AstraZeneca

Discussion Document	
Drug name	SEROQUEL™ (quetiapine fumarate)
Date	June 2007

'PRIVILEGED AND CONFIDENTIAL DRAFT FOR LEGAL REVIEW'

Discussion Document
SEROQUEL and Glucose dysregulation

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

Author: Lisa Boornazian BSN, RN
Safety Surveillance TA Team Leader
Drug Safety, Wilmington DE

Leigh Jefferies, MD
Global Drug Safety Physician
Drug Safety, Wilmington, DE, USA

Eileen Ming, Sc.D, M.P.H.
Director and Senior Research Scientist, Epidemiology
Discovery Medicine and Epidemiology, Wilmington, DE, USA

CONFIDENTIAL
AZSER14868252

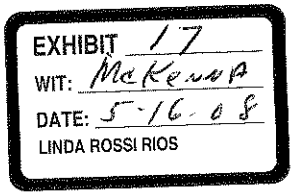


TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

SUMMARY

Having received the results of two placebo controlled clinical trialsdesigned to evaluate quetiapine and mood stabilizer as long-term maintenance therapy of bipolar disorder, the topic of glucose dysregulation including diabetes mellitus (DM), hyperglycemia, diabetic ketoacidosis (DKA), and diabetic coma was identified as a topic of review at SERM (Safety Evaluation and Review Meeting). This document provides a comprehensive review of the published literature, AstraZeneca sponsored clinical trials, and post-marketing reports regarding SEROQUEL and this topic.

According to the literature, the prevalence of DM in the schizophrenic population (up to 15.8% in one study [Mukherjee et al 1996] and 10.8-14.9% in another study [Dixon et al 2000]) has been noted to exceed that in the general population (7.3%/United States [US] [Mokdad et al 2001]) even prior to the introduction of atypical antipsychotic medications. Furthermore, a recent study (Ryan et al 2003) showed impaired fasting glucose tolerance in drug-naïve schizophrenic patients. In addition to schizophrenia, other studies have suggested that there is an increased prevalence of DM in patients with other psychiatric disorders (ie, bipolar disorder, anxiety, depression) compared to the general population (Regenold et al 2002, Everson Rose et al 2004).

The medical/scientific literature was inconsistent with regard to quetiapine and diabetes. The various data sources and analytic techniques used, each with its own strengths and weaknesses have contributed to an array of results. Some authors have found an increased risk for SEROQUEL and some have found no increased risk compared to a variety of different comparator groups. Limitations in these studies included in appropriate comparison groups, lack of information on major known risk factors for diabetes (e.g. obesity, family history, physical activity, co-morbidities, co-prescriptions), the potential for confounding by indication, lack of systematic screening for diabetes in the subject population, and questionable generalizability due to restrictive inclusion criteria. In sum, the epidemiology literature has been inconsistent with regard to quetiapine and diabetes. Inherent methodological issues contribute to the challenges of studying this complex question.

Trials 126 and 127 were two long term clinical trials designed to compare the efficacy and safety of quetiapine to placebo when used as adjunct to mood stabilizers (lithium or valproate) in the maintenance treatment of bipolar I disorder in adult patients. These two trials were not designed to evaluate diabetic status. The pre-planned analyses of glucose metabolism laboratory data, the summary of aggregated AE terms predefined by AstraZeneca as "potentially associated with diabetes" reported in the randomized treatment phase, the outcome of the post-hoc adjudication of cases of interest and the outcome of the post-hoc exploratory analyses all summarized here, were also presented to and discussed with an external diabetologist, Dr Robert Ratner.

Among patients treated with quetiapine and a mood stabilizer (lithium or valproate) for at least 12 weeks and then randomized to continue with quetiapine and a mood stabilizer or switch to placebo and a mood stabilizer and followed for up to 2 years:

- In the randomized phase quetiapine and a mood stabilizer was associated with a greater mean increase from baseline than placebo and a mood stabilizer in blood glucose (5.05 mg/dL) and HbA1c (0.14%). In patients whose last meal was at least 8 hours before venipuncture the mean difference between quetiapine and placebo was 5.49 mg/dL for glucose and 0.15% for HbA1c.

- The incidence density of a single emergent fasting blood glucose value ≥126 mg/dL was higher in patients randomized to quetiapine and mood stabilizer (18.03 patients per 100 patient-years) than in patients randomized to placebo and mood stabilizer (9.53 patients per 100 patient-years). The incidence of values ≥126 mg/dL was analyzed using a Poisson regression model adjusting for exposure time. The estimated ratio (quetiapine adjunct with lithium or valproate vs placebo adjunct with lithium or valproate) of incidence densities was 1.893 with a 95% confidence interval between 1.109 and 3.231.

- In the randomized phase there were 6 (0.93%) reported adverse events of diabetes (including one case of diabetic ketoacidosis) in the quetiapine and mood stabilizer group and 1 (0.15%) in the placebo and mood stabilizer group. When adjusting for treatment exposure in the randomized phase, the incidence densities were 1.6 cases per 100 patient-years for quetiapine compared to 0.4 cases per 100 patient-years for placebo.

Given the absence of definitive diagnostic testing for diabetes within the design of these studies (Trials 126 & 127), as hereafter described in detail , reliable and accurate determination of incidence and risk for diabetes for patients enrolled in these studies is not possible. Subject to the limitations hereafter described , the calculated absolute risk of onset of possible diabetes by adjudicated post-hoc analysis is low (0.72% - 23 patients divided by 3187 patients in the open-label safety population not classified as "diabetic" according to pre-defined criteria at enrollment). However during the randomized phase an approximately 2-fold increase in incidence density over placebo in observations of glucose values ≥126 mg/dL was observed.

Only one AstraZeneca clinical trial (Trial 125) to date had changes in glucose regulation as its primary endpoint. In this trial, the comparison groups were patients treated with olanzapine and those treated with risperidone. The primary objective of Trial 125 was to compare the safety/tolerability profile of quetiapine and olanzapine on glucose metabolism in schizophrenic patients by evaluating change from randomization in AUC (area under the curve) plasma glucose values following oral glucose tolerance test (OGTT). The analysis of mean glucose values at separate time points during the OGTT showed, that while fasting glucose and 30 min glucose levels were similar across the treatment groups at Week 24, the quetiapine group had lower plasma glucose values than both olanzapine and risperidone at 60, 90 and 120 minutes (2-hours) after the glucose load. For mean 2-hour-glucose value, no change from randomization at Week 24 was observed in the quetiapine group, while in the olanzapine and risperidone groups mean increases in 2-hour glucose from randomization at

Week 24 were seen. Thus, after 24 weeks of treatment, there appeared to be a difference between the patients in the three treatment groups in the ability to handle glucose challenge.

In addition, relevant data from AstraZeneca's cumulative clinical trial database (Safety 9.1) were reviewed. Since DM and hyperglycemia are medical diagnoses that are based on laboratory data, the laboratory data from the trials in the Safety 9.1 database were reviewed for information regarding glucose metabolism. Until recently, fasting glucoses were not obtained in the majority of AstraZeneca's clinical trials; the interpretative value of the non-fasting lab data is limited. In the majority of the trials the mean change from baseline in quetiapine-treated patients was similar to that which was seen in placebo-treated patients. For completeness, adverse event data from these trials were also reviewed, however it should be noted that in the majority of AstraZeneca clinical trials a pre-existing history of DM would not exclude a patient from participating in the trial.

A search of AstraZeneca's worldwide safety database (Clintrace) on 01 March 2007 identified 1679 (completed) adverse event reports of DM and/or diabetes related events. Assessment of causality was not possible in these cases because of incomplete clinical information, unclear temporal sequence of exposure and outcome, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (e.g. obesity or family history of DM), documented dietary non-compliance, and/or alternative explanations. Since the time of this search (01 March 2007) and as of 30 March 2007, AstraZeneca has received an additional 54 initial legal reports and 2503 follow-up legal reports. For almost all of these legal cases, the information provided is in the form of a civil complaint containing no clinical information or a plaintiff fact sheet. AstraZeneca is treating these plaintiff fact sheets as medically confirmed and submitting them to regulatory authorities as such.

It has been estimated that about 23.2 million patients worldwide (an estimate of almost 14.4 million patients in the US and 8.8 million patients in the rest of the world [ROW]) have been exposed to SEROQUEL for all time through February 2007 for the US and through 2006 for ROW.

1. INTRODUCTION

The purpose of this document is to review relevant information such as, pre-clinical and clinical study data, the scientific/medical literature, and post-marketing adverse event reports received by AstraZeneca regarding the association of glucose dysregulation including DM, DKA, diabetic coma, and/or exacerbation of DM with SEROQUEL treatment in adult patients and to assess whether the Core Data Sheet (CDS) for SEROQUEL requires amendment to reflect the company's current understanding of the subject.

2. BACKGROUND

2.1 Seroquel

SEROQUEL™ (quetiapine fumarate, quetiapine) was first approved for marketing in the United Kingdom on 31 July 1997 and was first launched in the United Kingdom on 22 September 1997 for the treatment of psychosis/schizophrenia and is currently approved in 85 countries for this indication. It was first approved for bipolar mania in Mexico in June 2003 and is currently approved in 77 countries for this indication. In October 2006 the United States (US) was the first country to approve SEROQUEL for bipolar depression.

SEROQUEL is indicated for the treatment of acute and chronic psychoses, including both positive and negative symptoms of schizophrenia, manic episodes in bipolar disorders, and bipolar depression. It is an atypical antipsychotic agent, which interacts with a broad range of neurotransmitter receptors. SEROQUEL exhibits affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. SEROQUEL also has high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

2.2 Core Data Sheet for Seroquel and DM or diabetes related events

The AstraZeneca CDS presents the company position on the prescribing information for SEROQUEL and provides a reference for consistency of product information documents in individual markets.

Glucose dysregulation including DM, hyperglycemia, DKA, diabetic coma, hyperglycemia, an/or exacerbation of DM is not referenced in the SEROQUEL CDS.

2.3 Exposure to SEROQUEL

It has been estimated that about 23.2 million patients worldwide (an estimate of almost 14.4 million patients in the US and 8.8 million patients in the rest of the world [ROW]) have been exposed to SEROQUEL for all time through February 2007 for the US and through 2006 for ROW.

2.4 Diabetes mellitus

Diabetes is one of the most common non-communicable diseases globally. (Diabetes Atlas 2003).

Globally, the prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030 (Wild et al 2004). Among adults, the prevalence is 5.1% in 2003, expected to increase to 6.3% by 2025 (Diabetes Atlas 2003). The total number of people with diabetes is projected to double between 2000 (171 million) and 2030 (366 million), based solely on demographic changes, assuming that age-specific prevalence remains constant. Given the increasing prevalence of obesity, it is likely that these figures provide an underestimate of future diabetes prevalence The greatest relative increases will occur in

Middle Eastern Crescent, sub-Saharan Africa, and India. The greatest absolute increase in the number of people with diabetes is projected to be in India. Most of the expected population growth between 2000 and 2030 is expected to be concentrated in the urban areas of the world, and the urban population in developing countries is projected to double between 2000 and 2030 (Wild et al 2004).

The estimated prevalence and number of cases in seven global regions in 2003 are: Africa (2.4%, 7.1 million), Eastern Mediterranean and Middle East (7.0%, 19.2 million), Europe (7.8%, 48.4 million), North America (7.9%, 23.0 million), South and Central America (5.6%, 14.2 million), South-East Asia (5.6%, 39.3 million), and Western Pacific (3.1%, 43.0 million) (Diabetes Atlas 2003). The 10 countries with the highest numbers of estimated cases of diabetes for 2000 are: India (32 million), China (21 million), US (18 million), Indonesia (8 million), Japan (6.8 million), Pakistan (5 million), Russian Federation (5 million), Brazil (5 million), Italy, (4 million) and Bangladesh (3 million) (Wild et al 2004). The highest prevalence of diabetes in 2003 can be found in Nauru (30.2%), United Arab Emirates (20.1%), Bahrain (14.9%), Kuwait (12.8%), Tonga (12.4%), Singapore (12.3%), Oman (11.4%), Mauritius (10.7%), Germany (10.2%) and Spain (9.9%) (Diabetes Atlas 2003). In 2003, Austria had a prevalence of 9.6%, Belgium 4.2%, Denmark 6.9%, Finland 7.2%, France 6.2%, Germany 10.2%, Greece 6.1%, Italy 6.6%, Netherlands 3.7%, Sweden 7.3%, Switzerland 9.5%, and UK 3.9% (Diabetes Atlas 2003). In developing countries, the majority of people with diabetes are in the 45- to 64-year age group; the majority of people with diabetes in developed countries are >64 years of age. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men (Wild et al 2004).

In the last 15 years, the number of people in the US with diagnosed diabetes has more than doubled, reaching 14.6 million in 2005. Although more than 20.8 million Americans have diabetes (7.0% of the population), 6.2 million do not know they have the disease. Among those age 20 or older, 20.6 million or 9.6% have diabetes (10.9 million or 10.5% of men, 9.7 million or 8.8% of all women). Among those age 60 or older, 10.3 million or 20.9% have diabetes (CDC 2005). The prevalence of diabetes varies considerably by ethnicity: 8.7% of all non-Hispanic whites aged 20 or older have diabetes, while 13.3% of adult non-Hispanic blacks, 9.5% of the adult Hispanic/Latino population, and 12.8% of adult American Indians and Alaska Natives do (CDC 2005). 1.5 million new cases of diabetes were diagnosed in people age 20 years or older in 2005 (CDC 2005).

2.4.1 Information from FDA AERS database

Using post marketing data sets, different quantitative signal detection tools can be employed to explore for a possible association between a drug and an event. Proportional reporting ratio (PRR) compares a target event drug rate with the rate of that event for all other drugs in a database. A PRR of ≥2.0 when the number of reports is ≥3 and the CHI square is ≥3.96 signifies a potential signal. AstraZeneca obtained PRR for SEROQUEL using the FDA's Adverse Event Reporting System (AERS) database. In addition, another signal detection method includes the Multi-item Gamma Poisson Shrinker (MGPS), which computes relative reporting rates (Observed/Expected [O/E] ratios) for drug-event pairs. Bayesian statistical modeling is used to obtain a more stable estimate of O/E (or MGPS) and this is called the

empiric Bayesian geometric mean (EBGM). An EB05 is the lower bounds of the two-sided 90% confidence interval around an EGBM. An EB05 greater than two suggests that there is a possible association between the drug and event.

For all events possibly related to DM (see Table A174 Appendix A) the PRR using AERS data through 31 December 2006 is 2.681 and the EB05 is 1.724 when SEROQUEL is listed as either a suspect or a concomitant medication. Thus, the disproportionality analysis using PRR suggested a possible association and the EB05 did not suggest a possible association between DM related events and SEROQUEL. (The EB05 scores and PRRs for other antipsychotics are listed in Appendix A Table A173).

2.4.2 Type I Diabetes

Although it may occur at any age, Type I DM most commonly develops in childhood or adolescence and is the predominant type of DM diagnosed before age 30. This type of DM accounts for 10% to 15% of all cases of DM and is characterized clinically by hyperglycemia and a propensity to DKA (Beers and Berkow 1999). Common symptoms of Type I DM include polyphagia, constant hunger, polyuria, unexplained weight loss, rapid, labored breathing, vision changes, drowsiness or exhaustion. DKA is a life-threatening complication of DM, which is characterized by increased glucose levels and acidosis. Frequently DKA is precipitated by other medical illnesses ranging from mild (e.g. flu) to serious (e.g. myocardial infarction). In Type I DM, the pancreas (via β cells) produces little or no insulin. The disease results in a genetically susceptible individual, from an immune-mediated, selective destruction of > 90% of the insulin-secreting β cells. The pancreatic islets exhibit insulitis, which is characterized by an infiltration of T lymphocytes accompanied by macrophages and B-lymphocytes, and by the loss of most of the β cells, without involvement of the glucagon-secreting α cells. The β cell destruction is carried out by cell-mediated immune mechanisms. The antibodies present at diagnosis usually become undetectable after a few years. They may be primarily a response to β cell destruction, but some are cytotoxic for β cells and may contribute to their loss. The clinical onset of Type I DM may occur in some patients, years after the insidious onset of the underlying autoimmune process. (Beers and Berkow 1999, Beaglehole and Lefebvre 2004)

2.4.3 Type II Diabetes

Type II DM is more commonly diagnosed in patients >30 years, but it also occurs in children and adolescents. Hyperglycemia and insulin resistance are the clinical characteristics of Type II DM. Symptoms of Type II DM are similar to those seen in Type I DM but are less obvious. Frequently patients are diagnosed many years after the onset of DM. Consequently, half of all people with Type II DM are undiagnosed. Although most patients are treated with diet, exercise, and oral drugs, some patients intermittently or persistently require insulin to control symptomatic hyperglycemia and prevent non-ketotic hyperglycemic-hyperosmolar coma (NKHHC). Type II DM is commonly associated with obesity, especially of the upper body (visceral/abdominal). Type II DM patients with visceral/abdominal obesity may have normal glucose levels after losing weight. (Beers and Berkow 1999, Beaglehole and Lefebvre 2004).

2.4.3.1 Risk factors for developing Type II DM

Type II DM results by the interaction between genetic pre-disposition and a number of life style factors (Ananth et al 2005). The following factors have been associated with the development of Type II DM (see Table 1).

Table 1 Major risk factors for Type II DM

Family history of DM (ie, parents or siblings with DM)	Cigarette smoking
Overweight (BMI ≥25 kg/m^2)	Previously identified impaired fasting glucose or impaired glucose tolerance
Habitual physical inactivity	Hypertension (≥140/90 mm Hg in adults)
HDL cholesterol ≤35 mg/dL (0.90 mmol/L) and/or a triglyceride level ≥250 mg/dL (2.82 mmol/L)	Race/ethnicity (e.g., African Americans, Hispanic Americans, Native Americans, Asian Americans and Pacific Islanders)
History of gestational DM or delivery of a baby weighing >9 lb	

BMI = body mass index, HDL = high density lipoprotein (Larsen et al 2003)

3. THE LITERATURE

3.1 Search strategy

A search of the scientific/medical literature through 27 February 2007 for SEROQUEL, to obtain information on or about glucose dysregulation , was performed utilizing AstraZeneca's in house database for indexing biomedical literature, which searches over 14,000 journals daily. Additional articles were found through other channels (reference lists, tables of contents of relevant journals, information from colleagues). Articles included contain an explicit statistical comparison of the prevalence or incidence of diabetes in patients prescribed quetiapine versus either conventional antipsychotics (an individual conventional antipsychotic or conventional antipsychotics as a group) or no exposure to antipsychotics. Studies without such an explicit statistical comparison, but that included some information about glucose metabolism or diabetes specifically for quetiapine patients were also explored briefly.

3.2 Overview

The purpose of this document is to review and analyze available epidemiologic literature assessing a potential relationship between quetiapine use and diabetes or glucose metabolism. Articles included contain an explicit statistical comparison of quetiapine versus either conventional antipsychotics (an individual conventional antipsychotic or conventional antipsychotics as a group) or no exposure to antipsychotics.

Clinicians have noticed a potential increased prevalence of diabetes among patients with schizophrenia and other psychiatric disorders for over a century, and mechanisms for this association have been hypothesized. Also, some have suggested a unique increased risk for diabetes associated with antipsychotics, and atypical antipsychotics in particular. Various pharmacoepidemiologic methods are available for exploring this association, and challenges

around data sources, methods, and specific exposure and outcome definitions have resulted in a range of studies of varying quality and varying conclusions.

Eighteen studies were found that specifically provide a formal statistical comparison between quetiapine and either conventional antipsychotics exposure or no antipsychotic exposure. Some found an increased risk for quetiapine compared to no antipsychotic exposure or conventional antipsychotic exposure. Some found no increased risk for quetiapine compared to no antipsychotic exposure or conventional antipsychotic exposure. In particular, two studies varied the analytic methods used to explore the relationship within their databases, and both showed that whether quetiapine is found to be associated with diabetes depends on the analytic methods used. Some studies also suggest that physicians may be "channelling" patients with pre-existing diabetes or at higher risk of developing diabetes to quetiapine.

In summary, the array of epidemiology studies examining the potential for a prospective association between quetiapine and diabetes are inconsistent. Inherent methodological issues contribute to the challenges of studying this complex question.

3.3 Prevalence of DM in psychiatric disorders

3.3.1 Prevalence of known diabetes in schizophrenia patients

Several studies have also shown a substantially higher prevalence of diabetes in populations with schizophrenia than in others. In the US, Medicare and Medicaid data from 1991 showed a prevalence rate of diabetes in schizophrenia patients of 12.5% and 11%, respectively (Dixon et al 2000). The prevalence of current diabetes in a cohort of patients being treated for schizophrenia that was part of a Schizophrenia Patient Outcomes Research Team (PORT) study was 11%; 15% of participants reported ever having diabetes (Dixon et al 2000). (Mukherjee et al 1996) found an overall prevalence of known diabetes of 15.8% in a cohort of patients with schizophrenia admitted to a long-term care facility in Italy, which is substantially higher than the estimated 2% to 3% prevalence of diabetes in the general population of Italy (Bruno et al 1992, Verrillo et al 1985). On the other hand, analysis of the National Hospital Discharge Survey from 1979-1989, before the introduction of atypical antipsychotics, found that schizophrenia inpatients and medical inpatients had similar diabetes prevalence rates (Basu and Meltzer 2006).

Age, ethnic origin, and geographical location all appear to alter the prevalence of diabetes mellitus and impaired glucose tolerance in those with psychiatric disorders. For example, in the Medicaid data, 6.7% of those ages 18-44 and 18.8% of those over age 44 had diabetes, 4.3% of men and 15.0% of women had diabetes, and 18.5% of blacks and 11.5% of whites had diabetes (Dixon et al 2000). The prevalence of known diabetes in Mukherjee's patient cohort increased with age, from 0% in individuals younger than 50 years, to 12.9% in the 50–59 years age group, and to 18.9% in the 60–69 years age group. The prevalence of diabetes decreased to 16.7% in patients aged 70–74 years and to 9.4% in those aged over 75 years, which likely indicates selective mortality (a healthy survivor effect) (Mukherjee et al 1996). Similarly, a study of 3474 patients with schizophrenia in France found that the incidence of

diabetes was twofold and fourfold higher than it was in the general population, for male and female patients, respectively (Casadebaig et al 1997).

A systematic evaluation of risk factor profiles of patients with treatment-emergent diabetes in data from 24 clinical trials database attempted to identify common characteristics of patients who developed diabetes during trials Cavazzoni et al 2004). In this database, 86 (1.8%) of 4820 schizophrenia patients without pre-existing diabetes developed diabetes. The majority of patients who were identified as developing diabetes were likely to have pre-existing, unrecognized glycemic abnormalities or to have had a greater burden of pre-existing risk factors for diabetes than patients who appeared to maintain normo-glycemia. In addition, elevated baseline non-fasting glucose level and prevalence of multiple risk factors for diabetes appear to have a major impact on the risk of developing diabetes, whereas the impact of treatment-emergent weight gain on short term (<6 months) risk of emergent diabetes was relatively small. Key baseline risk factors were age ≥45 years, baseline non-fasting glucose >120 mg/dL, non-Caucasian origin, baseline hypertension, female gender, and weight gain.

3.3.2 Prevalence of diabetes in screened schizophrenia populations

Studies assessing the prevalence of diabetes in people with schizophrenia broadly agree that there does appear to be increased risk, as described above. There is, however, significant variability in the reported prevalence rates from different studies. One major confounder when attempting to establish a true prevalence figure in schizophrenia and other populations is the number of people who have been actively screened. Lack of adequate access to health care, seeking care from no provider other than psychiatric specialists, and other biases (Gupta et al 2003) may lead to substantial underdetection. The symptoms of the psychosis itself may hinder the ability or willingness of the patient to communicate potential physical problems (Felker et al 1996; Jest et al 1996).

Screening for glucose tolerance will certainly produce a greater number of cases than the apparent prevalence based on usual care. A chart review of 607 schizophrenic residents of a long-term care ward in Singapore who were naïve to atypical antipsychotics found the prevalence of known diabetes to be 5%. After screening, another 16% were found to have diabetes, bringing the total diabetes prevalence rate to around 21%. In those age <60 years, the prevalence rate was double that of the general Singapore population, but in those aged 60 years and above, it was lower than the general population. In this study, the prevalence of impaired glucose tolerance was 31%, and the highest rate of diabetes (50%) was found in patients aged 50–59 years (Subramaniam et al 2003).

In 607 patients with schizophrenia at the Maudsley Hospital in London, the prevalence rate of diabetes and impaired glucose tolerance rose from 8.6% to 19.4% after prospective blood glucose testing (Bushe and Holt 2004; Taylor et al 2003). Another study that conducted active screening in a cohort of 153 patients who had been taking antipsychotics found that 31% of individuals had either diabetes or impaired glucose tolerance, and that in the majority (67%) the condition was previously unidentified (Cohn et al 2002). Similarly, of 200 patients with schizophrenia in the Netherlands, the prevalence of diabetes was 14.5%, of which 8% was previously known and 6.5% was newly diagnosed (Cohen et al 2006).

Further, a study of young (mean age = 33.6 years) patients with first-episode schizophrenia who were drug-naïve allowed a separation of the effects of the disease from the potential confounding effects of any antipsychotic medication. Despite being young and never having been exposed to neuroleptics, more than 15% of the individuals in this study had already developed impaired fasting glucose tolerance, compared with none of the matched healthy control groups (Ryan et al 2003).

3.3.3 Prevalence of diabetes in other psychiatric disorders

Schizophrenia is only one of several psychiatric disorders in which there appears to be a relatively high prevalence of abnormal glucose metabolism. Medical records of 254 inpatients aged 50-74 with a diagnosis of an Axis I psychiatric disorder found rates of type 2 diabetes of 50% in schizoaffective patients, 26% in bipolar I patients, 18% in major depression patients, 18% in dementia patients, and 13% in schizophrenia patients (Regenold et al 2002).

Affective disorders have been associated with diabetes in several studies. Among 345 inpatients with bipolar disorder, 9.9% were found to have diabetes; substantially more than the 3.4% expected prevalence based on age- and sex-adjusted national norms (Cassidy et al 1999). A Canadian case-control study found that those age 20-50 with diabetes were 30% more likely to have a history of depression than those who did not have diabetes; this association did not persist in those age ≥51 years (Brown et al 2005). Another study found an increased risk for diabetes in middle-aged women, primarily mediated through central adiposity; however, African-American women with depression had an increased risk for diabetes independent of central adiposity and other risk factors (Everson Rose et al 2004). The cross-sectional German National Health Interview and Examination Survey found that affective disorders (including depression, bipolar, etc.) and anxiety disorders were associated with an increased prevalence of diabetes; however, the increase was not statistically significant after controlling for age, sex, socioeconomic status, and marital status (Kruse et al 2003).

3.3.4 Potential mechanisms

Reasons for an increased prevalence of diabetes among patients with schizophrenia remain speculative. The mechanisms behind the association between schizophrenia and diabetes are likely to be multifactorial and to include environmental, genetic, and neuroendocrine factors.

3.3.4.1 Genetic factors

Genetic factors appear to have a key role in the association between schizophrenia and diabetes, since it has been reported that up to 50% of individuals with schizophrenia have a family history of type 2 diabetes, compared with just 4.6% of healthy adult controls (Cheta et al 1990, Dynes 1969, Lamberti et al 2003; Mukherjee et al 1989). A large chart review (Lamberti et al 2003) found a family history of type 2 diabetes in 17% of the total cohort of 436 schizophrenia patients. Importantly, in the cohort of patients who had a positive family history of diabetes, the prevalence of diabetes mellitus was 33%. In those with a negative family history of diabetes, its prevalence was just 10%. (Mukherjee et al 1989) investigated the incidence of diabetes in the parents and grandparents of patients with schizophrenia who were under 45 years old and had no signs of diabetes or impaired glucose tolerance. The

incidence of diabetes in the parents, who were all >50-year old, was 12%, twice that expected in an age-matched population. Of the 70 patients studied, 19% had at least one parent with type 2 diabetes and 16% of the remaining patients had at least one grandparent with type 2 diabetes, giving 31% of the study population a family history of the disease. These data suggest that genetic factors may explain to some extent the higher diabetes prevalence figures found in patients with schizophrenia compared with the general population.

It is possible that a family history of diabetes could constitute an independent risk factor for schizophrenia via, in the case of maternal diabetes, effects on brain development and maturation of the brain, as insulin is known to have a role in brain maturation and that fetal α-melatonin-stimulating hormone, thought to be a determinant of early fetal growth, has been reported to be abnormally high in infants of mothers with diabetes (Mukherjee et al 1989). Alternatively, a gestational zinc deficiency may be a common etiology for diabetes and schizophrenia, as this might damage organs with high zinc requirements such as the pancreas and the hippocampus (Andrews 1992).

3.3.4.2 Neuroendocrine factors

Patients with schizophrenia appear to show overactivation of both the hypothalamic-pituitary-adrenal and sympathoadrenal medullary axes, manifested by increased production of cortisol and adrenaline. Both of these hormones are known to be diabetogenic and may play a role in the onset of diabetes in schizophrenia (Dinan 2004). Thus, as people with schizophrenia are exposed to a broad range of psychological stressors (Dinan 2004), stress may play a critical role in the progression of schizophrenia and the development of diabetes (Ryan and Thakore 2002).

Obesity is highly prevalent among patients with schizophrenia, and excessive consumption of fast food (Peet 2004) has been implicated in the schizophrenia/obesity comorbidity. As one review suggests, "It has been hypothesized that brain reward function would be a relevant etiologic factor in both schizophrenia and overeating. A mesolimbic hyperdopaminergic state may render motivational/incentive reward system insensitive to low salience/palatability food. This, together with poor cognitive control from hypofunctional prefrontal cortex and enhanced hedonic impact of food, owing to exaggerated opioidergic drive (clinically manifested as pain insensitivity, may underlie unhealthy eating habits in patients with schizophrenia" (Elman et al 2006).

3.3.4.3 Environmental factors

Many people with schizophrenia exhibit poor health behaviors that may also contribute to their developing diabetes; these include (1) having less healthy diets (generally high in fat and low in fibre), (2) exercising less, and (3) smoking more than normal controls (Brown et al 1999). Various studies have reported that between 60% and 90% of patients with schizophrenia are nicotine dependent and that 20-70% indulge in substance abuse at some time in their lives (Ryan and Thakore 2002). Poverty, unstable living conditions and lower than expected educational attainment are all associated with schizophrenia, and also increase the risk of obesity and other adverse medical sequelae (Dixon et al 2000). There is also evidence that patients with schizophrenia have a higher waist-to-hip ratio than the general

population, an indication of increased visceral fat deposition (Ryan and Thakore 2002). Patients with schizophrenia generally have poorer physical health (Brown et al 1999; Osborn 2001), and less than adequate overall health care (Phelan et al 2001; Wang et al 2002) compared to the general population. Additional factors thought to predispose individuals with schizophrenia to developing diabetes include ethnicity, a history of glucose dysregulation, and pre-existing hypertension (Bushe and Holt 2004). All these characteristics are established risk factors for diabetes and might therefore help to explain the increased incidence of the disease among patients with schizophrenia (Rouillon and Sorbara 2005).

3.4 Epidemiological studies

3.4.1 Study designs

Several epidemiologic study designs have been used to explore the question of whether antipsychotics are associated with diabetes onset. Case-control studies compare those with diabetes (cases) with those without diabetes (controls), looking for differences in antecedent exposure to antipsychotics. Cohort studies identify people exposed to antipsychotics (specific antipsychotics, or antipsychotics in general) and a comparison group (other antipsychotics, or no exposure to antipsychotics), and follow them over time for differences in development of diabetes.

Most studies are retrospective, using data sources that already exist, such as medical records or insurance claims. As such, these studies are subject to limitations in the validity of retrospectively collected exposure and outcome information that was not collected for the purpose of research. A well-done prospective study, with or without intervention, has been prohibitively impractical thus far. The incidence rate of new onset diabetes in people with normal glucose is sufficiently low that a prospective study to assess whether antipsychotics are definitively associated with de novo diabetes would have to follow thousands of patients on different antipsychotic regimens for several months or years.

One investigator (Gianfrancesco et al 2006a) was able to illustrate the importance of study design by conducting multiple case-control and cohort studies, with slight variations in exposure or outcome definitions, within a single data source. This is described in Section 1.1.1.1.

3.4.1.1 Data sources and populations studied

Primary data collection

Ideally, to determine the true incidence rate of diabetes in psychiatric patients taking antipsychotics, one would randomize a very large population of people with various psychiatric disorders with normal glucose to various antipsychotics and prospectively follow them with periodic testing for several months or years. Such primary data collection, with the requisite sample size, has not occurred. The association between quetiapine and diabetes has only been assessed as a secondary or tertiary objective of small prospective studies, such as (Emsley et al 2005), which randomized schizophrenia patients with tardive dyskinesia to variable doses of quetiapine or haloperidol.

Electronic medical records

Electronic medical record systems, where a patient's medical records are recorded on the computer rather than on paper, are still relatively uncommon and are not generally set up to accommodate research. Such medical records would include demographic information, standard vital signs, diagnoses, prescriptions written, laboratory values, etc., and may include personal or family medical history.

In general, there are three types of medical record systems used for research: inpatient records for a single hospital system, records of general practitioners or primary care physicians using a particular brand of electronic medical record system, and an integrated inpatient and outpatient closed system. The inpatient and general practitioner record systems are obviously limited, as the information contained in them only includes inpatient experiences or visits to general practitioners, respectively; neither includes data from the other, and neither includes outpatient or ambulatory care specialist visits. In particular, without linkage to pharmacies, it is unknown whether a person fills a prescription given to them by their general practitioner. An example of the inpatient system is (Citrome et al 2004). An example of the general practitioner system is (Sacchetti et al 2005), which uses data from general practitioners in Italy, and (Koro et al 2002), which uses the General Practitioner Research Database in the UK.

The integrated inpatient and outpatient closed systems, such as Veterans Administration Health Systems and Cleveland Clinic, allow more thorough tracking of a patient through any health care resources used within the system, including pharmacy use. VA databases have been used in several studies, for example, (Cunningham et al 2003), (Sernyak et al 2002), (Lambert et al 2006b), and (Leslie and Rosenheck 2004).

Administrative database studies

Computerized administrative health databases have become widely used to study positive and negative effects of drugs in clinical practice, on a purely observational basis, with no intervention in medical care or interaction with patients. The data are collected for administrative purposes, such as reimbursement, and not for research. Such databases are readily available from a variety of sources, including pharmacy benefit managers (e.g., Advance PCS), government (e.g., Medicaid, Medicare, Saskatchewan Health Database), and managed care organizations (e.g., Ingenix Research Database, Pharmetrics).

In general, pharmacy databases contain only information that pharmacies would have available to them:

- Patient demographic information: year of birth, sex
- Prescriptions: date, specific drug & dose (NDC code), and quantity dispensed (number of doses), number of days supply dispensed

The government and managed care databases additionally contain the information that a health professional would submit to the health insurance company for payment.

- Medical encounters: date of service, type of place of service (outpatient, inpatient, ER, rehab, nursing home, etc.), and diagnoses (ICD9 codes) and procedures (CPT codes) that the health professional bills to the insurance company

- Insurance plan information (e.g., HMO, PPO, etc.), financial transactions (e.g., copayment), and dates of enrolment in the health plan

- Provider information: specialty (e.g., pediatrics, chiropractic, physical therapy)

Note that the information available from these databases is purely based on reimbursement claims for health-related services. Prescription data has been shown to be fairly accurate (West et al 2005), though prescription sampling would not be captured, and the extent of actual use of the prescription is unknown.

Diagnoses may be coded because the provider has diagnosed the patient with that condition, the provider merely examined the patient for that condition, or the provider has ruled out that condition. In some cases, patients request that the provider do not code for his/her actual condition if he/she is concerned about employment or insurability consequences. Further, providers or their coders may code for a similar condition, but not the exact condition the patient has, depending on reimbursement or patient insurance coverage limitations (Wynia et al 2000). Studies have shown that medical claims have limited sensitivity and specificity (Strom 2001); therefore, case adjudication is required if study results are to be considered valid.

These databases do not include any health care not reimbursed (whether because the services are not covered or a claim is not submitted); for example, if someone has Medicare plus additional coverage, the Medicare database only contains data on services Medicare covers, and the managed care organization's database often only contain data on services it covers, and the two cannot be linked to one another due to privacy concerns. There is important information that is not associated with reimbursement but could be important to the research question that is not included (ie, weight, disease severity, laboratory values, family history, etc.). Further, managed care databases under-represent those who are eligible for Medicaid or Medicare.

Studies using pharmacy databases include (Buse et al 2003), (Feldman et al 2004), and (Ostbye et al 2005). Studies using Medicaid data include (Gianfrancesco et al 2006*a*), (Lambert et al 2002) and (Lambert et al 2005). Studies using commercial claims databases were (Gianfrancesco et al 2003) and (Miller et al 2005).

3.4.1.2 Exposure and outcome definitions

Conflicting results from various studies may be related to the serious methodological limitations inherent to analyses involving insurance claims databases. These limitations include, but are not restricted to, the lack of any direct measure of glucose metabolism, high rates of polypharmacy, and the lack of verification of psychiatric diagnosis and whether the treatment(s) were even received (Haupt and Newcomer 2001).

Further, given the lack of randomization of patients in observational studies, selection bias often emerges as a potential threat to valid findings, particularly when studying drugs used to treat a very limited proportion of the population with specific conditions (Mamdani 2005). A major consequence is the difficulty in determining an appropriate comparison group to this unique patient population. In isolating the association between antipsychotics and diabetes relative to a comparison group in a valid manner, there needs to be a high level of confidence that potentially confounding variables are adequately identified and appropriately handled. Unfortunately, large administrative databases rarely contain sufficient levels of detailed clinical information to adequately assess the nature of selection bias that may be involved (Mamdani 2005). Some methods have evolved to adjust for selection bias, such as propensity score, but which have not been used in these studies.

How antipsychotic exposure is defined

There are several issues around defining drug exposure that may impact a study's results and interpretation. Some studies have applied less precise methods for associating diabetes with specific antipsychotics, whereas other studies have been more careful to match the time of diabetes onset with the time of specific antipsychotic use: because of real-world practices of switching antipsychotics and prolonged periods of non-use of antipsychotics, less timing-sensitive methods have a greater likelihood of false associations between antipsychotics and diabetes. Some investigators have attempted to account for this by using the treatment episode as the unit of observation rather than the person (Gianfrancesco et al 2006a).

Further, most studies base antipsychotic exposure measures on pharmacy prescriptions filled as a proxy for actual consumption. However, variable adherence, as well as use of samples, may lead to significant differences between true exposure and prescriptions filled. For example, an analysis of the agreement between VA computerized medication lists and a detailed history by a clinical pharmacist found complete agreement for less than 5% of patients (Kaboli et al 2004).

How diabetes is defined

The varying definitions of the outcome of interest may completely alter results in a study. In this case, some studies count diabetes events based on treatment (a pharmacy claim), others use diagnosis (a medical claim), and still others use elevated glucose or glucose tolerance testing (laboratory values). Studies that use the prescription of a hypoglycemic agent as the indicator for the presence of diabetes mellitus may underestimate the prevalence of diabetes mellitus due to the extensive under-diagnosis of diabetes, and may include a degree of error that undermines the ability to reliably detect differences between medications (Haupt and Newcomer 2001). On the other hand, using medical claims may reflect mild but relevant cases of glucose intolerance, but they may also reflect patients who tested negative for this condition. To reduce the extent of misclassification, some studies require diagnosis codes for diabetes to be present on 2 or more separate days. Because examination for diabetes may not be random, but may depend on perceptions of diabetes risk associated with the newly prescribed antipsychotic, dependence on medical claims may create bias (Gianfrancesco et al 2003). One study (Barner et al 2004) used multiple ways to find people with the outcome

(antidiabetic prescription, notation of new diabetes in the medical record, or elevated blood glucose), illustrating that each method misses people identified through the other methods.

Another major issue is whether any diabetes, or type 1, or type 2, should be assessed as outcomes (Gianfrancesco et al 2006a). As the mechanism is not fully understood, and given the limitations of data sources, various investigators have chosen to include or exclude Type 1. Thus, the ICD-9 code for diabetes used in most studies is 250.xx, which includes both Type 1 and Type 2, though some, such as (Lambert et al 2005), excluded 250.x1 and 250.x3, codes indicative of Type 1 diabetes, while (Gianfrancesco et al 2003) only allowed 250 x0 and 250.x2, thereby excluding diabetes cases that have not been explicitly identified as Type 2.

"New users" and "new events"

Including all users of a drug in analyses may introduce two types of bias: 1) underascertainment of events that occur early in therapy, and 2) the inability to control for disease risk factors that may be altered by the study drugs (Ray 2003). A "new-user" design avoids these biases by including only patients in a defined population who start a course of treatment with the study medication. Study follow-up begins at the same time as initiation of therapy (usually termed the "index date"). The study is further restricted to patients with a minimum period of non-use (washout) prior to drug initiation.

In addition to subjects being new users of the drugs of interest, they should also be free of the outcome at the beginning of the study. Study designs that fail to account for pre-existing diabetes can bias comparisons if prescribing behavior is sensitive to the perceived risks associated with antipsychotics. That is, patients who already have diabetes or are at greater risk for diabetes may be more likely to be prescribed antipsychotics perceived by the clinician to be safer (Gianfrancesco et al 2006a). To account for this, most studies either screen subjects for diabetes, or specify that there must be no evidence of diabetes in a reasonable period of time before the beginning of the exposure. Studies vary on the time period that should be free of evidence of diabetes, which may have impact on results.

3.4.1.3 Other design considerations

Explanations for the varying results in different studies may have many sources, in addition to those described above, such as:

> Differing settings and data sources (each with its own set of selection and detection biases, varying distribution of risk factors, etc.): VA database, Medicaid, managed care, outside US
>
> Inclusion criteria: all patients taking antipsychotic agents; persons with psychiatric diagnoses
>
> Comparison groups: typical versus atypicals, among typicals, antipsychotic use versus no antipsychotic use, among persons with psychoses, and among persons without psychoses

Controlling for demographic and personal characteristics: age, sex, race, body mass index, weight gain

Control for clinical characteristics: other antipsychotic use, psychiatric diagnoses, treatment exposure duration, dosage, other drugs that may cause diabetes (steroids, beta-blockers, anticonvulsants, hypertension, dyslipidemia

Accounting for dose (e.g., different doses may imply the same degree of antipsychotic exposure for patients with different body weights (Gianfrancesco et al 2003))

Year of study (e.g., improved awareness of the possibility of blood glucose abnormalities meant that more patients taking antipsychotic medications might have been screened for diabetes, which might account for the apparently higher prevalence rates being reported compared with 10 years ago)

Type of psychiatric disorders diagnosed in the patients enrolled

Statistical analysis approach (e.g., because the incidence of diabetes might not be linearly related to time with more cases being experienced early, annualization of incidence density could inflate the true incidence, and Cox proportional hazards models may be more appropriate (Buse et al 2003))

Duration of observation period (e.g., if an antipsychotic may induce excess weight gain, potentially leading to diabetes, this may require longer time frames to be detected [Gianfrancesco et al 2006a])

Monotherapy only or combination therapy allowed: where different antipsychotics are used concurrently or a switch is in progress, attribution of association of diabetes with both antipsychotics is unavoidable and can result in an overstatement of diabetes risk for the safer product (Gianfrancesco et al 2006a).

Number of metabolic panels: if glucose testing was done more frequently for some antipsychotics, then there is more opportunity to find a positive test, such that more intensive screening for diabetes would result in a higher incidence (Lambert et al 2006a).

Method of adjustment for confounding: most studies enter variables into the statistical analysis to adjust for potential confounders; some additionally match on confounders, as in case-control studies. In one study, propensity scoring altered the results for some covariates, but not for the primary comparisons among antipsychotics (Yang et al 2006a).

1.1.1.1 Study design does impact results

Decisions on each of the above study design considerations may impact a study's results, potentially leading to conflicting results from different studies, or even within the same study.

One investigator attempted to elucidate the impact of study design choices by analyzing the same data in different ways, and comparing the results (Gianfrancesco et al 2006a).

To demonstrate the sensitivity of results to study design, a study using Medicaid data (Gianfrancesco et al 2006a) conducted statistical comparisons using three designs reflecting progressively stronger controls for confounding influences:

> Study design 1: no screening for pre-existing diabetes, antipsychotic monotherapy not required, diabetes identified with medical or prescription claims
>
> Study design 2: screening for pre-existing diabetes eight months before observation or treatment, antipsychotic monotherapy required, diabetes identified with medical or prescription claims
>
> Study design 3: screening for pre-existing diabetes eight months before observation or treatment, antipsychotic monotherapy required, diabetes identified with prescription claims only

Frequencies of diabetes occurrence in the antipsychotic treatment groups were compared with each other and with those of untreated patients under the three study designs. Study design 1 is the weakest, and study design 3 is the most stringent.

A total of 54,529 patients with psychoses were newly started on an antipsychotic, and had at least 2 contiguous prescriptions for the same antipsychotic, during 1999-1Q03, and 37,867 patients with psychoses who were not treated with antipsychotics or were not treated for long periods. Under study design 1, 20.2% of quetiapine patients had diabetes; under study design 2, 6.0% had diabetes; and under study design 3, 3.1% had diabetes. Compared to those untreated with antipsychotics, under study design 1, quetiapine patients had a statistically significant increased risk of diabetes (OR 1.27, 95% CI 1.20-1.35), but not under study design 2 or 3 (study design 2: OR 0.89, 95% CI 0.77-1.03; study design 3: OR 1.00, 95% CI 0.83-1.20). Therefore, this study shows that less rigorous study designs lead to apparent increased risk for quetiapine relative to conventional antipsychotics, but more rigorous study designs show no increased risk.

Notably, quetiapine (and ziprasidone) users more frequently had prior excess weight gain and prior use of statins or another antipsychotic than users of other antipsychotics. Further, over time (1999-2000 versus 2001-1Q03), there was an increase in diabetes frequency, with a simultaneous increase in dose, in patients treated with quetiapine. An increase in the percentage of patients with pre-existing diabetes was also observed in patients treated with quetiapine. This suggests that quetiapine may be disproportionately prescribed to those with excess risk for diabetes, potentially leading to the apparent increased risk for diabetes associated with quetiapine in study design 1, the weakest study design explored.

A replication of this study (Gianfrencesco et al 2006b), conducted in a commercial claims database (Pharmetrics), examining study designs 1 and 3 only, found similar results. A total of 37,250 treatment episodes with risperidone, olanzapine, quetiapine, or conventional

antipsychotics were identified, during 1999-1Q02, including 6476 patients on quetiapine, and 33,263 patients with psychoses who were not treated with antipsychotics during the observation period. Under study design 1, 9.0% of quetiapine patients had diabetes; and under study design 3, 1.1% had diabetes. Compared to those untreated with antipsychotics, under study design 1, quetiapine patients had a statistically significant increased risk of diabetes (OR 1.39*, 95% CI 1.25-1.56), but not under study design 3 (OR 1.09, 95% CI 0.74-1.61). For low, medium, and high doses of quetiapine, the same results were found, that is, statistically significant OR for the weaker design, non-statistically significant OR for the more robust study design, showing no increased risk with increased dose. Therefore, this study also shows that less rigorous study designs lead to apparent increased risk for quetiapine relative to conventional antipsychotics, but more rigorous study designs show no increased risk.

1.1.2 Review of the literature

The epidemiological studies that were identified from the search of the literature will be discussed in the following manner:

Studies suggesting increased risk associated with quetiapine versus no antipsychotic

Studies suggesting increased risk associated with quetiapine versus conventional antipsychotics

Studies showing no risk associated with quetiapine versus no antipsychotic

Studies showing no risk associated with quetiapine versus conventional antipsychotics

Studies suggesting channelling

Other studies with quetiapine

In general, the "index date" refers to the first day of exposure to a drug of interest, and the "index drug" is the specific drug. An asterisk indicates statistical significance at the 0.05 level.

1.1.2.1 Studies suggesting increased risk associated with quetiapine versus no antipsychotic

Three studies were found that compared quetiapine directly with groups using no antipsychotics, finding an increased risk compared to no antipsychotics; however, none restricted the comparison group to those with psychiatric disorders (a study that did this is described in Section 3.4.1.5), and all three studies also found no increased risk compared to conventional antipsychotics.

(Buse et al 2003) and (Feldman et al 2004) used the same pharmacy database to find people who filled a prescription for an antipsychotic during December 1998 to February 2000, after at least 6 months with no prescriptions filled for antipsychotics, comparing them to people who filled a prescription for any other drug during January 2000 to February 2000, but no antipsychotic for the 6 months before and 6 months after their index prescription. All subjects

were in the database for at least 12 months before their index prescription, with no use of an antidiabetic in those 12 months. (Buse et al 2003) included all patients over age 18, while (Feldman et al 2004) limited analyses to age 60+. Mean dose of quetiapine was only 79.9±96.7 mg/day in Buse, and 64.6±83.5 mg/day in Feldman. Both studies found a statistically significant positive association between quetiapine and diabetes, compared with no antipsychotic use (Buse: OR = 1.7*, 95% CI 1.2-2.4; Feldman: OR = 1.9*, 95% CI 1.3-2.9), but found a negative association compared with conventional antipsychotic use (Buse: OR = 0.7*, 95% CI 0.5-0.97; Feldman: for age 60-74, OR = 0.3*, 95% CI 0.1-0.7, for age 75+, OR = 0.7, 95% CI 0.7-1.7). The major limitation of these studies is that the comparison group, people who filled a prescription for anything other than an antipsychotic, may not be appropriate, considering the evidence supporting an increased prevalence of diabetes in psychiatric populations in general. Another significant limitation is the reliance on prescription data only, and the subsequent lack of information on psychiatric diagnoses and known major risk factors for diabetes (e.g., obesity, family history, comorbidities). The exposure experienced by this population may not be representative, as inclusion required monotherapy only, the exposure duration was relatively short (ranging from 68 to 137 days, probably partly due to the monotherapy requirement) and the doses were low (e.g., average 80 mg/day for quetiapine). Further, the investigators did not account for exposure to other potentially diabetogenic drugs.

The third study (Sacchetti et al 2005), a matched case control study, used the electronic medical records of 550 general practitioners in Italy, collected in January 1996 to March 2002. Subjects had to have no antipsychotic prescription provided at their last office visit before the index date, did not have diabetes at the time of the index date, and were followed for up to two years. The exposed were prescribed an antipsychotic on the index date and were only prescribed that same antipsychotic during follow-up; the unexposed were randomly selected from the rest of database, and had no antipsychotics during follow-up. Compared to the unexposed, quetiapine was associated with an odds ratio of 33.7* (95% CI 9.2-123.6). No difference was found between quetiapine and haloperidol patients, though the number of subjects was small (evidenced by the wide confidence intervals). Similar to the previous studies, the major limitation is that the comparison group, people not prescribed an antipsychotic, may not be appropriate, considering the evidence supporting an increased prevalence of diabetes in psychiatric populations in general. Other limitations include the lack of information on known major risk factors (e.g., obesity, family history), on whether prescriptions written were filled, and on prescriptions written by providers other than general practitioners, and the requirement of monotherapy potentially reducing generalizability.

These studies are subject to confounding, and only show that people who are given antipsychotics are at increased risk for diabetes compared to the general population. This could be due to the background of increased risk for diabetes associated with psychiatric illness, for example.

3.4.1.4 Studies suggesting increased risk associated with quetiapine versus conventional antipsychotics

Eight published studies were found that suggest an increased risk for diabetes associated with quetiapine versus conventional antipsychotics, though in three of the studies, the finding was limited to specific subgroups, which, for one study (Lambert et al 2005), became non-significant after adjustment for confounders. Another three of the eight studies (Cunningham et al 2003; Gianfrancesco et al 2006a; Gianfrancesco et al 2006b) demonstrated that the risk associated with quetiapine compared to conventional antipsychotics is clearly dependent on the analysis plan, even using the same database; (Gianfrancesco et al 2006a; Gianfrancesco et al 2006b) are described in Section 1.1.1.1.

(Citrome et al 2004) observed psychiatric inpatients that had been in the hospital for at least 60 days during January 2000 to December 2002, had at least one dose of an antipsychotic medication, and were known to not have any prescriptions for an antidiabetic since January 1994, or, for new patients, in their first 30 days. Cases had a first prescription for an antidiabetic; the associated antipsychotic was that administered within the previous 45 days. Compared with those only exposed to conventional antipsychotics, quetiapine was associated with a crude OR of 3.2* (95% CI 1.6-6.1) and an adjusted OR of 3.1* (95% CI 1.6-6.0). Interestingly, the OR was statistically significant for men (3.9*, 95% CI 1.5-9.9) but not for women (2.0, 95% CI 0.6-2.0). Limitations include the potential for confounding by indication, lack of systematic screening for diabetes in the subject population (in particular, potential for surveillance bias where patients on certain agents may be more closely monitored for adverse effects), lack of information on major known risk factors for diabetes (e.g., obesity, elevated insulin, family history, physical activity, co-morbidities, co-prescriptions), and generalizability to the vast majority of psychiatric patients, who are not so chronically and severely impaired as to require long term hospitalization.

Two studies were conducted by Lambert (Lambert et al 2002; Lambert et al 2005) using California Medicaid data. The preliminary study (Lambert et al 2002) was a matched case-control study, using data from 1997-2000, and included people with schizophrenia, age 18+, on an antipsychotic monotherapy. Subjects were continuously eligible and without diabetes for 12 or more weeks before their first diabetes diagnosis code; controls had no diabetes code. The associated antipsychotic was that dispensed during those 12 weeks. The study found a non-statistically significant crude OR, but a statistically significant adjusted OR of 1.5* (1.1-1.9) comparing quetiapine to conventional antipsychotics (adjusted for ethnicity, exposure to other diabetes-inducing medications). The larger study (Lambert et al 2005) used data from 1995-2000, replicated the study using a 12-week, a 24-week, and a 52-week exposure window, this time requiring a 6-month period before the first diagnosis of diabetes. This study found no increased risk for quetiapine overall (crude OR = 1.2, 95% CI 0.9-1.7; adjusted OR = 1.2, 95% CI 0.8-1.7). For lower doses (<250 mg/day), the crude OR was statistically significant (OR = 2.6*, 95% CI 1.3-5.2), while the adjusted OR was not (OR = 1.9, 95% CI 0.9-4.1). Neither crude nor adjusted OR was statistically significant for moderate and high doses, nor for any dose in the 24- and 52-week exposure window. Thus, this more rigorous design (longer screening period for diabetes, broken down by dose, with different exposure

windows) did not conclude any increased risk for quetiapine compared to conventional antipsychotics.

VA patients diagnosed with schizophrenia in October 1998 to September 1999 were observed during June 1999 to September 1999 (Sernyak et al 2002). Those with any medical encounter with a primary or secondary diagnosis of diabetes during those 4 months were considered to have the outcome. The associated antipsychotic was the last antipsychotic prescribed during the June 1999 to September 1999 period. This study found an increased risk for quetiapine compared to conventional antipsychotics overall (OR = 1.3*, 95% CI 1.1-1.6), but this increased risk was limited to those under age 40 (OR = 1.8*, 95% CI 1.1-3.2) and age 40-49 (OR = 1.9*, 95% CI 1.4-2.4), and was not found for those age 50-59 (OR = 1.2, 95% CI 0.9-1.6), age 60-69 (OR = 0.9, 95% CI 0.6-1.5) or age 70+ (OR = 0.6, 95% CI 0.3-1.3). As the occurrence of diabetes did not necessarily have to occur after exposure to the associated antipsychotic, this study was cross-sectional, and may only reflect drug choices made after the diabetes was diagnosed, artificially increasing the risk associated with a drug that may actually have a lower risk.

A recently published study (Lambert et al 2006a), available previously as an abstract (Cunningham et al 2003) and its slides, as presented at the 2003 International Conference on Pharmacoepidemiology (ICPE) conference, attempted to determine the relative risk of developing diabetes in schizophrenic veterans on atypical antipsychotic monotherapy compared to those on haloperidol monotherapy, using three data analysis methods, using VA databases. The first method used data only from patients known to be starting an antipsychotic after at least three months of no exposure (inception cohort design); compared to new users of haloperidol, quetiapine was associated with an increased risk for diabetes (hazard ratio, HR 1.67, 95% CI 1.01-2.76). However, when this study was reported in the ICPE presentation, using all conventional antipsychotics as the comparator group, in the inception cohort design, quetiapine was associated with a statistically non-significant HR of 1.54 (95% CI 0.98-2.43). (Note: the original published abstract *incorrectly* reported HR for quetiapine of 3.34 (95%CI 2.51-4.45) - personal email communication, DR Miller, April 26, 2006) The abstract and presentation slides further investigated the association. Allowing all patients to be included (simple cohort design), regardless of prior use, the hazard ratio became closer to the null (HR 1.08, 95% CI 0.92-1.44). With a case-control design, identifying new cases of diabetes and looking in the previous 12 weeks and 52 weeks for antipsychotic exposure, quetiapine was associated with an increased risk (12 weeks: OR 1.50, 95% CI 1.16-1.93; 52 weeks: OR 1.91, 95% CI 1.34-2.72). The published article, combined with the abstract and presentation slides, demonstrate that varying results may arise by changing the study design and definition of comparison groups, even within the same database. According to the abstract and presentation slides, this study showed that quetiapine is not associated with diabetes using a cohort design, and is associated using the weaker case control designs, compared to conventional antipsychotics (Cunningham et al 2003).

Two studies, though in bipolar patients, were conducted by Guo and colleagues, using Pharmetrics data from January 1998 to December 2002, one limited to Medicaid data (Guo et al 2007), the other to commercial claims data (Guo et al 2005; Guo et al 2006). Patients in

both studies were those with a bipolar diagnosis (ICD9 code 296.0, 296.1, 296.4-296.8), who had at least 3 months' exposure to any antipsychotic or at least 3 prescriptions for bipolar-related treatment during the study period. Incident cases of diabetes were identified by either the earliest diagnosis code of 250.x in the medical record or treatment for diabetes; cases could not have a prior prescription filled for an oral anti-diabetic agent. In the commercial claims data, 123, 292 patients with a bipolar diagnosis were identified, 920 of whom had the outcome, who were matched to 5258 controls. 8.6% of cases and 3.2% of controls had taken quetiapine, for a statistically significant adjusted hazard ratio of 2.30 (95% CI 1.80-2.94) (Guo et al 2006). The abstract version of this study (Guo et al 2005) used 998 incident cases and 5701 controls, with HR 2.59 (95% CI 2.04-3.28). In the Medicaid data (Guo et al 2007), 13,471 patients with bipolar were identified, 283 of whom had the outcome, who were matched to 1134 controls. 6.4% of cases and 1.8% of controls had taken quetiapine, for a statistically significant hazard ratio of 2.48 (95% CI 1.43-4.30). Although patients could not have a prescription for an oral antidiabetic medication before their diabetes onset date, they could have had a diagnosis code, and this study does not sufficiently account for pre-existing diabetes or diabetes risk factors. Further, requiring only a single diagnosis code for diabetes to identify an outcome allows rule-out diagnoses to be counted as cases. Another limitation is that this study does not address the potentially large impact of channeling, as patients could have been on their medication for a long time, or could have switched from another medication.

3.4.1.5 Studies showing no risk associated with quetiapine versus no antipsychotic

Two studies were found that compared quetiapine directly with groups using no antipsychotics, finding no increased risk compared to no antipsychotic exposure.

A study that compared quetiapine exposure to no antipsychotic use in those with schizophrenia, bipolar, major depression, or any other psychotic disorder (ICD9 290-299) in a commercial claims database during April 1997 to October 2000 found no increased risk for quetiapine compared to those not exposed to any antipsychotic (Gianfrancesco et al 2003). This despite the characteristics of quetiapine patients appearing to predispose them to the outcome compared to the unexposed: they were more often schizophrenic or bipolar (unexposed group was more often depressed), exposed to diabetogenic beta-blockers (10.4% vs. 8.0%), and had a prior weight problem (4.0% vs. 1.4%). 33% of quetiapine users were also exposed to at least one other antipsychotic during the study. This study has a stronger design than many others, as exposed patients had to be exposed to drug for at least 60 days, with no exposure to the same drug in the previous 90 days, the diabetes diagnosis had to occur more than 30 days after the index date, and subjects had to have no diabetes in the previous 8 months. To ensure that the unexposed patients were comparable to the exposed patients, they had to have at least 4 medical claims with a psychiatric disorder.

Another study compared patients taking antipsychotics with patients taking corticosteroids (CSs) and proton pump inhibitors (PPIs) (Barnett et al 2006). Among patients who received an outpatient prescription from the VA in October 1998 to September 2000, 9705 received at least 30 days supply of CSs (18%), PPIs (73%), conventional antipsychotics (8%), or atypical antipsychotics (12%), and who had no diagnosis code for diabetes before drug initiation, back

to October 1997. An outcome was defined as a primary or secondary diagnosis of diabetes (ICD9 250.xx) during drug use or within 60 days of discontinuation. Cox regression models included a control for schizophrenia diagnosis. During the 2-year study, 12.9% developed diabetes. Relative to PPIs, CSs was associated with a statistically significant increased risk for diabetes, and both atypical and conventional antipsychotics were associated with a non-significant increased risk. Specifically, quetiapine was not associated with an increased risk relative to PPIs (RR=1.04, 95% CI 0.11-1.97), CSs (RR=0.86, 95% CI 0.21-1.55) or typical antipsychotics (RR=0.92, 95% CI 0.12-1.73). This study did not attempt to adjust for comorbidity, which is highly prevalent in VA populations. Limitations include the potential inaccuracy of diagnosis codes, lack of laboratory data, lack of data on risk factors, the likelihood that prescription data does not accurately reflect actual use, and the possibility that VA patients sought care outside of the VA (Barnett et al 2006).

3.4.1.6 Studies showing no risk associated with quetiapine versus conventional antipsychotics

Nine studies found no increased risk for quetiapine use compared to conventional antipsychotics. Three (Buse et al 2003; Feldman et al 2004; Sacchetti et al 2005) showing increased risk relative to no antipsychotic exposure have already been described in Section 0, one (Barnett et al 2006) showing no increased risk relative to no antipsychotic exposure in Section 3.4.1.5, and two (Gianfrancesco et al 2006a; Gianfrencesco et al 2006b) showing varying results depending on study design in Section 1.1.1.1.

(Lambert et al 2006b) used VA databases, including electronic medical records, to identify 100 initiators of quetiapine and 100 initiators of haloperidol who had at least 4 prescription fills for their index medication over one year. Monotherapy was required; a diabetes outcome could be from lab data (fasting glucose >126 mg/l), the medical record (notation of a new diagnosis of diabetes in any medical progress note) or prescription of an antidiabetic. In the subset with no baseline diabetes, quetiapine was associated with a non-significant OR of 2.7 (95% CI 0.5-14.7). This study also found that weight change and schizophrenia were not associated with development of diabetes. Strengths of this study include the multiple sources of potential diabetes diagnoses, and the requirement of multiple prescription fills, suggesting that the patients actually consumed some of the drug they were provided. Limitations common to other studies include the potential for confounding by indication, lack of systematic screening for diabetes in the subject population (in particular, potential for surveillance bias where patients on certain agents may be more closely monitored for adverse effects), lack of information on major known risk factors for diabetes (e.g., obesity, elevated insulin, family history, physical activity), missing information on any care received outside of the VA system, and generalizability to non-VA populations and to people using multiple antipsychotics.

Another VA database study (Leslie and Rosenheck 2004) included only those with a stable regimen of a single antipsychotic for at least 3 months during June 1999 to September 2000. Patients could not have diabetes, and must have had at least 2 medical primary care visits in the previous 6 months (to ensure that if someone did have diabetes, it would likely have been captured in their record). Compared to conventional antipsychotics, quetiapine users had no

increased risk (HR = 1.2, 95% CI 1.0-1.4). The same limitations as the above study apply to this as well. An additional limitation of this study is that exposures to antipsychotics other than the initial single antipsychotic are unknown, either before or after the "stable regimen", such that results could be confounded by intervening exposures. The 3-month "stable regimen" may be a strength as well as a limitation: it is a move toward isolating the effect of the index prescription from other prescriptions, but is it unknown whether this is a typical experience for patients, potentially further limiting generalizability.

A commercial database study (Miller et al 2005) used a similar approach of requiring a stable regimen of a single antipsychotic for at least 3 months, during January 1999 to October 2000 (patients could have been taking a different antipsychotic before or after the 3 month stable period). Subjects were those who had no diabetes before or during those 3 months, back to January 1999. Cases had their first diagnosis of diabetes after the end of the 3 months, to December 2000. This study found a decreased risk of diabetes associated with quetiapine: quetiapine was 10% of the study population, but only 7% of those who developed the outcome and 11% of those who did not ($p<0.04$). After adjustment, the hazard ratio for quetiapine was 0.7 (95% CI 0.5-1.1) in the total population, 0.5 in males (95% CI 0.2-1.1), and 0.9 in females (95% CI 0.5-1.6). Patients were exposed to conventional antipsychotics for a much longer duration than the atypical antipsychotics, which may be an issue if the likelihood of development of diabetes was found to be increased with increasing duration of antipsychotic exposure. The same limitations as the above study apply to this as well, including the questionable appropriateness of the 3-month stable period. Further, the authors speculate that severely mentally ill patients may have exhausted their commercial health plan benefits such that any health care beyond that would not have been reimbursed, and therefore not included in the database.

Finally, (Ostbye et al 2005) used a prescription database to identify patients continuously enrolled, and with at least one prescription fill for an antipsychotic and no other psychotropics, during June 2000 to May 2002. Subjects also had no antidiabetic prescriptions filled in the first 6 months of the observation period, or before the first antipsychotic prescription fill. Both the crude and adjusted odds ratios (ORs) were non-significantly lower for quetiapine compared to conventional antipsychotics (crude OR = 0.6, 95% CI 0.3-1.4; adjusted OR = 0.7, 95% CI 0.3-1.6). This study also compared atypical antipsychotics as a group to people taking antidepressants and antibiotics, but the individual comparisons involving quetiapine were only in comparison to conventional antipsychotics. Limitations common to other studies include the potential for confounding by indication, lack of systematic screening for diabetes in the subject population (in particular, potential for surveillance bias where patients on certain agents may be more closely monitored for adverse effects), lack of information on major known risk factors for diabetes (e.g., obesity, elevated insulin, family history, physical activity, co-morbidities), missing information on prescriptions filled outside of the health plan, generalizability to people without continuous prescription coverage with a single provider for 2 years, and generalizability to people without prescription coverage. An additional limitation is the particularly lenient requirement of only a single prescription fill, which assumes the patient actually consumed the medication, and that a single prescription is sufficient to induce diabetes.

3.4.1.7 Studies suggesting channelling

The indication for a prescription is probably the most important confounding factor in pharmacoepidemiology since, theoretically, there is always a reason for prescription and because the reason may be associated with the outcome of interest, resulting in channelling or confounding by indication (Csizmadi et al 2005). (Gianfrancesco et al 2006a), described above, and the following two studies, suggest that quetiapine may be preferentially prescribed to patients with diabetes or high risk for diabetes. This could lead to a possible misinterpretation of quetiapine being associated with increased risk for diabetes in the analysis, which may only be an artifact of prescribers prescribing quetiapine because of a perceived decreased risk for diabetes associated with it.

A chart review of 436 outpatients at a New York ambulatory care program in April 2001-September 2002 found that 14.2% of these patients had diabetes: 6.7% developed diabetes during treatment with their current antipsychotic, while 7.6% developed diabetes before beginning their current antipsychotic. 9 of the 57 patients on quetiapine (15.8%) had diabetes: 8 developed diabetes before starting to use quetiapine. This study provides evidence for channelling toward quetiapine for those who already have diabetes (Lamberti et al 2004).

A VA database study (Leslie and Rosenheck 2005) conducted similarly to one described above (Leslie and Rosenheck 2004), found that, though 3.0% of cases and 2.8% of matched controls were taking quetiapine before the date of diabetes onset, 11.2% of cases and 5.8% of matched controls were taking quetiapine 90 days after diabetes onset, suggesting that patients developing diabetes were disproportionately switched to quetiapine after diabetes onset.

3.4.1.8 Other studies with quetiapine

Several studies included quetiapine, though did not fulfil criteria to enter this review (a statistical comparison between quetiapine and either conventional antipsychotics or no antipsychotic exposure), including several abstracts. Not all are included here..

Studies of atypicals compared with no antipsychotics

One study (Etminan et al 2003) collected data on residents of long-term care facilities who were age 65+ from the Ontario Drug Benefit prescription claims database. Subjects were those who received 2 consecutive prescriptions for neuroleptic drugs who had no use of a neuroleptic or antidiabetic drug in the previous 1 year, and was not already diagnosed with diabetes. An outcome of diabetes occurred when an antidiabetic drug was prescribed. This study had three "control" groups: initiators of typicals, of benzodiazepines, and of corticosteroids. There were 11,104 patients in this study (3250 atypicals, 1888 typicals, 5326 benzodiazepines, and 640 corticosteroids). 3.4% of atypicals users were quetiapine users. Incidence of diabetes per 1000 person years was 31 among the atypicals, 47 for typicals, 40 for benzodiazepines, and 190 for corticosteroids. With benzodiazepines as the reference, the HR for atypicals was 0.9 (95% CI 0.7-1.2), for typicals was 1.3 (95% CI 0.9-1.8), and for corticosteroids was 2.2* (95% CI 1.4-3.1). In quetiapine users, 1.0% developed diabetes. Therefore, this study showed no increased risk associated with atypicals.

Studies of atypicals compared with conventional antipsychotics

A retrospective chart review from a clinical practice (Gupta et al 2003) included 208 patients from a variety of settings (inpatients, day treatment program, clinic outpatients, and private office patients). There were no differences between patients on risperidone, olanzapine, clozapine, quetiapine, or conventional antipsychotics regarding percent with diabetes (2 of 17 quetiapine patients, 11.8%), mean fasting glucose (109.1±45 for quetiapine), and triglycerides (243.8±200.9 for quetiapine. However, this study is difficult to interpret, as numbers given in text and in various tables were different and it is unknown which provide the actual results.

(Barner et al 2004) conducted a database cohort study using VA data in Texas in September 1995-November 2002. Of the 3469 included patients identified: 44.3% took atypical antipsychotics and 65.7% took conventional antipsychotics. Some patients did switch or add-on therapy during follow-up, such that 40% took atypicals only, 29% took typicals only, and 31% took both. Diabetes occurred in 7.1% of subjects (4.1% had elevated glucose, 3.0% had a relevant ICD9 code, and 2.1% had an antidiabetic prescription). Based on the initial drug prescribed, 6.8% of atypical antipsychotic users and 7.3% of conventional antipsychotic users developed diabetes (difference non-significant). Allowing for drug switching to occur, 6.8% of those taking atypicals only, 6.0% of those taking typicals only, and 7.7% of those taking both developed diabetes (combining "atypicals" with "both" resulted in 7.2% incidence). None of these differences were significant. The mean time to onset was 5 months (151.9±105.6 days). The incidence among quetiapine users was 5.8%, which was not statistically different from the other atypicals (7.5% for risperidone, 6.4% for olanzapine). This study demonstrates that using only ICD9 codes or only prescriptions to identify diabetes will miss a substantial proportion of people with diabetes.

An abstract was based on data from Taiwan's National Health Insurance claims database from 2000-2004. Patients were age ≥18 years, had at least 1 admission due to schizophrenia in the 2 years prior to the initiation of treatment with an antipsychotic, and no diabetes in the 1 year prior to treatment initiation. Diabetes outcomes were identified with medical claims or prescriptions for antidiabetic medications. Compared with users of haloperidol, those receiving quetiapine did not have a significantly higher odds of developing diabetes, though no statistic was provided (Cheng et al 2006).

All of these studies showed no increased risk for atypicals compared to conventional antipsychotics.

Studies of atypicals versus one another

The many various studies comparing atypicals to one another show absolutely conflicting results, with some showing increased risk for some atypicals, others showing increased risk for other atypicals, and some showing no increased risk for any atypical compared to others. Several comparisons are embedded within the articles in this literature review that gave statistics comparing quetiapine and patients with no antipsychotics or conventional antipsychotics exposure. Other studies (without comparison to no or conventional antipsychotics) that were found that had statistics for quetiapine are described here.

(Sun et al 2004) compared 581 schizophrenia patients taking atypical antipsychotic monotherapy (322 olanzapine, 44 quetiapine, 215 risperidone) identified from the North Carolina Medicaid Claims database during July 1998-October 2000. There were no statistically significant differences between olanzapine (OR = 0.9, 95% CI 0.3-3.2) or risperidone (OR = 1.0, 95% CI 0.5-1.9) versus quetiapine, though there was an apparent increased risk for those with prior use of antidepressants.

(Wilson et al 2003) identified 11,994 unique patients treated with an atypical antipsychotic through the Ohio Department of Mental Health in January 1994-July 2001, 619 (5.2%) of whom developed diabetes as documented by abnormal fasting glucose levels or treatment with a hypoglycemic medication. Only available in abstract form, this study reported a preliminary relative risk in confirmed cases of 6.4% for quetiapine; clearly, as relative risks are not to be reported as percentages, this study is uninterpretable.

Among 116 outpatients at a community mental health center in Tennessee in February 2001-May 2002 taking an atypical antipsychotic, with no diabetes before starting the current drug, 14 developed diabetes. None of the cases and 15 (14.7%) of the controls had been taking quetiapine; however, the length of treatment was much lower for quetiapine (359.8±264.7 days, which was statistically lower than for risperidone (661.9±442.8), and numerically lower than all others), and longer duration of treatment was associated with developing diabetes (1167.4±732.8 days for cases, 656.4±641.1 days for controls) such that the authors suggest the lack of cases in quetiapine may be due to the shorter exposure to the drug (Sumiyoshi et al 2004a, Sumiyoshi et al 2004b).

The following three studies are only available in abstract form, precluding substantial discussion of strengths and limitations.

An abstract describing a study that analyzed 8949 Texas VA patients from 1995-2004 using 7 different models, varying on design (cohort vs. case control), exposure duration definition (intent-to-treat vs. as-treated), and statistical model (propensity score, logistic regression, conditional logistic regression, and Cox proportional hazards), (Yang et al 2006a) found no increased risk for quetiapine compared to conventional antipsychotics across all models, but found different results (increased risk and no difference) across models when comparing quetiapine and risperidone: some models showed increased risk, others showed no difference (Yang et al 2006b). Upon publication of the full manuscript, this study may become another important example of how study design can impact results substantially, even within the same database.

An abstract investigating the difference in diabetes risk associated with medications, by diagnosis and dose using Texas Medicaid data (1997-2001), similarly found no difference between quetiapine and risperidone on the incidence of diabetes (OR 0.68, 95% CI 0.41-1.13). Among the 13,731 eligible patients, the baseline prevalence of diabetes was 16.9%, and incidence was 2.6%. While dose varied by treatment indication (273.2 mg for schizophrenia, 146.3 mg for bipolar, 79.6 mg for dementia) and patient age, none of treatment indication,

antipsychotic, or antipsychotic dose were associated with the development of diabetes (Harrington et al 2006).

Another abstract describes a study randomizing 199 patients with and without schizophrenia to atypical antipsychotics, with measurements every 3 months for 1 year. None of the 8 quetiapine patients developed fasting blood glucose above 6 mmol during the study (Amaladoss et al 2006).

None of these studies comparing quetiapine with other atypical antipsychotics show an increased risk for quetiapine.

Studies with outcomes other than diabetes (e.g., insulin, glucose, etc.)

(Sernyak et al 2005) conducted a case control study in a VA in Connecticut. Physicians of patients who received a prescription for an atypical antipsychotic during October 2000-September 2001 according to the administrative database were contacted to indicate the patient's current antipsychotic treatment regimen and whether the patient has diabetes. Fasting plasma glucose tests were requested from those without diabetes. Among 647 patients without diabetes identified, only 153 provided a fasting plasma glucose level, 12 of whom were taking quetiapine (7.8%). Of those taking quetiapine, 10 had normal glucose (9.4% of all study patients with normal glucose, <100 mg/dl), and 2 had elevated glucose (4.2% of all study patients with elevated glucose, ≥100 mg/dl), suggesting no disproportionately increased risk for quetiapine compared to other atypicals.

The following three studies are only available in abstract form, precluding substantial discussion of strengths and limitations. The strength of all three is that they are prospective, with blood drawn at pre-specified times.

Schizophrenia patients admitted to a psychiatric hospital in Greece, who were medication-free for at least 3 months, had serum lipids levels measured on the day of admission and 4 weeks later. Quetiapine patients did not show a statistically significant increase in triglycerides or cholesterol levels, while statistically significant increases were found for other atypicals (Rizos et al 2006).

In a trial of aripiprazole versus standard-of-care, with quetiapine as an option within the standard-of-care arm, at 26 weeks, 69% of quetiapine patients had abnormal cholesterol level, 62% for LDL, 30% for HDL, 52% for triglycerides, and 33% for glucose. These percentages significantly differed by agent (aripiprazole, olanzapine, and risperidone); quetiapine was neither the highest nor the lowest among the antipsychotics for any of these measures. The number of patients on quetiapine, and the definition of "abnormal" were not provided in this abstract (L'Italien et al 2006).

A pooling of data from 23 ziprasidone clinical trials of varying comparators and duration found that comparators of ziprasidone, including quetiapine, demonstrated higher rates of metabolic syndrome. (Newcomer et al 2006). However, no information about the quetiapine patients, including prevalence of metabolic syndrome, was given in this abstract.

Cross-sectional studies

Four cross-sectional studies were found that examine quetiapine and other antipsychotics. Cross-sectional studies do not contribute to understanding of the directionality of associations; that is, a drug being associated with an outcome could be a reflection of the drug preceding the outcome, or the outcome preceding the drug (which would suggest channeling). For completeness, these studies are included here.

Outpatients with serious mental disorders treated with an atypical antipsychotic in Bologna (n=76; 25% on quetiapine) were compared with a random sample of patients from a neurology department with idiopathic hyperhydrosis, without psychiatric history or antipsychotic treatment (n=36) in a cross-sectional study measuring metabolic risk factors in 2005. A greater proportion of quetiapine patients (90%) had been previously treated with another antipsychotic than risperidone (50%) or olanzapine (58%) patients. There were no difference in mean glucose or triglycerides levels among antipsychotics (Tarricone et al 2006). In addition to the cross-sectional design, major limitations include the small sample size, lack of information and adjustment for background variables, and the unique reference group.

A cross-sectional study of 415 inpatients and outpatients (26.3%) with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, at a university psychiatric hospital and its affiliates in Belgium, in November 2003, assessed prevalence of metabolic abnormalities by duration of illness. The prevalence of diabetes appeared to increase with increasing duration of illness, being present in 3% of first-episode patients, rising to 16.5% in patients with a duration of illness of more than 20 years), however, first episode patients had a mean age of 25.7 years, increasing to 49.8 years for chronic patients, so the association between duration of illness and diabetes is certainly confounded by age. Among the 415 patients, about 13% used quetiapine. Among the 314 with only one atypical being used, 6.7% had diabetes and 22.6% had prediabetes. Among the 44 using quetiapine only, 11.4% had diabetes and 9.1% had prediabetes; thus, quetiapine patients had a higher prevalence of diabetes and a lower prevalence of pre-diabetes than patients taking other atypical antipsychotics; thus quetiapine patients did have a higher prevalence of diabetes, but a lower prevalence of prediabetes than other atypical antipsychotics (DeHert et al 2006). This observation may well reflect channeling, and interpretation is hindered by the cross-sectional nature of the study.

A cross-sectional study of 24 subjects (7 quetiapine and 8 olanzapine from a community mental health clinic, and 9 normal controls) in Massachusetts, age 18 to 65 years and with BMI<30 kg/m^2, measured a variety of metabolic indicators, such as cholesterol, glucose, glucose clearance rates, and insulin, 38 times over 3.5 hours, during which glucose and human insulin were administered. The investigators found that quetiapine patients did not have fasting glucose, insulin sensitivity, or HOMA-IR different from olanzapine or controls. Glucose effectiveness (net fractional glucose clearance rate due to the increase in glucose independent of any increase in circulating insulin concentrations above baseline; low values suggest impairment of glucose metabolism) was similar to controls, but higher than olanzapine. HDL and alkaline phosphate, as well as activity levels, were lower than controls (Henderson et al 2005). The small sample size and questionable appropriateness of the control group are limitations. The exclusion of obese patients may limit generalizability.

An abstract describes a cross-sectional review of 441 clinical records of patients with a diagnosis of schizophrenia at a VA in Oregon: 16 patients used quetiapine, 2 of whom also had diabetes (12.5%) (Casey et al 2001). The authors compare rates for individual conventional and atypical antipsychotics to the rate of diabetes in the general population. This study has several limitations: the general population, in addition to being a completely unrelated external national comparison group whose data are not necessarily relevant, may not be an appropriate comparison group, considering the evidence supporting an increased prevalence of diabetes in psychiatric populations in general. Other major limitations include the very small sample size for quetiapine (n=16), lack of information on major known risk factors for diabetes (e.g., obesity, elevated insulin, family history, physical activity, comorbidities, co-prescriptions), lack of adjustment for other important potentially confounding variables (e.g., age, sex, etc.), the potential for confounding by indication, lack of systematic screening for diabetes in the subject population, and generalizability. Notably, the 12.5% diabetes prevalence in quetiapine patients is lower than that for thioridazine, clozapine, and olanzapine in the same study, and falls within the range of the prevalence of DM in the un-medicated schizophrenic population as described above in Section xx.

One-arm, small, and ecologic studies

Three studies were particularly limited, precluding drawing any conclusions for quetiapine.

An abstract describing a study of 23 parkinsonian patients taking quetiapine for at least three months in a movement disorders center found that, compared to the general population, parkinsonian patients treated with quetiapine had a greater prevalence (28% vs. 10.6%) and incidence (13% vs. 0.45%) of DM, and the risk of DM was greater in younger patients ($p<0.01$). The authors concluded that quetiapine might increase the risk of new-onset DM, especially in younger patients (Trieschmann et al 2003). However, the general population, in addition to being a completely unrelated external national comparison group whose data are not necessarily relevant, may not be an appropriate comparison group, considering the evidence supporting an increased prevalence of diabetes in psychiatric populations in general. Other major limitations include the very small sample size (n=23), lack of information on major known risk factors for diabetes (e.g., obesity, elevated insulin, family history, physical activity, comorbidities, co-prescriptions), lack of other important potentially confounding information (e.g., age, sex, etc.), the potential for confounding by indication, lack of systematic screening for diabetes in the subject population, and generalizability.

Another abstract describes a 12-week, prospective open-label study in 71 patients age 5-18 years with psychotic, mood, and/or disruptive behavior-spectrum disorders who were antipsychotic-naive (Correll et al 2004). Patients were given olanzapine, risperidone, or quetiapine (n=9) for 8 to 13 weeks. Results indicated that fasting glucose, insulin, and insulin resistance increased with atypical antipsychotic use, but that atypical antipsychotics did not differ among each other in their effect on glucose and insulin, or on absolute and relative HOMA-IR changes. Glucose increase was correlated with stimulant use, and increases in weight, BMI, and fat percentage. Insulin and HOMA-IR changes were correlated with disruptive behavior-spectrum disorders, non-Caucasian, non-Hispanic race, and weight gain. The percent increase in HOMA-IR was correlated with increased waist circumference, Asian

race, and stimulant co-treatment. This study reports insulin resistance in atypical antipsychotic initiators, but is a single-arm open-label, possibly non-randomized study, with no comparison group, which precludes any comparative inference. One pre-morbidly obese youngster developed diabetes, but baseline glucose metabolism status is not reported for this or any other subject. Notably, the effect on relative HOMA-IR was numerically smallest for quetiapine (24.5%) compared to risperidone (49.5%) and olanzapine (62.7%). The discrepancy between the absolute and relative changes in HOMA-IR suggests that the quetiapine patients may have had higher baseline HOMA-IR values.

A third study described in a Letter to the Editor used summary data from two different sources, spontaneously reported adverse events and total prescriptions dispensed in the country, again providing little useful information. (Firestone (2005) compared the number of prescriptions dispensed in Australia for the various antipsychotics with available adverse event data during the 10 year period, Jan 1994-Dec 2003. 271,957 prescriptions of quetiapine were dispensed. There were 3.7 reports of weight gain per million prescriptions dispensed, and 14.7 reports of diabetes per million prescriptions dispensed. For comparison, haloperidol had 1.3 and 0 reports of weight gain and diabetes, respectively, per million prescriptions. It is well recognized that comparisons of reporting rates are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used, such that comparison of two or more reporting rates should be viewed with extreme caution. While the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product, and other factors (e.g., publicity, newness of product to the market) (FDA 2005).

3.4.1.9 Summary of literature review

Eighteen published studies that specifically provide a formal statistical comparison between quetiapine and either conventional antipsychotics or no antipsychotic exposure were reviewed. Three (Buse et al 2003; Feldman et al 2004; Sacchetti et al 2005) showed increased risk compared to a general population, with no antipsychotic exposure and no psychiatric disorders; however, this increased risk could be due, at least in part, to an increased risk of developing diabetes in those with psychiatric disorders in general. Another eight studies showed increased risk for quetiapine relative to conventional antipsychotic exposure. However, in three of the studies, the association held only in a subgroup: men (Citrome et al 2004), lower dose (Lambert et al 2005), or younger (Sernyak et al 2002); in one of these (Lambert et al 2005), the results became non-significant after adjustment for confounders. This study was also the expansion of Lambert et al 2002, which was only in abstract form, such that details were not available and subpopulation analyses were not described. Another two studies found increased risk or no increased risk, depending on how the data were analyzed (Cunningham et al 2003; Gianfrancesco et al 2006a; Gianfrencesco et al 2006b).

Two studies comparing quetiapine users to those with a psychiatric disorder but no antipsychotic exposure found no increased risk for quetiapine (Barnett et al 2006; Gianfrancesco et al 2003), despite the quetiapine users having a higher prevalence of diabetic risk factors (Gianfrancesco et al 2003).

Nine studies found no increased risk for quetiapine compared to conventional antipsychotics, including three that did find increased risk relative to no antipsychotic exposure (Buse et al 2003, Feldman et al 2004; Sacchetti et al 2005), one with no increased risk relative to no antipsychotic exposure (Barnett et al 2006), and three that showed both increased and no increased risk for quetiapine, depending on the analytic methods. Three additional studies showing no increased risk required that patients be on monotherapy only, reducing the potential for inappropriate attribution of an outcome to one or another antipsychotic (Lambert et al 2006b, Leslie and Rosenheck 2004; Miller et al 2005), a strength compared to other studies that did not require monotherapy.

Importantly, at least three studies suggest that physicians may be "channelling" patients with pre-existing diabetes or at higher risk of developing diabetes to quetiapine (Gianfrancesco et al 2006a, Lamberti et al 2004; Leslie and Rosenheck 2005)

4. PRE-CLINICAL DATA

There is no evidence from preclinical data that SEROQUEL treatment in humans may be associated with DM. The only salient observation was small changes in glucagon secreting cells (hyperplasia) after 12 months administration of SEROQUEL in one rat study. These changes were minimal and were not seen in another rat study after two years of SEROQUEL dosing. No such changes were observed in the pancreatic islets of mice, dogs, or primates in studies of up to one year.

No changes in serum glucose levels and no degenerative pathology that would indicate the induction of a diabetic state were observed in any species throughout the preclinical toxicology program. Thus, the changes observed in the single rat study are considered to be of minimal pathological significance and would not be expected to have any clinical significance in humans.

5. CLINICAL STUDY DATA

AstraZeneca has thoroughly reviewed AE data and plasma glucose data from the AstraZeneca clinical trial program for information regarding disturbances in glucose metabolism in subjects who took SEROQUEL. In studies where it is available HOMA, QUICKI, and HbA_{1c} data was also reviewed. When discussing the clinical trial data below, the term "subject" will be used if data from Phase I studies (which included healthy volunteers) is included, otherwise the term "patient" will be used.

The clinical trial data will presented in the following manner:

> Results from two recently completed long-term clinical trials (Trials 126 & 127) (Section 5.2)

Cumulative data from the AstraZeneca SEROQUEL clinical trial database (Safety 9.1) (Section 5.3)

Other completed trials not contained in the safety database (Section 5.4)

5.1 Overview

Adverse event data

By convention, adverse event data are presented first, although laboratory data are more meaningful when making a diagnosis of hyperglycemia or DM. It should be noted that in the majority of AstraZeneca clinical trials a pre-existing history of DM would not exclude a patient from participating in the trial.

Laboratory data

Following the adverse event data, laboratory data from the trials mentioned above will be discussed. Until recently (starting July 2004), fasting glucoses were not obtained in the majority of AstraZeneca's clinical trials. Since DM and hyperglycemia are medical diagnoses that are based on fasting laboratory data, the interpretation of the non-fasting lab data is limited. The American Diabetes Association (ADA) recommends that in the absence of unequivocal hyperglycemia, the results should be confirmed by repeat testing on a different day (ADA 2004). Blood samples in most studies were collected in order to perform routine laboratory tests and the results were generally not confirmed by repeat testing. (Note: there is no relevant laboratory data available for mosapramine treated patients).

The glucose data that will be presented in this section were from both fasting and non-fasting samples. Given the limitations of non-fasting values, the interpretation of these data are limited. There are 23 trials that are believed to contain data from fasting samples. These trials are thought to contain true fasting data because the patients were either hospitalized, resided in a long term care facility or clinical research center (CRC), or information regarding the timing of the patient's last meal in relation to the time of the blood draw was available (documented fasting). The data from these 23 trials were combined and are presented in Section 5.3.1.2. In addition, data from just the trials that were placebo-controlled were combined and are presented in Section 5.3.2.2 below.

The following laboratory values will be discussed:

Glucose (mmol/L): To convert glucose from mmol/L to mg/dL multiply by 18 (ie, 5 mmol/L = 90 mg/dL). The following definitions are according to the ADA (ADA 2004):

Hyperglycemia: fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or 2h-glucose ≥11.1 mmol/L (200 mg/dL)

Impaired fasting glucose: fasting glucose ≥5.6 mmol/L (100 mg/dL) and <7.0 mmol/L (126 mg/dL)

Impaired glucose tolerance: 2h-glucose ≥7.8 mmol/L (140 mg/dL) and <11.1 mmol/L (200 mg/dL)

HbA_{1c} (%): (glycosylated hemoglobin): A laboratory test that is used to estimate plasma glucose control during the preceding one to three months. The normal level is about 6%. In poorly controlled diabetics, the level ranges from 9 to 12%. HbA_{1c} is not a specific test for diagnosing diabetes; however, elevated HbA_{1c} often indicates existing diabetes (Beers and Berkow 1999). AstraZeneca considers an HbA_{1c} >7.5% clinically important.

Insulin (pmol/L): Insulin levels may be used to monitor the amount of insulin produced by the body ('endogenous insulin') or to check if the body is not responding to insulin properly (insulin resistance'). Insulin levels are sometimes used in conjunction with the glucose tolerance test (GTT). Blood glucose and, sometimes, insulin levels are measured to evaluate insulin resistance, particularly in obese individuals.

$HOMA_R$ (homeostasis model assessment): This is a calculated measurement of insulin resistance (fasting plasma insulin (µlU/mL) X fasting plasma glucose (mmol/L)/22.5).

QUICKI: This is a calculated measurement of insulin sensitivity ((1/[log(insulin(µU/mL))+log(glucose(mg/dL))].

The lab data are separated into three prespecified groups:

"Non-diabetic patients": Using both fasting glucose and random glucose data, a non-diabetic is a patient not meeting the criteria for diabetic risk or diabetes (defined below).

"Diabetic risk": Documented fasting glucose ≥ 5.551 mmol/L (100 mg/dL) and <7 mmol/L (126 mg/dL) at baseline or a history of gestational diabetes or a BMI ≥35 and not meeting any of the criteria listed under diabetic patients.

"Diabetic patients" Documented fasting glucose ≥7 mmol/L (126 mg/dL) or a glucose value not confirmed as documented fasting ≥11.1 mmol/L (200 mg/dL) at baseline or HbA1c above ULN (6.10 %) at baseline or history of diabetes.

5.2 Trials 126/127

The information presented below has been taken from the DRAFT Summary of Clinical Safety (for Trials 126 & 127) including relevant draft appendices.

5.2.1 Background

Trial 126: A Multicenter, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400 mg to 800 mg daily in

divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Valproate) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients

Trial 127: A Multicenter, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400 mg to 800 mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Divalproex) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients

5.2.2 Adverse events potentially associated with diabetes mellitus

Patients with AEs potentially associated with DM are summarized by randomized treatment and by assigned mood stabilizer for the combined studies in Table 2 (See Table A1 in Appendix A for a list of PTs).

Table 2 **Trials 126 & 127: Adverse events potentially associated with diabetes mellitus (randomized safety population)**

	Randomized to QTP& LI/VAL (N=646)	PLA+LI/VAL (N=686)	Assigned mood stabilizer QTP+LI (N=274)	PLA+LI (N=287)	QTP+VAL (N=372)	PLA+VAL (N=393)
MEDDRA PREFERRED TERM [a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ANY ADVERSE EVENT	20 (3.1)	7 (1.0)	7 (2.6)	3 (1.0)	13 (3.5)	4 (1.0)
HYPERGLYCAEMIA	4 (0.6)	1 (0.1)	1 (0.4)	0	3 (0.8)	1 (0.3)
DIABETES MELLITUS	3 (0.5)	1 (0.1)	3 (1.1)	0	0	1 (0.3)
HYPERINSULINAEMIA	3 (0.5)	1 (0.1)	0	0	3 (0.8)	1 (0.3)
BLOOD GLUCOSE INCREASED	2 (0.3)	0	1 (0.4)	0	1 (0.3)	0
BLOOD INSULIN INCREASED	2 (0.3)	1 (0.1)	1 (0.4)	1 (0.3)	1 (0.3)	0
DIABETES MELLITUS NON-INSULIN-DEPENDENT	2 (0.3)	0	0	0	2 (0.5)	0
INSULIN RESISTANCE	2 (0.3)	0	0	0	2 (0.5)	0
DIABETIC KETOACIDOSIS	1 (0.2)	0	0	0	1 (0.3)	0
HBA1c INCREASED	1 (0.2)	1 (0.1)	0	0	1 (0.3)	1 (0.3)
POLYDIPSIA	1 (0.2)	1 (0.1)	1 (0.4)	0	0	1 (0.3)
THIRST	1 (0.2)	1 (0.1)	0	0	1 (0.3)	1 (0.3)
POLYURIA	0	2 (0.3)	0	2 (0.7)	0	0

a Patients with multiple events falling under the same preferred term are counted only once in that term.
PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate, N Number of patients in treatment group, n Number of patients.
MedDRA Medical Dictionary of Regulatory Activities 126 D1447C00126, 127 D1447C00127
Note Events emerging during randomized treatment phase by decreasing frequency in the QTP+LI/VAL group.

During randomized treatment, the incidence of AEs potentially associated with diabetes in the quetiapine treatment group was 3.1%, compared to 1.0% in the placebo group. For the AE preferred terms that are more specifically related to diabetes, there were three reports of "Diabetes mellitus" in the quetiapine group compared to one report in the placebo group, all of them in Study 127. Two patients in the quetiapine group in Study 127 had an AE of "Diabetes mellitus, non-insulin-dependent" reported during the randomized treatment phase. There was one AE of "Diabetic ketoacidosis" reported in the quetiapine treatment group in Study 127. These seven patients (6 quetiapine, 1 placebo) are summarized in Table 3 below (narratives are contained in Appendix D). Several of the AE terms were considered to be more related to glucose metabolism (eg, thirst, polydipsia, polyuria), and are not further discussed in this section.

Table 3 Seven patients with reported events of DKA, DM, or NIDDM in the randomized treatment phase

Patient ID PT	Age/Sex	Dose/FTO	Med hx	Adjunct therapy	Comments
			QUETIAPINE TREATED PATIENTS		
E0036019 DM	42/F	400 mg/day; 342 days	No hx of DM	Lithium	Baseline BMI=40.9, FBS=134 mg/dL, HbA1c=6.5% Tx for 117 days in OL phase. Lab values at visit prior to event: FBS=316 mg/dL, HbA1c=9.6%. Day 225 of randomization: event of DM reported. Tx=metformin. Seroquel & lithium contd. Pt recovered: Day 424 (FBS=117 mg/dL, HbA1c=6.6%).
E0062017 DM	46/F	700 mg/day; 126 days	No hx of DM	Lithium	Baseline BMI=34.0, FBS=115 mg/dL, HbA1c=6.0% Tx for 119 days in OL phase. Lab values prior to event: FBS=117 mg/dL, HbA1c=5.3% Day 7 of randomization event of DM reported. Tx=study drug dose changed, no glucose lowering med given. Day 21 Pt recvd (FBS=118 mg/dL, HbA1c=5.4%)
E0063001 DM	48/M	600 mg/day; 326 days	No hx of DM	Lithium	Baseline BMI=36.2, HbA1c=5.7%, random BG=117 mg/dL Tx for 118 days in OL phase. Day 208 of randomization: FBS=163 mg/dL, HbA1c=6.8% Tx=metformin, glipizide. Seroquel contd. AE contd tessl final visit (Day 687 of randomization): FBS=148 mg/dL, HbA1c=6.7%.
E0026002 NIDDM	33/M	600 mg/day; 308 days	No hx of DM	Valproate	Baseline BMI=29.8, HbA1c=5.5%, random BG=95 mg/dL Tx for 231 days in OL phase. On day 477 of randomization: BG=199 mg/dL, insulin=122 pmol/L, HbA1c=7.1%. No tx given. Seroquel contd. AE contd to final visit (Day 541 of randomization): FBS=92 mg/dL, insulin=19 pmol/L, HbA1c=6.6%
E0080036 NIDDM	29/M	800 mg/day; 329 days	Glucose intolerance	Valproate	Baseline BMI=38.4, FBS=92 mg/dL, HbA1c=5.9% Tx for 116 days in OL phase. Day 214 of randomization: FBS=238 mg/dL, HbA1c=15.6%. No tx given. Seroquel contd. AE contd to final visit (Day 276 of randomization): FBS=94 mg/dL, insulin=6 pmol/L, HbA1c=5.4%
E0059014 DKA	57/M	456 mg/day; 148 days	No hx of DM	Valproate	Baseline BMI=27.9, HbA1c=5.6%, random BG=130 mg/dL Tx for 116 days in OL phase. Day 21 of randomization: teeth extracted (reason unknown) Subsequent wt loss of 6 kg (unable to eat solid food). Day 30 of randomization: Pt had wt loss, polyuria, polydipsia, blurred vision, severe renal failure. Day 35 of randomization: Seroquel & valproate d/c'd. Day 44 of randomization: ER w/ nausea, fatigue, vomiting (no fever, chills, dysuria, cough, or SOB). BG=1445 mg/dL. Dx=hospitalized w/ DKA, IV hydration, IV insulin. Dx=new onset DM ("likely Type 1"). HbA1c=17.2%. Day 49 of randomization: DKA, renal failure resolved & Pt discharged from hospital. Day 51 of randomization: Blurred vision resolved.
			PLACEBO TREATED PATIENT		

Table 3 Seven patients with reported events of DKA, DM, or NIDDM in the randomized treatment phase

Patient ID PT	Age/Sex	Dose/TTO	Med hx	Adjunct therapy	Comments
D1050016 DM	43/F	250 days (1S placebo)	DM	Valproate	Baseline DM=34.3, FBS=95 mg/dL, HbA1c=5.6% Tx for 232 days in OL phase. Day 18 of randomization: FBS=94 mg/dL, HbA1c=6.0%. Tx=metformin. Study tx ceased. AE contd until final visit on Day 48 (FBS=83 mg/dL, HbA1c=5.8%)

In addition, there were 10 patients with AE of "Diabetes mellitus" and five patients with AE of "Diabetes mellitus, non-insulin-dependent" with an onset reported during the open-label treatment with quetiapine in combination with a mood stabilizer.

It is noteworthy that 18 of the 22 patients with AEs potentially associated with DMs mentioned in this section (7 in randomized, 15 open label) were found in patients in Study 127, where mean weight (92.7 kg) and mean BMI (31.9 kg/m^2) was greater than in Study 126 (84.1 kg and 29.2 kg/m^2, respectively). In fact, four of the six patients in the quetiapine group with AEs of "Diabetes mellitus", "Diabetes mellitus, non-insulin-dependent", or "Diabetic ketoacidosis" with an onset reported during randomized treatment had a baseline BMI >30 kg/m^2 at enrolment. In patients with an AE associated with diabetes with an onset reported during open-label treatment phase, 14 of 15 patients had a baseline BMI >30 kg/m^2 at enrolment. The range in those 14 patients with BMI >30 kg/m^2 was 32.0 kg/m^2 to 46.5 kg/m^2, with 4 patients having a BMI >40 kg/m^2.

5.2.3 Glucose regulation laboratory data

Glucose regulation laboratory data are presented for the total population and for three subgroups ("diabetics", "diabetic risk", "non-diabetics").

Change from randomization in glucose regulation laboratory data

Descriptive statistics for change from randomization to end of treatment in glucose regulation laboratory data are summarized by randomized treatment group and assigned mood stabilizer for the combined studies in Table 4.

]

Table 4 **Trials 126 & 127: Glucose regulation laboratory data, change from randomization to end of treatment (randomized safety population)**

		Randomized treatment			Assigned mood stabilizer		
		QTP & LI/VAL N = 646	PLA & LI/VAL N = 689	QTP &LI N = 274	PLA & LI N = 287	QTP &VAL N = 372	PLA &VAL N = 393
Glucose (mg/dL)							
N *		588	641	252	256	336	355
Randomization	Mean(SD)	93.78(19.970)	94.61(20.084)	94.83(18.630)	94.84(14.478)	92.99(20.911)	95.02(23.517)
End of treatment	Mean(SD)	98.78(41.837)	94.55(18.876)	100.10(28.885)	95.29(18.424)	97.78(49.393)	94.02(19.284)
Change	Mean(SD)	5.00(39.900)	-0.05(19.409)	5.27(26.412)	1.26(15.708)	4.78(47.611)	-1.00(21.662)
	Median	2.00	0.00	3.00	0.50	2.00	0.00
	Min to Max	-132.00 to 776.00	-121.00 to 87.00	-84.00 to 282.00	-52.00 to 75.00	-132.00 to 776.00	-121.00 to 87.00
HbA1C (%)							
N *		585	618	251	253	334	365
Randomization	Mean(SD)	5.44(0.643)	5.39(0.592)	5.26(0.536)	5.21(0.480)	5.52(0.692)	5.53(0.631)
End of treatment	Mean(SD)	5.59(0.723)	5.42(0.567)	5.43(0.639)	5.26(0.465)	5.73(0.760)	5.54(0.634)
Change	Mean(SD)	0.15(0.460)	0.04(0.346)	0.18(0.331)	0.05(0.304)	0.19(0.557)	0.03(0.373)
	Median	0.10	0.00	0.20	0.00	0.10	0.00
	Min to Max	-2.00 to 3.80	-2.80 to 2.30	-0.90 to 2.00	-2.10 to 1.40	-2.60 to 3.80	-2.80 to 2.30
Insulin (pmol/L)							
N *		501	531	211	214	290	317
Randomization	Mean(SD)	132.94(151.842)	135.13(154.995)	123.00(122.661)	121.78(134.202)	141.62(169.636)	144.14(167.185)
End of treatment	Mean(SD)	158.64(325.733)	145.91(262.396)	154.85(145.578)	143.15(157.738)	161.40(461.963)	147.56(227.876)
Change	Mean(SD)	25.70(161.479)	10.78(214.550)	33.85(149.963)	21.67(171.618)	19.77(309.376)	3.42(239.203)
	Median	7.00	0.00	14.00	7.00	0.00	0.00
	Min to Max	-882.00 to 795.00	-945.00 to 2125.00	-771.00 to 660.00	-945.00 to 1039.00	-882.00 to 795.00	-934.00 to 2125.00

Table 4 **Trials 126 & 127: Glucose regulation laboratory data, change from randomization to end of treatment (randomized safety population)**

		Randomized treatment		Assigned mood stabilizer			
		QTP & LI/VAL N = 646	PLA & LI/VAL N = 680	QTP &LI N = 274	PLA &LI N = 287	QTP &VAL N = 372	PLA &VAL N = 393
HOMA-B							
N [a]		505	523	215	214	290	309
Randomization	Mean(SD)	4.87(7.590)	4.93(7.509)	4.42(5.661)	4.30(6.051)	5.21(8.744)	5.37(8.355)
End of treatment	Mean(SD)	6.00(8.890)	5.56(9.756)	5.97(9.552)	5.30(7.187)	6.02(8.382)	5.76(11.203)
Change	Mean(SD)	1.13(8.929)	0.63(10.980)	1.55(9.843)	1.00(8.089)	0.81(8.190)	0.39(12.340)
	Median	0.23	0.04	0.47	0.08	0.19	0.00
	Min to Max	-50.60 to 103.32	-85.08 to 86.29	-41.47 to 103.32	-57.69 to 52.79	-50.50 to 33.99	-85.08 to 86.29
QUICKI							
N [a]		505	523	215	214	290	309
Randomization	Mean(SD)	0.3305(0.0425)	0.3299(0.0426)	0.3328(0.0434)	0.3337(0.0424)	0.3283(0.0419)	0.3273(0.0427)
End of treatment	Mean(SD)	0.3233(0.0438)	0.3277(0.0427)	0.3226(0.0448)	0.3273(0.0427)	0.3239(0.0432)	0.3280(0.0427)
Change	Mean(SD)	-.0073(0.0399)	-.0022(0.0400)	-.0103(0.0405)	-.0064(0.0390)	-.0048(0.0393)	0.0007(0.0405)
	Median	-.006	-.001	-.007	-.002	-.003	.0000
	Min to Max	-0.1477 to 0.1206	-0.1582 to 0.1246	-0.1477 to 0.0912	-0.1582 to 0.0889	-0.1476 to 0.1206	-0.1279 to 0.1246

a Number of patients with assessment at randomization and at least one assessment after randomization.
PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate, N Number of patients in treatment group. HOMA [insulin (uU/ml) x glucose (mmol/l)]/22.5.
QUICKI 1/[log10(insulin (uU/ml)) + log10 (glucose (mg/dl))]. HbA1c Hemoglobin A1c.
126 D1447C00126. 127 D1447C00127.

There were increases in mean glucose levels (QTP=5.00 mg/dL, PLA=-0.05 mg/dL) for the quetiapine group compared to the placebo group at end of treatment. However, the glucose data were highly variable, and the difference in median changes were smaller between treatment groups (QTP=2.00 mg/dL, PLA=0.00 mg/dL). A small difference between treatment groups was noted for HbA1c with a mean increase of 0.18% in the quetiapine treatment group, compared with an increase of 0.04% in the placebo group. Insulin levels increased by a mean of 25.70 pmol/L in the quetiapine treatment group, compared with an increase of 10.78 pmol/L in the placebo group. For both treatment groups, the median change was smaller (QTP=7.00 pmol/L, PLA=0.00 pmol/L). The mean change in the measure of insulin resistance (HOMA-R) was an increase of 1.13 in the quetiapine group and an increase of 0.63 in the placebo group. There was a small decrease in the measure of insulin sensitivity (QUICKI) in both treatment groups (-0.0071 in the quetiapine group and -0.0022 in the placebo group).

A detailed examination of the mean change from baseline in glucose regulation laboratory data for individual subgroups are presented by group in Table 5.

Table 5 Trials 126 & 127: Glucose regulation laboratory data, change to end of treatment, diabetic subgroups, by treatment group (randomized safety population)

		QTP+LI/VAL N=646				PLA+LI/VAL N=680			
		N[a]	Mean	SD	Median	N[a]	Mean	SD	Median
Glucose, fasting (mg/dL)	Diabetic	60	10.68	116.216	-5.50	65	-11.34	39.056	-8.00
	Diabetic risk	168	1.99	17.329	2.00	169	-1.48	15.055	-2.00
	Non diabetic	360	5.45	15.294	3.00	377	2.53	14.848	1.00
HbA1C (%)	Diabetic	59	0.25	0.998	0.20	64	-0.19	0.662	-0.20
	Diabetic risk	169	0.22	0.393	0.20	170	0.07	0.293	0.00
	Non diabetic	357	0.15	0.330	0.10	384	0.06	0.272	0.00
Insulin (pmol/L)	Diabetic	53	-37.96	222.503	-14.00	57	-78.91	223.622	-14.00
	Diabetic risk	144	27.51	213.209	0.00	147	13.23	211.298	7.00
	Non diabetic	304	35.95	110.739	7.00	327	25.31	213.260	0.00
HOMA-R	Diabetic	53	-1.30	20.432	-0.58	56	-5.06	15.320	-0.84
	Diabetic risk	145	1.24	8.924	0.06	144	1.32	11.730	0.20
	Non diabetic	307	1.49	4.664	0.38	323	1.31	9.032	0.05
QUICKI	Diabetic	53	0.0069	0.0392	0.0068	56	0.0101	0.0292	0.0087
	Diabetic risk	145	-0.0013	0.0365	-0.0014	144	-0.0008	0.0322	-0.0027
	Non diabetic	307	-0.0123	0.0407	-0.0083	325	-0.0050	0.0442	-0.0019

a Number of patients with assessment at baseline and at least one after baseline.
PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate N Number of patients in treatment group.
126 D1447C00126. 127 D1447C00127.

Changes in glucose regulation data were largest for diabetic patients, followed by smaller changes in patients at risk for diabetes; while non-diabetic patients remained relatively stable on most glycemic measures to end of randomized treatment. There was little change in measures of insulin resistance (HOMA-R) and insulin sensitivity (QUICKI).

There were relatively few diabetic patients (QTP=60, PLA=65), with great variability in data, thus comparisons of this subgroup should be made with caution. Nonetheless, in diabetic patients the mean glucose value was increased by 10.68 mg/dL at the end of treatment in the quetiapine group and decreased by -11.34 mg/dL in the placebo group. The median change was a decrease in both treatment groups: -5.50 mg/dL in the quetiapine group and –8.00 mg/dL in the placebo group. HbA1c in diabetic patients was increased in the quetiapine group at end of treatment by a mean change of 0.25%, and decreased -0.19% in the placebo group. Insulin values were decreased at end of treatment in diabetic patients in both treatment groups: with a mean change of -37.96 pmol/L in the quetiapine treatment group compared to –78.91 pmol/L in the placebo group. The median change was smaller, ie -14.00 pmol/L in both treatment groups. There was a mean decrease in HOMA-R in both treatment groups (-1.30 in the quetiapine group and –5.06 in the placebo group). In the measure of insulin sensitivity (QUICKI), the mean increase was 0.0069 in the quetiapine group and 0.0101 in the placebo group in diabetic patients.

For patients at risk for diabetes, glucose values were increased at end of treatment in the quetiapine treatment group (mean change of 1.99 mg/dL) compared with a small decrease (-1.48 mg/dL) in the placebo group. Median changes in glucose were similar to mean changes, with an increase by 2.00 mg/dL in the quetiapine group and a decrease by -2.00 mg/dL in the placebo group. HbA1c (measured in %) in patients at risk for diabetes was increased at end of treatment by a mean change of 0.22% in the quetiapine treatment group and 0.07% in the placebo group. Insulin values increased in patients at risk for diabetes in both treatment groups: mean change of 27.51 pmol/L in the quetiapine group and 13.23 pmol/L in the placebo group. However, the median insulin value was unchanged in the quetiapine group at end of treatment and increased by 7.00 pmol/L in the placebo group. There was a mean increase in HOMA-R in both treatment groups (1.24 in the quetiapine group and 1.32 in the placebo group). In the measure of insulin sensitivity (QUICKI), there was a mean decrease by –0.0013 in the quetiapine group and by –0.0008 in the placebo group in patients at risk for diabetes.

For non-diabetic patients, there were small differences between the quetiapine and placebo treatment groups on all of the glycemic measures. The mean increases in glucose was 5.45 mg/dL in the quetiapine group and 2.53 mg/dL in the placebo group. However, the median changes were smaller, with increases of 3.00 mg/dL in the quetiapine group and 1.00 mg/dL in the placebo group. The quetiapine patients showed an increase in HbA1c at end of treatment of 0.15% compared to an increase of 0.06% in the placebo group. The mean increase at end of treatment in insulin was 35.95 mg/dL in the quetiapine group compared to 25.31 mg/dl in the placebo group. The median change was smaller, with an increase by 7.00 mg/dl in the quetiapine group and no change in the placebo group. The mean change in measures of insulin resistance (HOMA-R) was similar in the quetiapine and placebo treatment

groups (1.49 and 1.31, respectively) in non-diabetic patients. There was a decrease in mean QUICKI in both treatment groups: -0.0123 in the quetiapine group and -0.0050 in the placebo group.

Change from randomization in glucose regulation laboratory data: observations following documented fasting

Glucose regulation laboratory data for change from randomization to end of treatment for observations (blood sampling) actively documented to be later than 8 hours after a meal are summarized in Table 6. A detailed examination of the mean change from baseline in glucose regulation laboratory data for individual subgroups ("non-diabetics", "diabetic risk", "diabetics") are contained in Table 7 below.

1

Table 6 **Trials 126 & 127: Glucose regulation laboratory data, change to end of treatment, >8 h fasting (randomized safety population)**

		Randomized treatment		Assigned mood stabilizer			
		QTP&LI/VAL N = 646	PLA& LI/VAL N = 680	QTP & LI N = 274	PLA & LI N = 287	QTP & VAL N = 372	PLA & VAL N = 393
Glucose (mg/dL)							
N [a]		520	493	228	203	292	290
Randomization	Mean(SD)	93.78(20.137)	94.77(19.419)	95.24(19.215)	94.63(14.468)	92.68(20.756)	94.87(22.263)
End of treatment	Mean(SD)	98.64(41.333)	94.14(18.288)	100.05(22.996)	95.14(18.017)	97.54(51.301)	93.44(18.473)
Change	Mean(SD)	4.86(39.723)	-0.63(18.296)	4.83(19.012)	0.52(14.870)	4.96(50.322)	-1.43(20.341)
	Median	2.50	0.00	4.00	0.00	2.00	-1.00
	Min to Max	-132.0 to 776.00	-121.0 to 87.00	-84.00 to 98.00	-52.00 to 75.00	-132.0 to 776.00	-121.0 to 87.00
HbA1C (%)							
N [a]		521	504	228	205	293	299
Randomization	Mean(SD)	5.41(0.647)	5.41(0.614)	5.26(0.543)	5.22(0.491)	5.52(0.697)	5.53(0.659)
End of treatment	Mean(SD)	5.59(0.712)	5.45(0.586)	5.45(0.642)	5.28(0.430)	5.73(0.742)	5.56(0.647)
Change	Mean(SD)	0.19(0.464)	0.03(0.362)	0.19(0.331)	0.05(0.307)	0.19(0.587)	0.04(0.395)
	Median	0.20	0.00	0.20	0.00	0.10	0.00
	Min to Max	-2.60 to 3.80	-2.80 to 2.30	-0.90 to 2.00	-2.10 to 0.90	-2.60 to 3.80	-2.80 to 2.30
Insulin (pmol/L)							
N [a]		445	432	191	172	254	260
Randomization	Mean(SD)	129.84(149.770)	127.37(139.107)	121.17(122.078)	119.15(157.379)	136.35(162.555)	132.78(140.248)
End of treatment	Mean(SD)	151.28(177.033)	130.05(136.856)	142.09(142.412)	123.95(120.949)	158.23(199.341)	134.07(228.049)
Change	Mean(SD)	21.44(163.085)	2.68(109.456)	20.86(153.400)	4.80(147.345)	21.88(179.304)	1.29(227.734)
	Median	7.00	0.00	7.50	0.00	3.50	0.00
	Min to Max	-882.0 to 799.00	-945.0 to 2125.0	-771.0 to 935.00	-945.0 to 646.00	-882.0 to 799.00	-895.0 to 2125.0
HOMA-R							

Table 6 **Trials 126 & 127: Glucose regulation laboratory data, change to end of treatment, >8 h fasting (randomized safety population)**

		Randomized treatment		Assigned mood stabilizer			
		QTP&LI/VAL N = 646	PLA& LI/VAL N = 680	QTP & LI N = 274	PLA & LI N = 287	QTP & VAL N = 372	PLA & VAL N = 393
N [a]		450	426	195	173	255	253
Randomization	Mean(SD)	4.75(7.470)	4.55(6.017)	4.42(5.662)	4.26(6.395)	5.00(8.603)	4.75(5.750)
End of treatment	Mean(SD)	5.58(7.640)	4.72(8.264)	5.34(6.656)	4.52(5.629)	5.76(8.323)	4.85(9.583)
Change	Mean(SD)	0.83(7.983)	0.17(8.983)	0.92(7.357)	0.26(7.129)	0.76(8.457)	0.10(10.070)
	Median	0.22	-0.02	0.24	0.04	0.21	-0.06
	Min to Max	-50.60 to 40.53	-57.69 to 86.29	-43.47 to 37.21	-57.69 to 29.09	-50.60 to 40.53	-31.28 to 86.29
QUICKI							
N [a]		450	426	195	173	255	253
Randomization	Mean(SD)	0.3309(0.0420)	0.3313(0.0420)	0.3324(0.0435)	0.3346(0.0423)	0.3297(0.0408)	0.3291(0.0418)
End of treatment	Mean(SD)	0.3258(0.0432)	0.3325(0.0421)	0.3251(0.0441)	0.3323(0.0431)	0.3255(0.0427)	0.3326(0.0416)
Change	Mean(SD)	-.0055(0.0385)	0.0012(0.0377)	-.0072(0.0391)	-.0024(0.0367)	-.0042(0.0387)	0.0036(0.0382)
	Median	-.005	.0005	-.005	-.001	-.004	.0013
	Min to Max	-.1477 to 0.1206	-.1152 to 0.1246	-.1477 to 0.0912	-.1152 to 0.0739	-.1476 to 0.1206	-.1138 to 0.1246

a Number of patients with assessment at randomization and at least one assessment after randomization.
PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate, N Number of patients in treatment group, HOMA Insulin (uU/ml) x glucose (mmol/l)/22.5, QUICKI 1/[log(Insulin n(uU/ml)) + log(Glucose n(mg/dl))], HbA1c Hemoglobin A1c.
Note: Change from randomization, >8 hours after a meal.
126 D1447C00126 127 D1447C0117.
/cere/prod/eroquel/edmaintenance/sp/output/tlfsx095.rtf chem212.sas 16APR2007:15:21 ksel497

1

Table 7 **Trials 126 & 127: Glucose regulation laboratory data, change to end of treatment, >8 h fasting, diabetic subgroups, by treatment group (randomized safety population)**

		QTP+LI/VAL N=646				PLA+LI/VAL N=680			
		N[a]	Mean	SD	Median	N[a]	Mean	SD	Median
Glucose, fasting (mg/dl.)	Diabetic	54	4.39	115.168	-7.00	52	-12.21	35.940	-8.00
	Diabetic risk	156	3.08	17.408	3.00	139	-2.83	13.874	-2.00
	Non diabetic	310	5.84	14.856	3.00	302	2.38	14.338	1.00
HbA1C (%)	Diabetic	52	0.20	1.004	0.20	54	-0.19	0.706	-0.20
	Diabetic risk	156	0.22	0.461	0.20	142	0.08	0.307	0.00
	Non diabetic	313	0.17	0.337	0.10	308	0.06	0.272	0.00
Insulin (pmol/L)	Diabetic	46	-68.20	207.587	-17.50	49	-50.55	166.627	-7.00
	Diabetic risk	135	22.10	215.819	0.00	122	-8.32	165.428	7.00
	Non diabetic	264	36.72	110.255	7.00	261	17.82	217.464	0.00
HOMA-R	Diabetic	46	-4.02	13.918	-0.64	48	-3.27	10.807	-0.67
	Diabetic risk	135	0.88	9.530	0.00	118	-0.19	7.157	0.14
	Non diabetic	269	1.63	4.914	0.38	260	0.97	9.231	-0.01
QUICKI	Diabetic	46	0.0124	0.0382	0.0074	48	0.0102	0.0272	0.0077
	Diabetic risk	135	0.0008	0.0367	-0.0000	118	0.0012	0.0330	-0.0019
	Non diabetic	269	-0.0118	0.0387	-0.0086	260	-0.0005	0.0410	0.0003

2 a Number of patients with assessment at baseline and at least one after baseline.
3 PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate, N Number of patients in treatment group.
4 /esre/prod/seroquel/clinmaintenance/sp/output/tl5%a096.rtf chemn263.sas 16APR2007:15:21 kscl497

Findings based on these more stringent fasting criteria were consistent with the results in the summary tables including all patients. The presentations covering documented fasting conditions (>8 h after the most recent meal) included approximately 80% to 90% of the patients in the tables summarizing results for all fasting patients.

Change from enrollment to end of randomized treatment in glucose regulation laboratory data

Descriptive statistics for change from enrollment to end of randomized treatment in glucose regulation laboratory data in patients randomized to quetiapine treatment are summarized for the separate and the combined studies in Table 8.

Table 8 **Glucose regulation laboratory data, change from enrolment to end of randomized treatment (LOCF, randomized safety population)**

		126 QTP+LI/VAL N = 336	127 QTP+LI/VAL N = 310	126 + 127 QTP+LI/VAL N = 646
Glucose (mg/dL)				
N [a]		307	267	574
Enrollment	Mean(SD)	92.89(18.193)	91.50(22.933)	92.24(20.526)
End of randomization treatment	Mean(SD)	97.27(19.027)	101.15(59.176)	99.07(42.693)
Change	Mean(SD)	4.38(19.286)	9.64(56.006)	6.83(40.763)
	Median	4.00	4.00	4.00
	Min to Max	-103.0 to 75.00	-147.0 to 770.00	-147.0 to 770.00
HbA1C (%)				
N [a]		311	268	579
Enrollment	Mean(SD)	5.37(0.494)	5.44(0.601)	5.40(0.547)
End of randomization treatment	Mean(SD)	5.54(0.619)	5.64(0.854)	5.59(0.739)
Change	Mean(SD)	0.17(0.455)	0.20(0.648)	0.18(0.553)
	Median	0.10	0.10	0.10
	Min to Max	-1.30 to 3.30	-1.50 to 4.40	-1.50 to 4.40
Insulin (pmol/L)				
N [a]		226	146	372
Enrollment	Mean(SD)	93.52(96.915)	115.73(161.147)	102.24(126.347)
End of randomization treatment	Mean(SD)	143.40(174.097)	179.16(174.678)	157.37(174.959)
Change	Mean(SD)	49.87(142.123)	62.17(227.980)	54.68(180.394)
	Median	14.00	27.00	20.00
	Min to Max	-389.0 to 896.00	-1590 to 764.00	-1590 to 896.00
HOMA-R				
N [a]		219	143	362
Enrollment	Mean(SD)	3.23(4.027)	4.74(14.749)	3.82(9.793)

Table 8 **Glucose regulation laboratory data, change from enrolment to end of randomized treatment (LOCF, randomized safety population)**

		126 QTP+LI/VAL N = 336	127 QTP+LI/VAL N = 310	126 + 127 QTP+LI/VAL N = 646
End of randomization treatment	Mean(SD)	5.16(6.749)	6.73(7.901)	5.77(7.255)
Change	Mean(SD)	1.93(5.903)	1.97(16.126)	1.95(11.105)
	Median	0.60	0.92	0.70
	Min to Max	-19.40 to 32.58	-166.0 to 42.34	-166.0 to 42.34
QUICKI				
N [a]		219	143	362
Enrollment	Mean(SD)	0.3424(0.0387)	0.3344(0.0384)	0.3392(0.0387)
End of randomization treatment	Mean(SD)	0.3272(0.0415)	0.3173(0.0447)	0.3233(0.0430)
Change	Mean(SD)	-.0151(0.0436)	-.0172(0.0462)	-.0159(0.0446)
	Median	-.014	-.013	-.014
	Min to Max	-.1597 to 0.1121	-.1484 to 0.0910	-.1597 to 0.1121

a Number of patients with assessment at enrollment and at least one assessment after enrollment.
Note: Patients randomized to quetiapine.
QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
HOMA [insulin (uU/ml) x glucose (mmol/l)]/22.5. QUICKI 1/[log10(insulin mU/ml) + log10 (glucose e(mg/dl))]. HbA1c Hemoglobin A1c.
/esre/prod/seroquel/ctdmaintenance/sp/output/tlf/sa197.rtf sa197.sas 16APR2007:15:27 kscl497

In the combined studies, glucose levels increased by a mean of 6.83 mg/dL with great variability (median change was 4.00 mg/dL) from enrollment to end of treatment. The mean change in HbA1c was an increase of 0.18% (median change 0.10). Insulin levels increased by a mean of 54.68 pmol/L (median change 20.00 pmol/L). The mean change in the measure of insulin resistance (HOMA-R) was an increase of 1.95 (median change 0.70); and there was a decrease in the measure of insulin sensitivity (QUICKI) of -0.0159 (median change -0.014) in the quetiapine patients in the randomized safety population.

Clinically important glucose regulation laboratory values emerging during randomized treatment phase

Patients with a clinically important glucose regulation laboratory value emerging at any time after randomization are summarized by randomized treatment group and by assigned mood stabilizer for the combined studies in Table 9.

Table 9 **Glucose regulation laboratory data, clinically important values at any time (randomized safety population)**

	Randomized treatment						Assigned mood stabilizer					
	QTP&LI/VAL N = 646		PLA&LI/VAL N = 680		QTP&LI N = 274		PLA & LI N = 287		QTP & VAL N = 372		PLA &VAL N = 393	
	N[a]	n(%)	N[a]	n(%)	N[a]	n(%)	N[a]	n(%)	N[a]	n(%)	N[a]	n(%)
Glucose (mg/dL)												
≤45	588	1 (0.2)	611	0	252	1 (0.4)	256	0	336	0	355	0
≥126	556	68 (12.2)	581	47 (8.1)	238	28 (11.8)	249	21 (8.4)	318	40 (12.6)	332	26 (7.8)
≥200	587	17 (2.9)	607	3 (0.5)	252	6 (2.4)	256	2 (0.8)	335	11 (3.3)	351	1 (0.3)
HbA1c (%)												
>7.5	576	12 (2.1)	611	5 (0.8)	248	3 (1.2)	253	1 (0.4)	328	9 (2.7)	358	4 (1.1)

a Number of patients at risk i.e. not fulfilling the criteria at randomization.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients. HbA1C Hemoglobin A1c.
126 D1447C00126. 127 D1447C00127.
Note: Clinically important values emerging during randomized treatment phase.
Note: Percentages are calculated as (n/Na)*100.
Note: Values at any time after randomization.

Treatment-emergent clinically important glucose regulation laboratory values at any time during randomized treatment were more common in the quetiapine group compared to the placebo group. There were shifts to high glucose values (≥126 mg/dL) in 68 patients (12.2%) in the quetiapine group, compared with 47 patients (8.1%) in the placebo group. Treatment emergent glucose values ≥200 mg/dL at any time during randomized treatment was reported in 17 patients (2.9%) in the quetiapine group and in 3 patients (0.5%) in the placebo group. HbA1c values were elevated (>7.5%) in 12 patients (2.1%) in the quetiapine group, compared with 5 patients (0.8%) in the placebo group.

Shift from randomization to clinically important glucose regulation laboratory values at any time after randomization is presented in Table 10 below and shift from randomization to end of treatment in glucose regulation laboratory data is presented in Table 11 below.

Table 10 **Trials 126 & 127: Glucose regulation laboratory data, shift to clinically important values at any time (randomized safety population)**

		QTP+LI/VAL N=646			PLA+LI/VAL N=680		
Lab Variable	Randomization	N[a] (%)	Low n[b] (%)	High n[b] (%)	N[a] (%)	Low n[b] (%)	High n[b] (%)
Glucose (mg/dL)							
Low: ≤45	Low	0	0	0	0	0	0

Table 10 **Trials 126 & 127: Glucose regulation laboratory data, shift to clinically important values at any time (randomized safety population)**

		QTP+LI/VAL N=646			PLA+LI/VAL N=680		
Lab Variable	Randomization	N[a] (%)	Low n[b] (%)	High n[b] (%)	N[a] (%)	Low n[b] (%)	High n[b] (%)
Normal	Normal	556 (94.6)	1 (0.2)	68 (12.2)	581 (95.1)	0	47 (8.1)
High: ≥126	High	32 (5.4)	0	20 (62.5)	30 (4.9)	0	13 (43.3)
	Total	588	1 (0.2)	88 (15.0)	611	0	60 (9.8)
Glucose (mg/dL)							
Low: ≤45	Low	0	0	0	0	0	0
Normal	Normal	587 (99.8)	1 (0.2)	17 (2.9)	607 (99.3)	0	3 (0.5)
High: ≥200	High	1 (0.2)	0	0	4 (0.7)	0	1 (25.0)
	Total	588	1 (0.2)	17 (2.9)	611	0	4 (0.7)
HbA1C (%)							
Normal	Normal	576 (98.5)	NA	12 (2.1)	611 (98.7)	NA	5 (0.8)
High: >7.5	High	9 (1.5)	NA	7 (77.8)	8 (1.3)	NA	5 (62.5)
	Total	585	NA	19 (3.2)	619	NA	10 (1.6)

a Distribution at randomization. b Patients are counted only once in each column.
NA Not applicable. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. HbA1C Hemoglobin A1c. N Number of patients in treatment group. n Number of patients.
126 D1447C00126. 127 D1447C00127.
Note: Percentages in the Na column are calculated as (Na /(Na in total row)*100
Note: Percentages are calculated as nb /Na *100
Note: Clinically important values are defined in table.
Note: Values at any time after randomization.
/esre/prod/seroquel/ctdmaintenance/sp/output/tlf/sa109.rtf chem231.sas 16APR2007:15:22 ksel497

Table 11 **Trials 126 & 127: Glucose regulation laboratory data, shift from randomization to end of treatment (randomized safety population)**

		QTP+LI/VAL N=646				PLA+LI/VAL N=680			
Lab Variable	Randomization	Low n (%)	Normal n (%)	High n (%)	Total n[a] (%)	Low n (%)	Normal n (%)	High n (%)	Total n[a] (%)
Glucose (mg/dL)									
Low: ≤45	Low	0	0	0	0	0	0	0	0
Normal	Normal	0	519 (93.3)	37 (6.7)	556 (94.6)	0	556 (95.7)	25 (4.3)	581 (95.1)
High: ≥126	High	0	19 (59.4)	13 (40.6)	32 (5.4)	0	20 (66.7)	10 (33.3)	30 (4.9)
	Total	0	538 (91.5)	50 (8.5)	588	0	576 (94.3)	35 (5.7)	611
Glucose (mg/dL)									
Low: ≤45	Low	0	0	0	0	0	0	0	0
Normal	Normal	0	579 (98.6)	8 (1.4)	587 (99.8)	0	605 (99.7)	2 (0.3)	607 (99.3)
High: ≥200	High	0	1 (100.0)	0	1 (0.2)	0	4 (100.0)	0	4 (0.7)

Table 11 Trials 126 & 127: Glucose regulation laboratory data, shift from randomization to end of treatment (randomized safety population)

		QTP+LI/VAL N=646				PLA+LI/VAL N=680			
Lab Variable	Randomization	Low n (%)	Normal n (%)	High n (%)	Total n[a] (%)	Low n (%)	Normal n (%)	High n (%)	Total n[a] (%)
	Total	0	580 (98.6)	8 (1.4)	588	0	609 (99.7)	2 (0.3)	611
HbA1c (%)									
Normal	Normal	NA	568 (98.6)	8 (1.4)	576 (98.5)	NA	608 (99.5)	3 (0.5)	611 (98.7)
High: >7.5	High	NA	4 (44.4)	5 (55.6)	9 (1.5)	NA	4 (50.0)	4 (50.0)	8 (1.3)
	Total	NA	572 (97.8)	13 (2.2)	585	NA	612 (98.9)	7 (1.1)	619

a Distribution at randomization.
NA Not applicable. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. HbA1C Hemoglobin A1c. N Number of patients in treatment group. n Number of patients.
126 D1447C00126. 127 D1447C00127.
Note: Percentages in the Na column are calculated as (Na /(Na in total row)*100
Note: Percentages are calculated as (n/Na)*100.
Note: Clinically important values are defined in table.
/csre/prod/seroquel/ctdmaintenance/sp/output/lif/sa131.rtf chem235.sas 16APR2007:15:22 kscl497

At the end of treatment, 37 patients (6.7%) in the quetiapine group and 25 patients (4.3%) in the placebo group presented with a shift to a glucose value ≥126 mg/dL. Eight patients (1.4%) in the quetiapine group and 3 patients (0.5%) in the placebo group showed shifts to clinically important high HbA1c at the end of treatment.

Patients with a clinically important glucose regulation laboratory value emerging at any time after randomization are summarized in Table 12 below by diabetic subgroup and randomized treatment group for the combined studies.

Table 12 Glucose regulation laboratory data, clinically important values at any time, diabetic subgroups, by treatment group (randomized safety population)

		QTP+LI/VAL N=646		PLA+LI/VAL N=680	
	N[a]	n(%)	N[a]	n(%)	
Glucose (mg/dL)					
≤45	Diabetic	60	0	65	0
	Diabetic risk	168	0	169	0
	Non diabetic	360	1 (0.3)	377	0
Glucose (mg/dL)					
≥126	Diabetic	30	14 (46.7)	37	12 (32.4)
	Diabetic risk	167	28 (16.8)	169	16 (9.5)
	Non diabetic	359	26 (7.2)	375	19 (5.1)

Table 12 Glucose regulation laboratory data, clinically important values at any time, diabetic subgroups, by treatment group (randomized safety population)

		QTP+LI/VAL N=646		PLA+LI/VAL N=680	
	N[a]	n(%)	N[a]	n(%)	
Glucose (mg/dL)					
≥200	Diabetic	59	14 (23.7)	61	3 (4.9)
	Diabetic risk	168	1 (0.6)	169	0
	Non diabetic	360	2 (0.6)	377	0
HbA1C (%)					
>7.5	Diabetic	50	7 (14.0)	56	4 (7.1)
	Diabetic risk	169	3 (1.8)	170	0
	Non diabetic	357	2 (0.6)	385	1 (0.3)

a Number of patients at risk i.e. not fulfilling the criteria at baseline.
PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate.
Note: Clinically important values emerging during randomized treatment phase. Note: Percentages are calculated as (n/Na)*100

In the quetiapine treatment group, the greatest proportion of treatment-emergent clinically important values at any time during randomized treatment within subgroups occurred in diabetic patients. Glucose values at any time were elevated ≥126 mg/dL in 14 of 30 (46.7%) diabetic patients with a glucose value <126 mg/dL at baseline (ie, randomization) in the quetiapine treatment group. Glucose values at any time were ≥126 mg/dL in 16.8% of the quetiapine patients at risk for diabetes and in 7.2% of the quetiapine non-diabetic patients. HbA1c values were elevated in 7 of 50 (14.0%) diabetic patients in the quetiapine treatment group at any time during randomized treatment, compared with 1.8% of patients at risk for diabetes, and 0.6% of non-diabetic patients. Incidences of high glucose and high HbA1c were in general lower in all 3 diabetic subgroups of patients randomized to placebo, compared with the corresponding quetiapine group.

At the end of treatment, the number of patients with a clinically important high glucose value was similar between treatment groups in the non-diabetic subgroup. In the diabetic subgroup, the incidence of glucose values ≥126 mg/dL was 33.3% in the quetiapine group and 16.2% in the placebo group. In patients in the diabetic risk subgroup, the incidence of glucose values ≥126 mg/dL was 9.0% in the quetiapine group and 4.1% in the placebo group. In the quetiapine group, 5 of 49 patients (10.2%) in the diabetic subgroup with a HbA1c value ≤7.5% at randomization had a HbA1c >7.5% at the end of treatment. Otherwise, few patients across treatment groups and across diabetic subgroups had treatment-emergent high HbA1c values at the end of treatment. (See Appendix A Table A5).

Clinically important glucose regulation laboratory values emerging during randomized treatment phase: observations following documented fasting

Clinically important glucose regulation laboratory values for observations (blood sampling) actively documented to be more than 8 hours after the most recent meal are summarized in Table 13 below.

Table 13 Glucose regulation laboratory data, clinically important values at any time, >8 h fasting (randomized safety population)

	Randomized treatment		Assigned mood stabilizer			
	QTP&LI/VAL N = 646 N [a] n(%)	PLA&LI/VAL N = 680 N [a] n(%)	QTP& LI N = 274 N [a] n(%)	PLA & LI N = 287 N [a] n(%)	QTP & VAL N = 372 N [a] n(%)	PLA &VAL N = 393 N [a] n(%)
Glucose (mg/dL)						
<= 45	448 1 (0.2)	431 0	199 1 (0.5)	177 0	249 0	254 0
>= 126	429 46 (10.7)	411 19 (4.6)	189 23 (12.2)	172 4 (2.3)	240 23 (9.6)	239 15 (6.3)
>= 200	448 9 (2.0)	429 3 (0.7)	199 4 (2.0)	177 2 (1.1)	249 5 (2.0)	252 1 (0.4)
HbA1C (%)						
> 7.5	441 9 (2.0)	434 4 (0.9)	195 2 (1.0)	178 1 (0.6)	246 7 (2.8)	256 3 (1.2)

a Number of patients at risk i.e. not fulfilling the criteria at randomization.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients. HbA1C Hemoglobin A1c.
126 D1447C00126. 127 D1447C00127.
Note: Clinically important values emerging during randomized treatment phase.
Note: Percentages are calculated as (n/Na)*100.
Note: Values at any time after randomization.
Note: >8 hours after last meal
/csrc/prod/seroquel/ctdmaintenance/sp/output/tlf/sa106.rtf chem271.sas 16APR2007:15:22 kscl497

A detailed examination of clinically important values for "diabetics", "diabetic risk", and "non-diabetics" is summarized by randomized treatment group in Appendix A Table A6.

Shift from randomization to clinically important glucose regulation laboratory values at any time after randomization for observations more than 8 hours after a meal is presented in Table 14.

Table 14 Trials 126 & 127: Glucose regulation laboratory data, shift to clinically important values at any time, >8 h fasting (randomized safety population)

		QTP+LI/VAL N=646			PLA+LI/VAL N=680		
Lab Variable	Randomization	N[a] (%)	Low n[b] (%)	High n[b] (%)	N[a] (%)	Low n[b] (%)	High n[b] (%)
Glucose (mg/dL)							
Low: ≤45	Low	0	0	0	0	0	0
Normal	Normal	429 (95.8)	1 (0.2)	46 (10.7)	411 (95.4)	0	19 (4.6)

Table 14 **Trials 126 & 127: Glucose regulation laboratory data, shift to clinically important values at any time, >8 h fasting (randomized safety population)**

		QTP+LI/VAL N=646			PLA+LI/VAL N=680		
Lab Variable	Randomization	N[a] (%)	Low n[b] (%)	High n[b] (%)	N[a] (%)	Low n[b] (%)	High n[b] (%)
High: ≥126	High	19 (4.2)	0	11 (57.9)	20 (4.6)	0	9 (45.0)
	Total	448	1 (0.2)	57 (12.7)	431	0	28 (6.5)
Glucose (mg/dL)							
Low: ≤45	Low	0	0	0	0	0	0
Normal	Normal	448 (100.0)	1 (0.2)	9 (2.0)	429 (99.5)	0	3 (0.7)
High: ≥200	High	0	0	0	2 (0.5)	0	1 (50.0)
	Total	448	1 (0.2)	9 (2.0)	431	0	4 (0.9)
HbA1c (%)							
Normal	Normal	441 (98.7)	NA	9 (2.0)	434 (98.2)	NA	4 (0.9)
High: >7.5	High	6 (1.3)	NA	5 (83.3)	8 (1.8)	NA	5 (62.5)
	Total	447	NA	14 (3.1)	442	NA	9 (2.0)

a Distribution at randomization. b Patients are counted only once in each column.
NA Not applicable, PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate, HbA1C Hemoglobin A1c, N Number of patients in treatment group, n Number of patients.
126 D1447C00126, 127 D1447C00127.
Note: Percentages in the Na column are calculated as (Na /(Na in total row)*100
Note: Percentages are calculated as nb /Na *100
Note: >8 hours after a meal.
Note: Clinically important values are defined in table. Values at any time after randomization.
/osr/prod/seroquel/ctdmaintenance/spvoutput/tlf/sa110.rtf chen236.sas 16APR2007:15:22 ksol497

Shift from randomization to end of treatment in glucose regulation laboratory data for observations more than 8 hours after a meal is presented in Table 15 below.

Table 15 Glucose regulation laboratory data, shift from randomization to end of treatment, >8 h fasting (randomized safety population)

		126+127 QTP+LI/VAL N=646				PLA+LI/VAL N=680			
Laboratory Safety Variable	Randomi-zation	Low n (%)	Normal n (%)	High n (%)	Total n[a] (%)	Low n (%)	Normal n (%)	High n (%)	Total n[a] (%)
Glucose (mg/dL)									
Low: <=45	Low	0	0	0	0	0	0	0	0
Normal	Normal	0	399 (93.0)	30 (7.0)	429 (95.8)	0	400 (97.3)	11 (2.7)	411 (95.4)
High: >=126	High	0	13 (68.4)	6 (31.6)	19 (4.2)	0	12 (60.0)	8 (40.0)	20 (4.6)
	Total	0	412 (92.0)	36 (8.0)	448	0	412 (95.6)	19 (4.4)	431
Glucose (mg/dL)									
Low: <=45	Low	0	0	0	0	0	0	0	0
Normal	Normal	0	443 (98.9)	5 (1.1)	448 (100.0)	0	427 (99.5)	2 (0.5)	429 (99.5)
High: >=200	High	0	0	0	0	0	2 (100.0)	0	2 (0.5)
	Total	0	443 (98.9)	5 (1.1)	448	0	429 (99.5)	2 (0.5)	431
HbA1C (%)									
Normal	Normal	NA	434 (98.4)	7 (1.6)	441 (98.7)	NA	432 (99.5)	2 (0.5)	434 (98.2)
High: >7.5	High	NA	2 (33.3)	4 (66.7)	6 (1.3)	NA	4 (50.0)	4 (50.0)	8 (1.8)
	Total	NA	436 (97.5)	11 (2.5)	447	NA	436 (98.6)	6 (1.4)	442

a Distribution at randomization. Note: Patients are counted only once in each column.
NA Not applicable. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. HbA1C Hemoglobin A1c. N Number of patients in treatment group. n Number of patients.
126 D1447C00126. 127 D1447C00127.
Note: Percentages in the Na column are calculated as (Na /(Na in total row))*100
Note: Percentages are calculated as (n/Na)*100
Note: Clinically important values are defined in table.
Note: >8 hours after last meal.

/sere/prod/seroquel/sdmaintenance/sp/output/df/sa112.rtf cbeg240.sas 16APR2007:15:22 ksd497

Findings based on these more stringent fasting criteria were consistent with the results in the presentation including all fasting patients.

Summary of glucose regulation laboratory data

During the randomized treatment phase there was a small increase in mean glucose level in the quetiapine group (5.00 mg/dL) compared to a small decrease in the placebo group (-0.05 mg/dL) at end of treatment. However, the glucose regulation data were highly variable, and the median changes and the difference between treatment groups were smaller (2.00 mg/dL in the quetiapine group vs 0.00 mg/dL in the placebo group). A slight difference between treatment groups was noted for HbA1c with small increases in both groups (0.18% and 0.04% in the quetiapine and placebo groups, respectively). The mean level of insulin increased with 25.70 pmol/L in the quetiapine treatment group and 10.78 pmol/L in the placebo group, and for both treatment groups, the median change was smaller; 7.00 pmol/L in the quetiapine group and no change in the placebo group. The mean changes in the measure of insulin resistance (HOMA-R) was an increase of 1.13 in the quetiapine group compared with 0.63 in the placebo group. There was a small decrease in the measure of insulin sensitivity (QUICKI) in both treatment groups (-0.006 in the quetiapine group and -0.001 in the placebo group).

Changes in glucose regulation data were largest for the subgroup of patients classified as "diabetic" at randomization (with a mean increase of 10.68 mg/dL in the quetiapine group [median value decreased -5.50 mg/dL] and a mean decrease of -11.34 mg/dL in the placebo group [median decrease -8.00 mg/dL], and a decrease in insulin in both groups [-37.96 pmol/L and -78.91 pmol/L in the quetiapine and placebo groups, respectively, with a median decrease of -14.00 in both groups]), with smaller changes in patients in the subgroup of patients classified as "at risk for diabetes" at randomization (with an increase in mean glucose value of 1.99 mg/dL [median 2.00 mg/dL] and an increase in mean insulin level of 27.51 pmol/L [median 0.00 pmol/L] in the quetiapine group); and similar small changes were noted for the subgroup of patients classified as "non-diabetic" at randomization (with an increase in mean glucose value of 5.45 mg/dL [median 3.00 mg/dL] and an increase in mean insulin level of 35.95 pmol/L [median 7.00 pmol/L] in the quetiapine group).

From enrollment to end of open-label treatment, the mean increase in glucose was 3.95 mg/dL (median 2.00 mg/dL). In HbA1c, there was an increase of 0.05% (median 0.00%) and the mean increase in insulin value was 49.45 pmol/L (median 14.00 pmol/L). These changes were seen in patients in the entire open-label safety population, all on treatment with quetiapine in combination with lithium or valproate.

From enrollment to open-label treatment to the end of randomized treatment (in patients randomized to quetiapine treatment), glucose levels increased by a mean of 6.83 mg/dL with great variability (median change was 4.00 mg/dL). The mean change in HbA1c was the same as during the randomized treatment phase, ie, an increase of 0.18% (median change 0.10). Insulin levels increased by a mean of 54.68 pmol/L (median change 20.00 pmol/L). The mean change in the measure of insulin resistance (HOMA-R) was an increase of 1.95 (median

change 0.70); and there was a decrease in the measure of insulin sensitivity (QUICKI) of 0.0159 (median change −0.014) in the quetiapine group in the randomized safety population.

The presentation of data on treatment-emergent clinically important (as defined by AstraZeneca: blood glucose ≥126 mg/dL in fasting patients: blood glucose ≥200 in non-fasting patients: HbA1c >7.5%) glucose regulation laboratory values is based on the "documented fasting" subset of patients. Such clinically important values at any time during randomized treatment were more common in the quetiapine group compared to the placebo group. 10.7% of the patients in the quetiapine group had a shift to a glucose value ≥126 mg/dL, compared to 4.6% in the placebo group. Treatment emergent glucose values ≥200 mg/dL at any time during randomized treatment was reported for 2.0% of the patients in the quetiapine group and for 0.7% in the placebo group. HbA1c values were elevated (>7.5%) in 2.0% of the patients in the quetiapine group, compared with 0.9% in the placebo group. At the end of treatment, 7.0% of the patients in the quetiapine group and 2.7% in the placebo group presented with a shift to a glucose value ≥126 mg/dL. Seven patients (1.6%) in the quetiapine group and 2 patients (0.5%) in the placebo group showed shifts to clinically important high HbA1c at the end of treatment.

The difference between treatment groups in shifts to clinically important high glucose values (≥126 mg/dL) emerging at any time during randomized treatment was most apparent in the subgroup of patients classified as "at risk for diabetes" at randomization (15.3% in the quetiapine group and 3.9% in the placebo group, in patients with >8 h documented fasting). The differences between the treatment groups may be influenced by the longer duration of exposure to study drug in the quetiapine group, and the higher number of assessments in this group as a consequence of the longer duration of exposure. The mean exposure time in the quetiapine treatment group [mean of 213 days] was 40% higher than in the placebo treatment group [mean of 152 days]). Also, part of the definition of "at risk for diabetes" was having a baseline glucose value of ≥100 to <126 mg/dL (documented fasting), close to the value considered to be clinically important (ie, ≥126 mg/dL), and this may have had an impact on the incidence of treatment emergent changes to high glucose values in the patients categorized to be "at risk for diabetes". To examine the effects of exposure duration and baseline glucose values on changes in glucose, a further analysis was undertaken.

Incidence density is calculated as the number of occurrences divided by "censored exposure" (total-patient years of exposure for all patients at risk) and multiplied by 100. For patients with an occurrence, exposure is calculated as the time from first dose to the time of the occurrence, and for patients without an occurrence, exposure is calculated as the time from first to last dose. In this analysis, the incidence densities of treatment emergent (ie, after randomization) glucose values ≥126 mg/ml were calculated. In all patients regardless of fasting status randomized to quetiapine, the incidence density was 21.58 observations per 100 patient-years, compared with 18.87 observations per 100 patient-years in patients randomized to placebo. The largest difference between treatment groups was noted in the patients in the "at risk for diabetes" subgroup with an incidence density of 27.03 observations per 100 patient-years in the quetiapine group compared with 19.75 observations per 100 patient-years in the placebo group. In the other 2 diabetic subgroups, the difference between

treatment groups was small. Patients in the "diabetic" subgroup had incidence densities of 93.16 and 94.54, respectively, in the quetiapine and the placebo groups. Patients in the "non-diabetic" subgroup had incidence densities of 13.24 and 12.23 respectively, in the quetiapine and the placebo groups. However, in all patients with documented fasting (>8 h), an approximately 2-fold increase in incidence density over placebo in observations of glucose values ≥126 mg/dL or ≥200 mg/dL was observed. The total incidence density of treatment emergent glucose values ≥126 mg/dL was 18.03 observations per 100 patient-years in the quetiapine group and 9.53 observations per 100 patient-years in the placebo group. These incidences of values ≥126 mg/dL were analyzed using a Poisson regression model adjusting for exposure time. The estimated ratio (quetiapine adjunct with a mood stabilizer vs placebo adjunct with a mood stabilizer) of incidence densities was 1.893 with a 95% confidence interval between 1.109 and 3.231. The total incidence density of treatment emergent glucose values ≥200 mg/dL was 3.19 and 1.45, respectively, in the quetiapine and the placebo groups.

5.2.3.1 Integrated post-hoc evaluation

The evaluation of adverse event data described in Section 5.2.2 included events reported by the investigator that were coded to MedDRA preferred terms that represent a diagnosis of diabetes ("diabetes mellitus", "diabetes mellitus, non-insulin-dependent", and "diabetic ketoacidosis") in 6 patients on quetiapine and a mood stabilizer, and in 1 patient on placebo and a mood stabilizer during the randomized treatment phase. The results described in Section 5.2.3 showed that quetiapine was associated with a greater mean increase of blood glucose from baseline, and more patients having treatment emergent blood glucose values ≥126 mg/dL, as compared with placebo. Because of these differences in glucose laboratory data and the imbalance in the number of AEs between treatment groups, an alternative approach was employed to examine whether data collected in the clinical studies (glucose metabolism laboratory data, concomitant medications, medical history) could identify additional cases of possible onset of possible diabetes.

The two studies were not designed to evaluate diabetic status, and the available data did not allow for the original American Diabetes Association (ADA) criteria to be applied in the diagnosis of onset of diabetes in cases of interest. Therefore, special methodologies were established post hoc to provide clinically relevant data regarding the use of quetiapine and glycemic status.

In an attempt to apply clinical input to assess whether the observed glucose data were associated with cases of interest, it was decided to perform an adjudication process at a case level. A very broad and inclusive screening for possible cases of interest was devised, which was then subjected to individual case adjudication by two AstraZeneca endocrinologists that were not involved with the study conduct. The adjudication decisions were collaborative between the two endocrinologists and 3 AstraZeneca physicians associated with the quetiapine project (the Medical Science Director, the Global Drug Safety Physician, and a senior research physician).

Methodology for integrated post-hoc screening of potential cases of interest

A broad post-hoc data search was conducted in order to identify patients who had an adverse event, glucose laboratory results, or initiation of medication that may be used for treatment of diabetes/hyperglycemia (ATC codes beginning with A10A and A10B) to identify possible onset of diabetes or exacerbation of existing diabetes. The listings were scrutinized to ascertain whether the patients showed data consistent with a possible onset of diabetes or possible exacerbation of diabetes (or possible diabetes). These patients are referred to as cases of interest in this document. Three separate and independent listings containing relevant data were prepared, all of which include information about patients' study drugs (in open-label and randomized treatment phase, respectively, and including mood stabilizer) medical history, BMI at baseline, age, sex, AEs potentially associated with diabetes, any concomitant medication at enrollment or initiated during the study (including those for treatments that may be prescribed for diabetes/hyperglycemia), laboratory data for glucose and HbA1c, and weight:

One listing was produced of patients for whom any of the following AEs (MedDRA preferred term) was reported at any time during the entire study: "diabetes mellitus", "diabetes mellitus non-insulin-dependent", "diabetic ketoacidosis", "diabetic complication", "blood glucose increased", "hyperglycaemia", "glucose tolerance impaired", "glycosylated hemoglobin increased", "blood insulin increased", "hyperinsulinaemia", and "insulin resistance". The listing was expanded beyond terms actually related to diabetes mellitus to facilitate identification of all potential cases of interest. In all, there were 43 patients in the listing (12 in Study 126, 31 in Study127).

A second listing was prepared of patients having medication that may be prescribed for treatment of diabetes/ hyperglycemia initiated or dose changed after enrollment. A total of 41 patients appeared in the 2 listings (12 in Study 126 and 29 in Study 127).

The third listing showed patients with 1 glucose value ≥126 mg/dL (regardless of whether documented fasting or not) as the final observation, or at least 2 glucose values ≥126 mg/dL (regardless of whether documented fasting or not) at any time during the study, or with an increase in HbA1c value ≥1.5 unit (%) at any time during the study (from minimum to maximum value. A total of 187 patients appeared in the 2 listings (76 in Study 126 and 111 in Study 127).

In total, 217 unique patients (88 from Study 126 and 129 from study 127) appear in at least 1 of the listings. These listings were then subjected to individual case review, as noted above, and discussed more fully below.

Approaches in the evaluation of potential cases of interest

I Initially, the information in these listings was reviewed to identify cases of interest during the placebo-controlled randomized treatment phase. During this review, the team was not blinded to treatment code. All patients with a relevant AE (MedDRA preferred term) search term (as listed above) reported during randomized treatment, all patients with medication that

may be prescribed for treatment of diabetes/ hyperglycemia initiated or dose changed during randomized treatment, and all patients with at least 1 glucose value ≥126 mg/dL (regardless of whether documented fasting or not) during randomized treatment were subject to review in the first step of the process.

Subsequently, the information in the data listings was reviewed to identify cases of interest during the non-controlled, open-label treatment phase. In this review, the data from the open-label treatment phase were reviewed for all patients in the open-label safety population (ie, including those in the randomized safety population).

The listings were reviewed by a team including the 2 AstraZeneca endocrinologists, and 3 other AstraZeneca physicians associated with the quetiapine project (the Medical Science Director, the Global Drug Safety Physician, and a senior research physician) post-hoc, and collaborative adjudication was then performed by the 2 endocrinologists who were not associated with the study design, implementation, or prior analysis.

Criteria for evaluating cases of interest were established collaboratively by the 2 AstraZeneca endocrinologists, with team input.

> ***ORIGINAL CRITERIA: From Diabetes Care 1997;20(7):1183-97***
>
> ***"The new criteria***
> *The diagnostic criteria for diabetes mellitus have been modified from those previously recommended by the NDDG or WHO. The revised criteria for the diagnosis of diabetes are shown in Table 3. Three ways to diagnose diabetes are possible, and each must be confirmed, on a subsequent day, by any one of the three methods given in Table 3. For example, one instance of symptoms with casual plasma glucose ≥200 mg/dl (11.1 mmol/l), confirmed on a subsequent day by 1) FPG ≥126 mg/dl (7.0 mmol/l), 2) an OGTT with the 2-h postload value ≥200 mg/dl (11.1 mmol/l), or 3) symptoms with a casual plasma glucose ≥200 mg/dl (11.1 mmol/l), warrants the diagnosis of diabetes.*
>
> ***Table 3 Criteria for the diagnosis of diabetes mellitus***
>
> *1. Symptoms of diabetes plus casual plasma glucose concentration 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.*
>
> *or*
>
> *2. FPG 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
>
> *or*
>
> *3. 2-h PG 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
>
> *In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use."*

FPG Fasting plasma glucose, NNDG National Diabetes Data Group, OGGT oral glucose tolerance test, PG postload glucose, WHO World Health Organization;

The ADA criteria for diagnosis of diabetes specify confirmation of a threshold glucose value "on a subsequent day," however, subsequent glucose values from the study were most commonly separated by a period of several weeks. Therefore, an adaptation of the ADA criteria was agreed upon by the endocrinologists to identify cases of interest where:

a confirming glucose value could be obtained on a subsequent proximal visit (not necessarily on a "subsequent day")

or

symptoms of diabetes plus documented fasting glucose ≥126 mg/dL or not documented fasting glucose ≥200 mg/dL

Oral glucose tolerance test (OGTT) was not part of the study design in Study 126 and Study 127, and was therefore not used as a diagnostic tool in the evaluation of cases of interest.

In the Case Report Form (CRF), date and time of blood sampling and date and time of the last meal prior to sampling was reported. This information was used to calculate the time elapsed between the last reported meal and blood draw, and to create a subset of patients only considering samples that met the more stringent fasting conditions, ie, with blood sampling documented in the CRF to be more than 8 hours after the last reported meal. "Documented fasting" is the term used in this document for describing this subset of glucose data. It should be noted that a "documented fasting" glucose value does not preclude that the patient had a caloric intake of fluids other than water during the period from the last meal to blood draw.

Criteria for identifying cases of interest regarding possible exacerbation of diabetes relied upon the clinical judgement of the 2 adjudicating endocrinologists, who considered the data available in the listings, including glucose, HbA1c, medication, and AEs potentially associated with diabetes.

General approach to analysis of cases of interest:

1. Any patient with a medical history of diabetes was considered to have pre-existing diabetes, and any patient with evidence of a glucose level at enrollment that reached ADA diagnostic threshold for diagnosis of diabetes was considered to have probable pre-existing diabetes, and therefore was excluded from evaluation of possible onset of diabetes during open-label or randomized treatment periods.

2. Any patient with a reported adverse event consistent with emerging diabetes and at least one glucose level that reached ADA diagnostic threshold for diagnosis of diabetes was considered to have onset of diabetes.

3. Any patient (without a medical history of diabetes or without a probable pre-existing diabetes at enrollment) who had a glucose level and a confirming level at the subsequent visit that reached ADA diagnostic threshold for diagnosis of diabetes, was considered to have a possible onset of possible diabetes.

4. Any patient with either probable pre-existing diabetes, or with onset or possible onset of diabetes (by approaches 1, 2 or 3 noted above) during open label treatment was evaluated for possible exacerbation of diabetes during the randomized treatment phase.*

5. Any patient with initiation of a medication that may be used for treatment of diabetes (or a change in dose of such medication) was evaluated for possible onset or possible exacerbation of diabetes.*

6. Any patient with probable pre-existing diabetes, or possible onset of diabetes (by approaches 1, 2 or 3 noted above) who had medication initiated for the treatment of diabetes (or a change in dose of such medication), was evaluated for possible exacerbation of possible diabetes.*

*Analysis of possible exacerbation was considered in the full context of AEs, glucose values, and HbA1c, based on clinical judgment of the 2 endocrinologists.

Methods for summarizing the post hoc adjudication of cases of interest

The cases of interest during each treatment phase were tabulated with respect to different baseline characteristics and key data for the identified patients were presented in listings, eg, including glucose data and weight at entry, at randomization and at end of treatment. Incidences and incidence densities for cases of interest relative to the study population were calculated. Incidence densities of cases of interest in the open label portion were contrasted with available epidemiologic data, while for the randomized portion, data from the 2 treatment groups were compared. In an attempt to thoroughly examine whether certain risk factors predispose to the occurrence of cases of interest, or to blood glucose values ≥126 mg/dL, an exploratory post-hoc analytic evaluation of Study 126 and Study 127 data was undertaken. [put this in to contrast with the post hoc adjudication, to limit confusion]The following potential risk factors were considered to be of key interest for the analysis of the post-hoc adjudicated cases: (i) impaired fasting glucose (IFG) at baseline, (ii) weight at enrollment and (iii) weight changes during the study. The analysis plan, the output from the analyses, and the detailed interpretation of the results are provided in Appendix C.

Results of the post hoc adjudication of cases of interest

For purposes of characterization of the cases of potential interest, the evaluation of the patient listings is summarized by 3 categories as shown in Table 16 for possible onset of diabetes, and in Table 18 for possible exacerbation of diabetes.

(a) Possible onset of diabetes

The results of the evaluation for possible onset of diabetes in the open label and randomized treatment phase are summarized in Table 16.

Table 16 Summary of post-hoc adjudication of cases for possible onset of diabetes (open-label and randomized treatment phase)

Evaluation categories	Open-label	Randomized treatment	
	QTP n=23	QTP n=11	PLA n=2
Patients with an AE of diabetes[a] and at least 1 glucose meeting adapted ADA criteria[b] (may include patients who initiate hypoglycemic agent)	6[c]	2[d]	0
No AE of DM: Patients with hypoglycemic medication initiated or changed and glucose meeting adapted ADA criteria[b]	1	0	1
No AE of DM and no initiation of hypoglycemic medication): Patients with glucose meeting adapted ADA criteria[b]	16	9	1

a AEs of diabetes include the following preferred terms; diabetes mellitus, diabetes mellitus non-insulin dependent, and diabetic ketoacidosis.

c Four of these patients also had hypoglycaemic medication initiated during the open-label phase of the study (Patients E0404003, E0108019, E0059014, and E0112015).

d Both of these patients also had hypoglycaemic medication initiated during the randomized phase of the study (Patients E0036019 and E0063001).

Note: Patients in this table adjudicated with possible onset of diabetes during the open label phase of the study could also be included in Table 17 if they were adjudicated to have experienced possible exacerbation of diabetes during the randomized phase of the study as well. (Patients E0059014, E0604021, E0080036, and E0048011).

Note: Patients E0026002 and E0062017 in the quetiapine group and Patient E0105016 in the placebo group had AEs of "diabetes mellitus" or "diabetes mellitus, non-insulin-dependent" reported during the randomized treatment phase, but were not considered in the adjudication process to have any evidence in laboratory results of an onset or an exacerbation of diabetes at any time during the study.

Note: Patients E0034005, E0040601, E0044056, and E0026009 had AEs of "diabetes mellitus" or "diabetes mellitus, non-insulin-dependent" reported during the open-label treatment phase, but were not considered in the adjudication process to have any evidence in laboratory results of an onset or an exacerbation of diabetes during open-label treatment.

Individual narratives for all the patients identified in Table 16 as representing a possible onset of diabetes are provided in Appendix D. A summary listing of patients identified in the randomized treatment phase is contained in Table 17 below.

This post-hoc approach of the open-label phase revealed an incidence of 0.72% (23 patients divided by 3187 patients at risk, ie, patients in the open-label safety population not classified as "diabetic" according to pre-defined criteria at enrollment) with possible onset of possible diabetes.

As shown in Table 16 the post-hoc approach identified the following for the open-label treatment phase:

> Six patients with reports of adverse events of diabetes during the open-label phase were adjudicated as onset of diabetes during the open-label treatment. These 6 adverse event reports of diabetes met a higher threshold of decision than strictly glucose/symptom driven adjudication and were more than "possible" diabetes.

Seventeen patients (with no adverse events of diabetes) were adjudicated as having possible onset of diabetes during the open-label phase based on glucose values and/or symptoms.

There were 53 patients in the quetiapine group and 57 patients in the placebo group classified as "diabetic" at randomization and thus not considered at risk for onset of possible diabetes during the randomized phase. During the randomized phase, 1.85% (11 patients divided by 593 patients at risk) treated with quetiapine had possible onset of possible diabetes, compared to 0.32% (2 patients divided by 623 patients at risk) treated with placebo. When adjusting for treatment exposure for patients at risk the incidence densities of possible onset of possible diabetes were 3.3 cases per 100 patient-years for quetiapine compared to 0.78 cases per 100 patient-years for placebo. As shown in Table 16, the post-hoc approach identified the following for the randomized treatment phase:

Two quetiapine patients and no placebo patients with adverse event reports of diabetes were adjudicated as onset of diabetes during the randomized phase. These 2 adverse event reports of diabetes met a higher threshold of decision than strictly glucose/symptom driven adjudication and were more than "possible" diabetes.

Nine quetiapine patients and 2 placebo patients (with no adverse events of diabetes) were adjudicated as having possible onset of possible diabetes during the randomized phase based on glucose values and/or symptoms.

Table 17 Patients with possible onset of DM in the randomized treatment phase

Study # Patient ID Tx group PT (if applicable)	Age/ Sex	Seroquel dose & TTO	Hx	Reported AE start/stop dates Comments
QTP patients: Emergence of diabetes during randomized phase				
D1447C00126 E0604029 QTP & LI	56/F	400 mg/day, 84 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 171 days. Baseline: BMI = 27.7, BG = 87 mg/dL (not documented fasting), HbA1c = 6.0%. Day 84 OL: BG = 129 mg/dL (documented fasting), HbA1c = 5.9% & AE of "BG ↑" reported. Day 85 RT: Wt ↑ 6 kg, BG = 345 mg/dL (documented fasting), HbA1c = 6.9%. Day 190 RT (final visit): BG = 127 mg/dL (documented fasting), HbA1c = 6.6%. No AE associated w/ DM during RT & no initiation of hypoglycemic med during trial **Post-hoc adjudicated evaluation:** Pt considered to have possible onset of DM during OL phase.
D1447C00126 E0605065 QTP & LI	60/M	400 mg/day, 197 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 112 days. Baseline: BMI = 29.1, BG = 98 mg/dL (documented fasting), HbA1c = 5.3% Day 85 RT: Wt ↑ 16 kg, BG = 128 mg/dL (documented fasting), HbA1c = 5.3%. No other lab values until Day 309 (final visit): Wt ↑ another 10 kg, BG = 155 mg/dL (documented fasting), HbA1c = 6.8%. No AE associated w/ DM during RT & no initiation of hypoglycemic med during trial. **Post-hoc adjudicated evaluation:** Pt considered to have possible onset of DM during RT.
D1447C00126 E1309003 QTP & LI	56/F	800 mg/day, 214 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 101 days. Baseline: Wt = 122 kg (no ht). At randomization: BG = 125 mg/dL (documented fasting), HbA1c = 6.3%. Day 113 RT: BG = 126 mg/dL (documented fasting), HbA1c = 6.3% Wt stable. Day 295 RT: Wt ↓ 13 kg. Day 463 RT: BG = 127 mg/dL (documented fasting), HbA1c = 6.5%. No AE associated w/ DM during RT & no hypoglycemic Tx initiated during trial **Post-hoc adjudicated evaluation:** Pt considered to have possible onset of DM during RT.
D1447C00126 E1301002 QTP & LI	59/M	400 mg/day, 281 days	No Hx of DM or oral hypoglycemic Tx @ enrollment	OL x 84 days. Baseline: BMI = 27.5, BG 94 mg/dl. (documented fasting), HbA1c = 5.5%. Day 197 RT: BG = 169 mg/dL (documented fasting), HbA1c = 6.8%. Day 197 RT: Wt ↑ 25 kg. Day 211 RT (last visit): BG = 169 mg/dL (documented fasting), HbA1c = 7.0%. **Post-hoc adjudicated evaluation:** Pt considered to have possible onset of DM during RT
D1447C00126 E0104067 QTP & LI	46/M	800 mg/day, 206 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 121 days. Baseline: BMI = 27.9, BG = 88 mg/dL (documented fasting), HbA1c = 5.1% Day 85 RT: Wt ↓ 9 kg, BG = 144 mg/dL (documented fasting), HbA1c = 5.2%. Day 365 RT: BG = 132 mg/dL (documented fasting), HbA1c = 5.4%. Day 378 RT: Wt ↓ another 6 kg, BG = 147 mg/dL (documented fasting), HbA1c = 5.2%. No AE associated w/ DM during RT & no hypoglycemic Tx initiated during trial. **Post-hoc adjudicated evaluation:** Pt considered to have possible onset of DM during RT

Table 17 Patients with possible onset of DM in the randomized treatment phase

Study # Patient ID Tx group PT (if applicable)	Age/ Sex	Seroquel dose & TTO	Hx	Reported AE start/stop dates Comments
D1447C00127 E0063008 QTF & LI DM	42/F	400 mg/day; 306 days	No hx of DM	OL x 112 days. Baseline: BMI = 40.9, BG = 134 mg/dL (not documented fasting), HbA1c = 6.5%. Day 196 RT: Wt ↑ 18 kg, BG = 316 mg/dL (documented fasting), HbA1c = 9.0%. From Day 274 RT & Day 278 RT: Dc'ed metformin & exenatide for AE of "DM". Day 312 RT: metformin & exenatide dose ↑. Day 424 RT: AE resolved (BG = 117 mg/dL [documented fasting], HbA1c = 6.6%), oral antidiabetic agents ongoing. **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT.
D1447C00127 E0063001 QTF & LI DM	48/ M	600 mg/day; 319 days	No hx of DM	OL x 111 days. Baseline: BMI = 36.2, BG = 112 mg/dL (not documented fasting), HbA1c = 5.7%. Day 208 RT: investigator reported "DM", Wt ↑ 3 kg, BG = 163 mg/dl, (documented fasting), HbA1c = 6.8%. Day 604 RT: dc'ed metformin & glipizide. Day 687 RT (last visit): BG = 143 mg/dL (documented fasting), HbA1c = 6.3%, oral antidiabetic agents ongoing. **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT.
D1447C00127 E0070006 QTP & VAL	43/F	400 mg/day; 237 days	Concurrent "renal glycosuria". No hx of DM/oral hypoglycemic Tx @ enrollment	OL x 168 days. Baseline: BMI = 44.2, BG = 146 mg/dL (not documented fasting), HbA1c = 8.1%. Day 169 RT: Wt ↓ 6 kg BG = 152 mg/dL (documented fasting), HbA1c = 5.8%. No AE reported w/ these labs. Day 447 RT: BG = 177 mg/dL (documented fasting). Day 561 RT: BG = 130 mg/dL (documented fasting). Day 673 RT (final visit): BG = 106mg/dL (documented fasting), HbA1c = 6.6%. **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT.
D1447C00127 E0083013 QTP & VAL	51/F	600 mg/day; Day 700	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 224 days. Baseline: BMI = 41.3, BG = 90 mg/dl. (documented fasting), HbA1c = 6.0%. Day 478 RT: Wt ↑ 10 kg, BG = 138 mg/dL (documented fasting), HbA1c = 7.6%. No AEs reported w/ these labs. Day 526 RT (final visit): BG = 126 mg/dL (documented fasting), HbA1c = 7.0%. **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT.
D1447C00127 E0089002 QTP & VAL	46/F	600 mg/day; 351 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 126 days. Baseline: BMI = 29.3, BG = 124 mg/dL. (not documented fasting), HbA1c = 6.3%. Day 225 RT: Wt ↑ 11 kg, BG = 228 mg/dL (not documented fasting), HbA1c = 7.3% No AEs reported w/ these labs. Day 268 RT (final visit): BG = 211 mg/dl. (not documented fasting), HbA1c = not available. **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT.
D1447C00127 E0120007 QTP & VAL	21/M	500 mg/day; 421 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 140 days. Baseline: BMI = 37.2, BG = 103 mg/dL. (not documented fasting), HbA1c = 5.2%. Day 281 RT: Wt ↑ 4 kg, BG = 137 mg/dL (documented fasting), HbA1c = 5.7 % Day 484 RT: BG = 176 mg/dl. (documented fasting), HbA1c = 7.7%. Day 595 RT: BG = 164 mg/dl. (documented fasting), HbA1c = 7.4%. No AEs reported w/ these labs. Day 602 RT (final visit): BG = 148 mg/dL (documented fasting), HbA1c = 7.7 %. **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT.

Table 17 Patients with possible onset of DM in the randomized treatment phase

Study # Patient ID Tx group PT (if applicable)	Age/ Sex	Seroquel dose & TTO	Hx	Reported AE start/stop dates Comments
D1447C00127 E0037014 QTP & LI	27/ M	500 mg/day; 302 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL: x 224 days. Baseline: BMI = 49.6, BG = 81 mg/dL (not documented fasting), HbA1c = 5.0 %. Day 78 RT: Wt ↑ 23 kg, BG = 151 mg/dL (documented fasting), HbA1c = 6.4%. AE of "Hyperglycemia" reported. Day 98 RT: AE resolved & Pt d/c'd from study d/t AE (BG = 131 mg/dL [documented fasting], &HbA1c = 6.3 %). **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT
PLA patients: Emergence of diabetes during randomized phase				
D1447C00127 E0026024 PLA & VAL	55/M	224 days OL; Day 15 of RT	No hx of DM or oral hypoglycemic Tx @ enrollment	OL: x 224 days. Baseline: BMI = 25.0, BG =90 mg/dL (not documented fasting), HbA1c = 5.1 %. Day 84 OL: BG = 170 mg/dL (documented fasting), HbA1c = 5.3%. Day 15 RT: Wt ↑ 16 kg, BG = 135 mg/dL (documented fasting), HbA1c = 5.7%, non-serious AEs of "hyperglycemia" & hypernatremia" reported by investigator. Resolved in 3 day. No action taken in response to these AEs. Day 43 RT (final visit) BG = 167 mg/dL (documented fasting). **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT.
D1447C00127 E0001012 PLA & VAL	54/M	168 days OL; Day 407 RT	No hx of DM or oral hypoglycemic Tx @ enrollment	OL: x 168 days. Baseline: BMI = 27.1, BG=119 mg/dL (not documented fasting), HbA1c = 6.8 % Day 368 RT: Wt ↑ 28 kg, BG = 167 mg/dL (documented fasting), HbA1c = 9.1%. Day 407 RT: metformin initiated for "↑ BG." Day 420 RT: metformin d/c'd. Day 465 RT: BG = 147 mg/dL (documented fasting), HbA1c = 8.2%. **Post-hoc adjudicated evaluation**: Pt considered to have possible onset of DM during RT

AE adverse event, BG Blood glucose, BMI body mass index, cont'd continued, d/c discontinued, d/t due to, DM diabetes mellitus, HbA1c glycosylated hemoglobin, hx history, LI lithium, info information, mo(s) months, OL open label, PLA placebo, pos positive, pt patient, QTP quetiapine, RT randomized treatment, Tx treatment, unk unknown, w/ with, w/drew withdrew, w/out without, wk(s) week(s), wt weight, yr(s) years)

(b) Possible exacerbation of diabetes

The results of the evaluation for possible exacerbation of diabetes in the open label and randomized treatment phase are summarized in Table 18.

Table 18 Summary of post-hoc adjudication of cases for possible exacerbation of diabetes (open label and randomized treatment phase)

Evaluation categories	Open-label	Randomized treatment	
	QTP n=20	QTP n=11	PLA n=4
Patients with an AE of diabetes[a] and at least 1 glucose meeting adapted ADA criteria[b]	5[c]	2[d]	0
No AE of diabetes: Patients with lab and clinical information consistent with exacerbation and hypoglycemic medication initiated or changed	2	2	0
No AE of DM and no hypoglycemic med initiated or changed: Patients with lab and clinical information consistent with exacerbation	13	7	4

[a] AEs of diabetes include the following preferred terms: diabetes mellitus, diabetes mellitus non-insulin dependent, and diabetic ketoacidosis.

[c] Two of these patients also had hypoglycaemic medication initiated during the open-label phase of the study (Patients E008004 and E0112006).

[d] One of these patients (E0059014) also had hypoglycaemic medication initiated during the randomized phase of the study.

Note: Patients in this table adjudicated with possible exacerbation of diabetes during the randomized phase of the study could also be included in Table 16 if they were adjudicated to have experienced possible onset of diabetes during the open-label phase. (Patients E0059014, E0604021, E0080036, and E0048011).

Note: Patients E0026002 and E0062017 in the quetiapine group and Patient E0105016 in the placebo group had AEs of "diabetes mellitus" or "diabetes mellitus, non-insulin-dependent" reported during the randomized treatment phase, but were not considered in the adjudication process to have any evidence in laboratory results of an onset or an exacerbation of diabetes at any time during the study.

Note: Patients E0034005, E0040001, E0044056, and E0026009 had AEs of "diabetes mellitus" or "diabetes mellitus, non-insulin-dependent" reported during the open-label treatment phase, but were not considered in the adjudication process to have any evidence in laboratory results of an onset or an exacerbation of diabetes during open-label treatment.

Individual narratives for all the patients identified in Table 18 as representing possible exacerbation of diabetes are provided in Appendix D. A summary listing of patients identified in the randomized treatment phase is contained in Table 19 below.

The post-hoc approach of the open-label phase revealed possible exacerbation of diabetes in 20 patients, corresponding to 0.59% of patients in the entire open-label safety population and 10.87% of the 184 patients classified as "diabetic" at enrollment. As shown in Table 18, the post-hoc approach identified the following for the open-label treatment phase:

> Five patients with reports of adverse events of diabetes during the open-label phase were adjudicated as having exacerbation of diabetes. These 5 adverse event reports

of diabetes met a higher threshold of decision than strictly glucose/symptom driven adjudication and were more than "possible" exacerbations.

Fifteen patients (with no adverse events of diabetes) were adjudicated as having possible exacerbation of diabetes during the open-label phase based on glucose values and/or symptoms.

During the randomization phase, 20.75% (11 patients divided by 53 patients classified as "diabetic" at randomization) in the quetiapine group and 7.02% (4 divided by the 57 patients classified as "diabetic") in the placebo group were adjudicated to have possible exacerbation of diabetes. When adjusting for treatment exposure for patients at risk, incidence densities were 40.81 cases per 100 patient-years for quetiapine compared to 22.64 cases per 100 patient-years for placebo. As shown in Table 18, the post-hoc approach identified the following for the randomized treatment phase:

Two quetiapine patients and no placebo patients with adverse event reports of diabetes that were adjudicated as exacerbation of diabetes. These 2 adverse event reports of diabetes met a higher threshold of decision than strictly glucose/symptom driven adjudication and were more than "possible" exacerbations.

Nine quetiapine patients and four placebo patients with no adverse events of diabetes were adjudicated as having possible exacerbation of diabetes during the randomized phase based on glucose values and/or symptoms.

Table 19 Adjudication of patients with possible exacerbation of DM

Study # Patient ID Tx group PT (if applicable)	Age/ Sex	Seroquel dose & TTO	Hx	Reported AE start/stop dates Comments
			QTP patients: Exacerbation of DM in randomized treatment phase	
D1447C00126 E0113002 QTP &VAL	28/F	400 mg/day; 197 mg/day	Hx of DM Oral hypoglycemic (metformin) Tx @ enrollment	OL x 112 days. Baseline: BMI = 50.1, BG = 120 mg/dL (documented fasting), HbA1c = 7.1 %. Day 85 RT: BG = 195 mg/dL (documented fasting), HbA1c = 7.6%. Day 198 RT: Wt ↓ 25 kg, BG = 235 mg/dL (not documented fasting). Day 208 RT: BG = 129 mg/dL (documented fasting), HbA1c = 8.1%. No AE associated w/ DM recorded during RT. Metformin not adjusted during trial. **Post-hoc adjudicated evaluation:** Pt considered to have probable pre-existing DM & possible exacerbation of DM during RT.
D1447C00126 E1004006 QTP & VAL	53/M	Dose unk; 226 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 143 days. Baseline: BMI = 39.4, BG = 164 mg/dL (documented fasting), HbA1c = 5.5 %. Day 85 RT: Wt ↑ 5 kg BG = 152 mg/dL (documented fasting), HbA1c = 6.4 %. Day 192 RT: BG = 148 mg/dL. Day 281 RT: BG = 173 mg/dL. Day 365 RT: BG = 167 mg/dL. Day 477 RT: BG = 186 mg/dL (all 4 values documented fasting). Day 477 RT: HbA1c = 8.8%. No AE associated w/ DM recorded during RT & no hypoglycemic Tx initiated during trial. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.
D1447C00127 E0055014 QTP & VAL DKA	57/M	400 mg/day; 143 days	No hx of DM or oral hypoglycemic tx @ enrollment	OL x 173 days. Baseline: BMI = 27.9, BG = 130 mg/dL (not documented fasting), HbA1c = 5.0 % Day 21 RT: Tooth extraction w/ subsequent Wt↓ of 6 kg. Day 28 RT: Wt 12 kg. "About Day 30 RT", pt w/ polyuria, polydipsia, wt. loss, mod. blurred vision, severe renal failure. Day 41 RT: n/v, fatigue. Day 42 RT: BG = 906 mg/dL. Presented to ER Day 44 RT: BG = 1445 mg/dL, HbA1c = 17.2% (obtained from local lab data). Dx = DKA. Tx = IVF & IV insulin. Day 49 RT: DKA resolved. Day 51 RT: blurred vision resolved. Pt withew from study d/t AE. **Post-hoc adjudicated evaluation:** Pt considered to have FBS suggestive of possible onset DM during OL (194 mg/dL) & exacerbation of DM with an AE report of "DKA" during the RT, w/ initiation of antidiabetic med.
D1447C00127 E0080036 QTP & VAL NIDDM	29/M	800 mg/day; 308 days	Hx of glucose intolerance, metabolic syndrome, obesity, but no hx of DM	OL x 109 days. Baseline: BMI = 38.4, BG = 92 mg/dl. (documented fasting), HbA1c = 5.9 %. Day 199 RT: Wt ↑ 2 kg, BG = 583 mg/dL (documented fasting) HbA1c = 13.6%. Day 206 RT: BG = 238 mg/dL (not documented fasting). No action taken by investigator in response to AE & no glucose lowering agents started. AE contd. to Day 275 RT (final visit): BG = 94 mg/dL (documented fasting), Insulin = 42 pmol/L, HbA1c = 9.4%. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.

Table 19 Adjudication of patients with possible exacerbation of DM

Study # Patient ID Tx group PT (if applicable)	Age/ Sex	Seroquel dose & TTO	Hx	Reported AE start/stop dates Comments
D1447C00127 E0004006? QTP & VAL	44/M	800 mg/day; 326 days	Hx of Type II DM concurrent tx w/ metformin & pioglitazone for Tx of DM @ enrollment	OL x 253 days. Baseline: BMI = 40.2, BG = 87 mg/dL (not documented fasting), HbA1c = 6.4 %. Day 91 RT: Wt ↓ 2.5 kg, BG = 404 mg/dL (documented fasting), HbA1c = 12.0%. Day 112 RT: insulin initiated for DM. Day 196 RT: BG = 179. Day 282 RT: BG = 169. Day 369 RT: BG = 172. Day 584 RT: BG = 261(all mg/dL & documented fasting). Day 562 RT (final visit): BG = 80 mg/dL (documented fasting), HbA1c = 9.4%. Insulin tx ongoing. **Post-hoc adjudicated evalution:** Pt considered to have probable pre-existing DM & possible exacerbation of DM during RT.
D1447C00127 E0048011 QTP & VAL	51/M	400 mg/day; 280 days	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 226 days. Baseline: BMI = 36.5, BG = 94 mg/dL (not documented fasting), HbA1c = 5.2 %. Day 54 RT: Wt ↑ 10 kg. Day 61 RT: Tx started w/ metformin, glibenclamide & glipizide. Day 62 RT: AE of hyperglycemia recorded. Day 68 RT: Pt d/c'd from trial dt AE. Day 85 RT: BG = 249 mg/dL (documented fasting), HbA1c = 9.6%. Hyperglycemic tx ongoing. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT
D1447C00127 E0007847 QTP & VAL	72/M	300 mg/day; 337 days	Current hx of DM, but no hypoglycemic meds ongoing @ enrollment	OL x 140 days. Baseline: BMI = 28.8, BG = 115 mg/dL (not documented fasting), HbA1c = 6.2 %. Day 197 RT: Wt ↑ 2kg, BG = 198 mg/dL (not documented fasting), HbA1c = 7.3 %. No AE associated w/ lab findings & no change in study med or start of DM Tx initiated during study. Day 435 RT (final visit) BG = 139 mg/dL (documented fasting), HbA1c = 7.5% w/o start of hyperglycemic med during study. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.
D1447C00127 E0004006 QTP & LIT	45/M	800 mg/day; 336 days	Current hx of DM Type II but no hypoglycemic meds ongoing @ enrollment	OL x 253 days. Baseline: BMI = 35.1, BG = 92 mg/dL (not documented fasting), HbA1c = 5.5%. Day 85 RT: BG = 129 mg/dL (documented fasting), HbA1c = 5.8%. Day 197 RT: BG = 132 mg/dL (documented fasting), HbA1c = 5.9 %. No AE associated w/ labs & no change in study med or start of DM Tx initiated during study. Day 245 RT: Wt ↑ 5 kg, BG = 381 mg/dL (not documented fasting) HbA1c = 6.5% w/o start of hyperglycemic med during study. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.
D1447C00127 F0051006 QTP & VAL	62/M	600 mg/day; 477 days	Current hx of DM w/ Tx of insulin (fast-acting & long-acting) ongoing @ enrollment & thru study	OL x 198 days. Baseline: BMI = 29.8, BG = 120 mg/dL (documented fasting), HbA1c = 6.6 %. Day 77 RT: BG = 136 mg/dL (documented fasting), HbA1c = 7.5 %. Day 279 RT (final visit): Wt ↑ 2 kg, BG = 214 mg/dL (not documented fasting), HbA1c = 9.3 % w/o change in hypoglycemic Tx. No AE associated w/ lab findings & no change in study med or DM therapy during study. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT

Table 19 Adjudication of patients with possible exacerbation of DM

Study # Patient ID Tx group PT (if applicable)	Age/ Sex	Seroquel dose & TTO	Hx	Reported AE start/stop dates Comments
D1447C00127 E0063011 QTP & LIT	52/F	500 mg/day; 436 days	Current hx of DM w/ Tx glipizide@ enrollment & thru study	OL x 238 days. Baseline: BMI = 37.0, BG = 92 mg/dL (documented fasting), HbA1c = 6.0 %. Day 85 RT: Wt ↑ 2 kg (then back to baseline @ final visit), BG = 174 mg/dL (documented fasting), HbA1c = 8.4%. Day 198 RT (final visit): BG = 248 mg/dL (documented fasting), HbA1c = 10.4% w/o change to hypoglycemic therapy. No AE associated with lab findings. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.
D1447C00127 E0080033 QTP & LIT	38/M	800 mg/day; 341 days	Current hx of DM, Type II w/ Tx of metformin @ enrollment & thru study	OL x 144 days. Baseline: BMI = 58.6, BG = 166 mg/dL (documented fasting), HbA1c = 7.3 % Day 197 RT: BG = 158 mg/dL dL (documented fasting), HbA1c = 7.1 %. Day 252 RT (final visit). Wt ↓ 2 kg, BG = 218 mg/dL (documented fasting), HbA1c = 8.0% w/o change in hypoglycemic tx. No AE associated w lab findings & no change in study med or DM therapy. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.
		PLA patients: Exacerbation of DM in randomized treatment phase		
D1447C00126 E0103011 PLA & VAL	42/F	253 days OL, Day 93 RT	Hx of DM but no oral hypoglycemic Tx @ enrollment	OL x 253 days. Baseline: BMI = 34.4, BG = 79 mg/dL (documented fasting), HbA1c = 6.0 %. Day 84 OL: BG = 129 mg/dL (documented fasting), HbA1c = 5.8%. Day 93 RT: Wt ↑ 5 kg, BG = 165 mg/dL (documented fasting), HbA1c = 7.0%. Day 155 RT (final visit) BG = 106 mg/dL (fasting status unknown), HbA1c = 6.8%. No AEs associated w/ DM reported during RT & no hypoglycemic Tx started. **Post-hoc adjudicated evaluation.** Pt considered to have possible exacerbation of DM during RT.
D1447C00126 E0118002 PLA & LI	33/M	309 days OL, Day 86 RT	Hx of DM Type II w/ ongoing tx w/ metformin @ enrollment	OL x 309 days. Baseline: BMI = 25.8, BG = 155 mg/dL (documented fasting), HbA1c = 6.8 %. Labs @ randomization: BG = 170 mg/dL (documented fasting), HbA1c = 7.3%. Day 86 RT: Wt↓ 1 kg, BG = 206 mg/dL (documented fasting), HbA1c = 7.8%. No AEs associated w/ DM reported during RT & metformin dose not changed during study. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.
D1447C00126 E0604021 PLA & VAL	42/M	119 days OL, Day 1 RT	No hx of DM. Hx of asthma tx w/ Gluco-corticosteroids thru study	OL x 119 days. Baseline: BMI = 28.8, BG =92 mg/dL (documented fasting), HbA1c = 6.1 %. Day 84 OL: BG = 129 mg/dL (documented fasting), HbA1c = 5.9%. Day 1 RT: Wt 121 kg from enrollment. Pt had AE = thirst & HbA1c ↑ (6.8%), BG = 114 mg/dL (documented fasting). No hypoglycemic agents initiated during trial. AE of HbA1c ↑. Day 87 RT (final visit) w/ BG = 137 mg/dL (documented fasting), HbA1c = 7.3%. Pt w/drew from study d/t AE. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.

CONFIDENTIAL
AZSER14866335

Table 19 Adjudication of patients with possible exacerbation of DM

Study # Patient ID Tx group PT (if applicable)	Age/ Sex	Seroquel dose & TTO	Hx	Reported AE start/stop dates Comments
D1442C00127 B0083028 PLA & VAL	57/M	224 days OL, Day 281 RT	No hx of DM or oral hypoglycemic Tx @ enrollment	OL x 224 days. Baseline: BMI = 36.3, BG = 134 mg/dL (documented fasting), HbA1c = 7.1 %. Day 82 OL: BG = 158 mg/dL (documented fasting), HbA1c = 6.9%. Day 168 OL: BG = 132 mg/dL (documented fasting), HbA1c = 6.5%. Day 281 RT: BG = 141 mg/dL (documented fasting), HbA1c = 7.4% Day 370 RT: Wt ↓ 6 kg from enrollment, BG = 118 mg/dL (documented fasting), HbA1c = 7.0%. Day 423 RT: Pt Tx w/ pioglitazone for "PBS". Day 443 RT (final visit): BG = 115 mg/dL, HbA1c =/ 9% w/ hypoglycemic Tx ongoing. **Post-hoc adjudicated evaluation:** Pt considered to have possible exacerbation of DM during RT.

Context of open-label findings of possible onsets of possible diabetes

As seen in Table 16, the post-hoc adjudication of cases of interest identified 23 patients considered to experience an onset or a possible onset of diabetes during the open-label treatment phase. The total quetiapine exposure in the open-label treatment period in the combined studies was 967.1 patient years. The 23 cases of interest are equivalent to 23.78 cases per 1000 patient-years.

The number of emergent diabetes cases that could be expected (based on the demographic features of the studied population) in the combined studies during the open-label treatment phase was approximated using diabetes incidence rates estimated from studies and surveys of the general population. The National Health Interview Survey (NHIS) is a multistage probabilistic health survey of the civilian, non-institutionalized, household population of the United States conducted annually by the Centers for Disease Control and Prevention (CDC). NHIS 2005 BMI-specific incidence rates calculated using CDC methodology based on self-reported age at diabetes onset (CDC 2005), weighted by the duration of exposure in each BMI (<25, 25-<30, 30-<40, ≥40) group within the study, results in 8.56 expected incident diabetes cases in the approximately 1000 person-years of open-label phase observation. Similarly, NHIS age-, sex-, and BMI-specific incidence rates weighted by the duration of exposure in each age (18-39, 40-64, ≥65), sex, and BMI (<25, 25-<30, ≥30) group within the study, results in 8.22 expected incident diabetes cases in 1000 person-years.

Expected number of diabetes cases during the open-label treatment period, adjusted for BMI, was also calculated using incidence rates reported in the literature. Using BMI-specific diabetes incidence rates among adults from CDC's National Health and Nutrition Examination Surveys (NHANES) I (1971-1975) and II (1992) (Ford et al 1997), 10.65 incident cases of diabetes could be expected. Similarly, using the incidence rates reported from the Framingham Offspring study of adults aged 40-55 years, the expected number of diabetes cases was 7.94 (Fox et al 2006).

All 4 of these estimates are based on incidence in the general population; however, the rates based on the general population may under-estimate the incidence of diabetes in bipolar patients as studies suggest that patients with bipolar disorder may have a higher prevalence of diabetes than the general population (Casey et al 2001), independent of BMI and psychotropic medication use (Regenold et al 2002). NHIS in particular may further underestimate the incidence of diabetes due to its use of self-reported diabetes (Rosamond et al 2007) , as it is believed that about one-third of persons with diabetes are undiagnosed (Harris et al 1998). In addition, studies conducting glucose tolerance tests in psychiatric patients identify many cases of unrecognized diabetes (Bushe and Holt 2004; Cohn et al 2002; Taylor et al 2003). For example, in a study that actively screened 153 patients taking antipsychotics, 31% had either diabetes or impaired glucose tolerance, in 67% of whom the condition was previously unidentified (Cohn et al 2002).

Therefore, a clinical study that actively monitors for diabetes in patients with bipolar disorder would reasonably be expected to find an incidence of diabetes higher than expected in the general population without proactive monitoring.

5.2.3.2 Post-hoc analysis of certain potential risk factors for diabetes-like events

In an attempt to thoroughly examine whether certain risk factors predispose to the occurrence of cases of interest, or to blood glucose values ≥126 mg/dL on study treatment, an exploratory post-hoc evaluation of Study 126 and Study 127 data was undertaken. The following potential risk factors were considered to be of interest: (i) impaired fasting glucose (IFG) at baseline, (ii) weight at enrollment and (iii) weight changes during the study. The analysis plan, the output from the analyses, and the detailed interpretation of the results are provided in Appendix C.

Instances of glucose ≥126 mg/dL were more common in patients with impaired fasting glucose (defined as a documented fasting glucose value ≥100 mg/dL and <126 mg/dL at baseline) in the open-label phase and in both treatment groups in the randomized phase (Table C11 in Appendix C). There were more observations of blood glucose values ≥126 mg/dL in the quetiapine group than in the placebo group in the randomized phase, both for patients with and without impaired fasting glucose at randomization. The results were consistent with the standard analyses of potentially clinically important glucose data . In the subset of patients with documented fasting (>8 h) glucose data, the incidence density of a single emergent fasting blood glucose value ≥126 mg/dL was higher in patients randomized to quetiapine and mood stabilizer (18.03 cases per 100 patient-years) than in patients randomized to placebo and mood stabilizer (9.53 cases per 100 patient-years).

In the open-label phase, there was an increase in the incidence density of blood glucose ≥126 mg/dL with increasing baseline BMI (Table C13 in Appendix C). In the randomized phase, there was an increase in relative risk with quetiapine compared to placebo as baseline BMI increased. In the BMI category <18.5 at randomization, the incidence density of documented fasting glucose values ≥126 mg/dL during randomized treatment was 28.42 and 0.00 in the quetiapine group and the placebo groups, respectively. In the BMI category 18.5 to <25, the incidence density of documented fasting glucose values ≥126 mg/dL was 12.17 and 8.05 in the quetiapine group and the placebo groups, respectively. The incidence density was similar in the BMI category ≥25 to <30 with 13.70 in the quetiapine group and 14.51 in the placebo group, respectively. In patients in the BMI category ≥30 to <40, the incidence density was 25.04 and 18.08 in the quetiapine and placebo groups, respectively. In the morbidly obese (baseline BMI ≥40) there was a clear increase in relative risk with quetiapine (42.65 vs 3.31 in the placebo group).

No consistent effect of weight gain was seen on the incidence of fasting glucose ≥126 mg/dL in the open-label phase or in either treatment group in the randomized phase (Table C15 in Appendix C).

Only weak correlations between change in weight and change in fasting blood glucose and HbA1c were observed in the open-label phase or in the randomized phase (Table C10 in Appendix C).

Although the numbers of patients with treatment emergent blood glucose ≥126 mg/dL in the open-label treatment phase are small, patients who had at least one fasting glucose value

≥126 mg/dL and were subsequently randomized to placebo showed a decrease in their average glucose values in the randomized phase, both in the combined data from the 2 studies (from 122.7 mg/dL to 115.7 mg/dL) and in Study 127 (from 134.0 mg/dL to 114.9 mg/dL) (Table C17 in Appendix C). Those randomized to quetiapine showed an increase, both in the combined data (from 128.8 mg/dL to 141.3 mg/dL) and in Study 127 (from 133.4 mg/dL to 163.7 mg/dL). In study 126, patients randomized to quetiapine showed a decrease (from 123.5 mg/dL to 111.5 mg/dL) in their average glucose values in the randomized phase while patients in the placebo group showed an increase (from 112.8 mg/dL to 116.4 mg/dL).

More details about the analyses, complete set of tables and additional interpretations of the data are provided in Appendix C.

No additional areas of concern were identified in the adjudicated post-hoc analysis or the post-hoc analysis of potential risk factors for having treatment emergent glucose values ≥126 mg/dL.

5.2.4 Integrated interpretation and conclusions on diabetes and glucose metabolism laboratory data

The pre-planned analyses of glucose metabolism laboratory data, the summary of aggregated AE terms potentially associated with diabetes reported in the randomized treatment phase, the outcome of the adjudication process of cases of interest, and the results of the post-hoc analysis of potential risk factors were presented to and discussed with an external diabetologist, Dr Robert Ratner. The outcome of those discussions is captured and summarized in the overall conclusions presented below.

Among patients treated with quetiapine and a mood stabilizer (lithium or valproate) for at least 12 weeks and then randomized to continue with quetiapine and a mood stabilizer or switch to placebo and a mood stabilizer and followed for up to 2 years:

In the randomized phase quetiapine and a mood stabilizer was associated with a greater mean increase from baseline than placebo and a mood stabilizer in blood glucose (5.05 mg/dL) and HbA1c (0.14%). In patients whose last meal was at least 8 hours before venipuncture the mean difference between quetiapine and placebo was 5.49 mg/dL for glucose and 0.15% for HbA1c.

The incidence density of a single emergent fasting blood glucose value ≥126 mg/dL was higher in patients randomized to quetiapine and mood stabilizer (18.03 patients per 100 patient-years) than in patients randomized to placebo and mood stabilizer (9.53 patients per 100 patient-years). The incidence of values ≥126 mg/dL was analyzed using a Poisson regression model adjusting for exposure time. The estimated ratio (quetiapine adjunct with lithium or valproate vs placebo adjunct with lithium or valproate) of incidence densities was 1.893 with a 95% confidence interval between 1.109 and 3.231.

In the randomized phase there were 6 (0.93%) reported adverse events of diabetes (including one case of diabetic ketoacidosis) in the quetiapine and mood stabilizer group and 1 (0.15%)

in the placebo and mood stabilizer group. When adjusting for treatment exposure in the randomized phase, the incidence densities were 1.6 cases per 100 patient-years for quetiapine compared to 0.4 cases per 100 patient-years for placebo

Given the absence of definitive diagnostic testing for diabetes within the design of these studies, reliable and accurate determination of incidence and risk for diabetes for patients enrolled in these studies is not possible. With this limitation, the calculated absolute risk of onset of possible diabetes by adjudicated post-hoc analysis is low (0.72% - 23 patients divided by 3187 patients in the open-label safety population not classified as "diabetic" according to pre-defined criteria at enrollment). However during the randomized phase an approximately 2-fold increase in incidence density over placebo in observations of glucose values ≥126 mg/dL was observed.

5.3 Trials from Safety 9.1 database

Safety data from SEROQUEL clinical trials is transferred to the SEROQUEL clinical trial safety database (Safety 9.1) after a study is completed and the clinical study report has been finalized.

The cumulative clinical trial data will be discussed in the following manner.

All trials

All data from all trials

All data from all trials thought to be fasted

Known fasting data from all trials thought to be fasted

All trials >12 weeks in duration

Placebo-controlled trials

All data from all placebo-controlled trials

All data from placebo-controlled trials thought to be fasted

Known fasting data from placebo-controlled trials thought to be fasted

Placebo-cotnrolled trials >12 weeks in duration

Placebo-controlled monotherapy trials

All data from all placebo-controlled monotherapy trials

All data from placebo-controlled monotherapy trials thought to be fasted

Known fasting data from placebo-controlled monotherapy trials thought to be fasted

Placebo-controlled monotherapy trials >12 weeks in duration

In addition, additional information will be presented with regards to Trial 125 (a trial designed to look a glucose metabolism) and Trial 04 (long term trial of quetiapine SR).

5.3.1 All Trials from Safety 9.1 database

Data from all trials are presented to give an overview of the relevant data from all AstraZeneca sponsored trials. These trials include all placebo-controlled, active drug comparator, open label, and open-label extension trials. Since it is a combination of trials of varying designs and comparison groups, the treatment groups are not directly comparable. For comparison to placebo refer to Section 5.3.2 Placebo-controlled trials.

5.3.1.1 All data from all trials from Safety 9.1 database

Adverse events potentially related to DM

The adverse event data are divided into 14 different categories. Table 20 below shows the categories and the MedDRA preferred terms that are contained within each. (These categories will be used in all AE tables in Section 5.3).

Table 20 Preferred terms used in adverse event search

Category	MedDRA preferred terms
DKA	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma
Diabetic coma	Diabetic hyperglycaemic coma, Diabetic coma, diabetic hyperosmolar coma, Hyperglycaemic hyperosmolar nonketotic syndrome
Gestational diabetes	Diabetes complicating pregnancy, gestational diabetes, glycosuria during pregnancy, glucose tolerance impaired in pregnancy
Polydipsia	Polydipsia
Polyuria	Polyuria
Thirst	Thirst
Hyperglycemia	Blood glucose fluctuation, Blood glucose increased, Glycosylated haemoglobin increased, Impaired fasting glucose, Hyperglycaemia
Impaired glucose tolerance	Glucose tolerance test decreased, Glucose tolerance impaired, Glucose tolerance test abnormal
Insulin resistance	Insulin resistance, Insulin resistance syndrome, Insulin tolerance test abnormal
Diabetes mellitus[a]	Increased insulin requirement, Insulin resistant diabetes, Insulin-requiring Type II Diabetes mellitus, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes mellitus insulin-dependent, Diabetes mellitus non-insulin dependent, Diabetes with hyperosmolarity, Dawn phenomenon, Somogyi phenomenon, Latent autoimmune diabetes in adults
Diabetic complications	Diabetic complications
Blood ketone abnormalities	Blood ketone body present, Blood ketone body increased

Table 20 Preferred terms used in adverse event search

Category	MedDRA preferred terms
Blood insulin abnormalities	Anti-insulin antibody increased, Anti-insulin antibody positive, Blood insulin abnormal, Blood insulin decreased, Blood insulin increased, Blood insulin C-peptide abnormal, Blood insulin C-peptide decreased, Blood insulin C-peptide increased, Blood proinsulin abnormal, Blood proinsulin decreased, Blood proinsulin increased, Hyperinsulinaemia, Hyperinsulinism, Impaired insulin secretion
Urine glucose abnormalities	Glucose urine present, Glucose urine, Urine glucose abnormality

a These terms may describe new onset or an exacerbation of pre-existing DM.

Table 21 below shows the AE data from subjects in all trials who reported events that may be potentially related to DM. The incidence rates are the percent of subjects with an event. The incidence density values are the number of subjects with an event per 100 patient years.

Table 21 Number of patients with adverse events related to diabetes (All trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Any[e]	Quetiapine	100 (10)	11013	3460.3 (3490.5)	0.91 (0.09)	2.9 (0.3)
	Placebo	10 (1)	1592	172.0 (172.9)	0.63 (0.06)	5.8 (0.6)
	Chlorpromazine	3 (0)	348	47.2 (47.6)	0.86 (0.00)	6.4 (0.0)
	Haloperidol	3 (0)	1028	179.6 (180.4)	0.29 (0.00)	1.7 (0.0)
	Lithium	5 (0)	98	17.1 (17.7)	5.10 (0.00)	29.3 (0.0)
	Mosapramine	1 (0)	90	10.4 (10.4)	1.11 (0.00)	9.6 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	8 (0)	888	178.2 (179.1)	0.90 (0.00)	4.5 (0.0)
Diabetic Ketoacidosis	Quetiapine	2 (2)	11013	3492.0 (3492.0)	0.02 (0.02)	0.1 (0.1)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	0 (0)	98	17.7 (17.7)	0.00 (0.00)	0.0 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	888	179.1 (179.1)	0.00 (0.00)	0.0 (0.0)
Polydipsia	Quetiapine	14 (0)	11013	3483.5 (3492.6)	0.13 (0.00)	0.4 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	2 (0)	348	47.3 (47.6)	0.57 (0.00)	4.2 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	1 (0)	98	17.6 (17.7)	1.02 (0.00)	5.7 (0.0)
	Mosapramine	1 (0)	90	10.4 (10.4)	1.11 (0.00)	9.6 (0.0)

Table 21 Number of patients with adverse events related to diabetes (All trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	2 (0)	888	178.8 (179.1)	0.23 (0.00)	1.1 (0.0)
Polyuria	Quetiapine	9 (0)	11013	3491.5 (3492.6)	0.08 (0.00)	0.3 (0.0)
	Placebo	2 (0)	1592	172.6 (172.9)	0.13 (0.00)	1.2 (0.0)
	Chlorpromazine	1 (0)	348	47.5 (47.6)	0.29 (0.00)	2.1 (0.0)
	Haloperidol	2 (0)	1028	179.6 (180.4)	0.19 (0.00)	1.1 (0.0)
	Lithium	1 (0)	98	17.5 (17.7)	1.02 (0.00)	5.7 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	1 (0)	888	179.1 (179.1)	0.11 (0.00)	0.6 (0.0)
Thirst	Quetiapine	24 (0)	11013	3487.5 (3492.6)	0.22 (0.00)	0.7 (0.0)
	Placebo	5 (0)	1592	172.3 (172.9)	0.31 (0.00)	2.9 (0.0)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	2 (0)	98	17.4 (17.7)	2.04 (0.00)	11.5 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	2 (0)	888	178.8 (179.1)	0.23 (0.00)	1.1 (0.0)
Hyperglycaemia	Quetiapine	40 (5)	11013	3482.8 (3492.5)	0.36 (0.05)	1.1 (0.1)
	Placebo	2 (0)	1592	172.8 (172.9)	0.13 (0.00)	1.2 (0.0)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	0 (0)	98	17.7 (17.7)	0.00 (0.00)	0.0 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	2 (0)	888	179.0 (179.1)	0.23 (0.00)	1.1 (0.0)
Diabetes mellitus	Quetiapine	34 (4)	11013	3486.7 (3493.1)	0.33 (0.04)	0.4 (0.1)
	Placebo	1 (1)	1592	172.9 (172.9)	0.06 (0.06)	0.6 (0.6)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	1 (0)	1028	180.4 (180.4)	0.10 (0.00)	0.6 (0.0)
	Lithium	1 (0)	98	17.7 (17.7)	1.02 (0.00)	5.6 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	2 (0)	888	178.9 (179.1)	0.23 (0.00)	1.1 (0.0)
Urine glucose abnormalities	Quetiapine	7 (0)	11013	3489.8 (3492.6)	0.06 (0.00)	0.2 (0.0)

Table 21 Number of patients with adverse events related to diabetes (All trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	0 (0)	98	17.7 (17.7)	0.00 (0.00)	0.0 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	888	179.1 (179.1)	0.00 (0.00)	0.0 (0.0)

a Patients must have received at least one dose of trial medication.
b Exposure in patient-years, censored at first event.
c 100 x total number of patients with event/total number of patients.
d 100 x total number of patients with event/total patient years of exposure.
e The number of patients with any of the adverse events. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Pgm: Reg-Def\Diabetes Mar 07 SERM\...\AE_all_trials.SAS. Data version: V9.1 User: Malin Dreyer 2007-05-02 20:19.

When all events were combined the incidence density for quetiapine-treated subjects (2.9) was higher than for the haloperidol-treated group (1.7) but not higher than for the placebo- (5.8), chlorpromazine- (6.4), lithium- (29.3), mosapramine (9.6), or risperidone-treated groups (4.5). There were no reports of any adverse event possibly related to DM in the olanzapine-treated group (incidence density = 0.0)

There were two patients among the quetiapine-treated subjects who reported DKA (incidence density = 0.1) compared to no subjects in any other comparator group (incidence densities = 0.0). Both of these quetiapine-treated subjects had pre-existing DM and neither report was considered related by the investigator. (Full narratives for these two reports are contained in Appendix D).

The first patient (5077IL/0056/0042/0013) was a 36-year-old male who after 28 weeks of therapy with SEROQUEL stopped taking his prescribed glipizide and SEROQUEL for 3 to 4 days. The patient was treated with intravenous fluids and insulin but later developed severe acidosis (BG = 419 mg/dL, amylase = 135 U/L, lipase = 1819 U/L, sodium = 130 mmol/L, chloride = 99 mmol/L, bicarbonate = 5 mmol/L, creatinine = 1.9 mg/dL, uric acid = 12.3 mg/dL, WBC = 17,000, beta hydroxyl butyrate = 182 mg/dL). The patient recovered about two weeks later, however therapy with SEROQUEL was not restarted. This patient also had a history of hyperlipidemia, hypertension, and drug abuse. Non-compliance with his antidiabetic medicine could have precipitated or contributed to precipitating the DKA.

The second patient (5077IL/0056/0051/0010) was a 45-year-old male patient who after 163 days on SEROQUEL reported an episode of uncontrolled DM (DKA). The patient was treated with intravenous fluids and a 2200-calorie diabetic diet and recovered two days later.

Therapy with SEROQUEL was continued. The patient also had a history of hypertension, alcohol abuse, and heroin abuse.

The incidence density of polydipsia in the quetiapine-treated group (0.4) was not higher than the incidence densities in the chlorpromazine (4.2), lithium- (5.7), mosapramine- (9.6), or risperidone-treated groups (1.1). There were no reports of polydipsia in the placebo, olanzapine, or haloperidol-treated groups (incidence densities = 0.0).

For the event of polyuria the incidence density for quetiapine-treated subjects (0.3) was not higher than the incidence densities for the placebo- (1.2), chlorpromazine- (2.1), haloperidol- (1.1), risperidone (0.6), or lithium-treated subjects (5.7). There were no reports of polyuria in the mosapramine or olanzapine-treated groups (incidence densities = 0.0).

The incidence density of thirst in the quetiapine-treated group(0.7) was not higher than the incidence densities in the placebo- (2.9), lithium- (11.5), or risperidone-treated groups (1.1). There were no reports of thirst in the chlorpromazine, olanzapine, or mosapramine- treated groups (incidence densities = 0.0).

The incidence density in the quetiapine-treated group of hyperglycemia (1.1) was not higher than in the placebo- (1.2) or risperidone-treated groups (1.1). There were no reports of hyperglycemia in the chlorpromazine-, olanzapine-, haloperidol-, lithium-, or mosapramine-treated groups (incidence densities = 0.0).

The incidence density of DM in the quetiapine-treated group (0.4) was not higher than in the placebo- (0.6), haloperidol- (0.6), lithium- (5.6), or risperidone-treated groups (1.1). There were no reports of DM in the olanzapine-, haloperidol-, or mosapramine-treated groups (incidence densities = 0.0).

The incidence density for urine glucose abnormalities was 0.2 in the quetiapine-treated group compared to 0.0 in all other comparator groups.

There were no reports of diabetic coma, gestational diabetes, impaired glucose tolerance, insulin resistance, diabetic complications, or blood ketone abnormalities in any treatment group in any SEROQUEL clinical trial.

It should be noted that in the majority of AstraZeneca clinical trials a pre-existing history of DM would not exclude a patient from participating in the trial. The two reports of DKA occurred in patients with a pre-existing history of diabetes.

Laboratory data

Data from diabetic subgroups ("non-diabetics", "diabetic risk", and "diabetics") are presented in Appendix A Tables A7 through A15.

Change from baseline in glucose regulation laboratory data

Table 22 below shows the mean changes in glucose, HbA_{1c}, insulin, $HOMA_R$, and QUICKI in all subjects (when available).

Table 22 Mean (SD) change from baseline to end of treatment (All trials)

		QTP N=11013	Pla N=1592	Chl N=348	Hal N=1028	Li N=98	Olz N=168	Ri N=888
Glucose (mmol/L)								
Patients[a]		5125	1342	92	228	93	168	426
Baseline	Mean (SD)	5.42 (1.45)	5.36 (1.36)	5.55 (1.11)	6.07 (2.15)	5.33 (1.21)	5.13 (0.82)	5.42 (1.56)
Last value	Mean (SD)	5.62 (1.83)	5.42 (1.42)	5.45 (1.21)	6.19 (2.15)	5.49 (1.81)	5.27 (0.62)	5.62 (1.60)
Change	Mean (SD)	0.20 (1.62)	0.059 (1.46)	-0.10 (1.43)	0.11 (1.83)	0.16 (1.73)	0.14 (0.80)	0.20 (1.47)
	Median	0.10	0	0	0.10	0	0.30	0.20
	Range	-9.83 to 29.67	-12.60 to 23.72	-4.50 to 3.80	-5.90 to 10.26	-5.40 to 5.85	-5.70 to 1.90	-7.83 to 14.83
HbA1c (%)								
Patients[a]		2111	443				168	172
Baseline	Mean (SD)	5.39 (0.53)	5.32 (0.50)				5.33 (0.40)	5.35 (0.44)
Last value	Mean (SD)	5.45 (0.61)	5.33 (0.50)				5.34 (0.43)	5.34 (0.45)
Change	Mean (SD)	0.055 (0.33)	0.012 (0.28)				0.0036 (0.34)	-0.013 (0.30)
	Median	0	0				0	0
	Range	-1.90 to 4.50	-1.70 to 1.10				-1.10 to 1.40	-0.90 to 3.00
Insulin (pmol/L)								
Patients[a]		2320	689				141	140
Baseline	Mean (SD)	104.48 (146.57)	95.25 (150.83)				242.30 (238.16)	224.27 (215.81)
Last value	Mean (SD)	131.27 (199.56)	108.70 (138.58)				305.13 (371.28)	254.09 (230.86)
Change	Mean (SD)	26.78 (195.95)	11.53 (182.41)				62.83 (350.06)	29.81 (244.84)
	Median	6.95	6.95				18.96	20.45
	Range	-1965 to 2730	-1875 to 1820				-1124 to 2822	-645.75 to 1492
HOMAR								
Patients[a]		2265	649				139	134
Baseline	Mean (SD)	3.35 (5.51)	3.42 (9.23)				1.46 (1.62)	1.62 (2.30)

Table 22 Mean (SD) change from baseline to end of treatment (All trials)

		QTP N=11013	Pla N=1592	Chl N=348	Hal N=1028	Li N=98	Olz N=168	Ri N=888
Last value	Mean (SD)	4.61 (9.38)	3.79 (6.66)				1.78 (1.51)	1.69 (1.40)
Change	Mean (SD)	1.26 (9.36)	0.37 (10.83)				0.32 (1.42)	0.072 (2.32)
	Median	0.21	0.18				0.15	0.13
	Range	-87.09 to 163.49	-137.15 to 87.11				-3.14 to 8.12	-22.57 to 10.63
QUICKI								
Patients*		2265	640				130	134
Baseline	Mean (SD)	0.3226 (0.0766)	0.3046 (0.0906)				0.3763 (0.0364)	0.3729 (0.0374)
Last value	Mean (SD)	0.3161 (0.0781)	0.2994 (0.0919)				0.3692 (0.0440)	0.3673 (0.0364)
Change	Mean (SD)	-0.0064 (0.0410)	-0.0052 (0.0382)				-0.0071 (0.0445)	-0.0056 (0.0322)
	Median	-0.0060	-0.0040				-0.0074	-0.0056
	Range	-0.2105 to 0.1807	-0.1830 to 0.1800				-0.1117 to 0.2593	-0.0995 to 0.0888

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Chl Chlorpromazine, Hal Haloperidol, Li Lithium, Olz Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone.
Pgm: Reg-DxT Diabetes Mar 07 SERM-LAB_chg_all_trials SAS. Data version: V91 User: Bengt Fransoo. 2007-05-03 12:22

The mean changes in glucose were small in all groups (quetiapine = 0.20 mmol/L, placebo = 0.059 mmol/L, chlorpromazine = -0.10 mmol/L, haloperidol = 0.11 mmol/L, lithium = 0.16 mmol/L, olanzapine = 0.14 mmol/L, risperidone = 0.20 mmol/L). The mean change in HbA_{1c} was 0.055% in the quetiapine group compared to 0.012% in the placebo group, 0.0036% in the olanzapine group, and –0.013% in the risperidone group. The mean change in insulin for the quetiapine-treated group (26.78 pmol/L) was higher than the mean change in the placebo-treated group (11.53 pmol/L) but not higher than the mean changes in the olanzapine- (62.83 pmol/L) or risperidone-treated groups (29.81 pmol/L). The mean change in $HOMA_R$ in the quetiapine-treated group (1.26) was higher than in the placebo- (0.37), olanzapine- (0.32), and risperidone-treated groups (0.072). The mean change in QUICKI was similar in all four groups (quetiapine = -0.0064, placebo = -0.0052, olanzapine = -0.0071, risperidone = -0.0056).

Table 23 and Table 24 below shows all subjects who had a shift to a clinically important glucose value at the end of treatment as compared to baseline. In the shift tables high is ≥7 mmol/L for a fasting sample and ≥11.1 mmol/L for a non-fasting sample, and low is ≤2.5 mmol/L.

Table 23 Shift from baseline to clinically important lab values at end of treatment (All trials, QTP to Chl)

	QTP N=1013 End of treatment			Pla N=1592 End of treatment			Chl N=348 End of treatment		
Lab test Baseline	Low n[a](%)	Norm n[a](%)	High n[a](%)	Low n[a](%)	Norm n[a](%)	High n[a](%)	Low n[a](%)	Norm n[a](%)	High n[a](%)
Glucose (mmol/L)									
Low	0 (0)	8 (100)	0 (0)	0 (0)	2 (100)	0 (0)	NA	NA	NA
Norm	8 (0.16)	4854 (97.5)	118 (2.4)	5 (0.38)	1281 (97.4)	29 (2.2)	1 (1.1)	91 (98.9)	0 (0)
High	0 (0)	65 (47.4)	72 (52.6)	0 (0)	19 (76.0)	6 (24.0)	NA	NA	NA
Total	8 (0.16)	4927 (96.1)	190 (3.7)	5 (0.32)	1302 (97.6)	35 (2.6)	1 (1.1)	91 (98.9)	0 (0)
HbA1c (%)									
Norm	NA	2085 (99.3)	15 (0.71)	NA	439 (99.8)	1 (0.23)	NA	NA	NA
High	NA	1 (9.1)	10 (90.9)	NA	0 (0)	3 (100)	NA	NA	NA
Total	NA	2086 (98.8)	25 (1.2)	NA	439 (99.1)	4 (0.90)	NA	NA	NA

a Patients who have received at least one dose of trial medication, have a valid at baseline and at least one value post baseline.
Chl Chlorpromazine, Pla Placebo, QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%): High: >=7.5
Pgm: Reg-Def\Diabetes Mar 07 SEVLAB-LAB sbc all trials SAS Data version: V91 User: Bergt Francois 2007-05-03 06:46.

Table 24 Shift from baseline to clinically important lab values at end of treatment (All trials, Hal to Ri)

	Hal N=1028 End of treatment			Li N=98 End of treatment			Olz N=168 End of treatment			Ri N=288 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	215 (97.7)	5 (2.3)	1 (1.1)	89 (97.8)	1 (1.1)	0 (0)	162 (97.0)	5 (3.0)	0 (0)	409 (97.8)	9 (2.2)
High	0 (0)	4 (50.0)	4 (50.0)	NA	NA	NA	0 (0)	1 (100)	0 (0)	0 (0)	4 (50.0)	4 (50.0)
Total	0 (0)	219 (96.1)	9 (3.9)	1 (1.1)	89 (97.8)	1 (1.1)	0 (0)	163 (97.0)	5 (3.0)	0 (0)	413 (95.9)	13 (3.1)
HbA1c (%)												
Norm	NA	NA	NA	NA	NA	NA	NA	168 (100)	0 (0)	NA	172 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	NA	NA	NA	NA	NA	NA	168 (100)	0 (0)	NA	172 (100)	0 (0)

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Hal Haloperidol, Li Lithium, Olz Olanzapine, Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=3.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: I:\eg-Def\Diabetes Mar 07 SEDAM\All_doc_all_trials\SAS Data version: V91 User: Bengt Fransson, 2007-05-03 06:55.

The percentage subjects who shifted from a normal baseline to a high glucose value by the end of treatment was 2.4% in the quetiapine-treated group compared to 2.2% in the placebo-, 2.3% in the haloperidol-, 1.1% in the lithium-, 3.0% in the olanzapine-, and 2.2% in the risperidone-treated groups (there were no patients in the chlorpromazine-treated group). The majority of subjects in all these groups had a normal glucose at baseline and at the end of treatment (quetiapine = 97.5%, placebo = 97.4%, chlorpromazine = 98.9%, haloperidol = 97.7%, lithium = 97.8%, olanzapine = 97.0%, risperidone = 97.8%). There were 15 quetiapine-treated (0.71%) patients with a normal baseline HbA_{1c} who shifted to a high value by the end of treatment compared to 1 placebo-treated patient (0.23%) (no patients in any other comparator group).

Treatment-emergent clinically important glucose laboratory values

Table 25 below shows all subjects who had a clinically important glucose value (low or high) at any point during a trial.

Table 25 Shift to clinically important lab values at any time (All trials)

	QTP N=11013		Pla N=1592		Chl N=348		Hal N=1628		Li N=98		Olz N=168		Ri N=888	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)														
Low[a]	5117	18 (0.35)	1340	10 (0.75)	92	1 (1.1)	228	0 (0)	91	2 (2.2)	168	0 (0)	426	0 (0)
High[b]	4004	198 (4.0)	1317	32 (2.4)	92	0 (0)	220	5 (2.3)	91	1 (1.1)	167	11 (6.6)	438	17 (4.1)
HbA1c (%)														
High[b]	2100	16 (0.76)	440	1 (0.23)	NA	NA	NA	NA	NA	NA	168	0 (0)	172	0 (0)

a N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
b N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time
Chl Chlorpromazine, Hal Haloperidol, Li Lithium, Olz Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting, HbA1c (%), High >=7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERMLAE_pla_all_trials.SAS, Data version: V91 User: Bengt Franzen, 2007-05-03 07:16.

The percentage of quetiapine treated subjects that had a high glucose value during a trial (4.0%) was higher than in the placebo- (2.4%), lithium- (1.1%), and haloperidol-treated groups (2.3%) but no higher than in the olanzapine- (6.6%) or risperidone-treated groups (4.1%). There was one quetiapine treated subject (0.76%) and one placebo-treated patient (0.23%) who had a high HbA_{1c} at some time during the trial. There were no patients who had a high HbA_{1c} in the other groups.

Summary of all trials from Safety 9.1 database

The number of adverse events possibly related to DM was small. The incidence densities across all treatment groups were similar. When all terms were combined the incidence density for quetiapine was not higher than the incidence density in placebo-, chlorpromazine, lithium-, mosapramine-, or risperidone-treated subjects. It should be noted, however that in these trials patients with a pre-existing history of DM were not excluded from participation.

When the data from all diabetic subgroups are combined the mean changes in glucose and HbA_{1c} (where available) were small in the placebo and quetiapine groups. The incidence of subjects who shifted from a normal baseline to a high value by the end of treatment was similar in both the quetiapine and placebo groups. The incidence of subjects who had a clinically important glucose value at any time during a trial was 4.0% in the quetiapine group compared to 2.4% in the placebo group.

Interpretation of the laboratory data from all patients in these trials, however, was limited because the data was from a combination of fasting and non-fasting samples. In addition, the results between treatment groups are not directly comparable, because they include trials of varying designs and comparator groups.

5.3.1.2 All data from trials in Safety 9.1 database thought to be fasted

Data from all trials that were thought to have fasting data are included in Appendix A Table16 through A28 . These trials included trials where the patients were hospitalized at a minimum the night prior to blood draws (D1441C00125), resided in a long term care facility (5077IL/0115, 5077US/0046), or resided in a CRC for the duration of the study (5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, D1441C00028). In addition, there were seven other trials that did not meet the criteria above but did have information regarding the patient's last meal in relation to the time of the blood draw, therefore, these trials are considered to be fasted trials (D1444C00001, D1444C0003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135). In more recent SEROQUEL clinical trials a tick box is marked if the BG value is known to be fasted, this was not used in earlier trials. The data presented in Section 5.3.1.3 below, represents only BG values that were confirmed to be fasting with a mark in the fasting tick box.

5.3.1.3 Documented fasting laboratory data from all trials thought to be fasted

Laboratory data

Data from individual diabetic subgroups ("non-diabetics", "diabetic risk", "diabetics") are contained in Appendix A Tables A29 through A37.

Change from baseline in glucose regulation laboratory data

Table 26 below shows the mean changes in glucose, HbA_{1c}, insulin, $HOMA_R$, and QUICKI in all subjects.

Table 26 **Mean (SD) change from baseline to end of treatment (All fasting trials, documented fasting)**

		QTP N=3031	Pla N=596	Olz N=168	Ri N=172
Glucose (mmol/L)					
Patients[a]		2189	469	163	164
Baseline	Mean (SD)	5.19 (1.06)	5.12 (0.81)	5.09 (0.84)	5.21 (0.73)
Last value	Mean (SD)	5.33 (1.26)	5.21 (1.08)	5.27 (0.62)	5.36 (0.88)
Change	Mean (SD)	0.15 (1.14)	0.089 (1.05)	0.18 (0.86)	0.16 (0.81)
	Median	0.100	0.056	0.20	0.20
	Range	-8.50 to 13.89	-4.20 to 5.16	-8.00 to 2.40	-3.70 to 5.10
HbA1c (%)					
Patients[a]		1872	384	164	165
Baseline	Mean (SD)	5.39 (0.52)	5.31 (0.51)	5.33 (0.39)	5.34 (0.45)
Last value	Mean (SD)	5.44 (0.61)	5.32 (0.51)	5.33 (0.43)	5.34 (0.47)
Change	Mean (SD)	0.053 (0.34)	0.015 (0.28)	0.0049 (0.34)	-0.0043 (0.32)
	Median	0	0	0	0
	Range	-1.90 to 4.50	-1.70 to 1.10	-0.90 to 1.40	-0.90 to 1.00
Insulin (pmol/L)					
Patients[a]		2025	474	140	140
Baseline	Mean (SD)	102.85 (147.20)	82.79 (85.21)	242.08 (238.94)	224.27 (215.81)
Last value	Mean (SD)	117.13 (183.12)	91.89 (118.35)	307.16 (371.83)	254.09 (230.86)
Change	Mean (SD)	14.28 (176.10)	9.10 (107.68)	65.08 (350.30)	29.81 (244.84)
	Median	2.08	0	19.03	20.45
	Range	-1965 to 2730	-620.26 to 1167	-1124 to 2822	-645.75 to 1492
$HOMA_R$					
Patients[a]		1864	445	130	134
Baseline	Mean (SD)	3.32 (5.46)	2.81 (3.06)	1.46 (1.02)	1.62 (2.30)
Last value	Mean (SD)	4.12 (8.64)	3.52 (6.07)	1.78 (1.51)	1.69 (1.46)
Change	Mean (SD)	0.80 (8.74)	0.72 (5.61)	0.32 (1.42)	0.072 (2.32)
	Median	0.13	0.070	0.15	0.13
	Range	-87.09 to 163.49	-23.06 to 71.49	-5.14 to 8.12	-22.57 to 10.63
QUICKI					
Patients[a]		1864	445	130	134
Baseline	Mean (SD)	0.3477 (0.0434)	0.3502 (0.0420)	0.3763 (0.0394)	0.3729 (0.0374)
Last value	Mean (SD)	0.3427 (0.0447)	0.3469 (0.0443)	0.3692 (0.0440)	0.3673 (0.0364)
Change	Mean (SD)	-0.0051 (0.0423)	-0.0034 (0.0394)	-0.0071 (0.0445)	-0.0056 (0.0322)
	Median	-0.0032	0.0000	-0.0074	-0.0056

Table 26 Mean (SD) change from baseline to end of treatment (All fasting trials, documented fasting)

	QTP N=3031	Pla N=596	Olz N=168	Ri N=172
Range	-0.2105 to 0.1807	-0.1830 to 0.1443	-0.1117 to 0.2593	-0.0896 to 0.0888

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/06-46, D1443C00028, D1443C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_all_trials_fast.SAS. Data version: V91 User: Bengt Franzen. 2007-05-16 08:18.

The mean changes in glucose were small in all groups (quetiapine = 0.15 mmol/L, placebo = 0.089 mmol/L, olanzapine = 0.18 mmol/L, risperidone = 0.16 mmol/L). The mean changes in HbA_{1c} were also small among the four groups (quetiapine = 0.053%, placebo = 0.015%, olanzapine = 0.0049%, risperidone = -0.0043%). The mean change in insulin for the quetiapine-treated group (14.28 pmol/L) was higher than the mean change in the placebo-treated group (9.10 pmol/L) but not higher than the mean changes in the olanzapine- (65.08 pmol/L) or risperidone-treated groups (29.81 pmol/L). The mean change in $HOMA_R$ in the quetiapine-treated group (0.80) was higher than in the placebo- (0.72), olanzapine- (0.32), and risperidone-treated groups (0.072). The mean change in QUICKI was small in all four groups (quetiapine = -0.0051, placebo = -0.0034, olanzapine = -0.0071, risperidone = -0.0056).

Table 27 below shows all subjects who had a shift to a clinically important glucose value at the end of treatment as compared to baseline. In the shift tables high is ≥7 mmol/L for a fasting sample and ≥11.1 mmol/L for a non-fasting sample; and low is ≤2.5 mmol/L.

Table 27 Shift from baseline to clinically important lab values at end of treatment (All fasting trials, documented fasting)

	QTP N=3031 End of treatment			Pla N=596 End of treatment			Olz N=168 End of treatment			Ri N=172 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	0 (0)	5 (100)	0 (0)	0 (0)	1 (100)	0 (0)	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	2 (0.095)	2017 (96.2)	78 (3.7)	1 (0.22)	434 (95.4)	20 (4.4)	0 (0)	157 (96.9)	5 (3.1)	0 (0)	156 (97.5)	4 (2.5)
High	0 (0)	44 (49.4)	45 (50.6)	0 (0)	9 (69.2)	4 (30.8)	0 (0)	1 (100)	0 (0)	0 (0)	2 (66.7)	1 (33.3)
Total	2 (0.091)	2066 (94.3)	123 (5.6)	1 (0.21)	444 (94.7)	24 (5.1)	0 (0)	158 (96.9)	5 (3.1)	0 (0)	159 (97.0)	5 (3.0)
HbA1c (%)												
Norm	NA	1848 (99.2)	14 (0.75)	NA	380 (99.7)	1 (0.26)	NA	164 (100)	0 (0)	NA	163 (100)	0 (0)
High	NA	1 (10.0)	9 (90.0)	NA	0 (0)	3 (100)	NA	NA	NA	NA	NA	NA
Total	NA	1849 (98.8)	23 (1.2)	NA	380 (99.0)	4 (1.0)	NA	164 (100)	0 (0)	NA	163 (100)	0 (0)

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone
Clinically important limits are Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting, HbA1c (%): High >=7.5.
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077IN/0046, D1441C/00028, D1441C/00125, D1444C/00001, D1444C/00003, D1444C/00064, D1444C/00132, D1444C/00133, D1444C/00146, D1447C/00135 are included in this table.
Pgm: Rep/Def/Diabetes Mar 07/SEKMil/LAE_shr_all_trials_final.SAS. Data version: V01 User: Bengt Franzen. 2007-05-03 06:59.

The percentage of subjects who shifted from a normal baseline to a high glucose value by the end of treatment was 3.7% in the quetiapine-treated group compared to 4.4% in the placebo-treated group, 3.1% in the olanzapine-treated group, and 2.5% in the risperidone-treated group. The majority of subjects in all these groups had a normal glucose at baseline and at the end of treatment (quetiapine = 96.2%, placebo = 95.4%, olanzapine = 96.9%, risperidone = 97.5%). There were 14 quetiapine-treated patients (0.75%) with a normal baseline HbA_{1c} who shifted to a high value by the end of treatment compared to one patient in the placebo-treated group (0.26%) (no patients in other groups).

Treatment emergent clinically important glucose laboratory values

Table 28 below shows all subjects who had a clinically important glucose value (low or high) at any point during a trial.

Table 28 Shift to clinically important lab values at any time (All fasting trials, documented fasting)

	QTP N=3031		Pla N=596		Olz N=168		Ri N=172	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	2186	3 (0.14)	468	1 (0.21)	163	0 (0)	163	0 (0)
High[b]	2100	127 (6.0)	456	23 (5.0)	162	10 (6.2)	161	10 (6.2)
HbA1c (%)								
High[b]	1862	15 (0.81)	381	1 (0.26)	164	0 (0)	163	0 (0)

a N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
b N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 For non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077USI/0046, D1441C00028, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERAYLAB_sha_all_trials_fast.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:18.

The percentage of quetiapine treated subjects that had a high glucose value during a trial (6.0%) was slightly higher than in the placebo-treated group (5.0%) but no higher than in the olanzapine- or risperidone-treated groups (6.2%). There were 15 quetiapine treated subjects (0.81%) who had a high HbA_{1c} at some time during the trial compared to one patient (0.26%) in the placebo-treated group (no patients in other groups).

Summary of known fasting data from all trials in Safety 9.1 database thought to be fasting

When all diabetic subgroups were combined the mean changes in glucose were similar among treatment groups. In addition, the incidence of subjects who shifted from a normal baseline to a high value by the end of treatment and the incidence of subjects who had a clinically important glucose value at any time during a trial was also similar across treatment groups.

5.3.1.4 Trials >12 weeks in Safety 9.1 database

The data from all SEROQUEL clinical trials trials where the planned duration of the trial (according to the protocol) was >84 days is contained in Appendix A Tables A38 through A51.

5.3.2 Placebo controlled trials in Safety 9.1 database

These trials include both fasting and non-fasting data, and trials where adjunct therapy was given (e.g. quetiapine plus lithium vs placebo plus lithium). Subsets of placebo-controlled trials that included only data believed to be fasting and monotherapy (ie, no adjunct treatment was given) are presented later in this document. Since this combined data represents trials of various sizes and design a direct comparison between placebo and quetiapine cannot necessarily be made.

5.3.2.1 All data from all placebo-controlled trials

Adverse events potentially related to DM

Table 29 below shows the AE data from patients in placebo-controlled trials that reported events that may be potentially related to DM.

Table 29 Number of patients with adverse events related to diabetes (All placebo-controlled trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Any[e]	Quetiapine	28 (0)	3437	371.3 (372.9)	0.81 (0.00)	7.5 (0.0)
	Placebo	10 (1)	1592	172.0 (172.9)	0.63 (0.06)	5.8 (0.6)
Diabetic Ketoacidosis	Quetiapine	0 (0)	3437	372.9 (372.9)	0.00 (0.00)	0.0 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
Polydipsia	Quetiapine	2 (0)	3437	372.8 (372.9)	0.06 (0.00)	0.5 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
Polyuria	Quetiapine	4 (0)	3437	372.8 (372.9)	0.12 (0.00)	1.1 (0.0)
	Placebo	2 (0)	1592	172.6 (172.9)	0.13 (0.00)	1.2 (0.0)
Thirst	Quetiapine	9 (0)	3437	371.9 (372.9)	0.26 (0.00)	2.4 (0.0)
	Placebo	5 (0)	1592	172.3 (172.9)	0.31 (0.00)	2.9 (0.0)
Hyperglycaemia	Quetiapine	12 (0)	3437	372.6 (372.9)	0.35 (0.00)	3.2 (0.0)
	Placebo	2 (0)	1592	172.8 (172.9)	0.13 (0.00)	1.2 (0.0)
Diabetes mellitus	Quetiapine	2 (0)	3437	372.9 (372.9)	0.06 (0.00)	0.5 (0.0)
	Placebo	1 (1)	1592	172.9 (172.9)	0.06 (0.06)	0.6 (0.6)
Urine glucose abnormalities	Quetiapine	0 (0)	3437	372.9 (372.9)	0.00 (0.00)	0.0 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)

a Patients must have received at least one dose of trial medication.
b Exposure in patient-years, censored at first event.
c 100 x total number of patients with event/total number of patients.

d 100 x total number of patients with event/total patient years of exposure.
e The number of patients with any of the adverse events. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Pgm: Reg-Def\Diabetes Mar 07 SERM\...\AE_pla_ctrl.SAS. Data version: V9.1 User: Malin Dreyer 2007-05-02 20:21.

When combined together the incidence density for quetiapine-treated patients was 7.5 compared to 5.8 in the placebo-group.

The incidence density of polydipsia in the quetiapine-treated group (0.5) was higher than in the placebo-treated group (0.0). The incidence density of polyuria in the quetiapine-treated group (1.1) was not higher than in the placebo-treated group (1.2). The incidence density of thirst in the quetiapine-treated group (2.4) was also not higher than in the placebo-treated group (2.9).

In the quetiapine-treated group there were 12 reports of hyperglycemia and 2 reports of DM corresponding to incidence densities of 3.2 and 0.5, respectively. There were two reports of hyperglycemia and one report of DM in the placebo group, corresponding to incidence densities of 1.2 and 0.6, respectively. (See Appendix A Table A52 for details of these 17 reports).

There were no reports of DKA, diabetic coma, gestational diabetes, impaired glucose tolerance, insulin resistance, diabetic complications, blood ketone abnormalities, or urine glucose abnormalities in placebo controlled trials.

Ten of the 14 reports of DM or hyperglycemia in quetiapine-treated patients were considered to be not related by the study investigator. Eight of these quetiapine-treated patients had or were suspected to have a prior history of DM. No information regarding the patients dietary habits or information about conditions (eg, infections), which could precipitate an exacerbation of DM were provided. In addition, not provided was the history of degree of diabetic control. Of these eight, two patients were clearly not under good control at baseline. The two other reports described one patient with a history of obesity and hyperlipidemia and another patient with a BG of 16 mmol/L on the day that therapy began. The four other reports in quetiapine-treated patients were considered related by the investigator. One patient was concomitantly receiving lithium for which hyperglycemia has been reported. The second report did not provide information about the patient's medical history. This patient's baseline glucose (fasting status unknown) was 4.9 mmol/L. After three weeks on quetiapine therapy was discontinued due to lack of efficacy. Three days later the patient's glucose was 9.1 mmol/L (fasting status unknown). No other information was provided. The third report described a patient who had an elevated baseline FBS. During the trial he patient's FBS were normal. One day after trial completion it was noted the patient's HbA_{1c} was elevated. This patient had a family history of DM (mother). The fourth patient developed an elevated FBS after one month of treatment. The patient's FBS was normal one week later and continued to be normal throughout the rest of the trial. No treatment was given. All three of the placebo-treated patients had a history of DM and did not have good diabetic control at baseline; all of these reports were considered to be not related by the study investigator. It should be noted,

however that in these trials patients with a pre-existing history of DM were not excluded from participation. The majority of patients who reported the adverse events of DM or hyperglycemia had a pre-existing history of DM.

Laboratory data

The laboratory data presented in Tables 44 through 52 below are from a combination of both fasting and non-fasting samples. Data from individual diabetic subgroups are contained in Appendix A Tables A53 through A61.

Change from baseline in glucose regulation laboratory data

Table 30 below shows the mean changes in glucose, HbA_{1c}, insulin, $HOMA_R$, and QUICKI in all subjects.

Table 30 Mean (SD) change from baseline to end of treatment (All placebo-controlled trials)

		QTP N=3437	Pla N=1592
Glucose (mmol/L)			
Patients[a]		2763	1342
Baseline	Mean (SD)	5.33 (1.39)	5.36 (1.36)
Last value	Mean (SD)	5.49 (1.65)	5.42 (1.42)
Change	Mean (SD)	0.15 (1.47)	0.059 (1.46)
	Median	0.100	0
	Range	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)			
Patients[a]		1173	443
Baseline	Mean (SD)	5.39 (0.53)	5.32 (0.50)
Last value	Mean (SD)	5.45 (0.61)	5.33 (0.50)
Change	Mean (SD)	0.056 (0.32)	0.012 (0.28)
	Median	0	0
	Range	-1.40 to 4.50	-1.70 to 1.10
Insulin (pmol/L)			
Patients[a]		1713	689
Baseline	Mean (SD)	95.11 (126.81)	93.23 (130.83)
Last value	Mean (SD)	131.99 (200.57)	104.76 (138.38)
Change	Mean (SD)	36.89 (197.65)	11.53 (182.41)
	Median	7.00	6.95
	Range	-1479 to 2299	-1875 to 1820
$HOMA_B$			
Patients[a]		1566	640
Baseline	Mean (SD)	3.32 (5.54)	3.42 (9.23)
Last value	Mean (SD)	4.93 (9.61)	3.79 (6.66)
Change	Mean (SD)	1.61 (9.83)	0.37 (10.85)
	Median	0.29	0.18
	Range	-87.09 to 127.84	-137.15 to 87.11
QUICKI			
Patients[a]		1566	640
Baseline	Mean (SD)	0.3123 (0.0855)	0.3046 (0.0906)
Last value	Mean (SD)	0.3039 (0.0864)	0.2994 (0.0919)
Change	Mean (SD)	-0.0084 (0.0408)	-0.0052 (0.0382)
	Median	-0.0090	-0.0040

Table 30 **Mean (SD) change from baseline to end of treatment (All placebo-controlled trials)**

	QTP N=3437	Pla N=1592
Range	-0.2105 to 0.1800	-0.1830 to 0.1800

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo, QTP Quetiapine.
Pgm: Reg-Def-Diabetes Mar 07 SERM-LAB_chg_pla_cm1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:38.

The mean changes in glucose were 0.15 mmol/L in the quetiapine-treated group compared to 0.059 mmol/L in the placebo-treated group. The mean changes in HbA_{1c} were small in both groups (quetiapine = 0.056%, placebo = 0.012%). The mean change in insulin in the quetiapine-treated group was 36.89 pmol/L compared to 11.53 pmol/L in the placebo-treated group. The mean changes in $HOMA_R$ were 1.61 in the quetiapine-treated group compared to 0.37 in the placebo-treated group. The mean change in QUICKI was similar in both groups (quetiapine = -0.0084, placebo = -0.0052). Because these data are from a combination of fasting and non-fasting samples, the interpretation of this data is limited.

Table 31 below shows all subjects who had a shift to a clinically important glucose value at the end of treatment as compared to baseline. In the shift tables high is ≥7 mmol/L for a fasting sample and ≥11.1 mmol/L for a non-fasting sample; and low is ≤2.5 mmol/L.

Table 31 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled trials)

	QTP N=3437 End of treatment			Pla N=1592 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)						
Low	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)
Norm	5 (0.19)	2614 (97.4)	66 (2.5)	5 (0.38)	1281 (97.4)	29 (2.2)
High	0 (0)	37 (48.7)	39 (51.3)	0 (0)	19 (76.0)	6 (24.0)
Total	5 (0.18)	2653 (96.0)	105 (3.8)	5 (0.37)	1302 (97.0)	35 (2.6)
HbA1c (%)						
Norm	NA	1159 (99.3)	8 (0.69)	NA	439 (99.8)	1 (0.23)
High	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	1160 (98.9)	13 (1.1)	NA	439 (99.1)	4 (0.90)

a. Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla: Placebo. QTP: Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def-Diabetes Mar 07 SERM/LAB_she_pla_ctrl.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:04.

The percentage of quetiapine-treated patients who shifted from a normal baseline to a high glucose value by the end of treatment (2.5%) was slightly higher than in the placebo-treated group (2.2%). The majority of patients had a normal glucose value at baseline and at the end of treatment (quetiapine = 97.4%, placebo = 97.4%). There were eight patients (0.69%) in quetiapine group who shifted from a normal baseline HbA_{1c} to a high value by the end of treatment compared to one patient in the placebo-group (0.23%). Because these data are from a combination of fasting and non-fasting samples, the interpretation of this data is limited.

Treatment emergent clinically important glucose laboratory values

Table 32 below shows all patients who had a clinically important glucose value (low or high) at any point during a trial.

Table 32 Shift to clinically important lab values at any time (All placebo-controlled trials)

	QTP N=3437		Pla N=1592	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	2761	10 (0.36)	1340	10 (0.75)
High[b]	2692	99 (3.7)	1317	32 (2.4)
HbA1c (%)				
High[b]	1167	8 (0.69)	440	1 (0.23)

a N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
b N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-DefDiabetes Mar 07 SERMLAB_sha_pla_ctrl SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:23.

The incidence of patients who had a high glucose value at any time during a trial was 3.7% in the quetiapine-treated group compared to 2.4% in the placebo-treated group. Because these data are from a combination of fasting and non-fasting samples, the interpretation of this data is limited. The incidence of quetiapine-treated patients who had a high HbA1c at any time was 0.69% compared to 0.23% in the placebo-group.

Summary of placebo-controlled trials in Safety 9.1 database

In placebo-controlled trials, the incidence densities for hyperglycemia, DM, and all events combined were higher in quetiapine-treated patients than those seen in placebo-treated patients. Ten reports were considered to be not related by the study investigator. Eight of these quetiapine-treated patients had or were suspected to have a prior history of DM. No information regarding the patient's dietary habits or information about condition (eg, infections), which could precipitate an exacerbation of DM were provided. In addition, not provided was the history of degree of diabetic control. Of these eight, two patients were clearly not under good control at baseline. The two other reports described one patient with a history of obesity and hyperlipidemia and another patient with a BG of 16 mmol/L on the day that therapy began. The four other reports in quetiapine-treated patients were considered related by the investigator. One patient was concomitantly receiving lithium for which hyperglycemia has been reported. The second report did not provide information about the patient's medical history. This patient's baseline glucose (fasting status unknown) was 4.9 mmol/L. After three weeks, quetiapine therapy was discontinued due to lack of efficacy. Three days later the patient's glucose was 9.1 mmol/L (fasting status unk). No other information was provided. The third report described a patient who had a high FBS at baseline which normalized during the study but had an HbA_{1c} that was slightly higher than at baseline. This patient had a family history of DM. The other patient had a high FBS after one month of therapy but recovered while continuing therapy with quetiapine.

When all diabetic subgroups are combined the mean changes in glucose and HbA_{1c} were small. The mean change in insulin and $HOMA_R$ were higher in the quetiapine group than in the placebo group. The mean change in QUICKI was similar in both groups. The incidence of patients who shifted from a normal baseline to a high glucose value by the end of treatment was similar in both groups. The incidence of patients who had a clinically important glucose value at anytime during the trial was slightly higher in the quetiapine group compared to placebo. (To see quetiapine IR and SR data shown separately see Appendix A Tables A62 through A73).

Interpretation of the laboratory data (except for HbA_{1c}) in these trials from all patient groups, however, was limited because the samples were both fasting and non-fasting.

5.3.2.2 All data from placebo-controlled trials in Safety 9.1 database thought to be fasted

The summary below is based on data from all placebo-controlled trials that were believed to have fasting data. These trials included 5077US/0046 where patients resided in a long term care facility and Trials D1444C00132, D1444C00133, D1447C00135 where there was information about the patient's last meal in relation to the time of the blood draw, therefore, these trials are considered to be fasted trials. In more recent SEROQUEL clinical trials a tick box is marked if the BG value is reported to be fasted (>8 hours since last meal); this was not used in earlier trials. The data for all of the laboratory data available in these trials, whether the tick box is checked or not are contained in Appendix A Tables A74 to A98. In Section 5.3.2.3 below, the data from those patients whose BG values were reported to be fasting with a mark in the fasting tick box are summarized.

5.3.2.3 Documented fasting data from placebo-controlled trials in Safety 9.1 database thought to be fasted

The data below is a subset of the data presented in Section 5.3.2.3 above. These data are only the laboratory values which were indicated by a tick box that they were fasted values.

Laboratory data

The data from individual diabetic subgroups ("non-diabetics", "diabetic risk", "diabetics") are contained in Appendix A (Tables A99 to A107).

Change from baseline in glucose regulation laboratory data

Table 33 below shows the mean changes in glucose, HbA_{1c}, insulin, $HOMA_R$, and QUICKI in all patients.

Table 33 Mean (SD) change from baseline to end of treatment (All placebo-controlled fasting trials, documented fasting)

		QTP N=1592	Pla N=596
Glucose (mmol/L)			
Patients[a]		1250	469
Baseline	Mean (SD)	5.17 (1.06)	5.12 (0.81)
Last value	Mean (SD)	5.33 (1.32)	5.21 (1.08)
Change	Mean (SD)	0.16 (1.22)	0.089 (1.05)
	Median	0.100	0.056
	Range	-8.22 to 13.89	-4.20 to 5.10
HbA1c (%)			
Patients[a]		1018	384
Baseline	Mean (SD)	5.39 (0.54)	5.31 (0.51)
Last value	Mean (SD)	5.44 (0.63)	5.32 (0.51)
Change	Mean (SD)	0.053 (0.33)	0.015 (0.28)
	Median	0	0
	Range	-3.40 to 4.50	-1.70 to 1.30
Insulin (pmol/L)			
Patients[b]		1253	474
Baseline	Mean (SD)	89.20 (118.09)	82.79 (85.21)
Last value	Mean (SD)	111.56 (175.67)	91.89 (118.35)
Change	Mean (SD)	22.36 (168.71)	9.10 (107.68)
	Median	6.95	0
	Range	-1479 to 2146	-620.26 to 1167
$HOMA_B$			
Patients[c]		1174	445
Baseline	Mean (SD)	3.25 (5.43)	2.81 (3.06)
Last value	Mean (SD)	4.30 (8.57)	3.52 (6.07)
Change	Mean (SD)	1.04 (8.79)	0.72 (5.61)
	Median	0.20	0.070
	Range	-87.09 to 127.84	-23.06 to 71.49
QUICKI			
Patients[a]		1174	445
Baseline	Mean (SD)	0.3490 (0.0433)	0.3502 (0.0420)
Last value	Mean (SD)	0.3419 (0.0452)	0.3469 (0.0443)
Change	Mean (SD)	-0.0071 (0.0430)	-0.0034 (0.0394)
	Median	-0.0094	0.0000

Table 33 **Mean (SD) change from baseline to end of treatment (All placebo-controlled fasting trials, documented fasting)**

	QTP N=1592	Pla N=596
Range	-0.2105 to 0.1800	-0.1830 to 0.1443

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_fast.SAS. Data version: V91 User: Bengt Franzon. 2007-05-16 08:20.

The mean changes in glucose were 0.16 mmol/L in the quetiapine-treated group compared to 0.089 mmol/L in the placebo-treated group. The mean changes in HbA_{1c} were small in both groups (quetiapine = 0.053%, placebo = 0.015%). The mean change in insulin in the quetiapine-treated group was 22.36 pmol/L compared to 9.10 pmol/L in the placebo-treated group. The mean changes in $HOMA_R$ were 1.04 in the quetiapine-treated group compared to 0.72 in the placebo-treated group. The mean change in QUICKI was similar in both groups (quetiapine = -0.0071, placebo = -0.0034).

Table 34 below shows the number and percentage of all patients who had a shift to a clinically important glucose value at the end of treatment as compared to baseline.

Table 34 **Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled fasting trials, documented fasting)**

	QTP N=1592 End of treatment			Pla N=596 End of treatment		
Lab test Baseline	Low n[a](%)	Norm n[a](%)	High n[a](%)	Low n[a](%)	Norm n[a](%)	High n[a](%)
Glucose (mmol/L)						
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	0 (0)	1145 (95.9)	49 (4.1)	1 (0.22)	434 (95.4)	20 (4.4)
High	0 (0)	28 (50.0)	28 (50.0)	0 (0)	9 (69.2)	4 (30.8)
Total	0 (0)	1173 (93.8)	77 (6.2)	1 (0.21)	444 (94.7)	24 (5.1)
HbA1c (%)						
Norm	NA	1004 (99.2)	8 (0.79)	NA	380 (99.7)	1 (0.26)
High	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	1005 (98.7)	13 (1.3)	NA	380 (99.0)	4 (1.0)

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shc_pla_ctrl_fast.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:05.

The percentage of quetiapine-treated patients who shifted from a normal baseline to a high glucose value by the end of treatment (4.1%) was not higher than in the placebo-treated group (4.4%). The majority of patients had a normal glucose value at baseline and at the end of treatment (quetiapine = 95.9%, placebo = 95.4%). There were eight patients (0.79%) in the quetiapine group who shifted from a normal baseline HbA_{1c} to a high value by the end of treatment compared to one patient (0.26%) in the placebo group.

Treatment-emergent clinically important glucose laboratory values

Table 35 below shows all patients who had a clinically important glucose value (low or high) at any point during a trial.

Table 35 Shift to clinically important lab values at any time (All placebo-controlled fasting trials, documented fasting)

	QTP N=1592		Pla N=596	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	1250	0 (0)	468	1 (0.21)
High[b]	1194	69 (5.8)	456	23 (5.0)
HbA1c (%)				
High[b]	1012	8 (0.79)	381	1 (0.26)

a N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
b N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def/Diabetes Mar 07 SERMM_AB_eha_pla_ctrl_fast.SAS. Data version: V91 User: Rengi Franzon. 2007-05-03 07:24.

The incidence of patients who had a high glucose value at any time during a trial was 5.8% in the quetiapine-treated group compared to 5.0% in the placebo-treated group. The incidence of quetiapine-treated patients who had a high HbA1c at any time during a trial was 0.79% compared to 0.26% in the placebo group.

Summary of documented fasting data from placebo-controlled trials in Safety 9.1 database thought to be fasted

When all diabetic subgroups are combined the mean changes in glucose and HbA_{1c} were small. The mean change in insulin and $HOMA_B$ were higher in the quetiapine group than in the placebo group. The mean change in QUICKI were small in both groups. The incidence of patients who shifted from a normal baseline to a high glucose value by the end of treatment was similar in both groups. The incidence of patients who had a clinically important glucose value at anytime during the trial was slightly higher in the quetiapine group compared to placebo. (To see quetiapine IR and SR data shown separately see Appendix A Tables A108 through A119).

5.3.2.4 Placebo-controlled trials >12 weeks in Safety 9.1 database

There was only one placebo-controlled trial where the planned duration of the trial (according to the protocol) was >84 days. This trial is Trial D1444C00004. The data from this trial is discussed separately in Section 5.3.4.2 below.

5.3.3 Placebo-controlled monotherapy trials in Safety 9.1 database

The data from all placebo-controlled monotherapy trials are contained in Appendix A Tables A135 to A159. The data from placebo-controlled monotherapy trials thought to be fasted and placebo-controlled monotherapy trials >12 weeks is the same as the data summarized in Section 5.3.2 above.

5.3.4 Trials of interest (contained in Safety database)

5.3.4.1 Trial D1441C00125

Objectives of the study

The primary objective of this study was to compare the safety/tolerability profile of quetiapine and olanzapine on glucose metabolism in schizophrenic patients by evaluating change from randomization in AUC plasma glucose values following OGTT.

The data presented below was taken from the clinical study report: A 24-Week, International, Multi-centre, Open-label, Flexible-dose, Randomised, Parallel-Group, Phase IV Study to Compare the Effect on Glucose Metabolism of Quetiapine, Olanzapine, and Risperidone in the Treatment of Patients with Schizophrenia.

Patient population

The patient populations analyzed and the numbers of patients in each population are summarized in Table 36.

Table 36 Analysis sets

	Quetiapine	Olanzapine	Risperidone	Total
	N	N	N	N
All patients enrolled				574
Randomised	168	169	173	510
Safety[a]	169	168	172	509
ITT[b]	168	169	172	509
PAP[c]	115	146	134	395
PP	98	126	106	330

a Safety included randomised patients who had taken at least one dose of medication.
b ITT was similar to safety but classified patients according to the randomised treatment.
c PAP (Primary Analysis Population) included all randomised patients who had randomization (baseline) and week 24 assessments.
SOURCE DOCUMENT: ST_DEM_ANALYSIS_SETS_339.SAS GENERATED: 17:34/46 26JAN2006 DB version prod: 13

In total, 510 of the 574 enrolled patients were randomised to the treatment groups: 168 to the quetiapine group, 169 to the olanzapine group, and 173 to the risperidone group. Almost all of them (with the exception of one patient in the risperidone group) received investigational products, and were included in the safety population. One patient, who was randomized to the olanzapine group, received quetiapine instead. This patient was included in the quetiapine group in the safety analysis set.

The primary analysis population (PAP) includes all randomised patients who were given study treatment and who had baseline and Week 24 (±4 weeks) assessments. The PAP was the population for the primary analysis and for the secondary analyses based on baseline and Week 24 results only. The classification was according to the treatment, which the patients were randomised.

The treatment groups were well matched with respect to demographic characteristics in all analysis populations. The demographic and key baseline characteristics of study patients in the PAP are shown in Appendix A Table A160.

Sex distribution in the PAP was similar across the groups, with about 66% male and 34% female patients. The mean age of patients entering the study was 39.5 years; the proportion of patients in age categories 18-50 and 51-65 years was 83% and 17%, respectively. As most of the patients were recruited in Europe, the majority of the patients were Caucasian (about 90 % in all groups). Mean weight of patients entering the study was 72.5 kg, and the predominant BMI categories were 18.5 to <25 (50%) and 25 to <30 (29%). There were no notable differences between the groups either in baseline weight and BMI, or in the proportions of patients in different BMI categories. The mean baseline BMI was relatively low in all treatment groups and reflected the predominance of patients from European countries in the study population. Overall, the treatment groups were well matched with respect to demographic characteristics.

Adverse event data

Patients with adverse events associated with DM are summarized by MedDRA preferred term and by randomised treatment in Table 37.

Table 37 Adverse events associated with diabetes mellitus (safety population)

	Quetiapine N = 169	Olanzapine N = 168	Risperidone N = 172	Total N = 509
MedDRA preferred term[a]	n (%)	n (%)	n (%)	n (%)
Any adverse event[b]	0	0	1 (0.6)	1 (0.2)
Polydipsia	0	0	1 (0.6)	1 (0.2)
Polyuria	0	0	1 (0.6)	1 (0.2)

a Patients with multiple events falling under the same term are counted only once in that term
b Patients with at least one adverse event potentially related to diabetes mellitus.
Note. Events emerging during randomised treatment phase by decreasing order of frequency as summarized over all treatment groups.
SOURCE DOCUMENT: ST_AE_DIABETES8.SAS GENERATED: 11:34:04 25JAN2006 DB version prod: 13

Only one patient in the risperidone group reported polydipsia and polyuria as an AE potentially associated with DM. No patients received the diagnosis of diabetes mellitus during the study, and none was excluded from the study due to diabetes, because the central laboratory failed to automatically flag for and notify the investigators on fasting glucose values ≥7.0 mmol/L or/and 2-hour glucose values ≥11.1 mmol/L. As a result, the laboratory results for these patients remained blinded throughout the study, and no additional plasma glucose measurements were conducted in order to confirm or reject the diagnosis of diabetes mellitus.

Definitions

Primary variable: AUC of plasma glucose values following OGTT

The primary outcome variable of this study was the change from randomization at Week 24 in AUC 0-2h of plasma glucose values following OGTT. Laboratory variables needed for calculation of the primary outcome variable were assessed at randomization, Week 12 and Week 24/end of treatment by the modified 2h-OGTT (Definition, Diagnosis and Classification of Diabetes Mellitus and its Complication 1999). The OGTT was performed in the morning after at least three days of unrestricted diet (>150 g of carbohydrate daily) and usual physical activity. A reasonable (30 to 50 g) carbohydrate containing meal had to be consumed on the evening before the test. The test was preceded by overnight fasting. To ensure fasting conditions for 8-14 h before the OGTT, an overnight hospitalisation at investigator site or at a day clinic centre was required. During the overnight fasting period, the patients were allowed to drink water. Smoking was not permitted during fasting and during the OGTT procedure until the last sampling of the OGTT was completed. Prior to the oral absorption of glucose, a venous catheter was put in place, and a blood sample was drawn for determination of fasting plasma glucose, fasting insulin, C-peptide, lipids, and HbA_{1c}. Then the patient drank 75 g of anhydrous glucose in 250-300 mL of water over the course of 5 minutes. Timing of the test was from the beginning of drinking. Four additional blood samples over 2 hours were collected via the venous catheter at 30, 60, 90, and 120 min after the glucose test load for determination of plasma glucose and insulin concentrations.

The primary outcome variable was calculated as change from randomization at Week 24 in AUC 0-2h of plasma glucose values following OGTT. The AUC was defined as the area under the linearly joint OGTT samples vs. time. It was computed with the trapezoidal method, using actual sampling times for the OGTT samples.

The first OGTT sample was taken in fasting condition. After that, the intake of glucose defines time 0 for the consecutive samples. The second, third, forth and fifth sample were scheduled at 30, 60, 90 and 120 minutes after glucose intake. The first fasting sample was treated as taken at 0 minutes, independent how long it was performed before the glucose intake. If the true sampling times was as planned at 0, 30, 60, 90, and 120 minutes, then the following formula was used for computing the AUC:

$$AUC(0\text{-}2h) \text{ in OGTT} = (15y_0+30y_{30}+30y_{60}+30y_{90}+15y_{120})/60$$

where y_t was the glucose measurement in mg/dL after t minutes.

Secondary variables based on plasma glucose values

Several secondary outcome variables were calculated on the basis of the plasma glucose values obtained during the OGTT procedure performed at randomization, Week 12, and Week 24. Change from randomization at Week 24 was assessed for the following variables:

- Fasting plasma glucose
- 2h-glucose (plasma glucose value taken at 120 min of OGTT)

Also, calculations were made to determine the proportion of patients at Week 24 with the following conditions:

- Hyperglycemia, defined as fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or 2h-glucose ≥11.1 mmol/L (200 mg/dL)
- IFG, defined as fasting glucose ≥5.6 mmol/L (100 mg/dL) and <7.0 mmol/L (126 mg/dL), or IGT, defined as 2h-glucose ≥7.8 mmol/L (140 mg/dL) and <11.1 mmol/L (200 mg/dL))

In the study protocol, IFG was defined as fasting glucose ≥ 6.1 mmol/L (110 mg/dL) and < 7.0 mmol/L (126 mg/dL). During the course of the study, the definition of IFG was changed by the American Diabetes Association to fasting glucose ≥5.6 mmol/L (100 mg/dL) and < 7.0 mmol/L (126 mg/dL). The new definition was used throughout this report, unless stated otherwise.

Secondary variables: insulin

Laboratory values for insulin were assessed in connection with the OGTT procedure at randomization, Week 12, and Week 24/end of treatment. The first blood sample for determination of insulin concentration was drawn via a venous catheter while the patient was in a fasting condition. Thereafter, four additional insulin measurements were performed at 30, 60, 90, and 120 min after the glucose load.

Change from randomization at Week 24 was calculated for fasting plasma insulin. Insulin levels were also assessed by calculation of change from randomization at Week 24 in following insulin indices:

- AUC 0-2h of plasma insulin values following OGTT, defined as the area under the linearly joint OGTT measurements vs. time. The calculations of the AUC of plasma insulin were performed in the same way as for the AUC of the plasma glucose values.
- ISI, defined as (10 000/square root of ([fasting glucose (mg/dL) x fasting insulin (μU/mL)] x [mean glucose (mg/dL) x mean insulin (μU/mL) during OGTT])) (Matsuda et al.)
- HOMA, defined as fasting plasma insulin (μIU/mL) x fasting plasma glucose (mmol/L)/22.5

Insulin and insulin sensitivity indices were analyzed using a log-transformation (geometric mean), since the distribution of data were expected to be highly skewed based on results from a previous study, while the log-transformed values were assumed to have normal distribution.

In addition, in several tables, the Quantitative Insulin Sensitivity Check Index (QUICKI) was included. QUICKI was defined as (1/[log(insulin(μU/mL))+log(glucose(mg/dL))]. This index was not considered one of the study's secondary variable.

Secondary variables: HbA_{1c}, C-peptide, lipids, and prolactin

HbA_{1c} and C-peptide were measured in connection with the OGTT procedure at randomization, Week 12 and Week 24. These variables were assessed while the patients were in fasting condition.

Calculation of the outcome variables related to HbA_{1c} and C-peptide were done as changes from baseline (randomization) to final visit at Week 24/end of treatment for each variable and treatment group. For HbA_{1c}, the proportion of patients with value ≥6.05% at Week 24 was calculated.

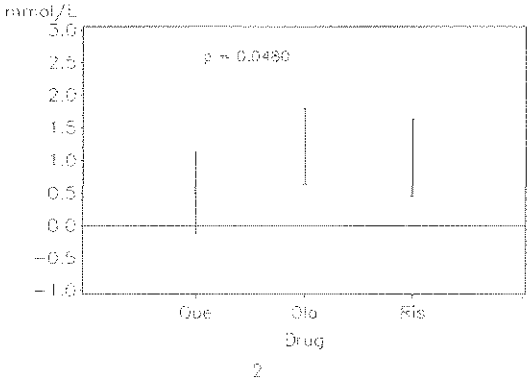
Clinical laboratory evaluation of glucose metabolism

Plasma glucose

The LS mean values and confidence intervals of the changes from randomization at Week 24 in AUC of plasma glucose values in the three treatment groups in the PAP are presented graphically in Figure 1.

The supporting data for changes from randomization in AUC of plasma glucose values is presented by treatment group in Table 38 and pairwise comparisons between the treatment groups with regard to this variable in Table 39.

Figure 1 (PAP) **AUC 0-2 h of plasma glucose values following OGTT, change from randomization**



SOURCE DOCUMENT: GLUC_01_PLOT.SAS GENERATED: 15:09:37 03FEB2006 DB version prod: 13

Table 38 **AUC 0-2h of plasma glucose values following OGTT, change from randomization (PAP)**

		Quetiapine	Olanzapine	Risperidone
AUC plasma glucose value (mmol/L x h)				
n[a]		111	144	130
Randomization	Mean (SD)	14.16 (3.02)	14.48 (3.83)	14.4 (3.63)
Change at Week 24	LS mean (SE)	0.506 (0.32)	1.218 (0.29)	1.041 (0.3)
	95% CI	(-0.13, 1.139)	(0.638, 1.798)	(0.45, 1.633)

a Number of patients with non-missing values at randomization and Week 24.
Note: Analysis using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.
SOURCE DOCUMENT: GLUC_01.SAS GENERATED: 8:37:46 18JAN2006 DB version prod: 13

Table 39 **AUC 0-2h of plasma glucose values following OGTT, treatment differences in change from randomization (PAP)**

		Quetiapine - Olanzapine	Quetiapine - Risperidone	Olanzapine - Risperidone
AUC plasma glucose value (mmol/L x h)				
Change at Week 24	LS mean (SE)	-0.71 (0.359)	-0.54 (0.368)	0.177 (0.344)
	95% CI	(-1.42, -0.01)	(-1.26, 0.188)	(-0.5, 0.853)
	p-value[a]	0.0480		

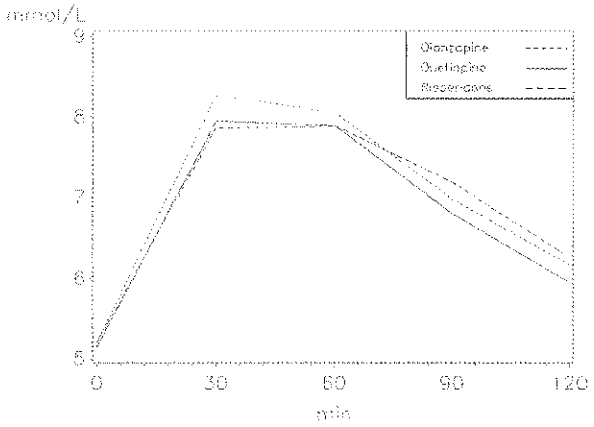
a No formal tests of quetiapine vs. risperidone or olanzapine vs. risperidone were planned for.

Note: Analysis using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.
SOURCE DOCUMENT: GLUC_02.SAS GENERATED: 8:38:07 18JAN2006 DB version prod: 13

At Week 24, the quetiapine group showed the smallest mean increase from baseline in AUC 0-2h (0.506 mmol/L x h). The mean change from randomization in AUC 0-2h of plasma glucose values at Week 24 in the PAP was significantly lower (p = 0.0480) in the quetiapine group than in the olanzapine group (1.218 mmol/L x h). The mean change from randomization in the risperidone group (1.041 mmol/L x h), though numerically greater than in the quetiapine group, did not show a statistically significant difference in comparison to the quetiapine group, as shown by a post-hoc analysis based on the confidence intervals coverage of 0.

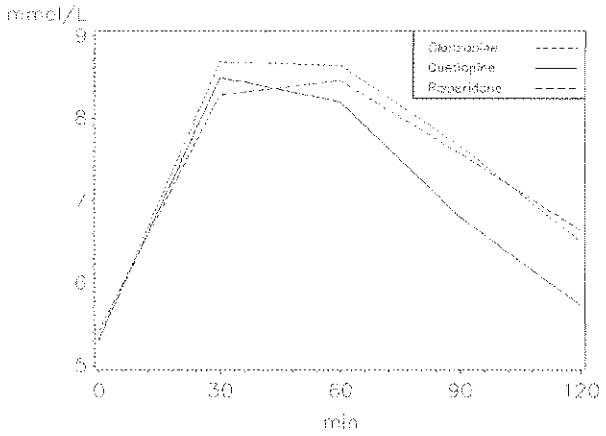
Figure 2 and Figure 3 present graphically the AUC the plasma glucose based on values taken at 0, 30, 60, 90, and 120 min of OGTT for PAP at randomization and at Week 24, respectively

Figure 2 **Plasma glucose values following OGTT at randomization (PAP)**



SOURCE DOCUMENT: GLUC_F01.SAS GENERATED: 11:33:56 03FEB2006 DB version prod: 13

Figure 3 **Plasma glucose values following OGTT at Week 24 (PAP)**



SOURCE DOCUMENT: GLUC_F03.SAS GENERATED: 11:34:35 03FEB2006 DB version prod: 13

At randomization, the curves for all three investigational products were similar. At Week 24, the curves looked almost identical from 0 to 30 min after the glucose load. However, at 30 min the quetiapine curve started to diverge, and at all later measurements (60, 90, and 120 min), the mean plasma glucose values in the quetiapine group were lower than those in the olanzapine and risperidone groups. At Week 12, this difference between the quetiapine on one hand, and olanzapine and risperidone on the other was similar or even greater than at Week 24 to the advantage of quetiapine.

The LS mean changes in fasting glucose and in 2-hour glucose from randomization at Week 24 are summarized by treatment in Table 40 below.

Table 40 **Fasting plasma glucose and two-hour glucose, change from randomization (PAP)**

		Quetiapine	Olanzapine	Risperidone
Fasting plasma glucose (mmol/L)				
n[a]		113	143	132
Randomization	Mean (SD)	5.14 (0.67)	5.199 (0.99)	5.203 (0.66)
Change at Week 24	LS mean (SE)	0.177 (0.08)	0.129 (0.08)	0.244 (0.08)
	95% CI	(0.013, 0.34)	(-0.02, 0.281)	(0.09, 0.399)
Two-hour glucose (mmol/L)				

Table 40 Fasting plasma glucose and two-hour glucose, change from randomization (PAP)

		Quetiapine	Olanzapine	Risperidone
n[a]		109	145	128
Randomization	Mean (SD)	5.934 (1.86)	6.163 (2.33)	6.266 (2.13)
Change at Week 24	LS mean (SE)	-0.1 (0.23)	0.543 (0.21)	0.587 (0.22)
	95% CI	(-0.56, 0.348)	(0.132, 0.953)	(0.162, 1.013)

a Number of patients with non-missing values at randomization and Week 24.
Note: Analysis using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.
SOURCE DOCUMENT: FGLUC_01.SAS GENERATED: 8:36:34 18JAN2006 DB version prod: 13

The baseline values of fasting plasma glucose and 2-hour glucose were similar across the treatment groups. At Week 24, there was a small increase from baseline in fasting glucose, which was comparable for all three treatment groups (0.177 mmol/L for quetiapine, 0.129 mmol/L for olanzapine, and 0.244 mmol/L for risperidone).

For the 2-hour glucose, no change from baseline at Week 24 was observed in the quetiapine group, while the olanzapine and risperidone groups showed an increase from baseline, which was of similar magnitude (0.543 and 0.587 mmol/L, respectively).

Hyperglycemia, impaired fasting glucose, impaired glucose tolerance, or diabetes

Table 41 summarizes by treatment group the proportion of patients in PAP with hyperglycemia (defined as fasting plasma glucose ≥7.0 mmol/L and/or 2h-glucose ≥11.1 mmol/L), the proportion of patients with fasting glucose ≥7.0 mmol/L, the proportion of patients with 2-hour glucose ≥11.1 mmol/L, and the proportion of patients with IFG (defined as fasting glucose ≥5.6 and <7.0 mmol/L) or IGT (defined as 2h-glucose ≥7.8 and <11.1 mmol/L) at randomization and at Week 24.

Table 41 Patients with hyperglycemia and impaired fasting glucose or impaired glucose tolerance (PAP)

	Quetiapine N = 115		Olanzapine N = 146		Risperidone N = 134	
	n[a]	n (%)	n[a]	n (%)	n[a]	n (%)
Proportion of patients with hyperglycemia						
Randomization	114	3 (2.6)	145	10 (6.9)	134	7 (5.2)
Week 24	115	5 (4.3)	146	10 (6.8)	133	9 (6.8)
Proportion of patients with fasting glucose ≥7.0 mmol/L						
Randomization	114	2 (1.8)	145	3 (2.1)	134	3 (2.2)
Week 24	115	3 (2.6)	146	5 (3.4)	134	4 (3.0)
Proportion of patients with 2h-glucose ≥11.1 mmol/L						
Randomization	114	1 (0.9)	145	8 (5.5)	134	5 (3.7)
Week 24	115	2 (1.7)	146	8 (5.5)	134	7 (5.2)

Table 41 Patients with hyperglycemia and impaired fasting glucose or impaired glucose tolerance (PAP)

	Quetiapine N = 115 n[a] n (%)	Olanzapine N = 146 n[a] n (%)	Risperidone N = 134 n[a] n (%)
Proportion of patients with impaired fasting glucose or impaired glucose tolerance			
Randomization	114 30 (26.3)	145 29 (20.0)	134 43 (32.1)
Week 24	115 37 (32.2)	146 43 (29.5)	133 54 (40.6)

a Number of patients with non-missing value.
SOURCE DOCUMENT: GLUC_03.SAS GENERATED: 17:48:05 04APR2006 DB version prod: 13

Several patients with hyperglycemia at randomization were incorrectly randomised for participation in the study, despite the fact that they fulfilled exclusion criteria. At randomization, there were three such patients in the quetiapine group, 10 in the olanzapine group, and seven in the risperidone group in the PAP.

At Week 24, the proportion of patients with hyperglycemia was small and similar to baseline (randomization) within each treatment group. The only patient in the quetiapine group, who had 2h-glucose ≥11.1 mmol/L at randomization, had a 2h-glucose value below 11.1 mmol/L at Week 24. The two patients with 2h-glucose values ≥11.1 mmol/L at Week 24 had normal values at randomization. In the olanzapine group, of the 8 patients with 2h-glucose values ≥11.1 mmol/L at randomization, 5 had normal values at Week 24, and 3 remained above 11.1 mmol/L. Of these, 1 patient got a higher value at Week 24 compared to randomization, and 2 remained unchanged. Five patients in the olanzapine group had normal 2h-glucose values at randomization, but ≥11.1 mmol/L at Week 24. In the risperidone group, of the 5 patients 2h-glucose ≥11.1 mmol/L at randomization, one remained unchanged, and others slightly worsened at Week 24.

The proportion of patients with IFG or IGT increased slightly from randomization to Week 24 in all treatment groups in the PAP. In the quetiapine group, it changed from 26.3 to 32.2%, in the olanzapine group from 20.0 to 29.5%, and in the risperidone group from 32.1 to 40.6%. The smallest increase was seen in the quetiapine group, and the greatest in the olanzapine group.

The proportions of patients in the PAP population with shift from randomization to Week 24 to higher or to lower category in fasting glucose or in 2h-glucose values are presented in Table 42. The proportion of patients with shift to higher category includes patients who shifted from normal to impaired, from normal to high, or from impaired to high. The proportion of patients with shift to lower category includes the patients with shift from high to impaired, from high to normal, or from impaired to normal.

Table 42 Patients with shift to higher or to lower category in fasting plasma glucose and two-hour glucose (PAP)

	Quetiapine N = 115 n[a] n (%)	Olanzapine N = 146 n[a] n (%)	Risperidone N = 134 n[a] n (%)
Proportion of patients with shift to higher fasting glucose category[b]			
Week 24	111 23 (20.7)	140 20 (14.3)	129 22 (17.1)
Proportion of patients with shift to higher 2h-glucose category[c]			
Week 24	108 10 (9.3)	137 20 (14.6)	123 23 (18.7)
Proportion of patients with shift to lower fasting glucose category[b]			
Week 24	20 11 (55.0)	23 7 (30.4)	35 9 (25.7)
Proportion of patients with shift to lower 2h-glucose category[c]			
Week 24	18 11 (61.1)	30 17 (56.7)	27 14 (51.9)

a Number of patients at risk at baseline, ie, Patients not in the highest category (for shift to higher category) or not in the normal category (for shift to lower category), and with non-missing value
b Categories for fasting glucose: normal <5.6 mmol/L; impaired ≥5.6 and < 7.0 mmol/L; high ≥7.0 mmol/L
c Categories for 2h-glucose: normal <7.8 mmol/L; impaired ≥7.8 and < 11.1 mmol/L; high ≥11.1 mmol/L
SOURCE DOCUMENT: GLUC_06.SAS GENERATED: 16:52:53 07APR2006 DB version prod: 13

With regard to 2h-glucose, about twice as many patients shifted at Week 24 to higher category in the risperidone group (18.7%), than in the quetiapine group (9.3%). In the olanzapine group, the shift to higher category was seen in 14.6% of patients. Shift to lower category was seen in a slightly higher proportion of patients in the quetiapine group in comparison to the risperidone and olanzapine groups.

For fasting glucose, shift to lower category at Week 24 was seen in 55% of patients in the quetiapine group, in comparison to 30.4% in the olanzapine group, and 25.7% in the risperidone group. A slightly higher proportion of patients moved to higher category in the quetiapine group compared to the other two groups.

No patients received the diagnosis of diabetes mellitus during the study, and none was excluded from the study due to diabetes, because the central laboratory failed to automatically flag for and notify the investigators on fasting glucose values ≥7.0 mmol/L or/and 2-hour glucose values ≥11.1 mmol/L. As a result, the laboratory results for these patients remained blinded throughout the study, and no additional plasma glucose measurements were conducted in order to confirm or reject the diagnosis of diabetes mellitus. Only one patient, who had a 2h-glucose value above the exclusion criteria for glucose, was excluded due to risk of diabetes after the central laboratory had manually disclosed the value. However, nine patients in the study had normal glucose values at randomization and at least two post-randomization values of fasting glucose ≥7.0 mmol/L and/or 2-hour glucose ≥11.1 mmol/L, revealed after

unblinding of the laboratory data. Of these, two patients were in the quetiapine treatment group, three in the olanzapine group, and four in the risperidone group.

Haemoglobin A1c

The LS mean changes in HbA_{1c} from randomization at Week 24 are summarized by treatment group in Table 43.

Table 43 Haemoglobin A_{1c}, change from randomization (PAP)

		Quetiapine	Olanzapine	Risperidone
HbA_{1c} (%)				
n[a]		106	140	128
Randomization	Mean (SD)	5.329 (0.43)	5.323 (0.39)	5.332 (0.49)
Change at Week 24	LS mean (SE)	0.122 (0.03)	0.05 (0.03)	0.065 (0.03)
	95% CI	(0.054, 0.191)	(-0.01, 0.112)	(0.001, 0.129)

a Number of patients with non-missing value.
Note: Analysis using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.
SOURCE DOCUMENT: HBA1C_01.SAS GENERATED: 17:49:30 04APR2006 DB version prod: 13

At randomization, all treatment groups had similar values (5.329% for the quetiapine, 5.323% for the olanzapine, and 5.332% for the risperidone group). At Week 24, the change in HbA_{1c} was small in all treatment groups: 0.122% in the quetiapine group, 0.065% in the risperidone group, and 0.05% in the olanzapine group.

Table 44 summarizes by treatment the number and percentage of patients with $HbA_{1c} \geq 6.05\%$ at randomization and at Week 24.

Table 44 Patients with haemoglobin $A_{1c} \geq 6.05\%$ (PAP)

	Quetiapine N = 115 n[a] n (%)	Olanzapine N = 146 n[a] n (%)	Risperidone N = 134 n[a] n (%)
Proportion of patients with $HbA_{1c} \geq 6.05\%$			
Randomization	112 5 (4.5)	143 6 (4.2)	132 9 (6.8)
Week 24	110 6 (5.5)	143 5 (3.5)	129 6 (4.7)

a Number of patients with non-missing value.
SOURCE DOCUMENT: HBA1C_03.SAS GENERATED: 17:56:09 04APR2006 DB version prod: 13

Across the treatment groups, approximately the same low proportion of patients had $HbA_{1c} \geq 6.05\%$ at randomization (4.5% for quetiapine, 4.2% for olanzapine, and 6.8% for risperidone). At Week 24, the proportion of patients with $HbA_{1c} \geq 6.05\%$ was very similar to the baseline for each of the treatment groups, and no meaningful difference between the treatments was seen.

Insulin

The relative changes from randomization at Week 24 in fasting plasma insulin, AUC 0-2h of plasma insulin values following OGTT, index of insulin sensitivity (ISI) according to Matsuda et al., and homeostasis model assessment (HOMA) are summarized in Table 45 below.

Table 45 Fasting plasma insulin and indices of insulin sensitivity, change from randomization (PAP)

		Quetiapine	Olanzapine	Risperidone
Fasting plasma insulin (µIU/mL)				
n[a]		82	117	113
Randomization	Geometric mean (CV)	5.209 (79.9)	5.363 (63.7)	5.442 (52.5)
Relative change at Week 24	Increase in %[b]	3.324	8.475	11.9
	95% CI	(-9.2, 17.58)	(-3.33, 21.73)	(-0.2, 25.47)
AUC based on plasma insulin values following OGTT (µIU/mL x h)				
n[a]		84	113	103
Randomization	Geometric mean (CV)	80.28 (64.9)	71.26 (68.7)	67.58 (56.9)
Relative change at Week 24	Increase in %[b]	13.15	24.45	10.74
	95% CI	(-0.14, 28.22)	(11.46, 38.96)	(-1.2, 24.13)
Index of insulin sensitivity (ISI)[c]				
n[a]		76	112	103
Randomization	Geometric mean (CV)	108.5 (64.4)	118 (69.6)	118.3 (64.5)
Relative change at Week 24	Increase in %[b]	-10.8	-19.1	-15.8
	95% CI	(-21.9, 1.847)	(-27.9, -9.33)	(-25.1, -5.41)
Homeostastasis model assessment (HOMA)[d]				
n[a]		82	117	112
Randomization	Geometric mean (CV)	1.183 (80.8)	1.227 (69.7)	1.257 (54.7)
Relative change at Week 24	Increase in %[b]	6.439	10.97	16.75
	95% CI	(-7.63, 22.65)	(-2.22, 25.94)	(2.945, 32.41)

a Number of patients with non-missing values at randomization and Week 24.
b Based on LS mean for log-transformed data
c ISI = 10,000/square root of ([fasting glucose (mg/dL) x fasting insulin (µU/mL)] x [mean glucose (mg/dL) x mean insulin (µU/mL) during OGTT])
d HOMA = fasting plasma insulin (µU/mL) x fasting plasma glucose (mmol/L)/22.5
Note: Analysis based on log-transformed data using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.
SOURCE DOCUMENT: INSU_01 SAS GENERATED: 11:34:40 19JAN2006 DB version prod: 13

Baseline values for fasting plasma insulin, AUC of plasma insulin values following OGTT, ISI and HOMA were similar across the treatment groups. At Week 24, there was a small relative increase in fasting insulin in all three groups that was not statistically significant. This increase was smallest in the quetiapine group (3.3%), compared to both the olanzapine (8.5%) and the risperidone (11.9%) groups.

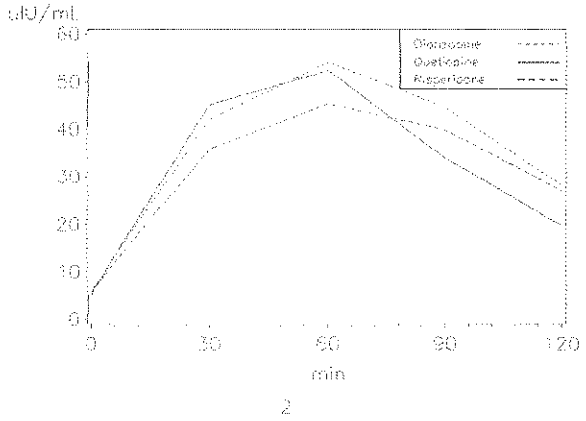
With regard to AUC, the olanzapine group had a considerably bigger increase (24.5%) than both quetiapine and risperidone (13.2% and 10.7% respectively). The change from randomization was statistically significant for the olanzapine group.

The ISI results showed the greatest change from randomization in the olanzapine group as well (decrease with 19.1%), followed by the risperidone group (15.8%). For both these groups, the decrease from baseline was statistically significant. The quetiapine group had a decrease from randomization of 10.8%, which was not statistically significant.

For HOMA, the greatest and statistically significant increase was observed in the risperidone group (16.8%), followed by the olanzapine group (11%). The quetiapine group showed the smallest increase (6.4%).

Figure 4 presents graphically the AUC of the plasma insulin based on values taken at 0, 30, 60, 90, and 120 min of OGTT at Week 24.

Figure 4 **Plasma values of insulin following OGTT at Week 24 (PAP)**



SOURCE DOCUMENT: INSU_F03.SAS GENERATED: 15:08:48 03FEB2006 DB version prod: 13

The dynamics of plasma insulin values resembled closely that of plasma glucose values (see Table xxi). Up to 60 min after the glucose load, the values for the quetiapine and olanzapine groups were very similar, and slightly lower for the risperidone group. However, the 90 min and 120 min values were lower for the quetiapine group, than both for olanzapine and risperidone. These results were in line with the results from the primary analysis.

C-peptide

The LS mean changes in C-peptide level from randomization at Week 24 are summarized by treatment group in Table 46 below.

Table 46 C-peptide level, change from randomization (PAP)

		Quetiapine	Olanzapine	Risperidone
Plasma C-peptide level (pmol/L)				
n*		90	118	110
Randomization	Mean (SD)	747.3 (366)	735.3 (300)	742.2 (346)
Change at Week 24	LS mean (SE)	120 (42.5)	142.5 (39.6)	139.7 (39.5)
	95% CI	(36.34, 203.7)	(64.53, 220.5)	(62.02, 217.5)

Note: Analysis using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.
SOURCE DOCUMENT: CPEPT_01 SAS GENERATED: 8:33:53 18JAN2006 DB version prod: 13

The baseline (randomization) values were comparable across the treatment groups. At Week 24, there was an increase from randomization in C-peptide level in all groups. The quetiapine group had the smallest change (120 pmol/L), while the olanzapine and risperidone groups increased by 142.5 and 139.7 pmol/L respectively. These results were consistent with the insulin data, and supported the primary analysis.

Potential issues affecting clinical laboratory results related to glucose metabolism and lipids

The results of the study were not confounded by the possibility that patients were not in good fasting condition when blood samples were drawn, as the patients were hospitalised overnight before the OGTT procedure in order to ensure adequate fasting condition.

Generally, the laboratory samples were of good quality and could be analyzed as planned. However, for insulin, samples were collected at site and sent in frozen condition in batches to the central laboratory and there were quite a few of these samples that could not be analyzed due to specimen received beyond stability or haemolysis. These cancellations are not considered to affect the analysis in any significant way, as the cancellations are most likely unrelated to the lab values of the patients.

Very few patients reported use of concomitant medication potentially affecting laboratory results related to metabolism during the study. In the quetiapine treatment group, one patient received simvastatin, one patient fish oil, one patient vitamin E, and one patient hydrocortisone.

Based on the reasons for patient withdrawals, there was no indication that the slightly higher withdrawal rate in the quetiapine group influenced the study results related to glucose metabolism and lipids.

Several patients with fasting plasma glucose ≥7.0 mmol/L and/or 2h-glucose ≥11.1 mmol/L at randomization were incorrectly randomised for participation in the study, despite the fact that they had hyperglycemia and thus fulfilled exclusion criteria. At randomization, there were three such patients in the quetiapine group, 10 in the olanzapine group, and seven in the risperidone group in the PAP. The incorrectly randomised patients did not have any substantial influence on the outcome of the study.

Summary of Trial 125 (glucose metabolism)

This study was conducted in a population mainly reflecting European chronic schizophrenic non-diabetic population with relatively normal insulin sensitivity at baseline. As the design of the study was randomized open-label, necessary precautions were taken to blind the key laboratory results for glucose metabolic variables, lipids and prolactin level to the investigators, patients, and sponsor until the database had been locked. The results were not confounded by the possibility that patients were not in good fasting condition when blood samples were drawn, as the patients were hospitalized overnight before the OGTT procedure in order to ensure fasting condition.

The study results suggest that there were differential effects between the investigational products in how the patients in the respective treatment group responded to stress condition provided by glucose load (OGTT). At Week 24, there was a statistically significant difference between the quetiapine and olanzapine groups in post-load glucose levels as measured by the AUC 0-2h of plasma glucose values, with the quetiapine group showing smaller mean increase from baseline (randomization) than the olanzapine group. This difference was statistically significant in both PAP and PP populations, which further supports the results. The mean change from baseline was smaller in the quetiapine group than in the risperidone group as well, but this difference was not statistically significant.

The analysis of mean glucose values at separate time points during the OGTT showed, that while fasting glucose and 30 min glucose levels were similar across the treatment groups at Week 24, the quetiapine group had lower plasma glucose values than both olanzapine and risperidone at 60, 90 and 120 min (2h) after the glucose load. For mean 2h-glucose value, no change from randomization at Week 24 was observed in the quetiapine group, while in the olanzapine and risperidone groups mean increases in 2h-glucose from randomization at Week 24 were seen. Thus, after 24 weeks of treatment, there appear to be a difference between the patients in the three treatment groups in the ability to handle glucose challenge. The 2h-glucose and AUC 0-2h data imply that in the olanzapine group and in a smaller degree in the risperidone group, there may be a trend towards developing an impairment of glucose tolerance, not seen in the patients who received quetiapine. From the clinical point of view, the change in 2h-glucose supported by change in AUC 0-2h in the olanzapine and possibly risperidone group might indicate a higher risk of diabetes.

The differential effects on handling of glucose load observed in the three treatment groups appeared rather quickly during the treatment. At Week 12, the changes in glucose variables described above were of the same magnitude as those observed at Week 24. After Week 12, the treatment effects on glucose metabolism seemed to stabilize, with almost no further change to Week 24. The fact that the results at Week 12 were similar to the results at Week 24 provides additional support to the primary analysis.

The results did not appear to be biased by a somewhat higher discontinuation rate in the quetiapine treatment group in comparison to the olanzapine and risperidone groups. The majority of discontinuations in the quetiapine group were related to worsening of schizophrenia, and did not suggest changes in glucose metabolism profile.

In the absence of stress condition provided by glucose load, the differences in glucose metabolic characteristics at Week 24 in the three treatment groups, as measured by fasting glucose and HbA_{1c} level, were small. With regard to mean fasting glucose levels, there was no meaningful difference between the three treatment groups at Week 24. The HbA_{1c} results were not in parallel with the AUC 0-2h of plasma glucose values and the 2h-glucose results, as the change from randomization at Week 24 in HbA_{1c} was slightly higher in the quetiapine group compared to that in the olanzapine and risperidone groups. However, as the changes from randomization were small and within the normal variability limits in all treatment groups, they probably had limited or no clinical significance. The interpretation of the absolute value of changes in the quetiapine group seen at Week 24 is limited due to the absence of a placebo control group, as psychiatric status per se can influence glucose tolerance and insulin resistance in patients.

The results accounted for above were supported by the shift in fasting glucose and 2h-glucose to a higher category (ie. shift from normal to impaired, from normal to high, or from impaired to high) at Week 24. With regard to 2h-glucose, about twice as many patients shifted to a higher category in the risperidone group compared to the quetiapine group, and about 50% more patients in the olanzapine group than in the quetiapine group. Shift to a lower category was seen in a slightly higher proportion of patients in the quetiapine group in comparison to the risperidone and olanzapine groups. For fasting glucose, shift to a lower category at Week 24 was seen in a higher proportion of patients in the quetiapine group, in comparison to the olanzapine and risperidone groups. A slightly higher proportion of patients moved to a higher category in the quetiapine group compared to the other two groups. However, there were no statistically significant differences between the groups, and these results should be interpreted with caution since the study was not designed for this kind of comparison. Also, it should be noticed that shift to high category in glucose values did not necessarily indicate that the patient had developed diabetes, as the values were not confirmed by repeated measurements necessary for the diagnosis of diabetes.

The underlying explanation for differences in glucose tolerance could be the difference in insulin secretion and/or insulin action. The pattern of the AUC 0-2h insulin curves followed the pattern seen in AUC 0-2h of plasma glucose values well. Up to 60 min after the glucose load, the values for the quetiapine and olanzapine groups were very similar, and slightly lower

for the risperidone group. However, the 90 min and 120 min values were lower for the quetiapine group, than both for olanzapine and risperidone, which was in line with the results from the primary analysis.

Overall, quetiapine did not appear to have a clinically relevant effect on glucose metabolism in chronic schizophrenic patients, when compared to the changes observed in olanzapine or risperidone treatment groups after 24 weeks of treatment. The results of the study on metabolic variables were reassuring, as the observed changes in these variables at Week 24 were small in all treatment groups, and most of them were not judged as clinically significant. Due to absence of a placebo control group, the interpretation of the absolute value of changes is limited.

5.3.4.2 D1444C00004 (Princess study)

This study was a one year, International, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Phase III Study to Evaluate Prevention of Relapse in Patients in Stable Condition with Chronic Schizophrenia Receiving Either Sustained-release Quetiapine Fumarate (SEROQUEL) or Placebo. This study evaluated the efficacy and safety of quetiapine SR compared to placebo in long-term use (up to one-year), by examining relapse in patient's psychiatric conditions.

All patients were treated with quetiapine SR for 16 weeks during the stabilization period. The placebo controlled randomized period was to be one year or until relapse for each patient or until the study was terminated. As the study was terminated after a positive interim analysis the mean duration of the double-blind, randomized treatment period with quetiapine SR was 4 months (120 days) and the maximum period was 9 months (270 days). During the whole study, including both stabilization and randomization period, 63 patients were treated with quetiapine SR for more than 6 months.

Adverse event data

There were no AEs associated with DM reported during the randomized treatment or the open label stabilization period.

Glucose regulation laboratory data; randomized treatment period

Glucose metabolism variables were evaluated for the open label safety population and the randomized safety population and for the three diabetic subgroups. These analyses were repeated for patients with a documented fasting value. To verify this further, the sampling time was plotted as cumulative percentage of patients having the sample taken by time of day for the open label safety population at enrollment and for the randomized treatment safety population at randomization and at last assessment. At all three occasions, more than 90% of the patients had the samples taken prior to 11.00 AM and close to 100% of the patients prior to 1.00 PM. In total, 99% of the glucose laboratory data was from patients with documented fasting condition. The data below are from the whole randomized safety population.

Changes in mean values over time in glucose regulation laboratory data during the *randomized treatment period*

Descriptive statistics for change from randomization to end of treatment in glucose regulation laboratory data are summarized for all patients by randomized treatment group in Table 47. The mean change from baseline for patients with diabetes, patients at risk for diabetes, and patients with no known diabetic risk is summarized by treatment group in Appendix A Table A161.

Table 47 Glucose regulation laboratory data, change from randomization to end of treatment (randomized safety population)

		PLA N=103	QTP SR N=94
Glucose (mmol/L)			
n[a]		76	78
Randomization	Mean (SD)	5.53 (0.68)	5.21 (0.94)
End of treatment	Mean (SD)	5.48 (1.11)	5.55 (1.30)
Change	Mean (SD)	0.15 (1.10)	0.34 (0.90)
	Median	0.10	0.30
	Min to max	-2.5 to 5.1	-1.7 to 5.1
HbA1C (%)			
n[a]		88	86
Randomization	Mean (SD)	5.24 (0.39)	5.29 (0.40)
End of treatment	Mean (SD)	5.28 (0.43)	5.34 (0.44)
Change	Mean (SD)	0.04 (0.31)	0.05 (0.35)
	Median	0.00	0.00
	Min to max	-0.8 to 0.8	-1.0 to 1.7
Insulin (pmol/L)			
n[a]		88	86
Randomization	Mean (SD)	87.15 (83.45)	83.49 (73.83)
End of treatment	Mean (SD)	118.33 (137.80)	97.28 (129.06)
Change	Mean (SD)	31.18 (112.38)	13.79 (128.50)
	Median	7.00	0.00
	Min to max	-243.0 to 507.0	-229.0 to 938.0
HOMA-R			
n[a]		72	75
Randomization	Mean (SD)	1.26 (1.26)	1.25 (1.26)
End of treatment	Mean (SD)	1.91 (3.30)	1.51 (2.67)
Change	Mean (SD)	0.65 (2.87)	0.26 (2.64)
	Median	0.06	0.02

Table 47 Glucose regulation laboratory data, change from randomization to end of treatment (randomized safety population)

		PLA N=103	QTP SR N=94
	Min to max	-4.3 to 16.3	-3.7 to 18.8
QUICKI			
n[a]		72	75
Randomization	Mean	0.1753	0.1753
	SD	0.0253	0.0268
End of treatment	Mean	0.1697	0.1737
	SD	0.0269	0.0256
Change	Mean	-0.0054	-0.0016
	SD	0.0226	0.0254
	Median	-0.0050	0.0000
	Min	-0.0600	-0.0600
	Max	0.0400	0.0600

a Number of patients with non-missing observations
HOMA-R homeostatic model assessment of insulin resistance. QUICKI quantitative insulin sensitivity check index.
HbA1C Hemoglobin A1C. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine. SR Sustained-release. SD Standard deviation.
Note: All patients with assessment at randomization and at least one assessment after randomization.
Study: D1444C00004 Source document: ST_LAB_GLUC_CHA73.SAS. Generated: 17:32:28 30Aug2006 D8 version prod: 6.

The changes in mean and median glucose values were small and similar in the two groups. Mean HbA1c values were relatively unchanged in both treatment groups. There was no median change from baseline for HbA1c in either group. Mean insulin levels were increased in both treatment groups with a larger increase observed in the placebo group (31.18 pmol/L) than in the quetiapine SR group (13.79 pmol/L). Median changes from baseline for insulin were lower than mean changes (7.00 pmol in the placebo group and no change in the quetiapine SR group). The mean increase in HOMA-R values was larger in the placebo group (0.65) compared to the quetiapine SR group (0.26). The median change from baseline for HOMA-R was small in both treatment groups. There was a small mean decrease from baseline in QUICKI values in both groups and the median change was even smaller.

Individual clinically important abnormalities in glucose regulation laboratory data during the *randomized treatment period*

Patients with clinically important fasting glucose regulation laboratory values emerging at any time after randomization are summarized in Table 48. Patients with a clinically important glucose regulation laboratory value emerging at any time after randomization are summarized by diabetic subgroups and treatment group in Appendix A Table A162.

Table 48 Glucose regulation laboratory data, clinically important values at any time (randomized safety population)

	PLA N = 103		QTP SR N = 94	
	n[a]	n (%)	n[a]	n (%)
Glucose (mmol/L)				
≤2.49795	76	0	78	0
≥6.99426	75	6 (8.0)	74	4 (5.4)
HbA1C (%)				
>7.5	88	0	86	0

a Number of patients at risk i.e. not fulfilling the criteria at randomization.
HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine SR Sustained-release.
Note: Clinically important values emerging during randomized treatment phase.
Note: All patients with assessment at randomization and at least one assessment after randomization.
Note: Percentages are calculated as (n/na)*100.
Study: D1444C00004 Source document: ST_LAB_GLUC_CL233.SAS. Generated: 17:35:37 30Aug2006 DB version prod: 6.

A slightly higher proportion of patients in placebo group (6 [8.0%]) than in the quetiapine SR group (4 [5.4%]) had clinically important high glucose values reported. There was no patient in any group recording a clinically important HbA1c level during the randomized treatment period.

Shift from randomization to clinically important glucose regulation laboratory values at any time after randomization and from randomization to end of treatment is presented for all patients in Table 49 and Table 50. Shift from randomization to end of treatment is presented for "non-diabetics", "diabetic risk", and "diabetics" in Appendix A Tables A163 through A165.

Table 49 Fasting glucose regulation laboratory data, shift to clinically important values at any time (randomized safety population)

	PLA N=103 At any time			QTP SR N=94 At any time		
Randomization	N[a] (%)	<L n[b] (%)	>U n[b] (%)	N[a] (%)	<L n[b] (%)	>U n[b] (%)
Glucose (mmol/L)						
<L	0	0	0	0	0	0
N	75 (98.7)	0	6 (8.0)	74 (94.9)	0	4 (5.4)
>U	1 (1.3)	0	0	4 (5.1)	0	2 (50.0)
Total	76 (100)	0	6 (7.9)	78 (100)	0	6 (7.7)
HbA1C (%)						

Table 49 Fasting glucose regulation laboratory data, shift to clinically important values at any time (randomized safety population)

	PLA N=103 At any time			QTP SR N=94 At any time		
Randomization	N[a] (%)	<L n[b] (%)	>U n[b] (%)	N[a] (%)	<L n[b] (%)	>U n[b] (%)
N	88 (100)	NA	0	86 (100)	NA	0
>U	0	NA	0	0	NA	0
Total	88 (100)	NA	0	86 (100)	NA	0

a Distribution at randomization.
b Patients are counted only once in each column.
NA Not applicable. PLA Placebo. QTP Quetiapine. SR Sustained-release. N Number of patients in treatment group. HbA1c Hemoglobin A1c. n Number of patients.
Note: Percentages in the na column are calculated as (na /na in total row)*100
Note: Percentages are calculated as nb /na *100
Note. Values at any time after randomization.
Study: D1444C00004 Source document: ST_LAB_GLUC_SH520.SAS. Generated: 19:14:37 30Aug2006 DB version prod: 6.

Table 50 Fasting glucose laboratory data, shift from randomization to end of treatment (randomized safety population)

	PLA N=103 End of treatment			QTP SR N=94 End of treatment		
Randomization	<L n(%)	N n (%)	>U n (%)	<L n(%)	N n (%)	>U n (%)
Glucose (mmol/L)						
<L	0	0	0	0	0	0
N	0	69 (92.0)	6 (8.0)	0	71 (95.9)	3 (4.1)
>U	0	1 (100.0)	0	0	2 (50.0)	2 (50.0)
Total	0	70 (92.1)	6 (7.9)	0	73 (93.6)	5 (6.4)
HbA_{1c} (%)						
N	NA	88 (100)	0	NA	86 (100)	0
>U	NA	0	0	NA	0	0
Total	NA	88 (100.0)	0	NA	86 (100.0)	0

HbA1c glycosylated hemoglobin. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA placebo. QTP quetiapine. SR sustained release.

The incidences of patients observed with shifts from normal glucose levels at baseline to high levels at end of treatment was 8.0% in the placebo group and 4.1% in the quetiapine SR groups. No patient had a shift to higher HbA1c levels at end of treatment.

Glucose shift plots from randomization to end of treatment for all quetiapine SR treated patients and placebo treated patients (all and individual subgroups) are shown Appendix A Figures A1 through A8.

Glucose regulation laboratory data; *open label stabilization period*

For glucose regulation laboratory data, descriptive statistics for change from enrolment to randomization and by visit are summarized for all patients in Table 51 below. Data for individual subgroups are contained in Appendix A Table A166 through A168.

Table 51 Fasting glucose regulation laboratory data, change from enrollment to end of stabilization period (open-label safety population)

		QTP SR N=327
Glucose (mmol/L)		
n[3]		252
Enrolment	Mean (SD)	5.27 (0.95)
Randomization	Mean (SD)	5.31 (0.87)
Change	Mean (SD)	0.04 (0.96)
	Median	0.10
	Min to max	-4.1 to 5.9
HbA1C (%)		
n[2]		278
Enrolment	Mean (SD)	5.25 (0.42)
Randomization	Mean (SD)	5.29 (0.40)
Change	Mean (SD)	0.04 (0.33)
	Median	0.00
	Min to max	-1.1 to 1.6
Insulin (pmol/L)		
n[3]		278
Enrolment	Mean (SD)	101.18 (139.30)
Randomization	Mean (SD)	106.27 (222.52)
Change	Mean (SD)	5.09 (219.44)
	Median	0.00
	Min to max	-917.0 to 2730.0
HOMA-R		
n[2]		223
Enrolment	Mean (SD)	1.61 (2.46)
Randomization	Mean (SD)	1.75 (5.03)
Change	Mean (SD)	0.15 (4.92)
	Median	-0.01

Table 51 Fasting glucose regulation laboratory data, change from enrollment to end of stabilization period (open-label safety population)

		QTP SR N=327
	Min to max	-16.8 to 63.0
QUICKI		
n[a]		223
Enrolment	Mean	0.1722
	SD	0.0256
Randomization	Mean	0.1734
	SD	0.0270
Change	Mean	0.0012
	SD	0.0269
	Median	0.0000
	Min	-0.0700
	Max	0.0900

a Number of patients with non-missing observations.
HOMA-R homeostatic model assessment of insulin resistance. QUICKI quantitative insulin sensitivity check index.
HbA1C Hemoglobin A1C. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine. SR Sustained-release. SD Standard deviation.
Note: All patients with assessment at enrollment and at least one assessment after enrollment.
Study: D1444C00004 Source document: ST_LAB_GLUC_CHA73_OL.SAS. Generated: 17:32:35 30Aug2006 DB version prod: 6.

Patients with clinically important glucose regulation laboratory values emerging at any time after enrolment and up to randomization are summarized in Table 52 (all patients) (individual subgroups contained in Appendix A Table A169).

Table 52 Fasting glucose regulation laboratory data, clinically important values at any time (open-label safety population)

	QTP SR N=327	
	n[a]	n (%)
Glucose (mmol/L)		
≤2.49795	252	0
≥6.99426	244	21 (8.6)
HbA1C (%)		
>7.5	278	0

a Number of patients at risk i.e. not fulfilling the criteria at enrollment.
HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: Clinically important values emerging during stabilization period.
Note: All patients with assessment at enrollment and at least one assessment after enrollment.
Note: Percentages are calculated as (n/na)*100.
Study: D1444C00004 Source document: ST_LAB_GLUC_CL233_OL.SAS. Generated: 12:35:43 30Aug2006 DB version prod: 6.

Shifts from enrolment to randomization are presented in Table 53 (all patients) and in Appendix A Table A170 through A172 for individual subgroups.

Table 53 Fasting glucose laboratory data, shift from enrolment to end of stabilization period (open-label safety population)

	QTP SR N=327 End of stabilization period		
Enrollment	**<L n (%)**	**N n (%)**	**>U n (%)**
Glucose (mmol/L)			
<L	0	0	0
N	0	237 (97.1)	7 (2.9)
>U	0	6 (75.0)	2 (25.0)
Total	0	243 (96.4)	9 (3.6)
HbA1C (%)			
N	NA	278 (100)	0
>U	NA	0	0
Total	NA	278 (100)	0

HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: For reference ranges, see Definitions of Clinically Important Laboratory Values, Vital Signs, and Electrocardiographic Data (Appendix 12.1.9, Statistical Analysis Plan).
Note: Denominators for percentages for below, normal, and above within a treatment are row totals.
Study: D1444C00004 Source document: ST_LAB_GLUC_SH79_OL.SAS. Generated: 17:36:36 30Aug2006 DB version prod 6

A shift plot for glucose from enrolment to randomization is shown in Appendix A Figure A9.

The mean changes in glucose regulation variables were small during the open label treatment period and not clinically meaningful. Nine patients (3.6%) had a clinically important high glucose at end of the stabilization period and seven of these shifted from a normal value at baseline (Table 53).

Conclusion

Mean and median changes in glucose during randomized treatment with quetiapine SR were small and similar to those seen with placebo treatment. Similar values were seen for patients with documented fasting. The incidences of patients observed with shifts from normal glucose levels at baseline to high levels at end of treatment was 8.0% in the placebo group and 4.1% in the quetiapine SR group. The mean changes in glucose regulation variables were small during the open label treatment period and not clinically meaningful.

Post-hoc analysis

The same post-hoc analysis that was performed for Study 126/127 was performed for Study D1444C0004.

Results of the post hoc evaluation, placebo-controlled, randomized treatment phase

Overall, the evaluation of the three listings combined identified one patient in the quetiapine group (Patient E1402001) and none in the placebo group with data suggesting emergence of diabetes during randomized treatment.

Results of the post hoc evaluation, open-label stabilization phase

During the open-label stabilization phase, the evaluation identified three patients with data suggesting emergence of diabetes during open-label treatment (Patients E1201011, E1303004, E1402013), and one patient with data suggesting exacerbation of pre-existing diabetes during open-label treatment (Patient E1104004).

5.4 Completed trials not contained in Safety 9

5.4.1 Trial D1441C00149 (Pediatric trial)

One study recently completed in pediatric patients (149) contains fasting glucose data. Since the focus of this document is glucose dysregulation in adult patients the data from this trial will not be discussed but is included in Appendix B. Data from an ongoing long term pediatric trial (150) will be available by second quarter of 2008 and the pediatric glucose data will subsequently be reviewed.

5.4.2 Trial 5077IL/0114 (CAFÉ study)

This was a 52-week, randomized, double-blind, flexible-dose, multicenter study comparing the efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of first episode psychosis.

5.4.2.1 Adverse event data

There were no reports of DKA or diabetic coma in any of the treatment groups. There was one report (0.7%) of "Glucose tolerance impaired" in a quetiapine (QTP) treated patients and there was one report each (0.8% each) of "Blood glucose increased", "Diabetes mellitus NOS", "Glucose urine present", and "Hyperglycaemia NOS" in the olanzapine group (OLZ). There were no glucose related adverse events reported in the risperidone (RIS) group.

5.4.2.2 Laboratory data

Fasting glucose and HbA_{1c} measurements were taken at baseline and weeks 12, 24, and 52.

Baseline glucose and HbA_{1c} data is presented in Table 54 below.

Table 54 Baseline fasting glucose and HbA_{1c} data

		Quetiapine N=134	Risperidone N=131	Olanzapine N=130	Total N=395	P value
Fasting glucose	Mean (SD)	85.77 (9.25)	86.53 (12.31)	8.33 (9.83)	85.88 (10.53)	0.6824
	Median	84.00	85.00	87.00	85.00	
	Min, max	64.00, 114.00	51.00, 157.00	56.00, 129.00	51.00, 157.00	
Fasting glucose ≥100 mg/dL	N (%)	8 (10.39)	6 (7.59)	4 (5.13)	18 (7.69)	0.4367
HbA_{1c}	Mean (SD)	5.17 (0.48)	5.22 (0.80)	5.15 (0.42)	5.18 (0.59)	0.8370
	Median	5.15	5.10	5.20	5.10	
	Min, max	3.90, 7.50	4.00, 11.20	3.90, 6.40	3.90, 11.20	
HbA_{1c} >6.1%	N (%)	4 (3.13)	4 (3.23)	1 (0.80)	9 (2.39)	0.3741

Table 55 below shows the mean change in fasting glucose and HbA_{1c} at 12 and 52 weeks and the number (%) of patients with a fasting glucose ≥100 mg/dL or an HbA_{1c} >6.1% at weeks 12 and 52.

Table 55 Change from baseline at 12 and 52 weeks

		QTP W12	QTP W52	RIS W12	RIS W52	OLZ W12	OLZ W52
Fasting ≥8 hours	N (%)	56 (62.9%)	74 (72.5%)	48 (58.5%)	70 (72.2%)	59 (62.1%)	78 (75.0%)
Fasting glucose	LSM (SE)	3.77 (1.42)	6.17 (1.67)	1.52 (1.50)	4.77 (1.70)	1.73 (1.39)	8.63 (1.59)
Fasting glucose ≥100 mg/dL	N (%)	5 (12.5%)	10 (20%)	1 (2.8%)	6 (12.5%)	5 (11.9%)	14 (25.5%)
HbA_{1c}	LSM (SE)	0.04 (0.03)	0.15 (0.04)	-0.02 (0.03)	0.06 (0.04)	0.00 (0.03)	0.16 (0.04)
HbA_{1c} >6.1%	N (%)	3 (3.4%)	5 (5.0%)	3 (3.7%)	4 (4.2%)	1 (1.1%)	4 (3.9%)

LSM least squares mean, OLZ olanzapine, QTP quetiapine, RIS risperidone, SE standard error W week.
All outcome variables for 12 and 52 week analyses were based on the maximum value for each patient up from baseline up to 74-94 or for each continuous outcome variable at each time point, we fit a univariate linear model with a predictor for therapy.
Note. Analysis included all subjects with both a baseline and at least one post-baseline observation for the analysis variable.

After 12 weeks of therapy the LSM change in fasting glucose was small in all three treatment groups (quetiapine = 3.77 mg/dL, risperidone = 1.52 mg/dL, olanzapine = 1.73 mg/dL). There were five patients each in the quetiapine and olanzapine group who had a fasting glucose ≥100 mg/dL (quetiapine = 12.5%, olanzapine = 11.9%) and one patient in the risperidone group (2.8%). The LMS change in HbA_{1c} was small at 12 weeks as well (quetiapine = 0.04%, risperidone = -0.02%, olanzapine = 0.00%). There were three patients in both the risperidone and quetiapine groups who had an HbA_{1c} >6.1% after 12 weeks of therapy (risperidone = 3.7%, quetiapine = 3.4%) and one patient in the olanzapine group (1.1%).

After 52 weeks of therapy the LMS change in fasting glucose was greatest in the olanzapine group (8.63 mg/dL) followed by the quetiapine (6.17 mg/dL) and risperidone groups (4.77 mg/dL). There were 14 patients (25.5%) in the olanzapine group, 10 patients (20%) in the quetiapine group, and six patients (12.5%) in the risperidone group who had a fasting glucose >100 mg/dL. The LMS change in HbA_{1c} at 52 weeks was similar in the olanzapine (0.16) and quetiapine groups (0.15). The LMS change in the risperidone group was 0.06. The number of patients who had an HbA_{1c} >6.1% after 52 weeks of therapy with similar in all three groups (quetiapine = 5 [5.0%], risperidone = 4 [4.2%], olanzapine = 4 [3.9%]).

6. IN-HOUSE SAFETY DATABASE

6.1 Clintrace

Clintrace is AstraZeneca's global clinical drug safety database that contains all adverse events reports, from spontaneous sources (eg, health care professionals, Regulatory Authorities, literature, consumers and others), whether or not they meet regulatory authorities' definition of serious, and reports from clinical study use that are defined as serious. Non-serious reports from clinical study use are usually only entered onto the clinical study database.

6.2 Search strategy

A search of the safety database on 01 March 2007 was performed to identify adverse event reports (completed) (from sources other than AstraZeneca sponsored studies) of glucose dysregulation (including DM, DKA, diabetic coma, and/or exacerbation of DM) associated with the use of SEROQUEL. The MedDRA (version 9.1) preferred terms used in the search are listed in Appendix A Table A174.

Since the time of this search (01 March 2007) and as of 30 March 2007, AstraZeneca has received an additional 54 initial legal reports and 2503 legal follow-up reports. For almost all of these legal cases, the information provided is in the form of a civil complaint containing no clinical information or a plaintiff fact sheet. AstraZeneca is treating these plaintiff fact sheets as report that are medically confirmed and they are submitted to regulatory authorities as such.

6.3 Search results

6.3.1 Overview

A total of 1679 reports were identified from the safety database search on 01 March 2007. These 1679 reports contained the following 2305 MedDRA preferred terms (Table 56 below).

Table 56 MedDRA preferred terms contained in 1679 reports of glucose dysregulation

Preferred term	Number of cases
Blood glucose	1
Blood glucose abnormal	15

Table 56 MedDRA preferred terms contained in 1679 reports of glucose dysregulation

Preferred term	Number of cases
Blood glucose fluctuation	14
Blood glucose increased	246
Diabetes mellitus	935
Diabetes mellitus inadequate control	12
Diabetes mellitus insulin-dependent	47
Diabetes mellitus non-insulin-dependent	194
Diabetic coma	186
Diabetic complication	1
Diabetic hyperglycaemic coma	1
Diabetic hyperosmolar coma	7
Diabetic ketoacidosis	243
Gestational diabetes	10
Glucose tolerance impaired	17
Glucose urine	1
Glucose urine present	3
Glycosylated haemoglobin increased	13
Hyperglycaemia	341
Insulin-requiring type II diabetes mellitus	2
Insulin resistance	5
Ketoacidosis	11
Total events	**2305**

NB: One report may contain multiple preferred terms, therefore the total number of events is larger than the total number of reports.

These reports will be discussed in the following manner:

Reports of DKA

Reports of diabetic coma

Reports of New onset of DM, hyperglycemia in patients with no known history of DM, and exacerbation of DM

Reports of gestational diabetes

Reports from clinical trials not sponsored by AstraZeneca

Within each of the first four categories outlined above, the reports will be divided into: 1) Medically confirmed reports, 2) Non-medically confirmed reports, and 3) Legal reports.

Non-medically confirmed reports are those reports that have been received from a consumer and have not been confirmed by a health care provider. Legal reports are divided into two sub –categories: Medically confirmed and Non-medically confirmed. Those reports received in the form of a civil complaint are considered not medically confirmed until follow-up information from a health care provider, in the form of medical records, or a plaintiff fact sheet has been received.

Table 57 below gives an overview of the diabetes related reports that will be discussed below.

Table 57 Overview of diabetes related reports

	Medically confirmed	Not medically confirmed	Legal	Total
DKA/ketoacidosis	65[a]	1	188	254
Diabetic coma	11	1	4	16
New onset DM or hyperglycemia	464	153	611	1228
Exacerbation of DM	91	46	3	140
Gestational DM	10	0	0	10
Post marketing study reports	31	0	0	31
Total	**672 (40%)**	**201 (12%)**	**806 (48%)**	**1679**

a Includes three reports of ketoacidosis, which do not describe DKA. DKA=diabetic ketoacidosis, DM=diabetes mellitus. Note: Reports are counted in only one category.

6.4 Diabetic ketoacidosis/Ketoacidosis

Two hundred forty-three reports contained the MedDRA preferred term "Diabetic ketoacidosis" and 11 reports contained the MedDRA preferred term "Ketoacidosis". Three of these reports containing the MedDRA preferred term "Ketoacidosis" did not describe DKA and will not be discussed further (2003UW08028, 2002GB01741, 2004SE04751). Thus, 251 reports will be discussed below. Full narratives for the medically confirmed and non-medically confirmed (non-legal) reports are contained in Appendix D. For legal cases, only those reports, which are medically confirmed have full narratives in Appendix D.

6.4.1.1 DKA in patients with no known history of DM (238 reports)

Two hundred thirty-eight reports described patients with no known history of DM or DKA. These reports are divided into the following categories: Medically confirmed (49), Non-medically confirmed (1), and Legal cases (188; some treated as "medically confirmed" by AstraZeneca as noted below).

6.4.1.2 Medically confirmed cases (49 reports)

Forty-nine of the 238 reports of DKA were medically confirmed and are summarized in Table 58 below. Seven of these reports described fatal outcomes (2001UW12078, 2002AP01772, 2002AP02883, 2002UW08229, 2003GB01346, 2004AP01695, 2005UW15699).

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
2006USW013390 Ketoacidosis	44/F	Both unk	Not provided	Unspecified anti-HTN meds	Baseline labs: Not provided After 3 days of polydipsia & feeling "a little different" Pt hospitalized w/ DKA. Outcome & if Seroquel contd, unk. No other info.
2006USW011090 DKA	28/F	200 mg/day; TTO unk	Not diabetic prior to Seroquel	None	Baseline labs: Not provided Pt taking ziprasidone & then started Seroquel. Pt hospitalized for DKA. Outcome & if Seroquel contd: unk. No other info
2006USW69586 DKA, DM	52/M	400 mg/day; about 2 y	Obesity (BMI=37.2), hypertipidemia, schizophrenia (Hx hx of smoking or alcohol use, no family hx of DM)	None	Baseline labs: Not provided After about 2 y on Seroquel FBS=126. About 2 mos later Pt hospitalized w/ 3 day hx of vomiting, polydipsia, & polyuria. Labs: pH of 7.09, HCO_3=9, BG=700, slight leukocytosis (WBC=14,000) w/ L side shift, urine++ ketones, 3+ sugar. Tx = insulin, hydration, & abx. Seroquel d/c'd about 1 mo later. 1 wk later BG reported to be stabilized (no lab values) but Pt not yet rec'd. No other info
2006USW67200 DKA	50/M	25-200 mg/day; 29 days	Polysubstance abuse, bipolar disorder	Lithium[c]	Baseline labs: Not provided Day 49: hospitalized w/ DKA. Seroquel alone d/c'd 2 days later. Pt rec'd (no lab values). Outcome unk. No other info.
2006USW04923 DKA	56/F	400 mg/day; 12-18 mos	"Moderately obese"	Clozapine[c,f]	Baseline labs: Not provided After 12-18 mos on Seroquel & 3 mos on clozapine, Pt hospitalized w/ DKA. Seroquel d/c'd, clozapine contd. Outcome unk. No other info.
2006USW04386 DKA	25/M	Both unk	Not provided	Not provided	Baseline labs: Not provided Pt hospitalized w/ spontaneous ketoacidosis-insulin dependent diabetes. Outcome & if Seroquel contd: unk. No other info.
2006GB000605 DKA	41/M	Both unk	Schizophrenia	Not provided	Baseline labs: Not provided Pt developed DKA. At time of report, Pt improving w/ unspecified tx but still unable to communicate. Unk if Seroquel contd. No other info.

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
2006AG01655 DKA	25/M	100-600 mg/day; 2-3 mos	Schizophrenia *No family or personal hx of DM*	chlorpromazine[6,6]	Baseline labs: BG = 100 mg/dL, BMI = 39.19. Pt *started haloperidol & biperiden*. 2 wks later Pt hospitalized w/ n/v, BG=546, urine=+ glucose & ketones, blood pH = 7.06. Seroquel d/c'd. Tx=insulin. Pt discharged 1 wk later; 4 mos later Pt continues on insulin, BMI=36.5, FBS=333 mg/dL. No other info.
2005UW05375 DKA	34/M	Both unk	Not provided	Not provided	Baseline labs: Not provided Pt developed DKA, pancreatitis. Outcome & if Seroquel contd. unk. No other info.
2004UW23264 DM, DKA	27/F	100 mg/day/ >4 y	HTN, diastolic dysfunction, wt ↑	lpratropium/ albuterol[6c]	Baseline labs: Not provided After 4 y on Seroquel Pt went to ER c/o not feeling well x 4 days, weakness, malaise, myalgia, excessive thirst, polyuria, ↓ appetite, blurry vision, mild headache, body ache, ↑ fatigue. BG = 1182, BUN = 39, creatinine = 1.7. Dx = new onset DM, DKA & ARF. Tx = IV insulin. Seroquel contd. Pt reportedly rec'd w/ sequelae (unspecified). No lab values or other info was provided.
2004UW22295 DKA	?/?	Both unk	Not provided	Not provided	Baseline labs: Not provided Pt developed DKA. Outcome & if Seroquel contd. unk. No other info.
2004UW18933 DKA	58/F	100 mg/day; 112 days	Family hx of DM	None	Baseline labs: Not provided After 3 mos on Seroquel: Pt w/ excessive sleepiness, ↑urination, ↑water consumption. Day 112: Slurred speech. Hospitalized w/ DKA & "almost diabetic coma" (BG = 577). Tx = IV insulin. Seroquel d/c'd. Pt rec'd & discharged from hospital on glucagon 3 days later. 1 mo later BG normal (no labs) & glucagon d/c'd. Another 2 mos later BG normal (no labs) w/o meds. No other info
2004UW14727 DKA Diabetic hyperosmolar coma NIDDM	62/F	300 mg/day; 103 days	Hyperlipidemia, HTN No family hx of DM	None	Baseline labs: BG = 80, [Hb] = 27.5 Day 103: severe DKA, hyperosmolar coma. Type II DM (BG = 700). Tx = insulin, metformin. Seroquel d/c'd. Pt rec'd 4 days later from DKA & hyperosmolar coma. 1 wk later Pt discharged from hospital. Pt contd on oral antidiabetics; BG about 120. Pt not rec'd from Type II DM. No other info.

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
2004USW13433 DKA	45/M	Dose unk/ >1 y	Not provided	None	Baseline labs: Not provided 1 y: Hospitalized w/ DKA. Seroquel d/c'd, risperidone started. Outcome unk. No other info.
2004GB02613 DKA	??/F	Both unk	Wt ↑	Not provided	Baseline labs: Not provided Wt gain on olanzapine. Olanzapine d/c'd. After unk time on Seroquel Pt had DKA. Seroquel d/c'd. Pt rec'd (no lab values). Seroquel restarted w/o problems. No other info.
2004GB00610 DKA	17/M	≤ 100 mg/day; 10 days	Smoker	None	Baseline labs: Not provided Day 11: ↑BP, confusion, drowsiness, polyuria, polydipsia, ketonuria, ↑thirst. BG = >50 mmol/L. Dx = DKA. Tx = IVF, insulin (sliding scale). Seroquel d/c'd. Pt rec'd 17 days later. Pt was concomitantly taking risperidone. No other info
2004AP01695 DKA	50/M	200 mg/day; 213 days	Hyperlipidemia (TRIG = 400 mg/dL)	None	Baseline labs: Not provided Day 217: Pt's father stated that Pt bed-ridden x 4 days. Since that time Pt had drunk water but not eaten full meals. Face swollen, pus running out of ears, vomiting. Reported that Pt may have taken non-prescription meds prior to Day 213. Hospitalized w/ ketoacidosis (total ketones = 12,000 mg/dL) & hypothermia (temp = 33.7°C). Next day Pt improved after tx w/ insulin & IVF. Pt developed fever (39°C), hypotension, shock. Condition worsened & Pt died next day. Autopsy not performed. COD = Acute circulatory failure, cardiac failure. No other info
2003USW14578 DKA	26/F	500 mg/day; TTO unk	Not provided	None	Baseline labs: Not provided Pt found confused, hospitalized w/ DKA. Outcome & if Seroquel contd. unk. No hx of DM. No other info.
2003USW05594 DKA	42/M	1000 mg/day; TTO unk	Not provided	Not provided	Baseline labs: Not provided Pt had diabetic acidosis. Seroquel contd. Outcome unk. No other info.

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
2003GB01346 DKA	18/F	200 mg/day; 97 days	Obesity	Not provided	Baseline labs: Not provided After ink time on Seroquel Pt switched to olanzapine. Pt had Wt ↑ on olanzapine & changed back to Seroquel after 106 days. After about 1 mo on Seroquel: Fungal infection of groin (noted to be associated w/ DM). Day 97 on Seroquel: Abdominal pain, vomiting. Hospitalized after collapsing. Labs showed HBG (no labs), very acidic blood (no lab values). Tx started (unspecified) Pt developed irregular HR & despite attempts to resuscitate Pt died on Day 5 of hospitalization. Autopsy: COD = DKA, 2° cause = atypical antipsychotic therapy. No other info
2003AP04434 DKA Hyperglycemia	72/M	50 mg/day; see comments	Hyperlipidemia	None	Baseline labs: BG = 132 mg/dL Day 12: ↓LOC, LOE, sleeping ↑. Seroquel & ibuprofen d/c'd. 2 days later Pt exhausted & rejected hospitalization. Next day Pt hospitalized. Tx = IVF (Pt had not eaten for 2-3 days). About 1 hr later BG = 897 mg/dL (repeat = 973 mg/dL). Dx = DKA, hyperglycemia. Serum ketone = >60 mg/dL. ABG: pH = 7.294, HCO_3 = 16.7, BE = -8.8 mEq/L. Tx = IVF, insulin. Pt switched to SC insulin followed by oral antidiabetics. Next day LOC improving, FBS = 198 mg/dL. Discharged from hospital on glibenclamide w/ good BG control (BG = 90 mg/dL). No other info
2003AP04386 DKA NIDDM	34/M	600 mg/day; ≈ 11 mos	Family hx DM, obesity No prior hx of HBG or DM	chlorpromazine[c1]	Baseline labs: HbA_{1c} = 5.2% Day 2: HbA_{1c} = 5.6%, FBS = 98 mg/dL. Day 71: FBS = 105 mg/dL, HbA_{1c} = 5.9%. Day 269: HbA_{1c} = 6.8%, Pt drinking soft drinks d/t extreme thirst, general malaise. 2 mos later: malaise ↑, Wt ↓ 10 kg. Day 331: Convulsive seizure w/loss of consciousness. BG = 799 mg/dL, urine ketone = 3+. Dx = DKA d/t soft drink. LOC improved. Tx = IVF, insulin drip. BG↓ (200s mg/dL). All meds d/c'd. Next day urine ketone neg & Pt rec'd. HbA_{1c} = 13.6%. Insulin switched to SC. 12 days later BG improved (100-250 mg/dL). No other info.
20021IW14814 DKA DM	Unk/F	400 mg/day; 328 days	Obesity (BMI = 36.51, ↑BG on olanzapine	Lithium[c]	Baseline labs: Not provided On olanzapine x 2-3 y. D/C'd olanzapine d/t ↑BG & started Seroquel. Day 328: DM, DI, pancreatitis. On ink date Pt had DKA: apnea, dyspnea, BG = 1400. All meds d/c'd. Pt not yet rec'd. No other info.

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
20021W09406 DKA	36/M	400 mg/day; 32 days	No family hx of DM	None	Baseline labs: Not provided Day 32: Hospitalized w/ DKA (BG = 1544 mg/dL, ABG pH = 7.24, K^+ = 6.1, BUN = 64, creatinine = 3.5, UA = ketones). Downstrtn infusion. Seroquel d/c'd temporarily. Pt rec'd in 3 days. Unk if therapy w/ Seroquel restarted. No other info.
2002UW08229 DKA Diabetic renal failure	40/F	200 mg/day; 286 days	Smoker; BMI = 28.3; cocaine/marijuana/crack abuse	None	Baseline labs: Reported that UA, FBS, metabolic panel "WNL" < 1 y before starting Seroquel 8 mos: Fatigue & lenergy. Pt went to MD but did not return for lab work. Day 286: Pt found dead. Neighbor reported: Pt traded drugs (cocaine/crack/marijuana) for use of her car. Autopsy: COD = DKA, diabetic renal failure, aspiration of vomitus. Other findings on autopsy: fatty liver, cholelithiasis, congestion of viscera, obesity. Labs on autopsy (vitreous): Na^+ = 146 mmol/L, K^+ = 25.5 mmol/L, Cl = 107 mmol/L, BUN = 86.5 mg/dL, BG = 947 mg/dL, creatinine = 2.7 mg/dL, UA = positive for cocaine metabolite. Heart blood positive for cocaine, ethanol, acetone & sertraline. No further blood tox done.
2002GB02627 DKA DM	44/M	400 mg/day; 99 days	Not provided	None	Baseline labs: Wt = 96.3 kg (8 mos prior to Seroquel) Day 99: DM & hospitalized dt early DKA. Tx = insulin. Pt also gained 32.2 kg over 1 y time. Seroquel contd. Pt not yet rec'd 1 mo later. No other info.
2002GB01254 DKA	?/M	300 mg/day; 14 mos	Obesity (BMI = 48.7)	Olanzapine[3,4]	Baseline labs: Not provided Clozapine d/c'd & therapy w/ Seroquel & olanzapine started. 14 mos later: Hospitalized w/ DKA, dehydration, acidosis. BG = 46 6, HbA_{1c} = >12%. Type I or II DM suspected. Pt reported to be increasingly obese. Tx = insulin. Both Seroquel & olanzapine contd. Pt not yet rec'd.

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
2002AP02883 DKA	36/F	200 mg/day; 452 days	Not provided	None	Baseline labs: Not provided 15 mos on Seroquel: Sxs of common cold (diarrhea, vomiting, retching, vomiting, pyrexia [38-39°C]). Next day: Fever resolved. GI sxs contd. & anorexia occurred. Next day: GI sxs contd., Tx = IVF. That evening Pt drinking "amazing" amount of water & developed difficulty breathing. Seen by MD next day, chest/abdominal x-rays = normal, BUN = 49, creatinine = 4.9. Dx = psychiatric sxs. Sent home. That evening Tdyspnea. Pt had "sudden change" in condition & ambulance called. Pt had cardiac arrest & died. Reported that body WI not recently changed, eating habits normal. Seroquel contd until death. Autopsy: COD = ARF. Reporter commented: Likely DIG followed ARF & dyspnea was sx of ketoacidosis or metabolic disturbance; DM may have been triggered by common cold; cardiac arrest probably occurred dt hyperkalemia. No other info.
2002AP02304 DKA	31/M	600 mg/day; 18 mos	Obesity (BMI = 30.9), excessive consumption of sweetened drinks. No family hx DM.	Chlorpromazine[b,c]	Baseline labs: Not provided *After >15 mos on Seroquel Pt did not visit MD. Mother picked up meds.* Pt's sxs had been ↑ing but was not reported to MD. Thought that Pt was drinking =5↑ sweetened drinks a day. Pt c/o thirst ↑IG & ↑Bx, urin. After 18 mos on Seroquel Pt c/o lisp & limb weakness. 2 days later dysarthria & limb weakness ↑. 3 days later Pt taken to hospital. Pt "almost conscious" & dehydrated. BP = 108/86, HR = 128 bpm, temp = 37.9°C, brain CT = normal, BG = 1280 mg/dL, urine ketone body = 60 mg/dL, urinary sugar = 4+. ABG: pH = 7.27, pCO2 = 22.3, pO2 = 155, HCO3 = 9.9, BE = 15.3, AG = 34.1, Lac = 14, Na+ = 147, K+ = 5.5, Cl = 103, Ca = 1.35, amylase = 96, BUN = 40, creatinine = 2.0, sOsm = 436, uOsm = 746), urinary ketone body = 3+, WBC = 16.7. Tx = insulin infusion, IVF. All meds d/c'd. Following day BG = 160-200 mg/dL. Na+ ↑, K+↓. Following day Seroquel restarted. Following day electrolytes stable. Pt rec'd & discharged. Family has not communicated w/ MD so Pt's status unk. No other info.

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
2002AP01772 DKA	51/M	300 mg/day; 292 days	Excessive consumption of sweetened drinks	None	Baseline labs: Wt = 57 kg (BMI = 21.6), urine=neg for glucose. Pt started tx w/ risperidone & 43 days later Seroquel added. Day 130 of Seroquel, Wt 14 kg (BMI = 26.9), mild anemia, HR86, BG = 123 mg/dL, HbA $_{1c}$ = 4.8% (not fasting). Day 292: Hospitalized w/ disturbed consciousness. BG = 1178 mg/dL, HCO$_3$ = 3.0 mmol/L, Na$^+$ = 116.3 mmol/L, K$^+$ = 6.55 mmol/L, ABG: BE = -25.2, pH = 7.055. Dx = DKA. All meds d/c'd. Tx = IVF, insulin. Next day BG = 239 mg/dL, Pt still comatose. That evening BG = 545 mg/dL, shock occurred. Tx = dopamine. Pt died next day of circulatory failure. No autopsy performed. Pt's sister reported Pt drinking 4L/day of Coca-cola everyday x 5 wks & Pt lost Wt rapidly during that time. No other info
2001UW14447 DKA	13/M	300 mg/day; 1-2 mos	Morbid obesity (BMI = 38.7) Possible family hx DM	None	Baseline labs: Not provided While on Seroquel (duration unk) Pt developed cardiac situation (starting w/ arrhythmia & progressing to ischemia). Pt scheduled for cardiac cath. Sometime later Pt hospitalized w/ DKA. Pt discharged on insulin. Pt in foster care (may be family hx of DM in grandparents & mother). Seroquel contd. Pt outcome unk. No other info.
2001UW12263 DKA Hyperglycemia	30/M	300 mg/day; TTO unk	Not provided	Olanzapine[b,c,f]	Baseline labs: Not provided Pt had abdominal pain, polydipsia, polyuria. That mo Pt developed DKA, hyperglycemia. Tx = glyburide, insulin. Pt reported to have received olanzapine (dates unk). Seroquel contd. Outcome unk. No other info.
2001UW12078 DKA	57/?	Both unk	Not provided	None	Baseline labs: Not provided After unk time on Seroquel & risperidone Pt developed DKA & died. No other info
2001UW02743 DKA	48/M	Dose unk; "few mos"	Hyperlipidemia	None	Baseline labs: Not provided *After few mos on Seroquel*, Pt returned to psych unit (following leave) lethargic. BG = 630 mg/dL, urine ketone positive. Pt hospitalized. Tx = IVF, insulin. C-peptide = "low normal". Anti-GAD = pending. Seroquel cont'd x 1-2 days & then switched to haloperidol. Pt discharged after 2 wks. BG = 150 mg/dL on insulin. No other info.

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
20001AW02905 DKA	18/?	Both unk	Not provided	None	Baseline labs: Not provided Pt hospitalized w/ DKA (BG = 1200), acute pancreatitis, ↑ lipids. Pt outcome & if Seroquel contd. unk. No other info.
2000LW01164 Ketoacidosis DM BG increased	43/M	200 mg/day; "few wks"	Not provided	None	Baseline labs: Not provided Over "a few wks" Pt developed polyuria, polydipsia, unexplained wt loss (>30 lbs). FBS = >200. Dx = DKA, new onset DM. Seroquel contd. Pt outcome unk. Pt has no family hx of DM. No other info.
1999AP05757 DM Ketoacidosis	25/M	750 mg/day; 21 mos	Not provided	Lithium[2]	Baseline labs: Not provided 21 mos: Hospitalized w/DM & ketoacidosis. Also reported Wt↑ (amount unk). Tx = insulin. Rec'd w/ "residual effects". Seroquel contd. No other info.
2005CH02396 DKA	33/M	600 mg/day; TTO unk	Not provided	Olanzapine[1,e,f]	Baseline labs: Not provided Pt on olanzapine for unk amount of time. Seroquel started, olanzapine dose↓ & dc'd 1 mo later. Unk time later: Pt developed DKA. Tx = insulin. Pt not yet rec'd. Unk if Seroquel contd. No other info.
2005LW15114 Ketoacidosis BG ↑	35/?	300 mg/day; TTO unk	Not provided	Not provided	Baseline labs: Not provided Pt developed ketoacidosis (BG = 3700). Outcome & if Seroquel contd. unk. No other info.
2005LW17274 DM Ketoacidosis	79/F	Dose unk; 4 mos	Not provided	Not provided	Baseline labs: Not provided 4 mos: DM & ketoacidosis. Pt not yet rec'd. Unk if Seroquel contd. No other info.
2005LW15699 DKA	45/M	Both unk	Not provided	Olanzapine[d,e,f]	Baseline labs: Not provided Pt hospitalized w/ DKA. Also had ↑lipids & developed severe respiratory complications. Pt died on unk date. Aspiration presumed COD. No other info.
2006LW14876 DKA UA	46/F	300 mg/day; >14 mos	HTN	None	Baseline labs: Not provided >14 mos: BG = 953, WBC = 16, Group D Enterococcus infection. Outcome & if Seroquel contd. unk. No other info

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
20051WI13318 DKA	48/M	600 mg/day, 20 days	Fatty liver, hyperlipidemia, obesity (BMI = 30.2)	None	Baseline labs: Not provided Day 20: DKA (ros = lethargy, "falling out"). Random BG = 609, ALT = 63, LDH = 159. Pt hospitalized. Seroquel d/c'd. Tx = metformin, insulin. Pt rec'd. No other info
20051WI09324 DKA DM	58/F	1000 mg/day, 1633 days	HTN, obesity (BMI = 50)	None	Baseline labs: Not provided 4 y 4 ½ mos: Wt ↑ 117 lbs (BMI = 68.9). 1 mo later: Weakness, unable to walk, thirst, ↑urination, SOB, ataxia. Pt denied n/v, abdominal pain, diarrhea, fever, chills, cough, sputum production, dysuria. Exam: tachypnea, mild distress, BP = 123/86, RR = 28, large amounts of redness in skin folds w/ small pustules likely d/t fungal infection & 2° bacterial infection. Hospitalized for morbid obesity, new onset DM w/ ketoacidosis & rash. Tx = IVF, abx, fluconazole, insulin. Pt improved & started on oral antidiabetics, Seroquel & carbamazepine d/c'd (date unk). Pt able to maintain BG ≤hrw 200s. No other info.
2005AP05975 DKA	52/M	200 mg/day; 7 days	Smoker (4 pks/day), obesity (BMI = 33.6) No family hx DM	Lithium[b]	Baseline labs: BG = 109 mg/dl. 3 wk: Hospitalized in "drowsy state". BG = 968 mg/dl., urine ketone body = 3+. ABG: pH = 7.248, pCO_2 = 17.6, HCO_3 = 7.5, BE = -16.54. Dx = metabolic acidosis. Tx = IVF, insulin. No polyuria, polydipsia, polyphagia, weakness, fatigue, blurred vision, Wt loss. Next day BG = 352 mg/dl. Seroquel d/c'd. Tx = insulin 6 days later: BG = 218 mg/dl. Another 2 days later: Started oral pioglitazone & 1 mo later metformin. BG gradually ↓ after that & insulin d/c'd. No other info.
2005AP04083 DKA	28/M	400 mg/day; 20 days	Not provided	Olanzapine[b,c]	Baseline labs: Not provided Seroquel & olanzapine started same day. After 20 days: DKA w/ 3 wk hx of Wt↓ (10 kg), polyuria. Both meds d/c'd & aripiprazole started. Tx = IVF, insulin. Reported that Pt's lab tests = ↑BG & ↓K+ on unk date (unk if prior to Seroquel). Pt rec'd. No other info.

Table 58 Reports of DKA in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose TTO	Relevant medical history	Relevant con meds	Comments
2005AP03905 DKA DM	29/F	200 mg/day; 352 days	Family hx of obesity & DM, hepatic steatosis, hyperlipidemia, smoker, obesity (BMI = 31.6)	None	Baseline labs: BG = 87 mg/dL, HbA_{1c} = 5.7% 9 mos: Nausea, thirst, polyuria. 1 mo later: Vomiting. Day 343: Endoscopy suggests gastritis. 4 days later: Echo = fatty liver. Day 352: BG = 436 mg/dL, ↓Na+, ABG = acidosis, ↑K+. Dx = DKA. Tx = IVF, insulin. Polyuria, polydipsia, polyphagia, fatigue reported. Seroquel, risperidone, carbamazepine d/c'd. Next day: Nausea improved. Pt able to eat. Following day: Urine ketone 4+. Next day: Pt rec'd from hypokalemia. DKA, hyponatremia, Risperidone had started 2 wks after Seroquel. No other info.
2005AC00445 Ketoacidosis Hyperglycaemia	46/F	300 mg/day; TTO unk	Not provided	Oral contraceptive[b,i]	Baseline labs: Not provided Pt had severe coma/shock, acetonemia, hyperglycaemia, ketoacidosis. BG = 58.1 mmol/L, ABG pH = 7.1. Tx = insulin infusion. Unk if Seroquel cont'd. Pt recovering. No other info.
2006AC00319 DKA	51/F	400 mg/day; >2 y	HTN, obesity (BMI = 31), hyperlipidemia No family hx DM	Lithium[c]	Baseline labs: BG = 6.1 mmol/L (date unk but reportedly prior to Seroquel) After about 2 y on Seroquel Pt had confusion x few days & became comatose. BG = 53 mmol/L, HbA_{1c} = 7.2%, urine ketones = 3+. No evidence of infection. Tx = insulin infusion (15-20 units/hr). Anti-GAD = normal x 2. Seroquel d/c'd. Pt hospitalized x 3 mos. Even after becoming euglycemic, urine output >3L/day w/ low specific gravity. Dx = diabetes insipidus d/t tx w/ lithium. 6 mos after onset Pt tx w/ diet alone. FBS <7 mmol/L, HbA_{1c} = 5.1 to 5.5%. No other info.

a PTs refers to diabetes related PTs only.
b Relevant med history refers to history which may contribute to development of DM/DKA.
c Relevant concomitant medications refers to those medications which may have contributed to the development of DM/DKA.
d For which hyperglycaemia has been reported.
e For which DKA has been reported.
f For which DM has been reported.
g For which altered glucose tolerance has been reported.
h For which reduced glucose tolerance has been reported.
i For which insulin resistance has been reported.

ABG arterial blood gas, abx antibiotics, AG glycemic glubylic, ALT alanine transaminase, ARF acute renal failure, BE base excess, BG blood glucose, BMI body mass index, BP blood pressure, BUN blood urea nitrogen, c-o complained of, Ca calcium, Cl chloride, COD cause of death, con meds concomitant medications, contd continued, CT computed tomography, d/c'd discontinued, d/t due to, DI diabetes insipidus, DKA diabetic ketoacidosis, DM diabetes mellitus, dx diagnosis, ER emergency room, FBS fasting blood sugar, GI gastrointestinal, HbA_{1c} glycosylated hemoglobin, HCO3 bicarbonate, HR heart rate, HR heart rate, HTN hypertension, hx history, info information, IV intravenous, IVF intravenous fluids, K+ potassium, L left, Lac lactate, LDH lactate dehydrogenase, LOC level of consciousness, LOE lack of energy, MD medical doctor, meds medications, mo(s) month(s), n/v nausea/vomiting, Na+ sodium, pCO2 partial carbon dioxide, pks packs, pO2 partial oxygen, Pt patient, PTs preferred terms, rec'd recovered, RR respiratory rate, SC subcutaneous, SOB shortness of breath, s/Sem serum

One report (2006UW07200) described a positive dechallenge (following the event therapy with SEROQUEL alone is discontinued or the dose is lowered and the patient recovers without further treatment). This report described a 50 year old male patient who was taking SEROQUEL (25-200 mg/day), lithium (for which hyperglycemia has been reported), and escitalopram for seven weeks. No laboratory data was provided. The only information provided was that the patient was hospitalized with DKA, SEROQUEL alone was discontinued two days later, and the patient recovered. No information was provided regarding possible risk factors (ie, family history, BMI, smoking, hyperlipidemia). Given the limited information provided assessment of causality in this reported was not possible.

Two reports described a negative rechallenge (after the patient recovers from the event SEROQUEL is restarted and the event does not reoccur). One report (2004GB02613) described a female patient who experienced weight gain on olanzapine prior to starting SEROQUEL. Therapy with olanzapine was discontinued and the patient started SEROQUEL. After an unspecified amount of time on SEROQUEL the patient developed DKA. Therapy with SEROQUEL was discontinued and the patient was reported to have recovered (no laboratory data provided). It was reported that therapy with SEROQUEL was restarted (date unspecified) without any problems. No information about the patient's concomitant medications or possible risk factors were provided. The other report (2002AP02304) described a 31-year-old male patient who had been taking SEROQUEL (600 mg/day) for 18 months. The patient was thought to have been drinking about five litres of sweetened drinks a day. The patient was hospitalized with DKA (BG~1280 mg/dL). All medications were discontinued and the patient was treated with an insulin infusion. The next day the patient's BG was 160-200 mg/dl. Therapy with SEROQUEL was restarted the following day. It was reported that the patient recovered fully and was discharged from the hospital. This patient had a history of obesity (BMI=30.9 kg/m^2) and was also taking chlorpromazine (for which hyperglycemia and altered glucose control has been reported).

Of the remaining 46 reports, six were confounded by both risk factors/medical history and concomitant medications (2006UW04923: moderate obesity, clozapine [for which hyperglycemia and DM has been reported], 2003AP04386: family history of DM, obesity, chlorpromazine [for which altered glucose tolerance and hyperglycemia has been reported], 2002UW14814: obesity, increased BG while on olanzapine, lithium [for which hyperglycemia has been reported], 2002GB01254: obesity, olanzapine [for which DKA, DM, and hyperglycemia has been reported], 2005AP05975: obesity, smoking four packs/day, lithium [for which hyperglycemia has been reported], 2006AC00319: obesity, hyperlipidemia, HTN, lithium [for which hyperglycemia has been reported]).

Fourteen reports were confounded by risk factors and/or medical history (2005AP03905, family history of DM, hyperlipidemia, smoker, obesity, 2002AP01772: excessive consumption of sweetened drinks, 2004GB00610: smoker, 2006AC01055: obesity (BMI=39 kg/m^2), 2006UW09586: obesity, suspected hyperlipidemia based on concomitant medications, 2003GB01346: obesity, 2001UW14447: morbid obesity, possible family history of DM, 2004UW14727: hyperlipidemia, 2001UW02143: hyperlipidemia, 2003AP04434: hyperlipidemia, 2005UW11318: hyperlipidemia, obesity, 2005UW09324: obesity, HTN,

2004UW18935: family history of DM, 2004AP01695: hyperlipidemia). One of these reports (2004AP01695) described a patient who may have had an infection as evidenced by "purulent drainage from his ears and swollen face". Infections are common precipitating events for DKA, which can be the initial presentation of previously undiagnosed DM. Thus, the pre-existing risk and infection as precipitating events may be responsible for the DKA, which can be fatal, as it was in this case.

Seven reports were confounded by concomitant medications (2004UW23764: albuterol [for which DKA and hyperglycemia have been reported], 2001UW12263: olanzapine [for which DKA, DM, and hyperglycemia have been reported], 1999AP05757: lithium [for which hyperglycemia has been reported], 2005GB02396: olanzapine [for which DKA, DM, and hyperglycemia have been reported], 2005UW15699: olanzapine [for which DKA, DM, and hyperglycemia have been reported], 2005AP04083: olanzapine [for which DKA, DM, and hyperglycemia have been reported], 2005AC00445: oral contraceptive [for which reduced glucose tolerance and insulin resistance have been reported].

One report (2002UW08229) described a patient who died from DKA and diabetic renal failure, whereby the diabetic renal failure suggests some degree of chronicity of the DM (although DM was not reported as part of the patient's medical history). In addition, this patient had a history of illicit drug abuse, obesity, smoking, and fatty liver, thus confounding the case.

In another report (2002GB02627) it was unclear if the patient was obese prior to starting SEROQUEL. However, the patient weighed 90.3 kg (no height) seven months prior to the start of SEROQUEL treatment, and went on to gain 32 kg over the next 11 months. No laboratory data to support a diagnosis of DM or DKA was provided. SEROQUEL was continued and at the time of the report the event was ongoing.

One report (2002AP02883) described possible DKA, however, there was no laboratory data to support a diagnosis of DM or DKA, and a viral illness could have accounted for many of the patient's symptoms (diarrhea, vomiting, retching, vomiting, pyrexia) or precipitated a possible DKA.

Six other reports provided limited information with regard to medical history, concomitant medications, lab data, and/or details regarding the event; therefore an assessment of causality was not possible (2006UW13390, 2006UW11090, 2002UW09406, 2000UW02905, 2000UW01164, 2005UW14876).

The remaining 10 reports contained scant clinical detail and did not lend themselves to analysis (2006UW04386, 2006GB00605, 2005UW05375, 2004UW22295, 2004UW13431, 2003UW14378, 2003UW05594, 2005UW18114, 2005UW17274, 2001UW12078).

6.4.1.3 Non-medically confirmed cases (1 report)

One report (2006UW02754) was received from a consumer and not confirmed by the patient's physician despite attempts to obtain additional information. The patient reported that she

experienced an increased blood sugar and "expected DKA" and was to be admitted to the hospital. No laboratory data or any other information was provided. The outcome was unknown. Thus, this report contained scant clinical detail and did not lend itself to analysis.

6.4.1.4 Legal Cases (188 reports; one treated by AstraZeneca as "medically confirmed")

One hundred eighty-eight reports of DKA/ketoacidosis were received from attorneys on behalf of patients in the form of a civil complaint. Only one of these reports has been medically confirmed upon the receipt of medical records. This report (2004UW01147) described an 11-year-old patient who reportedly developed DM (probable Type 1) after six months of therapy with SEROQUEL and experienced DKA nine months later (about one month after therapy with SEROQUEL was discontinued). This report was confounded by the patient's history of hyperglycemia and a family history of DM. The patient's outcome was not provided.

The remaining 187 reports provided no medical information about the patients and therefore will not be discussed further (see Appendix A Table A175 for Case IDs).

6.4.2 DKA in patients with a known history of DM (13 reports)

Thirteen reports described patients with a pre-existing history of DM who experienced DKA. All of these reports were medically confirmed.

6.4.2.1 Medically confirmed cases (13 reports)

Three of these 13 reports described a fatal outcome (1998UW49554, 2002AP01163, 2001UW05726). All 13 reports are summarized in Table 59 below.

Table 59 Reports of DKA in patients with a history of DM

Report # PT[a]	Age/ Sex	Dose TTO	Relevant med hx[b]	Relevant con meds[c]	Comments
20061AW08816 DKA	??/?	Both unk	DKA, family hx DM	None	Baseline labs: Not provided After ≤ 9 mos on Seroquel BG=180. Seroquel d/c'd 4 mos later & restarted 3 mos after that. Sometime in the same month Seroquel was restarted Pt had DKA. At time of report, Pt had not rec'd & Seroquel contd. Pt was concomitantly receiving risperidone. No other info.
2005SE06781 DKA	46/F	300 mg/day; ~6 mos	Type II DM, HTN	None	Baseline labs: Not provided Started Seroquel & risperidone at same time. 6 mos later DKA. Tx = all meds d/c'd. Next day Pt rec'd. No other info
2005AP00945 DKA, DM	48/M	600 mg/day; TTO unk	Type II DM (well-controlled)	None	Baseline labs: Not provided Aggravation of DM & DKA. Tx = insulin. Labs (date unk). Hgb = 14.5, BG = 77. Pt rec'd 3 wks later. Status of therapy w/ Seroquel unk. No other info
2004AP06389 DKA	36/F	600 mg/day, 3 y 7 mos	DM, obesity (BMI = 39), HTN, hyperlipidemia, fatty liver	Lithium[d]	Baseline labs: Not provided 3 wks: FBS = 83 mg/dL. Over next 3 y FBS = 131, 103, 106, 121 mg/dL. 3 y 3 mos: HbA_{1c} = 4.8%. >3 ½ y: anorexia, malaise, drank juice throughout day. 1 wk later Pt had difficulty breathing, dysphoria, FBS = 282 mg/dL, HbA_{1c} = 11.7%. Pt hospitalized w/ DKA. Pt had newly diagnosed DM (date unk). Pt also had fatigue & polydipsia on unk date. All meds d/c'd. Pt rec'd about 7 wks later (no labs). No other info.
2003AP00312 DKA, Hyperglycemia	32/F	100 mg/day; 6 mos	Obesity, type II DM	Chlorpromazine[d]	Baseline labs: FBS = 134 mg/dL, HbA_{1c} = 5.3%. Pt d/c'd olanzapine & started Seroquel next day. Day 9: HbA_{1c} = 6.4%. Day 198: HbA_{1c} = 7.2%, FBS = 100-199 mg/dL, Seroquel d/c'd. 2 mos later Pt had malaise & dry mouth. 2 days later Pt hospitalized w/ DKA (FBS = 487 mg/dL, HbA_{1c} = 12.4%, urine ketone +, glucose 3+). Tx = insulin. Pt improved 2 wks later (FBS = <100 mg/dL). Pt on diet therapy. Plan for insulin to be ↓ & d/c'd. No other info.
2002AP02329 DKA	21/F	600 mg/day; 57 days	Type I DM (since age 5)	None	Baseline labs: Not provided Day 53-56: Pt stopped all oral meds & insulin d/t aggravation of psych sxs. Day 57: Pt in ER d/t frequent vomiting & ↓mg consciousness. Dx = DKA (BG = 245 mg/dL, WBC = 29,200/mm³, CRP = 1.28 mg/dL). Tx = IVF (NS, electrolytes, glucose), insulin drip. Next day BG = 276 mg/dL, Pt still somnolent. Next day consciousness↑, BG = 200-300 mg/dL. Pt started risperidone, biperiden, carbamazepine, flunitrazepam, levomepromazine. Following day ketone bodies & sugar in urine negative. 5 days after onset of events insulin changed to SC. BG mean = 100-200 mg/dL. Reporter felt DKA d/t discontinuation of insulin by Pt. No other info.

Table 59 Reports of DKA in patients with a history of DM

Report # PT[a]	Age/ Sex	Dose TTO	Relevant med hx[b]	Relevant con meds[c]	Comments
2002AP01163 DKA *Diabetic coma*	36/M	75 mg/day; see comments	Type II DM (HG = 776 mg/dL; 2 y prior to Seroquel), drinks excessive consumption of soft drinks, non-compliance w/ oral diabetic meds	None	Baseline labs: BG = 109 mg/dL, HbA_{1c} = 5.3%, Wt = 67 kg. Day 65: HbA_{1c} = 13.9%, Wt = 60.1 kg, BG = 331 d/t drinking excessive amounts of coffee. Day 116: Seroquel d/c'd & clozapramide started. About 4 ½ mos later Pt d/c'd pioglitazone, BG = 117, HbA_{1c} = 4.5%, Wt = 59 kg. 7 mos after Seroquel d/c'd BG = 420, HbA_{1c} = 8.2%, Wt = 70 kg. 3 days later clozapramide switched back to Seroquel. 2 days later Pt had no complaints. Day 8 (of restarting Seroquel): Pt felt "terribly unwell". Day 13: Pt hospitalized in deep coma. *BP* = 60/36, *HR* = 120 bpm, *BG* = 3570, Temp = 40°C, urinary sugar = 4+, urinary Ketone = 1+. Pt had metabolic acidosis, pre-renal renal failure, severe dehydration causing R heart collapse. Tx = IVF, insulin drip, noradrenaline, abx, gabexate (for DIC), K+ (for hypokalaemia). Condition reported as "almost HHNC". Brain stem lesion suspected. All meds d/c'd. Next day respirations weak, ABG = CO_2 narcosis. Sputum test = sespected B.LNAR, haemophilus influenza, Strep A hemolyticus, candida albicans. Pt intubated & ventilated. Fever: contd., abs changed. Abdominal CT = no source of infection. NMS considered d/t sxs (but few muscle findings). Tx = dantrolene. ARF occurred d/t hypermyoglobinemia. Dialysis not possible d/t HBP & GI bleeding. Shock occurred & Pt died 5-½ hr later. COD = DKA. Reporter stated Pt always had several cans of soft drinks (sugar sweetened) in his pockets. No other info.
2001UW16978 DKA	32/M	800 mg/day; 2 wks	Borderline DM (diet-controlled)	None	Baseline labs: Not provided 2 wks: DKA (peak BG = 700 mg/dL). Pt had urinary incontinence, confusion, abnormal HR. 3 days prior to DKA Pt c/o upper respiratory sxs, dizziness. Pt also taking risperidone. Outcome & if Seroquel contd unk. No other info.
2001UW65726 *DKA*	43/M	≤600 mg/day; 188 days	DM, obesity	Chlorpromazine[d], clonidine[e]	Baseline labs: Not provided Day 188. Pt died from possible DKA. Pt took risperidone x 9 mos & stopped 3 mos after Seroquel started. No other info.
2003AP04688 DKA	24/M	300 mg/day; TTO unk	IDDM, obesity (BMI = 30), questionable med compliance, known drug abuse)	None	Baseline labs: Not provided Pt hospitalized w/ n/v after taking 5 ecstasy tabs & unk amount of alcohol. Treated for DKA, hypokalemia, metabolic acidosis. Pt had worsening renal function, hypotension, possible aspiration pneumonia. Pt intubated & developed ARF w/ ↑creatinine (peak = 527 µmol/L) 10 days after admission. Tx = albuterol, midazolam, propofol, haloperidol, epoprostenol, metronidazole. MRSA identified, Tx = abx. ARF resolved after 15 days. Metabolic acidosis & hypokalemia still resolving. Seroquel contd. No other info

Table 59 Reports of DKA in patients with a history of DM

Report # PT[a]	Age/ Sex	Dose TTO	Relevant med hx[b]	Relevant con meds[c]	Comments
2000AP03612 DKA	64/M	400 mg/day; 3 mos	FBS = 120 mg/dL (date unk), prostate CA, COPD, family hx of DM	None	Baseline labs: Not provided Pt hospitalized for unspecified reason. 12 days later Pt switched from risperidone to Seroquel. 2 mos later Pt found unresponsive after breakfast. Dx = DKA. Pt lost to follow-up. Outcome & if Seroquel contd. unk. No other info.
1998LW49554 DKA	58/M	800 mg/day; TTO unk	DM, CVA	None	Baseline labs: Not provided Pt had TIA & rec'd 5 mins later. Next day, Pt collapsed & died. Autopsy: COD = DKA. CVA. No other info
2005UW13179 DKA	14/F	300 mg/day 2 wks	Fragile Type I DM	None	Baseline labs: Not provided After 2 wks on Seroquel Pt developed DKA. Outcome & if Seroquel contd. unk. No other info.

a PTs refers to diabetes related PTs only.
b Relevant med history refers to history which may contribute to development of DM/DKA.
c Relevant concomitant medications refers to those medications which may have contributed to the development of DM/DKA.
d For which hyperglycaemia has been reported.
e For which DM has been reported.
f For which altered glucose tolerance has been reported.

ABG arterial blood gas. abx antibiotics. ampicillin-resistant. ARF acute renal failure. BG blood glucose. BLNAR beta-lactamase-negative. BP blood pressure. c/o complained of. CA cancer. CO_2 carbon dioxide. COD cause of death. con meds concomitant medications. contd. continued. COPD chronic obstructive pulmonary disease. CRP C-reactive protein. CT computed tomography. CVA cerebrovascular accident. d/c'd discontinued. dt due to. DIC disseminated intravascular coagulation. DKA diabetic ketoacidosis. DM diabetes mellitus. Dx diagnosis. ER emergency room. FBS fasting blood sugar. GI gastrointestinal. HbA$_{1c}$ glycosylated hemoglobin. High hemoglobin. HHNC hyperglycemic hyperosmolar non-ketotic coma. HR heart rate. HTN hypertension. hx history. IDDM insulin dependent diabetes mellitus. info information. IVF intravenous fluids. K+ potassium. meds medications. mo(s) months. MRSA methicillin resistant staphylococcus aureus. n/v nausea/vomiting. NMS neuroleptic malignant syndrome. NS normal saline. psych psychiatric. Pt patient. PTs preferred terms. R right. . rec'd recovered. SC subcutaneous. sx symptoms. tabs tablets. Temp temperature. TIA transient ischemic attack. TTO time to onset. Tx treatment. unk or ? unknown. w/ with. WBC white blood cells. wk(s) week(s). Wt weight. y year. NB. all BMI measurements are kg/m2. Lab units included when known.

One report (2002AP02329) described a patient with a history of Type I DM who experienced DKA after stopping all of her oral medications and insulin for three days. The patient recovered. The physician felt that the DKA was due to the patient discontinuing the insulin.

In two reports dietary non-compliance may have played a role. One report (2002AP01163) described a patient who was reported to drink excessive amounts of sweetened coffee and soft drinks. This patient also was non-compliant with oral antidiabetic medications and did not have stable blood sugars prior to starting SEROQUEL. The other patient (2004AP06389) "drank juice throughout the day". This patient was obese (BMI = 39 kg/m^2) and also taking a concomitant medication (lithium) for which hyperglycemia has been reported.

Another report (2001UW16478) described a patient who was a borderline diabetic. The patient experienced DKA following an upper respiratory infection. In addition, it was reported that the patient was diet-controlled, however no information regarding the patient's degree of dietary compliance was provided.

Another report (2006UW08816) suggested that the patient might have had a history of DKA prior to initiation of SEROQUEL. The sequence of events and the start and stop dates for SEROQUEL treatment were not clear. Two other reports (2001UW05726, 2003AP00312) were confounded by a concomitant medication (chlorpromazine) for which hyperglycemia and/or an exacerbation of DM has been reported.

Another report (2000AP04688) contained limited information about the event of DKA, therefore an assessment of causality was not possible. The remaining five reports (2005AP00945, 2000AP03612, 1998UW49554, 2005UW13179, 2005SE00781) contained scant clinical detail and did not lend themselves to analysis.

6.4.3 Summary of all reports of DKA

Assessment of causality was not possible in these cases because of incomplete clinical information, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (e.g. obesity or family history of DM), documented dietary non-compliance, and/or alternative explanations.

6.5 Diabetic coma

6.5.1 Search results

One hundred eighty-six reports contained the MedDRA preferred term "Diabetic coma", seven reports contained the MedDRA preferred term "Diabetic hyperosmolar coma", and one report contained the MedDRA preferred term "Diabetic hyperglycaemic coma". Two medically confirmed reports also contained the MedDRA preferred term "Diabetic ketoacidosis" (2004UW14727, 2002AP01163) and were discussed above. In addition, 176 legal reports containing the MedDRA preferred term "Diabetic coma" also contained the MedDRA preferred term "Diabetic ketoacidosis". These 176 case numbers are listed (and footnoted as such) in Appendix A Table xx and will not be discussed further.

In addition, seven other reports containing a diabetes related term also contained on the following MedDRA preferred terms "Coma", "Loss of consciousness", or "Unresponsive to stimuli". These seven reports were reviewed to determine if the coma might have been related to hyperglycemia or DM. One of these reports (2005AC00445) suggested a diabetic coma, however this report also contained the MedDRA preferred term "Ketoacidosis" and was discussed above. The other six reports did not suggest a diabetic coma and will be discussed in the appropriate sections below (2004AC00607, 2003UW02826, 2002AP02947, 2002AP02699, 1998UW49037, 2002UW16205).

Therefore 16 reports will be discussed. Full narratives for medically confirmed and non-medically confirmed reports are contained in Appendix D. For legal cases only those reports, which are medically confirmed have narratives in Appendix D.

6.5.1.1 Diabetic coma in patients with no known history of DM (13 reports)

Nine reports of diabetic coma described patients with no known history of DM. These reports are divided into the following categories: Medically confirmed (8), Non-medically confirmed (1), and Legal cases (4).

Medically confirmed reports (8 reports)

Eight medically confirmed reports described patients who had no known history of DM. These reports are summarized in Table 60 below. Three of these reports described a fatal outcome (1999UW00969, 2002UW05916, 2006AP00713).

Table 60 Reports of diabetic coma in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose/TTO	Relevant medical hx[b]	Relevant con meds[c]	Comments
20041AW09577 Diabetic coma DM	64/F	300 mg/day; ≤19 mos	Obesity	None	Baseline labs: Not provided Pt developed DM & subsequently hospitalized for diabetic coma (BG = 700) (unclear if prior to or while on Seroquel) 2-3 mos later Seroquel dose ↑ to 800 mg/day. Seroquel d/c'd unk time later d/t insomnia, anxiety. Endocrinologist felt DM not related to Seroquel Outcome unk. No other info.
1999LW00869 Diabetic hyperosmolar coma DM	28/M	Dose/TTO unk	3 wk hx of polydipsia, polyuria, 10-15 lb Wt loss	Lithium[d], albuterol[d,e]	Baseline labs: Not provided Pt had flu like sxs. Tx = azithromycin. 7 days later: Hospitalized w/ fever (102°F), arrhythmias, non-reactive pupils, bleeding from eyes/nose, BG = 2268 mg/dL, $\uparrow K^+$ (3.3 to 2 mEq/L.) Pt then developed DIC, v-fib. Tx = dantrolene, anti-arrhythmics, bicarb, insulin, FFP, whole blood, packed rbc. Pt died. Autopsy = new-onset DM w/ NKHC, NMS, metabolic acidosis, DIC, respiratory failure. No other info.
20021AW05916 Diabetic hyperosmolar coma NIDDM	42/F	600 mg/day; ≈9 mos	Tx non-compliance, obesity (BMI = 30.4)	Albuterol[d,e]	Baseline labs: Not provided Pt to residential facility d/t aggression & behavior problems. 6 days after being sent home Pt hospitalized w/ 2-day hx of mental status changes, polyuria, polydipsia, HEP, n/v, abdominal pain, sore throat. Pt afebrile, non-rigid, BG = 1739 mg/dL, WBC = 18.3K, creatinine = 3.2 mgAdL, BUN = 54 mg/dL, HbA_{1c} = 11.3%. Tx = K^+ phosphate, abx, midazolam, acetaminophen. Body temp = 101°F. Pt died d/t coma 2° to acute onset type II DM. Unspecified infectious process felt to have precipitated NKHHC. Autopsy showed no signs of infection. Autopsy = findings c/w leukoencephalopathy, etiology undetermined. No other info.
2002GB02176 Diabetic coma IDDM	56/F	2400 mg/day; ≈2 y	No family hx of DM, no other hx provided	Lithium[d]	Baseline labs: Not provided ≈2 y : Type I DM in diabetic coma. Pt also hypernatremic. Diabetic coma not precipitated by infection. Status of Seroquel & lithium unk. Pt improving. No other info.
2003AP01289 Diabetic hyperosmolar coma	36/M	See comments	Chronic pancreatitis	Loperamide[d]	Baseline labs: Not provided After surgery for rectal carcinoma Pt developed delirium & stunad on Seroquel. ≈12 days later BG = 420 mg/dL. 3 days later Seroquel d/c'd (reason unspecified) 1 wk later Pt comatose, BG = 500 mg/dL. Dx = nonketotic acidosis. Pt then developed DIC. An unk time later Pt recovering from nonketotic acidosis but had sequelae after DIC. No other info.

Table 60 Reports of diabetic coma in patients with no known history of DM

Report # PTs[a]	Age/ Sex	Dose/TTO	Relevant medical hx[b]	Relevant con meds[c]	Comments
2002AP04236 Diabetic hyperosmolar coma Hyperglycaemia	74/F	75 mg/day; 190 days	No family hx DM, regular dietary habits, BG not routinely monitored	Furosemide[f]	Baseline labs: Not provided Day 188: Loss of appetite. HR = 120 bpm. Day 190: trembling, temp = 37-38°C, $_1O_2$ sat, ↑HR, unresponsive, FBS = 1109 mg/dL, Na = 157 mEq/L, K = 5.1 mEq/L, Cl = 114 mEq/L, urine sugar = 4+, urine ketone = neg, ABG: pH = 7.37, BE = 1.5, pO_2 = 83, pCO_2 = 45.2, BUN = 103.2, creatinine = 2.38 mg/dL. Dx = left pneumonia, NKHHC. Tx = insulin, abx, IVF, all meds d/c'd. Next day BG = 82-280 mg/dL. Insulin d/c'd. Following day, FBS = 284 mg/dL, WBC = 16200/mm^3. Pt recovering.
2004AC00666 Diabetic coma	38/M	1100 mg/day; 180 days	HTN, BMI = 29.4	None	Baseline labs: Not provided Day 177: Pt developed pancreatitis. Day 180: Pt developed ketoacidotic coma that lasted 48 hrs. Seroquel dose ↑ next day to 600 mg/day. Ultrasound = acute respiratory infection, bronchopneumonia. While on Seroquel Pt wt ↑ from 83 kg to 120 kg. Pt rec'd from coma 2 days later & from pancreatitis 27 days after onset. Seroquel 600 mg/day contd. Outcome for wt gain, respiratory infection, bronchopneumonia unk. No other info.
2006AP00713 Diabetic hyperglycemic coma Hyperglycaemia	68/M	275 mg/day; 4 days	Hyperlipidemia, obesity, smoker (20 cigs/day), insulin resistance, ↑TRIG, HTN, 12 oz beer/day	None	Baseline labs: BG = 82 mg/dL Day 4: BG = 178 mg/dL. Day 57: disturbed consciousness, hyperglycemic coma (BG = 1204 mg/dL). Tx = dialysis. Hyperglycemia persisted. Seroquel d/c'd. 4 days later Pt died (BG = 1227 mg/dL). COD (autopsy): Septic shock d/t functional ileus (Pt had hx of ileus -- 3 ½ y prior to death). It was reported that Pt had hx of BG levels had occasionally been elevated d/t secretly eating prior to blood sampling. No other info

a PTs refers to diabetes related PTs only.
b Relevant med history refers to history which may contribute to development of DM/DKA.
c Relevant concomitant medications refers to those medications which may have contributed to the development of DM/DKA.
d For which hyperglycaemia has been reported.
e For which DKA has been reported.
f For which hyperglycaemia in Type II DM has been reported.

ABG arterial blood gas, abx antibiotics, DM diabetes mellitus, BE base excess, BG blood glucose, BMI body mass index, BUN blood urea nitrogen, cigs cigarettes, Cl chloride, COD cause of death, cncr concurrent with, con meds concomitant medications, d/c'd discontinued, d/t due to, DIC disseminated intravascular coagulation, Dkb diabetes mellitus, dx diagnose, FBS fasting blood sugar, FFP fresh frozen plasma, HbA_{1c} glycosylated hemoglobin, HR heart rate, HTN hypertension, hx history, IDDM insulin dependent diabetes mellitus, info information, IVF intravenous fluids, K potassium, mo(s) month(s), n/v nausea/vomiting, Na sodium, NIDDM non-insulin dependent diabetes mellitus, NKHHC non-ketotic hyperglycemic hyperosmolar coma, O2 sat oxygen saturation, pCO2 partial carbon dioxide, pO2 partial oxygen, Pt patient, PTs preferred terms, sxs symptoms, temp temperature, TRIG triglycerides, TTO time to onset, tx treatment, unk or ? unknown, US ultrasound, WBC white blood cells, wk(s) week(s), wt weight, y/o Lab units provided when known, WB all BMI measurements are kg/m2.

One report described a positive dechallenge (following the event, therapy with SEROQUEL alone is discontinued or the dose is lowered, and the patient recovers without additional treatment). This report (2004AC00666) described a 38-year-old male patient who developed pancreatitis after six months of therapy with SEROQUEL (1100 mg/day). Three days later the patient was reported to have experienced a "ketoacidotic coma". The dose of SEROQUEL was decreased to 600 mg/day and the patient recovered from the coma the following day. The patient recovered from the pancreatitis about four weeks after the onset. Therapy with SEROQUEL (600 mg/day) continued. During hospitalization it was discovered that the patient had an acute respiratory infection and bronchopneumonia which could have precipitated the hyperglycemia, leading to diabetic coma. In addition, the patient had a history of hypertension and the patient's BMI prior to the reported 27 kg weigh gain was 29.4 kg/m^2. No laboratory values (baseline or otherwise) were provided and the patient was taking a medication (timolol) for which an increased risk of developing Type II DM (in hypertensive patients receiving a beta blocker) has been reported.

Two reports were confounded by both medical history/risk factors and concomitant medications (2002UW05916: obesity, albuterol [for which DKA and hyperglycemia have been reported], 2003AP01289: chronic pancreatitis, loperamide [for which hyperglycemia has been reported]).

Two reports were confounded by risk factors/medical history (2004UW09577: obesity, 2006AP00713: hyperlipidemia, obesity, HTN, smoking). One other report was confounded by concomitant medications (1999UW00969: lithium [for which hyperglycemia has been reported], albuterol [for which DKA and hyperglycemia has been reported].

One report (2002AP04136) described a 74-year-old female patient who experienced hyperglycemia and diabetic coma. No information was provided regarding the patient's baseline blood glucose values, however it was reported that the patient's blood glucose was not monitored regularly. This patient concurrently experienced a respiratory infection, pneumonia, and dehydration. In addition, the patient was taking a concomitant medication (furosemide) for which hyperglycemia has been reported.

The last report (2002GB02176) contained limited information regarding the events. It was reported that the patient developed Type I DM after about two years of therapy with SEROQUEL and lithium (for which hyperglycemia has been reported). No laboratory information was provided and the status of therapy with the two medications was unknown.

Non-medically confirmed case (1 report)

One report (2006UW13575) was received from a patient's mother. The mother reported that after starting SEROQUEL almost two years ago the patient "almost died due to diabetic coma". The patient did not have a family history of diabetes. SEROQUEL was temporarily discontinued. The reporter also stated that the patient was currently being treated for diabetes and believed that it was in most part under control. After restarting SEROQUEL a few weeks later it was reported that the patient's BG had been fluctuating. No laboratory data or information about the patient's medical history was provided.

Legal cases (4 reports; two reports treated by AstraZeneca as "medically confirmed")

The first report (2006UW27335) originally received in the form a civil complaint was subsequently medically confirmed with medical records. This report described a 45-year-old female patient who claimed to have experienced diabetic coma and diabetes after two years of receiving SEROQUEL. She also claimed to have experienced pancreatitis (date unknown). This report was confounded by the patient's medical history of obesity (BMI = 30.9 kg/m^2), hyperglycemia, high cholesterol, high triglycerides, and family history of DM. In addition, the patient was also taking chlorpromazine (for which DM and hyperglycemia has been reported) and olanzapine (for which DM and hyperglycemia has been reported). The patient's outcome was not provided. The second report (2006UW21583) was initially received from an attorney in the form of a civil complaint and was later treated by AstraZeneca as medically confirmed upon the receipt of a patient fact sheet. This report was confounded by the patient's history of obesity and hyperglycemia and concomitant use of chlorpromazine (for which DM and hyperglycemia has been reported). It was reported that the patient died from an unknown cause on an unspecified date.

The other two reports received in the form of a civil complaint have not been medically confirmed. One of these reports contained no clinical detail and did not lend itself to analysis (2006UW17483). The other report (2006UW14368) was also received in the form of a civil complaint, however the complaint contained detailed medical information but was not supported with medical records. This report was confounded by the patient's history of HTN, hypertriglyceridemia, and family history of DM. It was also reported that the patient drank 18 cans of sugar-sweetened soft drinks the day prior to the event.

6.5.1.2 Diabetic coma in patients with a history of DM (3 reports)

Three reports of diabetic coma described patients with a history of DM. All three of these reports were medically confirmed and are summarized in Table 61 below.

Table 61 Reports of diabetic coma in patients with a history of DM

Report # PTs[a]	Age/ Sex	Dose/TTO	Relevant medical hx[b]	Relevant con meds[c]	Comments
2002AP04514 Diabetic hyperosmolar coma Hyperglycaemia	57/F	75 mg/day; 195 days	DM, risperidone therapy (x 2 mos) immediately prior to Seroquel	Chlorpromazine[d,e] prednisolone[d,f,g,h]	Baseline labs: BG = 210, FBS = 167 mg/dl. Pt started prednisolone 1 mo later. ↑BG (417-649 mg/dL). Tx = Seroquel d/c'd, diet control 9 days later Pt developed NKHHC Tx = all remaining meds d/c'd, insulin started, prednisolone ↓& d/c'd. Pt rec'd (BG = 95 mg/dL). No other info
2002SE05071 Diabetic coma, BG ↑	51/F	50-100 mg/day; TTO unk	Uncontrolled DM (HbA_{1c} = 11.02%), dietary non-compliance, olanzapine therapy (x 1 mo) immediately prior to Seroquel	Olanzapine[d,g]	Baseline labs: Not provided Olanzapine d/c'd & Seroquel started. Day 1 Seroquel: Fever, nausea/emesis, urinary incontinence. ↑BG Day 3: Diabetic coma (700 mg/dL), UTI. Tx = insulin, abx. Seroquel d/c'd. Pt rec'd from all events 3 days later. No other info.
2003SE04513 Diabetic coma	48/F	400 mg/day; 12 days	DM, olanzapine therapy prior to Seroquel d/c'd d/t Wt gain (duration unk)	Olanzapine[d,g]	Baseline labs: Not provided Therapy w/ olanzapine switched to Seroquel d/t Wt↑. Day 12 Seroquel; Diabetic coma (BG = 532 mg/dL, urine ketone bodies = 2+, no ketoacidosis). Seroquel d/c'd. Pt rec'd. Pt hospitalized x 4S days. During the hospitalization, following discontinuation of Seroquel Pt restarted olanzepine. 5 days prior to discharge BG = 196 mg/dL. No other info.

a PTs refers to diabetes related PTs only.
b Relevant med history refers to history which may contribute to development of DM/DKA.
c Relevant concomitant medications refers to those medications which may have contributed to the development of DM/DKA.
d For which hyperglycaemia has been reported.
e For which altered glucose tolerance has been reported.
f For which DKA has been reported
g For which DM has been reported.
h For which hyperosmolar coma has been reported.

Abx antibiotics, BG blood glucose, Con meds concomitant medications, D/C'd discontinued, D/t due to, DM diabetes mellitus, FBS fasting blood sugar, HbA_{1c} glycosylated haemaglobin, Hx history, Info information, mo(s) month(s), NKHHC non-ketotic hyperosmolar hyperglycemic coma, Pt patient, PTs preferred terms, Rec'd recovered, TTO time to onset, Tx treatment, Unk unknown, UTI urinary tract information, W/ with, Wt weight.

One report described a positive dechallenge (following the event therapy with SEROQUEL alone is discontinued or the dose is lowered and the patient recovers without additional treatment). This report (2003SE04513) described a 48-year-old female patient who discontinued therapy with olanzapine (for which hyperglycemia, DKA, and DM has been reported) due to weight gain and started SEROQUEL. After 12 days on SEROQUEL the patient developed diabetic coma (BG [reportedly] = 332 mg/dL, ketone bodies = +2). Therapy with SEROQUEL was discontinued and the patient was reported to have recovered (no laboratory data). During hospitalization the patient restarted olanzapine. Five days prior to discharge from the hospital (hospital day 43) the patient's BG was 196 mg/dL. No other information was provided.

Another report (2002AP04514) described a patient who was taking medications (chlorpromazine, prednisolone) for which hyperglycemia, DM, DKA, and hyperosmolar coma have been reported. The third report (2002SE05071) indicated that the patient's DM was poorly controlled prior to receiving SEROQUEL. This patient also had an infection and a history of non-compliance with diet.

6.5.1.3 Summary of all reports of diabetic coma

Assessment of causality was not possible in these cases because of incomplete clinical information, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (e.g. obesity or family history of DM), documented dietary non-compliance, and/or alternative explanations.

6.6 New onset DM, hyperglycemia, or exacerbation of pre-existing DM (1582 reports)

Two hundred fourteen reports of new-onset DM or exacerbation of DM were discussed in either the DKA or diabetic coma sections above. These reports will not be discussed further in this Section and are listed or referenced in Table 62 below.

Table 62 Reports discussed in other sections above

Section	Case IDs
DKA (medically confirmed)	2004UW23764, 2004UW14727, 2003AP04434, 2003AP04386, 2002UW14814, 2002GB02627, 2001UW12263, 1999AP05757, 2005UW18114, 2005UW17274, 2005UW14876, 2005UW09324, 2000UW01164, 2006UW09586, 2005AP03905, 2005AC00445, *2005AP00945, 2003AP00313*
DKA (not medically confirmed)	2006UW02754
DKA (Legal)	2004UW01147 (medically confirmed) 184[a] reports listed and footnoted in Table xx above (not medically confirmed)
Diabetic coma (medically confirmed)	1999UW00969, 2002GB02176, 2002AP04136, 2006AP00713, 2004UW09577, 2002UW05916, 2003AP01189, *2002AP04514, 2002SE05071*
Diabetic coma (Legal)	*2006UW14368* (not medically confirmed)

a 176 also contained the term "Diabetic coma"

NB Reports in italics describe patients with a pre-existing history of DM.

6.6.1 New onset (1228 reports)

One thousand two hundred twenty-eight reports described patients with new onset DM or patients who experienced hyperglycemia and did not have a prior history of DM. These 1228 reports will be discussed below and are divided into the following categories: Medically confirmed (464 reports), Non-medically confirmed (153 reports), and Legal cases (611 reports [some treated by AstraZeneca as "medically confirmed"]).

Medically confirmed (464 reports)

Fourteen reports (2007UW02514, 2001UW00363, 2000UW00266, 2002GB00282, 2005AP01154, 2006GB00066, 2006UW02750, 2006UW18010, 2006PK00223, 2006UW22127, 2006UW07337, 2006UW01876, 2006UW12109, 2006UW00204) described pediatric or young adult patients who developed Type I DM, which is considered not to be drug related because the disease results from an absence of insulin. One of these patients died. This patient (2002GB00282) was a 19-year-old who was diagnosed with Type I DM after experiencing a "hyperglycemic ketoacidotic pre-coma". The patient was treated with insulin and recovered, and therapy with SEROQUEL was discontinued. Four months later the patient died from an unknown cause. It was reported that the evening before his death his blood glucose had been normal and the patient had admitted to taking cocaine. An autopsy was not able to determine the patient's cause of death.

Another report (2007UW03020) described a case of neonatal hyperglycemia. The mother had been receiving SEROQUEL for more than a year for bipolar disorder; she was also receiving lithium. The patient had no relevant medical history except that she was a smoker. Several ultrasounds showed intra-uterine fetal growth retardation. Labor was induced prematurely because the baby was small for its gestational age and was in distress. The baby was born with a patent ductus arteriosus (PDA). Following birth the baby's BG rose beyond normal levels each time she was fed (lab values not provided). The outcome was not provided. No other information was available.

Of the remaining 449 reports, two described a positive rechallenge (following the event, therapy with SEROQUEL is discontinued or the dose is lowered and the patient recovers without further treatment and then when SEROQUEL therapy alone is restarted the event reoccurs). One report (2002UW15932) described a middle age female patient who had a family history of DM. It was reported that after an unspecified amount of time on SEROQUEL the patient experienced elevated BG and "almost diabetic coma". The patient was taken off all medications and her BG was controlled. Therapy with SEROQUEL alone was restarted (date unspecified) and the patient's BG started to rise again. SEROQUEL was discontinued. No information about this patient's medical history, concomitant medications, or laboratory values were provided. The second report (2004UW06083) described a 50-year-old female patient who after starting treatment (timing unspecified) with SEROQUEL experienced an elevated blood glucose of 120 and elevated LDL of 214. SEROQUEL was discontinued and the values improved (no lab values provided). The patient later tried

SEROQUEL again (timing unspecified) and the same elevations occurred (no lab values provided). SEROQUEL was again discontinued and the lab values normalized again (no lab values provided). As above, no information was provided about this patient's medical history or concomitant medications.

Thirty-three reports described a positive dechallenge, that is the patient experienced hyperglycemia/DM while on therapy with SEROQUEL, SEROQUEL alone was discontinued, and the patient recovered without additional treatment or with no additional treatment reported. Twenty-three of these reports contained scant clinical detail. In these 23 reports it is stated that the patient was on SEROQUEL, experienced hyperglycemia/DM, SEROQUEL was discontinued, and the patient recovered. The necessary information to assess causality in these reports is lacking. These reports contain no information about the patient's medical history, risk factors, and/or concomitant medications and in most cases do not provide any actual laboratory values to support the reported event. Therefore, these reports will not be discussed further (2004UW06025,2005UW09495, 2003GB00473, 2004GB01064, 2004UW06024, 2005UW11924, 2004UW23145, 2004UW17951, 2004AP06370, 2006UW06233, 2004AP00095, 2006UW08727, 2006UW10112, 2006UW16453, 2006UW18137, 2004UW01934, 2004SE00304, 2004PK02114, 2006UW01619, 2005UW02685, 2005UW03742, 2005AP01117, 2005SE00585). The remaining 10 reports describing a positive dechallenge are summarized in Table 63 below.

Table 63 New onset DM/hyperglycemia: Reports w/ a positive dechallenge

Case ID	Age/ Sex	Dose TTO	Relevant hx[a]	Relevant con meds[b]	Comments
2004UW03563	47/F	250 mg/day; 3 y 3 mos	Hypothyroidism	None	Baseline labs: Not provided BG ↑ from 14.4 to 25. Dose ↓ to 150 mg/day & BG improving (no lab values). Unclear timing in relation to Seroquel. No other info.
2004UW08948	7/M	300 mg/day; 4 mos	Wt=74 lb, Ht=52 in, asthma No family hx of DM	Lithium[c], olanzapine[d]	Baseline labs: Not provided After 4 mos on Seroquel & 2 mos on olanzapine Pt had ↓&↑BG ranging from 42 to 202 (1 h after eating fruit). Normal OGTT. Seroquel d/c'd. It was reported that BG normalized (range 85 to 186). No other info.
2004UW15424	12/M	800 mg/day; 15 mos	Family hx of DM	Albuterol[e]	Baseline labs: Not provided After 15 mos on Seroquel FBS=190. Sxs=polyuria, polydipsia, polyphagia, fatigue, weakness, dizziness, blurred vision, wt gain (42 lbs). Seroquel d/c'd next day. 3 days later FBS=122. FBS normalized w/in 2 wks (106). No other info.

Table 63 New onset DM/hyperglycemia: Reports w/ a positive dechallenge

Case ID	Age/ Sex	Dose TTO	Relevant hx[a]	Relevant con meds[b]	Comments
2003AP00833	43/F	150 mg/day; 33 wk	No family hx of DM	None	Baseline labs: Not provided Pt on risperidone x 6 mos. Risperidone d/c'd & Seroquel started next day. After 6 mos of Seroquel OGTT normal (107 mg/dL, 118 mg/dL (1 h), 110 mg/dL (90 min), 104 mg/dl (2 h), 105 mg/dL (3 h)). Urine=neg. About 2 mos later FBS=129 mg/dL. Seroquel d/c'd 2 wks later. One mo later Pt rec'd (OGTT: 109 mg/dL, 140 mg/dL (30 min), 124 mg/dL (1 h), 107 mg/dL (90 min), 109 mg/dL (2 h), 97 mg/dL (3 h).
2003AP00090	65/F	150 mg/day; 15 mos	None	None	Baseline labs: BG (after meal)=122 mg/dL. After 15 mos on Seroquel FBS=157 mg/dL. 2 wks later random BG=204 mg/dL. 2 wks later BG (2 h after meal)=155 mg/dL. Seroquel d/c'd. 2 wks later BG (2 h after meal)=189 mg/dL). FBS 6 wks after Seroquel d/c'd=155 mg/dL. 10 wks after Seroquel d/c'd FBS=142 mg/dL. Pt reported to be recovering.
2003AP00055	50/M	200 mg/day; 4.5 mos	Not provided	None	Baseline labs: FBS=133 mg/dL, HbA_{1c} = 6.3%, urine=negative Pt on olanzapine x 6 mos then d/c'd. Pt started Seroquel 3 wks later. After 4.5 mos on Seroquel FBS=234 mg/dL, HbA_{1c} =8.3%, urine=3+glucose. Seroquel d/c'd. One mo later FBS=145 mg/dL, HbA_{1c}=7.8%.
2002UW01476	60/M	Dose unk; 3 mos	Hyperlipidemia, HTN, obesity (BMI = 31.9)	None	Baseline labs: Reported "WNL" After 3 mos on Seroquel BG=500, HbA_{1c}=15%. Pt hospitalized. Seroquel d/c'd. Reported that BG almost returned to normal (no lab values).
2003PK02094	27/F	400 mg/day; 2.5 mos	Not provided	None	Baseline labs: Not provided After 2.5 mos on Seroquel BG=>25 mmol/L. Sxs=polyuria, nocturia, sweating, nausea, reported 15 kg wt gain. Dx=DM. Seroquel dose↓ to 200 mg/day. Next day BG=22.8 mmol/L. Seroquel contd 2 days later BG=10.5. 2 wks after dose ↓ BG=5.3 mmol/L. Seroquel d/c'd.

Table 63 New onset DM/hyperglycemia: Reports w/ a positive dechallenge

Case ID	Age/ Sex	Dose TTO	Relevant hx[a]	Relevant con meds[b]	Comments
2004AP01859	68/F	600 mg/day; TTO unk	Not provided	None	Baseline data: Not provided After unk time on Seroquel & risperidone BG=408 mg/dL. Seroquel contd. Next day FBS=84 mg/dL. BG was monitored 5x/day for 2 days & were WNL. Seroquel contd. About 2 mos later Pt had palpitations, HR=118 bpm. ECG: QT prolongation & hyperglycemia (random BG=327 mg/dL). Seroquel d/c'd. 3 h later QT prolongation resolved. Next day FBS=84 mg/dL. Pt received no tx for hyperglycemia. 3 wks later BG (2 h after meal)=195 mg/dL. No other info.
2005AP05990	64/F	600 mg/day; 11 mos	Obesity, hyperlipidemia, HTN, fatty liver	None	Baseline labs: Not provided After 5 ½ mos on Seroquel BG=82 mg/dL. After 11 mos on Seroquel FBS=350 mg/dL, HbA_{1c}=7%. Seroquel dose↓ to 300 mg/day. 4 days later Seroquel d/c'd. 34 days after Seroquel d/c'd BG=83 mg/dl, HbA_{1c}=6.6%. No other info.

a Relevant med history refers to history which may contribute to development of DM/DKA.
c Relevant concomitant medications refers to those medications which may have contributed to the development of DM/DKA.
c For which hyperglycemia has been reported.
d For which for which hyperglycemia, DM, and DKA has been reported.
e For which hyperglycemia and DKA has been reported.
BG blood glucose. BMI body mass index. Con meds concomitant medications. D/c'd discontinued. D/c'd discontinued. DM diabetes mellitus. ECG electrocardiogram. FBS fasting blood sugar. H hour. HbAIc glycosylated hemoglobin. Ht height. HTN hypertension. Hx history. Info information. Min minute(s). Mo(s) month(s). OGTT oral glucose tolerance test. Rec'd recovered. Sxs symptoms. TTO time to onset. W/in within. Wk(s) week(s). WNL within normal limits. Wt weight. Y year(s).

Seven of these 10 reports did not provide baseline glucose data, therefore it is not possible to know if the patient may have had an elevated glucose prior to starting SEROQUEL (2004UW03563, 2004UW08948, 2003AP00833, 2003PK02094, 2004AP01859, 2005AP05990, 2004UW15424). In addition, three of these seven reports were confounded by medical history and/or concomitant medications for which DM/hyperglycemia has been reported (2004UW08948: family history of DM, albuterol, 2005AP05990: obesity, hyperlipidemia, and hypertension, 2004UW0948: olanzapine, lithium). In another report (2002UW01476) the patient's baseline glucose was reported to be "within normal limits", however no actual values were provided. This report was confounded by the patient's history of obesity, hyperlipidemia, and hypertension. Of the two reports that provided actual baseline glucose values, one patient (2003AP00035) was receiving olanzapine for six months prior to starting SEROQUEL and had an elevated baseline FBS (133 mg/dL). After 4.5 months on SEROQUEL the patient's FBS was 234 mg/dL. Therapy with SEROQUEL was discontinued and one month later the patient's FBS was 145 mg/dL. It was not reported whether the patient started any type of diet modification following the event and in addition information about the patient's medical history was not provided. The second report (2003AP00090) described a patient whose had an elevated FBS after 15 months of therapy with SEROQUEL. The patient's subsequent random glucoses seem to fluctuate while still on SEROQUEL. Two weeks following the discontinuation of SEROQUEL the patient's random blood glucose

increased and over the next eight weeks the patient's FBS had decreased but had not reached a normal value (FBS=142 mg/dL).

Twenty-eight reports were confounded by both the patient's medical history and/or risk factors for DM and concomitant medications for which DM and/or hyperglycemia has been reported. The reports are listed in Appendix A Table A176.

One hundred seven reports were confounded by the patient's medical history and/or risk factors for DM. These reports are contained in appendix A Table A177.

Thirty-eight reports were confounded by concomitant medications for which DM and/or hyperglycemia has been reported. These reports are contained in Appendix A Table A178.

Another report (2003AP02635) described a patient who recovered while therapy with SEROQUEL was continued.

Eight other reports had alternate explanations and are discussed below:

> One report (2002AP02699) described a patient who while on SEROQUEL received an intravenous infusion of lactated ringers electrolyte/glucose solution and experienced elevated blood glucose. It was reported that the patient's blood glucose normalized within a few hours and no treatment was reported; which raises the possibility of a falsely elevated blood glucose level.
>
> One report (2002UW16205) described a patient who experienced a "blood sugar irregularity". The patient's blood sugar was reported to be "52" and increased to "140" after breakfast. Therefore there was no evidence of hyperglycemia.
>
> One report (2002AP02947) described a patient whose hyperglycemia occurred five days after the discontinuation of SEROQUEL. The patient's physician reported that he "considered the hyperglycemia to be chronic but not severe". In addition, the hyperglycemia occurred in the setting of dehydration and a possible infection (fever, increased WBC).
>
> One report (2004AP02038) described a patient with a history of alcohol use (1/2 glass sake twice/week) and increased liver enzymes (including gamma-glutamyl-transferase [γGT]). The alcohol use, prior liver enzyme elevation, and pre-SEROQUEL γGT raises a question of fatty liver, which is associated with diabetes.
>
> One report (2004PK02023) described a patient who developed DM after 12 weeks on SEROQUEL. Medical history was not provided and the only baseline BG reported (114 mg/dL [unknown if fasting]) was 10 months prior to starting SEROQUEL, thus it can not be ascertained whether the patient had DM or an abnormal fasting glucose immediately prior to starting therapy with SEROQUEL, or had any pre-existing risk factors. SEROQUEL was continued and the patient was successfully treated with diet and metformin.

One report (2005UW07527) was originally received from a consumer. The patient reported she had glucose problems and had received therapy with olanzapine for three years. Although the patient's physician provided follow-up, which indicated, "there were no abnormal glucose readings". The prior use of olanzapine raises the possibility of increased risk of DM due to olanzapine.

One report (2002AP01607) described a patient who reportedly was diagnosed with DM "after the initiation of quetiapine" with BG levels approaching 300 mg/dL. After three months of therapy, SEROQUEL was discontinued due to lack of effect. About one month after the discontinuation of SEROQUEL the patient's FBS ranged from 99 to 170 mg/dL. Given that DM progresses over time, it is possible that the patient had some degree of insulin resistance prior to starting therapy with SEROQUEL. In addition, no baseline glucose levels or information regarding risk factors for DM were provided.

One report (2004AP02094) described a 33-year-old male patient who developed DM after 16 months of therapy with SEROQUEL and 2.5 years of therapy with risperidone. The patient reportedly gained 11.2 kg during treatment with both medications and was subsequently diagnosed with DM (FBS=141 mg/dL), hepatic function disorder, and hyperlipidemia. Two months later SEROQUEL was discontinued and nine days later the patient's FBS was 215 mg/dL. It was reported the patient's DM was ongoing but the weight gain, hyperlipidemia, and hepatic function disorder were improving with diet. No further lab data was provided.

Thirty-nine reports provided limited information with regards to medical history, concomitant medications, lab data, and/or details regarding the event; therefore an assessment of causality was not possible. These case numbers are listed in Appendix A Table A179.

The remaining 193 reports contained scant clinical detail and did not lend themselves to analysis. These case numbers are listed in Appendix A Table A180.

Non-medically confirmed (153 reports)

Five reports were confounded by both the patient's medical history and concomitant medications for which DM or hyperglycemia has been reported (2002UW09024: obesity [BMI = 38.8], lithium, 2005UW09331: HTN, lithium, 2006UW04532: obesity [BMI=30.4 kg/m^2, hydrochlorothiazide, 2006UW07675: hypercholesterolemia, furosemide, clonidine, 2006UW13113: obesity [BMI=41.7 kg/m^2, furosemide, albuterol).

Thirty-six reports were confounded by the patient's medical history and/or risk factors for DM. These reports are contained in Appendix A Table A181.

One report (2003UW16660) was confounded by the patient's concurrent use of olanzapine (for which hyperglycemia, DM, and DKA has been reported) and another report (2006UW00496) described a patient who was concomitantly taking atorvastatin, which may suggest a history of hyperlipidemia. In addition, this report contained limited information.

Eleven reports were confounded by concomitant medications for which DM and/or hyperglycemia has been reported (2006UW28269: furosemide, 2004UW23522: albuterol, 2004UW14420: olanzapine, 2005UW07520: lithium, 2005UW04822: lithium, 2005UW02099: clonidine, 2006UW05934: olanzapine, 2006UW09433: olanzapine, 2006UW16682: olanzapine, 2006UW15662: clonidine, 2006UW14586: clonidine).

Seven reports provided limited information with regards to medical history, concomitant medications, lab data, and/or details regarding the event; therefore an assessment of causality was not possible (2006UW06797, 2004UW05602, 2006UW00051, 2007UW03984, 2007UW01839, 2006UW28226, 2006UW23395).

The remaining 92 reports contained scant clinical detail and did not lend themselves to analysis and are listed in Appendix A Table A182.

Legal cases (611 reports; seven treated by AstraZeneca as "medically confirmed")

Seven reports, initially received from an attorney (non-medically confirmed), were treated by AstraZeneca as medically confirmed upon the receipt of medical records or plaintiff fact sheets. Three reports were confounded by both the patient's medical history and concomitant medications (2005UW11955:obesity, hyperlipidemia, olanzapine, 2006UW13639: HTN, smoker, olanzapine, 2006UW09520: family history of DM, steroids). Two reports were confounded by the patient's medical history or risk factors (2006UW04485: HTN, chronic pancreatitis, tobacco abuse, 2006UW25304: family history of DM, hypertriglyceridemia, hyperglycemia). Another report (2003UW14499) described a patient who had a FBS of 122 after six months on SEROQUEL and was sent to a medical doctor for evaluation by her psychiatrist. About three months later the patient visited her psychiatrist and reported that an attorney contacted her about a class action lawsuit regarding SEROQUEL and DM. The patient asked her psychiatrist if SEROQUEL causes DM. The psychiatrist told her that it was not shown to cause DM but that it could cause weight gain, as could many of the other medications she was taking. The patient acknowledged that she wasn't sure her weight or high blood sugar could be blamed on SEROQUEL, as she was heavy prior to starting SEROQUEL. About two weeks later the patient told her psychiatrist that she had seen a medical doctor who performed lab tests. The patient reported that she had a normal HbA_{1c} and was not diabetic. This information was taken from medical records including the psychiatrist's progress notes. In the last report (2006UW05783) it was unclear at what point the patient actually received SEROQUEL in relation to the events.

The remaining 604 reports received from attorneys, in the form of civil complaints, contained no clinical detail. Many of these reports alleged injuries as a result of taking SEROQUEL, risperidone and/or olanzapine (for which DM has been reported). These case numbers are listed in Appendix A Table A183.

6.6.2 Summary of reports of new onset DM or hyperglycemia in patients with no history of DM

Assessment of causality was not possible in these cases because of incomplete clinical information, confounding by concomitant medications for which DM or related events have

been reported, risk factors for DM (e.g. obesity or family history of DM), and/or alternative explanations.

6.6.3 Exacerbation of DM (140 reports)

One hundred forty reports described patients with a history of DM who experienced an elevated blood glucose or who reported an exacerbation of their DM. These 140 reports will be discussed below and are divided into the following categories: Medically confirmed (91 reports), Non-medically confirmed (46 reports), and Legal cases (3 reports; some treated by AstraZeneca as "medically confirmed").

Medically confirmed (91 reports)

Seven reports described a positive dechallenge. Two of these reports (2003SE03028, 2006UW20487) contained scant clinical detail. The information in these reports was limited to the patient experienced hyperglycemia or DM, discontinued therapy with SEROQUEL, and recovered. No laboratory data (baseline or at time of event), information regarding medical history or concomitant medications, and/or sequence of events was provided. One of these reports mentioned that (2003SE03028) the patient was treating their diabetes "insufficiently". The other five reports are summarized in Table 64 below.

Table 64 Reports describing a possible positive dechallenge

Case ID	Age/ Sex	Dose TTO	Relevant hx	Relevant con meds	Comment
2005UW02117	67/F	300 mg/day; 17 mos	HTN, obesity, DM	Glyburide, metformin	Baseline labs: Not provided HbA_{1c} ↑ from 6.4% (5 mos after starting Seroquel) to 13.2% after 17 mos on Seroquel. BG=484 mg/dL. Seroquel d/c'd. BG reportedly returned to normal (no lab value). HbA_{1c}=5.7% 3 mos after Seroquel d/c'd. No other info. .
2006UW05701	70/F	50 mg/day; 2 wks	DM	None	Baseline labs: BG: 110-150 Pt reported not being able to regulate BG. BG after starting Seroquel was >200 everyday & as high as 350. Also had 1-2 BG below 70. After 14 days Seroquel d/c'd. Reported that BG returned to baseline of 110 (1 ½ days later). No other info
2002UW08675	37/F	25 mg/day; 2 days	Type 1 DM	Insulin	Baseline labs: BG=120 mg/dl. Day 2 of Seroquel BG=180-mg/dL. Glucose reportedly remained high until Seroquel d/c'd (no other lab values). No other info.
2004UW21796	52/M	100 mg/day; 1 mo	DM	Insulin, metformin	Baseline labs: Not provided Reported that BG levels uncontrolled after starting Seroquel. Seroquel d/c'd after one mo & BG normalized (no lab data provided).

Table 64 Reports describing a possible positive dechallenge

Case ID	Age/ Sex	Dose TTO	Relevant hx	Relevant con meds	Comment
2005UW16154	47/?	200 mg/day; 4 mos	DM, hepatitis C, borderline HTN	None	Baseline labs: Not provided Within 4 mos after starting Seroquel BG=500, TRIG=600, & Pt had asymptomatic pancreatitis. Seroquel d/c'd. BG returned to normal & TRIG ↓ (no lab values). No other info.

BG blood glucose. Con meds concomitant medications. D/c'd discontinued. DM diabetes mellitus. HbA1c glycosylated hemoglobin. HTN hypertension. Hx history. Info information. Info information. Mo(s) month(s). TRIG triglycerides. TTO time to onset. Wk(s) week(s). ? unknown.

In three of these five reports describing a positive dechallenge (2005UW02117, 2004UW21796, 2005UW16154), baseline BG values were not provided, therefore it is not possible to know the patient's degree of diabetic control prior to starting SEROQUEL. In addition, these reports stated the patient's BG returned to normal but no supporting BG values were provided. In another report (2006UW05701) limited information was provided about the patient's medical history, concurrent conditions (ie, stressors, infection), or method of diabetic control (ie, diet, medication). In addition, this patient also experienced BG below 70 while on SEROQUEL. In the fifth report (2002UW08675) it was reported that the patient's BG increased from 120 to 180 after two days of therapy with SEROQUEL. The report states the patient's BG remained high until SEROQUEL was discontinued. It is unclear how long the patient continued therapy with SEROQUEL and no other laboratory values were provided.

Twelve reports were confounded by the patient's dietary non-compliance (2005AP02811, 2005SE02278, 2004AP03383, 2003GB02774, 2001AP04051, 2002AP01913, 2002AP02570, 2002AP04372, 2005PK01582, 2003AP01248, 2006AP03851, 2006UW04338). Two of these 12 reports were also confounded by concomitant medications for which hyperglycemia has been reported (2002AP01913: chlorpromazine, 2002AP04372: lithium). Another of these 12 reports (2003AP01248) described a fatal outcome, however the patient's cause of death was unknown.

Three reports were confounded by the patient's non-compliance with their diabetic medications (2005UW17084, 2003SE05853, 1998AP45979). A fourth report (2002SE06379) described a patient who experienced both hypoglycemia and hyperglycemia. These fluctuations in blood sugar were reported to be due to changes in the patient's insulin dose.

Twelve reports were confounded by concomitant medications for which hyperglycemia and/or hyperglycemia in patients with Type II DM has been reported. These reports and the confounding medications are listed in Table 65 below.

Table 65 Medically confirmed reports confounded by concomitant medications

Report #	Confounding medications	Report #	Confounding medications
2005GB00361	Chlorpromazine[a]	2004AP05675[b]	Chlorpromazine[a], metoprolol[c]

Table 65 Medically confirmed reports confounded by concomitant medications

Report #	Confounding medications	Report #	Confounding medications
2005UW05754	Olanzapine[a]	2005GB00277[f]	Lithium[g]
2004GB00463	Lithium[g]	2004AC00675	Lithium[g]
2006AP00330	Hydrochlorothiazide[d]	2005UW12218[f]	Chlorpromazine[g,h]
2003UW03539	Chlorpromazine[g], fluticasone[d]	2002AP00855	Olanzapine[a]
2002AP03102	Chlorpromazine[a]	2002SI03085	Olanzapine[a]

a For which hyperglycemia has been reported.
b This report described a negative dechallenge to Seroquel.
c For which hyperglycemia in Type II DM has been reported.
d For which mild hyperglycemia has been reported
e This patient improved while continuing Seroquel.
f This patient also had a concurrent urinary tract infection.
g Patient's diet not well controlled prior to starting Seroquel.
h For which altered glucose tolerance has been reported.

Six reports described patients who had a history of brittle diabetes or whose diabetes was not well controlled prior to starting SEROQUEL (2004UW17777, 2004UW09502, 2004UW03459, 2003AP00123, 2004AC00924, 2005UW14279).

One report (2004AP00748) described a patient who had stopped smoking and had experienced an increase in appetite, which could have lead to an increase in the patient's weight and blood sugar level.

Five reports described a negative dechallenge (ie, the patient did not recover after the discontinuation of SEROQUEL). One of these reports (2002AP03075) described a patient that was possibly non-compliant with their diet, one (2004GB02958) had a history of DKA prior to starting SEROQUEL, thus indicating that the patient's DM was not always consistently controlled, and the remaining three (2006AP00920, 2004AP02229, 2003AP02502) did not provide any information about the patient's compliance with diabetic medications or diet. The patient's blood sugar continued to be elevated 13 weeks after the discontinuation of SEROQUEL.

Another report (2003UW09606) initially received from a consumer described a patient who experienced DM as well as other adverse events (anemia, hyponatremia, hypoosmolality, proteinuria, gastroduodenitis, joint pain, weight loss, urinary retention, gastritis, hyperlipidemia, abnormal gait, hypertension). Follow-up information received from the patient's physician, however stated, "All symptoms that he has are related to his underlying diabetes, renal disease, CVA and psychosis".

One report (2005AC01376) described a patient with a family history of DM who developed DM while receiving therapy with clozapine (for which DM has been reported). Clozapine was discontinued and the patient started a diabetic diet and exercise. Four weeks later the patient started SEROQUEL. At this time the patient's FBS was still elevated (7.2 mmol/L). An unspecified amount of time later, another OGTT was performed which showed a decrease in the patient's FBS and 1-hour post, but an increase in the patient's 2-hour post glucose blood

sugar. Given the limited information regarding the patient's concomitant medications and compliance with diabetic medications/exercise it is difficult to assess the meaning of the increase in the 2-hour post glucose result.

Thirteen reports provided limited information with regards to medical history, concomitant medications, lab data, and/or details regarding the event; therefore an assessment of causality was not possible (2007UW01888, 2005AP03604, 2005AP01119, 2005UW00308, 2005UW01845, 2004UW11560, 2006UW00973, 2001AP04784, 2000UW04457, 2004SE03645, 2001GB00231, 2004AP01990, 2006UW15578). One other report (2003UW16476) of blood glucose fluctuation did not provide any laboratory data therefore it was not possible to determine if the patient experienced hyperglycemia, hypoglycemia, or both.

The remaining 28 reports contained scant clinical detail and did not lend themselves to analysis. These reports are listed in Appendix A Table A184. One of these reports (2005AC00653) described a fatal outcome. The patient died from massive pancreatitis and an increased blood glucose level was found on autopsy; but no further details were provided.

Non-medically confirmed (46 reports)

Two reports were confounded by dietary non-compliance. In one report (2005UW11350) the reporter stated that he thought the patient was taking sugar because she didn't want to take SEROQUEL. In the second report (2004UW14487) the patient's wife stated that the patient was "eating all the crap that he possibly can - he eats pizza, sugar, cakes". Another report (2007UW02407) stated that the patient's blood sugar remained out of control indicating that the patient's diabetes was not under control prior to starting SEROQUEL.

Ten reports were confounded by concomitant medications (2006UW07512: HCTZ, 2006UW01252: lithium, 2007UW03572: hydrochlorothiazide [for which mild hyperglycemia has been reported], 2005UW06848: pentoxifylline [for which altered glucose tolerance in insulin treated diabetics has been reported], 2005UW07790: lithium [for which hyperglycemia has been reported], 2005UW13845: metoprolol [for which hyperglycemia in Type II DM has been reported], 2004UW19158: lithium [for which hyperglycemia has been reported], 2004UW21118: lithium [for which hyperglycemia has been reported], 2004UW24985: metoprolol [for which hyperglycemia in Type II DM has been reported], 2002UW10887: metoprolol [for which hyperglycemia in Type II DM has been reported]).

Ten reports provided limited information with regards to medical history, concomitant medications, lab data, and/or details regarding the event; therefore an assessment of causality was not possible (2005UW09811, 2005UW12599, 2002UW08863, 2000UW04142, 2004UW24606, 2005UW06154, 2006UW09816, 2006UW10098, 2006UW19234, 2006UW18308).

The remaining 23 reports contained scant clinical detail and did not lend themselves to analysis. These reports are listed in Appendix A Table A185.

Legal cases (3 reports [all treated by AstraZeneca as "medically confirmed")

Three reports initially received from an attorney (non-medically confirmed), were treated by AstraZeneca as medically confirmed upon the receipt of medical records or a plaintiff fact sheet. One report (2006UW01004) described a patient whose DM was poorly controlled (FBS = 164 mg/dL, HbA_{1c} = 7.1%) during the year prior to starting SEROQUEL, however no information about the patient's level of control immediately prior to starting SEROQUEL was provided. This report was confounded by a concomitant medication (lithium) for which hyperglycemia has been reported. The second report (2006UW27817) described an 18-year-old patient with Type I DM. This patient had a history of DKA, which may indicate a brittle diabetes. The third report (2006UW01799) contained scant clinical detail and did not lend itself to analysis.

6.6.4 Summary of reports of exacerbation of DM

Assessment of causality was not possible in these cases because of incomplete clinical information, confounding by concomitant medications for which hyperglycemia and/or an exacerbation of DM has been reported, concurrent illnesses, documented non-compliance with diet and/or antidiabetic medications, and/or alternative explanations.

6.7 Gestational diabetes (10 reports)

Ten reports described patients who developed gestational diabetes. All of these reports were medically confirmed.

Two reports were confounded by the patient's history of gestational diabetes (2004UW25674, 2002GB02814), one other report (2005UW06397) was confounded by concomitant cigarette smoking, and another report (2007UW01193) was confounded by concomitant cigarette smoking and a medical history of gestational diabetes. Another report (2002GB00947) described a patient who was treated with olanzapine (for which DM and hyperglycemia has been reported) and then switched to SEROQUEL because of excessive weight gain. The patient became pregnant and developed gestational DM in the third trimester.

One report (1999AP05218) was confounded by a concomitant medication (chlorpromazine) for which hyperglycemia and DM has been reported and in another report (2005GB01395) the patient was also taking olanzapine (for which DM has been reported), however the timing of olanzapine therapy related to the patient's pregnancy was unclear. Two reports (2005UW08732, 2006UW05055) contained limited information (no medical history or family history, lab data, weight, race and/or details regarding the event); therefore an assessment of causality was not possible. The last report (2004UW21521) contained scant clinical detail and did not lend itself to analysis.

6.7.1 Summary of reports of gestational diabetes

Assessment of causality was not possible in these cases because of incomplete clinical information, confounding by concomitant medications for which DM or related events have been reported, a history of gestational diabetes, and/or alternative explanations.

6.8 Non-AstraZeneca sponsored studies (31 reports)

Thirty-one reports were received from clinical trials that were not sponsored by AstraZeneca. Twenty-eight of these reports came from two post-marketing surveillance studies (one in Japan, one in Belgium). Two other reports came from clinical trials that were sponsored by other pharmaceutical companies and the last report was from the CATIE trial (Clinical Antipsychotic Trials of Intervention Effectiveness), which was sponsored by the National Institute of Mental Health (NIMH). These reports are discussed below.

6.8.1 Post marketing surveillance studies

6.8.1.1 Japan (19 reports)

A post-Marketing study was performed in Japan by Astellas Pharma, Inc, which is AstraZeneca's business partner in Japan. This study was performed to evaluate the safety and efficacy of SEROQUEL under actual clinical use. The follow-up survey was an actual-use investigation to evaluate the influence of SEROQUEL on blood sugar. The study included 1,047 patients that were captured across approximately 300-centers. A diagnosis of schizophrenia was the only inclusion criteria and no exclusion criteria were included. The observation period ranged from a minimum of eight weeks to a maximum of two years and laboratory tests regarding blood sugar were evaluated.

Nineteen adverse event reports involving glucose dysregulation from this study have been received by AstraZeneca and are discussed below.

New onset DM or hyperglycemia in patients with no known history of DM (11 reports)

Eleven reports describe patients who experienced a new onset of DM and/or experienced hyperglycemia and had no known history of DM.

Three reports were confounded by both the patient's medical history/risk factors and concomitant medications for which hyperglycemia and/or DM has been reported (2003AP04189: decreased activity, chlorpromazine, 2003AP03607: elevated FBS (130 mg/dL) on day SEROQUEL initiated, chlorpromazine, 2003AP02011: obesity, chlorpromazine).

Three reports were confounded by the patient's medical history/risk factors (2003AP03914: obesity, 2004AP00862: HTN, 2004AP00859: HTN, hyperlipidemia) and two reports were confounded by concomitant medications for which hyperglycemia and/or DM has been reported (2003AP01199: olanzapine, 2004AP00856: chlorpromazine).

Another report (2004AP00854) described a patient who recovered from hyperglycemia while continuing therapy with SEROQUEL and one report (2004AP00764) contained limited information (no baseline laboratory values, no information regarding sequence/treatment of events). The last report (2004AP00788) described a patient who experienced hyperglycemia eleven months after therapy with SEROQUEL was completed.

Exacerbation of pre-existing DM (8 reports)

Eight reports described an exacerbation of a patient's pre-existing DM.

Three reports were confounded by medications for which hyperglycemia and/or an exacerbation of DM has been reported (2003AP04406: olanzapine, 2003AP04186: chlorpromazine, 2003AP03672: chlorpromazine).

Three other reports described patients who were concomitantly receiving risperidone. One report (2003AP04510) described a negative dechallenge and another (2003AP01473) report described a patient who was not compliant with dietary instructions. In the third report (2003AP04476) no information regarding the patient's glucose control immediately prior to starting SEROQUEL was not provided.

One report (2003AP01034) described a patient who experienced an exacerbation of their diabetes one month after therapy with SEROQUEL was discontinued and while experiencing a concurrent infection (tinea pedis). The last report (2004AP00747) described a patient who experienced a "possible aggravation of DM". This patient also experienced an elevated WBC count at the same time, which may suggest a concurrent infection.

6.8.1.2 Belgium (9 reports)

A clinical study to evaluate metabolic disturbances in patients receiving antipsychotic treatment, which is not sponsored by AstraZeneca, is being conducted in Belgium. This is a multi-center observational, cross-sectional study with prospective follow-up for metabolic disturbances on the basis of good-clinical practice guidelines.

Patients in this study were divided into three groups: (1) Patients treated with antipsychotics for >6 months (n = 2000), (2) Patients who switched antipsychotic treatment (n = 300; 50 per antipsychotic treatment of 2nd generation), (3) Patients who received an antipsychotic for the first time (n = 300; 50 per antipsychotic treatment of 2nd generation). These patients were evaluated at baseline for metabolic risk factors, height, weight, abdominal and hip circumferences, blood pressure, and had blood drawn for glucose, insulin, and lipids. The frequency of follow-up evaluations depended on the patient's baseline values and guidelines. Follow-up visits included evaluation of height, weight, abdominal and hip circumferences, blood pressure, and blood samples were taken for glucose, insulin, and lipids.

Nine adverse event reports involving glucose dysregulation from this study have been received by AstraZeneca and are discussed below.

New onset DM or hyperglycemia in patients with no known history of DM (9 reports)

Nine reports describe patients who experienced a new onset of DM and/or experienced hyperglycemia and had no known history of DM.

One report (2005AC01949) described a patient who became pre-diabetic while taking SEROQUEL. This report was confounded by both the patient's history of obesity (BMI = 33.2) and by a concomitant medication (lithium) for which hyperglycemia has been reported.

One report (2005AC00287) was confounded by the patient's medical history (HTN, hyperlipidemia, smoking) and two concomitant medications (olanzapine, clozapine) for which DM has been reported.

The other seven reports were confounded by the patient's medical history/risk factors (2005AC01988: tobacco abuse, 2005AC01982: obesity [BMI = 34.5 kg/m^2], tobacco use, 2005AC00288: smoker, obesity [BMI = 46 kg/m^2], hyperlipidemia, HTN, 2005AC00285: metabolic syndrome, obesity [BMI = 38 kg/m^2], 2005AC00273: metabolic syndrome, HTN, obesity [BMI = 35.5 kg/m^2], 2005AC00060: obesity [BMI = 32.2 kg/m^2], metabolic syndrome, family history of DM, hyperlipidemia, increased appetite, 2005AC01981: obesity [BMI = 32.7 kg/m^2], tobacco abuse).

6.8.1.3 Summary of reports from two Phase IV post-marketing surveillance studies

Assessment of causality was not possible in these cases because of incomplete clinical information, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (e.g. obesity or family history of DM) or an exacerbation of DM (infection), and/or alternative explanations.

6.8.2 Study reports from other sources

New onset DM or hyperglycemia in patients with no known history of DM (3 reports)

All three reports describe patients who experienced a new onset of DM and/or experienced hyperglycemia and had no known history of DM

The first report (2006SE00445) described a patient enrolled in a Johnson & Johnson study (the Risperdal Consta trial of relapse prevention and effectiveness). This study is an open-label, multi-center, randomized two-year trial of Risperdal Consta versus SEROQUEL and aripiprazole in patients with schizophrenia or schizoaffective disorder. After two months on SEROQUEL it was reported that the patient had lost 26 kg and had hyperglycemia. The patient was treated with insulin and diabetic diet, therapy with SEROQUEL continued, and the patient recovered. This report contained limited information. No laboratory data or information about concomitant medications was provided.

The second report (2003UW10277) described a patient enrolled in the CATIE trial, which was a double-blind study comparing the effectiveness of antipsychotic medications in patients with schizophrenia. After about four months on "Phase I study drug" (code not broken) the patient had blurred vision, light-headedness, dizziness, weakness, and fatigue. The patient's serum glucose was reported to be 674 mg/dL and HbA_{1c} was >14%. The patient was hospitalized with new onset DM; the following day her glucose had decreased to 335 mg/dL. The patient was treated with intravenous insulin, oral antidiabetic medications, diabetic teaching, and diabetic diet. This report was confounded by the patient's history of HTN and by a family history of DM. In addition, since the study had not been unblinded, it was unknown if the patient actually received SEROQUEL.

The third report (2005SE02961) described a patient enrolled in a Bristol-Myers Squibb open-label study for the management of community-treated patients with schizophrenia. After four months of therapy with SEROQUEL the patient's blood glucose was 24.9 mmol/L. Eight days later the patient's blood glucose was 27 mmol/L without clinical symptoms. The patient was hospitalized, a diagnosis of DM was made, and the patient was started on oral antidiabetic medications. The patient recovered five weeks later. No baseline glucose laboratory data or medical history/risk factors were provided. In addition, the patient was concomitantly receiving fenofibrate, which may suggest a history of hypertriglyceridemia.

6.8.2.1 Summary of study reports from other sources

Assessment of causality was not possible in these cases because of incomplete clinical information, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (e.g. obesity or family history of DM), and/or alternative explanations.

7. DISCUSSION

Having received the results of two placebo controlled clinical trialsdesigned to evaluate quetiapine and mood stabilizer as long-term maintenance therapy of bipolar disorder, the topic of glucose dysregulation including diabetes mellitus (DM), hyperglycemia, diabetic ketoacidosis (DKA), and diabetic coma was identified as a topic of review at SERM (Safety Evaluation and Review Meeting). This document provides a comprehensive review of the published literature, AstraZeneca sponsored clinical trials, and post-marketing reports regarding SEROQUEL and this topic.

According to the literature, the prevalence of DM in the schizophrenic population (up to 15.8% in one study [Mukherjee et al 1996] and 10.8-14.9% in another study [Dixon et al 2000]) has been noted to exceed that in the general population (7.3%/United States [US] [Mokdad et al 2001]) even prior to the introduction of atypical antipsychotic medications. Furthermore, a recent study (Ryan et al 2003) showed impaired fasting glucose tolerance in drug-naïve schizophrenic patients. In addition to schizophrenia, other studies have suggested that there is an increased prevalence of DM in patients with other psychiatric disorders (ie, bipolar disorder, anxiety, depression) compared to the general population (Regenold et al 2002, Everson Rose et al 2004).

The medical/scientific literature was inconsistent with regard to quetiapine and diabetes. The various data sources and analytic techniques used, each with its own strengths and weaknesses have contributed to an array of results. Some authors have found an increased risk for SEROQUEL and some have found no increased risk compared to a variety of different comparator groups. Limitations in these studies included in appropriate comparison groups, lack of information on major known risk factors for diabetes (e.g. obesity, family history, physical activity, co-morbidities, co-prescriptions), the potential for confounding by indication, lack of systematic screening for diabetes in the subject population, and questionable generalizability due to restrictive inclusion criteria. In sum, the epidemiology

literature has been inconsistent with regard to quetiapine and diabetes. Inherent methodological issues contribute to the challenges of studying this complex question.

Trials 126 and 127 were two long term clinical trials designed to compare the efficacy and safety of quetiapine to placebo when used as adjunct to mood stabilizers (lithium or valproate) in the maintenance treatment of bipolar I disorder in adult patients. These two trials were not designed to evaluate diabetic status. The pre-planned analyses of glucose metabolism laboratory data, the summary of aggregated AE terms predefined by AstraZeneca as "potentially associated with diabetes" reported in the randomized treatment phase, the outcome of the post-hoc adjudication of cases of interest and the outcome of the post-hoc exploratory analyses all summarized here, were also presented to and discussed with an external diabetologist, Dr Robert Ratner.

Among patients treated with quetiapine and a mood stabilizer (lithium or valproate) for at least 12 weeks and then randomized to continue with quetiapine and a mood stabilizer or switch to placebo and a mood stabilizer and followed for up to 2 years:

- In the randomized phase quetiapine and a mood stabilizer was associated with a greater mean increase from baseline than placebo and a mood stabilizer in blood glucose (5.05 mg/dL) and HbA1c (0.14%). In patients whose last meal was at least 8 hours before venipuncture the mean difference between quetiapine and placebo was 5.49 mg/dL for glucose and 0.15% for HbA1c.

- The incidence density of a single emergent fasting blood glucose value ≥126 mg/dL was higher in patients randomized to quetiapine and mood stabilizer (18.03 patients per 100 patient-years) than in patients randomized to placebo and mood stabilizer (9.53 patients per 100 patient-years). The incidence of values ≥126 mg/dL was analyzed using a Poisson regression model adjusting for exposure time. The estimated ratio (quetiapine adjunct with lithium or valproate vs placebo adjunct with lithium or valproate) of incidence densities was 1.893 with a 95% confidence interval between 1.109 and 3.231.

- In the randomized phase there were 6 (0.93%) reported adverse events of diabetes (including one case of diabetic ketoacidosis) in the quetiapine and mood stabilizer group and 1 (0.15%) in the placebo and mood stabilizer group. When adjusting for treatment exposure in the randomized phase, the incidence densities were 1.6 cases per 100 patient-years for quetiapine compared to 0.4 cases per 100 patient-years for placebo.

Given the absence of definitive diagnostic testing for diabetes within the design of these studies (Trials 126 & 127), as hereafter described in detail , reliable and accurate determination of incidence and risk for diabetes for patients enrolled in these studies is not possible. Subject to the limitations hereafter described , the calculated absolute risk of onset of possible diabetes by adjudicated post-hoc analysis is low (0.72% - 23 patients divided by 3187 patients in the open-label safety population not classified as "diabetic" according to pre-defined criteria at enrollment). However during the randomized phase an approximately 2-

fold increase in incidence density over placebo in observations of glucose values ≥126 mg/dL was observed.

Only one AstraZeneca clinical trial (Trial 125) to date had changes in glucose regulation as its primary endpoint. In this trial, the comparison groups were patients treated with olanzapine and those treated with risperidone. The primary objective of Trial 125 was to compare the safety/tolerability profile of quetiapine and olanzapine on glucose metabolism in schizophrenic patients by evaluating change from randomization in AUC (area under the curve) plasma glucose values following oral glucose tolerance test (OGTT). The analysis of mean glucose values at separate time points during the OGTT showed, that while fasting glucose and 30 min glucose levels were similar across the treatment groups at Week 24, the quetiapine group had lower plasma glucose values than both olanzapine and risperidone at 60, 90 and 120 minutes (2-hours) after the glucose load. For mean 2-hour-glucose value, no change from randomization at Week 24 was observed in the quetiapine group, while in the olanzapine and risperidone groups mean increases in 2-hour glucose from randomization at Week 24 were seen. Thus, after 24 weeks of treatment, there appeared to be a difference between the patients in the three treatment groups in the ability to handle glucose challenge.

In addition, relevant data from AstraZeneca's cumulative clinical trial database (Safety 9.1) were reviewed. Since DM and hyperglycemia are medical diagnoses that are based on laboratory data, the laboratory data from the trials in the Safety 9.1 database were reviewed for information regarding glucose metabolism. Until recently, fasting glucoses were not obtained in the majority of AstraZeneca's clinical trials; the interpretative value of the non-fasting lab data is limited. In the majority of the trials the mean change from baseline in quetiapine-treated patients was similar to that which was seen in placebo-treated patients. For completeness, adverse event data from these trials were also reviewed, however it should be noted that in the majority of AstraZeneca clinical trials a pre-existing history of DM would not exclude a patient from participating in the trial.

A search of AstraZeneca's worldwide safety database (Clintrace) on 01 March 2007 identified 1679 (completed) adverse event reports of DM and/or diabetes related events. Assessment of causality was not possible in these cases because of incomplete clinical information, unclear temporal sequence of exposure and outcome, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (e.g. obesity or family history of DM), documented dietary non-compliance, and/or alternative explanations. Since the time of this search (01 March 2007) and as of 30 March 2007, AstraZeneca has received an additional 54 initial legal reports and 2503 follow-up legal reports. For almost all of these legal cases, the information provided is in the form of a civil complaint containing no clinical information or a plaintiff fact sheet. AstraZeneca is treating these plaintiff fact sheets as medically confirmed and submitting them to regulatory authorities as such.

It has been estimated that about 23.2 million patients worldwide (an estimate of almost 14.4 million patients in the US and 8.8 million patients in the rest of the world [ROW]) have been exposed to SEROQUEL for all time through February 2007 for the US and through 2006 for ROW.

8. REFERENCES

ADA 2004
American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care 27: 596-601, 2004.

Amaladoss et al 2006
Amaladoss AS, Balram C, Wang A. Incidence of glucose dysregulation induced by atypical antipsychotics (Abstract P122). European Psychiatry 21: S222, 2006. http://www.sciencedirect.com/science/article/B6VM1-4J5T5TS-2/2/cfc9f04d5517ad53739c181dda350e5d.

Ananth et al 2005
Ananth J, Venkatesh R, Burgoyne K, et al. Atypical antipsychotic induced weight gain: pathophysiology and management. Ann Clin Psychiatry 2004;16:75–85.

Andrews 1992
Andrews RCR. Diabetes and schizophrenia: genes or zinc deficiency. Lancet 340: 1160, 1992.

Barner et al 2004
Barner JC, Worchel J, Yang M. Frequency of new-onset diabetes mellitus and use of antipsychotic drugs among central Texas veterans. Pharmacotherapy 24: 1529-1538, 2004.

Barnett et al 2006
Barnett M, Argo T, Alexander B, Perry P. A regional comparison of developing diabetes among VA patients exposed to typical and atypical antipsychotics relative to corticosteroids and proton pump inhibitors. Annals of Clinical Psychiatry 18(1): 1-7, 2006. (not available on-line).

Basu and Meltzer 2006
Basu A and Meltzer HY. Differential trends in prevalence of diabetes and unrelated general medical illness for schizophrenia patients before and after the atypical antipsychotic era. Schizophrenia Research 86(1-3): 99-109, 2006. http://www.sciencedirect.com/science/article/B6TC2-4K48M8H-2/2/9c4dc743b112972f07a26f2412998faf.

Beaglehole and Lefebvre 2004
Beaglehole R and Lefebvre P (2004). Diabetes Action Now. Retrieved 06 March 2006 from http://www.who.int/diabetes/BOOKLET_HTML/en/print.html

Beers and Berkow 1999
Beers MH, Berkow R, editors. The Merck manual of diagnosis and therapy. 17th ed. Whitehouse Station, NJ: Merck Research Laboratories; 1999. p. 206-207.

Brown et al 2005
Brown LC, Majumdar SR, Newman SC, Johnson JA. History of Depression Increases Risk of Type 2 Diabetes in Younger Adults. Diabetes Care 28: 1063-1067, 5-1-2005.

Brown et al 1999
Brown S, Birtwistle J, Roe L, et al. The unhealthy lifestyle of people with schizophrenia. Psychological Medicine 29: 697-701, 1999.

Bruno et al 1992
Bruno G, Bargero G, Vuolo A, Pisu E, Pagano G. A population-based prevalence survey of known diabetes mellitus in Northern Italy based upon multiple independent sources of ascertainment. Diabetologia 35: 851-856, 1992.

Buse et al 2003
Buse JB, Cavazzoni P, Hornbuckle K, Hutchins D, Breier A, Jovanovic L. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. Journal of Clinical Epidemiology 56: 164-170, 2003.

Bushe and Holt 2004
Bushe C, Holt R. Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. British Journal of Psychiatry 184: s67-s71, 4-1-2004.

Casadebaig et al 1997
Casadebaig F, Philippe A, Guillaud-Bataille JM, Gausset MF, Quemada N, Terra JL. Schizophrenic patients: physical health and access to somatic care. European Psychiatry 12: 289-293, 1997.

Casey et al 2001
Casey DE, Danielson EM, Fishman NB. Prevalence of diabetes in schizophrenia patients treated with antipsychotics. 154th Annual Meeting of the American Psychiatric Association New Orleans, LA: May 7-10, 2001.

Cassidy et al 1999
Cassidy F, Ahearn E, Carroll BJ. Elevated Frequency of Diabetes Mellitus in Hospitalized Manic-Depressive Patients. American Journal of Psychiatry 156: 1417-1420, 9-1-1999.

Cavazzoni et al 2004
Cavazzoni P, Mukhopadhyay N, Carlson C, Breier A, Buse J. Retrospective analysis of risk factors in patients with treatment-emergent diabetes during clinical trials of antipsychotic medications. British Journal of Psychiatry 184: s94-101, 4-1-2004.

CDC 2005
CDC. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services, 2005.
http://www.cdc.gov/diabetes/pubs/factsheet05.htm.

Cheng et al 2006
Cheng JS, Huang WF, Tsai YW, Lin KM, Shih YT. New-onset diabetes mellitus associated with use of atypical antipsychotics among schizophrenic patients in Taiwan (Abstract PMH6). Value in Health 9(3): A65-A66, 2006. http://www.blackwell-synergy.com/doi/abs/10.1111/j.1524-4733.2006.00102_2.x.

Cheta et al 1990
Cheta D, Dumitrescu C, Georgescu M, Cocioaba G, Lichiardopol R, Stanoran M, et al. A study on the types of diabetes mellitus in first degree relatives of diabetic patients. Diabetes and Metabolism 16: 11-15, 1990.

Citrome et al 2004
Citrome L, Jaffi A, Levine J, Allingham B, Robinson J. Relationship Between Antipsychotic Medication Treatment and New Cases of Diabetes Among Psychiatric Inpatients. Psychiatric Services 55: 1006-1013, 9-1-2004.

Cohen et al 2006
Cohen D, Stolk RP, Grobbee DE, Gispen-de Wied CC. Hyperglycemia and Diabetes in Patients With Schizophrenia or Schizoaffective Disorders. Diabetes Care 29: 786-791, 4-1-2006.

Cohn et al 2002
Cohn T, Wolever T, Zipursky R, et al. Screening for diabetes and impaired glucose tolerance in patients on antipsychotic medication. International Journal of Neuropsychopharmacology 5: S168, 2002.

Correll et al 2004
Correll CU, Parikh UH, Kane JM, Malhotra AK. Second generation anti-psychotic-induced insulin resistance in anti-psychotic-naive children and adolescents. Biological Psychiatry 55: 16S-17S, 2004.

Csizmadi et al 2005
Csizmadi I, Collet J-P, Boivin J-F. Bias and confounding in pharmacoepidemiology. Chapter 47 In: Pharmacoepidemiology (eds. Strom, BL), Edition Fourth. West Sussex, England: John Wiley & Sons Ltd, 2005. Pages 791-809.

Cunningham et al 2003
Cunningham,F, Lambert B, Dalack G, Miller D, Hur K. Diabetes associated with antipsychotic use in veterans with schizophrenia. Pharmacoepidemiology and Drug Safety 12: S154-S155, 2003.

DeHert et al 2006
DeHert M, VanWinkel R, VanEyck D, Hanssens L, Wampers M, Scheen A, Peuskens J. Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study. Clinical Practice and Epidemiology in Mental Health 2: 14, 2006. http://www.biomedcentral.com/1471-244X/6/11.

Diabetes Atlas 2003
Diabetes Atlas (Second Edition). Brussels, Belgium: International Diabetes Federation, 2003. http://www.eatlas.idf.org/.

Dinan 2004
Dinan TG. Stress and the genesis of diabetes mellitus in schizophrenia. British Journal of Psychiatry 184: s72-s75, 4-1-2004.

Dixon et al 2000
Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, Lehman A. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophrenia Bulletin 26: 903-912, 2000.

Dynes 1969
Dynes JB. Diabetes in schizophrenia and diabetes in nonpsychotic medical patients. Diseases of the Nervous System 30: 341-344, 1969.

Elman et al 2006
Elman I, Borsook D, Lukas SE. Food intake and reward mechanisms in patients with schizophrenia: implications for metabolic disturbances and treatment with second-generation antipsychotic agents. Neuropsychopharmacology 31: ?, 2006.

Emsley et al 2005
Emsley R, Turner HJ, Schronen J, Botha K, Smit R, Oosthuizen PP. Effects of quetiapine and haloperidol on body mass index and glycaemic control: a long term, randomized, controlled trial. International Journal of Neuropsychopharmacology 8: 175-192, 2005.

Etminan et al 2003
Etminan M, Streiner DL, Rochon PA. Exploring the association between atypical neuroleptic agents and diabetes mellitus in older adults. Pharmacotherapy 23: 1411-1415, 2003.

Everson Rose et al 2004
Everson-Rose SA, Meyer PM, Powell LH, Pandey D, Torrens JI, Kravitz HM, Bromberger JT, Matthews KA. Depressive Symptoms, Insulin Resistance, and Risk of Diabetes in Women at Midlife. Diabetes Care 27: 2856-2862, 12-1-2004

FDA 2005
FDA. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Rockville, MD: Center for Drug Evaluation and Research, Food and Drug Administration, 2005. http://www.fda.gov/cder/guidance/6359OCC.pdf.

Feldman et al 2004
Feldman PD, Hay LK, Deberdt W, Kennedy JS, Hutchins DS, Hay DP, Hardy TA, Hoffmann VP, Hornbuckle K, Breier A. Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in a Geriatric Population in the United States. Journal of the American Medical Directors Association 5: 38-46, 2004.

Felker et al 1996
Felker B, Yazel JJ, Short D. Mortality and medical morbidity among psychiatric patients: a review. Psychiatric Services 47: 1356-1363, 1996.

Firestone (2005)
Firestone A. Weight gain and diabetes with "second-generation" antipsychotic drugs (letter). Medical Journal of Australia 182: 652-653, 2005.

Ford et al 1997
Ford ES, Williamson DF, Liu S. Weight Change and Diabetes Incidence: Findings from a National Cohort of US Adults. Am J Epidemiol 1997;146(3):214-22.

Fox et al 2006
Fox CS, Pencina MJ, Meigs JB, Vasan RS, Levitzky YS, D'Agostino RB Sr. Trends in the Incidence of Type 2 Diabetes Mellitus From the 1970s to the 1990s: The Framingham Heart Study. Circulation 2006;113:2914-18.

Gianfrancesco et al 2006a
Gianfrancesco F, Pesa J, Wang RH, Nasrallah H. Assessment of antipsychotic-related risk of diabetes mellitus in a Medicaid psychosis population: Sensitivity to study design. American Journal of Health-System Pharmacy 63: 431-441, 3-1-2006a.

Gianfrencesco et al 2006b
Gianfrancesco F, Wang R-H, Nasrallah HA. The influence of study design on the results of pharmacoepidemiologic studies of diabetes risk with antipsychotic therapy. Annals of Clinical Psychiatry 18(1): 9-17, 2006b. (not available on-line).

Gianfrancesco et al 2003
Gianfrancesco F, White RE, Wang R, Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. Journal of Clinical Psychopharmacology 23: 328-335, 2003.

Guo et al 2005
Guo JJ, Keck PE, Li H, Corey-Lisle P, Jiang DM, Jang R, L'Italien GJ. Risk of diabetes mellitus associated with atypical antipsychotic use among patients with bipolar disorders: population-based case-control study (Abstract P.2.046). European Neuropsychopharmacology 15 (suppl 3): S411, 2005.
http://www.sciencedirect.com/science?_ob=MImg&_imagekey=B6T26-4HJC4K4-94-1&_cdi=4910&_user=528388&_orig=browse&_coverDate=12%2F31%2F2005&_sk=999849999.8996&view=c&wchp=dGLbVzW-zSkzV&md5=d6276b811f2cbd5459353d2ecfbcd0a0&ie=/sdarticle.pdf.

Guo et al 2006
Guo JJ, Keck PE Jr, Corey-Lisle PK, Li H, Jiang D, Jang R, L'Italien GJ. Risk of diabetes mellitus associated with atypical antipsychotic use among patients with bipolar disorder: a

retrospective, population-based, case-control study. Journal of Clinical Psychiatry 67: 1055-1061, 2006. http://www.psychiatrist.com/privatepdf/2006/v67n07/v67n0707.pdf.

Guo et al 2007
Guo JJ, Keck PE Jr, Corey-Lisle PK, Li H, Jiang D, Jang R, L'Italien GJ. Risk of diabetes mellitus associated with atypical antipsychotic use among Medicaid patients with bipolar disorder: a nested case-control study. Pharmacotherapy 27(1): 27-35, 2007. http://www.atypon-link.com/PPI/doi/abs/10.1592/phco.27.1.27.

Gupta et al 2003
Gupta S, Steinmeyer C, Frank B, Madhusoodanan S, Lackwood K, Lentz B, Keller P. Hyperglycemia and hypertriglyceridemia in real world patients on antipsychotic therapy. American Journal of Therapeutics 10: 348-355, 2003.

Harrington et al 2006
Harrington P, Barner JC, Crismon ML, Lawson KIA, Mascarenas C, Rascati KL. Incident diabetes associated with use of second-generation antipsychotic (SGA) therapy: an evaluation of th eimpact of dose and treatment indication (abstract PMH5). Value in Health 9(3): A65, 2006. http://www.blackwell-synergy.com/doi/abs/10.1111/j.1524-4733.2006.00102_2.x.

Harris et al 1998
Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer H-M, Byrd-Holt DD. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults. Diabetes Care 1998;21(4):518-24.

Haupt and Newcomer 2001
Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. Journal of Clinical Psychiatry 62: 15-26, 2001.

Henderson et al 2005
Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, Weber MT, Anderson EJ, Allison DB, Daley TB, Schoenfeld D, Goff DC. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. Archives of General Psychiatry 62(1): 19-28, 2005. http://archpsyc.ama-assn.org/cgi/content/abstract/62/1/19

Jest et al 1996
Jest DV, Gladsjo JA, Lindamer LA, et al. Medical comorbidity in schizophrenia. Schizophrenia Bulletin 22: 413-430, 1996.

Kaboli et al 2004
Kaboli PJ, McClimon BJ, Hoth AB, Barnett MJ. Assessing the accuracy of computerized medication histories. American Journal of Managed Care 10: 872-877, 2004. http://www.ajmc.com/Article.cfm?Menu=1&ID=2762.

Koro et al 2002
Koro CE, Fedder DO, L'Italien GJ, Weiss SS, Magder LS, Kreyenbuhl J, Revicki DA, Buchanan RW. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. British Medical Journal 325: 243, 8-3-2002.

Kruse et al 2003
Kruse J, Schmitz N, Thefeld W. On the Association Between Diabetes and Mental Disorders in a Community Sample: Results from the German National Health Interview and Examination Survey. Diabetes Care 26: 1841-1846, 6-1-2003.

L'Italien et al 2006
L'Italien GJ, Blonde L, Hanssens L, McQuade R. Prevalence of diabetes/cardiovascular risk factors among schizophrenia patients treated with atypical antipsychotics in a multi-center, randomized, naturalistic, open-label study (Schizophrenia Trial of Aripiprazole: STAR study) (abstract 2329-PO). Diabetes 55 (suppl 1): A538, 2006.

Lambert et al 2002
Lambert B, Chou C-H, Chang K-Y, Iwamoto T, Tafesse E. Assessing the risk of antipsychotic-induced Type II diabetes among schizophrenics: a matched case-control study. ? 2002.

Lambert et al 2005
Lambert BL, Chou C-H, Chang K-Y, Tafesse E, Carson W. Antipsychotic exposure and type 2 diabetes among patients with schizophrenia: a matched case-control study of California Medicaid claims. Pharmacoepidemiology and Drug Safety 14: 417-425, 2005.

Lambert et al 2006a
Lambert BL, Cunningham FE, Miller DR, Dalack GW, Hur K. Diabetes risk associated with the use of olanzapine, quetipaine, and risperidone in Veterans Health Administration patients with schizophrenia. American Journal of Epidemiology 164(7): 672-681, 2006a.

Lambert et al 2006b
Lambert MT, Copeland LA, Sampson N, Duffy SA. New-onset type-2 diabetes associated with atypical antipsychotic medications. Progress in Neuro-Psychopharmacology and Biological Psychiatry In Press, Corrected Proof 2006b.

Lamberti et al 2003
Lamberti J, Crilly J, Maharaj K, Olson D, Costea O. Prevalence of adult-onset diabetes among outpatients receiving antipsychotic drugs. International Congress on Schizophrenia Research (ICOSR) 60: 360, 2003.

Lamberti et al 2004
Lamberti JS, Crilly JF, Maharaj K, Olson D, Wiener K, Dvorin S. Prevalence of diabetes mellitus among outpatients with severe mental disorders receiving atypical anti-psychotic drugs. Journal of Clinical Psychiatry 65: 702-706, 2004.

Larsen et al 2003
Larsen PR, Kronenberg HM, Melmed S, Polonsky KS. Type 2 Diabetes Mellitus. In: Williams Textbook of Endocrinology 10th ed. Saunders 2003 Philadelphia, PA. pp 1428-1433.

Leslie and Rosenheck 2004
Leslie DL, Rosenheck RA. Incidence of Newly Diagnosed Diabetes Attributable to Atypical Antipsychotic Medications. American Journal of Psychiatry 161: 1709-1711, 9-1-2004.

Leslie and Rosenheck 2005
Leslie DL, Rosenheck RA. Pharmacotherapy and Health Care Costs Among Patients With Schizophrenia and Newly Diagnosed Diabetes. Psychiatric Services 56: 803-809, 7-1-2005.

Mamdani 2005
Mamdani M. Antipsychotics and diabetes: is there an association? Pharmacoepidemiology and Drug Safety 14: 403-405, 2005.

Miller et al 2005
Miller EA, Leslie DL, Rosenheck RA. Incidence of new-onset diabetes mellitus among patients receiving atypical neuroleptics in the treatment of mental illness: evidence from a privately insured population. Journal of Nervous and Mental Disease 193: 387-395, 2005.

Mokdad et al 2001
Mokdad AH et al. The Continuing Epidemics of Obesity and Diabetes in the United States. Journal of the American Medical Association 2001: 286(10);1195.

Mukherjee et al 1996
Mukherjee S, Decina P, Bocola V, Saraceni, F, Scapicchio PL. Diabetes mellitus in schizophrenic patients. Comprehensive Psychiatry 37: 68-73, 1996.

Mukherjee et al 1989
Mukherjee S, Schur DB, Reddy R. Family history of type 2 diabetes in schizophrenic patients. Lancet 333: 495, 1989.

Newcomer et al 2006
Newcomer J, Meyer J, Loebel A, Parsons B. Differential effects of atypical antipsychotics on metabolic syndrome (Abstract P143). European Psychiatry 21: S228, 2006. http://www.sciencedirect.com/science/article/B6VM1-4J5T5TS-2/2/cfc9f04d5517ad53739c181dda350e5d.

Osborn 2001
Osborn DPJ. The poor physical health of people with mental illness. Western Journal of Medicine 175: 329, 2001.

Ostbye et al 2005
Ostbye T, Curtis LH, Masselink LE, Hutchison S, Wright A, Dans PE, Schulman KA, Krishnan RR. Atypical antipsychotic drugs and diabetes mellitus in a large outpatient

population: a retrospective cohort study. Pharmacoepidemiology and Drug Safety 14: 407-415, 2005.

Peet 2004
Peet M. Diet, diabetes and schizophrenia: review and hypothesis. British Journal of Psychiatry 184: s102-s105, 4-1-2004.

Phelan et al 2001
Phelan M, Stradins L, Morrison S. Physical health of people with severe mental illness. British Medical Journal 322: 444, 2001.

Ray 2003
Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. American Journal of Epidemiology 158: 915-920, 11-1-2003.

Regenold et al 2002
Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use [Erratum at J. Affect. Disorder. 70 (2002) 19--26]. Journal of Affective Disorders 70: 19-26, 2002.

Rizos et al 2006
Rizos EN, Sakellaropoulos KR, Papadopoulou AG, Ikonomakis EF, Finokaliotis EG, Katsafouros KA. Evaluation of serum lipids in a sample of schizophrenic patients, medicated with atypical antipsychotic treatment - a preliminary study (Abstract 152). European Psychiatry 21: S231, 2006. http://www.sciencedirect.com/science/article/B6VM1-4J5T5TS-2/2/cfc9f04d5517ad53739c181dda350e5d.

Rosamond et al 2007
Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al. The American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics--2007 Update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115(5):e69-e171.

Rouillon and Sorbara 2005
Rouillon F, Sorbara F. Schizophrenia and diabetes: Epidemiological data. European Psychiatry 20: S345-S348, 2005.

Ryan et al 2003
Ryan MCM, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. American Journal of Psychiatry 160: 284-289, 2003.

Ryan and Thakore 2002
Ryan MCM Thakore JH. Physical consequences of schizophrenia and its treatment: the metabolic syndrome. Life Science 71: 239-257, 2002.

Sacchetti et al 2005
Sacchetti E, Turrina C, Parrinello G, Brignoli O, Stefanini G, Mazzaglia G. Incidence of diabetes in a general practice population: a database cohort study on the relationship with haloperidol, olanzapine, risperidone, or quetiapine exposure. International Clinical Psychopharmacology 20: 33-37, 2005.

Sernyak et al 2005
Sernyak MJ, Gluanski B, Rosenheck R. Undiagnosed hyperglycemia in patients treated with atypical antipsychotics. Journal of Clinical Psychiatry 66: 1463-1467, 2005.

Sernyak et al 2002
Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R. Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia. American Journal of Psychiatry 159: 561-566, 4-1-2002.

Strom 2001
Strom BL. Data validity issues in using claims data. Pharmacoepidemiology and Drug Safety 10: 389-392, 2001.

Subramaniam et al 2003
Subramaniam M, Chong SA, Pek E. Diabetes Mellitus and Impaired Glucose Tolerance in patients with schizophrenia. Canadian Journal of Psychiatry 48: 345-347, 2003.

Sumiyoshi et al 2004a
Sumiyoshi T, Roy A, Anil AE, Jayathilaki K, Ertugrul A, Meltzer HY. A comparison of incidence of diabetes mellitus between atypical antipsychotic drugs. Journal of Clinical Psychopharmacology 24: 345-348, 2004a.

Sumiyoshi et al 2004b
Sumiyoshi T, Roy A, Jayathilaki K, Meltzer HY. The effect of hypertension and obesity on the development of diabetes mellitus in patients treated with atypical antipsychotic drugs. Journal of Clinical Psychopharmacology 24: 452-454, 2004b.

Sun et al 2004
Sun SX, Liu GG, Christensen DG. Anti-psychotic treatment and risk of diabetes: results from NC Medicaid population. Value in Health 7: 338, 2004.

Tarricone et al 2006
Tarricone I, Casoria M, Gozzi BF, Grieco D, Menchetti M, Serretti A, Ujkaj M, Pastorelli F, Berardi D. Metabolic risk factor profile associated with use of second generation antipsychotics: a cross-sectional study in a community mental health centre. BMC Psychiatry 6: 11, 2006. http://www.biomedcentral.com/1471-244X/6/11.

Taylor et al 2003
Taylor D, Young C, Mahomed R, et al. A prevalence study of impaired glucose tolerance and diabetes mellitus in hospitalised patients with schizophrenia. European Neuropsychopharmacology 13: S323, 2003.

Trieschmann et al 2003
Trieschmann ME, Fernandez HH, Friedman JH. New-onset diabetes in Parkinsonian patients on long-term quetiapine. Movement Disorders 18: 1095, 2003.

Verrillo et al 1985
Verrillo A, de Teresa A, La Rocca S, Giarrusso PC. Prevalence of diabetes mellitus and impaired glucose tolerance in a rural area of Italy. Diabetes Research 2: 301-306, 1985.

Wang et al 2002
Wang PS, Demler O, Kessler RC. Adequacy of treatment for serious mental illness in the United States. American Journal of Public Health 92: 92-98, 2002.

West et al 2005
West SL, Strom BL, Poole C. Validity of pharmacoepidemiologic drug and diagnosis data. Chapter 45 In: Pharmacoepidemiology (eds. Strom, BL), Edition Fourth. West Sussex, England: John Wiley & Sons Ltd, 2005. Pages 709-765.

Wild et al 2004
Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 27: 1047-1053, 5-1-2004.

Wilson et al 2003
Wilson DR, Petty F, Hammond C, Buckley P. Atypical antipsychotics and hyperglycemia: analysis of 11,994 Ohio DMH subjects. International Congress on Schizophrenia Research (ICOSR) 2003.

Wynia et al 2000
Wynia MK, Cummins DS, VanGeest JB, Wilson IB. Physician Manipulation of Reimbursement Rules for Patients: Between a Rock and a Hard Place. Journal of the American Medical Association 283: 1858-1865, 4-12-2000.

Yang et al 2006a
Yang M, Barner JC, Lawson KA, Rascati KL, Crismon ML, Wilson JP, Worchel J, Mascarenas C. Antipsychotic utilization and treatment-emergent diabetes: comparison of results with and without propensity scoring (Abstract PDB27). Value in Health 9(3): A39, 2006a. http://www.blackwell-synergy.com/doi/abs/10.1111/j.1524-4733.2006.00102_2.x.

Yang et al 2006b
Yang M, Barner JC, Rascati KL, Lawson KA, Wilson JP, Crismon ML, Worchel J, Mascarenas C. Antipsychotic utilization and treatment-emergent diabetes: a methodological

comparison using a claims database (Abstract PDB26). Value in Health 9(3): A38-A39, 2006b. http://www.blackwell-synergy.com/doi/abs/10.1111/j.1524-4733.2006.00102_2.x.

AstraZeneca

Discussion Document

Drug name	Quetiapine fumarate
Date	June 2007

'PRIVILEGED AND CONFIDENTIAL DRAFT FOR LEGAL REVIEW'

Addendum to Discussion Document
SEROQUEL and Glucose dysregulation

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

Author: Lisa Boornazian RN, BSN
Safety Surveillance Team Leader
Drug Safety, Wilmington, DE, USA

Leigh Jefferies, MD
Global Drug Safety Physician
Drug Safety, Wilmington, DE, USA

TABLE OF CONTENTS PAGE

SUMMARY

The following is an addendum to the 2007 Discussion Document "SEROQUEL and Glucose dysregulation" based on new significant safety information that has been generated. This document provides a comprehensive review of this new information.

1. INTRODUCTION

Additional clinical trial information was generated combining the data from all trials and Trials 126 and 127 and separately combining the data from all placebo-controlled trials and Trials 126 and 127. In addition, data from all placebo-controlled trials <12 weeks in duration contained in the Safety 9.1 database was generated.

2. BACKGROUND

No new information.

3. THE LITERATURE

No new information.

4. PRE-CLINICAL DATA

No new information.

5. CLINICAL STUDY DATA

5.1 All trials

Table 1 below shows in all SEROQUEL clinical trials (trials contained in Safety 9.1 database and Trials 126 and 127) the incidence of patients who had a high glucose value (≥7.0 mmol/L fasting, ≥11.1 mmol/L non-fasting) at any time during a trial. The incidence in the quetiapine group was 5.48% compared to 2.4% in the placebo group.

Table 1 **Shift to clinically important lab values at any time (All trials) – *including studies 126/127***

	QTP N=11659		Pla N=1592		Chl N=348		Hal N=1028		Li N=98		Ola N=168		Ri N=888	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)														
Low[a]	5689	20 (0.35)	1340	10 (0.75)	92	1 (1.1)	228	0 (0)	91	2 (2.2)	168	0 (0)	426	0 (0)
High[b]	5545	304 (5.48)	1317	32 (2.4)	92	0 (0)	220	5 (2.3)	91	1 (1.1)	167	11 (6.6)	418	17 (4.1)
HbA1c (%)														
High[b]	2673	38 (1.42)	440	1 (0.23)	NA	NA	NA	NA	NA	NA	168	0 (0)	172	0 (0)

a N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
b N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time
Chl Chlorpromazine, Hal Haloperidol, Li Lithium, Ola Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone.
Prespecified clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High >=7.5.

AstraZeneca

5.2 All placebo-controlled trials

Table 2 below shows in all SEROQUEL placebo-controlled clinical trials (trials contained in Safety 9.1 database and Trials 126 and 127) the incidence of patients who had a high glucose value (≥7.0 mmol/L fasting, ≥11.1 mmol/L non-fasting) at any time during the trial. The incidence in the quetiapine group was 5.14% compared to 4.16% in the placebo group.

Table 2 **Shift to clinically important lab values at any time (All placebo-controlled trials) – *including studies 126/127***

	QTP N=4083		Pla N=2272	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	3349	11 (0.33)	1951	10 (0.51)
High[b]	3248	167 (5.14)	1898	79 (4.16)
HbA1c (%)				
High[b]	1743	20 (1.15)	1051	6 (0.57)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Prespecified clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.

Note: In studies D1444C00004, D1447C00126 and D1447C00127, all patients received QTP prior to the placebo-controlled phase.

5.2.1 Placebo-controlled trials <12 weeks in duration

Table 3 below shows in all SEROQUEL placebo-controlled clinical trials (trials contained in Safety 9.1 database) with a planned duration of <12 weeks (per the protocol), the incidence of patients who had a high glucose value (≥7.0 mmol/L fasting, ≥11.1 mmol/L non-fasting) at any time during the trial. In the quetiapine group, the incidence was 3.5% compared to 2.1% in the placebo group.

Table 3 **Shift to clinically important lab values at any time (All placebo-controlled trials excluding D1444C00004)**

	QTP N=3342		Pla N=1490	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	2677	10 (0.37)	1264	10 (0.79)
High[b]	2609	92 (3.5)	1241	26 (2.1)
HbA1c (%)				
High[b]	1072	8 (0.75)	352	1 (0.28)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Prespecified important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.

Pgm: Reg-DefDiabetes Mar 07 SERMELAB_sbu_pla_ctrl_excl04.SAS. Data version: V91 User: Bengt Franzon. 2007-06-12 09:49.

6. DISCUSSION

This information revealed that the frequency of an elevation in blood glucose to a hyperglycemic level (≥7.0 mmol/L fasting or ≥11.1 mmol/L non-fasting) in these groups of quetiapine-treated patients ranged from 3.5% to 5.48%, which is consistent with the CIOMS definition of common (≥1% and <10%).

AstraZeneca

Appendix	A through D
Drug name	quetiapine fumarate
Date	June 2007

Appendices A through D
Discussion Document
SEROQUEL and Glucose dysregulation

LIST OF APPENDICES

LIST OF TABLES

LIST OF FIGURES

Appendix A Additional clinical trial tables

Trials 126/127

Table A1 Preferred terms used in search to identify AE reports of DM related events

Preferred terms		
Anti-insulin antibody increased	Anti-insulin antibody positive	Blood glucose abnormal
Blood glucose fluctuation	Blood glucose increased	Blood insulin abnormal
Blood insulin decreased	Blood insulin increased	Blood insulin c-peptide abnormal
Blood insulin C-peptide decreased	Insulin C-peptide increased	Blood proinsulin abnormal
Blood proinsulin decreased	Blood proinsulin increased	Dawn phenomenon
Diabetes mellitus	Diabetes mellitus inadequate control	Diabetes mellitus insulin dependent
Diabetes mellitus, non-insulin dependent	Diabetes with hyperosmolarity	Diabetic coma
Diabetic complication	Diabetic hyperglycaemic coma	Diabetic hyperosmolar coma
Diabetic hyperosmolar non-ketoacidosis	Diabetic ketoacidosis	Diabetic ketoacidotic hyperglycaemic coma
Glucose tolerance decreased	Glucose tolerance impaired	Glucose tolerance test abnormal
Glucose urine present	Glycosylated haemoglobin increased	Hyperglycaemia
Hyperinsulinaemia	Hyperinsulinism	Impaired fasting glucose
Impaired insulin secretion	Increased insulin requirement	Insulin resistance
Insulin resistance syndrome	Insulin resistant diabetes	Insulin-requiring type ii diabetes mellitus
Insulin tolerance test abnormal	Metabolic disorder	Somogyi phenomenon
Polydipsia	Polyuria	Thirst
Blood ketone body present	Blood ketone body increased	Neonatal diabetes mellitus
Glycosuria during pregnancy	Gestational diabetes	Glucose tolerance impaired in pregnancy
Diabetes complicating pregnancy		

Table A2 Glucose regulation laboratory data, change to end of treatment, >8 h fasting, "diabetics" (randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		126+127 QTP+ LI/VAL N = 646	PLA+ LI/VAL N = 680	QTP+ LI N = 274	PLA+ LI N = 287	QTP+ VAL N = 372	PLA+ VAL N = 393
Glucose (mg/dL)							
N [a]		54	52	24	12	30	40
Randomization	Mean(SD)	130.91(34.788)	125.38(38.225)	132.96(29.870)	128.33(25.163)	129.27(38.702)	124.50(41.578)
End of treatment	Mean(SD)	135.30(112.948)	113.17(33.564)	129.79(82.510)	123.25(43.497)	139.70(147.772)	110.15(28.894)
Change	Mean(SD)	4.38(115.168)	-12.23(35.940)	-3.17(45.952)	-5.08(29.959)	10.43(150.863)	-14.35(37.625)
	Median	-7.00	-8.00	1.50	-7.50	-9.50	-8.00
	Min to Max	-132.0 to 776.00	-121.0 to 67.00	-84.00 to 98.00	-52.00 to 55.00	-132.0 to 776.00	-121.0 to 67.00
HbA1C (%)							
N [a]		52	54	24	13	28	41
Randomization	Mean(SD)	6.569(1.193)	6.548(0.949)	6.079(0.957)	6.062(0.885)	6.988(1.229)	6.731(0.926)
End of treatment	Mean(SD)	6.776(1.212)	6.335(0.931)	6.332(1.240)	5.983(0.681)	7.146(1.069)	6.520(0.944)
Change	Mean(SD)	0.207(1.004)	-0.159(0.706)	0.253(0.650)	-0.138(0.649)	0.158(1.241)	-0.159(0.731)
	Median	0.20	-0.20	0.20	0.00	0.15	-0.20
	Min to Max	-2.60 to 3.20	-2.80 to 1.40	-0.90 to 2.00	-2.10 to 0.50	-2.60 to 3.20	-2.80 to 1.40
Insulin (pmol/L)							
N [a]		46	49	22	12	24	37
Randomization	Mean(SD)	223.96(210.242)	196.47(200.827)	262.05(232.217)	258.17(347.498)	189.64(187.078)	176.46(123.278)
End of treatment	Mean(SD)	155.76(126.322)	145.92(180.477)	166.50(121.871)	189.75(134.011)	145.92(132.992)	131.70(84.412)
Change	Mean(SD)	-68.20(207.587)	-50.55(166.627)	-95.55(253.673)	-68.42(295.937)	-43.13(155.515)	-44.76(100.589)

Table A2 Glucose regulation laboratory data, change to end of treatment, >8 h fasting, "diabetics" (randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		126+127 QTP+ LI/VAL N = 646	PLA+ LI/VAL N = 680	QTP+ LI N = 274	PLA+ LI N = 287	QTP+ VAL N = 372	PLA+ VAL N = 393
	Median	-17.5	-7.00	-21.0	10.50	-17.5	-20.0
	Min to Max	-771.0 to 285.00	-945.0 to 236.00	-771.0 to 285.00	-945.0 to 236.00	-569.0 to 181.00	-375.0 to 139.00
HOMA-R							
N [a]		46	48	22	11	24	37
Randomization	Mean(SD)	11.80(15.076)	9.39(11.433)	12.80(11.778)	13.89(19.796)	10.87(17.782)	8.05(7.333)
End of treatment	Mean(SD)	7.77(8.617)	6.12(6.313)	8.60(8.863)	9.56(11.166)	7.02(8.502)	5.10(3.615)
Change	Mean(SD)	-4.02(13.918)	-3.27(10.807)	-4.20(14.722)	-4.33(19.844)	-3.86(13.457)	-2.95(6.531)
	Median	-0.64	-0.67	-0.54	0.05	-1.19	-0.72
	Min to Max	-50.60 to 28.00	-57.69 to 23.90	-41.47 to 28.00	-57.69 to 23.90	-50.60 to 21.94	-31.28 to 3.08
QUICKI							
N [a]		46	48	22	11	24	37
Randomization	Mean(SD)	0.2924(0.0357)	0.2988(0.0362)	0.2886(0.0412)	0.2903(0.0352)	0.2959(0.0304)	0.3013(0.0366)
End of treatment	Mean(SD)	0.3048(0.0334)	0.3090(0.0288)	0.3001(0.0334)	0.2965(0.0318)	0.3090(0.0336)	0.3127(0.0272)
Change	Mean(SD)	0.0124(0.0382)	0.0102(0.0272)	0.0115(0.0382)	0.0062(0.0202)	0.0132(0.0389)	0.0114(0.0291)
	Median	.0074	.0077	.0065	-.001	.0085	.0080
	Min to Max	-.0586 to 0.1206	-.0659 to 0.0790	-.0465 to 0.0912	-.0238 to 0.0461	-.0586 to 0.1206	-.0659 to 0.0790

[a] Number of patients with assessment at randomization and at least one assessment after randomization.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. HOMA [insulin (uU/ml) x glucose (mmol/l)]/22.5. QUICKI 1/[log10(insulin o(uU/ml)) + log10 (glucose o(mg/dl))]. HbA1c Hemoglobin A1c.
Note: Change from randomization, >8 hours after a meal.
Note: "diabetics" defined as having documented fasting glucose >=126 mg/dL or non-documented fasting glucose >=200 mg/dL at baseline or a history of diabetes.
126 D1447C00126. 127 D1447C00127.
/sare/prod/seroquel/etdmaintenance/sp/output/ilPss098.rtf chem233.sas 16APR2007:15:21 kacl497

Table A3 Glucose regulation laboratory data, change to end of treatment, >8 h fasting, "diabetic risk" (randomized safety population).

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 646	PLA+ LI/VAL N = 680	QTP+ LI N = 274	PLA+ LI N = 287	QTP+ VAL N = 372	PLA+ VAL N = 393
Glucose (mg/dL)							
N *		156	139	79	67	86	72
Randomization	Mean(SD)	96.62(12.911)	98.56(12.836)	98.51(11.399)	99.60(11.110)	95.07(13.897)	97.65(13.154)
End of treatment	Mean(SD)	99.69(19.283)	95.70(13.200)	104.43(17.155)	96.97(11.392)	95.84(20.141)	94.64(14.675)
Change	Mean(SD)	3.08(17.408)	-2.85(13.874)	5.93(13.784)	-2.63(11.903)	0.77(19.656)	-3.01(15.568)
	Median	3.00	-2.00	6.50	-1.00	1.00	-4.50
	Min to Max	-60.00 to 63.00	-39.00 to 63.00	-28.00 to 58.00	-32.00 to 20.00	-60.00 to 63.00	-39.00 to 63.00
HbA1C (%)							
N *		156	142	71	68	85	74
Randomization	Mean(SD)	5.37(0.383)	5.38(0.354)	5.26(0.406)	5.29(0.376)	5.46(0.340)	5.47(0.317)
End of treatment	Mean(SD)	5.59(0.524)	5.47(0.341)	5.48(0.473)	5.40(0.305)	5.68(0.549)	5.53(0.362)
Change	Mean(SD)	0.22(0.401)	0.09(0.307)	0.22(0.302)	0.11(0.315)	0.23(0.470)	0.06(0.300)
	Median	0.20	0.00	0.20	0.05	0.10	0.00
	Min to Max	-0.60 to 3.00	-0.70 to 1.10	-0.60 to 1.10	-0.70 to 0.90	-0.30 to 3.00	-0.50 to 1.10
Insulin (pmol/L)							
N *		135	122	58	60	77	62
Randomization	Mean(SD)	186.71(202.327)	172.02(152.051)	148.64(105.313)	153.23(117.136)	215.59(248.837)	192.13(178.195)
End of treatment	Mean(SD)	208.81(245.758)	164.70(135.981)	173.58(149.248)	143.50(98.984)	235.51(296.821)	185.18(162.013)

Table A3 Glucose regulation laboratory data, change to end of treatment, >8 h fasting, "diabetic risk" (randomized safety population).

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 646	PLA+ LI/VAL N = 680	QTP+ LI N = 274	PLA+ LI N = 287	QTP+ VAL N = 372	PLA+ VAL N = 393
Change	Mean(SD)	22.10(215.819)	-8.32(165.428)	24.74(156.236)	-9.73(136.231)	20.12(255.317)	-6.95(190.605)
	Median	0.00	7.00	0.00	5.50	0.00	7.00
	Min to Max	-882.0 to 799.00	-646.0 to 570.00	-243.0 to 604.00	-405.0 to 341.00	-882.0 to 799.00	-646.0 to 570.00
HOMA-R							
N [a]		135	118	59	59	76	59
Randomization	Mean(SD)	6.65(8.397)	6.10(5.754)	5.11(3.753)	5.33(4.226)	7.85(10.572)	6.88(6.907)
End of treatment	Mean(SD)	7.53(9.894)	5.91(6.022)	6.33(6.286)	5.00(3.754)	8.46(11.951)	6.81(7.576)
Change	Mean(SD)	0.88(9.530)	-0.19(7.157)	1.23(6.288)	-0.32(5.137)	0.61(11.469)	-0.06(8.769)
	Median	0.00	0.14	0.20	0.25	-0.07	0.09
	Min to Max	-39.74 to 40.53	-23.44 to 38.40	-8.79 to 30.85	-15.70 to 16.48	-39.74 to 40.53	-23.44 to 38.40
QUICKI							
N [a]		135	118	59	59	76	59
Randomization	Mean(SD)	0.3113(0.0350)	0.3117(0.0349)	0.3125(0.0272)	0.3146(0.0334)	0.3101(0.0402)	0.3087(0.0364)
End of treatment	Mean(SD)	0.3120(0.0401)	0.3129(0.0344)	0.3124(0.0378)	0.3145(0.0295)	0.3117(0.0420)	0.3112(0.0388)
Change	Mean(SD)	0.0008(0.0367)	0.0012(0.0330)	-.0001(0.0319)	-.0001(0.0334)	0.0016(0.0402)	0.0025(0.0347)
	Median	-.000	-.002	-.003	-.003	.0017	-.002
	Min to Max	-.1476 to 0.1064	-.0724 to 0.0981	-.0991 to 0.0673	-.0648 to 0.0733	-.1476 to 0.1064	-.0724 to 0.0981

[a] Number of patients with assessment at randomization and at least one assessment after randomization.

PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. HOMA [insulin uU/ml) x glucose (mmol/l)]/22.5. QUICKI 1/[log10(insulin uU/ml) + log10 (glucose s(mg/dl))]. HbA1c Hemoglobin A1c.

Note: Change from randomization, >8 hours after a meal.

Diabetic risk defined as having a history of gestational diabetes or a BMI of >= 35 or impaired documented fasting glucose >=100 to <126 mg/dL;

126 D1447C00126, 127 D1447C00127.

/sre/prod/seroquel/cdmaintenance/sp/output/tlf/sa099.rtf chem214.sas 16APR2007:15:21 lxcl497

Table A4 Glucose regulation laboratory data, change to end of treatment, >8 h fasting, non-diabetics (randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 646	PLA+ LI/VAL N = 680	QTP+ LI N = 274	PLA+ LI N = 287	QTP+ VAL N = 372	PLA+ VAL N = 393
Glucose (mg/dL)							
N *		310	302	134	124	176	178
Randomization	Mean(SD)	88.88(9.002)	87.24(9.070)	86.77(8.589)	88.68(7.805)	88.21(9.271)	87.09(9.825)
End of treatment	Mean(SD)	91.73(14.544)	90.12(14.020)	92.43(14.458)	91.44(14.196)	91.19(14.627)	89.28(13.862)
Change	Mean(SD)	2.84(14.856)	2.38(14.338)	5.66(14.182)	2.76(13.985)	2.98(15.388)	2.11(14.686)
	Median	3.00	3.00	3.50	2.00	3.00	1.00
	Min to Max	-42.00 to 84.00	-76.00 to 87.00	-21.00 to 72.00	-25.00 to 75.00	-42.00 to 84.00	-76.00 to 87.00
HbA1C (%)							
N *		313	308	135	124	180	184
Randomization	Mean(SD)	5.23(0.374)	5.22(0.374)	5.11(0.349)	5.11(0.404)	5.32(0.368)	5.29(0.334)
End of treatment	Mean(SD)	5.40(0.452)	5.28(0.432)	5.27(0.394)	5.15(0.394)	5.50(0.469)	5.37(0.436)
Change	Mean(SD)	0.17(0.337)	0.06(0.272)	0.16(0.253)	0.05(0.231)	0.17(0.387)	0.08(0.296)
	Median	0.10	0.00	0.20	0.00	0.10	0.00
	Min to Max	-0.40 to 3.80	-0.80 to 2.30	-0.40 to 1.00	-0.80 to 0.60	-0.40 to 3.80	-0.50 to 2.30
Insulin (pmol/L)							
N *		264	261	111	100	153	161
Randomization	Mean(SD)	84.35(69.231)	93.52(104.342)	78.93(59.599)	83.28(83.088)	88.31(69.437)	99.88(115.828)
End of treatment	Mean(SD)	121.08(129.569)	114.34(215.634)	120.80(139.828)	105.58(127.983)	121.27(122.633)	114.93(255.714)

Table A4 Glucose regulation laboratory data, change to end of treatment, >8 h fasting, non-diabetics (randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 646	PLA+ LI/VAL N = 680	QTP+ LI N = 274	PLA+ LI N = 287	QTP+ VAL N = 372	PLA+ VAL N = 393
Change	Mean(SD)	36.72(110.255)	17.82(217.404)	41.90(116.190)	22.30(124.987)	32.97(105.972)	15.04(259.073)
	Median	7.00	0.00	14.00	0.00	7.00	0.00
	Min to Max	-222.0 to 695.00	-895.0 to 2125.0	-112.0 to 695.00	-271.0 to 646.00	-222.0 to 534.00	-895.0 to 2125.0
HOMA-R							
N [a]		269	260	114	103	155	157
Randomization	Mean(SD)	2.59(2.247)	2.95(3.569)	2.45(2.051)	2.62(2.648)	2.69(2.383)	3.17(4.055)
End of treatment	Mean(SD)	4.22(5.637)	3.92(9.229)	4.20(6.106)	3.71(5.457)	4.23(5.287)	4.05(11.040)
Change	Mean(SD)	1.63(4.914)	0.97(9.231)	1.75(5.098)	1.08(5.386)	1.54(4.788)	0.89(11.069)
	Median	0.38	-0.01	0.44	0.02	0.31	-0.04
	Min to Max	-10.81 to 37.21	-29.03 to 86.29	-3.76 to 37.21	-10.58 to 29.09	-10.81 to 33.46	-29.03 to 86.29
QUICKI							
N [a]		269	260	114	103	155	157
Randomization	Mean(SD)	0.3473(0.0375)	0.3463(0.0389)	0.3511(0.0402)	0.3508(0.0394)	0.3446(0.0352)	0.3432(0.0384)
End of treatment	Mean(SD)	0.3355(0.0433)	0.3457(0.0421)	0.3365(0.0453)	0.3463(0.0449)	0.3348(0.0418)	0.3454(0.0404)
Change	Mean(SD)	-.0118(0.0387)	-.0005(0.0410)	-.0146(0.0410)	-.0046(0.0406)	-.0098(0.0369)	0.0021(0.0412)
	Median	-.009	.0003	-.012	-.001	-.007	.0011
	Min to Max	-.1477 to 0.0959	-.1152 to 0.1246	-.1477 to 0.0897	-.1152 to 0.0739	-.1421 to 0.0959	-.1110 to 0.1246

[a] Number of patients with assessment at randomization and at least one assessment after randomization.
PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate, N Number of patients in treatment group. HOMA [insulin (uU/mL) x glucose (mmol/L)]/22.5. QUICKI 1/[log10(insulin mU/mL) + log10 (glucose mg/dL)]. HbA1c Haemoglobin A1c
126 D1447C00126, 127 D144700127.
Note: Change from randomization. >8 hours after a meal.

/ess/sprod/seroquel/chimeralstrmeco/sp/output/tlf/so100.rtf chem215.sas 16APR2007:15:21 kssf497

23

CONFIDENTIAL
AZSER14868485

Table A5 Glucose regulation laboratory data, clinically important values at end of treatment, diabetic subgroups (randomized safety population)

		126+127 QTP+LI/VAL N=646		PLA+LI/VAL N=680	
		N[a]	n(%)	N[a]	n(%)
Glucose (mg/dL)					
<=45	Diabetic	60	0	65	0
	Diabetic risk	168	0	169	0
	Non diabetic	360	0	377	0
Glucose (mg/dL)					
>=126	Diabetic	30	10 (33.3)	37	6 (16.2)
	Diabetic risk	167	15 (9.0)	169	7 (4.1)
	Non diabetic	359	12 (3.3)	375	12 (3.2)
Glucose (mg/dL)					
>=200	Diabetic	59	8 (13.6)	61	2 (3.3)
	Diabetic risk	168	0	169	0
	Non diabetic	360	0	377	0
HbA1C (%)					
>7.5	Diabetic	49	5 (10.2)	56	2 (3.6)
	Diabetic risk	169	2 (1.2)	170	0
	Non diabetic	357	1 (0.3)	384	1 (0.3)

[a] Number of patients at risk i.e. not fulfilling the criteria at baseline.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate.
Note: Clinically important values emerging during randomized treatment phase. Note: Percentages are calculated as (n/N[a])*100.
Note: Diabetics defined as having documented fasting glucose >= 126 mg/dL or non-documented fasting glucose >=200 mg/dL at baseline or a history of diabetes.
Diabetic risk defined as having a history of gestational diabetes or a BMI of >= 35 or impaired documented fasting glucose >=100 to <126 mg/dL;
Non-Diabetic defined as not meeting criteria for diabetes or diabetic risk.
/esrc/prod/seroquel/ctdmaintenance/sp/outputBF/sa182.rtf ar039.sas 20APR2007:10:53 kscl497

Table A6 Glucose regulation laboratory data, clinically important values at any time, >8 h fasting, diabetic subgroups, by treatment group, (randomized safety population)

		QTP+LI/VAL N=646		PLA+LI/VAL N=680	
		N*	n(%)	N*	n(%)
Glucose (mg/dL)					
<=45	Diabetic	45	0	50	0
	Diabetic risk	131	0	127	0
	Non diabetic	272	1 (0.4)	254	0
Glucose (mg/dL)					
>=126	Diabetic	26	10 (38.5)	30	8 (26.7)
	Diabetic risk	131	20 (15.3)	127	5 (3.9)
	Non diabetic	272	16 (5.9)	254	6 (2.4)
Glucose (mg/dL)					
>=200	Diabetic	45	8 (17.8)	48	3 (6.3)
	Diabetic risk	131	1 (0.8)	127	0
	Non diabetic	272	0	254	0
HbA1C (%)					
>7.5	Diabetic	38	6 (15.8)	43	4 (9.3)
	Diabetic risk	132	2 (1.5)	129	0
	Non diabetic	271	1 (0.4)	262	0

* Number of patients at risk i.e. not fulfilling the criteria at baseline.
PLA Placebo, QTP Quetiapine, LI Lithium, VAL Valproate.
Note: Clinically important values emerging during randomized treatment phase. Note: Percentages are calculated as (n/N*)*100.
Note: Diabetics defined as having documented fasting glucose >=126 mg/dL or non-documented fasting glucose >=200 mg/dL at baseline or a history of diabetes.
Diabetic risk defined as having a history of gestational diabetes or a BMI of >= 35 or impaired documented fasting glucose >=100 to <126 mg/dL;
Non-diabetic defined as not meeting criteria for diabetes or diabetic risk.
/users/prod/seroquel/ctdmaintenance/sp/output/tlf/sa107.rtf ctdmnt207.sas 16APR2007:15:22 ksch497

Data from the safety 9.1 database

All trials

Non-diabetic patients

Table A7 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All trials)

		QTP N=9486	Pla N=1282	Chl N=335	Hal N=967	Li N=96	Ola N=132	Ri N=746
Glucose (mmol/L)								
Patients[a]		4075	1024	91	213	89	132	322
Baseline	Mean (SD)	5.18 (1.00)	5.21 (1.04)	5.55 (1.11)	5.77 (1.36)	5.30 (1.20)	4.91 (0.54)	5.10 (0.82)
Last value	Mean (SD)	5.42 (1.28)	5.31 (1.18)	5.44 (1.21)	5.95 (1.53)	5.48 (1.83)	5.15 (0.54)	5.34 (0.95)
Change	Mean (SD)	0.23 (1.32)	0.098 (1.22)	-0.11 (1.42)	0.19 (1.68)	0.18 (1.74)	0.24 (0.64)	0.25 (1.13)
	Median	0.11	0.056	0	0.10	0	0.30	0.29
	Range	-7.46 to 22.06	-6.83 to 6.09	-4.50 to 3.80	-4.80 to 10.20	-5.40 to 5.83	-3.10 to 1.90	-4.22 to 9.33
HbA1c (%)								
Patients[a]		1464	305				132	122
Baseline	Mean (SD)	5.28 (0.38)	5.23 (0.37)				5.31 (0.37)	5.29 (0.41)
Last value	Mean (SD)	5.33 (0.38)	5.24 (0.36)				5.31 (0.40)	5.28 (0.46)
Change	Mean (SD)	0.037 (0.26)	0.016 (0.25)				0.0030 (0.34)	-0.0041 (0.30)
	Median	0	0				0	0
	Range	-0.90 to 1.10	-0.80 to 0.80				-1.00 to 1.40	-0.90 to 1.00
Insulin (pmol/L)								
Patients[a]		1785	486				112	166
Baseline	Mean (SD)	83.05 (211.70)	75.95 (140.22)				214.46 (1998.81)	225.30 (213.58)
Last value	Mean (SD)	113.78 (368.36)	92.71 (139.00)				301.38 (3994.69)	254.30 (239.16)
Change	Mean (SD)	30.71 (356.55)	16.76 (178.76)				86.93 (3980.89)	29.00 (250.88)
	Median	7.00	6.95				25.84	22.50
	Range	-770.90 to 2299	-1875 to 1820				-1124 to 2822	-645.75 to 1492
HOMA$_B$								
Patients[a]		1179	452				103	94
Baseline	Mean (SD)	2.23 (5.16)	2.70 (8.70)				1.35 (0.85)	1.38 (6.70)

Table A7 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All trials)

		QTP N=9486	Pla N=1282	Chl N=335	Hal N=967	Li N=96	Ola N=132	Ri N=746
Last value	Mean (SD)	3.71 (7.21)	3.27 (6.62)				1.60 (1.34)	1.53 (0.95)
Change	Mean (SD)	1.46 (6.98)	0.57 (10.55)				0.35 (1.37)	0.16 (0.83)
	Median	0.26	0.23				0.19	0.086
	Range	-35.70 to 127.84	-137.15 to 87.11				-3.14 to 8.12	-1.60 to 3.18
QUICKI								
Patients[a]		1570	452				103	97
Baseline	Mean (SD)	0.3200 (0.0810)	0.3092 (0.0949)				0.3791 (0.0386)	0.3745 (0.0349)
Last value	Mean (SD)	0.3183 (0.0826)	0.3012 (0.0959)				0.3791 (0.0429)	0.3766 (0.0362)
Change	Mean (SD)	-0.0106 (0.0400)	-0.0086 (0.0389)				-0.0090 (0.0460)	-0.0043 (0.0320)
	Median	-0.0100	-0.0076				-0.0085	-0.0051
	Range	-0.2105 to 0.1807	-0.1836 to 0.1810				-0.1117 to 0.2593	-0.0745 to 0.0888

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline
Chl Chlorpromazine, Hal Haloperidol, Li Lithium, Ola Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone
Pgm: Reg-Def Diabetes Mar 07 SERIAL\Alt_chg_all_trials_diab3.SAS. Data version: V91 User: Bengt Fransson. 2007-05-03 12:21.

Table A8 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All trials)

	QTP N=9486 End of tx			PLA N=1282 End of tx			CHL N=335 End of tx			HAL N=967 End of tx			LI N=96 End of tx			OLZ N=132 End of tx			RI N=746 End of tx		
	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)
Glucose (mmol/L)																					
L	0 (0)	7 (100)	0 (0)	0 (0)	1 (100	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
N	6 (0.15)	4005 (98.5)	53 (1.3)	4 (0.37)	1056 (98.4)	13 (1.2)	1 (1.1)	90 (98.9)	0 (0)	0 (0)	206 (97.6)	5 (2.4)	1 (1.1)	87 (97.8)	1 (1.1)	0 (0)	130 (98.5)	2 (1.5)	0 (0)	320 (99.4)	2 (0.62)
H	0 (0)	3 (75.0)	1 (25.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	6 (0.15)	4015 (98.5)	54 (1.3)	4 (0.37)	1057 (98.4)	13 (1.2)	1 (1.1)	90 (98.9)	0 (0)	0 (0)	206 (97.6)	5 (2.4)	1 (1.1)	87 (97.8)	1 (1.1)	0 (0)	130 (98.5)	2 (1.5)	0 (0)	320 (99.4)	2 (0.62)
HbA_{1c} (%)																					
N	NA	3464 (100)	0 (0)	NA	305 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	132 (100)	0 (0)	NA	122 (100)	0 (0)
H	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	3464 (100)	0 (0)	NA	305 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	132 (100)	0 (0)	NA	122 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Hal: Haloperidol. Li: Lithium. Olz: Olanzapine. Ri: Risperidone. Chl: Chlorpromazine. Pla: Placebo. QTP: Quetiapine.
Clinically important limits are: Glucose (mmol/L) Low: <=2.5. High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%). High: >7.5.

Pgm: Reg-Def\Diabetes Mar 07 SER\40_AB_shc_all_trials_diab3.SAS. Data version: V91 User: Bengt Frasson 2007-05-03 06:54

Table A9 Shift to clinically important lab values at any time in non-diabetic subjects (All trials)

	QTP N=9486		Pla N=1282		Chl N=335		Hal N=967		Li N=96		Olz N=132		Ri N=746	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)														
Low[a]	4068	15 (0.37)	1073	9 (0.84)	91	1 (1.1)	211	0 (0)	89	2 (2.2)	132	0 (0)	322	0 (0)
High[b]	4071	98 (2.4)	1074	13 (1.2)	91	0 (0)	211	5 (2.4)	89	1 (1.1)	132	6 (4.5)	322	7 (2.2)
HbA1c (%)														
High[b]	1464	1 (0.068)	305	0 (0)	NA	NA	NA	NA	NA	NA	132	0 (0)	122	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Chl Chlorpromazine. Hal Haloperidol. Li Lithium. Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone
Clinically important limits are: Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >7.5.
Pgm: Reg-Def/Diabetes Mar07 SERMPLAR_sha_all_trials_diab0 SAS. Data version: V91 User: Bengt Franzen 2007-05-03 07:15

Diabetic risk

Table A10 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All trials)

		QTP N=996	Pla N=220	Chl N=10	Hal N=35	Li N=2	Olz N=29	Ri N=90
Glucose (mmol/L)								
Patients[a]		727	183	1	9	2	29	77
Baseline	Mean (SD)	5.62 (0.81)	5.56 (0.75)	5.90	5.83 (1.47)	6.22 (1.02)	5.90 (0.54)	5.70 (0.92)
Last value	Mean (SD)	5.68 (1.69)	5.43 (1.08)	6.40	6.02 (1.03)	5.92 (0.12)	5.81 (0.76)	5.63 (0.96)
Change	Mean (SD)	0.062 (1.07)	0.086 (1.01)	0.50	0.19 (1.78)	-0.81 (1.14)	-0.083 (0.69)	-0.072 (0.99)
	Median	-0.100	0	0.50	-0.20	-0.81	-0.20	-0.17
	Range	-3.60 to 29.07	-3.66 to 4.50	0.50 to 0.50	-1.89 to 3.22	-1.61 to 0	-1.40 to 1.40	-3.33 to 2.89
HbA1c (%)								
Patients[b]		472	98				29	41
Baseline	Mean (SD)	5.40 (0.38)	5.32 (0.43)				5.42 (0.60)	5.43 (0.41)
Last value	Mean (SD)	5.45 (0.40)	5.35 (0.45)				5.44 (0.68)	5.41 (0.43)
Change	Mean (SD)	0.055 (0.29)	0.023 (0.27)				0.021 (0.34)	-0.017 (0.30)
	Median	0.100	0				0	0
	Range	-1.40 to 1.40	-0.90 to 0.80				-0.50 to 1.10	-0.90 to 0.70
Insulin (pmol/L)								
Patients[c]		330	144				22	34
Baseline	Mean (SD)	147.55 (193.90)	118.47 (103.42)				462.94 (358.68)	195.15 (154.05)
Last value	Mean (SD)	174.70 (274.35)	133.14 (134.22)				366.31 (288.00)	241.44 (205.30)
Change	Mean (SD)	27.15 (284.75)	14.67 (138.89)				-36.63 (190.75)	46.29 (222.45)
	Median	0	0				3.89	4.62
	Range	-1965 to 2730	-626.26 to 888.96				-598.51 to 269.46	-521.50 to 863.96
$HOMA_R$								
Patients[c]		496	134				20	53

Table A10 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All trials)

		QTP N=996	Pla N=220	Chl N=10	Hal N=35	Li N=2	Ola N=29	Ri N=90
Baseline	Mean (SD)	4.88 (6.18)	3.93 (3.51)				1.97 (1.42)	1.61 (1.05)
Last value	Mean (SD)	6.15 (13.34)	4.62 (5.83)				2.33 (2.29)	1.77 (1.05)
Change	Mean (SD)	1.27 (13.17)	0.69 (5.66)				0.36 (1.71)	0.17 (0.82)
	Median	-0.050	-0.025				0.086	0.13
	Range	-46.55 to 163.42	-21.59 to 40.41				-1.77 to 5.18	-2.26 to 1.57
QUICKI								
Patients*		496	131				20	33
Baseline	Mean (SD)	0.3089 (0.0644)	0.2882 (0.0859)				0.3633 (0.0431)	0.3694 (0.0383)
Last value	Mean (SD)	0.3116 (0.0706)	0.2878 (0.0881)				0.3620 (0.0485)	0.3610 (0.0322)
Change	Mean (SD)	0.0027 (0.0393)	-0.0032 (0.0312)				-0.0013 (0.0302)	-0.0084 (0.0298)
	Median	0.0000	0.0009				-0.0051	-0.0061
	Range	-0.1435 to 0.1366	-0.1229 to 0.0800				-0.0488 to 0.0749	-0.0896 to 0.0517

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Chl Chlorpromazine, Hal Haloperidol, Li Lithium, Ola Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone.
Pgm: Rep/Def/Diabetes Mar 07 SER3841/AE_chg_n8_trials_diab2.SAS Data version: V91 User: Bengt Pierzon, 2007-05-03 12:21.

Table A11 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All trials)

	QTP N=996 End of tx			PLA N=220 End of tx			CHL N=10 End of tx			HAL N=35 End of tx			LI N=2 End of tx			OLZ N=29 End of tx			RI N=90 End of tx		
	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)
Glucose (mmol/L)																					
L	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
N	0 (0)	698 (96.0)	29 (4.0)	0 (0)	176 (96.2)	7 (3.8)	0 (0)	1 (100)	0 (0)	0 (0)	9 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	26 (89.7)	3 (10.3)	0 (0)	74 (96.1)	3 (3.9)
H	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	698 (96.0)	29 (4.0)	0 (0)	176 (96.2)	7 (3.8)	0 (0)	1 (100)	0 (0)	0 (0)	9 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	26 (89.7)	3 (10.3)	0 (0)	74 (96.1)	3 (3.9)
HbA_{1c} (%)																					
N	NA	471 (100)	0 (0)	NA	98 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	29 (100)	0 (0)	NA	41 (100)	0 (0)
H	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	471 (100)	0 (0)	NA	98 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	29 (100)	0 (0)	NA	41 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication have a value at baseline and at least one value post baseline.
Chl Chlorpromazine. Pla Placebo. QTP Quetiapine. Hal Haloperidol. Li Lithium. Olz Olanzapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-?ref/Diabetes Mar 07 SERM/LAB_shr_all_trials_diab2.SAS. Data version: V91 User: Bengt Fransson. 2007-05-03 08:58

Table A12 Shift to clinically important lab values at any time in subjects with diabetic risk (All trials)

	QTP N=996		Pla N=220		Chl N=10		Hal N=35		Li N=2		Olz N=29		Ri N=90	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)														
Low[a]	727	1 (0.14)	183	0 (0)	1	0 (0)	9	0 (0)	2	0 (0)	29	0 (0)	77	0 (0)
High[b]	727	53 (7.3)	183	9 (4.9)	1	0 (0)	9	0 (0)	2	0 (0)	29	4 (13.8)	77	4 (5.2)
HbA1c (%)														
High[b]	471	0 (0)	98	0 (0)	NA	NA	NA	NA	NA	NA	29	0 (0)	41	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Chl Chlorpromazine, Hal Haloperidol, Li Lithium, Olz Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone
Clinically important limits are: Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High: >=7.5.
Pgm: Req-Def/Diabetes Mar 07 SER/M7LAT_glu_all_trials_diab2/SAS. Data version: V91 User: Bengt Fransen. 2007-05-03 07:14

Diabetic patients

Table A13 Mean (SD) change from baseline to end of treatment in diabetic subjects (All trials)

		QTP N=531	Pla N=90	Chl N=3	Hal N=26	Ola N=7	Ri N=52
Glucose (mmol/L)							
Patients[a]		325	85	0	8	7	27
Baseline	Mean (SD)	7.99 (3.46)	7.32 (3.19)		14.45 (2.96)	5.99 (2.54)	8.48 (4.19)
Last value	Mean (SD)	8.08 (4.37)	6.84 (3.07)		12.57 (5.46)	5.24 (0.42)	8.86 (4.02)
Change	Mean (SD)	0.092 (3.67)	-0.49 (3.53)		-1.88 (4.01)	-0.74 (2.24)	0.37 (4.04)
	Median	0	-0.28		-2.80	-0.100	0.10
	Range	-9.83 to 19.56	-12.00 to 13.72		-5.90 to 6.44	-3.70 to 0.80	-7.83 to 14.83
HbA1c (%)							
Patients[a]		176	40			7	9
Baseline	Mean (SD)	6.34 (0.86)	6.01 (0.85)			5.47 (0.77)	5.90 (0.50)
Last value	Mean (SD)	6.54 (1.20)	5.96 (0.91)			5.41 (0.74)	5.79 (0.38)
Change	Mean (SD)	0.20 (0.72)	-0.050 (0.45)			-0.057 (0.28)	-0.11 (0.43)
	Median	0.100	0			0	-0.10
	Range	-1.90 to 4.50	-1.70 to 1.10			-0.60 to 0.20	-0.70 to 0.50
Insulin (pmol/L)							
Patients[a]		211	59			2	6
Baseline	Mean (SD)	177.82 (208.83)	175.96 (261.50)			182.95 (143.96)	372.19 (456.40)
Last value	Mean (SD)	170.52 (198.48)	134.77 (130.45)			172.86 (99.20)	322.24 (253.42)
Change	Mean (SD)	-7.30 (228.63)	-39.19 (278.54)			-10.09 (77.72)	-49.96 (290.25)
	Median	0	-12.08			-57.09	19.72
	Range	-1679 to 1425	-1939 to 507.00			-89.33 to 92.23	-416.67 to 255.85
$HOMA_B$							
Patients[a]		199	57			2	4

Table A13 Mean (SD) change from baseline to end of treatment in diabetic subjects (All trials)

		QTP N=531	Pla N=90	Chl N=3	Hal N=26	Ola N=7	Ri N=52
Baseline	Mean (SD)	8.18 (11.58)	7.97 (17.54)			1.63 (1.48)	7.57 (12.61)
Last value	Mean (SD)	7.84 (11.24)	6.02 (8.65)			1.48 (0.77)	4.77 (5.81)
Change	Mean (SD)	-0.34 (14.46)	-1.95 (18.99)			-0.15 (1.38)	-2.80 (14.05)
	Median	0.000	-0.10			0.056	0.37
	Range	-87.09 to 92.99	-127.11 to 42.25			-2.66 to 1.89	-22.57 to 10.63
QUICKI							
Patients*		199	37			7	4
Baseline	Mean (SD)	0.3659 (0.0531)	0.3660 (0.0572)			0.3718 (0.0387)	0.3529 (0.0809)
Last value	Mean (SD)	0.3699 (0.0545)	0.3437 (0.0613)			0.3762 (0.0522)	0.3393 (0.0620)
Change	Mean (SD)	0.0059 (0.0469)	-0.0077 (0.0438)			0.0043 (0.0579)	-0.0136 (0.0595)
	Median	0.0050	-0.0080			-0.0020	-0.0280
	Range	-0.1619 to 0.1600	-0.1738 to 0.1443			-0.0936 to 0.0858	-0.0625 to 0.0649

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline
Chl Chlorpromazine Hal Haloperidol Ola Olanzapine Pla Placebo QTP Quetiapine Ri Risperidone
Note: Only treatments with existing patients are shown
Pgm: Reg-Del\Diabetes Mar 07 SERM\LAB_chg_all_trials_diab1.SAS. Data version: V91 User: Bengt Fransen. 2007-05-03 12:20

Table A14 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All trials)

	QTP N=531 End of tx			PLA N=90 End of tx			CHL N=3 End of tx			HAL N=26 End of tx			LI N=0 End of tx			OLZ N=7 End of tx			RI N=52 End of tx		
	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)
Glucose (mmol/L)																					
L	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	NA	NA	NA	NA	NA	NA	-	-	-	NA	NA	NA	NA	NA	NA
N	2 (1.1)	151 (79.9)	36 (19.0)	1 (1.7)	49 (83.1)	9 (15.3)	NA	NA	NA	NA	NA	NA	-	-	-	0 (0)	6 (100)	0 (0)	0 (0)	15 (78.9)	4 (21.1)
H	0 (0)	62 (46.6)	71 (53.4)	0 (0)	19 (76.0)	6 (24.0)	NA	NA	NA	0 (0)	4 (50.0)	4 (50.0)	-	-	-	0 (0)	1 (100)	0 (0)	0 (0)	4 (50.0)	4 (50.0)
Total	2 (0.62)	214 (66.3)	107 (33.1)	1 (1.2)	69 (81.2)	15 (17.6)	NA	NA	NA	0 (0)	4 (50.0)	4 (50.0)	-	-	-	0 (0)	7 (100)	0 (0)	0 (0)	19 (70.4)	8 (29.6)
HbA_{1c} (%)																					
N	NA	150 (90.9)	15 (9.1)	NA	36 (97.3)	1 (2.7)	NA	NA	NA	NA	NA	NA	-	-	-	NA	7 (100)	0 (0)	NA	9 (100)	0 (0)
H	NA	1 (9.1)	10 (90.9)	NA	0 (0)	3 (100)	NA	NA	NA	NA	NA	NA	-	-	-	NA	NA	NA	NA	NA	NA
Total	NA	151 (85.8)	25 (14.2)	NA	36 (90.0)	4 (10.0)	NA	NA	NA	NA	NA	NA	-	-	-	NA	7 (100)	0 (0)	NA	9 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Hal Haloperidol Olz Olanzapine Ri Risperidone, Chl Chlorpromazine, Plo Placebo, Q1P Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA_{1c} (%), High: >=7.5.
Note: Only treatments with existing patients are shown

Pgm: Reg\Def\Diabetes Mar 07 SERMLAB_shr_all_tr.lab_duh1.SAS, Data version: V91 User: Bengt Program: 2007-05-03 06:53

Table A15 Shift to clinically important lab values at any time in diabetic subjects (All trials)

	QTP N=531		Pla N=90		Chl N=3		Hal N=26		Ola N=7		Ri N=52	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)												
Low[a]	322	2 (0.62)	84	1 (1.2)	NA	NA	8	0 (0)	7	0 (0)	25	0 (0)
High[b]	196	48 (24.5)	60	10 (16.7)	NA	NA	NA	NA	6	1 (16.7)	19	6 (31.6)
HbA1c (%)												
High[b]	165	15 (9.1)	37	1 (2.7)	NA	NA	NA	NA	7	0 (0)	9	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time
Chl Chlorpromazine, Hal Haloperidol, Ola Olanzapine Pla Placebo, QTP Quetiapine, Ri Risperidone
Clinically important limits are: Glucose (mmol/L) Low: ≤2.8, High: >7 for fasting and ≥11.1 for non-fasting. HbA1c (%) High: ≥7.5.
Note: Only treatments with existing patients are shown
Prog: Reg-Def\Diabetes Mar 07\SER3001.AH_Abs_aR_trials_disbl.SAS. Data version: V81 User: Bangi Pran on: 2007-05-03 07:04

All fasting trials (all lab data)

Adverse event data

Table A16 Number of patients with adverse events related to diabetes (All fasting trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Any[e]	Quetiapine	20 (2)	3031	567.0 (570.1)	0.66 (0.07)	3.5 (0.4)
	Placebo	4 (1)	596	74.0 (74.3)	0.67 (0.17)	5.4 (1.3)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	1 (0)	172	67.1 (67.2)	0.58 (0.00)	1.5 (0.0)
Diabetic Ketoacidosis	Quetiapine	0 (0)	3031	570.2 (570.2)	0.00 (0.00)	0.0 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	172	67.2 (67.2)	0.00 (0.00)	0.0 (0.0)
Polydipsia	Quetiapine	2 (0)	3031	570.1 (570.2)	0.07 (0.00)	0.4 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	1 (0)	172	67.1 (67.2)	0.58 (0.00)	1.5 (0.0)
Polyuria	Quetiapine	4 (0)	3031	570.1 (570.2)	0.13 (0.00)	0.7 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	1 (0)	172	67.1 (67.2)	0.58 (0.00)	1.5 (0.0)
Thirst	Quetiapine	4 (0)	3031	569.9 (570.2)	0.13 (0.00)	0.7 (0.0)
	Placebo	3 (0)	596	74.0 (74.3)	0.50 (0.00)	4.1 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	172	67.2 (67.2)	0.00 (0.00)	0.0 (0.0)
Hyperglycaemia	Quetiapine	9 (1)	3031	569.0 (570.2)	0.30 (0.03)	1.6 (0.2)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	172	67.2 (67.2)	0.00 (0.00)	0.0 (0.0)
Diabetes mellitus	Quetiapine	3 (1)	3031	568.7 (570.2)	0.10 (0.03)	0.5 (0.2)
	Placebo	1 (1)	596	74.3 (74.3)	0.17 (0.17)	1.3 (1.3)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	172	67.2 (67.2)	0.00 (0.00)	0.0 (0.0)
Urine glucose abnormalities	Quetiapine	1 (0)	3031	570.2 (570.2)	0.03 (0.00)	0.2 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)

Table A16 Number of patients with adverse events related to diabetes (All fasting trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
	Risperidone	0 (0)	172	67.2 (67.2)	0.00 (0.00)	0.0 (0.0)

[a] Patients must have received at least one dose of trial medication.
[b] Exposure in patient-years, censored at first event.
[c] 100 x total number of patients with event/total number of patients.
[d] 100 x total number of patients with event/total patient years of exposure.
[e] The number of patients with any of the adverse events. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Trials D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135, 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, D1441C00028, 5077IL/0115, 5077US/0046 and D1441C00125 are included in this table.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Only rows with existing patients are shown.
Pgm: *Reg-Def\Diabetes Mar 07 SERM\...\AE_all_trials_fast.SAS.* Data version: V9.1 User: Malin Dreyer *2007-05-03 10:07.*

Non-diabetic patients

Table A17 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All fasting trials)

		QTP N=2188	Pla N=409	Olz N=132	Ri N=122
Glucose (mmol/L)					
Patients[a]		1879	358	132	121
Baseline	Mean (SD)	4.92 (0.66)	4.90 (0.66)	4.91 (0.54)	4.97 (0.67)
Last value	Mean (SD)	5.18 (0.91)	5.06 (0.79)	5.15 (0.54)	5.19 (0.55)
Change	Mean (SD)	0.26 (0.93)	0.16 (0.99)	0.24 (0.64)	0.21 (0.78)
	Median	0.17	0.100	0.30	0.30
	Range	-4.60 to 9.33	-6.83 to 4.72	-3.30 to 1.90	-3.00 to 1.80
HbA1c (%)					
Patients[a]		1444	305	132	122
Baseline	Mean (SD)	5.28 (0.38)	5.23 (0.37)	5.31 (0.37)	5.29 (0.41)
Last value	Mean (SD)	5.32 (0.38)	5.24 (0.36)	5.31 (0.40)	5.28 (0.46)
Change	Mean (SD)	0.037 (0.26)	0.016 (0.25)	0.0030 (0.34)	-0.0041 (0.30)
	Median	0	0	0	0
	Range	-0.90 to 1.10	-0.80 to 0.80	-1.00 to 1.40	-0.90 to 1.00
Insulin (pmol/L)					
Patients[a]		1540	369	112	100
Baseline	Mean (SD)	85.24 (118.15)	77.67 (154.45)	214.46 (199.81)	225.30 (213.58)
Last value	Mean (SD)	112.57 (361.93)	94.15 (153.91)	301.38 (394.69)	254.30 (239.16)
Change	Mean (SD)	27.32 (150.06)	16.48 (197.65)	86.93 (380.09)	29.00 (250.88)
	Median	7.00	6.95	25.84	22.50

Table A17 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All fasting trials)

		QTP N=2188	Pla N=409	Olz N=132	Ri N=122
	Range	-770.90 to 1632	-1875 to 1820	-1124 to 2822	-645.75 to 1492
HOMAR					
Patients[a]		1337	339	103	97
Baseline	Mean (SD)	2.28 (3.35)	2.88 (9.92)	1.35 (0.85)	1.38 (0.70)
Last value	Mean (SD)	3.61 (7.02)	3.40 (7.46)	1.69 (1.34)	1.53 (0.95)
Change	Mean (SD)	1.34 (6.83)	0.52 (12.00)	0.35 (1.37)	0.16 (0.83)
	Median	0.24	0.21	0.19	0.086
	Range	-35.70 to 127.84	-137.15 to 87.11	-3.14 to 8.12	-1.60 to 3.18
QUICKI					
Patients[a]		1337	339	103	97
Baseline	Mean (SD)	0.3592 (0.0399)	0.3595 (0.0416)	0.3791 (0.0386)	0.3749 (0.0349)
Last value	Mean (SD)	0.3480 (0.0448)	0.3515 (0.0447)	0.3701 (0.0429)	0.3706 (0.0362)
Change	Mean (SD)	-0.0112 (0.0425)	-0.0079 (0.0430)	-0.0090 (0.0460)	-0.0043 (0.0320)
	Median	-0.0100	-0.0100	-0.0085	-0.0051
	Range	-0.2105 to 0.1807	-0.1830 to 0.1860	-0.1317 to 0.2593	-0.0745 to 0.0888

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00028, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERA3_A13_chg_all_trials_ndfast_diab3 SAS. Data version: V91 User: Bengt Franzen 2007-05-03 12:33.

Table A18 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All fasting trials)

	QTP N=2188 End of treatment			Pla N=409 End of treatment			Olz N=132 End of treatment			Ri N=122 End of treatment		
Lab test **Baseline**	*Low* n[a] (%)	*Norm* n[a] (%)	*High* n[a] (%)	*Low* n[a] (%)	*Norm* n[a] (%)	*High* n[a] (%)	*Low* n[a] (%)	*Norm* n[a] (%)	*High* n[a] (%)	*Low* n[a] (%)	*Norm* n[a] (%)	*High* n[a] (%)
Glucose (mmol/L)												
Low	0 (0)	4 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	3 (0.16)	1841 (98.2)	31 (1.7)	0 (0)	350 (97.8)	8 (2.2)	0 (0)	130 (98.5)	2 (1.5)	0 (0)	120 (99.2)	1 (0.83)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	3 (0.16)	1845 (98.2)	31 (1.6)	0 (0)	350 (97.8)	8 (2.2)	0 (0)	130 (98.5)	2 (1.5)	0 (0)	120 (99.2)	1 (0.83)
HbA1c (%)												
Norm	NA	1444 (100)	0 (0)	NA	305 (100)	0 (0)	NA	132 (100)	0 (0)	NA	122 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	1444 (100)	0 (0)	NA	305 (100)	0 (0)	NA	132 (100)	0 (0)	NA	122 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone.
Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%): High >=7.5.
Note Trials 5077IL00016, 5077IL00017, 5077IL00020, 5077IL00024, 5077IL00027, 5077IL00035, 5077IL00048, 5077ILX0045, 5077IL00046, 5077IL00047, 5077IL00063, 5077IL00064, 5077IL00115, 5077USA0046, D1441C00028, D1441C00125, D1446C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00136, D1447C00135 are included in this table.
Pgm: Reg-Def-Diabetes Mar 07\SERM\LAB_sbe_all_trials_adhoc_diab1.SAS. Data version: V91 User: Bengt Fournier 2007-05-02 06:59

Table A19 Shift to clinically important lab values at any time in non-diabetic subjects (All fasting trials)

	QTP N=2188		Pla N=409		Olz N=132		Ri N=122	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	1875	4 (0.21)	358	1 (0.28)	132	0 (0)	121	0 (0)
High[b]	1879	56 (3.0)	358	8 (2.2)	132	6 (4.5)	121	6 (5.0)
HbA1c (%)								
High[b]	1444	1 (0.069)	305	0 (0)	132	0 (0)	122	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >=6.5.
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0046, D144GC00028, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_all_trials_udfast_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:19.

Diabetic risk patients

Table A20 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All fasting trials)

		QTP N=584	Pla N=127	Olz N=29	Ri N=41
Glucose (mmol/L)					
Patients[a]		526	110	29	40
Baseline	Mean (SD)	5.63 (0.66)	5.52 (0.63)	5.90 (0.54)	5.91 (0.53)
Last value	Mean (SD)	5.61 (1.66)	5.41 (0.94)	5.81 (0.76)	5.67 (0.68)
Change	Mean (SD)	-0.023 (1.66)	-0.11 (0.97)	-0.083 (0.69)	-0.24 (0.68)
	Median	-0.14	-0.11	-0.20	-0.30
	Range	-3.60 to 29.67	-3.06 to 4.30	-1.40 to 1.40	-1.70 to 1.50
HbA1c (%)					
Patients[a]		471	98	29	41
Baseline	Mean (SD)	5.40 (0.38)	5.32 (0.43)	5.42 (0.40)	5.43 (0.41)
Last value	Mean (SD)	5.45 (0.40)	5.35 (0.45)	5.44 (0.48)	5.41 (0.43)
Change	Mean (SD)	0.055 (0.29)	0.023 (0.27)	0.021 (0.34)	-0.017 (0.30)
	Median	0.100	0	0	0
	Range	-1.40 to 1.40	-0.90 to 0.80	-0.50 to 1.10	-0.60 to 0.70
Insulin (pmol/L)					
Patients[a]		482	113	22	34
Baseline	Mean (SD)	143.44 (189.89)	112.01 (107.87)	402.94 (358.68)	195.15 (154.05)
Last value	Mean (SD)	165.55 (275.06)	126.96 (143.20)	366.31 (288.00)	241.44 (205.30)

Table A20 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All fasting trials)

		QTP N=584	Pla N=127	Olz N=29	Ri N=41
Change	Mean (SD)	22.12 (278.22)	14.95 (147.81)	-36.63 (190.75)	46.29 (222.45)
	Median	0	0	3.89	4.62
	Range	-1965 to 2730	-620.26 to 888.96	-508.53 to 269.40	-521.50 to 863.96
$HOMA_B$					
Patients[a]		452	102	20	33
Baseline	Mean (SD)	4.72 (5.90)	3.80 (3.70)	1.97 (1.42)	1.61 (1.03)
Last value	Mean (SD)	5.84 (13.60)	4.53 (6.36)	2.33 (2.29)	1.77 (1.03)
Change	Mean (SD)	1.11 (13.29)	0.73 (6.14)	0.36 (1.71)	0.17 (0.82)
	Median	-0.13	-0.19	0.086	0.13
	Range	-40.55 to 163.49	-21.59 to 40.41	-1.77 to 5.18	-2.26 to 1.57
QUICKI					
Patients[a]		452	102	20	33
Baseline	Mean (SD)	0.3258 (0.0365)	0.3307 (0.0351)	0.3633 (0.0431)	0.3694 (0.0383)
Last value	Mean (SD)	0.3294 (0.0432)	0.3299 (0.0394)	0.3620 (0.0485)	0.3610 (0.0322)
Change	Mean (SD)	0.0036 (0.0408)	-0.0008 (0.0345)	-0.0013 (0.0302)	-0.0084 (0.0298)
	Median	0.0000	0.0000	-0.0051	-0.0061
	Range	-0.1433 to 0.1300	-0.1229 to 0.0800	-0.0488 to 0.0749	-0.0896 to 0.0517

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine Pla Placebo QTP Quetiapine Ri Risperidone.
Note: Trials 5077IL/0016, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0046, 5077IL/0047, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_all_trials_tdfast_diab2.SAS. Data version: V91 User: Bengt Fronzon. 2007-05-03 12:33.

Table A21 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All fasting trials)

	QTP N=584 End of treatment			Pla N=127 End of treatment			Olz N=29 End of treatment			Ri N=41 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	502 (95.4)	24 (4.6)	0 (0)	104 (94.5)	6 (5.5)	0 (0)	26 (89.7)	3 (10.3)	0 (0)	37 (92.5)	3 (7.5)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	502 (95.4)	24 (4.6)	0 (0)	104 (94.5)	6 (5.5)	0 (0)	26 (89.7)	3 (10.3)	0 (0)	37 (92.5)	3 (7.5)
HbA1c (%)												
Norm	NA	471 (100)	0 (0)	NA	98 (100)	0 (0)	NA	29 (100)	0 (0)	NA	41 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	471 (100)	0 (0)	NA	98 (100)	0 (0)	NA	29 (100)	0 (0)	NA	41 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline

Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.

Clinically important limits are: Glucose (mmol/L), Low <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High >7.5.

Note: Trials 5077IL/0016, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0046, 5077IL/0047, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00097, D1444C00003, D1444C00004, D1444C00137, D1444C00133, D1444C00146, D1447C00135 are included in this table.

Prg: Reg-Def-Diabetes Mar 07 SERSDLAB_she_all_trials_udfast_diab) SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 06:58

Table A22 Shift to clinically important lab values at any time in subjects with diabetic risk (All fasting trials)

	QTP N=584		Pla N=127		Olz N=29		Ri N=41	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	526	1 (0.19)	110	0 (0)	29	0 (0)	40	0 (0)
High[b]	526	47 (8.9)	110	8 (7.3)	29	4 (13.8)	40	4 (10.0)
HbA1c (%)								
High[b]	471	0 (0)	98	0 (0)	29	0 (0)	41	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High: >7.5.
Note: Trials 5077IL/0016, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5072IL/0046, 5077IL/0047, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def-Diabetes Mar 07 SERM-LAB_sha_all_trials_udfast_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:18.

Diabetic patients

Table A23 Mean (SD) change from baseline to end of treatment in diabetic subjects (All fasting trials)

		QTP N=259	Pla N=60	Olz N=7	Ri N=9
Glucose (mmol/L)					
Patients[a]		229	56	7	9
Baseline	Mean (SD)	6.92 (2.31)	6.04 (1.52)	5.99 (2.54)	5.60 (0.74)
Last value	Mean (SD)	6.99 (2.90)	6.08 (2.13)	5.24 (0.42)	6.46 (2.69)
Change	Mean (SD)	0.064 (2.79)	0.032 (2.03)	-0.74 (2.24)	0.86 (2.63)
	Median	0	-0.14	-0.100	0.10
	Range	-8.50 to 13.89	-4.20 to 5.10	-5.70 to 0.80	-1.40 to 7.50
HbA1c (%)					
Patients[a]		172	40	7	9
Baseline	Mean (SD)	6.32 (0.83)	6.01 (0.85)	5.47 (0.77)	5.90 (0.50)
Last value	Mean (SD)	6.51 (1.17)	5.96 (0.91)	5.41 (0.74)	5.79 (0.38)
Change	Mean (SD)	0.19 (0.72)	-0.050 (0.45)	-0.057 (0.28)	-0.11 (0.43)
	Median	0.100	0	0	-0.10
	Range	-1.90 to 4.50	-1.70 to 1.10	-0.60 to 0.20	-0.70 to 0.50
Insulin (pmol/L)					
Patients[a]		204	55	7	6
Baseline	Mean (SD)	178.68 (211.85)	143.81 (117.27)	182.95 (143.96)	372.19 (450.40)
Last value	Mean (SD)	172.49 (201.21)	133.71 (134.67)	172.86 (99.20)	322.24 (253.42)

Table A23 Mean (SD) change from baseline to end of treatment in diabetic subjects (All fasting trials)

		QTP N=259	Pla N=60	Olz N=7	Ri N=9
Change	Mean (SD)	-6.19 (232.39)	-10.09 (157.88)	-10.09 (77.72)	-49.96 (290.25)
	Median	0	-12.08	-57.09	19.72
	Range	-1479 to 1445	-493.00 to 507.00	-89.31 to 92.23	-416.07 to 255.85
$HOMA_R$					
Patients[a]		193	54	7	4
Baseline	Mean (SD)	8.29 (11.74)	5.82 (5.37)	1.63 (1.48)	7.57 (12.61)
Last value	Mean (SD)	7.98 (11.39)	6.06 (8.26)	1.48 (0.77)	4.77 (5.81)
Change	Mean (SD)	-0.31 (14.68)	0.24 (8.95)	-0.15 (1.38)	-2.80 (14.05)
	Median	0.10	-0.11	0.056	0.37
	Range	-87.09 to 92.99	-23.06 to 42.25	-2.66 to 1.89	-22.57 to 10.63
QUICKI					
Patients[a]		193	54	7	4
Baseline	Mean (SD)	0.3113 (0.0440)	0.3162 (0.0377)	0.3718 (0.0387)	0.3529 (0.0809)
Last value	Mean (SD)	0.3150 (0.0464)	0.3238 (0.0445)	0.3762 (0.0522)	0.3395 (0.0626)
Change	Mean (SD)	0.0037 (0.0475)	0.0076 (0.0448)	0.0043 (0.0379)	-0.0134 (0.0595)
	Median	0.0000	0.0001	-0.0020	-0.0280
	Range	-0.1619 to 0.1600	-0.0738 to 0.1443	-0.0976 to 0.0858	-0.0625 to 0.0649

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Note: Trials 5077IL/0024, 5077IL/0035, 5077IL/0044, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00001, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERML-AI3_chg_alf_trials_udfast_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:33.

Table A24 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All fasting trials)

	QTP N=259 End of treatment			Pla N=60 End of treatment			Olz N=7 End of treatment			Ri N=9 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)	NA	NA	NA	NA	NA	NA
Norm	2 (1.5)	107 (78.7)	27 (19.9)	1 (2.4)	34 (81.0)	7 (16.7)	0 (0)	6 (100)	0 (0)	0 (0)	6 (75.0)	2 (25.0)
High	0 (0)	46 (49.5)	47 (50.5)	0 (0)	9 (69.2)	4 (30.8)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Total	2 (0.87)	153 (66.8)	74 (32.3)	1 (1.8)	44 (78.6)	11 (19.6)	0 (0)	7 (100)	0 (0)	0 (0)	7 (77.8)	2 (22.2)
HbA1c (%)												
Norm	NA	148 (91.4)	14 (8.6)	NA	36 (97.3)	1 (2.7)	NA	7 (100)	0 (0)	NA	9 (100)	0 (0)
High	NA	1 (10.0)	9 (90.0)	NA	0 (0)	3 (100)	NA	NA	NA	NA	NA	NA
Total	NA	149 (86.6)	23 (13.4)	NA	36 (90.0)	4 (10.0)	NA	7 (100)	0 (0)	NA	9 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline

Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.

Clinically important limits are Glucose (mmol/L) Low <=2.5, High >=7.0 for fasting and >=11.1 for non-fasting. HbA1c (%) High >7.5.

Note. Trials 5077IL/0024, 5077IL/0035, 5077IL/0044, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00001, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.

Pgm: Reg-Def/Diabetes Mar 07 SERMLAB_shc_all_trials_adfast_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 06.58.

Table A25 Shift to clinically important lab values at any time in diabetic subjects (All fasting trials)

	QTP N=259		Pla N=60		Olz N=7		Ri N=9	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	229	2 (0.87)	55	1 (1.8)	7	0 (0)	9	0 (0)
High[b]	142	38 (26.8)	43	8 (18.6)	6	1 (16.7)	8	3 (37.5)
HbA1c (%)								
High[b]	162	14 (8.6)	37	1 (2.7)	7	0 (0)	9	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5
Note: Trials 5077IL/0024, 5077IL/0035, 5077IL/0044, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077IS/6046, D1441C00125, D1444C00001, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_all_trials_udfast_diab1.SAS. Data version: V91 User: Bengt Franzon 2007-05-03 07:18.

All diabetic subgroups

Table A26 Mean (SD) change from baseline to end of treatment (All fasting trials)

		QTP N=3031	Pla N=596	Olz N=168	Ri N=172
Glucose (mmol/L)					
Patients[a]		2634	524	168	170
Baseline	Mean (SD)	5.23 (1.10)	5.15 (0.89)	5.13 (0.82)	5.23 (0.75)
Last value	Mean (SD)	5.42 (1.46)	5.24 (1.09)	5.27 (0.62)	5.37 (0.88)
Change	Mean (SD)	0.18 (1.36)	0.092 (1.15)	0.14 (0.80)	0.14 (0.92)
	Median	0.10	0.056	0.30	0.20
	Range	-8.50 to 29.67	-6.83 to 5.10	-5.70 to 1.90	-3.00 to 7.50
HbA1c (%)					
Patients[a]		2087	443	168	172
Baseline	Mean (SD)	5.39 (0.52)	5.32 (0.50)	5.33 (0.40)	5.35 (0.44)
Last value	Mean (SD)	5.44 (0.60)	5.33 (0.50)	5.34 (0.43)	5.34 (0.46)
Change	Mean (SD)	0.054 (0.33)	0.012 (0.28)	0.0056 (0.34)	-0.013 (0.30)
	Median	0	0	0	0
	Range	-1.90 to 4.50	-1.70 to 1.10	-1.00 to 1.40	-0.90 to 1.00
Insulin (pmol/L)					
Patients[a]		2226	537	141	140
Baseline	Mean (SD)	106.41 (150.44)	91.67 (143.86)	242.30 (238.10)	224.27 (215.81)

Table A26 Mean (SD) change from baseline to end of treatment (All fasting trials)

		QTP N=3031	Pla N=596	Olz N=168	Ri N=172
Last value	Mean (SD)	129.53 (197.07)	105.11 (150.48)	305.13 (371.28)	254.09 (230.86)
Change	Mean (SD)	23.13 (193.20)	13.44 (184.29)	62.83 (350.06)	29.81 (244.84)
	Median	6.00	2.22	18.96	20.45
	Range	-1965 to 2730	-1875 to 1820	-1124 to 2822	-645.75 to 1492
HOMAR					
Patients[a]		1982	495	130	134
Baseline	Mean (SD)	3.42 (5.69)	3.39 (8.61)	1.46 (1.02)	1.62 (2.30)
Last value	Mean (SD)	4.54 (9.49)	3.92 (7.38)	1.78 (1.51)	1.69 (1.40)
Change	Mean (SD)	1.12 (9.63)	0.53 (10.71)	0.32 (1.42)	0.072 (2.32)
	Median	0.15	0.13	0.15	0.11
	Range	-87.09 to 163.49	-137.15 to 87.11	-3.14 to 8.12	-22.57 to 10.63
QUICKI					
Patients[a]		1982	495	130	134
Baseline	Mean (SD)	0.3469 (0.0435)	0.3488 (0.0430)	0.3763 (0.0394)	0.3729 (0.0374)
Last value	Mean (SD)	0.3406 (0.0460)	0.3441 (0.0450)	0.3692 (0.0440)	0.3673 (0.0364)
Change	Mean (SD)	-0.0064 (0.0432)	-0.0048 (0.0419)	-0.0071 (0.0445)	-0.0056 (0.0322)
	Median	-0.0057	-0.0034	-0.0074	-0.0056
	Range	-0.2105 to 0.1807	-0.1830 to 0.1800	-0.1117 to 0.2593	-0.0896 to 0.0888

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0546, D1441C00028, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1446C00346, D1447C00135 are included in this table.
Pgm: Reg-Def-Diabetes Mar 07 SERMULAB_chg_all_trials_usfast.SAS. Data version: V91 User: Bengt Fransen. 2007-05-03 12:34.

Table A27 Shift from baseline to clinically important lab values at end of treatment (All fasting trials)

	QTP N=3033 End of treatment			Pla N=596 End of treatment			Olz N=168 End of treatment			Ri N=172 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	0 (0)	4 (100)	0 (0)	0 (0)	1 (100)	0 (0)	NA	NA	NA	NA	NA	NA
Norm	5 (0.20)	2450 (96.6)	82 (3.2)	1 (0.20)	488 (95.7)	21 (4.1)	0 (0)	162 (97.0)	5 (3.0)	0 (0)	163 (96.4)	6 (3.6)
High	0 (0)	46 (49.5)	47 (50.5)	0 (0)	9 (69.2)	4 (30.8)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Total	5 (0.19)	2500 (94.9)	129 (4.9)	1 (0.19)	498 (95.0)	25 (4.8)	0 (0)	163 (97.0)	5 (3.0)	0 (0)	164 (96.5)	6 (3.5)
HbA1c (%)												
Norm	NA	2063 (99.3)	14 (0.67)	NA	439 (99.8)	1 (0.23)	NA	168 (100)	0 (0)	NA	172 (100)	0 (0)
High	NA	1 (10.0)	9 (90.0)	NA	0 (0)	3 (100)	NA	NA	NA	NA	NA	NA
Total	NA	2064 (98.9)	23 (1.1)	NA	439 (99.1)	4 (0.90)	NA	168 (100)	0 (0)	NA	172 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine Pla Placebo QTP Quetiapine Ri Risperidone
Clinically important limits are: Glucose (mmol/L), Low: <=3.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >=7.5.
Note: Trials 5077IL-0016, 5077IL-0017, 5077IL-0020, 5077IL-0024, 5077IL-0025, 5077IL-0035, 5077IL-0044, 5077IL-0045, 5077IL-0046, 5077IL-0047, 5077IL-0063, 5077IL-0064, 5077IL-0115, 5077IL-0046, D1441C00028, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00135, D1444C00146, D1447C00133 are included in this table.
Pgm: Reg-Def\Diabetes Mar07\SERM\LAB_she_alt_trials_tablist.SAS. Data version: V91 User: Bengt Fransson 2007-05-03 0u 59.

Table A28 Shift to clinically important lab values at any time (All fasting trials)

	QTP N=3031		Pla N=596		Olz N=168		Ri N=172	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	2630	7 (0.27)	523	2 (0.38)	168	0 (0)	170	0 (0)
High[b]	2547	143 (5.5)	511	24 (4.7)	167	11 (6.6)	169	13 (7.7)
HbA1c (%)								
High[b]	2077	15 (0.72)	440	1 (0.23)	168	0 (0)	172	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0664, 5077IL/0115, 5077US/0046, D1441C00028, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sho_all_trials_odfast.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:19

All fasting trials (documented fasting data only)

Non-diabetic patients

Table A29 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All fasting trials, documented fasting)

		QTP N=2188	Pla N=409	Olz N=132	Ri N=122
Glucose (mmol/L)					
Patients[a]		1494	318	129	116
Baseline	Mean (SD)	4.80 (0.47)	4.85 (0.46)	4.86 (0.36)	4.88 (0.43)
Last value	Mean (SD)	5.06 (0.78)	5.02 (0.75)	5.16 (0.54)	5.19 (0.56)
Change	Mean (SD)	0.26 (0.81)	0.16 (0.79)	0.30 (0.51)	0.31 (0.54)
	Median	0.17	0.100	0.30	0.30
	Range	-3.30 to 8.70	-2.10 to 4.72	-0.99 to 2.40	-1.40 to 2.20
HbA1c (%)					
Patients[a]		1284	265	130	115
Baseline	Mean (SD)	5.27 (0.37)	5.21 (0.37)	5.30 (0.37)	5.27 (0.43)
Last value	Mean (SD)	5.31 (0.38)	5.23 (0.37)	5.31 (0.40)	5.28 (0.47)
Change	Mean (SD)	0.037 (0.27)	0.011 (0.25)	0.0077 (0.33)	0.0087 (0.31)
	Median	0	0	0	0
	Range	-0.90 to 1.00	-0.80 to 0.80	-0.90 to 1.40	-0.90 to 1.00
Insulin (pmol/L)					
Patients[a]		1388	325	111	100
Baseline	Mean (SD)	79.92 (109.07)	66.29 (66.46)	213.93 (200.64)	225.30 (213.58)

Table A29 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All fasting trials, documented fasting)

		QTP N=2188	Pla N=409	Olz N=132	Ri N=122
Last value	Mean (SD)	101.16 (150.24)	82.74 (121.69)	303.91 (395.57)	254.30 (239.16)
Change	Mean (SD)	21.24 (133.48)	16.45 (99.33)	89.98 (380.43)	29.00 (250.88)
	Median	6.95	5.21	27.36	22.50
	Range	-757.00 to 1632	-327.00 to 1167	-1124 to 2822	-645.75 to 1492
HOMAR					
Patients[a]		1253	304	103	97
Baseline	Mean (SD)	2.11 (2.57)	2.11 (2.09)	1.35 (0.85)	1.38 (0.70)
Last value	Mean (SD)	3.25 (6.38)	3.06 (6.08)	1.69 (1.34)	1.53 (0.95)
Change	Mean (SD)	1.14 (6.11)	0.95 (5.35)	0.35 (1.37)	0.16 (0.83)
	Median	0.22	0.14	0.19	0.086
	Range	-26.01 to 127.84	-11.18 to 71.49	-3.14 to 8.12	-1.60 to 3.18
QUICKI					
Patients[a]		1253	304	103	97
Baseline	Mean (SD)	0.3606 (0.0391)	0.3610 (0.0402)	0.3791 (0.0386)	0.3749 (0.0349)
Last value	Mean (SD)	0.3506 (0.0434)	0.3543 (0.0442)	0.3701 (0.0429)	0.3706 (0.0362)
Change	Mean (SD)	-0.0101 (0.0419)	-0.0067 (0.0397)	-0.0090 (0.0460)	-0.0043 (0.0320)
	Median	-0.0100	-0.0051	-0.0085	-0.0051
	Range	-0.2105 to 0.1807	-0.1830 to 0.1100	-0.1117 to 0.2593	-0.0745 to 0.0888

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0026, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00028, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def-Diabetes Mar 07 SERM\LAB_chg_all_trials_fast_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-16 08:18.

Table A30 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All fasting trials, documented fasting)

	QTP N=2188 End of treatment			Pla N=409 End of treatment			Ol N=132 End of treatment			Ri N=122 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	0 (0)	3 (100)	0 (0)	NA	NA	NA	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	2 (0.13)	1461 (98.0)	28 (1.9)	0 (0)	311 (97.8)	7 (2.2)	0 (0)	127 (98.4)	2 (1.6)	0 (0)	114 (99.1)	1 (0.87)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	2 (0.13)	1464 (98.6)	28 (1.9)	0 (0)	311 (97.8)	7 (2.2)	0 (0)	127 (98.4)	2 (1.6)	0 (0)	115 (99.1)	1 (0.86)
HbA1c (%)												
Norm	NA	1284 (100)	0 (0)	NA	265 (100)	0 (0)	NA	130 (100)	0 (0)	NA	115 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	1284 (100)	0 (0)	NA	265 (100)	0 (0)	NA	130 (100)	0 (0)	NA	115 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Ol: Olanzapine Pla: Placebo QTP: Quetiapine Ri: Risperidone
Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting; HbA1c (%): High: >=7.5.
Note: Trials 5077IL-0016, 5077IL-0017, 5077IL-0020, 5077IL-0024, 5077IL-0027, 5077IL-0035, 5077IL-0044, 5077IL-0045, 5077IL-0046, 5077IL-0047, 5077IL-0063, 5077IL-0064, 5077IL-0115, 5077US-0046, D1441C00028, D1441C00125, D1446C00091, D1444C00033, D1444C00004, D1444C00132, D1444C00133, D1446C00146, D1447C00135 are included in this table.
Pgm: Reg-Det\Diabetes Mar07\STRMTLAB_ghe_all_trials_fast_diab5.SAS Data version: V91 User: Bengt Franzon 2007-05-03 09:53.

Table A31 Shift to clinically important lab values at any time in non-diabetic subjects (All fasting trials, documented fasting)

	QTP N=2188		Pla N=409		Olz N=132		Ri N=122	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	1491	2 (0.13)	318	0 (0)	129	0 (0)	115	0 (0)
High[b]	1494	49 (3.3)	318	7 (2.2)	129	6 (4.7)	116	6 (5.2)
HbA1c (%)								
High[b]	1284	1 (0.078)	265	0 (0)	130	0 (0)	115	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077IL/0016, 5077IL/0017, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0045, 5077IL/0046, 5077IL/0047, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00028, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SER3#LAB_sha_all_trials_fast_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:37.

Diabetic risk patients

Table A32 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All fasting trials, documented fasting)

		QTP N=584	Pla N=127	Olz N=29	Ri N=41
Glucose (mmol/L)					
Patients[a]		487	102	27	40
Baseline	Mean (SD)	5.64 (0.64)	5.50 (0.61)	5.88 (0.38)	5.92 (0.39)
Last value	Mean (SD)	5.50 (0.87)	5.42 (0.95)	5.80 (0.78)	5.67 (0.68)
Change	Mean (SD)	-0.14 (0.94)	-0.079 (0.97)	-0.078 (0.75)	-0.26 (0.75)
	Median	-0.20	-0.078	-0.20	-0.40
	Range	-3.00 to 5.89	-3.06 to 4.30	-1.40 to 1.80	-1.70 to 1.50
HbA1c (%)					
Patients[a]		432	86	27	40
Baseline	Mean (SD)	5.40 (0.37)	5.32 (0.44)	5.40 (0.40)	5.42 (0.41)
Last value	Mean (SD)	5.45 (0.40)	5.35 (0.46)	5.42 (0.48)	5.40 (0.43)
Change	Mean (SD)	0.050 (0.29)	0.034 (0.27)	0.026 (0.36)	-0.025 (0.32)
	Median	0	0	0	0
	Range	-1.40 to 1.40	-0.90 to 0.80	-0.50 to 1.10	-0.60 to 0.70
Insulin (pmol/L)					
Patients[a]		450	101	22	34

Table A32 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All fasting trials, documented fasting)

		QTP N=584	Pla N=127	Olz N=29	Ri N=41
Baseline	Mean (SD)	141.52 (189.63)	104.53 (98.01)	402.94 (358.68)	195.15 (154.05)
Last value	Mean (SD)	150.72 (260.00)	108.01 (103.96)	366.31 (288.00)	241.44 (205.30)
Change	Mean (SD)	9.20 (259.09)	3.48 (110.08)	-36.63 (190.75)	46.29 (222.45)
	Median	-1.88	-6.95	3.89	4.62
	Range	-1965 to 2730	-620.26 to 493.10	-508.51 to 269.40	-521.50 to 863.96
HOMAR					
Patients[a]		428	94	20	33
Baseline	Mean (SD)	4.67 (5.72)	3.43 (2.85)	1.97 (1.42)	1.61 (1.03)
Last value	Mean (SD)	5.31 (12.72)	4.01 (4.65)	2.35 (2.29)	1.77 (1.03)
Change	Mean (SD)	0.63 (12.23)	0.59 (4.14)	0.36 (1.71)	0.17 (0.82)
	Median	-0.18	-0.20	0.086	0.13
	Range	-40.55 to 163.49	-7.71 to 23.19	-1.77 to 5.18	-2.26 to 1.57
QUICKI					
Patients[a]		428	94	20	33
Baseline	Mean (SD)	0.3259 (0.0364)	0.3330 (0.0333)	0.3633 (0.0431)	0.3694 (0.0383)
Last value	Mean (SD)	0.3309 (0.0415)	0.3327 (0.0388)	0.3620 (0.0485)	0.3610 (0.0322)
Change	Mean (SD)	0.0051 (0.0391)	-0.0003 (0.0341)	-0.0013 (0.0302)	-0.0084 (0.0298)
	Median	0.0004	0.0042	-0.0051	-0.0061
	Range	-0.1433 to 0.1300	-0.1229 to 0.0800	-0.0488 to 0.0749	-0.0896 to 0.0517

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Note: Trials 5077IL/0016, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0046, 5077IL/0047, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1442C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_dl_trials_fast_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-16 08:17.

Table A33 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All fasting trials, documented fasting)

	QTP N=584 End of treatment			Pla N=127 End of treatment			Olz N=29 End of treatment			Ri N=41 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	463 (95.1)	24 (4.9)	0 (0)	96 (94.1)	6 (5.9)	0 (0)	24 (88.9)	3 (11.1)	0 (0)	37 (92.5)	3 (7.5)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	463 (95.1)	24 (4.9)	0 (0)	96 (94.1)	6 (5.9)	0 (0)	24 (88.9)	3 (11.1)	0 (0)	37 (92.5)	3 (7.5)
HbA1c (%)												
Norm	NA	432 (100)	0 (0)	NA	86 (100)	0 (0)	NA	27 (100)	0 (0)	NA	40 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	432 (100)	0 (0)	NA	86 (100)	0 (0)	NA	27 (100)	0 (0)	NA	40 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one valide post baseline

Olz Olanzapine Pla Placebo QTP Quetiapine Ri Risperidone

Clinically important limits are Glucose (mmol/L) Low =<4.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >=6.5.

Note: Trials 5077IL/0016, 5077IL/0027, 5077IL/0035, 5077IL/0048, 5077IL/0046, 5077IL/0047, 5077IL/0064, 5077IL/0315, 5077US/0046, D1444C00125, D1444C00081, D1444C00005, D1444C00004, D1444C00133, D1444C00133, D1444C00146, D1447C00135 are included in this table.

Pgm: Reg/Def/Diabetes Mar07 SERMLAB_dia_all_trials_fast_diab2 SAS Data version: V91 User: Bengt Fransson 2007-05-03 06:37

Table A34 **Shift to clinically important lab values at any time in subjects with diabetic risk (All fasting trials, documented fasting)**

	QTP N=584		Pla N=127		Olz N=29		Ri N=41	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	487	1 (0.21)	102	0 (0)	27	0 (0)	40	0 (0)
High[b]	487	44 (9.0)	102	8 (7.8)	27	4 (14.8)	40	4 (10.0)
HbA1c (%)								
High[b]	432	0 (0)	86	0 (0)	27	0 (0)	40	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting HbA1c (%) High: >=7.5.
Note: Trials 5077IL/0016, 5077IL/0027, 5077IL/0035, 5077IL/0044, 5077IL/0046, 5077IL/0047, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00001, D1444C00003, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_all_trials_fast_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:17.

Diabetic patients

Table A35 **Mean (SD) change from baseline to end of treatment in diabetic subjects (All fasting trials, documented fasting)**

		QTP N=259	Pla N=60	Olz N=7	Ri N=9
Glucose (mmol/L)					
Patients[a]		208	49	7	8
Baseline	Mean (SD)	6.88 (2.19)	6.10 (1.55)	6.34 (3.11)	6.38 (1.52)
Last value	Mean (SD)	6.88 (2.74)	6.05 (2.18)	5.24 (0.42)	6.34 (2.85)
Change	Mean (SD)	0.0049 (2.61)	-0.045 (2.14)	-1.10 (3.08)	-0.037 (2.46)
	Median	0	-0.39	-0.100	-0.10
	Range	-8.50 to 13.89	-4.20 to 5.10	-8.00 to 0.60	-3.70 to 5.10
HbA1c (%)					
Patients[a]		156	33	7	8
Baseline	Mean (SD)	6.33 (0.85)	6.05 (0.87)	5.54 (0.70)	5.94 (0.52)
Last value	Mean (SD)	6.53 (1.21)	6.05 (0.92)	5.41 (0.74)	5.85 (0.35)
Change	Mean (SD)	0.19 (0.75)	-0.0030 (0.42)	-0.13 (0.30)	-0.088 (0.43)
	Median	0	0	0	-0.0000
	Range	-1.90 to 4.50	-1.70 to 1.10	-0.60 to 0.20	-0.70 to 0.40
Insulin (pmol/L)					
Patients[a]		187	48	7	6
Baseline	Mean (SD)	179.99 (216.17)	148.75 (121.80)	182.95 (143.96)	372.19 (450.40)

Table A35 Mean (SD) change from baseline to end of treatment in diabetic subjects (All fasting trials, documented fasting)

		QTP N=259	Pla N=60	Olz N=7	Ri N=9
Last value	Mean (SD)	154.87 (165.29)	119.91 (118.09)	172.86 (99.20)	322.24 (253.42)
Change	Mean (SD)	-25.12 (201.43)	-28.84 (144.85)	-10.09 (77.72)	-49.96 (290.35)
	Median	0	-13.89	-57.09	19.72
	Range	-1479 to 548.66	-493.00 to 507.00	-89.31 to 92.23	-416.07 to 255.85
HOMAR					
Patients[a]		183	47	7	4
Baseline	Mean (SD)	8.45 (11.93)	6.05 (5.53)	1.63 (1.48)	7.57 (12.61)
Last value	Mean (SD)	7.30 (9.25)	5.50 (7.95)	1.48 (0.77)	4.77 (5.81)
Change	Mean (SD)	-1.15 (12.99)	-0.56 (8.89)	-0.15 (1.38)	-2.80 (14.05)
	Median	0.080	-0.19	0.056	0.37
	Range	-87.09 to 41.44	-23.06 to 42.25	-2.66 to 1.89	-22.57 to 10.63
QUICKI					
Patients[a]		183	47	7	4
Baseline	Mean (SD)	0.3107 (0.0444)	0.3148 (0.0386)	0.3718 (0.0387)	0.3529 (0.0809)
Last value	Mean (SD)	0.3164 (0.0455)	0.3268 (0.0437)	0.3762 (0.0522)	0.3395 (0.0620)
Change	Mean (SD)	0.0057 (0.0461)	0.0119 (0.0436)	0.0043 (0.0579)	-0.0134 (0.0595)
	Median	0.0000	0.0039	-0.0020	-0.0280
	Range	-0.1619 to 0.1600	-0.0738 to 0.1443	-0.0976 to 0.0858	-0.0625 to 0.0649

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Note: Trials 5077IL/0024, 5077IL/0035, 5077IL/0044, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00001, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_all_trials_fast_diab1.SAS. Data version: V91 User: Bengt Franzen. 2007-05-16 08:17.

Table A36 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All fasting trials, documented fasting)

	QTP N=259 End of treatment			Pla N=60 End of treatment			Ola N=7 End of treatment			Ri N=9 End of treatment		
Lab test Baseline	Low n* (%)	Norm n* (%)	High n* (%)	Low n* (%)	Norm n* (%)	High n* (%)	Low n* (%)	Norm n* (%)	High n* (%)	Low n* (%)	Norm n* (%)	High n* (%)
Glucose (mmol/L)												
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)	NA	NA	NA	NA	NA	NA
Norm	0 (0)	93 (78.2)	26 (21.8)	1 (2.9)	27 (77.1)	7 (20.0)	0 (0)	6 (100)	0 (0)	0 (0)	5 (100)	0 (0)
High	0 (0)	44 (49.4)	45 (50.6)	0 (0)	9 (69.2)	4 (30.8)	0 (0)	1 (100)	0 (0)	0 (0)	2 (66.7)	1 (33.3)
Total	0 (0)	137 (65.9)	71 (34.1)	1 (2.0)	37 (75.5)	11 (22.4)	0 (0)	7 (100)	0 (0)	0 (0)	7 (87.5)	1 (12.5)
HbA1c (%)												
Norm	NA	132 (90.4)	14 (9.6)	NA	29 (96.7)	1 (3.3)	NA	7 (100)	0 (0)	NA	8 (100)	0 (0)
High	NA	1 (10.0)	9 (90.0)	NA	0 (0)	3 (100)	NA	NA	NA	NA	NA	NA
Total	NA	133 (83.3)	23 (14.7)	NA	29 (87.9)	4 (12.1)	NA	7 (100)	0 (0)	NA	8 (100)	0 (0)

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline

Ola Olanzapine Pla Placebo QTP Quetiapine Ri Risperidone

Clinically important limits are Glucose (mmol/L) Low, <=2.5, High >=7 for fasting and >=11.1 for non-fasting, HbA1c (%) High >=7.5.

Note: Trials D1771L00024, D1771L00025, D1771L00044, D1771L00063, D1771L00064, D1771L00125, D1771US00046, D1443C00125, D1444C00001, D1444C00004, D1444C00132, D1444C00133, D1444C00136, D1447C00135 are included in this table.

Pgm: Berg/Def/Diabetes Mar 07 SER&MLA&_dbe_all_treate_fas_diabl.SAS. Data version: V01 User: Bengt Franzen. 2007-05-03 06:56.

Table A37 Shift to clinically important lab values at any time in diabetic subjects (All fasting trials, documented fasting)

	QTP N=259		Pla N=60		Olz N=7		Ri N=9	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	208	0 (0)	48	1 (2.1)	7	0 (0)	8	0 (0)
High[b]	119	34 (28.6)	36	8 (22.2)	6	0 (0)	5	0 (0)
HbA1c (%)								
High[b]	146	14 (9.6)	30	1 (3.3)	7	0 (0)	8	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077IL/0024, 5077IL/0035, 5077IL/0044, 5077IL/0063, 5077IL/0064, 5077IL/0115, 5077US/0046, D1441C00125, D1444C00001, D1444C00004, D1444C00132, D1444C00133, D1444C00146, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMGLAB_sha_all_trials_fast_diab1.SAS Data version: V91 User: Bengt Franzon. 2007-05-03 07:16.

All trials >12 weeks

Adverse event data

Table A38 Number of patients with adverse events related to diabetes (All trials >12 weeks)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Any[e]	Quetiapine	54 (8)	4277	2755.0 (2782.9)	1.26 (0.19)	2.0 (0.3)
	Placebo	0 (0)	102	17.8 (17.8)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	130	19.6 (19.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	3 (0)	229	84.5 (85.2)	1.31 (0.00)	3.5 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	3 (0)	347	112.4 (112.9)	0.86 (0.00)	2.7 (0.0)
Diabetic Ketoacidosis	Quetiapine	2 (2)	4277	2784.3 (2784.3)	0.05 (0.05)	0.1 (0.1)
	Placebo	0 (0)	102	17.8 (17.8)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	130	19.6 (19.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	229	85.2 (85.2)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	347	112.9 (112.9)	0.00 (0.00)	0.0 (0.0)
Polydipsia	Quetiapine	12 (0)	4277	2775.9 (2784.9)	0.28 (0.00)	0.4 (0.0)
	Placebo	0 (0)	102	17.8 (17.8)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	130	19.6 (19.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	229	85.2 (85.2)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)

Table A38 Number of patients with adverse events related to diabetes (All trials >12 weeks)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
	Risperidone	2 (0)	347	112.6 (112.9)	0.58 (0.00)	1.8 (0.0)
Polyuria	Quetiapine	2 (0)	4277	2784.0 (2784.9)	0.05 (0.00)	0.1 (0.0)
	Placebo	0 (0)	102	17.8 (17.8)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	130	19.6 (19.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	2 (0)	229	84.5 (85.2)	0.87 (0.00)	2.4 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	1 (0)	347	112.9 (112.9)	0.29 (0.00)	0.9 (0.0)
Thirst	Quetiapine	9 (0)	4277	2781.1 (2784.9)	0.21 (0.00)	0.3 (0.0)
	Placebo	0 (0)	102	17.8 (17.8)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	130	19.6 (19.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	229	85.2 (85.2)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	347	112.9 (112.9)	0.00 (0.00)	0.0 (0.0)
Hyperglycaemia	Quetiapine	22 (4)	4277	2775.5 (2784.8)	0.51 (0.09)	0.8 (0.1)
	Placebo	0 (0)	102	17.8 (17.8)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	130	19.6 (19.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	229	85.2 (85.2)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	347	112.9 (112.9)	0.00 (0.00)	0.0 (0.0)
Diabetes mellitus	Quetiapine	10 (3)	4277	2779.2 (2783.4)	0.23 (0.07)	0.4 (0.1)
	Placebo	0 (0)	102	17.8 (17.8)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	130	19.6 (19.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	1 (0)	229	85.2 (85.2)	0.44 (0.00)	1.2 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	1 (0)	347	112.8 (112.9)	0.29 (0.00)	0.9 (0.0)
Urine glucose abnormalities	Quetiapine	3 (0)	4277	2782.3 (2784.9)	0.07 (0.00)	0.1 (0.0)
	Placebo	0 (0)	102	17.8 (17.8)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	130	19.6 (19.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	229	85.2 (85.2)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	347	112.9 (112.9)	0.00 (0.00)	0.0 (0.0)

[a] Patients must have received at least one dose of trial medication.
[b] Exposure in patient-years, censored at first event.
[c] 100 x total number of patients with event/total number of patients.
[d] 100 x total number of patients with event/total patient years of exposure.

Appendix A Additional clinical trial tables
SEROQUEL and Glucose dysregulation
Drug name **quetiapine fumarate**
Date **June 2007**

[a] The number of patients with any of the adverse events. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Pgm: Reg-DefDiabetes Mar 07 SERM\...\AE_all_trials_long.SAS. Data version: V9.1 User: Malin Dreyer 2007-05-03 15:14.

Laboratory data

Non-diabetic patients

Table A39 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All trials >12 weeks)

		QTP N=3900	Pla N=78	Chl N=121	Hal N=207	Ola N=132	Ri N=284
Glucose (mmol/L)							
Patients[a]		1056	58	0	23	132	121
Baseline	Mean (SD)	5.55 (1.29)	5.21 (0.70)		5.38 (1.39)	4.91 (0.54)	4.97 (0.67)
Last value	Mean (SD)	5.80 (1.67)	5.33 (1.00)		5.46 (1.58)	5.15 (0.54)	5.19 (0.55)
Change	Mean (SD)	0.25 (1.80)	0.12 (1.06)		0.085 (1.07)	0.24 (0.64)	0.21 (0.78)
	Median	0.11	0.100		0	0.30	0.30
	Range	-7.40 to 22.00	-2.50 to 3.50		-3.28 to 2.33	-3.10 to 1.90	-3.00 to 1.80
HbA1c (%)							
Patients[b]		344	67			132	122
Baseline	Mean (SD)	5.24 (0.39)	5.19 (0.39)			5.31 (0.37)	5.29 (0.41)
Last value	Mean (SD)	5.29 (0.59)	5.19 (0.39)			5.31 (0.46)	5.28 (0.46)
Change	Mean (SD)	0.041 (0.29)	-0.0045 (0.31)			0.0030 (0.34)	-0.0041 (0.30)
	Median	0	0			0	0
	Range	-0.90 to 0.90	-0.86 to 0.80			-1.00 to 1.40	-0.90 to 1.06
Insulin (pmol/L)							
Patients[c]		314	67			132	100
Baseline	Mean (SD)	126.50 (179.50)	75.79 (76.82)			214.46 (199.81)	225.30 (213.58)
Last value	Mean (SD)	131.39 (186.21)	111.60 (133.71)			301.38 (394.69)	254.30 (239.16)
Change	Mean (SD)	4.90 (154.52)	35.81 (93.75)			86.93 (380.09)	29.00 (250.88)
	Median	0	7.00			25.84	22.50
	Range	-715.00 to 3194	-230.06 to 417.00			-1124 to 2822	-645.75 to 1492
$HOMA_B$							
Patients[d]		247	55			103	93
Baseline	Mean (SD)	2.38 (3.84)	2.83 (2.98)			1.35 (0.85)	1.38 (0.75)

Table A39 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All trials >12 weeks)

		QTP N=3900	Pla N=78	Chl N=121	Hal N=207	Ola N=132	Ri N=284
Last value	Mean (SD)	2.74 (9.42)	4.53 (7.40)			1.69 (3.34)	1.53 (0.95)
Change	Mean (SD)	0.36 (4.70)	1.22 (5.74)			0.35 (3.37)	0.16 (0.83)
	Median	0.10	0.30			0.19	0.086
	Range	-26.01 to 43.84	-11.18 to 34.05			-8.14 to 8.12	-1.69 to 3.38
QUICKI							
Patients*		247	55			103	97
Baseline	Mean (SD)	0.3611 (0.04203)	0.3495 (0.0411)			0.3791 (0.0386)	0.3749 (0.0349)
Last value	Mean (SD)	0.3572 (0.0455)	0.3384 (0.0465)			0.3761 (0.0429)	0.3766 (0.0362)
Change	Mean (SD)	-0.0039 (0.0436)	-0.0111 (0.0379)			-0.0090 (0.0460)	-0.0043 (0.0320)
	Median	-0.0042	-0.0100			-0.0085	-0.0051
	Range	-0.1300 to 0.1807	-0.1100 to 0.0800			-0.1117 to 0.2593	-0.0745 to 0.0888

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline
Chl Chlorpromazine, Hal Haloperidol, Ola Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone
Pgm: Reg/Def/Diabetes Mar 07/SER3401_AE_chg_all_trials_fcsg_diab3.SAS. Data version: V91 User: Bengt Francom 2007-05-03 12:35.

Table A40 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All trials >12 weeks)

	QTP N=3900 End of tx			PLA N=78 End of tx			CBL N=121 End of tx			HAL N=207 End of tx			OLZ N=132 End of tx			RI N=284 End of tx		
	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)	L n[a](%)	N n[a](%)	H n[a](%)
Glucose (mmol/L)																		
L	0 (0)	1 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
N	0 (0)	1030 (98.0)	21 (2.0)	0 (0)	54 (93.1)	4 (6.9)	NA	NA	NA	0 (0)	22 (95.7)	1 (4.3)	0 (0)	130 (98.5)	2 (1.5)	0 (0)	120 (99.2)	1 (0.83)
H	0 (0)	3 (75.0)	1 (25.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	1034 (97.9)	22 (2.1)	0 (0)	54 (93.1)	4 (6.9)	NA	NA	NA	0 (0)	22 (95.7)	1 (4.3)	0 (0)	130 (98.5)	2 (1.5)	0 (0)	120 (99.2)	1 (0.83)
HbA_{1c} (%)																		
N	NA	344 (100)	0 (0)	NA	67 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	132 (100)	0 (0)	NA	122 (100)	0 (0)
H	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	344 (100)	0 (0)	NA	67 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	132 (100)	0 (0)	NA	122 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Hal Haloperidol, Olz Olanzapine, Ris Risperidone, Chl Chlorpromazine, Pla Placebo, QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting, HbA1c (%), High: >7.5.
Pgm: Reg4DefOtaberax Mar 07 SERMOLAB_she_all_trials_long_diab5.SAS. Data version: V91 User: Bengt Fransson. 2007-05-08 07:01.

Table A41 Shift to clinically important lab values at any time in non-diabetic subjects (All trials >12 weeks)

	QTP N=3900		Pla N=78		Chl N=121		Hal N=207		Ola N=132		Ri N=284	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)												
Low[a]	1055	4 (0.38)	58	0 (0)	NA	NA	23	0 (0)	132	0 (0)	121	0 (0)
High[a]	1052	45 (4.3)	58	4 (6.9)	NA	NA	23	1 (4.3)	132	6 (4.5)	121	6 (5.0)
HbA1c (%)												
High[b]	344	1 (0.29)	67	0 (0)	NA	NA	NA	NA	132	0 (0)	122	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time
Chl Chlorpromazine, Hal Haloperidol, Ola Olanzapine Pla Placebo, QTP Quetiapine, Ri Risperidone
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >7.5.
Pgm: Reg-Def Diabetes Mar 07 SER/M1/All_sho_all_trials_long_diab3 SAS. Data version: V91 User: Bengt Tranten. 2007-05-03 07.21.

Diabetic risk patients

Table A42 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All trials >12 weeks)

		QTP N=231	Pla N=19	Chl N=7	Hal N=14	Ola N=29	Ri N=43
Glucose (mmol/L)							
Patients[a]		125	14	0	4	29	40
Baseline	Mean (SD)	5.98 (0.81)	5.68 (0.34)		5.53 (1.29)	5.90 (0.54)	5.91 (0.53)
Last value	Mean (SD)	6.25 (3.10)	5.67 (0.84)		6.42 (1.04)	5.81 (0.76)	5.67 (0.68)
Change	Mean (SD)	0.35 (3.09)	-0.0071 (0.39)		1.08 (2.29)	-0.083 (0.69)	-0.24 (0.68)
	Median	-0.100	0.050		1.50	-0.20	-0.30
	Range	-5.60 to 29.67	-0.60 to 0.80		-1.89 to 3.22	-1.40 to 1.40	-1.70 to 1.50
HbA1c (%)							
Patients[b]		94	17			29	41
Baseline	Mean (SD)	5.30 (0.40)	5.34 (0.32)			5.42 (0.40)	5.43 (0.41)
Last value	Mean (SD)	5.32 (0.36)	5.46 (0.41)			5.44 (0.48)	5.41 (0.43)
Change	Mean (SD)	0.019 (0.29)	0.12 (0.27)			0.021 (0.34)	-0.017 (0.30)
	Median	0	0.10			0	0
	Range	-1.00 to 0.70	-0.30 to 0.80			-0.50 to 1.10	-0.60 to 0.70
Insulin (pmol/L)							
Patients[b]		84	17			22	34
Baseline	Mean (SD)	196.37 (305.45)	103.41 (77.61)			402.94 (358.68)	195.15 (154.05)
Last value	Mean (SD)	193.65 (387.56)	124.94 (93.93)			366.31 (288.60)	241.44 (205.30)
Change	Mean (SD)	-2.73 (418.16)	21.53 (98.32)			-36.63 (190.75)	46.29 (222.45)
	Median	-7.00	6.00			3.89	4.62
	Range	-1905 to 2736	-153.00 to 292.00			-508.51 to 269.40	-521.50 to 863.98
$HOMA_B$							
Patients[b]		78	13			20	33

Table A42 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All trials >12 weeks)

		QTP N=231	Plb N=19	Chl N=7	Hal N=14	Ola N=29	Ri N=41
Baseline	Mean (SD)	4.44 (4.64)	3.66 (2.90)			1.97 (1.42)	1.61 (1.03)
Last value	Mean (SD)	6.18 (21.41)	4.15 (3.89)			2.33 (2.29)	1.77 (1.03)
Change	Mean (SD)	1.74 (19.95)	0.48 (4.46)			0.36 (1.71)	0.17 (0.82)
	Median	-0.22	0.14			0.086	0.13
	Range	-20.09 to 163.49	-6.48 to 13.43			-1.77 to 5.58	-2.56 to 1.57
QUICKI							
Patients*		78	13			20	33
Baseline	Mean (SD)	0.3316 (0.0457)	0.3331 (0.0435)			0.3633 (0.0431)	0.3694 (0.0383)
Last value	Mean (SD)	0.3378 (0.0648)	0.3246 (0.0341)			0.3629 (0.0485)	0.3619 (0.0322)
Change	Mean (SD)	0.0062 (0.0451)	-0.0085 (0.0303)			-0.0013 (0.0302)	-0.0084 (0.0298)
	Median	0.0013	0.0000			-0.0053	-0.0061
	Range	-0.1238 to 0.1300	-0.0700 to 0.0400			-0.0488 to 0.0749	-0.0896 to 0.0517

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Chl Chlorpromazine Hal Haloperidol Ola Olanzapine Plb Placebo QTP Quetiapine Ri Risperidone.
Pgm: I:\reg-Dat\Diabetes Mar 07 SER\M3\LAB_chg_all_trials_long_data2.SAS. Data version: V91 User: Bengt Francois 2007-05-02 12:35

Table A43 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All trials >12 weeks)

	QTP N=231 End of tx			PLA N=19 End of tx			CHL N=7 End of tx			HAL N=14 End of tx			OLZ N=29 End of tx			RI N=41 End of tx		
	L n[1](%)	N n[1](%)	H n[1](%)	L n[1](%)	N n[1](%)	H n[1](%)	L n[1](%)	N n[1](%)	H n[1](%)	L n[1](%)	N n[1](%)	H n[1](%)	L n[1](%)	N n[1](%)	H n[1](%)	L n[1](%)	N n[1](%)	H n[1](%)
Glucose (mmol/L)																		
L	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
N	0 (0)	112 (91.1)	11 (8.9)	0 (0)	13 (92.9)	1 (7.1)	NA	NA	NA	0 (0)	4 (100)	0 (0)	0 (0)	26 (89.7)	3 (10.3)	0 (0)	37 (92.5)	3 (7.5)
H	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	112 (91.1)	11 (8.9)	0 (0)	13 (92.9)	1 (7.1)	NA	NA	NA	0 (0)	4 (100)	0 (0)	0 (0)	26 (89.7)	3 (10.3)	0 (0)	37 (92.5)	3 (7.5)
HbA_{1c}(%)																		
N	NA	94 (100)	0 (0)	NA	17 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	29 (100)	0 (0)	NA	41 (100)	0 (0)
H	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	94 (100)	0 (0)	NA	17 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	29 (100)	0 (0)	NA	41 (100)	0 (0)

[1] Patients who have received at least one dose of trial medication; have a value at baseline and at least one value post baseline.
Bal Haloperidol Ola Olanzapine Ri Risperidone Chl Chlorpromazine Pla Placebo QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=3.5, High: >=7 for fasting and >=11.1 for non-fasting HbA1c (%), High: >=7.5.

Pgm: Reg\Del\Diabetes Mar 07\SUBMI_AR_sbu_all_trials_freq_diab2.SAS, Data version: V91 User: Bengt Frantzon, 2007-05-03 07:00.

Table A44 Shift to clinically important lab values at any time in subjects with diabetic risk (All trials >12 weeks)

	QTP N=231		Pla N=39		Chl N=7		Hal N=14		Olz N=29		Ri N=41	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)												
Low[a]	123	0 (0)	14	0 (0)	NA	NA	4	0 (0)	29	0 (0)	40	0 (0)
High[b]	123	19 (15.4)	14	1 (7.1)	NA	NA	4	0 (0)	29	4 (13.8)	40	4 (10.0)
HbA1c (%)												
High[b]	94	0 (0)	17	0 (0)	NA	NA	NA	NA	28	0 (0)	41	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time
Chl Chlorpromazine, Hal Haloperidol, Olz Olanzapine, Pla Placebo, QTP Quetiapine, Ri Risperidone
Clinically important limits are: Glucose (mmol/L), Low: <=3.5, High: >=7 for fasting and >=11.1 for non-fasting, HbA1c (%), High: >=7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAD_gka_all_trials_long_diab2.SAS, Data version: V91 User: Bengt Tranzon, 2007-05-03 07:20

Diabetic patients

Table A45 Mean (SD) change from baseline to end of treatment in diabetic subjects (All trials >12 weeks)

		QTP N=146	Pla N=5	Chl N=2	Hal N=8	Olz N=7	Ri N=22
Glucose (mmol/L)							
Patients[a]		48	4	0	5	7	9
Baseline	Mean (SD)	9.74 (3.91)	5.75 (0.60)		15.22 (2.79)	5.99 (2.54)	5.69 (0.74)
Last value	Mean (SD)	10.42 (6.39)	6.83 (2.80)		15.93 (4.72)	5.24 (0.42)	6.46 (3.69)
Change	Mean (SD)	0.68 (4.77)	1.08 (2.70)		0.72 (5.38)	-0.74 (2.24)	0.86 (2.63)
	Median	-0.572	-0.15		-0.056	-0.189	0.10
	Range	-8.89 to 15.00	-0.50 to 5.10		-4.22 to 6.44	-5.70 to 0.80	-4.40 to 7.50
HbA1c (%)							
Patients[b]		18	4			7	9
Baseline	Mean (SD)	5.89 (0.70)	5.65 (0.42)			5.47 (0.77)	5.90 (0.50)

Table A45 Mean (SD) change from baseline to end of treatment in diabetic subjects (All trials >12 weeks)

		QTP N=146	Pla N=5	Chl N=2	Hal N=8	Ola N=7	Ri N=22
Last value	Mean (SD)	5.95 (0.77)	5.88 (0.54)			5.41 (0.74)	5.79 (0.38)
Change	Mean (SD)	0.663 (0.58)	0.22 (0.22)			-0.957 (0.28)	-0.31 (0.45)
	Median	0.650	0.20			0	-0.45
	Range	-0.90 to 1.60	0 to 0.50			-0.60 to 0.20	-0.90 to 0.50
Insulin (pmol/L)							
Patients[a]		16	4			7	6
Baseline	Mean (SD)	337.23 (345.69)	180.50 (126.78)			182.95 (143.96)	372.19 (450.46)
Last value	Mean (SD)	238.73 (230.42)	226.50 (326.28)			172.86 (99.20)	322.24 (353.42)
Change	Mean (SD)	-98.50 (273.56)	40.00 (326.17)			-10.09 (77.72)	-49.96 (290.25)
	Median	-51.45	-52.00			-57.69	19.72
	Range	-917.00 to 243.00	-243.00 to 507.00			-89.31 to 92.23	-416.67 to 255.85
HOMAR							
Patients[b]		16	4			7	4
Baseline	Mean (SD)	12.60 (14.20)	6.86 (4.84)			4.63 (3.48)	7.57 (12.63)
Last value	Mean (SD)	5.86 (4.99)	13.98 (23.93)			3.48 (0.77)	4.77 (5.81)
Change	Mean (SD)	-6.74 (13.57)	7.13 (23.73)			-0.15 (1.38)	-2.80 (14.05)
	Median	-1.73	-2.13			0.056	0.37
	Range	-43.52 to 6.86	-9.49 to 42.25			-2.66 to 1.89	-22.57 to 10.63
QUICKI							
Patients[b]		16	4			7	4
Baseline	Mean (SD)	0.3607 (0.0588)	0.3106 (0.0483)			0.3718 (0.0387)	0.3529 (0.0809)
Last value	Mean (SD)	0.3215 (0.0486)	0.3225 (0.0650)			0.3762 (0.0522)	0.3395 (0.0620)
Change	Mean (SD)	-0.0208 (0.0527)	0.0125 (0.0819)			0.0043 (0.0579)	-0.0134 (0.0395)
	Median	-0.0260	0.0300			-0.0050	-0.0284

Table A45 Mean (SD) change from baseline to end of treatment in diabetic subjects (All trials >12 weeks)

	QTP N=146	Pla N=5	Chl N=2	Hal N=8	Ola N=7	Ri N=22
Range	-0.1200 to 0.1168	-0.0650 to 0.0590			-0.0976 to 0.0858	-0.0625 to 0.0649

[1] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Chl Chlorpromazine, Hal Haloperidol, Ola Olanzapine Pla Placebo, QTP Quetiapine, Ri Risperidone.
Pgm: /reg/del/Diabetes Mar 07 SUBMIT.APS chg_all_trials_long_diab1.SAS, Data version: V91 User: Bengt Fransson, 2007-05-03 12:34.

Table A46 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All trials >12 weeks)

	QTP N=146 End of tx			PLA N=5 End of tx			CHL N=2 End of tx			HAL N=8 End of tx			OLZ N=7 End of tx			RI N=22 End of tx		
	L n*(%)	N n*(%)	H n*(%)	L n*(%)	N n*(%)	H n*(%)	L n*(%)	N n*(%)	H n*(%)	L n*(%)	N n*(%)	H n*(%)	L n*(%)	N n*(%)	H n*(%)	L n*(%)	N n*(%)	H n*(%)
Glucose (mmol/L)																		
L	0 (0)	1 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
N	0 (0)	17 (85.0)	3 (15.0)	0 (0)	3 (75.0)	1 (25.0)	NA	NA	NA	NA	NA	NA	0 (0)	6 (100)	0 (0)	0 (0)	6 (75.0)	2 (25.0)
H	0 (0)	34 (51.9)	31 (48.1)	NA	NA	NA	NA	NA	NA	0 (0)	0 (0)	3 (100)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Total	0 (0)	52 (66.7)	26 (33.3)	0 (0)	3 (75.0)	1 (25.0)	NA	NA	NA	0 (0)	0 (0)	3 (100)	0 (0)	7 (100)	0 (0)	0 (0)	7 (77.8)	2 (22.2)
HbA_{1c} (%)																		
N	NA	18 (100)	0 (0)	NA	4 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	7 (100)	0 (0)	NA	9 (100)	0 (0)
H	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	18 (100)	0 (0)	NA	4 (100)	0 (0)	NA	NA	NA	NA	NA	NA	NA	7 (100)	0 (0)	NA	9 (100)	0 (0)

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Hal: Haloperidol, Olz: Olanzapine, Ri: Risperidone, Chl: Chlorpromazine, Pla: Placebo, QTP: Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.

Pgm: \Reg-Def\Diabetes Mar 07 SER\MULAB_shc_all_trials_long_diabl.SAS, Data version: V21 User: Bengt Franzon, 2007-05-03 07:00.

Table A47 Shift to clinically important lab values at any time in diabetic subjects (All trials >12 weeks)

	QTP N=146		Pla N=5		Chl N=2		Hal N=8		Olz N=7		Ri N=22	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)												
Low[a]	47	0 (0)	4	0 (0)	NA	NA	3	0 (0)	7	0 (0)	9	0 (0)
High[b]	21	5 (23.8)	4	1 (25.0)	NA	NA	NA	NA	6	1 (16.7)	8	3 (37.5)
HbA1c (%)												
High[b]	18	0 (0)	4	0 (0)	NA	NA	NA	NA	7	0 (0)	9	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Chl Chlorpromazine Hal Haloperidol Olz Olanzapine Pla Placebo QTP Quetiapine Ri Risperidone
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >=7.5.
Pgm: Reg-Def\Diabetes Mar 07 SER\bef\LAB_aba_all_trials_long_diab1.SAS. Data version: V91 User: Bengt Fransson, 2007-05-03 07:20.

All diabetic subgroups

Table A48 Mean (SD) change from baseline to end of treatment (All trials >12 weeks)

		QTP N=4277	Pla N=102	Chl N=130	Hal N=229	Olz N=168	Ri N=347
Glucose (mmol/L)							
Patients[a]		1227	29	6	30	168	370
Baseline	Mean (SD)	5.75 (1.65)	5.32 (0.67)		6.36 (3.35)	5.13 (0.82)	5.23 (0.75)
Last value	Mean (SD)	6.03 (2.39)	5.47 (1.11)		6.64 (3.69)	5.27 (0.63)	5.37 (0.88)
Change	Mean (SD)	0.28 (2.15)	0.15 (1.10)		0.28 (1.88)	0.14 (0.86)	0.14 (0.97)
	Median	0.10	0.100		0	0.30	0.20
	Range	-8.00 to 29.67	-2.30 to 3.30		-4.22 to 6.44	-5.70 to 1.90	-3.00 to 7.30
HbA1c (%)							
Patients[a]		456	88			168	172
Baseline	Mean (SD)	5.28 (0.43)	5.24 (0.30)			5.33 (0.40)	5.35 (0.44)

Table A48 Mean (SD) change from baseline to end of treatment (All trials >12 weeks)

		QTP N=4277	Pla N=402	Chl N=438	Ral N=229	Olz N=468	Ri N=347
Last value	Mean (SD)	5.32 (0.42)	5.27 (0.43)			5.34 (0.43)	5.34 (0.46)
Change	Mean (SD)	0.038 (0.31)	0.031 (0.30)			0.0036 (0.34)	-0.013 (0.30)
	Median	0	0			0	0
	Range	-1.00 to 1.60	-0.80 to 0.80			-1.00 to 1.40	-0.90 to 1.00
Insulin (pmol/L)							
Patients[a]		414	88			341	340
Baseline	Mean (SD)	148.82 (222.98)	85.89 (83.79)			242.30 (238.10)	224.27 (215.81)
Last value	Mean (SD)	148.17 (243.61)	119.13 (193.76)			305.13 (371.28)	254.09 (230.86)
Change	Mean (SD)	-0.64 (257.38)	33.24 (110.22)			62.83 (350.06)	29.81 (244.84)
	Median	0	7.00			18.96	28.45
	Range	-1965 to 2730	-243.00 to 507.00			-1124 to 2822	-645.75 to 1492
HOMA2							
Patients[a]		341	72			330	334
Baseline	Mean (SD)	3.33 (5.43)	3.19 (3.17)			3.46 (1.92)	3.62 (2.30)
Last value	Mean (SD)	3.67 (11.02)	4.99 (8.56)			3.78 (1.51)	3.89 (3.40)
Change	Mean (SD)	0.34 (10.82)	1.80 (7.36)			0.32 (1.42)	0.072 (2.32)
	Median	0.056	0.18			0.15	0.11
	Range	-43.52 to 163.49	-11.18 to 42.25			-3.16 to 8.12	-22.57 to 10.63
QUICKI							
Patients[a]		341	72			330	334
Baseline	Mean (SD)	0.3515 (0.0467)	0.3443 (0.0426)			0.3763 (0.0394)	0.3729 (0.0374)
Last value	Mean (SD)	0.3510 (0.0465)	0.3350 (0.0456)			0.3692 (0.0440)	0.3673 (0.0364)
Change	Mean (SD)	-0.0005 (0.0447)	-0.0092 (0.0382)			-0.0071 (0.0465)	-0.0056 (0.0322)
	Median	0.0000	0.0000			0.0074	0.0056

Table A48 Mean (SD) change from baseline to end of treatment (All trials >12 weeks)

	QTP N=4277	Pla N=102	Chl N=130	Hal N=229	Olz N=368	Ri N=347
Range	-0.1238 to 0.1807	-0.1100 to 0.0800			-0.1117 to 0.2593	-0.0896 to 0.0888

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Chl Chlorpromazine. Hal Haloperidol. Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Pgm: Reg-Del\Diabetes Mar07 SERM\LAB_chg_all_trials_long.SAS. Data version: V01 User: Bengt Franzen. 2007-05-03 12:36.

Table A49 Shift from baseline to clinically important lab values at end of treatment (All trials >12 weeks, QTP to Chl)

	QTP N=4277 End of treatment			Pla N=102 End of treatment			Chl N=130 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)									
Low	0 (0)	2 (100)	0 (0)	NA	NA	NA	NA	NA	NA
Norm	0 (0)	1159 (97.1)	35 (2.9)	0 (0)	79 (92.1)	6 (7.0)	NA	NA	NA
High	0 (0)	17 (54.8)	14 (45.2)	NA	NA	NA	NA	NA	NA
Total	0 (0)	1178 (96.0)	49 (4.0)	0 (0)	79 (92.1)	6 (7.0)	NA	NA	NA
HbA1c (%)									
Norm	NA	456 (100)	0 (0)	NA	88 (100)	0 (0)	NA	NA	NA
High	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	456 (100)	0 (0)	NA	88 (100)	0 (0)	NA	NA	NA

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Chl Chlorpromazine, Pla Placebo, QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L) Low <=2.5, High >=7 for fasting and >=11.1 for non-fasting, HbA1c (%) High >=7.5.
Pgm: Reg-DefDiabetes Mar 07 SER3001LAB_she_all_trials_long.SAS, Data version: V91 User: Bengt Franzon, 2007-05-03 07:02.

Table A50 Shift from baseline to clinically important lab values at end of treatment (All trials >12 weeks, Hal to Ri)

	Hal N=229 End of treatment			Ola N=168 End of treatment			Ri N=347 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)									
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	26 (96.3)	1 (3.7)	6 (0)	162 (97.0)	5 (3.0)	0 (0)	163 (96.4)	6 (3.6)

Table A50 Shift from baseline to clinically important lab values at end of treatment (All trials >12 weeks, *Hal* to Ri)

	Hal N=229 End of treatment			Olz N=168 End of treatment			Ri N=347 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
High	0 (0)	0 (0)	3 (100)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Total	0 (0)	26 (86.7)	4 (13.3)	0 (0)	163 (97.0)	5 (3.0)	0 (0)	164 (96.5)	6 (3.5)
HbA1c (%)									
Norm	NA	NA	NA	NA	168 (100)	0 (0)	NA	172 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	NA	NA	NA	168 (100)	0 (0)	NA	172 (100)	0 (0)

[a] Patients who have received at least one dose of trial medications, have a value at baseline and at least one value post baseline.
Hal Haloperidol, Olz Olanzapine, Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=3.3, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.0
Pgm: Reg.Def.Diabetes Mar 07 SERAFLAB_sbc_all_trials_long.SAS. Data version: V81 User: Bengt Pearson. 2007-05-03 07:02.

Table A51 Shift to clinically important lab values at any time (All trials >12 weeks)

	QTP N=4277		Pla N=102		Cbl N=130		Hal N=229		Olz N=168		Ri N=347	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)												
Low[a]	1225	4 (0.33)	76	0 (0)	NA	NA	30	0 (0)	168	0 (0)	170	0 (0)
High[b]	1196	69 (5.8)	76	6 (7.9)	NA	NA	27	1 (3.7)	167	11 (6.6)	169	13 (7.7)
HbA1c (%)												
High[b]	586	1 (0.22)	88	0 (0)	NA	NA	NA	NA	168	0 (0)	172	0 (0)

* N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time
* N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time
Chl Chlorpromazine, Hal Haloperidol, Ola Olanzepine, Pla Placebo, QTP Quetiapine, Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERMYLAB_sha_all_trials_long.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:21.

All Placebo controlled trials (adverse event data)

Table A52 Patients with AEs of hyperglycemia or DM in placebo-controlled studies

Study # Patient ID PT	Blinded treatment start	Blinded treatment end	Date lab drawn	Glucose (mmol/L)	Reported AE start and stop date Comments
			QUETIAPINE TREATED PATIENTS		
5077IL/0039 1705 BG increased*	30 April 1998	09 July 1998	24 Apr 1998 29 May 1998 09 Jul 1998 05 Aug 1998 03 Oct 1998	6.6 8.3 12.3 13.7 9.4	01 Jul 1998 to 01 Jul 1998. Fasting status unk. Pt seems to be diabetic (no med hx reported; concomitant insulin as of Day 1 of blinded therapy). Pt contd therapy in OLE portion of study through 01 Oct 1998. No causality provided
5077IL/0039 3202 Hyperglycemia*	05 June 1998	11 Aug 1998	20 May 1998 01 Jul 1998 12 Aug 1998 04 Nov 1998	5.4 5.9 8.1 4.9	30 Jul 1998 to 30 Sep 1998 Fasting status unk. Pt seems to be diabetic (concomitant insulin & troglitazone use as of Day 1 of blinded therapy). Pt contd therapy in OLE through 04 Nov 1998. Investigator causality=not related
5077IL/0043 637 Hyperglycemia*	10 Dec 2001	27 Dec 2001	05 Dec 2001 14 Dec 2001	17.17 31.28	14 Dec 2001 to unspecified date Fasting status unk. BG 1 before study. Started glyburide & glucophage on 12 Dec 2001. Pt dropped out of study d/t unk reason. History of DM, obesity. No other info. Investigator causality=not related
5077IL/0043 606 BG increased	15 Dec 2001	31 Dec 2001	12 Dec 2001 01 Jan 2002 14 Jan 2002	10.31 7.28 17.39	14 Jan 2002 to unspecified date Fasting status unk. History of DM, concomitant use of rosiglitazone (as of 12 Dec 2001). Investigator causality=not related
5077IL/0041 295 BG increased*	15 Feb 2002	08 Mar 2002	13 Feb 2002 11 Mar 2002 02 Apr 2002	4.72 8.61 5.11	11 Mar 2002 to 02 Apr 2002 Fasting status unk. FBG after 1 mo of treatment. Med hx of obesity, hyperlipidemia, hyperglycemides. Investigator causality=not related

Table A52 Patients with AEs of hyperglycemia or DM in placebo-controlled studies

Study # Patient ID PT	Blinded treatment start	Blinded treatment end	Date lab drawn	Glucose (mmol/L)	Reported AE start and stop date Comments
5077IL/0106 2403 Hyperglycemia	05 Apr 2001	15 May 2001	28 Mar 2001 14 May 2001 06 Aug 2001	5.6 8.7 4.9	14 May 2001 to 06 Aug 2001 Fasting status unk. Con med lithium. No med hx provided. No other info. Investigator causality=related
5077IL/0104 1160 BG increased	13 Sep 2000	05 Oct 2001	08 Sep 2001 06 Oct 2001	4.94 9.05	08 Oct 2001 to unspecified date Fasting status unk. No med hx provided. BG ↑ 2 days after tx stopped. Pt d/c'd from trial d/t LOE. Investigator causality= related
5077US/0046 228 BG increased[b]	28 Apr 2003	07 Jul 2003	23 Apr 2003 07 Jul 2003	6.22 7.56	15 May 2003 to 15 May 2003 Fasting sample. Hx of DM. Con meds include rosiglitazone (since 30 Sep 2002) & glipizide (since 31 Jan 2003). Other labs (23 Apr 2003: Insulin = 34.738 pmol/L, $HOMA_R$ = 1.37, QUICKI=0.367, 07 Jul 2003: Insulin = 55.56 pmol/L, $HOMA_R$ = 2.66, QUICKI = 0.33). No other info Investigator causality=not related
5077US/0046 499 BG increased[b]	28 Jul 2003	05 Oct 2003	21 Jul 2003 01 Aug 2003 06 Oct 2003	13.56 9.72 8.50	15 Oct 2003 to unspecified date Fasting samples. BG ↑ before study. PG ↑ while on therapy. Hx of DM. Con meds include rosiglitazone & glibenclamide (since 24 Nov 2002) & insulin (since 03 May 2003). Other labs (21 Jul 2003: Insulin = 145.85 pmol/L, 06 Oct 2003: Insulin = 62.51 pmol/L, $HOMA_R$ = 3.37, QUICKI = 0.32). Investigator causality=not related
5077US/0046 382 BG increased[b]	01 Sep 2003	09 Nov 2003	18 Aug 2003 12 Nov 2003	10.8 10.1	19 Oct 2003 to unspecified date Fasting samples. BG ↑ before study. Hx of DM. Con meds include glibenclamide (18 Oct 2003 to 29 Oct 2003) & metformin (29 Oct 2003). Other labs (18 Aug 2003: Insulin = 90.29 pmol/L, $HOMA_R$ = 6.21, QUICKI = 0.29; 12 Nov 2003: Insulin = 69.45 pmol/L, $HOMA_R$ = 4.46, QUICKI = 0.31) Investigator causality=not related

Table A52 Patients with AEs of hyperglycemia or DM in placebo-controlled studies

Study # Patient ID PT	Blinded treatment start	Blinded treatment end	Date lab drawn	Glucose (mmol/L)	Reported AE start and stop date Comments
5077IL/0100 1032 DM	26 Jun 2001	05 Jul 2001	22 Jun 2001 05 Jul 2001	9.80 6	27 Jun 2001 to unspecified date Fasting status unk. Tx w/ valproate started 17 Jun 2001. BG peaked on same day as start of therapy + was normal on day therapy d/c'd (Pt d/c'd from trial d/t worsening psych sxs) Metformin started 28 Jun 2001. Investigator causality=not related
5077US/0046 234 DM[a]	24 Dec 2002	31 Jan 2003	27 Dec 2002 07 Jan 2003 04 Feb 2003	6.39 6.78 12.39	04 Feb 2003 to 03 May 2003 Fasting samples. Elderly male Pt w/ hx of DM. On glipizide & rosiglitazone as of 03 Dec 2002. Other labs (07 Jan 2003: Insulin = 27.78 pmol/L, $HOMA_B$ = 1.26, QUICKI = 0.37, 04 Feb 2003: insulin = 20.84 pmol/L, $HOMA_B$ = 1.64, QUICKI = 0.35). No other info. Investigator causality=not related
D1444C00132 0321 Glycosylated hemoglobin ↑	15 Feb 2005	28 Mar 2005	10 Feb 2005 28 Mar 2005 29 Mar 2005	7.66 6.96 6.50	29 Mar 2005 to 11 Apr 2005 Fasting samples. No hx of DM. Family hx of DM (mother). Other labs (10 Feb 2005: insulin = 243.0 pmol/L, $HOMA_B$ = 11.82, QUICKI = 0.27, HbA_{1c} = 5.80%; 28 Mar 2005: insulin = 42.00 pmol/L, $HOMA_B$ = 1.32, QUICKI = 0.37; 29 Mar 2005: insulin = 104.00 pmol/L, $HOMA_B$ = 2.99, QUICKI = 0.32, HbA_{1c} = 6.40%). No other info. Investigator causality = related
D1447C00135 0985 Hyperglycemia	27 Sep 2004	21 Nov 2004	20 Sep 2004 25 Oct 2004 01 Nov 2004 22 Nov 2004	5.44 8.94 5.78 5.72	25 Oct 2004 to 01 Nov 2004 Fasting samples. No hx & no family hx of DM. Other labs (20 Sep 2004: Insulin = 38.54 pmol/L, $HOMA_B$ = 1.34, QUICKI = 0.37, HbA_{1c} = 5.20%, 25 Oct 2004: Insulin = 195.15 pmol/L, $HOMA_B$ = 11.16, QUICKI = 0.27, 22 Nov 2004: Insulin = 31.46 pmol/L, $HOMA_B$ = 1.15, QUICKI = 0.37, HbA_{1c} = 5.60%) Pt rec'd 4/4 de continuing quetiapine Investigator causality = related

[a] PLACEBO TREATED PATIENTS

Table A52 Patients with AEs of hyperglycemia or DM in placebo-controlled studies

Study # Patient ID PT	Blinded treatment start	Blinded treatment end	Date lab drawn	Glucose (mmol/L)	Reported AE start and stop date Comments
5077IL/0041 0077 BG increased[a]	25 Jun 2001	28 Jun 2001	21 Jun 2001 28 Jun 2001	12.67 4.61	23 Jun 2001 to 23 Jun 2001 & 25 Jun 2001 to 25 Jun 2001 & 27 Jun 2001 to 27 Jun 2001 Fasting status unk. Pt w/ hx of DM (on glibenclamide since 01 Jul 1991 & metformin since 01 Jul 1995. On olanzapine from 15 Apr 2001 to 21 Jun 2001. Pt had ↑ BG prior to study. Tx w/ insulin on 23 Jun 2001, 25 Jun 2001, & 27 Jun 2001. Investigator causality=not related
5077IL/0029 1172 Hyperglycemia	23 Aug 2001	12 Sep 2001	21 Aug 2001 13 Sep 2001	19.22 8.56	26 Aug 2001 to 28 Aug 2001 Fasting status unk. Pt w/ hx of DM on glibenclamide + metformin (since 07 Jan 1999). BG↑ before study Started rosiglitazone on 23 Aug 2001. Tx w/ insulin 23 Aug 2001 to 31 Aug 2001. Pt improved. Investigator causality=not related
D1444C00133 1642 DM	20 May 2005	26 Jun 2005	16 May 2005 16 Jun 2005 30 Jun 2005	4.78 5.17 5.11	23 Jun 2005 to 29 Jun 2005 Fasting samples. Pt w/ 6 mo hx of DM. Con meds included glyburide. Event tx w/ insulin (21 Jun 2005 to 29 Jun 2005). Other labs (16 May 2005: Insulin = 48.62 pmol/L, $HOMA_B$ = 1.49, QUICKI = 0.36, HbA_{1c} = 5.80%, 30 Jun 2005: Insulin = 104.18 pmol/L, $HOMA_B$ = 3.41, QUICKI = 0.32, HbA_{1c} = 5.70%). Investigator causality = not related

[a] Also discussed in placebo-controlled Monotherapy trial AE data, b Also discussed in AE data for Trials 96 and 115. BG = blood glucose, DM = diabetes mellitus, med hx = medical history, Pt = patient, con med = concomitant medications, cont = continued, disc'd = discontinued, info = information, unk = unknown, hx = history, OLE = open-label extension,

All Placebo–controlled trials (all lab data)

Non-diabetic patients

Table A53 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled trials)

		QTP N=2684	Pla N=1282
Glucose (mmol/L)			
Patients[a]		2127	1074
Baseline	Mean (SD)	5.08 (0.89)	5.21 (1.04)
Last value	Mean (SD)	5.28 (1.18)	5.31 (1.18)
Change	Mean (SD)	0.20 (1.18)	0.098 (1.22)
	Median	0.11	0.056
	Range	-4.90 to 9.50	-6.83 to 6.00
HbA1c (%)			
Patients[a]		801	305
Baseline	Mean (SD)	5.28 (0.39)	5.23 (0.37)
Last value	Mean (SD)	5.31 (0.39)	5.24 (0.36)
Change	Mean (SD)	0.034 (0.25)	0.016 (0.25)
	Median	0	0
	Range	-0.70 to 1.10	-0.80 to 0.80
Insulin (pmol/L)			
Patients[a]		1215	486
Baseline	Mean (SD)	74.16 (94.38)	75.95 (140.22)
Last value	Mean (SD)	111.87 (170.05)	92.71 (139.00)
Change	Mean (SD)	37.71 (163.53)	16.76 (178.76)
	Median	7.00	6.95
	Range	-770.90 to 2299	-1875 to 1820
$HOMA_B$			
Patients[a]		1096	452
Baseline	Mean (SD)	2.25 (3.28)	2.70 (8.70)
Last value	Mean (SD)	4.01 (8.03)	3.27 (6.62)
Change	Mean (SD)	1.76 (7.73)	0.57 (10.55)
	Median	0.32	0.23
	Range	-35.70 to 127.84	-137.15 to 87.11
QUICKI			
Patients[a]		1096	452
Baseline	Mean (SD)	0.3167 (0.0915)	0.3092 (0.0949)
Last value	Mean (SD)	0.3044 (0.0914)	0.3012 (0.0959)

Table A53 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled trials)

		QTP N=2684	Pla N=1282
Change	Mean (SD)	-0.0123 (0.0397)	-0.0080 (0.0389)
	Median	-0.0100	-0.0076
	Range	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:37.

Table A54 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled trials)

	QTP N=2684 End of treatment			Pla N=1282 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)						
Low	0 (0)	2 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Norm	4 (0.19)	2095 (98.6)	26 (1.2)	4 (0.37)	1056 (98.4)	13 (1.2)
High	NA	NA	NA	NA	NA	NA
Total	4 (0.19)	2097 (98.6)	26 (1.2)	4 (0.37)	1057 (98.4)	13 (1.2)
HbA1c (%)						
Norm	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA
Total	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L). Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%). High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\3_AB_shc_pla_ctrl_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:03.

Table A55 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled trials)

	QTP N=2684		Pla N=1282	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	2125	9 (0.42)	1073	9 (0.84)
High[b]	2127	41 (1.9)	1074	13 (1.2)
HbA1c (%)				
High[b]	801	0 (0)	305	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERMAB_sha_pla_enf_diab3.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 07:22.

Diabetic risk patients

Table A56 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled trials)

		QTP N=523	Pla N=220
Glucose (mmol/L)			
Patients[a]		443	183
Baseline	Mean (SD)	5.52 (0.82)	5.36 (0.75)
Last value	Mean (SD)	5.54 (1.23)	5.44 (1.08)
Change	Mean (SD)	0.017 (1.19)	0.086 (1.01)
	Median	-0.100	0
	Range	-3.44 to 8.22	-3.06 to 4.50
HbA1c (%)			
Patients[a]		272	98
Baseline	Mean (SD)	5.38 (0.38)	5.32 (0.43)
Last value	Mean (SD)	5.43 (0.41)	5.35 (0.45)
Change	Mean (SD)	0.056 (0.29)	0.023 (0.27)
	Median	0.100	0
	Range	-1.40 to 1.40	-0.90 to 0.80
Insulin (pmol/L)			
Patients[a]		349	144
Baseline	Mean (SD)	136.09 (160.54)	118.47 (103.42)
Last value	Mean (SD)	183.57 (271.75)	133.14 (134.22)
Change	Mean (SD)	47.48 (269.20)	14.67 (138.09)

Table A56 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled trials)

		QTP N=523	Pla N=220
	Median	6.00	0
	Range	-951.47 to 2146	-620.26 to 888.96
$HOMA_R$			
Patients[a]		331	131
Baseline	Mean (SD)	4.84 (6.19)	3.93 (3.51)
Last value	Mean (SD)	6.67 (12.52)	4.62 (5.83)
Change	Mean (SD)	1.83 (12.62)	0.69 (5.66)
	Median	0.17	-0.028
	Range	-34.93 to 119.88	-21.59 to 40.41
QUICKI			
Patients[a]		331	131
Baseline	Mean (SD)	0.3013 (0.0728)	0.2882 (0.0859)
Last value	Mean (SD)	0.3014 (0.0795)	0.2870 (0.0881)
Change	Mean (SD)	0.0002 (0.0384)	-0.0012 (0.0312)
	Median	-0.0006	0.0000
	Range	-0.1433 to 0.1287	-0.1229 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Pgm: Reg-Def-Diabetes Mar 07 SERMEL A8 chg pla ch1 diab2.SAS. Data version: V91 User: Bengt Granzon. 2007-05-03 12:37.

Table A57 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled trials)

	QTP N=523 End of treatment			Pla N=220 End of treatment		
Lab test Baseline	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**
Glucose (mmol/L)						
Low	NA	NA	NA	NA	NA	NA
Norm	0 (0)	427 (96.4)	16 (3.6)	0 (0)	176 (96.2)	7 (3.8)
High	NA	NA	NA	NA	NA	NA
Total	0 (0)	427 (96.4)	16 (3.6)	0 (0)	176 (96.2)	7 (3.8)
HbA1c (%)						
Norm	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA
Total	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:03.

Table A58 Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled trials)

	QTP N=523		Pla N=220	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	443	0 (0)	183	0 (0)
High[b]	443	28 (6.3)	183	9 (4.9)
HbA1c (%)				
High[b]	272	0 (0)	98	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:22.

Diabetic patients

Table A59 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled trials)

		QTP N=230	Pla N=90
Glucose (mmol/L)			
Patients[a]		193	85
Baseline	Mean (SD)	7.71 (3.32)	7.32 (3.19)
Last value	Mean (SD)	7.64 (3.90)	6.84 (3.07)
Change	Mean (SD)	-0.069 (3.51)	-0.49 (3.51)
	Median	0	-0.28
	Range	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)			
Patients[a]		100	40
Baseline	Mean (SD)	6.31 (0.88)	6.01 (0.85)
Last value	Mean (SD)	6.55 (1.19)	5.96 (0.91)
Change	Mean (SD)	0.23 (0.69)	-0.050 (0.45)
	Median	0.100	0
	Range	-0.90 to 4.50	-1.70 to 1.10

Table A59 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled trials)

		QTP N=230	Pla N=90
Insulin (pmol/L)			
Patients[a]		149	59
Baseline	Mean (SD)	169.87 (197.90)	173.96 (261.50)
Last value	Mean (SD)	175.26 (267.41)	134.77 (130.45)
Change	Mean (SD)	5.38 (246.71)	-39.19 (278.54)
	Median	6.95	-12.08
	Range	-1479 to 1445	-1799 to 507.00
HOMAR			
Patients[a]		139	57
Baseline	Mean (SD)	8.13 (11.52)	7.97 (17.54)
Last value	Mean (SD)	8.04 (11.73)	6.02 (8.05)
Change	Mean (SD)	-0.087 (15.40)	-1.95 (18.99)
	Median	0.20	-0.10
	Range	-87.09 to 92.99	-127.11 to 42.25
QUICKI			
Patients[a]		139	57
Baseline	Mean (SD)	0.3044 (0.0569)	0.3060 (0.0572)
Last value	Mean (SD)	0.3056 (0.0562)	0.3137 (0.0613)
Change	Mean (SD)	0.0012 (0.0495)	0.0077 (0.0438)
	Median	-0.0023	0.0000
	Range	-0.1619 to 0.1600	-0.0738 to 0.1443

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:36.

Table A60 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled trials)

	QTP N=230 End of treatment			Pla N=90 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)						
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	1 (0.85)	92 (78.6)	24 (20.5)	1 (1.7)	49 (83.1)	9 (15.3)
High	0 (0)	37 (48.7)	39 (51.3)	0 (0)	19 (76.0)	6 (24.0)
Total	1 (0.52)	129 (66.8)	63 (32.6)	1 (1.2)	69 (81.2)	15 (17.6)
HbA1c (%)						
Norm	NA	86 (91.5)	8 (8.5)	NA	36 (97.3)	1 (2.7)
High	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	87 (87.0)	13 (13.0)	NA	36 (90.0)	4 (10.0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shi_pla_ctrl_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:03.

Table A61 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled trials)

	QTP N=230		Pla N=90	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	193	3 (0.52)	84	1 (1.2)
High[b]	122	30 (24.6)	60	10 (16.7)
HbA1c (%)				
High[b]	94	8 (8.5)	37	1 (2.7)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:21.

All Placebo-controlled trials: IR vs SR data

Non-diabetic patients

Table A62 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled trials, separating immediate and sustained release)

		QTP SR N=746	QTP IR N=1938	All QTP N=2684	Pla N=1282
Glucose (mmol/L)					
Patients[a]		651	1476	2127	1074
Baseline	Mean (SD)	4.93 (0.56)	5.14 (0.99)	5.08 (0.89)	5.21 (1.34)
Last value	Mean (SD)	5.23 (0.97)	5.30 (1.26)	5.28 (1.18)	5.31 (1.18)
Change	Mean (SD)	0.30 (1.00)	0.16 (1.24)	0.20 (1.18)	0.098 (1.22)
	Median	0.17	0.10	0.11	0.056
	Range	-2.28 to 9.33	-4.90 to 9.50	-4.90 to 9.50	-6.83 to 6.00
HbA1c (%)					
Patients[a]		485	316	801	305
Baseline	Mean (SD)	5.38 (0.39)	5.28 (0.41)	5.28 (0.39)	5.23 (0.37)
Last value	Mean (SD)	5.33 (0.39)	5.29 (0.39)	5.31 (0.39)	5.24 (0.36)
Change	Mean (SD)	0.049 (0.26)	0.0095 (0.24)	0.034 (0.25)	0.016 (0.25)
	Median	0	0	0	0
	Range	-0.70 to 1.10	-0.70 to 0.90	-0.70 to 1.10	-0.80 to 0.80
Insulin (pmol/L)					
Patients[a]		495	720	1215	486
Baseline	Mean (SD)	80.08 (98.50)	70.10 (91.30)	74.16 (94.38)	75.95 (140.22)
Last value	Mean (SD)	112.25 (155.29)	111.61 (179.60)	111.87 (170.05)	92.71 (139.90)
Change	Mean (SD)	32.18 (146.15)	41.51 (174.47)	37.71 (163.53)	16.76 (178.76)
	Median	7.00	13.10	7.00	6.95
	Range	-757.00 to 1347	-770.90 to 2299	-770.90 to 2299	-1875 to 1820
HOMAR					
Patients[a]		445	651	1096	452
Baseline	Mean (SD)	2.51 (3.50)	2.07 (3.11)	2.25 (3.28)	2.70 (8.70)
Last value	Mean (SD)	4.04 (7.03)	3.98 (8.65)	4.01 (8.03)	3.27 (6.62)
Change	Mean (SD)	1.53 (6.49)	1.91 (8.48)	1.76 (7.73)	0.57 (10.55)
	Median	0.25	0.39	0.32	0.23
	Range	-23.99 to 64.09	-35.70 to 127.84	-35.70 to 127.84	-137.15 to 87.11
QUICKI					
Patients[a]		445	651	1096	452

Table A62 **Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled trials, separating immediate and sustained release)**

		QTP SR N=746	QTP IR N=1936	All QTP N=2684	Pla N=1282
Baseline	Mean (SD)	0.3530 (0.0379)	0.2919 (0.1077)	0.3167 (0.0915)	0.3092 (0.0949)
Last value	Mean (SD)	0.3425 (0.0442)	0.2784 (0.1052)	0.3044 (0.0914)	0.3012 (0.0959)
Change	Mean (SD)	-0.0105 (0.0420)	-0.0135 (0.0380)	-0.0123 (0.0397)	-0.0080 (0.0389)
	Median	-0.0100	-0.0100	-0.0100	-0.0076
	Range	-0.1600 to 0.1800	-0.2105 to 0.1262	-0.2105 to 0.1800	-0.1830 to 0.1800

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release, Pla Placebo, QTP Quetiapine SR Sustained release.

Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_SR_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:46.

Table A63 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled trials, separating immediate and sustained release)

	QTP SR N=746 End of treatment			QTP IR N=1938 End of treatment			All QTP N=2684 End of treatment			Pla N=1282 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Norm	0 (0)	643 (98.8)	8 (1.2)	4 (0.27)	1452 (98.5)	18 (1.2)	4 (0.19)	2095 (98.6)	26 (1.2)	4 (0.37)	1056 (98.4)	13 (1.2)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	643 (98.8)	8 (1.2)	4 (0.27)	1454 (98.5)	18 (1.2)	4 (0.19)	2097 (98.6)	26 (1.2)	4 (0.37)	1057 (98.4)	13 (1.2)
HbA1c (%)												
Norm	NA	485 (100)	0 (0)	NA	316 (100)	0 (0)	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	485 (100)	0 (0)	NA	316 (100)	0 (0)	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L) Low <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >7.5.
Pgm: Reg-Def Diabetes Mar 07 SERM\LAD_shc_plb_ctrl_SR_diab3.SAS. Data version: V91 User: Bengt Franzon 2007-05-03 07:11

Table A64 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled trials, separating immediate and sustained release)

	QTP SR N=746		QTP IR N=1938		All QTP N=2684		Pla N=1282	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	651	0 (0)	1474	9 (0.61)	2125	9 (0.42)	1073	9 (0.84)
High[b]	651	15 (2.3)	1476	26 (1.8)	2127	41 (1.9)	1074	13 (1.2)
HbA1c (%)								
High[b]	485	0 (0)	316	0 (0)	801	0 (0)	305	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\L_aB_shs_pla_ctrl_SR_diab3.SAS. Data version: V91 User: Bengt Frenzon 2007-05-03 07:30.

Diabetic risk patients

Table A65 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled trials, separating immediate and sustained release)

		QTP SR N=208	QTP IR N=315	All QTP N=523	Pla N=220
Glucose (mmol/L)					
Patients[a]		190	253	443	183
Baseline	Mean (SD)	5.59 (0.72)	5.47 (0.89)	5.52 (0.82)	5.36 (0.75)
Last value	Mean (SD)	5.67 (1.23)	5.44 (1.22)	5.54 (1.23)	5.44 (1.08)
Change	Mean (SD)	0.081 (1.18)	-0.030 (1.19)	0.017 (1.19)	0.086 (1.01)
	Median	-0.100	-0.056	-0.100	0
	Range	-2.56 to 4.89	-3.44 to 8.22	-3.44 to 8.22	-3.06 to 4.50
HbA1c (%)					
Patients[a]		153	319	272	98
Baseline	Mean (SD)	5.38 (0.41)	5.37 (0.34)	5.38 (0.38)	5.32 (0.43)
Last value	Mean (SD)	5.47 (0.42)	5.39 (0.38)	5.43 (0.41)	5.35 (0.45)
Change	Mean (SD)	0.086 (0.30)	0.017 (0.27)	0.056 (0.29)	0.023 (0.27)
	Median	0.100	0	0.100	0
	Range	-0.50 to 1.40	-1.40 to 0.70	-1.40 to 1.40	-0.90 to 0.80
Insulin (pmol/L)					
Patients[a]		153	196	349	144
Baseline	Mean (SD)	139.75 (140.40)	133.23 (174.96)	136.09 (160.54)	118.47 (103.42)
Last value	Mean (SD)	200.00 (330.30)	170.74 (215.34)	183.57 (271.75)	133.14 (134.22)

Table A65 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled trials, separating immediate and sustained release)

		QTP SR N=208	QTP IR N=315	All QTP N=523	Pla N=220
Change	Mean (SD)	60.25 (315.28)	37.51 (227.21)	47.48 (269.20)	14.67 (138.09)
	Median	7.00	4.65	6.00	0
	Range	-701.45 to 2146	-951.47 to 1049	-951.47 to 2146	-620.26 to 888.96
$HOMA_B$					
Patients[a]		147	184	331	131
Baseline	Mean (SD)	4.90 (5.43)	4.80 (6.76)	4.84 (6.19)	3.93 (3.51)
Last value	Mean (SD)	7.71 (16.46)	5.85 (8.06)	6.67 (12.52)	4.62 (5.83)
Change	Mean (SD)	2.81 (16.34)	1.05 (8.52)	1.83 (12.62)	0.69 (5.66)
	Median	0.13	0.17	0.17	-0.028
	Range	-34.93 to 119.88	-34.10 to 38.61	-34.93 to 119.88	-21.59 to 40.41
QUICKI					
Patients[a]		147	184	331	131
Baseline	Mean (SD)	0.3207 (0.0320)	0.2858 (0.0906)	0.3013 (0.0728)	0.2882 (0.0859)
Last value	Mean (SD)	0.3269 (0.0431)	0.2859 (0.0969)	0.3014 (0.0795)	0.2870 (0.0881)
Change	Mean (SD)	0.0002 (0.0382)	0.0001 (0.0386)	0.0002 (0.0384)	-0.0012 (0.0312)
	Median	0.0000	-0.0027	-0.0006	0.0000
	Range	-0.0900 to 0.1000	-0.1433 to 0.1287	-0.1433 to 0.1287	-0.1229 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Pgm: Reg-Def-Diabetes Mar 07 SERM-LAB_chg_pla_ctrl_SR_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:45.

Table A66 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled trials, separating immediate and sustained release)

	QTP SR N=208 End of treatment			QTP IR N=315 End of treatment			All QTP N=523 End of treatment			Pla N=220 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	179 (94.2)	11 (5.8)	0 (0)	248 (98.0)	5 (2.0)	0 (0)	427 (96.4)	16 (3.6)	0 (0)	176 (96.2)	7 (3.8)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	179 (94.2)	11 (5.8)	0 (0)	248 (98.0)	5 (2.0)	0 (0)	427 (96.4)	16 (3.6)	0 (0)	176 (96.2)	7 (3.8)
HbA1c (%)												
Norm	NA	153 (100)	0 (0)	NA	119 (100)	0 (0)	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	153 (100)	0 (0)	NA	119 (100)	0 (0)	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline

IR Immediate release Pla Placebo QTP Quetiapine SR Sustained release

Clinically important limits are: Glucose (mmol/L) Low <=2.5, High >=7 for fasting and >= 11.1 for non-fasting, HbA1c (%) High >=6.5.

Prgm: Reg-Def\Diabetes Mar 07 SLERM\LAE_ale_pla_cnt_SR_diab2.SAS, Data version: V91 User: Bengt Franzon 2007-05-03 07:11

Table A67 **Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled trials, separating immediate and sustained release)**

	QTP SR N=208		QTP IR N=315		All QTP N=523		Pla N=220	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	190	0 (0)	253	0 (0)	443	0 (0)	183	0 (0)
High[b]	190	19 (10.0)	253	9 (3.6)	443	28 (6.3)	183	9 (4.9)
HbA1c (%)								
High[b]	153	0 (0)	119	0 (0)	272	0 (0)	98	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def-Diabetes Mar 07 SERM3LAB_sha_pla_ctrl_SR_diab2.SAS. Data version: V91 User: Bengt Franzon 2007-05-03 07:29.

Diabetic patients

Table A68 **Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled trials, separating immediate and sustained release)**

		QTP SR N=92	QTP IR N=138	All QTP N=230	Pla N=90
Glucose (mmol/L)					
Patients[a]		84	109	193	85
Baseline	Mean (SD)	7.31 (2.86)	8.02 (3.63)	7.71 (3.32)	7.32 (3.19)
Last value	Mean (SD)	7.36 (3.89)	7.86 (3.91)	7.64 (3.90)	6.84 (3.07)
Change	Mean (SD)	0.045 (3.56)	-0.16 (3.49)	-0.068 (3.51)	-0.49 (3.51)
	Median	-0.028	0	0	-0.28
	Range	-9.83 to 15.72	-9.80 to 13.89	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)					
Patients[a]		71	29	100	40
Baseline	Mean (SD)	6.33 (0.84)	6.28 (0.97)	6.31 (0.88)	6.01 (0.85)
Last value	Mean (SD)	6.48 (0.99)	6.71 (1.58)	6.55 (1.19)	5.96 (0.91)
Change	Mean (SD)	0.15 (0.47)	0.43 (1.02)	0.23 (0.69)	-0.050 (0.45)
	Median	0.100	0.20	0.100	0
	Range	-0.90 to 1.70	-0.50 to 4.50	-0.90 to 4.50	-1.70 to 1.10
Insulin (pmol/L)					
Patients[a]		68	81	149	59

Table A68 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled trials, separating immediate and sustained release)

		QTP SR N=92	QTP IR N=138	All QTP N=230	Pla N=90
Baseline	Mean (SD)	204.46 (238.49)	140.84 (151.49)	169.87 (197.90)	173.96 (261.50)
Last value	Mean (SD)	230.11 (259.02)	129.20 (136.72)	175.26 (207.41)	134.77 (150.45)
Change	Mean (SD)	25.65 (310.84)	-11.64 (176.17)	5.38 (246.71)	-39.19 (278.54)
	Median	6.97	6.95	6.95	-12.08
	Range	-1479 to 1445	-757.01 to 625.05	-1479 to 1445	-1799 to 507.00
HOMAR					
Patients[a]		66	73	139	57
Baseline	Mean (SD)	9.76 (13.18)	6.65 (9.64)	8.13 (11.52)	7.97 (17.54)
Last value	Mean (SD)	10.96 (15.18)	5.40 (6.39)	8.04 (11.73)	6.02 (8.05)
Change	Mean (SD)	1.20 (19.05)	-1.25 (11.14)	-0.087 (15.40)	-1.95 (18.99)
	Median	0.79	0.17	0.20	-0.10
	Range	-87.09 to 92.99	-58.43 to 22.73	-87.09 to 92.99	-127.11 to 42.25
QUICKI					
Patients[a]		66	73	139	57
Baseline	Mean (SD)	0.3017 (0.0390)	0.3068 (0.0693)	0.3044 (0.0569)	0.3060 (0.0572)
Last value	Mean (SD)	0.3020 (0.0465)	0.3089 (0.0638)	0.3056 (0.0562)	0.3137 (0.0613)
Change	Mean (SD)	0.0003 (0.0495)	0.0020 (0.0499)	0.0012 (0.0495)	0.0077 (0.0438)
	Median	-0.0050	-0.0023	-0.0023	0.0000
	Range	-0.0800 to 0.1600	-0.1619 to 0.1293	-0.1619 to 0.1600	-0.0738 to 0.1443

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Pgm: Reg:Def:Diabetes Mar 07 SERM:LAB_chg_pla_ctrl_SR_diab1.SAS. Data version: V91 User: Bengt Franzon 2007-05-03 12:45.

Table A69 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled trials, separating immediate and sustained release)

	QTP SR N=92 End of treatment			QTP IR N=138 End of treatment			All QTP N=230 End of treatment			Pla N=90 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	1 (1.9)	38 (73.1)	13 (25.0)	0 (0)	54 (83.1)	11 (16.9)	1 (0.85)	92 (78.6)	24 (20.5)	3 (1.7)	49 (83.1)	9 (15.3)
High	0 (0)	17 (53.1)	15 (46.9)	0 (0)	20 (45.5)	24 (54.5)	0 (0)	37 (48.7)	39 (51.3)	0 (0)	19 (76.0)	6 (24.0)
Total	1 (1.2)	55 (65.5)	28 (33.3)	0 (0)	74 (67.9)	35 (32.1)	1 (0.52)	129 (66.8)	63 (32.6)	3 (1.2)	69 (81.2)	15 (17.6)
HbA1c (%)												
Norm	NA	62 (92.5)	5 (7.5)	NA	24 (88.9)	3 (11.1)	NA	86 (91.5)	8 (8.5)	NA	36 (97.3)	1 (2.7)
High	NA	1 (25.0)	3 (75.0)	NA	0 (0)	2 (100)	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	63 (88.7)	8 (11.3)	NA	24 (82.8)	5 (17.2)	NA	87 (87.0)	13 (13.0)	NA	36 (90.0)	4 (10.0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are Glucose (mmol/L): Low <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >=6.5.
Prgm: Reg-Def\Diabetes Mar 07 SER\ML\All_doc_pla_qui_SR_diab1.SAS Data version: V91 User: Bengt Franzen, 2007-05-05 07:11

Table A70 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled trials, separating immediate and sustained release)

	QTP SR N=92		QTP IR N=138		All QTP N=230		Pla N=90	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	84	1 (1.2)	109	0 (0)	193	1 (0.52)	84	1 (1.2)
High[b]	55	17 (30.9)	67	13 (19.4)	122	30 (24.6)	60	10 (16.7)
HbA1c (%)								
High[b]	67	5 (7.5)	27	3 (11.1)	94	8 (8.5)	37	1 (2.7)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-DefDiabetes Mar 07 SERM\LAB_sha_pla_ctrl_SR_diab1.SAS. Data version: V91 User: Bengt Fransen. 2007-05-03 07:29.

All diabetic subgroups

Table A71 Mean (SD) change from baseline to end of treatment (All placebo-controlled trials, separating immediate and sustained release)

		QTP SR N=1046	QTP IR N=2391	All QTP N=3437	Pla N=1592
Glucose (mmol/L)					
Patients[a]		925	1838	2763	1342
Baseline	Mean (SD)	5.29 (1.24)	5.36 (1.46)	5.33 (1.39)	5.36 (1.36)
Last value	Mean (SD)	5.52 (1.64)	5.47 (1.65)	5.49 (1.65)	5.42 (1.42)
Change	Mean (SD)	0.23 (1.46)	0.11 (1.47)	0.15 (1.47)	0.059 (1.46)
	Median	0.10	0.056	0.100	0
	Range	-9.83 to 15.72	-9.80 to 13.89	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)					
Patients[a]		709	464	1173	443
Baseline	Mean (SD)	5.41 (0.55)	5.37 (0.51)	5.39 (0.53)	5.32 (0.50)
Last value	Mean (SD)	5.47 (0.60)	5.41 (0.64)	5.45 (0.61)	5.33 (0.50)
Change	Mean (SD)	0.068 (0.30)	0.038 (0.36)	0.056 (0.32)	0.012 (0.28)
	Median	0	0	0	0
	Range	-0.90 to 1.70	-1.40 to 4.50	-1.40 to 4.50	-1.70 to 1.10
Insulin (pmol/L)					
Patients[a]		716	997	1713	689
Baseline	Mean (SD)	104.64 (133.61)	88.26 (121.30)	95.11 (126.81)	93.23 (150.83)
Last value	Mean (SD)	142.20 (219.57)	124.66 (185.49)	131.99 (200.57)	104.76 (138.38)

Table A71 Mean (SD) change from baseline to end of treatment (All placebo-controlled trials, separating immediate and sustained release)

		QTP SR N=1046	QTP IR N=2391	All QTP N=3437	Pla N=1592
Change	Mean (SD)	37.56 (212.34)	36.41 (186.50)	36.89 (197.65)	11.53 (182.41)
	Median	7.00	7.00	7.00	6.95
	Range	-1479 to 2146	-951.47 to 2299	-1479 to 2299	-1875 to 1820
HOMAR					
Patients[a]		658	908	1566	640
Baseline	Mean (SD)	3.77 (6.08)	2.99 (5.09)	3.32 (5.54)	3.42 (9.23)
Last value	Mean (SD)	5.55 (11.04)	4.47 (8.40)	4.93 (9.61)	3.79 (6.66)
Change	Mean (SD)	1.78 (11.13)	1.48 (8.76)	1.61 (9.83)	0.37 (10.83)
	Median	0.25	0.33	0.29	0.18
	Range	-87.09 to 119.88	-58.43 to 127.84	-87.09 to 127.84	-137.15 to 87.11
QUICKI					
Patients[a]		658	908	1566	640
Baseline	Mean (SD)	0.3406 (0.0411)	0.2918 (0.1019)	0.3123 (0.0855)	0.3046 (0.0906)
Last value	Mean (SD)	0.3336 (0.0462)	0.2823 (0.1011)	0.3039 (0.0864)	0.2994 (0.0919)
Change	Mean (SD)	-0.0070 (0.0422)	-0.0095 (0.0397)	-0.0084 (0.0408)	-0.0052 (0.0382)
	Median	-0.0100	-0.0080	-0.0090	-0.0040
	Range	-0.1600 to 0.1800	-0.2105 to 0.1293	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release, Pla Placebo, QTP Quetiapine, SR Sustained release.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_SR.SAS, Data version: V91 User: Bengt Franzon, 2007-05-03 12:46.

Table A72 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled trials, separating immediate and sustained release)

	QTP SR N=1046 End of treatment			QTP IR N=2391 End of treatment			All QTP N=3437 End of treatment			Pla N=1592 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)
Norm	1 (0.11)	860 (96.3)	32 (3.6)	4 (0.22)	1754 (97.9)	34 (1.9)	5 (0.19)	2614 (97.4)	66 (2.5)	5 (0.38)	1281 (97.4)	29 (2.2)
High	0 (0)	17 (53.1)	15 (46.9)	0 (0)	20 (45.5)	24 (54.5)	0 (0)	37 (48.7)	39 (51.3)	0 (0)	19 (76.0)	6 (24.0)
Total	1 (0.11)	877 (94.8)	47 (5.1)	4 (0.23)	1776 (96.6)	58 (3.2)	5 (0.18)	2653 (96.0)	105 (3.8)	5 (0.37)	1302 (97.6)	35 (2.6)
HbA1c (%)												
Norm	NA	709 (99.3)	5 (0.71)	NA	459 (99.4)	3 (0.65)	NA	1159 (99.3)	8 (0.69)	NA	439 (99.8)	1 (0.23)
High	NA	1 (25.0)	3 (75.0)	NA	0 (0)	2 (100)	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	701 (98.9)	8 (1.1)	NA	459 (98.9)	5 (1.1)	NA	1160 (98.9)	13 (1.1)	NA	439 (99.1)	4 (0.90)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L): Low <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >=6.5.
Path: Rep-DefDiabetes Mar 07 SLB34-LAD_qte_pla_chi_SR.SAS Data version: V91 User: Bengt Franzen 2007-05-03 07:12.

Table A73 Shift to clinically important lab values at any time (All placebo-controlled trials, separating immediate and sustained release)

	QTP SR N=1046		QTP IR N=2391		All QTP N=3437		Pla N=1592	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	925	1 (0.11)	1836	9 (0.49)	2761	10 (0.36)	1340	10 (0.75)
High[b]	896	51 (5.7)	1796	48 (2.7)	2692	99 (3.7)	1317	32 (2.4)
HbA1c (%)								
High[b]	705	5 (0.71)	462	3 (0.65)	1167	8 (0.69)	440	1 (0.23)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERAFLAB_she_pla_ctrl_SR.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:30.

Placebo-controlled fasting trials (all values)

Adverse event data

Table A74 Number of patients with adverse events related to diabetes (All placebo-controlled fasting trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Any[e]	Quetiapine	10 (0)	1592	190.4 (191.1)	0.63 (0.00)	5.3 (0.0)
	Placebo	4 (1)	596	74.0 (74.3)	0.67 (0.17)	5.4 (1.3)
Diabetic Ketoacidosis	Quetiapine	0 (0)	1592	191.1 (191.1)	0.00 (0.00)	0.0 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
Polydipsia	Quetiapine	1 (0)	1592	191.0 (191.1)	0.06 (0.00)	0.5 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
Polyuria	Quetiapine	1 (0)	1592	191.0 (191.1)	0.06 (0.00)	0.5 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
Thirst	Quetiapine	2 (0)	1592	190.9 (191.1)	0.13 (0.00)	1.0 (0.0)
	Placebo	3 (0)	596	74.0 (74.3)	0.50 (0.00)	4.1 (0.0)
Hyperglycaemia	Quetiapine	5 (0)	1592	190.8 (191.1)	0.31 (0.00)	2.6 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)
Diabetes mellitus	Quetiapine	1 (0)	1592	191.1 (191.1)	0.06 (0.00)	0.5 (0.0)
	Placebo	1 (1)	596	74.3 (74.3)	0.17 (0.17)	1.3 (1.3)
Urine glucose abnormalities	Quetiapine	0 (0)	1592	191.1 (191.1)	0.00 (0.00)	0.0 (0.0)
	Placebo	0 (0)	596	74.3 (74.3)	0.00 (0.00)	0.0 (0.0)

[a] Patients must have received at least one dose of trial medication.
[b] Exposure in patient-years, censored at first event.

[c] 100 x total number of patients with event/total number of patients.
[d] 100 x total number of patients with event/total patient years of exposure.
[e] The number of patients with any of the adverse events. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Trials 5077US0046, D1444C00132, D1444C00133, D1447C00135 and D1444C00004 are included in this table.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Pgm: Reg-Def\Diabetes Mar 07 SERM\...\AE_pla_ctrl_fast.SAS. Data version: V9.1 User: Malin Dreyer 2007-05-02 20:38.

Laboratory data

Non-diabetic patients

Table A75 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled fasting trials)

		QTP N=1092	Pla N=409
Glucose (mmol/L)			
Patients[a]		944	358
Baseline	Mean (SD)	4.80 (0.31)	4.90 (0.66)
Last value	Mean (SD)	5.08 (0.90)	5.06 (0.79)
Change	Mean (SD)	0.27 (0.90)	0.16 (0.99)
	Median	0.17	0.100
	Range	-2.39 to 9.33	-6.83 to 4.72
HbA1c (%)			
Patients[a]		801	305
Baseline	Mean (SD)	5.28 (0.39)	5.23 (0.37)
Last value	Mean (SD)	5.31 (0.39)	5.24 (0.36)
Change	Mean (SD)	0.034 (0.25)	0.016 (0.25)
	Median	0	0
	Range	-0.70 to 1.10	-0.80 to 0.80
Insulin (pmol/L)			
Patients[a]		970	369
Baseline	Mean (SD)	75.44 (102.01)	77.67 (154.45)
Last value	Mean (SD)	109.55 (160.35)	94.15 (153.91)
Change	Mean (SD)	34.11 (155.65)	16.48 (197.65)
	Median	7.00	6.95
	Range	-770.90 to 1632	-1875 to 1820
HOMAR			
Patients[a]		863	339
Baseline	Mean (SD)	2.29 (3.59)	2.88 (9.92)
Last value	Mean (SD)	3.94 (7.97)	3.40 (7.46)
Change	Mean (SD)	1.64 (7.73)	0.52 (12.00)
	Median	0.29	0.21

Table A75 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled fasting trials)

		QTP N=1092	Pla N=409
	Range	-35.70 to 127.84	-137.15 to 87.11
QUICKI			
Patients[a]		863	339
Baseline	Mean (SD)	0.3602 (0.0402)	0.3595 (0.0416)
Last value	Mean (SD)	0.3466 (0.0458)	0.3515 (0.0447)
Change	Mean (SD)	-0.0136 (0.0433)	-0.0079 (0.0430)
	Median	-0.0100	-0.0100
	Range	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMIL_AB_chg_pla_ctrl_udfast_diab3.SAS Data version: V91 User: Bengt Franzon, 2007-05-03 12:40.

Table A76 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled fasting trials)

	QTP N=1092 End of treatment			Pla N=409 End of treatment		
Lab test Baseline	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**
Glucose (mmol/L)						
Low	0 (0)	1 (100)	0 (0)	NA	NA	NA
Norm	1 (0.11)	926 (98.2)	16 (1.7)	0 (0)	350 (97.8)	8 (2.2)
High	NA	NA	NA	NA	NA	NA
Total	1 (0.11)	927 (98.2)	16 (1.7)	0 (0)	350 (97.8)	8 (2.2)
HbA1c (%)						
Norm	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA
Total	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMIL_AB_shc_pla_ctrl_udfast_diab3.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 07:07.

Table A77 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled fasting trials)

	QTP N=1092		Pla N=409	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	943	1 (0.11)	358	1 (0.28)
High[b]	944	26 (2.8)	358	8 (2.2)
HbA1c (%)				
High[b]	801	0 (0)	305	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMAB_sha_pla_ctrl_udfast_diab3.SAS. Data version: V91 User: Bangi Franzon. 2007-05-03 07:25.

Diabetic risk patients

Table A78 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials)

		QTP N=339	Pla N=127
Glucose (mmol/L)			
Patients[a]		303	110
Baseline	Mean (SD)	5.51 (0.67)	5.52 (0.63)
Last value	Mean (SD)	5.47 (1.00)	5.41 (0.94)
Change	Mean (SD)	-0.039 (1.02)	-0.11 (0.97)
	Median	-0.11	-0.11
	Range	-2.56 to 4.72	-3.06 to 4.30
HbA1c (%)			
Patients[a]		272	98
Baseline	Mean (SD)	5.38 (0.38)	5.32 (0.43)
Last value	Mean (SD)	5.43 (0.41)	5.35 (0.45)
Change	Mean (SD)	0.056 (0.29)	0.023 (0.27)
	Median	0.100	0
	Range	-1.40 to 1.40	-0.90 to 0.80
Insulin (pmol/L)			
Patients[a]		301	113
Baseline	Mean (SD)	127.68 (145.60)	112.01 (107.87)
Last value	Mean (SD)	170.34 (272.86)	126.96 (143.20)

Table A78 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials)

		QTP N=339	Pla N=127
Change	Mean (SD)	42.66 (261.68)	14.95 (147.81)
	Median	0	0
	Range	-701.45 to 2146	-620.26 to 888.96
HOMAR			
Patients[a]		287	102
Baseline	Mean (SD)	4.59 (5.75)	3.80 (3.70)
Last value	Mean (SD)	6.26 (12.85)	4.53 (6.36)
Change	Mean (SD)	1.67 (12.73)	0.73 (6.14)
	Median	-0.052	-0.19
	Range	-34.93 to 119.88	-21.59 to 40.41
QUICKI			
Patients[a]		287	102
Baseline	Mean (SD)	0.3266 (0.0353)	0.3307 (0.0351)
Last value	Mean (SD)	0.3280 (0.0443)	0.3299 (0.0394)
Change	Mean (SD)	0.0013 (0.0408)	-0.0008 (0.0345)
	Median	0.0000	0.0000
	Range	-0.1433 to 0.1287	-0.1229 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trials 5077IS0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def-Diabetes Mar 07 SERAT-LAB_chg_pla_ctrl_udfast_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:46.

Table A79 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials)

	QTP N=339 End of treatment			Pla N=127 End of treatment		
Lab test Baseline	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**
Glucose (mmol/L)						
Low	NA	NA	NA	NA	NA	NA
Norm	0 (0)	289 (95.4)	14 (4.6)	0 (0)	103 (94.5)	6 (5.5)
High	NA	NA	NA	NA	NA	NA
Total	0 (0)	289 (95.4)	14 (4.6)	0 (0)	103 (94.5)	6 (5.5)
HbA1c (%)						
Norm	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)

Table A79 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials)

	QTP N=339 End of treatment			Pla N=127 End of treatment		
Lab test Baseline	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**
High	NA	NA	NA	NA	NA	NA
Total	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMJLAB_shs_pla_ctrl_udfast_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:06.

Table A80 Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled fasting trials)

	QTP N=339		Pla N=127	
	N	**n (%)**	**N**	**n (%)**
Glucose (mmol/L)				
Low[a]	303	0 (0)	110	0 (0)
High[b]	303	25 (8.3)	110	8 (7.3)
HbA1c (%)				
High[b]	272	0 (0)	98	0 (0)

[a] N is the number of patients with normal or high at baseline. n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline. n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMJLAB_shs_pla_ctrl_udfast_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:25.

Diabetic patients

Table A81 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled fasting trials)

		QTP N=161	Pla N=60
Glucose (mmol/L)			
Patients[a]		144	56
Baseline	Mean (SD)	6.73 (2.14)	6.04 (1.52)
Last value	Mean (SD)	6.93 (2.77)	6.08 (2.13)
Change	Mean (SD)	0.20 (2.86)	0.032 (2.03)

Table A81 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled fasting trials)

		QTP N=161	Pla N=60
	Median	0.056	-0.14
	Range	-8.22 to 13.89	-4.20 to 5.10
HbA1c (%)			
Patients[a]		100	40
Baseline	Mean (SD)	6.31 (0.88)	6.01 (0.85)
Last value	Mean (SD)	6.55 (1.19)	5.96 (0.91)
Change	Mean (SD)	0.23 (0.69)	-0.050 (0.45)
	Median	0.100	0
	Range	-0.90 to 4.50	-1.70 to 1.10
Insulin (pmol/L)			
Patients[a]		142	55
Baseline	Mean (SD)	170.72 (201.96)	143.81 (117.27)
Last value	Mean (SD)	178.32 (211.52)	133.71 (134.67)
Change	Mean (SD)	7.60 (252.46)	-10.09 (157.88)
	Median	6.95	-12.08
	Range	-1479 to 1445	-493.00 to 507.00
HOMAR			
Patients[a]		133	54
Baseline	Mean (SD)	8.28 (11.75)	5.82 (5.37)
Last value	Mean (SD)	8.24 (11.95)	6.06 (8.26)
Change	Mean (SD)	-0.036 (15.75)	0.24 (8.95)
	Median	0.27	-0.11
	Range	-87.09 to 92.99	-23.06 to 42.25
QUICKI			
Patients[a]		133	54
Baseline	Mean (SD)	0.3121 (0.0445)	0.3162 (0.0377)
Last value	Mean (SD)	0.3129 (0.0451)	0.3238 (0.0445)
Change	Mean (SD)	0.0008 (0.0505)	0.0076 (0.0448)
	Median	-0.0070	0.0001
	Range	-0.1619 to 0.1600	-0.0738 to 0.1443

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trials 5072US/0045, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg:Def:Diabetes Mar 07 SER9LAB_chg_pla_cvl_udfast_diab1.SAS. Data version: V01 User: Bengt Franzon. 2007-05-03 12:46.

Table A82 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled fasting trials)

	QTP N=161 End of treatment			Pla N=60 End of treatment		
Lab test Baseline	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**
Glucose (mmol/L)						
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	1 (1.1)	68 (76.4)	20 (22.5)	1 (2.4)	34 (81.0)	7 (16.7)
High	0 (0)	27 (49.1)	28 (50.9)	0 (0)	9 (69.2)	4 (30.8)
Total	1 (0.69)	95 (66.0)	48 (33.3)	1 (1.8)	44 (78.6)	11 (19.6)
HbA1c (%)						
Norm	NA	86 (91.5)	8 (8.5)	NA	36 (97.3)	1 (2.7)
High	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	87 (87.0)	13 (13.0)	NA	36 (90.0)	4 (10.0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMYLAB_shs_pla_ctrl_udfast_diab1.SAS. Data version: V91 User: Bengt Pranzon. 2007-05-03 07:06.

Table A83 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled fasting trials)

	QTP N=161		Pla N=60	
	N	**n (%)**	**N**	**n (%)**
Glucose (mmol/L)				
Low[a]	144	1 (0.69)	55	1 (1.8)
High[b]	94	26 (27.7)	43	8 (18.6)
HbA1c (%)				
High[b]	94	8 (8.5)	37	1 (2.7)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMYLAB_shs_pla_ctrl_udfast_diab1.SAS. Data version: V91 User: Bengt Pranzon. 2007-05-03 07:24.

All diabetic subgroups

Table A84 Mean (SD) change from baseline to end of treatment (All placebo-controlled fasting trials)

		QTP N=1592	Pla N=596
Glucose (mmol/L)			
Patients[a]		1391	524
Baseline	Mean (SD)	5.16 (1.05)	5.15 (0.89)
Last value	Mean (SD)	5.35 (1.37)	5.24 (1.09)
Change	Mean (SD)	0.20 (1.28)	0.092 (1.15)
	Median	0.10	0.056
	Range	-8.22 to 13.89	-6.83 to 5.10
HbA1c (%)			
Patients[a]		1173	443
Baseline	Mean (SD)	5.39 (0.53)	5.32 (0.50)
Last value	Mean (SD)	5.45 (0.61)	5.33 (0.50)
Change	Mean (SD)	0.056 (0.32)	0.012 (0.28)
	Median	0	0
	Range	-1.40 to 4.50	-1.70 to 1.10
Insulin (pmol/L)			
Patients[a]		1413	537
Baseline	Mean (SD)	96.14 (129.56)	91.67 (143.86)
Last value	Mean (SD)	129.41 (196.98)	105.11 (150.48)
Change	Mean (SD)	33.27 (193.97)	13.44 (184.29)
	Median	6.95	2.22
	Range	-1479 to 2146	-1875 to 1826
$HOMA_R$			
Patients[a]		1283	495
Baseline	Mean (SD)	3.43 (5.82)	3.39 (8.61)
Last value	Mean (SD)	4.90 (9.82)	3.92 (7.38)
Change	Mean (SD)	1.47 (10.10)	0.53 (10.71)
	Median	0.25	0.13
	Range	-87.09 to 127.84	-137.15 to 87.11
QUICKI			
Patients[a]		1283	495
Baseline	Mean (SD)	0.3477 (0.0437)	0.3488 (0.0430)
Last value	Mean (SD)	0.3390 (0.0468)	0.3441 (0.0450)
Change	Mean (SD)	-0.0088 (0.0441)	-0.0048 (0.0419)

Table A84 Mean (SD) change from baseline to end of treatment (All placebo-controlled fasting trials)

		QTP N=1592	Pla N=596
	Median	-0.0100	-0.0034
	Range	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo QTP Quetiapine.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_adfast.SAS. Data version: V91 User: Bengt Franzen. 2007-05-03 12:41.

Table A85 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled fasting trials)

	QTP N=1592 End of treatment			Pla N=596 End of treatment		
Lab test Baseline	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**
Glucose (mmol/L)						
Low	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Norm	2 (0.15)	1283 (96.1)	50 (3.7)	1 (0.20)	488 (95.7)	21 (4.1)
High	0 (0)	27 (49.1)	28 (50.9)	0 (0)	9 (69.2)	4 (30.8)
Total	2 (0.14)	1311 (94.2)	78 (5.6)	1 (0.19)	498 (95.0)	25 (4.8)
HbA1c (%)						
Norm	NA	1159 (99.3)	8 (0.69)	NA	439 (99.8)	1 (0.23)
High	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	1160 (98.9)	13 (1.1)	NA	439 (99.1)	4 (0.90)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >=7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shc_pla_ctrl_adfast.SAS. Data version: V91 User: Bengt Franzen. 2007-05-03 07:07.

Table A86 Shift to clinically important lab values at any time (All placebo-controlled fasting trials)

	QTP N=1592		Pla N=596	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	1390	2 (0.14)	523	2 (0.38)
High[b]	1341	77 (5.7)	511	24 (4.7)
HbA1c (%)				
High[b]	1167	8 (0.69)	440	1 (0.23)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00094, D1444C00132, D1444C00133, D1447C00135 are included in this table.

Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shs_pla_ctrl_tdfast.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 07:26.

Placebo controlled fasting trials: IR vs SR data

Non-diabetic patients

Table A87 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, separating immediate and sustained release)

		QTP SR N=537	QTP IR N=555	All QTP N=1092	Pla N=309
Glucose (mmol/L)					
Patients[a]		472	472	944	358
Baseline	Mean (SD)	4.85 (0.48)	4.76 (0.53)	4.80 (0.51)	4.90 (0.66)
Last value	Mean (SD)	5.12 (0.91)	5.03 (0.89)	5.08 (0.90)	5.06 (0.79)
Change	Mean (SD)	0.28 (0.92)	0.27 (0.89)	0.27 (0.90)	0.16 (0.99)
	Median	0.14	0.17	0.17	0.100
	Range	-1.56 to 9.33	-2.39 to 6.83	-2.39 to 9.33	-6.83 to 4.72
HbA1c (%)					
Patients[a]		485	316	801	305
Baseline	Mean (SD)	5.28 (0.39)	5.28 (0.41)	5.28 (0.39)	5.23 (0.37)
Last value	Mean (SD)	5.33 (0.39)	5.29 (0.39)	5.31 (0.39)	5.24 (0.36)
Change	Mean (SD)	0.049 (0.26)	0.0095 (0.24)	0.034 (0.25)	0.016 (0.25)
	Median	0	0	0	0
	Range	-0.70 to 1.10	-0.70 to 0.90	-0.70 to 1.10	-0.80 to 0.80
Insulin (pmol/L)					

Table A87 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, separating immediate and sustained release)

		QTP SR N=537	QTP IR N=555	All QTP N=1092	Pla N=409
Patients[a]		495	475	970	369
Baseline	Mean (SD)	80.08 (98.50)	70.61 (105.44)	75.44 (102.01)	77.67 (154.45)
Last value	Mean (SD)	112.25 (155.29)	106.73 (165.59)	109.55 (160.35)	94.15 (153.91)
Change	Mean (SD)	32.18 (146.15)	36.12 (165.10)	34.11 (155.65)	16.48 (197.65)
	Median	7.00	7.00	7.00	6.95
	Range	-757.00 to 1347	-770.90 to 1632	-770.90 to 1632	-1875 to 1820
HOMAR					
Patients[a]		445	418	863	339
Baseline	Mean (SD)	2.51 (3.50)	2.06 (3.67)	2.29 (3.59)	2.88 (9.92)
Last value	Mean (SD)	4.04 (7.93)	3.83 (8.87)	3.94 (7.97)	3.40 (7.46)
Change	Mean (SD)	1.53 (6.49)	1.76 (8.86)	1.64 (7.73)	0.52 (12.00)
	Median	0.25	0.32	0.29	0.21
	Range	-23.99 to 64.09	-35.70 to 127.84	-35.70 to 127.84	-137.15 to 87.13
QUICKI					
Patients[a]		445	418	863	339
Baseline	Mean (SD)	0.3530 (0.0379)	0.3680 (0.0413)	0.3602 (0.0402)	0.3595 (0.0416)
Last value	Mean (SD)	0.3425 (0.0442)	0.3510 (0.0471)	0.3466 (0.0458)	0.3515 (0.0447)
Change	Mean (SD)	-0.0105 (0.0426)	-0.0170 (0.0446)	-0.0136 (0.0433)	-0.0079 (0.0430)
	Median	-0.0100	-0.0168	-0.0100	-0.0100
	Range	-0.1600 to 0.1800	-0.2105 to 0.1262	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Note: Trials 5077US0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SER\PLAB_chg_pla_ctrl_adfast_SR_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:49.

Table A88 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, separating immediate and sustained release)

	QTP SR N=537 End of treatment			QTP IR N=555 End of treatment			All QTP N=1092 End of treatment			Pla N=609 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	NA	NA	NA
Norm	0 (0)	465 (98.5)	7 (1.5)	1 (0.21)	461 (97.9)	9 (1.9)	1 (0.11)	926 (98.2)	16 (1.7)	0 (0)	350 (97.8)	8 (2.2)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	465 (98.5)	7 (1.5)	1 (0.21)	462 (97.9)	9 (1.9)	1 (0.11)	927 (98.2)	16 (1.7)	0 (0)	350 (97.8)	8 (2.2)
HbA1c (%)												
Norm	NA	485 (100)	0 (0)	NA	316 (100)	0 (0)	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	485 (100)	0 (0)	NA	316 (100)	0 (0)	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR: Immediate release. Pla: Placebo. QTP: Quetiapine. SR: Sustained release.
Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >= 11.1 for non-fasting. HbA1c (%): High: >=7.5.
Note: Trials 3079US3046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg/Def/Diabetes Mar 07 SER3051AH_she_pla_ctrl_edfast_SR_Alab3.SAS Data version: V91 User: Bergé François. 2007-05-03 02:15.

Table A89 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled fasting trials, separating immediate and sustained release)

	QTP SR N=537		QTP IR N=555		All QTP N=1092		Pla N=409	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	472	0 (0)	471	1 (0.21)	943	1 (0.11)	358	1 (0.28)
High[b]	472	14 (3.0)	472	12 (2.5)	944	26 (2.8)	358	8 (2.2)
HbA1c (%)								
High[b]	485	0 (0)	316	0 (0)	801	0 (0)	305	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release, Pla Placebo, QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\3_AB_sha_pla_ctrl_adfast_SR_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:33.

Diabetic risk patients

Table A90 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, separating immediate and sustained release)

		QTP SR N=164	QTP IR N=175	All QTP N=339	Pla N=127
Glucose (mmol/L)					
Patients[a]		153	150	303	110
Baseline	Mean (SD)	5.56 (0.66)	5.46 (0.67)	5.51 (0.67)	5.52 (0.63)
Last value	Mean (SD)	5.58 (1.06)	5.36 (0.91)	5.47 (1.00)	5.41 (0.94)
Change	Mean (SD)	0.022 (1.09)	-0.10 (0.95)	-0.039 (1.02)	-0.11 (0.97)
	Median	-0.100	-0.11	-0.11	-0.11
	Range	-2.56 to 4.72	-1.94 to 3.72	-2.56 to 4.72	-3.06 to 4.30
HbA1c (%)					
Patients[a]		153	119	272	98
Baseline	Mean (SD)	5.38 (0.41)	5.37 (0.34)	5.38 (0.38)	5.32 (0.43)
Last value	Mean (SD)	5.47 (0.42)	5.39 (0.38)	5.43 (0.41)	5.35 (0.45)
Change	Mean (SD)	0.086 (0.30)	0.017 (0.27)	0.056 (0.29)	0.025 (0.27)
	Median	0.100	0	0.100	0
	Range	-0.50 to 1.40	-1.40 to 0.70	-1.40 to 1.40	-0.90 to 0.80
Insulin (pmol/L)					
Patients[a]		153	148	301	113

Table A90 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, separating immediate and sustained release)

		QTP SR N=164	QTP IR N=175	All QTP N=339	Pla N=127
Baseline	Mean (SD)	139.75 (340.40)	115.21 (150.24)	127.68 (145.60)	112.01 (107.87)
Last value	Mean (SD)	200.00 (330.30)	139.68 (193.07)	170.34 (272.86)	126.96 (143.20)
Change	Mean (SD)	60.25 (315.28)	24.47 (190.54)	42.66 (261.68)	14.95 (147.81)
	Median	7.00	0	0	0
	Range	-701.45 to 2146	-513.93 to 1049	-701.45 to 2146	-620.26 to 888.96
HOMAR					
Patients[a]		147	140	287	102
Baseline	Mean (SD)	4.90 (5.43)	4.27 (6.08)	4.59 (5.75)	3.80 (3.70)
Last value	Mean (SD)	7.71 (16.46)	4.74 (7.10)	6.26 (12.85)	4.53 (6.36)
Change	Mean (SD)	2.81 (16.34)	0.47 (7.16)	1.67 (12.73)	0.73 (6.14)
	Median	0.13	-0.069	-0.032	-0.19
	Range	-34.93 to 119.88	-19.78 to 36.23	-34.93 to 119.88	-21.59 to 40.41
QUICKI					
Patients[a]		147	140	287	102
Baseline	Mean (SD)	0.3207 (0.0320)	0.3329 (0.0375)	0.3266 (0.0353)	0.3307 (0.0351)
Last value	Mean (SD)	0.3269 (0.0431)	0.3354 (0.0445)	0.3280 (0.0443)	0.3299 (0.0394)
Change	Mean (SD)	0.0002 (0.0382)	0.0025 (0.0435)	0.0013 (0.0408)	-0.0008 (0.0345)
	Median	0.0000	0.0000	0.0000	0.0000
	Range	-0.0909 to 0.1000	-0.1433 to 0.1287	-0.1433 to 0.1287	-0.1229 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM1.AB_chg_pla_ctrl_udfast_SR_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:49.

Table A91 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, separating immediate and sustained release)

	QTP SR N=164 End of treatment			QTP IR N=175 End of treatment			All QTP N=339 End of treatment			Pla N=127 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	143 (93.5)	10 (6.5)	0 (0)	146 (97.3)	4 (2.7)	0 (0)	289 (95.4)	14 (4.6)	0 (0)	104 (94.5)	6 (5.5)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	143 (93.5)	10 (6.5)	0 (0)	146 (97.3)	4 (2.7)	0 (0)	289 (95.4)	14 (4.6)	0 (0)	104 (94.5)	6 (5.5)
HbA1c (%)												
Norm	NA	153 (100)	0 (0)	NA	119 (100)	0 (0)	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	153 (100)	0 (0)	NA	119 (100)	0 (0)	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically suggested limits are: Glucose (mmol/L) Low <=5.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >=7.5.
Note: Trials 26775IS/0046, D1444C00004, D1444C00125, D1444C00175, D1447C00135 are included in this table.
Pgm: Reg-Def Diabetes May 07 SEPAR-LAB_sbc_pla_qtr_edtest_SR_Exp2 SAS (Beta version: V9.1 User: Bengt Franzen. 2007-05-03 07:14.

Table A92 Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled fasting trials, separating immediate and sustained release)

	QTP SR N=164		QTP IR N=175		All QTP N=339		Pla N=127	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	153	0 (0)	150	0 (0)	303	0 (0)	110	0 (0)
High[b]	153	18 (11.8)	150	7 (4.7)	303	25 (8.3)	110	8 (7.3)
HbA1c (%)								
High[b]	153	0 (0)	119	0 (0)	272	0 (0)	98	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00094, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_ndfast_SR_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:33.

Diabetic patients

Table A93 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled fasting trials, separating immediate and sustained release)]

		QTP SR N=73	QTP IR N=88	All QTP N=161	Pla N=60
Glucose (mmol/L)					
Patients[a]		70	74	144	56
Baseline	Mean (SD)	6.72 (2.05)	6.74 (2.24)	6.73 (2.14)	6.04 (1.52)
Last value	Mean (SD)	6.69 (2.16)	7.16 (3.24)	6.93 (2.77)	6.08 (2.13)
Change	Mean (SD)	-0.023 (2.38)	0.42 (3.26)	0.20 (2.86)	0.032 (2.03)
	Median	0	0.17	0.056	-0.14
	Range	-7.10 to 8.28	-8.22 to 13.89	-8.22 to 13.89	-4.20 to 5.10
HbA1c (%)					
Patients[a]		71	29	100	40
Baseline	Mean (SD)	6.33 (0.84)	6.28 (0.97)	6.31 (0.88)	6.01 (0.85)
Last value	Mean (SD)	6.48 (0.99)	6.71 (1.58)	6.55 (1.19)	5.96 (0.93)
Change	Mean (SD)	0.15 (0.47)	0.43 (1.02)	0.23 (0.69)	-0.050 (0.45)
	Median	0.100	0.20	0.100	0
	Range	-0.90 to 1.70	-0.50 to 4.50	-0.90 to 4.50	-1.70 to 1.10
Insulin (pmol/L)					
Patients[a]		68	74	142	55
Baseline	Mean (SD)	204.46 (238.49)	139.71 (156.68)	170.72 (201.96)	143.81 (117.27)
Last value	Mean (SD)	230.11 (259.02)	136.72 (141.59)	178.32 (211.52)	133.71 (134.67)
Change	Mean (SD)	25.65 (310.84)	-8.98 (183.97)	7.69 (252.46)	-10.09 (137.88)
	Median	6.97	6.95	6.95	-12.08
	Range	-1479 to 1445	-757.01 to 625.05	-1479 to 1445	-493.00 to 507.00
$HOMA_B$					
Patients[a]		66	67	133	54
Baseline	Mean (SD)	9.76 (13.18)	6.82 (10.04)	8.28 (11.75)	5.82 (5.37)
Last value	Mean (SD)	10.96 (15.18)	5.57 (6.65)	8.24 (11.95)	6.06 (8.26)
Change	Mean (SD)	1.20 (19.05)	-1.25 (11.63)	-0.036 (15.75)	0.24 (8.95)
	Median	0.79	0.20	0.27	-0.11
	Range	-87.09 to 92.99	-58.43 to 22.73	-87.09 to 92.99	-23.06 to 42.25
QUICKI					
Patients[a]		66	67	133	54
Baseline	Mean (SD)	0.3017 (0.0390)	0.3224 (0.0473)	0.3121 (0.0445)	0.3162 (0.0377)
Last value	Mean (SD)	0.3020 (0.0465)	0.3237 (0.0412)	0.3129 (0.0451)	0.3258 (0.0445)

Table A93 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled fasting trials, separating immediate and sustained release)[]

		QTP SR N=73	QTP IR N=88	All QTP N=161	Pla N=60
Change	Mean (SD)	0.0003 (0.0495)	0.0013 (0.0518)	0.0008 (0.0505)	0.0076 (0.0448)
	Median	-0.0050	-0.0070	-0.0070	0.0001
	Range	-0.0800 to 0.1600	-0.1619 to 0.1293	-0.1619 to 0.1600	-0.0738 to 0.1443

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_udfast_SR_diab1.SAS Data version: V91 User: Bengt Franzon, 2007-05-03 12:49.

Table A94 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled fasting trials, separating immediate and sustained release)

	QTP SR N=73 End of treatment			QTP IR N=88 End of treatment			All QTP N=161 End of treatment			Pla N=60 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	1 (2.3)	31 (72.1)	11 (25.6)	0 (0)	37 (80.4)	9 (19.6)	1 (1.1)	68 (76.4)	20 (22.5)	1 (2.4)	34 (81.0)	7 (16.7)
High	0 (0)	15 (55.6)	12 (44.4)	0 (0)	12 (42.9)	16 (57.1)	0 (0)	27 (49.1)	28 (50.9)	0 (0)	9 (69.2)	4 (30.8)
Total	1 (1.4)	46 (65.7)	23 (32.9)	0 (0)	49 (66.2)	25 (33.8)	1 (0.69)	95 (66.0)	48 (33.3)	1 (1.8)	44 (78.6)	11 (19.6)
HbA1c (%)												
Norm	NA	62 (92.5)	5 (7.5)	NA	24 (88.9)	3 (11.1)	NA	86 (91.5)	8 (8.5)	NA	36 (97.3)	1 (2.7)
High	NA	1 (25.0)	3 (75.0)	NA	0 (0)	2 (100)	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	63 (88.7)	8 (11.3)	NA	24 (82.8)	5 (17.2)	NA	87 (87.0)	13 (13.0)	NA	36 (90.0)	4 (10.0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline

IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.

Clinically important limits are: Glucose (mmol/L): Low <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%): High >7.5.

Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1444C00135 are included in this table.

Pgm: Reg-Def Diabetes Mar 07 SEKMEL331_ske_pla_cni_udfast_SR_Aab1.SAS Data version: V93 User: Henga Franzen 2007-05-03 07:14.

Table A95 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled fasting trials, separating immediate and sustained release)

	QTP SR N=73		QTP IR N=88		All QTP N=161		Pla N=60	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	70	1 (1.4)	74	0 (0)	144	1 (0.69)	55	1 (1.8)
High[b]	46	15 (32.6)	48	11 (22.9)	94	26 (27.7)	43	8 (18.6)
HbA1c (%)								
High[b]	67	5 (7.5)	27	3 (11.1)	94	8 (8.5)	37	1 (2.7)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_tdfast_SR_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:32.

All diabetic subgroups

Table A96 Mean (SD) change from baseline to end of treatment (All placebo-controlled fasting trials, separating immediate and sustained release)

		QTP SR N=774	QTP IR N=818	All QTP N=1592	Pla N=596
Glucose (mmol/L)					
Patients[a]		695	696	1391	524
Baseline	Mean (SD)	5.19 (1.01)	5.12 (1.10)	5.16 (1.05)	5.15 (0.89)
Last value	Mean (SD)	5.38 (1.22)	5.33 (1.50)	5.35 (1.37)	5.24 (1.09)
Change	Mean (SD)	0.19 (1.19)	0.20 (1.37)	0.20 (1.28)	0.092 (1.15)
	Median	0.100	0.11	0.10	0.056
	Range	-7.10 to 9.33	-8.22 to 13.89	-8.22 to 13.89	-6.83 to 5.10
HbA1c (%)					
Patients[a]		709	464	1173	443
Baseline	Mean (SD)	5.41 (0.55)	5.37 (0.51)	5.39 (0.53)	5.32 (0.50)
Last value	Mean (SD)	5.47 (0.60)	5.41 (0.64)	5.45 (0.61)	5.33 (0.50)
Change	Mean (SD)	0.068 (0.30)	0.038 (0.36)	0.056 (0.32)	0.012 (0.28)
	Median	0	0	0	0
	Range	-0.90 to 1.70	-1.40 to 4.50	-1.40 to 4.50	-1.70 to 1.10
Insulin (pmol/L)					
Patients[a]		716	697	1413	537
Baseline	Mean (SD)	104.64 (133.61)	87.41 (124.75)	96.14 (129.56)	91.67 (143.86)
Last value	Mean (SD)	142.20 (219.57)	116.27 (169.85)	129.41 (196.98)	105.11 (150.48)
Change	Mean (SD)	37.56 (212.34)	28.86 (173.13)	33.27 (193.97)	13.44 (184.29)
	Median	7.00	6.95	6.95	2.22
	Range	-1479 to 2146	-770.90 to 1632	-1479 to 2146	-1875 to 1820
$HOMA_R$					
Patients[a]		658	625	1283	495
Baseline	Mean (SD)	3.77 (6.08)	3.07 (5.51)	3.43 (5.82)	3.39 (8.61)
Last value	Mean (SD)	5.55 (11.04)	4.22 (8.30)	4.90 (9.82)	3.92 (7.38)
Change	Mean (SD)	1.78 (11.13)	1.15 (8.89)	1.47 (10.10)	0.53 (10.71)
	Median	0.25	0.25	0.25	0.13
	Range	-87.09 to 119.88	-58.43 to 127.84	-87.09 to 127.84	-137.15 to 87.11
QUICKI					
Patients[a]		658	625	1283	495
Baseline	Mean (SD)	0.3406 (0.0411)	0.3552 (0.0450)	0.3477 (0.0437)	0.3488 (0.0430)
Last value	Mean (SD)	0.3336 (0.0462)	0.3446 (0.0469)	0.3390 (0.0468)	0.3441 (0.0450)
Change	Mean (SD)	-0.0070 (0.0422)	-0.0106 (0.0460)	-0.0088 (0.0441)	-0.0048 (0.0439)

Table A96 Mean (SD) change from baseline to end of treatment (All placebo-controlled fasting trials, separating immediate and sustained release)

		QTP SR N=774	QTP IR N=818	All QTP N=1592	Pla N=596
	Median	-0.0100	-0.0100	-0.0100	-0.0034
	Range	-0.1600 to 0.1800	-0.2105 to 0.1293	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: *Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_odfast_SR.SAS. Data version: V91 User: Bengt Franzen. 2007-05-03 12:50.*

Table A97 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled fasting trials, separating immediate and sustained release)

	QTP SR N=774 End of treatment			QTP IR N=818 End of treatment			All QTP N=1592 End of treatment			Pla N=596 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Norm	1 (0.15)	639 (95.7)	28 (4.2)	1 (0.15)	644 (96.6)	22 (3.3)	2 (0.15)	1283 (96.1)	50 (3.7)	1 (0.20)	488 (95.7)	21 (4.1)
High	0 (0)	15 (55.6)	12 (44.4)	0 (0)	12 (42.9)	16 (57.1)	0 (0)	27 (49.1)	28 (50.9)	0 (0)	9 (69.2)	4 (30.8)
Total	1 (0.14)	654 (94.1)	40 (5.8)	1 (0.14)	657 (94.4)	38 (5.5)	2 (0.14)	1311 (94.2)	78 (5.6)	1 (0.17)	498 (95.0)	25 (4.8)
HbA1c (%)												
Norm	NA	703 (99.3)	5 (0.71)	NA	459 (99.4)	3 (0.65)	NA	1159 (99.3)	8 (0.69)	NA	439 (99.8)	1 (0.23)
High	NA	1 (25.0)	3 (75.0)	NA	0 (0)	2 (100)	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	701 (98.9)	8 (1.1)	NA	459 (99.6)	5 (1.1)	NA	1160 (99.3)	13 (1.1)	NA	439 (99.3)	4 (0.90)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L): Low <= 2.5, High >= 7 for fasting and >= 11.1 for non-fasting. HbA1c (%): High >= 7.5.
Note: Trials D1443C00004, D1444C00002, D1444C00132, D1448C00135, D1447C00133 are included in this table.
Pgm: Reg42ef Diabetes May 07 SER3dFL_A3j_ste_pla_ctr_edffset_SR.S.AS. Date version: V31 User: Bengt Francon 2007-05-23 07:15

Table A98 Shift to clinically important lab values at any time (All placebo-controlled fasting trials, separating immediate and sustained release)

	QTP SR N=774		QTP IR N=818		All QTP N=1592		Pla N=596	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	695	1 (0.14)	695	1 (0.14)	1390	2 (0.14)	523	2 (0.38)
High[b]	671	47 (7.0)	670	30 (4.5)	1341	77 (5.7)	511	24 (4.7)
HbA1c (%)								
High[b]	705	5 (0.71)	462	3 (0.65)	1167	8 (0.69)	440	1 (0.23)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-DefDiabetes Mar 07 SERM\LAB_sba_pla_ctd_udfast_SR.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:34.

Placebo-controlled fasting trials (documented fasting data)

Non-diabetic patients

Table A99 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, documented fasting)

		QTP N=1092	Pla N=409
Glucose (mmol/L)			
Patients[a]		839	318
Baseline	Mean (SD)	4.79 (0.44)	4.85 (0.46)
Last value	Mean (SD)	5.04 (0.80)	5.02 (0.75)
Change	Mean (SD)	0.24 (0.80)	0.16 (0.79)
	Median	0.17	0.100
	Range	-1.94 to 8.70	-2.10 to 4.72
HbA1c (%)			
Patients[a]		690	265
Baseline	Mean (SD)	5.27 (0.39)	5.21 (0.37)
Last value	Mean (SD)	5.30 (0.38)	5.23 (0.37)
Change	Mean (SD)	0.028 (0.25)	0.011 (0.25)
	Median	0	0
	Range	-0.70 to 0.90	-0.80 to 0.80
Insulin (pmol/L)			
Patients[a]		853	325
Baseline	Mean (SD)	66.30 (79.69)	66.29 (66.46)
Last value	Mean (SD)	93.81 (146.30)	82.74 (121.69)
Change	Mean (SD)	27.51 (137.01)	16.45 (99.33)
	Median	6.95	5.21
	Range	-757.00 to 1632	-327.00 to 1167
$HOMA_R$			
Patients[a]		787	304
Baseline	Mean (SD)	2.03 (2.38)	2.11 (2.09)
Last value	Mean (SD)	3.43 (7.27)	3.06 (6.08)
Change	Mean (SD)	1.39 (6.88)	0.95 (5.35)
	Median	0.26	0.14
	Range	-22.09 to 127.84	-11.18 to 71.49
QUICKI			
Patients[a]		787	304
Baseline	Mean (SD)	0.3623 (0.0389)	0.3610 (0.0402)
Last value	Mean (SD)	0.3503 (0.0439)	0.3543 (0.0442)

Table A99 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, documented fasting)

		QTP N=1092	Pla N=409
Change	Mean (SD)	-0.0119 (0.0426)	-0.0067 (0.0397)
	Median	-0.0100	-0.0051
	Range	-0.2105 to 0.1800	-0.1830 to 0.1100

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trials *5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135* are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_fast_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-16 08:19.

Table A100 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, documented fasting)

	QTP N=1092 End of treatment			Pla N=409 End of treatment		
Lab test Baseline	**Low** n^{a} (%)	**Norm** n^{a} (%)	**High** n^{a} (%)	**Low** n^{a} (%)	**Norm** n^{a} (%)	**High** n^{a} (%)
Glucose (mmol/L)						
Low	NA	NA	NA	NA	NA	NA
Norm	0 (0)	825 (98.3)	14 (1.7)	0 (0)	311 (97.8)	7 (2.2)
High	NA	NA	NA	NA	NA	NA
Total	0 (0)	825 (98.3)	14 (1.7)	0 (0)	311 (97.8)	7 (2.2)
HbA1c (%)						
Norm	NA	690 (100)	0 (0)	NA	265 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA
Total	NA	690 (100)	0 (0)	NA	265 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shc_pla_ctrl_fast_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:05

Table A101 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled fasting trials, documented fasting)

	QTP N=1092		Pla N=409	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	839	0 (0)	318	0 (0)
High[b]	839	22 (2.6)	318	7 (2.2)
HbA1c (%)				
High[b]	690	0 (0)	265	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_fast_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:24.

Diabetic risk patients

Table A102 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, documented fasting)

		QTP N=339	Pla N=127
Glucose (mmol/L)			
Patients[a]		279	102
Baseline	Mean (SD)	5.52 (0.66)	5.50 (0.61)
Last value	Mean (SD)	5.46 (0.93)	5.42 (0.95)
Change	Mean (SD)	-0.055 (0.98)	-0.079 (0.97)
	Median	-0.11	-0.078
	Range	-1.94 to 5.89	-3.06 to 4.30
HbA1c (%)			
Patients[a]		240	86
Baseline	Mean (SD)	5.37 (0.39)	5.32 (0.44)
Last value	Mean (SD)	5.43 (0.41)	5.35 (0.46)
Change	Mean (SD)	0.053 (0.29)	0.034 (0.27)
	Median	0.100	0
	Range	-1.40 to 1.40	-0.90 to 0.80
Insulin (pmol/L)			
Patients[a]		273	101
Baseline	Mean (SD)	122.71 (138.05)	104.53 (98.01)
Last value	Mean (SD)	148.84 (245.46)	108.01 (103.96)
Change	Mean (SD)	26.13 (224.91)	3.48 (110.08)
	Median	0	-6.95
	Range	-548.66 to 2146	-620.26 to 493.10
$HOMA_R$			
Patients[a]		263	94
Baseline	Mean (SD)	4.44 (5.34)	3.43 (2.85)
Last value	Mean (SD)	5.51 (11.22)	4.01 (4.65)
Change	Mean (SD)	1.07 (10.82)	0.59 (4.14)
	Median	-0.660	-0.20
	Range	-21.59 to 119.88	-7.71 to 23.19
QUICKI			
Patients[a]		263	94
Baseline	Mean (SD)	0.3270 (0.0348)	0.3330 (0.0333)
Last value	Mean (SD)	0.3297 (0.0421)	0.3327 (0.0388)
Change	Mean (SD)	0.0027 (0.0387)	-0.0003 (0.0341)

Table A102 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, documented fasting)

		QTP N=339	Pla N=127
	Median	0.0000	0.0042
	Range	-0.1433 to 0.1287	-0.1229 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo QTP Quetiapine
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_fast_diab2.SAS. Data version: V91 User: Bengt Franzon, 2007-05-16 08:19.

Table A103 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, documented fasting)

	QTP N=339 End of treatment			Pla N=127 End of treatment		
Lab test Baseline	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**	**Low n[a] (%)**	**Norm n[a] (%)**	**High n[a] (%)**
Glucose (mmol/L)						
Low	NA	NA	NA	NA	NA	NA
Norm	0 (0)	263 (94.3)	16 (5.7)	0 (0)	96 (94.1)	6 (5.9)
High	NA	NA	NA	NA	NA	NA
Total	0 (0)	263 (94.3)	16 (5.7)	0 (0)	96 (94.1)	6 (5.9)
HbA1c (%)						
Norm	NA	240 (100)	0 (0)	NA	86 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA
Total	NA	240 (100)	0 (0)	NA	86 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_she_pla_ctrl_fast_diab2.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 07:04.

Table A104 Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled fasting trials, documented fasting)

	QTP N=339		Pla N=127	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	279	0 (0)	102	0 (0)
High[b]	279	24 (8.6)	102	8 (7.8)
HbA1c (%)				
High[b]	240	0 (0)	86	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_fast_diab2.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 07:23.

Diabetic patients

Table A105 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled fasting trials, documented fasting)

		QTP N=161	Pla N=60
Glucose (mmol/L)			
Patients[a]		132	49
Baseline	Mean (SD)	6.85 (2.15)	6.10 (1.55)
Last value	Mean (SD)	6.90 (2.77)	6.05 (2.18)
Change	Mean (SD)	0.057 (2.80)	-0.045 (2.14)
	Median	0	-0.39
	Range	-8.22 to 13.89	-4.20 to 5.10
HbA1c (%)			
Patients[a]		88	33
Baseline	Mean (SD)	6.35 (0.90)	6.05 (0.87)
Last value	Mean (SD)	6.59 (1.23)	6.05 (0.92)
Change	Mean (SD)	0.24 (0.73)	-0.0030 (0.42)
	Median	0.100	0
	Range	-0.90 to 4.50	-1.70 to 1.10
Insulin (pmol/L)			
Patients[a]		127	48
Baseline	Mean (SD)	171.02 (205.93)	148.75 (121.80)
Last value	Mean (SD)	150.67 (158.63)	119.91 (118.09)
Change	Mean (SD)	-20.35 (211.29)	-28.84 (144.85)
	Median	6.94	-13.89
	Range	-1479 to 548.66	-493.00 to 507.00
$HOMA_B$			
Patients[a]		124	47
Baseline	Mean (SD)	8.47 (12.00)	6.05 (5.53)
Last value	Mean (SD)	7.23 (8.82)	5.50 (7.95)
Change	Mean (SD)	-1.24 (13.39)	-0.56 (8.89)
	Median	0.21	-0.19
	Range	-87.09 to 41.44	-23.06 to 42.25
QUICKI			
Patients[a]		124	47
Baseline	Mean (SD)	0.3117 (0.0451)	0.3148 (0.0386)
Last value	Mean (SD)	0.3148 (0.0434)	0.3268 (0.0437)
Change	Mean (SD)	0.0031 (0.0489)	0.0119 (0.0436)

Table A105 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled fasting trials, documented fasting)

	QTP N=161	Pla N=60
Median	-0.0022	0.0039
Range	-0.1619 to 0.1600	-0.0738 to 0.1443

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_fast_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-16 08.19.

Table A106 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled fasting trials, documented fasting)

	QTP N=161 End of treatment			Pla N=60 End of treatment		
Lab test Baseline	**Low n[a](%)**	**Norm n[a](%)**	**High n[a](%)**	**Low n[a](%)**	**Norm n[a](%)**	**High n[a](%)**
Glucose (mmol/L)						
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	0 (0)	57 (75.0)	19 (25.0)	1 (2.9)	27 (77.1)	7 (20.0)
High	0 (0)	28 (50.0)	28 (50.0)	0 (0)	9 (69.2)	4 (30.8)
Total	0 (0)	85 (64.4)	47 (35.6)	1 (2.0)	37 (75.5)	11 (22.4)
HbA1c (%)						
Norm	NA	74 (90.2)	8 (9.8)	NA	29 (96.7)	1 (3.3)
High	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	75 (85.2)	13 (14.8)	NA	29 (87.9)	4 (12.1)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_she_pla_ctrl_fast_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:04.

Table A107 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled fasting trials, documented fasting)

	QTP N=161		Pla N=60	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	132	0 (0)	48	1 (2.1)
High[b]	76	23 (30.3)	36	8 (22.2)
HbA1c (%)				
High[b]	82	8 (9.8)	30	1 (3.3)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shu_pla_ctrl_fast_diab1.SAS. Data version: V93 User: Bengt Franzon, 2007-05-03 07:23.

IR vs SR data

Non-diabetic patients

Table A108 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

		QTP SR N=537	QTP IR N=555	All QTP N=1092	Pla N=409
Glucose (mmol/L)					
Patients[a]		433	406	839	318
Baseline	Mean (SD)	4.84 (0.43)	4.75 (0.45)	4.79 (0.44)	4.85 (0.46)
Last value	Mean (SD)	5.06 (0.75)	5.01 (0.85)	5.04 (0.80)	5.02 (0.75)
Change	Mean (SD)	0.23 (0.77)	0.26 (0.83)	0.24 (0.80)	0.16 (0.79)
	Median	0.10	0.17	0.17	0.100
	Range	-1.40 to 8.70	-1.94 to 6.83	-1.94 to 8.70	-2.10 to 4.72
HbA1c (%)					
Patients[a]		425	265	690	265
Baseline	Mean (SD)	5.26 (0.39)	5.29 (0.39)	5.27 (0.39)	5.21 (0.37)
Last value	Mean (SD)	5.30 (0.38)	5.29 (0.38)	5.30 (0.38)	5.23 (0.37)
Change	Mean (SD)	0.045 (0.26)	0.0023 (0.24)	0.028 (0.25)	0.011 (0.23)
	Median	0	0	0	0
	Range	-0.70 to 6.90	-0.70 to 0.70	-0.70 to 6.90	-0.80 to 0.80
Insulin (pmol/L)					
Patients[a]		449	404	853	325
Baseline	Mean (SD)	73.45 (86.04)	58.35 (69.81)	66.30 (79.09)	66.29 (66.46)
Last value	Mean (SD)	94.38 (134.60)	93.18 (158.46)	93.81 (146.30)	82.74 (121.69)
Change	Mean (SD)	20.93 (128.78)	34.83 (145.41)	27.51 (137.01)	16.45 (99.33)
	Median	6.95	7.00	6.95	5.21
	Range	-757.00 to 1347	-680.61 to 1632	-757.00 to 1632	-327.00 to 1167
$HOMA_B$					
Patients[a]		408	379	787	304
Baseline	Mean (SD)	2.24 (2.40)	1.81 (2.33)	2.03 (2.38)	2.11 (2.09)
Last value	Mean (SD)	3.31 (5.10)	3.56 (9.05)	3.43 (7.27)	3.06 (6.08)
Change	Mean (SD)	1.07 (4.55)	1.75 (8.71)	1.39 (6.88)	0.95 (5.35)
	Median	0.23	0.31	0.26	0.14
	Range	-14.95 to 51.16	-22.09 to 127.84	-22.09 to 127.84	-11.18 to 71.49
QUICKI					
Patients[a]		408	379	787	304
Baseline	Mean (SD)	0.3552 (0.0365)	0.3699 (0.0400)	0.3623 (0.0389)	0.3610 (0.0402)

Table A108 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

		QTP SR N=537	QTP IR N=555	All QTP N=1092	Pla N=409
Last value	Mean (SD)	0.3463 (0.0420)	0.3546 (0.0456)	0.3503 (0.0439)	0.3543 (0.0442)
Change	Mean (SD)	-0.0089 (0.0420)	-0.0152 (0.0430)	-0.0119 (0.0426)	-0.0067 (0.0397)
	Median	-0.0100	-0.0140	-0.0100	-0.0051
	Range	-0.1600 to 0.1800	-0.2105 to 0.1262	-0.2105 to 0.1800	-0.1830 to 0.1100

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release, Pla Placebo, QTP Quetiapine SR Sustained release.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERMULAB_dtg_pla_ctrl_fast_SR_diab3.SAS. Data version: V91 User: Bengt Franzon, 2007-05-16 08:21.

Table A.109 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

	QTP SR N=537 End of treatment			QTP IR N=555 End of treatment			All QTP N=1092 End of treatment			Pla N=409 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	428 (98.8)	5 (1.2)	0 (0)	397 (97.8)	9 (2.2)	0 (0)	825 (98.3)	14 (1.7)	0 (0)	311 (97.8)	7 (2.2)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	428 (98.8)	5 (1.2)	0 (0)	397 (97.8)	9 (2.2)	0 (0)	825 (98.3)	14 (1.7)	0 (0)	311 (97.8)	7 (2.2)
HbA1c (%)												
Norm	NA	425 (100)	0 (0)	NA	265 (100)	0 (0)	NA	690 (100)	0 (0)	NA	265 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	425 (100)	0 (0)	NA	265 (100)	0 (0)	NA	690 (100)	0 (0)	NA	265 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%): High >=7.5.
Note: Trials 30776/B0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: I:\eg-12cf\Diabetes Mar 07 SERAF\LAB_shr_pla_ctrl_fast_SR_div63.SAS Data version: V5 User: Bengt Franzon 2007-05-03 07:13

Table A110 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

	QTP SR N=537		QTP IR N=555		All QTP N=1092		Pla N=409	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	433	0 (0)	406	0 (0)	839	0 (0)	318	0 (0)
High[b]	433	11 (2.5)	406	11 (2.7)	839	22 (2.6)	318	7 (2.2)
HbA1c (%)								
High[b]	425	0 (0)	265	0 (0)	690	0 (0)	265	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_fast_SR_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:31.

Diabetic risk patients

Table A111 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

		QTP SR N=164	QTP IR N=175	All QTP N=339	Pla N=127
Glucose (mmol/L)					
Patients[a]		145	134	279	102
Baseline	Mean (SD)	5.56 (0.67)	5.48 (0.65)	5.52 (0.66)	5.50 (0.61)
Last value	Mean (SD)	5.61 (1.04)	5.31 (0.78)	5.46 (0.93)	5.42 (0.95)
Change	Mean (SD)	0.049 (1.06)	-0.17 (0.86)	-0.055 (0.98)	-0.079 (0.97)
	Median	-0.10	-0.17	-0.11	-0.078
	Range	-1.94 to 5.89	-1.94 to 3.72	-1.94 to 5.89	-3.06 to 4.30
HbA1c (%)					
Patients[a]		139	101	240	86
Baseline	Mean (SD)	5.38 (0.41)	5.37 (0.35)	5.37 (0.39)	5.32 (0.44)
Last value	Mean (SD)	5.46 (0.42)	5.38 (0.39)	5.43 (0.41)	5.35 (0.46)
Change	Mean (SD)	0.083 (0.30)	0.012 (0.27)	0.053 (0.29)	0.034 (0.27)
	Median	0.100	0	0.100	0
	Range	-0.50 to 1.40	-1.40 to 0.70	-1.40 to 1.40	-0.90 to 0.80
Insulin (pmol/L)					
Patients[a]		140	133	273	101

Table A111 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

		QTP SR N=164	QTP IR N=175	All QTP N=339	Pla N=127
Baseline	Mean (SD)	125.29 (117.28)	120.00 (157.39)	122.71 (138.05)	104.53 (98.01)
Last value	Mean (SD)	178.69 (307.07)	117.42 (151.38)	148.84 (245.46)	108.01 (103.96)
Change	Mean (SD)	53.40 (278.19)	-2.58 (145.34)	26.13 (224.91)	3.48 (110.08)
	Median	6.97	-2.43	0	-6.95
	Range	-548.66 to 2146	-513.93 to 667.00	-548.66 to 2146	-620.26 to 493.10
HOMAR					
Patients[a]		137	126	263	94
Baseline	Mean (SD)	4.41 (4.22)	4.48 (6.36)	4.44 (5.34)	3.43 (2.85)
Last value	Mean (SD)	6.74 (14.38)	4.17 (5.95)	5.51 (11.22)	4.01 (4.65)
Change	Mean (SD)	2.33 (13.82)	-0.30 (5.80)	1.07 (10.82)	0.59 (4.14)
	Median	0.11	-0.076	-0.060	-0.20
	Range	-21.59 to 119.88	-19.78 to 24.99	-21.59 to 119.88	-7.71 to 23.19
QUICKI					
Patients[a]		137	126	263	94
Baseline	Mean (SD)	0.3228 (0.0310)	0.3316 (0.0381)	0.3270 (0.0348)	0.3330 (0.0353)
Last value	Mean (SD)	0.3234 (0.0421)	0.3366 (0.0411)	0.3297 (0.0423)	0.3327 (0.0388)
Change	Mean (SD)	0.0006 (0.0372)	0.0050 (0.0403)	0.0027 (0.0387)	-0.0003 (0.0341)
	Median	0.0000	0.0002	0.0000	0.0042
	Range	-0.1000 to 0.1000	-0.1433 to 0.1287	-0.1433 to 0.1287	-0.1229 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Note: Trials 5077US0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def:Diabetes Mar 07 SERMLAB_chg_pla_ctrl_fast_SR_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-16 08:20.

Table A112 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

	QTP SR N=164 End of treatment			QTP IR N=175 End of treatment			All QTP N=339 End of treatment			Pla N=127 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	132 (91.0)	13 (9.0)	0 (0)	131 (97.8)	3 (2.2)	0 (0)	263 (94.3)	16 (5.7)	0 (0)	96 (94.1)	6 (5.9)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	132 (91.0)	13 (9.0)	0 (0)	131 (97.8)	3 (2.2)	0 (0)	263 (94.3)	16 (5.7)	0 (0)	96 (94.1)	6 (5.9)
HbA1c (%)												
Norm	NA	139 (100)	0 (0)	NA	101 (100)	0 (0)	NA	240 (100)	0 (0)	NA	86 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	139 (100)	0 (0)	NA	101 (100)	0 (0)	NA	240 (100)	0 (0)	NA	86 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def Diabetes Mar 07 SERM/LAB_shc_pla_cnl_fast_SR_diab2.SAS. Data version: V5 User: Bengt Franzon. 2007-05-03 07:15

Table A113 Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

	QTP SR N=164		QTP IR N=175		All QTP N=339		Pla N=127	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	145	0 (0)	134	0 (0)	279	0 (0)	102	0 (0)
High[b]	145	18 (12.4)	134	6 (4.5)	279	24 (8.6)	102	8 (7.8)
HbA1c (%)								
High[b]	139	0 (0)	101	0 (0)	240	0 (0)	86	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_fast_SR_diab2.SAS. Data version: V91 User: Bengt Franzen. 2007-05-03 07:31.

Diabetic subjects

Table A114 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

		QTP SR N=73	QTP IR N=88	All QTP N=161	Pla N=60
Glucose (mmol/L)					
Patients[a]		65	67	132	49
Baseline	Mean (SD)	6.74 (2.09)	6.95 (2.21)	6.85 (2.15)	6.10 (1.55)
Last value	Mean (SD)	6.61 (1.97)	7.19 (3.37)	6.90 (2.77)	6.05 (2.18)
Change	Mean (SD)	-0.14 (2.12)	0.24 (3.34)	0.057 (2.80)	-0.045 (2.14)
	Median	0	0.056	0	-0.39
	Range	-7.10 to 5.17	-8.22 to 13.89	-8.22 to 13.89	-4.20 to 5.10
HbA1c (%)					
Patients[a]		61	27	88	33
Baseline	Mean (SD)	6.34 (0.88)	6.36 (0.97)	6.35 (0.90)	6.05 (0.87)
Last value	Mean (SD)	6.50 (1.03)	6.80 (1.61)	6.59 (1.23)	6.05 (0.92)
Change	Mean (SD)	0.15 (0.50)	0.44 (1.06)	0.24 (0.73)	-0.0030 (0.42)
	Median	0	0.20	0.100	0
	Range	-0.90 to 1.70	-0.50 to 4.50	-0.90 to 4.50	-1.70 to 1.10
Insulin (pmol/L)					
Patients[a]		62	65	127	48
Baseline	Mean (SD)	209.02 (245.57)	134.77 (152.57)	171.02 (205.93)	148.75 (121.80)
Last value	Mean (SD)	194.58 (191.28)	108.78 (104.96)	150.67 (158.63)	119.91 (118.09)
Change	Mean (SD)	-14.43 (250.11)	-25.99 (167.92)	-20.35 (211.29)	-28.84 (144.85)
	Median	3.47	6.95	6.94	-13.89
	Range	-1479 to 548.66	-757.03 to 409.76	-1479 to 548.66	-493.60 to 507.00
$HOMA_B$					
Patients[a]		61	63	124	47
Baseline	Mean (SD)	9.89 (13.48)	7.09 (10.30)	8.47 (12.00)	6.03 (5.53)
Last value	Mean (SD)	8.95 (10.32)	5.56 (6.74)	7.23 (8.82)	5.50 (7.95)
Change	Mean (SD)	-0.94 (14.88)	-1.53 (11.90)	-1.24 (13.39)	-0.56 (8.89)
	Median	0.41	0.18	0.21	-0.19
	Range	-87.09 to 41.44	-58.43 to 22.73	-87.09 to 41.44	-23.06 to 42.25
QUICKI					
Patients[a]		61	63	124	47
Baseline	Mean (SD)	0.3016 (0.0397)	0.3215 (0.0482)	0.3117 (0.0451)	0.3148 (0.0386)
Last value	Mean (SD)	0.3054 (0.0440)	0.3239 (0.0411)	0.3148 (0.0434)	0.3268 (0.0437)

Table A114 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

		QTP SR N=73	QTP IR N=88	All QTP N=161	Plu N=60
Change	Mean (SD)	0.0038 (0.0454)	0.0024 (0.0524)	0.0031 (0.0489)	0.0119 (0.0436)
	Median	0.0000	-0.0032	-0.0022	0.0039
	Range	-0.0800 to 0.1600	-0.1619 to 0.1293	-0.1619 to 0.1600	-0.0738 to 0.1443

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Note: Trials 5077IR/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm. Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_cut_fast_SR_diab1.SAS Data version. V91 User: Bengt Franzon. 2007-05-16 08:20.

Table A115 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

	QTP SR N=73 End of treatment			QTP IR N=88 End of treatment			All QTP N=161 End of treatment			Pla N=60 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	0 (0)	28 (73.7)	10 (26.3)	0 (0)	29 (76.3)	9 (23.7)	0 (0)	57 (75.0)	19 (25.0)	1 (2.9)	27 (77.1)	7 (20.0)
High	0 (0)	15 (55.6)	12 (44.4)	0 (0)	13 (44.8)	16 (55.2)	0 (0)	28 (50.0)	28 (50.0)	0 (0)	9 (69.2)	4 (30.8)
Total	0 (0)	43 (66.2)	22 (33.8)	0 (0)	42 (62.7)	25 (37.3)	0 (0)	85 (64.4)	47 (35.6)	1 (2.0)	37 (75.5)	11 (22.4)
HbA1c (%)												
Norm	NA	52 (91.2)	5 (8.8)	NA	22 (88.0)	3 (12.0)	NA	74 (90.2)	8 (9.8)	NA	29 (96.7)	1 (3.3)
High	NA	1 (25.0)	3 (75.0)	NA	0 (0)	2 (100)	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	53 (86.9)	8 (13.1)	NA	22 (81.5)	5 (18.5)	NA	75 (85.2)	13 (14.8)	NA	29 (87.9)	4 (12.1)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release, Pla Placebo, QTP Quetiapine, SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=3.5, High >=7 for fasting and >=11.1 for non-fasting, HbA1c (%), High >=6.5.
Note: Trials 5077IR49046, D1444C00004, D1444C00122, D1444C00123, D1447C00153 are included in this table.
Pgm: Reg-DoD\Diabetes Mar 07 SER\SER1_AD_sbe_pla_ctrl_fast_SR_diab1.SAS, Data version: 179: User: Bengt Fransson: 2007-05-03 07:12

Table A116 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

	QTP SR N=73		QTP IR N=88		All QTP N=161		Pla N=60	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	65	0 (0)	67	0 (0)	132	0 (0)	48	1 (2.1)
High[b]	38	13 (34.2)	38	10 (26.3)	76	23 (30.3)	36	8 (22.2)
HbA1c (%)								
High[b]	57	5 (8.8)	25	3 (12.0)	82	8 (9.8)	30	1 (3.3)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_fast_SR_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:31.

All diabetic subgroups

Table A117 Mean (SD) change from baseline to end of treatment (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

		QTP SR N=774	QTP IR N=818	All QTP N=1592	Pla N=596
Glucose (mmol/L)					
Patients[a]		643	607	1250	469
Baseline	Mean (SD)	5.19 (1.01)	5.15 (1.12)	5.17 (1.06)	5.12 (0.81)
Last value	Mean (SD)	5.34 (1.11)	5.32 (1.52)	5.33 (1.32)	5.21 (1.08)
Change	Mean (SD)	0.15 (1.05)	0.17 (1.37)	0.16 (1.22)	0.089 (1.05)
	Median	0.100	0.11	0.100	0.056
	Range	-7.10 to 8.70	-8.22 to 13.89	-8.22 to 13.89	-4.20 to 5.10
HbA1c (%)					
Patients[a]		625	393	1018	384
Baseline	Mean (SD)	5.39 (0.56)	5.38 (0.52)	5.39 (0.54)	5.31 (0.51)
Last value	Mean (SD)	5.46 (0.60)	5.42 (0.67)	5.44 (0.63)	5.32 (0.51)
Change	Mean (SD)	0.064 (0.30)	0.035 (0.38)	0.053 (0.33)	0.015 (0.28)
	Median	0	0	0	0
	Range	-0.90 to 1.70	-1.40 to 4.50	-1.40 to 4.50	-1.70 to 1.10
Insulin (pmol/L)					
Patients[a]		651	602	1253	474
Baseline	Mean (SD)	97.51 (124.32)	80.22 (110.37)	89.20 (118.09)	82.79 (85.21)
Last value	Mean (SD)	122.06 (194.44)	100.22 (152.15)	111.56 (175.67)	91.89 (118.35)
Change	Mean (SD)	24.55 (184.89)	20.06 (149.37)	22.36 (168.71)	9.10 (107.68)
	Median	6.95	6.49	6.95	0
	Range	-1479 to 2146	-757.01 to 1632	-1479 to 2146	-620.26 to 1167
$HOMA_R$					
Patients[a]		606	568	1174	445
Baseline	Mean (SD)	3.50 (5.59)	2.99 (5.24)	3.25 (5.43)	2.81 (3.06)
Last value	Mean (SD)	4.65 (8.87)	3.91 (8.23)	4.30 (8.57)	3.52 (6.07)
Change	Mean (SD)	1.15 (8.92)	0.93 (8.66)	1.04 (8.79)	0.72 (5.61)
	Median	0.20	0.20	0.20	0.070
	Range	-87.09 to 119.88	-58.43 to 127.84	-87.09 to 127.84	-23.06 to 71.49
QUICKI					
Patients[a]		606	568	1174	445
Baseline	Mean (SD)	0.3425 (0.0404)	0.3560 (0.0451)	0.3490 (0.0433)	0.3502 (0.0420)
Last value	Mean (SD)	0.3370 (0.0445)	0.3472 (0.0455)	0.3419 (0.0452)	0.3469 (0.0443)

Table A117 Mean (SD) change from baseline to end of treatment (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

		QTP SR N=774	QTP IR N=818	All QTP N=1592	Pla N=596
Change	Mean (SD)	-0.0055 (0.0416)	-0.0088 (0.0444)	-0.0071 (0.0430)	-0.0034 (0.0394)
	Median	-0.0100	-0.0090	-0.0094	0.0000
	Range	-0.1600 to 0.1800	-0.2105 to 0.1293	-0.2105 to 0.1800	-0.1830 to 0.1443

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Note: Trials 5077US00046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM3LAB_chg_pla_cut_fast_SR.SAS. Data version: V91 User: Bengt Franzon. 2007-05-16 08:21.

Table A118 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

	QTP SR N=774 End of treatment			QTP IR N=818 End of treatment			All QTP N=1592 End of treatment			Pla N=596 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	6 (0)	388 (95.5)	28 (4.5)	0 (0)	557 (96.4)	21 (3.6)	0 (0)	1145 (95.9)	49 (4.1)	1 (0.22)	434 (95.4)	20 (4.4)
High	0 (0)	15 (55.6)	12 (44.4)	0 (0)	13 (44.8)	16 (55.2)	0 (0)	28 (50.0)	28 (50.0)	0 (0)	9 (69.2)	4 (30.8)
Total	6 (0)	603 (93.8)	40 (6.2)	0 (0)	570 (93.9)	37 (6.1)	0 (0)	1173 (93.8)	77 (6.2)	1 (0.21)	444 (94.7)	24 (5.1)
HbA1c (%)												
Norm	NA	616 (99.2)	5 (0.81)	NA	388 (99.2)	3 (0.77)	NA	1004 (99.2)	8 (0.79)	NA	380 (99.7)	1 (0.26)
High	NA	1 (25.0)	3 (75.0)	NA	0 (0)	2 (100)	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	617 (98.7)	8 (1.3)	NA	388 (98.7)	5 (1.3)	NA	1005 (98.7)	13 (1.3)	NA	380 (99.0)	4 (1.0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >=7.5.
Note: Trials 5077IR0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg:/Gef/Diabetes Mar07/SERM/LAb_she_pbl_uni_fast_SR.SAS Data version: V81 User: Hengs Francois. 2007-05-03 02:13.

Table A119 Shift to clinically important lab values at any time (All placebo-controlled fasting trials, documented fasting, separating immediate and sustained release)

	QTP SR N=774		QTP IR N=818		All QTP N=1592		Pla N=596	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	643	0 (0)	607	0 (0)	1250	0 (0)	468	1 (0.21)
High[b]	616	42 (6.8)	578	27 (4.7)	1194	69 (5.8)	456	23 (5.0)
HbA1c (%)								
High[b]	621	5 (0.81)	391	3 (0.77)	1012	8 (0.79)	381	1 (0.26)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Trials 5077US/0046, D1444C00004, D1444C00132, D1444C00133, D1447C00135 are included in this table.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_fast_SR.SAS. Data version: V9I User: Bengt Franzon. 2007-05-03 07:32.

Placebo-controlled trials >12 weeks

All diabetic subgroups

Table A120 Mean (SD) change from baseline to end of treatment (All placebo-controlled trials >12 weeks)

		QTP N=95	Pla N=102
Glucose (mmol/L)			
Patients[a]		84	76
Baseline	Mean (SD)	5.15 (0.75)	5.32 (0.67)
Last value	Mean (SD)	5.52 (1.26)	5.47 (1.11)
Change	Mean (SD)	0.37 (1.23)	0.15 (1.10)
	Median	0.100	0.100
	Range	-1.60 to 8.70	-2.50 to 5.10
HbA1c (%)			
Patients[a]		95	88
Baseline	Mean (SD)	5.19 (0.45)	5.24 (0.39)
Last value	Mean (SD)	5.34 (0.42)	5.27 (0.43)
Change	Mean (SD)	0.14 (0.31)	0.031 (0.30)
	Median	0.10	0
	Range	-0.50 to 0.90	-0.80 to 0.80
Insulin (pmol/L)			
Patients[a]		94	88
Baseline	Mean (SD)	92.76 (100.07)	85.89 (81.79)
Last value	Mean (SD)	95.66 (127.44)	119.13 (137.76)
Change	Mean (SD)	2.90 (147.09)	33.24 (110.22)
	Median	0	7.00
	Range	-424.00 to 952.00	-243.00 to 507.00
$HOMA_B$			
Patients[a]		77	72
Baseline	Mean (SD)	3.42 (4.13)	3.19 (3.17)
Last value	Mean (SD)	4.06 (6.90)	4.99 (8.56)
Change	Mean (SD)	0.64 (7.52)	1.80 (7.36)
	Median	0.11	0.18
	Range	-14.95 to 49.76	-11.18 to 42.25
QUICKI			
Patients[a]		77	72
Baseline	Mean (SD)	0.3438 (0.0427)	0.3443 (0.0426)
Last value	Mean (SD)	0.3409 (0.0433)	0.3350 (0.0456)

Table A120 Mean (SD) change from baseline to end of treatment (All placebo-controlled trials >12 weeks)

		QTP N=95	Pla N=102
Change	Mean (SD)	-0.0029 (0.0472)	-0.0093 (0.0382)
	Median	0.0000	0.0000
	Range	-0.1000 to 0.1800	-0.1100 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_long.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:42.

Table A121 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled trials >12 weeks)

	QTP N=95 End of treatment			Pla N=102 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)						
Low	NA	NA	NA	NA	NA	NA
Norm	0 (0)	79 (95.2)	4 (4.8)	0 (0)	70 (92.1)	6 (7.9)
High	0 (0)	0 (0)	1 (100)	NA	NA	NA
Total	0 (0)	79 (94.0)	5 (6.0)	0 (0)	70 (92.1)	6 (7.9)
HbA1c (%)						
Norm	NA	95 (100)	0 (0)	NA	88 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA
Total	NA	95 (100)	0 (0)	NA	88 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shc_pla_ctrl_long.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:09.

Table A122 Shift to clinically important lab values at any time (All placebo-controlled trials >12 weeks)

	QTP N=95		Pla N=102	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	84	0 (0)	76	0 (0)
High[b]	83	7 (8.4)	76	6 (7.9)
HbA1c (%)				
High[b]	95	0 (0)	88	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L). Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%). High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_long.SAS. Data version: V91 User: Bengt Franzen. 2007-05-03 07:27.

IR vs SR data

Non-diabetic subjects

Table A123 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

		QTP SR N=70	All QTP N=70	Pla N=78
Glucose (mmol/L)				
Patients[a]		59	59	58
Baseline	Mean (SD)	4.81 (0.46)	4.81 (0.46)	5.21 (0.70)
Last value	Mean (SD)	5.28 (1.33)	5.28 (1.33)	5.33 (1.00)
Change	Mean (SD)	0.48 (1.30)	0.48 (1.30)	0.12 (1.06)
	Median	0.20	0.20	0.100
	Range	-0.90 to 8.70	-0.90 to 8.70	-2.50 to 3.50
HbA1c (%)				
Patients[a]		70	70	67
Baseline	Mean (SD)	5.20 (0.44)	5.20 (0.44)	5.19 (0.39)
Last value	Mean (SD)	5.34 (0.37)	5.34 (0.37)	5.19 (0.39)
Change	Mean (SD)	0.14 (0.30)	0.14 (0.30)	-0.0045 (0.31)
	Median	0.10	0.10	0
	Range	-0.50 to 0.90	-0.50 to 0.90	-0.80 to 0.80
Insulin (pmol/L)				
Patients[a]		69	69	67
Baseline	Mean (SD)	79.65 (87.11)	79.65 (87.11)	75.79 (76.82)
Last value	Mean (SD)	80.48 (70.25)	80.48 (70.25)	111.60 (131.71)
Change	Mean (SD)	0.83 (92.76)	0.83 (92.70)	35.81 (93.75)
	Median	0	0	7.00
	Range	-424.00 to 326.00	-424.00 to 326.00	-230.00 to 417.00
$HOMA_B$				
Patients[a]		52	52	55
Baseline	Mean (SD)	2.58 (2.93)	2.58 (2.93)	2.81 (2.98)
Last value	Mean (SD)	3.24 (3.77)	3.24 (3.77)	4.53 (7.40)
Change	Mean (SD)	0.66 (4.23)	0.66 (4.23)	1.72 (5.74)
	Median	0.21	0.21	0.30
	Range	-14.95 to 19.71	-14.95 to 19.71	-11.18 to 34.05
QUICKI				
Patients[a]		52	52	55
Baseline	Mean (SD)	0.3537 (0.0413)	0.3537 (0.0413)	0.3495 (0.0411)

Table A123 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

		QTP SR N=70	All QTP N=70	Pla N=78
Last value	Mean (SD)	0.3448 (0.0414)	0.3448 (0.0414)	0.3384 (0.0465)
Change	Mean (SD)	-0.0088 (0.0487)	-0.0088 (0.0487)	-0.0111 (0.0379)
	Median	-0.0050	-0.0050	-0.0100
	Range	-0.1000 to 0.1800	-0.1000 to 0.1800	-0.1100 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Note: Only treatments with existing patients are shown.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_long_SR_diab3.SAS. Data version: V91 User: Bengt Franzen. 2007-05-03 12:51.

Table A124 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

	QTP SR N=70 End of treatment			All QTP N=70 End of treatment			Pla N=78 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)									
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	58 (98.3)	1 (1.7)	0 (0)	58 (98.3)	1 (1.7)	0 (0)	54 (93.1)	4 (6.9)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	58 (98.3)	1 (1.7)	0 (0)	58 (98.3)	1 (1.7)	0 (0)	54 (93.1)	4 (6.9)
HbA1c (%)									
Norm	NA	70 (100)	0 (0)	NA	70 (100)	0 (0)	NA	67 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	70 (100)	0 (0)	NA	70 (100)	0 (0)	NA	67 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L) Low <=2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >7.5.
Note: Only treatments with existing patients are shown.
Pgm: Reg-Def/Diabetes Mar 07 SERM-LAB_shc_plo_chi_long_SR_diab3.SAS. Data version: V01 User: Bengt Franzon 2007-05-03 07:16.

Table A125 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

	QTP SR N=70		All QTP N=70		Pla N=78	
	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)						
Low[a]	59	0 (0)	59	0 (0)	58	0 (0)
High[b]	59	2 (3.4)	59	2 (3.4)	58	4 (6.9)
HbA1c (%)						
High[b]	70	0 (0)	70	0 (0)	67	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Only treatments with existing patients are shown
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_long_SR_diab3.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:55.

Diabetic risk subjects

Table A126 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

		QTP SR N=23	All QTP N=23	Pla N=19
Glucose (mmol/L)				
Patients[a]		23	23	14
Baseline	Mean (SD)	5.89 (0.58)	5.89 (0.58)	5.68 (0.34)
Last value	Mean (SD)	6.03 (0.84)	6.03 (0.84)	5.67 (0.44)
Change	Mean (SD)	0.14 (1.08)	0.14 (1.08)	-0.0071 (0.39)
	Median	-0.100	-0.100	0.050
	Range	-1.60 to 2.50	-1.60 to 2.50	-0.60 to 0.80
HbA1c (%)				
Patients[a]		23	23	17
Baseline	Mean (SD)	5.13 (0.43)	5.13 (0.43)	5.34 (0.32)
Last value	Mean (SD)	5.23 (0.33)	5.23 (0.33)	5.46 (0.41)
Change	Mean (SD)	0.10 (0.28)	0.10 (0.28)	0.12 (0.27)
	Median	0.10	0.10	0.10
	Range	-0.40 to 0.60	-0.40 to 0.60	-0.30 to 0.80
Insulin (pmol/L)				
Patients[a]		23	23	17
Baseline	Mean (SD)	114.17 (105.12)	114.17 (105.12)	103.41 (77.61)
Last value	Mean (SD)	124.78 (219.14)	124.78 (219.14)	124.94 (93.93)
Change	Mean (SD)	10.61 (242.39)	10.61 (242.39)	21.53 (98.32)
	Median	-6.00	-6.00	6.00
	Range	-389.00 to 952.00	-389.00 to 952.00	-153.00 to 292.00
$HOMA_R$				
Patients[a]		23	23	13
Baseline	Mean (SD)	4.38 (4.14)	4.38 (4.14)	3.66 (2.90)
Last value	Mean (SD)	5.63 (11.22)	5.63 (11.22)	4.15 (3.89)
Change	Mean (SD)	1.25 (12.00)	1.25 (12.00)	0.48 (4.46)
	Median	-0.47	-0.47	0.14
	Range	-12.68 to 49.76	-12.68 to 49.76	-6.48 to 13.43
QUICKI				
Patients[a]		23	23	13
Baseline	Mean (SD)	0.3270 (0.0372)	0.3270 (0.0372)	0.3331 (0.0435)
Last value	Mean (SD)	0.3361 (0.0472)	0.3361 (0.0472)	0.3246 (0.0341)

Table A126 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

		QTP SR N=23	All QTP N=23	Pla N=19
Change	Mean (SD)	0.0091 (0.0439)	0.0091 (0.0439)	-0.0085 (0.0363)
	Median	0.0100	0.0100	0.0000
	Range	-0.0800 to 0.0800	-0.0800 to 0.0800	-0.0700 to 0.0400

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Note: Only treatments with existing patients are shown.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_long_SR_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:51.

Table A127 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

	QTP SR N=23 End of treatment			All QTP N=23 End of treatment			Pla N=19 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)									
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	20 (87.0)	3 (13.0)	0 (0)	20 (87.0)	3 (13.0)	0 (0)	13 (92.9)	1 (7.1)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	20 (87.0)	3 (13.0)	0 (0)	20 (87.0)	3 (13.0)	0 (0)	13 (92.9)	1 (7.1)
HbA1c (%)									
Norm	NA	23 (100)	0 (0)	NA	23 (100)	0 (0)	NA	17 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	23 (100)	0 (0)	NA	23 (100)	0 (0)	NA	17 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline

Pla Placebo. QTP Quetiapine. SR Sustained release.

Clinically important limits are: Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >=7.5.

Note: Only treatment with existing patients are shown

Pgm: Reg-DiaPDiabetes Mar07 SEROMH_MH_dbc_pla_str_long_SR_diab7.SAS. Data version: V01 User: Bengt Fraszon 2007-05-03 07:16.

Table A128 Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

	QTP SR N=23		All QTP N=23		Pla N=19	
	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)						
Low[a]	23	0 (0)	23	0 (0)	14	0 (0)
High[b]	23	5 (21.7)	23	5 (21.7)	14	1 (7.1)
HbA1c (%)						
High[b]	23	0 (0)	23	0 (0)	17	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Only treatments with existing patients are shown
Pgm. Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_long_SR_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:54.

Diabetic subjects

Table A129 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

		QTP SR N=2	All QTP N=2	Pla N=5
Glucose (mmol/L)				
Patients[a]		2	2	4
Baseline	Mean (SD)	6.85 (1.34)	6.85 (1.34)	5.75 (0.60)
Last value	Mean (SD)	6.65 (1.34)	6.65 (1.34)	6.83 (2.80)
Change	Mean (SD)	-0.20	-0.20	1.08 (2.70)
	Median	-0.20	-0.20	-0.15
	Range	-0.20 to -0.20	-0.20 to -0.20	-0.50 to 5.10
HbA1c (%)				
Patients[a]		2	2	4
Baseline	Mean (SD)	5.85 (0.92)	5.85 (0.92)	5.65 (0.42)
Last value	Mean (SD)	6.55 (1.20)	6.55 (1.20)	5.88 (0.54)
Change	Mean (SD)	0.70 (0.28)	0.70 (0.28)	0.22 (0.22)
	Median	0.70	0.70	0.20
	Range	0.50 to 0.90	0.50 to 0.90	0 to 0.50
Insulin (pmol/L)				
Patients[a]		2	2	4
Baseline	Mean (SD)	298.50 (255.27)	298.50 (255.27)	180.50 (126.78)
Last value	Mean (SD)	284.50 (108.19)	284.50 (108.19)	220.50 (326.28)
Change	Mean (SD)	-14.00 (363.45)	-14.00 (363.45)	40.00 (326.17)
	Median	-14.00	-14.00	-52.00
	Range	-271.00 to 243.00	-271.00 to 243.00	-243.00 to 507.00
$HOMA_B$				
Patients[a]		2	2	4
Baseline	Mean (SD)	14.19 (13.75)	14.19 (13.75)	6.86 (4.84)
Last value	Mean (SD)	7.21 (4.12)	7.21 (4.12)	13.98 (23.93)
Change	Mean (SD)	-6.98 (9.64)	-6.98 (9.64)	7.13 (23.73)
	Median	-6.98	-6.98	-2.13
	Range	-13.79 to -0.16	-13.79 to -0.16	-9.49 to 42.25
QUICKI				
Patients[a]		2	2	4
Baseline	Mean (SD)	0.2800 (0.0424)	0.2800 (0.0424)	0.3100 (0.0483)
Last value	Mean (SD)	0.2950 (0.0212)	0.2950 (0.0212)	0.3225 (0.0680)

Table A129 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

		QTP SR N=2	All QTP N=2	Pla N=5
Change	Mean (SD)	0.0150 (0.0212)	0.0150 (0.0212)	0.0125 (0.0519)
	Median	0.0150	0.0150	0.0300
	Range	0.0000 to 0.0300	0.0000 to 0.0300	-0.0600 to 0.0500

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Note: Only treatments with existing patients are shown.

Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl_long_SR_diabl.SAS. Data version: V91 User: Bengt Franzen. 2007-05-03 12:50

Table A130 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

	QTP SR N=2 End of treatment			All QTP N=2 End of treatment			Pla N=5 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)									
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	3 (75.0)	1 (25.0)
High	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	NA	NA	NA
Total	0 (0)	1 (50.0)	1 (50.0)	0 (0)	1 (50.0)	1 (50.0)	0 (0)	3 (75.0)	1 (25.0)
HbA1c (%)									
Norm	NA	2 (100)	0 (0)	NA	2 (100)	0 (0)	NA	4 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	2 (100)	0 (0)	NA	2 (100)	0 (0)	NA	4 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%): High: >7.5.
Note. Only treatments with existing patients are shown
Pgm: Reg-Def/Diabetes Mar 07 SERSI-LSH_shc_pls_cni_long_SR_diab1.SAS. Data version: V91 User: Bengt Franzon 2007-05-03 07.16

Table A131 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

	QTP SR N=2		All QTP N=2		Pla N=5	
	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)						
Low[a]	2	0 (0)	2	0 (0)	4	0 (0)
High[b]	1	0 (0)	1	0 (0)	4	1 (25.0)
HbA1c (%)						
High[b]	2	0 (0)	2	0 (0)	4	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Only treatments with existing patients are shown
Pgm: Reg-Def-Diabetes Mar 07 SER4001_AB_sha_pla_ctrl_long_SR_diabt.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:54.

All diabetic subgroups

Table A132 Mean (SD) change from baseline to end of treatment (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

		QTP SR N=95	All QTP N=95	Pla N=102
Glucose (mmol/L)				
Patients[a]		84	84	76
Baseline	Mean (SD)	5.15 (0.75)	5.15 (0.75)	5.32 (0.67)
Last value	Mean (SD)	5.52 (1.26)	5.52 (1.26)	5.47 (1.11)
Change	Mean (SD)	0.37 (1.23)	0.37 (1.23)	0.15 (1.10)
	Median	0.100	0.100	0.100
	Range	-1.60 to 8.70	-1.60 to 8.70	-2.50 to 5.10
HbA1c (%)				
Patients[a]		95	95	88
Baseline	Mean (SD)	5.19 (0.45)	5.19 (0.45)	5.24 (0.39)
Last value	Mean (SD)	5.34 (0.42)	5.34 (0.42)	5.27 (0.43)
Change	Mean (SD)	0.14 (0.31)	0.14 (0.31)	0.031 (0.30)
	Median	0.10	0.10	0
	Range	-0.50 to 0.90	-0.50 to 0.90	-0.80 to 0.80
Insulin (pmol/L)				
Patients[a]		94	94	88
Baseline	Mean (SD)	92.76 (100.07)	92.76 (100.07)	85.89 (81.79)
Last value	Mean (SD)	95.66 (127.44)	95.66 (127.44)	119.13 (137.76)
Change	Mean (SD)	2.90 (147.09)	2.90 (147.09)	33.24 (110.22)
	Median	0	0	7.60
	Range	-424.00 to 952.00	-424.00 to 952.00	-243.00 to 567.00
$HOMA_{IR}$				
Patients[a]		77	77	72
Baseline	Mean (SD)	3.42 (4.13)	3.42 (4.13)	3.19 (3.17)
Last value	Mean (SD)	4.06 (6.90)	4.06 (6.90)	4.99 (8.56)
Change	Mean (SD)	0.64 (7.52)	0.64 (7.52)	1.80 (7.36)
	Median	0.11	0.11	0.18
	Range	-14.95 to 49.76	-14.95 to 49.76	-11.18 to 42.25
QUICKI				
Patients[a]		77	77	72
Baseline	Mean (SD)	0.3438 (0.0427)	0.3438 (0.0427)	0.3443 (0.0426)
Last value	Mean (SD)	0.3409 (0.0433)	0.3409 (0.0433)	0.3350 (0.0456)

Table A132 Mean (SD) change from baseline to end of treatment (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

		QTP SR N=95	All QTP N=95	Pla N=102
Change	Mean (SD)	-0.0029 (0.0472)	-0.0029 (0.0472)	-0.0093 (0.0382)
	Median	0.0000	0.0000	0.0000
	Range	-0.1000 to 0.1800	-0.1000 to 0.1800	-0.1100 to 0.0800

* Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla: Placebo, QTP: Quetiapine, SR: Sustained release.
Note: Only treatments with existing patients are shown
Pgm: Reg-Def\Diabetes Mar 07 SERMUAB_chg_pla_ctrl_long_SR.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:52.

Table A133 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

	QTP SR N=95 End of treatment			All QTP N=95 End of treatment			Pla N=102 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)									
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	79 (95.2)	4 (4.8)	0 (0)	79 (95.2)	4 (4.8)	0 (0)	70 (92.1)	6 (7.9)
High	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	NA	NA	NA
Total	0 (0)	79 (94.0)	5 (6.0)	0 (0)	79 (94.0)	5 (6.0)	0 (0)	70 (92.1)	6 (7.9)
HbA1c (%)									
Norm	NA	95 (100)	0 (0)	NA	95 (100)	0 (0)	NA	88 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	95 (100)	0 (0)	NA	95 (100)	0 (0)	NA	88 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline
Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L) Low < =2.5, High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >7.5.
Note: Only treatments with existing patients are shown
Pgm: Reg/Def/Diabetes Mar 07 SERAFL33I_shc_pla_ctrl_long_SR.SAS. Data version: V91 User: Bengt Fransson. 2007-05-03 07:17.

Table A134 Shift to clinically important lab values at any time (All placebo-controlled trials >12 weeks, separating immediate and sustained release)

	QTP SR N=95		All QTP N=95		Pla N=102	
	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)						
Low[a]	84	0 (0)	84	0 (0)	76	0 (0)
High[b]	83	7 (8.4)	83	7 (8.4)	76	6 (7.9)
HbA1c (%)						
High[b]	95	0 (0)	95	0 (0)	88	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: Only treatments with existing patients are shown
Pgm: Reg-DefDiabetes Mar 07 SERMVLAB_sha_pla_ctrl_long_SR.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:35.

Placebo-controlled monotherapy trials

Adverse event potentially related to DM

Table A135 Number of patients with adverse events related to diabetes (Placebo-controlled monotherapy trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Any[e]	Quetiapine	24 (0)	3242	357.8 (359.3)	0.74 (0.00)	6.7 (0.0)
	Placebo	9 (1)	1389	159.6 (160.4)	0.55 (0.07)	5.6 (0.6)
Diabetic Ketoacidosis	Quetiapine	0 (0)	3242	359.3 (359.3)	0.00 (0.00)	0.0 (0.0)
	Placebo	0 (0)	1389	160.4 (160.4)	0.00 (0.00)	0.0 (0.0)
Polydipsia	Quetiapine	2 (0)	3242	359.2 (359.3)	0.06 (0.00)	0.6 (0.0)
	Placebo	0 (0)	1389	160.4 (160.4)	0.00 (0.00)	0.0 (0.0)
Polyuria	Quetiapine	3 (0)	3242	359.2 (359.3)	0.09 (0.00)	0.8 (0.0)
	Placebo	2 (0)	1389	160.1 (160.4)	0.14 (0.00)	1.2 (0.0)
Thirst	Quetiapine	8 (0)	3242	358.4 (359.3)	0.25 (0.00)	2.2 (0.0)
	Placebo	5 (0)	1389	159.8 (160.4)	0.36 (0.00)	3.1 (0.0)
Hyperglycaemia	Quetiapine	11 (0)	3242	359.0 (359.3)	0.34 (0.00)	3.1 (0.0)
	Placebo	1 (0)	1389	160.4 (160.4)	0.07 (0.00)	0.6 (0.0)
Diabetes mellitus	Quetiapine	1 (0)	3242	359.3 (359.3)	0.03 (0.00)	0.3 (0.0)
	Placebo	1 (1)	1389	160.4 (160.4)	0.07 (0.07)	0.6 (0.6)
Urine glucose abnormalities	Quetiapine	0 (0)	3242	359.3 (359.3)	0.00 (0.00)	0.0 (0.0)

Table A135 Number of patients with adverse events related to diabetes (Placebo-controlled monotherapy trials)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
	Placebo	0 (0)	1389	160.4 (160.4)	0.00 (0.00)	0.0 (0.0)

[a] Patients must have received at least one dose of trial medication.
[b] Exposure in patient-years, censored at first event.
[c] 100 x total number of patients with event/total number of patients.
[d] 100 x total number of patients with event/total patient years of exposure.
[e] The number of patients with any of the adverse events. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Pgm: Reg-Def.Diabetes Mar 07 SERM\...\AE_pla_mono_cnl SAS. Data version: V9.1 User: Malin Dreyer 2007-05-02 20:24.

Laboratory data

Non-diabetic patients

Table A136 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled monotherapy trials)

		QTP N=2518	Pla N=1115
Glucose (mmol/L)			
Patients[a]		1990	937
Baseline	Mean (SD)	5.06 (0.85)	5.21 (1.04)
Last value	Mean (SD)	5.28 (1.17)	5.29 (1.16)
Change	Mean (SD)	0.22 (1.14)	0.078 (1.21)
	Median	0.11	0
	Range	-4.80 to 9.50	-6.83 to 8.00
HbA1c (%)			
Patients[a]		801	305
Baseline	Mean (SD)	5.28 (0.39)	5.23 (0.37)
Last value	Mean (SD)	5.31 (0.39)	5.24 (0.36)
Change	Mean (SD)	0.034 (0.25)	0.016 (0.25)
	Median	0	0
	Range	-0.70 to 1.10	-0.80 to 0.80
Insulin (pmol/L)			
Patients[a]		1215	486
Baseline	Mean (SD)	74.36 (94.38)	75.95 (140.22)
Last value	Mean (SD)	111.87 (170.05)	92.71 (139.00)
Change	Mean (SD)	37.71 (163.53)	16.76 (178.76)
	Median	7.00	6.95
	Range	-730.90 to 2290	-1875 to 1820
$HOMA_B$			
Patients[a]		1096	452
Baseline	Mean (SD)	2.25 (3.28)	2.70 (8.70)
Last value	Mean (SD)	4.01 (8.03)	3.27 (6.62)
Change	Mean (SD)	1.76 (7.73)	0.57 (10.55)
	Median	0.32	0.23
	Range	-35.70 to 127.84	-137.15 to 87.11
QUICKI			
Patients[a]		1096	452
Baseline	Mean (SD)	0.3167 (0.0915)	0.3092 (0.0949)
Last value	Mean (SD)	0.3044 (0.0914)	0.3012 (0.0959)

Table A136 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled monotherapy trials)

		QTP N=2518	Pla N=1115
Change	Mean (SD)	-0.0123 (0.0397)	-0.0080 (0.0389)
	Median	-0.0100	-0.0076
	Range	-0.2105 to 0.1800	-0.1830 to 0.1860

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Pgm: Reg-Def\Diabetes Mar 07 SER\MLAB_chg_pla_mono_diab3.SAS. Data version: V93 User: Bengt Franzon. 2007-05-03 12:44.

Table A137 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled monotherapy trials)

	QTP N=2518 *End of treatment*			Pla N=1115 *End of treatment*		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)						
Low	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Norm	4 (0.20)	1960 (98.5)	25 (1.3)	2 (0.21)	921 (98.4)	13 (1.4)
High	NA	NA	NA	NA	NA	NA
Total	4 (0.20)	1961 (98.5)	25 (1.3)	2 (0.21)	922 (98.4)	13 (1.4)
HbA1c (%)						
Norm	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA
Total	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SER\MLAB_she_pla_mono_diab3.SAS. Data version: V93 User: Bengt Franzon. 2007-05-03 07:16.

Table A138 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled monotherapy trials)

	QTP N=2518		Pla N=1115	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	1989	9 (0.45)	936	6 (0.64)
High[b]	1990	40 (2.0)	937	13 (1.4)
HbA1c (%)				
High[b]	801	0 (0)	305	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: > 7.5.
Pgm: Reg-DefDiabetes Mar 07 SERM/LAB_sbs_pla_mono_diab3.SAS. Data version: V9I User: Bengt Fristrom. 2007-05-03 07.28.

Diabetic risk patients

Table A139 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled monotherapy trials)

		QTP N=502	Pla N=194
Glucose (mmol/L)			
Patients[a]		426	162
Baseline	Mean (SD)	5.50 (0.80)	5.37 (0.71)
Last value	Mean (SD)	5.53 (1.22)	5.35 (1.04)
Change	Mean (SD)	0.031 (1.16)	-0.014 (0.94)
	Median	-0.056	-0.056
	Range	-3.30 to 8.22	-3.06 to 4.50
HbA1c (%)			
Patients[a]		272	98
Baseline	Mean (SD)	5.38 (0.38)	5.32 (0.43)
Last value	Mean (SD)	5.43 (0.41)	5.35 (0.45)
Change	Mean (SD)	0.056 (0.29)	0.023 (0.27)
	Median	0.100	0
	Range	-1.40 to 1.40	-0.90 to 0.80
Insulin (pmol/L)			
Patients[a]		349	144
Baseline	Mean (SD)	136.09 (160.54)	118.47 (103.42)
Last value	Mean (SD)	183.57 (271.75)	133.14 (134.22)
Change	Mean (SD)	47.48 (269.20)	14.67 (138.09)

Table A139 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled monotherapy trials)

		QTP N=502	Pla N=194
	Median	6.00	0
	Range	-951.47 to 2146	-620.26 to 888.96
$HOMA_R$			
Patients[a]		331	131
Baseline	Mean (SD)	4.84 (6.39)	3.93 (3.51)
Last value	Mean (SD)	6.67 (12.52)	4.62 (5.83)
Change	Mean (SD)	1.83 (12.62)	0.69 (5.66)
	Median	0.17	-0.028
	Range	-34.93 to 119.88	-21.59 to 40.41
QUICKI			
Patients[a]		331	131
Baseline	Mean (SD)	0.3013 (0.0728)	0.2882 (0.0859)
Last value	Mean (SD)	0.3014 (0.0795)	0.2870 (0.0881)
Change	Mean (SD)	0.0002 (0.0384)	-0.0012 (0.0312)
	Median	-0.0006	0.0000
	Range	-0.1435 to 0.1287	-0.1229 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Pgm: Reg-Def-Diabetes Mar 07 SERMAB_chg_pla_mono_diab2.SAS, Data version: V91 User: Bengt Franzon, 2007-05-03 12:43.

Table A140 Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled monotherapy trials)

	QTP N=502 End of treatment			Pla N=194 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)						
Low	NA	NA	NA	NA	NA	NA
Norm	0 (0)	410 (96.2)	16 (3.8)	0 (0)	155 (95.7)	7 (4.3)
High	NA	NA	NA	NA	NA	NA
Total	0 (0)	410 (96.2)	16 (3.8)	0 (0)	155 (95.7)	7 (4.3)
HbA1c (%)						
Norm	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA
Total	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%): High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_she_pla_mono_diab2.SAS. Data version: V91 User: Bengt Franzon 2007-05-03 07:09.

Table A141 Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled monotherapy trials)

	QTP N=502		Pla N=194	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	426	0 (0)	162	0 (0)
High[b]	426	28 (6.6)	162	9 (5.6)
HbA1c (%)				
High[b]	272	0 (0)	98	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_mono_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:2

Diabetic patients

Table A142 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled monotherapy trials)

		QTP N=222	Pla N=80
Glucose (mmol/L)			
Patients[a]		187	76
Baseline	Mean (SD)	7.58 (3.17)	7.06 (2.84)
Last value	Mean (SD)	7.53 (3.86)	6.74 (3.10)
Change	Mean (SD)	-0.051 (3.53)	-0.32 (3.27)
	Median	0	-0.25
	Range	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)			
Patients[a]		100	40
Baseline	Mean (SD)	6.31 (0.88)	6.03 (0.85)
Last value	Mean (SD)	6.55 (1.19)	5.96 (0.91)
Change	Mean (SD)	0.23 (0.69)	-0.050 (0.45)
	Median	0.100	0
	Range	-0.90 to 4.50	-1.70 to 1.10
Insulin (pmol/L)			
Patients[a]		149	59
Baseline	Mean (SD)	169.87 (197.90)	173.96 (261.50)
Last value	Mean (SD)	175.36 (207.41)	134.77 (130.45)
Change	Mean (SD)	5.38 (246.71)	-39.19 (278.54)

Table A142 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled monotherapy trials)

		QTP N=222	Pla N=80
	Median	6.95	-12.08
	Range	-1479 to 1445	-1799 to 507.00
$HOMA_B$			
Patients[a]		139	57
Baseline	Mean (SD)	8.13 (11.52)	7.97 (17.54)
Last value	Mean (SD)	8.04 (11.73)	6.02 (8.05)
Change	Mean (SD)	-0.087 (15.46)	-1.95 (18.99)
	Median	0.20	-0.10
	Range	-87.09 to 92.99	-127.11 to 42.25
QUICKI			
Patients[a]		139	57
Baseline	Mean (SD)	0.3044 (0.0569)	0.3060 (0.0572)
Last value	Mean (SD)	0.3056 (0.0562)	0.3137 (0.0613)
Change	Mean (SD)	0.0012 (0.0495)	0.0077 (0.0438)
	Median	-0.0023	0.0000
	Range	-0.1619 to 0.1600	-0.0738 to 0.1443

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo, QTP Quetiapine.
Pgm: Reg-DefDiabetes Mar 07 SERMLAB_chg_pla_mono_diab1.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 12:43

Table A143 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled monotherapy trials)

	QTP N=222 End of treatment			Pla N=80 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)						
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	1 (0.87)	90 (78.3)	24 (20.9)	1 (1.9)	44 (83.0)	8 (15.1)
High	0 (0)	36 (50.0)	36 (50.0)	0 (0)	16 (72.7)	6 (27.3)
Total	1 (0.53)	126 (67.4)	60 (32.1)	1 (1.3)	61 (80.3)	14 (18.4)
HbA1c (%)						
Norm	NA	86 (91.5)	8 (8.5)	NA	36 (97.3)	1 (2.7)
High	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	87 (87.0)	13 (13.0)	NA	36 (90.0)	4 (10.0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5
Pgm: Reg-Def-Diabetes Mar 07 SERMLAB_she_pla_mono_diab1.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 07:09.

Table A144 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled monotherapy trials)

	QTP N=222		Pla N=80	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	187	1 (0.53)	75	1 (1.3)
High[b]	120	30 (25.0)	54	9 (16.7)
HbA1c (%)				
High[b]	94	8 (8.5)	37	1 (2.7)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def-Diabetes Mar 07 SERMLAB_sha_pla_mono_diab1.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 07:27.

All diabetic subgroups

Table A145 Mean (SD) change from baseline to end of treatment (All placebo-controlled monotherapy trials)

		QTP N=3242	Pla N=1389
Glucose (mmol/L)			
Patients[a]		2603	1175
Baseline	Mean (SD)	5.31 (1.34)	5.35 (1.29)
Last value	Mean (SD)	5.48 (1.64)	5.39 (1.40)
Change	Mean (SD)	0.17 (1.45)	0.040 (1.41)
	Median	0.100	0
	Range	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)			
Patients[a]		1173	443
Baseline	Mean (SD)	5.39 (0.53)	5.32 (0.50)
Last value	Mean (SD)	5.45 (0.61)	5.33 (0.50)
Change	Mean (SD)	0.056 (0.32)	0.012 (0.28)
	Median	0	0
	Range	-1.40 to 4.50	-1.70 to 1.10
Insulin (pmol/L)			
Patients[a]		1713	689
Baseline	Mean (SD)	95.11 (126.81)	93.23 (130.83)
Last value	Mean (SD)	131.99 (200.57)	104.76 (138.38)
Change	Mean (SD)	36.89 (197.63)	11.53 (182.41)
	Median	7.00	6.95
	Range	-1479 to 2299	-1875 to 1820
$HOMA_B$			
Patients[a]		1566	640
Baseline	Mean (SD)	3.32 (5.54)	3.42 (9.23)
Last value	Mean (SD)	4.93 (9.61)	3.79 (6.66)
Change	Mean (SD)	1.61 (9.83)	0.37 (10.83)
	Median	0.29	0.18
	Range	-87.09 to 127.84	-137.15 to 87.11
QUICKI			
Patients[a]		1566	640
Baseline	Mean (SD)	0.3123 (0.0855)	0.3046 (0.0906)
Last value	Mean (SD)	0.3039 (0.0864)	0.2994 (0.0919)
Change	Mean (SD)	-0.0084 (0.0408)	-0.0052 (0.0382)

Table A145 Mean (SD) change from baseline to end of treatment (All placebo-controlled monotherapy trials)

		QTP N=3242	Pla N=1389
	Median	-0.0090	-0.0040
	Range	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_mono.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:44.

Table A146 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled monotherapy trials)

	QTP N=3242 End of treatment			Pla N=1389 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)						
Low	0 (0)	1 (100)	0 (0)	0 (0)	2 (100)	0 (0)
Norm	5 (0.20)	2460 (97.2)	65 (2.6)	3 (0.26)	1120 (97.3)	28 (2.4)
High	0 (0)	36 (50.0)	36 (50.0)	0 (0)	16 (72.7)	6 (27.3)
Total	5 (0.19)	2497 (95.9)	101 (3.9)	3 (0.26)	1138 (96.9)	34 (2.9)
HbA1c (%)						
Norm	NA	1159 (99.3)	8 (0.69)	NA	439 (99.8)	1 (0.23)
High	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	1160 (98.9)	13 (1.1)	NA	439 (99.1)	4 (0.90)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shc_pla_mono.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:16

Table A147 Shift to clinically important lab values at any time (All placebo-controlled monotherapy trials)

	QTP N=3242		Pla N=1389	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	2602	10 (0.38)	1173	7 (0.60)
High[b]	2536	98 (3.9)	1153	31 (2.7)
HbA1c (%)				
High[b]	1167	8 (0.69)	440	1 (0.23)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm. Reg-Def\Diabetes Mar 07 SERMOLAB_shs_pla_meeto.SAS. Data version: V91 User Bengt Franzon, 2007-05-03 07:38.

IR vs SR data

Non-diabetic subjects

Table A148 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled monotherapy trials, separating immediate and sustained release)

		QTP SR N=746	QTP IR N=1772	All QTP N=2518	Pla N=1115
Glucose (mmol/L)					
Patients[a]		651	1339	1990	937
Baseline	Mean (SD)	4.93 (0.56)	5.12 (0.95)	5.06 (0.85)	5.21 (1.04)
Last value	Mean (SD)	5.23 (0.97)	5.30 (1.26)	5.28 (1.17)	5.29 (1.16)
Change	Mean (SD)	0.30 (1.00)	0.18 (1.20)	0.22 (1.14)	0.078 (1.21)
	Median	0.17	0.11	0.11	0
	Range	-2.28 to 9.33	-4.80 to 9.50	-4.80 to 9.50	-6.83 to 6.00
HbA1c (%)					
Patients[a]		485	316	801	305
Baseline	Mean (SD)	5.28 (0.39)	5.28 (0.41)	5.28 (0.39)	5.23 (0.37)
Last value	Mean (SD)	5.33 (0.39)	5.29 (0.39)	5.31 (0.39)	5.24 (0.36)
Change	Mean (SD)	0.049 (0.26)	0.0095 (0.24)	0.034 (0.25)	0.016 (0.25)
	Median	0	0	0	0
	Range	-0.70 to 1.10	-0.70 to 0.90	-0.70 to 1.10	-0.80 to 0.80
Insulin (pmol/L)					
Patients[a]		495	720	1215	486
Baseline	Mean (SD)	80.08 (98.50)	70.40 (91.30)	74.16 (94.38)	75.95 (140.22)
Last value	Mean (SD)	112.25 (155.29)	111.61 (179.60)	111.87 (170.05)	92.71 (139.00)
Change	Mean (SD)	32.18 (146.15)	41.51 (174.47)	37.71 (163.53)	16.76 (178.76)
	Median	7.00	13.10	7.00	6.95
	Range	-757.00 to 1347	-770.90 to 2299	-770.90 to 2299	-1875 to 1820
$HOMA_B$					
Patients[a]		445	651	1096	452
Baseline	Mean (SD)	2.51 (3.50)	2.07 (3.11)	2.25 (3.28)	2.70 (8.70)
Last value	Mean (SD)	4.04 (7.03)	3.98 (8.65)	4.01 (8.03)	3.27 (6.62)
Change	Mean (SD)	1.53 (6.49)	1.91 (8.48)	1.76 (7.73)	0.57 (10.55)
	Median	0.25	0.39	0.32	0.23
	Range	-23.99 to 64.09	-35.70 to 127.84	-35.70 to 127.84	-137.15 to 87.11
QUICKI					
Patients[a]		445	651	1096	452
Baseline	Mean (SD)	0.3530 (0.0379)	0.2919 (0.1077)	0.3167 (0.0915)	0.3092 (0.0949)

Table A148 Mean (SD) change from baseline to end of treatment in non-diabetic subjects (All placebo-controlled monotherapy trials, separating immediate and sustained release)

		QTP SR N=746	QTP IR N=1772	All QTP N=2518	Pla N=1115
Last value	Mean (SD)	0.3425 (0.0442)	0.2784 (0.1052)	0.3044 (0.0914)	0.3012 (0.0959)
Change	Mean (SD)	-0.0105 (0.0420)	-0.0135 (0.0380)	-0.0123 (0.0397)	-0.0080 (0.0389)
	Median	-0.0100	-0.0100	-0.0100	-0.0076
	Range	-0.1600 to 0.1800	-0.2105 to 0.1262	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release, Pla Placebo, QTP Quetiapine, SR Sustained release.
Pgm: Reg-Def\Diabetes Mar 07 SER\FLAB_chg_pla_mono_SR_diab3.SAS. Data version: V91 User: Bengt Franzon, 2007-05-03 12:53

Table A149 Shift from baseline to clinically important lab values at end of treatment in non-diabetic subjects (All placebo-controlled monotherapy trials, separating immediate and sustained release)

	QTP SR N=746 End of treatment			QTP IR N=1772 End of treatment			All QTP N=2518 End of treatment			Pla N=1135 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Norm	0 (0)	643 (98.8)	8 (1.2)	4 (0.30)	1317 (98.4)	17 (1.3)	4 (0.20)	1960 (98.5)	25 (1.3)	2 (0.21)	921 (98.4)	13 (1.4)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	643 (98.8)	8 (1.2)	4 (0.30)	1318 (98.4)	17 (1.3)	4 (0.20)	1961 (98.5)	25 (1.3)	2 (0.21)	922 (98.4)	13 (1.4)
HbA1c (%)												
Norm	NA	485 (100)	0 (0)	NA	316 (100)	0 (0)	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	485 (100)	0 (0)	NA	316 (100)	0 (0)	NA	801 (100)	0 (0)	NA	305 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L) Low <=2.5 High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM-LAB_shc_pla_mono_SR_diab3.SAS Data version: V01 User: Bang Frozhoo 2007-05-03 07:18.

Table A150 Shift to clinically important lab values at any time in non-diabetic subjects (All placebo-controlled monotherapy trials, separating immediate and sustained release)

	QTP SR N=746		QTP IR N=1772		All QTP N=2518		Pla N=1115	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	651	0 (0)	1338	9 (0.67)	1989	9 (0.45)	936	6 (0.64)
High[b]	651	15 (2.3)	1339	25 (1.9)	1990	40 (2.0)	937	13 (1.4)
HbA1c (%)								
High[b]	485	0 (0)	316	0 (0)	801	0 (0)	305	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_shs_pla_mono_SR_diab3.SAS. Data version: V91 User: Bengt Franzon 2007-05-03 07:37.

Diabetic risk subjects

Table A151 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled monotherapy trials, separating immediate and sustained release)

		QTP SR N=208	QTP IR N=294	All QTP N=502	Pla N=194
Glucose (mmol/L)					
Patients[3]		190	236	426	162
Baseline	Mean (SD)	5.59 (0.72)	5.43 (0.85)	5.50 (0.80)	5.37 (0.71)
Last value	Mean (SD)	5.67 (1.23)	5.42 (1.21)	5.53 (1.22)	5.35 (1.04)
Change	Mean (SD)	0.081 (1.18)	-0.0087 (1.14)	0.031 (1.16)	-0.014 (0.94)
	Median	-0.160	-0.056	-0.056	-0.056
	Range	-2.56 to 4.89	-3.30 to 8.22	-3.30 to 8.22	-3.06 to 4.50
HbA1c (%)					
Patients[4]		153	119	272	98
Baseline	Mean (SD)	5.38 (0.41)	5.37 (0.34)	5.38 (0.38)	5.32 (0.43)
Last value	Mean (SD)	5.47 (0.42)	5.39 (0.38)	5.43 (0.41)	5.35 (0.45)
Change	Mean (SD)	0.086 (0.30)	0.017 (0.27)	0.056 (0.29)	0.023 (0.27)
	Median	0.100	0	0.100	0
	Range	-0.50 to 1.40	-1.40 to 0.70	-1.40 to 1.40	-0.90 to 0.80
Insulin (pmol/L)					
Patients[5]		153	196	349	144
Baseline	Mean (SD)	139.75 (140.40)	133.23 (174.96)	136.09 (160.54)	118.47 (103.42)
Last value	Mean (SD)	200.00 (330.30)	170.74 (215.34)	183.57 (271.75)	133.14 (134.22)
Change	Mean (SD)	60.25 (315.28)	37.51 (227.21)	47.48 (269.20)	14.67 (138.09)
	Median	7.00	4.65	6.00	0
	Range	-701.45 to 2146	-951.47 to 1049	-951.47 to 2146	-620.26 to 888.96
$HOMA_B$					
Patients[4]		147	184	331	131
Baseline	Mean (SD)	4.90 (5.43)	4.80 (6.76)	4.84 (6.19)	3.93 (3.51)
Last value	Mean (SD)	7.71 (16.46)	5.85 (8.06)	6.67 (12.52)	4.62 (5.83)
Change	Mean (SD)	2.81 (16.34)	1.05 (8.52)	1.83 (12.62)	0.69 (5.66)
	Median	0.13	0.17	0.17	-0.028
	Range	-34.93 to 119.88	-34.10 to 38.61	-34.93 to 119.88	-21.59 to 40.41
QUICKI					
Patients[4]		147	184	331	131
Baseline	Mean (SD)	0.3207 (0.0320)	0.2858 (0.0906)	0.3013 (0.0728)	0.2882 (0.0859)
Last value	Mean (SD)	0.3209 (0.0431)	0.2859 (0.0969)	0.3014 (0.0795)	0.2870 (0.0881)

Table A151 Mean (SD) change from baseline to end of treatment in subjects with diabetic risk (All placebo-controlled monotherapy trials, separating immediate and sustained release)

		QTP SR N=208	QTP IR N=294	All QTP N=502	Pla N=194
Change	Mean (SD)	0.0002 (0.0382)	0.0003 (0.0386)	0.0002 (0.0384)	-0.0012 (0.0312)
	Median	0.0000	-0.0027	-0.0006	0.0000
	Range	-0.0900 to 0.1000	-0.1433 to 0.1287	-0.1433 to 0.1287	-0.1229 to 0.0800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_mono_SR_diab2.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:52.

Table A152 **Shift from baseline to clinically important lab values at end of treatment in subjects with diabetic risk (All placebo-controlled monotherapy trials, separating immediate and sustained release)**

	QTP SR N=208 End of treatment			QTP IR N=294 End of treatment			All QTP N=502 End of treatment			Pla N=194 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norm	0 (0)	179 (94.2)	11 (5.8)	0 (0)	231 (97.9)	5 (2.1)	0 (0)	410 (96.2)	16 (3.8)	0 (0)	155 (95.7)	7 (4.3)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	0 (0)	179 (94.2)	11 (5.8)	0 (0)	231 (97.9)	5 (2.1)	0 (0)	410 (96.2)	16 (3.8)	0 (0)	155 (95.7)	7 (4.3)
HbA1c (%)												
Norm	NA	153 (100)	0 (0)	NA	119 (100)	0 (0)	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)
High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	NA	153 (100)	0 (0)	NA	119 (100)	0 (0)	NA	272 (100)	0 (0)	NA	98 (100)	0 (0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%) High: >7.5.
Pgm: Reg-Def Diabetes Mar 07 SbRM-LAB_shs_pla_mono_SR_diab2.SAS. Data version: V93 User: Bangt Franzon 2007-05-03 07:18.

Table A153 Shift to clinically important lab values at any time in subjects with diabetic risk (All placebo-controlled monotherapy trials, separating immediate and sustained release)

	QTP SR N=208		QTP IR N=294		All QTP N=502		Pla N=194	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	190	0 (0)	236	0 (0)	426	0 (0)	162	0 (0)
High[b]	190	19 (10.0)	236	9 (3.8)	426	28 (6.6)	162	9 (5.6)
HbA1c (%)								
High[b]	153	0 (0)	119	0 (0)	272	0 (0)	98	0 (0)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SER\#LAB_sha_pla_mono_SR_diab2.SAS. Data version: V91 User: Bengt Fronzon 2007-05-03 07:36.

Diabetic subjects

Table A154 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled monotherapy trials, separating immediate and sustained release)

		QTP SR N=92	QTP IR N=130	All QTP N=222	Pla N=80
Glucose (mmol/L)					
Patients[a]		84	103	187	76
Baseline	Mean (SD)	7.31 (2.86)	7.80 (3.40)	7.58 (3.17)	7.06 (2.84)
Last value	Mean (SD)	7.36 (3.89)	7.67 (3.84)	7.53 (3.86)	6.74 (3.10)
Change	Mean (SD)	0.045 (3.56)	-0.13 (3.52)	-0.051 (3.53)	-0.32 (3.27)
	Median	-0.028	0	0	-0.25
	Range	-9.83 to 15.72	-9.80 to 13.89	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)					
Patients[a]		71	29	100	40
Baseline	Mean (SD)	6.33 (0.84)	6.28 (0.97)	6.31 (0.88)	6.01 (0.85)
Last value	Mean (SD)	6.48 (0.99)	6.71 (1.58)	6.55 (1.19)	5.96 (0.91)
Change	Mean (SD)	0.15 (0.47)	0.43 (1.02)	0.23 (0.69)	-0.050 (0.45)
	Median	0.100	0.20	0.100	0
	Range	-0.90 to 1.70	-0.50 to 4.50	-0.90 to 4.50	-1.70 to 1.10
Insulin (pmol/L)					
Patients[a]		68	81	149	59
Baseline	Mean (SD)	204.46 (238.49)	140.84 (151.49)	169.87 (197.90)	173.96 (261.50)
Last value	Mean (SD)	230.11 (259.02)	129.20 (136.72)	175.26 (207.41)	134.77 (130.45)
Change	Mean (SD)	25.65 (310.84)	-11.64 (176.17)	5.38 (246.71)	-39.19 (278.54)
	Median	6.97	6.95	6.95	-12.08
	Range	-1479 to 1445	-757.01 to 625.05	-1479 to 1445	-1799 to 507.00
$HOMA_B$					
Patients[a]		66	73	139	57
Baseline	Mean (SD)	9.76 (13.18)	6.65 (9.64)	8.13 (11.52)	7.97 (17.54)
Last value	Mean (SD)	10.96 (15.18)	5.40 (6.39)	8.04 (11.73)	6.02 (8.05)
Change	Mean (SD)	1.20 (19.05)	-1.25 (11.14)	-0.087 (15.40)	-1.95 (18.99)
	Median	0.79	0.17	0.20	-0.10
	Range	-87.09 to 92.99	-58.43 to 22.73	-87.09 to 92.99	-127.11 to 42.25
QUICKI					
Patients[a]		66	73	139	57
Baseline	Mean (SD)	0.3017 (0.0390)	0.3068 (0.0693)	0.3044 (0.0569)	0.3060 (0.0572)
Last value	Mean (SD)	0.3020 (0.0465)	0.3089 (0.0638)	0.3056 (0.0562)	0.3137 (0.0613)

Table A154 Mean (SD) change from baseline to end of treatment in diabetic subjects (All placebo-controlled monotherapy trials, separating immediate and sustained release)

		QTP SR N=92	QTP IR N=130	All QTP N=222	Pla N=80
Change	Mean (SD)	0.0003 (0.0495)	0.0020 (0.0499)	0.0012 (0.0495)	0.0077 (0.0438)
	Median	-0.0050	-0.0023	-0.0023	0.0000
	Range	-0.0800 to 0.1600	-0.1619 to 0.1293	-0.1619 to 0.1600	-0.0738 to 0.1443

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release, Pla Placebo, QTP Quetiapine, SR Sustained release.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_mono_SR_diab1.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:52.

Table A155 Shift from baseline to clinically important lab values at end of treatment in diabetic subjects (All placebo-controlled monotherapy trials, separating immediate and sustained release)

	QTP SR N=92 End of treatment			QTP IR N=130 End of treatment			All QTP N=222 End of treatment			Pla N=80 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	0 (0)	1 (100)	0 (0)
Norm	1 (1.9)	38 (73.1)	13 (25.0)	0 (0)	52 (82.5)	11 (17.5)	1 (0.87)	90 (78.3)	24 (20.9)	1 (1.9)	44 (83.0)	8 (15.1)
High	0 (0)	17 (53.1)	15 (46.9)	0 (0)	19 (47.5)	21 (52.5)	0 (0)	36 (50.0)	36 (50.0)	0 (0)	16 (72.7)	6 (27.3)
Total	1 (1.2)	55 (65.5)	28 (33.3)	0 (0)	71 (68.9)	32 (31.1)	1 (0.53)	126 (67.4)	60 (32.1)	1 (1.3)	61 (80.3)	14 (18.4)
HbA1c (%)												
Norm	NA	62 (92.5)	5 (7.5)	NA	24 (88.9)	3 (11.1)	NA	86 (91.5)	8 (8.5)	NA	36 (97.3)	1 (2.7)
High	NA	1 (25.0)	3 (75.0)	NA	0 (0)	2 (100)	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	63 (88.7)	8 (11.3)	NA	24 (82.8)	5 (17.2)	NA	87 (87.0)	13 (13.0)	NA	36 (90.0)	4 (10.0)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline

IR Immediate release, Pla Placebo, QTP Quetiapine, SR Sustained release.

Clinically important limits are: Glucose (mmol/L): Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%): High >=7.5.

Pgm: Reg-Def\Diabetes Mar 07 SER\MULAD_dbe_pla_mono_SR_diab1.SAS. Data version: V01 User: Ekangi Ivanova. 2007-05-03 07.17.

Table A156 Shift to clinically important lab values at any time in diabetic subjects (All placebo-controlled monotherapy trials, separating immediate and sustained release)

	QTP SR N=92		QTP IR N=130		All QTP N=222		Pla N=80	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	84	1 (1.2)	103	0 (0)	187	1 (0.53)	75	1 (1.3)
High[b]	55	17 (30.9)	65	13 (20.0)	120	30 (25.0)	54	9 (16.7)
HbA1c (%)								
High[b]	67	5 (7.5)	27	3 (11.1)	94	8 (8.5)	37	1 (2.7)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L) Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def-Diabetes Mar 07 SER\4\LAB_sha_pla_mono_SR_diab1.SAS. Data version: V91 User: Bengt Franzon 2007-05-03 07:36.

All diabetic subgroups

Table A157 Mean (SD) change from baseline to end of treatment (All placebo-controlled monotherapy trials, separating immediate and sustained release)

		QTP SR N=1046	QTP IR N=2196	All QTP N=3242	Pla N=1389
Glucose (mmol/L)					
Patients[a]		925	1678	2603	1175
Baseline	Mean (SD)	5.29 (1.24)	5.33 (1.39)	5.31 (1.34)	5.35 (1.29)
Last value	Mean (SD)	5.52 (1.64)	5.46 (1.64)	5.48 (1.64)	5.39 (1.40)
Change	Mean (SD)	0.23 (1.46)	0.13 (1.45)	0.17 (1.45)	0.040 (1.43)
	Median	0.10	0.100	0.100	0
	Range	-9.83 to 15.72	-9.80 to 13.89	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)					
Patients[a]		709	464	1173	443
Baseline	Mean (SD)	5.41 (0.55)	5.37 (0.51)	5.39 (0.53)	5.32 (0.50)
Last value	Mean (SD)	5.47 (0.60)	5.41 (0.64)	5.45 (0.61)	5.33 (0.50)
Change	Mean (SD)	0.068 (0.30)	0.038 (0.36)	0.056 (0.32)	0.012 (0.28)
	Median	0	0	0	0
	Range	-0.90 to 1.70	-1.40 to 4.50	-1.40 to 4.50	-1.70 to 1.10
Insulin (pmol/L)					
Patients[a]		716	997	1713	689
Baseline	Mean (SD)	104.64 (133.61)	88.26 (121.30)	95.11 (126.81)	93.23 (150.83)
Last value	Mean (SD)	142.20 (219.57)	124.66 (185.49)	131.99 (200.57)	104.76 (138.38)
Change	Mean (SD)	37.56 (212.34)	36.41 (186.50)	36.89 (197.65)	11.53 (182.41)
	Median	7.00	7.00	7.00	6.95
	Range	-1479 to 2146	-951.47 to 2299	-1479 to 2299	-1875 to 1820
$HOMA_B$					
Patients[a]		658	908	1566	640
Baseline	Mean (SD)	3.77 (6.08)	2.99 (5.09)	3.32 (5.54)	3.42 (9.23)
Last value	Mean (SD)	5.55 (11.04)	4.47 (8.40)	4.93 (9.61)	3.79 (6.66)
Change	Mean (SD)	1.78 (11.13)	1.48 (8.76)	1.61 (9.83)	0.37 (10.83)
	Median	0.25	0.33	0.29	0.18
	Range	-87.09 to 119.88	-58.43 to 127.84	-87.09 to 127.84	-137.15 to 87.11
QUICKI					
Patients[a]		658	908	1566	640
Baseline	Mean (SD)	0.3406 (0.0411)	0.2918 (0.1019)	0.3123 (0.0855)	0.3046 (0.0906)
Last value	Mean (SD)	0.3336 (0.0462)	0.2823 (0.1011)	0.3039 (0.0864)	0.2994 (0.0919)

Table A157 Mean (SD) change from baseline to end of treatment (All placebo-controlled monotherapy trials, separating immediate and sustained release)

		QTP SR N=1046	QTP IR N=2196	All QTP N=3242	Pla N=1389
Change	Mean (SD)	-0.0070 (0.0422)	-0.0095 (0.0397)	-0.0084 (0.0408)	-0.0052 (0.0382)
	Median	-0.0100	-0.0080	-0.0090	-0.0040
	Range	-0.1600 to 0.1800	-0.2105 to 0.1293	-0.2105 to 0.1800	-0.1830 to 0.1800

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Pgm: Reg-Def-Diabetes Mar 07 SERMULAB_chg_pla_mono_SR.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:53.

Table A158 Shift from baseline to clinically important lab values at end of treatment (All placebo-controlled monotherapy trials, separating immediate and sustained release)

	QTP SR N=1046 End of treatment			QTP IR N=2196 End of treatment			All QTP N=3242 End of treatment			Pla N=1389 End of treatment		
Lab test Baseline	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)	Low n[a] (%)	Norm n[a] (%)	High n[a] (%)
Glucose (mmol/L)												
Low	NA	NA	NA	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	2 (100)	0 (0)
Norm	1 (0.11)	866 (96.3)	32 (3.6)	4 (0.24)	1600 (97.7)	33 (2.0)	5 (0.20)	2466 (97.2)	65 (2.6)	3 (0.26)	1120 (97.3)	28 (2.4)
High	0 (0)	17 (53.1)	15 (46.9)	0 (0)	19 (47.5)	21 (52.5)	0 (0)	36 (50.0)	36 (50.0)	0 (0)	16 (72.7)	6 (27.3)
Total	1 (0.11)	877 (94.8)	47 (5.1)	4 (0.24)	1620 (96.5)	54 (3.2)	5 (0.19)	2497 (95.9)	101 (3.9)	3 (0.26)	1138 (96.9)	34 (2.9)
HbA1c (%)												
Norm	NA	708 (99.3)	5 (0.71)	NA	459 (99.4)	3 (0.65)	NA	1159 (99.3)	8 (0.69)	NA	439 (99.8)	1 (0.23)
High	NA	1 (25.0)	3 (75.0)	NA	0 (0)	2 (100)	NA	1 (16.7)	5 (83.3)	NA	0 (0)	3 (100)
Total	NA	701 (98.9)	8 (1.1)	NA	459 (98.9)	5 (1.1)	NA	1160 (98.9)	13 (1.1)	NA	439 (99.1)	4 (0.90)

[a] Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are Glucose (mmol/L): Low: <=2.5 High >=7 for fasting and >=11.1 for non-fasting. HbA1c (%): High >=7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAll_she_pla_mono_SR.SAS Data version: V01 User: Bengt Fransson 2007-05-03 05:19.

Table A159 Shift to clinically important lab values at any time (All placebo-controlled monotherapy trials, separating immediate and sustained release)

	QTP SR N=1046		QTP IR N=2196		All QTP N=3242		Pla N=1389	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)								
Low[a]	925	1 (0.11)	1677	9 (0.54)	2602	10 (0.38)	1173	7 (0.60)
High[b]	896	51 (5.7)	1640	47 (2.9)	2536	98 (3.9)	1153	31 (2.7)
HbA1c (%)								
High[b]	705	5 (0.71)	462	3 (0.65)	1167	8 (0.69)	440	1 (0.23)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
IR Immediate release. Pla Placebo. QTP Quetiapine. SR Sustained release.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_mono_SR.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 07:37.

Trial 125

Table A160 Demographic and baseline characteristics (PAP)

	Quetiapine N = 115	Olanzapine N = 146	Risperidone N = 134	Total N = 395
Sex: n (%)				
Male	76 (66.1)	97 (66.4)	87 (64.9)	260 (65.8)
Female	39 (33.9)	49 (33.6)	47 (35.1)	135 (34.2)
Age (years)[a]				
n[b]	115	146	134	395
Mean (SD)	39.4 (11.1)	40.5 (10.4)	38.3 (11.1)	39.5 (10.9)
Median	39.0	41.0	37.0	40.0
Min to max	20 to 63	19 to 65	19 to 62	19 to 65
Age distribution[a]: n (%)				
18 to 50	95 (82.6)	121 (82.9)	110 (82.1)	326 (82.5)
51 to 65	20 (17.4)	25 (17.1)	24 (17.9)	69 (17.5)
Race/ethnicity: n (%)				
Caucasian	104 (90.4)	134 (91.8)	116 (86.6)	354 (89.6)
Black	9 (7.8)	11 (7.5)	15 (11.2)	35 (8.9)
Other[d]	2 (1.7)	1 (0.7)	3 (2.2)	6 (1.5)
Weight (kg)				
n[b]	115	146	134	395
Mean (SD)	73.6 (15.4)	71.9 (14.6)	72.1 (15.8)	72.5 (15.2)
Median	69.5	70.1	69.0	69.5

Table A160 Demographic and baseline characteristics (PAP)

	Quetiapine N = 115	Olanzapine N = 146	Risperidone N = 134	Total N = 395
Min to max	43 to 116	46 to 121	42 to 117	42 to 121
BMI (kg/m^2): n (%)				
<18.5	8 (7.0)	10 (6.8)	9 (6.7)	27 (6.8)
18.5 to <25	54 (47.0)	72 (49.3)	70 (52.2)	196 (49.6)
25 to <30	37 (32.2)	43 (29.5)	35 (26.1)	115 (29.1)
≥ 30	16 (13.9)	21 (14.4)	20 (14.9)	57 (14.4)
Smoking[c]	67 (58.3)	86 (58.9)	86 (64.2)	239 (60.5)

a At randomization.
b Number of patients with non-missing values.
c Current smoker or any other nicotine use at enrolment. d Other race was mixed race
SOURCE DOCUMENT: ETI_DEM_CHAR32.SAS GENERATED: 11:33:16 25JAN2006 DB version prod. 13

D1444C00004

Table A161 Fasting glucose laboratory data, change from randomization to end of treatment for diabetic subgroups (randomized safety population)

			PLA N=103	QTP SR N=94
Glucose (mmol/l)	Diabetics	n[b]	3	4
		Mean	0.70	0.33
		SD	3.94	3.20
		Median	-0.50	-1.05
		Min	-2.50	-1.70
		Max	5.10	5.10
	Diabetic-risk	n[b]	27	18
		Mean	-0.13	0.28
		SD	1.00	0.79
		Median	-0.40	0.15
		Min	-2.10	-0.90
		Max	2.40	2.00
	Non-diabetic	n[b]	46	56
		Mean	0.28	0.37
		SD	0.82	0.62
		Median	0.20	0.30
		Min	-1.40	-1.00
		Max	3.50	2.40
HbA1C (%)	Diabetics	n[b]	3	4

Table A161 Fasting glucose laboratory data, change from randomization to end of treatment for diabetic subgroups (randomized safety population)

			PLA N=103	QTP SR N=94
		Mean	0.30	-0.05
		SD	0.20	0.37
		Median	0.30	-0.05
		Min	0.10	-0.50
		Max	0.50	0.40
	Diabetic-risk	n[a]	29	20
		Mean	0.07	0.05
		SD	0.25	0.47
		Median	0.00	0.00
		Min	-0.30	-0.60
		Max	0.80	1.70
	Non-diabetic	n[a]	56	62
		Mean	0.01	0.05
		SD	0.33	0.30
		Median	0.00	0.10
		Min	-0.80	-1.00
		Max	0.80	0.80
Insulin (pmol/L)	Diabetics	n[a]	3	4
		Mean	155.00	-29.50
		SD	377.11	129.18
		Median	201.00	-52.00
		Min	-243.00	-153.00
		Max	507.00	139.00
	Diabetic-risk	n[a]	29	20
		Mean	22.00	41.95
		SD	117.00	241.95
		Median	6.00	0.00
		Min	-230.00	-229.00
		Max	292.00	938.00
	Non-diabetic	n[a]	56	62
		Mean	29.30	7.50
		SD	83.38	59.41
		Median	7.00	6.50
		Min	-111.00	-181.00

Table A161 Fasting glucose laboratory data, change from randomization to end of treatment for diabetic subgroups (randomized safety population)

			PLA N=103	QTP SR N=94
		Max	417.00	167.00
HOMA-R	Diabetics	n[a]	3	4
		Mean	4.41	-0.05
		SD	10.50	4.35
		Median	0.61	-1.35
		Min	-3.66	-3.67
		Max	16.29	6.17
	Diabetic-risk	n[c]	25	16
		Mean	0.38	1.16
		SD	2.24	5.15
		Median	-0.07	0.11
		Min	-4.31	-3.38
		Max	5.56	18.84
	Non-diabetic	n[b]	44	55
		Mean	0.55	0.03
		SD	2.15	0.93
		Median	0.10	0.02
		Min	-1.31	-2.84
		Max	13.14	2.91
QUICKI	Diabetics	n[a]	3	4
		Mean	-0.0033	0.0050
		SD	0.0306	0.0238
		Median	-0.0100	0.0150
		Min	-0.0300	-0.0300
		Max	0.0300	0.0200
	Diabetic-risk	n[c]	25	16
		Mean	-0.0028	0.0006
		SD	0.0239	0.0254
		Median	0.0000	0.0000
		Min	-0.0500	-0.0500
		Max	0.0400	0.0600
	Non-diabetic	n[b]	44	55
		Mean	-0.0070	-0.0027
		SD	0.0218	0.0258

Table A161 Fasting glucose laboratory data, change from randomization to end of treatment for diabetic subgroups (randomized safety population)

		PLA N=103	QTP SR N=94
	Median	-0.0100	0.0000
	Min	-0.0600	-0.0600
	Max	0.0400	0.0600

[a] Number of patients with non-missing observations

N Number of patients in treatment group. PLA Placebo. QTP Quetiapine. SR Sustained-release. SD Standard deviation.

Note: All patients with assessment at randomization and at least one after randomization.

Note: Diabetics defined as having baseline glucose >=6.99426 mmol/L at baseline or a history of diabetes. Diabetic risk defined as having a history of gestational diabetes or a BMI of >35 or impaired glucose>=5.5551 to <6.99426 mmol/L; Non-diabetic defined as not meeting criteria for diabetes or diabetic risk.

Study: D1444C00006 Source document: ST_LAB_GLUC_DSU3525.SAS. Generated: 17:34:29 30Aug2006 DB version prod: 6.

Table A162 Glucose and HbA1c, clinically important values at any time for diabetic subgroups (randomized safety population)

			PLA N=103	QTP SR N=94
Glucose (mmol/L)				
<= 2.49795	Diabetic	n[a]	3	4
		n(%)	0	0
	Diabetic risk	n[a]	27	18
		n(%)	0	0
	Non-Diabetic	n[a]	46	56
		n(%)	0	0
>= 6.99426	Diabetic	n[a]	2	0
		n(%)	1 (50.0)	0
	Diabetic risk	n[a]	27	18
		n(%)	3 (11.1)	4 (22.2)
	Non-Diabetic	n[a]	46	56
		n(%)	2 (4.3)	0
HbA1C (%)				
> 7.5	Diabetic	n[a]	3	4
		n(%)	0	0
	Diabetic risk	n[a]	29	20
		n(%)	0	0
	Non-Diabetic	n[a]	56	62
		n(%)	0	0

[a] Number of patients at risk, ie, not fulfilling the criteria at baseline.

PLA Placebo. QTP Quetiapine. SR Sustained-release. N Number of patients in treatment group. n Number of patients.

Note: Diabetics defined as having a baseline fasting glucose assessment >6.99426 mmol/L or a history of diabetes. Diabetic risk defined as having a history of gestational diabetes or a BMI of >35 or a baseline fasting glucose assessment >5.5551 mmol/L but <6.99426 mmol/L. Non-diabetic defined as not meeting criteria for diabetes or diabetic risk.
Percentages are calculated as n/n* x 100, where n is the number of patients meeting criterion at last visit.
Study: D1444C00004 Source document: ST_LAB_GLUC_DSUB526.SAS. Generated: 17:34:42 30Aug2006 DB version prod: 6.

Table A163 Fasting glucose regulation laboratory data for non-diabetic subgroup (randomized safety population), shift from randomization to end of treatment

	PLA N=67 End of treatment			QTP SR N=67 End of treatment		
Randomization	<L n (%)	N n (%)	>U n (%)	<L n (%)	N n (%)	>U n (%)
Glucose (mmol/L)						
<L	0	0	0	0	0	0
N	0	44 (95.7)	2 (4.3)	0	56 (100)	0
>U	0	0	0	0	0	0
Total	0	44 (95.7)	2 (4.3)	0	56 (100)	0
HbA1C (%)						
N	NA	56 (100)	0	NA	62 (100)	0
>U	NA	0	0	NA	0	0
Total	NA	56 (100)	0	NA	62 (100)	0

HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: For reference ranges, see Definitions of Clinically Important Laboratory Values, Vital Signs, and Electrocardiographic Data (Appendix 12.1.9 Statistical Analysis Plan).
Note: Denominators for percentages for below, normal, and above within a treatment are row totals.

Study: D1444C00004 Source document: ST_LAB_GLUC_SH290.SAS. Generated: 17:37:11 30Aug2006 DB version prod: 6.

Table A164 Fasting glucose regulation laboratory data, shift from randomization to end of treatment for diabetic risk subgroup (randomized safety population)

	PLA N=31 End of treatment			QTP SR N=23 End of treatment		
Randomization	<L n (%)	N n (%)	>U n (%)	<L n (%)	N n (%)	>U n (%)
Glucose (mmol/L)						
<L	0	0	0	0	0	0
N	0	24 (88.9)	3 (11.1)	0	15 (83.3)	3 (16.7)
>U	0	0	0	0	0	0
Total	0	24 (88.9)	3 (11.1)	0	15 (83.3)	3 (16.7)
HbA1C (%)						

Table A164 Fasting glucose regulation laboratory data, shift from randomization to end of treatment for diabetic risk subgroup (randomized safety population)

	PLA N=31 End of treatment			QTP SR N=23 End of treatment		
Randomization	<L n (%)	N n (%)	>U n (%)	<L n (%)	N n (%)	>U n (%)
N	NA	29 (100)	0	NA	20 (100)	0
>U	NA	0	0	NA	0	0
Total	NA	29 (100)	0	NA	20 (100)	0

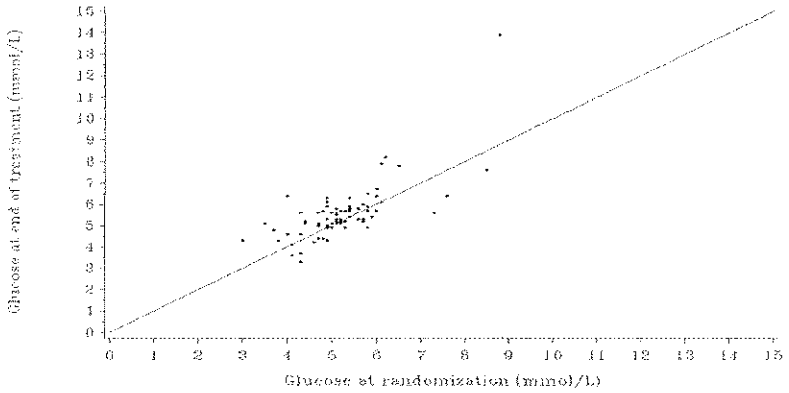
HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: For reference ranges, see Definitions of Clinically Important Laboratory Values, Vital Signs, and Electrocardiographic Data (Appendix 12.1.9. Statistical Analysis Plan).
Note: Denominators for percentages for below, normal, and above within a treatment are row totals.
Note: Diabetic risk defined as having either fasting glucose >=5.5551 and 6.99426 (mmol/L) at randomization, history of gestational diabetes or BMI >=35.
Study: D1444C00004 Source document: ST_LAB_GLUC_SH291.SAS. Generated: 17:36:57 30Aug2006 DB version prod: 6.

Table A165 Fasting glucose regulation laboratory data for diabetic subgroup (randomized safety population), shift from randomization to end of treatment

	PLA N=5 End of treatment			QTP SR N=4 End of treatment		
Randomization	<L n (%)	N n (%)	>U n (%)	<L n (%)	N n (%)	>U n (%)
Glucose (mmol/L)						
<L	0	0	0	0	0	0
N	0	1 (50.0)	1 (50.0)	0	0	0
>U	0	1 (100)	0	0	2 (50.0)	2 (50.0)
Total	0	2 (66.7)	1 (33.3)	0	2 (50.0)	2 (50.0)
HbA1C (%)						
N	NA	3 (100)	0	NA	4 (100)	0
>U	NA	0	0	NA	0	0
Total	NA	3 (100)	0	NA	4 (100)	0

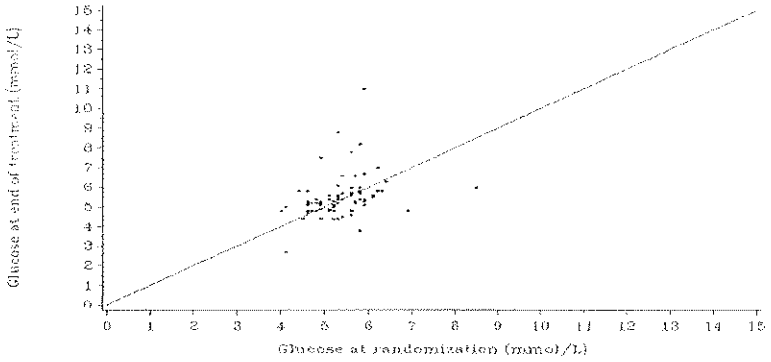
HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: For reference ranges, see Definitions of Clinically Important Laboratory Values, Vital Signs, and Electrocardiographic Data (Appendix 12.1.9. Statistical Analysis Plan).
Note: Denominators for percentages for below, normal, and above within a treatment are row totals.
Note: Diabetic defined as having either fasting glucose >=6.99426 (mmol/L) at randomization, HbA1c above ULN at randomization or history of diabetes.
Study: D1444C00004 Source document: ST_LAB_GLUC_SH289.SAS. Generated: 17:36:44 30Aug2006 DB version prod: 6.

Figure A1 **Shift plot: fasting glucose at randomization vs end of treatment, QTP SR (randomized safety population)**



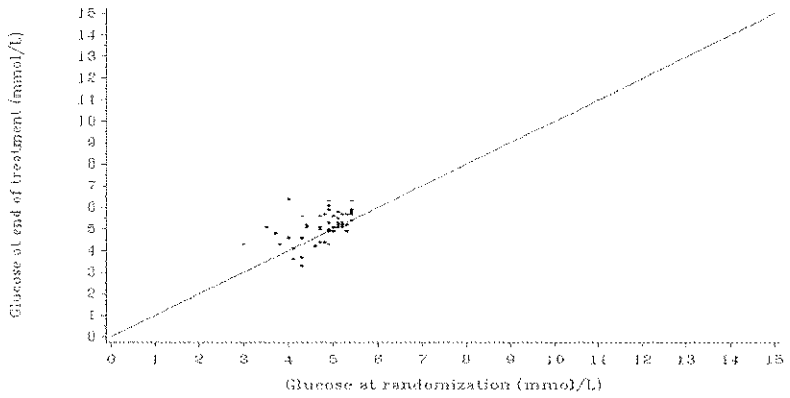
QTP Quetiapine. SR Sustained-release.
Note: Last assessment is used as end of treatment.
Study: D1444C00004 Source document: S_LAB_PLOT1.SAS. Generated: 17:38:24 30Aug2006 DB version prod: 6.

Figure A2 **Shift plot: fasting glucose at randomization vs end of treatment, PLA (randomized safety population)**



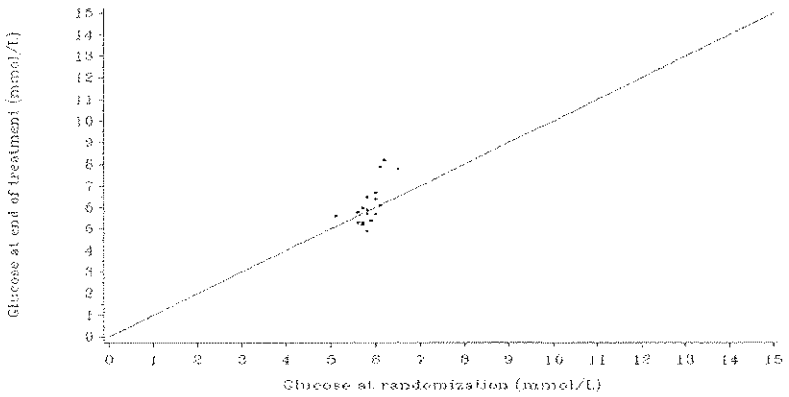
PLA Placebo.
Note: Last assessment is used as end of treatment.
Study: D1444C00004 Source document: S_LAB_PLOT3.SAS. Generated: 17:38:36 30Aug2006 DB version prod: 6.

Figure A3 Shift plot: fasting glucose at randomization vs end of treatment, QTP SR for non-diabetic subgroup (randomized safety population)



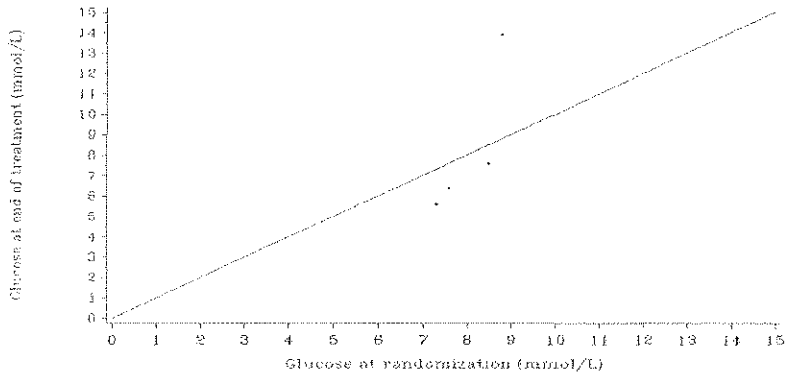
QTP Quetiapine. SR Sustained-release.
Note: Last assessment is used as end of treatment.
Study: D1444C00004 Source document: S_LAB_PLOT8.SAS. Generated: 17:39:08 30Aug2006 DB version prod: 6.

Figure A4 **Shift plot: fasting glucose at randomization vs end of treatment, QTP SR for diabetic risk subgroup (randomized safety population)**



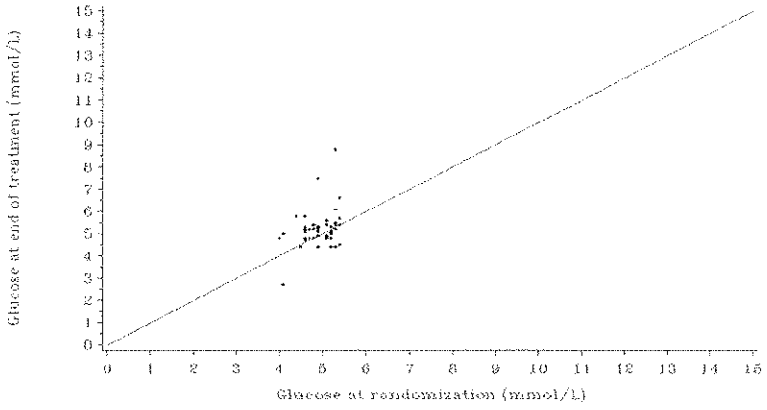
QTP Quetiapine. SR Sustained-release.
Note: Last assessment is used as end of treatment.
Study: D1444C00004 Source document: S_LAB_PLOT6.SAS. Generated. 17.38.56 30Aug2006 DB version prod: 6.

Figure A5 **Shift plot: fasting glucose at randomization vs end of treatment (randomized safety population), QTP SR for diabetic subgroup**



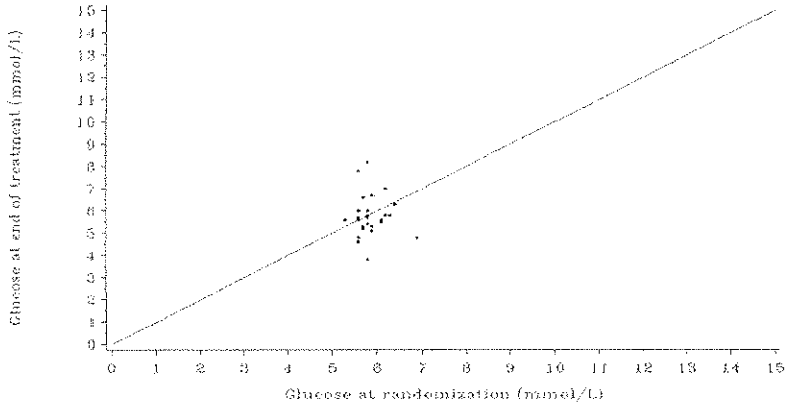
QTP Quetiapine. SR Sustained-release.
Note: Last assessment is used as end of treatment.
Study: D1444C00004 Source document: S_LAB_PLOT4.SAS. Generated: 17:38:44 30Aug2006 DB version prod: 6.

Figure A6 **Shift plot: fasting glucose at randomization vs end of treatment (randomized safety population), PLA for non-diabetic subgroup**



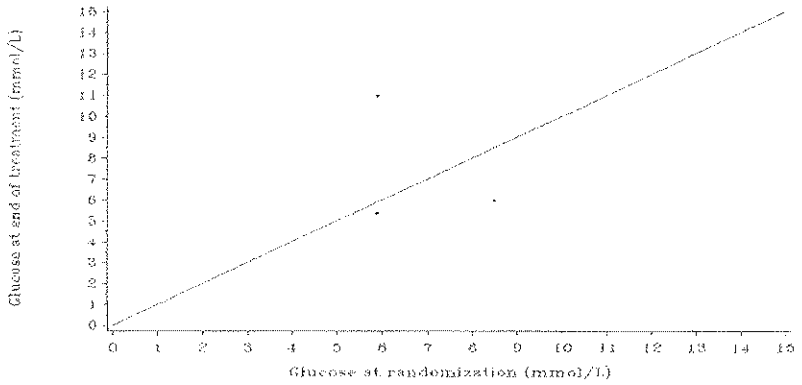
PLA Placebo.
Note: Last assessment is used as end of treatment.
Study: D1444C00038 Source document: S_LAB_PLOT9.SAS. Generated: 17:39:14 36Aug2006 DB version prod: 6.

Figure A7 Shift plot: fasting glucose at randomization vs end of treatment (randomized safety population), PLA for diabetic risk subgroup



PLA Placebo.
Note: Last assessment is used as end of treatment.
Study: D1444C00004 Source document: S_LAB_PLOT7.SAS. Generated: 17:39:02 30Aug2006 DB version prod: 6.

Figure A8 **Shift plot: fasting glucose at randomization vs end of treatment, PLA for diabetic subgroup (randomized safety population)**



PLA Placebo.
Note: Last assessment is used as end of treatment.
Study: D1444C00004 Source document: S_LAB_PLOT5.SAS. Generated: 17:38:49 30Aug2006 DB version prod: 6.

Table A166 **Fasting glucose laboratory data, change from enrolment to end of stabilization period for non-diabetic subgroup (open-label safety population)**

		QTP SR N=239
Glucose (mmol/L)		
n[a]		178
Enrolment	Mean (SD)	4.88 (0.44)
Randomization	Mean (SD)	5.12 (0.77)
Change	Mean (SD)	0.24 (0.86)
	Median	0.15
	Min to max	-3.5 to 5.9
HbA1C (%)		
n[b]		203
Enrolment	Mean (SD)	5.22 (0.37)
Randomization	Mean (SD)	5.26 (0.36)
Change	Mean (SD)	0.04 (0.29)

Table A166 Fasting glucose laboratory data, change from enrolment to end of stabilization period for non-diabetic subgroup (open-label safety population)

		QTP SR N=239
	Median	0.00
	Min to max	-0.9 to 0.9
Insulin (pmol/L)		
n[a]		206
Enrolment	Mean (SD)	82.11 (122.29)
Randomization	Mean (SD)	89.11 (130.17)
Change	Mean (SD)	7.00 (140.29)
	Median	0.00
	Min to max	-715.0 to 1194.0
HOMA-R		
n[a]		156
Enrolment	Mean (SD)	1.12 (1.76)
Randomization	Mean (SD)	1.32 (2.01)
Change	Mean (SD)	0.20 (2.16)
	Median	0.02
	Min to max	-10.0 to 16.9
QUICKI		
n[a]		156
Enrolment	Mean	0.1788
	SD	0.0233
Randomization	Mean	0.1774
	SD	0.0269
Change	Mean	-0.0014
	SD	0.0260
	Median	0.0000
	Min	-0.0600
	Max	0.0700

[a] Number of patients with non-missing observations.
HOMA-R homeostatic model assessment of insulin resistance. QUICKI quantitative insulin sensitivity check index
HbA1C Hemoglobin A1C. N Number of patients in treatment group. QTP Quetiapine. SR Sustained-release. SD Standard deviation.
Note: All patients with an assessment at enrollment and at least one assessment after enrollment.
Note: Non-diabetic defined as not meeting criteria for diabetes or diabetic risk.
Study: D1444C00004 Source document: ST_LAB_GLUC_CHA76_OL.SAS. Generated: 17:33:14 30Aug2006 DB version prod: 6.

Table A167 Fasting glucose laboratory data, change from enrolment to end of stabilization period for diabetic risk subgroup (open-label safety population)

		QTP SR N=73
Glucose (mmol/L)		
n[a]		62
Enrolment	Mean (SD)	5.90 (0.52)
Randomization	Mean (SD)	5.64 (0.73)
Change	Mean (SD)	-0.26 (0.80)
	Median	-0.25
	Min to max	-2.1 to 2.1
HbA1C (%)		
n[b]		63
Enrolment	Mean (SD)	5.25 (0.36)
Randomization	Mean (SD)	5.30 (0.39)
Change	Mean (SD)	0.05 (0.36)
	Median	0.00
	Min to max	-1.1 to 0.9
Insulin (pmol/L)		
n[c]		60
Enrolment	Mean (SD)	123.12 (113.21)
Randomization	Mean (SD)	149.98 (407.51)
Change	Mean (SD)	26.87 (369.89)
	Median	-7.00
	Min to max	-403.0 to 2730.0
HOMA-R		
n[d]		55
Enrolment	Mean (SD)	3.95 (1.83)
Randomization	Mean (SD)	2.71 (9.45)
Change	Mean (SD)	0.75 (8.71)
	Median	-0.08
	Min to max	-7.8 to 63.0
QUICKI		
n[e]		55
Enrolment	Mean	0.1607
	SD	0.0216
Randomization	Mean	0.1664
	SD	0.0239

Table A167 Fasting glucose laboratory data, change from enrolment to end of stabilization period for diabetic risk subgroup (open-label safety population)

		QTP SR N=73
Change	Mean	0.0056
	SD	0.0260
	Median	0.0000
	Min	-0.0600
	Max	0.0800

[a] Number of patients with non-missing observations.
HOMA-R homeostatic model assessment of insulin resistance. QUICKI quantitative insulin sensitivity check index.
HbA1C Hemoglobin A1C. N Number of patients in treatment group. QTP Quetiapine. SR Sustained-release. SD Standard deviation.
Note: All patients with an assessment at enrollment and at least one assessment after enrollment.
Note: Diabetic risk defined as having either fasting glucose ≥5.5551 and 6.9944 (mmol/L) at randomization, history of gestational diabetes or BMI ≥35.
Study: D1444C00004 Source document: ST_LAB_GLUC_CHA12_OL.SAS. Generated: 17:33:01 30Aug2006 DB version prod: 6.

Table A168 Fasting glucose laboratory data, change from enrolment to end of stabilization period for diabetic subgroup (open-label safety population)

		QTP SR N=15
Glucose (mmol/L)		
n[a]		12
Enrolment	Mean (SD)	7.72 (2.13)
Randomization	Mean (SD)	6.48 (1.36)
Change	Mean (SD)	-1.24 (1.64)
	Median	-0.70
	Min to max	-4.1 to 0.7
HbA1C (%)		
n[a]		12
Enrolment	Mean (SD)	5.88 (0.75)
Randomization	Mean (SD)	5.79 (0.76)
Change	Mean (SD)	-0.09 (0.65)
	Median	-0.05
	Min to max	-0.9 to 1.6
Insulin (pmol/L)		
n[a]		12
Enrolment	Mean (SD)	318.83 (283.08)
Randomization	Mean (SD)	182.33 (134.51)

Table A168 Fasting glucose laboratory data, change from enrolment to end of stabilization period for diabetic subgroup (open-label safety population)

		QTP SR N=15
Change	Mean (SD)	-136.50 (295.66)
	Median	-55.00
	Min to max	-917.0 to 180.0
HOMA-R		
n[b]		12
Enrolment	Mean (SD)	6.38 (5.76)
Randomization	Mean (SD)	3.04 (2.43)
Change	Mean (SD)	-3.33 (5.95)
	Median	-1.23
	Min to max	-16.8 to 2.7
QUICKI		
n[c]		12
Enrolment	Mean	0.1392
	SD	0.0278
Randomization	Mean	0.1542
	SD	0.0284
Change	Mean	0.0150
	SD	0.0373
	Median	0.0150
	Min	-0.0700
	Max	0.0800

[a] Number of patients with non-missing observations.
HOMA-R homeostatic model assessment of insulin resistance. QUICKI quantitative insulin sensitivity check index.
HbA1C Hemoglobin A1C. N Number of patients in treatment group. QTP Quetiapine. SR Sustained-release. ULN Upper limit of normal.
Note: All patients with an assessment at enrollment and at least one assessment after enrollment
Note: Diabetic defined as having either fasting glucose ≥6.99426 (mmol/L) at randomization, HbA1c above ULN at randomization or history of diabetes.

Study: D1444C00004 Source document: ST_LAB_GLUC_CHA75_OL.SAS. Generated: 17:32:48 30Aug2006 DB version prod: 6.

Table A169 Glucose and HbA1c, clinically important values at any time for diabetic subgroups (open-label safety population)

			QTP SR N=327
Glucose (mmol/L)			
<= 2.49795	Diabetic	n[a]	12
		n(%)	0

Table A169 Glucose and HbA1c, clinically important values at any time for diabetic subgroups (open-label safety population)

			QTP SR N=327
	Diabetic risk	n[a]	62
		n(%)	0
	Non-Diabetic	n[a]	178
		n(%)	0
>= 6.99426	Diabetic	n[b]	4
		n(%)	1 (25.0)
	Diabetic risk	n[c]	62
		n(%)	8 (12.9)
	Non-Diabetic	n[c]	178
		n(%)	12 (6.7)
HbA1C (%)			
> 7.5	Diabetic	n[d]	12
		n(%)	0
	Diabetic risk	n[e]	63
		n(%)	0
	Non-Diabetic	n[e]	203
		n(%)	0

[a] Number of patients at risk, ie, not fulfilling the criteria at baseline.
PLA Placebo. QTP Quetiapine. SR Sustained-release. N Number of patients in treatment group, n Number of patients.
Note: Diabetics defined as having a baseline fasting glucose assessment >=6.99426 mmol/L or a history of diabetes. Diabetic risk defined as having a history of gestational diabetes or a BMI of >35 or a baseline fasting glucose assessment >=5.5551 mmol/L but <6.99426 mmol/L. Non-diabetic defined as not meeting criteria for diabetes or diabetic risk.
Percentages are calculated as $n/N \times 100$, where n is the number of patients meeting criterion at last visit.
Study: D1444C00004 Source document: ST_LAB_GLUC_DS\B526_GL.SAS. Generated: 17:34:48 30Aug2006 DB version prod: 6.

Table A170 Fasting glucose regulation laboratory data for non-diabetic subgroup (open-label safety population), shift from enrolment to end of stabilization period

		QTP SR N=239 End of stabilization period	
Enrollment	<L n (%)	N n (%)	>U n (%)
Glucose (mmol/L)			
<L	0	0	0
N	0	173 (97.2)	5 (2.8)
>U	0	0	0
Total	0	173 (97.2)	5 (2.8)

Table A170 Fasting glucose regulation laboratory data for non-diabetic subgroup (open-label safety population), shift from enrolment to end of stabilization period

	QTP SR N=239 End of stabilization period		
Enrollment	<L n (%)	N n (%)	>U n (%)
HbA1C (%)			
N	NA	203 (100)	0
>U	NA	0	0
Total	NA	203 (100)	0

HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: For reference ranges, see Definitions of Clinically Important Laboratory Values, Vital Signs, and Electrocardiographic Data (Appendix 12.1.9, Statistical Analysis Plan).
Note: Denominators for percentages for below, normal, and above within a treatment are row totals.
Study: D1444C00004 Source document: ST_LAB_GLUC_SH290_OL.SAS. Generated: 17:37:17 30Aug2006 DB version prod: 6.

Table A171 Fasting glucose regulation laboratory data for diabetic risk subgroup (open-label safety population), shift from enrolment to end of stabilization period

	QTP SR N=73 End of stabilization period		
Enrollment	<L n (%)	N n (%)	>U n (%)
Glucose (mmol/L)			
<l	0	0	0
N	0	60 (96.8)	2 (3.2)
>U	0	0	0
Total	0	60 (96.8)	2 (3.2)
HbA1C (%)			
N	NA	63 (100)	0
>U	NA	0	0
Total	NA	63 (100)	0

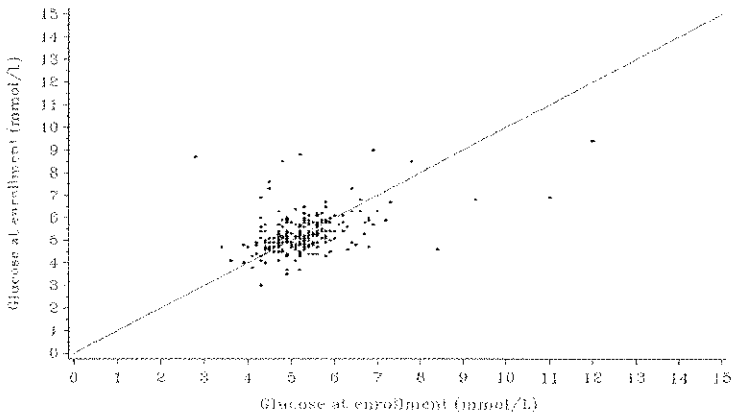
HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: For reference ranges, see Definitions of Clinically Important Laboratory Values, Vital Signs, and Electrocardiographic Data (Appendix 12.1.9, Statistical Analysis Plan).
Note: Denominators for percentages for below, normal, and above within a treatment are row totals.
Study: D1444C00004 Source document: ST_LAB_GLUC_SH291_OL.SAS. Generated: 17:37:03 30Aug2006 DB version prod: 6.

Table A172 Fasting glucose regulation laboratory data for diabetic subgroup (open-label safety population), shift from enrolment to end of stabilization period

		QTP SR N=15 End of stabilization period	
Enrollment	<L n (%)	N n (%)	>U n (%)
Glucose (mmol/L)			
<L	0	0	0
N	0	4 (100)	0
>U	0	6 (75.0)	2 (25.0)
Total [a]	0	10 (83.3)	2 (16.7)
HbA1C (%)			
N	NA	12 (100)	0
>U	NA	0	0
Total	NA	12 (100)	0

HbA1C Hemoglobin A1C. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: For reference ranges, see Definitions of Clinically Important Laboratory Values, Vital Signs, and Electrocardiographic Data (Appendix 12.1.9, Statistical Analysis Plan).
Note: Denominators for percentages for below, normal, and above within a treatment are row totals.
Study: D1444C00004 Source document: ST_LAB_GLUC_SH289_OL.SAS. Generated: 17:36:50 30Aug2006 DB version prod: 6.

Figure A9 **Shift plot: fasting glucose at enrolment vs end of stabilization period, QTP SR (open-label safety population)**



QTP Quetiapine SR Sustained-release.
Note: Last assessment is used as end of stabilization period
Study: D1444C00004 Source document: S_LAB_PLOT2.SAS. Generated: 17:38:31 30Aug2006 DB version prod: 6.

Table A173 **Signal detection for atypical antipsychotics and DM related events**

Drug name	N	EB05	EBGM	EB95	P value	PRR	PRR CHISQ
Amisulpiride	30	1.068	1.441	1.91	0.000001554	2.324	23.08
Aripiprazole	232	1.433	1.597	1.777	1.881 -28	2.025	122.406
Clozapine	1019	1.389	1.462	1.429	0	1.657	266.702
Olanzapine	2517	4.075	4.211	4.351	0	6.045	10370.86
Quetiapine	640	1.724	1.84	1.962	0	2.681	681.071
Risperidone	1052	1.776	1.869	1.966	0	2.117	622.239
Ziprasidone	177	1.245	1.41	1.592	4.541 -26	1.956	84.17
Zotepine	14	1.322	2.028	3.06	3.786 -08	3.859	30.256

Post-marketing tables

Table A174 MedDRA 9.1 Preferred terms

Blood glucose increased	Blood glucose abnormal	Blood glucose	Blood glucose fluctuation
Glucose tolerance decreased	Glucose tolerance test	Glucose tolerance test abnormal	Glycosylated haemoglobin
Glycosylated haemoglobin increased	Diabetic coma	Diabetic hyperglycaemic coma	Diabetic hyperosmolar coma
Diabetic ketoacidotic hyperglycaemic coma	Decreased insulin requirement	Insulin resistance syndrome	Diabetes mellitus
Diabetes mellitus inadequate control	Diabetes mellitus insulin-dependent	Diabetes mellitus malnutrition-related	Diabetes mellitus non-insulin-dependent
Diabetes with hyperosmolarity	Insulin resistance	Increased insulin requirement	Insulin autoimmune syndrome
Insulin resistant diabetes	Insulin sparing effect	Insulin-requiring type II diabetes mellitus	Neonatal diabetes mellitus
Diabetic complication	Diabetic ketoacidosis	Somogyi phenomenon	Hyperglycaemic hyperosmolar nonketotic syndrome
Dawn phenomenon	Glucose tolerance impaired	Impaired fasting glucose	Impaired insulin secretion
Hyperglycaemia	Hypoinsulinaemia postoperative	Glucose urine	Ketoacidosis
Glucose urine present	Glycosuria	Glycosuria during pregnancy	Gestational diabetes
Glucose tolerance impaired in pregnancy	Diabetes complicating pregnancy		

Table A175 Legal cases (non-medically confirmed) of DKA/ketoacidosis containing no clinical detail

Case IDs					
2007UW03186[a]	2007UW03185[a]	2007UW03184[a]	2007UW03183[a]	2007UW03182[a]	2007UW03181[a]
2007UW03180[a]	2007UW03177[a]	2007UW03176[a]	2007UW03175[a]	2007UW03174[a]	2007UW03173[a]
2007UW03172[a]	2007UW03171[a]	2007UW03170[a]	2007UW03168[a]	2007UW03167[a]	2007UW03166[a]
2007UW03162[a]	2007UW03153[a]	2007UW02353[a]	2007UW02352[a]	2007UW02351[a]	2007UW02350[a]
2007UW02349[a]	2007UW02347[a]	2007UW02346[a]	2007UW02345[a]	2007UW02344[a]	2007UW02343[a]
2007UW02342[a]	2007UW02341[a]	2007UW02340[a]	2007UW02339[a]	2007UW02337[a]	2007UW02336[a]
2007UW02335[a]	2007UW02334[a]	2007UW02333[a]	2007UW02332[a]	2007UW02331[a]	2007UW02330[a]
2007UW02329[a]	2007UW02328[a]	2007UW02248[a]	2007UW01267[a]	2007UW01266[a]	2007UW01265[a]
2007UW01264[a]	2007UW01263[a]	2007UW01262[a]	2007UW01261[a]	2007UW01260[a]	2007UW01259[a]
2007UW01258[a]	2007UW01257[a]	2007UW01256[a]	2007UW01255[a]	2007UW01254[a]	2007UW01253[a]
2007UW01252[a]	2007UW01251[a]	2007UW01245[a]	2007UW01239[a]	2007UW01238[a]	2007UW01237[a]
2007UW01235[a]	2007UW01234[a]	2007UW01233[a]	2007UW01232[a]	2007UW01231[a]	2007UW01230[a]

Table A175 Legal cases (non-medically confirmed) of DKA/ketoacidosis containing no clinical detail

Case IDs					
2007UW01229[b]	2007UW01228[a]	2007UW01226[a]	2007UW01225[a]	2007UW01223[a]	2007UW01222[a]
2007UW01221[a]	2007UW01220[a]	2007UW01219[a]	2007UW01218[a]	2007UW01217[a]	2007UW01216[a]
2007UW01215[a]	2007UW01214[a]	2007UW01213[a]	2007UW01212[a]	2007UW01209[a]	2007UW01208[a]
2007UW01207[a]	2007UW01206[a]	2007UW01205[a]	2007UW01204[a]	2007UW01203[a]	2007UW01202[a]
2007UW01201[a]	2007UW01200[a]	2007UW01199[a]	2007UW01198[a]	2007UW01197[a]	2007UW01196[a]
2007UW01195[a]	2007UW01194[a]	2007UW01192[a]	2007UW01191[a]	2007UW01190[a]	2007UW01189[a]
2007UW01187[a]	2007UW01185[a]	2007UW01184[a]	2007UW01183[a]	2007UW01182[a]	2007UW01181[a]
2007UW01180[a]	2007UW01179[a]	2007UW01178[a]	2007UW01177[a]	2007UW01176[a]	2007UW01175[a]
2007UW01174[a]	2007UW01173[a]	2007UW01172[a]	2007UW01171[a]	2007UW01170[a]	2007UW01169[a]
2007UW01168[a]	2007UW01165[a]	2007UW01164[a]	2007UW01163[a]	2007UW01161[a]	2007UW01159[a]
2007UW01158[a]	2007UW01154[a]	2007UW01153[a]	2007UW01152[a]	2007UW01151[a]	2007UW01150[a]
2007UW01148[a]	2007UW01147[a]	2007UW01146[a]	2007UW01144[a]	2007UW01139[a]	2007UW01138[a]
2007UW01136[a]	2007UW01135[a]	2007UW01134[a]	2007UW01133[a]	2007UW01132[a]	2007UW01131[a]
2007UW01128[a]	2007UW01127[a]	2007UW01126[a]	2007UW01125[a]	2007UW01123[a]	2007UW01122[a]
2007UW01121[a]	2007UW01119[a]	2007UW01118[a]	2007UW01117[a]	2007UW01116[a]	2007UW01113[a]
2007UW01109[a]	2007UW01106[a]	2007UW01105[a]	2007UW01104[a]	2007UW01103[a]	2007UW01096[a]
2007UW01049[a]	2007UW01047[a]	2007UW01042[a]	2007UW01034[a]	2007UW01031[a]	2007UW01030[a]
2007UW01025[c]	2006UW14191[a]	2006UW26626[c]	2006UW19446	2006UW19444	2006UW19253
2006UW19006[a]	2006UW17489[b]	2006UW17474[b]	2006UW03654[b]	2007UW02614[b]	2006UW02726[b]
2007UW03643[c]					

[a] Reports also containing the MedDRA preferred terms "Diabetic coma", "Diabetes mellitus", and "Hyperglycaemia".
[b] Reports also containing the MedDRA preferred term "Diabetes mellitus".
[c] Reports also containing the MedDRA preferred term "Diabetes mellitus non-insulin dependent".
[d] Reports also containing the MedDRA preferred term "Diabetes mellitus insulin dependent".
[e] Reports also containing the MedDRA preferred term "Blood glucose increased".

Table A176 Medically confirmed reports of new onset DM/hyperglycemia confounded by medical history/risk factors and concomitant medications

Report #	Confounding med hx and/or risk factors	Confounding concomitant medications
2007UW00346	Obesity	Lithium[a]
2006AC01221	Obesity (BMI = 34.1)	Lithium[a]
2006UW09292	Obesity (BMI = 38.7), HTN, hypercholesterolemia, hyperglycaemia	Lithium[a]
2006UW14052	Obesity (BMI = 38.1), smoker, family hx of DM	Olanzapine[a,b,c]
2006AP01111	Obesity, hyperlipidemia	Chlorpromazine[a,d]
2005SI02169	Family hx of DM, smoker	Lithium[a]

Table A176 Medically confirmed reports of new onset DM/hyperglycemia confounded by medical history/risk factors and concomitant medications

Report #	Confounding med hx and/or risk factors	Confounding concomitant medications
2005AP01924	Hyperlipidemia, smoker, obesity (BMI = 31.9)	Olanzapine[a,b,c]
2005AP00758	Smoker, insulin resistance, dyslipidemia, HTN	Furosemide[a]
2004UW17950	HTN, obesity	Lithium[a]
2005AP06252[e]	PET bottle syndrome	Chlorpromazine[a,d]
2005GB01302	Poor diet, obesity	Clozapine[a,b]
2004UW04505	Family hx of DM	Lithium[a]
2005AP00216	Hyperlipidemia, obesity, "eating large amounts of snacks"	Olanzapine[a,b,c], chlorpromazine[a,d]
2004AP00417	HTN	Furosemide[a]
2004UW21030	Obesity, hyperlipidemia, HTN	Glucocorticosteroids[a]
2004UW19465	Hyperlipidemia, obesity	Olanzapine[a,b,c]
2003UW05910	HTN, obesity (BMI = 37.4)	Olanzapine[a,b,c]
2003AP02732	Excessive drinking of juice and soft drinks	Chlorpromazine[a,d]
2003AP02835	Obesity	Chlorpromazine[a,d]
2002AP04011	Obesity (BMI = 37.9)	Chlorpromazine[a,d]
2000UW02019	HTN	Lithium[a]
2000AP02609	Family hx of DM, family hx of HTN	Furosemide[a]
2003AP01545	Hyperlipidemia	Olanzapine[a,b,c]
2003AP01768	Hyperlipidemia	Chlorpromazine[a,d]
2003AP01846	Dumping syndrome	Chlorpromazine[a,d]
2005UW13880	Smoker	Olanzapine[a,b,c]
2003GB00633	Obesity (BMI = 38.5), family hx of DM	"Steroids"[a]
2001UW00231	FBG before Seroquel (while on olanzapine)	Medroxyprogesterone[a,i]

[a] For which hyperglycemia has been reported.
[b] For which DM has been reported.
[c] For which DKA has been reported
[d] For which altered glucose tolerance has been reported
[e] This report described a fatal outcome, however the patient's cause of death was unknown.
[f] This report described a negative rechallenge.
[g] For which hyperglycemia with accentuation or precipitation of the diabetic state has been reported.
[h] For which reduced glucose tolerance has been reported.
[i] For which insulin resistance has been reported.

BMI body mass index. DM diabetes mellitus. FBS fasting blood sugar. HTN hypertension. Hx history. NB: all BMI measurements are kg/m^2.

Table A177 Medically confirmed reports of new onset DM/hyprglycemia confounded by medical history/risk factors

Report #	Confounding med hx/risk factors	Report #	Confounding med hx/risk factors
2003AP00095	Glucose tolerance impaired, excessive eating/drinking soft drinks	2005UW07492	Obesity (BMI = 31.1), family hx of DM, Wt gain/polydipsia/polyuria on olanzapine
2006AP01403	Dietary non-compliance	2005UW14363	↑BG
2005UW16973	Family hx of DM	2005UW18526	Family hx of DM
2005UW17565	Family hx of DM, obesity	2005UW18626	Family hx of DM, obesity (BMI = 40.4)
2005UW04800	Obesity	2005UW03396	Hyperglycemia on olanzapine
2005GB01698	Hyperlipidemia, obesity	2005GB00171	↑cholesterol, obesity (BMI = 34.2)
2004AP05420	Obesity, hyperlipidemia	2003AP00040	"Inactive w/ promiscuous eating habits"
2004AP06118	Family hx of DM	2004AP02574	HTN
2005AP04567	Family hx of DM, smoker	2005AP04033	Smoker, HTN, glucose tolerance abnormal
2005SE00747	Family hx of DM	2005SE04735	Family hx of DM
2006UW02597	Family hx of DM	2003AP04185	"Predisposition to DM"
2005UW05846	Lipid + glucose abnormalities	2004UW03589	HTN, obesity (BMI = 38.8), family hx of DM
2004UW02604	Obesity	2005UW08902	Obesity, family hx of DM
2004UW09786	Hyperlipidemia, obesity, family hx of DM	2004AP01181	Obesity (BMI = >30)
2004UW10393	Obesity	2004UW11908	Family hx of DM
2004UW22845	Obesity (BMI = 46.8)	2004UW21767	Obesity (BMI = 35), HTN
2004AP03416	Obesity (BMI = 34.9), hyperlipidemia	2004AP04163	Obesity (BMI = 38.9), insulin resistance, HTN, hyperlipidemia, excessive eating/drinking
2004AP00918	Obesity, uncontrolled eating	2006UW18795	Family history of DM
2003UW06459	Obesity (BMI = 34.8)	2003UW03980	HTN
2003UW02826	Obesity (BMI = 33.5), hyperlipidemia	2003SE04779	Family hx of DM
2003UW01302	Borderline diabetes	2003AP03200	Family hx of DM
2003GB00465	Family hx of DM	2004UW06215	Family hx of DM
2003GB00857	"Will not stop eating sugar"	2003AP00034	Obesity (BMI = 36.1), hyperlipidemia
2003AP00844	Family hx of DM, hyperlipidemia	2003AP01950	↑FBS before Seroquel
2003AP01955	Obesity, "drinking cola"	2002AP04003	Family hx of DM
2002AP04183	Family hx of DM, "tendency to obesity" (BMI = 29.4)	2002AP04184	Hyperlipidemia, obesity (BMI = 31.8)
2002AP04245	Obesity (BMI = 31.9)	2006AP01651	Obesity (BMI = 30.1), smoker
2002AP00269	Obesity (BMI = 35.5)	2002GB01293	Family hx of DM, family hx of obesity
2001UW13180	Family hx of DM	2001AP05019	Hypercholesterolemia, obesity
2000AP05293	Obesity (BMI = 32.3)	1999UW03532	HTN
1999AP02989	Obesity (BMI = 30.0)	2005AP03229	Consuming "massive amounts" of soft drinks (sugar-sweetened).

Table A177 Medically confirmed reports of new onset DM/hyprglycemia confounded by medical history/risk factors

Report #	Confounding med hx/risk factors	Report #	Confounding med hx/risk factors
2005UW19528	Pre-Seroquel BG=141 mg/dL	2005UW19530	Obesity, family hx of DM
2003AP06571	Obesity (BMI=30)	2005UW14822	Obesity, family hx of DM, HTN, smoker
2004SB00328	Obesity (BMI = 31.7)	2004AP02848	Obesity, hyperlipidemia
2004AP02946	Hypercholesterolemia, smoker	2004AP04586	Family hx of DM, obesity
2003AP00033	Obesity (BMI = 34.7)	2003AP02271	HTN, hyperlipidemia, obesity
2002AP04524	Family hx of DM	2001SE07046	Obesity (BMI = 36.2)
2006UW27153	HTN	2006GB01136	Family hx of DM, hyperlipidemia
2006AP04120	Obesity (BMI= 27.3), smoker, polypliagia, family hx of DM	2006AC01835	Family hx of DM, smoker
2006UW12086	Obesity	2006AP02235	Hyperlipidemia, smoker
2006AP02396	HTN, smoker,	2006AP06131	HTN
2006UW02335	Obesity (BMI = 34.6), hyperlipidemia, "random glucose greater than 200"	2006UW03503	Family hx of diabetes
2006UW05160	Family hx of diabetes	2006UW05436	Obesity
2006UW05622	Obesity (BMI = 31.6), HTN, polyuria, polydipsia	2006UW06824	Obesity (BMI = 32.3), HTN, ↑ cholesterol
2006UW06739	Family hx of diabetes	2006UW07135	Family hx of diabetes
2006UW09165	Gestational diabetes, ↑BG on Olanzapine	2006UW09517	Obesity
2006UW14429	Obesity (BMI = 50.4)	2007UW01802	Morbid obesity
2007UW01289	Obesity (BMI = 33.7), dyslipidemia	2007AP00590	Obesity (BMI = 30.1), hyperlipidemia, smoker
2006UW25578	Obesity	2006UW27162	Family hx of diabetes
2006UW25558	Family hx of diabetes	2006UW19874	Family hx of diabetes
2006UW17285	Morbid obesity (BMI = 43.3), family hx of diabetes, non-compliance to diet	2006UW15871	Family hx of diabetes
2006UW21691	Obesity (BMI = 34.7), hyperlipidemia, smoker	2006UW20591	Obesity (BMI = 35)
2006UW17555	Obesity	2005AP02543	"Consumes 7-8 cans of juice a day"
2006AP01404	Obesity (BMI = 36.5), hyperlipidemia, metabolic syndrome, prior use of glucocosteroids		

BG blood glucose. BMI body mass index. DM diabetes mellitus. HTN hypertension. Hx history. Wt weight. NB: All BMI measurements are kg/m^2.

Table A178 Medically confirmed reports of new onset DM/hyperglycemia confounded by concomitant medications

Report #	Confounding concomitant medications	Report #	Confounding concomitant medications
2006UW08704	Lithium[a]	2004AP01183	Olanzapine[a,b]
2006UW12419	Olanzapine[a,b]	2006AP03115	Olanzapine[a,b], furosemide[a]
2006AP02227	Olanzapine[a,b]	2007UW01529	Clozapine[a,b]
2005UW06041	Lithium[a], olanzapine[a,b]	2005UW14299	Olanzapine[a,b]
2005UW19267	Olanzapine[a,b]	2004AP06088	Lithium[a]
2005AP02911	Furosemide[a]	2004AP02849	Chlorpromazine[a,d]
2005AP02438	Chlorpromazine[a,d]	2005GB01163	Lithium[a]
2005SE01088	Lithium[a]	2006UW02431	"Steroids"[a,b]
2006UW03144	Lithium[a]	2004AP01247	Chlorpromazine[a,d]
2003SE02056[e]	Progesterone/estrogen[b,g,h]	2004UW17477	Lithium[a]
2004UW22418	Lithium[a]	2004UW20259	Furosemide[a]
2003UW14175	Clozapine[a,b]	2003UW11698	Lithium[a]
2003GB02288	Chlorpromazine[a,d]	2005UW08218	Lithium[a]
2003AP00109[f]	Lithium[a], chlorpromazine[a,d]	2003AP01151	Olanzapine[a,b]
2001AP02034	Chlorpromazine[a,d]	2003AP01546	Lithium[a], chlorpromazine[a,d]
2002UW13371	Olanzapine[a,b]	2002AP04278	Chlorpromazine[a,d]
2002AP00323	Olanzapine[a,b]	2001UW13265	Olanzapine[a,b]
2001UW07693	Prednisone[a]	2001GB00094	Lithium[a]
1998UW48512	Lithium[a]	2005AP00531	Furosemide[a]

[a] For which hyperglycemia has been reported.
[b] For which DM has been reported.
[c] For which DKA has been reported.
[d] For which altered glucose tolerance has been reported.
[e] Patient recovered while continuing Seroquel.
[f] This report described a negative dechallenge.
[g] For which reduced glucose tolerance has been reported.
[h] For which insulin resistance has been reported.
[i] For which hyperglycemia or DM have been reported.

Table A179 Medically confirmed reports containing limited information

Case IDs					
2006UW07207	2005UW03577	2004AP03941	2004UW15170	2003UW05396	2003UW01256
2006UW25884	2005UW04553	2004UW04704	2004UW22011	1999AP01985	2005SE02084
2006UW04994	2004UW10036	2004UW12279	2004UW18638	1998UW49037	1999UW03387
2002GB02591	2004AP01224	2006UW14277	2005AP02542	2006UW15023	2006UW15601
2006UW17186	2006AC00858	2006AC01949	2007UW02992	2007UW03915	2007UW03843

Table A179 Medically confirmed reports containing limited information

Case IDs					
2007UW02348	2007UW01698	2007AP00921	2007AC00300	2007AP01350	2006UW03133
2006UW00106	2006SE05501	2004UW16815			

Table A180 Medically confirmed reports of new onset DM/hyperglycemia containing scant clinical detail

2001UW02046	2003UW11934	2005UW11287	2004UW21192	2005UW02298	2005UW18517
1998AP50408	2003UW14174	2004UW03266	2004UW21169	2005UW02561	2005UW18552
2001SE08506	2003UW11521	2004UW01756	2004UW21213	2005UW02950	2005UW18353
2001AP04437	2003UW11520	2004UW04695	2004UW21255	2005GB00584	2005UW18145
2003AP03248	2003UW05429	2004UW04671	2004UW21571	2005UW01015	2005UW18059
2000UW04533	2003UW07379	2004UW04522	2004UW19366	2005UW01100	2005UW17841
2000UW04346	2003UW08142	2004UW25289	2004UW17889	2005UW05563	2005UW17017
1999UW00967	2003UW08145	2004UW24577	2005AC00788	2005UW05603	2002UW16580
1998UW48844	2003UW09218	2004UW05539	2005AC00782	2005UW08333	2003UW19525
2002UW14927	2003UW09399	2006UW01524	2005AP02193	2005UW10118	2005UW02641
2002UW15169	2003UW03250	2003UW02110	2002UW02227	2005UW09719	2005UW13683
2002UW15836	2003UW03648	2004UW05804	2005PK00254	2005UW04550*	2005UW12229
2005UW13214	2003UW03853	2004UW08038	2004UW09151	2005UW11269	2004AP06365
2002UW16583	2003UW00329	2004UW10326	2005GB00818	2005UW11071	2002UW14549
2002UW16588	2004SE05328	2004UW09771	2005GB00660	2005UW10734	2005UW01464
2002UW10490	2005UW01420	2004UW09556	2005AP04504	2004UW09179	2004AP06367
2002UW11778	2004AP03990	2004UW09532	2002UW14319	2005UW12089	2004AP00410
2002UW03965	2004AP00015	2004UW15502	2005UW01153	2005UW13192	2004UW16508
2003AP01273	2005UW01915	2004UW16310	2005UW04012	2005UW12769	2004AC00697
2003SI302724	2003UW05599	2004UW16509	2005UW04289	2005UW14019	2006UW02604
2003GB00705	2004AC00102	2006UW10596	2005UW02691	2005UW14793	2006UW12443
2003UW13780	2006UW12007	2004UW22878	2006UW08634	2005UW15296	2005UW15863
2003UW13872	2004UW03302	2004UW22678	2003GB00604	2006UW22488	2006UW20606
2006UW20339	2006UW19890	2006UW19873	2006UW19464	2006UW19419	2006UW18601
2006UW03510	2006UW17932	2006UW16290	2006UW16195	2006UW16066	2006UW15522
2006UW15424	2007UW02554	2007UW03717	2007AP01352	2007UW00143	2006UW15365
2006UW15113	2006UW14915	2006UW14858	2006UW14104	2006UW13387	2006UW12794
2006UW07673	2006UW06847	2006UW06671	2006UW06636	2006UW06555	2006UW06553
2006UW06514	2006GB02217	2006UW05947	2006UW05907	2006UW05474	2006UW05458
2006UW04929	2006GB01459	2006UW03142	2006UW02685	2006UW02536	2006UW02347

Table A180 Medically confirmed reports of new onset DM/hyperglycemia containing scant clinical detail

2006UW02211	2006AP05858	2006UW01539	2006UW01314	2006UW01299	2006UW00205
2006PK02561	2006UW00632	2006AP04351	2006PK01639	2006AP01919	2006AP05289
2006AP04830					

* This report described a fatal outcome, however the patient's cause of death was unknown.

Table A181 Non-medically confirmed reports of new onset DM/hyperglycemia confounded by medical history/risk factors

Report #	Confounding med hx/risk factor	Report #	Confounding med hx/risk factor
2005UW00133	HTN, obesity (BMI = 36.2)	2005UW02698	HTN
2004UW12192	Obesity (BMI = 35.5)	2005UW07355	Obesity (BMI = 38.8), hyperlipidemia
2005UW10599	Family history of DM	2005UW12391	HTN, obesity (BMI = 36.7)
2004UW17047	Obesity (BMI = 32.4)	2006UW02962	Obesity (BMI = 44)
2005UW01840	Obesity (BMI = 32.7), HTN	2006UW00461	Obesity (BMI = 35.3), history of hyperglycemia
2005UW14369	Obesity (BMI = 31), hypercholesterolemia	2005UW09668	Polycystic ovarian syndrome, HTN, hyperlipidemia, obesity (BMI = 39.3)
2002UW14620	"Blood sugar changes"	2005UW08632	Obesity (BMI = 34.8), HTN
2005UW06918	Obesity (BMI = 37.3)	2005UW09706	HTN, hypercholesterolemia
2007UW02310	Obesity (BMI=34.5)	2007UW00385	Family history of DM, obesity (BMI=31.2)
2006UW04676	HTN, family history of DM	2006UW08048	Family history of DM
2006UW20514	Obesity (BMI=38)	2006UW21855	Obesity (BMI=32.2)
2006UW24319	HTN, obesity (BMI=38)	2006UW25829	Obesity (BMI=43.9)
2006UW18655	Family history of DM	2006UW17008	Family history of DM
2006UW17263	Family history of DM	2006UW17358	Obesity (BMI=39.4)
2006UW17924	Obesity (BMI=35.7)	2006UW12618	HTN
2006UW13930	HTN, hypercholesterolemia	2006UW13992	Obesity (BMI=40.9), hypercholesterolemia
2006UW14013	Obesity (BMI=36.3)	2006UW14206	HTN
2006UW15343	Obesity (BMI=34.9)	2004UW19506	HTN, obesity [BMI = 44.7 kg/m2]

BMI body mass index, DM diabetes mellitus, HTN hypertension, Hx history. NB All BMI measurements are kg/m^2.

Table A182 Non-medically confirmed reports of new onset DM/hyperglycemia containing scant clinical detail

Case IDs					
2006UW02098	2006UW05364	2007UW01632	2006UW15593	2006UW16023	2006UW15114
2006UW19259	2006UW11130	2006UW12515	2006UW14296	2006UW14585	2006UW13996

Table A182 Non-medically confirmed reports of new onset DM/hyperglycemia containing scant clinical detail

Case IDs					
2006UW19130	2006UW19007	2006UW20745	2006UW22524	2006UW20522	2006UW28429
2006UW28202	2006UW27459	2006UW27264	2006UW11040	2006UW09819	2006UW09601
2006UW09438	2006UW07255	2006UW06901	2006UW06698	2006UW06655	2006UW05944
2006UW05900	2006UW05828	2006UW05676	2006UW05634	2006UW05594	2006UW05560
2006UW05414	2006UW05348	2006UW05185	2006UW04851	2006UW04814	2006UW04674
2006AC02345	2007UW02326	2007UW02376	2007UW02479	2007UW03037	2005UW06946
2005UW07805	2005UW09571	2005UW11707	2005UW11731	2005UW11953	2005UW11967
2005UW12374	2005UW12648	2005UW15763	2005UW16980	2005UW18872	2005UW03840
2005GB01942	2005AP05998	2004UW26262	2004UW22096	2004UW19755	2006UW02819
2006UW02799	2006UW03232	2006UW02285	2006UW00847	2006UW01663	2006UW01024
2004UW03479	2004UW06618	2004UW12849	2004UW13072	2004UW15964	2004UW17850
2003UW02469	2003UW03127	2003UW10204	2003UW12728	2003UW17274	2002UW09743
2001UW13414	2002UW05977	2000UW01047	2006GB01749	2006AP04877	2006UW04018
2006UW03831	2006UW03872				

Table A183 Legal reports (non medically confirmed) of new onset DM/hyperglycemia containing no clinical detail

2006UW03318	2006UW03296	2006UW03268	2006UW03025	2006UW03007	2006UW02145
2006UW03319	2006UW03297	2006UW03270	2006UW03026	2006UW03008	2006UW02146
2006UW03317	2006UW03295	2006UW03260	2006UW03024	2006UW03006	2006UW02142
2006UW03316	2006UW03294	2006UW03259	2006UW03023	2006UW03005	2006UW02024
2006UW03315	2006UW03293	2006UW03258	2006UW03022	2006UW03004	2006UW01927
2006UW03314	2006UW03291	2006UW03256	2006UW03021	2006UW03003	2006UW01925
2006UW03313	2006UW03288	2006UW03253	2006UW03020	2006UW03002	2006UW01882
2006UW03312	2006UW03287	2006UW03251	2006UW03019	2006UW03001	2006UW01816
2006UW03307	2006UW03286	2006UW03036	2006UW03018	2006UW03000	2006UW01766
2006UW03306	2006UW03285	2006UW03035	2006UW03017	2006UW02384	2006UW01660
2006UW03305	2006UW03283	2006UW03034	2006UW03016	2006UW02378	2006UW01649
2006UW03304	2006UW03280	2006UW03033	2006UW03015	2006UW02377	2006UW01647
2006UW03303	2006UW03279	2006UW03032	2006UW03014	2006UW02376	2006UW01616
2006UW03302	2006UW03277	2006UW03031	2006UW03013	2006UW02375	2006UW01577
2006UW03301	2006UW03276	2006UW03030	2006UW03012	2006UW02374	2006UW01567
2006UW03300	2006UW03274	2006UW03029	2006UW03011	2006UW02373	2006UW01475

Table A183 Legal reports (non medically confirmed) of new onset DM/hyperglycemia containing no clinical detail

2006UW03299	2006UW03273	2006UW03028	2006UW03010	2006UW02372	2006UW01463
2006UW03298	2006UW03272	2006UW03027	2006UW03009	2006UW02150	2006UW01461
2006UW00983	2005UW15263	2005UW15595	2005UW14815	2005UW14261	2005UW13877
2006UW00981	2005UW16052	2005UW15589	2006UW00985	2005UW13288	2005UW13876
2006UW00980	2005UW16027	2005UW15425	2005UW14265	2005UW14037	2005UW13875
2006UW01798	2005UW15691	2005UW15413	2005UW14264	2005UW13297	2005UW13872
2006UW00794	2005UW15686	2005UW14907	2005UW14263	2005UW13878	2005UW13870
2005UW13867	2005UW13389	2005UW13362	2005UW13285	2005UW13295	2006UW00791
2005UW13504	2005UW13308	2005UW13323	2005UW13236	2005UW13294	2006UW00434
2005UW13503	2005UW13306	2005UW13301	2005UW13298	2005UW13292	2006UW00027
2005UW13489	2005UW13382	2005UW13286	2007UW00007	2007UW00009	2007UW00011
2007UW00108	2007UW00344	2007UW00736	2007UW00739	2007UW00750	2007UW00826
2007UW00829	2007UW00833	2007UW00836	2007UW00839	2007UW00848	2007UW00849
2007UW00851	2007UW00862	2007UW00864	2007UW00865	2007UW00867	2007UW00868
2007UW00990	2007UW01032	2007UW01041	2007UW01081	2007UW01083	2006UW01930
2006UW03269	2007UW03160	2006UW03310	2006UW03311	2006UW03526	2006UW03653
2006UW03657	2006UW03665	2006UW03808	2006UW04341	2006UW04344	2006UW04346
2006UW04347	2006UW04348	2006UW04349	2006UW04435	2006UW04560	2006UW04575
2006UW04576	2006UW04578	2006UW04579	2006UW04581	2006UW04582	2006UW04584
2006UW04825	2006UW04335	2006UW05632	2006UW05781	2006UW06078	2006UW06083
2006UW06084	2006UW06085	2006UW06087	2006UW06091	2006UW06092	2006UW06093
2006UW06094	2006UW06095	2006UW06096	2006UW06097	2006UW06099	2006UW06191
2006UW06820	2006UW06955	2006UW06956	2006UW06978	2006UW06982	2006UW06984
2006UW06987	2006UW06988	2006UW06989	2006UW06991	2006UW06992	2006UW06993
2006UW06996	2006UW06997	2006UW06999	2006UW07000	2006UW07003	2006UW07004
2006UW07006	2006UW07007	2006UW07008	2006UW07009	2006UW07010	2006UW07011
2006UW07013	2006UW07015	2006UW07016	2006UW07017	2006UW07021	2006UW07022
2006UW07023	2006UW07024	2006UW07025	2006UW07026	2006UW07027	2006UW07028
2006UW07029	2006UW07030	2006UW07031	2006UW07032	2006UW07033	2006UW07034
2006UW07035	2006UW07036	2006UW07037	2006UW07038	2006UW07039	2006UW07040
2006UW07041	2006UW07042	2006UW07043	2006UW07044	2006UW07045	2006UW07046
2006UW07047	2006UW07156	2006UW07925	2006UW08785	2006UW09112	2006UW09311
2006UW09629	2006UW09633	2006UW09758	2006UW09760	2006UW09762	2006UW09764
2006UW09853	2006UW09855	2006UW09856	2006UW09861	2006UW09862	2006UW09863
2006UW09865	2006UW09867	2006UW09869	2006UW09870	2006UW09872	2006UW09873
2006UW09876	2006UW09878	2006UW10153	2006UW10161	2006UW10190	2006UW10191

Table A183 Legal reports (non medically confirmed) of new onset DM/hyperglycemia containing no clinical detail

2006UW10192	2006UW10491	2006UW10919	2006UW09111	2006UW26605	2006UW26608
2006UW26613	2006UW26616	2006UW26623	2006UW26625	2006UW26627	2006UW26628
2006UW26629	2006UW27627	2006UW27731	2006UW27805	2006UW27806	2006UW28167
2006UW28248	2006UW20482	2006UW20483	2006UW21045	2006UW21804	2006UW22125
2006UW23421	2006UW23772	2006UW24276	2006UW25695	2006UW19373	2006UW19374
2006UW19375	2006UW19377	2006UW19378	2006UW19550	2006UW20181	2006UW20184
2006UW20466	2006UW20468	2006UW20469	2006UW20470	2006UW20471	2006UW20473
2006UW20476	2006UW20477	2006UW20478	2006UW20479	2006UW20481	2006UW18801
2006UW18803	2006UW18871	2006UW18885	2006UW18889	2006UW18922	2006UW18926
2006UW19010	2006UW19017	2006UW19018	2006UW19019	2006UW19020	2006UW19247
2006UW19248	2006UW19250	2006UW19252	2006UW19255	2006UW19256	2006UW19257
2006UW19372	2006UW17237	2006UW17331	2006UW17393	2006UW17478	2006UW17479
2006UW17482	2006UW17484	2006UW17485	2006UW17555	2006UW17561	2006UW18086
2006UW12967	2006UW13041	2006UW14652	2006UW14784	2006UW15596	2006UW15780
2006UW16029	2006UW16345	2006UW16346	2006UW01642	2007UW01967	2007UW01968
2007UW01969	2007UW01996	2007UW02003	2007UW02004	2007UW02008	2007UW02010
2007UW02012	2007UW02014	2007UW02015	2007UW02018	2007UW02019	2007UW02022
2007UW02024	2007UW02025	2007UW02026	2007UW02027	2007UW02028	2007UW02032
2007UW02033	2007UW02034	2007UW02035	2007UW02036	2007UW02037	2007UW02039
2007UW02040	2007UW02041	2007UW02043	2007UW02044	2007UW02046	2007UW02048
2007UW02049	2007UW02051	2007UW02052	2007UW02053	2007UW02054	2007UW02055
2007UW02057	2007UW02058	2007UW02059	2007UW02060	2007UW02061	2007UW02069
2007UW02070	2007UW02071	2007UW02072	2007UW02073	2007UW02074	2007UW02076
2007UW02077	2007UW02078	2006UW19376	2007UW02081	2007UW02082	2007UW02083
2007UW02084	2007UW02086	2007UW02087	2007UW02089	2007UW02092	2007UW02094
2007UW02099	2007UW02100	2007UW02101	2007UW02108	2007UW02117	2007UW02118
2007UW02119	2007UW02121	2007UW02123	2007UW02124	2007UW02125	2007UW02126
2007UW02129	2007UW02130	2007UW02132	2007UW021333	2007UW02138	2007UW02141
2007UW02145	2007UW02146	2007UW02147	2007UW02152	2007UW02153	2007UW02156
2007UW02159	2007UW02162	2007UW02167	2007UW02168	2007UW02170	2007UW02174
2007UW02182	2007UW02195	2007UW02197	2007UW02275	2007UW02276	2007UW02290
2007UW02306	2007UW02307	2007UW02309	2007UW01409	2007UW01412	2007UW01413
2007UW01517	2007UW01564	2007UW01566	2007UW01569	2007UW01573	2007UW01899
2007UW01966	2007UW01900	2007UW01901	2007UW01918	2007UW01931	2007UW01932
2007UW01933	2007UW01934	2007UW01935	2007UW01936	2007UW01937	2007UW01938
2007UW01939	2007UW01940	2007UW01941	2007UW01942	2007UW01943	2007UW01944

Table A183 Legal reports (non medically confirmed) of new onset DM/hyperglycemia containing no clinical detail

2007UW01945	2007UW01946	2007UW01947	2007UW01948	2007UW01949	2007UW01950
2007UW01951	2007UW01952	2007UW01954	2007UW01955	2007UW01956	2007UW01957
2007UW01958	2007UW01960	2007UW01961	2007UW01962	2007UW01963	2007UW01964
2007UW01965	2007UW01391	2007UW01398	2007UW01400	2007UW01404	2007UW01407
2006UW06088	2007UW03190	2007UW03197	2007UW03198	2007UW03200	2007UW03201
2007UW03578	2007UW03580	2007UW03596	2007UW03599	2007UW03600	2007UW03602
2007UW03603	2007UW03615	2007UW03618	2007UW03626	2007UW03660	2006UW06953
2006UW03309	2006UW20474	2007UW02338	2007UW02356	2007UW02359	2007UW02360
2007UW02368	2007UW02372	2007UW02387	2007UW02389	2007UW02392	2007UW02397
2007UW02400	2007UW02499	2007UW02405	2007UW02406	2007UW02431	2007UW02433
2007UW02440	2007UW02447	2007UW02448	2007UW02451	2007UW02452	2007UW02496
2007UW02497	2007UW02564	2007UW02573	2007UW02575	2007UW02577	2007UW02584
2007UW02621	2007UW02670	2007UW02680	2007UW02681		

Table A184 Medically confirmed cases of exacerbation of DM containing scant clinical detail

Case IDs					
2005AC00653	2004UW21792	2005SE05065	2005UW01209	2005UW01229	2005UW03227
2005UW16326	2005UW14031	2004UW15531	2004UW00640	2003UW06840	2003UW11996
1999AP06660	2001UW07793	2001UW08041	2002GB03159	2002UW14424	2003AP00038
2003AP04402	2003GB01220	2005UW03200	2002UW12946	2004UW13432	2003UW17164
2006UW09328	2006UW16570	2006UW21474	2006UW14161		

Table A185 Non-medically confirmed report of exacerbation of DM containing scant clinical detail

Case IDs					
2005UW09726	2005UW12779	2005UW02096	2004UW24075	2005UW19103	2006UW01185
2006UW03255	1999UW00288	2003UW02626	2006UW04564	2006UW04607	2006UW04651
2006UW04860	2006UW04918	2006UW05878	2006UW05940	2006UW07132	2006UW10478
2006UW28562	2006UW20586	2006UW17567	2006UW15194	2006UW15652	

Appendix B Pediatric data (Trial D1441C00149)

Study design

This was a 3-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 600 mg/day) and placebo, given in divided doses (either twice daily [bid] or three times daily [tid], per the judgement of the investigator), in patients aged 10 to 17 years with Bipolar I mania. The study design and age range were dictated by a Written Request from the FDA. Patients were randomly assigned to blinded study treatment in a 1:1:1 ratio and stratified by age group (10 to 12 years and 13 to 17 years). Double-blind treatment was preceded by a medication washout period of 1 to 28 days (depending on the medications involved and at the discretion of the investigator) during which time the patient could have been hospitalized if deemed clinically necessary. The patient could have been treated as an inpatient or outpatient throughout the course of the study, according to the clinical judgment of the investigator.

Diabetic subgroups and glucose related laboratory values

Diabetics were defined as those with fasting glucose ≥126 mg/dL at randomization, or $HbA1_c$ above ULN at randomization, or a history of diabetes.

Diabetic risk group were those with fasting glucose ≥100 and <126 mg/dL at randomization, or history of gestational diabetes, or BMI ≥35 kg/m^2.

Non-diabetics were those not meeting criteria for diabetes or diabetic risk.

Potentially important glucose values were defined as:

Fasting glucose: ≤2.5 mmol/L (≤45 mg/dL); ≥7 mmol/L (≥126 mg/dL)

Random glucose: ≤2.5 mmol/L (≤45 mg/dL); ≥11.1 mmol/L (≥200 mg/dL)

Insulin resistance, assessed by HOMA-R calculated as (insulin value (mU/mL) x glucose value (mmol/L)) divided by 22.5, are summarized.

Insulin sensitivity, assessed by QUICKI calculated as 1 divided by the following value (log10(insulin value (μU/mL)) + $\log_{10}$(glucose value (mg/dL))), is summarized.

Adverse events potentially associated with DM

Adverse events potentially associated with DM are summarized by preferred term in Table B1.

Table B1 Adverse events coded to diabetes mellitus (safety population)

Preferred term	Quetiapine 400 mg (N=95)		Quetiapine 600 mg (N=98)		Placebo (N=90)	
	n	%	n	%	n	%
Total[a]	3	3.2	1	1.0	0	0.0
Blood insulin increased	1	1.1	1	1.0	0	0.0
Glycosylated hemoglobin increased	0	0.0	1	1.0	0	0.0
Thirst	2	2.1	0	0.0	0	0.0

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.
NOTE: Data are ordered by descending incidence in the quetiapine 600 mg group.
Data derived from D1441C00149 draft CSR

Four patients experienced AEs potentially related to diabetes One patient, a 12-year-old boy in the 400 mg quetiapine group, experienced thirst on Day 7 of treatment, which was judged by the investigator to be mild in intensity and not related to study medication. His serum glucose, insulin, and HbA1c values were normal at Day –6 (baseline) and Day 23 (final visit); he was fasting (≥8 hours since his last meal) at both of these time points. Thirst resolved in 5 days without change in study medication. The second patient, a 15-year-old boy in the 400 mg quetiapine group, experienced thirst on Day 2 of treatment, which was judged by the investigator to be mild in intensity and related to study medication. His serum glucose and HbA1c values were normal at Day –1 (baseline) and Day 3 (final visit); he was fasting at both of these timepoints. His insulin concentration was elevated on Day -1 (48 µIU/mL) and normal on Day 3 (20 µIU/mL). Thirst resolved without change in study medication. Neither of these patients had a known family history of diabetes nor did they have any biological family members with diabetes. There is no evidence to suggest that in these two reports the event of thirst was an indication of diabetes or sign and symptoms of diabetes. The third patient, a 13-year-old girl in the 400 mg quetiapine group, experienced blood insulin increased on Day 19, which was judged by the investigator to be mild in intensity and not related to study medication. Her blood insulin levels were 22 µIU/mL on Day –8 (baseline), 40 µIU/mL on Day 19, and 52 µIU/mL on Day 39 (final visit) She was confirmed fasting at all 3 visits, and her serum glucose and HbA1c concentrations were normal at each of the laboratory evaluations (HbA1c was not taken at the Day 39 visit). The fourth patient, a 14-year-old boy in the 600 mg quetiapine group, had an AE of blood insulin increased, which was judged by the investigator to be mild in intensity and not related to study medication, and an AE of glycosylated hemoglobin increased, which was judged by the investigator to be mild in intensity and related to study medication; both of which occurred on Day 22. On Day –9 (baseline) and Day 21 (final visit), his serum glucose concentrations were 104 mg/dL (normal) and 120 mg/dL (high), blood insulin concentrations were 46 µIU/mL (high) and 48 µIU/mL (high), and HbA1c concentrations were 6.5% (high) and 7.4% (high). He was confirmed fasting at both of these time points.

All AEs potentially related to diabetes were mild in intensity, and none resulted in discontinuation from the study.

Laboratory values

Changes in mean values over time in clinical chemistry

Changes from baseline to Day 21 are shown in Table B2.

Table B2 Clinical chemistry changes from baseline (safety population)

	Quetiapine 400 mg (N=95)			Quetiapine 600 mg (N=98)			Placebo (N=90)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Glucose, fasting[a] (mg/dL)	87	3.4828	11.49708	83	3.7590	13.10240	81	-1.1728	11.03040
HOMA-R	67	1.9501	12.35612	73	2.8898	7.02099	67	-0.0210	3.77324
Insulin (µIU/mL)	76	6.7500	46.00409	83	10.5060	26.58093	76	-1.3816	23.88750
HbA1c (%)	88	-0.0011	0.25708	85	0.0494	0.23023	81	0.0123	0.16154
QUICKI	67	-0.0115	0.03723	73	-0.0197	0.04365	67	0.0006	0.04381

[a] Fasting was defined as ≥8 hours between time of last meal and time of blood draw.
ALAT (or ALT) Alanine aminotransferase. ASAT (or AST) Aspartate aminotransferase. HbA1c Glycosylated hemoglobin. HDL High density lipoprotein. HOMA Homeostasis model assessment. LDL Low density lipoprotein. QUICKI Quantitative insulin sensitivity check index. SD Standard deviation. TSH Thyroid stimulating hormone. T4 Thyroxine.
Data derived from D1441C00149 draft CSR.

Mean and median values at baseline and Day 21 for fasting glucose (defined as ≥8 hours between time of last meal and time of blood draw) and HbA1c were similar for the 3 treatment groups. Mean and median changes from baseline for HbA1c were similar for the 3 groups. Mean and median changes from baseline showed increases for the two quetiapine groups in fasting glucose (mean: 400 mg quetiapine: 3.4828 mg/dL; 600 mg quetiapine: 3.7590 mg/dL) that were not seen in the placebo group (mean: -1.1728 mg/dL). For other parameters reflecting glucose metabolism (HOMA-R, QUICKI, insulin), mean and median values at baseline were similar for the 3 treatment groups. Mean values at Day 21 were higher for HOMA-R and insulin and lower for QUICKI in the quetiapine groups; mean and median changes from baseline showed increases for the 2 quetiapine groups in HOMA-R (mean: 400 mg quetiapine: 1.9501; 600 mg quetiapine: 2.8898) and insulin (mean: 400 mg quetiapine: 6.7500 µIU/L; 600 mg quetiapine: 10.5060 µIU/L) values and decreases in QUICKI (mean: 400 mg quetiapine: -0.0115; 600 mg quetiapine: -0.0197) that were not seen in the placebo group (mean: HOMA-R: -0.0210; insulin: -1.38166 µIU/L; QUICKI: 0.0006).

Subgroup analyses of non-diabetics indicated that quetiapine-treated patients had greater mean changes from baseline in fasting glucose (400 mg quetiapine: 4.09 mg/dL; 600 mg quetiapine: 5.19 mg/dL) and insulin levels (400 mg quetiapine: 5.69 µIU/mL; 600 mg quetiapine: 11.55 µIU/mL) compared to placebo-treated patients (fasting glucose: 0.67 mg/dL; insulin:

-2.71 µIU/mL). Of those patients who were fasting (defined as ≥8 hours between the time of their last meal and the time of their blood draw), quetiapine-treated patients had greater mean changes from baseline in fasting glucose levels (400 mg quetiapine: 2.75 mg/dL; 600 mg quetiapine: 4.05 mg/dL) and insulin levels (400 mg quetiapine: 7.51 mg/dL; 600 mg quetiapine: 6.80 mg/dL) compared to placebo-treated patients (fasting glucose: -0.83 mg/dL; insulin: -3.14 µIU/mL). There were very few patients with diabetes (3 overall), with risk factors for diabetes (22 overall), or who were not fasting (34 overall), thus no conclusions could be made regarding insulin and fasting glucose levels in these populations.

Clinical chemistry by age group

Laboratory values are summarized by treatment group for patients aged 10-12 years old and patients aged 13-17 years old in Table B3 below.

Table B3 Glucose related labs by age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	PLA N=90
Glucose (mg/dL)	≤12 years	Baseline	N	42	42	36
			Mean	81.9286	86.1429	85.3889
			SD	6.22502	10.85733	10.60936
			Median	82.00	85.50	84.00
			Min to max	64.0 to 97.0	67.0 to 127.0	71.0 to 116.0
		Final	N	41	37	31
			Mean	89.0732	89.3784	85.0968
			SD	12.13958	10.20716	8.32808
			Median	88.0	87.0	86.0
			Min to max	67.0 to 131.0	72.0 to 116.0	68.0 to 100
		Change	N		40	37
			Mean	7.2250	2.7838	0.1290
			SD	12.67642	14.62140	10.94149
			Median	5.5	3.0	0.0
			Min to max	-12.0 to 54.0	-43.0 to 31.0	-27.0 to 21.0
	13-17 years	Baseline	N	52	55	54
			Mean	86.0192	83.7091	87.0852
			SD	7.61189	10.55615	10.25123
			Median	86.0	85.0	85.0
			Min to max	70.0 to 110.0	61.0 to 112.0	71.0 to 118.0
		Final	N	47	47	50
			Mean	86.2766	88.7660	85.6400
			SD	7.31497	10.87721	9.63573
			Median	85.0	86.0	85.0

Table B3 Glucose related labs by age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	PLA N=90
			Min to max	70.0 to 101.0	63.0 to 126.0	51.0 to 112.0
		Change	N	47	46	50
			Mean	0.2979	4.5435	-1.9800
			SD	9.39916	11.84850	11.11809
			Median	0.00	6.50	-0.50
			Min to max	-33.0 to 16.0	-30.0 to 32.0	-34.0 to 18.0
HOMA-R	≤12 years	Baseline	N	34	42	32
			Mean	1.1625	1.2984	1.9175
			SD	1.02545	1.21497	3.02075
			Median	0.7849	0.7886	1.0088
			Min to max	0.1416 to 4.6066	0.1485 to 4.5953	0.1547 to 11.8422
		Final	N	39	34	28
			Mean	2.6629	2.2895	1.4077
			SD	4.42492	2.91504	1.53284
			Median	1.0436	1.1487	0.9000
			Min to max	0.1485 to 24.1580	0.2487 to 13.3323	0.1589 to 7.0313
		Change	N	31	34	24
			Mean	1.5865	0.9746	0.1573
			SD	4.32693	2.31619	1.39499
			Median	0.2003	0.2565	-0.0744
			Min to max	-1.0280 to 20.5343	-1.5659 to 8.9828	-3.4781 to 3.6336
	13-17 years	Baseline	N	49	51	50
			Mean	2.0406	1.5505	1.7564
			SD	2.97546	1.32377	1.32861
			Median	1.0658	1.0263	1.3406
			Min to max	0.2021 to 17.0359	0.1416 to 5.1780	0.3247 to 6.5647
		Final	N	37	44	47
			Mean	2.2256	2.5885	1.8132
			SD	3.97164	3.10206	1.52342
			Median	1.2059	1.2703	1.5728
			Min to max	0.3039 to 24.2083	0.4145 to 14.6579	0.1623 to 7.5410
		Change	N	36	39	43
			Mean	0.0323	1.2360	-0.0996
			SD	5.05803	3.02937	1.49308
			Median	0.1715	0.4330	-0.2038

Table B3 Glucose related labs by age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	PLA N=90
			Min to max	-14.7551 to 21.9272	-3.9087 to 11.1563	-2.8705 to 4.8617
HbA_{1c}	≤12 years	Baseline	N	43	42	36
			Mean	5.2372	5.3048	5.2917
			SD	0.31850	0.36888	0.26118
			Median	5.30	5.25	5.30
			Min to max	4.70 to 6.10	4.60 to 6.20	4.60 to 5.70
		Final	N	41	38	31
			Mean	5.2634	5.3000	5.3258
			SD	0.33148	0.38061	0.33062
			Median	5.30	5.25	5.40
			Min to max	4.4 to 6.1	4.5 to 6.2	4.6 to 5.8
		Change	N	41	38	31
			Mean	0.0293	0.0000	0.0484
			SD	0.15206	0.24824	0.15678
			Median	0.000	0.000	0.000
			Min to max	-0.30 to 0.30	-1.10 to 0.30	-0.200to 0.30
	13-17 years	Baseline	N	52	55	54
			Mean	5.2365	5.2364	5.2722
			SD	0.29308	0.40660	0.29615
			Median	5.20	5.20	5.30
			Min to max	4.6 to 5.7	4.4 to 6.5	4.7 to 5.9
		Final	N	47	48	50
			Mean	5.2213	5.3354	5.2720
			SD	0.34949	0.47512	0.30841
			Median	5.30	5.30	5.30
			Min to max	3.9 to 5.8	4.6 to 7.4	4.6 to 5.8
		Change	N	47	47	50
			Mean	-0.2077	0.0894	-0.0100
			SD	0.32148	0.20876	0.16194
			Median	0.00	0.10	0.00
			Min to max	-1.5 to 0.4	-0.3 to 09	-0.5 to 0.3
Insulin (uIU/mL)	≤12 years	Baseline	N	36	42	35
			Mean	15.6389	14.8333	22.5429
			SD	13.63	13.74669	30.73161
			Median	10.00	10.0	14.0

Table B3 Glucose related labs by age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	PLA N=90
			Min to max	2.0 to 56.0	2.0 to 59.0	2.0 to 144.0
		Final	N	41	36	30
			Mean	28.6341	24.6111	19.9333
			SD	42.00581	28.90702	29.47814
			Median	13.0	14.0	11.0
			Min to max	2.0 to 235.0	3.0 to 139.0	2.0 to 156.0
		Change	N	35	36	29
			Mean	13.1429	10.3056	-3.0000
			SD	37.3750	20.44340	29.23794
			Median	3.00	3.50	-1.00
			Min to max	-16.0 to 191.0	-15.0 to 80.0	-127.0 to 63.0
	13-17 years	Baseline	N	51	56	53
			Mean	26.0196	20.0714	21.7358
			SD	31.35506	22.69630	16.78386
			Median	15.00	14.00	16.00
			Min to max	3.0 to 163.0	2.0 to 157.0	4.0 to 79.0
		Final	N	42	47	48
			Mean	26.7381	31.0426	21.4167
			SD	43.77830	34.24843	16.35749
			Median	14.0	16.0	18.5
			Min to max	4.0 to 277.0	5.0 to 145.0	2.0 to 80.0
		Change	N	41	47	47
			Mean	1.2927	10.6596	-0.3830
			SD	52.10146	3068301	20.18238
			Median	1.00	4.00	-1.00
			Min to max	-152.0 to 248.0	-42.0 to 126.0	-61.0 to 58.0
QUICKI	≤12 years	Baseline	N	34	42	32
			Mean	0.3464	0.3434	0.3417
			SD	0.04684	0.04695	0.05446
			Median	0.3433	0.3429	0.3306
			Min to max	0.2715 to 0.4620	0.2714 to 0.4560	0.2410 to 0.4646
		Final	N	39	34	28
			Mean	0.3238	0.3224	0.3425
			SD	0.04632	0.04158	0.04772
			Median	0.3286	0.3242	0.3361

Table B3 Glucose related labs by age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	PLA N=90
			Min to max	0.2268 to 0.4560	0.2414 to 0.4147	0.2587 to 0.4515
		Change	N	31	34	24
			Mean	-0.0219	-0.0229	-0.0075
			SD	0.03646	0.04125	0.05444
			Median	-0.0137	-0.0192	0.0061
			Min to max	-0.1187 to 0.0406	-0.1437 to 0.0549	-0.1347 to 0.0829
	13-17 years	Baseline	N	49	51	50
			Mean	0.3265	0.3282	0.3209
			SD	0.03957	0.03676	0.3412
			Median	0.3275	0.3297	0.3178
			Min to max	0.2351 to 0.4306	0.2675 to 0.4620	0.2603 to 0.3950
		Final	N	37	44	47
			Mean	0.3199	0.3145	0.3233
			SD	0.03217	0.03751	0.04136
			Median	0.3220	0.3199	0.3111
			Min to max	0.2272 to 0.4001	0.2389 to 0.3790	0.2564 to 0.4494
		Change	N	36	39	43
			Mean	-0.0026	-0.0169	0.0052
			SD	0.03603	0.04599	0.03652
			Median	-0.0074	-0.0157	0.0076
			Min to max	-0.0690 to 0.1012	-0.1121 to 0.1015	-0.0907 to 0.0876

Evaluations of glucose and insulin are summarized by treatment group and status of fasting confirmation for patients aged 10-12 years old and patients aged 13-17 years old in Table B4. There were too few patients who were not fasting to make meaningful comparisons between the age groups. For patients who were fasting, mean and median values at baseline and changes from baseline were similar for the two age groups.

Table B4 Glucose and insulin data by meal confirmed fasting and age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	Placebo N=90
CONFIRMED FASTING BY MEAL TIME DATA						
Fasting glucose (mg/dL)	≤12 years	Baseline	N	27	26	19
			Mean (SD)	82.15 (6.292)	83.77 (6.452	84.00 (8.609)

Table B4 Glucose and insulin data by meal confirmed fasting and age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	Placebo N=90
			Median	81.00	84.00	84.00
			Min to max	73.0 to 97.0	67.0 to 98.0	71.0 to 101.0
		Final	N	27	26	19
			Mean (SD)	87.44 (9.881)	88.69 (9.899)	83.68 (7.696)
			Median	86.00	86.50	85.00
			Min to max	67.0 to 119.0	73.0 to 116.0	68.0 to 93.0
		Change	N	27	26	19
			Mean (SD)	5.30 (9.988)	4.92 (10.688)	-0.32 (10.122)
			Median	3.00	3.50	0.00
			Min to max	-12.0 to 36.0	-11.0 to 27.0	-21.0 to 19.0
	13 to 17 years	Baseline	N	33	29	22
			Mean (SD)	85.24 (7.758)	84.24 (9.018)	86.95 (8.162)
			Median	86.00	86.00	85.00
			Min to max	70.0 to 101.0	62.0 to 104.0	75.0 to 118.0
		Final	N	33	29	22
			Mean (SD)	85.58 (7.562)	87.52 (8.567)	85.50 (5.189)
			Median	84.00	85.00	85.00
			Min to max	70.0 to 99.0	78.0 to 120.0	77.0 to 95.0
		Change	N	33	29	22
			Mean (SD)	0.33 (7.765)	3.28 (8.876)	-1.45 (7.903)
			Median	0.00	4.00	-1.00
			Min to max	-21.0 to 16.0	-12.0 to 23.0	-31.0 to 9.0
Insulin (uIU/mL)	≤12 years	Baseline	N	23	24	17
			Mean (SD)	12.61 (10.978)	9.79 (7.627)	13.94 (10.353)
			Median	9.00	8.50	12.00
			Min to max	2.0 to 44.0	2.0 to 33.0	2.0 to 44.0
		Final	N	23	24	17
			Mean (SD)	24.48 (47.419)	14.38 (11.765)	12.29 (10.652)
			Median	11.00	10.00	11.00
			Min to max	2.0 to 235.0	3.0 to 50.0	2.0 to 45.0
		Change	N	23	24	17
			Mean (SD)	11.87 (40.011)	4.58 (9.537)	-1.65 (8.238)
			Median	1.00	3.00	-2.00
			Min to max	-16.0 to 191.0	-11.0 to 40.0	-17.0 to 16.0
	13 to 17 years	Baseline	N	29	25	19

Table B4 Glucose and insulin data by meal confirmed fasting and age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	Placebo N=90
			Mean (SD)	16.97 (13.860)	12.08 (8.396)	19.84 (14.698)
			Median	12.00	10.00	14.00
			Min to max	4.0 to 68.0	2.0 to 46.0	4.0 to 53.0
		Final	N	29	25	19
			Mean (SD)	21.03 (21.031)	21.00 (27.582)	16.47 (10.824)
			Median	14.00	14.00	16.00
			Min to max	4.0 to 85.0	5.0 to 142.0	3.0 to 39.0
		Change	N	29	25	19
			Mean (SD)	4.07 (21.767)	8.92 (24.933)	-3.37 (10.910)
			Median	2.00	4.00	2.00
			Min to max	-45.0 to 65.0	-9.0 to 120.0	-37.0 to 17.0
		DATA NOT CONFIRMED WITH MEAL TIME DATA				
Fasting glucose (mg/dL)	≤12 years	Baseline	N	5	6	1
			Mean (SD)	78.60 (9.044)	96.33 (21.750)	107.00
			Median	80.00	86.00	107.00
			Min to max	64.0 to 86.0	78.0 to 127.0	107.0
		Final	N	5	6	1
			Mean (SD)	95.40 (22.523)	93.83 (12.703)	102.0
			Median	92.00	95.50	102.0
			Min to max	75.0 to 131.0	76.0 to 111.0	102.0
		Change	N	5	6	1
			Mean (SD)	16.80 (21.742)	-2.50 (27.501)	-5.00
			Median	11.00	-2.50	-5.00
			Min to max	-2.0 to 54.0	-43.0 to 31.0	-5.00
	13 to 17 years	Baseline	N	2	4	8
			Mean (SD)	99.00 (15.556)	88.00 (9.557)	95.38 (16.698)
			Median	99.00	89.50	94.00
			Min to max	88.0 to 110.0	77.0 to 96.0	73.0 to 117.0
		Final	N	2	4	8
			Mean (SD)	80.00 (4.243)	95.75 (20.982)	89.75 (6.671)
			Median	80	89.50	90.00
			Min to max	77.0 to 83.0	78.0 to 126.0	79.0 to 102.0
		Change	N	2	4	8
			Mean (SD)	-19.00 (19.799	7.75 (20.205)	-5.63 (15.146)
			Median	-19.00	9.50	-2.50

Table B4 Glucose and insulin data by meal confirmed fasting and age group

Lab test	Age group		Statistic	QTP 400 mg N=95	QTP 600 mg N=98	Placebo N=90
			Min to max	-33.0 to -5.0	-18.0 to 30.0	-31.0 to 12.0
Insulin (uIU/mL)	≤12 years	Baseline	N	8	7	2
			Mean (SD)	22.25 (13.895)	26.43 (20.173)	114.00 (59.397)
			Median	25.50	16.00	114.0
			Min to max	5.0 to 41.0	5.0 to 59.0	72.0 to 156.0
		Final	N	8	7	2
			Mean (SD)	44.00 (36.50)	56.00 45.884)	114.00 (59.397)
			Median	35.50	42.00	114.00
			Min to max	8.0 to 110.0	13.0 to 139.0	72.0 to 156.0
		Change	N	8	7	2
			Mean (SD)	21.75 (39.568)	29.57 (30.314)	15.50 (67.175)
			Median	8.50	24.00	15.50
			Min to max	-16.0 to 102.0	1.0 to 80.0	-32.0 to 63.0
	13 to 17 years	Baseline	N	2	7	8
			Mean (SD)	101.50 (86.974)	49.57 (51.127)	33.75 (18.148)
			Median	101.50	38.00	25.00
			Min to max	40.0 to 163.0	8.0 to 157.0	18.0 to 65.0
		Final	N	2	7	8
			Mean (SD)	22.50 (12.021)	69.71 (50.891)	32.25 (18.398)
			Median	22.50	56.00	27.00
			Min to max	14.0 to 31.0	6.0 to 145.0	14.0 to 71.0
		Change	N	2	7	8
			Mean (SD)	-79.00 (74.953)	20.14 (53.856)	-1.50 (28.839)
			Median	-79.00	-1.00	-5.00
			Min to max	-132.0 to -26.0	-42.00 to 117.0	-40.0 to 53.0

Changes in individual patients over time in clinical chemistry

The numbers of patients with normal clinical chemistry values at baseline and abnormal low or abnormal high values at Day 21 are summarized by treatment group in Table B5 below.

Table B5 Shifts in chemistry values from normal at baseline to out-of-range values - incidence (safety population)

	Shift to low, n (%)			Shift to high, n (%)[a]		
	Quetiapine 400 mg (N=95)	Quetiapine 600 mg (N=98)	Placebo (N=90)	Quetiapine 400 mg (N=95)	Quetiapine 600 mg (N=98)	Placebo (N=90)
Glucose, fasting[b]	1 (1.2)	1 (1.3)	1 (1.2)	2 (2.3)	2 (2.6)	0
HOMA-R	0	0	0	0	0	0
Insulin	1 (2.1)	3 (5.1)	6 (12.5)	9 (19.1)	16 (27.1)	9 (18.8)
HbA1c	1 (1.1)	0	0	0	2 (2.4)	0
QUICKI	0	0	0	0	0	0

[a] Percentages are based on all patients with values at baseline and Day 21
[b] Fasting was defined as ≥8 hours between time of last meal and time of blood draw.
ALAT (or ALT) Alanine aminotransferase. ASAT (or AST) Aspartate aminotransferase. HbA1c Glycosylated hemoglobin. HDL High density lipoprotein. HOMA Homeostasis model assessment. LDL Low density lipoprotein. QUICKI Quantitative insulin sensitivity check index. TSH Thyroid stimulating hormone. T4 Thyroxine.
Data derived from D1441C00149 draft CSR.

Similar numbers of patients changed from normal to abnormal low fasting glucose (defined as ≥8 hours between time of last meal and time of blood draw) between the 3 treatment groups and more quetiapine-treated patients shifted to abnormal high fasting glucose levels and to abnormal high HbA1c than placebo-treated patients. Changes from normal to abnormal high or low insulin were observed in similar numbers of patients in all 3 treatment groups.

Individual potentially clinically important abnormalities in clinical chemistry

The numbers of patients in each treatment group with baseline values that were not in the range of potentially clinically important and who recorded values at Day 21 in the potentially clinically important range are summarized in Table B6.

Table B6 Clinically important shifts in chemistry values from baseline - incidence (safety population)

	Shift to low, n (%)[a]			Shift to high, n (%)[a]		
	Quetiapine 400 mg (N=95)	Quetiapine 600 mg (N=98)	Placebo (N=90)	Quetiapine 400 mg (N=95)	Quetiapine 600 mg (N=98)	Placebo (N=90)
Glucose, fasting[b]	0	0	0	1 (1.1)	1 (1.2)	0
HOMA-R	0	0	0	0	0	0
Insulin	0	0	0	0	0	0
HbA1c	0	0	0	0	0	0
QUICKI	0	0	0	0	0	0

[a] Percentages are based on all patients with values at baseline and Day 21.
[b] Fasting was defined as ≥8 hours between time of last meal and time of blood draw.

ALAT (or ALT) Alanine aminotransferase. ASAT (or AST) Aspartate aminotransferase. BbA1c Glycosylated hemoglobin. HDL High density lipoprotein. HOMA Homeostasis model assessment. LDL Low density lipoprotein. QUICKI Quantitative insulin sensitivity check index. TSH Thyroid stimulating hormone. T4 Thyroxine.
Data derived from D1441C00149 draft CSR.

Two patients had potentially clinically important elevations of fasting glucose at the Day 21 windowed visit (fasting defined as ≥8 hours between time of last meal and time of blood draw); however, neither patient was fasting at the time of the elevations. The first patient, a 12-year-old boy in the 400 mg quetiapine group, had glucose values of 77 mg/dL and 131 mg/dL at Day –10 (baseline) and Day 22 (final visit), respectively. The other patient, a 15-year-old boy in the 600 mg quetiapine group, had glucose values of 96 mg/dL and 126 mg/dL at Day –9 (baseline) and Day 19 (final visit), respectively.

Discussion of clinical laboratory values

Changes in mean and median values for fasting glucose (defined as ≥8 hours between time of last meal and time of blood draw), insulin, and two derived measures of glucose metabolism (HOMA-R and QUICKI) showed greater changes in the quetiapine groups than in the placebo group. Patients in the quetiapine groups had larger mean increases in change from baseline of fasting glucose (400 mg quetiapine: 3.4828 mg/dL; 600 mg quetiapine: 3.7590 mg/dL), HOMA-R (400 mg quetiapine: 1.9501; 600 mg quetiapine: 2.8898), and insulin (400 mg quetiapine: 6.7500 µIU/L; 600 mg quetiapine: 10.5060 µIU/L), and larger decreases in change from baseline in QUICKI (400 mg quetiapine: -0.0115; 600 mg quetiapine: -0.0197), relative to the placebo group (fasting glucose: -1.1728 mg/dL; HOMA-R: -0.0210; insulin: -1.38166 µIU/L; QUICKI: 0.0006). Few patients in the quetiapine groups experienced potentially clinically important elevations of fasting glucose or reported AEs related to diabetic measures. Elevations in glucose and diabetic parameters are consistent with changes seen in the adult population (Haupt & Newcomer 2001). Further analysis of long-term exposure to quetiapine in Study 150 will help clarify differences between the adult and children/adolescent populations.

Overall summary

Low rates of AEs potentially related to DM were seen in quetiapine-treated patients, including mild AEs of thirst, blood insulin increased, and glycosylated hemoglobin in4565 bncreased, but none of these AEs resulted in discontinuation from the study. There was no evidence to suggest that the two events of thirst were either an indication of diabetes or a sign or symptom of diabetes. While two quetiapine-treated patients experienced potentially clinically important elevations in fasting glucose, neither patient was confirmed fasting; thus these elevations are not clinically meaningful. Laboratory data suggest that quetiapine may cause changes in diabetic indices (mean increases in insulin and HOMA-R and decreases in QUICKI), compared to placebo. Further analysis of these patients during the long-term study (Study 150) will provide increased understanding of the effect of quetiapine on glucose homeostasis.

Appendix C Post hoc analysis of Trials 126 & 127

1. SCOPE

Studies 126 and 127 were multicenter, randomized, parallel-group, double-blind studies to evaluate the efficacy of quetiapine versus placebo when used as adjunct to lithium or valproate in the maintenance treatment of adult patients with Bipolar I Disorder for up to 104 weeks.

Study 126 and Study 127 were unblinded for analysis and the primary endpoint was met in both studies. Evaluation of combined safety data from the two studies revealed an imbalance in the number of adverse events potentially associated with diabetes between treatments. Since these studies were not designed to thoroughly evaluate diabetic status, it was decided to undertake a clinical post hoc re-evaluation of unblinded data in an attempt to refine the pre-specified protocol definition. During this process a number of clinical questions have arisen that require further exploratory data analysis.

The purpose of this document is to (i) briefly describe the process for the clinical post-hoc re-evaluation and definition of cases of interest and (ii) to list out the additional questions this process has raised and (iii) to describe how these additional questions will be addressed via further exploratory evaluation of study data and (iv) to present the results of the analyses and summarize the findings related to each question.

2. DEFINITIONS

The following definitions were used in the post-hoc analyses:

- "Baseline" refers to enrollment or randomization depending on the purpose of the analysis
- All analyses of glucose data in this document will be performed using the "Documented fasting" subset, only considering samples that met the more stringent fasting conditions, ie, blood sampling documented in the CRF to be more than 8 h after the last meal.
- Impaired fasting glucose: a documented fasting glucose value $\geq$100 mg/dL and <126 mg/dL at baseline.
- BMI categories:
  - Underweight: <18.5
  - Normal weight: $\geq$18.5 and <25
  - Overweight: $\geq$25 and <30

- Obese: ≥30 and <40
- Morbid obesity: ≥40

- Weight change (change from baseline to last value in the randomized phase):
  - ≥1% decrease
  - <1% increase or decrease (no significant change)
  - 1%-<5% increase
  - ≥5% increase

3. POST-HOC EVALAUTION OF PROTOCOL DEFINITION OF A POSSIBLE DIABETIC EVENT

Adjudicated possible onset of, or exacerbation of possible diabetes were identified in the post-hoc clinical evaluation. The entire data set was examined using three distinct criteria and resultant patients meeting those criteria were listed. These criteria are summarized below:

1. All patients with adverse events emerging after enrollment and potentially associated with diabetes mellitus (except "polyuria", "polydipsia" and "thirst") (based on project-specific search of MedDRA preferred terms: anti-insulin antibody increased, anti-insulin antibody positive, blood glucose abnormal, blood glucose fluctuation, blood glucose increased, blood insulin abnormal, blood insulin decreased, blood insulin increased, blood insulin C-peptide abnormal, blood insulin C-peptide decreased, blood insulin C-peptide increased, blood proinsulin abnormal, blood proinsulin decreased, blood proinsulin increased, dawn phenomenon, diabetes mellitus, diabetes mellitus inadequate control, diabetes mellitus insulin dependent, diabetes mellitus non-insulin-dependent, diabetes with hyperosmolarity, diabetic coma, diabetic complication, diabetic hyperglycaemic coma, diabetic hyperosmolar coma, diabetic hyperosmolar non-ketoacidosis, diabetic ketoacidosis, diabetic ketoacidotic hyperglycaemic coma, glucose tolerance decreased, glucose tolerance impaired, glucose tolerance test abnormal, glucose urine present, glycosylated haemoglobin increased, hyperglycaemia, hyperinsulinaemia, hyperinsulinism, impaired fasting glucose, impaired insulin secretion, increased insulin requirement, insulin resistance, insulin resistance syndrome, insulin resistant diabetes, insulin-requiring type II diabetes mellitus, insulin tolerance test abnormal, metabolic disorder, somogyi phenomenon, polydipsia, polyuria, thirst, blood ketone body present, blood ketone body increased, neonatal diabetes mellitus, glycosuria during pregnancy, gestational diabetes, glucose tolerance impaired in pregnancy, diabetes complicating pregnancy).
2. Patients with medication that may be used for treatment of diabetes/hyperglycemia initiated or dose changed after enrollment (search criteria: ATC codes beginning with A10A and A10B)

3. Patients with at least 1 glucose value ≥126 mg/dL regardless of whether documented fasting or not documented fasting as the final observation, or at least 2 glucose values ≥126 mg/dL regardless of whether documented fasting or not documented fasting at any time during the study, or with an increase in HbA1c value ≥1.5 percentage points at any time during the study (from minimum to maximum value)

The open-label safety population consisted of 3371 patients and the randomized safety population consisted of 646 patients randomized to quetiapine and 680 randomized to placebo. There were 217 unique patients fulfilling at least one of the criteria. In total, 43 patients appeared on the adverse event-listing, 41 patients on the medication listing, and 187 patients on the glucose listing. These individual patients were further reviewed for possible onset or exacerbation of possible diabetes during the study. The post-hoc review process involved endocrinology experts from AstraZeneca, and used as a basis the American Diabetes Association (ADA) diabetes criteria below:

ORIGINAL CRITERIA: Diabetes Care, 1997;20(7):1183-97

"The new criteria

The diagnostic criteria for diabetes mellitus have been modified from those previously recommended by the NDDG or WHO. The revised criteria for the diagnosis of diabetes are shown in Table 3. Three ways to diagnose diabetes are possible, and each must be confirmed, on a subsequent day, by any one of the three methods given in Table 3. For example, one instance of symptoms with casual plasma glucose ≥ 200 mg/dL (11.1 mmol/l), confirmed on a subsequent day by 1) FPG ≥126 mg/dL (7.0 mmol/l), 2) an OGTT with the 2-h postload value ≥200 mg/dL (11.1 mmol/l), or 3) symptoms with a casual plasma glucose ≥200 mg/dL (11.1 mmol/l), warrants the diagnosis of diabetes.

Table 3- Criteria for the diagnosis of diabetes mellitus

1. Symptoms of diabetes plus casual plasma glucose concentration 200 mg/dL (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. FPG 126 mg/dL (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

or

3. 2-h PG 200 mg/dL (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO (2), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use."

FPG: Fasting plasma glucose; NNDG: National Diabetes Data Group; OGGT: oral glucose tolerance test; PG postload glucose; WHO: World Health Organization

The ADA criteria for diagnosis of diabetes specify confirmation of threshold glycemia "on a subsequent day," however, subsequent glycemic values from the study were most commonly separated by a period of several weeks. Therefore, an adaptation of the ADA criteria was agreed upon by the 2 AstraZeneca endocrinologists. The definitions for possible onset of possible diabetes where:

- a confirming glycemic value was obtained on a subsequent proximal visit (rather than the subsequent day)

or

- symptoms of diabetes plus documented fasting glucose ≥126 mg/dL or not documented fasting glucose ≥200 mg/dL.

Criteria for identifying cases of exacerbation of possible diabetes relied primarily upon the clinical judgment of the 2 adjudicating endocrinologists, and were usually based on clinically relevant increases in glucose or HbA1c, or other adverse event or medication information available from the study data.

4. QUESTIONS RAISED AND INTENDED FURTHER EXPLORATORY ANALYSIS OF DATA

The main purpose of the further exploratory, post-hoc evaluation of Study 126 and Study 127 data is to examine whether certain risk factors predispose to the occurrence of cases of interest or treatment emergent documented fasting blood glucose values ≥126 mg/dL on study treatment. Key potential risk factors are (i) impaired fasting glucose at enrollment, (ii) weight at enrollment and (ii) weight changes during the study.

Specific questions to answer are listed in Table C-1, with a short summary of proposed post-hoc analyses (mainly frequency and rate tables) and a reference to pre-defined and finalized analyses (mainly summary statistics on a group-level). Definitions and details around the planned analyses are outlined in following Table C-1. The analyses are based on the full set of patients receiving study drug (open-label and randomized safety populations) and on subsets.

Table C-1 Questions and proposed analyses

Question	Analyses	Table	Conclusions
Does impaired fasting glucose predispose to onset of fasting glucose ≥126 mg/dL during the study?	Incidence table for patients with and without impaired fasting glucose at baseline, with an onset of any documented fasting glucose ≥126 mg/dL during the study	Table C-11	Instances of glucose ≥126 mg/dL were more common in patients with impaired fasting glucose (defined as a documented fasting glucose value >100 mg/dL and <126 mg/dL at baseline) in the open-label phase and in both treatment groups in the randomized phase. There were more observations of blood glucose values ≥126 mg/dL in the quetiapine group than in the placebo group in the randomized phase, both for patients with and without impaired fasting glucose at randomization. The results were consistent with the standard analyses of potentially clinically important glucose data.
For the cases identified by the adjudication process to have possible onset of possible diabetes, how many of the patients had impaired fasting glucose at baseline?	No. of patients with and without impaired fasting glucose at baseline of the patients with adjudicated possible onset of possible diabetes in the OL or RD phases	Table C-12	Of the 7 patients adjudicated to have possible onset of possible diabetes in the randomized phase who had a documented fasting value at randomization, 5 patients had impaired fasting glucose at randomization.
Does weight/BMI at baseline predispose to onset of fasting glucose ≥126 mg/dL during the study?	Incidence table for patients with an onset of any fasting glucose ≥126 mg/dL during the study, by BMI category at study entry	Table C-13	In the open-label phase there was an increase in the incidence density of glucose ≥126 mg/dL with increasing baseline BMI. In the randomized phase there was no consistent increase in relative risk with quetiapine compared to placebo as baseline BMI category increases. In the morbidly obese (baseline BMI ≥40) there is an increase in relative risk with quetiapine

Question	Analyses	Table	Conclusions
For the cases identified by the adjudication process to have possible onset of possible diabetes, how many of the patients were in the different BMI categories at baseline?	No. of patients with adjudicated possible onset of possible diabetes in the OL or RD phase in different BMI categories at baseline	Table C-14	8 of 11 quetiapine patients with possible onset of possible diabetes in the randomized phase had baseline BMI ≥30. In the open-label phase, 15 of 23 patients had baseline BMI ≥30.
Does weight change correlate with the onset of fasting glucose ≥126 mg/dL during the study?	Incidence table for patients with any fasting glucose ≥126 mg/dL during the study, who had a weight decrease (>1%), no significant weight change (<1% increase or decrease), >1-<5% increase or >5% increase	Table C-15	No consistent effect of weight gain was seen in the open-label phase or in either group in the randomized phase.
For the cases identified by the adjudication process to have possible onset of possible diabetes, how many of the patients had changes in weight during the study?	No. of patients with adjudicated possible onset of possible diabetes in the OL or RD phase in different categories of weight change	Table C-16	7 of 11 adjudicated possible quetiapine cases in the randomized phase had a weight increase ≥5% since enrollment. 3 of 11 quetiapine patients had increase of ≥5% since randomization.

Question	Analyses	Table	Conclusions
What is the correlation between change in weight and changes in documented fasting glucose and HbA1c?	Correlation coefficients of change from enrollment to randomization and from randomization to end of treatment in weight and glucose, as reference to corresponding analyses in previous studies	Table C-10	Only weak correlations between change in weight and change in fasting glucose and HbA1c were observed in the open-label phase or in the randomized phase.
	Descriptive statistics of change in weight vs. changes in documented fasting glucose and HbA1c over time (from enrolment to randomization in the open-label phase and from randomization to last visit in the randomized phase)		

Question	Analyses	Table	Conclusions
Are increases in glucose during the open-label phase reversible when patients shift from open-label quetiapine to randomized study drug, and is there a difference in glycemic levels during the subsequent randomized phase for patients randomized to quetiapine vs. placebo?	Mean glucose during the open-label phase and randomized phase, respectively, for subgroups of patients with/without at least one glucose value ≥126 mg/dL during the open-label phase	Table C-17	Although the numbers of patients with treatment emergent blood glucose ≥126 mg/dL in the open-label treatment phase are small, patients who had at least one fasting glucose value ≥126 mg/dL and were subsequently randomized to placebo showed a decrease in their average glucose values in the randomized phase, both in the combined data from the 2 studies and in Study 127. Those randomized to quetiapine showed an increase, both in the combined data and in Study 127. In study 126, patients randomized to quetiapine showed a decrease (from 123.5 mg/dL to 111.5 mg/dL) in their average glucose values in the randomized phase while patients in the placebo group showed an increase (from 112.8 mg/dL to 116.4 mg/dL).
	Shift tables/plots of patients with low/normal/high values at baseline, shifting to low/normal/high post-baseline		
	Mean changes from randomization in the quetiapine group vs. the placebo group		

Question	Analyses	Table	Conclusions
For the cases identified by the adjudication process to have possible onset of possible diabetes in the open label phase, what was the subsequent glycemic status of the patients randomized to quetiapine vs placebo?	Listing of patients with adjudicated possible onset and exacerbation of possible diabetes. To facilitate the review, simple tabulations may also be used if necessary.		Of the 23 patients adjudicated to have possible onset of possible diabetes during the open-label phase, 6 were subsequently randomized to quetiapine and 11 to placebo. 3 of the 6 quetiapine patients and 1 of the 11 placebo patients exacerbated. Of the patients that did not exacerbate, 1 patient in each treatment group received additional medication.
What is the temporal profile of weight and glucose data?	A linear mixed model with the slope for each patient as a random effect to analyse the change in documented fasting glucose and weight data over time	Table C-38	Slopes for weight, fasting glucose and HbA1c over time were positive suggesting a time-dependent increase. This was also confirmed by mean plots and tables of descriptive statistics at each time point from enrollment to end of treatment

Question	Analyses	Table	Conclusions
	Descriptive statistics of changes in glucose, HbA1c and weight over time (during the randomized phase and from enrollment to end of randomized quetiapine treatment). Tables will also be produced for the subsets of patients with at least 48 weeks treatment and at least 60 weeks treatment, respectively, to reduce variability in estimates caused by patients with early withdrawal.		
	Box-plots for glucose and weight data and a mean plot of HbA1c vs weight data to display the simultaneous developments over time	Figure C-1 Figure C-2 Figure C-3 Figure C-4 Figure C-5	

Question	Analyses	Table	Conclusions
How many patients had insulin therapy initiated or insulin dose changed during the study?	Listing of patients searched by ATC-code, including age and gender and glucose, HbA1c and weight at entry and randomization.	Table C-19	7 patients had insulin therapy during the study, whereof 2 during the OL phase and 5 during the RD phase (3 PLA, 2 QTP)

5. TABLES AND FIGURES

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
Glucose (mg/dL)					
1 week	N [a]		1	2	3
	Enrollment	Mean(SD)	97.00	84.50(14.849)	88.67(12.741)
	At time point	Mean(SD)	103.00	86.00(1.414)	91.67(9.866)
	Change	Mean(SD)	6.00	1.50(13.435)	3.00(9.849)
		Median	6.00	1.50	6.00
		Min to Max	6.00 to 6.00	-8.00 to 11.00	-8.00 to 11.00
12 weeks	N [a]		118	100	218
	Enrollment	Mean(SD)	94.08(17.672)	92.09(24.728)	93.17(21.174)
	At time point	Mean(SD)	94.93(16.553)	93.89(19.978)	94.45(18.168)
	Change	Mean(SD)	0.85(18.654)	1.80(19.235)	1.28(18.885)
		Median	0.00	2.00	1.00
		Min to Max	-96.00 to 59.00	-125.0 to 59.00	-125.0 to 59.00
24 weeks	N [a]		117	109	226
	Enrollment	Mean(SD)	95.26(19.636)	89.49(15.148)	92.47(17.812)
	At time point	Mean(SD)	95.80(17.306)	93.13(19.755)	94.51(18.535)
	Change	Mean(SD)	0.55(21.613)	3.64(21.550)	2.04(21.590)
		Median	1.00	2.00	2.00
		Min to Max	-93.00 to 75.00	-46.00 to 142.00	-93.00 to 142.00
36 weeks	N [a]		97	75	172
	Enrollment	Mean(SD)	92.13(13.954)	90.37(26.321)	91.37(20.245)
	At time point	Mean(SD)	94.98(15.069)	92.93(16.689)	94.09(15.781)
	Change	Mean(SD)	2.85(14.441)	2.56(23.637)	2.72(18.944)
		Median	2.00	4.00	2.00
		Min to Max	-33.00 to 75.00	-139.0 to 72.00	-139.0 to 75.00
48 weeks	N [a]		127	113	240
	Enrollment	Mean(SD)	94.41(18.977)	92.38(23.854)	93.45(21.390)
	At time point	Mean(SD)	95.75(17.444)	103.23(44.493)	99.27(33.198)
	Change	Mean(SD)	1.34(20.076)	10.85(44.245)	5.82(33.948)

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
		Median	0.00	4.00	2.00
		Min to Max	-98.00 to 85.00	-147.0 to 317.00	-147.0 to 317.00
60 weeks	N [a]		80	74	154
	Enrollment	Mean(SD)	96.71(22.260)	89.76(14.129)	93.37(19.060)
	At time point	Mean(SD)	94.30(17.355)	100.16(29.670)	97.12(24.170)
	Change	Mean(SD)	-2.41(20.228)	10.41(26.176)	3.75(24.041)
		Median	0.00	6.00	2.00
		Min to Max	-103.0 to 57.00	-33.00 to 156.00	-103.0 to 156.00
72 weeks	N [b]		41	54	95
	Enrollment	Mean(SD)	97.73(21.668)	91.50(14.574)	94.19(18.143)
	At time point	Mean(SD)	98.49(18.597)	98.85(42.849)	98.69(34.386)
	Change	Mean(SD)	0.76(21.937)	7.35(40.367)	4.51(33.680)
		Median	-1.00	2.50	1.00
		Min to Max	-61.00 to 59.00	-54.00 to 263.00	-61.00 to 263.00
84 weeks	N [b]		29	40	69
	Enrollment	Mean(SD)	100.90(24.541)	91.50(13.853)	95.45(19.490)
	At time point	Mean(SD)	98.83(20.900)	105.78(50.264)	102.86(40.507)
	Change	Mean(SD)	-2.07(20.653)	14.28(44.241)	7.41(36.936)
		Median	2.00	4.00	3.00
		Min to Max	-76.00 to 32.00	-48.00 to 256.00	-76.00 to 256.00
96 weeks	N [b]		8	23	31
	Enrollment	Mean(SD)	99.88(30.829)	88.17(9.277)	91.19(17.662)
	At time point	Mean(SD)	103.38(21.367)	93.65(16.612)	96.16(18.100)
	Change	Mean(SD)	3.50(41.525)	5.48(16.605)	4.97(24.603)
		Median	14.00	2.00	2.00
		Min to Max	-79.00 to 56.00	-19.00 to 49.00	-79.00 to 56.00
108 weeks	N [b]		6	20	26
	Enrollment	Mean(SD)	104.17(35.165)	93.35(17.394)	95.69(22.353)
	At time point	Mean(SD)	88.67(9.395)	100.60(32.641)	97.85(29.217)
	Change	Mean(SD)	-15.50(30.592)	7.45(34.748)	2.15(34.671)
		Median	-11.5	2.50	-3.00
		Min to Max	-71.00 to 21.00	-41.00 to 114.00	-71.00 to 114.00

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
120 weeks	N [a]			14	14
	Enrollment	Mean(SD)		92.36(17.482)	92.36(17.482)
	At time point	Mean(SD)		94.43(13.472)	94.43(13.472)
	Change	Mean(SD)		2.07(15.633)	2.07(15.633)
		Median		4.00	4.00
		Min to Max		-40.00 to 36.00	-40.00 to 36.00
HbAIC (%)					
1 week	N [a]		1	1	2
	Enrollment	Mean(SD)	5.80	5.70	5.75(0.071)
	At time point	Mean(SD)	5.70	5.50	5.60(0.141)
	Change	Mean(SD)	-0.10	-0.20	-0.15(0.071)
		Median	-0.10	-0.20	-0.15
		Min to Max	-0.10 to -0.10	-0.20 to -0.20	-0.20 to -0.10
12 weeks	N [a]		117	98	215
	Enrollment	Mean(SD)	5.36(0.440)	5.44(0.459)	5.40(0.449)
	At time point	Mean(SD)	5.31(0.441)	5.38(0.546)	5.34(0.492)
	Change	Mean(SD)	-0.06(0.305)	-0.06(0.360)	-0.06(0.331)
		Median	-0.10	-0.10	-0.10
		Min to Max	-0.90 to 0.60	-1.20 to 1.60	-1.20 to 1.60
24 weeks	N [a]		117	112	229
	Enrollment	Mean(SD)	5.35(0.468)	5.46(0.500)	5.40(0.486)
	At time point	Mean(SD)	5.34(0.490)	5.45(0.555)	5.40(0.524)
	Change	Mean(SD)	-0.01(0.341)	-0.00(0.489)	-0.01(0.419)
		Median	0.00	0.00	0.00
		Min to Max	-1.00 to 0.90	-2.10 to 1.70	-2.10 to 1.70
36 weeks	N [a]		103	79	182
	Enrollment	Mean(SD)	5.31(0.430)	5.41(0.442)	5.35(0.437)
	At time point	Mean(SD)	5.40(0.438)	5.49(0.607)	5.44(0.518)
	Change	Mean(SD)	0.09(0.353)	0.08(0.510)	0.09(0.427)
		Median	0.10	0.00	0.10
		Min to Max	-1.30 to 1.30	-1.40 to 2.40	-1.40 to 2.40
48 weeks	N [a]		131	113	244

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Enrollment	Mean(SD)	5.35(0.428)	5.47(0.504)	5.41(0.468)
	At time point	Mean(SD)	5.50(0.502)	5.72(1.377)	5.60(1.011)
	Change	Mean(SD)	0.15(0.404)	0.25(1.241)	0.20(0.894)
		Median	0.10	0.00	0.10
		Min to Max	-0.90 to 1.60	-2.20 to 9.70	-2.20 to 9.70
60 weeks	N [a]		81	76	157
	Enrollment	Mean(SD)	5.34(0.505)	5.44(0.535)	5.39(0.520)
	At time point	Mean(SD)	5.54(0.621)	5.69(0.915)	5.61(0.779)
	Change	Mean(SD)	0.20(0.405)	0.25(0.737)	0.22(0.588)
		Median	0.10	0.20	0.10
		Min to Max	-0.50 to 2.00	-1.60 to 4.40	-1.60 to 4.40
72 weeks	N [a]		44	54	98
	Enrollment	Mean(SD)	5.30(0.461)	5.46(0.545)	5.39(0.513)
	At time point	Mean(SD)	5.47(0.656)	5.85(1.222)	5.68(1.021)
	Change	Mean(SD)	0.18(0.471)	0.39(0.994)	0.29(0.806)
		Median	0.10	0.25	0.20
		Min to Max	-0.50 to 2.30	-1.50 to 5.60	-1.50 to 5.60
84 weeks	N [a]		30	40	70
	Enrollment	Mean(SD)	5.38(0.407)	5.53(0.596)	5.46(0.526)
	At time point	Mean(SD)	5.75(0.902)	5.97(1.206)	5.87(1.085)
	Change	Mean(SD)	0.37(0.859)	0.44(1.096)	0.41(0.995)
		Median	0.10	0.25	0.20
		Min to Max	-0.50 to 3.30	-1.90 to 4.80	-1.90 to 4.80
96 weeks	N [a]		9	24	33
	Enrollment	Mean(SD)	5.42(0.399)	5.44(0.415)	5.43(0.404)
	At time point	Mean(SD)	5.61(0.437)	5.60(0.582)	5.60(0.540)
	Change	Mean(SD)	0.19(0.506)	0.16(0.411)	0.17(0.431)
		Median	0.20	0.10	0.10
		Min to Max	-0.30 to 1.30	-0.30 to 1.60	-0.30 to 1.60
108 weeks	N [a]		6	22	28
	Enrollment	Mean(SD)	5.13(1.052)	5.45(0.717)	5.39(0.789)
	At time point	Mean(SD)	5.22(0.933)	5.94(1.221)	5.79(1.189)

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Change	Mean(SD)	0.08(0.248)	0.49(1.109)	0.40(0.998)
		Median	0.05	0.30	0.25
		Min to Max	-0.20 to 0.50	-1.90 to 4.20	-1.90 to 4.20
120 weeks	N [a]			14	14
	Enrollment	Mean(SD)		5.59(0.865)	5.59(0.865)
	At time point	Mean(SD)		5.91(1.157)	5.91(1.157)
	Change	Mean(SD)		0.33(0.955)	0.33(0.955)
		Median		0.25	0.25
		Min to Max		-1.50 to 3.00	-1.50 to 3.00
Insulin (pmol/L)					
12 weeks	N [a]		85	69	154
	Enrollment	Mean(SD)	84.51(68.354)	135.96(221.491)	107.56(158.202)
	At time point	Mean(SD)	115.92(123.355)	135.36(125.130)	124.63(124.125)
	Change	Mean(SD)	31.41(130.797)	-0.59(223.515)	17.07(178.470)
		Median	7.00	7.00	7.00
		Min to Max	-409.0 to 743.00	-1541 to 659.00	-1541 to 743.00
24 weeks	N [a]		73	59	132
	Enrollment	Mean(SD)	92.08(84.027)	116.25(116.209)	102.89(100.026)
	At time point	Mean(SD)	113.62(99.371)	124.05(98.253)	118.28(98.633)
	Change	Mean(SD)	21.53(117.826)	7.80(130.513)	15.39(123.364)
		Median	14.00	7.00	13.00
		Min to Max	-402.0 to 500.00	-479.0 to 479.00	-479.0 to 500.00
36 weeks	N [a]		63	36	99
	Enrollment	Mean(SD)	93.25(80.797)	155.58(291.345)	115.92(188.025)
	At time point	Mean(SD)	105.22(77.229)	181.31(165.343)	132.89(122.026)
	Change	Mean(SD)	11.97(87.464)	25.72(320.332)	16.97(203.792)
		Median	7.00	34.00	7.00
		Min to Max	-430.0 to 216.00	-1527 to 771.00	-1527 to 771.00
48 weeks	N [a]		81	65	146
	Enrollment	Mean(SD)	85.49(61.298)	127.23(227.145)	104.08(158.994)
	At time point	Mean(SD)	94.42(81.080)	151.12(140.377)	119.66(114.561)
	Change	Mean(SD)	8.93(83.916)	23.89(255.319)	15.59(180.868)

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
		Median	0.00	21.00	14.00
		Min to Max	-146.0 to 410.00	-1590 to 764.00	-1590 to 764.00
60 weeks	N [a]		46	43	89
	Enrollment	Mean(SD)	95.04(61.853)	106.70(111.095)	100.67(88.776)
	At time point	Mean(SD)	98.50(73.718)	215.79(223.028)	155.17(173.186)
	Change	Mean(SD)	3.46(81.847)	109.09(228.362)	54.49(176.446)
		Median	7.00	20.00	13.00
		Min to Max	-195.0 to 320.00	-229.0 to 1056.0	-229.0 to 1056.0
72 weeks	N [a]		25	20	45
	Enrollment	Mean(SD)	108.76(104.797)	113.60(115.751)	110.93(108.545)
	At time point	Mean(SD)	141.80(194.827)	154.95(133.875)	147.64(168.781)
	Change	Mean(SD)	33.04(135.183)	41.35(181.793)	36.73(155.744)
		Median	-7.00	21.00	0.00
		Min to Max	-69.00 to 493.00	-541.0 to 382.00	-541.0 to 493.00
84 weeks	N [a]		13	12	25
	Enrollment	Mean(SD)	109.62(71.737)	73.58(30.563)	92.32(57.782)
	At time point	Mean(SD)	102.69(52.063)	154.08(185.562)	127.36(133.506)
	Change	Mean(SD)	-6.92(53.794)	80.50(186.235)	35.04(139.035)
		Median	-7.00	20.50	14.00
		Min to Max	-105.0 to 84.00	-55.00 to 625.00	-105.0 to 625.00
96 weeks	N [a]		2	6	8
	Enrollment	Mean(SD)	118.00(19.799)	87.83(33.469)	95.38(32.421)
	At time point	Mean(SD)	198.00(103.238)	233.83(206.748)	224.88(179.804)
	Change	Mean(SD)	80.00(83.439)	146.00(175.115)	129.50(154.375)
		Median	80.00	73.00	73.00
		Min to Max	21.00 to 139.00	42.00 to 493.00	21.00 to 493.00
108 weeks	N [a]			1	1
	Enrollment	Mean(SD)		63.00	63.00
	At time point	Mean(SD)		28.00	28.00
	Change	Mean(SD)		-35.00	-35.00
		Median		-35.0	-35.0
		Min to Max		-35.00 to -35.00	-35.00 to -35.00

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
HOMA-R					
12 weeks	N [a]		83	68	151
	Enrollment	Mean(SD)	2.80(2.345)	6.55(21.193)	4.49(14.392)
	At time point	Mean(SD)	4.29(6.049)	5.26(6.687)	4.72(6.341)
	Change	Mean(SD)	1.49(6.147)	-1.29(20.838)	0.24(14.715)
		Median	0.34	0.46	0.37
		Min to Max	-12.65 to 40.20	-162.4 to 33.90	-162.4 to 40.20
24 weeks	N [a]		69	57	126
	Enrollment	Mean(SD)	2.80(2.209)	4.12(6.407)	3.40(4.635)
	At time point	Mean(SD)	4.24(4.921)	4.12(4.234)	4.19(4.605)
	Change	Mean(SD)	1.45(4.866)	-0.00(6.724)	0.79(5.802)
		Median	0.52	0.27	0.48
		Min to Max	-12.23 to 23.69	-32.21 to 24.44	-32.21 to 24.44
36 weeks	N [a]		59	35	94
	Enrollment	Mean(SD)	3.16(3.267)	8.95(29.163)	5.31(18.042)
	At time point	Mean(SD)	3.61(3.379)	7.19(8.253)	4.94(5.921)
	Change	Mean(SD)	0.45(3.391)	-1.76(29.484)	-0.37(18.059)
		Median	0.15	1.35	0.22
		Min to Max	-13.17 to 13.42	-162.5 to 41.64	-162.5 to 41.64
48 weeks	N [a]		78	62	140
	Enrollment	Mean(SD)	3.03(2.924)	6.46(22.191)	4.55(14.959)
	At time point	Mean(SD)	3.33(3.285)	6.09(7.194)	4.55(5.530)
	Change	Mean(SD)	0.30(3.632)	-0.37(22.646)	0.00(15.247)
		Median	0.06	0.98	0.35
		Min to Max	-10.68 to 15.93	-166.0 to 42.34	-166.0 to 42.34
60 weeks	N [a]		45	42	87
	Enrollment	Mean(SD)	3.47(3.065)	3.80(6.435)	3.63(4.957)
	At time point	Mean(SD)	3.50(3.244)	8.79(11.151)	6.06(8.470)
	Change	Mean(SD)	0.03(3.251)	5.00(10.211)	2.43(7.832)
		Median	0.22	0.86	0.38
		Min to Max	-8.65 to 13.88	-4.51 to 50.65	-8.65 to 50.65
72 weeks	N [a]		22	19	41

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Enrollment	Mean(SD)	3.51(3.626)	4.06(5.718)	3.77(4.657)
	At time point	Mean(SD)	4.56(5.357)	5.25(4.533)	4.88(4.943)
	Change	Mean(SD)	1.05(5.202)	1.19(7.743)	1.12(6.418)
		Median	-0.20	0.63	0.16
		Min to Max	-2.72 to 22.68	-25.88 to 12.61	-25.88 to 22.68
84 weeks	N [a]		13	12	25
	Enrollment	Mean(SD)	4.34(4.414)	2.29(0.969)	3.36(3.357)
	At time point	Mean(SD)	4.10(3.279)	5.26(6.539)	4.66(5.032)
	Change	Mean(SD)	-0.25(2.089)	2.97(6.704)	1.30(5.046)
		Median	-0.15	0.72	0.38
		Min to Max	-4.47 to 3.09	-1.74 to 22.71	-4.47 to 22.71
96 weeks	N [a]		2	6	8
	Enrollment	Mean(SD)	3.48(0.685)	2.62(1.025)	2.83(0.989)
	At time point	Mean(SD)	8.84(6.619)	8.13(8.864)	8.31(7.905)
	Change	Mean(SD)	5.36(5.933)	5.51(7.865)	5.48(7.015)
		Median	5.36	2.43	2.43
		Min to Max	1.16 to 9.55	1.04 to 21.35	1.04 to 21.35
QUICKI					
12 weeks	N [a]		83	68	151
	Enrollment	Mean(SD)	0.3449(0.0396)	0.3296(0.0369)	0.3380(0.0390)
	At time point	Mean(SD)	0.3342(0.0430)	0.3245(0.0410)	0.3298(0.0422)
	Change	Mean(SD)	-.0108(0.0455)	-.0051(0.0312)	-.0082(0.0397)
		Median	-.008	-.009	-.008
		Min to Max	-.1374 to 0.0957	-.0642 to 0.0836	-.1374 to 0.0957
24 weeks	N [a]		69	57	126
	Enrollment	Mean(SD)	0.3431(0.0372)	0.3311(0.0323)	0.3377(0.0355)
	At time point	Mean(SD)	0.3300(0.0388)	0.3271(0.0349)	0.3287(0.0370)
	Change	Mean(SD)	-.0131(0.0433)	-.0040(0.0324)	-.0090(0.0388)
		Median	-.012	-.004	-.007
		Min to Max	-.1370 to 0.0878	-.0780 to 0.0799	-.1370 to 0.0878
36 weeks	N [a]		59	35	94
	Enrollment	Mean(SD)	0.3434(0.0417)	0.3284(0.0389)	0.3378(0.0411)

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	At time point	Mean(SD)	0.3379(0.0448)	0.3155(0.0507)	0.3295(0.0486)
	Change	Mean(SD)	-.0055(0.0405)	-.0129(0.0518)	-.0083(0.0449)
		Median	-.003	-.016	-.011
		Min to Max	-.0908 to 0.1236	-.1144 to 0.1318	-.1144 to 0.1318
48 weeks	N [b]		78	62	140
	Enrollment	Mean(SD)	0.3421(0.0380)	0.3346(0.0378)	0.3388(0.0380)
	At time point	Mean(SD)	0.3395(0.0394)	0.3167(0.0389)	0.3294(0.0406)
	Change	Mean(SD)	-.0026(0.0371)	-.0179(0.0426)	-.0094(0.0402)
		Median	-.001	-.016	-.009
		Min to Max	-.0954 to 0.0794	-.1281 to 0.0910	-.1281 to 0.0910
60 weeks	N [b]		45	42	87
	Enrollment	Mean(SD)	0.3348(0.0393)	0.3356(0.0343)	0.3352(0.0368)
	At time point	Mean(SD)	0.3353(0.0384)	0.3133(0.0503)	0.3247(0.0456)
	Change	Mean(SD)	0.0005(0.0437)	-.0223(0.0500)	-.0105(0.0480)
		Median	-.002	-.013	-.010
		Min to Max	-.1273 to 0.1121	-.1484 to 0.0676	-.1484 to 0.1121
72 weeks	N [b]		22	19	41
	Enrollment	Mean(SD)	0.3351(0.0376)	0.3313(0.0340)	0.3334(0.0356)
	At time point	Mean(SD)	0.3288(0.0399)	0.3213(0.0424)	0.3253(0.0407)
	Change	Mean(SD)	-.0064(0.0475)	-.0100(0.0503)	-.0081(0.0483)
		Median	.0021	-.009	-.004
		Min to Max	-.1597 to 0.0700	-.1108 to 0.1307	-.1597 to 0.1307
84 weeks	N [b]		13	12	25
	Enrollment	Mean(SD)	0.3250(0.0372)	0.3423(0.0222)	0.3333(0.0315)
	At time point	Mean(SD)	0.3221(0.0282)	0.3290(0.0504)	0.3254(0.0397)
	Change	Mean(SD)	-.0029(0.0272)	-.0133(0.0573)	-.0079(0.0436)
		Median	.0033	-.016	-.006
		Min to Max	-.0543 to 0.0405	-.1368 to 0.1056	-.1368 to 0.1056
96 weeks	N [b]		2	6	8
	Enrollment	Mean(SD)	0.3180(0.0087)	0.3334(0.0142)	0.3295(0.0143)
	At time point	Mean(SD)	0.2887(0.0300)	0.2981(0.0264)	0.2957(0.0254)
	Change	Mean(SD)	-.0293(0.0213)	-.0353(0.0156)	-.0338(0.0157)

Table C- 2 Glucose regulation laboratory data, change from enrollment over time (patients with at least 48 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment		126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Median	-.029	-.035	-.035
	Min to Max	-.0444 to -.0143	-.0564 to -.0164	-.0564 to -.0143

[a] Number of patients with assessment at enrollment and at specified time point.
Note: Patients randomized to quetiapine.
Note: Time points define total duration of quetiapine treatment (open-label and randomized).
OC Observed cases. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
HOMA [insulin (uU/ml) x glucose (mmol/l)]/22.5. QUICKI 1/[log10(insulin o(uU/ml) + log10 (glucose o(mg/dL))].
HbA1c Hemoglobin A1c.
126 D1447C00126. 127 D1447C00127.
/esr/dev/seroquel/ctdmsiotexance/sp/output/tlf/tab-10.rtf tab10.sas 11MAY2007:14:47 kscl497

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
Glucose (mg/dL)					
1 week	N [a]		1	1	2
	Enrollment	Mean(SD)	97.00	74.00	85.50(16.263)
	At time point	Mean(SD)	103.00	85.00	94.00(12.728)
	Change	Mean(SD)	6.00	11.00	8.50(3.536)
		Median	6.00	11.00	8.50
		Min to Max	6.00 to 6.00	11.00 to 11.00	6.00 to 11.00
12 weeks	N [a]		75	68	143
	Enrollment	Mean(SD)	95.76(21.085)	93.28(18.276)	94.58(19.769)
	At time point	Mean(SD)	95.08(18.250)	94.65(19.818)	94.87(18.945)
	Change	Mean(SD)	-0.68(19.261)	1.37(16.407)	0.29(17.927)
		Median	0.00	2.00	1.00
		Min to Max	-96.00 to 34.00	-64.00 to 59.00	-96.00 to 59.00
24 weeks	N [a]		76	75	151
	Enrollment	Mean(SD)	96.70(23.681)	92.97(17.822)	94.85(20.990)
	At time point	Mean(SD)	97.64(24.611)	94.77(28.470)	96.22(26.548)
	Change	Mean(SD)	0.95(26.114)	1.80(24.955)	1.37(25.463)
		Median	0.00	-2.00	0.00
		Min to Max	-93.00 to 75.00	-46.00 to 142.00	-93.00 to 142.00
36 weeks	N [a]		60	54	114
	Enrollment	Mean(SD)	93.45(15.495)	89.67(15.275)	91.66(15.440)
	At time point	Mean(SD)	94.47(12.811)	92.80(17.358)	93.68(15.090)
	Change	Mean(SD)	1.02(10.011)	3.13(17.305)	2.02(13.925)
		Median	1.50	2.00	2.00
		Min to Max	-33.00 to 26.00	-33.00 to 72.00	-33.00 to 72.00
48 weeks	N [a]		76	80	156
	Enrollment	Mean(SD)	96.61(22.168)	92.23(16.610)	94.36(19.576)
	At time point	Mean(SD)	96.09(17.176)	105.24(48.563)	100.78(36.957)
	Change	Mean(SD)	-0.51(21.473)	13.01(44.948)	6.42(36.039)
		Median	-0.50	4.00	2.00

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
		Min to Max	-98.00 to 85.00	-46.00 to 317.00	-98.00 to 317.00
60 weeks	N [a]		87	80	167
	Enrollment	Mean(SD)	96.72(22.432)	90.68(16.132)	93.83(19.843)
	At time point	Mean(SD)	95.66(18.329)	98.60(29.206)	97.07(24.128)
	Change	Mean(SD)	-1.07(20.172)	7.93(28.426)	3.24(24.813)
		Median	1.00	4.50	2.00
		Min to Max	-103.0 to 57.00	-82.00 to 156.00	-103.0 to 156.00
72 weeks	N [a]		45	54	99
	Enrollment	Mean(SD)	97.02(20.946)	90.17(14.037)	93.28(17.757)
	At time point	Mean(SD)	99.00(17.973)	98.63(42.889)	98.80(33.762)
	Change	Mean(SD)	1.98(21.412)	8.46(39.852)	5.52(32.792)
		Median	1.00	3.50	2.00
		Min to Max	-61.00 to 59.00	-54.00 to 263.00	-61.00 to 263.00
84 weeks	N [a]		31	41	72
	Enrollment	Mean(SD)	100.45(23.771)	90.46(13.777)	94.76(19.248)
	At time point	Mean(SD)	99.23(20.276)	105.20(49.737)	102.63(39.702)
	Change	Mean(SD)	-1.23(20.245)	14.73(43.589)	7.86(36.151)
		Median	3.00	6.00	4.00
		Min to Max	-76.00 to 32.00	-18.00 to 256.00	-76.00 to 256.00
96 weeks	N [a]		9	24	33
	Enrollment	Mean(SD)	99.22(28.904)	87.13(8.384)	90.42(17.009)
	At time point	Mean(SD)	105.11(20.655)	95.33(17.380)	98.00(18.529)
	Change	Mean(SD)	5.89(39.498)	8.21(17.260)	7.58(24.602)
		Median	16.00	2.50	5.00
		Min to Max	-79.00 to 56.00	-19.00 to 49.00	-79.00 to 56.00
108 weeks	N [a]		6	20	26
	Enrollment	Mean(SD)	104.17(35.165)	90.60(15.853)	93.73(21.732)
	At time point	Mean(SD)	88.67(9.395)	101.60(32.858)	98.62(29.480)
	Change	Mean(SD)	-15.50(30.592)	11.00(33.528)	4.88(34.222)
		Median	-11.5	4.00	1.50
		Min to Max	-71.00 to 21.00	-36.00 to 114.00	-71.00 to 114.00
120 weeks	N [a]			17	17

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Enrollment	Mean(SD)		91.29(16.054)	91.29(16.054)
	At time point	Mean(SD)		94.41(12.227)	94.41(12.227)
	Change	Mean(SD)		3.12(14.624)	3.12(14.624)
		Median		5.00	5.00
		Min to Max		-40.00 to 36.00	-40.00 to 36.00
HbA1C (%)					
1 week	N [a]		1		1
	Enrollment	Mean(SD)	5.80		5.80
	At time point	Mean(SD)	5.70		5.70
	Change	Mean(SD)	-0.10		-0.10
		Median	-0.10		-0.10
		Min to Max	-0.10 to -0.10		-0.10 to -0.10
12 weeks	N [a]		76	68	144
	Enrollment	Mean(SD)	5.36(0.541)	5.48(0.548)	5.42(0.545)
	At time point	Mean(SD)	5.31(0.567)	5.42(0.709)	5.36(0.638)
	Change	Mean(SD)	-0.06(0.285)	-0.06(0.406)	-0.06(0.346)
		Median	-0.10	-0.10	-0.10
		Min to Max	-0.70 to 0.60	-1.20 to 1.60	-1.20 to 1.60
24 weeks	N [a]		78	78	156
	Enrollment	Mean(SD)	5.33(0.578)	5.54(0.580)	5.44(0.587)
	At time point	Mean(SD)	5.35(0.709)	5.54(0.751)	5.44(0.734)
	Change	Mean(SD)	0.02(0.362)	-0.01(0.562)	0.01(0.471)
		Median	0.00	0.00	0.00
		Min to Max	-0.70 to 1.40	-2.10 to 2.40	-2.10 to 2.40
36 weeks	N [a]		64	58	122
	Enrollment	Mean(SD)	5.27(0.475)	5.44(0.484)	5.35(0.484)
	At time point	Mean(SD)	5.36(0.474)	5.50(0.682)	5.43(0.583)
	Change	Mean(SD)	0.09(0.345)	0.06(0.528)	0.08(0.440)
		Median	0.10	0.00	0.10
		Min to Max	-1.30 to 0.90	-1.40 to 2.40	-1.40 to 2.40
48 weeks	N [a]		79	79	158
	Enrollment	Mean(SD)	5.34(0.460)	5.52(0.529)	5.43(0.502)

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	At time point	Mean(SD)	5.47(0.547)	5.75(1.534)	5.61(1.156)
	Change	Mean(SD)	0.13(0.394)	0.23(1.388)	0.18(1.018)
		Median	0.10	0.00	0.10
		Min to Max	-0.90 to 1.60	-2.20 to 9.70	-2.20 to 9.70
60 weeks	N [a]		88	83	171
	Enrollment	Mean(SD)	5.35(0.564)	5.45(0.579)	5.40(0.572)
	At time point	Mean(SD)	5.56(0.672)	5.68(0.927)	5.62(0.806)
	Change	Mean(SD)	0.21(0.398)	0.23(0.730)	0.22(0.582)
		Median	0.10	0.20	0.10
		Min to Max	-0.50 to 2.00	-1.60 to 4.40	-1.60 to 4.40
72 weeks	N [a]		48	54	102
	Enrollment	Mean(SD)	5.27(0.462)	5.44(0.552)	5.36(0.516)
	At time point	Mean(SD)	5.46(0.630)	5.80(1.236)	5.64(1.008)
	Change	Mean(SD)	0.19(0.466)	0.36(1.000)	0.28(0.796)
		Median	0.10	0.20	0.20
		Min to Max	-0.50 to 2.30	-1.50 to 5.60	-1.50 to 5.60
84 weeks	N [a]		32	41	73
	Enrollment	Mean(SD)	5.37(0.395)	5.49(0.605)	5.44(0.524)
	At time point	Mean(SD)	5.74(0.875)	5.91(1.213)	5.83(1.074)
	Change	Mean(SD)	0.37(0.833)	0.42(1.085)	0.40(0.976)
		Median	0.10	0.20	0.20
		Min to Max	-0.50 to 3.30	-1.90 to 4.80	-1.90 to 4.80
96 weeks	N [a]		10	25	35
	Enrollment	Mean(SD)	5.41(0.378)	5.44(0.412)	5.43(0.398)
	At time point	Mean(SD)	5.60(0.414)	5.59(0.591)	5.59(0.540)
	Change	Mean(SD)	0.19(0.477)	0.14(0.402)	0.16(0.418)
		Median	0.20	0.10	0.10
		Min to Max	-0.30 to 1.30	-0.30 to 1.60	-0.30 to 1.60
108 weeks	N [a]		6	22	28
	Enrollment	Mean(SD)	5.13(1.052)	5.45(0.706)	5.38(0.781)
	At time point	Mean(SD)	5.22(0.933)	5.82(1.234)	5.69(1.186)
	Change	Mean(SD)	0.08(0.248)	0.37(1.126)	0.31(1.006)

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
		Median	0.05	0.25	0.20
		Min to Max	-0.20 to 0.50	-1.90 to 4.20	-1.90 to 4.20
120 weeks	N [a]			17	17
	Enrollment	Mean(SD)		5.54(0.794)	5.54(0.794)
	At time point	Mean(SD)		5.85(1.080)	5.85(1.080)
	Change	Mean(SD)		0.31(0.872)	0.31(0.872)
		Median		0.20	0.20
		Min to Max		-1.50 to 3.00	-1.50 to 3.00
Insulin (pmol/L)					
12 weeks	N [a]		51	48	99
	Enrollment	Mean(SD)	88.63(65.100)	121.60(127.989)	104.62(101.454)
	At time point	Mean(SD)	103.16(69.919)	133.21(101.645)	117.73(87.619)
	Change	Mean(SD)	14.53(63.386)	11.60(105.464)	13.11(85.944)
		Median	6.00	14.00	7.00
		Min to Max	-125.0 to 187.00	-500.0 to 195.00	-500.0 to 195.00
24 weeks	N [a]		45	40	85
	Enrollment	Mean(SD)	93.82(88.943)	128.00(135.962)	109.91(114.109)
	At time point	Mean(SD)	105.29(86.191)	116.48(70.197)	110.55(78.808)
	Change	Mean(SD)	11.47(94.898)	-11.53(128.713)	0.65(111.989)
		Median	13.00	7.00	7.00
		Min to Max	-382.0 to 319.00	-479.0 to 277.00	-479.0 to 319.00
36 weeks	N [a]		36	25	61
	Enrollment	Mean(SD)	94.08(75.776)	116.24(140.652)	103.16(106.693)
	At time point	Mean(SD)	104.28(79.313)	186.44(187.485)	137.95(139.247)
	Change	Mean(SD)	10.19(60.316)	70.20(202.636)	34.79(139.398)
		Median	3.50	34.00	7.00
		Min to Max	-111.0 to 194.00	-340.0 to 771.00	-340.0 to 771.00
48 weeks	N [a]		49	42	91
	Enrollment	Mean(SD)	95.47(66.075)	108.40(131.797)	101.44(101.409)
	At time point	Mean(SD)	90.16(68.521)	148.71(112.432)	117.19(95.521)
	Change	Mean(SD)	-5.31(68.554)	40.31(135.574)	15.75(106.783)
		Median	-14.0	28.00	7.00

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
		Min to Max	-146.0 to 305.00	-479.0 to 361.00	-479.0 to 361.00
60 weeks	N [a]		48	46	94
	Enrollment	Mean(SD)	97.46(67.390)	113.02(112.771)	105.07(92.249)
	At time point	Mean(SD)	96.85(72.994)	212.87(216.273)	153.63(169.484)
	Change	Mean(SD)	-0.60(84.718)	99.85(223.938)	48.55(174.474)
		Median	3.50	17.00	10.00
		Min to Max	-195.0 to 320.00	-229.0 to 1056.0	-229.0 to 1056.0
72 weeks	N [a]		25	21	46
	Enrollment	Mean(SD)	108.76(104.797)	116.48(113.588)	112.28(107.734)
	At time point	Mean(SD)	141.80(194.827)	159.81(152.372)	150.02(167.672)
	Change	Mean(SD)	33.04(135.183)	43.33(177.423)	37.74(154.155)
		Median	-7.00	28.00	3.00
		Min to Max	-69.00 to 493.00	-541.0 to 382.00	-541.0 to 493.00
84 weeks	N [a]		13	13	26
	Enrollment	Mean(SD)	109.62(71.737)	81.31(40.397)	95.46(58.838)
	At time point	Mean(SD)	102.69(52.063)	186.00(211.676)	144.35(156.884)
	Change	Mean(SD)	-6.92(53.794)	104.69(198.499)	48.88(153.436)
		Median	-7.00	27.00	14.00
		Min to Max	-105.0 to 84.00	-55.00 to 625.00	-105.0 to 625.00
96 weeks	N [a]		2	6	8
	Enrollment	Mean(SD)	118.00(19.799)	87.83(33.469)	95.38(32.421)
	At time point	Mean(SD)	198.00(103.238)	233.83(206.748)	224.88(179.804)
	Change	Mean(SD)	80.00(83.439)	146.00(175.115)	129.50(154.375)
		Median	80.00	73.00	73.00
		Min to Max	21.00 to 139.00	42.00 to 493.00	21.00 to 493.00
108 weeks	N [a]			1	1
	Enrollment	Mean(SD)		63.00	63.00
	At time point	Mean(SD)		28.00	28.00
	Change	Mean(SD)		-35.00	-35.00
		Median		-35.0	-35.0
		Min to Max		-35.00 to -35.00	-35.00 to -35.00

HOMA-R

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
12 weeks	N [a]		51	46	97
	Enrollment	Mean(SD)	3.11(2.804)	4.72(7.170)	3.87(5.371)
	At time point	Mean(SD)	3.69(3.294)	5.10(5.710)	4.36(4.630)
	Change	Mean(SD)	0.58(2.241)	0.38(5.844)	0.49(4.317)
		Median	0.11	0.35	0.29
		Min to Max	-3.85 to 6.50	-24.39 to 16.87	-24.39 to 16.87
24 weeks	N [a]		42	38	80
	Enrollment	Mean(SD)	2.91(2.707)	4.89(7.693)	3.85(5.702)
	At time point	Mean(SD)	4.29(5.633)	3.70(2.457)	4.01(4.403)
	Change	Mean(SD)	1.38(4.321)	-1.19(6.811)	0.16(5.752)
		Median	0.48	0.11	0.28
		Min to Max	-3.12 to 23.69	-32.21 to 6.90	-32.21 to 23.69
36 weeks	N [a]		36	23	59
	Enrollment	Mean(SD)	3.37(3.493)	4.76(8.600)	3.91(5.990)
	At time point	Mean(SD)	3.70(3.490)	7.91(9.825)	5.34(6.947)
	Change	Mean(SD)	0.32(2.423)	3.15(11.274)	1.43(7.328)
		Median	0.11	1.35	0.20
		Min to Max	-3.68 to 9.11	-23.52 to 41.64	-23.52 to 41.64
48 weeks	N [a]		46	41	87
	Enrollment	Mean(SD)	3.45(3.106)	4.22(7.450)	3.81(5.569)
	At time point	Mean(SD)	2.97(2.422)	5.96(5.762)	4.38(4.557)
	Change	Mean(SD)	-0.48(2.296)	1.74(6.098)	0.57(4.614)
		Median	-0.58	1.18	0.12
		Min to Max	-9.45 to 6.15	-18.29 to 17.61	-18.29 to 17.61
60 weeks	N [a]		48	44	92
	Enrollment	Mean(SD)	3.61(3.482)	3.94(6.340)	3.77(5.028)
	At time point	Mean(SD)	3.45(3.187)	8.69(10.899)	5.96(8.265)
	Change	Mean(SD)	-0.16(3.465)	4.75(10.049)	2.19(7.747)
		Median	0.22	0.86	0.38
		Min to Max	-10.01 to 13.88	-4.51 to 50.65	-10.01 to 50.65
72 weeks	N [a]		22	20	42
	Enrollment	Mean(SD)	3.51(3.626)	4.09(5.566)	3.78(4.602)

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	At time point	Mean(SD)	4.56(5.357)	5.38(4.452)	4.95(4.904)
	Change	Mean(SD)	1.05(5.202)	1.29(7.552)	1.17(6.348)
		Median	-0.20	0.79	0.21
		Min to Max	-2.72 to 22.68	-25.88 to 12.61	-25.88 to 22.68
84 weeks	N [7]		13	13	26
	Enrollment	Mean(SD)	4.34(4.414)	2.47(1.120)	3.41(3.297)
	At time point	Mean(SD)	4.10(3.279)	6.34(7.375)	5.22(5.707)
	Change	Mean(SD)	-0.25(2.089)	3.87(7.204)	1.81(5.605)
		Median	-0.15	0.86	0.49
		Min to Max	-4.47 to 3.09	-1.74 to 22.71	-4.47 to 22.71
96 weeks	N [7]		2	6	8
	Enrollment	Mean(SD)	3.48(0.685)	2.62(1.025)	2.83(0.989)
	At time point	Mean(SD)	8.84(6.619)	8.13(8.864)	8.31(7.905)
	Change	Mean(SD)	5.36(5.933)	5.51(7.865)	5.48(7.015)
		Median	5.36	2.43	2.43
		Min to Max	1.16 to 9.55	1.04 to 21.35	1.04 to 21.35
QHICK1					
12 weeks	N [8]		51	46	97
	Enrollment	Mean(SD)	0.3416(0.0407)	0.3280(0.0336)	0.3351(0.0387)
	At time point	Mean(SD)	0.3333(0.0400)	0.3248(0.0425)	0.3293(0.0412)
	Change	Mean(SD)	-.0083(0.0428)	-.0032(0.0321)	-.0059(0.0389)
		Median	-.005	-.007	-.005
		Min to Max	-.1374 to 0.0712	-.0642 to 0.0836	-.1374 to 0.0836
24 weeks	N [8]		42	38	80
	Enrollment	Mean(SD)	0.3457(0.0419)	0.3265(0.0335)	0.3366(0.0391)
	At time point	Mean(SD)	0.3323(0.0406)	0.3279(0.0333)	0.3302(0.0371)
	Change	Mean(SD)	-.0133(0.0384)	0.0014(0.0317)	-.0063(0.0359)
		Median	-.012	-.003	-.005
		Min to Max	-.1336 to 0.0725	-.0661 to 0.0799	-.1336 to 0.0799
36 weeks	N [8]		36	23	59
	Enrollment	Mean(SD)	0.3414(0.0435)	0.3330(0.0382)	0.3381(0.0414)
	At time point	Mean(SD)	0.3388(0.0477)	0.3203(0.0595)	0.3316(0.0529)

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment			126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Change	Mean(SD)	-.0027(0.0390)	-.0126(0.0583)	-.0065(0.0472)
		Median	-.002	-.011	-.002
		Min to Max	-.0885 to 0.1106	-.1144 to 0.1318	-.1144 to 0.1318
48 weeks	N [a]		46	41	87
	Enrollment	Mean(SD)	0.3338(0.0348)	0.3361(0.0363)	0.3349(0.0353)
	At time point	Mean(SD)	0.3440(0.0418)	0.3163(0.0402)	0.3309(0.0431)
	Change	Mean(SD)	0.0102(0.0306)	-.0198(0.0390)	-.0040(0.0378)
		Median	.0120	-.017	-.004
		Min to Max	-.0656 to 0.0794	-.1281 to 0.0745	-.1281 to 0.0794
60 weeks	N [a]		48	44	92
	Enrollment	Mean(SD)	0.3359(0.0418)	0.3336(0.0348)	0.3348(0.0384)
	At time point	Mean(SD)	0.3362(0.0387)	0.3123(0.0493)	0.3248(0.0455)
	Change	Mean(SD)	0.0004(0.0429)	-.0213(0.0491)	-.0100(0.0470)
		Median	-.005	-.013	-.010
		Min to Max	-.1273 to 0.1121	-.1484 to 0.0676	-.1484 to 0.1121
72 weeks	N [a]		22	20	42
	Enrollment	Mean(SD)	0.3351(0.0376)	0.3301(0.0336)	0.3327(0.0354)
	At time point	Mean(SD)	0.3288(0.0399)	0.3195(0.0420)	0.3244(0.0407)
	Change	Mean(SD)	-.0064(0.0475)	-.0106(0.0490)	-.0084(0.0477)
		Median	.0021	-.010	-.004
		Min to Max	-.1597 to 0.0700	-.1108 to 0.1307	-.1597 to 0.1307
84 weeks	N [a]		13	13	26
	Enrollment	Mean(SD)	0.3250(0.0372)	0.3395(0.0235)	0.3322(0.0314)
	At time point	Mean(SD)	0.3221(0.0282)	0.3234(0.0523)	0.3228(0.0411)
	Change	Mean(SD)	-.0029(0.0272)	-.0161(0.0558)	-.0095(0.0435)
		Median	.0033	-.020	-.007
		Min to Max	-.0543 to 0.0405	-.1368 to 0.1056	-.1368 to 0.1056
96 weeks	N [a]		2	6	8
	Enrollment	Mean(SD)	0.3180(0.0087)	0.3334(0.0142)	0.3295(0.0143)
	At time point	Mean(SD)	0.2887(0.0300)	0.2981(0.0264)	0.2957(0.0254)
	Change	Mean(SD)	-.0293(0.0213)	-.0353(0.0156)	-.0338(0.0157)
		Median	-.029	-.035	-.035

Table C- 3 Glucose regulation laboratory data, change from enrollment over time (patients with at least 60 weeks treatment), >8 h fasting (OC, randomized safety population)

Time on QTP treatment		126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Min to Max	-.0444 to -.0143	-.0564 to -.0164	-.0564 to -.0143

[a] Number of patients with assessment at enrollment and at specified time point.
Note: Patients randomized to quetiapine.
Note: Time points define total duration of quetiapine treatment (open-label and randomized).
OC Observed cases. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
HOMA {insulin (uU/ml) x glucose (mmol/l)}/22.5. QUICKI 1/[log10(insulin u(uU/ml) + log10 (glucose e(mg/dl))].
HbA1c Hemoglobin A1c.
126 D1447C00126. 127 D1447C00127.
/esre/dev/seroquel/cdmaintenance/sp/output-tlf/tab-11.rtf tab11.sas 11MAY2007:14:29 ksel497

Table C- 4 Weight data, change from enrollment over time (patients with at least 48 weeks treatment) (OC, randomized safety population)

Time on QTP treatment		Weight (kg)	126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
1 week	N [a]		114	133	247
	Enrollment	Mean(SD)	80.25(17.453)	92.05(23.495)	86.60(21.700)
	At time point	Mean(SD)	80.88(16.886)	92.34(22.990)	87.22(21.237)
	Change	Mean(SD)	0.45(1.733)	1.47(2.637)	0.99(2.319)
		Median	0.30	1.30	0.70
		Min to Max	-6.00 to 8.00	-5.00 to 14.40	-6.00 to 14.40
12 weeks	N [a]		161	154	315
	Enrollment	Mean(SD)	80.35(17.862)	91.50(22.873)	85.80(21.181)
	At time point	Mean(SD)	83.30(17.681)	94.52(22.409)	88.94(20.935)
	Change	Mean(SD)	2.84(4.466)	3.61(5.150)	3.22(4.821)
		Median	2.00	2.70	2.00
		Min to Max	-6.80 to 18.20	-6.10 to 24.80	-6.80 to 24.80
24 weeks	N [a]		164	167	331
	Enrollment	Mean(SD)	83.08(17.503)	94.11(22.352)	88.64(20.813)
	At time point	Mean(SD)	84.69(18.023)	96.08(22.464)	90.45(21.145)
	Change	Mean(SD)	1.72(4.593)	2.21(4.592)	1.97(4.592)
		Median	0.30	1.00	0.60
		Min to Max	-7.90 to 20.90	-5.90 to 21.80	-7.90 to 21.80
36 weeks	N [a]		127	122	249
	Enrollment	Mean(SD)	84.55(17.817)	96.85(22.490)	90.57(21.118)
	At time point	Mean(SD)	85.07(17.980)	97.56(22.986)	91.16(21.466)
	Change	Mean(SD)	0.52(4.307)	0.71(3.311)	0.62(3.845)
		Median	0.00	0.40	0.00
		Min to Max	-26.60 to 22.40	-7.00 to 15.80	-26.60 to 22.40
48 weeks	N [a]		170	172	342
	Enrollment	Mean(SD)	84.25(18.074)	95.79(22.426)	90.05(21.154)
	At time point	Mean(SD)	85.41(18.358)	96.62(23.540)	91.04(21.827)
	Change	Mean(SD)	1.16(7.288)	0.83(4.954)	0.99(6.218)
		Median	0.80	1.30	0.95
		Min to Max	-51.90 to 41.00	-15.70 to 17.10	-51.90 to 41.00
60 weeks	N [a]		95	115	210
	Enrollment	Mean(SD)	81.82(18.683)	98.32(23.751)	90.86(23.074)

Table C- 4 Weight data, change from enrollment over time (patients with at least 48 weeks treatment) (OC, randomized safety population)

Time on QTP treatment		Weight (kg)	126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	At time point	Mean(SD)	82.55(18.682)	99.81(25.588)	92.00(24.255)
	Change	Mean(SD)	0.72(4.776)	1.49(5.509)	1.14(5.192)
		Median	0.50	1.80	0.70
		Min to Max	-17.90 to 21.00	-12.20 to 18.50	-17.90 to 21.00
72 weeks	N [a]		51	70	121
	Enrollment	Mean(SD)	81.46(18.925)	100.46(21.690)	92.45(22.549)
	At time point	Mean(SD)	81.66(17.878)	101.36(21.879)	93.03(22.459)
	Change	Mean(SD)	0.13(4.427)	0.90(4.637)	0.58(4.547)
		Median	0.30	0.80	0.60
		Min to Max	-14.00 to 11.60	-10.00 to 11.40	-14.00 to 11.60
84 weeks	N [a]		33	51	84
	Enrollment	Mean(SD)	76.04(17.528)	96.86(19.504)	88.68(21.266)
	At time point	Mean(SD)	75.74(17.040)	98.52(20.584)	89.57(22.193)
	Change	Mean(SD)	-0.30(5.038)	1.66(7.451)	0.89(6.646)
		Median	-1.00	1.10	0.70
		Min to Max	-13.10 to 8.20	-19.10 to 17.60	-19.10 to 17.60
96 weeks	N [a]		11	36	47
	Enrollment	Mean(SD)	75.32(12.905)	100.82(20.362)	94.85(21.698)
	At time point	Mean(SD)	74.69(12.828)	101.60(21.159)	95.30(22.561)
	Change	Mean(SD)	-0.63(3.577)	0.78(7.090)	0.45(6.433)
		Median	-0.20	0.60	0.20
		Min to Max	-6.00 to 7.60	-13.50 to 16.80	-13.50 to 16.80
108 weeks	N [a]		6	25	31
	Enrollment	Mean(SD)	76.40(15.946)	106.31(22.273)	100.52(24.157)
	At time point	Mean(SD)	73.45(13.572)	107.79(24.442)	101.14(26.435)
	Change	Mean(SD)	-2.95(3.682)	1.48(9.553)	0.62(8.856)
		Median	-2.15	2.40	-0.30
		Min to Max	-9.30 to 1.00	-18.70 to 19.50	-18.70 to 19.50
120 weeks	N [a]		2	14	16
	Enrollment	Mean(SD)	75.20(5.374)	114.06(24.837)	109.21(26.697)
	At time point	Mean(SD)	82.50(7.778)	115.99(26.667)	111.80(27.407)
	Change	Mean(SD)	7.30(2.404)	1.92(7.490)	2.59(7.238)
		Median	7.30	1.60	3.40

Table C- 4 Weight data, change from enrollment over time (patients with at least 48 weeks treatment) (OC, randomized safety population)

Time on QTP treatment	Weight (kg)	126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Min to Max	-5.60 to 9.00	-12.70 to 16.60	-12.70 to 16.60

[a] Number of patients with assessment at enrollment and at specified time point.
Note: Patients randomized to quetiapine.
Note: Time points define total duration of quetiapine treatment (open-label and randomized).
OC Observed cases. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
126 D1447C00126. 127 D1447C00127.
/csre/dew/seroquel/ctdmaintenance/sp/output/lil/tab-12.rtf tab12.sas 14MAY2007:09:57 kscl497

Table C- 5 Weight data, change from enrollment over time (patients with at least 60 weeks treatment) (OC, randomized safety population)

Time on QTP treatment		Weight (kg)	126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
1 week	N [a]		65	98	163
	Enrollment	Mean(SD)	78.46(17.825)	95.64(24.264)	88.79(23.437)
	At time point	Mean(SD)	78.86(17.322)	96.15(24.409)	89.75(23.540)
	Change	Mean(SD)	0.44(1.603)	1.62(2.811)	1.15(2.466)
		Median	0.50	1.55	0.90
		Min to Max	-5.50 to 4.50	-5.00 to 14.40	-5.50 to 14.40
12 weeks	N [a]		98	114	212
	Enrollment	Mean(SD)	79.39(18.950)	95.08(23.634)	87.82(22.928)
	At time point	Mean(SD)	81.65(18.810)	97.92(23.888)	90.80(23.221)
	Change	Mean(SD)	2.31(3.936)	3.31(5.035)	2.85(4.577)
		Median	1.45	2.35	1.70
		Min to Max	-6.80 to 15.20	-6.10 to 21.00	-6.80 to 21.00
24 weeks	N [a]		99	126	225
	Enrollment	Mean(SD)	81.86(18.497)	97.19(22.581)	90.44(22.190)
	At time point	Mean(SD)	83.13(18.805)	99.33(23.644)	92.28(23.077)
	Change	Mean(SD)	1.35(4.357)	2.07(4.482)	1.75(4.432)
		Median	0.20	1.00	0.80
		Min to Max	-7.90 to 20.90	-5.90 to 18.80	-7.90 to 20.90
36 weeks	N [a]		78	97	175
	Enrollment	Mean(SD)	85.21(20.370)	99.59(23.857)	93.18(23.431)
	At time point	Mean(SD)	85.05(20.328)	99.99(23.797)	93.29(23.460)
	Change	Mean(SD)	-0.00(3.912)	0.41(3.012)	0.23(3.438)
		Median	0.00	0.40	0.00
		Min to Max	-26.60 to 6.80	-7.30 to 9.60	-26.60 to 9.60
48 weeks	N [a]		95	115	210
	Enrollment	Mean(SD)	81.82(18.683)	98.32(23.751)	90.86(23.074)
	At time point	Mean(SD)	82.44(18.320)	99.76(25.095)	91.93(23.856)
	Change	Mean(SD)	0.62(6.755)	1.44(4.898)	1.07(5.812)
		Median	0.90	1.40	1.25
		Min to Max	-51.90 to 20.00	-15.70 to 17.10	-51.90 to 20.00
60 weeks	N [a]		103	131	234
	Enrollment	Mean(SD)	83.12(19.553)	98.96(23.629)	91.99(23.259)

Table C- 5 Weight data, change from enrollment over time (patients with at least 60 weeks treatment) (OC, randomized safety population)

Time on QTP treatment		Weight (kg)	126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	At time point	Mean(SD)	83.56(19.250)	100.40(25.057)	92.95(24.129)
	Change	Mean(SD)	0.52(4.781)	1.44(5.724)	1.03(5.338)
		Median	0.50	1.80	0.55
		Min to Max	-17.90 to 23.00	-12.20 to 18.50	-17.90 to 21.00
72 weeks	N [a]		53	77	130
	Enrollment	Mean(SD)	82.95(19.451)	102.00(22.264)	94.24(23.084)
	At time point	Mean(SD)	83.24(18.768)	102.66(21.821)	94.75(22.679)
	Change	Mean(SD)	0.29(4.427)	0.66(5.343)	0.51(4.975)
		Median	0.30	0.60	0.50
		Min to Max	-14.00 to 11.60	-12.10 to 16.50	-14.00 to 16.50
84 weeks	N [a]		34	59	93
	Enrollment	Mean(SD)	77.11(17.534)	99.22(20.723)	91.34(22.261)
	At time point	Mean(SD)	76.71(16.778)	100.33(20.530)	91.69(22.188)
	Change	Mean(SD)	-0.41(4.683)	1.11(8.416)	0.55(7.284)
		Median	-1.00	1.10	-0.40
		Min to Max	-13.10 to 8.20	-24.40 to 19.00	-24.40 to 19.00
96 weeks	N [a]		11	38	49
	Enrollment	Mean(SD)	76.41(13.728)	104.28(22.431)	98.02(23.772)
	At time point	Mean(SD)	75.16(13.394)	103.46(20.949)	97.11(22.759)
	Change	Mean(SD)	-1.25(2.410)	-0.81(9.352)	-0.91(8.286)
		Median	-0.20	-0.20	-0.20
		Min to Max	-6.00 to 1.50	-35.70 to 16.80	-35.70 to 16.80
108 weeks	N [a]		5	29	34
	Enrollment	Mean(SD)	71.84(12.723)	109.84(23.069)	104.25(25.647)
	At time point	Mean(SD)	70.16(12.210)	109.26(22.570)	103.46(25.441)
	Change	Mean(SD)	-1.68(2.202)	-0.64(11.940)	-0.79(11.031)
		Median	-1.90	-1.60	-1.70
		Min to Max	-4.80 to 1.00	-39.90 to 19.50	-39.90 to 19.50
120 weeks	N [a]		1	20	21
	Enrollment	Mean(SD)	71.40	112.69(26.145)	110.72(27.029)
	At time point	Mean(SD)	77.00	111.45(24.919)	109.81(25.425)
	Change	Mean(SD)	5.60	-1.24(11.776)	-0.91(11.575)
		Median	5.60	-0.10	0.70

Table C- 5 Weight data, change from enrollment over time (patients with at least 60 weeks treatment) (OC, randomized safety population)

Time on QTP treatment	Weight (kg)	126 QTP+ LI/VAL N = 336	127 QTP+ LI/VAL N = 310	126 + 127 QTP+ LI/VAL N = 646
	Min to Max	-5.60 to 5.60	-42.30 to 16.60	-42.30 to 16.60

[a] Number of patients with assessment at enrollment and at specified time point.
Note: Patients randomized to quetiapine.
Note: Time points define total duration of quetiapine treatment (open-label and randomized).
OC Observed cases. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
126 D1447C00126. 127 D1447C00127.
/asre/devseroquel/ctdmaintenance/sp/output/tlf/tab-13.rtf tab13.sas 14MAY2007:09:59 kscl497

Table C- 6 Listing of patients adjudicated to have possible diabetes emerging during the randomized treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[b]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[a] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
D1447C00126	E0805097	QTP+LI/QTP+LI	NO	Enrollment	98.00	YES	5.50	25.00	6.00	88
			YES	Randomization	116.00	YES	5.70		2.15	93
				End of treatment	155.00	YES	6.80		6.70	114
	E1104007	QTP+LI/QTP+LI	NO	Enrollment	88.00	YES	5.10	5.00	1.09	80
			NO	Randomization	89.00	YES	5.80			79
				End of treatment	147.00	YES	5.20	12.00	4.37	65
	E1309003	QTP+LI/QTP+LI	YES	Enrollment	117.00	YES	5.90	18.00	5.20	122
			YES	Randomization	125.00	YES	6.30	15.00	4.60	115
				End of treatment	127.00	YES	6.50	20.00	6.22	120
	E1801002	QTP+LI/QTP+LI	NO	Enrollment	94.00	YES	5.50	7.00	1.62	88
			NO	Randomization		YES		8.00		90
				End of treatment	169.00	YES	7.60		13.55	112
D1447C00127	E0301012	QTP+VAL/PLA+VAL	YES	Enrollment	119.00	NO	6.80	24.06	7.04	91
			NO	Randomization	93.00	NO	5.90	14.00	3.17	102
				End of treatment	143.00	YES	8.20	18.00	6.56	171
	E0026024	QTP+VAL/PLA+VAL	NO	Enrollment	99.00	NO	5.10	21.00	4.67	83
			YES	Randomization	104.00	YES	5.60	29.00	7.48	93
				End of treatment	167.00	YES	5.70	111.00	45.88	91
	E0036019	QTP+LI/QTP+LI	NO	Enrollment	134.00	NO	6.50	82.00	26.97	122
			NO	Randomization	157.00	NO	6.70	95.00	36.73	131
				End of treatment	117.00	YES	6.60	9.00	2.60	131
	E0037014	QTP+LI/QTP+LI	NO	Enrollment	83.00	NO	5.60			343
			YES	Randomization	117.00	YES	5.60	36.00	10.40	358
				End of treatment	131.00	YES	6.30	32.00	11.05	353

Table C- 6 Listing of patients adjudicated to have possible diabetes emerging during the randomized treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[b]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[a] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
	E0063001	QTP+LI/QTP+LI	YES	Enrollment	137.00	NO	5.70			108
			YES	Randomization	124.00	YES	5.80	50.00	15.33	111
				End of treatment	143.00	YES	6.70	28.00	9.83	109
	E0070006	QTP+VAL/QTP+VAL	NO	Enrollment	146.00	NO	8.10			109
			YES	Randomization	104.00	YES	6.00	60.00	15.47	104
				End of treatment	108.00	YES	6.60	80.00	20.98	100
	E0083013	QTP+VAL/QTP+VAL	NO	Enrollment	90.00	YES	6.00			109
			NO	Randomization	95.00	YES	6.60	21.00	4.95	119
				End of treatment	126.00	YES	7.00	30.00	9.33	134
	E0089002	QTP+VAL/QTP+VAL	NO	Randomization	131.00	NO	7.30			79
				End of treatment	211.00	NO	7.30	98.00	53.06	77
	E0120007	QTP+VAL/QTP+VAL	YES	Enrollment	103.00	NO	5.20			118
			NO	Randomization	89.00	NO	5.10	28.00	6.10	121
				End of treatment	148.00	YES	7.70	56.00	20.41	140

[a] Blood sampling >8 hours after last meal
[b] Impaired fasting glucose = documented fasting glucose >=100 to <126 mg/dL at enrollment/randomization
/cara/dev/seroquel/clda/ontinuance/sp/output/tlf/tab-14.rtf tab14.sas 29MAY2007:11:41 kkerr835

Table C- 7 Listing of patients adjudicated to have possible diabetes exacerbating during the randomized treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[a]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[a] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
D1447C00126	E0103011	QTP+VAL/PLA+VAL	NO	Enrollment	79.00	YES	6.00	6.00	1.17	88
			NO	Randomization	78.00	YES	6.30	4.00	0.76	92
				End of treatment	106.00	YES	6.80	9.00	2.36	93
	E0113002	QTP+VAL/QTP+VAL	YES	Enrollment	120.00	YES	7.10	22.00	6.55	131
			YES	Randomization	113.00	YES	7.30	18.00	5.04	132
				End of treatment	129.00	YES	8.10	15.00	4.80	107
	E0118002	QTP+LI/PLA+LI	NO	Enrollment	155.00	YES	6.80	16.00	6.12	82
			NO	Randomization	170.00	YES	7.30	25.00	9.61	82
				End of treatment	206.00	YES	7.80	28.00	14.19	81
	E0604021	QTP+VAL/PLA+VAL	NO	Enrollment	92.00	YES	6.10	14.00	3.17	104
			YES	Randomization	134.00	YES	6.80	34.00	3.92	125
				End of treatment	137.00	YES	7.30	12.00	4.05	121
	E1104066	QTP+VAL/QTP+VAL	NO	Enrollment	164.00	YES	5.50	45.00	18.20	110
			YES	Randomization	123.00	YES	5.80			114
				End of treatment	186.00	YES	8.80	30.00	13.75	113
D1447C00127	E0007047	QTP+VAL/QTP+VAL	YES	Enrollment	115.00	NO	6.20	12.00	3.41	89
			YES	Randomization	121.00	YES	6.80	13.00	3.87	90
				End of treatment	136.00	YES	7.50	9.00	3.08	85
	E0044006	QTP+LI/QTP+LI	NO	Enrollment	92.00	NO	5.50			113
			NO	Randomization	94.00	YES	5.20	48.00	11.09	113
				End of treatment	281.00	NO	6.50	122.00	114.41	118

Table C- 7 Listing of patients adjudicated to have possible diabetes exacerbating during the randomized treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[a]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[b] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
	E00440607	QTP+VAL/QTP+VAL	NO	Enrollment	87.00	NO	6.40			119
			NO	Randomization	127.00	YES	8.10	26.00	8.09	145
				End of treatment	89.00	YES	9.40	23.00	4.50	152
	E00485011	QTP+VAL/QTP+VAL	NO	Enrollment	94.00	YES	5.20			76
			YES	Randomization	121.00	YES	7.60	19.00	5.66	89
				End of treatment	249.00	YES	9.60	45.50	27.60	83
	E00531006	QTP+VAL/QTP+VAL	YES	Enrollment	120.00	YES	6.60	15.00		111
			NO	Randomization	130.00	YES	7.20	14.00	4.48	111
				End of treatment	234.00	NO	9.30	25.00	13.22	109
	E00559014	QTP+VAL/QTP+VAL	NO	Enrollment	150.00	NO	5.00			84
			YES	Randomization	124.00	YES	7.10	27.00	8.28	95
				End of treatment	900.00	YES		6.00	13.33	86
	E00636011	QTP+LI/QTP+LI	NO	Enrollment	92.00	YES	6.00	23.00	5.21	104
			NO	Randomization	163.00	YES	8.40	42.00	16.88	108
				End of treatment	248.00	YES	10.40	33.00	20.24	104
	E00800033	QTP+LI/QTP+LI	NO	Enrollment	166.00	YES	7.30	105.00	42.93	186
			YES	Randomization	126.00	YES	6.80	36.00	10.72	182
				End of treatment	218.00	YES	8.90	72.00	38.72	184
	E00800036	QTP+VAL/QTP+VAL	NO	Enrollment	92.00	YES	5.90	26.00	5.89	118
			NO	Randomization	147.00	YES	6.20	88.00	32.07	116
				End of treatment	95.00	YES	9.30	6.00	1.39	112
	E00830038	QTP+VAL/PLA+VAL	NO	Enrollment	134.00	YES	7.10	32.00	10.52	113
			YES	Randomization	118.00	YES	6.20	18.00	5.20	115

Table C- 7 Listing of patients adjudicated to have possible diabetes exacerbating during the randomized treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[b]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[a] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
				End of treatment	115.00	YES	6.96	55.00	4.27	116

[a] Blood sampling >8 hours after last meal.
[b] Impaired fasting glucose = documented fasting glucose >=100 to <126 mg/dL at enrollment/randomization.
/sere/dev/seroquel/eidnamsmaanea/sp/output/dl/tab-15a1f tab15.sas 21MAY2007 07:43 lachen

Table C- 8 Listing of patients adjudicated to have possible diabetes emerging during the open-label treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[2]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[3] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
D1447C00126	E0101014	QTP+VAL	NO	Enrollment	95.00	YES	5.70	45.00	10.46	96
	E0103026	QTP+VAL/PLA+VAL	YES	Enrollment	109.00	YES	6.30	4.00	1.07	152
			NO	Randomization	130.00	YES	7.60	27.00	8.64	148
				End of treatment	88.00	YES	6.80	7.00	1.52	148
	E0119015	QTP+VAL/PLA+VAL	NO	Enrollment	95.00	YES	6.30	38.00	8.95	136
			YES	Randomization	109.00	YES	6.80	61.00	16.27	135
				End of treatment	116.00	YES	6.90	45.00	12.80	135
	E0122014	QTP+L/PLA+L	NO	Enrollment	99.00	YES	5.50	7.00	1.71	78
			NO	Randomization	105.00	YES	5.60	8.00	2.07	81
				End of treatment	111.00	YES	5.70	7.00	1.93	78
	E0208007	QTP+VAL/PLA+VAL	YES	Enrollment	114.00	YES	6.00	17.00	4.76	108
			NO	Randomization	180.00	YES	7.10	58.00	16.89	110
				End of treatment	152.00	YES	6.80	43.00	16.65	108
	E0403008	QTP+VAL/PLA+VAL	YES	Enrollment	113.00	YES	6.00			97
			NO	Randomization	131.00	YES	6.00			107
				End of treatment	198.00	YES	6.40			107
	E0404003	QTP+VAL/PLA+VAL	YES	Enrollment	107.00	YES	6.90			111
			YES	Randomization	123.00	YES	6.70	40.00	12.09	110
				End of treatment	134.00	YES	6.30	27.00	7.56	103
	E0604021	QTP+VAL/PLA+VAL	NO	Enrollment	92.00	YES	6.10	14.00	3.17	164
			YES	Randomization	134.00	YES	6.80	14.00	3.92	125
				End of treatment	137.00	YES	7.30	12.00	4.05	121

Table C- 8 Listing of patients adjudicated to have possible diabetes emerging during the open-label treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[b]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[a] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
	E0604029	QTP+LI/QTP+LI	NO	Enrollment	87.00	NO	6.00	18.00	3.84	79
			YES	Randomization	113.00	YES	6.20	26.00	7.28	87
				End of treatment	127.00	YES	6.60	22.00	6.84	84
	E1120001	QTP+LI/QTP+LI	YES	Enrollment	116.00	YES	6.60	14.00	3.98	98
			NO	Randomization	128.00	YES	6.50	19.00	6.00	98
				End of treatment	121.00	YES	6.90	60.00	17.87	98
	E1309007	QTP+VAL/PLA+VAL	NO	Enrollment	89.00	YES	4.80	9.00	1.96	78
			NO	Randomization	138.00	YES	5.80	22.00	7.58	78
				End of treatment	123.00	YES	5.70	29.00	8.76	78
D1447C00127	E0066069	QTP+VAL	NO	Enrollment	97.00	YES	6.30	47.00	11.28	131
	E0097015	QTP+LI	YES	Enrollment	106.00	NO	6.40			95
	E0038023	QTP+VAL/PLA+VAL	YES	Enrollment	102.00	YES	7.90	10.00	2.76	87
			NO	Randomization	143.00	YES	8.20	13.00	4.56	95
				End of treatment	128.00	YES	7.30	12.00	3.57	87
	E0035022	QTP+VAL	YES	Enrollment	115.00	NO	6.30	28.00	8.21	102
	E0048011	QTP+VAL/QTP+VAL	NO	Enrollment	94.00	YES	5.20			76
			YES	Randomization	121.00	YES	7.00	19.00	5.66	89
				End of treatment	249.00	YES	9.60	45.00	27.60	83
	E0059014	QTP+VAL/QTP+VAL	NO	Enrollment	130.00	NO	5.00			84
			YES	Randomization	124.00	YES	7.10	27.00	8.28	99
				End of treatment	989.00	YES		6.00	13.55	86
	E0059017	QTP+VAL/PLA+VAL	NO	Enrollment	88.00	NO	5.20			109
			NO	Randomization	195.00	YES	7.60	32.00	34.56	119
				End of treatment	74.00	YES	4.80	18.00	3.28	102

Table C- 8 Listing of patients adjudicated to have possible diabetes emerging during the open-label treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[b]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[a] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
	E0064037	QTP+VAL	NO	Enrollment	77.00	NO	6.60	15.00	2.87	
	E0067005	QTP+VAL	NO	Enrollment	91.00	YES	6.00			113
	E0070029	QTP+VAL/PLA+VAL	NO	Enrollment	83.00	YES	6.60	25.00	5.11	105
			NO	Randomization	168.00	YES	6.90	69.00	28.52	121
				End of treatment	114.00	YES	6.70	38.00	10.64	117
	E0080036	QTP+VAL/QTP+VAL	NO	Enrollment	92.00	YES	5.90	26.00	5.89	138
			NO	Randomization	147.00	YES	6.20	88.00	32.07	139
				End of treatment	94.00	YES	9.40	6.00	1.39	132
	E0108019	QTP+VAL/QTP+VAL	YES	Enrollment	112.00	NO	6.20			90
			NO	Randomization	150.00	NO	7.90	8.00	5.58	106
				End of treatment	121.00	YES	6.70	4.00	1.19	99

[a] Blood sampling ≥8 hours after last meal.
[b] Impaired fasting glucose = documented fasting glucose >=100 to <126 mg/dL at enrollment/randomization.
/sro/dev/seroquel/clinmaintenance/sy/output/tl/tab-16.rtf tab16.sas 29MAY2007:12:54 tkm035

Table C- 9 Listing of patients adjudicated to have possible diabetes exacerbating during the open-label treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[b]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[a] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
D1447C00126	E01030001	QTP+VAL	NO	Enrollment	145.00	YES	6.50	6.00	2.15	152
	E01180016	QTP+VAL/QTP+VAL	NO	Enrollment	153.00	YES	7.80	41.00	15.39	145
			NO	Randomization	195.00	YES	9.90	54.00	16.32	145
				End of treatment	159.00	YES	8.30	14.00	5.48	134
	E01170029	QTP+VAL/QTP+VAL	NO	Enrollment	153.00	YES	7.80	56.00	21.16	95
			NO	Randomization	295.00	NO	9.20	121.00	85.20	105
				End of treatment	163.00	YES	8.20	94.00	37.60	106
	E00807005	QTP+VAL	NO	Enrollment	256.00	NO	6.10			79
	E01311006	QTP+LI/QTP+LI	NO	Enrollment		YES	6.60	56.00		103
			NO	Randomization	395.00	YES	8.00	53.00	15.84	113
				End of treatment	227.00	YES	8.40	55.00	19.00	111
D1447C00127	E00906005	QTP+LI	YES	Enrollment	115.00	NO	5.70			83
	E00908004	QTP+LI/QTP+LI	NO	Enrollment	137.00	YES	6.60			85
			NO	Randomization	249.00	NO	8.00	65.00	39.87	169
	E00920014	QTP+VAL	NO	Enrollment	129.00	YES	5.90			98
	E00931012	QTP+VAL	NO	Enrollment	223.00	NO	7.30			169
	E00942013	QTP+VAL	NO	Enrollment	95.00	YES	7.20	32.00	7.54	118
	E00958003	QTP+VAL	NO	Enrollment	75.00	YES	5.90			114
	E00965011	QTP+LI/QTP+LI	NO	Enrollment	92.00	YES	6.00	23.00	5.21	104
			NO	Randomization	163.00	YES	8.40	42.00	16.99	108
				End of treatment	248.00	YES	10.40	33.00	20.24	104
	E00700035	QTP+VAL	NO	Enrollment	155.00	YES	8.30	46.00	15.33	140

Table C- 9 Listing of patients adjudicated to have possible diabetes exacerbating during the open-label treatment phase

STUDY	PATIENT	TREATMENT (OL/RD)	IMPAIRED FASTING GLUCOSE[b]	TIME OF ASSESSMENT	GLUCOSE (MG/DL)	FASTING SAMPLE[a] (YES/NO)	HBA1C (%)	INSULIN (PMOL/L)	HOMA-R	WEIGHT (KG)
	E0073002	QTP+VAL/QTP+VAL	NO	Enrollment	95.00	YES	7.80			105
			YES	Randomization	125.00	YES	10.10			105
				End of treatment	124.00	YES	7.80	52.00	11.35	106
	E0078013	QTP+VAL/QTP+VAL	NO	Enrollment	159.00	YES	7.30	11.00	4.30	67
			NO	Randomization	158.00	YES	8.80	5.00	1.96	71
				End of treatment		NO			2.61	67
				End of treatment	77.00	YES	6.40			67
	E0080032	QTP+LI	YES	Enrollment	118.00	YES	5.80	31.00	8.96	77
	E0195003	QTP+VAL	NO	Enrollment	217.00	YES	9.60			86
	E0112006	QTP+LI/PLA+LI	YES	Enrollment	132.00	YES	6.10	21.00	5.79	145
			YES	Randomization	102.00	YES	5.30	12.00	3.36	152
				End of treatment	105.00	YES	5.30	16.00	4.12	135
	E0116029	QTP+VAL/QTP+VAL	NO	Enrollment	133.00	YES	6.70	43.00	14.33	109
			NO	Randomization	140.00	NO	6.30	74.00	25.65	107
				End of treatment	190.00	NO	7.00	43.00	20.07	111
	E0125005	QTP+VAL	YES	Enrollment	124.00	YES	6.00	43.00	13.19	130

[a] Blood sampling >8 hours after last meal
[b] Impaired fasting glucose = documented fasting glucose >=100 to <126 mg/dL at enrollment/randomization
/cars/dev/seroquel/oldmaintenance/sprendpu/tlf/tab-17.rtf(tab17.sas 23MAY2007:14:34 kbm635

Table C- 10 Correlation of change in weight and change in documented fasting glucose data (randomized safety population)

		126 + 127 QTP + LI/VAL N=646	PLA + LI/VAL N=680
Change from enrollment to randomization	N[a]	377	378
	Correlation (glucose - weight)[c]	-0.0015	0.0979
	N[a]	382	385
	Correlation (HbA1c - weight)[c]	0.1162	0.1809
Change from randomization to end of treatment	N[b]	404	401
	Correlation (glucose - weight)[d]	0.0658	0.1344
	N[b]	405	408
	Correlation (HbA1c - weight)[d]	0.1163	0.2159

[a] Number of patients who had value at enrollment and a value at randomization.
[b] Number of patients who had value at randomization and at least one value after randomization.
[c] Pearson correlation coefficient of individual change from enrollment to randomization in weight and glucose/HbA1c.
[d] Pearson correlation coefficient of individual change from randomization to end of treatment in weight and glucose/HbA1c.
Note: Documented fasting glucose (sampling ≥8 hours after a meal).
Note: Values at end of treatment may not coincide on the same day.

Table C- 11 Any documented fasting glucose >=126 mg/dL during the study, for patients with normal or impaired fasting glucose at baseline (open-label and randomized safety populations)

126 + 127		OL safety population	RD safety population		RD safety population	
		Documented fasting glucose at enrollment and >= 126 in OL phase	Documented fasting glucose at enrollment and >= 126 in RD phase		Documented fasting glucose at randomization and >= 126 in RD phase	
		QTP + LI/VAL N=3371	QTP + LI/VAL N=646	PLA + LI/VAL N=680	QTP + LI/VAL N=646	PLA + LI/VAL N=680
Impaired fasting glucose (IFG)[a]	N[e]	166	47	41	64	77
	Patients with glucose >=126[d]: n(%)	16(9.64%)	4(8.51%)	4(9.76%)	14(21.88%)	7(9.09%)
	Exposure[e]	109.1	50.9	33.5	38.2	36.3
	Incidence density[f]	14.66	7.85	11.94	36.67	19.31
Normal fasting glucose[b]	N[e]	1148	298	276	337	309
	Patients with glucose >=126[d]: n(%)	43(3.75%)	25(8.39%)	8(2.90%)	22(6.53%)	6(1.94%)
	Exposure[e]	708.9	287.8	246.8	205.9	154.2
	Incidence density[f]	6.07	8.69	3.24	10.68	3.89

[a] Doc fasting glucose >=100 to <126 mg/dL at baseline (enrollment or randomization) and no history of diabetes.
[b] Doc fasting glucose <100 at baseline (enrollment or randomization).
[c] Number of patients with/without IFG at time point (enrollment or randomization).
[d] Patients with at least one post-baseline documented fasting glucose >=126mg/dL in the specified treatment phase.
[e] Exposure in patient-years: time until first value >=126 or until last dose for patients with no value >=126
[f] 100*(patients with at least one documented fasting glucose >=126/exposure in patient-years)
Note: Percentages are calculated as (n/Nb)*100.
Note: Patients with missing doc fasting value not included in subgroups (IFG or Normal fasting glucose).
/cere/dev/seroquel/ctdmaintenance/by/output/tlf/tab-19.rtf tab19.sas 23JUL07:15:22 lse3497

Table C- 12 Impaired fasting glucose at baseline for patients with adjudicated emerging possible diabetes

126 + 127	Emerging possible diabetes in the OL phase (IFG at enrollment)	Emerging possible diabetes in the RD phase (IFG at enrollment)		Emerging possible diabetes in the RD phase (IFG at randomization)	
	QTP+LI/VAL N[a]=(23)	QTP+LI/VAL N[a]=(11)	PLA+LI/VAL N[a]=(2)	QTP+LI/VAL N[a]=(11)	PLA+LI/VAL N[a]=(2)
No. of patients with impaired fasting glucose (IFG)[b]	6	1	0	5	1
No. of patients with normal fasting glucose[c]	10	4	0	2	0
No. of patients with documented fasting glucose at baseline	16	5	0	7	1
No. of patients without documented fasting glucose at baseline[d]	7	6	2	4	1

[a] Number of patients with adjudicated emerging possible diabetes in the specified phase.
[b] Doc fasting glucose >=100 to <126 mg/dL at baseline (enrollment or randomization) and no history of diabetes.
[c] Doc fasting glucose <100 at baseline (enrollment or randomization).
[d] Patients without documented fasting value not included in subgroups (IFG or Normal fasting glucose).
/core/dev/se.squel/cdmaintenance/sp/output/IFGtab-20.rtf tab20.sas 29MAY2007.13.07 kbqa035

Table C- 13 Any documented fasting glucose >=126 mg/dL during the study, by baseline BMI category (open-label and randomized safety populations)

126 + 127		OL safety population BMI at enrollment, documented fasting glucose >= 126 in OL phase	RD safety population BMI at enrollment, documented fasting glucose >= 126 in RD phase		RD safety population BMI at randomization, documented fasting glucose >= 126 in RD phase	
		QTP + LI/VAL N=3371	QTP + LI/VAL N=646	PLA + LI/VAL N=680	QTP + LI/VAL N=646	PLA + LI/VAL N=680
< 18.5	N[b]	27	5	9	4	2
	Patients with glucose >=126[c] : n(%)	0(0.00%)	1(20.00%)	1(11.11%)	1(25.00%)	0(0.00%)
	Exposure[d]	17.3	5.4	8.5	3.5	1.1
	Incidence density[e]	0.00	18.57	12.09	28.42	0.00
>=18.5 and < 25	N[b]	517	133	136	97	105
	Patients with glucose >=126[c] : n(%)	19(3.68%)	9(6.77%)	6(4.41%)	7(7.22%)	4(3.81%)
	Exposure[d]	324.1	133.8	117.7	52.3	49.9
	Incidence density[e]	5.86	6.73	5.10	12.17	8.02
>= 25 and < 30	N[b]	377	162	144	178	165
	Patients with glucose >=126[c] : n(%)	41(7.13%)	20(12.35%)	11(7.64%)	15(8.43%)	11(6.67%)
	Exposure[d]	361.1	161.6	126.1	109.5	75.8
	Incidence density[e]	11.36	12.37	8.72	13.70	14.51
>= 30 and < 40	N[b]	559	150	153	213	195
	Patients with glucose >=126[c] : n(%)	65(11.63%)	24(16.00%)	13(8.27%)	33(15.49%)	17(8.72%)
	Exposure[d]	343.9	161.2	122.8	131.8	94.0
	Incidence density[e]	18.79	14.89	8.96	25.04	18.08
>= 40	N[b]	119	32	24	45	30
	Patients with glucose >=126[c] : n(%)	24(20.17%)	12(37.50%)	2(8.33%)	16(35.56%)	1(2.50%)

Table C- 13 Any documented fasting glucose >=126 mg/dL during the study, by baseline BMI category (open-label and randomized safety populations)

126 + 127		OL safety population BMI at enrollment, documented fasting glucose >= 126 in OL phase QTP + LI/VAL N=3371	RD safety population BMI at enrollment, documented fasting glucose >= 126 in RD phase QTP + LI/VAL N=646	 PLA + LI/VAL N=680	RD safety population BMI at randomization, documented fasting glucose >= 126 in RD phase QTP + LI/VAL N=646	 PLA + LI/VAL N=680
	Exposure[d]	79.2	42.1	26.3	37.5	30.2
	Incidence density[e]	30.30	28.54	7.62	42.65	3.31

[a] BMI at baseline (enrollment or randomization).
[b] Number of patients in BMI subgroup at time point (enrollment or randomization).
[c] Patients with at least one post-baseline documented fasting glucose >=126mg/dL in the specified treatment phase.
[d] Exposure in patient-years=time until first value >=126 or until last dose for patients with no value >=126.
[e] 100*(patients with at least one documented fasting glucose >=126/exposure in patient-years)
Note: Percentages are calculated as (n/Nb)*100.
/sasro/dev/seroquel/cidmaintenance/sp/output/lft/lab-21.rtf lab21.sas 23MAY2007:16:17 kscl497

CONFIDENTIAL
AZSER14868757

Table C- 14 BMI at enrollment and at randomization for patients with adjudicated emerging possible diabetes

126 + 127	Emerging possible diabetes in the OL phase (BMI at enrollment)	Emerging possible diabetes in the RD phase (BMI at enrollment)		Emerging possible diabetes in the RD phase (BMI at randomization)	
BMI category[b]	QTP+LI/VAL N[a]=(23)	QTP+LI/VAL N[a]=(11)	PLA+LI/VAL N[a]=(2)	QTP+LI/VAL N[a]=(11)	PLA+LI/VAL N[a]=(2)
>= 18.5 and < 25	2	0	0	0	0
>= 25 and < 30	6	4	2	2	1
>= 30 and < 40	12	2	0	4	1
>= 40	3	4	0	4	0
No. patients with BMI classification missing at baseline	0	1	0	1	0

[a] Number of patients with adjudicated emerging possible diabetes in the specified phase
[b] BMI at baseline (enrollment or randomization).
/core/dev/sas/spad/adnaintesearce/sp/output/ICtab-22.rtf tab22.sas 29MAY2007:15:06 kfqsp035

CONFIDENTIAL
AZSER14868758

Table C- 15 Any documented fasting glucose >=126 mg/dL and weight change during the study (open-label and randomized safety populations)

126 + 127		OL safety population	RD safety population		RD safety population	
		Documented fasting glucose at enrollment and >= 126 in OL phase	Documented fasting glucose at enrollment and >= 126 in RD phase		Documented fasting glucose at randomization and >= 126 in RD phase	
		QTP + LI/VAL N=3371	QTP + LI/VAL N=646	PLA + LI/VAL N=680	QTP + LI/VAL N=646	PLA + LI/VAL N=680
>= 1% decrease	N[b]	664	150	204	187	288
	Patients with glucose >=126[c]: n(%)	56(8.43%)	20(13.33%)	8(3.92%)	32(17.11%)	18(6.25%)
	Exposure[d]	425.4	162.8	186.9	132.1	341.9
	Incidence density[e]	13.16	12.29	4.28	24.23	12.68
< 1% increase or decrease	N[b]	275	47	61	105	102
	Patients with glucose >=126[c]: n(%)	28(10.18%)	8(17.02%)	8(13.11%)	10(9.52%)	8(7.84%)
	Exposure[d]	124.2	45.6	52.5	50.8	40.1
	Incidence density[e]	22.54	17.76	15.25	19.99	19.93
>= 1 - 5% increase	N[b]	509	105	130	167	91
	Patients with glucose >=126[c]: n(%)	35(6.88%)	7(6.67%)	6(5.45%)	13(7.78%)	5(5.49%)
	Exposure[d]	277.5	100.9	96.0	90.7	46.3
	Incidence density[e]	12.61	6.94	6.25	14.34	10.80
>= 5% increase	N[b]	599	236	152	79	26
	Patients with glucose >=126[c]: n(%)	40(6.68%)	37(15.68%)	11(8.33%)	17(21.52%)	2(7.69%)
	Exposure[d]	418.8	250.4	123.1	67.6	22.5
	Incidence density[e]	8.91	14.78	8.93	25.15	8.91

[b] Change in weight from baseline (enrollment or randomization) to end of randomized treatment.
[c] Number of patients in subgroup (patients must have baseline and a post-baseline weight assessment to be included)

[c] Patients with at least one post-baseline documented fasting glucose >= 126mg/dL in the specified treatment phase
[d] Exposure in patient-years=time until first value >=126 or until last dose for patients with no value >=126
[e] 100*(patients with at least one documented fasting glucose >=126/exposure in patient-years)
Note: Percentages are calculated as (n/Nb)* 100.
/ccre/dev/seroquel/cdmaintenance/sp/output/II/tab-23.rtf tab23.sas 23MAY2007:16:34 kxel497

Table C- 16 Weight change during the study for patients with adjudicated emerging possible diabetes

126 + 127	Emerging possible diabetes in the OL phase (Weight change from enrollment)	Emerging possible diabetes in the RD phase (Weight change from enrollment)		Emerging possible diabetes in the RD phase (Weight change from randomization)	
Weight change[b]	QTP+LI/VAL N[a]=(23)	QTP+LI/VAL N[a]=(11)	PLA+LI/VAL N[a]=(2)	QTP+LI/VAL N[a]=(11)	PLA+LI/VAL N[a]=(2)
>= 1% decrease	12	3	0	6	1
< 1% increase or decrease	4	1	0	1	0
>= 1 - < 5% increase	1	0	0	1	0
>= 5% increase	6	7	2	3	1
No. patients with missing weight change classification[c]	0	0	0	0	0

[a] Number of patients with adjudicated emerging possible diabetes in the specified phase.
[b] Change in weight from baseline (enrollment or randomization) to end of treatment.
[c] Patients must have baseline and a post-baseline weight assessment to be classified
/ccre/dev/seroquel/cdmaintenance/sp/output/II/tab-24.rtf tab24.sas 29MAY2007:13:04 kleu035

Table C- 17 Mean documented fasting glucose during the randomization phase for placebo vs. quetiapine, compared with mean glucose in the open-label phase(randomized safety population)

Study	Documented fasting glucose		Open-label phase QTP + LI/VAL N=646	Open-label phase PLA + LI/VAL N=680	Randomized phase QTP + LI/VAL N=646	Randomized phase PLA + LI/VAL N=680
126	>= 126[a]	N[b]	7	8	6	7
		Mean glucose[c] : mean	123.5	112.8	111.5	116.4
	< 126	N[b]	284	290	287	311
		Mean glucose[c] : mean	90.6	91.1	93.4	93.1
127	>= 126[a]	N[b]	8	7	8	7
		Mean glucose[c] : mean	133.4	134	163.7	134.9
	< 126	N[b]	214	223	247	248
		Mean glucose[c] : mean	86.6	87.4	92.3	89.1
126 + 127	>= 126[a]	N[b]	15	15	14	14
		Mean glucose[c] : mean	128.8	122.7	141.3	115.7
	< 126	N[b]	498	513	534	559
		Mean glucose[c] : mean	88.9	89.5	92.9	91.3

[a] Patients with at least 1 doc. fasting glucose>=126 mg/dL any time in the OL (after enrollment) and no history of diabetes
[b] Number of patients in subgroup
[c] Mean of intra-individual mean glucose based on all assessments in respective phase.
/esr/dev/seroquel/csrmaintenance/sp/output/dl/tab-25.rtf tab25.sas 23MAY2007:09:11 1xcl497

Table C- 18 Analysis of change in weight and glucose data from enrollment to end of treatment for patients randomized to QTP (randomized safety population)

		126 + 127 QTP + LI/VAL N=646
Slope estimate and 95% confidence interval	Weight (Kg)	0.509(0.430, 0.588)
	Glucose[a] (mg/dL)	0.723(0.109, 1.337)
	HBA1c (%)	0.071(0.062, 0.080)
	Insulin (pmol/L)	0.482(-0.209, 1.173)
	HOMA-R	0.106(-0.177, 0.389)
	QUICKI	-0.001(-0.002, 0.000)

a Documented fasting glucose (sampling >8 hours after a meal).
Note: Analysis of change over time (slope estimate and corresponding confidence interval) using a mixed model with random patient effect.
/csre/dev/seroquel/cdmaintenance/sp/output/dl/tab-26.rtf tab26.sas 23MAY2007:13:37 kscl497

Table C- 19 Patients with insulin therapy initiated or insulin dose changed during the study

STUDY	SUBJECT	RD TRT	AGE	SEX	WEIGHT (ENR/RD)	GLUCOSE (ENR/RD)	HBA1C (ENR/RD)	MEDICATION CLASS	GENERIC NAME	MED START DAY FR RD	DOSE	REASON FOR THERAPY
D1447C00126	E020180 1	PLA+VAL	55	Male	116/107	120/113	6.1/5.9	Insulins And Analogues, Fast-Acting	INSULIN ASPART	-99	15	Diabetes
								Insulins And Analogues, Fast-Acting	INSULIN ASPART	-158	32	Diabetes
								Insulins And Analogues, Fast-Acting	INSULIN ASPART	-126	20	Diabetes
	E030630 2	PLA+VAL	66	Female	82.2/82.1	108/85	6.3/6.9	Insulins And Analogues, Intermediate-A	INSULIN HUMAN INJECTION, ISOPHANE	234	4	Diabetes
								Insulins/Analogues, Intermed-Acting Co	INSULIN HUMAN	234	26	Diabetes
D1447C00127	E003109 2		50	Female	78.5/	72/	6.4/	INSULINS AND ANALOGUES, FAST-ACTING	INSULIN		10	DIABETES
	E004409 7	QTP+VAL	44	Male	118.8/114.7	87/127	6.4/8.1	INSULINS AND ANALOGUES, FAST-ACTING	INSULIN	112	30	DIABETES MELLITI
	E007309 2	QTP+VAL	51	Female	104.5/105	93/125	7.8/10.1	INSULINS AND ANALOGUES, LONG-ACTING	INSULIN GLARGINE	155	15	TYPE 1 DIABETES

Table C- 19 Patients with insulin therapy initiated or insulin dose changed during the study

STUDY	SUBJECT	RD TRT	AGE	SEX	WEIGHT (ENR/RD)	GLUCOSE (ENR/RD)	HBA1C (ENR/RD)	MEDICATION CLASS	GENERIC NAME	MED START DAY FR RD	DOSE	REASON FOR THERAPY
	E007800 2	PLA+VAL	44	Female	68.1/75.9	139/101	8.6/9.2	INSULINS AND ANALOGUES, FAST-ACTING	INSULIN ASPART	167	8	DIABETES
								INSULINS AND ANALOGUES, FAST-ACTING	INSULIN ASPART	169	8	DIABETES
								INSULINS AND ANALOGUES, FAST-ACTING	INSULIN ASPART	170	4	DIABETES
								INSULINS AND ANALOGUES, LONG-ACTING	INSULIN GLARGINE	162	20	DIABETES
	E008003 0	PLA+LI	41	Male	114.3/114.5	262/165	6.9/8.2	INSULINS AND ANALOGUES, LONG-ACTING	INSULIN GLARGINE	68	140	TYPE 2 DIABETES

Figure C-1 **Mean plot of weight and Hba1c from enrollment to end of randomized treatment (patients randomized to QTP) 126 + 127 (randomized safety population)**

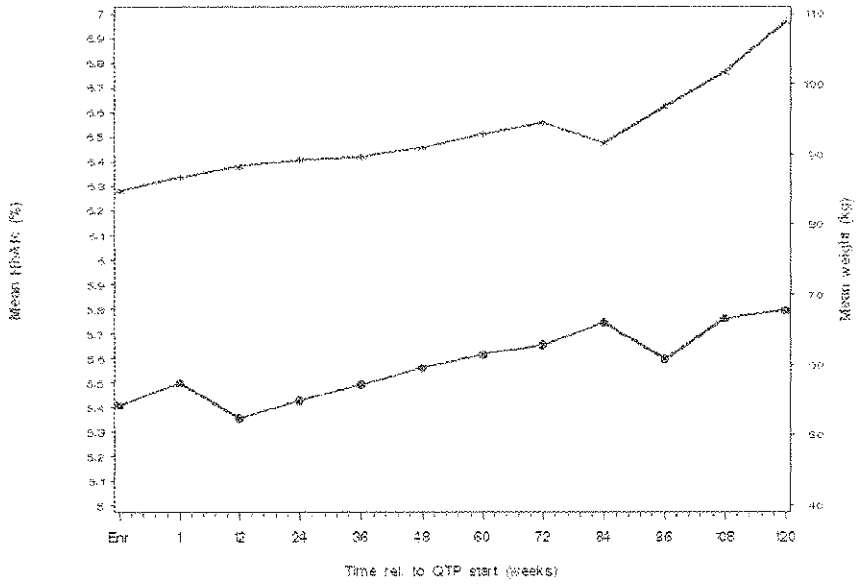


Figure C- 2 Mean plot of weight and glucose from enrollment to end of randomized treatment (patients randomized to QTP) 126 + 127 (randomized safety population)

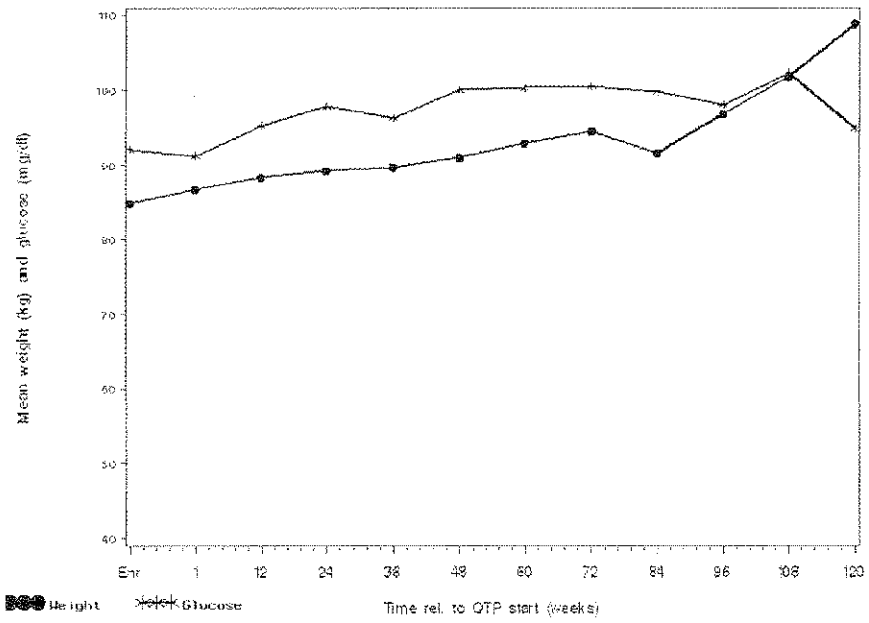


Figure C-3 **Box-whisher plot of glucose from enrollment to end of randomized treatment (patients randomized to QTP) 126 + 127 (randomized safety population**

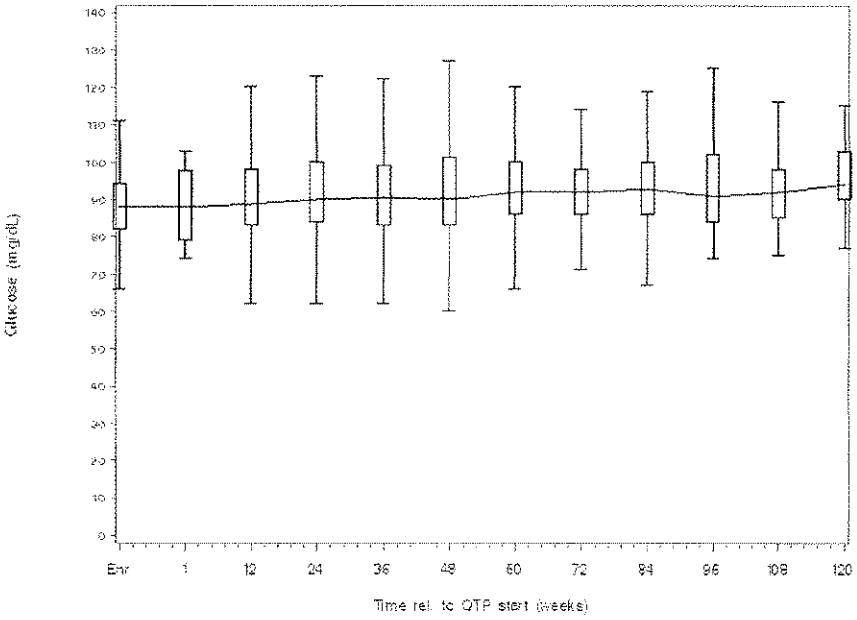


Figure C-4 **Box-whisker plot of HbA1c from enrollment to end of randomized treatment (patients randomized to QTP) 126 + 127 (randomized safety population**

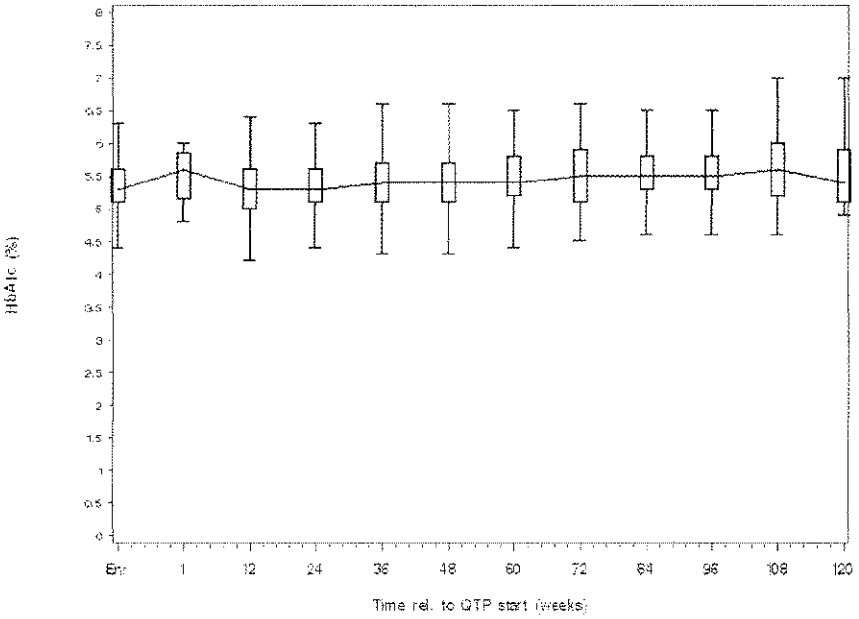
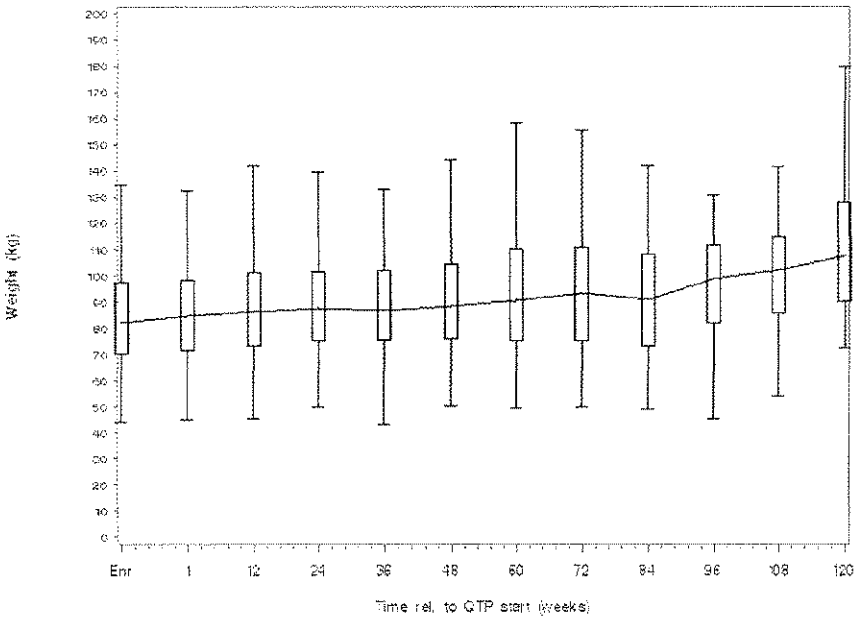


Figure C-5 **Box-whisher plot of weight from enrollment to end of randomized treatment (patients randomized to QTP) 126 + 127 (randomized safety population**



Appendix D Clinical trial narratives

Trials 126/127 Narratives

Quetiapine group: Cases suggestive of possible onset of diabetes during randomized treatment, limited narratives with glycemic data (11 patients)

Patient E0036019; Study 127
The adverse event "diabetes mellitus" (verbatim term) was reported for a 42-year-old morbidly obese Black female (with no evidence of pre-existing diabetes) on Day 225 of randomized quetiapine treatment (QTP 400 mg/day adjunct with lithium). The AE was considered by the reporting investigator to be of moderate intensity and unrelated to study drug.

Study treatment exposure was 112 days of open-label treatment and 423 days of randomized treatment (quetiapine 400 mg/day and lithium).

At enrollment blood glucose was not "documented fasting" (134.0 mg/dL), HbA1c was 6.5%, and BMI was 40.9 kg/m^2. From enrollment to Day 196 of randomized treatment the patient had a weight increase of 18 kg (from 122 kg to 140 kg). On Day 196 of randomized treatment "documented fasting" blood glucose was 316 mg/dL and HbA1c was 9.0%. On Day 225 the AE "diabetes mellitus" was reported. Treatment was initiated with glucose lowering medications metformin hydrochloride and exenatide on Day 274 and Day 278, respectively. On Day 312 exenatide was increased from 10 mg to 20 mg and metformin hydrochloride was increased from 500 mg to 1000 mg. The AE diabetes mellitus was reported resolved on Day 424 with "documented fasting" blood glucose of 117 mg/dL and HbA1c 6.6%, with oral diabetes treatment ongoing.

Summary: This patient with morbid obesity at the time of enrollment (BMI 40.9 kg/m^2), and no evidence of pre-existing diabetes, had an adverse event of "diabetes mellitus" associated with an elevated fasting glucose value of 316 mg/dL, and also experienced a 18 kg weight gain during study participation. Oral antihyperglycemic therapy was initiated with good therapeutic results (decrease in glucose values from 316 mg/dL to 117 mg/dL and decrease in HbA1c from 9.0%. to 6.6%) while study medication was continued. Upon post-hoc adjudicated analysis this patient was considered to have onset of diabetes during randomized treatment. .

Patient E0063001; Study 127
The adverse event "diabetes mellitus" (verbatim term) was reported for a 48-year-old obese Caucasian male (with no evidence of pre-existing diabetes) on Day 208 of randomized quetiapine treatment (QTP 600 mg/day adjunct with lithium). The AE was considered by the reporting investigator to be of moderate intensity and related to study drug.

Study treatment exposure was 111 days of open-label treatment and 687 days of randomized treatment (quetiapine 600 mg/day and lithium).

At enrollment, blood glucose was not "documented fasting" (117 mg/dL), HbA1c was 5.7%, and BMI was 36.2 kg/m^2. From the time of enrollment to Day 208 (date of AE "diabetes mellitus"), the patient had a weight increase of 3 kg (108 kg to 111 kg). Day 208 values were "documented fasting" blood glucose 163 mg/dL and HbA1c 6.8%. The patient received glucose lowering medication (metformin hydrochloride and glipizide) on Day 604. The AE continued to the final visit on Day 687 when "documented fasting" values were reported for blood glucose of 143 mg/dL and HbA1c 6.7%, with antihyperglycemic treatment still ongoing.

Summary: This patient with obesity at the time of enrollment (BMI 36.2 kg/m^2), and no evidence of pre-existing diabetes, had an adverse event of "diabetes mellitus" associated with an elevated fasting glucose 163 mg/dL, an increase in HbA1c from 5.7% to 6.8%, and a 3 kg weight increase during study participation. Oral antihyperglycemic treatment was initiated with therapeutic results (decrease in glucose from 163 mg/dL to 143 mg/dL and decrease in HbA1c from 6.8%. to 6.7%) while the patient was continued on study medication. Upon post-hoc adjudicated evaluation this patient was considered to have onset of diabetes during randomized treatment.

Patient E0037014; Study 127
The adverse event "hyperglycaemia" was reported for a 27-year-old morbidly obese Caucasian male (with no evidence of pre-existing diabetes) on Day 78 of randomized treatment (QTP 500 mg/day adjunct with lithium). The AE was considered by the reporting investigator to be of mild intensity and related to study drug.

Study treatment exposure was 224 days of open-label treatment and 85 days of randomized treatment (quetiapine 500 mg/day and lithium).

At enrollment blood glucose was not "documented fasting" (81 mg/dL), HbA1c was 5.0%, and BMI was 49.6 kg/m^2. From enrollment to Day 78 (date of the reported AE), the patient had a weight increase of 23 kg (143 kg to 166 kg). Day 78 "documented fasting" blood glucose was 151 mg/dL and HbA1c was 6.4%. On Day 98 the patient was withdrawn from the study due to the AE and the investigator considered the event resolved. At the final visit (Day 98), "documented fasting" blood glucose was 131 mg/dL and HbA1c was 6.3%. A clinical narrative for this DAE is provided in the CSR for Study 127, Section 11.3.10, Module 5.3.5.1.

Summary: This patient with morbid obesity at the time of enrollment (BMI 49.6 kg/m^2), and no evidence of pre-existing diabetes, had an adverse event of "hyperglycaemia" associated with elevated fasting glucose values of 151 mg/dL and 131 mg/dL, an increase in HbA1c from 5.0% to 6.4% and 6.3%, and a 23 kg weight increase, during study participation. The patient was withdrawn from the study due to the AE. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

Patient E0070006; Study 127
A 43-year-old morbidly obese Caucasian female with a medical history of "renal glycosuria" at the time of enrollment (with no history of pre-existing diabetes) had elevated glucose values

during randomized treatment (QTP 400 mg/day adjunct with valproate) that were not associated with any AEs.

Study treatment exposure was 168 days of open-label treatment and 672 days of randomized treatment (quetiapine 400 mg/day and valproate).

At enrollment blood glucose was not "documented fasting" (146 mg/dL), HbA1c was 8.1%, and BMI 44.2 kg/m^2. From enrollment to Day 169, the patient had a weight decrease of 6 kg (109 kg to 103 kg). At randomization "documented fasting" blood glucose was 104 mg/dL and HbA1c was 6.0%. Day 169 "documented fasting" blood glucose was 152 mg/dL and HbA1c was 5.9%. Day 447 and Day 561 "documented fasting" blood glucose values were 177 mg/dL and 130 mg/dL, respectively. Final visit (Day 673) "documented fasting" values were blood glucose of 106 mg/dL and HbA1c of 6.6%. No adverse events were reported by the investigator in association with these laboratory findings.

Summary: This patient with morbid obesity at the time of enrollment (BMI 44.2 kg/m^2), and a medical history of "renal glycosuria" with no evidence of pre-existing diabetes, had fasting glucose values during randomization from 104 mg/dL to 177 mg/dL, 130 mg/dL, and 106 mg/dL; HbA1c from 6.0% to 8.1%, 5.9%, and 6.6% associated with a 6 kg weight decrease during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

Patient E0083013; Study 127
A 51-year-old morbidly obese Caucasian female with no evidence of pre-existing diabetes at the time of enrollment had elevated glucose values during randomized treatment (QTP 600 mg/day adjunct with valproate) that were not associated with any AEs.

Study treatment exposure was 224 days of open-label treatment and 626 days of randomized treatment (quetiapine 600 mg/day and valproate).

At enrollment blood glucose was "documented fasting" 90 mg/dL, HbA1c was 6.0%, BMI was 41.3 kg/m^2. From enrollment to Day 478, the patient had a weight increase of 10 kg (109 kg to 119 kg). Day 478 "documented fasting" blood glucose was 138 mg/dL and HbA1c was 7.6%. At the final visit (Day 626), "documented fasting" blood glucose was 126 mg/dL and HbA1c was 7.0%. No adverse events were reported by the investigator in association with these laboratory findings.

Summary: This patient with morbid obesity at the time of enrollment (BMI 41.3 kg/m^2), and no evidence of pre-existing diabetes, had increases in fasting glucose (from 90 mg/dL to 138 mg/dL and 126 mg/dL; HbA1c from 6.0% to 7.6% and 7.0%) associated with a weight increase of 10 kg during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

Patient E0089002; Study 127
A 46-year-old overweight Black female with no evidence of pre-existing diabetes had elevated glucose values during randomized treatment (QTP 600 mg/day adjunct with valproate) that were not associated with any AEs.

Study treatment exposure was 126 days of open-label treatment and 267days of randomized treatment (quetiapine 600 mg/day and valproate).

At enrollment blood glucose was not "documented fasting" (124 mg/dL), HbA1c was 6.3% and BMI was 29.3 kg/m^2. From the time of study enrollment to Day 225 the patient had a weight increase of 11 kg (68 kg to 79 kg). Day 225 of randomized treatment not "documented fasting" blood glucose was 228 mg/dL and HbA1c was 7.3%. At the final visit (Day 268) the not "documented fasting" blood glucose was 211 mg/dL, there was no HbA1c value reported for this visit. No adverse events were reported by the investigator in association with these laboratory findings.

Summary: This overweight patient (BMI 29.3 kg/m^2) with no evidence of pre-existing diabetes at the time of enrollment, had increases in non fasting glucose from 124 mg/dL to 228 mg/dL and 211 mg/dL; HbA1c from 6.3% to 7.3%, associated with a weight increase of 11 kg during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

Patient E0120007; Study 127
A 21-year-old obese Caucasian male with no evidence of pre-existing diabetes at enrollment had increases in glucose values during randomized treatment (QTP 500 mg/day adjunct with valproate) that were not associated with any AEs. Study treatment exposure was 140 days of open-label treatment and 601 days of randomized treatment (quetiapine 500 mg/day and valproate). At enrollment blood glucose was not "documented fasting" 103 mg/dL, HbA1c was 5.2%, and BMI was 37.2 kg/m^2. From the time of enrollment to Day 281, the patient had a weight increase of 4 kg (118 kg to 122 kg). Day 281 "documented fasting" blood glucose was 137 mg/dL and HbA1c was 5.7%. Day 484 "documented fasting" blood glucose was 176 mg/dL and HbA1c was 7.7%, on the subsequent visit (Day 595) "documented fasting" blood glucose was 164 mg/dL and HbA1c was 7.4%. At the final visit (Day 602), "documented fasting" blood glucose was 148 mg/dL and HbA1c was 7.7%. No adverse events were reported by the investigator in association with these laboratory findings.

Summary: This patient with obesity at the time of enrollment (BMI 37.2 kg/m^2), and no evidence of pre-existing diabetes, had elevated fasting glucose during randomization (137 mg/dL, 176 mg/dL, and 164 mg/dL) and increases from baseline in HbA1c (from 5.2% to 5.7%, 7.7%, and 7.4%) associated with a weight increase of 4 kg during study participation. Upon post-hoc adjudicated evaluation this patient was considered to possible onset of diabetes during randomized treatment.

Patient E0805007; Study 126
A 60-year-old overweight Caucasian male with no evidence of pre-existing diabetes had an

elevated glucose value during randomized treatment (QTP 400 mg/day adjunct with lithium) that was not associated with any AE.

Study treatment exposure was 112 days of open-label treatment and 309 days of randomized treatment (quetiapine 400 mg/day with lithium).

At enrollment blood glucose was "documented fasting" 98 mg/dL, HbA1c was 5.5%, BMI was 29.1 kg/m^2. From the time of enrollment to the final visit (Day 309) the patient had a weight increase of 26 kg (from 88 kg to 114 kg). At the final visit (Day 309), "documented fasting" blood glucose was 155 mg/dL and HbA1c was 6.8%. No adverse events were reported by the investigator in association with these laboratory findings.

Summary: This overweight patient (BMI of 29.1 kg/m^2) with no evidence of pre-existing diabetes, had increases in fasting glucose (from 98 mg/dL to 128 mg/dL, 132 mg/dL, and 155 mg/dL), and HbA1c changes from 5.5% to 5.3%, and 6.8% associated with a weight increase of 26 kg during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

Patient E1104007; Study 126
A 46-year-old overweight Caucasian male with no evidence of pre-existing diabetes at the time of enrollment, had elevated glucose values during randomized treatment (QTP 500 mg/day adjunct with lithium) that were not associated with any AEs.

Study treatment exposure was 121 days of open-label treatment and 378 days of randomized treatment (quetiapine 500 mg/day with lithium).

At enrollment blood glucose "documented fasting" 88 mg/dL, HbA1c was 5.1%, and BMI was 27.9 kg/m2. From the time of enrollment to the final visit (Day 378) the patient had a weight decrease of 15 kg (from 80 kg to 65 kg). Day 85 "documented fasting" blood glucose was 144 mg/dL and HbA1c was 5.2% and Day 365 "documented fasting" blood glucose was 132 mg/dL and HbA1c was 5.4%. At the final visit (Day 378) "documented fasting" blood glucose was 147 mg/dL and was 5.2%. No adverse events were reported by the investigator in association with these laboratory findings.

Summary: This overweight patient (BMI of 27.9 kg/m^2) with no evidence of pre-existing diabetes, had an increase in glucose values (fasting glucose from 88 mg/dL to 144 mg/dL, 132 mg/dL, and 147 mg/dL) and HbA1c values of 5.1% to 5.2%, 5.4%, and 5.2%) associated with a weight decrease of 15 kg during study participation. Upon post-hoc adjudicated analysis this patient was considered to possible onset of diabetes during randomized treatment.

Patient E1309003; Study 126
A 56-year-old Caucasian female with an increased fasting glucose at the time of enrollment suggestive of impaired glucose tolerance and no other evidence of pre-existing diabetes had elevated glucose values during randomized treatment (QTP 800 mg/day adjunct with lithium) that were not associated with any AEs.

Study treatment exposure was 101 days of open-label treatment and 461 days of randomized treatment (quetiapine 800 mg/day with lithium).

At enrollment blood glucose was "documented fasting" 117 mg/dL, HbA1c was 5.8%, and weight was 122 kg (BMI unavailable as height not recorded). From the time of enrollment to the Day 113 and thereafter the patient had a weight decrease of 11 kg to Day 293(from 121 kg to 110 kg). Day of randomization "documented fasting" blood glucose was 125 mg/dL and HbA1c was 6.3%. Day 113 "documented fasting" blood glucose values were 126 mg/dL and HbA1c was 6.3%. At the final visit (Day 461) "documented fasting" blood glucose was 127 mg/dL and HbA1c was 6.5%. No adverse events were reported by the investigator in association with these laboratory findings.

Summary: This patient with a weight of 122 kg at the time of enrollment and possible evidence of impaired fasting glucose at screening (117 mg/dL) with no other evidence of pre-existing diabetes, had an increase in glucose values (fasting glucose from 117 mg/dL to 125 mg/dL, 126 mg/dL, and 127 mg/dL; HbA1c from 5.8% to 6.3%, 6.3%, and 6.5%), associated with a weight decrease of 11 kg during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

Patient E1801002; Study 126
A 59-year-old overweight Caucasian male with no evidence of pre-existing diabetes had elevated glucose values during randomized treatment (QTP 400 mg/day adjunct with lithium) that were not associated with any AEs.

Study treatment exposure was 84 days of open-label treatment and 211 days of randomized treatment (quetiapine 400 mg/day with lithium).

At enrollment blood glucose was "documented fasting" 94 mg/dL, HbA1c was 5.5%, and BMI was 27.5 kg/m^2. From the time of enrollment to Day 197 of randomized treatment the patient had a weight increase of 24 kg (from 88 kg to 112 kg). Day 197 "documented fasting" blood glucose was 169 mg/dL and HbA1c was 6.8%. At the final visit (Day 211) "documented fasting" blood glucose was 169 mg/dL and HbA1c was 7.0%. No adverse events were reported by the investigator in association with these laboratory findings.

Summary: This overweight patient (BMI of 27.5 kg/m^2 at the time of enrollment), with no evidence of pre-existing diabetes, had an increase in fasting glucose from 94 mg/dL to 169 mg/dL on two occasions; HbA1c from 5.5% to 6.8%, and 7.0%, associated with a weight increase of 24 kg during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

Placebo group: Cases suggestive of possible onset of diabetes during randomized treatment, limited narratives with glycemic data (2 patients)

Patient E0001012; Study 127
A 54-year-old overweight Caucasian male had no history of diabetes and no hypoglycemic

treatment ongoing at enrollment. This patient was treated for 168 days during the open-label phase of the study, and the screening visit BMI, blood glucose and HbA1c values were 27.1 kg/m^2, 119 mg/dL (not "documented fasting") and 6.8%; respectively. On Day 407 of randomized treatment with placebo adjunct with valproate as the mood stabilizer, the patient had treatment with metformin hydrochloride initiated, with "elevated blood sugar" given as reason for treatment. The oral diabetes treatment was stopped on Day 420 (ie, the duration of metformin therapy was 13 days). The blood glucose and HbA1c values closest to the initiation of hypoglycemic treatment (Day 368) were 167 mg/dL ("documented fasting") and 9.1%, respectively. Weight increased by 28 kg from enrollment (91 kg) to day 368 (119 kg). At the final visit on Day 465 of randomized treatment, the blood glucose and HbA1c values were 147 mg/dL ("documented fasting") and 8.2%, respectively.

Summary: This overweight patient (BMI 27.1 kg/m^2), with no evidence of pre-existing diabetes, had oral diabetes treatment initiated for 13 days during randomization. Fasting glucose values during the randomized phase of the study were 167 mg/dL (pre diabetes treatment) and 147 mg/dL (post diabetes treatment), and HbA1c values were 9.1% (pre diabetes treatment) and 8.2% (post diabetes treatment). The patient had a 28 kg weight gain during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

Patient E0026024; Study 127
A 35-year-old overweight Caucasian male had no history of diabetes and no hypoglycemic treatment ongoing at enrollment. This patient was treated for 224 days during the open-label phase of the study, and for 14 days during randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 25.0 kg/m^2, 90 mg/dL (not "documented fasting") and 5.1%; respectively. On Day 84 of open-label treatment with quetiapine 600 mg/day, the patient had a blood glucose value of 170 mg/dL ("documented fasting"), when the HbA1c was 5.3%. On Day 15 of randomized treatment with placebo, the blood glucose was 135 mg/dL ("documented fasting") and the HbA1c was 5.7%; and AEs of "hyperglycemia" and "hyperinsulinemia" were reported by the investigator. Both AEs were non-serious, 1 day in duration, considered by the investigator to be of moderate intensity and considered by the investigator to be related to study drug, and no action was recorded by the investigator in response to these AEs. Weight increased by 10 kg from enrollment (81 kg) to Day 15 of randomized treatment (91 kg). At the final visit on Day 43 of randomized treatment, the blood glucose was 167 mg/dL ("documented fasting"), but no HbA1c value was available for that visit.

Summary: This overweight patient (BMI 25.0 kg/m^2), with no evidence of pre-existing diabetes had AEs of hyperglycemia and hyperinsulinemia reported during randomized treatment and changes in fasting glucose values of 170 mg/dL (open-label), 135 mg/dL and 167 mg/dL (randomized treatment), and HbA1c of 5.3% (open-label) and 5.7% (randomized treatment). The patient had a 10 kg weight gain during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes during randomized treatment.

? **Quetiapine group: Cases suggestive of possible exacerbation of diabetes during randomized treatment, limited narratives with glycemic data (11 patients)**

Patient E0059014; Study 127 (also referenced in possible onset of diabetes in open-label treatment phase)
The SAE, "diabetic ketoacidosis" was reported for a 57-year-old overweight Black male (with no evidence of pre-existing diabetes) on Day 30 of randomized treatment (QTP 400 mg/day adjunct with valproate). The AE was considered by the investigator to be of severe intensity and unrelated to study drug. The patient was subsequently hospitalized for DKA and discharged as newly diagnosed diabetes.

Study treatment exposure was 113 days of open-label treatment and 38 days of randomized treatment (quetiapine 400 mg/day and valproate).

At enrollment blood glucose was not "documented fasting" 130 mg/dL, HbA1c was 5.0%, and BMI was 27.9 kg/m^2. On Day 84 of open-label treatment a "documented fasting" blood glucose was reported as 194 mg/dL. Weight was stable from enrollment (84 kg) to Day 28 (86 kg). During randomized treatment on Day 21 the patient had teeth extracted and a subsequent weight loss of 6 kg due to liquid diet, Day 30 the patient reported polyuria and polydipsia, weight loss, moderate blurred vision and severe renal failure, from Day 41 the patient experienced fatigue, nausea, and vomiting (denied fever chills, dysuria, cough and shortness of breath). Day 42 "documented fasting" blood glucose was 900 mg/dL. Day 44 the patient presented to the emergency room and was subsequently admitted to intensive care with diabetic ketoacidosis. Upon hospitalization glucose was 1445 mg/dL and 1051 mg/dL, and HbA1c was 17.2% (obtained from local laboratory data). Treatment included IV hydration and IV insulin and the patient was newly diagnosed with "diabetes, likely Type 1". By Day 48 of randomized treatment, the event of diabetic ketoacidosis (and an SAE of "renal failure") was reported to be resolved and the patient was discharged from the hospital. The patient discontinued from the study due to AEs, a clinical narrative for the events is provided in the CSR for Study 127, Section 11.3.10, Module 5.3.5.1.

Summary: This overweight patient with a BMI of 27.9 kg/m^2 at enrollment (with no evidence of pre-existing diabetes) had an adverse event of "diabetic ketoacidosis" associated with changes in glucose values (from non-fasting glucose at enrollment of 130 mg/dL to a fasting value during open-label treatment of 194 mg/dL, fasting randomization values of 124 mg/dL, and 900 mg/dL, and hospitalization values of 1445 mg/dL and 1051 mg/dL; HbA1c values of 5.0% to 17.2%). This patient also had a 6 kg weight loss during study participation. Upon post-hoc adjudicated analysis this patient was considered to have fasting glucose levels consistent with onset of diabetes during the open label phase of the study and exacerbation of diabetes with an AE report of "diabetic ketoacidosis" during the randomized phase of the study, with initiation of antihyperglycemic medication.

Patient E0080036; Study 127 (also referenced in possible onset of diabetes in the open-label phase)
A 29-year-old obese Caucasian male with prior medical history of glucose intolerance,

metabolic syndrome, and obesity (with no medical history of diabetes) had an adverse event with the verbatim term "type II diabetes" (MedDRA preferred term "diabetes mellitus non-insulin-dependent") on Day 214 of randomized treatment (QTP 800 mg/day adjunct with valproate). The investigator considered the AE to be of moderate intensity and unrelated to study drug.

Study treatment exposure was 109 days of open-label treatment and 275 days of randomized treatment (quetiapine 800 mg/day with valproate).

At enrollment blood glucose was "documented fasting" 92 mg/dL, HbA1c was 5.9%, and BMI was 38.4 kg/m^2. Weight was stable from enrollment to Day 199 (118 kg to 120 kg). The "documented fasting" blood glucose at randomization was 147 mg/dL. Day 199 "documented fasting" glucose was 583 mg/dL and non "documented fasting" HbA1c was 15.6%. On Day 214 the adverse event of "type II diabetes" was reported. Day 206 non "documented fasting" blood glucose was 238 mg/dL and no HbA1c value was reported. At the final visit (Day 275) "documented fasting" glucose was 94 mg/dL, insulin 42 pmol/L, and HbA1c 9.4%; the AE was reported as continuing.

Summary: This obese patient (BMI 38.4 kg/m^2) with a medical history of glucose intolerance, metabolic syndrome, and obesity (with no medical history of diabetes) at enrollment had an adverse event "type II diabetes" during randomized treatment associated with increases in glucose (fasting blood glucose values from 92 mg/dL to 147 mg/dL [day of randomization], 583 mg/dL and non-fasting glucose value of 238 mg/dL; HbA1c values of 5.9% to 15.6%) with no glucose lowering therapy initiated. Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes in the open-label phase, and exacerbation of diabetes during randomized treatment.

Patient E0044007; Study 127
A 44-year-old morbidly obese Caucasian male with prior history of "diabetes mellitus type II" had ongoing treatment with metformin and pioglitazone for treatment of diabetes mellitus at enrollment.

Study treatment exposure was 253 days of open-label treatment and 562 days of randomized treatment (quetiapine 800 mg/day and valproate).

At enrollment blood glucose was not "documented fasting" 87 mg/dL, HbA1c was 6.4%, and BMI was 40.2 kg/m^2. From enrollment to Day 91 of randomized treatment the patient had a weight increase of 25 kg (from 119 kg to 144 kg). Day 91 "documented fasting" glucose was 404 mg/dL and HbA1c was 12.0%. On Day 112 of randomized treatment insulin was initiated for "diabetes mellitus". During randomization "documented fasting" blood glucose values were Day 196: 179 mg/dL, Day 282: 169 mg/dL, Day 369: 172 mg/dL, and Day 484: 201 mg/dL. At the final visit (Day 562) "documented fasting" blood glucose was 80 mg/dL and HbA1c was 9.4%, with insulin treatment still ongoing.

Summary: This patient with morbid obesity (BMI 40.2 kg/m^2), prior history of "diabetes mellitus type II", and ongoing antihyperglycemic treatment at enrollment, had changes in

fasting glucose values during randomization (from 169 mg/dL to 404 mg/dL to 80 mg/dL at the final visit; changes in HbA1c values from 6.4% to 12.0% to 9.4%), and a 25 kg weight increase during study participation. Insulin was initiated and continued throughout the study. Upon post-hoc adjudicated analysis this patient had pre-existing diabetes and possible exacerbation of diabetes during randomized treatment.

Patient E0048011; Study 127 (also referenced in possible onset of diabetes in the open-label phase)
The AE "hyperglycemia" was reported and antihyperglycemic therapy was initiated for a 51-year-old overweight Caucasian male (with no evidence of pre-existing diabetes) during randomized treatment (QTP 400 mg/day adjunct with valproate). The AE was considered by the reporting investigator to be of severe intensity and related to study drug.

Study treatment exposure was 226 days of open-label treatment and 68 days of randomized treatment (quetiapine 400 mg/day adjunct with valproate).

At enrollment blood glucose was "documented fasting" 94 mg/dL, HbA1c was 5.2%, and BMI was 26.3 kg/m^2. From the time of screening to Day 54 the patient had a weight increase of 10 kg (from 76 kg to 86 kg). Day 168 (open-label "documented fasting" blood glucose was 167 mg/dL and HbA1c was 6.9%. On Day 61 of randomized treatment was initiated with metformin hydrochloride, glibenclamide, and glipizide for "hyperglycemia". On Day 62, the patient had an AE of "hyperglycemia". On Day 68 the patient withdrew from the study due to the AE. At the final visit (Day 83) "documented fasting" glucose was 249 mg/dL and HbA1c was 9.6%, respectively, with hyperglycemic treatment still ongoing.

Summary: This overweight patient (BMI 26.3 kg/m^2) with no evidence of pre-existing diabetes, had an AE of "hyperglycemia" and fasting glucose values of 94 mg/dL (at enrollment), 167 mg/dL (open label), and 249 mg/dL (during randomized treatment at the final visit). This patient had a 10 kg weight increase during study participation. Upon post-hoc adjudicated evaluation was considered to have possible onset during open-label treatment and possible exacerbation of diabetes during randomized treatment.

Patient E0007047; Study 127
A 72-year-old overweight Caucasian man, with a medical history of diabetes, but no antihyperglycemic medications ongoing at enrollment, had elevated glucose values during randomized treatment. No adverse event was recorded by the investigator in association with any of the laboratory assessments, and no change in study medication or initiation of diabetes therapy were recorded during the study.

Study treatment exposure was 140 days of open-label treatment and for 435 days of randomized treatment (quetiapine 500 mg/day with valproate).

At enrollment blood glucose was not "documented fasting" 115 mg/dL, HbA1c values were 6.2%, and BMI was 28.8 kg/m^2. From enrollment to Day 197 of randomized treatment the patient had a weight increase of 2 kg (from 89 kg to 91 kg). Day 197 "documented fasting"

blood glucose was 198 mg/dL and HbA1c was 7.3%. At the final visit (Day 435), "documented fasting" blood glucose was 139 mg/dL and HbA1c was 7.5%.

Summary: This overweight patient with a BMI of 28.8 kg/m^2 at enrollment (with medical history of diabetes) had elevated fasting glucose values of 115 mg/dL (enrollment), 198 mg/dL, and 139 mg/dL (final visit); HbA1c values of 6.2% (enrollment), 7.3%, and 7.5% (final visit), and a 2 kg weight gain during study participation. Upon post-hoc adjudicated analysis this patient was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0044006; Study 127
A 43-year-old obese Caucasian male with medical history of "diabetes mellitus type II" and no antihyperglycemic medications ongoing at enrollment had elevated glucose values during randomized treatment. No adverse event was recorded by the investigator in association with any of the laboratory assessments, and no change in study medication or initiation of diabetes therapy was recorded by the investigator at any time during the study.

Study treatment exposure was 251 days during the open-label treatment and for 231 days of randomized treatment (quetiapine 800 mg/day with lithium).

At enrollment blood glucose was not "documented fasting" 92 mg/dL, HbA1c was 5.5%; and BMI was 35.1 kg/m^2. From enrollment to the final visit of randomized treatment (Day 245) the patient had a weight increase of 5 kg (from 113 kg to 118 kg). Day 85 "documented fasting" blood glucose was 129 mg/dL and HbA1c was 5.8%. Day 197 "documented fasting" blood glucose was 132 mg/dL and HbA1c of 5.9%. No adverse event was recorded by the investigator in association with any of the laboratory assessments, and no change in study medication or initiation of diabetes therapy was recorded by the investigator at any time during the study. Day 245 not "documented fasting" blood glucose was 381 mg/dL and HbA1c was 6.5%; without initiation of hyperglycemic medication at any time during the study.

Summary: This obese patient (BMI 35.1 kg/m^2) with a medical history of "diabetes mellitus type II" and no antihyperglycemic treatment at enrollment, had elevated fasting glucose values during randomization (ranging from 129 mg/dL to 132 mg/dL and 381 mg/dL; and HbA1c values ranging from 5.5% to 5.8%, 5.9%, and 6.5%), associated with a 5 kg weight increase during study participation. Upon post-hoc adjudicated evaluation this patient was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0051006; Study 127
A 62-year-old overweight Caucasian male with a medical history of "diabetes", and treatment with insulin (fast-acting and long-acting) ongoing at enrollment and continuing throughout the study, had elevated glucose values during randomized treatment. No adverse event was recorded by the investigator in association with any of the laboratory assessments, and no change in study medication or diabetes therapy was recorded by the investigator at any time during the study.

Study treatment exposure was 198 days of open-label treatment and for 279 days of randomized treatment (quetiapine 600 mg/day and valproate).

At enrollment blood glucose was "documented fasting" 120 mg/dL, HbA1c was 6.6%, and BMI was 29.8 kg/m^2. From enrollment to Day 77 the patient had a weight loss of 7 kg (from 111 kg to 104 kg). Day 77 "documented fasting" blood glucose was 136 mg/dL and HbA1c was 7.3%. At the final visit (Day 279), not "documented fasting" blood glucose was 214 mg/dL and HbA1c was 9.3%; without any change in the antihyperglycemic therapy.

Summary: This overweight patient (BMI 29.8 kg/m^2) with a medical history of "diabetes" and ongoing insulin treatment at enrollment, had elevated glucose values during randomization (fasting glucose values of 120 mg/dL and 136 mg/dL, and non-fasting glucose of 214 mg/dL; and HbA1c values ranging from 6.6% to 7.3%, and 9.3%), associated with a 7 kg weight loss during study participation. Upon post-hoc adjudicated evaluation this patient was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0063011; Study 127
A 52-year-old obese Caucasian woman, with a medicalhistory of "diabetes" and treatment with glipizide ongoing at enrollment that continued throughout the study, had elevated glucose values during randomized treatment. No adverse events were recorded by the investigator in association with the laboratory assessments.

Study treatment exposure was 238 days of open-label treatment and 198 days of randomized treatment (quetiapine 500 mg/day and lithium).

At enrollment blood glucose was "documented fasting" 92 mg/dL, HbA1c was 6.0%; and BMI was 37.0 kg/m^2. Weight varied throughout the study (104 kg at enrollment, 106 kg at Day 85, and returning to 104 kg at final visit). Day 85 "documented fasting" blood glucose was 174 mg/dL and HbA1c was 8.4%. At the final visit (Day 198), "documented fasting" blood glucose was 248 mg/dL and HbA1c was 10.4%, without any change in the antihyperglycemic therapy

Summary: This obese patient (BMI 37.0 kg/m^2), with a medicalhistory of "diabetes" and ongoing antihyperglycemic treatment at enrollment, had elevated fasting glucose values of 174 mg/dL and 248 mg/dL; and HbA1c values ranging from 8.4% and 10.4% during randomized treatment. Upon post-hoc adjudicated evaluation this patient was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0080033; Study 127
A 38-year-old morbidly obese Caucasian man with a medical history of "diabetes type 2" and treatment with metformin ongoing at enrollment that continued throughout the study, had elevated glucose values during randomized treatment. No adverse event was recorded by the investigator in association with any of the laboratory assessments, and no change in study medication or diabetes therapy was recorded by the investigator.

Study treatment exposure was 144 days of open-label treatment and 252 days of randomized treatment (quetiapine 800 mg/day and lithium).

At enrollment blood glucose was "documented fasting" 166 mg/dL, HbA1c was 7.3%, and BMI was 58.6 kg/m^2. From enrollment to Day 252 (final visit) the patient had a weight loss of 2 kg (from 186 kg to 184 kg). Day 197 "documented fasting" blood glucose was 158 mg/dL and HbA1c was 7.1%. At the final visit (Day 252) "documented fasting" blood glucose was 218 mg/dL and HbA1c was 8.0%, without any change in the antihyperglycemic therapy.

Summary: This morbidly obese patient (BMI 58.6 kg/m^2) with a medicalhistory of "diabetes type 2" and ongoing antihyperglycemic treatment at enrollment, had elevated fasting glucose values of 166 mg/dL (enrollment), 158 mg/dL (Day 197), and 218 mg/dL (final visit); and corresponding HbA1c values of 7.3%, 7.1%, and 8.0%, associated with a 2 kg weight loss during study participation. Upon post-hoc adjudicated evaluation this patient was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0113002; Study 126
A morbidly obese 28-year-old Black woman, with a history of diabetes and ongoing antihyperglycemic treatment with metformin at enrollment, had elevated glucose values during randomized treatment. No AE associated with diabetes was recorded during the randomized treatment phase and metformin dose was not adjusted during the study.

Study treatment exposure was 112 days of open-label treatment and 298 days of randomized treatment (quetiapine 400 mg/day and valproate).

At enrollment blood glucose was "documented fasting" 120 mg/dL, HbA1c was 7.1%, and BMI was 50.1 kg/m^2. From enrollment to Day 195 the patient had a weight loss of 25 kg (from 132 kg to 107 kg). Day 85 "documented fasting" blood glucose was 195 mg/dL and HbA1c was 7.6%. Day 198 not "documented fasting" blood glucose was 235 mg/dL and final visit (Day 298) "documented fasting" blood glucose was 129 mg/dL and HbA1c was 8.1%.

Summary: This morbidly obese patient (BMI 50.1 kg/m^2) with a medicalhistory of "diabetes" and ongoing antihyperglycemic treatment at enrollment, had elevated glucose values during randomization (fasting 195 mg/dL, 129 mg/dL, and non-fasting 235 mg/dL), and HbA1c values of 7.6% and 8.1% during randomized treatment, associated with a 25 kg weight loss during study participation. Upon post-hoc adjudicated evaluation this patient was considered to have pre-existing diabetes and possible exacerbation of diabetes during randomized treatment.

Patient E1104006; Study 126
A 53-year-old obese Caucasian man, with no evidence of diabetes at enrollment, had fasting elevated glucose values at enrollment and during randomized.

Study treatment exposure was 141 days of open-label treatment and 476 days of randomized treatment (quetiapine 500 mg and valproate).

At enrollment blood glucose was 164 mg/dL, HbA1c was 5.5%, and BMI was 39.4 kg/m^2. Day 85 "documented fasting" blood glucose was 159 mg/dL and HbA1c was 6.4%. From enrollment to Day 85 the patient had a weight gain of 5 kg (from 110 kg to 115 kg) and weight was stable thereafter. The patient had "documented fasting" glucose values on Day 197 of 148 mg/dL, on Day 281 of 173 mg/dL, on Day 365 of 167 mg/dL, and on Day 477 of 186 mg/dL. The HbA1c value on Day 477 was 8.8%. No AE associated with diabetes was recorded during randomized treatment phase and no antihyperglycemic treatment was initiated during the study.

Summary: This obese patient (BMI 39.4 kg/m^2) with no evidence of pre-existing diabetes had a fasting blood glucose value consistent with diabetes (164 mg/dL) at the time of enrollment and changes in fasting glucose values during randomization (from 148 mg/dL to 186 mg/dL), changes in HbA1c values from 6.4% and 8.8% during randomized treatment, and a 5 kg weight gain during study participation. Upon post-hoc adjudicated evaluation this patient was considered to have probable pre-existing diabetes and possible exacerbation of diabetes during randomized treatment.

Placebo group: Cases suggestive of possible exacerbation of diabetes during randomized treatment, limited narratives with glycemic data (4 patients)

Patient E0103011; Study 126
A 42-year-old obese Caucasian woman had a history of diabetes mellitus but no hypoglycemic treatment ongoing at enrollment. This patient was treated for 253 days during the open-label phase of the study, and the screening visit BMI, blood glucose and HbA1c values were 34.4 kg/m^2, 79 mg/dL ("documented fasting") and 6.0%, respectively. On Day 84 of open-label treatment, the blood glucose and HbA1c values were 129 mg/dL ("documented fasting") and 5.8%, respectively. On Day 93 of randomized treatment with placebo adjunct with valproate as the mood stabilizer, the blood glucose and HbA1c values were 165 mg/dL ("documented fasting") and 7.0%, respectively. Weight increased by 5 kg (from 88 kg to 93 kg) from enrollment to Day 93. At the last visit (Day 135), blood glucose and HbA1c were 106 mg/dL and 6.8%, respectively. No AE associated with diabetes was recorded during the randomized treatment phase, and no hypoglycaemic treatment was initiated.

Summary: This obese patient (BMI 34.4 kg/m^2), with a history of pre-existing diabetes, had fasting glucose values of 79 mg/dL (enrollment), 129 mg/dL (open-label), and 165 mg/dL and 106 mg/dL (randomized treatment) and HbA1c values of 6.0% (enrollment), 5.8% (open-label), and 7.0% and 6.8% (randomized treatment). The patient had a 5 kg weight gain during study participation. Upon post-hoc adjudicated analysis, this patient was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0118002; Study 126
A 33-year-old overweight Caucasian man had a history of "Type 2 diabetes mellitus" and ongoing treatment with metformin at enrollment. This patient was treated for 109 days during the open-label phase of the study, and the screening visit BMI, blood glucose and HbA1c values were 25.8 kg/m^2, 155 mg/dL ("documented fasting") and 6.8%, respectively. At randomization, the blood glucose and HbA1c values were 170 mg/dL ("documented fasting")

and 7.3%, respectively. On Day 86 of randomized treatment with placebo adjunct with lithium as the mood stabilizer, the blood glucose and HbA1c values were 206 mg/dL ("documented fasting") and 7.8%, respectively. The weight was stable from enrollment (82 kg) to Day 86 (81 kg). No AE associated with diabetes was recorded during the randomized treatment phase, and the dose of metformin was not adjusted during the study.

Summary: This overweight patient (BMI 25.8 kg/m^2), with a medical history of pre-existing diabetes and ongoing antihyperglycemic medication, had fasting glucose values of 155 mg/dL (enrollment) 170 mg/dL (randomization) and 206 mg/dL (Day 86), and HbA1c values of 6.8% (enrollment), 7.3% (randomization) and 7.8% (Day 86). Upon post-hoc adjudicated analysis, this patient was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0604021; Study 126 (also referenced in possible onset of diabetes in the open-label phase)
A 42-year-old Caucasian man (with no evidence of pre-existing diabetes at the time of enrollment) had a medical history of asthma and was taking glucocorticoids throughout the study due to the asthma. The patient was recorded by the investigator as having an adverse event of "thirst" on Day 9 of randomized treatment while receiving placebo adjunct with valproate as the mood stabilizer. The investigator considered the AE to be of mild intensity and related to study drug. There was also an adverse event of "glycosylated haemoglobin increased" recorded on Day 1 of randomized treatment. The investigator considered the AE to be initially of mild intensity and related to study drug. On Day 73, the intensity of this AE was changed to moderate. This patient was treated for 119 days during the open-label phase of the study, and the screening visit BMI, blood glucose and HbA1c values were 28.8 kg/m^2, 92 mg/dL ("documented fasting") and 6.1%, respectively. On day 84 of open-label treatment, the blood glucose was 129 mg/dL ("documented fasting") and HbA1c was 5.9%. The blood glucose and HbA1c values at the time of the AE (Day 1) were 114 mg/dL ("documented fasting") and 6.8%, respectively. Weight increased by 21 kg from enrollment (104 kg) to Day 1 (125 kg). No glucose lowering medications were administered to this patient at any time during the study. The AE of "glycosylated haemoglobin increased" was still present at the final visit on Day 87 when the blood glucose and HbA1c values were 137 mg/dL ("documented fasting") and 7.3%, respectively. The patient withdrew from the study due to this AE.

Summary: This overweight patient (BMI 28.8 kg/m^2), with a history of asthma and ongoing treatment with gluco-corticosteroids (with no evidence of pre-existing diabetes) had AEs of thirst and "glycosylated haemoglobin increased" during randomized treatment. The fasting blood glucose and HbA1c values at the time of the AE (Day 1) were 114 mg/dL ("documented fasting") and 6.8%, respectively. The patient had a 21 kg weight gain during study participation. Upon post-hoc adjudicated analysis, this patient was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0083038; Study 127
A 57-year-old Caucasian male had no history of diabetes and no oral diabetes treatment

ongoing at enrollment. This patient was treated for 224 days during the open-label phase of the study, and the screening visit BMI, blood glucose and HbA1c values were 36.3 kg/m^2, 134 mg/dL ("documented fasting") and 7.1%; respectively. During open-label treatment, the patient had a blood glucose value of 158 mg/dL ("documented fasting") on Day 82, when HbA1c was 6.9%. On Day 168 of open-label treatment, the glucose and HbA1c values were 132 mg/dL ("documented fasting") and 6.5% respectively. On Day 281 of randomized treatment with placebo adjunct with valproate as the mood stabilizer, the blood glucose and HbA1c were reported to be 141 mg/dL ("documented fasting") and 7.4%, respectively. On Day 423, the patient had treatment with pioglitazone hydrochloride initiated, with "elevated fasting plasma glucose" given as reason for treatment. The blood glucose and HbA1c values closest to the initiation of hypoglycemic treatment (Day 370) were 118 mg/dL ("documented fasting") and 7.6%, respectively. Weight decreased by 6 kg from enrollment (119 kg) to Day 370 (113 kg). At the final visit on Day 443 of randomized treatment, the blood glucose and HbA1c values were 115 mg/dL ("documented fasting") and 6.9%, respectively, while the hypoglycemic treatment was still ongoing.

Summary: This obese patient (BMI 36.3 kg/m^2), with no history of pre-existing diabetes, had fasting glucose values of 134 mg/dL (enrollment), 158 mg/dL and 132 mg/dL (during open-label), 141 mg/dL (during randomized treatment) and 118 mg/dL (before initiation of hypoglycemic treatment), and HbA1c values of 7.1% (enrollment), 6.9% and 6.5% (during open-label), 7.4% (during randomized treatment), and 7.6% (before initiation of hypoglycemic treatment). The patient had a 6 kg weight loss during study participation. Upon post-hoc adjudicated analysis, this patient was considered to have a probable pre-existing diabetes and possible exacerbation of diabetes during randomized treatment.

Results of the post hoc adjudicated case evaluation, open-label treatment phase

Overall, the evaluation by individual adjudication of patients, as previously described, of the combined data from the 3 listings identified 23 patients who met criteria for possible onset of possible diabetes in the open-label treatment phase, and identified 20 patients who met criteria for possible exacerbation of diabetes pre-existing at entry. Four of the patients with possible onset of possible diabetes in the open-label treatment phase, were also identified as possible exacerbations in the randomized treatment phase and are part of the 15 exacerbating cases in that period. A brief narrative and summary of findings for these patients is presented below.

Possible onset of possible diabetes during open-label treatment (23 patients)

Patient E0059014; Study 127;
Upon post-hoc adjudicated analysis this patient was considered to have fasting glucose levels consistent with onset of diabetes during the open label phase of the study and exacerbation of diabetes with an AE report of "diabetic ketoacidosis" during the randomized phase of the study, with initiation of antihyperglycemic medication. The narrative for this patient is found in Section

Patient E0604029; Study 126
A 50-year-old overweight Caucasian female with no evidence of pre-existing diabetes at enrollment had an adverse event of "blood glucose increased" during open-label treatment and

subsequent increases in blood glucose during randomized treatment (QTP 400 mg/day adjunct with lithium) that were not associated with any AEs.

Study treatment exposure was 171 days of open-label treatment and 190 days of randomized treatment (quetiapine 400 mg/day with lithium).

At enrollment blood glucose was not "documented fasting" 87 mg/dL, HbA1c was 6.0%, BMI was 27.7 kg/m^2. From the time of study enrollment to Day 85 of randomized treatment, the patient had a weight increase of 6 kg (79 kg to 85 kg). The adverse event of "blood glucose increased" was reported 87 days prior to randomization and was associated with a "documented fasting" blood glucose of 129 mg/dL and HbA1c of 5.9%. Day 85 of randomized treatment "documented fasting" blood glucose was 145 mg/dL and HbA1c was 6.9%. At the final visit (Day 190), the "documented fasting" blood glucose was 127 mg/dL and HbA1c was 6.6%. There were no AEs associated with diabetes during randomized treatment, and no antihyperglycemic treatment was initiated during the study.

- This overweight patient (BMI of 27.7 kg/m2) with no evidence of pre-existing diabetes, had an adverse event of "blood glucose increased" during open-label treatment, elevated fasting glucose of 129 mg/dL, 145 mg/dL, and 127 mg/dL and HbA1c values of 6.0%, 5.9%, 6.9%, and 6.6%, associated with a weight increase of 6 kg during study participation. Upon post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during the open-label phase of the study."

Patient E0101014 in Study 126
A 32-year-old Caucasian woman, had no history of diabetes and no hypoglycemic treatment at enrollment. This patient was treated for 183 days during the open-label phase of the study with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, but was not randomized. The screening visit BMI, blood glucose and HbA1c values were 33.9 kg/m^2, 93 mg/dL ("documented fasting") and 5.7%, respectively. On Day 183 of open-label treatment with quetiapine 400 mg/day, the investigator reported a non-serious AE of "diabetes mellitus" that was considered by the investigator to be of mild intensity, related to study drug, and the patient was withdrawn from the study due to this AE. On Day 85 of open-label treatment, the blood glucose and HbA1c values were 131 mg/dL ("documented fasting") and 6.4%, respectively. On Day 163, blood glucose was 114 mg/dL ("documented fasting") and HbA1c was 6.6%. The AE was reported as continuing at the final visit, no hypoglycaemic medications were recorded. Weight increased by 3 kg from enrollment (96 kg) to Day 163 of open-label treatment (99 kg). At the final visit (Day 191 of open-label treatment), blood glucose was 85 mg/dL ("documented fasting") and HbA1c was 6.2%.

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment, with no evidence of diabetes at enrolment.

Patient E0119015 in Study 126
A 49-year-old Caucasian man, had no history of diabetes and no hypoglycemic treatment at

enrollment. This patient was treated for 113 days during the open-label phase of the study with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and for 141 days of randomized treatment with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 42.5 kg/m^2, 95 mg/dL ("documented fasting") and 6.1%, respectively. On Day 23 of open-label treatment with quetiapine 400 mg/day, the investigator reported a non-serious AE of "diabetes mellitus" that was considered by the investigator to be of mild intensity, not related to study drug, and the patient was not withdrawn from the study due to this AE. The patient was started on the oral hypoglycaemic agent metformin on Day 23 of open-label treatment. On Day 84 of open-label treatment, the blood glucose and HbA1c values were 109 mg/dL ("documented fasting") and 6.8%, respectively. The AE was reported as continuing at the final visit, metformin treatment continued throughout the study. Weight increased by 16 kg from enrollment (146 kg) to Day 84 of open-label treatment (162 kg). At the final visit (Day 141 of randomized treatment), blood glucose was 116 mg/dL ("documented fasting") and HbA1c was 6.9%.

- In the post-hoc adjudicated evaluation, this patient was considered to have possible onset of diabetes during the open-label treatment phase, with no evidence of diabetes at enrollment.

Patient E0404003 in Study 126
A 58-year-old Caucasian man, had no history of diabetes and no hypoglycemic treatment at enrollment. This patient was treated for 196 days during the open-label phase of the study with quetiapine 600 mg/day adjunct with valproate as the mood stabilizer, and for 155 days of randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 38.4 kg/m^2, 107 mg/dL ("documented fasting") and 6.9%, respectively. On Day 119 of open-label treatment with quetiapine 600 mg/day, the investigator reported a non-serious AE of "diabetes mellitus, non-insulin-dependent" that was considered by the investigator to be of moderate intensity, not related to study drug, and the patient was not withdrawn from the study due to this AE. The patient was started on the oral hypoglycaemic agent gliclazide on Day 119 of open-label treatment. On Day 84 of open-label treatment, the blood glucose and HbA1c values were 145 mg/dL ("documented fasting") and 7.4%, respectively. On the next visit, Day 168 of open-label treatment, the blood glucose was 132 mg/dL ("documented fasting") and the HbA1c was 6.7%. The AE was reported as continuing at the final visit, gliclazide treatment continued throughout the study. Weight decreased by 1 kg from enrollment (111 kg) to Day 84 of open-label treatment (110 kg). At the final visit (Day 141 of randomized treatment), blood glucose was 116 mg/dL ("documented fasting") and HbA1c was 6.9%.

- In the post-hoc adjudicated evaluation, this patient was considered to have possible onset of diabetes during the open-label treatment phase, with no evidence of diabetes at enrollment.

Patient E0604021 in Study 126
Upon post-hoc adjudicated analysis, this patient was considered to have possible onset of

diabetes during the open-label treatment phase, and was considered to have possible exacerbation of diabetes during randomized treatment.

Patient E0064037 in Study 127

A 39-year-old Black woman, had no history of diabetes and no hypoglycemic treatment at enrollment. This patient was treated for 205 days during the open-label phase of the study with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit weight (BMI was not available), blood glucose and HbA1c values were 100 kg, 77 mg/dL (not "documented fasting") and 6.6%, respectively. On Day 168 of open-label treatment, the investigator reported a non-serious AE of "diabetes mellitus, non-insulin-dependent" of 44 days duration that was considered by the investigator to be of severe intensity, related to study drug, and the patient was withdrawn from the study due to this AE. There was no report of initiation of any hypoglycaemic medication at any time during the study. On the day the AE was reported as starting (Day 168 of open-label treatment), the blood glucose and HbA1c values were 196 mg/dL (not "documented fasting") and 8.1%, respectively. On the next visit, Day 196 of open-label treatment, the blood glucose was 208 mg/dL (not "documented fasting") and the HbA1c was 10.1%. The AE was reported as continuing at the final visit. Weight increased by 6 kg from enrollment (100 kg) to Day 168 of open-label treatment (106 kg). At the final visit (Day 217 of open-label treatment), blood glucose was 86 mg/dL (not "documented fasting") and HbA1c was 8.9%.

- In the post-hoc adjudicated evaluation, this patient was considered to have possible onset of diabetes during the open-label treatment phase, with no evidence of diabetes at enrolment.

Patient E0108019 in Study 127

A 52-year-old Caucasian man, had no history of diabetes and no hypoglycemic treatment at enrollment. This patient was treated for 218 days during the open-label phase of the study with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and for 83 days of randomized treatment with quetiapine 600 mg/day adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 24.8 kg/m^2, 112 mg/dL (not "documented fasting") and 6.2%, respectively. On Day 28 of open-label treatment, the investigator reported a non-serious AE of "diabetes mellitus" of 280 days duration that was considered by the investigator to be of moderate intensity, not related to study drug, and the patient was not withdrawn from the study due to this AE. The dose of quetiapine was lowered due to this AE from 500 mg/day to 400 mg/day on Day 36 of open-label treatment, then increased on Day 196 of open-label treatment to 600 mg/day quetiapine, and the patient was randomized to that dose (600 mg/day quetiapine). Treatment with metformin was recorded as initiating on Day 2 of randomized treatment. After the AE was reported as starting (Day 28 of open-label treatment), the next available blood glucose and HbA1c values were on Day 90 of open-label treatment, and were 138 mg/dL ("documented fasting") and 6.9%, respectively. On the next visit, Day 174 of open-label treatment, the blood glucose was 282 mg/dL (not "documented fasting") and the HbA1c was 7.3%. The AE was reported as continuing at the final visit. Weight increased by 19 kg from enrollment (90

kg) to Day 90 of open-label treatment (109 kg). At the final visit (Day 90 of randomized treatment), blood glucose was 121 mg/dL ("documented fasting") and HbA1c was 6.7%.

- In the post-hoc adjudicated evaluation, this patient was considered to have possible onset of diabetes during the open-label treatment phase, with no evidence of diabetes at enrolment.

Patient E0080036 in Study 127
Upon post-hoc adjudicated analysis this patient was considered to have possible onset of diabetes in the open-label phase, and exacerbation of diabetes during randomized treatment.

Patient E1120001 in Study 127
A 63-year-old Caucasian man, had no recorded history of diabetes but did have a history of "impaired glucose tolerance" and concomitant treatment with metformin at enrollment. This patient was treated for 184 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with lithium as the mood stabilizer, and was treated for 200 days of randomized treatment with quetiapine 500 mg/day adjunct with lithium as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 33.4 kg/m^2, 116 mg/dL ("documented fasting") and 6.6%; respectively. On Day 100 of open-label treatment, the blood glucose and HbA1c values were 141 mg/dL ("documented fasting") and 6.4%; respectively. On the next visit (randomization visit, Day 184 of open-label treatment), blood glucose was 128 mg/dL ("documented fasting") and the HbA1c was 6.5%. Weight was not available at the enrollment visit.

- In the post-hoc adjudicated evaluation, this patient was considered to have possible onset of diabetes during the open-label treatment phase.

Patient E0103026 in Study 126
A 24-year-old Black woman, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medication at enrollment. This patient was treated for 252 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and for 28 days of randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 55.8 kg/m^2, 109 mg/dL ("documented fasting") and 6.3%; respectively. On Day 84 of open-label treatment, the blood glucose and HbA1c values were 134 mg/dL ("documented fasting") and 7.1%; respectively. At the next visit (Day 168 of open-label treatment), the blood glucose was 263 mg/dL ("documented fasting") and the HbA1c was 8.1%. On the final visit, (Day 28 of randomized treatment), blood glucose was 88 mg/dL ("documented fasting") and the HbA1c was 6.8%. There was no record of initiation of any hypoglycaemic medication at any time during the study. Weight increased by 1 kg from the enrollment visit (152 kg) to Day 84 (153 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have possible onset of diabetes during the open-label treatment phase.

Patient E0122014 in Study 126

A 41-year-old Caucasian woman, had no recorded history of diabetes but did have a recorded medical history of "Diabetes (gestational)", and no concomitant treatment with hypoglycaemic medication at enrollment. This patient was treated for 231 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with lithium as the mood stabilizer, and for 30 days of randomized treatment with placebo adjunct with lithium as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 30.3 kg/m^2, 99 mg/dL ("documented fasting") and 5.5%; respectively. On Day 172 of open-label treatment, the blood glucose value was 163 mg/dL ("documented fasting"), and the HbA1c was unavailable at that visit. At the next visit (randomization visit, corresponding to Day 231 of open-label treatment), the blood glucose was 135 mg/dL ("documented fasting") and the HbA1c was 5.6%. On the final visit, (Day 31 of randomized treatment), blood glucose was 111 mg/dL ("documented fasting") and the HbA1c was 5.7%. There was no record of initiation of any hypoglycaemic medication at any time during the study. Weight increased by 2 kg from the enrollment visit (79 kg) to Day 172 (81 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E0208007 in Study 126

A 47-year-old Caucasian man, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medication at enrollment. This patient was treated for 228 days during the open-label phase of the study with a median dose of quetiapine 300 mg/day adjunct with valproate as the mood stabilizer, and for 84 days of randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 35.3 kg/m^2, 114 mg/dL ("documented fasting") and 6.0%; respectively. On Day 87 of open-label treatment, the blood glucose value was 130 mg/dL ("documented fasting"), and the HbA1c was 6.4%. At the next visit (Day 171 of open-label treatment), the blood glucose was 151 mg/dL ("documented fasting") and the HbA1c was 6.8%. On the final visit, (Day 84 of randomized treatment), blood glucose was 157 mg/dL ("documented fasting") and the HbA1c was 6.8%. There was no record of initiation of any hypoglycaemic medication at any time during the study. Weight increased by 3 kg from the enrollment visit (108 kg) to Day 87 (111 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E0403008 in Study 126

A 45-year-old Caucasian man, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medication at enrollment. This patient was treated for 98 days during the open-label phase of the study with a median dose of quetiapine 600 mg/day adjunct with valproate as the mood stabilizer, and for 85 days of randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 29.9 kg/m^2, 113 mg/dL ("documented fasting") and 6.0%; respectively. On the randomization visit (corresponding to Day 98 of open-label treatment), the blood

glucose value was 131 mg/dL ("documented fasting"), and the HbA1c was 6.0%. At the next visit (Day 8 of randomized treatment), the blood glucose was 108 mg/dL (not "documented fasting") and the HbA1c was 6.1%. On the final visit, (Day 85 of randomized treatment), blood glucose was 198 mg/dL ("documented fasting") and the HbA1c was 6.4%. There was no record of initiation of any hypoglycaemic medication at any time during the study. Weight increased by 3 kg from the enrollment visit (97 kg) to Day 98 of open-label treatment (100 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E1309007 in Study 126
A 59-year-old Caucasian woman, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medication at enrollment. This patient was treated for 82 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and for 35 days of randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 28.2 kg/m^2, 89 mg/dL ("documented fasting") and 4.8%; respectively. On Day 75 of open-label treatment, the blood glucose value was 140 mg/dL ("documented fasting"), and the HbA1c was 7.7%. At the next visit (the randomization visit, corresponding to Day 82 of open-label treatment), the blood glucose was 138 mg/dL (not "documented fasting") and the HbA1c was 5.8%. On the final visit, (Day 35 of randomized treatment), blood glucose was 123 mg/dL ("documented fasting") and the HbA1c was 5.7%. There was no record of initiation of any hypoglycaemic medication at any time during the study. Weight decreased by 2 kg from the enrollment visit (79 kg) to Day 75 of open-label treatment (77 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E0006069 in Study 127
A 49-year-old Black woman, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medications at enrollment. This patient was treated for 227 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 45.2 kg/m^2, 97 mg/dL ("documented fasting") and 6.3%; respectively. On Day 211 of open-label treatment, the blood glucose and HbA1c values were 230 mg/dL (not "documented fasting") and 6.9%; respectively. At the next visit (Day 227 of open-label treatment), the blood glucose was 188 mg/dL ("documented fasting") and the HbA1c was 7.1%. On the final visit, (Day 240 of open-label treatment), blood glucose was 94 mg/dL ("documented fasting") and the HbA1c was not available. Weight increased by 10 kg from the enrollment visit (131 kg) to Day 227 (141 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatmenT.

Patient E0007015 in Study 127

A 48-year-old Hispanic woman, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medications at enrollment. This patient was treated for 225 days during the open-label phase of the study with a median dose of quetiapine 500 mg/day adjunct with lithium as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 33.5 kg/m^2, 106 mg/dL (not "documented fasting") and 6.4%, respectively. On Day 169 of open-label treatment, the blood glucose and HbA1c values were 224 mg/dL (not "documented fasting") and 7.2%, respectively. At the next visit (final visit, Day 224 of open-label treatment), the blood glucose was 127 mg/dL ("documented fasting") and the HbA1c was 6.8%. There was no recorded initiation of hypoglycaemic medication at any time during the study for this patient. Weight increased by 18 kg from the enrollment visit (95 kg) to Day 168 (113 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E0008021 in Study 127

A 55-year-old Caucasian man, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medications at enrollment. This patient was treated for 258 days during the open-label phase of the study with a median dose of quetiapine 500 mg/day adjunct with valproate as the mood stabilizer, and for 199 days of randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 24.7 kg/m^2, 112 mg/dL ("documented fasting") and 7.0%; respectively. On Day 83 of open-label treatment, the blood glucose and HbA1c values were 138 mg/dL ("documented fasting") and 6.3%; respectively; but the subsequent values at Day 112 of open-label treatment were within the normal range (blood glucose of 122 mg/dL [not "documented fasting"] and HbA1c of 6.5%). At the next visit (Day 168 of open-label treatment), the blood glucose was 133 mg/dL (not "documented fasting") and the HbA1c was 6.9%. On the subsequent visit (randomization, Day 258 of open-label treatment), the blood glucose was 143 ("documented fasting") and the HbA1c was 8.3%. On the final visit, (Day 86 of randomized treatment), blood glucose was 120 mg/dL ("documented fasting") and the HbA1c was 7.3%. Weight increased by 1 kg from the enrollment visit (87 kg) to Day 168 (88 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E0035022 in Study 127

A 58-year-old Caucasian man, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medications at enrollment. This patient was treated for 136 days during the open-label phase of the study with a median dose of quetiapine 600 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 30 kg/m^2, 119 mg/dL ("documented fasting") and 6.3%; respectively. On Day 109 of open-label treatment, the blood glucose and HbA1c values were 130 mg/dL ("documented fasting") and 6.7%; respectively. At the next

visit (Day 111 of open-label treatment), the blood glucose was 127 mg/dL ("documented fasting") and the HbA1c was 6.9%. On the final visit, (Day 137 of open-label treatment), blood glucose was 130 mg/dL ("documented fasting") and the HbA1c was 7.0%. Weight increased by 6 kg from the enrollment visit (102 kg) to Day 136 (108 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E0048011 in Study 127
Upon post-hoc adjudicated evaluation this patient was considered to have possible onset during open-label treatment and possible exacerbation of diabetes during randomized treatment.

Patient E0059017 in Study 127
A 48-year-old Caucasian man, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medications at enrollment. This patient was treated for 112 days during the open-label phase of the study with a median dose of quetiapine 600 mg/day adjunct with valproate as the mood stabilizer, and for 600 days of randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 34.4 kg/m^2, 88 mg/dL ("documented fasting") and 5.2%; respectively. On Day 84 of open-label treatment, the blood glucose and HbA1c values were 172 mg/dL ("documented fasting") and 7.3%; respectively. At the next visit (randomization visit, corresponding to Day 112 of open-label treatment), the blood glucose was 195 mg/dL ("documented fasting") and the HbA1c was 7.9%. On the final visit, (Day 624 of randomized treatment), blood glucose was 74 mg/dL ("documented fasting") and the HbA1c was 4.8%. There was no record of any hypoglycaemic medication at any time during the study. Weight increased by 11 kg from the enrollment visit (109 kg) to Day 84 (120 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E0067006 in Study 127
A 44-year-old Caucasian man, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medications at enrollment. This patient was treated for 203 days during the open-label phase of the study with a median dose of quetiapine 800 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 35.5 kg/m^2, 91 mg/dL ("documented fasting") and 6.0%; respectively. On Day 171 of open-label treatment, the blood glucose and HbA1c values were 137 mg/dL ("documented fasting") and 7.6%; respectively. At the next visit (Day 204 of open-label treatment), the blood glucose was 202 mg/dL ("documented fasting") and the HbA1c was 8.9%. On the final visit, (Day 218 of open-label treatment), blood glucose was 321 mg/dL ("documented fasting") and the HbA1c was 9.7%. There was no record of any hypoglycaemic medication at any time during the study. Weight increased by 4 kg from the enrollment visit (119 kg) to Day 90 (123 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Patient E0070029 in Study 127

A 38-year-old Black man, had no recorded history of diabetes and no concomitant treatment with hypoglycaemic medications at enrollment. This patient was treated for 113 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and for 14 days of randomized treatment with placebo adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 30.8 kg/m^2, 83 mg/dL ("documented fasting") and 6.0%; respectively. On Day 83 of open-label treatment, the blood glucose and HbA1c values were 185 mg/dL ("documented fasting") and 6.9%; respectively. At the next visit (randomization visit, corresponding to Day 113 of open-label treatment), the blood glucose was 168 mg/dL ("documented fasting") and the HbA1c was 6.9%. On the final visit, (Day 15 of randomized treatment), blood glucose was 114 mg/dL ("documented fasting") and the HbA1c was 6.7%. There was no record of any hypoglycaemic medication at any time during the study. Weight increased by 13 kg from the enrollment visit (105 kg) to Day 83 (118 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have possible onset of diabetes during open-label treatment.

Possible exacerbation of pre-existing diabetes during open-label treatment (20 patients)

Patient E0008004 in Study 127

A 47-year-old Black woman, had no recorded history of diabetes and no hypoglycemic treatment at enrollment. This patient was treated for 253 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with lithium as the mood stabilizer, and for 2 days of randomized treatment with quetiapine 700 mg/day adjunct with lithium as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 32.3 kg/m^2, 137 mg/dL ("documented fasting") and 6.6%; respectively. On Day 168 of open-label treatment, the investigator reported a non-serious AE of "diabetes mellitus" of 254 days duration that was considered by the investigator to be of moderate intensity, related to study drug, and the patient was not withdrawn from the study due to an AE. The dose of quetiapine was lowered due to this AE from 500 mg/day to 400 mg/day on Day 9 of open-label treatment, then increased on Days 143, 197, and 225 of open-label treatment to 500, 600, and 700 mg/day quetiapine; and the patient was randomized to that dose (700 mg/day quetiapine). Treatment with metformin was recorded as initiating on Day 2 of randomized treatment. On the day that the AE was reported as starting (Day 168 of open-label treatment), the blood glucose and HbA1c values were 188 mg/dL (not "documented fasting") and 7.2%; respectively. On the next visit, Day 224 of open-label treatment, the blood glucose was 154 mg/dL (not "documented fasting") and the HbA1c was unavailable at that visit. Weight increased by 10 kg from enrollment (85 kg) to Day 168 of open-label treatment (95 kg). At the final visit (randomization visit, Day -1 of randomized treatment), blood glucose was 249 mg/dL (not "documented fasting") and HbA1c was 8.0%.

- In the post-hoc adjudicated evaluation this patient was considered to have probable pre-existing diabetes and exacerbation of diabetes during the open-label treatment phase.

Patient E0020014 in Study 127

A 36-year-old Caucasian woman, had no recorded history of diabetes and no hypoglycemic treatment at enrollment. This patient was treated for 224 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 36.8 kg/m^2, 129 mg/dL ("documented fasting") and 5.9%; respectively. On Day 165 of open-label treatment, the investigator reported a non-serious AE of "diabetes mellitus non-insulin-dependent" of 61 days duration that was considered by the investigator to be of moderate intensity, related to study drug, and the patient was withdrawn from the study due to this AE. No hypoglycaemic medication was recorded for this patient at any time during the study. On the day that the AE was reported as starting (Day 165 of open-label treatment), the blood glucose and HbA1c values were 160 mg/dL ("documented fasting") and 6.6%, respectively. There were no recorded glucose measurements between the enrollment visit and Day 165, and on the next visit (Day 200 of open-label treatment), the blood glucose was 173 mg/dL ("documented fasting") and the HbA1c was 6.6%. Weight increased by 1 kg from enrollment (95 kg) to Day 165 of open-label treatment (94 kg). At the last visit with glucose measurements recorded (Day 225 of open-label treatment), blood glucose was 207 mg/dL ("documented fasting") and HbA1c was 7.6%.

- In the post-hoc adjudicated evaluation this patient was considered to have probable pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase associated with an AE of diabetes.

Patient E0105003 in Study 127

A 24-year-old Caucasian woman, had a recorded history of "diabetes" and concomitant treatment with metformin at enrollment. This patient was treated for 208 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 32.8 kg/m^2, 217 mg/dL ("documented fasting") and 9.6%; respectively. On Day 50 of open-label treatment, the investigator reported a non-serious AE of "diabetes mellitus" of 159 days duration that was considered by the investigator to be of mild intensity, not related to study drug, and no action was recorded by the investigator in response to this AE although treatment with rosiglitazone was initiated on Day 50 of open-label treatment and continued to the final visit. The next available glucose measurement after the AE was reported as starting was on the final visit (Day 208 of open-label treatment), when the blood glucose and HbA1c values were 328 mg/dL ("documented fasting") and 10.0%; respectively. Weight decreased by 5 kg from enrollment (86 kg) to Day 208 of open-label treatment (81 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0112006 in Study 127

A 51-year-old Caucasian man, had a recorded history of "type 2 diabetes" and concomitant treatment with metformin at enrollment. This patient was treated for 245 days during the open-label phase of the study with a median dose of quetiapine 800 mg/day adjunct with lithium as the mood stabilizer, and was treated for 40 days of randomized treatment with quetiapine 800 mg/day adjunct with lithium as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 45.8 kg/m^2, 112 mg/dL ("documented fasting") and 6.1%; respectively. On Day 101 of open-label treatment, the investigator reported a non-serious AE of "diabetes mellitus" of 5 days duration that was considered by the investigator to be of mild intensity, related to study drug, and no action was recorded by the investigator in response to this AE although treatment with glibenclamide was initiated on Day 101 of open-label treatment and the dose of metformin was changed on the same day. The glucose measurement prior to the AE was reported as starting was on Day 83 of open-label treatment, when the blood glucose and HbA1c values were 167 mg/dL ("documented fasting") and 7.3%; respectively. On the next visit (Day 171 of open-label treatment), blood glucose was 128 mg/dL ("documented fasting") and the HbA1c was 6.6%. Weight decreased by 2 kg from enrollment (145 kg) to Day 171 of open-label treatment (143 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes, and possible exacerbation of diabetes during the open-label treatment phase associated with a reported AE of diabetes.

Patient E0116029 in Study 127

A 36-year-old Caucasian woman, had no recorded history of diabetes or treatment with any hypoglycaemic medication at enrollment. This patient was treated for 222 days during the open-label phase of the study with a median dose of quetiapine 500 mg/day adjunct with valproate as the mood stabilizer, and was treated for 201 days of randomized treatment with quetiapine 500 mg/day adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 34.0 kg/m^2, 135 mg/dL ("documented fasting") and 6.7%; respectively. On Day 115 of open-label treatment, the investigator reported a non-serious AE of "diabetes mellitus" of 308 days duration that was considered by the investigator to be of moderate intensity, related to study drug, and no action was recorded by the investigator in response to this AE although treatment with metformin was initiated on Day 121 of open-label treatment. The glucose measurement prior to the AE was reported as starting was on Day 83 of open-label treatment, when the blood glucose and HbA1c values were 194 mg/dL ("documented fasting") and 7.4%; respectively. On Day 86 of open-label treatment, blood glucose was 173 mg/dL ("documented fasting") and the HbA1c was unavailable from that visit. Weight was unchanged from enrollment (100 kg) to Day 83 of open-label treatment (100 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have probable pre-existing diabetes, , and possible exacerbation of diabetes during the open-label treatment phase associated with a reported AE of diabetes.

Patient E0103001 in Study 126
A 49-year-old Caucasian man, had a recorded history of "diabetes" but no concomitant treatment with any hypoglycaemic medication at enrollment. This patient was treated for 260 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. There were no screening visit data available for this patient, the first data for BMI and blood glucose values were from the Day 85 visit, and were 48 kg/m^2 and 95 mg/dL ("documented fasting"). HbA1c was unavailable at the Day 85 visit, and the initial HbA1c value at Day 169 of open-label treatment was 7.7%. On Day 119 of open-label treatment, treatment with glipizide was initiated. The blood glucose and HbA1c values at the next visit (Day 169 of open-label treatment) were 161 mg/dL ("documented fasting") and 7.7%; respectively. On the next visit (final visit, Day 260 of open-label treatment), blood glucose was 210 mg/dL ("documented fasting") and the HbA1c was 8.3%. Weight increased by 2 kg from enrollment visit (151 kg) to Day 169 (153 kg).

- In the adjudicated post-hoc evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes.

Patient E0137029 in Study 126
A 60-year-old Caucasian man, had a recorded history of "diabetes mellitus type 2" and concomitant treatment with both fast-acting and long-acting insulin at enrollment. This patient was treated for 153 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and was treated for 84 days during randomized treatment with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 30.1 kg/m^2, 153 mg/dL ("documented fasting") and 7.8%; respectively. On Day 2 of randomized treatment, treatment with metformin was initiated. The blood glucose and HbA1c values at the previous visit (randomization visit, after 153 days of open-label treatment) were 295 mg/dL (not "documented fasting") and 9.0%; respectively. On the final visit, (Day 85 of randomized treatment), blood glucose was 163 mg/dL ("documented fasting") and the HbA1c was 8.2%. Weight was unchanged from the enrollment visit (104 kg) to the randomization visit (104 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes and was receiving treatment with insulin at enrollment, and possible exacerbation of diabetes during the open-label treatment phase for which metformin was started on Day 2 of randomized treatment.

Patient E0118016 in Study 126
A 45-year-old Caucasian woman, had a recorded medical history of "diabetes mellitus, type 2" and concomitant treatment with glipizide at enrollment. This patient was treated for

205 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and for 221 days of randomized treatment with quetiapine 700 mg/day adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 47.8 kg/m^2, 153 mg/dL ("documented fasting") and 7.8%, respectively. On Day 173 of open-label treatment, the blood glucose value was 228 mg/dL ("documented fasting"), and the HbA1c was 9.2%. At the next visit (Day 197 of open-label treatment), the blood glucose was not available, but the HbA1c was 10.0%. On the final visit, (Day 222 of randomized treatment), blood glucose was 159 mg/dL ("documented fasting") and the HbA1c was 8.3%. There was no record of any changes in dose of glipizide, nor initiation of any other hypoglycaemic medication at any time during the study. Weight increased by 2 kg from the enrollment visit (143 kg) to Day 173 of open-label treatment (145 kg).

- In the post-hoc adjudicated evaluation this patient was considered to have pre-existing diabetes and was treated with glipizide at enrollment, and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0807003 in Study 126
A 57-year-old Caucasian man, had a recorded medical history of "diabetes mellitus" and concomitant treatment with metformin and gliclazide at enrollment. This patient was treated for 201 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with lithium as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 28.3 kg/m^2, 256 mg/dL (not "documented fasting") and 6.1%, respectively. On Day 202 (the final visit) of open-label treatment, the blood glucose value was 311 mg/dL ("documented fasting"), and the HbA1c was 8.7%. There was no record of any changes in dose of gliclazide or metformin, nor initiation of any other hypoglycaemic medication at any time during the study. Weight was only available at the enrollment visit for this patient.

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during open-label treatment based on a single elevation in blood glucose and HbA1c at Day 202 of open-label treatment.

Patient E1311006 in Study 127
A 57-year-old Caucasian man, had a medical history of "diabetes mellitus type 2" and concomitant treatment with glibenclamide at enrollment. This patient was treated for 91 days during the open-label phase of the study with a median dose of quetiapine 800 mg/day adjunct with lithium as the mood stabilizer, and for 35 days of randomized treatment with quetiapine 800 mg/day adjunct with lithium as the mood stabilizer. The screening visit BMI and HbA1c values were 38.3 kg/m^2 and 6.6%, respectively; blood glucose was not available at the enrollment visit. On Day 80 of open-label treatment, the blood glucose and HbA1c values were 142 mg/dL ("documented fasting") and 7.9%, respectively. At the next visit (the randomization visit, corresponding to Day 91 of open-label treatment), the blood glucose was 195 mg/dL ("documented fasting") and the HbA1c was 8.0%. On the final visit, (Day 133 of

randomized treatment), blood glucose was 227 mg/dL ("documented fasting") and the HbA1c was 8.4%. There was no record of any change in glibenclamide dosage or initiation of any other hypoglycaemic medication at any time during the study. Weight increased by 9 kg from the enrollment visit (103 kg) to Day 80 (112 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0073002 in Study 127
A 51-year-old Black woman, had a recorded history of "diabetes type II" and concomitant treatment with metformin at enrollment. This patient was treated for 111 days during the open-label phase of the study with a median dose of quetiapine 500 mg/day adjunct with valproate as the mood stabilizer, and was treated for 197 days during randomized treatment with quetiapine 500 mg/day adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 39.3 kg/m^2, 93 mg/dL ("documented fasting") and 7.8%; respectively. On the randomization visit (corresponding to Day 111 of open-label treatment), the blood glucose and HbA1c values were 125 mg/dL ("documented fasting") and 10.0%; respectively. On the final visit, (Day 85 of randomized treatment), blood glucose was 124 mg/dL ("documented fasting") and the HbA1c was 7.5%. Weight was unchanged from the enrollment visit (105 kg) to the randomization visit (105 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0078013 in Study 127
A 58-year-old Black man, had a recorded history of "diabetes mellitus type II" and concomitant treatment with metformin and glibenclamide at enrollment. This patient was treated for 91 days during the open-label phase of the study with a median dose of quetiapine 500 mg/day adjunct with valproate as the mood stabilizer, and was treated for 287 days during randomized treatment with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 19.9 kg/m^2, 159 mg/dL ("documented fasting") and 7.3%; respectively. On the randomization visit (corresponding to Day 91 of open-label treatment), the blood glucose and HbA1c values were 158 mg/dL ("documented fasting") and 8.8%; respectively. On the final visit, (Day 288 of randomized treatment), blood glucose was 77 mg/dL ("documented fasting") and the HbA1c was 6.4%. Weight increased by 3 kg from the enrollment visit (67 kg) to the randomization visit (70 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0006003 in Study 127
A 50-year-old Black woman, had a medical history of "insulin dependent diabetic", but no

recorded concomitant treatment with hypoglycaemic medications at enrollment. This patient was treated for 153 days during the open-label phase of the study with a median dose of quetiapine 700 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 29.2 kg/m^2, 115 mg/dL (not "documented fasting") and 5.7%; respectively. On Day 153 of open-label treatment, the blood glucose and HbA1c values were 145 mg/dL (not "documented fasting") and 6.9%; respectively. At the next visit (the final visit, Day 168 of open-label treatment), the blood glucose was 162 mg/dL (not "documented fasting") and the HbA1c was not available. There was no record of any hypoglycaemic medication at any time during the study. Weight increased by 9 kg from the enrollment visit (83 kg) to Day 156 (92 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes with insulin therapy ongoing, and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0031012 in Study 127
A 45-year-old Black man, had a medical history of "diabetes" and concomitant treatment with metformin at enrollment. This patient was treated for 252 days during the open-label phase of the study with a median dose of quetiapine 800 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 47 kg/m^2, 223 mg/dL (not "documented fasting") and 7.3%; respectively. On Day 169 of open-label treatment, the blood glucose and HbA1c values were 279 mg/dL ("documented fasting") and 11.6%; respectively. At the next visit (Day 198 of open-label treatment), the blood glucose was 171 mg/dL ("documented fasting") and the HbA1c was 10.3%. On the final visit, (Day 253 of open-label treatment), blood glucose was 166 mg/dL ("documented fasting") and the HbA1c was 10.2%. There was no record of any change in metformin dosage or initiation of any other hypoglycaemic medication at any time during the study. Weight increased by 3 kg from the enrollment visit (109 kg) to Day 168 (112 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and a possible exacerbation of diabetes during the open-label treatment phase.

Patient E0042013 in Study 127
A 38-year-old Caucasian woman, had a medical history of "non-insulin dependent diabetes" and concomitant treatment with metformin and glibenclamide at enrollment. This patient was treated for 253 days during the open-label phase of the study with a median dose of quetiapine 450 mg/day adjunct with lithium as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 40.8 kg/m^2, 95 mg/dL (not "documented fasting") and 7.2%; respectively. On Day 176 of open-label treatment, the blood glucose and HbA1c values were 162 mg/dL ("documented fasting") and 7.2%; respectively. At the next visit (final visit, Day 253 of open-label treatment), the blood glucose was 199 mg/dL ("documented fasting") and the HbA1c was 8.0%. There was no record of any change in metformin or glibenclamide dosage or initiation of any other hypoglycaemic

medication at any time during the study. Weight increased by 10 kg from the enrollment visit (118 kg) to Day 169 (128 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0048003 in Study 127

A 51-year-old Black woman, had a medical history of "diabetes mellitus" but no record of concomitant treatment with any hypoglycaemic medications at enrollment. This patient was treated for 251 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 36 kg/m^2, 75 mg/dL ("documented fasting") and 5.9%; respectively. On Day 168 of open-label treatment, the blood glucose and HbA1c values were 187 mg/dL ("documented fasting") and 7.4%; respectively. At the next visit (the final visit, Day 252 of open-label treatment), the blood glucose was 299 mg/dL ("documented fasting") and the HbA1c was 7.8%. There was no record of initiation of any hypoglycaemic medication at any time during the study. Weight increased by 11 kg from the enrollment visit (114 kg) to Day 167 (125 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes, and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0063011 in Study 127

A 52-year-old Caucasian woman, had a medical history of "diabetes" and concomitant treatment with pioglitazone, glipizide, and metformin at enrollment. This patient was treated for 238 days during the open-label phase of the study with a median dose of quetiapine 500 mg/day adjunct with lithium as the mood stabilizer, and for 198 days of randomized treatment with quetiapine 500 mg/day adjunct with lithium as the mood stabilizer. The screening visit BMI, blood glucose and HbA1c values were 37 kg/m^2, 92 mg/dL ("documented fasting") and 6.0%; respectively. On Day 14 of open-label treatment, the blood glucose and HbA1c values were 153 mg/dL ("documented fasting") and 7.6%, respectively. At the next visit (Day 86 of open-label treatment), the blood glucose was 135 mg/dL ("documented fasting") and the HbA1c was unavailable. The next visit at which HbA1c was available was Day 182 of open-label treatment, at which time the HbA1c was 7.5%. On the final visit, (Day 198 of randomized treatment), blood glucose was 248 mg/dL ("documented fasting") and the HbA1c was 10.4%. There was no record of any change in metformin or glipizide dosage; pioglitazone treatment was halted on Day 51 of open-label treatment. Weight increased by 8 kg from the enrollment visit (104 kg) to Day 14 (112 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes was and on combined treatment with pioglitazone, glipizide, and metformin at enrollment, and possible exacerbation of diabetes based on increases in blood glucose and HbA1c during the open-label treatment phase.

Patient E0070035 in Study 127
A 56-year-old Caucasian man, had a medical history of "diabetes, type II" and concomitant treatment with metformin at enrollment. This patient was treated for 124 days during the open-label phase of the study with a median dose of quetiapine 600 mg/day, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 41.7 kg/m^2, 135 mg/dL ("documented fasting") and 8.3%; respectively. On Day 85 of open-label treatment (the final visit with glucose measurements recorded), the blood glucose and HbA1c values were 274 mg/dL ("documented fasting") and 9.2%; respectively. There was no record of any change in metformin dosage or initiation of any other hypoglycaemic medication at any time during the study. Weight increased by 5 kg from the enrollment visit (140 kg) to Day 84 (145 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0080032 in Study 127
A 42-year-old Caucasian man, had a medical history of "diabetes, type 2" and concomitant treatment with glimepiride and pioglitazone at enrollment. This patient was treated for 168 days during the open-label phase of the study with a median dose of quetiapine 400 mg/day adjunct with lithium as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 25.9 kg/m^2, 118 mg/dL ("documented fasting") and 5.8%; respectively. On Day 86 of open-label treatment, the blood glucose and HbA1c values were 200 mg/dL ("documented fasting") and 6.3%; respectively. At the next visit (the final visit, Day 168 of open-label treatment), the blood glucose was 202 mg/dL ("documented fasting") and the HbA1c was 8.3%. There was no record of any change in glimepiride or pioglitazone dosage or initiation of any other hypoglycaemic medication at any time during the study. Weight increased by 2 kg from the enrollment visit (77 kg) to Day 85 (79 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase.

Patient E0125005 in Study 127
A 49-year-old Caucasian man, had a medical history of "diabetes" and concomitant treatment with metformin at enrollment. This patient was treated for 205 days during the open-label phase of the study with a median dose of quetiapine 500 mg/day adjunct with valproate as the mood stabilizer, and was not randomized. The screening visit BMI, blood glucose and HbA1c values were 42.4 kg/m^2, 124 mg/dL ("documented fasting") and 6.0%; respectively. On Day 85 of open-label treatment, the blood glucose and HbA1c values were 269 mg/dL ("documented fasting") and 9.5%; respectively. At the next visit (Day 170 of open-label treatment), the blood glucose was 143 mg/dL ("documented fasting") and the HbA1c was 8.3%. On the final visit, (Day 205 of open-label treatment), blood glucose was 123 mg/dL ("documented fasting") and the HbA1c was 7.3%. There was no record of any change in

metformin dosage or initiation of any other hypoglycaemic medication at any time during the study. Weight increased by 5 kg from the enrollment visit (130 kg) to Day 84 (135 kg).

- In the post-hoc adjudicated evaluation, this patient was considered to have pre-existing diabetes , and possible exacerbation of diabetes during the open-label treatment phase.

Patients not considered to represent possible onset or possible exacerbation of possible diabetes during the randomized treatment phase

The remaining patients captured in the listings for post-hoc evaluation were not considered to demonstrate possible onset or possible exacerbation of diabetes during the placebo-controlled randomized treatment phase. For 15 of the patients, a brief description is presented below, giving the rationale for the decision not to include the patient in one of the categories possible onset or possible exacerbation of diabetes in the randomized treatment phase. Three of the patients (E0026002 and E0062017 in the quetiapine treatment group and E0105016 in the placebo group) had investigator reported AEs which were coded to the MedDRA preferred terms "diabetes mellitus" or "diabetes mellitus, non-insulin-dependent" and did not meet the adapted ADA criteria for a possible onset of possible diabetes in the adjudicated process. These 3 patients are described first in each treatment group.

Patients in the quetiapine treatment group

Patient E0026002 in Study 127, a 33-year-old Caucasian man, was recorded by the investigator as having an adverse event with the verbatim term "type II diabetes" (MedDRA preferred term "diabetes mellitus, non-insulin-dependent") on Day 533 of randomized treatment with quetiapine adjunct with valproate as the mood stabilizer. The AE was reported to be resolved Day 540. The patient did not have a medical history of diabetes, did not have any hypoglycemic treatment initiated, and had a transient increase in glucose value (318 mg/dL, not "documented fasting") on Day 533 that normalized without initiation of any hypoglycemic treatment and was considered to be most likely associated with an infection.

Patient E0062017 in Study 127, a 46-year-old Caucasian woman, was recorded by the investigator as having an adverse event with the verbatim term "diabetes mellitus" (MedDRA preferred term "diabetes mellitus") on Day 7 of randomized treatment with quetiapine adjunct with lithium as the mood stabilizer. This patient did not have a medical history of diabetes. The AE was reported to be resolved on Day 21 of randomized treatment. The investigator changed the dose of study medication in response to this AE, but no glucose lowering medication was administered due to this AE and the patient did not have any evidence in laboratory results of onset of diabetes at any time during the study.

Patient E0008015 in Study 127, a 54-year-old Black woman, had no medical history of diabetes at enrollment. On Day 197 of randomized treatment with quetiapine adjunct with valproate as the mood stabilizer, the blood glucose was 146 mg/dL ("documented fasting") and the HbA1c was 6.8%. All other glucose values were within the normal range during the study.

Patient E0010014 in Study 127, a 23-year-old Caucasian man, had no medical history of diabetes at enrolment, and no glucose lowering medication was ongoing at enrollment or initiated at any time during the study. On Day 85 of randomized treatment with quetiapine adjunct with valproate as the mood stabilizer, the blood glucose was 239 mg/dL (not "documented fasting") and the HbA1c was 5.0%. On Day 364, the patient had a blood glucose of 195 mg/dL ("documented fasting") and the HbA1c was 5.2%. When the study site was contacted, the investigator stated that the patient was not fasting on Day 85 or on Day 364. No subsequent confirmatory fasting samples were taken. The investigator did not think this was a case of emergent diabetes, but recommended the patient to follow up his glucose level with his primary care physician. There were a couple of normal blood glucose levels in between Day 85 and Day 364, and no other evidence of onset of diabetes at any time during the study.

Patient E0020009 in Study127, a 21-year-old Hispanic woman, was recorded by the investigator as having an adverse event with the verbatim term "insulin resistance" (MedDRA preferred term "insulin resistance") on Day 476 of randomized treatment with quetiapine adjunct with valproate as the mood stabilizer. The patient did not have a medical history of diabetes, did not have any hypoglycemic treatment initiated, and did not have any evidence in laboratory results of onset of diabetes at any time during the study.

Patient E0020087 in Study 127, a 49-year-old Caucasian man, was recorded by the investigator as having an adverse event with the verbatim term "insulin resistance" (MedDRA preferred term "insulin resistance") on Day 82 of randomized treatment with quetiapine adjunct with valproate as the mood stabilizer. The patient did not have a medical history of diabetes, did not have any hypoglycemic treatment initiated, and did not have any evidence in laboratory results of onset of diabetes at any time during the study.

Patient E0037020 in Study 127, a 29-year-old Caucasian woman, had a medical history of "dysmenorrhea". The patient was randomized to quetiapine adjunct with lithium as the mood stabilizer. Treatment with metformin hydrochloride 500 mg was initiated on Day 283 of randomized treatment. The reason for treatment was recorded as "oligomenorrhea". The dose of metformin was increased to 1000 mg on Day 290 and again on day 297 to 1500, on both occasions with "oligomenorrhea" given as reason for dose adjustment. There was no evidence in this patient of onset of diabetes during randomized treatment although there was a single high blood glucose value (166 mg/dL, "documented fasting") on Day 180.

Patient E0073002 in Study 127, a 51-year-old Black woman, had a medical history of diabetes type 2, and ongoing treatment with metformin hydrochloride at enrollment. On day 155 of randomized treatment with quetiapine adjunct with valproate as mood stabilizer, the patient was administered 15 units of insulin clargine. According to the investigator at the site, this dose was administered by a primary care physician to treat a transient elevated glucose level attributed to an ongoing upper respiratory infection. There is no evidence in the data in the study database of an exacerbation of diabetes during the randomized treatment phase.

Patient E0080002 in Study 127, a 54-year-old Caucasian man, had no medical history of diabetes at enrollment. On Day 175 of open-label treatment (15 days before randomization)

with quetiapine 400 mg/day adjunct with lithium as the mood stabilizer, there was an isolated elevated blood glucose value of 158 mg/dL ("documented fasting") and the HbA1c was 5.4%. There were no other glucose or HbA1c values reported during the open-label treatment phase. On Day 197 of randomized treatment with quetiapine 400 mg/day adjunct with lithium as the mood stabilizer, the blood glucose was 192 mg/dL ("documented fasting") and the HbA1c was 5.0%. In the randomized treatment phase, the remaining blood glucose values were 91 mg/dL at randomization, 106 mg/dL on Day 85, 112 mg/dL on Day 281, 93 mg/dL on Day 366, 83 mg/dL on Day 478, 96 mg/dL on Day 589, and 106 mg/dL on Day 589, all values "documented fasting".

Patient E0138011 in Study 126, a 72-year-old Caucasian woman, had treatment with cyamopsis tetragonolobus gum initiated on Day 37 of randomized treatment with quetiapine adjunct with lithium as the mood stabilizer. The reason for treatment recorded by the investigator was "constipation". The patient did not have a medical history of diabetes and had no evidence in laboratory results of onset of diabetes at any time during the study.

Patient E1120001 in Study 126, a 63-year-old Caucasian man, had a medical history of "impaired glucose tolerance" and treatment with metformin hydrochloride ongoing at enrollment. The dose of metformin was increased on Day 57 (from 500 mg to 800 mg) of randomized treatment with quetiapine adjunct with lithium as the mood stabilizer and again on Day 87 (from 800 mg to 1000 mg). The patient had a glucose value of 141 mg/dL ("documented fasting") 84 days prior to randomization and 128 mg/dL ("documented fasting") at randomization. There was no evidence of onset of diabetes or exacerbation of the existing condition at any time during randomized treatment. During the randomized treatment, blood glucose was 126 mg/dL ("documented fasting") on Day 112, and 121 mg/dL ("documented fasting") on Day 197, the final visit.

Patients in the placebo group

Patient E0105016 in Study 127, a 45-year-old Caucasian woman, had a medical history of diabetes mellitus and was on treatment with metformin hydrochloride at enrollment. The patient was recorded by the investigator as having an adverse event with the verbatim term "worsening of diabetes" (MedDRA preferred term "diabetes mellitus") on Day 18 of randomized treatment with placebo adjunct with valproate as the mood stabilizer, because of an exacerbation of symptoms. The patient had the dose of metformin hydrochloride increased (from 1000 mg to 1500 mg) at the time of the onset of the AE. The blood glucose and HbA1c values at randomization were 94 mg/dl ("documented fasting") and 6.0%, respectively. The AE continued to the final visit on Day 48 of randomized treatment when the blood glucose and HbA1c values were 83 mg/dl ("documented fasting") and 5.8%, respectively. The patient did not have any evidence in laboratory results of an exacerbation of diabetes at any time during the study.

Patient E0070013 in Study 127, a 62-year-old Black woman, had a medical history of "diabetes, type 1" at enrollment, and the blood sugar and HbA1c values at the screening visit were 183 mg/dL ("documented fasting") and 12.4%; respectively. On Day 364 of randomized treatment with placebo adjunct with valproate as the mood stabilizer, the blood sugar and

HbA1c values were 341 mg/dL ("documented fasting") and 10.6%. However, by the final visit (Day 672) the blood sugar was 138 mg/dL ("documented fasting") and the HbA1c was 8.6%; so this case was not considered to be an exacerbation of diabetes during randomized treatment.

Patient E0070027 in Study 127, a 38-year-old Black woman, had no medical history of diabetes at enrollment, and the blood sugar and HbA1c values at the screening visit were 75 mg/dL ("documented fasting") and 5.1%; respectively. On Day 84 (56 days prior to randomization) of open-label treatment with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer, the blood glucose was 126 mg/dL ("documented fasting") and the HbA1c was 5.1%. At randomization, blood glucose was 72 mg/dL ("documented fasting") and the HbA1c was 4.9%. On Day 85 of randomized treatment with placebo adjunct with valproate as the mood stabilizer, the blood sugar and HbA1c values were 146 mg/dL ("documented fasting") and 5.0%. This patient may have had glucose metabolism abnormality that began to emerge during open-label treatment, but the isolated abnormal glucose during randomized treatment was not confirmed on repeat testing and not considered to be associated with onset of diabetes.

Patient E0401006 in Study 126, a 28-year-old Caucasian man, had no history of diabetes and no hypoglycaemic treatment ongoing at enrollment. The patient was randomized to placebo adjunct with lithium as mood stabilizer. On Day 414 of randomized treatment, the patient had treatment with metformin initiated. The reason for starting treatment was recorded as "elevated levels of insulin". There were no high blood glucose or HbA1c values at any time during open-label or randomized treatment phase, and the initiation of metformin treatment was therefore not considered to be associated with an onset of diabetes.

Patients not considered to represent possible onset or possible exacerbation of possible diabetes during the open-label treatment phase

The remaining patients captured in the listings for post-hoc evaluation were not considered to demonstrate possible onset or possible exacerbation of possible diabetes during the placebo-controlled randomized treatment phase. For 17 of the patients, a brief description is presented below, giving the rationale for the decision not to include the patient in one of the categories possible onset or possible exacerbation of diabetes in the open-label treatment phase. Four of the patients (E0026009, E0034005, E0040001, and E0044056) had investigator reported AEs which were coded to the MedDRA preferred terms "diabetes mellitus" or "diabetes mellitus, non-insulin-dependent" and did not meet the adapted ADA criteria for a possible onset of possible diabetes in the adjudicated process. These 4 patients are described first below. For 13 of the patients who probably had pre-existing diabetes, a brief description is presented , giving the rationale for the decision that the patient probably had pre-existing diabetes.

Patient E0026009 in Study 127, a 47-year-old Caucasian woman, was recorded by the investigator as having an adverse event with the verbatim term "Type II diabetes" (MedDRA preferred term "diabetes mellitus, non-insulin dependent") on Day 83 of open label treatment with quetiapine 400 mg/day adjunct with valproate as the mood stabilizer. The patient had no prior history of diabetes mellitus. The patient did not have glucose lowering medications

administered during the study and there was no evidence in laboratory results of a possible onset of diabetes at any time during the study.

Patient E0034005 in Study 127, a 59-year-old Caucasian man, was recorded by the investigator as having an adverse event with the verbatim term "diabetes mellitus" (MedDRA preferred term "diabetes *mellitus*") on Day 40 of open label treatment with 100 mg/day quetiapine adjunct with lithium as the mood stabilizer. This patient was treated for a total of 62 days during the open-label phase of the study, and the screening visit blood glucose and HbA1c values were 164 mg/dL ("documented fasting") and 8.3%, respectively. The patient had no prior history of diabetes mellitus despite the screening visit blood glucose and HbA1c in the diabetic range. The patient was treated with glucose lowering medication (metformin and glipizide) that were started on Day 40 of open-label treatment, the same day as the AE start date. The patient had fasting glucose and HbA1c values of 149 mg/dL and 8.5 %, respectively, on the final visit of the study, Day 62 of open label treatment. The patient was considered to be a probable pre-existing diabetes (based on screening glucose and HbA1c values), and did not have any evidence in laboratory results of possible exacerbation of diabetes at any time during the study.

Patient E0040001 in Study 127, a 47-year-old Caucasian woman, was recorded by the investigator as having an adverse event with the verbatim term "diabetes mellitus" (MedDRA preferred term "diabetes mellitus") on Day 73 of open label treatment with quetiapine 600 mg/day adjunct with lithium as the mood stabilizer. The patient had no prior history of diabetes mellitus. The patient was treated with glucose lowering medication (metformin) beginning on Day 73, the start date of this AE. The patient had non-fasting glucose and HbA1c values of 65 mg/dL and 5.1%, respectively, on Day 87, the day of the final visit. There was no evidence in laboratory results of a possible onset of diabetes at any time during the study.

Patient E0044056 in Study 127, a 64-year-old Caucasian man, was recorded by the investigator as having an adverse event with the verbatim term "diabetes mellitus" (MedDRA preferred term "diabetes *mellitus*") on Day 16 of open label treatment with 300 mg/day quetiapine adjunct with valproate as the mood stabilizer. The patient had no prior medical history of diabetes mellitus. The screening visit blood glucose and HbA1c values were 137 mg/dL ("documented fasting"), and 7.1%, respectively. The patient was treated with glucose lowering medication (glipizide) starting on Day 115 of open-label treatment and ongoing at the final study visit. The patient had fasting glucose and HbA1c values of 133 mg/dL and 7.0 %, respectively, on Day 224 of randomized treatment, the final visit for this patient. The patient was considered to be a probable pre-existing diabetes (based on screening glucose and HbA1c values), and did not have any evidence in laboratory results of possible exacerbation of diabetes at any time during the study.

Patient E0001011 in Study 127, a 57-year-old Caucasian woman, had blood glucose and HbA1c values at the enrollment visit of 142 mg/dL ("documented fasting") and 5.7%, respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0024041 in Study 127, a 41-year-old Caucasian woman, had blood glucose and HbA1c values at the enrollment visit of 241 mg/dL ("documented fasting") and 7.1%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0031026 in Study 127, a 37-year-old Black woman, had blood glucose and HbA1c values at the enrollment visit of 259 mg/dL ("documented fasting") and 9.7%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0083038 in Study 127, a 57-year-old Caucasian man, had blood glucose and HbA1c values at the enrollment visit of 134 mg/dL ("documented fasting") and 7.1%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0146006 in Study 126, a 45-year-old Caucasian man, had blood glucose and HbA1c values at the enrollment visit of 129 mg/dL ("documented fasting") and 6.7%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0707006 in Study 126, a 28-year-old Caucasian man, had blood glucose and HbA1c values at the enrollment visit of 181 mg/dL ("documented fasting") and 5.2%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0805019 in Study 126, a 61-year-old Caucasian woman, had blood glucose and HbA1c values at the enrollment visit of 126 mg/dL ("documented fasting") and 5.9%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0902001 in Study 126, a 64-year-old Caucasian woman, had blood glucose and HbA1c values at the enrollment visit of 146 mg/dL ("documented fasting") and 6.3%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0911007 in Study 126, a 57-year-old Caucasian man, had blood glucose and HbA1c values at the enrollment visit of 138 mg/dL ("documented fasting") and 5.8%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E0919005 in Study 126, a 38-year-old Caucasian man, had blood glucose and HbA1c values at the enrollment visit of 244 mg/dL ("documented fasting") and 8.0%; respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E1114011 in Study 126, a 53-year-old Caucasian woman, had blood glucose and HbA1c values at the enrollment visit of 128 mg/dL ("documented fasting") and 6.0%, respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E1121001 in Study 126, a 45-year-old Caucasian woman, had blood glucose and HbA1c values at the enrollment visit of 131 mg/dL ("documented fasting") and 6.4%, respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Patient E1311001 in Study 126, a 54-year-old Caucasian man, had blood glucose and HbA1c values at the enrollment visit of 131 mg/dL ("documented fasting") and 5.5%, respectively. The patient did not have a medical history of diabetes, and did not have any evidence in laboratory results of exacerbation of diabetes at any time during the study.

Safety 9.1 data (cumulative clinical trial database)

Clinical trial reports of DKA

5077IL/0056/0042/0013: This serious report of "Diabetic ketoacidosis" described a 36 year-old male patient who has been receiving SEROQUEL (up to 500 mg/day) for the treatment of schizophrenia as part of a clinical trial. Medical history included DM, hypertension, dyspepsia, drug abuse, and hyperlipidemia. Concomitant medications included glipizide, gemfibrozil, metoclopramide, and hydrochlorothiazide. Twenty-eight weeks after starting SEROQUEL the patient was admitted to the hospital with a decreased level of consciousness. The patient had not been taking his glipizide or SEROQUEL for 3-4 days prior to admission. The patient was treated with intravenous fluids and insulin but later developed severe acidosis due to increased lipase (1819u/l [NR=25-229]) and amylase (135u/l [NR=27-92]). Other abnormal laboratory findings included: sodium (130 mmol/l [NR=135-146]), chloride (99 mmol/l [NR=100-107]), bicarbonate (5mmol/l [NR=22-32]), creatinine (1.9 mg/dL [NR=0.4-1.4]), glucose (413mg/dL [NR=70-160]), uric acid (12.3mg/dL [NR=2.2-7.2]), white blood count (17,000 [NR=4,000-11000]), beta-hydroxy butyrate (182mg/dlL [NR=0.4-4]). The patient was started on subcutaneous insulin and food was started once amylase and lipase were within normal range. At the time of reporting the patient had not restarted SEROQUEL. The event resolved two weeks after the onset of events. The study investigator felt that there was not a reasonable possibility that the event was related to SEROQUEL. No baseline laboratory data was provided.

5077IL/0056/0051/0010: This serious report of "Diabetic ketoacidosis" described a 45-year-old male patient who received SEROQUEL (600 mg/day) for the treatment of schizoaffective disorder as part of a clinical trial. Medical history included DM, hypertension, gastroesophageal reflux, insomnia, gonorrhoea, genital herpes, and alcohol/heroin abuse. Concomitant medications included clonazepam, amitriptyline, famotidine, and lisinopril. On day 163 of treatment the patient had a "moderately severe" episode of uncontrolled DM requiring hospitalization. The patient was treated with intravenous fluids and a 220-calorie diabetic diet. The patient recovered two days later and remained in the trial. The study

investigator considered the event not related to trial therapy. No laboratory data was provided.

Narratives

DKA: Patients with no history of DM

Medically confirmed

2006UW11090: This serious report of "Diabetic ketoacidosis" described a 28-year-old femal patient who was receiving SEROQUEL (200 mg/day; duration unknown) for the treatment of an unspecified condition. Medical history was not provided. Concomitant medications included dexmethylphenidate. The patient was taking ziprasidone and then started SEROQUEL. An unspecified amount of time later, this nursing home patient experienced DKA. It was also reported that the patient started having behavioral problems that were worse than usual. The patient was not diabetic prior to starting SEROQUEL. The patient's outcome and whether therapy with SEROQUEL continued was not provided. No other information was available.

2006UW09586: This serious report of "Diabetic ketoacidosis" and "Diabetes mellitus" described a 52-year-old male patient who was receiving SEROQUEL (400 mg/day; about 2 years) for the treatment of schizophrenia. Medical history included depression, obesity [BMI 37.2 kg/m^2], back pain, knee pain, two back surgeries, and hyperlipidemia. Concomitant medications included omeprazole, magnesium, gemfibrozil, acetaminophen/codeine, cyclobenzaprine, trazodone, and duloxetine. After about two years on SEROQUEL the patient had a fasting blood glucose of 126 mg/dL (baseline not provided). Two months later the patient was hospitalized with a three day history of vomiting, polydipsia, and polyuria. The patient did not have a fever but complained of generalized weakness. Labs were as follows: pH = 7.09, bicarbonate = 9, BG = 700, and WBC = 14,000 with a left side shift. His urine was positive for ketones and 3+ sugar. The patient was started on insulin (25 units in the am and 27 units in the pm), liberal fluid hydration, and a broad spectrum antibiotic. The patient was weaned off Seroquel and discontinued one month after the onset of events. About six weeks later the patient's BG while on insulin was 98 mg/dL. The reporter indicated that there were no other lifestyle, nutritional or medical issues that could have contributed to the diagnosis of hyperglycemia or diabetes. No other information was available.

2006UW07200: This serious report of "Diabetic ketoacidosis" described a 50-year-old male patient who was receiving SEROQUEL (dose unknown; 52 days) for the treatment of bipolar disorder. Medical history included depression, brain injury, and polysubstance abuse. Concomitant medications include lithium and escitalopram. After 52 days of therapy with SEROQUEL the patient was hospitalized with DKA. Two days later SEROQUEL was discontinued and the patient recovered. No laboratory data was provided. No other information was available.

2006UW04923: This serious report of "Diabetic ketoacidosis" described a 56-year-old female patient who was receiving SEROQUEL (400mg/day; 12-18 months) for the treatment of psychotic symptoms. Medical history included moderate obesity. Concomitant medications include clozapine (for which hyperglycemia, DM has been reported). After about a year on SEROQUEL the patient started treatment with clozapine. Three months later the patient presented to the emergency room complaining of not feeling well and was diagnosed with DKA and admitted to the ICU. Therapy with SEROQUEL was discontinued. The patient's condition was reported to be improving. Therapy with clozapine continued. No laboratory data was provided. No other information was available.

2006UW04386: This serious report of "Diabetic ketoacidosis" described a 25-year-old male who was receiving SEROQUEL (dose/duration unknown) for the treatment of an unspecified condition. Medical history and concomitant medications were not provided. After starting treatment the patient experienced spontaneous "ketoacidosis-insulin dependent diabetes". The patient's outcome and whether therapy with SEROQUEL continued was not provided. No other information was available.

2006GB00605: This serious report of "Diabetic ketoacidosis" described a 41-year-old male who was receiving SEROQUEL (dose/duration unknown) for the treatment of schizophrenia. Medical history and concomitant medications were not provided. After an unspecified amount of time on SEROQUEL the patient developed DKA. The patient received an unspecified treatment and was reported to be recovering. No laboratory data was provided. No other information was available.

2006UW13390: This serious report of "Ketoacidosis" described a 44-year-old-female who was receiving SEROQUEL (dose/duration unknown) for the treatment of an unspecified condition. Medical history was not provided. Concomitant medications included "hypertensive medications." After an unspecified amount of time on SEROQUEL the patient was extremely thirsty and " a little different". Three days later the patient was found in bed at home dazed and confused and was admitted to the hospital with DKA. The patient's outcome and whether therapy with SEROQUEL continued was not provided. No other information was available.

2006AC01055: This serious report of "Diabetic ketoacidosis" described a 25-year-old male patient who was receiving SEROQUEL (100-600mg/day; about 3 months) for the treatment of schizophrenia. Medical history included obesity (BMI=39.19 kg/m^2). It was reported that the patient had no personal or family history of DM. Concomitant medications included haloperidol and biperiden. The patient was "irregulary" treated with chlorpromazine for four months until the month prior to starting SEROQUEL. The patient's baseline BG (fasting status not provided) was 100 mg/dL. After two months on SEROQUEL therapy with haloperidol and biperiden was added. Two weeks later the patient was taken to the emergency room with suspected DKA. The patient had nausea and vomiting, random BG was 546 mg/dL, there was glucose and ketones in his urine, and blood pH was 7.06. SEROQUEL was discontinued and the patient was treated with insulin. The status of the patient's other medications was unspecified. The patient improved and the patient was discharged from the

hospital one week later on NPH insulin and was referred to an endocrinologist. Three months after then event the patient was reported to be taking metformin, NPH insulin, regular insulin, haloperidol, biperiden, clonazepam, and sertraline. His BMI was 36.54 kg/m^2 and his fasting glucose was 333mg/dL at this time. No other information was available.

2005UW05375: This serious report of "Pancreatitis" and "Diabetic ketoacidosis" described a 34-year-old male patient who was receiving SEROQUEL (dose/duration unknown) for the treatment of an unspecified condition. Medical history and concomitant medications were not provided. After an unknown amount of time on SEROQUEL the patient developed pancreatitis and DKA. The patient's outcome and if SEROQUEL continued was unknown. No other information was provided.

2003UW14378: This serious report of "Diabetic ketoacidosis" described a 26-year-old female patient who was receiving SEROQUEL (500 mg/day). The patient had no previous history of DM. Concomitant medication included ziprasidone. The patient was found in her house in a state of confusion and was hospitalized. At the time of the report, the patient had not recovered. This report contained scant clinical detail (i.e. no glucose data or pH levels, no baseline laboratory values, no dates of SEROQUEL therapy, and no medical history). No further information was provided; however, follow-up has been requested but not yet received.

2003UW05594: This serious report of "Diabetic ketoacidosis" described a 42-year-old male patient receiving SEROQUEL (1000 mg/day; duration and indication unknown). Medical history and concomitant medications were not provided. The patient developed diabetic acidosis. The outcome was unknown. It was reported that SEROQUEL was continued. No additional information was provided; however, follow-up has been requested but not yet received.

2003GB01346: This serious report of "Diabetic ketoacidosis" and "Tinea cruris" described an 18-year-old female patient receiving SEROQUEL (200 mg/day x 5 months) for the treatment of psychotic symptoms. Medical history and concomitant medications were not provided. The patient had previously received SEROQUEL for an unknown amount of time and then switched to olanzapine (for which DKA and DM has been reported) for an unspecified reason. Olanzapine was continued for approximately four months and the patient experienced weight gain. The olanzapine was discontinued and SEROQUEL restarted. After about REDACTE on SEROQUEL the patient died suddenly due to DKA. REDACTED before her death the patient developed a fungal infection of the groin (tinea cruris), which was noted to be associated with DM. REDACTE prior to her death, the patient was admitted to the hospital with abdominal pain and vomiting. Laboratory tests revealed high blood glucose and acidosis (no data). Treatment was initiated (unspecified) and the patient developed an irregular heartbeat. Subsequently, she could not be resuscitated. Post mortem determined the cause of death as DKA with secondary cause reported as atypical antipsychotic therapy. The coroner believed that DKA due to SEROQUEL treatment was the most likely cause of death but that it was impossible to be certain. Post mortem blood analysis did not show the presence of olanzapine, SEROQUEL or any common drugs of abuse. Post-mortem showed that the

cardiovascular, genitourinary, lymphoreticular and endocrine systems were all normal. DKA in a 19-year-old suggests the patient may have had Type I or Insulin Dependent DM. Since there are no blood glucose or HbA_{1c} values reported, it is unknown when the patient developed DM. The absence of SEROQUEL in the postmortem blood tests raises the question of whether the patient was actually taking SEROQUEL. But since the timing of the blood sampling in relation to SEROQUEL dosing was not provided, it cannot be determined with certainty whether the patient was noncompliant. Concomitant medications were not provided. Follow-up information has been requested but not yet received.

2002UW14814: This serious report of "Diabetic ketoacidosis", "Diabetes mellitus", "Diabetes insipidus", "Pancreatitis", "Apnoea", and "Dyspnoea" described a female patient who was receiving SEROQUEL (400 mg/day) for irritability, insomnia, and mania. Medical history included obesity since treatment with atypical antipsychotics and increased blood glucose while taking olanzapine immediately prior to starting therapy with SEROQUEL. Concomitant medications included lithium (for which hyperglycemia has been reported), clonazepam, and gabapentin (for which blood glucose fluctuation in diabetic patients has been reported). Olanzapine was discontinued on the day that SEROQUEL therapy was started. After 17 months of SEROQUEL therapy the patient experienced pancreatitis, DM, diabetes insipidus, DKA, apnea, and dyspnea. The blood glucose level was reported to be 1400 (no units) on an unknown date. SEROQUEL, clonazepam, and lithium were all discontinued. The patient recovered from the pancreatitis, however, the outcome for the other events was unknown at the time of the report.

2002GB02627: This serious report of "Diabetes Mellitus" and "Diabetic ketoacidosis" described a 44-year-old male who began SEROQUEL therapy (200 mg 2x/day) on 05-Jul-2002 for the treatment of schizophrenia and experienced DM three months later. Medical history was not provided. Concomitant medications included lactulose and orphenadrine "for schizophrenia", which was discontinued two months prior to the event. The patient was hospitalized with "early DKA" and was treated with insulin. A hemoglobinopathy screen about three weeks prior to commencing SEROQUEL "detected HbA and HbA4" (no values). No evidence of sickle cell or thalassemia was observed. The patient's weight had also increased from 90.3 kg on 26-Nov-2001 to 122.5 kg on 19-Oct-2002. SEROQUEL was continued and the event was ongoing at the time of the report. No further information was provided.

2002AP01772: This serious report of "Diabetic ketoacidosis", "Hyponatremia", "Hyperkalemia", "Hypokalemia" and "Anaemia" described a 51-year-old male patient who was receiving SEROQUEL and risperidone (for which hyponatremia has been reported) for schizophrenic psychosis, and developed DKA. Medical history included hepatic failure and acute hepatitis, which were suspected to be drug induced (drug not identified), prior to the DKA. Concomitant medications included ethyl loflazepate and nitrazepam. Family history for DM was unknown. The patient was hospitalized for four months for an unspecified reason. Urinary glucose levels were analyzed monthly and remained negative during this time. Risperidone (2 mg/day) was initiated upon hospitalization and increased to 4 mg/day by two months. About six weeks later, SEROQUEL (200 mg/day) was initiated and titrated to

300 mg/day within eight days. About six weeks after discharge blood tests revealed mild anemia, slightly increased triglycerides, and normal glucose (not fasting) and HbA_{1c} values (123 mg/dL and 4.8 %, respectively). About six months later, the patient's condition seemed uneventful except for a complaint of insomnia, for which his nitrazepam dose was increased (as outpatient). REDACTED after beginning SEROQUEL and risperidone, respectively) the patient experienced "disturbed consciousness" and was hospitalized. Laboratory results included BS level (1179 mg/dL), HCO3 (3.0 mmol/L), sodium (116.3 mmol/L), and potassium (6.55 mmol/L). Results of the blood gas analysis were: BE (base excess) was -25.2, and pH was 7.055. DKA was diagnosed. Hydration status prior to hospitalization was unknown. All medications were discontinued and the patient was given normal saline, sodium bicarbonate, and insulin. The following day, blood glucose improved (233 mg/dL) but the patient remained comatose. Potassium levels had decreased (2.73 mmol/L) before increasing again (3.98 mmol/L) by the evening. During the evening, the patient's BS increased to 545 mg/dL. Shock occurred and was unsuccessfully treated with a large volume of dopamine. The following day the patient died of circulatory failure (not confirmed that the patient died from a hyperosmolar coma). An autopsy was not performed. The patient's sister confirmed that the patient drank about 4 liters of Coca-Cola (regular formula) every day for the last five weeks, and that the patient had lost weight rapidly in the last few weeks.

2002AP02304: This serious report of "Diabetic ketoacidosis" described a 31-year-old male patient who was receiving SEROQUEL for treatment of schizophrenia. Medical history included obesity. Concomitant medications included haloperidol, biperiden, trihexyphenidyl, levomepromazine, and chlorpromazine/promethazine/phenobarbital combination (hyperglycemia and DM have been reported for chlorpromazine). Three months after SEROQUEL was increased to 600 mg/day, the patient complained of limb weakness and a limp, which were not recognized objectively. Two days later the dysarthria and limb weakness worsened. The next day, approximately one and one-half years after commencing SEROQUEL, the patient was hospitalized (he could not hold a cup in his hand). On admission, the patient was "almost conscious", deep reflex was mildly increased, BP was 138/86, pulse 100 bpm, BS 1348 mg/dL, and temperature was 37.9°C. Two days later, a brain computed tomography (CT) scan was normal, BS level was 1280 mg/dL, and urinary sugar was 4+. Treatment included insulin and an infusion solution. The event resolved the following day. It was unknown if the patient was discharged on insulin. The reporting physician considered that the event was related to "PET bottle syndrome" (drinking large amounts of sweetened soft drink; other details are unknown).

2002AP02883: This serious report of "Diabetic ketoacidosis", "Renal failure acute", "Dyspnoea", Diarrhoea", Retching", "Vomiting", "Polydipsia" and "Pyrexia" described a 30-year-old female patient who was receiving SEROQUEL for the treatment of schizophrenic psychoses. Medical history included hyperprolactinemia with haloperidol. The patient did not have a history of drinking or alcoholism, it is unknown whether her family had a history of DM, but the patient did not. Concomitant medications included haloperidol (30 mg/day gradually reduced to 5 mg/day), bromperidol (12 mg/day), biperiden (3 mg/day), triazolam (0.5 mg/day), flunitrazepam (1 mg/day), and distigmine. SEROQUEL treatment (75 mg/day)

was commenced in June 2001. This was titrated upwards to 200 mg while haloperidol was reduced from 30 mg to 5 mg. On REDACTED 2002, one year and three months after commencing SEROQUEL treatment the patient developed symptoms of what was reported to be a common cold (diarrhea, retching, vomiting and pyrexia) and her body temperature increased to 38-39 °C. On REDACTED 2002, her fever resolved but gastrointestinal symptoms continued and anorexia occurred. On REDACTED 2002 her diarrhea and vomiting continued and she received treatment with a drip infusion to prevent dehydration. During the evening her family recognized she was drinking a large amount of water and later that night the patient complained of difficulty breathing. On REDACTED 2002, her difficultly breathing continued and she visited a local internist. Chest and abdominal X-ray results were normal; laboratory tests were not performed. The internist diagnosed the condition as psychiatric symptoms. She returned home after treatment with a drip infusion. During the evening her difficulty breathing increased. Her family recognized a sudden change in her condition and called an ambulance. At this time the patient possibly experienced a cardiac arrest. She underwent intubation, no vomit was recognized at the time and she died at approximately REDACTED. Her body weight had not markedly changed recently and she had a normal physique, due to this her BS level had not been analyzed recently. Her eating habits were normal for a person of her age. The patient continued to receive SEROQUEL until the day of her death. An autopsy was performed, and the cause of death was determined to be acute renal failure. The reporting physician considered that the diarrhea, pyrexia, retching, and vomiting were related to a common cold and commented that the patient was healthy. It was assumed, however, that the hyperglycemia, which may have occurred after DM, was triggered by the common cold. The physician considered that SEROQUEL caused the condition, since another patient developed hyperglycemia during SEROQUEL therapy. However, it is only a matter of speculation, since there was no objective data. Since excessive drinking and breathing difficulty occurred, the reporter also suspected that ketoacidosis possibly occurred and advanced to induce deterioration of her condition and death. It was considered that cardiac arrest possibly occurred due to hyperkalemia in such a condition.

2001UW12078: This serious report of "Diabetic ketoacidosis" described a 57-year-old patient (sex unknown) who was receiving SEROQUEL (dose/duration unknown) for an unknown indication. Medical history was not provided. Concomitant medications included risperidone, which was also considered a suspect medication. The patient experienced DKA and died. No further information was obtainable.

2002UW08229: This serious report of "Diabetic ketoacidosis", "Renal failure", "Suicidal ideation", "Drug administration error", "Fatigue", "Aspiration", "Hepatic steatosis", "Cholelithiasis" and "Obesity" described a 40-year-old female patient who was receiving SEROQUEL for the treatment of schizoaffective disorder and a depressed mood. Medical history included mental illness, smoker, obesity (weight 186 lb./height 68 inches, BMI = 28.3 kg/m^2), and cocaine, crack, and marijuana abuse. Concomitant medications included buspirone, sertraline, and gatifloxacin. The patient's SEROQUEL dose was gradually titrated to 300 mg/day over several months. Five months later the dose was increased to 200 mg 2x/day. The patient misunderstood the directions and took 200 mg/day from that time on. Approximately REDACTED later the patient was found dead on the floor of her apartment.

The police investigator's report stated that the patient's neighbor disclosed that the patient traded drugs, namely cocaine, crack, and marijuana, to let others drive her car, and that the patient was very depressed and hated herself, and spoke of wanting to commit suicide. Marijuana residue and seeds were found in her car. The autopsy report indicated that the cause of death was DKA, with a contributing factor of diabetic renal failure. The report also revealed that the patient had severe fatty liver metamorphosis, cholelithiasis, congestion of the viscera, and obesity. Lab values at autopsy from a vitreous specimen included Na 146 mmol/L, K 25.5 mmol/L, chloride 107 mmol/L, BUN 86.5 mg/dL, glucose 997 mg/dL, and creatinine 2.7 mg/dL. The patient's urine was positive for cocaine metabolites, and her heart blood was positive for cocaine, ethanol, acetone, and sertraline.

2002UW09406: This serious report of "Diabetic ketoacidosis" described a 36-year-old male patient who was prescribed SEROQUEL (400 mg/day) for the treatment of schizophrenia. Medical history included gastroesophageal reflux disease and no family history of DM. Concomitant medications included lansoprazole, ibuprofen, multivitamins, and Metamucil. One month after starting SEROQUEL the patient was hospitalized for DKA. Treatment included 10 units of insulin IV and then 10 units/hour IV. SEROQUEL was discontinued and it was not reported if SEROQUEL was restarted. Laboratory values on admission included: blood gas pH 7.26, glucose 1544 mg/dL, K^+ 6.1, BUN 64, creatinine 3.5, and urine positive for ketones. (Units listed whenever they were provided). The patient did recover from the event and was discharged from the hospital. No further information was provided.

2002GB01254: This serious report of "Diabetic ketoacidosis" described a male patient (age unknown) who was receiving SEROQUEL (300 mg/day) for the treatment of schizophrenia. Medical history included obesity. Concomitant medications included clozapine (for which hyperglycemia and ketoacidosis has been reported) and olanzapine (for which hyperglycemia, DM, DKA/coma, elevated plasma glucose and risk factor for weight gain has been reported). One year and two months after starting SEROQUEL the patient was hospitalized with DKA. On admission, the glucose level was 46.6 (no units); the patient was dehydrated, and acidotic. The patient's HbA_{1c} was >12%. Type I or Type II DM was suspected. The patient had become increasingly obese (BMI 48.7 kg/m2). Treatment included insulin, but at the time of the report, the event was ongoing.

2001UW14447: This serious report of "Diabetic ketoacidosis", "Arrhythmia", and "Myocardial ischemia" described a 13-year-old male patient who was receiving SEROQUEL (300 mg/day) for the treatment of bipolar disorder to control his fear, aggression, and mood swings. Medical history included morbid obesity. Concomitant medications included valproate. Once on SEROQUEL, the patient developed a "cardiac situation" that started with an arrhythmia and progressed to ischemia. A stress test revealed ischemia and the patient was scheduled for cardiac catheterization. Approximately one month later, the patient was hospitalized for DKA and was discharged on insulin. The patient was in foster care and there was little information about family history, however, it was thought that there might be a family history of DM (several grandparents and mother). Additional information was requested.

2001UW12263: This serious report of "Diabetic ketoacidosis" "Abdominal pain", "Polydipsia", "Polyuria" and "Hyperglycaemia" described a 30-year-old male patient who was receiving SEROQUEL (300 mg/day) for an unknown indication. Medical history was not provided. Concomitant medications included olanzapine (for which hyperglycemia, DM, DKA/coma, elevated plasma glucose and risk factor of weight gain has been reported). The patient experienced abdominal pain, polydipsia, and polyuria. Later that month DKA and hyperglycemia occurred. Treatment included glyburide and insulin. SEROQUEL was continued.

2001UW02143: This serious report of "Diabetic ketoacidosis" described a 48-year-old male patient who was receiving SEROQUEL (dose unknown) for a few months for treatment of an unspecified psychiatric disorder. Medical history included hyperlipidemia. Concomitant medications included lorazepam and an unspecified "statin" medication. The patient experienced DKA. The patient "was on a day of leave and returned lethargic" (report did not specify if the patient was in a long term care setting). The patient was seen in the emergency room and his blood glucose was found to be 630 mg/dL and ketones were found in his urine; the patient was admitted to the hospital. Treatment included insulin and intravenous fluids. Laboratory results revealed a low-normal C-peptide (no value given) and Anti-GAD results were pending. SEROQUEL was continued for a day or two before the patient was switched to haloperidol. At the time of this report the patient's BS was reported to be 250 mg/dL on insulin 70/30 2x/day. The patient was discharged from the hospital 13 days after admission.

2000UW02905: This serious report of "Diabetic ketoacidosis", "Pancreatitis acute" and "Lipids increased" described an 18-year-old patient (sex unknown) who was receiving SEROQUEL (dose/duration/indication unknown). Medical history was not provided. Concomitant medications included sertraline. The patient was hospitalized with DKA, a BS of 1200 (no units), acute pancreatitis, and elevated lipids. Outcome of events is unknown. Additional information has been requested.

2000UW01164: This serious report of "Ketoacidosis", "Diabetes mellitus", "Polyuria", "Polydipsia", "Weight increased" and "Blood glucose increased" described a 43-year-old male patient who was receiving SEROQUEL (200 mg/day) for treatment of an unspecified mental illness. Medical history was not provided. Concomitant medications included venlafaxine (for which risk factor of weight gain and increased serum cholesterol has been reported). Over a period of a few weeks the patient developed polyuria, polydipsia, and an unexplained weight loss of over 30 pounds. FBS showed glucose level over 700 (no units). The patient developed ketoacidosis and was hospitalized where a diagnosis of new onset DM was made. SEROQUEL therapy continued. Outcome of the events is unknown. Additional information has been requested.

2004UW14727: This serious report of "Diabetic ketoacidosis", "Diabetic hyperosmolar coma", and "Diabetes mellitus non-insulin-dependant" described a 62-year-old female patient who was receiving SEROQUEL (50-100 mg/day) for depression. Medical history included a malignant breast lump removal, hypertension, and hyperlipidemia. Concomitant medications included atorvastatin, gabapentin (for which blood glucose fluctuation in diabetic patients has

been reported), tramadol, rofecoxib (for which risk factor of weight gain has been reported), montelukast sodium, tamoxifen, esomeprazole, and losartan (for which hypertension has been reported). On day 67 of therapy with SEROQUEL, the patient experienced severe DKA, severe hyperosmolar coma, and moderate Type II DM. The patient was admitted to the hospital. Her blood sugar was 700 (no units). Therapy with SEROQUEL was discontinued. Treatment included NPH insulin (25 units in the morning, 20 units in the evening) and metformin. The patient recovered from the DKA and hyperosmolar coma and was discharged. She began therapy with pioglitazone. Her glucose dropped to 120 (no units). The patient continues to take metformin. The patient has not recovered from Type II DM.

2004AP01695: This serious report of "Diabetic ketoacidosis" and "Shock" described a 50-year-old male who was receiving SEROQUEL (200 mg/day; approximately 7 months) for schizophrenia. Medical history included hyperlipidemia and high triglyceride levels Concomitant medications included biperiden, bezafibrate, and bromperidol lactate. The patient had drunk water, but not eaten full meals for 6 days before his death. He had a swollen face and pus exuding from his ears. On [redacted] of therapy with SEROQUEL, the patient was found to be ketoacidotic (total ketones 12600 mg/dL) and hypothermic (body temperature 33.7°C) on admission to the hospital. Treatment included insulin and infusion solution. The patient's condition worsened; he developed a fever (39°C) and hypotension, and went into shock. The patient died.

2004GB00610: This serious report of "Diabetic ketoacidosis" described a 17-year-old male who was receiving SEROQUEL (25-100 mg/day; 10 days) for schizophrenia. Medical history included sedation and smoking. Concomitant medications included valproate, procyclidine, haloperidol, lorazepam, risperidone, valproate, and clonazepam. On day 10 of therapy with SEROQUEL, the patient experienced high blood pressure, confusion, drowsiness, polyuria, polydipsia, ketonuria, and increased thirst. Upon admittance to an accident and emergency facility, the patient's glucose was greater than 50 mmol/L. The patient was diagnosed with severe DKA. Treatment included IV fluids and sliding scale insulin. Therapy with SEROQUEL was discontinued. The patient was discharged from the hospital. The patient's outcome is unknown.

2004GB02613: This serious report of "Diabetic ketoacidosis" described a female patient of an unspecified age who was receiving SEROQUEL (dose/duration unknown) for an unspecified indication. Medical history and concomitant medications were not provided. The patient experienced DKA and therapy with SEROQUEL was discontinued until the event stabilised, and then the therapy was restarted without incident. Additional information has been requested.

2004UW13431: This serious report of "Diabetic ketoacidosis" described a 45-year-old male who was receiving SEROQUEL (dose unknown; approximately 1 year) for post traumatic stress disorder. Medical history was not provided. Concomitant medication included sertraline hydrochloride. After starting therapy with SEROQUEL, the patient was hospitalized with DKA. Therapy with SEROQUEL was discontinued, and the patient was started on therapy

with risperidone. The patient's outcome is unknown. Additional information has been requested.

2004UW18935: This serious report of "Diabetic ketoacidosis" and "Somnolence" described a 58-year-old female who was receiving SEROQUEL (100 mg/day; 4 months) for sleep disorder. Medical history included arthritis, depression, anxiety, and a family history of DM. Concomitant medications included clonazepam, escitalopram, and valproate. On day 74 of therapy with SEROQUEL, the patient experienced excessive sleepiness, increased urination, and heavily increased water consumption. The patient went to her doctor's office and was deemed as having "slurred speech." The patient was sent to the emergency room and was diagnosed with DKA and "almost" a diabetic coma. Her glucose level was 577 (no units). Treatment included intravenous insulin. Therapy with SEROQUEL was discontinued. The patient was discharged, and she was prescribed oral glucagon. One month later, the patient's glucose levels were normal and therapy with oral glucagon was discontinued. Additional information has been requested.

2004UW22295: This serious report of "Diabetic ketoacidosis" described a patient of unspecified age and sex who was receiving SEROQUEL (dose/duration unknown) for an unspecified indication. Medical history and concomitant medications were not reported. After starting treatment with SEROQUEL the patient experienced DKA. The patient's outcome is unknown. Additional information has been requested.

2003AP04434: This serious report of "Hyperglycemia", "Depressed level of consciousness" and "Diabetic ketoacidosis" described a 72-year-old patient who was receiving SEROQUEL (50mg/day; 11 days) for the treatment of schizophrenia. Medical history included hyperlipidemia, mental disorder, Korsakoff syndrome, disorientation, confabulation, cerebral atrophy and cerebral ventricle dilation. Concomitant medication included tiapride. One week and five days after commencing SEROQUEL therapy, the patient developed a depressed level of consciousness. It was reported that he had a lack of energy and was sleeping more than usual. SEROQUEL was discontinued. 3 days later the patient was hospitalized and given an electrolyte transfusion due to him not eating for two to three days. An hour later the patient had high glucose levels (897 mg/dL) and he was diagnosed with life threatening diabetic ketoacidosis and hyperglycemia. The next day the patient received glycemic control and his level of consciousness and responsiveness improved.

2004UW23764: This serious report of "Diabetes mellitus insulin dependent", Diabetic Ketoacidosis", "Renal failure acute", "Liver function test abnormal", "Liver function test abnormal" and "Hepatic cyst" described a 77-year-old female patient who was receiving SEROQUEL (100mg/day) for the treatment of schizoaffective disorder. Concurrent illnesses included depression, hypertension, diastolic dysfunction, COPD, chronic pelvic pain, weight gain, and medical history consisted of laparoscopic cholecystectomy. Concomitant medications included diltiazem, clonidine (for which hyperglycemia is patients with NIDDM or IDDM has been reported), pantoprazole, senna, ipratropium/albuterol inhaler, fluticasone propionate (for which hyperglycemia has been reported), albuterol (for which hyperglycemia and DKA has been reported) and ipratropium via nebulizer and oxygen. Four years after

commencing therapy with SEROQUEL, the patient presented to the ER with complaints of not feeling well, weakness, malaise, myalgia, excessive thirst, polyuria, decreased appetite, blurry vision, mild headache, body ache and increased fatigue. The patient's glucose level was 1182 (anion gap 20), BUN was 30, and creatinine was 1.7. The patient was diagnosed with new onset DM, DKA and acute renal failure. She was treated with intravenous insulin and intravenous hydration. The patient's lab values normalized but liver function tests increased: AST (from 34 to 50), ALT (from 40 to 53) and alkaline phosphatase (from 80 to 93). The patient was discharged 8 days later and SEROQUEL was continued.

1999AP05757: This serious report of "Diabetes mellitus", "Ketoacidosis" and "Weight increased" described a 25-year-old male patient who was receiving SEROQUEL (750mg/day) for the treatment of psychosis. Concomitant medication included lithium (for which hyperglycemia has been reported), acamprosate, and flupenthixol (for which interaction with lithium resulting in hyperglycemia has been reported). One year and 9 months after commencing SEROQUEL therapy the patient was hospitalized due to the development of DM and DKA. The patient also experienced weight gain. The patient was treated with insulin. The patient recovered and treatment with SEROQUEL is still continuing.

2003AP04386: This serious report of "Diabetes mellitus non insulin dependent", "Diabetic ketoacidosis" and "Convulsion" described a 34-year-old male patient who was receiving SEROQUEL (600mg/11 months) for the treatment of schizophrenia. Medical history included family history of DM and obesity. Concomitant medications consisted of sulpiride (for which hyperglycemia and risk factor for obesity and hyperlipidemia reported), biperiden, lorazepam, fluphenazine, proheparum, chlorpromazine (for which hyperglycemia, DM and risk factor of obesity has been reported), flunitrazepam, promethazine and allopurinol. Approximately 2 months after commencing treatment with SEROQUEL, the patient had fasting blood glucose of 105 mg/dL and HbA_{1c} of 6.8%. At this time the patient drank soft drinks due to extreme thirst. 8 months later the patient developed a convulsive seizure with loss of consciousness and was hospitalized. His BS was 799 mg/dL and ketone body in urine was 3+. The patient was diagnosed with DKA due to consumption of soft drinks. The patient was treated with large amounts of fluid and small amounts of insulin drip infusion. The patient's blood sugar levels normalized and SEROQUEL was discontinued. The next day the patient recovered from the DKA, however his HbA1c was elevated (13.6%). No further information provided.

2005GB02396: This serious report of "Diabetic ketoacidosis" described a 33-year-old male patient who was receiving SEROQUEL (600 mg/day) for the treatment of schizophrenia. Medical history was not provided however it was reported that the patient did not have a history of DM. Concomitant medications included olanzapine (for which DKA has been reported) and folic acid. The patient began SEROQUEL treatment on 20-JUN-2005 and was having olanzapine reduced and withdrawn on 21-JUL-2005. The reporter stated a possible drug interaction between the two atypical antipsychotics leading to ketoacidosis after an unknown time. The patient was treated with insulin for the event of diabetic ketoacidosis. At the time of the report the patient had not yet recovered from the events. No laboratory data was provided.

2005UW18114: This serious report of "Ketoacidosis" described a 35-year- old patient (sex unknown) who was receiving SEROQUEL (300 mg/day) for the treatment of an unspecified condition. Medical history and concomitant medications were not provided. It was reported that after starting treatment the patient experienced ketoacidosis and blood sugars of 1700. The patient's outcome and whether therapy with SEROQUEL continued was not provided. No other information was provided. .

2005UW17274: This serious report of "Diabetes mellitus insulin-dependent" and "Ketoacidosis" was received as a civil complaint from an attorney on behalf of a female patient, whom the attorney alleges has suffered DM and ketoacidosis as a result of ingesting SEROQUEL. According to the civil complaint, the patient took SEROQUEL as prescribed in June 2003, and as a result was diagnosed with DM and ketoacidosis. The complaint alleged the patient suffered and continues to suffer from "serious permanent physical injuries as well as pain and emotional anguish". Follow-up information was received in the form of medical records in connection with the lawsuit. The following reflects the information that was stated in these records. Medical history included hypertension, severe depression, obesity, myocardial infarction, total abdominal hysterectomy, one ovary removed, and smoking. The patient's father died of diabetic complications in his 70's. Concomitant medication included escitalopram, amlodipine, and valsartan. On 21-Oct-2003 the patient was found at home with an altered level of consciousness and high blood sugar. The patient had no known history of diabetes or ketoacidosis. She was last seen by her family four hours prior to the event. For approximately one week prior to the event the patient experienced stomach pains. She denied any alcohol intake and her alcohol level was 0. She also complained of polydipsia, polyuria, and thirst. Several days prior to the event the patient experienced nausea, vomiting, and vague dysuria. The paramedics noted the patient's blood sugar was high. She was transported to the hospital emergency department. Treatment medications received in the emergency department included intravenous insulin, naloxone, and flumazenil with no response. She was also given two liters normal saline boluses. She was started on an insulin drip. A repeat accu-check was extremely high. Arterial blood gas indicated severe metabolic acidosis with a PH of 7.12, CO2 of 8, PO2 129, and bicarbonate 2. Oxygenation saturation was 98-99%. Ammonia was within normal limits at 19. The acidotic blood gas and elevated blood sugar were indicative of DKA. Other significant abnormal laboratory findings included glucose 425-731, potassium 6.1, chloride 89, and bicarbonate 5.8. The patient's white blood cell count was 19,500, hematocrit 45.7, blood urea nitrogen 37 and creatinine 2.1, possibly indicating severe dehydration. Intravenous fluids were maintained for rehydration. Additional treatment medications included bicarbonate. By 2:00 am the patient was improving. She was lethargic but oriented and recognized family members at the bedside. She was admitted to intensive care with a diagnosis of new onset diabetes mellitus with acute altered mental status, probable ketoacidosis/metabolic acidosis. By 28-Oct-2003 the patient's BUN and creatinine were normal. Her glucose, which took several days to control, was at a reasonable level. She was placed on glyburide and Actos therapy. The acidosis cleared as well. She was mildly anemic with a hematocrit of 34.1. The physician noted that the etiology of the patient's decompensation was unclear. On 28-Oct-2003 she was discharged to home on long-acting and regular insulin and was taught to administer her own insulin and to perform accu-checks. The patient's discharge diagnosis was acute onset type I diabetes with diabetic ketoacidosis,

now resolved. On 24-Feb-2004 the patient was given a prescription for SEROQUEL 100 mg, one tablet three times a day and five tablets at bedtime. On 04-Apr-2004 the patient's dosage was reduced to one tablet in the morning, two at bedtime for five days. Following five days at this dosage the patient was instructed to discontinue SEROQUEL therapy.

2005UW15699: This serious report of "Diabetic ketoacidosis" described a 45-year-old male patient who was receiving SEROQUEL (dose unknown) for the treatment of schizophrenia. Medical history was not provided. Concomitant medications included olanzapine (for which DKA has been reported). After an unspecified amount of time on SEROQUEL the patient was hospitalized due to DKA. While in the hospital the patient's lipids "shot up" and he developed severe respiratory complications. The patient died. Aspiration was the presumed cause of death. No other information was provided.

2005UW14876: This serious report of "Diabetes mellitus" and "Diabetic ketoacidosis" described a 46-year-old female patient who was receiving SEROQUEL (300 mg/day) for the treatment of schizophrenia. Medical history included hypertension. Concomitant medications included valproate. After more than one year on SEROQUEL the patient was hospitalized for new onset of diabetes, DKA, and somnolence. The patient's BG (fasting status unknown) was 963 (units not provided), white blood cell count was 16, and the patient was positive for Group D Enterococcus infection. The patient's outcome and if therapy with SEROQUEL continued was not provided. No other information was available.

2005UW11318: This serious report of "Diabetic ketoacidosis" described a 48-year-old male patient who was receiving SEROQUEL (600mg/day) for the treatment of schizophrenia. Medical history included fatty liver, hyperlipidemia, obesity (BMI=29), significant alcohol use, and a positive tuberculin test. Concomitant medications included isoniazide (for which hyperglycemia has been reported), multivitamin, and vitamin B6. After two months of therapy with isoniazide and 20 days of therapy with SEROQUEL the patient experienced severe DKA. Symptoms included lethargy, and "falling out". The patient's random BG was 600. The patient was hospitalized for five days for stabilization. Therapy with SEROQUEL was discontinued that day due to the event and therapy with isoniazide was continued. Abnormal lab values included increased ALT (63) and LDH (159). Treatment included metformin and insulin. The patient had no previous history of diabetes. The patient has continued to take oral hypoglycemic medication following the DKA and recovered four days after the start of the event.

2005UW09324: This serious report of "Infection", "Weight increased", "Diabetes mellitus", and "Ketoacidosis" described a 58-year-old female patient who was receiving SEROQUEL (dose/duration unknown) for the treatment of an unspecified condition. Medical history and concomitant medications were not provided. After an unknown amount of time on SEROQUEL the patient experienced a "large amount of weight gain" (she now weighs 427 pounds) and developed an infection in her buttocks. The patient also experienced diabetes and ketoacidosis. The patient's outcome and if SEROQUEL continued was unknown. No other information was provided.

2005AP05975: This serious report of "Diabetic ketoacidosis" described a 52 year-old male patient who was receiving SEROQUEL (200 mg/day) for the treatment of manic-depressive psychosis. Medical history included obesity (BMI=33.6), hypothyroidism, hyperlipidemia, and smoking (80 cigarettes/day). Concomitant medications included lithium (for which hyperglycemia has been reported), levomepromazine, carbamazepine, biperiden, flunitrazepam, nitrazepam; levothyroxine; and simvastatin. The patient had no family history of diabetes. After one week on SEROQUEL the patient was found in a dreamy state, and was taken to a nearby hospital. Blood and urine tests conducted at the hospital on the same day revealed blood sugar 968 mg/dL (baseline before SEROQUEL=109 mg/dL) and urinary ketone body 3+. Blood gas analysis showed pH7.248, partial pressure of carbon dioxide 17.6, bicarbonate 7.5 and base excess -16.54. Based on these findings, the presence of metabolic acidosis was confirmed, and the patient was referred to the reporter's hospital on the same day. The patient was subsequently treated with fluid replacement, with saline and insulin 1 unit/hour, following which his consciousness returned. At 14:00 on the same date, the patient's BG was measured again, and urine tests showed urinary ketone body 4+. Saline loading and continuous drip infusion were conducted and the patient received an intravenous injection of insulin. The total administration of insulin on the day amounted to 42 units. The patient did not experience any polyuria, polydipsia, polyphagia, fatigue, weakness, blurred vision or weight loss. The following morning blood tests showed BG of 352 mg/dL, and therapy with SEROQUEL was discontinued in response to the event. Saline loading and intravenous injection of 27 units of insulin were provided on the same day. The patient also received 10 units of an unspecified drug, plus 4 units of unspecified drug via subcutaneous injection on the same date. The next day the continuous drip infusion of insulin was discontinued and changed to sliding scale therapy. One week after the onset of events the event was ongoing (BG=219 mg/dl in the morning). Two days later the patient commenced therapy with pioglitazone and about one month later started metformin. Two days later insulin therapy was discontinued and the patient's blood sugar level gradually decreased (no laboratory values provided). One and one-half months after being hospitalized (40 days after SEROQUEL discontinued) the event was considered to have resolved, and the patient was discharged from hospital

2005AP04083: This serious report of "Diabetic ketoacidosis", "Weight decreased", and "Polyuria" described a 28-year-old male patient who was receiving SEROQUEL (400 mg/day; one year three weeks) for the treatment of an unspecified condition. Medical history was not provided. Concomitant medications included olanzapine (for which DKA has been reported). After about one year on SEROQUEL and olanzapine the patient was hospitalized with DKA following a three-week history of weight loss (10 kg) and polyuria. SEROQUEL and olanzapine were discontinued and aripiprazole was started. The patient was treated with fluid and electrolyte replacement and insulin. The patient recovered after an unknown amount of time. No laboratory data was provided. No other information was available.

2005AP03905: This serious report of "Diabetic ketoacidosis" and "Diabetes mellitus" described a 29 year-old female patient who was receiving SEROQUEL (200 mg/day) for the treatment of schizophrenia. Medical history included hepatic steatosis, hyperlipidemia, candida albicans vaginitis, vulvitis, a fracture of the femur, smoking, obesity (BMI 31.6), and

risk factors also included obese parents with DM. Concomitant medications included risperidone, carbamazepine, milnacipran, biperiden, flunitrazepam, zopiclone, nizatidine, and metoclopramide. The patient's baseline FBS and HbA_{1c} one month before starting SEROQUEL were 87mg/dL and 5.7% After two weeks of therapy with SEROQUEL the patient commenced therapy with risperidone. Three weeks later therapy with carbamazepine was started. About 8 ½ months later the patient developed symptoms including nausea, thirst and polyuria. One month later she developed repeated vomiting. About two weeks later the patient was referred from the psychiatric to an internal medicine doctor. Three days later endoscopic examination by gastrocamera revealed findings suggestive of gastritis and four days later an echo showed findings of hepatic steatosis. Another four days later the patient visited the emergency department for palpitation and nausea and received and unspecified drip infusion. The next day (after one year of SEROQUEL) blood tests revealed DM (BG=436 mg/dL, HbA_{1c}=12.9%) and hyponatraemia (sodium=128 mEq/L). Arterial blood gas showed acidosis (pH=7.23). Additional lab tests on the same day revealed hypokalemia (K^+=2.8). Based on the test results, a diagnosis of DKA was made and the patient was hospitalized and treated with fluid replacement and insulin therapy. Clinical symptoms of polyuria, polydipsia, polyphagia, and fatigue were also reported. Treatment with SEROQUEL, risperidone, and carbamazepine were discontinued in response to the events. The following day lab tests showed pH of 7.31 and potassium of 3.0. The nausea improved which allowed the patient to take food. The next day lab tests revealed urinary ketone 4+ and potassium of 3.3. After six days in the hospital her potassium improved to 3.5, and the patient was considered to have recovered from the hypokalemia. Three days after, a urinary ketone test was negative. As of the same day, the patient recovered from the DKA and hyponatremia (sodium=141 mEq/L). Subsequently, the patient practiced self-injection of insulin during hospitalisation and the daily-injected insulin volume finally reached 62 units per day. The patient was discharged after being hospitalized for 24 days. One month later it was reported that the DM had abated.

2005AC00445: This serious report of "Hyperglycaemia", "Coma", "Ketoacidosis", "Acetonaemia", and "Shock" described a 46-year-old female who was receiving SEROQUEL (300 mg/day; duration unknown) for the treatment of an unspecified condition. Medical history was not provided. Concomitant medications included estrogens. After an unknown amount of time on SEROQUEL the patient experienced coma/shock, acetonemia, hyperglycemia (BG=58.1 mmol/L), and ketoacidosis. The patient's outcome and status of therapy with SEROQUEL was unknown. No other information was provided.

2006AC00319: This serious literature report of "Diabetic ketoacidosis" described a 51-year-old female patient who was receiving SEROQUEL (400 mg/day) for the treatment of chronic schizophrenia. Medical history included obesity (BMI=31), hypothyroidism, hyperlipidemia, and hypertension but no history of DM, IFG, or IGT. There was no family history of DM. Concomitant medications included levothyroxine, lithium (for which hyperglycemia has been reported), simvastatin, acetylsalicylic acid, and atenolol. After about two years on SEROQUEL, over a period of a few days, the patient became confused and then comatose. Blood glucose was found to be 53 mmol/l, HbA_{1c} was 7.2%, and she was ketoacidotic (pH 7.1; urine ketones +++). There was no evidence of infection. She initially required management in an intensive care unit where she was paralyzed and ventilated. Her insulin

requirements were very high (15-20 units/hour intravenously). There was no clear evidence of anti-islet cell antibodies during the acute stage of illness. Antiglutamic acid decarboxylase titres were normal on two occasions. It was decided to discontinue SEROQUEL. The patient spent three months in hospital. Even after she became euglycemic, her urine output remained above 3L/day, and was of very low specific gravity. Accordingly, she was given an additional diagnosis of diabetes insipidus, thought to be due to treatment with lithium. After transfer to a psychiatric ward, symptoms of psychotic relapse were apparent and she was also noted to be disorientated. Both the psychosis and confusion improved over approximately three months. Six months after the onset of DM the patient was being treated with diet alone. The patient however did not follow the recommended diet or engage in any form of exercise and subsequently gained 4 kg. Despite this, FBS were mainly <7 mmol/l and haHbA$_{1c}$ values were between 5.1% and 5.5%.

Non-medically confirmed

2006UW02754: This serious report of "Diabetic ketoacidosis" described a 32-year-old male patient who was receiving SEROQUEL (dose/duration unknown) for the treatment of an unspecified condition. Medical history and concomitant medications were not provided. After an unspecified amount of time on SEROQUEL the patient experienced elevated blood sugar levels and possible DKA (no lab values provided). The patient was hospitalized and at the time of the report had not yet recovered. It is unknown if the patient continued therapy with SEROQUEL. No other information was available.

Legal reports(medically confirmed)

2004UW01147: This serious report of "Diabetes mellitus insulin-dependent", "Diabetic ketoacidosis", "Dermatitis contact", Urinary tract infection", Hyperglycemia", "Pharyngitis", "Bronchitis acute", "Sinusitis", "Weight increased", "Infectious mononucleosis", "Dehydration", "Vomiting", "Ketonuria", "Influenza like illness", "Hypokalemia", "Vaginitis bacterial" and "Self injurious behaviour" described a 14-year-old female patient who was receiving SEROQUEL (25-75mg/day; 20 months) for the treatment of depression and mood swings secondary to post traumatic stress disorder. Medical history included pneumonia, decreased energy, hyperglycemia, family history of DM, emotional/physical abuse, mood swings, post traumatic stress disorder, panic disorder, adjustment disorder, conversion disorder, attention-deficit hyperactive disorder, stomach spasms, asthma, impulse control, depression. Concomitant medication included citalopram and mirtazapine (for which DM has been reported). Five months after commencing therapy with SEROQUEL the patient experienced blood sugars in the 240 range, sleepiness and thirst. Approximately 7 months later the patient presented to the ER with polydipsia and polyuria for four days. Her blood glucose was 601 (no units), sodium was 132 and she was negative for serum ketones. The patient was diagnosed with new onset DM and experienced slight weight gain (from 51.2 to 51.7 kg). She was treated with intravenous half normal saline with potassium and started on isophane insulin, insulin/lispro and a controlled diet. The patient received SEROQUEL while in the hospital. Treatment with SEROQUEL was discontinued on an unknown date. After that the patient presented to the ER 10 more times. She was diagnosed with hyperglycemia her 3rd trip to the ER. One month after the discontinuation of SEROQUEL, the patient presented to

the ER (9th time) and was diagnosed with DKA. The patient's blood sugar was 431 (no units) along with glucose and ketones spilling in her urine. The patient's acidosis resolved.

DKA: Patients with a history of DM

Medically confirmed

2006UW08816: This serious report of "Diabetic ketoacidosis" and "Blood glucose increased" described a patient (age/gender unknown) who received SEROQUEL (dose/duration unknown) for the treatment of an unspecified condition. Medical history included DKA and a family history of DM. Concomitant medications included risperidone. After no more than nine months on SEROQUEL (dates not provided) the patient began experienced an elevated glucose of 180 mg/dL (fasting status unspecified). Therapy with SERQOUEL continued for another 16 months and then was discontinued for an unspecified reason. At the time of the report, the patient had not recovered. No other information was available.

2005SE00781: This serious report of "Diabetic ketoacidosis" described a 46-year-old female patient who was receiving SEROQUEL (300 mg/day; about 6 months) for the treatment of an unspecified condition. Medical history included DM, depression, and hypertension. Concomitant medications included risperidone, nirtazapine, metformin, insulin, atenolol, and trimetazidine. The patient started therapy with both SEROQUEL and risperidone around the same time. After about six months of therapy with both medications the patient developed DKA and all of the patient's medications (including SEROQUEL) were discontinued. The patient recovered the next day. Information regarding the patient's level of diabetic control was not provided. No other information was available.

2005AP00945: This serious report of "Diabetes mellitus", "Diabetic ketoacidosis", and "Insulin resistance" described a 48-year-old male patient who was receiving SEROQUEL (600 mg/day; duration unknown) for the treatment of an unspecified condition. Medical history included well-controlled Type II DM. Concomitant medications included metformin, glimepiride, glibenclamide, enalapril, gemfibrozil, venlafaxine, and diltiazem. After an unknown amount of time on SEROQUEL the patient experienced insulin resistance, which resulted in an aggravation of DM and DKA. The patient was treated with insulin. The patient's BG=77 (no units provided) and HbA_{1c}=14.5% (no baseline BG or HbA_{1c} values provided). The patient recovered from the events three weeks later. It was unknown if SEROQUEL or any other medications were discontinued. No other information was provided.

2004AP06389: This serious report of "Diabetic ketoacidosis" described a 36-year-old female patient who was receiving SEROQUEL (600 mg/day; 3 ½ years) for the treatment of schizophrenia. Medical history included hyperlipidemia, hypertension, obesity (BMI=39 kg/m^2), fatty liver, and hypothyroidism. Concomitant medications included lithium (for which hyperglycemia has been reported), carbamazepine, promethazine, levomepromazine, flurazepam, zopiclone, diazepam, amlodipine, atorvastatin, and fenofibrate. After three and one-half years on SEROQUEL the patient had anorexia, malaise, and lay down drinking juice throughout the day. One week later she experienced breathing difficulty and aggravated

dysphoria. The patient's fasting blood sugar (FBS) was 282 mg/dL (FBS one month after start of SEROQUEL=83 mg/dL) and her glycosylated hemoglobin (HbA_{1c}) was 11%. The patient was admitted to the hospital with DKA and newly diagnosed DM. The patient reportedly also experienced polydipsia and fatigue on an unspecified date. Six days later all of the patient's medications, including SEROQUEL, were discontinued. The patient was reported to have recovered about seven weeks after the onset of symptoms. No other information was provided.

2003AP00312: This serious report of "Diabetic ketoacidosis" and "Hyperglycemia" described a 32-year-old female patient who was receiving SEROQUEL (100 mg/day) for the treatment of panic disorder, dissociated disturbance, dysthymia, and post-traumatic stress disorder. Medical history included DM (Type II, diet controlled). Height and weight were 163.9 cm and 123 kg, respectively (BMI = 45.7 kg/m^2). The patient has weighed over 80kg since high school. No concomitant medications were taken during SEROQUEL treatment. Initially, the patient had taken olanzapine for three months and then discontinued it due to a 'Dear Doctor' letter regarding DM. Subsequently, treatment with SEROQUEL (100 mg/day) was initiated (no other antipsychotics were used at this time). Three months prior to starting SEROQUEL the patient's HbA_{1c} was 5.3%. Eight days after starting SEROQUEL the FBS and HbA_{1c} were 134 mg/dL and 6.4%, respectively. Six and one-half months after starting SEROQUEL the HbA_{1c} was 7.7% and SEROQUEL was discontinued due to a 'Dear doctor' letter issued regarding SEROQUEL and hyperglycemia. Chlorpromazine (for which hyperglycemia has been reported) was then started and after two months of chlorpromazine the patient experienced dry mouth and general malaise. Two days later the patient went to the emergency department for an acute aggravation of DM. The patient reported polydipsia and polyuria for the prior two weeks. Infection was ruled out due a CRP (C-reactive protein) of 0.26 (normal range <0.3 mg/dL. The patient's HbA_{1c} was 12.4% at this time and FBS was 487 mg/dL. The patient's BS gradually decreased with insulin treatment and her FBS was reported to be less than 100 mg/dL.

2002AP02329: This serious report of "Diabetic ketoacidosis" described a 21-year-old female who was receiving SEROQUEL (600 mg/day) for the treatment of schizophrenia. Medical history included insulin dependent DM (IDDM) since age five. Concomitant medications included trihexyphenidyl, carbamazepine, haloperidol, clonazepam, flunitrazepam, zotepine, levomepromazine, and human insulin. The patient stopped oral medications and insulin, as her psychiatric symptoms were aggravated and vomiting occurred. Three days later (about eight weeks after starting SEROQUEL) the patient was hospitalized with vomiting, "deterioration of consciousness", BS level of 745 mg/dL, WBC of 29,2000/mm3, CRP of 1.28 mg/dL, and moderate dehydration. DKA was diagnosed. Treatment included drip infusion of normal saline, electrolytes with glucose drip infusion, and insulin infusion. BS, blood gases and mental status all improved. The next day the BS was 276 mg/dL. The following day oral drugs (risperidone, biperiden, carbamazepine, flunitrazepam, and levomepromazine) were started. The day after that, auditory hallucinations and delusion "continued" BS was stable with a mean BS of 200-300 mg/dL; urine ketones and sugar were both negative. Two days later the BS again improved with a mean of 100-200 mg/dL. Auditory hallucinations and

delusions still continued but insomnia did not occur. On the seventh day of admission the event had improved.

2002AP01163: This serious report of "Diabetic ketoacidosis" and "Diabetic coma" described a 36-year-old male patient receiving SEROQUEL (75 mg/day) for the treatment of schizophrenic psychosis. Medical history included Type II DM and drinking excessive amounts of soft drinks and coffee. The patient had been drinking large volumes of soft drink and his blood glucose level and in June 2000 HbA_{1c} were 776 and 10.7 %, respectively. Treatment included a drip infusion with added insulin and eventually oral pioglitazone. After six months of pioglitazone therapy, the blood glucose level was 109 (2 hour value, no units) and HbA_{1c} was 5.3%. On 18 July 2001, the blood glucose was increased to 331 (4 hour value, no units) due to drinking excessive amounts of coffee and the HbA_{1c} was 13.9%. On 28 January 2002, the patient reported that he stopped taking pioglitazone but the blood glucose was 117 (4 hour value, no units); HbA_{1c} was 4.9% and body weight was 59 kg. On 15 April 2002, blood glucose was 420 (2 hour value, no units) and HbA_{1c} was 8.2%. The patient was being treated with clocapramine and on 15 May 2001, SEROQUEL (25 mg/day) was added. The dosage of SEROQUEL was increased and decreased over the next few months until it was discontinued on 07 September 2001 when it was switched to clocapramine. On 18 April 2002, clocapramine (75 mg/day) was switched to SEROQUEL (75 mg/day). Two days later the patient's mental status was unchanged and he had no physical complaints. On 25 April 2002, his mental status was still unchanged, though he felt terribly unwell. On REDACT 2002, the patient was admitted to the hospital in a deep coma. Blood pressure was 60/36 mmHg, pulse was 120 bpm, and blood glucose was 1570 (no units). Renal failure developed secondary to severe dehydration and right heart collapse or shock. Treatment included continuous large volume infusion with a drip infusion of insulin and noradrenaline; which resulted in systolic BP of 90-100 mmHg. Immediately after, a fever (~ 40 ^{O}C) was recorded and antibiotic therapy of ampicillin, sulbactam, and clindamycin started. FOY (gabexate mesylate) was started for disseminated intravascular coagulation (DIC) and L-Aspartate potassium was given for hypokalemia. "The condition was almost hyperglycemic hyperosmolar nonketotic coma (NKHHC)." On hospital day two, his respirations were weak. Blood gas analysis revealed carbon dioxide narcosis. The urinary ketone body test was negative with a pH of 5, and the microbial tests showed the urinary was negative, however, the sputum test result revealed suspected beta-lactamase negative ampicillin resistant (BLNAR), haemophilus influenza (1+), streptococcus a-haemolyticus (1+), and candida albicans (1+). The patient was intubated and put on a respirator. The fever continued. Antibiotics were changed to imipenem and cilastatin. Abdominal CT scan and echography were carried out to detect the cause of the fever, but infection could not be detected. Blood analysis also excluded the possibility of infection. CNS disorder was suspected due to anisocoria and weak/absent spontaneous respiration. Brain stem lesion was suspected, since brain edema, hemorrhage, and major infarction were not recognized on brain CT. Concerning the fever, hypermyoglobinemia was recognized on blood gas analysis data, and it was considered necessary to rule out NMS since he was taking SEROQUEL, though muscle findings were few. Dantrolene was given with injection for diagnostic treatment. Acute renal failure occurred due to the hypermyoglobinemia, but dialysis could not be started because the BP was decreased (around 60-70 mmHg) and gastrointestinal (GI) bleeding occurred due to

DIC. Catecholamine resistant hypotension (shock) occurred and the patient subsequently died. The cause of death was DKA. The physician commented that the patient had not been compliant with his diet. NMS was suspected to have caused the hypermyoglobinemia but there were few clinical or physical findings. Rhabdomyolysis may have occurred after peripheral circulatory failure, dehydration severe enough to cause shock in the condition of ketoacidosis, and central fever. No further information was provided.

2001UW16478: This serious report of "Diabetic ketoacidosis" described a 32-year-old male patient who was receiving SEROQUEL (800 mg/day x 2 weeks) for the treatment of schizophrenia and mental retardation. Medical history included borderline DM (diet controlled). Concomitant medications included risperidone, mesoridazine, valproate, and lorazepam. The patient experienced DKA. Three days prior to the incident the patient complained of upper respiratory symptoms and dizziness. On the day of the event the patient had an episode of urinary incontinence, confusion, and an abnormal heart rate. The blood glucose on chemstrip was abnormal (no value given). The peak glucose level was 700 mg (no other unit). It was not reported whether SEROQUEL was continued. The patient remained hospitalized at the time of the report. Additional information has been requested.

2001UW05726: This serious report of "Diabetic ketoacidosis" described a 43-year-old male patient who was receiving SEROQUEL (dose unknown) for the treatment of atypical psychosis. After REDACTE of SEROQUEL therapy the patient died from possible DKA. Medical history included obesity, DM, Tourette's syndrome, borderline personality, and mild manic-depressive disorder. Concomitant medications included Haldol (haloperidol; for which a drug interaction with lithium resulting in a hyperglycemic reaction has been reported), lithium (for which hyperglycemia has been reported), pimozide (for which a drug interaction with lithium resulting in a hyperglycemic reaction has been reported), tetrabenazine, clonidine (for which hyperglycemia in NIDDM and IDDM has been reported), carbamazepine, clomipramine, lorazepam, clonazepam, propranolol, goserelin, chlorpromazine (for which DM and hyperglycemia has been reported), and chloral hydrate. It was also noted that the patient had been on risperidone at the same time that SEROQUEL was started; Risperdal was discontinued three to four months prior to the patient's death. The reporter also stated that the patient's lab values, in reference to DM, changed drastically (not indicated if they improved or worsened) once the patient started SEROQUEL (no values given). Additional information was requested.

2000AP04688: This serious report of "Diabetic ketoacidosis" described a 24-year-old male patient who was receiving SEROQUEL (300 mg/day) for the treatment of schizophrenia. Medical history included insulin dependent DM, depression, and learning difficulties. Concomitant medications included paroxetine. It was reported that the patient took five "ecstasy" tablets and then consumed an unknown amount of alcohol on a Saturday evening. The patient was admitted to the hospital the next day with nausea, vomiting, hypokalemia, and metabolic acidosis, and was treated for DKA. Following worsening renal function, increasing aggression, and possible aspiration pneumonia, the patient was intubated and transferred to the intensive care unit. Ten days after admission, the patient developed acute renal failure with increased creatinine levels, reaching a maximum of 327 µmol/L (normal range = 55 -150

µmol/L). Treatment included hemodiafiltration, and alfentanil, midazolam, propofol, haloperidol, epoprostenol, and metronidazole. Vancomycin and ciprofloxacin were initiated after methicillin-resistant Staphylococcus aureus (MRSA) and coliform were identified. The acute renal failure resolved after two weeks and two days but the metabolic acidosis and hypokalemia were resolving slowly at the time of this report. The patient was unable to take SEROQUEL and paroxetine after taking the "ecstasy" due to the initial symptoms of nausea and vomiting. There was a possibility that the patient took an overdose of SEROQUEL but this was not confirmed. Follow-up information revealed that the patient was regularly prescribed SEROQUEL and paroxetine but his compliance was questionable.

2000AP03612: This serious literature report of "Diabetic ketoacidosis" described a 64-year-old male patient with schizophrenia, who was switched from risperidone to SEROQUEL monotherapy (50 mg/day) 12 days after admission to the hospital (reason unknown). Medical history included chronic obstructive airways disease, prostate cancer, and DM. Concomitant medications included propranolol. FBS on an unknown date was 120 mg/dL. SEROQUEL was then increased to 100 mg in the morning and 300 mg at night. Two months later the patient was found unresponsive after breakfast and was transferred to a tertiary care center with a diagnosis of acute DKA. The patient was then lost to follow-up. The authors commented that the basal rate of DM in the Cincinnati area and among psychotic persons is higher than the national median.

19981UW49554: This serious report of "Diabetic ketoacidosis" described a 58-year-old male patient who was receiving SEROQUEL (800 mg/day; duration unknown) for the treatment of schizoaffective disorder. Medical history included DM and CVA. Concomitant medications included gabapentin (for which BS fluctuation in diabetic patients has been reported). The patient experienced a TIA and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The REDACTED, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary CVA.

2005UW13179: This serious report of "Diabetic ketoacidosis" described 14-year-old female patient who was receiving SEROQUEL (300 mg/day) for the treatment of bipolar disorder I (mixed) without psychotic features. Medical history included fragile Type 1 DM. Concomitant medications included oxcarbazepine. After two weeks of therapy with SEROQUEL the patient experienced DKA. No other information was provided.

Diabetic coma: No known history of DM

Medically confirmed

2004UW09577: This serious report of "Diabetic coma" "Diabetes mellitus", "Hypertension", "Anxiety", "Psychiatric symptom", "Insomnia", "Painful respiration", and "Speech disorder" described a 64-year-old female patient who was receiving SEROQUEL (300 mg/day; ≤6 months) for the treatment of post-traumatic stress disorder with psychotic features, tactile hallucinations, and sleep disorder. Medical history included insomnia, speech disorder, anxiety, and weight of 229 pounds (height not provided). The patient reportedly had no family history of DM. Concomitant medications included escitalopram, amlodipine,

valsartan, citalopram, zolpidem, unspecified hypertension medications, and unspecified inhalers (including steroids). After ≤6 months on SEROQUEL the patient developed DM and was subsequently hospitalized for diabetic coma with a BG of 700 (units not provided). Two to three months later the patient's dose of SEROQUEL was increased to 800 mg/day, however she continued to have insomnia and pain with deep breathing. Other adverse events reported (dates unknown) included hypertension, lack of confidence, "wasn't calm enough", and "felt as if she was going to jump out of her skin". Therapy with SEROQUEL was discontinued. The patient's outcome was unknown. No baseline glucose values or any other information was provided.

1999UW00969: This serious report of "Diabetes mellitus" and "Diabetic hyperosmolar coma" described a 28-year-old male patient who was receiving SEROQUEL (dose and duration unknown) for the treatment of schizophrenia. Medical history included bipolar disease, hallucinations, and asthma. Concomitant medications included albuterol (for which hyperglycemia and DKA have been reported), lithium (for which hyperglycemia has been reported), and omeprazole. The patient presented to the emergency room with a temperature of 107°F, cardiac arrhythmias, focal twitching, increased tone, pupils were non-reactive, no reaction to noxious stimuli, bleeding from eyes and nose, liver enzymes twice normal (no values given), blood glucose 2240 (no units), low potassium (no values), CPK normal, and Lithium level was not elevated. There was no report of increase or decrease of body temperature before presentation. The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. Lorazepam, dantrolene, and anti-arrhythmics (unspecified) were started. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from onset. He died on hospital REDAC. A tentative diagnosis of NMS was made with complete autopsy reports pending.

Follow-up information was received from the county coroner in the form of an autopsy final report and indicated the cause of death was complications of DM. The final findings were: 1) findings consistent with DM, 2) hepatomegaly with severe fatty metamorphosis, and 3) severe pulmonary congestion and hemorrhage. Comment from autopsy report: "This 28-year-old male died from multiple complications of a severe metabolic disorder of diabetic origin. He developed nonketotic hyperosmolar status which was followed by acidosis, hyperkalemia, hyperthermia, disseminated intravascular coagulation and cardiovascular instability." The autopsy report contained a clinical history as follows. "This patient was admitted to the hospital on the evening of REDACT 1999. He stayed in the hospital less than 12 hours and died on REDACT 1999. He was brought to the emergency room by ambulance, stuporous and with respiratory difficulty. He had a clinical history of mental disorder considered to be schizophrenia due to auditory hallucinations. His treatment included valproate and lithium, but the valproate had been changed for SEROQUEL. He also had a history of asthma for which he used an albuterol inhaler. One week before the event the patient had flu-like symptoms and was seen by his primary doctor who prescribed azithromycin. However, he continued feeling poor, with progressive weakness until he collapsed in the bathroom. There was also a history of polydipsia, polyuria, and anorexia (10-15 lb. weight loss) for the three

weeks prior to the event. On the day of admission the patient became confused. Upon admission the patient was febrile, dehydrated, and had labored respirations without evidence of bronchial obstruction. He developed hypoxemia and required intubation. Intravenous fluids were given, chest x-ray was unremarkable, and drug screen showed only acetaminophen. Laboratory evaluation revealed severe acidosis with a pH of 7.19, potassium of 3.3, sodium of 114 (no units given), and a blood glucose of 2,200 mg/dL. Insulin treatment was started with the presumption of DKA, however ketones were not significantly elevated. The serum osmolality was 377 (no units). Body temperature increased as high as 109 °F and he required physical means for cooling. The possibility of NMS was entertained and dantrolene was started. Potassium determination indicated hypokalemia of less than 2 mEq/l and he received potassium chloride. Further complications occurred, with widening of the QRS complex on the EKG and apparent disseminated intravascular coagulation, evidenced by multiple sources of bleeding (unspecified). He was transfused with eight units of packed cells. Amiodarone was given for his wide complex tachycardia, but he continued worsening and arrested with ventricular fibrillation. He was defibrillated and converted temporarily. After several shocks, a pacemaker was installed due to profound bradycardia. After he arrested again and required defibrillation, it was requested that no further shocks were given. The patient was pronounced dead at [redacted]. The most important clinical diagnoses were: 1) new onset DM with nonketotic hyperosmolar coma, 2) malignant neuroleptic syndrome with hyperthermia, 3) metabolic acidosis and severe hypokalemia, 4) disseminated intravascular coagulation, 5) respiratory failure, 6) wide complex tachyarrhythmia." Additional information from the autopsy report included the following. The patient's height and weight were reported as 69 inches and 200 pounds, respectively. Autopsy showed the lungs to be heavy and markedly congested with generalized acute pulmonary congestion and areas of alveolar hemorrhage; liver to be bulky and markedly enlarged with the hepatic parenchyma showing fatty metamorphosis of microvesicular type involving approximately 90% of the hepatocytes and acute congestion with increased number of red cells in the sinusoid; spleen to be somewhat enlarged; and heart to have focal interstitial hemorrhage in sections from the right ventricle.

2002UW05916: This serious report of "Diabetic hyperosmolar coma" and "Diabetes mellitus" described a 12-year-old female patient who was receiving SEROQUEL while in a residential facility for nine months for the treatment of behavior problems and aggression. Medical history included mild mental retardation, seizure disorder, exceptionally tall and obese, and medical non-compliance (medical neglect). Concomitant medications included citalopram, desmopressin, oxybutynin, and albuterol (for which hyperglycemia and DKA have been reported). One month prior to discharge, the dose of SEROQUEL was increased from 400 to 600 mg/day. Six days after discharge, the patient was hospitalized after experiencing a two-day history of mental status changes, polyuria, polydipsia, increased blood pressure, nausea, vomiting, abdominal pain, and sore throat. Blood glucose level was 1779 mg/dL. Abnormal lab tests included WBC = 18.3K, creatinine = 3.2 mg/dL, and BUN = 54 mg/dL. Plasma was negative for ketones. The patient was treated with potassium phosphate, cefotaxime, midazolam for agitation, and acetaminophen. Despite the treatment, less than 12 hours later the patient became unconscious and died with a body temperature of 111°F. Cause of death was nonketotic hyperosmolar coma secondary to newly diagnosed DM. The patient

also had an "unspecified" infectious process, which was felt to have precipitated the nonketotic hyperosmolar coma. An autopsy showed no evidence of infection, or any specific abnormalities other than the patient's height and weight.

2002GB02176: This serious report of "Diabetic coma" and "Diabetes mellitus insulin-dependent" described a female patient in her fifties who had been receiving SEROQUEL (no more than 400 mg/day) for an unknown indication. Medical history was not provided. Concomitant medications included lithium (for which hyperglycemia has been reported). The patient developed Type I DM and was admitted to the intensive care unit in a diabetic coma. The patient had received a combination of lithium and SEROQUEL for two years with no ill effect. During hospitalization, the patient was found to be hypernatremic, for which the reporter suspected lithium. The patient was reported to have no history or family history of DM. At the time of this report the patient's condition was improving. No treatment measures, other medical history, or concomitant medications were provided. Additional information was requested. Follow-up information indicated that the event of diabetic coma was the initial presentation for DM and that the patient had no known infection that might have precipitated the coma.

2003AP01289: This serious report of "Diabetic hyperosmolar coma" described a male patient in his 70s who was receiving SEROQUEL for the treatment of delirium. Medical history included rectal carcinoma, alcoholic liver disease, chronic pancreatitis, and schizophrenia. Concomitant medications included distigmine, loperamide (for which hyperglycemia has been reported), streptococcus faecalis/bacillus subtilis/lactobacillus, clostridium butyricum, and polycarbophil. This patient had been diagnosed with rectal carcinoma and underwent an unspecified operation. After the surgery, the patient experienced delirium and was given SEROQUEL (25 mg). The dosage was increased to 50 mg the next day and 75 mg the following day, but then decreased to 50 mg on the fourth day of therapy. Eight days later the BS was 120 mg/dL (unspecified if FBS). Three days later SEROQUEL was discontinued for an unspecified reason. One week later, the patient became comatose and was transferred to another hospital. The BS was 500 mg/dL and nonketotic acidosis was diagnosed. Thereafter the patient developed disseminated intravascular coagulation (DIC). On an unspecified date the patient was said to be recovering from the nonketotic acidosis but had sequelae after DIC.

2002AP04136: This report of "Diabetic hyperosmolar coma" described a 74-year-old female patient who was receiving SEROQUEL (75 mg/day) for the treatment of schizophrenia. Medical history included stage II breast cancer and concomitant diseases included mild renal function disorder, respiratory infection, and dehydration. Concomitant medications included furosemide (for which hyperglycemia and dehydration has been reported), spironolactone, haloperidol, nemonapride, trihexyphenidyl, levomepromazine, magnesium oxide, and rilmazafone. Six months after starting SEROQUEL the patient developed a loss of appetite. Two days later her consciousness level decreased and trembling was observed. Body temperature was 37.8°C, oxygen saturation was 87%, and the heart rate was 120 bpm. The patient was not responsive when her name was called. Laboratory data showed FBS 1100 mg/dL, sodium 157 mEq/L, potassium 5.1 mEq/L, chloride 114 mEq/L, urine sugar 4+, and negative urine ketone. Arterial blood gas analysis showed the following values: pH 7.37,

base excess 1.5, pO_2 45.2, blood urea nitrogen (BUN) 103.2 mg/dL, and creatinine 2.38 mg/dL. Left pneumonia was diagnosed according to chest x-ray and hyperosmolar (non-ketotic) coma was diagnosed according to laboratory data. Immediately a rapid infusion of 0.45% saline solution and antibiotic therapy were started. When an infusion of 2 liters was given, urination was observed. The BS was still 735 mg/dL and insulin 4 units/hour was started. All medications including SEROQUEL were discontinued. The next day, BS was 82-280 mg/dL and the following values were noted: BUN 89.8 mg/dL, creatinine 1.67 mg/dL, sodium 157 mEq/L, potassium 4.7 mEq/L, and chloride 121 mEq/L. The patient was responsive to calling, and the infusion was continuing. Insulin was discontinued. The following day she could talk clearly, her temperature was 36.7°C, heart rate was 60 bpm, fasting blood sugar was 284 mg/dL, WBC 16,200/mm^3, and CRP 20.9. SEROQUEL was not restarted.

2004AC00666: This serious report of "Pancreatitis", "Diabetic coma", "Bronchopneumonia", "Respiratory tract infection", and "Weight increased" described a 38-year-old male patient who was receiving SEROQUEL (1100 mg/day; 180 days) for the treatment of schizophrenia. Medical history included hypertension, hepatitis B, glaucoma, and insomnia. Concomitant medications included flurazepam, propanolol, aldactazine, latanoprost, and timolol. On Day 177 of therapy with SEROQUEL the patient developed pancreatitis and three days later fell into a ketoacidosis coma that lasted for approximately 48 hours. The patient's dose of SEROQUEL was reduced to 600 mg/day. An abdominal ultrasound revealed acute respiratory infection and bronchopneumonia. While on SEROQUEL the patient also experienced weight gain. After taking SEROQUEL for one month the patient's weight was 93 kg (body mass index [BMI]=29.4 kg/m^2 and four months later the patient's weight was 120 kg (BMI=35.7 kg/m^2). The patient remained hospitalized and recovered from the Pancreatitis 27 days after onset. The patient continued therapy with SEROQUEL. Information regarding the outcome of the events of respiratory infection and bronchopneumonia was not provided. No baseline or laboratory data was provided.

2006AP00713: This serious report of "Diabetic hyperglycaemic coma" described a 68-year-old male patient who was receiving SEROQUEL (275 mg/day) for the treatment of organic psychosis. Medical history included hypoxic encephalopathy, ileus, hyperlipidemia, smoking 20 cigarettes/day, drinking beer (350 ml/day), obesity, insulin resistance, dyslipidemia, hypertriglyceridemia and hypertension. Concomitant drugs included imidapril, levomepromazine, carbamazepine, clonazepam, and valproate. The patient's BG two months before starting SEROQUEL was 82 mg/dL. After four days of SEROQUEL therapy, the patient developed hyperglycaemia (BG=178 mg/dL). REDACTED after starting SEROQUEL, the patient developed disturbed consciousness and it was considered to be due to a hyperglycaemic coma (BG=1204mg/dL). At 13:30 on the same day, dialysis was performed however the hyperglycaemia persisted. SEROQUEL was discontinued. REDACTE after discontinuing SEROQUEL, the patient died. An autopsy was performed and confirmed that the cause of death was septic shock caused by a functional ileus. At the time of death the hyperglycaemia was ongoing and the outcome of the hyperglycemic coma was not reported. No other information was available.

Legal reports (medically confirmed)

2006UW21583: This serious report of "Diabetic coma" and "Diabetes mellitus" was received in the form of a civil complaint from an attorney on behalf of a female patient whom the attorney alleges suffered "death" as a result of taking SEROQUEL. According to the civil complaint, the patient took SEROQUEL (dates and doses not provided) and suffered "severe, permanent and disabling injuries" and "death." Follow-up information was obtained in the form of Plaintiff Fact Sheet received in connection with the litigation. The following reflects the information stated in these records, and does not contain information obtained directly from medical records: This 50 year old female patient was receiving SEROQUEL (300 mg/day) for the treatment of depression. Medical history included hyperglycemia and obesity. Concomitant medications included chlorpromazine. After an unspecified amount of time on SEROQUEL the patient experienced diabetic coma and diabetes. The patient died on RE RED -2005. The cause of death was unknown. No other information was available.

Diabetic coma: Patients with a history of DM

Medically confirmed

2002AP04514: This serious report of "Diabetic coma" described a 57-year-old female who was receiving SEROQUEL (75 mg/day) for the treatment of schizophrenia. Medical history included DM, ovarian cancer, and idiopathic thrombocytopenic purpura. Concomitant medications included levomepromazine, chlorpromazine (for which hyperglycemia, DM has been reported), trihexyphenidyl, bromisoval, amobarbital, and haloperidol. After five months of SEROQUEL therapy the patient began taking prednisolone (20 mg/day; for which hyperglycemia, DM, DKA, and hyperosmolar coma have been reported). About one month later, the patient developed hyperglycemia (417-649; no units). SEROQUEL was discontinued and the patient began diet control. Nine days later the patient developed hyperosmolar non-ketotic diabetic coma. Chlorpromazine and risperidone were discontinued and insulin was started. Prednisolone was decreased to 10 mg/day, then to 7.5 mg/day, and then discontinued. The patient recovered from the coma and the hyperglycemia resolved.

2002SE05071: This serious report of "Diabetic coma" described a 51-year-old female patient who was receiving SEROQUEL for the treatment of agitation. Concurrent conditions included Alzheimer's type dementia, DM, and non-compliance with diet control during the last three months. Concomitant medications included phenytoin (for which hyperglycemia has been reported), rivastigmine (precaution for use in diabetic patients), sertraline, acarbose, and olanzapine (for which hyperglycemia, DM, and diabetic acidosis have been reported). The patient was initially treated with olanzapine (5 mg/day) for the treatment of agitation. Four days later generalized tonic-clonic seizure occurred and olanzapine was discontinued. The patient experienced agitation again six days later, so olanzapine (5 mg/day) was restarted and a second seizure followed. The dose was increased to 10 mg/day, and phenytoin (300 mg/day) was started, as epileptic seizure was suspected. The agitation persisted. Eighteen days later, olanzapine was discontinued and SEROQUEL (25 mg/day) was initiated. Four days after the first intake of SEROQUEL the patient experienced high fever, unconsciousness, urinary incontinence, and elevated blood glucose level (700 mg/dL). Diabetic coma, urinary tract infection (UTI), and mild leukocytosis (urine) were diagnosed during the third day of the

titration period with SEROQUEL. Initial body temperature was 40°C. Treatment included infusion of crystalline insulin and then 30 % mixtard insulin 2x/day, and cyprofloxacine. (Glucose levels remained between 100 and 200 mg/dL.) The fever persisted for two days. (Conflicting information included that according to urine culture and antibiogram results, Amox and Clavulonate were started instead of cyprofloxacine.) The fever resolved. SEROQUEL was discontinued and one week after the events started the patient recovered with sequelae. It was found that the dementia was increased. "Decreased glucose absorption inhibitor" and high HbA_{1c} (11.02 %; no other date) indicated poor control of blood glucose levels in this patient prior to receiving SEROQUEL.

2003SE04513: This serious report of "Diabetic coma" described a 48-year-old female patient receiving SEROQUEL (400 mg/day x 12 days) for the treatment of schizophrenia. Medical history included DM. Concomitant medications included metformin and diamicron. Prior to the start of SEROQUEL the patient was treated with olanzapine (for which DKA and DM have been reported) but was switched to SEROQUEL due to weight gain. After 12 days of SEROQUEL the patient experienced diabetic coma; blood glucose during the event was 332 mg/dL, urine ketone bodies were ++, but there was no signs of ketoacidosis. SEROQUEL was discontinued and the patient was improving. No further information was provided.

Non-medically confirmed

2006UW13575: This serious report of "Diabetic coma", "Diabetes mellitus", and "Blood glucose fluctuation" was received from the mother of a 47-year-old male patient. The patient was in a mental health facility. The patient was being treated with SEROQUEL (dose unknown) for the treatment of schizophrenia. Medical history was not provided. Concomitant medications included haloperidol. An unspecified amount of time after taking SEROQUEL it was reported that the patient "almost died due to a diabetic coma." There was no history of diabetes in his family. SEROQUEL treatment was temporarily discontinued. The mother could not provide timelines or previous medications. The mother stated that the patient currently was being treated for diabetes and believed it was for the most part in control. A few weeks ago, the patient restarted SEROQUEL therapy. The mother stated that the patient does daily blood sugar monitoring and the other week he mentioned that his blood sugar was going up and down. No other information was available.

Legal reports (medically confirmed)

2006UW27335: This serious report of "Diabetic coma" and "Diabetes mellitus" was received in the form of a civil complaint from an attorney on behalf of a female patient whom the attorney alleges developed "injuries" as a result of taking SEROQUEL. According to the civil complaint, the patient took Seroquel (dates and dose not provided). The civil complaint alleges that the patient suffered "severe, permanent, and disabling injuries." Follow-up information was obtained in the form of a "Fact Sheet" completed by the patient, received in connection with the lawsuit. The following reflects the information that was stated in the Fact Sheet: The patient was being treated with SEROQUEL (900 mg/day) for mental health. Medical history included hallucinations, panic attacks, anemia, bowel infection, schizophrenia, bipolar disorder, depression, glycosuria, hyperglycemia, high cholesterol, high

triglycerides, and obesity. In addition, the patient had a family history of schizophrenia, bipolar disorder, alcoholism, glandular disease, diabetes, and obesity. Concomitant medications included aripiprazole, ziprasidone hydrochloride, chlorpromazine, and olanzapine. After about two years on SEROQUEL the patient claimed to have experienced diabetic coma, pancreatitis, and diabetes. Therapy with SEROQUEL was discontinued on an unspecified date and the patient's outcome was not provided. No other information was available.

Fatal reports (other than DKA/diabetic coma)

Medically confirmed

2007UW01888: This serious report of "Pneumonia" and "Diabetes mellitus" described a 64-year-old male patient who was receiving SEROQUEL (300mg/day; about 5 years) for the treatment of bipolar disorder. Medical history included DM. Concomitant medications include diazepam and hydroxyzine. After starting treatment with SEROQUEL the patient experienced a worsening of his DM. After about 2 years on SEROQUEL the patient's daily dose of SEROQUEL was decreased (reason unspecified). About four years later the patient died from complications of pneumonia. No additional information was provided.

2006UW15424: This serious report of "Accidental overdose" and "Blood glucose increased" described a 40-year-old female patient who was receiving SEROQUEL (200mg/day; duration unknown) for the treatment of borderline personality disorder. Medical history included substance abuse. Concomitant medications were not provided. After starting treatment the patient experienced an accidental overdose and died. The physician stated, "While taking SEROQUEL (about 200 mg), the first blood sugar they got for me six to twelve months after initiation of SEROQUEL was 700; SEROQUEL was tapered". The physician reported that the coroner ruled her death an accidental overdose. No other information was provided.

2005UW04550: This serious report of "Death" and "Hyperglycemia" described a female patient in her seventies who was receiving SEROQUEL (dose/duration unknown) for the treatment of an unspecified condition. Medical history was not provided. The patient was on multiple concomitant medications that were not provided. After starting treatment the patient's blood sugar levels were significantly elevated. The patient subsequently died. The cause of death was unknown. No other information was provided.

2005AP06252: This serious report of "Hyperglycemia" and "Death" described a male patient (age unknown) who was receiving SEROQUEL (100mg/day; > 12 months) for the treatment of schizophrenia. Medical history included hepatitis. Concomitant medications included risperidone, chlorpromazine (for which DM has been reported), trihexyphenidyl, naftopidil, and propiverine. After more than one year on SEROQUEL the patient started naftopidil and propiverine. The patient subsequently developed a dry mouth, which was considered to be an anticholinergic side effect. This symptom later led to PET bottle syndrome. About three months later blood tests revealed hyperglycemia. The patient was hospitalized and treated (unspecified). The patient's BG subsequently increased to 1700. Two weeks later the patient died. At the time of reporting to AstraZeneca it was unknown whether the patient was receiving Seroquel at the time of his death. No other information was available.

2005AC00653: This serious report of "Pancreatitis" and "Blood glucose increased" described a female patient (age unknown) who was receiving SEROQUEL (dose unknown; about 28-36 months) for the treatment of an unspecified condition. Medical history included DM and overweight. Concomitant medications include diazepam. After about three years on SEROQUEL the patient experienced massive pancreatitis and died. An autopsy was performed and revealed a lot of fat deposition in the stomach and an increased glucose level (values not provided). The report stated that she "probably died of massive pancreatitis". No other information was available.

2003AP01248: This serious report of "Sudden death," "Haematemesis," and "Glycosylated haemoglobin increased" described a 43-year-old female patient who was receiving SEROQUEL (37.5-75mg/day; about 6 months) for the treatment of schizophrenia. Medical history includes DM, HTN, insomnia and constipation. Concomitant medications included glibenclamide, atorvastatin, pioglitazone, acarbose, amlodipine, flunitrazepam, promethazine, nitrazepam, etizolam, levomepromazine, bromisoval, amobarbital, senna leaf, and brotizolam. The patient visited the reporter's clinic with a prescription, which had been issued at another clinic. She explained that she had had insomnia for 30 years, for which she had been treated with several drugs. She had no symptoms other than insomnia but seemed to have chronic mild schizophrenia from the prescription, her speech and general impression. At first she requested her drugs to be decreased in dose but later she asked for them to be increased. About one and one-half months later she visited the clinic again saying that she had lost her prescribed drugs. At this time, Seroquel 75 mg daily was added to her drug regime, after which she reported to be able to obtain a deep sleep. About 4 months later she attended the clinic where no abnormal findings were noted and she was given a repeat prescription of the previous drugs. Six days later it was reported that the patient had died after vomiting blood. Cause of death and whether an autopsy had been performed was unknown. The reporting physician commented that the patient's HbA_{1c} had increased after administration of SEROQUEL (7.4% after 1 ½ months on SEROQUEL, 9.8% AFTER 2 ½ months on SEROQUEL, 10.7% after 4 months on SEROQUEL) but the patient had sometimes not attended her clinic appointments and her diet control was poor. No other information was available.

2002GB00282: This serious report of "Diabetes mellitus" and "Death" described a 19-year-old male who was receiving SEROQUEL (dose/duration unknown) for the treatment of schizophrenic illness. Medical history included obesity, psychiatric disorder, and cocaine abuse. Concomitant medications included risperidone. The patient commenced treatment with SEROQUEL and four months later was admitted to hospital with hyperglycaemic keto-acidotic pre-coma. He was transferred to intensive care and diagnosed with type I DM. The possibility that the patient was suffering from type II diabetes due to, or at least precipitated by, SEROQUEL was entertained but not actively pursued. During his stay in intensive care, a very high creatine kinase level was revealed but no cause was established. Diabetes was controlled with insulin and the patient was discharged. Seroquel treatment was eventually discontinued and replaced by other anti-psychotic drugs but the diabetes remained unresolved. Four months later, the patient died unexpectedly of an unknown cause. The night before his death he was noted to be very restless and slept badly. On questioning that evening, the

patient stated that he took cocaine. In the morning he had his BG level measured, which was normal, and received his injection of insulin. Later that morning, he retired to bed, was noted to be snoring at about midday and did not appear for lunch. That afternoon he was observed to be no longer snoring and had no pulse. Attempts to resuscitate the patient were unsuccessful and he was pronounced dead. An autopsy failed to identify the cause of death and an open verdict was returned at the inquest. Post-mortem blood analysis detected the presence of carbamazepine although this was a drug neither prescribed nor taken illicitly. No further information is expected.