CLINICAL REVIEW

CHANGES IN WEIGHT, LIPIDS, AND GLUCOSE WITH QUETIAPINE

Application Type	NDA 20-639 and NDA 22-047
Submission Number	000
Drugs	SEROQUEL (Quetiapine fumarate) SEROQUEL XR (Quetiapine Extended Release)
Submission Date	June 26, 2008
Name of Reviewer	Kavneet Kohli-Chhabra, M.D. Medical Officer Cara L. Alfaro, Pharm.D. Clinical Analyst
Review Completion Date	March 26, 2009
Therapeutic Class	Atypical Antipsychotic
Subject	Metabolic Parameters (Hyperglycemia, Hyperlipidemia, and Weight Gain)
Sponsor	AstraZeneca
Formulation	Oral
Dosing Regimen	Multiple (50 - 800 mg)
Indications	Multiple

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1 Executive Summary Section

1.1 Recommendation on Regulatory Action

In response to a request from the Division of Psychiatry Products, the Sponsor submitted data for the effect of quetiapine on several metabolic parameters for adult and pediatric/adolescent subjects in their clinical trials database. The adult data is contained in this review and the pediatric/adolescent review is in progress. Recommendations on regulatory action will be made when all reviews have been completed. Though the Sponsor has submitted a Changes Being Effected labeling supplement that has incorporated some of the pediatric/adolescent metabolic data, it is likely that further changes to product labeling will be recommended based on these reviews. These metabolic data from adults will be presented at the Psychopharmacological Drugs Advisory Committee meeting scheduled for April 8, 2009.

1.2 Recommendation on Postmarketing Actions

No recommendations at this time.

1.3 Summary of Clinical Findings

Weight

Placebo-Controlled Trials

In the clinical trials database, quetiapine was associated with significant weight gain. In the placebo-controlled trials, subjects receiving quetiapine (modal dose = 347 mg, median exposure 43 days) gained 1.2 (SD 3.5) kg compared to 0.2 (SD 3.3) kg in the placebo group.

An analysis of the fixed-dose placebo-controlled trials showed that quetiapine 50 mg/day was not associated with weight gain that was different from placebo (0.8 kg vs. 0.2 kg), but that all other doses were associated with statistically significant weight gain though not strongly linearly related to dose over the range of 150 to 800 mg/day.

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**QTP** 400 mg	**QTP** 600 mg	**QTP** 800 mg	**Placebo**
All Trials							
N	656	1286	1915	340	1182	451	2319
Mean (SD) Change	**0.8 (2.2)**	**1.0 (2.5)**	**1.1 (2.9)**	**1.1 (2.8)**	**1.4 (4.4)**	**1.2 (5.0)**	**0.2 (3.4)**
p-value (vs. placebo)	NS	< 0.001	< 0.001	0.004	< 0.001	< 0.001	
Median Exp days	49	53	53	42	44	42	54

In general, subjects with lower baseline BMI had greater increases in weight.

	Mean (SD) Weight Change		
Baseline BMI (kg/m2)	Quetiapine	Placebo	
≤ 18.5	1.8 (2.6)	1.1 (2.6)	p = 0.021
18.5 – 25	1.4 (2.7)	0.3 (3.5)	p < 0.001
25 – 30	1.1 (3.3)	0.1 (2.5)	p < 0.001
≥ 30	0.9 (3.9)	0.1 (3.7)	p < 0.001

There was a suggestion that weight gain increased over time (i.e., 0.9 kg at week 2, 1.2 kg at week 4 and 8, 2.4 kg at week 12 in quetiapine treated group compared to 0.2 - 0.5 kg for the placebo group), however, the sample sizes in the placebo-controlled trials at 12 weeks is significantly less than sample sizes at earlier weeks.

In the categorical analyses, 58% of quetiapine-treated subjects gained 0-5 kg at week 6 compared to 48% of subjects in the placebo group. Nearly 8% of quetiapine-treated subjects gained > 5 to 10 kg at week 6 compared to 2% of subjects in the placebo group. Approximately 4% of subjects gain > 5 to 10 kg in the 50 and 150 mg dose groups compared to ~8% in the 300 and 600 mg dose groups and 12-15% in the 600 and 800 mg/day groups. Similarly, in the > 10 to 15 kg category, the proportions of subjects in the placebo, quetiapine 50-300 mg/day groups are similar (< 1%) compared to 1.8% and 2.1% in the quetiapine 600 and 800 mg/day groups respectively.

Comparator-Controlled Trials

In comparator-controlled trials, quetiapine was associated with less mean weight gain compared to olanzapine, greater weight gain compared to haloperidol and similar weight gain to risperidone and chlorpromazine.

	QTP	OLZ	QTP	RIS	QTP	CHL	QTP	HAL
N	295	286	702	695	326	330	1035	730
Mean (SD) Wt Change	3.3(6.5)	6.1(8.0)	2.2(6.1)	2.3(6.9	1.1(4.2)	1.2(6.2)	1.3(5.1)	0(4)
Mean (SD) Modal Dose (mg)	563(191)	14(5)	552 (207)	5 (2)	549 (129)	627 (225)	439 (227)	11 (6)
Median Exposure (days)	167	168	56	56	65	63	42	42
p-value	<0.001	-	0.701	-	0.699	-	<0.001	-

The comparator-controlled data also indicate that weight gain increased over time for quetiapine-treated subjects – though, sample sizes at 48 weeks are very small. Consistent across comparator trials, the weight gain for quetiapine-treated subjects at week 24 is approximately 4 kg compared to 6 kg for olanzapine-treated subjects and similar 4 kg for risperidone-treated subjects. Limited sample sizes were available for haloperidol-treated subjects > 12 weeks and the chlorpromazine comparator-controlled trial was < 12 weeks.

Comparing the categorical weight gain for 6 week and 6 month time points also indicated increases in weight over time in quetiapine-treated subjects (little data was available for the 12 month time point for these requested analyses). While a greater proportion of olanzapine treated patients gained weight at 6 months (i.e., 28% of olanzapine-treated subjects and 18% of quetiapine-treated subjects gained > 5 to 10 kg at 6 months, > 15 to 20 kg for 10.9% of olanzapine vs. 5.2% of quetiapine) a similar proportion (17%) of both olanzapine and quetiapine-treated subjects gained > 10 to 15 kg (modal dose 569 mg of quetiapine; 13 mg of olanzapine).

Glucose

Placebo-Controlled Trials

In the clinical trials database, quetiapine was associated with an increase in fasting glucose. In the placebo-controlled trials, subjects receiving quetiapine (modal dose = 331 mg, median

exposure 54 days) had a significant increase of 2.4 (18.1) mg/dL in mean fasting glucose compared to a 1.6 (13.6) mg/dL increase in the placebo group.

The mean change in fasting glucose from baseline to endpoint did not follow a linear dose-related signal. Quetiapine 50, 150, 400 mg/day and placebo had numerically similar increases in fasting glucose while the 300, 600 and 800 mg/day groups were associated with a greater increase in glucose. However, the mean increase in fasting glucose was only significantly different from the placebo group for the 600 mg/day group.

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**QTP** 400 mg	**QTP** 600 mg	**QTP** 800 mg	**Placebo**
All Trials							
n	439	832	1004	287	578	266	1489
Mean (SD) Change	**0.2 (13.6)**	**1.8 (13.6)**	**3.3 (16.4)**	**1.7 (17.2)**	**3.4 (19.9)**	**2.4 (23.4)**	**1.7 (13.8)**
p-value (vs. placebo)	NS	NS	NS (0.075)	NS (0.094)	0.02	NS	
Median Exposure (days)	56	56	56	42	56	42	56

The effects on fasting glucose variable in that the quetiapine 300 mg/day groups increased mean fasting glucose by 1.9 and 3.4 mg/dL in the GAD and MDD trials respectively - though neither of these changes in mean fasting glucose were significantly different from placebo. The quetiapine 50 mg/day group increased mean fasting glucose by 2.4 mg/dL in the MDD trials – again, this was not significantly different from placebo.

A more consistent dose-related linear increase in mean fasting glucose was noted for the 8-week time point in the by-week analysis (excluding the 400 and 800 mg/day dose groups due to small sample sizes).

		QTP 50 mg N = 656	**QTP** 150 mg N = 1286	**QTP** 300 mg N = 1915	**QTP** 400 mg N = 340	**QTP** 600 mg N = 1182	**QTP** 800 mg N = 451	**Placebo** N = 2319
Week 2	n	5	15	16	11	9	11	19
	Mean (SD) Change	**-3.2 (17.5)**	**4.1 (4.6)**	**1.6 (10.6)**	**-0.3 (15.8)**	**-0.5 (8.2)**	**7.5 (7.4)**	**2.7 (13.1)**
	p-value (vs. placebo)	NS	NS	NS	NS	NS	0.032	
Week 4	n	375	711	551	245	246	214	1090
	Mean (SD) Change	**1.1 (14.4)**	**1.9 (13.5)**	**4.6 (14.7)**	**0.2 (18.7)**	**4.7 (21.5)**	**3.5 (19.9)**	**2.0 (14.4)**
	p-value (vs. placebo)	NS	NS	NS (0.068)	NS	NS (0.090)	NS	
Week 8	n	235	498	636	2	335	0	871
	Mean (SD) Change	**-1.0 (10.9)**	**1.5 (13.0)**	**2.8 (17.3)**	**5.4 (7.6)**	**3.5 (21.1)**	**NA**	**1.6 (13.1)**
	p-value (vs. placebo)	0.023	NS	NS	NS	0.049	NA	

Shift changes in mean fasting glucose were analyzed and showed that 2.4% of quetiapine-treated subjects had a significant shift from normal baseline (< 100 mg/dL) to high (> 126 mg/dL) compared to 1.4% in the placebo group. Shifts from normal baseline to ≥ 140 mg/dL were not different between the treatment groups.

Similar proportions (~12%) of subjects in the quetiapine and placebo groups had shift changes from impaired (≥ 100 - < 126 mg/dL) to high (≥ 126 mg/dL) fasting glucose. The percentage of subjects with an increase from normal to high fasting glucose (< 100 to ≥ 126 mg/dL) was 0.5% in the 50 mg/day group with similar percentages in the 150 – 600 mg/day groups (2.6% - 3.3%, not linear) and 1% in the 800 mg/day group compared to 1.4% in the placebo group. No dose-

related signal emerged when evaluating the percentages of subjects with shifts from impaired to high fasting glucose (100-125 to ≥ 126 mg/dL).

Similar proportions of subjects in both quetiapine and placebo groups (~27%) had a > 10 mg/dL shift in fasting glucose. The dose-related analyses showed that similar percentages of subjects had shifts in fasting glucose ≥ 10 mg/dL in the placebo (26%) and quetiapine 50 – 600 mg/day groups (~24 – 28%); compared to 37% in the quetiapine 800 mg/day group.

A greater proportion of quetiapine-treated subjects had a shift in HbA1c > 6.1% compared to placebo (4.1% vs. 2.8%). A dose-related signal was evident with 4.9% and 7.7% of subjects in the 600 mg/day and 800 mg/day groups exhibiting this shift.

Glycosuria was noted in 2.3% of quetiapine-treated subjects compared to 0.2% in the placebo group. Few data were available for the 50 and 150 mg/day quetiapine groups, but it is noteworthy that 4.7% of subjects experienced glycosuria in the 800 mg/day group.

Comparator-Controlled Trials

Similar mean increases in fasting glucose were noted in the comparator-controlled trials with olanzapine and risperidone.

	QTP	**OLZ**	QTP	RIS
N	198	212	198	207
Mean (SD) Glucose Change	3.0 (14.9)	3.9 (15.3)	3.0 (14.9)	2.5 (14.2)
p-value	0.572	-	0.692	-
Modal (SD) Dose (mg)	602.5 (160.2)	14.8 (3.8)	602.5 (160.2)	4.7 (1.6)
Median Exposure (days)	168	168	168	168

The analysis for mean fasting glucose change at 2, 4, 8, 12, 24 and 48 weeks were only informative for weeks 12 and 24 due to sample size limitations.

Shift changes in mean fasting glucose were analyzed and showed that similar proportions of subjects in the quetiapine-treated, olanzapine-treated and risperidone-treated subjects had a shift from normal baseline (< 100 mg/dL) to high (> 126 mg/dL) [~2.5 – 4%]. No differences were noted between these treatment groups for shifts from impaired baseline (≥ 100 - < 126 mg/dL) to high (≥ 126 mg/dL) fasting glucose [~10-14%]; though a greater proportion of subjects with impaired baseline fasting glucose had a shift to high compared to those with a normal baseline fasting glucose.

There were no significant differences in the proportion of subjects with shifts in HbA1c to ≥ 6.1%: 2.5% and 4.7% in the quetiapine and olanzapine groups and 2.5% and 3.3% in the quetiapine and risperidone groups. Similar proportions of subjects in the quetiapine, olanzapine and risperidone treatment groups experienced glycosuria (1.7 – 2.7%). Of note, in the comparator controlled trials with haloperidol, 16% of quetiapine-treated subjects experienced glycosuria compared to 7% of haloperidol-treated subjects.

Long Term Controlled and Uncontrolled Clinical Trials

The mean change in fasting glucose from 2 to 48 weeks indicated a trend for increasing glucose over time.

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	121	2741	2360	2963	788	201
Mean (SD) Glucose Change	1.7 (11)	2.8 (18)	2.7 (17)	2.7 (17)	3.8 (21)	4.9 (17)
Mean (SD) Modal Dose (mg)	362 (231)	317 (223)	339 (216)	436 (234)	491(214	397 (203)

Little long-term data for shifts in HbA1c are available from clinical trials – likely these assessments were not included in many trials. The data presented for the long term controlled and uncontrolled trials indicate that 6% of subjects had a shift to > 6.1%; however the median exposure is only 72 days (range 55 – 137). Glycosuria occurred in 3.2% of quetiapine-treated subjects.

Lipids

Placebo-Controlled Trials

In the clinical trials database, quetiapine was associated primarily with an increase in total cholesterol and fasting triglycerides with lesser effects on LDL and HDL. The quetiapine-treated subjects (modal daily dose =349 mg, median exposure 52 days) had a 2.6 (30.8) mg/dL increase in total cholesterol compared to a decrease of 3.0 (28.2) mg/dL in placebo-treated subjects. Subjects receiving quetiapine (mean modal daily dose = 346 mg, median exposure 55 days) had a 13 (95) mg/dL increase in fasting triglycerides compared to a decrease of 5.4 (75.2) mg/dL in subjects receiving placebo.

For the mean change in total cholesterol from baseline to endpoint, all doses of quetiapine were significantly different from placebo; however, only doses $\geq$ 300 were associated with increases in total cholesterol. The increase did not follow a linear trend; the greatest increases in total cholesterol were in the 400 and 800 mg/day groups.

For the mean change in fasting triglycerides from baseline to endpoint, all quetiapine doses were associated with significant increases except for the 50 mg/day dose. Again, no clear linear trend was seen, all other doses produced fairly similar increases in fasting triglycerides.

The proportion of quetiapine-treated subjects with shifts from normal total cholesterol (< 200 mg/dL) to high (> 240 mg/dL) was 3.5% compared to 1.4% of placebo-treated subjects . The proportion of quetiapine-treated subjects with shifts from borderline (> 200 to < 240 mg/dL) to high (> 240 mg/dL) was 21% compared to 16% of placebo-treated subjects. A robust dose-related effect was not noted for the shift from normal to high total cholesterol. Across all dose groups, similar proportions of subjects experienced a shift from borderline to high (~15 – 21%) and the 800 mg/day group had the highest proportion of subjects with this shift (36.8%).

The proportion of quetiapine-treated subjects with shifts from normal fasting triglycerides (< 150 mg/dL) to high (> 200 mg/dL) was 8% compared to 4% of placebo-treated subjects. The

proportion of quetiapine-treated subjects with shifts from borderline fasting triglycerides (> 150 to < 200 mg/dL) to high (> 200 mg/dL) was 32% compared to 19% of placebo-treated subjects. A robust dose-related effect was not noted for the shift from normal to high fasting triglycerides. Similar proportions of subjects in each dose group experienced a shift from borderline to high (~30-38%) with the exception of the 50 mg/day group (19.4%).

Comparator-Controlled Trials

Quetiapine was associated with less mean increase in total cholesterol compared to olanzapine, greater mean increase compared to risperidone and similar mean increases compared to chlorpromazine and haloperidol. Reliable comparison data for fasting triglycerides is not available due to very small sample sizes for this parameter (~20/group).

Measurements in mg/dl	QTP	OLZ	QTP	RIS	QTP	CHL	QTP	HAL
N =	234	245	435	450	68	76	94	89
Mean (SD) T-C Change	**8.0 (38.0)**	**15.9 (41)**	**7 (38)**	**-2 (36)**	**29 (53)**	**20 (31)**	**2.4 (25.3)**	**-0.3 (27)**
p-value	0.029	-	<0.001	-	0.188	-	0.473	-
Mean Modal (SD) Dose (mg)	592.7 (175)	14.5 (4.1)	595(193	5	588(71	584(58	256(153	8.0 (5)
Median Exp (days)	168	168	58	57	70	70	56	56

In analyses of treatment-emergent significant changes comparing fasting baseline and post-baseline lipid measurements in the active-comparator controlled trials with haloperidol, chlorpromazine, olanzapine or risperidone, no significant differences were observed in most of these outlier categories between the active-comparator and quetiapine; except that in the risperidone controlled trials, some increases in outliers percentage regarding treatment emergent shifts in total cholesterol measures were noted for the quetiapine group with normal baseline cholesterol.

2 Introduction and Background

On 1/8/2008, FDA requested AstraZeneca for information of Seroquel (quetiapine fumarate) and Seroquel XR (quetiapine fumarate) Extended-Release tablets with respect to metabolic parameters of body weight, lipids and glucose data based upon FDA specified criteria of each entity. The specified criteria for mean change analyses and categorical analyses are listed at the beginning of each section regarding evaluation of weight, glucose and lipid data. The Sponsor submitted the requested information on June 26, 2008.

The Division requested these data for all clinical trials involving adults and pediatric/adolescent subjects. This review pertains to the adult data only. The pediatric data is currently under review by Cara Alfaro, Pharm.D. In December 2008, the Sponsor submitted a Changes Being Effected labeling supplement to primarily include safety data from pediatric/adolescent clinical trials in bipolar disorder and schizophrenia. The Division provided some feedback and suggestions for changes which were incorporated into labeling by the Sponsor. The bipolar disorder and schizophrenia clinical trials data were submitted as a supplemental NDA and are currently under review. Therefore, this review will not comment specifically on labeling issues as these will be addressed upon completion of the reviews of the pediatric/adolescent metabolic analyses and clinical trials per the sNDA.

The development program for quetiapine and quetiapine XR included many trials using a fixed-dose design. Though not included in the original request, the Division requested that the Sponsor perform an analysis of the dose-related effects of quetiapine and quetiapine XR on metabolic parameters. The Division requested that the analyses be provided for the following groups: all clinical trials, schizophrenia clinical trials, bipolar disorder clinical trials, generalized anxiety disorder clinical trials, major depressive disorder clinical trials and generalized anxiety disorder + major depressive disorder clinical trials. The Division requested these additional analyses on 2/5/2009 and the Sponsor submitted these data on 2/18/2009.

3 Method

3.1 Dose-Related Analyses

For the dose-related analyses, the Division requested that these analyses be performed for all fixed-dose trials (excluding flexible-dose trials). Since these analyses are a subset of the entire clinical trials database, the sample sizes in these data tables will be less than the sample sizes in the data tables pertaining to all clinical trials.

The fixed dose trials in schizophrenia, bipolar disorder, generalized anxiety disorder and major depressive disorder included quetiapine doses in the range of 50 – 800 mg/day:

Schizophrenia: 50, 150, 300, 400, 600 and 800 mg/day (one clinical trial had a 75 mg and 750 mg dose arm, these data were combined into the 50 and 800 mg dose arms respectively)
Bipolar disorder: 400 and 600 mg/day
Generalized anxiety disorder: 50, 150 and 300 mg/day
Major depressive disorder: 50, 150 and 300 mg/day

The majority of the data for the 50 and 150 mg/day doses come from the GAD and MDD trials since very few subjects received these doses in fixed dose trials in schizophrenia.

Evaluating the dose-related effects of drugs on safety signals is helpful to assess risk: benefit and inform clinicians. Dose-relatedness might be viewed as a surrogate for concentration-relatedness; however, plasma concentrations were not always obtained in these clinical trials. It should be noted that for drugs that are extensively metabolized, there is tremendous variability in plasma concentrations achieved and this is somewhat obscured by focusing on doses only. As an example, from the original NDA for quetiapine, trough plasma concentrations were obtained in fixed dose trial 0013 (~50 subjects per group, number with plasma concentrations not available at the time of this review):

Dose (mg/day)	Mean [SD] Trough Plasma Concentration (ng/ml)
75	14 [11]
150	28 [16]
300	44 [34]
600	91 [59]
750	94 [72]

These data would indicate that for subjects in this clinical trial, the plasma concentrations between the 600 and 750 mg/day dose groups were essentially the same.

For all clinical trials, quetiapine was titrated to the target fixed dose. Though most of the protocols for the clinical trials in schizophrenia were not too specific about the titration scheme, some protocols indicate that the target dose of 750 mg/day should be reached by Day 7. Therefore, for the dose-related analyses that evaluated effects over time (starting at week 2), these data should reflect the target dose.

4 Study Population

As can be seen in Table 1 below, the study population consisted of:

- All adult subjects: age ≥18 at time of enrollment in 24 placebo-controlled trials, 17 comparator controlled trials (3 Chlorpromazine, 7 Haloperidol, 2 Olanzapine and 5 Risperidone) and all adult quetiapine-treated subject data from a total of 84 controlled and uncontrolled trials
- Pediatric and Adolescents: age <18 at time of enrollment – review of the data from this population will not be covered in this review
- Subjects with first episode psychosis and antipsychotic naïve subjects in placebo-controlled, comparator-controlled and uncontrolled trials - Antipsychotic naïve subjects were obtained by excluding patients with any record of a specific antipsychotic medication and information from psychiatric history modules

We requested that the exclusion of subjects from trials that meet the following criteria:

- Studies without a source drug monotherapy arm
- Studies with duration under 7 days
- Studies with a relapse-prevention study design, in which subjects had source drug exposure prior to randomization
- Studies evaluating the source drug using routes of drug delivery other than oral drug delivery (e.g., intramuscular, intravenous)

According to the FDA request, the sponsor provided tabulations on glucose and lipids for the following conditions: fasting, non-fasting and random fasting. For analyses under a specific fasting condition a patient had to be in the same fasting condition at post-baseline assessments as in baseline assessment. It was noted that the earliest studies of quetiapine were not designed to evaluate glucose metabolism. Fasting glucose measurements were requested in all of clinical trials starting in July 2004.

It should be noted that the subject stratification and specified criteria for mean change analyses and categorical analyses used are listed at the beginning of each section regarding evaluation of weight, glucose and lipid data in section 5, 6, and 7, respectively.

The baseline demographic tables highlighting the details about the study population and a list of all the quetiapine clinical trials included in the analyses for this metabolic data submission by the sponsor are presented in the Appendix.

Table 1: Subject groups summarized for metabolic data

Subject group	Number of trials	Total number of subjects	
		Quetiapine	Comparato
All adult subjects			
1. Adult subjects in placebo-controlled trials	24	6870	3000
2. Adult subjects in comparator-controlled trials[a]			
Chlorpromazine	3	346	349
Haloperidol	7	1276	849
Olanzapine	2	297	289
Risperidone	5	1385	1014
3. All adult quetiapine-treated subject data, controlled and uncontrolled	84	20021	NA
Pediatric and adolescent subjects (age <18 at time of enrollment)			
1. Pediatric and adolescent subjects in placebo-controlled trials	2	340	165
2. Pediatric and adolescent subjects in comparator-controlled trials[b]	0	NA	NA
3. Pediatric and adolescent quetiapine-treated subject data, controlled and uncontrolled	7	385	NA
Subjects with first episode psychosis and antipsychotic-naïve subjects			
1. Subjects with first episode psychosis and antipsychotic-naïve subjects in placebo-controlled trials	9	2489	1207
2. Subjects with first episode psychosis and antipsychotic-naïve subjects in comparator-controlled trials[c]			
Olanzapine	1	66	72
Risperidone	1	66	66
3. All data for subjects with first episode psychosis or antipsychotic-naïve subjects, controlled and uncontrolled	13	5021	NA

This table is extracted from sponsor's submission

5 Weight Gain

5.1 Adult Subjects in Placebo-Controlled Trials

5.1.1 Mean Change Analyses

Analyses of mean changes in weight (in kg) and in body mass index (BMI) from baseline to last observation carried forward (LOCF) endpoint for all patients in each subject group was evaluated. Similar mean change analyses of subgroups divided according to World Health Organization categories of baseline BMI: Underweight (BMI<18.5), Normal Weight (18.5≤BMI<25), Overweight (25≤BMI<30), and Obese (BMI≥30) was also reviewed. Treatment effect assessment was based on an analysis of variance (ANOVA) model with terms for protocol and treatment.

Observed case analyses of mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks were reviewed. For these analyses, mean weight change was reported for all patients who completed the study time up to the time point specified for that analysis. Comparison between treatment groups was conducted and p-values were reported by the sponsor.

1. Mean Body Weight Change (in Kg)

The quetiapine-treated subjects (N = 6412) who received a modal daily dose of 347 mg, gained an average of 1.2 kg (2.6 lbs), compared to an increase of 0.2 kg (0.4 lbs) in placebo-treated subjects (N = 2817) with a median exposure of 43-49 days.

Table 2: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) (placebo-controlled trials)

	QTP N = 6412	**Placebo** N = 2817
Mean (SD) Weight at BL	80.6 (21.2)	80.3 (21.9)
Mean (SD) Weight at EOT	81.8 (21.2)	80.5 (22.0)
Mean (SD) Weight Change	1.2 (3.5)	0.2 (3.3)
p-value	<0.001	-
Modal (SD) Dose in mg	347 (224)	-
Median Exposure (days)	43	49

Information obtained from Sponsor table 14 in Clinical Study Report

Dose-Related Analyses

The mean change in weight from baseline to endpoint was fairly consistent between doses for the fixed-dose placebo controlled trials. In the all clinical trials analyses, quetiapine 50 mg/day was associated with the least weight gain (0.8 kg) and this was not different from placebo (0.2 kg). For the 150, 300, 400, 600 and 800 mg/day groups, the mean change in weight was 1 to 1.4 kg (vs. 0.2 kg for placebo) and not linearly related to dose. This finding was consistent when evaluating the fixed dose trials by indication – with the exception of the schizophrenia trials. In the schizophrenia trials, all doses were statistically different from placebo and 50 mg/day was associated with a 1.4 kg increase in weight and the greatest weight gain was in the 150 mg/day group (2.9 kg). However, it should be noted that these lower dose groups (50 and 150 mg/day) also have significantly fewer subjects compared to the other dose groups.

Table 3: Weight (kg) - Change from Baseline to Endpoint, Fixed-Dose Placebo-Controlled Trials (LOCF)

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**QTP** 400 mg	**QTP** 600 mg	**QTP** 800 mg	**Placebo**
All Trials							
N	656	1286	1915	340	1182	451	2319
Mean (SD) Change	**0.8 (2.2)**	**1.0 (2.5)**	**1.1 (2.9)**	**1.1 (2.8)**	**1.4 (4.4)**	**1.2 (5.0)**	**0.2 (3.4)**
p-value (vs. placebo)	NS	< 0.001	< 0.001	0.004	< 0.001	< 0.001	-
Median Exp days	49	53	53	42	44	42	54
Schizophrenia							
N	29	29	205	340	422	451	337
Mean (SD) Change	**1.4 (4.1)**	**2.9 (4.4)**	**1.5 (3.3)**	**1.1 (2.8)**	**1.9 (5.7)**	**1.2 (5.0)**	**0.2 (3.4)**
p-value (vs. placebo)	0.020	< 0.001	0.002	0.002	< 0.001	0.001	-
Median Exposure (days)	41	42	31	42	42	42	41
Bipolar Disorder							
N	-	-	894	-	760	-	679
Mean (SD) Change	-	-	**1.0 (3.1)**	-	**1.2 (3.4)**	-	**0.0 (2.5)**
p-value (vs. placebo)	-	-	< 0.001	-	< 0.001	-	-
Median Exposure (days)	-	-	56	-	56	-	56
GAD							
N	448	674	445	-	-	-	664
Mean (SD) Change	**0.7 (2.2)**	**1.1 (2.5)**	**1.1 (2.5)**	-	-	-	**0.3 (2.4)**
p-value (vs. placebo)	0.011	< 0.001	< 0.001	-	-	-	-
Median Exposure (days)	56	56	56	-	-	-	56
MDD							
N	179	583	371	-	-	-	639
Mean (SD) Change	**0.8 (2.0)**	**0.9 (2.4)**	**1.2 (2.5)**	-	-	-	**0.4 (4.8)**
p-value (vs. placebo)	NS	0.015	0.003	-	-	-	-
Median Exposure (days)	42	45	43	-	-	-	49
MDD + GAD							
N	627	1257	816	-	-	-	1303
Mean (SD) Change	**0.7 (2.1)**	**1.0 (2.4)**	**1.2 (2.5)**	-	-	-	**0.3 (3.8)**
p-value (vs. placebo)	NS	< 0.001	< 0.001	-	-	-	-
Median Exposure (days)	54	54	48	-	-	-	56

From Sponsor Tables 8, 12, 16, 20, 24, 28 in 2/18/09 submission

2. Mean Body Weight Change by BMI Category

The mean weight gain by baseline BMI category was 1.8 kg, 1.4 kg, 1.1 kg and 0.9 kg, for quetiapine-treated subjects, and 1.1 kg, 0.3 kg, 0.1 kg and 0.1 kg for placebo-treated subjects for the underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively. It seemed that subjects with lower baseline BMI had greater increases in weight.

Table 4: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by BMI category (placebo-controlled trials)

BMI category (kg/m^2)		**QTP**	**Placebo**
Underweight BMI ≤ 18.5	N	189	106
	Mean (SD) Weight at BL	48.0 (7.2)	47.6 (6.8)
	Mean (SD) Weight at EOT	49.8 (7.7)	48.8 (7.4)
	Mean (SD) Weight Change	1.8 (2.6)	1.1 (2.6)
	p-value	0.021	-
	Modal (SD) Dose (mg)	417 (240)	-
	Median Exposure (days)	43	43
Normal weight BMI 18.5 to 25	N	2157	915
	Mean (SD) Weight at BL	63.8 (9.1)	63.6 (9.1)
	Mean (SD) Weight at EOT	65.2 (9.5)	63.9 (9.7)
	Mean (SD) Weight Change	1.4 (2.7)	0.3 (3.5)
	p-value	<0.001	-

	Modal (SD) Dose (mg)	348 (229)	-
	Median Exposure (days)	43	49
Overweight BMI 25 to 30	N	1863	835
	Mean (SD) Weight at BL	79.6 (10.0)	79.7 (10.2)
	Mean (SD) Weight at EOT	80.7 (10.5)	79.8 (10.6)
	Mean (SD) Weight Change	1.1 (3.3)	0.1 (2.5)
	p-value	<0.001	-
	Modal (SD) Dose (mg)	340 (220)	-
	Median Exposure (days)	44	52
Obese BMI ≥30	N	2072	895
	Mean (SD) Weight (kg) at BL	102.0 (18.6)	102.0 (20.5)
	Mean (SD) Weight at EOT	102.8 (18.9)	102.1 (20.7)
	Mean (SD) Weight (kg) Change	0.9 (3.9)	0.1 (3.7)
	p-value	<0.001	-
	Modal (SD) Dose (mg)	347 (222)	-
	Median Exposure (days)	43	49

Information obtained from Sponsor table 15 in Clinical Study Report

Dose-Related Analyses

There was no linear dose-related change in weight from baseline to endpoint by baseline BMI category.

Table 5: Weight (kg) - Change from Baseline to Endpoint by Baseline BMI Category, All Fixed-Dose Placebo-Controlled Trials (LOCF)

BMI category (kg/m^2)		**QTP** 50 mg N = 656	**QTP** 150 mg N = 1286	**QTP** 300 mg N = 1915	**QTP** 400 mg N = 340	**QTP** 600 mg N = 1182	**QTP** 800 mg N = 451	**Placebo** N = 2319
BMI < 18.5 (Underweight)	n	20	25	27	30	39	19	74
	Mean (SD) Change	**0.9 (1.3)**	**1.0 (1.6)**	**1.8 (2.1)**	**1.3 (1.6)**	**2.5 (2.8)**	**1.7 (4.0)**	**0.8 (2.4)**
	p-value (vs. placebo)	NS	NS	0.021	NS	0.007	NS	-
	Median Exposure (days)	56	56	56	42	43	42	44
18.5 ≤ BMI < 25 (Normal weight)	n	251	433	596	154	384	150	757
	Mean (SD) Change	**0.8 (2.2)**	**1.2 (2.3)**	**1.4 (2.5)**	**1.5 (2.7)**	**1.8 (3.0)**	**1.6 (2.7)**	**0.4 (3.6)**
	p-value (vs. placebo)	NS	0.001	< 0.001	NS	< 0.001	0.002	-
	Median Exposure (days)	55	54	55	42	43	42	54
25 ≤ BMI < 30 (Overweight)	n	200	388	600	67	361	122	702
	Mean (SD) Change	**0.8 (2.2)**	**1.1 (2.4)**	**1.0 (2.7)**	**0.6 (2.8)**	**1.1 (3.4)**	**1.4 (2.8)**	**0.2 (2.5)**
	p-value (vs. placebo)	0.009	< 0.001	< 0.001	0.034	< 0.001	0.003	
	Median Exposure (days)	45	54	51	42	48	42	55
BMI ≥30 (Obese)	n	185	438	689	87	394	157	781
	Mean (SD) Change	**0.6 (2.4)**	**0.8 (2.9)**	**1.0 (3.4)**	**0.8 (3.2)**	**1.1 (4.5)**	**0.5 (7.4)**	**0.1 (3.9)**
	p-value (vs. placebo)	NS	0.007	< 0.001	NS	< 0.001	NS	-
	Median Exposure (days)	44	50	52	42	46	41	54

From Sponsor Table nine in 2/18/09 submission

3. Mean Body Weight Change by Time (in Weeks)

The mean weight gain from baseline to endpoint for quetiapine-treated subjects was 0.9 kg, 1.2 kg, 1.2 kg, and 2.4 kg, compared to 0.2 kg, 0.2 kg, 0.2 kg, and 0.5 kg in the placebo group at Weeks 2, 4, 8, and 12, respectively.

Table 6: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by week (short-term placebo-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**
QTP= N	3779	3685	2591	164
Mean (SD) Weight at BL	79.6 (21.5)	79.6 (21.4)	79.6 (20.6)	69.8 (17.3)
Mean (SD) Weight at EOT	80.5 (21.6)	80.7 (21.4)	80.9 (20.7)	72.1 (16.8)
Mean (SD) Weight Change	0.9 (2.4)	1.2 (2.9)	1.2 (3.0)	2.4 (4.2)
p-value	<0.001	<0.001	<0.001	<0.001
Modal (SD) Dose (mg)	322 (237)	328 (237)	311 (200)	585 (216)
Median Exposure (days)	15	29	57	84

Placebo = N	1734	1731	1302	91
Mean (SD) Weight at BL	78.6 (21.9)	79.7 (22.5)	79.9 (22.0)	67.0 (16.6)
Mean (SD) Weight at EOT	78.8 (22.0)	79.9 (22.5)	80.1 (22.1)	67.5 (16.7)
Mean (SD) Weight Change	0.2 (2.2)	0.2 (2.5)	0.2 (2.6)	0.5 (4.1)
p-value	-	-	-	-
Mean Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	15	29	57	84

Information obtained from Sponsor table 16 in Clinical Study Report

Dose-Related Analyses

In Table 6, above, weight increased from weeks 4 -8 to week 12. However, for the dose-related analyses, there were no fixed-dose trials of 12 weeks duration. Additionally, virtually no data is available for quetiapine 400 and 800 mg/day at week 8. Therefore, the dose-related changes in weight over time analyses are not very informative.

For the 2, 4 and 8 week time points, mean changes in weight for all quetiapine doses were significantly different from placebo. There is a suggestion of a linear dose-relationship for the 8 week time point for the dose groups for which there are reasonable sample sizes.

Table 7: Weight Change (kg) from Baseline to Endpoint By Week, All Fixed-Dose Placebo-Controlled Trials

		QTP 50 mg N = 656	**QTP** 150 mg N = 1286	**QTP** 300 mg N = 1915	**QTP** 400 mg N = 340	**QTP** 600 mg N = 1182	**QTP** 800 mg N = 451	**Placebo** N = 2319
Week 2	n	551	1063	783	313	339	352	1449
	Mean (SD) Change	**0.5 (1.7)**	**0.8 (1.8)**	**1.0 (1.9)**	**0.8 (2.2)**	**1.4 (2.5)**	**1.1 (4.4)**	**0.2 (2.2)**
	p-value (vs. placebo)	0.015	< 0.001	< 0.001	0.009	< 0.001	0.005	-
Week 4	n	526	1014	772	291	309	320	1388
	Mean (SD) Change	**0.6 (1.9)**	**0.9 (2.2)**	**1.2 (3.2)**	**1.2 (2.6)**	**1.5 (3.3)**	**1.4 (4.6)**	**0.3 (2.4)**
	p-value (vs. placebo)	0.011	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	-
Week 8	n	322	639	938	4	542	3	1211
	Mean (SD) Change	**0.8 (2.2)**	**1.1 (2.7)**	**1.2 (3.0)**	**0.3 (1.7)**	**1.5 (3.6)**	**2.0 (2.0)**	**0.2 (2.6)**
	p-value (vs. placebo)	0.045	< 0.001	< 0.001	NS	< 0.001	NS	-

From Sponsor Table 10 in 2/18/09 submission

4. Mean BMI Change (kg/m^2)

The quetiapine-treated subjects (N = 6281, mean daily dose of 347 mg) showed a mean increase in BMI from baseline to endpoint of 0.4 kg/m^2, compared to 0.1 kg/m^2 in placebo-treated subjects (Table 8).

Table 8: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) (placebo-controlled trials)

	QTP N = 6281	**Placebo** N = 2751
Mean (SD) BMI at BL	28.2 (7.0)	28.2 (7.3)
Mean (SD) BMI at EOT	28.6 (7.0)	28.3 (7.4)
Mean (SD) BMI Change	0.4 (1.2)	0.1 (1.2)
p-value	<0.001	-
Modal (SD) Dose (mg)	347.2 (225.0)	-
Median Exposure (days)	43	49

Information obtained from Sponsor table 17 in Clinical Study Report

Dose-Related Analyses

There was no strong linear relationship to dose. Overall, most quetiapine dose groups had a mean change in BMI of 0.4 kg/m2, the 50 mg/day group had a mean change of 0.3 kg/m2. All quetiapine dose groups had a mean change in BMI that was statistically different from placebo (0.1 kg/m2). Similar to the mean change in weight data, the change in BMI was most variable in the schizophrenia trials where the 50 mg/day group had a mean BMI change of 0.5 kg/m2 and the dose group with the largest mean change was 150 mg/day with a BMI change of 1.0 kg/m2 (it should be noted, however, that these lower dose groups also have significantly fewer subjects compared to the other dose groups).

Table 9: BMI (kg/m^2) - Change from Baseline to Endpoint, Fixed-Dose Placebo-Controlled Trials (LOCF)

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**QTP** 400 mg	**QTP** 600 mg	**QTP** 800 mg	**Placebo**
All Trials							
N	656	1284	1912	338	1178	448	2314
Mean (SD) Change	**0.3 (0.8)**	**0.4 (0.9)**	**0.4 (1.0)**	**0.4 (1.0)**	**0.5 (1.3)**	**0.4 (1.9)**	**0.1 (1.2)**
p-value (vs. placebo)	0.046	< 0.001	< 0.001	0.007	< 0.001	< 0.001	-
Median Exposure (days)	49	53	53	42	44	42	54
Schizophrenia							
N	29	28	204	338	418	448	336
Mean (SD) Change	**0.5 (1.4)**	**1.0 (1.5)**	**0.5 (1.1)**	**0.4 (1.0)**	**0.6 (1.5)**	**0.4 (1.9)**	**0.1 (1.2)**
p-value (vs. placebo)	0.031	< 0.001	0.005	0.004	< 0.001	0.006	-
Median Exposure (days)	41	42	30.5	42	42	42	41
Bipolar Disorder							
N	-	-	893	-	760	-	678
Mean (SD) Change	-	-	**0.4 (1.1)**	-	**0.4 (1.2)**	-	**0.0 (0.9)**
p-value (vs. placebo)	-	-	< 0.001	-	< 0.001	-	-
Median Exposure (days)	-	-	56	-	56	-	56
GAD							
N	448	674	445	-	-	-	663
Mean (SD) Change	**0.3 (0.8)**	**0.4 (0.9)**	**0.4 (0.9)**	-	-	-	**0.1 (0.9)**
p-value (vs. placebo)	0.008	< 0.001	< 0.001	-	-	-	-
Median Exposure (days)	56	56	56	-	-	-	56
MDD							
N	179	582	370	-	-	-	637
Mean (SD) Change	**0.3 (0.7)**	**0.3 (0.9)**	**0.4 (0.9)**	-	-	-	**0.1 (1.7)**
p-value (vs. placebo)	NS	0.008	0.002	-	-	-	-
Median Exposure (days)	42	45	43	-	-	-	49
MDD + GAD							
N	627	1256	815	-	-	-	1300
Mean (SD) Change	**0.3 (0.7)**	**0.4 (0.9)**	**0.4 (0.9)**	-	-	-	**0.1 (1.3)**
p-value (vs. placebo)	NS	< 0.001	< 0.001	-	-	-	-
Median Exposure (days)	54	54	48	-	-	-	56

From Sponsor Tables 36, 38, 40, 42, 44, 46 in 2/18/09 submission

5. Mean BMI Change by BMI Category

The mean BMI change from baseline to endpoint by baseline BMI category showed an increase of 0.7, 0.5, 0.4 and 0.3 kg/ m^2 for quetiapine-treated subjects, and 0.4, 0.1, 0 and 0 kg/ m^2 for placebo-treated subjects in the underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

Table 10: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) by BMI category (placebo-controlled trials)

BMI category (kg/m^2)		QTP	Placebo
Underweight BMI ≤ 18.5	N	189	106
	Mean (SD) BMI at BL	17.2 (1.0)	17.3 (1.0)
	Mean (SD) BMI at EOT	17.9 (1.5)	17.7 (1.3)
	Mean (SD) BMI Change	0.7 (0.9)	0.4 (0.9)
	p-value	0.015	-
	Modal (SD) Dose (mg)	417 (239)	-
	Median Exposure (days)	43	43
Normal weight BMI 18.5 to 25	N	2157	915
	Mean (SD) BMI at BL	22.3 (1.7)	22.3 (1.8)
	Mean (SD) BMI at EOT	22.8 (1.9)	22.4 (2.1)
	Mean (SD) BMI Change	0.5 (0.9)	0.1 (1.2)
	p-value	<0.001	-
	Modal (SD) Dose (mg)	348 (229)	-
	Median Exposure (days)	43	49
Overweight BMI 25 to 30	N	1863	835
	Mean (SD) BMI at BL	27.3 (1.4)	27.3 (1.4)
	Mean (SD) BMI at EOT	27.7 (1.9)	27.4 (1.7)
	Mean (SD) BMI Change	0.4 (1.2)	0.0 (0.9)
	p-value	<0.001	-
	Modal (SD) Dose (mg)	340 (220)	-
	Median Exposure (days)	44	52
Obese BMI ≥ 30	N	2072	895
	Mean (SD) BMI at BL	36.1 (5.8)	36.4 (6.4)
	Mean (SD) BMI at EOT	36.4 (5.9)	36.5 (6.5)
	Mean (SD) BMI Change	0.3 (1.4)	0.0 (1.3)
	p-value	<0.001	-
	Modal (SD) Dose (mg)	347 (222)	-
	Median Exposure (days)	43	49

Information obtained from Sponsor table 18 in Clinical Study Report

Dose-Related Analyses

No strong dose-related signal emerged in the evaluation of mean change in BMI by baseline BMI category. In subjects with BMI < 25 kg/m2, the quetiapine 50 and 150 mg/day groups appeared to be associated with a lesser increase in BMI compared to the other dose groups. This same pattern was not evident in overweight (25 ≤ BMI < 30) or obese (BMI ≥ 30) subjects.

Table 11: BMI (kg/m2): Change from Baseline to Endpoint by Baseline BMI Category, All Fixed-Dose Placebo-Controlled Trials (LOCF)

BMI category (kg/m^2)		QTP 50 mg N = 656	QTP 150 mg N = 1286	QTP 300 mg N = 1915	QTP 400 mg N = 340	QTP 600 mg N = 1182	QTP 800 mg N = 451	Placebo N = 2319
BMI < 18.5 (Underweight)	n	20	25	27	30	39	19	74
	Mean (SD) Change	**0.3 (0.5)**	**0.4 (0.6)**	**0.6 (0.7)**	**0.5 (0.6)**	**0.9 (1.0)**	**0.6 (1.4)**	**0.3 (0.9)**
	p-value (vs. placebo)	NS	NS	0.027	NS	0.008	NS	-
	Median Exposure (days)	56	56	56	42	43	42	44
18.5 ≤ BMI < 25 (Normal weight)	n	251	433	596	154	384	150	757
	Mean (SD) Change	**0.3 (0.8)**	**0.4 (0.8)**	**0.5 (0.9)**	**0.5 (1.0)**	**0.6 (1.0)**	**0.5 (0.9)**	**0.1 (1.3)**
	p-value (vs. placebo)	NS	< 0.001	< 0.001	NS	< 0.001	0.002	-
	Median Exposure (days)	55	54	55	42	43	42	54
25 ≤ BMI < 30 (Overweight)	n	200	388	600	67	361	122	702
	Mean (SD) Change	**0.3 (0.8)**	**0.4 (0.8)**	**0.3 (0.9)**	**0.2 (1.0)**	**0.4 (1.2)**	**0.5 (1.0)**	**0.1 (0.9)**
	p-value (vs. placebo)	0.011	< 0.001	< 0.001	0.050	< 0.001	0.002	-
	Median Exposure (days)	45	54	51	42	48	42	55
BMI ≥30 (Obese)	n	185	438	689	87	394	157	781
	Mean (SD) Change	**0.2 (0.9)**	**0.3 (1.0)**	**0.4 (1.2)**	**0.3 (1.1)**	**0.4 (1.6)**	**0.1 (2.8)**	**0.0 (1.4)**
	p-value (vs. placebo)	NS	0.005	< 0.001	NS	< 0.001	NS	-
	Median Exposure (days)	44	50	52	42	46	41	54

From Sponsor Table 37 in 2/18/09 submission

5.1.2 Categorical Analyses

1. Weight Gain Outliers

In a pooled analysis of placebo-controlled trials, among quetiapine-treated subjects (N = 3102 at a modal daily dose of 319 mg), the majority (58%) had a mean weight gain of 0-5 kg, compared to 48% in the placebo-controlled subjects (N = 1405) at Week 6. Nearly 8% of subjects in the quetiapine group compared to 2% of subjects in the placebo group gained > 5 to 10 kg at week 6. About 1% of the quetiapine treated patients gained >10 to 15 kg at week 6 compared to 0.4% in the placebo group.

Table 12: Proportion of Patients with Weight (in kg) Change at Week 6 (placebo-controlled trials)

	QTP N = 3102	**Placebo** N = 1405
Weight change (kg)	N (%)	N (%)
≤0	1035 (33.4)	693 (49.3)
0 to ≤5 (0-11 lb)	1785 (57.5)	677 (48.2)
>5 to ≤10 (11-22 lb)	242 (7.8)	26 (1.9)
>10 to ≤15 (22-33 lb)	34 (1.1)	5 (0.4)
>15 to ≤20 (33-44 lb)	3 (0.1)	2 (0.1)
>20 to ≤25 (44-55 lb)	1 (0.0)	1 (0.1)
>25 to ≤30 (55-66 lb)	2 (0.1)	1 (0.1)
Modal (SD) Dose (mg)	319 (237)	0
Median Exposure (days)	43	43

Information obtained from Sponsor table 19 in Clinical Study Report

Dose-Related Analysis

Similar proportions of subjects gained > 0 to 5 kg between the quetiapine dose groups. However, a dose-related signal emerges when evaluating the > 5 to 10 kg weight gain. Approximately 4% of subjects gain > 5 to 10 kg in the 50 and 150 mg dose groups compared to 8% in the 300 and 600 mg dose groups and 12-15% in the 600 and 800 mg/day groups. Similarly, in the > 10 to 15 kg category, the proportions of subjects in the placebo, quetiapine 50-300 mg/day groups are similar (< 1%) compared to 1.8% and 2.1% in the quetiapine 600 and 800 mg/day groups respectively.

Table 13: Proportion of Subjects with Weight Change by Prespecified Weight Change Categories, Fixed-Dose Placebo-Controlled Trials

Weight (kg) Change at Week 6	**QTP** 50 mg N = 477	**QTP** 150 mg N = 900	**QTP** 300 mg N = 639	**QTP** 400 mg N = 246	**QTP** 600 mg N = 280	**QTP** 800 mg N = 291	**Placebo** N = 1231
≤0 kg	190 (39.8%)	281 (31.2%)	185 (29.0%)	97 (39.4%)	91 (32.5%)	112 (38.5%)	605 (49.1%)
> 0 to 5 kg	269 (56.4%)	574 (63.8%)	400 (62.6%)	129 (52.4%)	140 (50.0%)	136 (46.7%)	601 (48.8%)
>5 to 10 kg	16 (3.4%)	39 (4.3%)	51 (8.0%)	19 (7.7%)	42 (15.0%)	35 (12.0%)	17 (1.4%)
>10 to 15 kg	1 (0.2%)	6 (0.7%)	3 (0.5%)	1 (0.4%)	5 (1.8%)	6 (2.1%)	5 (0.4%)
>15 to 20 kg	0	0	0	0	1 (0.4%)	1 (0.3%)	1 (0.1%)
>20 to 25 kg	0	0	0	0	0	1 (0.3%)	1 (0.1%)
>25 kg	1 (0.2%)	0	0	0	1 (0.4%)	0	1 (0.1%)

From Sponsor Table 11 in 2/18/09 submission

5.2 Adult Subjects in Comparator-Controlled Trials

5.2.1 Mean Change Analyses

1. Mean Body Weight Change (in Kg)

In a pooled analysis of comparator-controlled trials, olanzapine-treated subjects had the highest mean weight gain of 6.1 kg (13.4 lbs) at a modal olanzapine dose of 14 mg per day, compared to 3.3 kg (7.3 lbs) in quetiapine-treated subjects at a modal quetiapine dose of 562 mg per day with a median exposure of 167-168 days. Similar mean increase in weight of 2.2 kg was observed between the quetiapine group (modal daily dose 552 mg) and the risperidone group (modal daily dose 5 mg); both drugs with median exposure of 56 days. See table 14 below for mean weight change observed in the olanzapine, risperidone, chlorpromazine and haloperidol groups.

Table 14: Weight (in Kg) - change from baseline (BL) to end of treatment (EOT) (comparator-controlled trials)

	QTP	OLZ	QTP	RIS	QTP	CHL	QTP	HAL
N	295	286	702	695	326	330	1035	730
Mean (SD) Wt at BL	74.1 (17.4)	74.3 (16.9)	79.2 (20.3)	81.0 (20.5)	73.2 (15.7)	73.0 (15.0)	76.0 (17.3)	72.6 (16.5)
Mean (SD) Wt at EOT	77.4 (19.0)	80.3 (19.1)	81.3 (20.7)	83.3 (19.6)	74.2 (15.8)	74.3 (15.3)	77.4 (17.4)	72.7 (16.0)
Mean (SD) Wt Change	3.3 (6.5)	6.1 (8.0)	2.2 (6.1)	2.3 (6.9)	1.1 (4.2)	1.2 (6.2)	1.3 (5.1)	0.0 (4.0)
Modal (SD) Dose (mg)	563 (191)	14 (5)	552 (207)	5 (2)	549 (129)	627 (225)	439 (227)	11 (6)
Median Exp (days)	167	168	56	56	65	63	42	42
p-value	<0.001	-	0.701	-	0.699	-	<0.001	-

Information obtained from Sponsor tables 20, 26, 32 and 38 in Clinical Study Report
QTP- quetiapine, CHL - Chlorpromazine, OlZ – olanzapine, RIS - risperidone, HAL – haloperidol

2. *Mean Body Weight Change by BMI Category*

The mean weight gain by baseline BMI category was 6.0-6.5 kg in olanzapine–treated subjects and 3.2-3.7 kg in quetiapine–treated subjects. For each category [underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30)]. As can be seen in table 15 below for mean weight gain observed in the quetiapine group compared to olanzapine, risperidone, chlorpromazine and haloperidol groups, the greatest mean increase was seen in the olanzapine treated group for all BMI categories while similar mean changes were noted in other antipsychotic treatment groups including quetiapine.

Table 15: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by BMI category (comparator-controlled trials)

BMI category (kg/m2)	QTP	OLZ	QTP	RIS	QTP	CHL	QTP	HAL
Underweight BMI ≤ 18.5 (N)	19	18	29	23	10	13	20	24
Mean (SD) Wt at BL	54.0 (8.4)	50.7 (4.2)	53.2 (7.8)	50.7 (5.7)	53.8 (7.2)	51.4 (6.8)	50.4 (7.5)	51.1 (5.4)
Mean (SD) Wt at EOT	57.7 (8.5)	56.7 (5.4)	56.6 (7.8)	55.7 (5.8)	56.3 (7.2)	52.7 (7.2)	51.6 (9.0)	54.0 (6.1)
Mean (SD) Wt Change	3.7 (4.9)	6.0 (5.2)	3.3 (4.6)	4.9 (3.5)	2.5 (3.0)	1.3 (2.9)	1.2 (3.5)	2.9 (3.3)
p-value	0.167	-	0.201	-	0.147	-	0.178	-
Modal (SD) Dose (mg)	542 (187)	156 (4)	528 (205)	5 (2)	495 (157)	546 (217)	487 (196)	12 (4)
Median Exposure (days)	168	168	58	163	44	42	42	42

Normal Weight BMI 18.5 to 25 (N)	143	140	281	264	125	124	344	232
Mean (SD) Wt at BL	64.2 (9.0)	66.4 (8.4)	66.3 (9.2)	67.2 (9.1)	64.5 (8.8)	64.9 (8.5)	67.0 (8.8)	65.4 (8.5)
Mean (SD) Wt at EOT	67.4 (11.2)	72.3 (10.7)	68.6 (10.5)	70.3 (9.6)	66.1 (9.2)	67.4 (12.4)	69.0 (9.7)	66.1 (9.0)
Mean (SD) Wt Change	3.2 (5.8)	6.0 (6.8)	2.3 (5.3)	3.1 (4.3)	1.7 (3.9)	2.5 (8.4)	2.1 (4.6)	0.8 (3.4)
p-value	<0.001	-	0.073	-	0.297		0.004	-
Modal (SD) Dose (mg)	558 (198)	14 (4)	553 (211)	5 (2)	520 (158)	548 (200)	466 (227)	10 (5)
Median Exposure (days)	164	168	57	70	42	42	42	42

Overweight BMI 25 to 30 (N)	84	85	203	184	63	72	270	162
Mean (SD) Wt at BL	82.2 (11.1)	80.5 (10.5)	81.6 (10.7)	82.4 (9.8)	79.1 (10.5)	80.2 (10.6)	79.7 (9.1)	78.7 (9.1)
Mean (SD) Wt at EOT	85.5 (12.6)	86.4 (14.7)	83.8 (11.4)	85.1 (11.8)	80.1 (12.1)	80.9 (10.9)	80.9 (10.4)	78.0 (9.6)
Mean (SD) Wt Change	3.3 (6.9)	6.0 (9.2)	2.2 (5.5)	2.7 (5.9)	1.1 (4.3)	0.7 (3.8)	1.2 (5.5)	-0.7 (3.8)
p-value	0.011	-	0.554	-	0.625	-	0.004	-
Modal (SD) Dose (mg)	571 (187)	14 (5)	553 (209)	5 (2)	566 (110)	576 (188)	442 (236)	10 (5)
Median Exposure (days)	168	168	56	56	69	69	42	42

Obese BMI > 30 (N)	48	43	163	188	51	41	170	97
Mean (SD) Wt at BL	95.5 (14.7)	97.7 (19.9)	103.4 (19.8)	104.0 19.6)	94.2 (13.3)	93.0 (14.3)	99.3 (15.3)	95.4 (14.7)
Mean (SD) Wt at EOT	99.2 (19.1)	104.2 (23.1)	104.9 (21.4)	104.4 (18.2)	94.4 (14.5)	92.0 (14.3)	99.3 (16.1)	93.8 (14.5)
Mean (SD) Wt Change	3.6 (8.3)	6.5 (10.1)	1.5 (8.1)	0.5 (10.4)	0.2 (4.8)	-1.0 (5.5)	0.0 (5.3)	-1.6 (5.8)
p-value	0.118	-	0.385	-	0.233	-	0.079	-
Modal (SD) Dose (mg)	569 (188)	145 (5)	564 (205)	5.3 (2)	563 (108)	593 (180)	403 (242)	107 (5)
Median Exposure (days)	168	168	56	56	65	69	42	42

Information obtained from Sponsor tables 21, 27, 33 and 39 in Clinical Study Report
QTP- quetiapine, CHL - Chlorpromazine, OlZ – olanzapine, RIS – risperidone, HAL – haloperidol

3. Mean Body Weight Change by Time (in Weeks)

The mean weight gain from baseline to endpoint for olanzapine–treated subjects showed 2.3, 2.6, 4.0, 4.8, 6.2, and 13.2 kg; and for quetiapine-treated subjects was 1.4, 1.6, 2.4, 2.9, 4.1 and 7.1 kg, at Weeks 2, 4, 8, 12, 24 and 48, respectively. Weight gain increased over time for quetiapine-treated subjects although sample sizes at 48 weeks are very small. Consistent across comparator trials, the weight gain for quetiapine-treated subjects at week 24 is approximately 4 kg compared to 6 kg for olanzapine-treated subjects. But, similar weight gain (4 kg) was observed for risperidone-treated subjects. Limited sample sizes were available for haloperidol-treated subjects > 12 weeks and the chlorpromazine comparator-controlled trial was < 12 weeks.

Table 16: Weight increase over time by week (comparator-controlled trials)

	Week 2		**Week 4**		**Week 8**		**Week 12**		**Week 24**		**Week 48**	
	OLZ N =106	**QTP N=113**	**OLZ N=271**	**QTP N=265**	**OLZ N=254**	**QTP N=233**	**OLZ N=253**	**QTP N=223**	**OLZ N=214**	**QTP N=171**	**OLZ N=40**	**QTP N=37**
Mean (SD) Wt Change	2.3 (2.2)	1.4 (2.0)	2.6 (3.3)	1.6 (2.7)	4.0 (4.5)	2.4 (3.7)	4.8 (5.7)	2.9 (4.5)	6.2 (7.6)	4.1 (6.5)	13.2 (9.5)	7.1 (11.3)
p-value	0.001	-	<0.001	-	<0.001	-	<0.001	-	0.001	-	0.011	-

	Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 48**

	RIS N=361	QTP N=358	RIS N=466	QTP N=477	RIS N=408	QTP N=392	RIS N=295	QTP N=284	RIS N=190	QTP N=171	RIS N=34	QTP N=37
Mean (SD) Wt Change	1.6 (4.4)	1.5 (4.9)	1.8 (3.2)	1.5 (4.6)	2.0 (3.7)	1.9 (5.6)	2.7 (3.8)	2.7 (4.5)	4.2 (5.6)	4.1 (6.5)	6.0 (10.7)	7.1 (11.3)
p-value	0.674	-	0.287	-	0.791	-	0.982	-	0.733	-	0.692	-

	Week 2		Week 4		Week 8		Week 12		Week 24		Week 48	
	HAL N= 219	QTP N=311	HAL N=220	QTP N=299	HAL N=241	QTP N=300	HAL N= 90	QTP N=187	HAL N=17	QTP N=75	HAL N=6	QTP N=18
Mean (SD) Wt Change	-0.5 (2.7)	0.1 (3.0)	-0.4 (2.2)	0.7 (2.7)	0.4 (3.8)	1.6 (4.3)	0.1 (3.7)	2.5 (5.2)	-1.7 (6.1)	3.9 (8.0)	1.0 (5.6)	7.2 (9.4)
p-value	0.086	-	<0.001	-	0.002	-	0.001	-	0.047	-	0.110	-

See table 17 below for mean weight gain (by time category) observed in the quetiapine, olanzapine, risperidone, chlorpromazine and haloperidol groups.

Table 17:Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by week (comparator-controlled trials)

	Week 2		Week 4		Week 8		Week 12		Week 24		Week 48	
	OLZ N =106	QTP N=113	OLZ N=271	QTP N=265	OLZ N=254	QTP N=233	OLZ N=253	QTP N=223	OLZ N=214	QTP N=171	OLZ N=40	QTP N=37
Mean (SD) Wt at BL	77.1 (16.9)	77.2 (19.4)	74.0 (16.6)	74.2 (17.8)	74.1 (16.7)	74.2 (17.2)	3.8 (15.5)	7 74.2 (16.9)	73.7 (15.0)	74.7 (15.8)	76.0 (13.6)	77.1 (21.8)
Mean (SD) Wt at EOT	79.4 (16.8)	78.5 (19.4)	76.6 (17.1)	75.9 (17.9)	78.1 (17.3)	76.6 (17.6)	78.6 (16.5)	77.1 (17.4)	80.0 (17.0)	78.8 (16.6)	89.2 (16.9)	84.2 (28.3)
Mean (SD) Wt Change	2.3 (2.2)	1.4 (2.0)	2.6 (3.3)	1.6 (2.7)	4.0 (4.5)	2.4 (3.7)	4.8 (5.7)	2.9 (4.5)	6.2 (7.6)	4.1 (6.5)	13.2 (9.5)	7.1 (11.3)
p-value	0.001	-	<0.001	-	<0.001	-	<0.001	-	0.001	-	0.011	
Modal (SD) Dose	13 (5)	504 (226)	14 (4)	580 (177)	14 (4)	597 (171)	14 (4)	594 (173)	14 (4)	605 (159)	12.5 (4.9)	583 (168)
Median Exp (days)	15	15	29	29	56	57	85	85	168	169	337.0	336.0
	RIS N=361	QTP N=358	RIS N=466	QTP N=477	RIS N=408	QTP N=392	RIS N=295	QTP N=284	RIS N=190	QTP N=171	RIS N=34	QTP N=37
Mean (SD) Wt at BL	84.9 (20.3)	82.7 (21.1)	80.5 (19.7)	78.7 (19.8)	80.1 (19.4)	78.3 (19.7)	74.2 (16.4)	73.6 (16.6)	74.1 (17.1)	74.7 (15.8)	81.2 (19.9)	77.1 (21.8)
Mean (SD) Wt at EOT	86.6 (20.3)	84.2 (21.1)	82.3 (19.7)	80.3 (19.8)	82.1 (19.0)	80.3 (19.9)	76.9 (16.0)	76.3 (16.9)	78.3 (17.1)	78.8 (16.6)	87.2 (21.7)	84.2 (28.3)
Mean (SD) Wt Change	1.6 (4.4)	1.5 (4.9)	1.8 (3.2)	1.5 (4.6)	2.0 (3.7)	1.9 (5.6)	2.7 (3.8)	2.7 (4.5)	4.2 (5.6)	4.1 (6.5)	6.0 (10.7)	7.1 (11.3)
p-value	0.674	-	0.287	-	0.791	-	0.982	-	0.733	-	0.692	-
Modal (SD) Dose	5 (2)	593 (203)	5 (2)	599 (180)	5 (2)	609 (173)	5 (2)	561 (180)	4 (2)	605 (159)	2.3 (0.9)	583 (168)
Median Exp (days)	15	15	28	28	56	56	84	84	169	169	336.0	337
	HAL N= 219	QTP N=311	HAL N=220	QTP N=299	HAL N=241	QTP N=300	HAL N= 90	QTP N=187	HAL N=17	QTP N=75	HAL N=6	QTP N=18
Mean (SD) Wt at BL	69.1 (15.8)	73.2 (18.8)	68.1 (15.0)	72.6 (18.1)	70.1 (16.6)	72.8 (17.5)	75.6 (17.9)	78.3 (18.0)	82.3 (20.3)	80.0 (17.8)	72.0 (13.2)	74.7 (14.4)
Mean (SD) Wt at EOT	68.6 (15.5)	73.4 (18.7)	67.7 (14.7)	73.2 (17.9)	70.5 (16.2)	74.4 (17.6)	75.7 (16.4)	80.8 (17.7)	80.7 (18.3)	84.0 (18.6)	72.9 (12.2)	8.9 (13.8)
Mean (SD) Wt Change	-0.5 (2.7)	0.1 (3.0)	-0.4 (2.2)	0.7 (2.7)	0.4 (3.8)	1.6 (4.3)	0.1 (3.7)	2.5 (5.2)	-1.7 (6.1)	3.9 (8.0)	1.0 (5.6)	7.2 (9.4)
p-value	0.086	-	<0.001	-	0.002	-	0.001	0	-	-	0.047	0.110
Modal (SD) Dose	8 (4.2)	385 (240)	9 (4.4)	402 (234)	13 (7)	467 (206)	8 (4.1)	421 (231)	12 (2)	353 (219	13 (3)	396 (204)
Median Exp (days)	14	14	28	28	56	56	84	84	169	168	336.0	336
	CHL N = 103	QTP N = 93	CHL N = 95	QTP N = 93	CHL N = 20	QTP N = 22	CHL N =129	QTP N =122	-	-	-	-
Mean (SD) Wt at BL	68.8 (13.6)	69.3 (13.8)	68.9 (13.7)	68.4 (13.6)	73.7 (16.5)	77.3 (15.6)	75.8 (16.0)	74.3 (15.3)	-	-	-	-

Mean (SD) Wt at EOT	69.3 (13.0)	70.4 (13.4)	70.1 (13.2)	69.7 (13.3)	75.5 (17.0)	76.3 (15.5)	76.8 (15.8)	75.9 (16.1)	-	-	-	-
Mean (SD) Wt Change	0.6 (2.4)	1.0 (2.5)	1.2 (3.1)	1.2 (3.2)	1.8 (3.7)	-1.0 (5.3)	1.0 (4.4)	1.6 (4.5)	-	-	-	-
p-value	0.211	-	0.861	-	0.106	-	0.303		-	-	-	-
Modal (SD) Dose	455 (167)	481 (148)	504 (175)	482 (145)	840 (123)	600	728 (157)	603 (19)	-	-	-	-
Median Exp (days)	14	14	28	28	62	56	70	70	-	-	-	-

Information obtained from Sponsor table 22, 28, 34 and 40 in Clinical Study Report baseline assessment
QTP- quetiapine, CHL - Chlorpromazine, OlZ – olanzapine, RIS – risperidone, HAL – haloperidol

4. Mean BMI Change (kg/m^2)

The olanzapine-treated subjects had a mean increase in BMI (kg/m^2) from baseline of 2.0 kg/ m^2 at a modal olanzapine dose of 14 mg per Day, compared to 1.1 kg/ m^2 in quetiapine–treated subjects with a median exposure of 168 days. As can be seen in table 18 below for mean BMI change observed in the risperidone, chlorpromazine and haloperidol groups, the greatest mean increase was seen in the olanzapine treated group for all BMI categories while similar mean changes were noted in other antipsychotic treatment groups including quetiapine.

Table 18: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) (comparator-controlled trials)

	QTP N = 294	**OLZ** N =286	**QTP** N =676	**RIS** N =659	**QTP** N =249	**CHL** N =250	**QTP** N =804	**HAL** N =515
Mean (SD) BMI at BL	25 (5)	25.2 (5.2)	26.7 (6.4)	27.2 (6.6)	25.6(5.5)	25.2 (5.1)	26.4(5.3)	25.7(5.1)
Mean (SD) BMI at EOT	26 (5)	27.2 (5.9)	27.4 (6.5)	28.0 (6.3)	26.0(5.4)	25.7 (5.2)	26.8(5.3)	25.7(5.0)
Mean (SD) BMI Change	1.1(2.2)	2.0 (2.7)	0.7 (2.2)	0.8 (2.3)	0.4(1.4)	0.5(2.2)	0.4(1.8)	0.0(1.4)
p-value	<0.001	-	0.565	-	0.716	-	<0.001	-
Modal (SD) Dose	562 (192)	14 (5)	555	5	539 (139)	563 (194)	445 (233)	10 (5)
Median Exposure (days)	168	168	56	56	49.0	51	42	42

Information obtained from Sponsor table 23, 29, 35 and 41 in Clinical Study Report
QTP- quetiapine, CHL - Chlorpromazine, OlZ – olanzapine, RIS - risperidone, HAL – haloperidol

5. Mean BMI Change by BMI Category

The mean BMI change by baseline BMI category was an increase of 2.2, 2.0, 1.9 and 2.3 kg/ m^2, for olanzapine–treated subjects; an increase of 1.3,1.0, 1.1 and 1.3 kg/ m^2 for quetiapine–treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively. See table 19 below for mean BMI change (by BMI Category) observed in the quetiapine group compared to the olanzapine, risperidone, chlorpromazine and haloperidol groups.

Table 19: BMI (kg/m2) - change from baseline (BL) to end of treatment (EOT) by BMI category (comparator-controlled trials)

BMI category (kg/m2)	**QTP**	**OLZ**	**QTP**	**RIS**	**QTP**	**CHL**	**QTP**	**HAL**
Underweight BMI ≤ 18.5 (N)	19	18	29	23	10	13	20	-
Mean (SD) BMI at BL	17.2 (1.1)	17.7(0.8)	17.2(1.1)	17.5(0.9)	17.9(0.6)	17.4(1.5)	17.5(0.6)	17.3(0.9)
Mean (SD) BMI at EOT	18.5 (2.3)	19.8(2.2)	18.4(1.9)	19.3(1.3)	18.7(1.0)	17.9(1.9)	17.9(1.5)	18.3(1.1)
Mean (SD) BMI Change	1.3(1.8)	2.2(1.9)	1.2 (1.6)	1.7(1.3)	0.8(1.1)	0.5(10)	0.4(1.2)	1.0(1.1)
p-value	0.155	-	0.191	-	0.166	-	0.168	-
Modal (SD) Dose (mg)	542 (186)	16(4)	528(205)	5	495(157)	546(217)	488(196)	12(4)
Median Exp (days)	168	168	58	163	44	42	42	42
Normal weight BMI 18.5 to 25(N)	143	140	281	264	125	124	344	
Mean (SD) BMI at BL	22.0(1.7)	22.2(1.7)	22.3(1.8)	22.3(1.8)	17.9(0.6)	17.4(1.5)	22.3(1.7)	22.1(1.8)
Mean (SD) BMI at EOT	23.1 (2.7)	24.2(2.8)	23.0(2.4)	23.3(2.3)	18.7(1.0)	17.9(1.9)	23.0(2.2)	22.4(2.0)
Mean Modal (SD) BMI Change	1.0 (2.0)	2.0 (2.3)	0.8 (1.8)	1.1(1.5)	0.8(1.1)	0.5(1.0)	0.7(1.6)	0.3(1.1)
p-value	<0.001	-	0.028	-	0.166	-	0.002	-

Modal (SD) Dose (mg)	558 (198)	14 (4)	553	5	495(157)	546(217)	466(227)	10 (5)
Median Exp (days)	164	168	57	70	42	42	42	42
Overweight BMI 25 to 30 (N)	84	85	203	184	63	72	270	162
Mean (SD) BMI at BL	27.2 (1.5)	27.2(1.5)	27.2(1.5)	27.2(1.3)	27.3(1.4)	27.1(1.3)	27.3(1.4)	27.2(1.4)
Mean (SD) BMI at EOT	28.4 (2.6)	29.2(3.2)	27.9(2.2)	28.1(2.3)	27.7(2.0)	27.4(1.8)	27.7(2.3)	27.0(2.0)
Mean (SD) BMI Change	1.1 (2.3)	1.9 (3.0)	0.8 (1.9)	0.8(2.0)	0.3(1.4)	0.3(1.3)	0.4(1.9)	-0.2(1.3)
p-value	0.018	-	0.866	-	0.769	-	0.005	-
Modal (SD) Dose (mg)	571 (187)	14(5)	553	5.0	566(110)	576(188)	442(236)	10(5)
Median Exp (days)	168	168	56	56	69	69	42	42
Obese BMI $\geq$ 30 (N)	48	43	163	188	51	41	170	97
Mean (SD) BMI at BL	33.2 (3.5)	34.1(5.3)	35.5(5.9)	35.4(5.7)	33.9(4.5)	33.9(3.5)	34.2(4.3)	33.8(3.3)
Mean (SD) BMI at EOT	34.5 (5.1)	36.4(6.4)	36.0(6.3)	35.6(5.4)	33.9(4.6)	33.6(4.0)	34.2(4.6)	33.3(3.8)
Mean Modal (SD) BMI Change	1.3 (2.7)	2.3 (3.8)	0.5 (3.0)	0.2(3.4)	0.0(1.7)	-0.3(2.0)	0.0(1.8)	-0.5(1.9)
p-value	0.146	-	0.499	-	0.347	-	0.138	-
Modal (SD) Dose (mg)	569(188)	15 (5)	563(205)	5(2)	563(108)	593(180)	403(242)	11 (5)
Median Exp (days)	168	168	56	56	65	69	42	42

Information obtained from Sponsor tables 24, 30, 36 and 42 in Clinical Study Report
QTP- quetiapine, CHL - Chlorpromazine, OlZ – olanzapine, RIS – risperidone, HAL – haloperidol

5.2.2 Categorical Analyses

1. Weight Gain Outliers in olanzapine-controlled trials

In a pooled analysis of olanzapine-controlled trials, 47%, 21% and 11% of olanzapine-treated subjects had a mean weight gain of > 0-5 kg (0-11 lb) at a modal olanzapine dose of 11 mg per Day, compared to 65%, 30 % and 14% of quetiapine- treated subjects had a mean weight gain of > 0-5 kg (0-11 lb) at a modal quetiapine dose of 569 mg per Day at 6 week, 6 month and 12 month time-points. For the outlier analysis of the higher weight categories of >5 kg, the proportion of subjects increases with over time for both in the quetiapine and olanzapine treated groups.

Table 20: Proportion of Patients with Weight (in kg) Change at 6 Weeks, 6 and 12 Months (comparator-controlled trials)

	QTP			**OLZ**		
	6 Weeks N = 106	6 Months N = 116	12 Months N = 37	6 Weeks N = 112	6 Months N = 119	12 Months N = 44
Weight change	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
≤0	19 (17.9)	35 (30.2)	12 (32.4)	14 (12.5)	17 (14.3)	4 (9.1)
0 to ≤5 (0-11 lb)	69 (65.1)	34 (29.3)	5 (13.5)	53 (47.3)	25 (21.0)	5 (11.4)
>5 to ≤10 (11-22 lb)	16 (15.1)	21 (18.1)	8 (21.6)	31 (27.7)	33 (27.7)	10 (22.7)
>10 to ≤15 (22-33 lb)	2 (1.9) 20	20 (17.2)	4 (10.8)	12 (10.7)	21 (17.6)	11 (25.0)
>15 to ≤20 (33-44 lb)	0	6 (5.2)	4 (10.8)	2 (1.8)	13 (10.9)	4 (9.1)
>20 to ≤25 (44-55 lb)	0	0	3 (8.1)	0	4 (3.4)	5 (11.4)
>25 to ≤30 (55-66 lb)	0	0	1 (2.7)	0	6 (5.0)	5 (11.4)
Modal (SD) Dose in mg	569 (192)			13 (5)		
Median Exp (days)	170			172		

Information obtained from Sponsor tables 25, 31, 37, and 43 in Clinical Study Report, OlZ – olanzapine

2. Weight Gain Outliers in risperidone-controlled trials

In a pooled analysis of risperidone-controlled trials, 52%, 42% and 28% of risperidone-treated subjects had a mean weight gain of > 0-5 kg (0-11 lb) at a mean risperidone dose of 5 mg per Day, compared to 56%, 29 % and 13% of quetiapine-treated subjects had a mean weight gain of

> 0-5 kg (0-11 lb) at a mean quetiapine dose of 599 mg per Day at 6 week, 6 and 12 month intervals. Although the same sizes were noted to be small, for the outlier analysis of the higher weight categories of >5 kg, the proportion of subjects seems to increase over time for both in the quetiapine and risperidone treated groups.

Table 21: Proportion of Patients with Weight (in kg) Change at 6 Weeks, 6 and 12 Months (comparator-controlled trials)

	QTP			RIS		
	6 Wks N = 275	6 Mths N = 116	12 Mths N = 37	6 Wks N = 307	6 Mths N = 117	12 Mths N = 36
Weight change	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
≤0	74 (26.9)	35 (30.2)	12 (32.4	92 (30.0)	21 (17.9)	7 (19.4)
0 to ≤5 (0-11 lb)	154 (56.0)	34 (29.3)	5 (13.5)	160 (52.1)	49 (41.9)	10 (27.8)
>5 to ≤10 (11-22 lb)	40 (14.5)	21 (18.1)	8 (21.6)	50 (16.3)	29 (24.8)	7 (19.4)
>10 to ≤15 (22-33 lb)	6 (2.2)	20 (17.2)	4 (10.8)	3 (1.0)	11 (9.4)	5 (13.9)
>15 to ≤20 (33-44 lb)	1 (0.4)	6 (5.2)	4 (10.8)	1 (0.3)	5 (4.3)	5 (13.9)
>20 to ≤25 (44-55 lb)	0	0	3 (8.1)	0	0	0
>25 to ≤30 (55-66 lb)	0	0	1 (2.7)	1 (0.3)	2 (1.7)	2 (5.6)
Modal (SD) Dose in mg	599 (188)			5 (2)		
Median Exp (days)	43			43		

Information obtained from Sponsor tables 25, 31, 37, and 43 in Clinical Study Report, RIS – risperidone

3. Weight Gain Outliers in chlorpromazine-controlled trials

In a pooled analysis of chlorpromazine-controlled trials, the proportions of patients with weight gain for each category was noted to be similar between the chlorpromazine-treated subjects and the quetiapine-treated subjects at week 6.

Table 22: Proportion of Patients with Weight (in kg) Change at Week 6 (comparator-controlled trials)

Chlorpromazine	**QTP** (N = 168)	**CHL**(N = 161)
Weight change (kg)	N (%)	N (%)
≤0	60(35.7)	63(39.1)
0 to ≤5 (0-11 lb)	86(51.2)	79(49.1)
>5 to ≤10 (11-22 lb)	19(11.3)	16 (9.9)
>10 to ≤15 (22-33 lb)	2 (1.2)	2 (1.2)
>15 to ≤20 (33-44 lb)	1 (0.6)	0
>20 to ≤25 (44-55 lb)	0	0
Modal (SD) Dose (mg)	538.2(115.7)	545.3(120.1)
Median Exposure (days)	42.0	42.0

Information obtained from Sponsor tables 25, 31, 37 and 43 in Clinical Study Report
QTP- quetiapine, CHL -Chlorpromazine

4. Weight Gain Outliers in haloperidol-controlled trials

In a pooled analysis of haloperidol -controlled trials, 40%, 46% and 35% of haloperidol -treated subjects had a mean weight gain of > 0-5 kg (0-11 lb) at a modal haloperidol dose of 9 mg per Day, compared to 45%, 37 % and 31% of quetiapine- treated subjects had a mean weight gain of > 0-5 kg (0-11 lb) at a modal quetiapine dose of 449 mg per Day at 6 week, 6 and 12 month intervals. For the outlier analysis of the higher weight categories of >5-10, and >10-15 kg, the proportion of subjects seems to be increased over time in the quetiapine treated group.

Table 23: Proportion of Patients with Weight (in kg) Change at 6 Weeks, 6 and 12 Months (comparator-controlled trials)

	QTP			HAL		
	6 Weeks N = 420	6 Months N = 57	12 Months N = 73	6 Weeks N = 307	6 Months N = 11	12 Months N = 52
Weight change	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
≤0	156 (37.1)	11 (19.3)	20 (27.4)	168 (54.7)	5 (45.5)	22 (42.3)
0 to ≤5 (0-11 lb)	190 (45.2)	21 (36.8)	23 (31.5)	124 (40.4)	5 (45.5)	18 (34.6)
>5 to ≤10 (11-22 lb)	64 (15.2)	20 (35.1)	13 (17.8)	15 (4.9)	1 (9.1)	9 (17.3)
>10 to ≤15 (22-33 lb)	9 (2.1)	3 (5.3)	12 (16.4)	0	0	1 (1.9)
>15 to ≤20 (33-44 lb)	1 (0.2)	0	0	0	0	1 (1.9)
>20 to ≤25 (44-55 lb)	0	0	4 (5.5)	0	0	0
>25 to ≤30 (55-66 lb)	0	2 (3.5)	1 (1.4)	0	0	1 (1.9)
Modal (SD) Dose	449 (228)			9 (5)		
Median Exp (days)	43			43		

Information obtained from Sponsor tables 25, 31, 37 and 44 in Clinical Study Report
EOT – end of treatment, PLA - placebo, QTP- quetiapine, HAL – haloperidol

5.3 Adult Subjects in Long Term Controlled and Uncontrolled Trials

5.3.1 Mean Change Analyses

1. Mean Body Weight Change

The quetiapine-treated subjects (N = 17515) who received a mean daily dose of 397 mg, gained an average of 1.3 kg (2.9 lbs) with a median exposure of 61 days.

Table 24: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) (all QTP trials)

	QTP (N = 17515)
Mean (SD) Weight at BL	77.9 (20.3)
Mean (SD) Weight at EOT	79.3 (20.5)
Mean (SD) Weight Change	1.3 (4.6)
Modal (SD) Dose (mg)	397.3 (241.5)
Median Exposure (days)	61

Information obtained from Sponsor table 44 in Clinical Study Report

2. *Mean Body Weight Change by BMI Category*

The mean weight gain by baseline BMI category was 2.3 kg, 1.7 kg, 1.2 kg and 0.8 kg for quetiapine–treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

Table 25: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by BMI category (all QTP trials)

BMI category (kg/m2)		**QTP**
Underweight BMI ≤ 18.5	N	570
	Mean (SD) Weight at BL	48.5 (6.9)
	Mean (SD) Weight at EOT	50.8 (8.1)
	Mean (SD) Weight Change	2.3 (4.0)
	Modal (SD) Dose (mg)	459.9 (238.6)
	Median Exposure (days)	68
Normal weight BMI 18.5 to 25	N	6088
	Mean (SD) Weight at BL	63.9 (9.2)
	Mean (SD) Weight at EOT	65.6 (9.9)
	Mean (SD) Weight Change	1.7 (4.1)
	Modal (SD) Dose (mg)	410.1 (242.6)
	Median Exposure (days)	64

Overweight BMI 25 to 30	N	4932
	Mean (SD) Weight at BL	79.1 (10.0)
	Mean (SD) Weight at EOT	80.3 (10.8)
	Mean (SD) Weight Change	1.2 (4.5)
	Modal (SD) Dose (mg)	394.3 (243.0)
	Median Exposure (days)	63
Obese BMI ≥30	N	4673
	Mean (SD) Weight (kg) at BL	100.8 (18.4)
	Mean (SD) Weight (kg) at EOT	101.6 (18.9)
	Mean (SD) Weight (kg) Change	0.8 (5.1)
	Modal (SD) Dose (mg)	380.7 (244.6)
	Median Exposure (days)	57

Information obtained from Sponsor table 45 in Clinical Study Report

3. Mean Body Weight Change by Time (in Weeks)

The mean weight gain from baseline to endpoint for quetiapine–treated subjects was 0.8 kg, 1.0 kg, 1.3 kg, 1.5 kg, 2.2 kg and 3.1 kg (0.8 to 6.8 lbs) at the 2, 4, 8, 12, 24 and 48 weeks interval, respectively.

Table 26: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by week (all QTP trials)

	Wk 2	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**	**Wk 48**
Seroquel = N	5865	8800	7884	6025	1659	383
Mean (SD) Weight at BL	77.7 (21.0)	76.5 (20.4)	76.8 (20.4)	75.8(19.8)	74.1 (17)	75.1 (18)
Mean (SD) Weight at EOT	78.5 (21.1)	77.4 (20.4)	78.1(20.5)	77.3 (19.8)	76.4 (18)	78.2 (19)
Mean (SD) Weight Change	0.8 (2.7)	1.0 (3.2)	1.3 (3.7)	1.5 (4.4)	2.2(5)	3.1 (7.9)
Modal (SD) Dose (mg)	373(246)	448 (252)	413 (235)	451(254)	478 (23)	427 (222)
Median Exposure (days)	15	29	57	85	169	337

Information obtained from Sponsor table 46 in Clinical Study Report

4. Mean BMI Change (kg/m2)

The quetiapine-treated subjects (N = 16263) had a mean increase in BMI (kg/m^2) from baseline of 0.5 kg/ m^2 at a modal quetiapine dose of 399 mg per Day with a median exposure of 62 days.

Table 27: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) (all QTP trials)

	QTP (N = 16263)
Mean (SD) BMI at BL	27.5 (6.7)
Mean (SD) BMI at EOT	28.0 (6.7)
Mean (SD) BMI Change	0.5 (1.6)
Modal (SD) Dose (mg)	398.6 (243.7)
Median Exposure (days)	62

Information obtained from Sponsor table 47 in Clinical Study Report

5. Mean BMI Change by BMI Category

The mean BMI change by baseline BMI category was 0.8, 0.6, 0.4 and 0.3 kg/ m^2, for quetiapine–treated subjects for underweight (BMI < 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively. A decreasing trend was observed here.

Table 28: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) by BMI category (all QTP trials)

BMI category (kg/m2)		**QTP**
Underweight BMI ≤ 18.5	N	570
	Mean (SD) BMI at BL	17.3 (1.2)
	Mean (SD) BMI at EOT	18.1 (1.9)
	Mean (SD) BMI Change	0.8 (1.5)

	Modal (SD) Dose (mg)	459.9 (238.6)
	Median Exposure (days)	68
Normal weight BMI 18.5 to 25	N	6088
	Mean (SD) BMI at BL	22.3 (1.7)
	Mean (SD) BMI at EOT	22.9 (2.2)
	Mean (SD) BMI Change	0.6 (1.4)
	Modal (SD) Dose (mg)	410.1 (242.6)
	Median Exposure (days)	64
Overweight BMI 25 to 30	N	4932
	Mean (SD) BMI at BL	27.3 (1.4)
	Mean (SD) BMI at EOT	27.7 (2.1)
	Mean (SD) BMI Change	0.4 (1.6)
	Modal (SD) Dose (mg)	394.3 (243.0)
	Median Exposure (days)	63
Obese BMI ≥ 30	N	4673
	Mean (SD) BMI at BL	35.8 (5.7)
	Mean (SD) BMI at EOT	36.0 (5.9)
	Mean (SD) BMI Change	0.3 (1.8)
	Modal (SD) Dose (mg)	380.7 (244.6)
	Median Exposure (days)	57

Information obtained from Sponsor table 48 in Clinical Study Report

5.3.2 Categorical Analyses

1. Weight Gain Outliers

In a pooled analysis of all quetiapine trials 53%, 42%, 35%, 28% and 23% had a mean weight gain of > 0-5 kg (0-11 lb) at a mean quetiapine dose of 405 mg per Day at Week 6 and at 6, 12, 24 and 36 months interval, respectively.

Table 29: Proportion of Patients with Weight Change at 6 Weeks, 6, 12, 24 and 36 Months (all QTP trials)

QTP	**6 Weeks** N = 5703	**6 Months** N = 1531	**12 Months** N = 900	**24 Months** N = 229	**36 Months** N = 148
Weight change (kg)	N (%)	N (%)	N (%)	N (%)	N (%)
≤0	2117 (37.1)	562 (36.7)	314 (34.9)	60 (26.2)	32 (21.6)
0 to ≤5 (0-11 lb)	3043 (53.4)	636 (41.5)	311 (34.6)	64 (27.9)	34 (23.0)
>5 to ≤10 (11-22 lb)	467 (8.2)	212 (13.8)	147 (16.3)	47 (20.5)	34 (23.0)
>10 to ≤15 (22-33 lb)	61 (1.1)	89 (5.8)	77 (8.6)	28 (12.2)	24 (16.2)
>15 to ≤20 (33-44 lb)	9 (0.2)	22 (1.4)	24 (2.7)	20 (8.7)	13 (8.8)
>20 to ≤25 (44-55 lb)	2 (0.0)	4 (0.3)	20 (2.2)	2 (0.9)	6 (4.1)
>25 to ≤30 (55-66 lb)	4 (0.1)	6 (0.4)	7 (0.8)	8 (3.5)	5 (3.4)
Modal (SD) Dose	405.0 (235.6)				
Median Exp (days)	43				

Information obtained from Sponsor table 49 in Clinical Study Report

5.4 Antipsychotic-Naïve Subjects in Placebo-Controlled Trials

5.4.1 Mean Change Analyses

1. Mean Body Weight Change

The quetiapine-treated subjects (N = 2410) who received a modal daily dose of 167 mg, gained an average of 1.0 kg (2.2 lbs), compared to an increase of 0.3 kg (0.7 lbs) in placebo-treated subjects (N = 1141) with a median exposure of 49-55 days.

Table 30: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) (naïve subjects, placebo-controlled trials)

	QTP (N = 2410)	**Placebo** (N = 1141)

Mean (SD) Weight at BL	80.2 (20.8)	80.7 (22.2)
Mean (SD) Weight at EOT	81.2 (20.9)	81.0 (22.3)
Mean (SD) Weight Change	1.0 (2.4)	0.3 (3.9)
p-value	<0.001	-
Modal (SD) Dose (mg)	176.0 (116.3)	-
Median Exposure (days)	49	55

Information obtained from Sponsor table 64 in Clinical Study Report

2. *Mean Body Weight Change by BMI Category*

The mean weight gain by baseline BMI category was 1.2 kg, 1.1 kg, 1.1 kg and 0.8 kg, for quetiapine–treated subjects and 0.8 kg, 0.5 kg, 0.2 kg and 0.2 kg for placebo–treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

Table 31: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by BMI category (naïve subjects, placebo-controlled trials)

BMI category (kg/m2)		**QTP**	**Placebo**
Underweight BMI ≤ 18.5	N	64	40
	Mean (SD) Weight at BL	48.8 (7.1)	47.7 (7.1)
	Mean (SD) Weight at EOT	50.0 (7.5)	48.5 (7.9)
	Mean (SD) Weight Change	1.2 (1.8)	0.8 (2.9)
	p-value	0.423	-
	Modal (SD) Dose (mg)	222.7 (190.4)	-
	Median Exposure (days)	56	54
Normal weight BMI 18.5 to 25	N	822	357
	Mean (SD) Weight at BL	63.5 (8.9)	62.9 (8.7)
	Mean (SD) Weight at EOT	64.6 (9.2)	63.4 (9.7)
	Mean (SD) Weight Change	1.1 (2.1)	0.5 (4.5)
	p-value	0.004	-
	Modal (SD) Dose (mg)	177.6 (131.6)	-
	Median Exposure (days)	50	55
Overweight BMI 25 to 30	N	717	358
	Mean (SD) Weight at BL	78.8 (10.2)	79.1 (10.2)
	Mean (SD) Weight at EOT	79.9 (10.6)	79.4 (10.3)
	Mean (SD) Weight Change	1.1 (2.3)	0.2 (2.2)
	p-value	<0.001	-
	Modal (SD) Dose (mg)	170.0 (100.7)	-
	Median Exposure (days)	49	55
Obese BMI ≥30	N	805	384
	Mean (SD) Weight at BL	100.9 (18.1)	102.1 (20.3)
	Mean (SD) Weight at EOT	101.7 (18.4)	102.3 (20.5)
	Mean (SD) Weight Change	0.8 (2.7)	0.2 (4.6)
	p-value	0.005	-
	Modal (SD) Dose (mg)	175.9 (103.5)	-
	Median Exposure (days)	49	55

Information obtained from Sponsor table 65 in Clinical Study Report

3. Mean Body Weight Change by Time (in Weeks)

The mean weight gain from baseline to endpoint for quetiapine–treated subjects showed 0.8 kg, 0.9 kg, 1.0 kg, and 0.3 kg and for placebo-treated subjects showed 0.2 kg, 0.2 kg, 0.3 kg, and 0.5 kg at 2, 4, 8, and 12 weeks, respectively.

Table 32: Weight (in kg) - change from baseline to end of treatment by week (naïve subjects, placebo-controlled trials)

	Wk 2	Wk 4	Wk 8	Wk 12
Quetiapine= N	2017	1925	1099	8
Mean (SD) Weight at Baseline	80.5 (21.0)	80.1 (20.8)	78.8 (20.5)	80.9 (16.0)
Mean (SD) Weight at EOT	81.2 (21.0)	81.0 (20.8)	79.8 (20.6)	81.2 (14.8)
Mean (SD) Weight Change	0.8 (1.8)	0.9 (2.4)	1.0 (2.6)	0.3 (2.8)
p-value	<0.001	<0.001	<0.001	0.930
Modal (SD) Dose (mg)	180.7 (119.0)	180.9 (119.5)	161.4 (90.9)	162.5 (95.4)
Median Exposure (days)	15	29	57	70
Placebo= N	1024	977	635	3
Mean (SD) Weight at Baseline	80.7 (22.3)	80.7 (22.2)	80.0 (22.5)	94.6 (36.2)
Mean (SD) Weight at EOT	80.9 (22.3)	80.9 (22.2)	80.3 (22.5)	95.1 (35.4)
Mean (SD) Weight Change	0.2 (2.1)	0.2 (2.2)	0.3 (2.5)	0.5 (1.5)
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	15	29	57	71

Information obtained from Sponsor table 66 in Clinical Study Report

4. Mean BMI Change (kg/m^2)

The quetiapine-treated subjects (N = 2408) had a mean increase in BMI (kg/m^2) from baseline of 0.4 kg/ m^2 at a modal quetiapine dose of 176 mg per Day, compared to 0.1 kg/ m^2 in placebo–treated subjects (N = 1139) with a median exposure of 49-55 days.

Table 33: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) (naïve subjects, placebo-controlled trials)

	QTP (N = 2408)	**Placebo** (N = 1139)
Mean (SD) BMI at BL	28.2 (7.0)	28.5 (7.4)
Mean (SD) BMI at EOT	28.6 (7.0)	28.6 (7.5)
Mean (SD) BMI Change	0.4 (0.8)	0.1 (1.4)
p-value	<0.001	-
Modal (SD) Dose (mg)	176.0 (116.3)	-
Median Exposure (days)	49	55

Information obtained from Sponsor table 47 in Clinical Study Report

5. Mean BMI Change by BMI Category

The mean BMI change by baseline BMI category showed 0.4, 0.4, 0.4 and 0.3 kg/ m^2, for quetiapine–treated subjects and showed 0.3, 0.2, 0.1 and 0.1 kg/ m^2 for placebo–treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

Table 34: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) by BMI category (naïve subjects, placebo-controlled trials)

BMI category (kg/m2)		**QTP**	**Placebo**
Underweight BMI ≤ 18.5	N	64	40
	Mean (SD) BMI at BL	17.4 (1.0)	17.6 (0.7)
	Mean (SD) BMI at EOT	17.8 (1.3)	17.9 (1.3)
	Mean (SD) BMI Change	0.4 (0.6)	0.3 (1.0)
	p-value	0.459	-
	Modal (SD) Dose (mg)	222.7 (190.4)	-
	Median Exposure (days)	56	54
Normal weight BMI 18.5 to 25	N	822	357
	Mean (SD) BMI at BL	22.2 (1.8)	22.2 (1.8)
	Mean (SD) BMI at EOT	22.6 (1.9)	22.4 (2.3)
	Mean (SD) BMI Change	0.4 (0.7)	0.2 (1.6)
	p-value	0.002	-
	Modal (SD) Dose (mg)	177.6 (131.6)	-

	Median Exposure (days)	50	55
Overweight BMI 25 to 30	N	717	358
	Mean (SD) BMI at BL	27.3 (1.4)	27.3 (1.4)
	Mean (SD) BMI at EOT	27.7 (1.6)	27.4 (1.6)
	Mean (SD) BMI Change	0.4 (0.8)	0.1 (0.8)
	p-value	<0.001	-
	Modal (SD) Dose (mg)	170.0 (100.7)	-
	Median Exposure (days)	49	55
Obese BMI ≥ 30	N	805	384
	Mean (SD) BMI at BL	36.0 (5.7)	36.6 (6.5)
	Mean (SD) BMI at EOT	36.3 (5.8)	36.7 (6.6)
	Mean (SD) BMI Change	0.3 (1.0)	0.1 (1.6)
	p-value	0.003	-
	Modal (SD) Dose (mg)	175.9 (103.5)	-
	Median Exposure (days)	49	55

Information obtained from Sponsor table 68 in Clinical Study Report

5.4.2 Categorical Analyses

1. Weight Gain Outliers

Among quetiapine-treated subjects (N = 1677) 62% had a mean weight gain of > 0-5 kg (0-11 lb) at a mean quetiapine dose of 180 mg per Day, compared to 52% had a mean weight gain of > 0-5 kg (0-11 lb) in the placebo-controlled subjects (N = 881) at Week 6.

Table 35: Proportion of Patients with Weight Change at Week 6 (naïve subjects, placebo-controlled trials)

	QTP (N = 1677)	**Placebo** (N = 881)
Weight change (kg)	N (%)	N (%)
≤0	556 (33.2)	420 (47.7)
0 to ≤5 (0-11 lb)	1044 (62.3)	454 (51.5)
>5 to ≤10 (11-22 lb)	71 (4.2)	4 (0.5)
>10 to ≤15 (22-33 lb)	5 (0.3)	1 (0.1)
>15 to ≤20 (33-44 lb)	0	1 (0.1)
>20 to ≤25 (44-55 lb)	0	0
>25 to ≤30 (55-66 lb)	1 (0.1)	1 (0.1)
Modal (SD) Dose (mg)	180 (119)	-
Median Exposure (days)	43	43

Information obtained from Sponsor table 69 in Clinical Study Report

5.5 Antipsychotic-Naïve Subjects in Comparator-Controlled Trials

5.5.1 Mean Change Analyses

1. Mean Body Weight Change (in Kg)

The olanzapine-treated subjects (N = 65) gained an average of 8.8 kg (19 lbs) at a mean olanzapine dose of 12 mg per Day, compared to a 4.5 kg (10 lbs) weight gain in antipsychotic naïve quetiapine-treated subjects (N = 67) with a median exposure of 179-238 days.

The risperidone-treated subjects (N = 62) gained an average of 5.4 kg (12 lbs) at a mean olanzapine dose of 12 mg per Day, compared to a 4.5 kg (10 lbs) weight gain in antipsychotic naïve quetiapine-treated subjects (N = 67) with a median exposure of 150-238 days.

Table 36: Weight (in Kg) - change from baseline (BL) to end of treatment (EOT) (naïve subjects, comparator-controlled trials)

	QTP (N = 65)	**OLZ** (N = 67)	**QTP** (N =65)	**RIS** (N = 62)
Mean (SD) Wt at BL	77.2 (19.2)	79.2 (22.0)	77.2 (19.2)	79.1 (20.4)
Mean (SD) Wt at EOT	81.7 (22.7)	88.1 (23.1)	81.7 (22.7)	84.5 (21.4)
Mean (SD) Wt Change	4.5 (7.9)	8.8 (8.4)	4.5 (7.9)	5.4 (6.7)
p-value	0.003	-	0.505	-
Modal (SD) Dose (mg)	503 (210.0)	12 (5)	503 (210)	2 (1)
Median Exposure (days)	238	179	238	150

Information obtained from Sponsor tables 70 and 76 in Clinical Study Report
QTP- quetiapine, OlZ – olanzapine, RIS - risperidone

2. *Mean Body Weight Change by BMI Category*

The mean weight gain by baseline BMI category showed 14.5 kg, 7.6 kg, 12.5 kg and 7.0 kg, for olanzapine–treated subjects and showed 3.8 kg, 4.0 kg, 4.7 kg and 5.8 kg for antipsychotic naïve quetiapine-treated subjects for underweight (BMI < 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.
The mean weight gain by baseline BMI category showed 9.1 kg, 5.2 kg, 4.1 kg and 7.8 kg, for risperidone–treated subjects and showed 3.8 kg, 4.0 kg, 4.7 kg and 5.8 kg for antipsychotic naïve quetiapine-treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

Table 37: **Weight (in kg) - change from baseline to end of treatment by BMI category (naïve subjects, comparator-controlled trials)**

BMI category (kg/m2)	**QTP**	**OLZ**	**QTP**	**RIS**
Underweight BMI ≤ 18.5 = N	3	2	3	1
Mean (SD) Wt at BL	51.7 (8.6)	51.5 (2.2)	51.7 (8.6)	59.9
Mean (SD) Wt at EOT	55.5 (8.7)	66.0 (2.9)	55.5 (8.7)	68.9
Mean (SD) Wt Change	3.8 (3.0)	14.5 (0.6)	3.8 (3.0)	9.1
p-value	0.018	-	0.268	-
Modal (SD) Dose (mg)	433.3 (208.2)	10.0 (0.0)	433.3 (208.2)	2.0
Median Exposure (days)	367	235	367	139
Normal weight BMI 18.5 to 25 =N	33	38	33	30
Mean (SD) Wt at BL	65.8 (9.5)	69.1 (8.0)	65.8 (9.5)	67.3 (8.7)
Mean (SD) Wt at EOT	69.8 (11.4)	76.8 (10.2)	69.8 (11.4)	72.5 (9.2)
Mean (SD) Wt Change	4.0 (6.7)	7.6 (8.4)	4.0 (6.7)	5.2 (5.3)
p-value	0.050	-	0.448	-
Modal (SD) Dose (mg)	496.9 (197.5)	12.6	496.9 (197.5)	2.2 (0.9)
Median Exposure (days)	307	166	307	172
Overweight BMI 25 to 30 = N	16	15	16	17
Mean (SD) Wt at BL	85.0 (9.4)	87.3 (13.5)	85.0 (9.4)	81.4 (10.7)
Mean (SD) Wt at EOT	89.7 (14.2)	99.8 (14.6)	89.7 (14.2)	85.5 (11.2)
Mean (SD) Wt Change	4.7 (7.3)	12.5 (9.7)	4.7 (7.3)	4.1 (9.1)
p-value	0.017	-	0.852	-
Modal (SD) Dose (mg)	493.8 (235.1)	10.8 (4.5)	493.8 (235.1)	2.3 (1.1)
Median Exposure (days)	183	198	183	104
Obese BMI ≥ 30 = N	13	11	13	11
Mean (SD) Wt at BL	102.4 (17.9)	110.4 (30.7)	102.4 (17.9)	110.9 (23.1)
Mean (SD) Wt at EOT	108.3 (27.1)	117.4 (32.2)	108.3 (27.1)	118.7 (24.1)
Mean (SD) Wt Change	5.8 (11.9)	7.0 (5.7)	5.8 (11.9)	7.8 (6.9)
p-value	0.774	-	0.633	-
Modal (SD) Dose (mg)	546.2 (225.9)	11.6 (6.4)	546.2 (225.9)	2.5 (0.9)
Median Exposure (days)	305	179	305	181

Information obtained from Sponsor tables 71 and 77 in Clinical Study Report, OlZ – olanzapine, RIS - risperidone

3. Mean Body Weight Change by Time (in Weeks)

Mean body weight increases over time of exposure for both active comparators and quetiapine treated antipsychotic naive patients. The magnitude of weight gain was relatively smaller in the quetiapine group compared to olanzapine or risperidone treatment in this population during the same treatment time points.

The mean weight gain from baseline to endpoint for olanzapine–treated subjects showed 2.7 kg, 4.1 kg, 6.3 kg, 7.8 kg, 11.2 kg, and 14.1 kg and for antipsychotic naïve quetiapine-treated subjects showed 1.4 kg, 2.3 kg, 3.9 kg, 4.2 kg, 5.2 kg and 7.9 kg at 2, 4, 8, 12, 24 and 48 weeks, respectively. The mean weight gain from baseline to endpoint for risperidone–treated subjects showed 1.2 kg, 2.1 kg, 3.4 kg, 3.9 kg, 6.4 kg, and 10.6 kg and for antipsychotic naïve quetiapine-treated subjects showed 1.4 kg, 2.3 kg, 3.9 kg, 4.2 kg, 5.2 kg, 7.9 kg at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 38: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by week (naïve subjects, comparator-controlled trials)

	Week 2		**Week 4**		**Week 8**		**Week 12**		**Week 24**		**Week 48**	
Olanzapine	QTP N=56	OLZ N= 55	QTP N=60	OLZ N=60	QTP N=49	OLZ N=52	QTP N=50	OLZ N=53	QTP N= 36	OLZ N= 36	QTP N=24	OLZ N=18
Mean (SD) Wt at BL	77.1 (19.9)	77.8 (18.4)	77.5 (19.5)	78.3 (21.1)	77.5 (19.1)	78.2 (21.6)	77.2 (20.1)	76.5 (17.1)	75.3 (16.4)	75.9 (14.9)	77.8 (24.5)	73.8 (13.2)
Mean (SD) Wt at EOT	78.5 (20.3)	80.5 (18.2)	79.8 (19.8)	82.3 (21.4)	81.4 (19.8)	84.5 (21.9)	81.5 (21.0)	84.3 (17.9)	80.5 (18.2)	87.0 (16.0)	85.7 (32.3)	87.8 (14.4)
Mean (SD) Wt Change	1.4 (1.9)	2.7 (2.3)	2.3 (2.3)	4.1 (3.3)	3.9 (3.4)	6.3 (4.9)	4.2 (4.4)	7.8 (5.6)	5.2 (6.4)	11.2 (7.3)	7.9 (12.4)	14.1 (8.1)
p-value	0.002	-	<0.001	-	0.005	-	<0.001	-	<0.001	-	0.074	-
Modal (SD) Dose	518.2 (209.1)	12.4 (4.7)	522.0 (203)	12.4 (4.9)	539.6 (202)	13.1 (4.7)	540.8 (202)	12.8 (4.6)	580.0 (184.4)	13.1 (4.8)	582.6 (178)	12.5 5(4.6)
Median Exp (days)	15	15	29	29	57	57	86	85	170	169	336	337
Risperidone	QTP N=56	RIS N=52	QTP N=60	RIS N=58	QTP N=49	RIS N=46	QTP N=50	RIS N=41	QTP N=36	RIS N=23	QTP N=24	RIS N=13
Mean (SD) Wt at BL	77.1 (19.9)	81.7 (20.7)	77.5 (19.5)	80.0 (20.7)	77.5 (19.1)	79.9 (18.1)	77.2 (20.1)	79.9 (18.7)	75.3 (16.4)	80.4 (19.9)	77.8 (24.5)	84.4 (21.0)
Mean (SD) Wt at EOT	78.5 (20.3)	82.9 (20.7)	79.8 (19.8)	82.1 (21.3)	81.4 (19.8)	83.3 (18.4)	81.5 (21.0)	83.8 (18.9)	80.5 (18.2)	86.8 (19.4)	85.7 (32.3)	95.0 (22.7)
Mean (SD) Wt Change	1.4 (1.9)	1.2 (1.8)	2.3 (2.3)	2.1 (2.6)	3.9 (3.4)	3.4 (3.7)	4.2 (4.4)	3.9 (4.2)	5.2 (6.4)	6.4 (6.4)	7.9 (12.4)	10.6 (8.5)
p-value	0.497	-	0.741	-	0.515	-	0.724	-	0.476	-	0.499	-
Modal (SD) Dose	518.2 (209.1)	2.4 (1.0)	522.0 (203)	2.4 (1.0)	539.6 (202)	2.5 (0.9)	540.8 (202)	2.4 (0.8)	580.0 (184)	2.6 (0.9)	582 (178)	2.2 (1.0)
Median Exp (days)	15	15	29	29	57	57	86	85	169	173	336	337

Information obtained from Sponsor table 72 and 78 in Clinical Study Report
QTP- quetiapine, OlZ – olanzapine, Exp –exposure, RIS - risperidone

4. Mean BMI Change (kg/m2)

The olanzapine-treated subjects (N = 66) had a mean increase in BMI (kg/m^2) from baseline of 2.9 kg/m^2 at a modal olanzapine dose of 12 mg per Day, compared to 1.4 kg/m^2 in antipsychotic naïve quetiapine–treated subjects (N = 65) with a median exposure of 181-238 days.

The risperidone-treated subjects (N = 59) had a mean increase in BMI (kg/m^2) from baseline of 2.0 kg/m^2 at a modal risperidone dose of 2.3 mg per Day, compared to 1.4 kg/m^2 in antipsychotic naïve quetiapine–treated subjects (N = 65) with a median exposure of 169-238 days.

Table 39: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) (naïve subjects, comparator-controlled trials)

	QTP (N = 65)	**OLZ** (N = 66)	**QTP** (N = 65)	**RIS** (N = 59)
Mean (SD) BMI at BL	25.7 (5.8)	25.9 (7.0)	25.7 (5.8)	26.5 (6.2)
Mean (SD) BMI at EOT	27.1 (6.8)	28.8 (7.1)	27.1 (6.8)	28.5 (7.0)
Mean (SD) BMI Change	1.4 (2.5)	2.9 (2.8)	1.4 (2.5)	2.0 (2.6)
p-value	0.002	-	0.230	-
Modal (SD) Dose (mg)	503.1 (210.0)	11.9 (5.3)	503.1 (210.0)	2.3 (1.0)
Median Exposure (days)	238	181	238	169

Information obtained from Sponsor table 79 in Clinical Study Report
QTP- quetiapine, OlZ – olanzapine, RIS - risperidone

5. Mean BMI Change by BMI Category

The mean BMI change by baseline BMI category showed 5.1, 2.6, 3.9 and 1.9 kg/ m^2, for olanzapine–treated subjects and 1.4, 1.2,1.4 and 2.0 kg/ m^2 for antipsychotic naïve quetiapine–treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

The mean BMI change by baseline BMI category showed 2.8,1.9, 1.5 and 2.8 kg/ m^2, for risperidone–treated subjects and 1.4, 1.2,1.4 and 2.0 kg/ m^2 for antipsychotic naïve quetiapine–treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

Table 40: BMI (kg/m2) - change from baseline (BL) to end of treatment (EOT) by BMI category (naïve subjects, comparator-controlled trials)

BMI category (kg/m2)	**QTP**	**OLZ**	**QTP**	**RIS**
Underweight BMI ≤ 18.5 = N	3	2	3	1
Mean (SD) Wt at BL	16.7 (0.5)	18.0 (0.4)	16.7 (0.5)	18.4
Mean (SD) Wt at EOT	18.2 (0.8)	23.1 (0.5)	18.2 (0.8)	21.2
Mean (SD) Wt Change	1.4 (0.9)	5.1 (0.1)	1.4 (0.9)	2.8
p-value	0.013	-	0.326	-
Modal (SD) Dose (mg)	433.3 (208.2)	10.0 (0.0)	433.3 (208.2)	2.0
Median Exposure (days)	367.0	235.5	367.0	139.0
Normal weight BMI 18.5 to 25 =N	33	38	33	30
Mean (SD) Wt at BL	22.2 (1.7)	22.3 (1.5)	22.2 (1.7)	22.4 (2.0)
Mean (SD) Wt at EOT	23.3 (2.8)	24.9 (3.0)	23.3 (2.8)	24.3 (2.9)
Mean (SD) Wt Change	1.2 (2.4)	2.6 (2.7)	1.2 (2.4)	1.9 (1.8)
p-value	0.026	-	0.205	-
Modal (SD) Dose (mg)	496.9 (197.5)	12.6 (5.4)	496.9 (197.5)	2.2 (0.9)
Median Exposure (days)	307.0	166.0	307.0	172.0
Overweight BMI 25 to 30 = N	16	15	16	17
Mean (SD) Wt at BL	27.6 (1.6)	27.2 (1.7)	27.6 (1.6)	27.6 (1.3)
Mean (SD) Wt at EOT	29.0 (2.9)	31.1 (2.8)	29.0 (2.9)	29.1 (3.9)
Mean (SD) Wt Change	1.4 (1.9)	3.9 (3.2)	1.4 (1.9)	1.5 (3.6)
p-value	0.013	-	0.899	-
Modal (SD) Dose (mg)	493.8 (235.1)	10.8 (4.5)	493.8 (235.1)	2.3 (1.1)
Median Exposure (days)	183.5	198.0	183.5	104.0
Obese BMI ≥ 30 = N	13	11	13	11
Mean (SD) Wt at BL	34.4 (5.0)	38.3 (8.5)	34.4 (5.0)	36.6 (6.0)
Mean (SD) Wt at EOT	36.4 (7.5)	40.2 (8.3)	36.4 (7.5)	39.4 (6.5)
Mean (SD) Wt Change	2.0 (3.6)	1.9 (2.1)	2.0 (3.6)	2.8 (2.7)
p-value	0.931	-	0.555	-
Modal (SD) Dose (mg)	546.2 (225.9)	11.6 (6.4)	546.2 (225.9)	2.5 (0.9)
Median Exposure (days)	305.0	179.0	305.0	181.0

Information obtained from Sponsor tables 74 and 80 in Clinical Study Report
QTP- quetiapine, OlZ – olanzapine, RIS - risperidone

5.5.2 Categorical Analyses

1. Weight Gain Outliers in olanzapine-controlled trials

In a pooled analysis of olanzapine-controlled trials, 49%, 10 %, and 15% had a mean weight gain of > 0-5 kg (0-11 lb) at a modal olanzapine dose of 13 mg per Day, compared to 64%, 26%, and 13% had a mean weight gain of > 0-5 kg (0-11 lb) in the antipsychotic naïve quetiapine-treated subjects at a modal quetiapine dose of 538 mg per Day for Week 6, 6 and 12 months. Although the sample sizes were small, the proportion of outliers appeared to be increased over time for other higher weight categories as well.

Table 41: Proportion of Patients with Weight (in kg) Change at 6 Weeks, 6 and 12 Months (naïve subjects, olanzapine-controlled trials)

	QTP			**OLZ**		
	6 Weeks N = 56	**6 Months** N = 38	**12 Months** N = 23	**6 Weeks** N = 57	**6 Months** N = 30	**12 Months** N = 20
Weight change	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
≤0	7 (12.5)	13 (34.2)	7 (30.4)	6 (10.5)	2 (6.7)	1 (5.0)
0 to ≤5 (0-11 lb)	36 (64.3)	10 (26.3)	3 (13.0)	28 (49.1)	3 (10.0)	3 (15.0)
>5 to ≤10 (11-22 lb)	12 (21.4)	7 (18.4)	5 (21.7)	15 (26.3)	7 (23.3)	4 (20.0)
>10 to ≤15 (22-33 lb)	1 (1.8)	6 (15.8)	4 (17.4)	7 (12.3)	9 (30.0)	6 (30.0)
>15 to ≤20 (33-44 lb)	0	2 (5.3)	2 (8.7)	1 (1.8)	5 (16.7)	2 (10.0)
>20 to ≤25 (44-55 lb)	0	0	1 (4.3)	0	3 (10.0)	2 (10.0)
>25 to ≤30 (55-66 lb)	0	0	1 (4.3)	0	1 (3.3)	2 (10.0)
Modal (SD) Dose	538.2 (202.3)			12.6 (4.8)		
Median Exp (days)	195.5			173.0		

Information obtained from Sponsor tables 75 in Clinical Study Report, QTP- quetiapine, OlZ – olanzapine, Exp - exposure

2. Weight Gain Outliers in risperidone-controlled trials

In a pooled analysis of risperidone-controlled trials, 70%, 40 %, and 21% had a mean weight gain of > 0-5 kg (0-11 lb) at a modal risperidone dose of 2.4 mg per Day, compared to 64%, 26%, and 26% had a mean weight gain of > 0-5 kg (0-11 lb) in the antipsychotic naïve quetiapine-treated subjects at a modal quetiapine dose of 538 mg per Day for Week 6, 6 and 12 months. Although the sample sizes were small, the proportion of outliers appeared to be increased over time in other higher weight categories.

Table 42: Proportion of Patients with Weight (in kg) Change at 6 Weeks, 6 and 12 Months (naïve subjects, risperidone-controlled trials)

	QTP			**RIS**		
	6 Wks N = 56	**6 Mths** N = 38	**12 Mths** N = 23	**6 Wks** N = 56	**6 Mths** N = 25	**12 Mths** N =14
Weight change	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
≤0	7 (12.5)	13 (34.2)	7 (30.4)	9 (16.1)	2 (8.0)	1 (7.1)
0 to ≤5 (0-11 lb)	36 (64.3)	10 (26.3)	10 (26.3)	39 (69.6)	10 (40.0)	3 (21.4)
>5 to ≤10 (11-22 lb)	12 (21.4)	7 (18.4)	5 (21.7)	7 (12.5)	6 (24.0)	4 (28.6)
>10 to ≤15 (22-33 lb)	1 (1.8)	6 (15.8)	4 (17.4)	1 (1.8)	4 (16.0)	3 (21.4)
>15 to ≤20 (33-44 lb)	0	2 (5.3)	2 (8.7)	0	2 (8.0)	2 (14.3)
>20 to ≤25 (44-55 lb)	0	0	1 (4.3)	0	0	0
>25 to ≤30 (55-66 lb)	0	0	1 (4.3)	0	1 (4.0)	1 (7.1)
Modal (SD) Dose in mg	538.2 (202.3)			2.4 (0.9)		
Median Exp (days)	195.5			46.5		

Information obtained from Sponsor table 81 in Clinical Study Report, QTP- quetiapine, RIS – risperidone, Exp - exposure

5.6 Antipsychotic-Naïve Subjects Controlled and Uncontrolled Trials

5.6.1 Mean Change Analyses

1. *Mean Body Weight Change*

The antipsychotic naïve quetiapine-treated subjects (N = 4509) gained an average of 1.3 kg (2.9 lbs) at a modal quetiapine dose of 174 mg per Day with a median exposure of 57 days.

Table 43: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) (naïve subjects, all QTP trials)

	QTP (N = 4509)
Mean (SD) Weight at BL	81.0 (21.3)
Mean (SD) Weight at EOT	82.2 (21.4)
Mean (SD) Weight Change	1.3 (3.4)
Modal (SD) Dose (mg)	174.1 (116.0)
Median Exposure (days)	57.0

Information obtained from Sponsor table 82 in Clinical Study Report

2. *Mean Body Weight Change by BMI Category*

The mean weight gain by baseline BMI category months 1.7 kg, 1.5 kg 1.3 kg and 1.0 kg, for antipsychotic naïve quetiapine–treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

Table 44: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by BMI category (naïve subjects, all QTP trials)

BMI category (kg/m2)		**QTP**
Underweight BMI ≤ 18.5	N	104
	Mean (SD) Weight at BL	48.7 (6.8)
	Mean (SD) Weight at EOT	50.4 (7.7)
	Mean (SD) Weight Change	1.7 (3.5)
	Modal (SD) Dose (mg)	207.2 (170.0)
	Median Exposure (days)	56.0
Normal weight BMI 18.5 to 25	N	1488
	Mean (SD) Weight at BL	63.6 (8.9)
	Mean (SD) Weight at EOT	65.1 (9.3)
	Mean (SD) Weight Change	1.5 (3.1)
	Modal (SD) Dose (mg)	175.6 (127.8)
	Median Exposure (days)	57.0
Overweight BMI 25 to 30	N	1380
	Mean (SD) Weight at BL	78.9 (10.3)
	Mean (SD) Weight at EOT	80.2 (10.8)
	Mean (SD) Weight Change	1.3 (2.9)
	Modal (SD) Dose (mg)	169.3 (106.0)
	Median Exposure (days)	57.0
Obese BMI ≥30	N	1533
	Mean (SD) Weight at BL	101.9 (18.8)
	Mean (SD) Weight at EOT	102.8 (19.2)
	Mean (SD) Weight Change	1.0 (3.9)
	Modal (SD) Dose (mg)	174.8 (107.4)
	Median Exposure (days)	57.0

Information obtained from Sponsor table 83 in Clinical Study Report

3. Mean Body Weight Change by Time (in Weeks)

The mean weight gain from baseline to endpoint for antipsychotic naïve quetiapine–treated subjects months 0.8 kg, 1.0 kg, 1.2 kg, 1.5 kg, 1.8 kg and 3.9 kg and for 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 45: Weight (in kg) - change from baseline (BL) to end of treatment (EOT) by week (naïve subjects, all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
N	2147	2098	2023	1417	223	86
Mean (SD) Weight at BL	80.4 (20.9)	80.2 (20.7)	80.8 (21.6)	81.6 (22.1)	79.9 (19.6)	80.0 (21.4)
Mean (SD) Weight at EOT	81.1 (20.9)	81.1 (20.7)	81.9 (21.6)	83.1 (22.0)	81.7 (19.7)	83.9 (24.3)
Mean (SD) Weight Change	0.8 (1.8)	1.0 (2.4)	1.2 (3.5)	1.5 (3.9)	1.8 (4.7)	3.9 (8.1)
Modal (SD) Dose (mg)	186.2(132.9)	188.2(134.2)	173.1(112.2)	180.4(119.4)	246.6(182.5)	280.6(224.2)
Median Exposure (days)	15.0	29.0	57.0	85.0	169.0	336.0

Information obtained from Sponsor table 84 in Clinical Study Report

4. Mean BMI Change (kg/m^2)

The antipsychotic naïve quetiapine-treated subjects (N = 4505) had a mean increase in BMI (kg/m^2) from baseline of 0.4 kg/ m^2 at a modal quetiapine dose of 174 mg per Day with a median exposure of 57 days.

Table 46: BMI (kg/m^2) - change from baseline (BL) to end of treatment (EOT) (naïve subjects, all QTP trials)

	QTP (N = 4505)
Mean (SD) BMI at BL	28.5 (7.1)
Mean (SD) BMI at EOT	28.9 (7.1)
Mean (SD) BMI Change	0.4 (1.2)
Modal (SD) Dose (mg)	174.1 (116.0)
Median Exposure (days)	57.0

Information obtained from Sponsor table 85 in Clinical Study Report

5. Mean BMI Change by BMI Category

The mean BMI change by baseline BMI category months 0.6, 0.5, 0.5 and 0.3 kg/ m^2, for antipsychotic naïve quetiapine-treated subjects for underweight (BMI< 18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI > 30) groups, respectively.

Table 47: BMI (kg/m^2) - change from baseline to end of treatment by BMI category (naïve subjects, all QTP trials)

BMI category (kg/m2)		**QTP**
Underweight BMI ≤ 18.5	N	104
	Mean (SD) BMI at BL	17.4 (1.0)
	Mean (SD) BMI at EOT	18.0 (1.6)
	Mean (SD) BMI Change	0.6 (1.3)
	Modal (SD) Dose (mg)	207.2 (170.0)
	Median Exposure (days)	56.0
Normal weight BMI 18.5 to 25	N	1488
	Mean (SD) BMI at BL	22.3 (1.7)
	Mean (SD) BMI at EOT	22.8 (2.0)
	Mean (SD) BMI Change	0.5 (1.1)
	Modal (SD) Dose (mg)	175.6 (127.8)
	Median Exposure (days)	57.0
Overweight BMI 25 to 30	N	1380
	Mean (SD) BMI at BL	27.4 (1.4)
	Mean (SD) BMI at EOT	27.8 (1.7)
	Mean (SD) BMI Change	0.5 (1.0)
	Modal (SD) Dose (mg)	169.3 (106.0)

	Median Exposure (days)	57.0
Obese BMI ≥ 30	N	1533
	Mean (SD) BMI at BL	36.3 (5.9)
	Mean (SD) BMI at EOT	36.7 (6.1)
	Mean (SD) BMI Change	0.3 (1.4)
	Modal (SD) Dose (mg)	174.8 (107.4)
	Median Exposure (days)	57.0

Information obtained from Sponsor table 86 in Clinical Study Report

5.6.2 Categorical Analyses

1. Weight Gain Outliers

In a pooled analysis, among antipsychotic naïve quetiapine-treated subjects 62%, 46% and 42% had a mean weight gain of > 0-5 kg (0-11 lb) at a modal quetiapine dose of 188 mg per Day, at Week 6, 6 and 12 month interval, respectively. The proportion of outliers appeared to be increased over time in other higher weight categories.

Table 48: Proportion of Patients with Weight (in kg) Change at 6 Weeks, 6 and 12 Months (naïve subjects, all QTP trials)

	6 Weeks N = 1812	**6 Months** N = 238	**12 Months** N = 160
Weight change	N (%)	N (%)	N (%)
≤0	590 (32.6)	93 (39.1)	49 (30.6)
0 to ≤5 (0-11 lb)	1126 (62.1)	110 (46.2)	68 (42.5)
>5 to ≤10 (11-22 lb)	88 (4.9)	21 (8.8)	22 (13.8)
>10 to ≤15 (22-33 lb)	7 (0.4)	10 (4.2)	13 (8.1)
>15 to ≤20 (33-44 lb)	0	3 (1.3)	6 (3.8)
>20 to ≤25 (44-55 lb)	0	1 (0.4)	1 (0.6)
>25 to ≤30 (55-66 lb)	1 (0.1)	0	1 (0.6)
Modal (SD) Dose(mg)	187.6 (130.5)		
Median Exp (days)	43.0		

Information obtained from Sponsor table 87 in Clinical Study Report

6 Glucose

6.1 Adult Subjects in Placebo-Controlled Trials

6.1.1 Mean Change Analyses

The mean change analyses in glucose (in mg/dl) (baseline to endpoint [last observation carried forward (LOCF)] and baseline to highest measurement for fasting and non-fasting data) was evaluated. Stratification according to baseline serum glucose measurement for each of the six categories (Fasting Serum Glucose: normal <100 mg/dL, impaired 100-125 mg/dL, Diabetes ≥126 mg/dL and Non-Fating Serum Glucose: Normal <140 mg/dL, Borderline 140-199 mg/dL, High ≥200 mg/dL) was evaluated. Observed case analyses of mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks were reviewed.

Comparing the proportions of subjects with clinically significant changes was conducted using Fisher's exact test. Comparison between treatment groups was conducted and p-values reported.

The criteria for analyses of proportions of subjects with treatment-emergent changes of interest at any time post-baseline are as per table below.

Criteria for Clinically Significant Changes	Baseline	Post-Treatment
Fasting Serum Glucose		
Normal to High <100 mg/dL	<100 mg/dL	≥126 mg/dL
Impaired Fasting Glucose to High	100-125 mg/dL	≥126 mg/dL
Normal/Impaired Fasting Glucose to High	<126 mg/dL	≥126 mg/dL
Change in fasting serum glucose ≥10 mg/dL at any time post-baseline*	Any value	Fasting glucose increased ≥10 mg/dL
Non-Fasting Serum Glucose		
Normal to High	<140 mg/dL	≥200 mg/dL
Borderline to High	140-199 mg/dL	≥200 mg/dL
Normal to Borderline/High	<140 mg/dL	≥140 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Change in non-fasting serum glucose ≥20 mg/dL at any time post baseline*	Any value	Non-fasting glucose increased ≥20 mg/dL

* Additional subgroup analyses dividing according to baseline glucose levels (Fasting Serum Glucose: post-treatment levels of 140 mg/dL, 200 mg/dL, 300 mg/dl and Non-Fasting Glucose: post-treatment level of 300 mg/dL).

Analyses of the proportion of subjects with post-baseline hemoglobin A1c ≥ 6.1%, 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1% and analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each fasting and non-fasting subject database was evaluated.

The sponsor provided non-fasting data results. This review will not cover this analysis as the number of subjects is too small (QTP=80; placebo=36) presenting difficulty in interpreting results.

1. Mean Glucose Change (in mg/dl)

The mean change from baseline and the highest mean change from baseline seen in fasting glucose levels in quetiapine-treated subjects (N = 3564) compared to placebo- treated subjects (N = 1657) showed 2.4 mg/dL compared to 1.6 mg/dL, and 5.3 mg/dL compared 4.4 mg/dL, respectively at a modal daily dose of 331 mg per Day with a mean exposure of 54-55 days.

Table 49: Fasting Glucose (mg/dl) change from baseline (BL) to end of treatment (EOT) (placebo-controlled trials)

	QTP	Placebo
N	3564	1657
Mean (SD) Glucose at BL	92.1 (14.2)	91.6 (13.3)
Mean (SD) Glucose at EOT	94.6 (20.0)	93.2 (16.0)
Mean (SD) Glucose Change	2.4 (18.1)	1.6 (13.6)
p-value	0.044	-
		-
Mean (SD) Highest Glucose	97.4 (21.1)	96.0 (16.3)
Mean (SD) Highest Glucose Change	5.3 (18.8)	4.4 (14.0)
Modal (SD) Dose (mg)	331.4 (221.6)	
Median Exposure (days)	54	55

Information obtained from Sponsor table 329 in Clinical Study Report

Dose-Related Analyses

The mean change in fasting glucose from baseline to endpoint did not follow a linear dose-related signal. In general, quetiapine 50 mg/day and 150 mg/day did not appear to increase mean fasting glucose compared to placebo while doses ≥ 300 mg/day did increase mean fasting glucose. The quetiapine 400 mg/day group, however, was not associated with an increase in mean fasting glucose compared to placebo – the finding is somewhat unexpected. The mean increase in fasting glucose was only statistically different from the placebo group for the 600 mg/day group.

The effects are variable in that the quetiapine 300 mg/day groups increased mean fasting glucose by 1.9 and 3.4 mg/dL in the GAD and MDD trials respectively - though neither of these changes in mean fasting glucose were significantly different from placebo. Interestingly, the quetiapine 50 mg/day group increased mean fasting glucose by 2.4 mg/dL in the MDD trials – again, this was not significantly different from placebo.

Table 50: Fasting Glucose (mg/dL), Change from Baseline to Endpoint, Placebo-Controlled Trials

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**QTP** 400 mg	**QTP** 600 mg	**QTP** 800 mg	**Placebo**
All Trials							
n	439	832	1004	287	578	266	1489
Mean (SD) Change	**0.2 (13.6)**	**1.8 (13.6)**	**3.3 (16.4)**	**1.7 (17.2)**	**3.4 (19.9)**	**2.4 (23.4)**	**1.7 (13.8)**
p-value (vs. placebo)	NS	NS	NS (0.075)	NS (0.094)	0.02	NS	
Median Exposure (days)	56	56	56	42	56	42	56
Schizophrenia							
n	NA	NA	NA*	287	169	266	181
Mean (SD) Change	**NA**	**NA**	**NA**	**1.7 (17.2)**	**3.5 (19.3)**	**2.4 (23.4)**	**0.0 (16.6)**
p-value (vs. placebo)	NA	NA	NA	NS	NS (0.067)	NS	
Median Exposure (days)	NA	NA	NA	42	42	42	42
Bipolar Disorder							
n	-	-	498	-	409	-	367
Mean (SD) Change	-	-	**4.0 (18.5)**	-	**3.4 (20.2)**	-	**2.9 (15.3)**
p-value (vs. placebo)	-	-	NS	-	NS	-	
Median Exposure (days)	-	-	56	-	57	-	56
GAD							
n	315	446	259	-	-	-	456
Mean (SD) Change	**-0.6 (14.0)**	**1.8 (12.9)**	**1.9 (13.1)**	-	-	-	**1.2 (12.3)**
p-value (vs. placebo)	NS (0.064)	NS	NS	-	-	-	
Median Exposure (days)	59	56	58	-	-	-	57
MDD							
n	124	386	247	-	-	-	485
Mean (SD) Change	**2.4 (12.2)**	**1.9 (14.4)**	**3.4 (14.9)**	-	-	-	**1.8 (12.6)**
p-value (vs. placebo)	NS	NS	NS	-	-	-	
Median Exposure (days)	42	49	48	-	-	-	50
MDD + GAD							
n	439	832	506	-	-	-	941
Mean (SD) Change	**0.2 (13.6)**	**1.8 (13.6)**	**2.6 (14.0)**	-	-	-	**1.5 (12.5)**
p-value (vs. placebo)	NS	NS	NS	-	-	-	
Median Exposure (days)	56	56	53	-	-	-	56

*Sponsor indicated that no fasting glucose measurements were taken in clinical trials that included the 300 mg dose arm
From Sponsor Tables 90, 92, 94, 96, 98, 100 in 2/18/09 submission

2. Mean Fasting Glucose Change (in mg/dl) by Time (in Weeks)

The mean fasting glucose change from baseline to endpoint for quetiapine–treated subjects showed 2.1, 3.0, and 2.0 mg/dl compared to placebo-treated subjects 1.7, 2.0, and 1.6 mg/dl at 2, 4, and 8 weeks, respectively. Data for week 12 is shown in Table 51; however, too few data are available for meaningful interpretation.

Table 51: Fasting Glucose (mg/dl) change from baseline (BL) to end of treatment (EOT), by week (placebo-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**
Seroquel = N	68	2436	1706	16
Mean (SD) Glucose at BL	91.7 (12.6)	91.7 (13.3)	92.3 (13.1)	97.2 (17.3)
Mean (SD) Glucose at EOT	93.7 (11.3)	94.7 (19.8)	94.3 (18.7)	100.1(15.3)
Mean (SD) Glucose Change	2.1 (10.6)	3.0 (18.1)	2.0 (16.3)	2.9 (7.2)
p-value	0.803	0.042	0.338	0.722
Modal (SD) Dose (mg)	387.5 (247)	312 (228)	279 (179)	391 (208)
Median Exposure (days)	15	29	57	73
Placebo = N	23	1182	871	4
Mean (SD) Glucose at BL	91.5 (13)	91.5 (13.4)	92.0 (14.4)	85.1 (9.9)
Mean (SD) Glucose at EOT	93.1 (12.7)	93.5 (14.5)	93.6 (16.5)	90.0 (10.4)
Mean (SD) Glucose Change	1.7 (12)	2.0 (14.3)	1.6 (13.1)	4.9 (7.0)
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	13	29	57	73

Information obtained from Sponsor table 330 in Clinical Study Report

Dose-Related Analysis

Few subjects had fasting glucose data at week 2 and virtually no fasting glucose data are available for the 400 and 800 mg/day groups at week 8; therefore, these data are not very informative from a dose-related analysis over time perspective.

However, for the 8 week time point, a linear dose-relationship is noted with a decrement in mean fasting glucose for the quetiapine 50 mg/day group and increases of 1.5, 2.8 and 3.5 mg/dL for the 150, 300 and 600 mg/day groups.

Table 52: Fasting Glucose (mg/dL): Change from Baseline to Endpoint By Week, All Fixed-Dose Placebo-Controlled Trials

		QTP 50 mg N = 656	**QTP** 150 mg N = 1286	**QTP** 300 mg N = 1915	**QTP** 400 mg N = 340	**QTP** 600 mg N = 1182	**QTP** 800 mg N = 451	**Placebo** N = 2319
Week 2	n	5	15	16	11	9	11	19
	Mean (SD) Change	**-3.2 (17.5)**	**4.1 (4.6)**	**1.6 (10.6)**	**-0.3 (15.8)**	**-0.5 (8.2)**	**7.5 (7.4)**	**2.7 (13.1)**
	p-value (vs. placebo)	NS	NS	NS	NS	NS	0.032	
Week 4	n	375	711	551	245	246	214	1090
	Mean (SD) Change	**1.1 (14.4)**	**1.9 (13.5)**	**4.6 (14.7)**	**0.2 (18.7)**	**4.7 (21.5)**	**3.5 (19.9)**	**2.0 (14.4)**
	p-value (vs. placebo)	NS	NS	NS (0.068)	NS	NS (0.090)	NS	
Week 8	n	235	498	636	2	335	0	871
	Mean (SD) Change	**-1.0 (10.9)**	**1.5 (13.0)**	**2.8 (17.3)**	**5.4 (7.6)**	**3.5 (21.1)**	**NA**	**1.6 (13.1)**
	p-value (vs. placebo)	0.023	NS	NS	NS	0.049	NA	

From baseline to highest mean glucose change for quetiapine–treated subjects showed -0.6, 3.0, 5.8, and 4.2 mg/dl compared to placebo-treated subjects 2.7, 2.1, 4.8, and 7.7 mg/dl at 2, 4, 8,

and 12 weeks, respectively. Interpretation of the week 12 data is limited due to the small numbers of subjects at this time point.

Table 53: Fasting Glucose (mg/dl) change from baseline (BL) to highest mean glucose change, by week (placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	305	2498	2763	59
Mean (SD) Glucose at BL	93.4 (16.9)	91.8 (14)	92.3 (14.2)	93.2 (14.1)
Mean (SD) Highest Glucose	92.8 (17.3)	94.9 (20)	98.0 (20.3)	97.3 (15.1)
Mean (SD) Highest Glucose Change	-0.6 (14.9)	3.0 (18)	5.8 (17.8)	4.2 (10.0)
p-value	0.206	0.049	0.106	0.454
Modal (SD) Dose (mg)	392 (250)	315(229)	326 (217)	314 (186)
Median Exposure (days)	8	29	44	64
Placebo = N	152	1208	1224	22
Mean (SD) Glucose at BL	92.3 (12.8)	92 (13)	91.5 (13.6)	90.6 (13.8)
Mean (SD) Highest Glucose	95.0 (17.1)	94 (14)	96.3 (15.9)	98.4 (15.4)
Mean (SD) Highest Glucose Change	2.7 (15.4)	2.1(14.2)	4.8 (13.4)	7.7 (17.9)
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	8	29	44	64

Information obtained from Sponsor table 330 in Clinical Study Report

3. Mean Fasting Glucose Change (mg/dl) from 'Normal' Baseline

The mean change from 'normal' baseline and the highest mean change from 'normal' baseline seen in fasting glucose levels in quetiapine-treated subjects (N = 2907) compared to placebo-treated subjects (N = 1346) showed 3.8 mg/dL compared to 3.1 mg/dL, and 6.5 mg/dL compared to 5.8 mg/dL, respectively at a modal quetiapine dose of 325 mg per Day and at a mean exposure of 54-55 days.

Table 54:Fasting Glucose (mg/dl) change from normal baseline (BL) to end of treatment (EOT) (placebo-controlled trials)

	QTP	Placebo
N	2907	1346
Mean (SD) Glucose at BL	87.4 (7.0)	87.1 (7.2)
Mean (SD) Glucose at EOT	91.2 (14.2)	90.2 (10.5)
Mean (SD) Glucose Change	3.8 (14.3)	3.1 (11.1)
p-value	0.090	-
		-
Mean (SD) Highest Glucose	93.9 (14.9)	92.9 (11.0)
Mean (SD) Highest Glucose Change	6.5 (15.0)	5.8 (11.6)
Modal (SD) Dose (mg)	325 (218)	-
Median Exposure (days)	54	55

Information obtained from Sponsor table 331 in Clinical Study Report

Dose-Related Analyses

Similar to the above analysis, due to the increase in mean fasting glucose from normal baseline to endpoint in the placebo group, few of the results analyzed by dose are significant. However, in general, it appears that the dose relationship noted previously for change in mean fasting glucose from baseline (normal/impaired) is similar. For doses $\geq$ 300 mg/day a more consistent increase in fasting glucose was demonstrated. The 50 mg/day group had very different effects on mean fasting glucose when analyzed by indication. In the GAD trials, mean fasting glucose increased by 0.5 mg/dL while in the MDD trials, mean fasting glucose increased by 4.0 mg/dL –

similar to the effects noted at 150 and 300 mg/day. None of these increases in mean fasting glucose in the MDD and GAD trials were significantly different from placebo however.

Table 55: Fasting Glucose (mg/dL), Change from Normal Baseline to Endpoint, Placebo-Controlled Trials

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**QTP** 400 mg	**QTP** 600 mg	**QTP** 800 mg	**Placebo**
All Trials							
n	368	689	835	242	452	196	1210
Mean (SD) Change	**1.5 (10.1)**	**3.2 (11.3)**	**3.8 (12.3)**	**3.6 (12.0)**	**5.4 (15.3)**	**4.3 (11.7)**	**3.1 (11.1)**
p-value (vs. placebo)	NS (0.099)	NS	NS	NS	0.015	NS	
Median Exposure (days)	56	56	56	42	55.5	42	56
Schizophrenia							
n	NA	NA	NA*	242	139	196	141
Mean (SD) Change	**NA**	**NA**	**NA**	**3.6 (12.0)**	**5.2 (15.7)**	**4.3 (11.7)**	**2.4 (13.3)**
p-value (vs. placebo)	NA	NA	NA	NS	NS (0.083)	NS	
Median Exposure (days)	NA	NA	NA	42	42	42	42
Bipolar Disorder							
n	-	-	402	-	313	-	290
Mean (SD) Change	-	-	**3.8 (12.7)**	-	**5.5 (15.2)**	-	**4.2 (11.5)**
p-value (vs. placebo)	-	-	NS	-	NS	-	
Median Exposure (days)	-	-	56	-	57	-	56
GAD							
n	261	365	220	-	-	-	374
Mean (SD) Change	**0.5 (9.7)**	**3.1 (11.3)**	**3.3 (10.6)**	-	-	-	**2.8 (10.9)**
p-value (vs. placebo)	0.006	NS	NS	-	-	-	
Median Exposure (days)	59	56	58.5	-	-	-	57
MDD							
n	107	324	213	-	-	-	405
Mean (SD) Change	**4.0 (10.8)**	**3.4 (11.3)**	**4.4 (13.3)**	-	-	-	**2.9 (10.1)**
p-value (vs. placebo)	NS	NS	NS (0.091)	-	-	-	
Median Exposure (days)	42	49	48	-	-	-	50
MDD + GAD							
n	368	689	433	-	-	-	779
Mean (SD) Change	**1.5 (10.1)**	**3.2 (11.3)**	**3.8 (12.0)**	-	-	-	**2.9 (10.5)**
p-value (vs. placebo)	NS (0.083)	NS	NS	-	-	-	
Median Exposure (days)	56	56	52	-	-	-	56

*Sponsor indicated that no fasting glucose measurements were taken in clinical trials that included the 300 mg dose arm
From Sponsor Tables 102, 105, 106, 108, 110, 112 in 2/18/09 submission

4. Mean Fasting Glucose Change from 'Normal' Baseline by Time (in Weeks)

The mean fasting glucose change from 'normal' baseline to endpoint for quetiapine–treated subjects showed 4.3, 4.4, 3.0, and 3.9 mg/dl compared to placebo-treated subjects showed 4.2, 3.6 ,3.2, and 4.9 mg/dl at 2, 4, 8, and 12 weeks, respectively. Interpretation of the week 12 data is limited due to the small numbers of subjects at this timepoint.

Table 56: Fasting Glucose change from normal baseline (BL) to end of treatment (EOT), by week (placebo-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**
Seroquel = N	54	2018	1376	11
Mean (SD) Glucose at BL	86.8 (7.4)	87.4 (6.9)	87.7 (6.8)	88.4 (7.2)
Mean (SD) Glucose at EOT	91.2 (10.2)	91.8 (15.5)	90.7 (11.9)	92.3 (5.6)
Mean (SD) Glucose Change	4.3 (8.9)	4.4 (15.7)	3.0 (11.9)	3.9 (6.4)
p-value	0.979	0.056	0.572	0.258
Modal (SD) Dose (mg)	394 (248)	307 (223)	273 (176)	400 (206)
Median Exposure (days)	15	29	57	71
Placebo = N	17	971	699	4
Mean (SD) Glucose at BL	85.6 (8.6)	87.2 (7.2)	87.1 (7.3)	85.1 (9.9)

Mean (SD) Glucose at EOT	89.8 (12.0)	90.8 (11.1)	90.4 (10.2)	90.0 (10.4)
Mean (SD) Glucose Change	4.2 (12.8)	3.6 (11.7)	3.2 (10.9)	4.9 (7.0)
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	13	29	57	74

Information obtained from Sponsor table 332 in Clinical Study Report

From baseline to highest mean glucose change for quetiapine–treated subjects showed 2.0, 4.5, 6.9, and 5.0 mg/dl compared to placebo-treated subjects showed 3.6, 3.7, 6.3, and 10.4 mg/dl at 2, 4, 8, and 12 weeks, respectively. Interpretation of the week 12 data is limited due to the small numbers of subjects at this timepoint.

Table 57:Fasting Glucose (mg/dl) at normal baseline (BL) to highest mean glucose change, by week (placebo-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**
Seroquel = N	240	2065	2233	43
Mean (SD) Glucose at BL	87.4 (7.2)	87.4 (6.9)	87.4 (6.9)	86.9 (7.1)
Mean (SD) Highest Glucose	89.4 (12.5)	91.9 (15.4)	94.3 (13.0)	91.9 (9.5)
Mean (SD) Highest Glucose Change	2.0 (12.2)	4.5 (15.7)	6.9 (13.2)	5.0 (8.1)
p-value	0.834	0.053	0.528	0.407
Modal (SD) Dose (mg)	399 (252)	309 (223)	318 (212)	319 (176)
Median Exposure (days)	8	29	43	65
Placebo = N	119	992	997	19
Mean (SD) Glucose at BL	87.2 (7.7)	87.2 (7.2)	87.0 (7.3)	86.1 (6.8)
Mean (SD) Highest Glucose	90.8 (10.9)	90.9 (11.1)	93.3 (10.8)	96.5 (13.6)
Mean (SD) Highest Glucose Change	3.6 (11.1)	3.7 (11.7)	6.3 (11.5)	10.4 (14.5)
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	7	29	44	64

Information obtained from Sponsor table 332 in Clinical Study Report

5. Mean Fasting Glucose Change (mg/dl) from 'High' Baseline

The mean change from 'high' baseline and the highest mean change from 'high' baseline seen in fasting glucose levels in quetiapine-treated subjects (N = 85) compared to placebo- treated subjects (N = 32) was -6.5 mg/dL compared to -7.0 mg/dL and 2.3 mg/dL compared to -5.1 mg/dL, respectively at a modal quetiapine dose of 448 mg per Day with a mean exposure of 45-56 days.

Table 58: Fasting Glucose (mg/dl) change from high baseline (BL) to end of treatment (EOT) (placebo-controlled trials)

	QTP	**Placebo**
N	85	32
Mean (SD) Glucose at BL	150.6 (28.9)	146.3 (26.3)
Mean (SD) Glucose at EOT	144.1 (56.8)	139.3 (50.5)
Mean (SD) Glucose Change	-6.5 (58.8)	-7.0 (37.4)
p-value	0.876	-
Mean (SD) Highest Glucose	152.9 (61.0)	141.1 (50.8)
Mean (SD) Highest Glucose Change	2.3 (63.2)	-5.1 (37.1)
Modal (SD) Dose (mg)	448 (257)	-
Median Exposure (days)	45	56

Information obtained from Sponsor table 333 in Clinical Study Report

6. Mean Fasting Glucose Change from 'High' Baseline by Time (in Weeks)

The mean fasting glucose change from 'high' baseline to endpoint for quetiapine–treated subjects showed -37.8, -2.2, 3.3, and -1.8 mg/dl at 2, 4, 8, and 12 weeks respectively, compared to placebo-treated subjects -23.0 at 4 weeks and -5.6 at 8 weeks.

Table 59: Fasting Glucose change from high baseline (BL) to end of treatment (EOT), by week (placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	1	54	34	1
Mean (SD) Glucose at BL	142.2	146.8 (22.9)	145.4 (29.3)	142.2
Mean (SD) Glucose at EOT	104.4	144.6 (53.8)	148.8 (57.2)	140.4
Mean (SD) Glucose Change	-37.8	-2.2 (53.4)	3.3 (60.8)	-1.8
p-value	-	0.279	0.481	-
Modal (SD) Dose (mg)	400	419 (280)	371 (209)	600.0
Median Exposure (days)	15	29	57	78
Placebo = N	0	20	20	0
Mean (SD) Glucose at BL	-	151.2 (31.9)	151.2 (31.5)	-
Mean (SD) Glucose at EOT	-	128.3 (35.8)	145.5 (54.8)	-
Mean (SD) Glucose Change	-	-23.0 (46.8)	-5.6 (35.5)	-
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	-	29	57	-

Information obtained from Sponsor table 332 in Clinical Study Report

From baseline to highest mean glucose change for quetiapine–treated subjects showed -16.4, -4.1, 5.9, and -0.9 mg/dl compared to placebo-treated subjects -20.3, -22.3, -3.4, and -16.2 mg/dl at 2, 4, 8, and 12 weeks, respectively.

Table 60: Fasting Glucose (mg/dl) at high baseline (BL) to highest mean glucose change, by week (placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	12	59	66	2
Mean (SD) Glucose at BL	151.2 (34.0)	148.3 (25.8)	149.8 (30.1)	142.2 (0.0)
Mean (SD) Highest Glucose	134.9 (39.0)	144.2 (53.4)	155.7 (63.3)	141.3 (36.9)
Mean (SD) Highest Glucose Change	-16.4 (37.7)	-4.1 (52.1)	5.9 (66.7)	-0.9 (36.9)
p-value	0.483	0.311	0.611	-
Modal (SD) Dose (mg)	450 (210)	427(276)	466 (265)	600
Median Exposure (days)	6.5	29	43	31
Placebo = N	4	21	23	1
Mean (SD) Glucose at BL	129.6 (4.4)	150.3 (31.4)	149.8 (29.6)	129.6
Mean (SD) Highest Glucose	109.4 (30.0)	128.0 (34.9)	146.4 (52.7)	113.4
Mean (SD) Highest Glucose Change	-20.3 (25.6)	-22.3 (45.7)	-3.4 (34.6)	-16.2
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	4.5	29	571	64

Information obtained from Sponsor table 333 in Clinical Study Report

7. Mean Fasting Glucose Change (mg/dl) from 'impaired fasting glucose' Baseline

The mean change from 'impaired fasting' baseline and the highest mean change from 'impaired fasting' baseline seen in fasting glucose levels in quetiapine-treated subjects (N = 572) compared to placebo- treated subjects (N = 279) showed -3.1 mg/dL compared to -4.4 mg/dL and -5.1 mg/dL compared to -1.2 mg/dL, respectively at a modal quetiapine dose of 448 mg per Day with a mean exposure of 55 days.

Table 61: Fasting Glucose (mg/dl) change from impaired fasting glucose at baseline (BL) to end of treatment (EOT) (placebo-controlled trials)

	QTP	Placebo
N	572	279
Mean (SD) Glucose at BL	107.3 (6.5)	107.0 (6.2)
Mean (SD) Glucose at EOT	104.3 (22.0)	102.6 (18.0)
Mean (SD) Glucose Change	-3.1 (20.9)	-4.4 (17.4)
p-value	0.266	-
Mean (SD) Highest Glucose	107.2 (21.9)	105.8 (18.3)
Mean (SD) Highest Glucose Change	-0.2 (20.6)	-1.2 (17.5)
Modal (SD) Dose (mg)	346 (230)	-
Median Exposure (days)	55	55

Information obtained from Sponsor table 335 in Clinical Study Report

Dose-Related Analyses

All dose groups showed decrements in mean fasting glucose change from impaired baseline to endpoint. No strong dose-relationship emerged.

Table 62: Fasting Glucose (mg/dL), Change from Impaired Baseline to Endpoint, Placebo-Controlled Trials

	QTP 50 mg	QTP 150 mg	QTP 300 mg	QTP 400 mg	QTP 600 mg	QTP 800 mg	Placebo
All Trials							
n	65	126	155	40	104	52	248
Mean (SD) Baseline	107.7 (7.0)	106.4 (5.5)	107.7 (6.8)	108.8 (7.0)	106.6 (5.9)	108.1 (7.2)	107.1 (6.3)
Mean (SD) EOS	104.1 (22.6)	101.4 (14.6)	105.9 (24.7)	104.4 (27.1)	106.4 (23.0)	103.5 (17.4)	103.0 (18.5)
Mean (SD) Change	**-3.7 (22.0)**	**-5.0 (14.9)**	**-1.8 (22.6)**	**-4.4 (26.2)**	**-0.2 (22.9)**	**-4.7 (15.4)**	**-4.1 (17.7)**
p-value (vs. placebo)	NS	NS	NS	NS	NS	NS	-
Median Exposure (days)	56	56	56	42	56	42	56

From Sponsor Table 126 in 2/18/09 submission

8. Mean Fasting Glucose Change from 'impaired fasting glucose' Baseline by Time (in Weeks)

The mean fasting glucose change from 'impaired fasting glucose' baseline to endpoint for quetiapine–treated subjects showed -4.4 at 2 weeks, -4.0 at 4 weeks, -2.7 at 8 weeks and 1.4 mg/dl at 12 weeks compared to placebo-treated subjects -5.7 at 2 weeks, -3.4 at 4 weeks, -5.1 at 8 weeks.

Table 63: Fasting Glucose change from impaired fasting glucose at baseline to end of treatment, by week (placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	13	364	296	4
Mean (SD) Glucose at BL	108.0 (6.1)	107.3 (6.5)	107.2 (6.4)	110.3 (11.5)
Mean (SD) Glucose at EOT	103.6(10.0)	103.3(19.4)	104.5(22.3)	111.6 (11.1)
Mean (SD) Glucose Change	-4.4 (8.7)	-4.0 (18.4)	-2.7 (20.9)	1.4 (10.3)
p-value	0.740	0.711	0.163	-
Modal (SD) Dose (mg)	358 (233)	325 (246)	293 (188)	313 (225)
Median Exposure (days)	14	29	57	74
Placebo = N	6	191	152	0
Mean (SD) Glucose at BL	108.3 (8.3)	107.2 (6.2)	106.8 (6.0)	-
Mean (SD) Glucose at EOT	102.6 (9.9)	103.7 (16.5)	101.7 (15.2)	-
Mean (SD) Glucose Change	-5.7 (6.8)	-3.4 (15.3)	-5.1 (14.8)	-
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	14	29	57	-

Information obtained from Sponsor table 336 in Clinical Study Report

From baseline to highest mean glucose change for quetiapine–treated subjects showed -8.8, -3.9, 0.4, and 2.3 mg/dl compared to placebo-treated subjects -2.0, 3.3, -1.9, and -5.4 mg/dl at 2, 4, 8, and 12 weeks, respectively.

Table 64: Fasting Glucose from impaired fasting glucose at baseline (BL) to highest mean glucose change, by week (placebo-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**
Seroquel = N	53	374	464	14
Mean (SD) Glucose at BL	107.5 (6.8)	107.3 (6.5)	107.3 (6.4)	105.6 (7.3)
Mean (SD) Highest Glucose	98.7 (14.5)	103.4(19.3)	107.7 (21.0)	107.9 (10.1)
Mean (SD) Highest Glucose Change	-8.8 (12.8)	-3.9 (18.3)	0.4 (19.6)	2.3 (10.9)
p-value	0.017	0.645	0.068	0.394
Modal (SD) Dose (mg)	348 (246)	327 (246)	344 (228)	279(200)
Median Exposure (days)	8	29	44	65
Placebo = N	29	195	204	2
Mean (SD) Glucose at BL	108.2 (7.8)	107.2 (6.2)	107.0 (6.0)	114.5 (9.2)
Mean (SD) Highest Glucose	110.2 (25.3)	103.9 (16.4)	105.1 (16.0)	109.1 (34.1)
Mean (SD) Highest Glucose Change	2.0 (24.6)	-3.3 (15.1)	-1.9 (15.7)	-5.4 (43.3)
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	9	29	54	62

Information obtained from Sponsor table 336 in Clinical Study Report

6.1.2 Categorical Analyses

1. Fasting Glucose Increase Outliers

Results showed that the 2.4% of quetiapine-treated subjects compared to 1.4% of placebo-treated subjects had a mean treatment emergent increase in fasting glucose from baseline values of glucose <100 mg/dL to >126 mg/dL post-baseline. Similar proportions of increase in glucose outliers of ≥126 or ≥140 mg were observed in both quetiapine-treated and placebo-treated subjects who had baseline values of glucose ≥100 mg/dL and <126 mg/dL, and glucose >126 mg/dL. The modal quetiapine dose was 329 mg per Day with a median exposure of 55 Days.

Table 65: Proportion of Patients with treatment emergent fasting Glucose (mg/dL) change (placebo-controlled trials)

Baseline	**Treatment Arm Post-baseline**	**N =**	**≥300 N (%)**	**≥200 N (%)**	**≥140 N (%)**	**≥126 N (%)**
<100 mg/dL	Quetiapine	2907	2 (0.1)	4 (0.1)	26 (0.9)	71 (2.4)
	Placebo	1346	0	0	8 (0.6)	19 (1.4)
	p-value		1.000	0.315	0.359	0.030
≥100 mg/dL and <126 mg/dL	Quetiapine	572	1 (0.2)	6 (1.0)	30 (5.2)	67 (11.7)
	Placebo	279	0	0	13 (4.7)	33(11.8)
	p-value		1.000	0.185	0.868	1.000
< 126 mg/dL	Quetiapine	3479	3 (0.1)	10 (0.3)	56 (1.6)	138 (4.0)
	Placebo	1625	0	0	21 (1.3)	52 (3.2)
	p-value		0.556	0.037	0.460	0.204
Modal (SD) Dose (mg)	329(220)					
Median Exposure(days)	55					

Information obtained from Sponsor table 339 in Clinical Study Report

Dose-Related Analyses

The percentage of subjects with an increase from normal to high fasting glucose (< 100 to ≥ 126 mg/dL) was 0.5% in the 50 mg/day group with similar percentages in the 150 – 600 mg/day groups (2.6% - 3.3%, not linear) and 1% in the 800 mg/day group compared to 1.4% in the placebo group. No dose-related signal emerged when evaluating the percentages of subjects with shifts from impaired to high fasting glucose (100-125 to ≥ 126 mg/dL).

Table 66: Shifts in Fasting Glucose (mg/dL), All Fixed-Dose Placebo-Controlled Trials

	QTP 50 mg N = 656			QTP 150 mg N = 1286			QTP 300 mg N = 1915			QTP 400 mg N = 340		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Increase by ≥ 10 mg/dL	439	107	24.4%	832	229	27.5%	1004	279	27.8%	287	74	25.8%
Normal to High (< 100 to ≥ 126 mg/dL)	368	2	0.5%	689	18	2.6%	835	23	2.8%[a]	242	8	3.3%[b]
Normal to ≥ 140 mg/dL	368	0	0	689	7	1%	835	7	0.8%	242	3	1.2%
Normal to ≥ 200 mg/dL	368	0	0	689	0	0	835	0	0	242	0	0
Normal to ≥ 300 mg/dL	368	0	0	689	0	0	835	0	0	242	0	0
Impaired to High (100 – 125 to ≥ 126 mg/dL)	65	7	10.8%	126	6	4.8%	155	22	14.2%	40	8	20%
Impaired to ≥ 140 mg/dL	65	3	4.6%	126	2	1.6%	155	8	5.2%	40	4	10%
Impaired to ≥ 200 mg/dL	65	1	1.5%	126	0	0	155	1	0.6%	40	1	2.5%
Impaired to ≥ 300 mg/dL	65	0	0	126	0	0	155	1	0.6%	40	0	0

	QTP 600 mg N = 1182			QTP 800 mg N = 451			Placebo N = 2319		
	N	n	(%)	N	n	(%)	N	n	(%)
Increase by ≥ 10 mg/dL	578	166	28.7%	266	99	37.2%[a]	1489	391	26.3%
Normal to High (< 100 to ≥ 126 mg/dL)	452	13	2.9%[b]	196	2	1%	1210	17	1.4%
Normal to ≥ 140 mg/dL	452	7	1.5%	196	0	0	1210	7	0.6%
Normal to ≥ 200 mg/dL	452	2	0.4%	196	0	0	1210	0	0
Normal to ≥ 300 mg/dL	452	0	0	196	0	0	1210	0	0
Impaired to High (100 – 125 to ≥ 126 mg/dL)	104	13	12.5%	52	8	15.4%	248	31	12.5%
Impaired to ≥ 140 mg/dL	104	6	5.8%	52	5	9.6%	248	12	4.8%
Impaired to ≥ 200 mg/dL	104	2	1.9%	52	0	0	248	0	0
Impaired to ≥ 300 mg/dL	104	0	0	52	0	0	248	0	0

[a] statistically significant versus placebo
[b] borderline statistically significant versus placebo (p ≤ 0.06)
From Sponsor Tables 138 and 144 in 2/18/09 submission

2. Fasting Glucose Increase of more than ≥10 mg/dL Outliers

Results showed that the 28%, 29%, 18%, 37% of quetiapine-treated subjects had a mean treatment emergent increase in fasting glucose of ≥ 10 mg/dl at categories any value, <100 mg/dl, ≥100 mg/dL and <126 mg/dL respectively with modal quetiapine dose of 331 mg per Day and a median exposure of 54-55 Days.

Table 67: Proportion of Patients with treatment emergent increase (≥10 mg/dL) in fasting glucose (placebo-controlled trials)

Baseline	**Treatment Arm**	**N =**	**≥10 mg/dL increase post-baseline n (%)**
Any value	Quetiapine	3564	989 (27.7)
	Placebo	1657	430 (26.0)
	p-value = 0.181		

<100 mg/dL	Quetiapine	2907	855 (29.4)
	Placebo	1346	375 (27.9)
	p-value = 0.309		
≥100 mg/dL and <126 mg/dL	Quetiapine	572	103 (18.0)
	Placebo	279	45 (16.1)
	p-value = 0.563		
<126 mg/dL	Quetiapine	85	31 (36.5)
	Placebo	32	10 (31.3)
	p-value = 0.668		
Modal (SD) Dose (mg)	331 (221)		
Median Exposure(days)	54 - 55		

Information obtained from Sponsor table 340 in Clinical Study Report

Dose-Related Analyses

See Table 67 above. Similar percentages of subjects had shifts in fasting glucose ≥ 10 mg/dL in the placebo (26%) and quetiapine 50 – 600 mg/day groups (~24 – 28%); compared to 37% in the quetiapine 800 mg/day group.

3. Fasting HbA1c (%) Increase of more than ≥6.1 Outliers

Results showed that the 4.1% of quetiapine-treated (N = 3481) subjects had a mean HbA1c increase (> 6.1) from baseline compared to 2.8 % of placebo-treated subjects (N = 1595) (median exposure 55-56 days).

Table 68: Proportion of Patients with treatment emergent fasting HbA1c (%) increase (placebo-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	≥ 6.1 N (%)	≥8 N (%)	≥10 N (%)	≥12 N (%)
HbA1c(%) <6.1	Quetiapine	3481	144 (4.1)	0	0	0
	Placebo	1595	44 (2.8)	0	0	0
	p-value = 0.016					
Modal (SD) Dose	340 (221)					
Median Exposure(days)	55 - 56					

Information obtained from Sponsor table 341 in Clinical Study Report

Dose-Related Analyses

A dose-related signal emerged for the HbA1c analysis. In the quetiapine 600 and 800 mg/day groups, 4.9% and 7.7%, respectively, of subjects had an increase in HbA1c of ≥ 6.1% compared to 2.5% in the placebo group.

Table 69: HbA1c, Shifts from Baseline, All Fixed Dose Trials

	QTP 50 mg N = 656	QTP 150 mg N = 1286	QTP 300 mg N = 1915	QTP 400 mg N = 340	QTP 600 mg N = 1182	QTP 800 mg N = 451	Placebo N = 2319
N	388	789	997	276	616	261	1450
Increase to ≥ 6.1%	13 (3.4%)	30 (3.8%)	33 (3.3%)	3 (1.1%)	30 (4.9%)	20 (7.7%)	36 (2.5%)
p-value (vs. placebo)	NS	NS	NS	NS	0.006	< 0.001	
Median Exposure (days)	56	56	56	42	56	42	56

From Sponsor Table 158 in 2/18/09 submission

4. Glycosuria Outliers

Results showed that the 2.3% of quetiapine-treated subjects (N = 1588) had glycosuria (any amount of glucose seen in urine) from baseline compared to 0.2 % of placebo-treated subjects (N = 439) (median exposure 43 -44 days).

Table 70: Proportion of Patients with treatment emergent glycosuria (placebo-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	N (%)
Glycosuria	Quetiapine	1588	36 (2.3)
	Placebo	439	1 (0.2)
Mean Modal (SD) Dose (mg)	500 (192)		
Median Exposure(days)	43 - 44		

Information obtained from Sponsor table 342 in Clinical Study Report

Dose-Related Analyses

A dose-related signal did appear to emerge for the percentage of subjects experiencing glycosuria; however, too few data are available for the quetiapine 50 and 150 mg/day groups to interpret the effect of these lower doses on this variable.

Table 71: Glycosuria, All Fixed Dose Trials

	QTP 50 mg N = 656	QTP 150 mg N = 1286	QTP 300 mg N = 1915	QTP 400 mg N = 340	QTP 600 mg N = 1182	QTP 800 mg N = 451	Placebo N = 2319
N	4	7	275	293	450	276	283
N (%) with Glycosuria	0	0	5 (1.8%)	5 (1.7%)	11 (2.4%)	13 (4.7%)	1 (0.4%)
Median Exposure (days)	35	50	68	42	54	42	42

From Sponsor Table 165 in 2/18/09 submission

6.2 Adult Subjects in Comparator-Controlled Clinical Trials

6.2.1 Mean Change Analyses

1. Mean Fasting Glucose Change (mg/dl) from 'Any' Baseline

The mean change from baseline (any glucose level) to endpoint and the highest mean change from baseline in olanzapine-treated subjects (N = 212, modal daily dose of 15 mg) were 3.9 mg/dL and 9.1 mg/dL compared to 3.0 mg/dL and 6.9 mg/dL in quetiapine-treated subjects (N = 198, modal daily dose of 602 mg) respectively, with a mean exposure of 168 days.

The mean change from baseline (any glucose level) to endpoint and the highest mean change from baseline in risperidone-treated subjects (N = 207, modal daily dose of 4.7 mg) were 2.5 mg/dL and 6.5 mg/dL compared to 3.0 mg/dL and 6.9 mg/dL in quetiapine-treated subjects (N = 198, modal daily dose of 602 mg) respectively, with a mean exposure of 168 days.

Table 72: Mean glucose (mg/dl) change from baseline (BL) to end of treatment (EOT) (comparator-controlled trials)

	QTP	OLZ	QTP	RIS
N	198	212	198	207
Mean (SD) Glucose at BL	90.7 (11.8)	89.8 (14.1)	90.7 (11.8)	92.0 (12.6)
Mean (SD) Glucose at EOT	93.7 (14.6)	93.7 (12.1)	93.7 (14.6)	94.5 (15.4)
Mean (SD) Glucose Change	3.0 (14.9)	3.9 (15.3)	3.0 (14.9)	2.5 (14.2)

p-value	0.572	-	0.692	-
Mean (SD) Highest Glucose	97.6 (15.2)	98.9 (16.1)	97.6 (15.2)	98.5 (17.2)
Mean (SD) Highest Glucose Change	6.9 (15.0)	9.1 (19.1)	6.9 (15.0)	6.5 (16.2)
Modal (SD) Dose (mg)	602.5 (160.2)	14.8 (3.8)	602.5 (160.2)	4.7 (1.6)
Median Exposure (days)	168	168	168	168

Information obtained from Sponsor table 350 and 370 in Clinical Study Report, OLZ-olanzapine, and RIS- risperidone

2. Mean Fasting Glucose Change (mg/dl) from 'Normal' Baseline

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoint and the highest mean change from baseline in olanzapine-treated subjects (N = 182, modal daily dose of 15 mg) were 5.7 mg/dL and 10.8 mg/dL compared to 5.6 mg/dL and 9.2 mg/dL in quetiapine-treated subjects (N = 162, modal daily dose of 605 mg) respectively, with a mean exposure of 168 days.

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoint and the highest mean change from baseline in risperidone-treated subjects (N = 164, modal daily dose of 4.5 mg) were 4.5 mg/dL and 8.7 mg/dL compared to 5.6 mg/dL and 9.2 mg/dL in quetiapine-treated subjects (N = 166, modal daily dose of 604 mg) respectively, with a mean exposure of 168 days.

Table 73: Mean glucose (mg/dl) change from 'normal' baseline (BL) to end of treatment (EOT) (comparator-controlled trials)

	QTP	**OLZ**	**QTP**	**RIS**
N	166	182	166	164
Mean (SD) Glucose at BL	86.9 (7.3)	86.4 (6.9)	86.9 (7.3)	87.3 (7.7)
Mean (SD) Glucose at EOT	92.5 (14.6)	92.1 (11.1)	92.5 (14.6)	91.8 (10.7)
Mean (SD) Glucose Change	5.6 (13.4)	5.7 (10.7)	5.6 (13.4)	4.5 (10.6)
p-value	0.931	-	0.425	-
Mean (SD) Highest Glucose	96.1 (14.9)	97.2 (14.6)	96.1 (14.9)	96.1 (14.3)
Mean (SD) Highest Glucose Change	9.2 (13.4)	10.8 (14.9)	9.2 (13.4)	8.7 (13.8)
Modal (SD) Dose (mg)	605 (163)	15 (4)	604.8 (163.4)	4.5 (1.6)
Median Exposure (days)	168	168	168	168

Information obtained from Sponsor table 352 and 372 in Clinical Study Report, OLZ-olanzapine, and RIS- risperidone

3. Mean Fasting Glucose Change (mg/dl) from 'Impaired' Baseline

The mean change from impaired baseline (fasting glucose level of 100-125 mg/dl) to endpoint and the highest mean change from baseline in olanzapine-treated subjects (N = 29, modal daily dose of 15 mg) were 2.3 mg/dL and 3.7 mg/dL compared to -7.7 mg/dL and -3.2 mg/dL in quetiapine-treated subjects (N = 30, modal daily dose of 577 mg) respectively, with a mean exposure of 168 days.

The mean change from impaired baseline (fasting glucose level of 100-125 mg/dl) to endpoint and the highest mean change from baseline in risperidone-treated subjects (N = 40, modal daily dose of 5.3 mg) were -5.5 mg/dL and -2.4 mg/dL compared to -7.7 mg/dL and -3.2 mg/dL in quetiapine-treated subjects (N = 30, modal daily dose of 577 mg) respectively, with a mean exposure of 168 days.

Table 74: Mean glucose (mg/dl) change from 'impaired' baseline (BL) to end of treatment (EOT) (comparator-controlled trials)

	QTP	OLZ	QTP	RIS
N	30	29	30	40
Mean (SD) Glucose at BL	107.8 (5.7)	106.1 (5.9)	107.8 (5.7)	107.3 (6.4)
Mean (SD) Glucose at EOT	100.1 (12.1)	103.8 (13.6)	100.1 (12.1)	101.8 (12.1)
Mean (SD) Glucose Change	-7.7 (12.5)	-2.3 (13.3)	-7.7 (12.5)	-5.5 (12.9)
p-value	0.198		0.696	
Mean (SD) Highest Glucose	104.6 (13.5)	109.8 (21.0)	104.6 (13.5)	104.9 (11.8)
Mean (SD) Highest Glucose Change	-3.2 (14.6)	3.7 (20.7)	-3.2 (14.6)	-2.4 (12.6)
Modal (SD) Dose (mg)	576.7 (138.2)	14.8 (3.1)	576.7 (138.2)	5.3 (1.1)
Median Exposure (days)	168	168	168	168

Information obtained from Sponsor table 356 and 376 in clinical Study Report, OLZ-olanzapine, and RIS- risperidone

4. Mean Fasting Glucose Change (mg/dl) from 'High' Baseline

The mean change from high baseline (fasting glucose level of ≥126 mg/dl) to endpoint and the highest mean change from baseline in olanzapine-treated subjects (N = 1, modal daily dose of 10 mg) were -144 mg/dL and -144 mg/dL compared to -45 mg/dL and -39 mg/dL in quetiapine-treated subjects (N = 2, modal daily dose of 800 mg) respectively, with a mean exposure of 93-169 days.

The mean change from high baseline (fasting glucose level of ≥126 mg/dl) to endpoint and the highest mean change from baseline in risperidone-treated subjects (N = 3, modal daily dose of 3 mg) were 0 mg/dL and 3.0 mg/dL compared to -45.9 mg/dL and -39.6 mg/dL in quetiapine-treated subjects (N = 2, modal daily dose of 800 mg) respectively, with a mean exposure of 93-169 days.

Table 75: Mean glucose (mg/dl) change from 'high' baseline (BL) to end of treatment (EOT) (comparator-controlled trials)

	QTP	**OLZ**	**QTP**	**RIS**
N	2	1	2	3
Mean (SD) Glucose at BL	148.5 (14.0)	239.4	148.5 (14.0)	144.6 (15.5)
Mean (SD) Glucose at EOT	102.6 (28.0)	95.4	102.6 (28.0)	144.6 (82.3)
Mean (SD) Glucose Change	-45.9 (14.0)	-144.0	-45.9 (14.0)	0
p-value	0.110	-	0.511	-
Mean (SD) Highest Glucose	108.9 (36.9)	95.4	108.9 (36.9)	147.6 (80.1)
Mean (SD) Highest Glucose Change	-39.6 (22.9)	-144.0	-39.6 (22.9)	3.0 (80.9)
Modal (SD) Dose (mg)	800	10	800	5
Median Exposure (days)	93	169	93	168

Information obtained from Sponsor table 354 and 374 in Clinical Study Report, OLZ-olanzapine, and RIS- risperidone

5. Mean Fasting Glucose Change (mg/dl) from 'Any' Baseline by Time (in Weeks)

Please see tables 76 and 77 below for comparison of mean glucose change from baseline and highest glucose change from baseline for quetiapine compared to olanzapine and quetiapine compared to risperidone at the 2, 4, 8, and 12 weeks endpoints.

Table 76: Mean glucose (mg/dl) change from baseline (BL) to end of treatment (EOT), by week (comparator-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 48**
quetiapine = N	0	5	6	163	136	0
Mean (SD) Glucose at BL	-	84 (19)	89.2 (10.3)	90.7 (11.1)	91.4 (12)	-
Mean (SD) Glucose at EOT	-	87 (11)	94.3 (8.4)	92.3 (11.4)	94.7 (15.8)	-

Mean (SD) Glucose Change	-	2.7 (15)	5.1 (3.5)	1.6 (11.5)	3.2 (15.9)	-
p-value	-	-	0.249	0.081	0.706	-
Modal (SD) Dose (mg)	-	500	600	615	617	-
Median Exposure (days)	-	28	59	85	169	-
olanzapine = N	0	0	1	188	170	1
Mean (SD) Glucose at BL	-	-	95.4	90.0 (14.3)	90.5 (15)	70.0
Mean (SD) Glucose at EOT	-	-	106.2	94.5 (15.0)	94.4 (11.9)	86.0
Mean (SD) Glucose Change	-	-	10.8	4.5 (18.3)	4.0 (15.6)	16.0
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	-	-	30	15	15.0 (3.4)	15.0
Median Exposure (days)	-	-	53	84	168	350
quetiapine = N	0	5	6	163	136	0
Mean (SD) Glucose at BL	-	84.2 (19)	89.2 (10.3)	90.7 (11.1)	91.4 (11.9)	-
Mean (SD) Glucose at EOT	-	87 (11)	94.3 (8.4)	92.3 (11.4)	94.7 (15.8)	-
Mean (SD) Glucose Change	-	2.7 (15)	5.1 (3.5)	1.6 (11.5)	3.2 (15.9)	-
p-value	-	0.746	0.800	0.539	0.863	-
Modal (SD) Dose (mg)	-	500 (141)	600 (167)	614.8 (152)	617 (143)	-
Median Exposure (days)	-	28	58	85	169	-
risperidone = N	1	3	4	108	152	0
Mean (SD) Glucose at BL	81.0	92.5 (12)	85.1 (9.6)	92.5 (13.0)	92.1 (11.7)	-
Mean (SD) Glucose at EOT	91.8	91(9)	88.7 (4.0)	95.0 (14.6)	95.8 (16.4)	-
Mean (SD) Glucose Change	10.8	-1.6 (12)	3.6 (10.9)	2.6 (15.7)	3.7 (13.9)	-
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	94.6 (12.0)	4.7 (1.2)	4.9 (1.3)	4.8 (1.6)	4.8 (1.5)	-
Median Exposure (days)	94.7 (11.6)	30	50	85	169	-

Information obtained from Sponsor table 351 and 371 in Clinical Study Report

Table 77: Highest mean glucose change from baseline (BL), by week (comparator trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 48**
quetiapine = N	108	101	99	164	146	6
Mean (SD) Glucose at BL	92.5 (11)	92.0 (11)	92.0 (10.0)	90.7 (11.1)	91.4 (11.6)	87.6 (8)
Mean (SD) Glucose at EOT	93.2 (11.5)	93.1 (11)	93.4 (11.3)	94.5 (12.0)	98.8 (15.8)	96.0 (12)
Mean (SD) Glucose Change	0.7 (12.4)	1.1 (12)	1.4 (11.4)	3.8 (11.4)	7.4 (15.5)	8.4 (11)
p-value	0.378	0.448	0.342	0.084	0.528	0.246
Modal (SD) Dose (mg)	598 (149)	601 (139)	608 (139)	615 (15)	612 (147)	533 (151)
Median Exposure (days)	1	1	1	84	163	89
olanzapine = N	117	110	109	190	183	9
Mean (SD) Glucose at BL	90.7 (9)	90.0 (9)	90.2 (9.2)	90.1 (14.3)	89.9 (14.6)	80 (7)
Mean (SD) Glucose at EOT	92.5 (14)	92.3 (14)	92.6 (13.9)	96.1 (16.2)	99.3 (16.4)	101 (25)
Mean (SD) Glucose Change	1.9 (12)	2.3 (12)	2.5 (11.6)	6.0 (19.0)	9.4 (19.4)	21 (24)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	15.4 (3)	16 (3)	16 (3)	15 (4)	15(4)	13 (4)
Median Exposure (days)	1	1	1	84	120	183

quetiapine = N	108	101	99	164	146	6
Mean (SD) Glucose at BL	92.5 (11.1)	92.0 (11)	92.0 (10.0)	90.7 (11.1)	91.4 (11.6)	87.6 (8)
Mean (SD) Glucose at EOT	93.2 (11.5)	93 (11)	93.4 (11.3)	94.5 (12.0)	98.8 (15.8)	96.0 (12)
Mean (SD) Glucose Change	0.7 (12.4)	1.1 (12)	1.4 (11.4)	3.8 (11.4)	7.4 (15.5)	8.4 (11)
p-value	0.744	0.563	0.635	0.548	0.716	0.747
Modal (SD) Dose (mg)	598.1 (149)	601 (139)	608 (139)	614.7 (152)	612 (147)	533.3 (151)
Median Exposure (days)	1	11	1	84	163	89
risperidone = N	119	107	108	171	161	5
Mean (SD) Glucose at BL	94.6 (12.0)	94.3 (12)	94.2 (11.8)	92.4 (12.9)	91.9 (11.6)	81.8 (2)
Mean (SD) Glucose at EOT	94.7 (11.6)	94.4 (11)	94.3 (11.0)	96.8 (15.3)	100.1 (18)	87.6 (5)
Mean (SD) Glucose Change	0.2 (11.5)	0.1 (12)	0.1 (11.5)	4.3 (15.5)	8.3 (15.7)	5.7 (6.0)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	5.2 (1.2)	5.2 (1.2)	5.2 (1.3)	4.8 (1.6)	4.7 (1.6)	2.6 (1.1)

Median Exposure (days)	1	1	1	84	91	184

Information obtained from Sponsor table 351 and 371 in Clinical Study Report

6. Mean Fasting Glucose Change (mg/dl) from 'Normal' Baseline by Time (in Weeks)

Please see tables 78 and 79 below for comparison of mean glucose change from baseline and highest glucose change from baseline for quetiapine compared to olanzapine and quetiapine compared to risperidone at the 2, 4, 8, and 12 weeks endpoints.

Table 78: Mean glucose (mg/dl) change from 'normal' baseline (BL) to end of treatment (EOT), by week (comparator-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 48**
quetiapine = N	0	4	6	140	112	0
Mean (SD) Glucose at BL	-	77 (13)	89.2 (10.3)	87.4 (6.9)	87.4 (6.9)	-
Mean (SD) Glucose at EOT	-	86 (13)	94.3 (8.4)	91.0 (10.5)	93.4 (16.2)	-
Mean (SD) Glucose Change	-	8 (10)	5.1 (3.5)	3.6 (9.9)	6.0 (15.0)	-
p-value	-	-	0.249	0.079	0.751	-
Mean Modal (SD) Dose (mg)	-	475 (150)	600 (167)	617 (156.8)	626 (146)	-
Median Exposure (days)	-	25.5	59	85	169	
olanzapine = N	0	0	1	163	146	1
Mean (SD) Glucose at BL	-	-	95.4	86.7 (6.7)	87.0 (6.6)	70.0
Mean (SD) Glucose at EOT	-	-	106.2	92.9 (14.6)	92.5 (10.5)	86.0
Mean (SD) Glucose Change	-	-	10.8	6.1 (15.0)	5.6 (10.1)	16.0
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	-	-	30.0	15.0 (3.7)	15.0 (3.5)	15.0
Median Exposure (days)	-	-	53	84	168	350
quetiapine = N	0	4	6	140	112	0
Mean (SD) Glucose at BL	-	77.4 (12.9)	89.2 (10.3)	87.4 (6.9)	87.4 (6.9)	-
Mean (SD) Glucose at EOT	-	85.7 (12.7)	94.3 (8.4)	91.0 (10.5)	93.4 (16.2)	-
Mean (SD) Glucose Change	-	8.3 (10.2)	5.1 (3.5)	3.6 (9.9)	6.0 (15.0)	-
p-value	-	0.692	0.800	0.136	0.621	-
Modal (SD) Dose (mg)	-	475 (150)	600 (167)	616.5 (157)	626 (146)	-
Median Exposure (days)	-	26	59	85	169	-
risperidone = N	1	2	4	133	121	0
Mean (SD) Glucose at BL	81.0	85.6 (3.7)	85.1 (9.6)	87.7 (8.0)	87.9 (7.4)	-
Mean (SD) Glucose at EOT	91.8	89.5 (13.4)	88.7 (4.0)	93.5 (14.1)	93.1 (10.6)	-
Mean (SD) Glucose Change	10.8	3.9 (9.8)	3.6 (10.9)	5.8 (13.9)	5.3 (10.4)	-
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	4.0	4.0	4.9 (1.3)	4.6 (1.6)	4.7 (1.6)	-
Median Exposure (days)	17	28	51	85	169	-

Information obtained from Sponsor table 353 and 373 in Clinical Study Report

Table 79: Highest mean glucose change from 'normal' baseline (BL), by week (comparator-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 48**
quetiapine = N	86	82	81	140	121	5
Mean (SD) Glucose at BL	88.2 (6.5)	88.2 (7)	88.4 (6.6)	87.4 (6.9)	87.5 (6.8)	84.7 (4)
Mean (SD) Glucose at EOT	91.1 (9.3)	91 (9.7)	91.7 (9.6)	92.9 (10.5)	97.4 (15.6)	95 (14)
Mean (SD) Glucose Change	2.9 (9.1)	3.1 (9.4)	3.2 (9.2)	5.5 (9.4)	9.9 (14.3)	11 (11)
p-value	0.908	0.605	0.902	0.085	0.983	0.329
Modal (SD) Dose (mg)	598 (155)	606 (144)	615 (143)	617 (157)	623 (146)	560 (152)
Median Exposure (days)	1	1	1	84	164	86
olanzapine = N	96	93	92	164	158	9
Mean (SD) Glucose at BL	87.3 (6.3)	87 (6)	87.3 (6.4)	86.8 (6.7)	86.5 (6.9)	80.1 (7)
Mean (SD) Glucose at EOT	89.8 (8.7)	89.6 (9)	89.9 (9.0)	94.1 (14.4)	97.2 (14.6)	101 25)
Mean (SD) Glucose Change	2.5 (7.9)	2.5 (7.9)	2.6 (8.0)	7.3 (14.6)	10.8 (14.8)	21 (24)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	15.5 (3.2)	15.6 (3)	15.7 (3.5)	15.0 (3.7)	14.9 (3.7)	13.3 (4)

Median Exposure (days)	1	1	1	84	120	183
quetiapine = N	86	82	81	140	121	5
Mean (SD) Glucose at BL	88.2 (7)	88.2 (7)	88.4 (6.6)	87.4 (6.9)	87.5 (6.8)	84.7 (4)
Mean (SD) Glucose at EOT	91 (9)	91.3 (9)	91.7 (9.6)	92.9 (10.5)	97.4 (15.6)	95.2 (14)
Mean (SD) Glucose Change	2.9 (9.1)	3.1 (9.4)	3.2 (9.2)	5.5 (9.4)	9.9 (14.3)	10.5 (11)
p-value	0.705	0.776	0.628	0.160	0.768	0.861
Modal (SD) Dose (mg)	597.7 (155)	606 (144)	614.8 (143)	616.5 (157)	622.5 (146)	560 (152)
Median Exposure (days)	1	1	1	84	164	86
risperidone = N	84	77	79	135	129	5
Mean (SD) Glucose at BL	88.8 (8)	88.9 (8)	89.0 (8.3)	87.7 (7.9)	87.7 (7.3)	81.8 (2)
Mean (SD) Glucose at EOT	92.2 (11)	92.4 (11)	92.4 (11.0)	94.7 (15.0)	97.8 (14.4)	87.6 (5)
Mean (SD) Glucose Change	3.5 (10)	3.5 (11)	3.4 (10.5)	7.0 (14.6)	10.1 (13.7)	5.7 (6.0)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	5.2 (1.3)	5.2 (1.3)	5.2 (1.3)	4.6 (1.6)	4.6 (1.6)	2.6 (1.1)
Median Exposure (days)	1	1	1	85	99	184

Information obtained from Sponsor table 353 and 373 in Clinical Study Report

7. Mean Fasting Glucose Change (mg/dl) from 'Impaired' Baseline by Time (in Weeks)

Please see tables 80 and 81 below for comparison of mean glucose change from baseline and highest glucose change from baseline for quetiapine compared to olanzapine and quetiapine compared to risperidone at the 2, 4, 8, and 12 weeks endpoints (limited sample size).

Table 80: Mean glucose change from 'impaired' baseline (BL) to end of treatment (EOT), by week (comparator-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 48**
quetiapine = N	0	1	0	22	23	0
Mean (SD) Glucose at BL	-	111.6	-	108.1 (6.0)	108.3 (5.9)	-
Mean (SD) Glucose at EOT	-	91.8	-	98.0 (12.3)	99.8 (11.6)	-
Mean (SD) Glucose Change	-	-19.8	-	-10.1 (14)	-8.5 (12.9)	-
p-value	-	-	-	0.020	0.076	-
Modal (SD) Dose (mg)	-	600.0	-	596 (117)	565.2 (115)	-
Median Exposure (days)	-	29	-	85	169	-
olanzapine = N	0	0	0	24	23	0
Mean (SD) Glucose at BL	-	-	-	106.2 (6.4)	106.4 (6.5)	-
Mean (SD) Glucose at EOT	-	-	-	105.6 (13)	106.6 (13)	-
Mean (SD) Glucose Change	-	-	-	-0.6 (11.6)	0.2 (13.2)	-
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	14.8 (3.1)	14.8 (2.8)	-
Median Exposure (days)	-	-	-	22	168	-
quetiapine = N	0	1	0	22	23	0
Mean (SD) Glucose at BL	-	111.6	-	108.1 (6.0)	108.3 (5.9)	-
Mean (SD) Glucose at EOT	-	91.8	-	98.0 (12.3)	99.8 (11.6)	-
Mean (SD) Glucose Change	-	-19.8	-	-10.1 (14)	-8.5 (12.9)	-
p-value	-	-	-	0.678	0.618	-
Mean Modal (SD) Dose (mg)	-	600	-	596 (117)	565.2 (115)	-
Median Exposure (days)	-	29	-	85	169	-
risperidone = N	0	1	0	33	29	0
Mean (SD) Glucose at BL	-	106.2	-	107.0 (6.8)	106.9 (7.2)	-
Mean (SD) Glucose at EOT	-	93.6	-	99.1 (10.6)	101.9 (12)	-
Mean (SD) Glucose Change	-	-12.6	-	-7.9 (12.0)	-5.0 (13.4)	-
p-value	-	-	-	-	-	-
Mean Modal (SD) Dose (mg)	-	6	-	5.3 (1.1)	5.3 (1.1)	-
Median Exposure (days)	-	30	-	84	169	-

Information obtained from Sponsor table 357 and 377 in Clinical Study Report

Table 81: Highest mean glucose change from 'impaired' baseline (BL), by week (comparator-controlled trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
quetiapine = N	21	19	18	23	24	1
Mean (SD) Glucose at BL	108.0 (6.1)	108.3 (6)	108.1 (6.2)	107.8 (5.9)	108.2 (5.9)	102.0
Mean (SD) Glucose at EOT	102.3 (15)	101 (15)	101.1 (15)	102.4 (15)	104.6 (14)	100.0
Mean (SD) Glucose Change	-5.7 (15.8)	-7.7 (16)	-7.0 (16.3)	-5.4 (16.2)	-3.6 (15.6)	-2.0
p-value	0.421	0.177	0.220	0.021	0.098	-
Mean Modal (SD) Dose (mg)	591	579	578 (116)	595.7 (115)	550 (135)	400.0
Median Exposure (days)	1	1	1	82	131	204
olanzapine = N	21	17	17	25	24	0
Mean (SD) Glucose at BL	105.9 (5.3)	105.9 (6)	105.9 (5.8)	106.1 (6.3)	106.2 (6.4)	-
Mean (SD) Glucose at EOT	105.1 (22)	107 (24)	107.4 (24)	109.1 (22)	113.0 (21)	-
Mean (SD) Glucose Change	-0.9 (22.0)	1.5 (23)	1.5 (23.4)	3.0 (20.8)	6.8 (21.1)	-
p-value	-	-	-		-	-
Mean Modal (SD) Dose (mg)	15.0 (3.2)	15 (3)	15	14.8 (3.1)	15.0 (2.9)	-
Median Exposure (days)	1	1	1	84	86	-
quetiapine = N	21	19	18	23	24	1
Mean (SD) Glucose at BL	108.0 (6.1)	108.3 (6)	108.1 (6.2)	107.8 (5.9)	108.2 (5.9)	102.0
Mean (SD) Glucose at EOT	102.3 (15)	100 (15)	101.1 (15)	102.4 (15)	104.6 (14)	100.0
Mean (SD) Glucose Change	-5.7 (15.8)	-7.7 (16)	-7.0 (16.3)	-5.4 (16.2)	-3.6 (15.6)	-2.0
p-value	0.612	0.807	0.707	0.728	0.634	-
Mean Modal (SD) Dose (mg)	590.5 (118)	579 (113)	578 (117)	596(114)	550.0 (135)	400.0
Median Exposure (days)	1	1	1	82	130	204
risperidone = N	34	29	28	33	30	0
Mean (SD) Glucose at BL	107.9 (6.8)	107.5 (7)	107.6 (7.2)	107.0 (6.8)	106.7 (7.1)	-
Mean (SD) Glucose at EOT	100.5 (10)	98.9 (9)	99.1 (9)	102.7 (9.3)	105.3 (12)	-
Mean (SD) Glucose Change	-7.5 (10.5)	-8.6 (9)	-8.4 (9.2)	-4.3 (10.2)	-1.4 (12.7)	-
p-value	-	-	-	-	-	-
Mean Modal (SD) Dose (mg)	5.2 (1.0)	5.2 (1.0)	5.2 (1.0)	5.3 (1.1)	5.3 (1.1)	-
Median Exposure (days)	1	1	1	84	85	-

Information obtained from Sponsor table 357 and 377 in Clinical Study Report

6.2.2 Categorical Analyses

1. Fasting Glucose Increase Outliers

Similar percentages of subjects had shifts in fasting glucose outliers in the quetiapine and active-comparator treatment groups.

Table 82: Proportion of Patients with treatment emergent fasting glucose (mg/dL) change (comparator-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	≥300 N (%)	≥200 N (%)	≥140 N (%)	≥126 N (%)
<100 mg/dL	Quetiapine	166	0	1 (0.6)	1 (0.6)	4 (2.4)
	Olanzapine	182	0	0	4 (2.2)	7 (3.8)
	p-value		-	0.477	0.374	0.547
	Quetiapine	166	0	1 (0.6)	1 (0.6)	4 (2.4)
	risperidone	164	0	0	3 (1.8)	7 (4.3)
	p-value		-	1.000	0.370	0.377
≥100 mg/dL and <126 mg/dL	Quetiapine	30	0	0	0	3 (10.0)
	Olanzapine	29	0	0	2 (6.9)	4 (13.8)
	p-value		-	-	0.237	0.706
	Quetiapine	30	0	0	0	3 (10.0)
	risperidone	40	0	0	0	4 (10.0)

	p-value		-	-	-	1.000
< 126 mg/dL	Quetiapine	196	0	1 (0.5)	1 (0.5)	7 (3.6)
	Olanzapine	211	0	0	6 (2.8)	11 (5.2)
	p-value		-	0.482	0.124	0.476
	Quetiapine	196	0	1 (0.5)	1 (0.5)	7 (3.6)
	risperidone	204	0	0	3 (1.5)	11 (5.4)
	p-value		-	0.490	0.623	0.472
Modal (SD) Dose (mg)	QTP – 600 mg vs. OLZ – 15 mg QTP - 600 mg vs. RISP – 4.7 mg					
Median Exposure(days)	QTP – 168 days vs. OLZ – 168 days QTP - 168 days vs. RISP -168 days					

Information obtained from Sponsor table 360 and 380 in Clinical Study Report

2. Fasting Glucose Increase of more than ≥10 mg/dL Outliers

Similar percentages of subjects had shifts in fasting glucose ≥ 10 mg/dL outliers in the quetiapine and the active-comparator treated groups.

Table 83: Proportion of Patients with treatment emergent increase in fasting glucose (>10 mg/dL) (comparator-controlled trials)

Baseline	Treatment Arm	N =	>10 mg/dL increase post-baseline n (%)
Any value	quetiapine	198	65 (32.8)
	olanzapine	212	83 (39.2)
	p-value = 0.217		
	quetiapine	198	65 (32.8)
	risperidone	207	63 (30.4)
	p-value = 0.669		
<100 mg/dL	quetiapine	166	60 (36.1)
	olanzapine	182	77 (42.3)
	p-value = 0.272		
	quetiapine	166	60 (36.1)
	risperidone	164	58 (35.4)
	p-value = 0.909		
≥100 mg/dL and <126 mg/dL	quetiapine	30	5 (16.7)
	olanzapine	29	6 (20.7)
	p-value = 0.748		
	Quetiapine	30	5 (16.7)
	risperidone	40	4 (10.0)
	p-value = 0.483		
<126 mg/dL	quetiapine	2	0
	olanzapine	1	0
	p-value = -		
	quetiapine	2	0
	risperidone	3	1 (33.3)
	p-value = 1.000		
Modal (SD) Dose (mg)	QTP – 603 mg vs. OLZ – 15 mg QTP - 602 mg vs. RISP – 4.7 mg		
Median Exposure(days)	QTP – 168 days vs. OLZ – 168 days QTP - 168 days vs. RISP – 168 days		

Information obtained from Sponsor table 361 and 381 in Clinical Study Report

3. Fasting HbA1c (%) Increase of more than ≥6.1 Outliers

Olanzapine-treated subjects (N = 255, modal daily dose of 13 mg) had a greater mean HbA1c increase from baseline of 4.7% compared to a mean HbA1c increase of 2.5 % in quetiapine-treated subjects (N = 240, modal daily dose of 563 mg) with a median exposure of 198-321 days.

Risperidone-treated subjects (N = 241, modal daily dose of 4.3 mg) had a greater mean HbA1c increase from baseline of 3.3% compared to a mean HbA1c increase of 2.5 % in quetiapine-treated subjects (N = 240, modal daily dose of 590 mg) with a median exposure of 168 days.

Table 84: Proportion of Patients with treatment emergent fasting HbA1c (%) increase (comparator-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	≥ 6.1 N (%)	≥8 N (%)	≥10 N (%)	≥12 N (%)
HbA1c(%) <6.1	Quetiapine	240	6 (2.5)	1 (0.4)	0	0
	Olanzapine	255	12 (4.7)	1 (0.4)	0	0
	p-value =		0.233	1.000	-	-
	Quetiapine	240	6 (2.5)	1 (0.4)	0	0
	risperidone	241	8 (3.3)	0	0	0
	p-value =		0.787	0.499	-	-
Modal (SD) Dose (mg)	QTP – 563 mg vs. OLZ – 13 mg QTP - 590 mg vs. RISP - 4.3 mg					
Median Exposure(days)	QTP – 321 days vs. OLZ – 198 days QTP - 168 days vs. RISP - 168 days					

Information obtained from Sponsor table 362 and 382 in Clinical Study Report

4. Glycosuria Outliers

About 2.3% of quetiapine-treated subjects (N = 221, modal daily dose of 588 mg) had greater treatment emergent glycosuria (any amount of glucose seen in urine from baseline) compared to 1.7 % in olanzapine-treated subjects (N = 238) with a median exposure of 335-337 days.

About 2.7% of risperidone-treated subjects (N = 222, modal daily dose of 588 mg) had greater treatment emergent glycosuria (any amount of glucose seen in urine from baseline) compared to 2.3 % in quetiapine-treated subjects (N = 221) with a median exposure of 169 days.

Table 85: Proportion of Patients with treatment emergent glycosuria (comparator-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	N(%)
Glycosuria	Quetiapine	221	5 (2.3)
	Olanzapine	238	4 (1.7)
	Quetiapine	221	5 (2.3)
	Risperidone	222	6 (2.7)
Modal (SD) Dose (mg)	QTP – 588 mg vs. OLZ – 14 mg QTP - 588 mg vs. RISP – 4.3 mg		
Median Exposure(days)	QTP – 337 days vs. OLZ – 335 days QTP - 169 days vs. RISP -169 days		

Information obtained from Sponsor table 363 and 383 in Clinical Study Report

About 16% of quetiapine-treated subjects (N = 98, mean daily dose of 265 mg) had treatment emergent glycosuria (any amount of glucose seen in urine from baseline) compared to 6.7 % in haloperidol-treated subjects (N = 89) with a median exposure of 56 days.

Table 86: Proportion of Patients with treatment emergent glycosuria (haloperidol-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	N (%)
Glycosuria	Quetiapine	98	16 (16.3)
	haloperidol	89	6 (6.7)
Modal (SD) Dose (mg)	Quetiapine - 264.8 (157.4) / haloperidol - 8.1 (4.7)		
Median Exposure(days)	56		

Information obtained from Sponsor table 343 in Clinical Study Report

6.3 Adults Subjects in Long Term Controlled and Uncontrolled Clinical Trials

6.3.1 Mean Change Analyses

1. Mean Glucose Change (in mg/dl) from All subjects at any baseline glucose level

The mean change from baseline (any glucose level) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 8567, modal daily dose of 379 mg) was 2.9 mg/dL and 6.1 mg/dL with a mean exposure of 71 days.

Table 87: Mean glucose change (in mg/dl) from baseline (BL) to end of treatment (EOT) (all QTP trials)

	QTP
N	8567
Mean (SD) Glucose at BL	92.4 (14.6)
Mean (SD) Glucose at EOT	95.3 (19.5)
Mean (SD) Glucose Change	2.9 (17.7)
p-value	-
Mean (SD) Highest Glucose	98.6 (20.9)
Mean (SD) Highest Glucose Change	6.1 (18.8)
Modal (SD) Dose (mg)	379 (234)
Median Exposure (days)	71

Information obtained from Sponsor table 390 in Clinical Study Report

2. Mean Glucose Change (in mg/dl) from 'Normal Fasting Glucose' (<100 mg/dL) at Baseline

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 6832, modal daily dose of 373 mg) was 4.6 mg/dL and 7.6 mg/dL with a mean exposure of 71 days.

Table 88: Mean glucose change (in mg/dl) from 'normal' baseline (BL) to end of treatment (EOT) (all QTP trials)

	QTP
N	6832
Mean (SD) Glucose at BL	87.3 (7.2)
Mean (SD) Glucose at EOT	91.9 (14.0)
Mean (SD) Glucose Change	4.6 (14.1)
p-value	-
Mean (SD) Highest Glucose	94.9 (15.3)
Mean (SD) Highest Glucose Change	7.6 (15.4)
Modal (SD) Dose (mg)	373 (232)
Median Exposure (days)	71

Information obtained from Sponsor table 392 in Clinical Study Report

3. Mean Glucose Change (in mg/dl) from 'Impaired Fasting Glucose' (100-125 mg/dL) at Baseline

The mean change from impaired baseline (fasting glucose level of 100-125 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 1511, modal daily dose of 395 mg) was-2.5 mg/dL and 1.0 mg/dL with a mean exposure of 75 days.

Table 89:Mean glucose change from' impaired' fasting glucose at baseline (BL) to end of treatment (EOT) (all QTP trials)

	QTP
N	1510
Mean (SD) Glucose at BL	107.0 (6.3)
Mean (SD) Glucose at EOT	104.5 (20.9)
Mean (SD) Glucose Change	-2.5 (20.3)
p-value	-
Mean (SD) Highest Glucose	108.0 (21.3)
Mean (SD) Highest Glucose Change	1.0 (20.6)
Modal (SD) Dose (mg)	395.3 (239.9)
Median Exposure (days)	75

Information obtained from Sponsor table 396 in Clinical Study Report

4. Mean Glucose Change (in mg/dl) from 'High Fasting Glucose' (≥126 mg/dL) at Baseline

The mean change from high baseline (fasting glucose level of ≥126 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 225, modal daily dose of 449 mg) were -12.2 mg/dL and -4.3 mg/dL with a mean exposure of 71 days.

Table 90: Mean glucose change (in mg/dl) from 'high' baseline (BL) to end of treatment (EOT) (all QTP trials)

	QTP
N	225
Mean (SD) Glucose at BL	149.8 (27.4)
Mean (SD) Glucose at EOT	137.5 (54.0)
Mean (SD) Glucose Change	-12.2 (50.8)
p-value	-
Mean (SD) Highest Glucose	145.5 (57.1)
Mean (SD) Highest Glucose Change	-4.3 (54.5)
Modal (SD) Dose (mg)	449 (235)
Median Exposure (days)	71

Information obtained from Sponsor table 394 in Clinical Study Report

5. Mean Fasting Glucose Change (in mg/dl) from All subjects at any baseline glucose level by Time (in Weeks)

The mean change from baseline (any fasting glucose level) to endpoints (in weeks) in quetiapine-treated subjects showed -1.7, 2.8, 3, 3, 4 and 5 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 91: Mean glucose change (in mg/dl) from baseline (BL) to end of treatment (EOT), by week (all QTP trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 48**
Seroquel = N	121	2741	2360	2963	788	201
Mean (SD) Glucose at BL	92 (12)	92 (14)	93 (14)	92 (14)	93 (15)	93 (13)
Mean (SD) Glucose at EOT	93 (12)	95 (20)	95 (20)	95 (18)	96 (21)	98 (17)
Mean (SD) Glucose Change	1.7 (11)	2.8 (18)	3 (17)	3 (17)	4 (21)	5 (17)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	362 (231)	317 (223)	339 (216)	436 (234)	491(214	397 (203)

Median Exposure (days)	15	29	57	84	169	337

Information obtained from Sponsor table 391 in Clinical Study Report

The mean change from any baseline (any fasting glucose level) to the highest mean change in quetiapine-treated subjects showed -0.6, 3, 5, 4, 7 and 10 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 92: Highest mean glucose change (in mg/dl) from baseline (BL), by week (all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	526	2924	3805	3385	2188	1045
Mean (SD) Glucose at BL	94 (17)	92 (14)	93 (15)	93 (15)	93 (15)	93 (14)
Mean (SD) Highest Glucose	93 (17)	95 (20)	98 (20)	96 (18)	100 (20)	102 (21)
Mean (SD) Highest Glucose Change	-0.6 (16)	3(18)	5 (18)	4 (17)	7 (19)	10 (20)
p-value	-	-	-	-	-	
Modal (SD) Dose (mg)	410 (243)	328 (226)	365 (225)	438 (231)	397(233	357(215)
Median Exposure (days)	8	29	46	83	113	228

Information obtained from Sponsor table 391 in Clinical Study Report

6. Mean Glucose Change (in mg/dl) from 'Normal Fasting Glucose' (<100 mg/dL) at Baseline by Time (in Weeks)

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoints (in weeks) in quetiapine-treated subjects showed 3.8, 4.4, 3.9, 5, 7 and 8 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 93: Mean glucose change (in mg/dl) from 'normal' baseline (BL) to end of treatment (EOT), by week (all quetiapine trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	95	2242	1872	2349	624	153
Mean (SD) Glucose at BL	86.9 (7.1)	87.4 (7.0)	87.5 (7.2)	87 (7.4)	87 (6.9)	87 (6)
Mean (SD) Glucose at EOT	90.7 (9.9)	91.8 (15.2)	91.4 (12.7)	92 (13)	94 (18.3)	95 (16)
Mean (SD) Glucose Change	3.8 (9.6)	4.4 (15.4)	3.9 (12.7)	5 (13.8)	7(18.1)	8(15.4)
p-value	-	-	-	-	--	-
Modal (SD) Dose (mg)	352 (234)	311 (218)	330 (212)	435 (234)	7(18.1)	385 (194)
Median Exposure (days)	15	29	57	84	169	337

Information obtained from Sponsor table 393 in Clinical Study Report

The mean change from any normal baseline (fasting glucose level of < 100 mg/dl) to the highest mean change in quetiapine-treated subjects showed 2.1, 4.5, 6.5, 6, 9 and 12 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 94: Highest mean glucose change (in mg/dl) from 'normal' baseline (BL), by week (all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	409	2386	3017	2664	1724	810
Mean (SD) Glucose at BL	87.8 (7)	87.5 (7)	87.4 (7.2)	87 (7.3)	87 (7)	88 (7)
Mean (SD) Highest Glucose	90 (11.3)	91.9 (15)	93.9 (13.3)	93 (13.6)	97 (16)	99 (17)
Mean (SD) Highest Glucose Change	2.1 (11)	4.5 (15)	6.5 (13.5)	6(13.9)	9 (16)	12 (17)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	416(246)	323 (222)	356 (222)	437 (231)	398(234)	349 (213)
Median Exposure (days)	7	29	46	83	114	232

Information obtained from Sponsor table 393 in Clinical Study Report

7. Mean Glucose Change (in mg/dl) from 'Impaired Fasting Glucose' (100 -125 mg/dL) at Baseline by Time (in Weeks)

The mean change from impaired baseline (fasting glucose level of ≥125 mg/dl) to endpoints (in weeks) in quetiapine-treated subjects showed -5.6, -4.5, -1.9,-2, -4.6 and -3.3 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 95: Mean glucose change (in mg/dl) from 'impaired' baseline (BL) to end of treatment (EOT), by week (all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	24	432	430	536	143	43
Mean (SD) Glucose at BL	106.9 (5.9)	107.6 (6.7)	107.2 (6.6)	106.9 (6)	108(6.1)	108.0 (7)
Mean (SD) Glucose at EOT	101.3 (11)	103(18.5)	105 (22.8)	104(20.0)	103 (23)	105 (11)
Mean (SD) Glucose Change	-5.6 (9.9)	-4.5 (17.8)	-1.9 (21.7)	-2 (19.5)	-4.6 (24)	-3.3 (13)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	404 (225.0)	330 (236.3)	365(228)	438(239)	489 (200)	443 (231)
Median Exposure (days)	15	29	57	84	169	337

Information obtained from Sponsor table 397 in Clinical Study Report

The mean change from any impaired baseline (fasting glucose level of 100 - 125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -6.8, -4.3,-0.2, -1.4, 1.9 and 3 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 96: Highest mean glucose change (in mg/dl) from 'impaired' baseline (BL), by week (all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	101	465	688	630	405	207
Mean (SD) Glucose at BL	107(6.1)	107.5 (6)	107.3 (6.5)	107(6.3)	107 (6)	106 (6)
Mean (SD) Highest Glucose	100 (14)	103 (18)	107 (20.9)	106 (19)	109(20)	109 (15)
Mean (SD) Highest Glucose Change	-6.8 (13)	-4.3 (18)	-0.2 (19.8)	-1.4 (19)	1.9(20)	3(15)
p-value	-	-	-	-	-	-
Mean Modal (SD) Dose (mg)	388(238)	343 (238)	390 (232.5)	439 (235)	392(232	387(227)
Median Exposure (days)	8	29	50	83	113	212

Information obtained from Sponsor table 397 in Clinical Study Report

8. Mean Glucose Change (in mg/dl) from 'High Fasting Glucose' (≥126 mg/dL) at Baseline by Time (in Weeks)

The mean change from any impaired baseline (fasting glucose level of 100 - 125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -14, -4, -2,-21, -24 and -11 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 97: Mean glucose change (in mg/dl) from 'high' baseline (BL) to end of treatment (EOT), by week (all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	2	67	58	78	21	5
Mean (SD) Glucose at BL	139.5 (3.8)	148 (22.7)	146.6 (29)	148 (24)	150 (28)	140 (14)
Mean (SD) Glucose at EOT	126.0 (31)	144 (51.3)	145(52.4)	127.(49)	126 (38)	129(35)
Mean (SD) Glucose Change	-13.5 (34)	-3.5 (49.0)	-1.9 (50.5)	-21 (41)	-24 (49)	-11(45)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	350 (71)	422(269.7)	434(214.5)	478(223)	483 (225)	360(227)
Median Exposure (days)	15	29	57	83	169	338

Information obtained from Sponsor table 395 in Clinical Study Report

The mean change from any high baseline (fasting glucose level of ≥125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -29, -6, 0, -20, -9 and 3 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 98: Highest mean glucose change (in mg/dl) from 'high' baseline (BL), by week (all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	16	73	100	91	59	28

Mean (SD) Glucose at BL	162 (41)	150 (27)	148 (29)	149 (27)	149(26)	144 (27)
Mean (SD) Highest Glucose	132 (53)	144 (53)	148 (57.5)	129 (51)	139(40)	147(53)
Mean (SD) Highest Glucose Change	-29 (57)	-6.4 (52)	0.0 (57.1)	-20 (42)	-9 (46)	3.(58)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	403 (217)	417 (265)	468.0 (240)	475 (218)	425(221	375.(191)
Median Exposure (days)	7	29	50	81	108	214

Information obtained from Sponsor table 395 in Clinical Study Report

6.3 2 Categorical Analyses

1. Fasting Glucose Increase Outliers

In the Quetiapine-treated subjects (modal daily dose of 376 mg, median exposure of 71 days) 4.7% had treatment emergent increase in glucose from <126 mg/dl at baseline to >126 mg/dl post baseline. 12% had treatment emergent increase in glucose from >100 - <126 mg/dl at baseline to >126 mg/dl post baseline; and 5.9% had >140 mg post-baseline.

Table 99: Proportion of Patients with treatment emergent fasting glucose change (in mg/dL) (all QTP trials)

Baseline	Treatment Arm Post-baseline	N =	≥300 N (%)	≥200 N (%)	≥140 N (%)	≥126 N (%)
<100 mg/dL	Quetiapine	6832	3 (0.0)	15 (0.2)	97 (1.4)	210 (3.1)
≥100 mg/dL and <126 mg/dL	Quetiapine	1510	3 (0.2)	13 (0.9)	89 (5.9)	184 (12.2)
<126 mg/dL	Quetiapine	8342	6 (0.1)	28 (0.3)	186 (2.2)	394 (4.7)
Modal (SD) Dose (mg)	376.9 (233.4)					
Median Exposure(days)	71					

Information obtained from Sponsor table 400 in Clinical Study Report

2. Fasting Glucose Increase of more than ≥10 mg/dL Outliers

30 % of Quetiapine-treated subjects (modal daily dose of 379 mg, median exposure of 71 days) showed treatment emergent increase in glucose (≥10 mg/dL) regardless of the baseline glucose value.

Table 100: Proportion of Patients with treatment emergent increase (≥10 mg/dL) in fasting glucose (all QTP trials)

Baseline	Treatment Arm	N =	≥10 mg/dL increase post-baseline n (%)
Any value	Quetiapine	8567	2597 (30.3)
<100 mg/dL	Quetiapine	6832	2221 (32.5)
≥100 mg/dL and <126 mg/dL	Quetiapine	1510	305 (20.2)
<126 mg/dL	Quetiapine	225	71 (31.6)
Modal (SD) Dose (mg)	378.8 (233.8)		
Median Exposure(days)	71		

Information obtained from Sponsor table 401 in Clinical Study Report

3. Fasting HbA1c (%) Increase of more than ≥6.1 Outliers

About 6 % of quetiapine-treated (N = 8698, modal daily dose of 394 mg) subjects had a treatment emergent HbA1c increase (> 6.1%) from baseline with a median exposure of 72 days.

Table 101: Proportion of Patients with treatment emergent fasting HbA1c (%) increase (all QTP trials)

Baseline	Treatment Arm Post-baseline	N =	≥ 6.1 N (%)	≥8 N (%)	≥10 N (%)	≥12 N (%)
HbA1c(%) <6.1	Quetiapine	8698	526 (6.0)	5 (0.1)	1 (0.0)	0
Modal (SD) Dose in mg	394.4 (249.4)					
Median Exposure(days)	72					

Information obtained from Sponsor table 402 in Clinical Study Report

4. Glycosuria Outliers

About 3.2% of quetiapine-treated subjects (N = 5679, modal daily dose of 507 mg with median exposure of 77 days) had treatment emergent glycosuria (any amount of glucose seen in urine).

Table 102: Proportion of Patients with treatment emergent glycosuria (all QTP trials)

Baseline	Treatment Arm Post-baseline	N =	N (%)
Glycosuria	Quetiapine	5679	179 (3.2)
Modal (SD) Dose (mg)	507.2 (200.0)		
Median Exposure(days)	77		

Information obtained from Sponsor table 403 in Clinical Study Report

6.4 Antipsychotic-Naïve Subjects in Placebo-Controlled Trials

6.4.1 Mean Change Analyses

1. Mean Glucose Change (in mg/dl) from All subjects at any baseline glucose level

The mean change from baseline (any glucose level) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 1652, modal daily dose of 180 mg) were 1.2 mg/dL and 4.6 mg/dL compared to 1.6 mg/dL and 4.4 mg/dL in placebo-treated subjects (N = 890) respectively, with a mean exposure of 56 days.

Table 103: Mean glucose change (mg/dl) from baseline (BL) to end of treatment (EOT) (naïve subjects, placebo-controlled trials)

	QTP	Placebo
N	1652	890
Mean (SD) Glucose at BL	91.2 (12.1)	91.0 (13.2)
Mean (SD) Glucose at EOT	92.5 (14.4)	92.4 (15.6)
Mean (SD) Glucose Change	1.2 (13.8)	1.4 (12.7)
p-value	0.654	-
Mean (SD) Highest Glucose	95.8 (14.9)	95.9 (16.0)
Mean (SD) Highest Glucose Change	4.6 (14.3)	4.8 (12.9)
Modal (SD) Dose (mg)	179.4 (118.8)	-
Median Exposure (days)	56	56

Information obtained from Sponsor table 441 in Clinical Study Report

2. Mean Glucose Change (in mg/dl) from 'Normal Fasting Glucose' (<100 mg/dL) at Baseline

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 1378, mean daily dose of 181 mg) were 3 mg/dL and 6 mg/dL compared to 3 mg/dL and 6 mg/dL in placebo-treated subjects (N = 740) respectively, with a mean exposure of 56 days.

Table 104: Mean glucose change (mg/dl) from 'normal' baseline to end of treatment (EOT) (naïve subjects, placebo-controlled trials)

	QTP	Placebo
N	1378	740
Mean (SD) Glucose at BL	87.4 (7.0)	87.0 (7.2)
Mean (SD) Glucose at EOT	90.1 (11.2)	89.8 (10.3)
Mean (SD) Glucose Change	2.7 (11.5)	2.8 (10.9)
p-value	0.732	-

Mean (SD) Highest Glucose	93.5 (12.0)	93.0 (10.7)
Mean (SD) Highest Glucose Change	6.1 (12.2)	6.0 (11.2)
Modal (SD) Dose (mg)	181.3 (121.4)	-
Median Exposure (days)	56	56

Information obtained from Sponsor table 442 in Clinical Study Report

3. Mean Glucose Change (in mg/dl) from 'Impaired Fasting Glucose' (100-125 mg/dL) at Baseline

The mean change from impaired baseline (fasting glucose level of 100-125 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 252, modal daily dose of 171 mg) were -5.4 mg/dL and -2.3 mg/dL compared to -5.9 mg/dL and -1.1 mg/dL in placebo-treated subjects (N = 137) respectively, with a mean exposure of 56 days.

Table 105: Mean glucose change from' Impaired' baseline to end of treatment (naïve subjects, placebo-controlled trials)

	QTP	**Placebo**
N	252	137
Mean (SD) Glucose (mg/dl) at Baseline	107.4 (6.4)	107.4 (6.5)
Mean (SD) Glucose (mg/dl)at End of treatment	101.9 (18.0)	101.5 (15.1)
Mean (SD) Glucose (mg/dl) Change	-5.4 (17.4)	-5.9 (14.7)
p-value	0.639	
Mean (SD) Highest Glucose(mg/dl)	105.1 (17.5)	106.3 (15.7)
Mean (SD) Highest Glucose (mg/dl) Change	-2.3 (16.9)	-1.1 (15.3)
Modal (SD) Dose (mg)	170.6 (106.0)	-
Median Exposure (days)	56	56

Information obtained from Sponsor table 446 in Clinical Study Report

4. Mean Glucose Change (in mg/dl) from High Fasting Glucose' (≥126 mg/dL) at Baseline

The mean change from high baseline (fasting glucose level of ≥126 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 22, modal daily dose of 448 mg) were-15 mg/dL and -10 mg/dL compared to-4 mg/dL and -1 mg/dL in placebo-treated subjects (N = 13) respectively, with a mean exposure of 55-56 days.

Table 106: Mean glucose change (mg/dl) from 'high' baseline (BL) to end of treatment (EOT) (naïve subjects, placebo-controlled trials)

	QTP	**Placebo**
N	22	13
Mean (SD) Glucose at BL	145.9 (23.2)	149.1 (38.0)
Mean (SD) Glucose at EOT	130.9 (35.5)	145.5 (66.8)
Mean (SD) Glucose Change	-15.0 (43.7)	-3.6 (38.0)
p-value	0.555	
Mean (SD) Highest Glucose	136.1 (34.9)	148.0 (66.2)
Mean (SD) Highest Glucose Change	-9.8 (44.6)	-1.1 (37.5)
Modal (SD) Dose (mg)		
Median Exposure (days)	55	56

Information obtained from Sponsor table 444 in Clinical Study Report

5. Mean Glucose Change (in mg/dl) from All subjects at any baseline glucose level by Time (in Weeks)

The mean change from baseline (any fasting glucose level) to endpoints (in weeks) in quetiapine-treated subjects showed 1, 2, 0.7, and -7 mg/dl compared to 10, 2, 1, and 0 mg/dl in placebo-treated subjects at 2, 4, 8, and 12 weeks, respectively.

Table 107: Mean glucose change from baseline (BL) to end of treatment (EOT), by week (naïve subjects, placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	21	1376	835	3
Mean (SD) Glucose at BL	91.6 (9.9)	91.2 (11.9)	91.6 (11.0)	105.6 (16.3)
Mean (SD) Glucose at EOT	92.7 (12.3)	93.4 (14.4)	92.3 (13.6)	99.6 (12.0)
Mean (SD) Glucose Change	1.1 (9.3)	2.3 (14.1)	0.7 (12.6)	-6.0 (5.5)
p-value	0.216	0.470	0.459	-
Mean Modal (SD) Dose (mg)	197.6 (162.4)	181.4 (119.7)	161.3 (87.7)	83.3 (57.7)
Median Exposure (days)	15	29	57	71
Placebo = N	6	731	492	1
Mean (SD) Glucose at BL	94.5 (13.8)	91.1 (13.4)	92.0 (15.0)	77.4
Mean (SD) Glucose at EOT	104.4 (5.7)	92.8 (12.9)	93.3 (17.5)	77.4
Mean (SD) Glucose Change	9.9 (10.5)	1.7 (13.4)	1.3 (13.3)	0
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	15	29	57	71

Information obtained from Sponsor table 441 in Clinical Study Report

The mean change from any baseline (any fasting glucose level) to the highest mean change in quetiapine-treated subjects showed -4, 2, 5, and 2 mg/dl compared to 5, 2, 5, and 11 mg/dl in placebo-treated subjects at 2, 4, 8, and 12 weeks, respectively.

Table 108: Highest mean glucose change (in mg/dl) at baseline (BL), by week (naïve subjects, placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	108	1393	1288	18
Mean (SD) Glucose at BL	95.5 (15.3)	91.2 (12.0)	91.0 (11.4)	94.3 (14.3)
Mean (SD) Highest Glucose	91.7 (16.6)	93.4 (14.3)	96.5 (14.0)	96.6 (12.1)
Mean (SD) Highest Glucose Change	-3.8 (17.2)	2.2 (14.1)	5.4 (13.2)	2.3 (9.8)
p-value	0.032	0.494	1.000	0.105
Mean Modal (SD) Dose (mg)	170.4 (93.2)	180.9 (119.7)	179.1 (121.0)	138.9 (99.3)
Median Exposure (days)	8	29	43	64
Placebo = N	71	738	697	10
Mean (SD) Glucose at BL	91.8 (12.8)	91.1 (13.4)	91.2 (13.7)	86.0 (10.0)
Mean (SD) Highest Glucose	96.8 (16.2)	92.8 (12.8)	96.3 (16.3)	96.7 (15.6)
Mean (SD) Highest Glucose Change	5.0 (15.1)	1.7 (13.3)	5.1 (12.7)	10.6 (7.0)
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	9	29	43	58

Information obtained from Sponsor table 441 in Clinical Study Report

6. Mean Glucose Change (in mg/dl) from 'Normal Fasting Glucose' (<100 mg/dL) at Baseline by Time (in Weeks)

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoints (in weeks) in quetiapine-treated subjects showed 1, 4, 2, and -4 mg/dl compared to 14, 3, 3, and 0 mg/dl in placebo-treated subjects at 2, 4, 8, and 12 weeks, respectively.

Table 109: Mean glucose change from 'normal' baseline (BL) to end of treatment, by week (naïve subjects, placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	16	1154	691	2
Mean (SD) Glucose at BL	87.3 (6.3)	87.4 (6.9)	87.9 (6.8)	96.3 (3.8)
Mean (SD) Glucose at EOT	88.7 (9.9)	91.3 (11.9)	89.9 (10.6)	92.7 (1.3)

Mean (SD) Glucose Change	1.3 (9.7)	3.9 (12.1)	2.0 (10.5)	-3.6 (5.1)
p-value	0.149	0.326	0.138	-
Modal (SD) Dose (mg)	178.1 (93.0)	183.2 (122.6)	162.7 (88.7)	100.0 (71)
Median Exposure (days)	14	29	57	71
Placebo = N	4	610	401	1
Mean (SD) Glucose at BL	87.3 (8.1)	87.1 (7.2)	87.2 (7.3)	77.4
Mean (SD) Glucose at EOT	101.7 (2.3)	90.4 (10.6)	90.3 (10.4)	77.4
Mean (SD) Glucose Change	14.4 (9.9)	3.3 (11.1)	3.1 (11.1)	0
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	15	29	57	71

Information obtained from Sponsor table 443 in Clinical Study Report

The mean change from any normal baseline (fasting glucose level of < 100 mg/dl) to the highest mean change in quetiapine-treated subjects showed -0.8, 4.5, 7, and 5.0 mg/dl compared to 7, 3, 7, and 9 mg/dl in placebo-treated subjects at 2, 4, 8, and 12 weeks, respectively.

Table 110: Highest mean glucose change (in mg/dl) at 'normal' baseline (BL), by week (naïve subjects, placebo-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**
Seroquel = N	77	1166	1074	13
Mean (SD) Glucose at BL	88.7 (7.4)	87.4 (6.9)	87.3 (6.9)	87.9 (10.2)
Mean (SD) Highest Glucose	87.9 (13.3)	91.3 (11.9)	94.2 (11.5)	93.3 (11.6)
Mean (SD) Highest Glucose Change	-0.8 (13.9)	3.9 (12.1)	6.9 (11.6)	5.4 (8.2)
p-value	0.127	0.299	0.896	0.385
Modal (SD) Dose (mg)	167.5 (79.0)	182.9 (122.7)	181.7 (124.2)	157.7 (107.7)
Median Exposure (days)	8	29	43	64
Placebo = N	44	617	582	9
Mean (SD) Glucose at BL	86.3 (7.3)	87.1 (7.2)	87.1 (7.1)	83.6 (6.8)
Mean (SD) Highest Glucose	92.8 (11.7)	90.5 (10.6)	93.5 (10.4)	92.6 (9.4)
Mean (SD) Highest Glucose Change	6.5 (12.7)	3.4 (11.0)	6.4 (10.8)	9.0 (5.0)
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	8	29	43	58

Information obtained from Sponsor table 443 in Clinical Study Report

7. Mean Glucose Change (in mg/dl) from 'Impaired Fasting Glucose' (100 -125 mg/dL) at Baseline by Time (in Weeks)

The mean change from impaired baseline (fasting glucose level of $\geq$125 mg/dl) to endpoints (in weeks) in quetiapine-treated subjects showed 0.4, -6, -6, and -11 mg/dl at 2, 4, 8, and 12 weeks respectively, compared to placebo-treated subjects 0.9 at 2 weeks, -4.5 at 4 weeks and -6.5 at 8 weeks.

Table 111: Mean glucose change from 'impaired' baseline (BL) to end of treatment, by week (naïve subjects, placebo-controlled trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**
Seroquel = N	5	205	133	1
Mean (SD) Glucose at BL	105.5 (4.7)	107.7 (6.6)	107.2 (6.4)	124.2
Mean (SD) Glucose at EOT	105.8 (10.5)	102.0 (16.6)	101.7 (16.5)	113.4
Mean (SD) Glucose Change	0.4 (8.9)	-5.7 (16.4)	-5.5 (15.8)	-10.8
p-value	-	0.540	0.401	-
Modal (SD) Dose (mg)	260.0 (305.0)	173.9 (104.9)	155.3 (82.6)	50
Median Exposure (days)	15	29	57	74
Placebo = N	2	111	80	0
Mean (SD) Glucose at BL	108.9 (11.5)	107.7 (6.6)	107.7 (6.4)	-
Mean (SD) Glucose at EOT	109.8 (7.6)	103.2 (14.4)	101.3 (13.4)	-
Mean (SD) Glucose Change	0.9 (3.8)	-4.5 (13.3)	-6.5 (13.4)	-
p-value	-	-	-	-

Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	15	29	57	-

Information obtained from Sponsor table 447 in Clinical Study Report

The mean change from any impaired baseline (fasting glucose level of 100 - 125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -10, -6, -1.6, and -6 mg/dl compared to -2,-5, -1 and 25 mg/dl in placebo-treated subjects at 2, 4, 8, and 12 weeks, respectively.

Table 112: Highest mean glucose change (in mg/dl) at 'impaired' baseline (BL), by week (naïve subjects, placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	27	209	198	5
Mean (SD) Glucose at BL	107.1 (5.9)	107.7 (6.6)	107.2 (6.3)	110.9 (8.6)
Mean (SD) Highest Glucose	96.9 (12.6)	101.9 (16.6)	105.6 (14.9)	105.1 (9.5)
Mean (SD) Highest Glucose Change	-10.3 (11.3)	-5.7 (16.3)	-1.6 (14.3)	-5.8 (9.4)
p-value	0.056	0.519	0.544	0.207
Modal (SD) Dose (mg)	170.4 (127.3)	173.2 (104.9)	167.7 (104.2)	90
Median Exposure (days)	8	29	43	64
Placebo = N	15	111	103	1
Mean (SD) Glucose at BL	106.4 (7.3)	107.7 (6.6)	107.6 (6.4)	108.0
Mean (SD) Highest Glucose	108.4 (20.1)	103.2 (14.4)	106.6 (14.6)	133.2
Mean (SD) Highest Glucose Change	2.0 (19.5)	-4.5 (13.3)	-1.0 (14.8)	25.2
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	9	29	41	58

Information obtained from Sponsor table 447 in Clinical Study Report

8. Mean Glucose Change (in mg/dl) from 'High Fasting Glucose' (≥126 mg/dL) at Baseline by Time (in Weeks)

The mean change from any high baseline (fasting glucose level of ≥125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -14 and -9 mg/dl compared to -30, and -7 mg/dl in placebo-treated subjects at 2, 4, 8, and 12 weeks, respectively.

Table 113: Mean glucose change from 'high' baseline (BL) to end of treatment, by week (naïve subjects, placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	0	17	11	0
Mean (SD) Glucose at BL	-	145.8 (24.4)	134.5 (9.1)	-
Mean (SD) Glucose at EOT	-	132.0 (33.3)	125.7 (36.0)	-
Mean (SD) Glucose Change	-	-13.8 (42.2)	-8.8 (40.9)	-
p-value	-	0.309	0.809	-
Modal (SD) Dose (mg)	-	150.0 (68.5)	150.0 (86.6)	-
Median Exposure (days)	-	29	11	-
Placebo = N	0	10	11	0
Mean (SD) Glucose at BL	-	152.8 (43.1)	152.2 (40.8)	-
Mean (SD) Glucose at EOT	-	123.1 (23.0)	145.6 (73.1)	-
Mean (SD) Glucose Change	-	-29.7 (49.3)	-6.5 (40.8)	-
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	-	29	11	-

Information obtained from Sponsor table 445 in Clinical Study Report

The mean change from any high baseline (fasting glucose level of ≥125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -19, -15 and -4 mg/dl compared to -13, -30 and -2 mg/dl in placebo-treated subjects at 2, 4, 8, and 12 weeks, respectively.

Table 114: Highest mean glucose change (in mg/dl) at 'high' baseline (BL), by week (naïve subjects, placebo-controlled trials)

	Week 2	Week 4	Week 8	Week 12
Seroquel = N	4	18	16	0
Mean (SD) Glucose at BL	148.1 (24.3)	145.0 (23.9)	139.6 (17.6)	-
Mean (SD) Highest Glucose	129.6 (37.4)	130.0 (33.4)	135.3 (36.9)	-
Mean (SD) Highest Glucose Change	-18.5 (60.6)	-15.0 (41.3)	-4.3 (41.8)	-
p-value	0.645	0.296	0.906	-
Modal (SD) Dose (mg)	225.0 (86.6)	144.4 (70.5)	143.8 (75.0)	-
Median Exposure (days)	8	29	44	-
Placebo = N	2	10	12	0
Mean (SD) Glucose at BL	130.5 (6.4)	152.8 (43.1)	150.3 (39.5)	-
Mean (SD) Highest Glucose	117.9 (42.0)	123.1 (23.0)	148.1 (69.2)	-
Mean (SD) Highest Glucose Change	-12.6 (35.6)	-29.7 (49.3)	-2.2 (38.9)	-
p-value	-	-	-	-
Modal (SD) Dose (mg)	-	-	-	-
Median Exposure (days)	5	29	47	-

Information obtained from Sponsor table 445 in Clinical Study Report

6.4.2 Categorical Analyses

1. Fasting Glucose Increase Outliers

Results showed that the 2.3% of quetiapine-treated subjects (modal daily dose of 180 mg, median exposure of 56 days) compared to 1.1% of placebo-treated subjects had a mean treatment emergent increase in fasting glucose from baseline values of glucose <100 mg/dL to >126 mg/dL.

Table 115: Proportion of Patients with treatment emergent fasting glucose change (mg/dL) (naïve subjects, placebo-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	≥300 N (%)	≥200 N (%)	≥140 N (%)	≥126 N (%)
<100 mg/dL	Quetiapine	1378	0	0	8 (0.6)	32 (2.3)
	Placebo	740	0	0	4 (0.5)	8 (1.1)
	p-value		-	-	1.000	0.046
≥100 mg/dL and <126 mg/dL	Quetiapine	252	0	0	8 (3.2)	22 (8.7)
	Placebo	137	0	0	5 (3.6)	14(10.2)
	p-value		-	1.000	0.776	0.715
<126 mg/dL	Quetiapine	1630	0 (0.0)	1 (0.1)	16 (1.0)	54(3.3)
	Placebo	877	0	0	9 (1.0)	22 (2.5)
	p-value		-	1.000	1.000	0.275
Modal (SD) Dose (mg)	179.7(119.2)					
Median Exposure(days)	56					

Information obtained from Sponsor table 450 in Clinical Study Report

2. Fasting Glucose Increase of more than ≥10 mg/dL Outliers

Similar percentages of patients with fasting glucose increase of more than 10 mg/dl were seen in both quetiapine and placebo treated patients.

Table 116: Proportion of Patients with treatment emergent increase in glucose (≥10 mg/dL) (naïve subjects, placebo-controlled trials)

Baseline	Treatment Arm	N =	≥10 mg/dL increase post-baseline n (%)
Any value	Quetiapine	1652	439 (26.6)
	Placebo	890	234 (26.3)
	p-value = 0.888		
<100 mg/dL	Quetiapine	1378	394 (28.6)
	Placebo	740	209 (28.2)
	p-value = 0.880		
≥100 mg/dL and <126 mg/dL	Quetiapine	252	39 (15.5)
	Placebo	137	20 (14.6)
	p-value = 0.883		
<126 mg/dL	Quetiapine	22	6 (27.3)
	Placebo	13	5 (38.5)
	p-value = 0.708		
Modal (SD) Dose (mg)	179.4 (118.8)		
Median Exposure(days)	56		

Information obtained from Sponsor table 451 in Clinical Study Report

3. Fasting HbA1c (%) Increase of more than ≥6.1 Outliers

Similar percentages of patients with fasting HbA1c increase of more than 6.1% were seen in both quetiapine and placebo treated patients.

Table 117: Proportion of Patients with treatment emergent fasting HbA1c (%) increase (naïve subjects, placebo-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	≥ 6.1 N (%)	≥8 N (%)	≥10 N (%)	≥12 N (%)
HbA1c(%) <6.1	Quetiapine	1523	46 (3.0)	0	0	0
	Placebo	820	21 (2.6)	0	0	0
	p-value = 0.604					
Modal (SD) Dose in mg	182.4 (124.0)					
Median Exposure(days)	56					

Information obtained from Sponsor table 452 in Clinical Study Report

4. Glycosuria

Similar percentages of patients with treatment emergent glycosuria were noted in both quetiapine and placebo treated patients.

Table 118: Proportion of Patients with treatment emergent glycosuria (naïve subjects, placebo-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	N (%)
Glycosuria	Quetiapine	126	1 (0.8)
	Placebo	81	1 (1.2)
Modal (SD) Dose (mg)	327.0 (248.2)		
Median Exposure(days)	8-14		

Information obtained from Sponsor table 453 in Clinical Study Report

6.5 Antipsychotic-Naïve Subjects in Comparator-Controlled Trials

6.5.1 Mean Change Analyses

1. Mean Glucose Change (in mg/dl) from All subjects at any baseline glucose level

The mean change from baseline (any glucose level) to endpoint and the highest mean change from baseline in olanzapine-treated subjects (N = 27, modal daily dose of 13 mg) were 6.3 mg/dL and 7.3 mg/dL compared to 3.7 mg/dL and 7.1 mg/dL in quetiapine-treated subjects (N = 24, modal daily dose of 565 mg) respectively, with a mean exposure of 198-347 days.

The mean change from baseline (any glucose level) to endpoint and the highest mean change from baseline in risperidone-treated subjects (N = 22, modal daily dose of 2.3 mg) were 1.7 mg/dL and 3.6 mg/dL compared to 3.0 mg/dL and 6.9 mg/dL in quetiapine-treated subjects (N = 24, modal daily dose of 565 mg) respectively, with a mean exposure of 252-347 days.

Table 119: Mean glucose change (in mg/dl) from baseline (BL) to end of treatment (EOT) (naïve subjects, comparator-controlled trials)

	QTP	OLZ	QTP	RIS
N	24	27	24	22
Mean (SD) Glucose at BL	86.9 (10.0)	84.6 (8.0)	86.9 (10.0)	88.7 (7.9)
Mean (SD) Glucose at EOT	90.6 (12.6)	90.9 (15.5)	90.6 (12.6)	90.4 (14.0)
Mean (SD) Glucose Change	3.7 (13.3)	6.3 (16.7)	3.7 (13.3)	1.7 (12.9)
p-value	0.553	-	0.603	-
Mean (SD) Highest Glucose	94.0 (11.0)	92.0 (15.4)	94.0 (11.0)	92.3 (16.1)
Mean (SD) Highest Glucose Change	7.1 (12.6)	7.3 (16.6)	7.1 (12.6)	3.6 (14.0)
Modal (SD) Dose (mg)	565.2 (177.4)	13.2 (4.0)	565.2 (177.4)	2.3 (0.9)
Median Exposure (days)	347.0	198.0	347.0	252.5

Information obtained from Sponsor table 460 and 478 in Clinical Study Report, OLZ-olanzapine, and RIS- risperidone

2. Mean Glucose Change (in mg/dl) from 'Normal Fasting Glucose' (<100 mg/dL) at Baseline

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoint and the highest mean change from baseline in olanzapine-treated subjects (N = 26, modal daily dose of 13 mg) were 7 mg/dL and 8 mg/dL compared to 6 mg/dL and 10 mg/dL in quetiapine-treated subjects (N = 21, modal daily dose of 590 mg) respectively, with a mean exposure of 198-357 days.

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoint and the highest mean change from baseline in risperidone-treated subjects (N = 20, modal daily dose of 2.3 mg) were 2.2 mg/dL and 3.2 mg/dL compared to 6.3 mg/dL and 10.2 mg/dL in quetiapine-treated subjects (N = 166, modal daily dose of 604 mg) respectively, with a mean exposure of 206-357 days.

Table 120: Mean glucose change from 'normal' baseline (BL) to end of treatment (EOT) (naïve subjects, comparator-controlled trials)

	QTP	OLZ	QTP	RIS
N	21	26	21	20
Mean (SD) Glucose at BL	84.1 (6.6)	83.9 (7.3)	84.1 (6.6)	86.9 (5.7)
Mean (SD) Glucose at EOT	90.4 (12.9)	91.0 (15.8)	90.4 (12.9)	89.1 (13.2)
Mean (SD) Glucose Change	6.3 (11.5)	7.0 (16.5)	6.3 (11.5)	2.2 (12.9)
p-value	0.860	-	0.285	-
Mean (SD) Highest Glucose	94.3 (11.0)	92.1 (15.7)	94.3 (11.0)	90.1 (12.4)
Mean (SD) Highest Glucose Change	10.2 (9.3)	8.2 (16.3)	10.2 (9.3)	3.2 (12.5)
Modal (SD) Dose (mg)	590.0 (165.1)	13.4 (4.0)	590	2.3
Median Exposure (days)	357.0	198.0	357	206

Information obtained from Sponsor table 462 and 482 in Clinical Study Report, OLZ-olanzapine, and RIS- risperidone

3. Mean Glucose Change (in mg/dl) from 'Impaired Fasting Glucose' (100-125 mg/dL) at Baseline

It should be noted that there was a very small number patients (N=<3 in each treatment group) of this category.

In this submission there are no data tables of fasting Mean Glucose Change for the following categories:

- 'High' Baseline
- 'High' Baseline to highest change
- 'High' Baseline by Time (in Weeks)

4. Mean Glucose Change (in mg/dl) by Time (in Weeks)

Although the sponsor provided some data tables for this analysis, the number of subjects are too small (<20) to interpret the results.

6.5.2 Categorical Analyses

1. Fasting Glucose Increase Outliers

Although the sponsor provided some data tables for this analysis, the number of subjects are too small to interpret the results.

2. Fasting Glucose Increase of more than >10 mg/dL Outliers

In this analysis, 38 % of Quetiapine-treated subjects (mean daily dose of 565 mg, median exposure of 347 days) showed treatment emergent increase in glucose (>10 mg/dL) compared to 26 % in olanzapine-treated subjects (modal daily dose of 13 mg, median exposure of 198 days) and 18 % in risperidone-treated subjects (modal daily dose of 2.3 mg, median exposure of 252 days) regardless of their baseline glucose level.

Table 121: Proportion of Patient with treatment emergent increase in fasting glucose >10 mg/dL (naïve subjects, comparator-controlled trials)

Baseline	Treatment Arm	N =	>10 mg/dL increase post-baseline n (%)
Any value	quetiapine	24	9 (37.5)
	olanzapine	27	7 (25.9)
	p-value	0.546	
	quetiapine	24	9 (37.5)
	risperidone	22	4 (18.2)
	p-value	0.197	
<100 mg/dL	quetiapine	21	9 (42.9)
	olanzapine	26	7 (26.9)
	p-value	0.355	
	quetiapine	21	9 (42.9)
	risperidone	20	3 (15.0)
	p-value	0.085	
≥100 mg/dL and <126 mg/dL	quetiapine	3	0

	olanzapine	1	0
	p-value	-	
	quetiapine	3	0
	risperidone	2	1 (50.0)
	p-value	0.400	
<126 mg/dL	quetiapine	0	0
	olanzapine	0	0
	p-value	-	
	quetiapine	0	0
	risperidone	0	0
	p-value	-	
Modal (SD) Dose (mg)	QTP – 565 mg vs. OLZ – 13 mg QTP - 562 mg vs. RISP – 2.3 mg		
Median Exposure(days)	QTP – 347 days vs. OLZ – 198 days QTP - 347 days vs. RISP – 252 days		

Information obtained from Sponsor table 469 and 487 in Clinical Study Report

3. Fasting HbA1c (%) Increase of more than ≥6.1 Outliers

Approximately 2% in quetiapine-treated subjects (N = 48) with a median exposure of 198-322 days had a treatment-emergent HbA1c increase >6.1%, compared to 6.4% of Olanzapine-treated subjects (N = 47, modal daily dose of 13 mg) and 5.4% of risperidone-treated subjects (N = 37, modal daily dose of 2.5 mg).

Table 122: Proportion of Patients with treatment emergent fasting HbA1c (%) increase (naïve subjects, comparator-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	≥ 6.1 N (%)	≥8 N (%)	≥10 N (%)	≥12 N (%)
HbA1c(%) <6.1	Quetiapine	48	1 (2.1)	0	0	0
	Olanzapine	47	3 (6.4)	0	0	0
	p-value = -		0.362	0.495	-	-
	Quetiapine	48	1 (2.1)	0	0	0
	risperidone	37	2 (5.4)	0	0	0
	p-value = -		0.577	-	-	-
Modal (SD) Dose	QTP – 563 mg vs. OLZ – 13 mg QTP - 564 mg vs. RISP – 2.5 mg					
Median Exposure(days)	QTP – 321 days vs. OLZ – 198 days QTP - 322 days vs. RISP – 198 days					

information obtained from Sponsor table 470 and 488 in Clinical Study Report

4. Glycosuria

In this small group of antipsychotic naïve subjects in comparator controlled trials, similar proportion of subjects experienced glycosuria among all treatment groups.

Table 123: Proportion of Patients with treatment emergent glycosuria (naïve subjects, comparator-controlled trials)

Baseline	Treatment Arm Post-baseline	N =	N (%)
Glycosuria	Quetiapine	49	1 (2.0)
	Olanzapine	41	2 (4.9)
	Quetiapine	49	1 (2.0)
	Risperidone	31	1 (3.2)
Mean Modal (SD) Dose (mg)	QTP – 564 mg vs. OLZ – 13 mg QTP - 564 mg vs. RISP – 2.4 mg		
Median Exposure(days)	QTP – 337 days vs. OLZ – 335 days QTP - 337 days vs. RISP – 294 days		

Information obtained from Sponsor table 471 and 489 in Clinical Study Report

6.6 Antipsychotic-Naïve Subjects in Controlled and Uncontrolled Trials

6.6.1 Mean Change Analyses

1. Mean Glucose Change (in mg/dl) from All subjects at any baseline glucose level

The mean change from baseline (any glucose level) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 3077, modal daily dose of 179 mg) was 2 mg/dL and 5 mg/dL with a mean exposure of 63 days.

Table 124: Mean glucose change (mg/dl) from baseline (BL) to end of treatment (EOT) (naïve subjects, all QTP trials)

	QTP
N	3077
Mean (SD) Glucose at BL	91.4 (12.7)
Mean (SD) Glucose at EOT	93.4 (16.2)
Mean (SD) Glucose Change	2.0 (14.9)
p-value	-
Mean (SD) Highest Glucose	96.5 (16.7)
Mean (SD) Highest Glucose Change	5.1 (15.3)
Modal (SD) Dose (mg)	179.4 (114.1)
Median Exposure (days)	63

Information obtained from Sponsor table 496 in Clinical Study Report

2. Mean Glucose Change (in mg/dl) from 'Normal Fasting Glucose' (<100 mg/dL) at Baseline

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 2531, modal daily dose of 181 mg) was 3 mg/dL and 6 mg/dL with a mean exposure of 63 days.

Table 125: Mean glucose change (mg/dl) from 'normal' baseline to end of treatment (naïve subjects, all QTP trials)

	QTP
N	2531
Mean (SD) Glucose at BL	87.3 (7.0)
Mean (SD) Glucose at EOT	90.6 (12.0)
Mean (SD) Glucose Change	3.3 (12.2)
p-value	-
Mean (SD) Highest Glucose	93.7 (12.7)
Mean (SD) Highest Glucose Change	6.4 (12.9)
Modal (SD) Dose (mg)	180.7 (116.6)
Median Exposure (days)	63

Information obtained from Sponsor table 498 in Clinical Study Report

3. Mean Glucose Change (in mg/dl) from 'Impaired Fasting Glucose' (100-125 mg/dL) at Baseline

The mean change from impaired baseline (fasting glucose level of 100-125 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 493, modal daily dose of 173 mg) was-3.6 mg/dL and -0.8 mg/dL with a mean exposure of 63 days.

Table 126: Mean glucose change from 'impaired' baseline (BL) to end of treatment (EOT) (naïve subjects, all QTP trials)

	QTP
N	493
Mean (SD) Glucose at BL	106.7 (6.0)
Mean (SD) Glucose at EOT	103.1 (18.9)
Mean (SD) Glucose Change	-3.6 (18.6)
p-value	-
Mean (SD) Highest Glucose	105.9 (18.7)
Mean (SD) Highest Glucose Change	-0.8 (18.4)
Modal (SD) Dose (mg)	172.9 (103.0)
Median Exposure (days)	63

Information obtained from Sponsor table 502 in Clinical Study Report

4. Mean Glucose Change (in mg/dl) from 'High Fasting Glucose' (≥126 mg/dL) at Baseline

The mean change from high baseline (fasting glucose level of ≥126 mg/dl) to endpoint and the highest mean change from baseline in quetiapine-treated subjects (N = 53, modal daily dose of 174 mg) were -9.7 mg/dL and -4.4 mg/dL with a mean exposure of 81 days.

Table 127: Mean glucose change (mg/dl) from 'high' baseline to end of treatment (naïve subjects, all QTP trials)

	QTP
N	53
Mean (SD) Glucose at BL	147.5 (23.7)
Mean (SD) Glucose at EOT	137.8 (42.5)
Mean (SD) Glucose Change	-9.7 (45.3)
p-value	-
Mean (SD) Highest Glucose	143.2 (42.9)
Mean (SD) Highest Glucose Change	-4.4 (45.1)
Modal (SD) Dose (mg)	174.5 (83.6)
Median Exposure (days)	81

Information obtained from Sponsor table 500 in Clinical Study Report

5. Mean Glucose Change (in mg/dl) from All subjects at any baseline glucose level by Time (in Weeks)

The mean change from baseline (any fasting glucose level) to endpoints (in weeks) in quetiapine-treated subjects showed 1.1, 2.2, 0.8, 2.3, 3.8 and 3.3 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 128:Mean glucose change (mg/dl) from baseline to end of treatment, by week (naïve subjects, all QTP trials)

	Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 48**
Seroquel = N	32	1411	958	719	112	46
Mean (SD) Glucose at BL	90.7 (8.8)	91.2 (12.3)	91.7 (11.9)	91.6 (13.1)	91.7 (14)	90.0 (1)
Mean (SD) Glucose at EOT	91.7 (12.0)	93.4 (14.7)	92.5 (14.3)	94.0 (15.0)	95.5 (26)	93.3 (12)
Mean (SD) Glucose Change	1.1 (11.7)	2.2 (14.1)	0.8 (13.0)	2.3 (14.3)	3.8 (24)	3.3 (17)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	162.5 (143)	181.1 (119)	167.6 (92)	176.0 (108)	233(167)	177.2 (103)
Median Exposure (days)	15	29	57	84	169	337

Information obtained from Sponsor table 497 in Clinical Study Report

The mean change from any baseline (any fasting glucose level) to the highest mean change in quetiapine-treated subjects showed -3.2, 2.2, 5.1, 2.3, 6.3 and 7.9 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 129: Highest mean glucose change (mg/dl) from baseline, by week (naïve subjects, all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	145	1433	1433	746	625	349
Mean (SD) Glucose at BL	95.7 (16.2)	91.3 (12.4)	91.2 (12.0)	91.7 (13.9)	92 (15)	91.4 (12
Mean (SD) Highest Glucose	92.5 (20.1)	93.5 (15.3)	96.2 (14.5)	94.1 (14.9)	98.2 (19)	99.3 (17
Mean (SD) Highest Glucose Change	-3.2 (16.7)	2.2 (14.2)	5.1 (13.4)	2.3 (14.7)	6.3 (17)	7.9 (16)
p-value	-	-	-	-	-	
Modal (SD) Dose (mg)	163.4 (93	180.7 (119)	182.7 (120)	175.4 (107)	178(114)	173(104)
Median Exposure (days)	8	29	46	85	113	232

Information obtained from Sponsor table 497 in Clinical Study Report

6. Mean Glucose Change (in mg/dl) from 'Normal Fasting Glucose' (<100 mg/dL) at Baseline by Time (in Weeks)

The mean change from normal baseline (fasting glucose level of <100 mg/dl) to endpoints (in weeks) in quetiapine-treated subjects showed 1.2, 3.9, 2.0, 4, 5.3 and 7 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 130: Mean glucose change from 'normal' baseline to end of treatment, by week (naïve subjects, all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	27	1181	792	580	91	37
Mean (SD) Glucose at BL	87.9 (6.2)	87.3 (6.9)	87.9 (6.8)	87 (7)	87(6.3)	85 (6.5)
Mean (SD) Glucose at EOT	89.1 (10.5)	91.2 (12.0)	89.9 (10.6)	91 (12.8)	92 (14.4)	92 (12)
Mean (SD) Glucose Change	1.2 (12.3)	3.9 (12.1)	2.0 (10.4)	4(13.4)	5.3 (14)	7 (12)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	144.4 (88)	183 (122)	169(93)	177 (109)	237 (176)	177 (105)
Median Exposure (days)	15	29	57	84	169	336

Information obtained from Sponsor table 499 in Clinical Study Report

The mean change from any normal baseline (fasting glucose level of < 100 mg/dl) to the highest mean change in quetiapine-treated subjects showed -1.0, 4, 6.5, 4, 7.5 and 10 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 131: Highest mean glucose change (mg/dl) from 'normal' baseline, by week (naïve subjects, all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	104	1197	1192	601	497	285
Mean (SD) Glucose at BL	89 (7)	87 (7)	87.3 (6.9)	87 (7.2)	86.8 (7)	87 (7)
Mean (SD) Highest Glucose	88 (12.3)	91 (12)	93.8 (11.5)	91 (12)	94.3 (13)	97 (13)
Mean (SD) Highest Glucose Change	-1.0 (14)	4 (12)	6.5 (11.5)	4 (13.2)	7.5 (13)	10(12)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	162 (82)	183(122)	185 (123)	177 (107)	178(118)	170 (106)
Median Exposure (days)	7	29	43	83	114	232

Information obtained from Sponsor table 499 in Clinical Study Report

7. Mean Glucose Change (in mg/dl) from Impaired Fasting Glucose' (100 -125 mg/dL) at Baseline by Time (in Weeks)

The mean change from impaired baseline (fasting glucose level of $\geq$125 mg/dl) to endpoints (in weeks) in quetiapine-treated subjects showed 0.4, -5.8, -5.1,-1.7, -0.9 and -6 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 132: Mean glucose change from 'impaired' baseline to end of treatment, by week (naïve subjects, all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	5	212	152	125	17	8
Mean (SD) Glucose at BL	105.5 (4.7)	107.8 (6.7)	107.0 (6.3)	106 (5.7)	105.5 (4)	105.5 (5)
Mean (SD) Glucose at EOT	105.8 (10)	102 (17)	101.9 (16)	105 (14)	105 (52)	99.7 (7)
Mean (SD) Glucose Change	0.4 (8.9)	-5.8 (16.4)	-5.1 (15.5)	-1.7 (12)	-0.9 (53)	-6 (9.8)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	260 (305)	173 (105)	160 (87.0)	172 (103)	224(131)	181 (107)
Median Exposure (days)	15	29	57	85	169	343

Information obtained from Sponsor table 503 in Clinical Study Report

The mean change from any impaired baseline (fasting glucose level of 100 - 125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -9.6, -5.8,-1.6, -1.6, 2 and -1 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 133: Highest mean glucose change (mg/dl) from 'impaired' baseline, by week (naïve subjects, all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	36	216	221	130	114	55
Mean (SD) Glucose at BL	107(6)	108 (6.7)	107.1 (6.2)	106 (5.7)	107 (6)	105 (4.5)
Mean (SD) Highest Glucose	97 (13)	102 (16)	105.5 (15)	105(13.7)	109 (25)	104 (13)
Mean (SD) Highest Glucose Change	-9.6 (11)	-5.8 (16)	-1.6 (14.2)	-1.6 (13)	2	-1 (14)
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	163(121)	172 (105)	171(104.4)	169 (103)	174(102)	177(92)
Median Exposure (days)	8	29	43	85	113	223

Information obtained from Sponsor table 503 in Clinical Study Report

8. Mean Glucose Change (in mg/dl) from High Fasting Glucose' (≥126 mg/dL) at Baseline by Time (in Weeks)

The mean change from any impaired baseline (fasting glucose level of 100 - 125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -14, -4, -2,-21, -24 and -11 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 134: Mean glucose change from 'high' baseline to end of treatment, by week (naïve subjects, all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	0	18	14	14	4	1
Mean (SD) Glucose at BL	-	148.5 (26)	143 (26)	148.(23)	147(12)	147.6
Mean (SD) Glucose at EOT	-	136.4 (37)	134 (43.6)	128 (23)	136(22)	73.8
Mean (SD) Glucose Change	-	-12 (41.6)	-8.5 (49.9)	-19 (33)	-11 (22)	-73.8
p-value	-	-	-	-	-	-
Modal (SD) Dose (mg)	-	150 (66)	171 (93.5)	150.(76)	188 (75)	150.0
Median Exposure (days)	-	29	57	86	169	349

Information obtained from Sponsor table 501 in Clinical Study Report

The mean change from any high baseline (fasting glucose level of ≥125 mg/dl) to the highest mean change in quetiapine-treated subjects showed -4, -8.5,-4.4, -25, -11 and -0.4 mg/dl at 2, 4, 8, 12, 24 and 48 weeks, respectively.

Table 135: Highest mean glucose change (mg/dl) from 'high' baseline, by week (naïve subjects, all QTP trials)

	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48
Seroquel = N	5	20	20	15	14	9
Mean (SD) Glucose at BL	157 (29)	149 (25)	144 (25)	153 (30)	155 (30)	135.2 (9)
Mean (SD) Highest Glucose	153(62)	140 (44)	140 (40.2)	128 (22)	144 (29)	135(61)
Mean (SD) Highest Glucose Change	-4.0 (62)	-8.5 (44)	-4.4 (47.0)	-25.(39)	-11 (36)	-0.4 (62)
p-value	-	-	-	-	-	-

Modal (SD) Dose (mg)	210 (82)	145 (67)	167 (87.8)	160 (83)	182(64)	206 (95)
Median Exposure (days)	8	29	50	81	108	238

Information obtained from Sponsor table 501 in Clinical Study Report

6.6.2 Categorical Analyses

1. Fasting Glucose Increase Outliers

Quetiapine-treated subjects (modal daily dose of 179 mg, median exposure of 63 days) showed treatment emergent increase in glucose of 3.7 % for glucose levels <126 mg/dl at baseline.

Table 136: Proportion of Patients with treatment emergent fasting glucose change (mg/dL) (naïve subjects, all QTP trials)

Baseline	Treatment Arm Post-baseline	N =	≥300 N (%)	≥200 N (%)	≥140 N (%)	≥126 N (%)
<100 mg/dL	Quetiapine	2531	0	1 (0)	20 (0.8)	64 (2.5)
≥100 mg/dL and <126 mg/dL	Quetiapine	493	1 (0.2)	2 (0.4)	19 (3.9)	47 (9.5)
<126 mg/dL	Quetiapine	3024	1 (0.0)	3 (0.1)	39 (1.3)	111 (3.7)
Modal (SD) Dose (mg)	179.4 (114.5)					
Median Exposure(days)	63					

Information obtained from Sponsor table 506 in Clinical Study Report

2. Fasting Glucose Increase of more than ≥10 mg/dL Outliers

Quetiapine-treated subjects (modal daily dose of 179 mg, median exposure of 63 days) showed treatment emergent increase in glucose (≥10 mg/dL) of 27 % for any glucose level at baseline.

Table 137: Proportion of Patients with treatment emergent increase in glucose (≥10 mg/dL) (naïve subjects, all QTP trials)

Baseline	Treatment Arm	N =	≥10 mg/dL increase post-baseline n (%)
Any value	Quetiapine	3077	829 (26.9)
<100 mg/dL	Quetiapine	2531	727 (28.7)
≥100 mg/dL and <126 mg/dL	Quetiapine	493	84 (17.0)
<126 mg/dL	Quetiapine	53	18 (34.0)
Modal (SD) Dose (mg)	179.4 (114.1)		
Median Exposure(days)	63		

Information obtained from Sponsor table 507 in Clinical Study Report

3. Fasting HbA1c (%) Increase of more than ≥6.1 Outliers

About 5 % of all quetiapine-treated subjects (N = 2982, modal daily dose of 181 mg) had a mean HbA1c increase (> 6.1) from baseline with a median exposure of 63 days.

Table 138: Proportion of Patients with treatment emergent fasting HbA1c (%) increase (naïve subjects, all QTP trials)

Baseline	Treatment Arm Post-baseline	N =	≥ 6.1 N (%)	≥8 N (%)	≥10 N (%)	≥12 N (%)
HbA1c(%) <6.1	Quetiapine	2982	149 (5.0)	0	1 (0.0)	0
Modal (SD) Dose (mg)	181.8 (121.9)					
Median Exposure(days)	63					

Information obtained from Sponsor table 508 in Clinical Study Report

4. Glycosuria Outliers

About 1.5 % of all quetiapine-treated subjects (N = 194, modal daily dose of 370 mg) had treatment emergent glycosuria (any amount of glucose seen in urine from baseline) with a median exposure of 45 days.

Table 139: Proportion of Patients with treatment emergent glycosuria (naïve subjects, all QTP trials)

Baseline	Treatment Arm Post-baseline	N =	N (%)
Glycosuria	Quetiapine	194	3 (1.5)
Modal (SD) Dose (mg)	370.5 (252.3)		
Median Exposure(days)	45		

Information obtained from Sponsor table 509 in Clinical Study Report

7 Lipids

7.1 Adult Subjects in Placebo-Controlled Trials

Mean changes in the following lipid parameters were performed: total cholesterol (combined fasting and non-fasting), HDL cholesterol (combined fasting and non-fasting), fasting LDL cholesterol, fasting triglycerides and non-fasting triglycerides. The mean baseline lipid value, post-treatment lipid value, and magnitude of change were reported. Because exposure time is essential to interpreting lipid results, each group analyses were conducted for all subjects, and subjects with at least 12 and 24 weeks of exposure. Median exposure at time of lipid measurement was also listed with each table related to lipids. Treatment effect assessment was based on an analysis of variance (ANOVA) model with terms for protocol and treatment. Comparisons between treatment groups were conducted and p-values were reported by the sponsor.

7.1.1 Mean Change Analyses

1. Mean lipid Change (in mg/dl) from baseline to endpoint

The quetiapine-treated subjects (N = 4675) with a modal daily dose of 349 mg, had a mean total cholesterol increase of 2.6 mg/dL compared to a decrease of 3.0 in placebo-treated subjects (N = 2128) with a median exposure of 52-55 days. The fasting triglyceride mean increase of 13 mg/dL was seen in the QTP treated group (modal daily dose of 346 mg) compared to a decrease of 5.4 in placebo treated subjects with a median exposure of 55-56 days. The fasting LDL mean change was -0.1 mg/dL in QTP treated subjects compared to -2.1 in placebo treated subjects. The fasting HDL mean change was -1.2 mg/dL in QTP treated subjects compared to -0.6 in placebo treated subjects.

Table 140: Lipids, change from baseline (BL) to end of treatment (EOT) (placebo-controlled trials)

	QTP	Placebo
N =	4675	2128
Mean (SD) Total cholesterol (mg/dL) at BL	195.1 (43.0)	194.0 (42.5)
Mean (SD) Total cholesterol (mg/dL) at EOT	197.7 (44.4)	191.0 (41.9)
Mean (SD) Total cholesterol (mg/dL) Change	2.6 (30.8)	-3.0 (28.2)
p-value	<0.001	-
Modal (SD) Dose (mg)	349.2 (218.6)	-
Median Exposure (days)	52	55

N =	2057	963
Mean (SD) LDL fasting (mg/dL) at BL	114.7 (37.1)	113.3 (35.5)
Mean (SD) LDL fasting (mg/dL) at EOT	114.6 (37.6)	111.3 (34.9)
Mean (SD) LDL fasting (mg/dL) Change	-0.1 (26.0)	-2.1 (24.4)
p-value	0.084	-
Modal (SD) Dose (mg)	345.9 (222.0)	-
Median Exposure (days)	55	56

N =	4497	2015
Mean (SD) HDL (mg/dL) at BL	52.8 (15.3)	52.4 (14.9)
Mean (SD) HDL (mg/dL) at EOT	51.6 (15.2)	51.8 (14.9)
Mean (SD) HDL (mg/dL) Change	-1.2 (9.7)	-0.6 (8.3)
p-value	0.011	-
Modal (SD) Dose (mg)	349.9 (219.8)	-
Median Exposure (days)	54	55

N =	2070	966
Mean (SD) Triglycerides, fasting (mg/dL) at BL	140.0 (97.7)	137.4 (92.9)
Mean (SD) Triglycerides, fasting (mg/dL)at EOT	153.0 (126.3)	132.0 (91.9)
Mean (SD) Triglycerides, fasting (mg/dL) Change	13.0 (95.0)	-5.4 (75.2)
p-value	<0.001	-
Modal (SD) Dose (mg)	346.4 (221.7)	-
Median Exposure (days)	55	56

Information obtained from Sponsor table 88 in Clinical Study Report

Dose-Related Analyses

Table 152 contains lipid changes from baseline to endpoint for all fixed-dose placebo-controlled trials while Tables 153-157 provide lipid changes from baseline to endpoint by indication. For the mean change in total cholesterol from baseline to endpoint, all doses of quetiapine were significantly different from placebo, however, only doses ≥ 300 were associated with increases in total cholesterol. The increase did not follow a linear trend, the greatest increases in total cholesterol were in the 400 and 800 mg/day groups.

For the mean change in fasting triglycerides from baseline to endpoint, all quetiapine doses were associated with significant increases except for the 50 mg/day dose. Again, no clear linear trend was seen, all other doses produced fairly similar increases in fasting triglycerides.

Dose-related analyses by indication were mostly consistent with the pooled fixed-dose trials. Interestingly, the quetiapine 50 mg/day group in MDD trials did increase fasting triglycerides (8.5 vs. -4.1 mg/dL); however, this was not statistically significant.

Table 141: Lipids, Change from Baseline to Endpoint, All Fixed-Dose Placebo-Controlled Trials

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**QTP** 400 mg	**QTP** 600 mg	**QTP** 800 mg	**Placebo**
Cholesterol							
n	452	902	1408	302	913	351	1821
Mean (SD) Change	**-1.0 (26.7)**	**-1.5 (26.7)**	**0.8 (30.6)**	**7.0 (31.4)**	**3.3 (33.8)**	**7.1 (32.4)**	**-3.6 (27.6)**
p-value (vs. placebo)	0.021	0.046	< 0.001	< 0.001	< 0.001	< 0.001	
Median Exposure (days)	56	56	56	42	55	42	56
LDL, fasting							
n	241	437	611	167	380	151	884
Mean (SD) Change	**1.5 (24.0)**	**-1.6 (24.4)**	**-0.8 (26.2)**	**4.2 (25.9)**	**-1.7 (28.1)**	**3.7 (28.3)**	**-2.5 (24.6)**
p-value (vs. placebo)	0.014	NS	NS (0.079)	NS (0.072)	NS	NS	
Median Exposure (days)	56	56	56	42	56	42	56

HDL							
n	452	902	1403	302	912	350	1820
Mean (SD) Change	**-1.3 (9.7)**	**-2.0 (9.4)**	**-1.2 (9.6)**	**-0.5 (9.6)**	**-1.0 (10.0)**	**-0.2 (9.7)**	**-0.6 (8.3)**
p-value (vs. placebo)	NS	0.005	NS (0.094)	NS	NS	NS	
Median Exposure (days)	56	56	56	42	55	42	56
Triglycerides, fasting							
n	241	437	616	169	386	151	887
Mean (SD) Change	**0.0 (58.5)**	**13.2 (105.8)**	**17.4 (106.4)**	**15.8 (80.8)**	**8.7 (84.4)**	**16.3 (103.5)**	**-5.0 (76.5)**
p-value (vs. placebo)	NS	0.003	< 0.001	0.004	0.005	0.003	
Median Exposure (days)	56	56	56	42	55	42	56
Triglycerides, nonfasting							
n	49	120	118	61	85	39	202
Mean (SD) Change	**-10.9 (53.8)**	**7.0 (66.8)**	**5.3 (84.9)**	**40.7 (79.9)**	**21.1 (97.3)**	**51.2 (109.3)**	**-1.8 (70.3)**
p-value (vs. placebo)	NS	NS	NS	< 0.001	0.039	< 0.001	
Median Exposure (days)	56	56	56	42	53	42	56

From Sponsor Table 172 in 2/18/09 submission

Table 142: Lipids, Change from Baseline to Endpoint, Fixed-Dose Placebo-Controlled "Schizophrenia" Trials

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**QTP** 400 mg	**QTP** 600 mg	**QTP** 800 mg	**Placebo**
Schizophrenia							
Cholesterol							
n	NA	NA	140	302	313	351	252
Mean (SD) Change	**NA**	**NA**	**11.6 (36.0)**	**7.0 (31.4)**	**8.7 (35.6)**	**7.1 (32.4)**	**-3.1 (32.0)**
p-value (vs. placebo)	NA	NA	NS	< 0.001	< 0.001	< 0.001	
Median Exposure (days)	NA	NA	36.5	42	42	42	42
LDL, fasting							
n	NA	NA	NA	167	100	151	111
Mean (SD) Change	**NA**	**NA**	**NA**	**4.2 (25.9)**	**0.7 (27.6)**	**3.7 (28.3)**	**-1.6 (26.5)**
p-value (vs. placebo)	NA	NA	NA	NS (0.089)	NS	NS	
Median Exposure (days)	NA	NA	NA	42	42	42	42
HDL							
n	NA	NA	139	302	313	350	252
Mean (SD) Change	**NA**	**NA**	0.4 (10.2)	-0.5 (9.6)	-0.9 (10.6)	-0.2 (9.7)	-0.6 (8.4)
p-value (vs. placebo)	NA	NA	NS	NS	NS	NS	NS
Median Exposure (days)	NA	NA	41	42	42	42	42
Triglycerides, fasting							
n	NA	NA	NA	169	100	151	111
Mean (SD) Change	**NA**	**NA**	**NA**	**15.8 (80.8)**	**7.4 (102.3)**	**16.3 (103.5)**	**-13.4 (83.7)**
p-value (vs. placebo)	NA	NA	NA	0.006	NS	0.012	
Median Exposure (days)	NA	NA	NA	42	42	42	42
Triglycerides, nonfasting							
n	NA	NA	NA	61	37	39	38
Mean (SD) Change	**NA**	**NA**	NA	**40.7 (79.9)**	**27.4 (68.6)**	**51.2 (109.3)**	**-12.7 (67.4)**
p-value (vs. placebo)	NA	NA	NA	< 0.001	0.012	0.002	
Median Exposure (days)	NA	NA	NA	42	42	42	42

From Sponsor Table 173 in 2/18/09 submission

Table 143: Lipids, Change from Baseline to Endpoint, Fixed-Dose Placebo-Controlled "Bipolar" Trials

	QTP 300 mg	**QTP** 600 mg	**Placebo**
Cholesterol			
n	703	600	542
Mean (SD) Change	**-0.9 (32.5)**	**0.5 (32.5)**	**-3.3 (29.2)**
p-value (vs. placebo)	NS	NS (0.085)	
Median Exposure (days)	56	56	56
LDL, fasting			

n	330	280	237
Mean (SD) Change	**-1.9 (27.2)**	**-2.5 (28.4)**	**-4.5 (25.2)**
p-value (vs. placebo)	NS	NS	
Median Exposure (days)	56	56	57
HDL			
n	699	599	541
Mean (SD) Change	-0.7 (9.6)	-1.0 (9.8)	-0.1 (8.7)
p-value (vs. placebo)	NS	NS	
Median Exposure (days)	56	56	56
Triglycerides, fasting			
n	335	286	238
Mean (SD) Change	**18.2 (127.7)**	**9.1 (77.3)**	**-4.0 (105.3)**
p-value (vs. placebo)	0.018	NS (0.064)	
Median Exposure (days)	56	56	57
Triglycerides, nonfasting			
n	51	48	39
Mean (SD) Change	**0.3 (102.3)**	**16.2 (115.1)**	**2.2 (75.9)**
p-value (vs. placebo)	NS	NS	
Median Exposure (days)	NA	42	42

From Sponsor Table 174 in 2/18/09 submission

Table 144: Lipids, Change from Baseline to Endpoint, Fixed-Dose Placebo-Controlled "GAD" Trials

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**Placebo**
Cholesterol				
n	320	475	296	516
Mean (SD) Change	**-1.3 (27.3)**	**-1.1 (27.3)**	**0.4 (24.3)**	**-2.3 (25.7)**
p-value (vs. placebo)	NS	NS	0.031	
Median Exposure (days)	59.5	56	57	57
LDL, fasting				
n	171	226	147	259
Mean (SD) Change	**1.2 (24.3)**	**-1.7 (24.6)**	**1.5 (24.6)**	**-2.3 (24.2)**
p-value (vs. placebo)	NS (0.059)	NS	NS (0.075)	
Median Exposure (days)	62	57	57	57
HDL				
n	320	475	296	516
Mean (SD) Change	-1.5 (9.6)	-2.1 (10.1)	-3.1 (8.6)	
p-value (vs. placebo)	NS (0.067)	0.002	0.001	
Median Exposure (days)	59.5	56	57	57
Triglycerides, fasting				
n	171	226	147	259
Mean (SD) Change	**-3.4 (60.9)**	**11.2 (70.5)**	**20.6 (69.2)**	**-3.2 (55.3)**
p-value (vs. placebo)	NS	0.013	0.001	
Median Exposure (days)	62	57	57	57
Triglycerides, nonfasting				
n	38	64	29	72
Mean (SD) Change	**-6.6 (46)**	**12.4 (74.9)**	**18.5 (57.3)**	**1.7 (64.4)**
p-value (vs. placebo)	NS	NS	NS	
Median Exposure (days)	57	56	56	57

From Sponsor Table 175 in 2/18/09 submission

Table 145: Lipids, Change from Baseline to Endpoint, Fixed-Dose Placebo-Controlled "MDD" Trials

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**Placebo**
Cholesterol				
n	132	427	269	511
Mean (SD) Change	**-0.1 (25.3)**	**-1.8 (25.7)**	**0.2 (27.7)**	**-5.7 (25.2)**
p-value (vs. placebo)	0.006	0.020	0.007	
Median Exposure (days)	42	49	48	50

LDL, fasting				
n	70	211	134	277
Mean (SD) Change	**2.2 (23.6)**	**-1.5 (24.2)**	**-0.8 (25.0)**	**-1.2 (23.6)**
p-value (vs. placebo)	NS (0.089)	NS	NS	
Median Exposure (days)	42	49	47	50
HDL				
n	132	427	269	511
Mean (SD) Change	-1.0 (9.9)	-1.9 (8.6)	-1.2 (10.0)	-1.5 (8.3)
p-value (vs. placebo)	NS	NS	NS	
Median Exposure (days)	42	49	48	50
Triglycerides, fasting				
n	70	211	134	279
Mean (SD) Change	**8.5 (51.6)**	**15.4 (133.8)**	**12.0 (78.0)**	**-4.1 (59.7)**
p-value (vs. placebo)	NS	0.033	NS	
Median Exposure (days)	42	49	47	50
Triglycerides, nonfasting				
n	11	56	38	53
Mean (SD) Change	**-25.7 (76.1)**	**0.9 (56.1)**	**2.0 (77.2)**	**-1.7 (76.5)**
p-value (vs. placebo)	NS	NS	NS	
Median Exposure (days)	41	50	49	56

From Sponsor Table 176 in 2/18/09 submission

Table 146: Lipids, Change from Baseline to Endpoint, Fixed-Dose Placebo-Controlled "GAD and MDD" Trials

	QTP 50 mg	**QTP** 150 mg	**QTP** 300 mg	**Placebo**
Cholesterol				
n	452	902	565	1027
Mean (SD) Change	**-1.0 (26.7)**	**-1.5 (26.5)**	**0.3 (25.9)**	**-4.0 (25.5)**
p-value (vs. placebo)	0.015	0.036	< 0.001	
Median Exposure (days)	56	56	53	56
LDL, fasting				
n	241	437	281	536
Mean (SD) Change	**1.5 (24.0)**	**-1.6 (24.4)**	**0.4 (24.8)**	**-1.7**
p-value (vs. placebo)	0.012	NS	NS	
Median Exposure (days)	56	56	55	56
HDL				
n	452	902	565	1027
Mean (SD) Change	-1.3 (9.7)	-2.0 (9.4)	-2.2 (9.4)	-0.9 (8.1)
p-value (vs. placebo)	NS	0.005	NS (0.072)	
Median Exposure (days)	56	56	53	56
Triglycerides, fasting				
n	241	437	281	538
Mean (SD) Change	**0.0 (58.5)**	**13.2 (105.8)**	**16.5 (73.5)**	**-3.7 (57.6)**
p-value (vs. placebo)	NS	0.002	< 0.001	
Median Exposure (days)	56	56	55	56
Triglycerides, nonfasting				
n	49	120	67	125
Mean (SD) Change	**-10.9 (53.8)**	**7.0 (66.8)**	**9.1 (69.3)**	**0.3 (69.5)**
p-value (vs. placebo)	NS	NS	NS	
Median Exposure (days)	56	56	50	56

From Sponsor Table 177 in 2/18/09 submission

7.1.2 Categorical Analyses

Analyses of treatment-emergent significant changes (fasting baseline and post-baseline lipid measurements) were performed according to the National Cholesterol Education Program (NCEP) classifications.

Table 147: Treatment-Emergent Significant Changes in Lipids

	Baseline	Post-baseline
Total Cholesterol (Fasting and Non-Fasting)*		
Normal to High	<200 mg/dL	≥240 mg/dL
Borderline to High	≥200 and <240 mg/dL	≥240 mg/dL
Normal/Borderline to High	<240 mg/dL	≥240 mg/dL
Normal to Borderline/High	<200 mg/dL	≥200 mg/dL
LDL Cholesterol (Fasting)		
Normal to High	<100 mg/dL	≥160 mg/dL
Borderline to High	≥100 and <160 mg/dL	≥160 mg/dL
Normal/Borderline to High	<160 mg/dL	≥160 mg/dL
Normal to Borderline/High	<100 mg/dL	≥100 mg/dL
HDL Cholesterol (Fasting and Non-fasting)*		
Normal to Low	≥40 mg/dL	<40 mg/dL
Triglycerides (Fasting)		
Normal to High	<150 mg/dL	≥200 mg/dL
Normal to Very High	<150 mg/dL	≥500 mg/dL
Borderline to High	≥150 and <200b mg/dL	≥200 mg/dL
Borderline to Very High	≥150 and <200 mg/dL	≥500 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Normal/Borderline to Very High	<200 mg/dL	≥500 mg/dL
Normal to Borderline/High/Very High	<150 mg/dL	≥150 mg/dL

* given that total cholesterol and HDL cholesterol measurements are not significantly changed by fasting status and that the majority of clinical trial lipid data is non-fasting, we elect to include fasting and nonfasting values for total cholesterol and HDL cholesterol in combined analyses.

Table 148: Treatment-Emergent Significant Changes in Lipids: Additional Analyses

	Baseline	Post-baseline
Treatment- emergent very high triglycerides (fasting)	Fasting triglycerides <500 mg/dL	Fasting triglycerides ≥500 mg/dL
Treatment-emergent very high triglycerides (nonfasting and random)	NF and random Trig <500 mg/dL	Non-fasting and random Triglycerides ≥500 mg/dL
Treatment-emergent triglycerides >1000 mg/dL (All cases fasting, non-fasting, and random)	Triglycerides <1000 mg/dL	Triglycerides ≥1000 mg/dL
Change in fasting or non-fasting total cholesterol ≥40 mg/dL at any time post-baseline [1]	Any value	Increased fasting or non-fasting total cholesterol ≥40 mg/dL
Change in fasting LDL cholesterol ≥ 30 mg/dL at anytime post-baseline [2]	Any value	Increased fasting LDL cholesterol ≥ 30 mg/dL
Change in fasting or non-fasting HDL cholesterol ≥20 mg/dL at any time post-baseline [3]	Any value	Decreased fasting or NF HDL cholesterol ≥ 20 mg/dL
Change in fasting triglycerides ≥50 mg/dL at any time post-baseline [4]	Any value	Increased fasting triglycerides ≥50 mg/dL

[1] subgroup analyses based on the following categories of baseline fasting or nonfasting total cholesterol for adults: Normal (<200 mg/dL), Borderline (≥200 and <240 mg/dL), and High (≥240 mg/dL).
[2] subgroup analyses based on the following categories of baseline fasting LDL cholesterol for adults: Normal (<100 mg/dL), Borderline (≥100 and <160 mg/dL), and High (≥160 mg/dL).
[3] subgroup analyses based on the following categories of baseline fasting or nonfasting HDL cholesterol: Normal (≥40 mg/dL) and Low (<40 mg/dL).
[4] subgroup analyses based on the following categories of baseline fasting triglycerides: Normal (<150 mg/dL), Borderline (≥150 and <200 mg/dL), High (≥200 and <500 mg/dL), and Very High (≥500 mg/dL).

1. Total Cholesterol outliers

A greater proportion of QTP treated patients who had total cholesterol from normal (<200), borderline (≥200 to <240), or normal/borderline (<240 mg/dL) at baseline was noted with treatment emergent shift to post-baseline (≥240 mg/dL) as compared to placebo treated group.

Table 149: Proportion of Patients with treatment emergent shifts of total cholesterol (placebo-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline			Placebo Post-baseline			p-value	
Baseline (BL)	n (%)	≥240	≥200	n (%)	≥240	≥200	≥240	≥200
Normal <200	2759	96 (3.5)	584(21)	1260	18 (1.4)	211(16)	<0.001	0.001
Borderline ≥200 to <240	1239	264 (21)	-	580	93 (16.0)	-	0.009	-
Normal/Borderline <240	3998	360 (9.0)	-	1840	111 (6.0)	-	<0.001	-
Mean (SD) BL value for Normal/Borderline	3998	183 (31)	-	1840	182 (31)	-	-	
Mean (SD) value at EOT for Normal/Borderline	3998	189 (37)	-	1840	183 (35)	-	-	
Mean (SD) change for Normal/Borderline	3998	6 (28)	-	1840	0.4 (25)	-	-	
Modal (SD) Dose (mg)	349.6 (219.4)			-				
Median Exposure (days)	51			55				

Information obtained from Sponsor table 89 in Clinical Study Report

2. Total Cholesterol ≥40 mg/dl outliers

A greater proportion of QTP treated patients who had changes in total cholesterol >40 mg/dL from normal, borderline or high baseline categories as compared to the placebo patients.

Table 150: Proportion of Patients with treatment emergent shifts of total cholesterol ≥ 40 mg/dl increase (placebo-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline		Placebo Post-baseline		p-value
Baseline (BL)	n (%)	≥40	n (%)	≥40	≥40
Any value	4675	493 (10.5)	2128	123 (5.8)	<0.001
Normal <200	2759	325 (11.8)	1260	80 (6.3)	<0.001
Borderline ≥200 to <240	1239	121 (9.8)	580	32 (5.5)	0.002
High ≥240	677	47 (6.9)	288	11 (3.8)	0.075
Mean (SD) BL value for Any value	4675	195.1 (43.0)	2128	194.0 (42.5)	-
Mean (SD) value at EOT for Any value	4675	197.9 (44.6)	2128	191.1 (42.0)	-
Mean (SD) change for Any value	4675	2.9 (31.0)	2128	-2.8 (28.4)	-
Modal (SD) Dose (mg)	349.2 (218.6)		-		
Median Exposure (days)	52		55		

Information obtained from Sponsor table 90 in Clinical Study Report

3. Total HDL outliers

There is a slight numerical increase in the proportion of patients who had treatment emergent shift in HDL from normal >40 mg/dL to low at post-baseline in the QTP treated patients as compared to the placebo-groups.

Table 151: Proportion of Patients with treatment emergent shifts of total HDL (placebo-controlled trials)

Total HDL (mg/dL) (fasting and non-fasting)	QTP Post-baseline		Placebo Post-baseline		p-value
Baseline (BL)	n (%)	<40	n (%)	<40	<40
Normal ≥ 40 mg/dL	3653	381 (10.4)	1639	145 (8.8)	0.082
Mean (SD) Normal at BL	3653	57.0 (13.7)	1639	56.5 (13.4)	-
Mean (SD) Normal at EOT	3653	55.0 (14.3)	1639	55.2 (14.1)	-
Mean (SD) change for Normal	3653	-2.0 (9.9)	1639	-1.2 (8.7)	-
Modal (SD) Dose (mg)	344.0 (220.1)		-		
Median Exposure (days)	54		55		

Information obtained from Sponsor table 91 in Clinical Study Report

4. Total HDL ≥ 20 mg/dl decrease outliers

Shift changes in total HDL≥20 mg/dL decrease were analyzed and showed that 3.7% of quetiapine-treated subjects who had normal baseline (>40 mg/dL) showed a significant shift post-baseline (decrease in total HDL≥20 mg/dL) compared to 2.1% in the placebo group. Shifts from low baseline to ≤ 40 mg/dL were not different between the treatment groups.

Table 152: Proportion of Patients with treatment emergent shifts of total HDL ≥ 20 mg/dL decrease (placebo-controlled trials)

Total HDL (mg/dL) ≥ 20 mg/dL decrease	QTP Post-baseline		Placebo Post-baseline		p-value
Baseline (BL)	n (%)	≥20 mg/dL decrease	n (%)	≥20 mg/dL decrease	≥20
Any value	4497	137 (3.0)	2015	35 (1.7)	0.002
Normal >40	3653	135 (3.7)	1639	35 (2.1)	0.002
Low ≤ 40	844	2 (0.2)	376	0	1.000
Mean (SD) BL value for Any value	4497	52.8 (15.3)	2015	52.4 (14.9)	-
Mean (SD) value at EOT for Any value	4497	51.6 (15.2)	2015	51.8 (14.9)	-
Mean (SD) change for Any value	4497	-1.2 (9.7)	2015	-0.6 (8.3)	-
Modal (SD) Dose (mg)	349.9 (219.8)		-		
Median Exposure (days)	54		55		

Information obtained from Sponsor table 92 in Clinical Study Report

5. Total fasting LDL Outliers

Shift changes in total LDL were analyzed and showed that 28% of quetiapine-treated subjects who had normal baseline (<100 mg/dL) showed a significant shift post-baseline (≥100 mg/dL) compared to 21% in the placebo group. No significant different between the treatment groups for shifts from baseline to ≥ 160 mg/dL regardless of baseline fasting LDL status.

Table 153: Proportion of Patients with treatment emergent shifts of fasting LDL (placebo-controlled trials)

Fasting LDL (mg/dL)	QTP Post-baseline			placebo Post-baseline			p-value	
Baseline (BL)	n (%)	≥160	≥100	n (%)	≥160	≥100	≥160	≥100
Normal <100	742	8 (1.1)	206(28)	383	1 (0.3)	82(21)	0.287	0.021
Borderline ≥100 to <160	1101	103 (9.4)	-	491	35 (7.1)	-	0.149	-
Normal/Borderline <160	1843	111 (6.0)	-	874	36 (4.1)	-	0.045	-
Mean (SD) BL value for Normal/Borderline	1843	106 (27)	-	874	106 (27)	-	-	
Mean (SD) value at EOT for Normal/Borderline	1843	109 (32)	-	874	106 (31)	-	-	
Mean (SD) change for Normal/Borderline	1843	2.2 (4)	-	874	0.5 (22)	-	-	

Modal (SD) Dose	344.3 (222.7)	-
Median Exposure (days)	55	55

Information obtained from Sponsor table 93 in Clinical Study Report

6. *Total fasting LDL ≥ 30 mg/dl outliers*

No significant different between the treatment groups for shifts from baseline to this outlier category regardless of baseline fasting LDL status.

Table 154: Proportion of Patients with treatment emergent shifts of fasting LDL ≥ 30 mg/dL increase (placebo-controlled trials)

fasting LDL ≥ 30 mg/dL increase	QTP Post-baseline		Placebo Post-baseline		p-value
Baseline (BL)	n (%)	≥30 mg/dL increase	n (%)	≥30 mg/dL increase	≥30
Any Value	2057	209 (10.2)	963	71 (7.4)	0.015
Normal <100	742	82 (11.1)	383	29 (7.6)	0.073
Borderline ≥100 to <160	1101	114 (10.4)	491	41 (8.4)	0.234
Normal/Borderline <160	214	13 (6.1)	89	1 (1.1)	0.073
Mean (SD) BL value for Any value	2057	114.7 (37.1)	963	113.3 (35.5)	-
Mean (SD) value at EOT for Any value	2057	114.7 (37.7)	963	111.3 (34.9)	-
Mean (SD) change for Any value	2057	-0.1 (26.2)	963	-2.1 (24.4)	-
Modal (SD) Dose (mg)	345.9 (222.0)		-		
Median Exposure (days)	55		56		

Information obtained from Sponsor table 94 in Clinical Study Report

7. Fasting Triglycerides outliers

Outlier analysis for shift changes in fasting triglyceride showed that a greater percentage of quetiapine-treated subjects in all baseline categories (normal <150 mg/dL, borderline >150-<200 or normal/borderline <200) showed a significant shift post-baseline to ≥200 mg/dL, compared to the placebo group.

Table 155: Proportion of Patients with treatment emergent shifts of fasting triglycerides (placebo-controlled trials)

Triglycerides, fasting mg/dL	QTP Post-baseline				placebo Post-baseline				p-value		
Baseline (BL)	n (%)	≥500	≥200	≥150	n (%)	≥500	≥200	≥150	≥500	≥200	≥150
Normal <150	1416	2(0.1)	109(8)	273(19)	667	0	26(4)	86(13)	1.000	<0.001	<0.001
Borderline ≥150 to <200	297	4 (1)	94(32)	-	138	0	26(19)	-	0.312	0.006	-
Normal/Borderline <200	1713	6(0.4)	203(12)	-	805	0	52 (7)	-	0.186	<0.001	-
Mean (SD) BL value for Normal/Borderline	1713	106.3 (40.7)	106.3 (40.7)	-	805	105.4 (41.3)	105.4 (41.3)	-	-		
Mean (SD) value at EOT for Normal/Borderline	1713	124.2 (71.5)	124.2 (71.3)	-	805	110.1 (55.9)	110.2 (56.0)	-	-		
Mean (SD) change for Normal/Borderline	1713	17.9 (60.8)	17.9 (60.6)	-	805	4.8 (46.4)	4.8 (46.5)	-	-		
Modal (SD) Dose	342(222)				-						
Median Exposure (days)	55				56						

Information obtained from Sponsor table 95 in Clinical Study Report

8. Fasting Triglycerides ≥ 50 mg/dL increase outliers (QTP vs. placebo)

The treatment emergent shift changes were analyzed for Fasting Triglycerides of ≥ 50 mg/dL and showed that a significant proportion (19-26%) of quetiapine-treated subjects who had normal

baseline (<150 mg/dL), borderline (≥150 to <200), or high (≥200 to < 500) showed this post-baseline shift compared to the placebo group (11-13%).

Table 156: Proportion of Patients with treatment emergent shifts of fasting triglycerides ≥ 50 mg/dL increase (placebo-controlled trials)

Fasting triglycerides ≥ 50 mg/dL increase	QTP Post-baseline		Placebo Post-baseline		p-value
Baseline (BL)	n (%)	≥50 mg/dL increase	n (%)	≥50 mg/dL increase	≥50
Any Value	2070	432 (20.9)	966	115 (11.9)	<0.001
Normal <150	1416	268 (18.9)	667	77 (11.5)	<0.001
Borderline ≥150 to <200	297	76 (25.6)	138	17 (12.3)	0.002
High ≥200 to < 500	334	82 (24.6)	153	20 (13.1)	0.004
Very High ≥ 500	23	6 (26.1)	8	1 (12.5)	0.642
Mean (SD) BL value for Any value	2070	140.0 (97.7)	966	137.4 (92.9)	-
Mean (SD) value at EOT for Any value	2070	153.1 (126.3)	966	132.7 (93.6)	-
Mean (SD) change for Any value	2070	13.1 (94.9)	966	-4.7 (75.3)	-
Modal (SD) Dose (mg)	346.4 (221.7)		-		
Median Exposure (days)	55		56		

Information obtained from Sponsor table 96 in Clinical Study Report

Dose-Related Analyses

There is a suggestion of a dose-related effect on total cholesterol when analyzed by categorical shift data. Approximately 4% of subjects receiving doses > 400 mg/day experienced a shift from normal to high compared to ~1-3% of subjects at lower doses. Across all dose groups, similar proportions of subjects experienced a shift from borderline to high – the 800 mg/day group had the highest proportion of subjects with this shift (36.8%).

Similar proportions of subjects in each dose group experienced a shift from normal to high fasting triglycerides (~7-8%) with the exception of the 50 mg/day group (3.5%) and the 300 mg/day group (21.6%). Similar proportions of subjects in each dose group experienced a shift from borderline to high (~30-38%) with the exception of the 50 mg/day group (19.4%).

Table 157: Shifts in Lipids, All Fixed-Dose Placebo-Controlled Trials

	QTP 50 mg N = 656			QTP 150 mg N = 1286			QTP 300 mg N = 1915			QTP 400 mg N = 340		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Cholesterol												
Increase by ≥ 40 mg/dL	452	21	4.6%	902	45	5%	1408	117	8.3%[a]	302	42	13.9%[a]
Normal to High (< 200 to ≥ 240)	259	3	1.2%	534	12	2.2%b	804	23	2.9%[a]	199	4	2%
Borderline to High (200 – 239 to ≥ 240 mg/dL)	126	20	15.9%	234	28	12%	402	86	21.4%[a]	70	14	20%
Normal/Borderline to High (< 240 to ≥ 240 mg/dL)	385	23	6%	768	40	5.2%	1206	109	9%[a]	269	18	6.7%
Normal to Borderline/High (< 200 to ≥ 200 mg/dL)	259	49	18.9%	534	90	16.9%	804	135	16.8%	199	40	20.1%
LDL, fasting												
Increase by ≥ 30 mg/dL	241	27	11.2%[b]	437	35	8.0%	611	49	8.0%	167	22	13.2%[a]
Normal to High (< 100 to ≥ 160 mg/dL)	88	0	0	156	3	1.9%	202	2	1%	71	2	2.8%
Borderline to High (100 – 159 to > 160 mg/dL)	129	13	10.1%	244	13	5.3%	342	34	9.9%	77	9	11.7%
Normal/Borderline to High (< 160 to ≥ 160 mg/dL)	217	13	6%	400	16	4%	544	36	6.6%[b]	148	11	7.4%

Normal to Borderline/High (< 100 to ≥ 100 mg/dL)	88	27	30.7%[a]	156	34	21.8%	202	60	29.7%[a]	71	30	42.3%[a]
HDL												
Decrease by ≥ 20 mg/dL	452	16	3.5%[a]	902	29	3.2%[a]	1403	37	2.6%	302	11	3.6%[a]
Normal to Low (≥ 40 to < 40 mg/dL)	389	36	9.3%	768	76	9.9%	1118	107	9.6%	237	31	13.1%[a]
Triglycerides, fasting												
Increase by ≥ 50 mg/dL	241	26	10.8%	437	94	21.5%[a]	616	129	20.9%[a]	169	41	24.3[a]
Normal to High (< 150 to ≥ 200 mg/dL)	173	6	3.5%	308	25	8.1%[a]	417	37	21.6%[a]	113	10	8.8%[b]
Normal to Very High (< 150 to ≥ 500 mg/dL)	173	0	0	308	0	0	417	0	0	113	1	0.9%
Borderline to High (150 – 199 to ≥ 200 mg/dL)	36	7	19.4%	62	20	32.3%[a]	84	30	35.7%[a]	32	11	34.4%[b]
Borderline to Very High (150 – 199 to ≥ 500 mg/dL)	36	0	0	62	0	0	84	1	1.2%	32	0	0
Normal/Borderline to High (< 200 to ≥ 200 mg/dL)	209	13	6.2%	370	45	12.2%[a]	501	67	13.4%[a]	145	21	14.5%[a]
Normal/Borderline to Very High (< 200 to ≥ 500 mg/dL)	209	0	0	370	0	0	501	1	0.2%	145	1	0.7%
Normal to Borderline/High/Very High (< 150 to ≥ 150 mg/dL)	173	16	9.2%	308	58	18.8%[a]	417	90	21.6%[a]	113	26	23%[a]

	QTP 600 mg N = 1182			**QTP 800 mg N = 451**			**Placebo N = 2319**		
	N	n	(%)	N	n	(%)	N	n	(%)
Cholesterol									
Increase by ≥ 40 mg/dL	913	109	11.9%[a]	351	55	15.7%[a]	1821	84	4.6%
Normal to High (< 200 to ≥ 240)	510	21	4.1%[a]	224	8	3.6%[a]	1079	11	1%
Borderline to High (200 – 239 to ≥ 240 mg/dL)	246	52	21.1%[a]	87	32	36.8%[a]	495	68	13.7%
Normal/Borderline to High (< 240 to ≥ 240 mg/dL)	756	73	9.7%[a]	311	40	12.9%[a]	1574	79	5%
Normal to Borderline/High (< 200 to ≥ 200 mg/dL)	510	132	25.9%[a]	224	56	25%[a]	1079	166	15.4%
LDL, fasting									
Increase by ≥ 30 mg/dL	380	42	11.1%[a]	151	26	17.2%[a]	884	65	7.4%
Normal to High (< 100 to ≥ 160 mg/dL)	138	1	0.7%	59	0	0	337	1	0.3%
Borderline to High (100 – 159 to > 160 mg/dL)	192	18	9.4%	77	14	18.2%[a]	463	33	7.1%
Normal/Borderline to High (< 160 to ≥ 160 mg/dL)	330	19	5.8%	136	14	10.3%[a]	800	34	4.3%
Normal to Borderline/High (< 100 to ≥ 100 mg/dL)	138	35	25.4%	59	12	20.3%	337	68	20.2%
HDL									
Decrease by ≥ 20 mg/dL	912	26	2.9%[b]	350	15	4.3%[a]	1820	31	1.7%
Normal to Low (≥ 40 to < 40 mg/dL)	725	87	12%[a]	276	22	8%	1484	131	8.8%
Triglycerides, fasting									
Increase by ≥ 50 mg/dL	386	88	22.8%[a]	151	39	25.8%[a]	887	106	12%
Normal to High (< 150 to ≥ 200 mg/dL)	259	20	7.7%[a]	96	7	7.3%	615	25	4.1%
Normal to Very High (< 150 to ≥ 500 mg/dL)	259	0	0	96	1	1%	615	0	0
Borderline to High (150 – 199 to ≥ 200 mg/dL)	52	16	30.8%	26	10	38.5%[a]	125	23	18.4%
Borderline to Very High (150 – 199 to ≥ 500 mg/dL)	52	1	1.9%	26	2	7.7%[a]	125	0	0
Normal/Borderline to High (< 200 to ≥ 200 mg/dL)	311	36	11.6%[a]	122	17	13.9%[a]	740	48	6.5%
Normal/Borderline to Very High (< 200 to ≥ 500 mg/dL)	311	1	0.3%	122	3	2.5%[a]	740	0	0

Normal to Borderline/High/Very High (< 150 to ≥ 150 mg/dL)	259	52	20.1%[a]	96	20	20.8%[b]	615	80	13%

[a] statistically significant versus placebo
[b] borderline statistically significant versus placebo ($p \leq 0.06$)
From Sponsor Tables 179, 185, 193, 199, 207, 213, 221, 227 in 2/18/09 submission

7.2 Adult Subjects in Comparator-Controlled Trials

7.2.1 Mean Change Analyses

1. Mean lipid change (in mg/dl) from baseline to endpoint

In comparison of mean lipid change of total cholesterol, fasting LDL, HDL, and fasting triglycerides from baseline to endpoint of quetiapine compared with olanzapine, risperidone, chlorpromazine and haloperidol, only difference noted was a greater mean increase in total cholesterol: 8.0 vs. 16 mg in QTP vs. olanzapine; 7 vs. 2 mg/dL in QTP vs. risperidone (~SD 40)

Table 158: Lipids, change from baseline (BL) to end of treatment (EOT) (comparator-controlled trials)

Measurements in mg/dl	QTP	OLZ	QTP	RIS	QTP	CHL	QTP	HAL
N =	234	245	435	450	68	76	94	89
Mean (SD) T-C at BL	187.3 (46.2)	185 (43)	191(46)	193(44	179(38	177(37	180.5 (34)	176 (33)
Mean (SD) T-C at EOT	195.4 (48.1)	201 (50)	198(46)	191(41	209(59	197(42	183 (38.0)	176 (33)
Mean (SD) T-C Change	**8.0 (38.0)**	**15.9 (41)**	**7 (38)**	**-2 (36)**	**29 (53)**	**20 (31)**	**2.4 (25.3)**	**-0.3 (27)**
p-value	0.029	-	<0.001	-	0.188	-	0.473	-
Modal (SD) Dose (mg)	592.7 (175)	14.5 (4.1)	595(193	5	588(71	584(58	256(153	8.0 (5)
Median Exp (days)	168	168	58	57	70	70	56	56
N =	22	31	22	23	-	-	-	-
Mean (SD) F-LDL at BL	109.2 (37.3)	108.9 (28)	109 (37)	108(31	-	-	-	-
Mean (SD) F-LDL at EOT	114.1 (41.0)	115 33)	114 (41)	109(41	-	-	-	-
Mean (SD) F-LDL Change	4.9 (36.3)	6.7 (29.8)	5 (36)	2 (28)	-	-	-	-
p-value	0.841	-	0.725	-	-	-	-	-
Modal (SD) Dose (mg)	627 (161)	13.1 (4.4)	627 (161)	3(1)	-	-	-	-
Median Exp (days)	325	253	352	364	-	-	-	-
N =	217	236	417	437	-	-	-	-
Mean (SD) HDL at BL	45.5 (13.3)	44.7 (11)	47 (14	47(14)	-	-	-	-
Mean (SD) HDL at EOT	44.5 (11.7)	42.5 (12)	47 (13)	47(13)	-	-	-	-
Mean (SD) HDL Change	-1.0 (10.1)	-2.1 (11)	-0.9	0	-	-	-	-
p-value	0.206	-	0.246		-	-	-	-
Modal (SD) Dose (mg)	591 (177)	591 (177)	595(195	5	-	-	-	-
Median Exp (days)	168	168	57	57	-	-	-	-
N =	23	32	23	23	-	-	-	-
Mean (SD) F-Trig at BL	122.4 (62.2)	96.5 (53)	122 (62)	110(73	-	-	-	-
Mean (SD) F-Trig at EOT	141.7 (82.0)	137.4 (90)	142(82)	111(66	-	-	-	-
Mean (SD) F-Trig Change	**19.3 (58.6)**	**40.9 (87)**	**19 (59)**	**0.8(59)**	-	-	-	-
p-value	0.304	-	0.293	-	-	-	-	-
Modal (SD) Dose (mg)	613.0 (171)	13.3 (4.5)	613	2.6	-	-	-	-
Median Exp (days)	350	348	350	364	-	-	-	-

Information obtained from Sponsor table 98, 100, 103 and 133 in Clinical Study Report, TC - Total cholesterol, BL – Baseline, EOT – End of treatment, Exp – Exposure, F-LDL – Fasting LDL, F-Trig – Fasting triglycerides, NF – Trig – Non fasting triglycerides, OLZ – olanzapine, RIS – risperidone, CHL – chlorpromazine, HAL - haloperidol, QTP - quetiapine

2. Mean lipid change (in mg/dl) from baseline to endpoint(≥12 weeks and ≥24 weeks exposure)

For comparison of mean lipid change of total cholesterol, fasting LDL, HDL, and fasting triglycerides from baseline to endpoint over time (≥12 weeks and ≥24 weeks exposure) of quetiapine compared with olanzapine and risperidone, no significant differences were noted.

Table 159: lipids, change from baseline (BL) to end of treatment (EOT), exposure at > 12 and ≥ 24 weeks (comparator-controlled trials)

	Exposure at > 12 weeks		Exposure at ≥ 24 weeks	
	QTP	OLZ	QTP	RIS
N =	201	236	138	165
Mean (SD) Total cholesterol (mg/dL) at BL	187.1(45.1)	184.8 (43.7)	190.6 (46)	184 (41)
Mean (SD) Total cholesterol (mg/dL) at EOT	196.7 (47)	201.3 (50.7)	199 (47.3)	199 (45)
Mean (SD) Total cholesterol (mg/dL) Change	9.7 (39.3)	16.5 (41.3)	8.4 (37.7)	15.7 (36)
p-value	0.086		0.095	
Modal (SD) Dose (mg)	607.0 (164)	14.5 (3.9)	600.7 (161)	14 (4.1)
Median Exposure (days)	169	169	175	172
N =	20	29	18	25
Mean (SD) LDL fasting (mg/dL) at BL	106.3 (37)	109.1 (28.4)	101(26.1)	105 (27)
Mean (SD) LDL fasting (mg/dL) at EOT	110.1 (39)	117.2 (33.7)	106 (38.7)	111 (30)
Mean (SD) LDL fasting (mg/dL) Change	3.9 (37.9)	8.1 (30.2)	4.9 (36.5)	6.4 (28)
p-value	0.664		0.886	
Modal (SD) Dose (mg)	635 (159.9)	13.3 (4.3)	622.2 (163)	12.8 (4)
Median Exposure (days)	359	346	363	360
N =	189	227	130	158
Mean (SD) HDL (mg/dL) at BL	44.9 (13.3)	44.6 (11.3)	45.8 (13.4)	45 (11)
Mean (SD) HDL (mg/dL) at EOT	44.3 (11.7)	42.5 (11.8)	44.6 (11.6)	42.8 (12)
Mean (SD) HDL (mg/dL) Change	0.6 (10.2)	-2.1 (10.8)	1.3 (10.0)	-1.9 (11)
p-value	0.140		0.534	
Modal (SD) Dose (mg)	604.3 (166)	14.5 (4.0)	596.1 (165)	14.1 (4)
Median Exposure (days)	169	169	176	173
N =	21	30	18	25
Mean (SD) Triglycerides, fasting (mg/dL) at BL	121.0 (65)	98.7 (53.6)	112.7 (52)	99.2 (56)
Mean (SD) Triglycerides, fasting (mg/dL)at EOT	135.3 (83)	137.4 (92.5)	125.8 (56)	126 (56)
Mean (SD) Triglycerides, fasting (mg/dL) Change	14.4 (58.7)	38.7 (87.4)	13.8 (56.3)	26.6 (56)
p-value	0.272		0.463	
Modal (SD) Dose (mg)	619 (172)	13.5 (4.4)	622.2 (163)	12.8 (4)
Median Exposure (days)	355	300	363	360

Information obtained from Sponsor table 104 and 105 in Clinical Study Report

7.2.2 Categorical Analyses

In analyses of treatment-emergent significant changes (fasting baseline and post-baseline lipid measurements) for active-comparator controlled trials with chlorpromazine, haloperidol, olanzapine or risperidone controlled trials, no significant differences were observed in most of these outlier categories between the active-comparator and QTP except that some trends of increase in outliers percentage were noted the QTP group in risperidone controlled trials for the following categories:

1. Total Cholesterol outliers

Table 160: Proportion of Patients with treatment emergent shifts in cholesterol (risperidone-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline			risperidone Post-baseline			p-value	
Baseline (BL)	n(%)	≥240	≥200	n(%)	≥240	≥200	≥240	≥200
Normal <200	270	22 (8.1)	86 (32)	266	10 (4)	65 (24)	0.044	0.068
Borderline ≥200 to <240	105	23 (22)	-	125	19 (15)	-	0.231	-
Normal/Borderline <240	375	45 (12)	-	391	29 (7)	-	0.037	-
Mean (SD) BL Nl	270	163 (23)	163 (23	266	165(24)	165 (24	-	
Mean (SD) BL Brd	105	217 (11)	-	125	216 (11	-	-	
Mean (SD) BL Nl/Brd	375	178 (32)	-	391	181 (31	-	-	
Mean (SD) EOT Nl	270	180 (38	181 (38	266	174 (35	176 (36	-	
Mean (SD) EOT Brd	105	217 (32)	-	125	207 (36	-	-	
Mean (SD) EOT Nl/Brd	375	191(40)	-	391	185(38)	-	-	
Mean (SD) change Nl	270	17 (33)	18(33)	266)	10 (29)	11 (29)	-	
Mean (SD) change Brd	105	0.3 (32)	-	125	8.1 (36	-	-	
Mean (SD) change Nl/Brd	375	12 (34)	-	391	4 (32)	-	-	

Modal (SD) Dose (mg)	597.3 (197.0)	5.0 (2.0)
Median Exposure (days)	57	57

Information obtained from Sponsor table 136 in Clinical Study Report

2. Total Cholesterol outliers Over Time of Exposure (≥12 and ≥24 weeks)

Table 161: Proportion of Patients with treatment emergent shifts of total cholesterol at ≥12 weeks (risperidone-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline			Risperidone Post-baseline			p-value	
Baseline (BL)	n(%)	≥240	≥200	n(%)	≥240	≥200	≥240	≥200
Normal <200	136	17 (12.5)	52 (38.2)	132	7 (5.3)	41 (31)	0.053	0.25
Borderline ≥200 to <240	37	8 (21.6)	-	55	12 (21.8)	-	-	-
Normal/Borderline <240	173	25 (14.5)	-	187	19 (10.2)	-	-	-

Modal (SD) Dose in mg	613.4 (164)	4.3 (1.7)
Median Exposure (days)	173	187

Information obtained from Sponsor table 137 in Clinical Study Report

Table 162: Proportion of Patients with treatment emergent shifts of total cholesterol at ≥24 weeks (risperidone-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline			Risperidone Post-baseline			p-value	
Baseline (BL)	n(%)	≥240	≥200	n(%)	≥240	≥200	≥240	≥200
Normal <200	88	13 (15)	38 (43)	111	7 (6.3)	47 (42)	0.045	0.13
Borderline ≥200 to <240	28	7 (25.0)	-	40	17 (42)	-	-	-
Normal/Borderline <240	116	20 (17)	-	151	24 (16)	-	-	-

Modal (SD) Dose (mg)	613.0 (158.1)	4.2 (1.8)
Median Exposure (days)	177	173

Information obtained from Sponsor table 138 in Clinical Study Report

3. Total Cholesterol ≥40 mg/dl outliers

Table 163: Proportion of Patients with treatment emergent shifts of total cholesterol ≥ 40 mg/dl increase (Risperidone-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	Post-baseline total cholesterol ≥ 40 mg/dl increase			
	QTP		risperidone	
Baseline (BL)	N	n (%)	N	n (%)
Any value	435	86 (19.8)	450	64 (14.2) p=0.031
Normal <200 mg/dL	270	70 (50.9)	266	48 (18) p=0.029

Borderline ≥200 to <240	105	11 (10.5)	125	13 (10.4)
High ≥240	60	5 (8.3)	59	3 (5.1)
Modal (SD) Dose in mg	595.1 (193.4)		5.0 (2.0)	
Median Exposure (days)	58		57	

Information obtained from Sponsor table 139 in Clinical Study Report

4. Total Cholesterol ≥40 mg/dl outliers over time (≥12 weeks of exposure)

Table 164: Proportion of Patients with treatment emergent shifts of total cholesterol ≥ 40 mg/dl increase (Risperidone-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	Post-baseline at ≥12 wks exposure			
	QTP		risperidone	
Baseline (BL)	n (%)	≥40	n (%)	≥40
Any value	201	55 (27)	236	78 (33)
Normal <200	136	48 (35)	160	62 (39) p=0.044
Borderline ≥200 to <240	37	4 (11)	54	11 (20)
High ≥240	28	3 (11)	22	5 (23)
Modal (SD) Dose in mg	607.0 (164.3)		4.3 (1.7)	
Median Exposure (days)	169		169	

Information obtained from Sponsor table 140 in Clinical Study Report

7.3 Adult Subjects in Long Term Controlled and Uncontrolled Clinical Trials

7.3.1 Mean Change Analyses

1. Mean lipid Change (in mg/dl) from baseline to endpoint

The quetiapine-treated subjects (N = 11103) with a mean modal daily dose of 389 mg, had a mean total cholesterol change of 2.7 with a median exposure of 65 days. The fasting triglyceride mean change was 13 in QTP treated (mean modal daily dose of 382 mg) with a median exposure of 74 days. The fasting LDL mean change was 0.4 in QTP treated subjects. The fasting HDL mean change was -1.5 in QTP treated subjects.

Table 165: Lipids, change from baseline (BL) to end of treatment (EOT) (All QTP trials)

	QTP
N =	11103
Mean (SD) Total cholesterol (mg/dL) at BL	194.4 (43.9)
Mean (SD) Total cholesterol (mg/dL) at EOT	197.0 (44.6)
Mean (SD) Total cholesterol (mg/dL) Change	2.7 (32.8)
p-value	-
Modal (SD) Dose (mg)	389.3 (244.3)
Median Exposure (days)	65
N =	5293
Mean (SD) LDL fasting (mg/dL) at BL	114.7 (37.4)
Mean (SD) LDL fasting (mg/dL) at EOT	115.1 (37.4)
Mean (SD) LDL fasting (mg/dL) Change	0.4 (27.4)
p-value	-
Modal (SD) Dose (mg)	382.4 (232.3)
Median Exposure (days)	74
N =	10250
Mean (SD) HDL (mg/dL) at BL	52.4 (15.2)
Mean (SD) HDL (mg/dL) at EOT	50.9 (15.1)
Mean (SD) HDL (mg/dL) Change	-1.5 (10.0)
p-value	-
Modal (SD) Dose (mg)	393.6 (246.8)
Median Exposure (days)	69

N =	5318
Mean (SD) Triglycerides, fasting (mg/dL) at BL	144.3 (102.9)
Mean (SD) Triglycerides, fasting (mg/dL)at EOT	157.2 (124.1)
Mean (SD) Triglycerides, fasting (mg/dL) Change	12.8 (98.2)
p-value	-
Modal (SD) Dose (mg)	382.4 (232.2)
Median Exposure (days)	74

Information obtained from Sponsor table 163 in Clinical Study Report

2. Mean lipid Change (in mg/dl) from baseline to endpoint (≥12 and ≥24 weeks)

The quetiapine-treated subjects (N = 4331) with a modal daily dose of 411 mg, had a mean total cholesterol change of 2.4 with a median exposure time of ≥12 weeks compared to quetiapine-treated subjects (N = 1893) with a modal daily dose of 398 mg, had a mean total cholesterol change of 2.5 with a exposure time of ≥24 weeks. Please see below table for mean changes related to fasting triglyceride, fasting LDL, fasting HDL at ≥12 and ≥ 24 weeks of exposure.

Table 166: Lipids, change from baseline (BL) to end of treatment (EOT), exposure ≥ 12 and ≥ 24 weeks (All QTP trials)

	QTP exposure ≥ 12 weeks	QTP exposure ≥ 24 weeks
N =	4331	1893
Mean (SD) Total cholesterol (mg/dL) at BL	193.1 (44.9)	193.5 (44.8)
Mean (SD) Total cholesterol (mg/dL) at EOT	195.5 (44.8)	196.0 (45.6)
Mean (SD) Total cholesterol (mg/dL) Change	2.4 (35.4)	2.5 (37.4)
p-value	-	-
Modal (SD) Dose (mg)	411.1 (264.0)	398.0 (228.5)
Median Exposure (days)	152	260
N =	2415	1090
Mean (SD) LDL fasting (mg/dL) at BL	113.2 (37.9)	113.5 (37.8)
Mean (SD) LDL fasting (mg/dL) at EOT	113.9 (37.1)	114.1 (38.0)
Mean (SD) LDL fasting (mg/dL) Change	0.7 (29.0)	0.6 (29.5)
p-value	-	-
Modal (SD) Dose (mg)	384.4 (236.7)	381.4 (224.7)
Median Exposure (days)	154	276
N =	4094	1712
Mean (SD) HDL (mg/dL) at BL	52.4 (15.2)	52.8 (15.1)
Mean (SD) HDL (mg/dL) at EOT	50.2 (15.1)	50.4 (15.4)
Mean (SD) HDL (mg/dL) Change	-2.1 (10.7)	-2.4 (11.2)
p-value	-	-
Modal (SD) Dose (mg)	411.0 (266.2)	399.3 (230.5)
Median Exposure (days)	147	257
N =	2424	1092
Mean (SD) Triglycerides, fasting (mg/dL) at BL	144.5 (103.6)	147.5 (106.0)
Mean (SD) Triglycerides, fasting (mg/dL)at EOT	157.7 (121.9)	155.0 (122.6)
Mean (SD) Triglycerides, fasting (mg/dL) Change	13.2 (99.7)	7.6 (103.5)
p-value	-	-
Modal (SD) Dose (mg)	384.2 (236.7)	381.6 (224.6)
Median Exposure (days)	154	275

Information obtained from Sponsor table 164 and 165 in Clinical Study Report

7.3.2 Categorical Analyses

1. Total Cholesterol outliers

Regardless of baseline total cholesterol value, the proportion of total cholesterol outliers increased in all QTP treated patients.

Table 167: Proportion of Patients with treatment emergent shifts of total cholesterol (All QTP trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline		
Baseline (BL)	n (%)	>240	≥200
Normal <200	6565	278 (4.2)	1591 (24.2)
Borderline ≥200 to <240	2944	674 (23)	-
Normal/Borderline <240	9509	952 (10)	-
Mean (SD) BL value for Normal	6565	166 (24)	165.9 (23.5)
Mean (SD) BL value for Borderline	2944	218 (11.0)	-
Mean (SD) BL value for Normal/Borderline	9509	181.8 (31)	-
Mean (SD) value at EOT for Normal	6565	176.2 (34)	176.7 (33.9)
Mean (SD) value at EOT for Borderline	2944	216.6 (32)	-
Mean (SD) value at EOT for Normal/Borderline	9509	188.7 (38)	-
Mean (SD) change for Normal	6565	10.3 (28.8)	10.8 (28.7)
Mean (SD) change for Borderline	2944	-0.8 (31.3)	-
Mean (SD) change for Normal/Borderline	9509	6.9 (30.0)	-
Modal (SD) Dose (mg)	389.8 (244.0)		
Median Exposure (days)	65		

Information obtained from Sponsor table 166 in Clinical Study Report

2. Total Cholesterol outliers over time

Regardless of baseline total cholesterol value, the proportion of total cholesterol outliers increased in the QTP treated patient s increases over time of exposure.

Table 168: Proportion of Patients with treatment emergent shifts of total cholesterol at ≥12 and ≥24 wks exposure (All QTP trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline exposure ≥12 wks			QTP Post-baseline exposure ≥24 wks		
Baseline (BL)	n (%)	>240	>200	n (%)	>240	>200
Normal <200	2601	150 (6)	723 (28)	1125	91(8)	361(32)
Borderline ≥200 to <240	1121	287 (26)	-	499	151(30)	-
Normal/Borderline <240	3722	437 (12)	-	1624	242(15)	-
Mean (SD) BL value for Normal	2601	165 (24)	165 (24)	1125	164(24)	164(24)
Mean (SD) BL value for Borderline	1121	218 (11)	-	499	218(11)	-
Mean (SD) BL value for Normal/Borderline	3722	181 (32)	-	1624	181(32)	-
Mean (SD) value at EOT for Normal	2601	176 (37)	178(37)	1125	178(39)	180(39)
Mean (SD) value at EOT for Borderline	1121	216 (33)	-	499	218(35)	-
Mean (SD) value at EOT for NL/Borderline	3722	188 (40)	-	1624	190(42)	-
Mean (SD) change for Normal	2601	12 (32)	13 (32)	1125	13 (35)	15(34)
Mean (SD) change for Borderline	1121	-1.5(32)	-	499	-0(34)	-
Mean (SD) change for Normal/Borderline	3722	7.8 (33)	-	1624	9 (35)	-
Modal (SD) Dose (mg)	413.1 (262.4)			399.0 (227.3)		
Median Exposure (days)	151			261		

Information obtained from Sponsor table 167 and 168 in Clinical Study Report,

3. Total Cholesterol ≥ 40 mg/dl increase outliers

Regardless of baseline total cholesterol value, the proportion of total cholesterol >40 mg increase in the QTP treated patient s increases over time of exposure as compared to the placebo group.

Table 169: Proportion of Patients with treatment emergent shifts of total cholesterol ≥ 40 mg/dl increase and by time (All QTP trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP - Post-baseline		QTP - Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	>40	n (%)	>40	n (%)	>40
Any value	11103	1380 (12)	4331	654 (15.1)	1893	364 (19.2)
Normal <200	6565	970 (14.8)	2601	484 (18.6)	1125	270 (24.0)
Borderline ≥200 to <240	2944	296 (10.1)	1121	119 (10.6)	499	67 (13.4)
High ≥240	1594	114 (7.2)	609	51 (8.4)	269	27 (10.0)
Mean (SD) BL value for Any value	11103	194.4 (44)	4331	193.1 (45)	1893	193 (45)
Mean (SD) BL value for Normal	6565	165.9 (23)	2601	164.5 (24)	1125	164.4 (24.0)
Mean (SD) BL value for Borderline	2944	217.5 (11)	1121	218.0 (11)	499	218.1 (11.0)
Mean (SD) BL value for High	1594	269.0 (32)	609	269.1 (34)	269	269.5 (33.0)
Mean (SD) value at EOT for Any value	11103	197.8 (45)	4331	196.9 (46)	1893	198.6 (46.8)
Mean (SD) value at EOT for Normal	6565	176.6 (34)	2601	177 (36)	1125	179.3 (38.2)
Mean (SD) value at EOT for Borderline	2944	216.2 (32)	1121	215.3 (33)	499	216.6 (36.2)
Mean (SD) value at EOT for High	1594	250.9 (46)	609	247.2 (47)	269	245.8 (50.0)
Mean (SD) change for Any value	11103	3.4 (33.5)	4331	3.8 (36.7)	1893	5.1 (39.2)
Mean (SD) change for Normal	6565	10.8 (29)	2601	12.7 (32.3)	1125	14.9 (34.8)
Mean (SD) change for Borderline	2944	-1.2 (32)	1121	-2.6 (32.6)	499	-1.5 (35.7)
Mean (SD) change for High	1594	-18.1 (42)	609	-22.0 (45)	269	-23.7 (45.8)
Modal (SD) Dose (mg)	389.3 (244.3)		411.1 (264.0)		398.0 (228.5)	
Median Exposure (days)	65		152		260	

Information obtained from Sponsor table 169, 170 and 171 in Clinical Study Report

4. Total HDL outliers

Table 170: Proportion of Patients with treatment emergent shifts of total HDL (All QTP trials)

Total HDL (mg/dL) (fasting and non-fasting)	QTP -Post-baseline		QTP- Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	<40	n (%)	<40	n (%)	<40
Normal ≥ 40	8311	1126 (14)	3325	608(18)	1412	302 (21.4)
Mean (SD) Normal at BL	8311	57 (13.6)	3325	57 (14)	1412	56.7 (13.6)
Mean (SD) Normal at EOT	8311	54 (14.5)	3325	53 (15)	1412	52.6 (15.0)
Mean (SD) change for Nl	8311	-2.6 (10)	3325	-4 (11)	1412	-4.1 (11.3)
Modal (SD) Dose (mg)	380.7 (243.5)		391.0 (259.0)		381.6 (225.4)	
Median Exposure (days)	69		147		259	

Information obtained from Sponsor table 173 and 174 in Clinical Study Report

5. Total HDL ≥ 20 mg/dL decrease outliers

Table 171: Proportion of Patients with treatment emergent shifts of total HDL ≥ 20 mg/dL decrease (All QTP trials)

Total HDL (mg/dL) ≥ 20 mg/dL decrease	QTP - Post-baseline		QTP - Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	≥20 mg/dL	n (%)	≥20 mg/dL	n (%)	≥20 mg/dL
Any value	10250	398 (3.9)	4094	233 (5.7)	1712	127 (7.4)
Normal >40	8311	394 (4.7)	3325	230 (6.9)	1412	124 (8.8)
Low ≤ 40	1939	4 (0.2)	769	3 (0.4)	300	3 (1.0)
Mean (SD) BL value for Any value	10250	52.4 (15.2)	4094	52.4 (15.2)	1712	52.8 (15.1)
Mean (SD) BL value for Normal value	8311	56.6 (13.6)	3325	56.6 (13.7)	1412	56.7 (13.6)
Mean (SD) BL value for Low value	1939	34.3 (4)	769	34.1 (4.2)	300	34.1 (4.0)
Mean (SD) value at EOT for Any value	10250	50.8 (15.1)	4094	50.0 (15.0)	1712	49.9 (15.2)
Mean (SD) value at EOT for Normal value	8311	54.1 (14.4)	3325	53.1 (14.3)	1412	52.7 (14.3)
Mean (SD) value at EOT for Low value	1939	36.6 (9)	769	36.5 (9.7)	300	36.6 (11.6)
Mean (SD) change for Any value	10250	-1.6 (10.2)	4094	-2.4 (11.1)	1712	-2.8 (11.8)
Mean (SD) change for Normal value	8311	-2.5 (10.3)	3325	-3.5 (11.1)	1412	-4.0 (11.6)
Mean (SD) change for Low value	1939	2.4 (8)	769	2.4 (9.6)	300	2.5 (11.6)
Modal (SD) Dose	393.6 (246.8)		411.0 (266.2)		399.3 (230.5)	
Median Exp (days)	69		147		257	

Information obtained from Sponsor table 175, 176 and 177 in Clinical Study Report

6. Total fasting LDL outliers

Table 172: Proportion of Patients with treatment emergent shifts of fasting LDL (All QTP trials)

Fasting LDL(mg/dL)	QTP -Post-baseline			QTP- Post-baseline at ≥12 wks exposure			QTP - Post-baseline at ≥24 wks exposure		
Baseline (BL)	n (%)	>160	>100	n (%)	>160	>100	n %)	>160	>100
Normal <100	1943	24 (1)	615(32)	951	16 (1.7)	337(35)	435	10 (2.3)	170(39)
Borderline ≥100 to<160	2802	285(10)	-	1228	145 (11)	-	544	76 (14)	-
Normal/Borderline<160	4745	309 (6)	-	2179	161 (7.4)	-	979	86 (8.8)	-
Mean (SD) BL value for Any value	1943	79 (16)	79 (16)	951	78.6 (16.3)	78.6 (16.3)	435	78.5 (16.6)	78.5 (16.6)
Mean (SD) BL value for Normal value	2802	125 (16)	-	1228	125.9 (16.6)	-	544	126.5 (16.3)	-
Mean (SD) BL value for Low value	4745	106 (28)	-	2179	105.2 (28.7)	-	979	105.2 (29.0)	-
Mean (SD) value at EOT for Any value	1943	88.3 (26.4)	88.9 (26.4)	951	89.2 (27.9)	90.3 (27.8)	435	89.0 (29.2)	90.9 (29.1)
Mean (SD) value at EOT for Normal value	2802	124.3 (28.0)	-	1228	124.9 (28.6)	-	544	126.1 (29.7)	-
Mean (SD) value at EOT for Low value	4745	109.6 (32.6)	-	2179	109.3 (33.4)	-	979	109.7 (34.8)	-
Mean (SD) change for Any value	1943	9.4 (23)	10.0 (23)	951	10.6 (24.9)	11.7 (24.6)	435	10.6 (25.7)	12.4 (25.3)
Mean (SD) change for Normal value	2802	-1.1 (26)	-	1228	-1.0 (26.8)	-	544	-0.4 (28.7)	-
Mean (SD) change for Low value	4745	3.2 (25)	-	2179	4.0 (26.6)	-	979	4.5 (27.9)	-

Modal (SD) Dose	382.7 (233.2)	388.4 (237.8)	387.6 (226.4)
Median Exp (days)	74	154	278

Information obtained from Sponsor table 178, 179 and 180 in Clinical Study Report

7. Total fasting LDL ≥ 30 mg/dl increase outliers

Table 173: Proportion of Patients with treatment emergent shifts of fasting LDL ≥ 30 mg/dL increase (All QTP trials)

fasting LDL ≥ 30 mg/dL increase	QTP -Post-baseline		QTP- Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	>30 mg/dL	n (%)	>30 mg/dL	n (%)	>30 mg/dL
Any Value	5293	687 (13.0)	2415	398 (16.5)	1090	214 (19)
Normal <100	1943	333 (17.1)	951	212 (22.3)	435	114 (26)
Borderline ≥100 to <160	2802	318 (11.3)	1228	167 (13.6)	544	90 (16.5)
Normal/Borderline <160	548	36 (6.6)	236	19 (8.1)	111	10 (9.0)
Mean (SD) BL value for Any value	5293	114.7 (37)	2415	113.2 (37.9)	1090	113.5 (37.8)
Mean (SD) BL value for Normal value	1943	78.9 (16)	951	78.6 (16.3)	435	78.5 (16.6)
Mean (SD) BL value for Borderline value	2802	125.4 (16.3)	1228	125.9 (16.6)	544	126.5 (16.3)
Mean (SD) BL value for NL/BL value	548	186.7 (30.8)	236	186.9 (33.4)	111	186.7 (25.9)
Mean (SD) value at EOT for Any value	5293	115.6 (37.6)	2415	115.1 (37.6)	1090	116.2 (38.7)
Mean (SD) value at EOT for Normal value	1943	88.9 (26.6)	951	90.3 (28.1)	435	91.1 (29.6)
Mean (SD) value at EOT for Borderline value	2802	124.3 (28.1)	1228	125.0 (28.7)	544	126.5 (29.8)
Mean (SD) value at EOT for NL/BL value	548	165.9 (41.3)	236	163.3 (40.8)	111	163.7 (41.3)
Mean (SD) change for Any value	5293	1.0 (27.9)	2415	1.9 (29.9)	1090	2.7 (30.9)
Mean (SD) change for Normal value	1943	10.0 (23.5)	951	11.8 (25.2)	435	12.7 (26.2)
Mean (SD) change for Borderline value	2802	-1.1 (25.7)	1228	-0.9 (27.1)	544	-0.1 (28.9)
Mean (SD) change for NL/BL value	548	-20.8 (37.2)	236	-23.6 (41.1)	111	-22.9 (38.9)
Modal (SD) Dose (mg)	382.4 (232.3)		384.4 (236.7)		381.4 (224.7)	
Median Exposure (days)	74		154		276	

Information obtained from Sponsor table 181, 182 and 183 in Clinical Study Report

8. Fasting Triglycerides outliers Over Time

Table 174: Proportion of Patients with treatment emergent shifts of fasting triglycerides (All QTP trials)

Triglycerides, Fasting (mg/dL)	QTP -Post-baseline				QTP- Post-baseline at ≥12 wks exposure				QTP - Post-baseline at ≥24 wks exposure			
Baseline (BL)	n (%)	≥500	≥200	≥150	n (%)	≥500	≥200	≥150	n (%)	≥500	≥200	≥150
Normal <150	3559	6 (0)	341 (10)	821 (23)	1629	3 (0.2)	184 (11.3)	423 (26)	720	1 (0.1)	89 (12.4)	199 (27.6)
Borderline ≥150 to <200	806	17 (2)	297 (37)	-	362	10 (2.8)	152 (42.0)	-	166	5 (3.0)	69 (41.6)	-
Normal/Borderline <200	4365	23 (0)	638 (15)	-	1991	13 (0.7)	336 (16.9)	-	886	6 (0.7)	158 (17.8)	-
Mean (SD) BL value for Normal	3559	93.8 (28.5)	93.8 (28.5)	93.8 (28)	1629	94.3 (27.7)	94.3 (27.7)	94 (27)	720	93.6 (27.9)	93.6 (27.9)	93.6 (27.9)
Mean (SD) BL value for Bl	806	173.0 (14.6)	173.0 (14.6)	-	362	172.8 (14.6)	172.8 (14.6)	-	166	172.3 (15.0)	172.3 (15.0)	-
Mean (SD) BL value for Nl/Bl	4365	108.4 (40.6)	108.4 (40.6)	-	1991	108.5 (39.8)	108.5 (39.8)	-	886	108.4 (40.2)	108.4 (40.2)	-

Mean (SD) value at EOT for Normal	3559	115.4 (63.0)	116.9 (65.6)	117.6 (65)	1629	117.5 (65.6)	120.8 (70.8)	122 (70)	720	116.1 (61.6)	121.7 (70.9)	124.1 (70.8)
Mean (SD) value at EOT for Bl	806	187.5 (97.1)	191.4 (97.0)	-	362	186.6 (99.8)	195.6 (100.1)	-	166	177.1 (97.7)	193.8 (101.8)	-
Mean (SD) value at EOT for Nl/Bl	4365	128.7 (75.9)	130.7 (78.0)	-	1991	130.1 (77.7)	134.4 (82.1)	-	886	127.5 (73.7)	135.2 (82.5)	-
Mean (SD) change for Nl	3559	21.7 (56.9)	23.2 (59.4)	23.9 (59)	1629	23.3 (60.1)	26.6 (65.0)	28 (64)	720	22.5 (56.0)	28.1 (64.8)	30.5 (64.4)
Mean (SD) change for Bl	806	14.5 (96.6)	18.4 (96.5)	-	362	13.8 (99.6)	22.8 (100.0)	-	166	4.8 (97.5)	21.5 (101.5)	-
Mean (SD) change for Nl/Bl	4365	20.3 (66.1)	22.3 (67.8)	-	1991	21.5 (69.1)	25.9 (72.6)	-	886	19.1 (66.1)	26.9 (73.1)	-
Modal (SD) Dose (mg)		378.2 (232.6)				381.0 (237.0)				377.3 (224.4)		
Median Exp (days)		74				153				272		

Information obtained from Sponsor table 184, 185 and 186 in Clinical Study Report

9. Fasting Triglycerides of ≥50 mg/dL increase outliers

Table 175: Proportion of Patients with treatment emergent shifts of fasting triglycerides ≥ 50 mg/dL increase (All QTP trials)

Fasting triglycerides ≥ 50 mg/dL increase	QTP -Post-baseline		QTP- Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	>50	n (%)	>50	n (%)	>50
Any Value	5318	1279 (24)	2424	665 (27)	1092	303 (27.7)
Normal <150	3559	818 (23)	1629	433 (26)	720	204 (28.3)
Borderline ≥150 to<200	806	215 (26)	362	108 (29)	166	46 (27.7)
High ≥200 to < 500	887	232 (26)	405	118 (29)	188	49 (26.1)
Very High ≥ 500	66	14 (21)	28	6 (21)	18	4 (22.2)
Mean (SD) BL value for Any value	5318	144.3 (103)	2424	144.5 (103)	1092	147.5 (106.0)
Mean (SD) BL value for Normal value	3559	93.8 (28)	1629	94.3 (27)	720	93.6 (27.9)
Mean (SD) BL value for Borderline value	806	173 (15)	362	172.8 (15)	166	172.3 (15.0)
Mean (SD) BL value for High value	887	279 (70)	405	281.7 (71)	188	282.5 (71.4)
Mean (SD) BL value for Very high value	66	696 (202)	28	714.2 (240)	18	662.2 (134.9)
Mean (SD) value at EOT for Any value	5318	159 (125)	2424	163.1 (124)	1092	164.5 (127.6)
Mean (SD) value at EOT for Normal value	3559	117 (65)	1629	122.1 (70)	720	123.8 (70.0)
Mean (SD) value at EOT for BL value	806	191 (98)	362	195.2 (102)	166	193.9 (105.4)
Mean (SD) value at EOT for high value	887	272 (151)	405	277.6 (160)	188	264.9 (168.2)
Mean (SD) value at EOT for Very high	66	526 (443)	28	471.1 (385)	18	475.0 (354.6)
Mean (SD) change for Any value	5318	15.4 (99)	2424	18.6 (100)	1092	17.1 (106.9)
Mean (SD) change for Normal value	3559	23.9 (59)	1629	27.9 (64)	720	30.2 (63.7)
Mean (SD) change for BL value	806	18.2 (97)	362	22.5 (101)	166	21.6 (105.0)
Mean (SD) change for High value	887	-7.5(137)	405	-4.0 (144)	188	-17.7 (155.3)
Mean (SD) change for Very high value	66	-170(427)	28	-243(347)	18	-187.2 (352)
Modal (SD) Dose	382.4 (232.2)		384.2 (236.7)		381.6 (224.6)	
Median Exp (days)	74		154		275	

Information obtained from Sponsor table 187, 188 and 189 in Clinical Study Report

10. Fasting Triglycerides of ≥50 mg/dL increase outliers Over Time

Table 176: Proportion of Patients with treatment emergent shifts of very high fasting triglycerides (All QTP trials)

Fasting triglycerides ≥ 500 Very High	QTP -Post-baseline		QTP- Post-baseline at ≥12 wks exposure		QTP - Post-baseline at >24 wks exposure	
Baseline (BL)	n (%)	> 500	n (%)	>500	n (%)	>500
Very High > 500	5252	92 (1.8)	2396	52 (2.2)	1074	22 (2.0)
Mean (SD) BL value for Very high value	5252	137.4 (79.6)	2396	137.8 (79.8)	1074	138.8 (81.3)
Mean (SD) value at EOT for Very high	5252	152.9 (107.7)	2396	154.8 (112.1)	1074	151.3 (110.8)
Mean (SD) change for Very high value	5252	15.5 (83.9)	2396	17.0 (88.5)	1074	12.4 (90.6)
Modal (SD) Dose	381.8 (231.9)		383.7 (236.2)		380.1 (223.5)	
Median Exp (days)	74		154		276	

Information obtained from Sponsor table 190, 191 and 192 in Clinical Study Report

7.4 Antipsychotic-Naïve Subjects in Placebo-Controlled Trials

7.4.1 Mean Change Analyses

1. Mean lipid Change (in mg/dl) from baseline to endpoint

The quetiapine-treated subjects (N = 1784) with a mean modal daily dose of 180 mg, had a mean total cholesterol change of 0.3 compared to -3.2 in placebo-treated subjects (N = 963) with a median exposure of 56 days. The fasting triglyceride mean change was 11 in QTP treated (modal daily dose of 183 mg) compared to -2.6 in placebo treated subjects with a median exposure of 56 days. The fasting LDL mean change was -0.1 in QTP treated subjects compared to -2.1 in placebo treated subjects. The fasting HDL mean change was -1.8 in QTP treated subjects compared to -0.9 in placebo treated subjects.

Table 177: Lipids, change from baseline (BL) to end of treatment (EOT) (naïve subjects, placebo-controlled trials)

	QTP	Placebo
N =	1784	963
Mean (SD) Total cholesterol (mg/dL) at BL	192.7 (41.5)	192.4 (40.1)
Mean (SD) Total cholesterol (mg/dL) at EOT	193.0 (42.4)	189.3 (40.0)
Mean (SD) Total cholesterol (mg/dL) Change	0.3 (26.2)	-3.2 (25.5)
p-value	<0.001	-
Modal (SD) Dose (mg)	180.4 (118.1)	0
Median Exposure (days)	56	56
N =	878	476
Mean (SD) LDL fasting (mg/dL) at BL	112.6 (34.6)	112.4 (34.0)
Mean (SD) LDL fasting (mg/dL) at EOT	112.5 (35.4)	110.3 (33.3)
Mean (SD) LDL fasting (mg/dL) Change	-0.1 (23.7)	-2.1 (23.2)
p-value	0.119	-
Modal (SD) Dose (mg)	182.9 (123.8)	0
Median Exposure (days)	56	56
N =	1784	963
Mean (SD) HDL (mg/dL) at BL	54.7 (15.7)	53.6 (14.3)
Mean (SD) HDL (mg/dL) at EOT	52.8 (15.9)	52.7 (14.8)
Mean (SD) HDL (mg/dL) Change	-1.8 (9.3)	-0.9 (8.2)
p-value	0.018	-
Modal (SD) Dose (mg)	180.4 (118.1)	0

Median Exposure (days)	56	56

N =	878	478
Mean (SD) Triglycerides, fasting (mg/dL) at BL	132.3 (92.9)	125.7 (75.9)
Mean (SD) Triglycerides, fasting (mg/dL)at EOT	143.1 (121.3)	123.0 (74.9)
Mean (SD) Triglycerides, fasting (mg/dL) Change	10.8 (86.8)	-2.6 (56.2)
p-value	0.004	-
Modal (SD) Dose (mg)	182.9 (123.8)	0
Median Exposure (days)	56	56

N =	197	104
Mean (SD) Triglycerides non-fasting (mg/dL) at BL	130.8 (86.8)	126.9 (70.7)
Mean (SD) Triglycerides non-fasting (mg/dL) at EOT	134.5 (86.4)	128.1 (79.6)
Mean (SD) Triglycerides non-fasting (mg/dL) Change	3.7 (64.4)	1.3 (61.0)
p-value	0.688	-
Modal (SD) Dose (mg)	169.3 (91.0)	0
Median Exposure (days)	56	57

Information obtained from Sponsor table 225 in Clinical Study Report

7.4.2 Categorical Analyses

*1. Total Cholesterol outli*ers

The treatment emergent shifts

Table 178: Proportion of Patients with treatment emergent shifts of total cholesterol (naïve subjects, placebo-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline			Placebo Post-baseline			p-value	
Baseline (BL)	n (%)	≥240	≤200	n (%)	≥240	≤200	≥240	≤200
Normal <200	1042	23 (2.2)	172(17)	568	8 (1.4)	93 (16)	0.343	1.000
Borderline ≥200 to <240	460	71 (15.4)	-	258	31 (12.0)	-	0.222	-
Normal/Borderline <240	1502	94 (6.3)	-	826	39 (4.7)	-	0.136	-
Mean (SD) BL value for Normal	1079	166.6 (23.3)	166.6 (23.3)	581	167.1 (22.3)	167.1 (22.3)	-	
Mean (SD) BL value for Borderline	470	216.2 (11.8)	-	265	215.9 (12.2)	-	-	
Mean (SD) BL value for Normal/Borderline	1502	182.6 (30.3)	-	826	183.0 (29.9)	-	-	
Mean (SD) value at EOT for Normal	1079	172.0 (30.3)	172.0 (30.4)	581	169.4 (29.6)	169.4 (29.6)	-	
Mean (SD) value at EOT for Borderline	470	211.4 (28.3)	-	265	209.2 (27.3)	-	-	
Mean (SD) value at EOT for Normal/Borderline	1502	184.8 (34.6)	-	826	182.7 (34.2)	-	-	
Mean (SD) change for Normal	1079	5.4 (22.9)	5.4 (22.9)	581	2.3 (20.7)	2.3 (20.7)	-	
Mean (SD) change for Borderline	470	-4.7 (26.5)	-	265	-6.7 (25.8)	-	-	
Mean (SD) change for Normal/Borderline	1502	2.2 (24.5)	-	826	-0.3 (22.9)	-	-	
Modal (SD) Dose (mg)	182.6 (120.8)			-				
Median Exposure (days)	56			56				

Information obtained from Sponsor table 226 in Clinical Study Report

2. *Total Cholesterol outliers*

Table 179: Proportion of Patients with treatment emergent shifts of total cholesterol (naïve subjects, placebo-controlled trials)

Total cholesterol (mg/dL) (fasting and non-fasting) ≥ 40 mg/dl increase	QTP - Post-baseline		Placebo -Post-baseline		p-value
Baseline (BL)	n (%)	>40	n (%)	>40	>40
Any value	1734	99 (5.7)	942	41 (4.4)	0.146
Normal <200	1042	68 (6.5)	568	27 (4.8)	0.184
Borderline ≥200 to <240	460	19 (4.1)	258	12 (4.7)	0.849
High ≥240	232	12 (5.2)	116	2 (1.7)	0.154
Mean (SD) BL value for Any value	1784	192.7 (41.5)	963	192.4 (40.1)	-
Mean (SD) BL value for Normal	1079	166.6 (23.3)	581	167.1 (22.3)	-
Mean (SD) BL value for Borderline	470	216.2 (11.8)	265	215.9 (12.2)	-
Mean (SD) BL value for High	232	265.9 (27.8)	116	265.3 (27.8)	-
Mean (SD) value at EOT for Any value	1784	193.0 (42.4)	963	189.4 (40.1)	-
Mean (SD) value at EOT for Normal	1079	172.0 (30.3)	581	169.4 (29.6)	-
Mean (SD) value at EOT for Borderline	470	211.3 (28.2)	265	209.2 (27.3)	-
Mean (SD) value at EOT for High	232	253.0 (40.1)	116	244.5 (36.4)	-
Mean (SD) change for Any value	1784	0.3 (26.2)	963	-3.0 (25.7)	-
Mean (SD) change for Normal	1079	5.4 (22.9)	581	2.3 (20.7)	-
Mean (SD) change for Borderline	470	-4.9 (26.6)	265	-6.7 (25.8)	-
Mean (SD) change for High	232	-12.8 (32.7)	116	-20.7 (36.3)	-
Modal (SD) Dose (mg)	180.4 (118.1)		-		
Median Exposure (days)	56		56		

Information obtained from Sponsor table 227 in Clinical Study Report

3. *Total HDL outliers*

Table 180: Proportion of Patients with treatment emergent shifts of total HDL (naïve subjects, placebo-controlled trials)

Total HDL (mg/dL) (fasting and non-fasting)	QTP - Post-baseline		Placebo - Post-baseline		p-value
Baseline (BL)	n (%)	<40	n (%)	<40	<40
Normal ≥ 40	1519	158 (10.4)	810	66 (8.1)	0.089
Mean (SD) BL value for Normal	1519	58.2 (14.3)	810	57.1 (12.7)	-
Mean (SD) EOT value for Normal	1519	55.8 (15.1)	810	55.8 (13.9)	-
Mean (SD) Change value for Normal	1519	-2.4 (9.6)	810	-1.3 (8.6)	-
Modal (SD) Dose (mg)	179.1 (117.5)		-		
Median Exposure (days)	56		56		

Information obtained from Sponsor table 228 in Clinical Study Report

4. *Total HDL ≥ 20 mg/dl decrease outliers*

Table 181:Proportion of Patients with treatment emergent shifts of total HDL ≥ 20 mg/dL decrease (naïve subjects, placebo-controlled trials)

Total HDL (mg/dL)≥ 20 mg/dL decrease	QTP - Post-baseline		Placebo - Post-baseline		p-value
Baseline (BL)	n (%)	>20 mg/dL	n (%)	>20 mg/dL	>20
Any value	1784	51 (2.9)	963	17 (1.8)	0.094
Normal >40	1519	50 (3.3)	810	17 (2.1)	0.118
Low ≤ 40	265	1 (0.4)	153	0	1.000
Mean (SD) BL value for Any	1784	54.7 (15.7)	963	53.6 (14.3)	-
Mean (SD) BL value for Normal	1519	58.2 (14.3)	810	57.1 (12.7)	-
Mean (SD) BL value for low	265	34.7 (3.7)	153	34.9 (3.7)	-
Mean (SD) value at EOT for Any	1784	53 (15.9)	963	52.7 (14.8)	
Mean (SD) value at EOT for Normal	1519	55.8 (15.1)	810	55.8 (13.9)	-

Mean (SD) value at EOT for Low	265	36 (7.6)	153	36.2 (5.5)	-
Mean (SD) change for Any	1784	-1.8(9.3)	963	-0.9 (8.2)	-
Mean (SD) change for Normal	1519	-2.4(9.6)	810	-1.3 (8.6)	-
Mean (SD) change for Low	265	1.2 (7.0)	153	1.3 (4.7)	-

Modal (SD) Dose (mg)	180.4 (118.1)	-
Median Exposure (days)	56	56

Information obtained from Sponsor table 229 in Clinical Study Report

5. Total fasting LDL outliers

Table 182: Proportion of Patients with treatment emergent shifts of fasting LDL (naïve subjects, placebo-controlled trials)

Fasting LDL(mg/dL)	QTP - Post-baseline			Placebo - Post-baseline			p-value	
Baseline (BL)	n(%)	>160/>130	>100/<130	n(%)	>160/>130	>100/<130	>160/>130	>100/<130
Normal <100	310	4 (1.3)	80 (26)	178	0	37 (21)	0.302	0.227
Borderline ≥100 to <160	469	29 (6.2)	-	248	13 (5.2)	-	0.739	-
Normal/Borderline <160	779	33 (4.2)	-	426	13 (3.1)	-	0.348	-
Mean (SD) BL for Normal	334	79.8 (15.2)	79.8 (15.2)	188	81.4 (13.9)	81.4 (13.9)	-	
Mean (SD) BL for Borderline	473	125.1 (16.2)	-	250	124.5 (15.4)	-	-	
Mean (SD) BL Normal/Borderline	779	107.2 (27.1)	-	426	106.7 (25.8)	-	-	
Mean (SD) at EOT - Normal	334	87.0 (26.1)	87.0 (26.1)	188	84.5 (20.7)	84.5 (20.7)	-	
Mean (SD) at EOT - Borderline	473	122.2 (24.5)	-	250	122.1 (24.4)	-	-	
Mean (SD) at EOT N/Borderline	779	108.4 (30.5)	-	426	106.8 (29.2)	-	-	
Mean (SD) change for Normal	334	7.2 (22.4)	7.2 (22.4)	188	3.1 (15.9)	3.1 (15.9)	-	
Mean (SD) change for Borderline	473	-2.9 (21.8)	-	250	-2.4 (22.9)	-	-	
Mean (SD) change for Nl/Borderline	779	1.2 (22.6)	-	426	0.1 (20.4)	-	-	

Modal (SD) Dose	183.7 mg (125.6)	-
Median Exp(days)	56	56

Information obtained from Sponsor table 230 in Clinical Study Report

6. Total fasting LDL > 30 mg/dL increase outliers

The treatment emergent shifts of Total fasting LDL ≥ 30 mg/dL increase showed a mean change of 7.2 in QTP treated subjects compared to 3.1 seen in placebo treated subjects. See table 194 below for QTP dose (in mg) and median exposure days.

Table 183: Proportion of Patients with treatment emergent shifts fasting LDL ≥ 30 mg/dL increase (naïve subjects, placebo-controlled trials)

fasting LDL ≥ 30 mg/dL increase	QTP - Post-baseline		Placebo - Post-baseline		p-value
Baseline (BL)	n (%)	≥30 mg/dL increase	n (%)	≥30 mg/dL increase	≥30
Any Value	848	67 (7.9)	463	31 (6.7)	0.445
Normal <100	310	30 (9.7)	178	10 (5.6)	0.126
Borderline ≥100 to <160	469	32 (6.8)	248	20 (8.1)	0.548
Normal/Borderline <160	69	5 (7.2)	37	1 (2.7)	0.662

Mean (SD) BL value for Any value	878	112.6 (34.6)	476	112.4 (34.0)	-
Mean (SD) BL value for Normal value	334	79.8 (15.2)	188	81.4 (13.9)	-
Mean (SD) BL value for Borderline value	473	125.1 (16.2)	250	124.5 (15.4)	-
Mean (SD) BL value for NL/BL value	69	184.4 (27.5)	37	187.2 (28.6)	-
Mean (SD) value at EOT for Any value	878	112.5 (35.4)	476	110.3 (33.3)	-
Mean (SD) value at EOT for Normal value	334	87.0 (26.1)	188	84.5 (20.7)	-
Mean (SD) value at EOT for Borderline value	473	122.2 (24.5)	250	122.1 (24.4)	-
Mean (SD) value at EOT for NL/BL value	69	168.5 (39.6)	37	161.1 (34.3)	-
Mean (SD) change for Any value	878	-0.1 (23.7)	476	-2.1 (23.2)	-
Mean (SD) change for Normal value	334	7.2 (22.4)	188	3.1 (15.9)	-
Mean (SD) change for Borderline value	473	-2.9 (21.8)	250	-2.4 (22.9)	-
Mean (SD) change for NL/BL value	69	-15.9 (31.0)	37	-26.1 (37.7)	-
Modal (SD) Dose (mg)	182.9 (123.8)		-		
Median Exposure (days)	56		56		

Information obtained from Sponsor table 231 in Clinical Study Report

7. Fasting Triglycerides outliers

Table 184: Proportion of Patients with treatment emergent shifts of fasting triglycerides (naïve subjects, placebo-controlled trials)

Triglycerides, Fasting (mg/dL)	QTP -Post-baseline				Placebo- Post-baseline				P-value		
Baseline (BL)	n(%)	>500	>200	>150	n(%)	>500	>200	>150	>500	>200	>150
Normal <150	625	0	46 (7.4)	107 (17.1)	354	0	13 (3.7)	42 (11.9)	-	0.025	0.033
Borderline ≥150 to <200	120	0	34 (28.3)	-	60	0	10 (16.7)	-	-	0.100	-
Normal/Borderline <200	745	0	80 (10.7)	-	414	0	23 (5.6)	-	-	0.003	-
Mean (SD) BL value for Normal	625	89.7 (30.1)	89.7 (30.1)	89.7 (30.1)	354	89.8 (29.8)	89.8 (29.8)	89.8 (29.8)	-	-	-
Mean (SD) BL value for Bl	120	172.2 (13.9)	172.2 (13.9)	-	60	173.3 (14.1)	173.3 (14.1)	-	-	-	-
Mean (SD) BL value for Nl/Bl	745	103.0 (41.4)	103.0 (41.4)	-	414	101.9 (40.7)	101.9 (40.7)	-	-	-	-
Mean (SD) value at EOT for NL	625	105.8 (52.9)	105.8 (52.9)	105.8 (52.9)	354	97.4 (45.9)	97.4 (45.9)	97.4 (45.9)	-	-	-
Mean (SD) value at EOT for Bl	120	174.9 (74.2)	174.9 (74.2)	-	60	160.0 (56.2)	160.0 (56.2)	-	-	-	-
Mean (SD) value at EOT for Nl/Bl	745	116.9 (62.3)	116.9 (62.3)	-	414	106.5 (52.4)	106.5 (52.4)	-	-	-	-
Mean (SD) change for Nl	625	16.1 (45.1)	16.1 (45.1)	16.1 (45.1)	354	7.5 (38.0)	7.5 (38.0)	7.5 (38.0)	-	-	-
Mean (SD) change for Bl	120	2.7 (75.1)	2.7 (75.1)	-	60	-13.3 (58.9)	-13.3 (58.9)	-	-	-	-
Mean (SD) change for Nl/Bl	745	13.9 (51.3)	13.9 (51.3)	-	414	4.5 (42.2)	4.5 (42.2)	-	-	-	-
Modal (SD) Dose	184.6 mg(128.4)				0				-		
Median Exp (days)	56				56				-		

Information obtained from Sponsor table 232 in Clinical Study Report

8. Fasting Triglycerides ≥ 50 mg/dL increase outliers

Table 185: Proportion of Patients , treatment emergent shifts triglycerides ≥ 50 mg/dL increase (naïve subjects, placebo-controlled trials)

Fasting triglycerides ≥ 50 mg/dL increase	QTP -Post-baseline		Placebo - Post-baseline		p-value
Baseline (BL)	n (%)	≥50	n (%)	≥50	≥50
Any Value	878	162 (18)	478	57 (11.9)	0.002
Normal <150	625	101(16.2)	354	41 (11.6)	0.059
Borderline ≥150 to<200	120	28 (23.3)	60	8 (13.3)	0.166
High ≥200 to < 500	127	32 (25.2)	63	8 (12.7)	0.058
Very High ≥ 500	6	1 (16.7)	1	0	1.000
Mean (SD) BL Any	878	132 (93)	478	125.7 (76)	-
Mean (SD) BL Normal	625	89.7 (30)	354	89.8 (29.8)	-
Mean (SD) BL Borderline	120	172 (14)	60	173.3 (14)	-
Mean (SD) BL High	127	274 (67)	63	275.0 (64)	-
Mean (SD) BL Very high	6	767 (137)	1	541	-
Mean (SD) EOT Any	878	143 (121)	478	124.2 (79)	-
Mean (SD) EOT Nl	625	106(52.9)	354	97.4 (45.9)	-
Mean (SD) EOT BL	120	175 (74)	60	160.0 (56)	-
Mean (SD) EOT high	127	264 (126)	63	235.3 (114)	-
Mean (SD) EOT Very high	6	832 (746)	1	487.3	-
Mean (SD) change Any	878	10.8 (89)	478	-1.4 (56.1)	-
Mean (SD) change Nl	625	16.1 (45)	354	7.5 (38.0)	-
Mean (SD) change BL	120	2.7 (75)	60	-13.3 (59)	-
Mean (SD) change High	127	-10 (116)	63	-39.7 (103)	-
Mean change Very high	6	65 (758)	1	-54.0	-
Modal (SD) Dose	182.9 (123.8)		0		-
Median Exp (days)	-		-		

Information obtained from Sponsor table 233 in Clinical Study Report

9. Fasting Triglycerides "Very high" outliers

Table 186: Proportion of Patients with treatment emergent shifts of very high fasting triglycerides (naïve subjects, placebo-controlled trials)

Fasting triglycerides ≥ Very High	QTP -Post-baseline		Placebo - Post-baseline		p-value
Baseline (BL)	n (%)	≥ 500	n (%)	≥500	≥500
Very High < 500	872	8 (0.9)	477	3 (0.6)	0.756
Mean (SD) BL value for Very high value	872	128(76)	477	124 (73)	-
Mean (SD) value at EOT for Very high	872	138(91)	477	123 (77)	-
Mean (SD) change for Very high value	872	10 (65)	477	-1.3 (56)	-
Modal (SD) Dose (mg)	182.9 (124.0)		-		-
Median Exp (days)	56		56		-

Information obtained from Sponsor table 234 in Clinical Study Report

7.5 Antipsychotic-Naïve Subjects in Comparator-Controlled Trials

7.5.1 Mean Change Analyses

1. Mean lipid change (in mg/dl) from baseline to endpoint

Please see table 198 below for comparison of mean lipid change of total cholesterol, fasting LDL, HDL, and fasting triglycerides from baseline to endpoint of quetiapine compared with olanzapine and risperidone.

Table 187: Lipids, change from baseline (BL) to end of treatment (EOT) (naïve subjects, comparator-controlled trials)

Measurements in mg/dl	QTP	OLZ	QTP	RIS
N =	234	245	435	450
Mean (SD) TC at BL	187.3 (46.2)	185 (43)	191(46)	193(44
Mean (SD) TC at EOT	195.4 (48.1)	201 (50)	198(46)	191(41
Mean (SD) TC Change	8.0 (38.0)	15.9 (41)	7 (38)	-2 (36)
p-value	0.029	-	<0.001	-
Modal (SD) Dose (mg)	592.7 (175)	14.5 (4.1)	595(193	5
Median Exp (days)	168	168	58	57
N =	22	31	22	23
Mean (SD) F-LDL at BL	109.2 (37.3)	108.9 (28)	109 (37)	108(31
Mean (SD) F-LDL at EOT	114.1 (41.0)	115 33)	114 (41)	109(41
Mean (SD) F-LDL Change	4.9 (36.3)	6.7 (29.8)	5 (36)	2 (28)
p-value	0.841	-	0.725	-
Modal (SD) Dose (mg)	627 (161)	13.1 (4.4)	627 (161)	3(1)
Median Exp (days)	325	253	352	364
N =	217	236	417	437
Mean (SD) HDL at BL	45.5 (13.3)	44.7 (11)	47 (14	47(14)
Mean (SD) HDL at EOT	44.5 (11.7)	42.5 (12)	47 (13)	47(13)
Mean (SD) HDL Change	-1.0 (10.1)	-2.1 (11)	-0.9	0
p-value	0.206	-	0.246	
Modal (SD) Dose (mg)	591 (177)	591 (177)	595(195	5
Median Exp (days)	168	168	57	57
N =	23	32	23	23
Mean (SD) F-Trig at BL	122.4 (62.2)	96.5 (53)	122 (62)	110(73
Mean (SD) F-Trig at EOT	141.7 (82.0)	137.4 (90)	142(82)	111(66
Mean (SD) F-Trig Change	19.3 (58.6)	40.9 (87)	19 (59)	0.8(59)
p-value	0.304	-	0.293	-
Modal (SD) Dose (mg)	613.0 (171)	13.3 (4.5)	613	2.6
Median Exp (days)	350	348	350	364
N =	42	40	42	45
Mean (SD) NF - Trig at BL	147.8 (102)	121.7 (76)	148 (102)	159 (165)
Mean (SD) NF - Trig at EOT	173.9 (142)	184 (112)	174(142)	150 (97)
Mean (SD) NF -Trig Change	26.1 (150.2)	62.5 (86)	26 (150)	-8.5(185)
p-value	0.186	-	0.342	-
Modal (SD) Dose (mg)	546 (213)	12.2 (5.0)	546	2.5
Median Exp (days)	330	346	330	268

Information obtained from Sponsor table 235 and 265 in Clinical Study Report
TC - Total cholesterol, BL – Baseline, EOT – End of treatment, Exp – Exposure, F-LDL – Fasting LDL, F-Trig – Fasting triglycerides, NF – Trig – Non fasting triglycerides, OLZ – olanzapine, RIS – risperidone, QTP - quetiapine

7.5.2 Categorical Analyses

In analyses of treatment-emergent significant changes (fasting baseline and post-baseline lipid measurements) for active-comparator controlled trials with olanzapine or risperidone controlled trials, no significant differences were observed in these outlier categories between the active-comparator and QTP.

7.6 Antipsychotic-Naïve Subjects in Controlled and Uncontrolled Trials

7.6.1 Mean Change Analyses

1. Mean lipid Change (in mg/dl) from baseline to endpoint

The quetiapine-treated antipsychotic naïve subjects (N = 3454) with a mean modal daily dose of 181 mg, had a mean total cholesterol change a decrease of -1.3 mg/dL with a median exposure of 63 days. The fasting triglyceride mean change was an increase of 12 mg/dL in QTP treated (modal daily dose of 183 mg) with a median exposure of 64 days. The fasting LDL mean change was -1.3 and the fasting HDL mean change was -2.6 in these QTP treated patients.

Table 188:Lipids, change from baseline (BL) to end of treatment (EOT) (naïve subjects, all QTP trials)

	QTP
N =	3454
Mean (SD) Total cholesterol (mg/dL) at BL	195.5 (42.4)
Mean (SD) Total cholesterol (mg/dL) at EOT	194.2 (42.0)
Mean (SD) Total cholesterol (mg/dL) Change	-1.3 (28.6)
p-value	-
Modal (SD) Dose (mg)	180.8 (118.2)
Median Exposure (days)	63

N =	1848
Mean (SD) LDL fasting (mg/dL) at BL	114.5 (35.1)
Mean (SD) LDL fasting (mg/dL) at EOT	113.2 (35.3)
Mean (SD) LDL fasting (mg/dL) Change	-1.3 (24.9)
p-value	-
Modal (SD) Dose (mg)	183.1 (116.2)
Median Exposure (days)	64

N =	3453
Mean (SD) HDL (mg/dL) at BL	55.0 (15.6)
Mean (SD) HDL (mg/dL) at EOT	52.5 (15.7)
Mean (SD) HDL (mg/dL) Change	-2.6 (9.5)
p-value	-
Modal (SD) Dose (mg)	180.9 (118.2)
Median Exposure (days)	63

N =	1851
Mean (SD) Triglycerides, fasting (mg/dL) at BL	137.3 (100.7)
Mean (SD) Triglycerides, fasting (mg/dL)at EOT	148.8 (119.1)
Mean (SD) Triglycerides, fasting (mg/dL) Change	11.5 (85.8)
p-value	-
Modal (SD) Dose (mg)	183.0 (116.2)
Median Exposure (days)	64

Information obtained from Sponsor table 295 in Clinical Study Report

2. Mean lipid Change (in mg/dl) from baseline to endpoint by ≥ 12 and ≥ 24 weeks exposure

The quetiapine-treated subjects (N = 1340) at a mean modal daily dose of 180 mg, had a mean total cholesterol change of -3.5 at ≥ 12 weeks exposure. The QTP treated subjects (N=513) had a mean total cholesterol change of -4.1 at a modal daily dose of 199 mg at ≥ 24 weeks exposure. The fasting triglyceride mean change was 11.3 in QTP treated (mean modal daily dose of 180 mg) at ≥ 12 weeks exposure. The QTP treated subjects (N=513) had a mean total cholesterol

change of 1.1 at a mean modal daily dose of 193 mg at ≥ 24 weeks exposure. Please see table 268 for LDL and HDL mean changes.

Table 189: Lipids, change from baseline (BL) to end of treatment (EOT), exposure ≥ 12 and ≥ 24 weeks (naïve subjects, all QTP trials)

At exposure ≥ 12 and ≥ 24 weeks	QTP exposure ≥ 12 weeks	QTP exposure ≥ 24 weeks
N =	1340	513
Mean (SD) Total cholesterol (mg/dL) at BL	197.7 (42.9)	200.5 (44.7)
Mean (SD) Total cholesterol (mg/dL) at EOT	194.2 (41.2)	196.4 (40.9)
Mean (SD) Total cholesterol (mg/dL) Change	-3.5 (31.4)	-4.1 (33.1)
p-value	-	-
Modal (SD) Dose (mg)	180.3 (119.1)	199.0 (150.2)
Median Exposure (days)	141	270
N =	814	336
Mean (SD) LDL fasting (mg/dL) at BL	115.6 (35.0)	116.8 (37.1)
Mean (SD) LDL fasting (mg/dL) at EOT	112.7 (34.7)	114.1 (36.8)
Mean (SD) LDL fasting (mg/dL) Change	-3.0 (26.0)	-2.8 (27.1)
p-value	-	-
Modal (SD) Dose (mg)	179.9 (108.9)	193.0 (126.2)
Median Exposure (days)	143	273
N =	1340	513
Mean (SD) HDL (mg/dL) at BL	55.4 (15.6)	55.8 (15.5)
Mean (SD) HDL (mg/dL) at EOT	51.8 (15.6)	51.7 (15.0)
Mean (SD) HDL (mg/dL) Change	-3.6 (10.1)	-4.1 (10.6)
p-value	-	-
Modal (SD) Dose (mg)	180.3 (119.1)	199.0 (150.2)
Median Exposure (days)	141	270
N =	816	336
Mean (SD) Triglycerides, fasting (mg/dL) at BL	141.5 (108.5)	143.9 (104.8)
Mean (SD) Triglycerides, fasting (mg/dL)at EOT	152.8 (118.9)	145.1 (97.7)
Mean (SD) Triglycerides, fasting (mg/dL) Change	11.3 (81.9)	1.1 (74.8)
p-value	-	-
Modal (SD) Dose (mg)	179.7 (108.9)	193.0 (126.2)
Median Exposure (days)	143	273

Information obtained from Sponsor table 296 and 297 in Clinical Study Report

7.6.2 Categorical Analyses

1. Total Cholesterol outliers

Table 190: Proportion of Patients with treatment emergent shifts of total cholesterol (naïve subjects, All QTP trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP - Post-baseline		
Baseline (BL)	n (%)	≥240/≥200	≥200/≥ 170 to ≤200
Normal <200	1956	61 (3.1)	366 (18.7)
Borderline ≥200 to <240	949	164 (17.3)	-
Normal/Borderline <240	2905	225 (7.7)	-
Mean (SD) BL value for Normal	1993	167.2 (22.8)	167.2 (22.8)
Mean (SD) BL value for Borderline	960	216.9 (11.5)	-
Mean (SD) BL value for Normal/Borderline	2905	183.9 (30.4)	-
Mean (SD) value at EOT for Normal	1993	173.0 (31.4)	173.4 (31.6)
Mean (SD) value at EOT for Borderline	960	212.2 (28.8)	-
Mean (SD) value at EOT for Normal/Borderline	2905	186.2 (35.6)	-
Mean (SD) change for Normal	1993	5.7 (25.4)	6.1 (25.5)
Mean (SD) change for Borderline	960	-4.7 (27.2)	-
Mean (SD) change for Normal/Borderline	2905	2.3 (26.5)	-

Modal (SD) Dose (mg)	182.7 (120.0)
Median Exposure (days)	63

Information obtained from Sponsor table 298 in Clinical Study Report

2. Total Cholesterol outliers

Table 191: Proportion of Patients with treatment emergent shifts of total cholesterol by time (naïve subjects, all QTP trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP Post-baseline exposure ≥12 wks			QTP Post-baseline exposure ≥24 wks		
Baseline (BL)	n (%)	≥240/≥200	≥200/≥ 170 to ≤200	n (%)	≥240/≥200	≥200/≥ 170 to ≤200
Normal <200	747	34 (4.6)	165 (22.1)	277	20 (7)	73 (26.4)
Borderline ≥200 to <240	390	75 (19.2)	-	155	32 (21)	-
Normal/Borderline <240	1137	109 (9.6)	-	432	52 (12)	-
Mean (SD) BL value for Normal	747	168 (22)	168.0 (22.1)	277	170(21)	169.6 (20.7)
Mean (SD) BL value for Bl	390	218 (11)	-	155	218(12)	-
Mean (SD) BL value for Normal/Bl	1137	185 (30)	-	432	187(29)	-
Mean (SD) value at EOT for Normal	747	174 (33)	175.1 (33.7)	277	178(34)	180(34)
Mean (SD) value at EOT for Bl	390	212 (29)	-	155	212(30)	-
Mean (SD) value at EOT for NL/Bl	1137	187 (37)	-	432	190(36)	-
Mean (SD) change for Normal	747	6.1 (29)	7.1 (29.1)	277	8 (32)	10.6 (31.8)
Mean (SD) change for Bl	390	-6.0 (28)	-	155	-6 (29)	-
Mean (SD) change for Normal/Bl	1137	1.9 (29)	-	432	3.1(31)	-
Modal (SD) Dose (mg)	182.4 (120.7)			203.5 (153.8)		
Median Exposure (days)	140			269		

Information obtained from Sponsor table 299 and 300 in Clinical Study Report,

3. Total Cholesterol ≥ 40 mg/dl increase outliers

Table 192:Proportion of Patient, treatment emergent shifts of total cholesterol ≥ 40 mg/dl increase and by time (naïve subjects, all QTP trials)

Total cholesterol (mg/dL) (fasting and non-fasting)	QTP - Post-baseline		QTP - Post-baseline at ≥12 wks exposure		QTP - Post-baseline at≥24 wks exposure	
Baseline (BL)	n (%)	≥40	n (%)	≥40	n (%)	≥40
Any value	3403	246 (7.2)	1339	123 (9.2)	512	62 (12.1)
Normal <200	1956	176 (9.0)	747	89 (11.9)	277	48 (17.3)
Borderline ≥200 to <240	949	44 (4.6)	390	20 (5.1)	155	7 (4.5)
High ≥240	498	26 (5.2)	202	14 (6.9)	80	7 (8.8)
Mean (SD) BL for Any	3403	195 (42)	1339	197.7 (43)	512	200.5 (44.7)
Mean (SD) BL for Nl	1956	167.2 (23)	747	168 (22)	277	169.6 (20.7)
Mean (SD) BL for Bl	949	216.9 (12)	390	218 (11)	155	218.0 (11.6)
Mean (SD) BL High	498	267 (29)	202	268.6 (33)	80	273.2 (43.3)
Mean (SD) EOT for Any	3403	194.7 (42)	1339	195.4 (42)	512	198.8 (42.6)
Mean (SD) EOT for Nl	1956	173.3 (32)	747	174.8 (33)	277	179.7 (33.7)
Mean (SD) EOT for Bl	949	211.5 (28)	390	210.5 (28)	155	209.6 (28.9)
Mean (SD) EOT for High	498	247.8 (41)	202	242 (43.5)	80	244.0 (50.4)
Mean (SD) change Any	3403	-0.8 (29)	1339	-2.3 (33.0)	512	-1.7 (36.0)
Mean (SD) change Nl	1956	6.0 (25)	747	6.9 (29.2)	277	10.1 (32.0)
Mean (SD) change Bl	949	-5.4 (27)	390	-7.5 (27.0)	155	-8.4 (27.7)
Mean (SD) change High	498	-19.3 (37)	202	-26.3 (41)	80	-29.1 (44.7)
Modal (SD) Dose	180.8 (118.2)		180.3 (119.1)		199.0 (150.2)	
Median Exposure (days)	63		141		270	

Information obtained from Sponsor table 301, 302 and 303 in Clinical Study Report

4. Total HDL outliers

Table 193: Proportion of Patients with treatment emergent shifts of total HDL(naïve subjects, all QTP trials)

Total HDL (mg/dL) (fasting and non-fasting)	QTP -Post-baseline		QTP- Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	<40	n (%)	<40	n (%)	<40
Normal ≥ 40	2978	392 (13)	1168	207(18)	449	97 (21.6)
Mean (SD) Normal at BL	2978	58.3 (14)	1168	59 (14)	449	58.9 (14.0)
Mean (SD) Normal at EOT	2978	54.9 (15)	1168	54(15)	449	52.8 (14.8)
Mean (SD) change for Nl	2978	-3.4 (10)	1168	-5 (11)	449	-6.1 (10.7)
Modal (SD) Dose (mg)	177.8 (114.4)		174.2 (109.8)		188.1 (132.8)	
Median Exposure (days)	63		141		266	

Information obtained from Sponsor table 304, 305 and 306 in Clinical Study Report

5. Total HDL ≥ 20 mg/dL decrease outliers

Table 194: Proportion of Patients with treatment emergent shifts of total HDL ≥ 20 mg/dL decrease (naïve subjects, all QTP trials)

Total HDL (mg/dL) ≥ 20 mg/dL decrease	QTP - Post-baseline		QTP - Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	≥20 mg/dL	n (%)	≥20 mg/dL	n (%)	≥20 mg/dL
Any value	3453	152 (4.4)	1340	94 (7.0)	513	50 (9.7)
Normal >40	2978	150 (5.0)	1168	93 (8.0)	449	49 (10.9)
Low ≤ 40	475	2 (0.4)	172	1 (0.6)	64	1 (1.6)
Mean (SD) BL value for Any value	3453	55(16)	1340	55.4 (16)	513	55.8 (15)
Mean (SD) BL value for Normal value	2978	58 (14)	1168	58.5 (14)	449	58.9 (14)
Mean (SD) BL value for Low value	475	35 (4)	172	34.2 (4)	64	34 (4)
Mean (SD) value at EOT for Any value	3453	52 (16)	1340	51.4 (16)	513	50.9 (15)
Mean (SD) value at EOT for Normal value	2978	55 (15)	1168	53.8 (15)	449	53 (14)
Mean (SD) value at EOT for Low value	475	35 (9)	172	35 (10.4)	64	36.2 (14)
Mean (SD) change for Any value	3453	-2.8 (9.8)	1340	-4.0 (11)	513	-4.9 (12)
Mean (SD) change for Normal value	2978	-3.3 (9.9)	1168	-4.7 (11)	449	-5.9 (11)
Mean (SD) change for Low value	475	0.9 (8.2)	172	0.4 (10)	64	2.2 (14)
Modal (SD) Dose	180.9 (118.2)		180.3 (119.1)		199.0 (150.2)	
Median Exp (days)	63		141		270	

Information obtained from Sponsor table 307, 308 and 309 in Clinical Study Report

6. Total fasting LDL outliers

Table 195: Proportion of Patients with treatment emergent shifts of fasting LDL (naïve subjects, all QTP trials)

Fasting LDL(mg/dL)	QTP -Post-baseline			QTP- Post-baseline at ≥12 wks exposure			QTP - Post-baseline at ≥24 wks exposure		
Baseline (BL)	n (%)	≥160/ ≥130	≥100/ ≤130	n(%)	≥160/ ≥130	≥100/ ≤130	n(%)	≥160/ ≥130	≥100 /≤130
Normal <100	650	9 (1)	186 (28)	294	5 (2)	96 (33)	118	3 (2.5)	47 (40)
Borderline ≥100 to<160	997	71 (7)	-	437	36 (8)	-	180	15 (8)	-
Normal/Borderline<160	1647	80 (5)	-	731	41 (6)	-	298	18 (6)	-
Mean (SD) BL Any	674	80 (15)	80 (15)	294	81 (15)	81 (15)	118	81 (15)	81 (15)

Mean (SD) BL Nl	1001	125 (16	-	437	126 (17	-	180	125 (16	-
Mean (SD) BL Low	1647	107(27	-	731	108 (27	-	298	108 (27	-
Mean (SD) EOT Any	674	87 (25	88 (26)	294	88 (25)	90 (25)	118	88 (26)	92 (27)
Mean (SD) EOT Nl	1001	122 (26	-	437	121 (28	-	180	122(28)	-
Mean (SD) EOT Low	1647	109 (31	-	731	108 (31	-	298	108(32)	-
Mean (SD) change Any	674	7 (22	8 (22)	294	7 (22)	9 (22)	118	8 (23)	12 (23)
Mean (SD) change Nl	1001	-3 (23)	-	437	-4 (24)	-	180	-4 (25)	-
Mean (SD) change Low	1647	0.8 (23	-	731	0	-	298	0.8 (25)	-
Modal (SD) Dose	183.4 (117.1)			181.5 (110.1)			196.8 (129.5)		
Median Exp (days)	64			142			276		

Information obtained from Sponsor table 310, 311 and 312 in Clinical Study Report

7. Total fasting LDL ≥ 30 mg/dl increase outliers

Table 196: Proportion of Patients with treatment emergent shifts of fasting LDL ≥ 30 mg/dL increase (naïve subjects, all QTP trials)

fasting LDL ≥ 30 mg/dL increase	QTP -Post-baseline		QTP- Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	≥30 mg/dL	n (%)	≥30 mg/dL	n (%)	≥30 mg/dL
Any Value	1818	176 (9.7)	814	100 (12.3)	336	52 (15.5)
Normal <100	650	89 (13.7)	294	53 (18.0)	118	27 (22.9)
Borderline ≥100 to <160	997	75 (7.5)	437	40 (9.2)	180	21 (11.7)
Normal/Borderline <160	171	12 (7.0)	83	7 (8.4)	38	4 (10.5)
Mean (SD) BL Any	1848	114 (35)	814	115.6 (35)	336	116 (37)
Mean (SD) BL Nl	674	80.5 (15)	294	81.3 (15.0)	118	80.7 (15)
Mean (SD) BL Low	1001	125 (16.4)	437	125.9 (17)	180	125 (16)
Mean (SD) BL Any	171	184 (25.1)	83	183 (21.4)	38	188 (26)
Mean (SD) EOT Any	1848	113.6 (35)	814	113.6 (35)	336	116 (38)
Mean (SD) EOT Nl	674	88.3 (26)	294	89.5 (25.8)	118	91.3 (28)
Mean (SD) EOT Low	1001	121.9 (26)	437	121 (27)	180	121 (28)
Mean (SD) EOT Any	171	164.8 (38)	83	160.5 (38)	38	164 (43)
Mean (SD) change Any	1848	-0.9 (25)	814	-2.0 (27.1)	336	-0.8 (29)
Mean (SD) change Nl	674	7.8 (22.3)	294	8.2 (22.5)	118	10.6 (25)
Mean (SD) change Low	1001	-3.5 (23)	437	-4.9 (24.3)	180	-3.6 (25)
Mean (SD) change Any	171	-19.6 (35)	83	-22.8 (39)	38	-23 (40)
Modal (SD) Dose (mg)	183.1 (116.2)		179.9 (108.9)		193.0 (126.2)	
Median Exposure (days)	64		143		273	

Information obtained from Sponsor table 313, 314 and 315 in Clinical Study Report

8. Fasting Triglycerides outliers

The QTP treated subjects with treatment emergent shifts of Fasting Triglycerides show a mean change of 20, 22 and 23 at post baseline, ≥ 12 weeks exposure and ≥ 24 weeks exposure for the normal Fasting Triglycerides (>200) respectively. See table below for QTP dose (in mg) and median exposure days.

Table 197: Proportion of Patients with treatment emergent shifts of fasting (naïve subjects, all QTP trials)

Triglycerides, Fasting (mg/dL)	QTP -Post-baseline				QTP- Post-baseline at ≥12 wks exposure				QTP - Post-baseline at ≥24 wks exposure			
Baseline (BL)	n (%)	≥500	≥200	≥150	n (%)	≥500	≥200	≥150	n (%)	≥500	≥200	≥150
Normal <150	1287	1 (0)	113 (8.8)	272 (21.1)	559	1 (0.2)	56 (10.0)	134 (24.0)	226	0	26 (11.5)	64 (28.3)
Borderline ≥150 to <200	273	4 (1.5)	101 (37.0)	-	127	3 (2.4)	59 (46.5)	-	54	1 (1.9)	21 (38.9)	-
Normal/Borderline <200	1560	5 (0.3)	214 (13.7)	-	686	4 (0.6)	115 (16.8)	-	280	1 (0.4)	47 (16.8)	-

Mean (SD) BL value for Normal	1287	91.4 (29.0)	91.4 (29.0)	91.4 (29.0)	559	93.3 (27.9)	93.3 (27.9)	93.3 (27.9)	226	93.4 (27.1)	93.4 (27.1)	93.4 (27.1)
Mean (SD) BL value for Bl	273	172.6 (14.9)	172.6 (14.9)	-	127	172.8 (15.7)	172.8 (15.7)	-	54	173.1 (16.9)	173.1 (16.9)	-
Mean (SD) BL value for Nl/Bl	1560	105.6 (41.1)	105.6 (41.1)	-	686	108.0 (40.4)	108.0 (40.4)	-	280	108.8 (40.5)	108.8 (40.5)	-
Mean (SD) value at EOT Normal	1287	109.8 (57.0)	111.2 (59.4)	112.1 (59.3)	559	111.5 (58.7)	114.9 (63.9)	117.0 (63.6)	226	110.4 (56.5)	116.5 (65.1)	120.4 (65.7)
Mean (SD) value at EOT for Bl	273	186.0 (96.6)	189.2 (94.7)	-	127	193.8 (102.3)	200.5 (97.8)	-	54	171.0 (81.5)	186.7 (88.2)	-
Mean (SD) value at EOT for Nl/Bl	1560	123.1 (71.7)	124.9 (73.2)	-	686	126.8 (75.9)	130.8 (78.7)	-	280	122.1 (66.4)	130.0 (75.3)	-
Mean (SD) change for Nl	1287	18.4 (49.8)	19.9 (52.4)	20.8 (51.9)	559	18.2 (52.9)	21.6 (58.3)	23.7 (57.3)	226	16.9 (51.2)	23.1 (60.1)	26.9 (60.1)
Mean (SD) change for Bl	273	13.4 (96.0)	16.5 (94.0)	-	127	21.0 (102.6)	27.8 (97.8)	-	54	-2.1 (84.0)	13.6 (90.1)	-
Mean (SD) change for Nl/Bl	1560	17.5 (60.5)	19.3 (61.7)	-	686	18.7 (64.9)	22.8 (67.3)	-	280	13.3 (59.3)	21.2 (66.9)	-
Mean Modal (SD) Dose	182.2 (118.3) mg				177.6 (108.1) mg				189.5 (125.2) mg			
Median Exp	64 days				142 days				270 days			

Information obtained from Sponsor table 316, 317 and 318 in Clinical Study Report

9. Fasting Triglycerides of ≥ 50 mg/dL increase outliers

Table 198: Proportion of Patients with treatment emergent shifts of fasting triglycerides ≥ 50 mg/dL increase (naïve subjects, all QTP trials)

Fasting triglycerides ≥ 50 mg/dL increase	QTP -Post-baseline		QTP- Post-baseline at ≥12 wks exposure		QTP - Post-baseline at ≥24 wks exposure	
Baseline (BL)	n (%)	≥50	n (%)	≥50	n (%)	≥50
Any Value	1851	424 (23)	816	220 (27.0)	336	84 (25.0)
Normal <150	1287	267 (21)	559	135 (24.2)	226	60 (26.5)
Borderline ≥150 to<200	273	75 (27.5)	127	42 (33.1)	54	12 (22.2)
High ≥200 to < 500	272	78 (28.7)	119	40 (33.6)	50	11 (22.0)
Very High ≥ 500	19	4 (21.1)	11	3 (27.3)	6	1 (16.7)
Mean (SD) BL Any	1851	137 (101)	816	141.5 (109)	336	143.9 (104.8)
Mean (SD) BL Nl	1287	91.4 (29)	559	93.3 (27.9)	226	93.4 (27.1)
Mean (SD) BL BRD	273	173 (15)	127	172.8 (16)	54	173.1 (16.9)
Mean (SD) BL HIGH	272	278(72)	119	281.1 (76)	50	278.5 (68.1)
Mean (SD) BL LOW	19	729 (252)	11	720.1 (318)	6	662.1 (163.4)
Mean (SD) EOT Any	1851	152 (121)	816	159.0 (122)	336	156.2 (105.8)
Mean (SD) EOT Nl	1287	112 (59)	559	116.8 (63)	226	119.9 (64.4)
Mean (SD) EOT BRD	273	188 (94)	127	199.0 (99)	54	185.2 (87.9)
Mean (SD) EOT HIGH	272	272 (129)	119	282.6 (134)	50	254.4 (99.1)
Mean (SD) EOT LOW	19	582 (561)	11	506.1 (469)	6	443.4 (348.1)
Mean (SD) change Any	1851	14.3 (87)	816	17.5 (83.6)	336	12.2 (83.7)
Mean (SD) change Nl	1287	20.7 (52)	559	23.5 (56.9)	226	26.5 (59.2)
Mean (SD) change BRD	273	15.8 (94)	127	26.3 (98.1)	54	12.1 (90.2)
Mean (SD) change HIGH	272	-6 (114)	119	1.5 (115.7)	50	-24.1 (100.0)
Mean (SD) change LOW	19	-147(463)	11	-214(212)	6	-218.7 (203.1)
Modal (SD) Dose (mg)	183.0 (116.2)		179.7 (108.9)		193.0 (126.2)	
Median Exp (days)	64		143		273	

Information obtained from Sponsor table 319, 320 and 321 in Clinical Study Report

10. Fasting Triglycerides of ≥ 500 mg/dL "very high" increase outliers

Table 199: Proportion of Patients with treatment emergent shifts of very high fasting triglycerides (naïve subjects, all QTP trials)

Fasting triglycerides ≥ Very High	QTP -Post-baseline		QTP- Post-baseline at ≥ 12 wks exposure		QTP - Post-baseline at ≥ 24 wks exposure	
Baseline (BL)	n (%)	≥ 500	n (%)	≥500	n (%)	≥500
Very High < 500	1832	22 (1)	805	12 (1.5)	330	3 (0.9)
Mean (SD) BL Very high	1832	131(77)	805	133 (77)	330	134.5 (76.1)
Mean (SD) EOT Very high	1832	145 (98)	805	149 (103)	330	141.0 (84.4)
Mean (SD) change Very high	1832	14 (72)	805	15 (76.0)	330	6.5 (68.1)
Modal (SD) Dose (mg)	182.8 (116.4)		179.6 (109.0)		192.3 (126.5)	
Median Exp (days)	64		143		273	

Information obtained from Sponsor table 322, 323 and 324 in Clinical Study Report

8 APPENDIX

8.1 Tables summarizing subject demographic Information

8.1.1 Adult subjects in placebo-controlled trials

Table 200: Baseline demographics (adult subjects, placebo-controlled trials)

		QTP N=6870	PLA N=3000
Sex n (%)	Male	3336 (48.6)	1365 (45.5)
	Female	3534 (51.4)	1635 (54.5)
Age (years)	n	6870	3000
	Mean (SD)	39.4 (11.4)	39.5 (11.9)
Race/ethnicity n (%)	White	4725 (68.8)	2058 (68.6)
	Black	1359 (19.8)	571 (19.0)
	Asian	409 (6.0)	201 (6.7)
	Hispanic	232 (3.4)	97 (3.2)
	Mixed, Other	140 (2.0)	71 (2.4)
	Not specified	5 (0.1)	2 (0.1)
Treatment indication n (%)	Dementia	0 (0.0)	0 (0.0)
	Schizoaffective	0 (0.0)	0 (0.0)
	Schizophrenia	1875 (27.3)	525 (17.5)
	Bipolar mania	297 (4.3)	287 (9.6)
	Bipolar depression	1734 (25.2)	687 (22.9)
	Bipolar mixed, etc.	178 (2.6)	126 (4.2)
	Major depressive disorder (MDD)	1149 (16.7)	648 (21.6)
	Generalized anxiety disorder (GAD)	1572 (22.9)	665 (22.2)
	Others	0 (0.0)	0 (0.0)
	Healthy volunteers	65 (0.9)	62 (2.1)
Modal dose (mg)	n	6870	3000
	Mean (SD)	345.1 (223.6)	0.0 (0.0)
Exposure (days)	n	6870	3000
	Median (Q1, Q3)	42.0 (21, 56)	45.0 (22, 56)

8.1.2 Adult subjects in comparator-controlled trials

Table 201: Baseline demographics (adult subjects, chlorpromazine-controlled trials)

		QTP N=346	CHL N=349
Sex n (%)	Male	228 (65.9)	237 (67.9)
	Female	118 (34.1)	112 (32.1)
Age (years)	n	346	349
	Mean (SD)	37.8 (10.9)	38.3 (10.5)
Race/ethnicity n (%)	White	245 (70.8)	260 (74.5)
	Black	55 (15.9)	38 (10.9)
	Asian	5 (1.4)	3 (0.9)
	Hispanic	25 (7.2)	29 (8.3)
	Mixed, Other	16 (4.6)	19 (5.4)
	Not specified	0 (0.0)	0 (0.0)
Treatment indication n (%)	Dementia	0 (0.0)	0 (0.0)
	Schizoaffective	0 (0.0)	0 (0.0)
	Schizophrenia	346 (100.0)	349 (100.0)
	Bipolar mania	0 (0.0)	0 (0.0)
	Bipolar depression	0 (0.0)	0 (0.0)
	Bipolar mixed, etc.	0 (0.0)	0 (0.0)
	Major depressive disorder (MDD)	0 (0.0)	0 (0.0)
	Generalized anxiety disorder (GAD)	0 (0.0)	0 (0.0)
	Others	0 (0.0)	0 (0.0)
	Healthy volunteers	0 (0.0)	0 (0.0)
Modal dose (mg)	n	346	349
	Mean (SD)	548.0 (130.7)	620.8 (230.8)
Exposure (days)	n	346	349
	Median (Q1, Q3)	62.5 (42, 70)	62.0 (35, 70)
	Min to max	1 to 124	2 to 96

		QTP N=346	CHL N=349
Reasons for discontinuation n (%)	Lack of efficacy	17 (4.9)	15 (4.3)
	Side effects	23 (6.6)	42 (12.0)
	Metabolic side effects	0 (0.0)	0 (0.0)
Weight (kg)	n	346	346
	Mean (SD)	73.6 (16.0)	73.1 (14.9)
BMI (kg/m^2)	n	264	260
	Mean (SD)	25.9 (5.6)	25.2 (5.1)

Note: Percentages calculated as 100*n/N.
Studies included 204636/0007, 5077IL/0031, 5077IL/0054
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Table 202: Baseline demographics (adult subjects, haloperidol-controlled trials)

		QTP N=1276	HAL N=849
Sex n (%)	Male	879 (68.9)	544 (64.1)
	Female	397 (31.1)	305 (35.9)
Age (years)	n	1276	849
	Mean (SD)	38.2 (10.9)	38.7 (11.9)
Race/ethnicity n (%)	White	921 (72.2)	634 (74.7)
	Black	133 (10.4)	38 (4.5)
	Asian	143 (11.2)	131 (15.4)
	Hispanic	44 (3.4)	18 (2.1)
	Mixed, Other	35 (2.7)	28 (3.3)
	Not specified	0 (0.0)	0 (0.0)
Treatment indication n (%)	Dementia	0 (0.0)	0 (0.0)
	Schizoaffective	28 (2.2)	33 (3.9)
	Schizophrenia	1146 (89.8)	717 (84.5)
	Bipolar mania	102 (8.0)	99 (11.7)
	Bipolar depression	0 (0.0)	0 (0.0)
	Bipolar mixed, etc.	0 (0.0)	0 (0.0)
	Major depressive disorder (MDD)	0 (0.0)	0 (0.0)
	Generalized anxiety disorder (GAD)	0 (0.0)	0 (0.0)
	Others	0 (0.0)	0 (0.0)
	Healthy volunteers	0 (0.0)	0 (0.0)
Modal dose (mg)	n	1276	849
	Mean (SD)	416.2 (229.6)	11.0 (5.6)
Exposure (days)	n	1276	849
	Median (Q1, Q3)	42.0 (21, 59)	42.0 (22, 57)
	Min to max	1 to 426	1 to 442
Reasons for discontinuation n (%)	Lack of efficacy	201 (15.8)	61 (7.2)
	Side effects	82 (6.4)	103 (12.1)
		QTP N=1276	**HAL N=849**
	Metabolic side effects	1 (0.1)	0 (0.0)
Weight (kg)	n	1246	839
	Mean (SD)	76.2 (17.2)	73.5 (16.9)
BMI (kg/m^2)	n	972	575
	Mean (SD)	26.4 (5.3)	25.8 (5.1)

N Number of patients in treatment group. n Number of patients. NA Not applicable. HAL Haloperidole. QTP Quetiapine. Q1 Lower quartile. Q3 Upper quartile. SD standard deviation.
Note: Percentages calculated as 100*n/N.
Studies included 5077IL/0013, 5077IL/0014, 5077IL/0015, 5077IL/0050, 5077IL/0052, 5077IL/0104, H-15-31
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Table 203: Baseline demographics (adult subjects, olanzapine-controlled trials)

		QTP N=297	OLZ N=298
Sex n (%)	Male	193 (65.0)	209 (70.1)
	Female	104 (35.0)	89 (29.9)
Age (years)	n	297	298
	Mean (SD)	32.8 (11.5)	33.2 (11.8)
Race/ethnicity n (%)	White	210 (70.7)	209 (70.1)
	Black	75 (25.3)	76 (25.5)
	Asian	7 (2.4)	8 (2.7)
	Hispanic	0 (0.0)	0 (0.0)
	Mixed, Other	5 (1.7)	5 (1.7)
	Not specified	0 (0.0)	0 (0.0)
Treatment indication n (%)	Dementia	0 (0.0)	0 (0.0)
	Schizoaffective	17 (5.7)	17 (5.7)
	Schizophrenia	280 (94.3)	281 (94.3)
	Bipolar mania	0 (0.0)	0 (0.0)
	Bipolar depression	0 (0.0)	0 (0.0)
	Bipolar mixed, etc.	0 (0.0)	0 (0.0)
	Major depressive disorder (MDD)	0 (0.0)	0 (0.0)
	Generalized anxiety disorder (GAD)	0 (0.0)	0 (0.0)
	Others	0 (0.0)	0 (0.0)
	Healthy volunteers	0 (0.0)	0 (0.0)
Modal dose (mg)	n	295	295
	Mean (SD)	561.4 (192.2)	13.7 (4.8)
Exposure (days)	n	297	298
	Median (Q1, Q3)	167.0 (72, 175)	168.0 (157, 176)
	Min to max	4 to 396	1 to 444
Reasons for discontinuation n (%)	Lack of efficacy	25 (8.4)	22 (7.4)
	Side effects	38 (12.8)	23 (7.7)
	Metabolic side effects	0 (0.0)	1 (0.3)
Weight (kg)	n	297	295
	Mean (SD)	74.1 (17.5)	74.5 (17.3)
BMI (kg/m^2)	n	296	295
	Mean (SD)	25.1 (5.0)	25.2 (5.4)

N Number of patients in treatment group. n Number of patients. NA Not applicable. OLZ Olanzapine. QTP Quetiapine. Q1 Lower quartile. Q3 Upper quartile. SD standard deviation.
Note: Percentages calculated as 100*n/N.
Studies included D1441C00125, D1441L00002
Table ID: A2103_DEM_1B_OLZ. Program: \Demo tables\Program\MakeDemoTable.sas. User: kjwm515. Data created: 21MAY2008:12:56. Table created: 21MAY2008:12:56.

Table 204: Baseline demographics (adult subjects, risperidone-controlled trials)

		QTP N=1385	RI N=1014
Sex n (%)	Male	859 (62.0)	680 (67.1)
	Female	526 (38.0)	334 (32.9)
Age (years)	n	1385	1014
	Mean (SD)	39.6 (12.5)	38.1 (12.3)
Race/ethnicity n (%)	White	915 (66.1)	661 (65.2)
	Black	346 (25.0)	287 (28.3)
	Asian	30 (2.2)	11 (1.1)
	Hispanic	63 (4.5)	32 (3.2)
	Mixed, Other	31 (2.2)	23 (2.3)
	Not specified	0 (0.0)	0 (0.0)
Treatment indication n (%)	Dementia	13 (0.9)	5 (0.5)
	Schizoaffective	174 (12.6)	76 (7.5)
	Schizophrenia	1023 (73.9)	884 (87.2)
	Bipolar mania	83 (6.0)	21 (2.1)
	Bipolar depression	0 (0.0)	0 (0.0)
	Bipolar mixed, etc.	2 (0.1)	0 (0.0)
	Major depressive disorder (MDD)	72 (5.2)	25 (2.5)
	Generalized anxiety disorder (GAD)	0 (0.0)	0 (0.0)
	Others	18 (1.3)	3 (0.3)
	Healthy volunteers	0 (0.0)	0 (0.0)
Modal dose (mg)	n	1383	1013
	Mean (SD)	425.5 (229.7)	5.2 (2.4)
Exposure (days)	n	1385	1014
	Median (Q1, Q3)	70.0 (36, 121)	65.0 (37, 122)
	Min to max	1 to 396	1 to 447
Reasons for discontinuation n (%)	Lack of efficacy	139 (10.0)	81 (8.0)
	Side effects	127 (9.2)	85 (8.4)
		QTP N=1385	**RI N=1014**
	Metabolic side effects	1 (0.1)	2 (0.2)
Weight (kg)	n	828	833
	Mean (SD)	77.9 (19.7)	79.8 (19.7)
BMI (kg/m^2)	n	683	678
	Mean (SD)	26.7 (6.4)	27.2 (6.5)

N Number of patients in treatment group. n Number of patients. NA Not applicable. QTP Quetiapine. Q1 Lower quartile. Q3 Upper quartile. RI Risperidone. SD standard deviation.
Note: Percentages calculated as 100*n/N.
Studies included 5077IL/0053, 5077US/0004, 5077US/0043, D1441C00125, D1441L00002
Table ID: A2101_DEM_1B_RI. Program: \Demo tables\Program\MakeDemoTable.sas. User: kjwm515. Data created: 21MAY2008:12:56. Table created: 21MAY2008:12:56.

8.1.3 Adult subjects in Controlled and Uncontrolled trials

Table 205: Baseline demographics (adult subjects, quetiapine-treated, all trials)

		QTP N=20021
Sex n (%)	Male	10543 (52.7)
	Female	9478 (47.3)
Age (years)	n	20021
	Mean (SD)	39.4 (11.8)
Race/ethnicity n (%)	White	14045 (70.2)
	Black	2776 (13.9)
	Asian	1783 (8.9)
	Hispanic	837 (4.2)
	Mixed, Other	489 (2.4)
	Not specified	91 (0.5)
Treatment indication n (%)	Dementia	13 (0.1)
	Schizoaffective	463 (2.3)
	Schizophrenia	8489 (42.4)
	Bipolar mania	1592 (8.0)
		QTP N=20021
	Bipolar depression	2685 (13.4)
	Bipolar mixed, etc.	736 (3.7)
	Major depressive disorder (MDD)	3075 (15.4)
	Generalized anxiety disorder (GAD)	2797 (14.0)
	Others	64 (0.3)
	Healthy volunteers	107 (0.5)
Modal dose (mg)	n	20018
	Mean (SD)	385.5 (240.5)
Exposure (days)	n	20021
	Median (Q1, Q3)	57.0 (29, 113)
	Min to max	1 to 2253
Reasons for discontinuation n (%)	Lack of efficacy	1407 (7.0)
	Side effects	2272 (11.3)
	Metabolic side effects	59 (0.3)
Weight (kg)	n	19333
	Mean (SD)	78.2 (20.3)
BMI (kg/m^2)	n	17765
	Mean (SD)	27.5 (6.7)

N Number of patients in treatment group. n Number of patients. NA Not applicable. NA Not applicable. QTP Quetiapine. Q1 Lower quartile. Q3 Upper quartile. SD standard deviation.
Note: Percentages calculated as 100*n/N.
Studies included 204636/0003, 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0005, 5077IL/0006, 5077IL/0008, 5077IL/0012, 5077IL/0013, 5077IL/0014, 5077IL/0015, 5077IL/0016, 5077IL/0020, 5077IL/0024, 5077IL/0027, 5077IL/0029, 5077IL/0031, 5077IL/0033, 5077IL/0035, 5077IL/0036, 5077IL/0037, 5077IL/0041, 5077IL/0044, 5077IL/0045, 5077IL/0047, 5077IL/0050, 5077IL/0052, 5077IL/0053, 5077IL/0054, 5077IL/0056, 5077IL/0061, 5077IL/0062, 5077IL/0065, 5077IL/0066, 5077IL/0072, 5077IL/0084, 5077IL/0086, 5077IL/0093, 5077IL/0097, 5077IL/0104, 5077IL/0105, 5077IL/0107, 5077IL/0109, 5077IL/0118, 5077US/0004, 5077US/0043, 5077US/0049, D1441C00023, D1441C00125, D1441C00130, D1441L00002, D1444C00001, D1444C00004, D1444C00132, D1444C00133, D1444C00145, D1444C00146, D1444C00147, D1447C00001, D1447C00134, D1447C00135, D1447C00144, D1448C00001, D1448C00002, D1448C00003, D1448C00004, D1448C00005, D1448C00008, D1448C00009, D1448C00010, D1448C00011, D1448C00012, D1448C00017, D144CC00002, D144CC00004
, H-15-21, H-15-22, H-15-31, H-15-32, H-15-33, H-15-34, H-15-35, H-15-36, H-15-37
Table ID: A3101_DEM_1C. Program: \Demo tables\Program\MakeDemoTable.sas. User: kjwm515. Data created: 22MAY2008:13:08. Table created: 22MAY2008:13:08.

8.1.4 Subjects with first episode psychosis and antipsychotic-naïve subjects in placebo-controlled trials

Table 206: Baseline demographics (naïve subjects, placebo-controlled trials)

		QTP N=2489	PLA N=1207
Sex n (%)	Male	973 (39.1)	457 (37.9)
	Female	1516 (60.9)	750 (62.1)
Age (years)	n	2489	1207
	Mean (SD)	39.4 (12.4)	39.0 (12.5)
Race/ethnicity n (%)	White	1918 (77.1)	883 (73.2)
	Black	409 (16.4)	232 (19.2)
	Asian	54 (2.2)	36 (3.0)
	Hispanic	85 (3.4)	48 (4.0)
	Mixed, Other	23 (0.9)	8 (0.7)
	Not specified	0 (0.0)	0 (0.0)
Treatment indication n (%)	Dementia	0 (0.0)	0 (0.0)
	Schizoaffective	0 (0.0)	0 (0.0)
	Schizophrenia	60 (2.4)	23 (1.9)
	Bipolar mania	0 (0.0)	0 (0.0)
	Bipolar depression	0 (0.0)	0 (0.0)
	Bipolar mixed, etc.	0 (0.0)	0 (0.0)
	Major depressive disorder (MDD)	976 (39.2)	542 (44.9)
	Generalized anxiety disorder (GAD)	1393 (56.0)	582 (48.2)
	Others	0 (0.0)	0 (0.0)
	Healthy volunteers	60 (2.4)	60 (5.0)
Modal dose (mg)	n	2489	1207
	Mean (SD)	174.7 (114.9)	0.0 (0.0)
Exposure (days)	n	2489	1207
	Median (Q1, Q3)	49.0 (27, 57)	55.0 (40, 58)
	Min to max	1 to 79	1 to 75
Reasons for discontinuation n (%)	Lack of efficacy	7 (0.3)	6 (0.5)
		QTP N=2489	PLA N=1207
	Side effects	401 (16.1)	52 (4.3)
	Metabolic side effects	5 (0.2)	1 (0.1)
Weight (kg)	n	2488	1207
	Mean (SD)	80.0 (20.6)	80.3 (21.8)
BMI (kg/m^2)	n	2486	1205
	Mean (SD)	28.2 (6.9)	28.3 (7.3)

N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. QTP Quetiapine. Q1 Lower quartile. Q3 Upper quartile. SD standard deviation.
Note: Percentages calculated as 100*n/N.
Studies included D1441C00112, D1448C00001, D1448C00002, D1448C00003, D1448C00004, D1448C00008, D1448C00009, D1448C00010, D1448C00011
Table ID: C1101_DEM_3A_PLA. Program: \Demo tables\Program\MakeDemoTable.sas. User: kjwm515. Data created: 21MAY2008:12:58. Table created: 21MAY2008:12:58.

8.1.5 Subjects with first episode psychosis and antipsychotic-naïve subjects in comparator-controlled trials

Table 207: Baseline demographics (naïve subjects, olanzapine-controlled trials)

		QTP	OLZ
		N=66	N=72
Sex n (%)	Male	46 (69.7)	54 (75.0)
	Female	20 (30.3)	18 (25.0)
Age (years)	n	66	72
	Mean (SD)	24.8 (5.8)	25.0 (6.3)
Race/ethnicity n (%)	White	30 (45.5)	33 (45.8)
	Black	30 (45.5)	32 (44.4)
	Asian	4 (6.1)	5 (6.9)
	Hispanic	0 (0.0)	0 (0.0)
	Mixed, Other	1 (1.5)	2 (2.8)
	Not specified	1 (1.5)	0 (0.0)
Treatment indication n (%)	Dementia	0 (0.0)	0 (0.0)
		QTP	OLZ
		N=66	N=72
	Schizoaffective	8 (12.1)	12 (16.7)
	Schizophrenia	58 (87.9)	60 (83.3)
	Bipolar mania	0 (0.0)	0 (0.0)
	Bipolar depression	0 (0.0)	0 (0.0)
	Bipolar mixed, etc.	0 (0.0)	0 (0.0)
	Major depressive disorder (MDD)	0 (0.0)	0 (0.0)
	Generalized anxiety disorder (GAD)	0 (0.0)	0 (0.0)
	Others	0 (0.0)	0 (0.0)
	Healthy volunteers	0 (0.0)	0 (0.0)
Modal dose (mg)	n	64	70
	Mean (SD)	503.1 (210.0)	11.5 (5.4)
Exposure (days)	n	66	72
	Median (Q1, Q3)	235.0 (72, 364)	166.0 (81, 358)
	Min to max	6 to 396	1 to 384
Reasons for discontinuation n (%)	Lack of efficacy	8 (12.1)	11 (15.3)
	Side effects	9 (13.6)	12 (16.7)
	Metabolic side effects	0 (0.0)	0 (0.0)
Weight (kg)	n	66	70
	Mean (SD)	77.0 (19.2)	79.5 (22.7)
BMI (kg/m^2)	n	66	69
	Mean (SD)	25.7 (5.7)	26.1 (7.2)

N Number of patients in treatment group. n Number of patients. NA Not applicable. OLZ Olanzapine. QTP Quetiapine. Q1 Lower quartile. Q3 Upper quartile. SD standard deviation.
Note: Percentages calculated as 100*n/N.
Studies included D1441L00002
Table ID: C2103_DEM_3B_OLZ. Program: \Demo tables\Program\MakeDemoTable.sas. User: kjwm515. Data created: 21MAY2008:12:59. Table created: 21MAY2008:12:59.

Table 208: Baseline demographics (naïve subjects, risperidone-controlled trials)

		QTP N=66	RI N=66
Sex n (%)	Male	46 (69.7)	46 (69.7)
	Female	20 (30.3)	20 (30.3)
Age (years)	n	66	66
	Mean (SD)	24.8 (5.8)	23.3 (6.2)
Race/ethnicity n (%)	White	30 (45.5)	41 (62.1)
	Black	30 (45.5)	23 (34.8)
	Asian	4 (6.1)	1 (1.5)
	Hispanic	0 (0.0)	0 (0.0)
	Mixed, Other	1 (1.5)	1 (1.5)
	Not specified	1 (1.5)	0 (0.0)
Treatment indication n (%)	Dementia	0 (0.0)	0 (0.0)
	Schizoaffective	8 (12.1)	12 (18.2)
	Schizophrenia	58 (87.9)	54 (81.8)
	Bipolar mania	0 (0.0)	0 (0.0)
	Bipolar depression	0 (0.0)	0 (0.0)
	Bipolar mixed, etc.	0 (0.0)	0 (0.0)
	Major depressive disorder (MDD)	0 (0.0)	0 (0.0)
	Generalized anxiety disorder (GAD)	0 (0.0)	0 (0.0)
	Others	0 (0.0)	0 (0.0)
	Healthy volunteers	0 (0.0)	0 (0.0)
Modal dose (mg)	n	64	64
	Mean (SD)	503.1 (210.0)	2.3 (1.0)
Exposure (days)	n	66	66
	Median (Q1, Q3)	235.0 (72, 364)	143.5 (49, 294)
	Min to max	6 to 396	7 to 447
Reasons for discontinuation n (%)	Lack of efficacy	8 (12.1)	5 (7.6)
	Side effects	9 (13.6)	6 (9.1)
	Metabolic side effects	0 (0.0)	0 (0.0)
Weight (kg)	n	66	66
	Mean (SD)	77.0 (19.2)	78.6 (20.0)
BMI (kg/m^2)	n	66	63
	Mean (SD)	25.7 (5.7)	26.5 (6.1)

N Number of patients in treatment group. n Number of patients. NA Not applicable. QTP Quetiapine. Q1 Lower quartile. Q3 Upper quartile. RI Risperidone. SD standard deviation.
Note: Percentages calculated as 100*n/N.
Studies included D1441L00002
Table ID: C2101_DEM_3B_RI. Program: \Demo tables\Program\MakeDemoTable.sas. User: kjwm515. Data created: 21MAY2008:12:59. Table created: 21MAY2008:12:59.

8.1.6 Subjects with first episode psychosis and antipsychotic naïve in controlled and uncontrolled trials

Table 209: Baseline demographics (naïve subjects, quetiapine-treated, all trials)

		QTP N=5021
Sex n (%)	Male	1927 (38.4)
	Female	3094 (61.6)
Age (years)	n	5021
	Mean (SD)	40.7 (12.5)
Race/ethnicity n (%)	White	4034 (80.3)
	Black	654 (13.0)
	Asian	127 (2.5)
	Hispanic	157 (3.1)
	Mixed, Other	48 (1.0)
	Not specified	1 (0.0)
Treatment indication n (%)	Dementia	0 (0.0)
	Schizoaffective	8 (0.2)
	Schizophrenia	118 (2.4)
		QTP N=5021
	Bipolar mania	0 (0.0)
	Bipolar depression	0 (0.0)
	Bipolar mixed, etc.	0 (0.0)
	Major depressive disorder (MDD)	2486 (49.5)
	Generalized anxiety disorder (GAD)	2339 (46.6)
	Others	0 (0.0)
	Healthy volunteers	70 (1.4)
Modal dose (mg)	n	5019
	Mean (SD)	170.1 (113.6)
Exposure (days)	n	5021
	Median (Q1, Q3)	56.0 (31, 103)
	Min to max	1 to 503
Reasons for discontinuation n (%)	Lack of efficacy	33 (0.7)
	Side effects	893 (17.8)
	Metabolic side effects	29 (0.6)
Weight (kg)	n	5014
	Mean (SD)	81.1 (21.3)
BMI (kg/m^2)	n	5010
	Mean (SD)	28.6 (7.1)

N Number of patients in treatment group. n Number of patients. NA Not applicable. NA Not applicable. QTP Quetiapine. Q1 Lower quartile. Q3 Upper quartile. SD standard deviation.
Note: Percentages calculated as 100*n/N.
Studies included D1441C00112, D1441L00002, D1448C00001, D1448C00002, D1448C00003, D1448C00004, D1448C00005, D1448C00008, D1448C00009, D1448C00010, D1448C00011, D1448C00012, D1448C00017
Table ID: C3101_DEM_3C. Program: \Demo tables\Program\MakeDemoTable.sas. User: kjwm515. Data created: 21MAY2008:12:59. Table created: 21MAY2008:12:59.

8.2 List of clinical trials included in the analyses for the metabolic submission

Table 210:List of Metabolic clinical trials

Study	Indication	Quetiapine N	Quetiapine Dose Range	Placebo N	Comparator	Comparator N	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides	Glucose	HbA1c	UA glucose	Weight	Duration Controlled	Duration Uncont
Clinical Trial Name/Number	Trial Indication	# receiving QTP	Range of doses used	# receiving Pbo (If none leave blank)	Name all comp. used	# receiving comp	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	Hemoglobin A1c. If no leave blank. If yes enter Y	Urine glucose. If no leave blank. If yes enter Y	If no leave blank. If yes enter Y	Duration controlled in weeks	Duration uncontrolled in weeks
Adult subjects in Placebo-Controlled Trials																
204636/0003	Healthy volunteers	5	25 mg	2			NF			NF	NF		NF	Y	2 weeks	
204636/0008	Schizophrenia	low dose = 94 high dose = 96	low dose = up to 250 high dose = 75-750 mg	96			NF			NF	NF			Y	6 weeks	
50771U0004	Schizophrenia	8	25 to 250	4			NF			NF	NF			Y	3 weeks	
50771U0006	Schizophrenia	54	75-750 mg	55			NF			NF	NF			Y	6 weeks	
50771U0013	Chronic/Sub-chronic Schizophrenia	258	75-750		Haloperidol	52					NF			Y		6 weeks
50771U0041	Schizophrenia	448	50-800 mg	84			NF	NF	NF	NF	F			Y	6 weeks	
50771U0104	bi-polar	101	50-400mg	100	Haloperidol	98					NF			Y	12 weeks	
50771U0106	Bi-polar	72	50-800 mg	35	Lithium	67					NF			Y	12 weeks	
5077US0049	Bipolar Depression	342	25 mg - 800 mg	169			F	F	F	F	F			Y	8 weeks	
D1444C00132	acute schizophrenia	IR: 123 XR: 347	IR: 400 XR: 400-800	118			F	F	F	F	F	Y	Y	Y	6 weeks	
D1444C00133	acute schizophrenia	IR: 116 XR: 342	IR: 800 XR: 400-800	117			F	F	F	F	F	Y	Y	Y	6 weeks	
D1447C00001	Bipolar Depression	518 in acute phase, 301(from the acute phase) in continuation phase	300-600 mg	129 in acute phase, 165 in continuation phase	Lithium	136 in acute phase, 74 in continuation phase	F	F	F	F	F	Y	Y	Y	8 weeks - Acute Phase; 26-52 weeks - Continuation Phase	
D1447C00134	Bipolar disorder	487 in acute phase, 237(from the acute phase) in continuation phase	50-600 mg	124 in acute phase, 129 (NOT from the placebo group in acute phase) in continuation phase	Paroxetine	121in acute phase	NF	NF	NF	NF	F	Y	Y	Y	49 weeks	3 weeks
D1447C00135	Bipolar disorder	339	50-600 mg	167			NF	NF	NF	NF	F	Y		Y	7 weeks	1 weeks
D1448C0001	MDD	535	50, 150 or 300mg	181			F	F	F	F	F	Y	Y	Y	6 weeks	
D1448C0002	MDD	304	150 or 300 mg	157	Duloxetine	148	F	F	F	F	F	Y	Y	Y	6 weeks	
D1448C0003	MDD	152	150 or 300 mg	156			F	F	F	F	F	Y	Y	Y	8 Weeks	
D1448C0004	MDD	157	150 or 300 mg	155	Escitalopram (10 mg)	156	F	F	F	F	F	Y	Y	Y	8 Weeks	
D1448C00008	Healthy volunteers	57	150 mg (SR)				NF	NF	NF	NF	F		Y	Y	2 weeks	0
D1448C00009	GAD	709	50, 150 or 300mg	234			F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00010	GAD		150 or 300 mg		Escitalopram (10 mg)		F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00011	GAD	438	50, 150 mg	217	Paroxetine 20 mg/day	215	F	F	F	F	F	Y	Y	Y	9 weeks	
D144CC00002	Acute Bipolar Depression	139	XR: 300	138			F	F	F	F	F	Y		Y	8 weeks	
D144CC00004	Acute Bipolar Mania	151	XR: 400-800	160			F	F	F	F	F	Y		Y	3 weeks	
Adult subject in Comparator-Controlled Trials																
204699/0007	Schizophrenia	101	75 mg-750 mg		Chlorpromazine	100					NF			Y	6 weeks	
50771U0031	Treatment-resistant schizophrenia	18 subjects	5 segments: A)Placebo for 1 wk; B) 40 mg/day haloperidol for 4 wks; C) Placebo single blind for 1 wk; D) double-blind fixed dose 600-1200 mg/day for 6 wk; E) double-blind flexible dose; 75-1500 mg/day for 4 wks		Chloropromazine		NF				NF			Y	16 weeks	
50771U0054	Schizophrenia	117	50-600 mg		Chlorpromazine	119								Y	8 weeks	2 weeks
50771U0013	Chronic/Sub-chronic Schizophrenia	258	75-750		Haloperidol	52					NF			Y		6 weeks
50771U0014	Chronic/Sub-chronic Schizophrenia	221	50-800		Haloperidol	227								Y		6 weeks
50771U0015	Chronic/Sub-chronic Schizophrenia	260	75-600		Haloperidol	41					NF			Y		up to 52 weeks
50771U0050	Schizophrenia	193	50-600 mg		Haloperidol	188								Y	51 weeks	1 week
50771U0052	Schizophrenia	143	50-600 mg		Haloperidol	145								Y	7 weeks	1 week
50771U0104	bi-polar	101	50-400mg	100	Haloperidol	98					NF			Y	12 weeks	
H-15-31	Schizophrenia	100	50 -600 mg	97	Haloperidol 1.5 -18 mg/day		NF							Y	8 weeks	

Study	Indication	Quetiapine N	Quetiapine Dose Range	Placebo N	Comparator	Comparator N	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides	Glucose	HbA1c	UA glucose	Weight	Duration Controlled	Duration Uncont
Clinical Trial Name/Number	Trial Indication	# receiving QTP	Range of doses used	# receiving Pbo (if none leave blank)	Name all comp. used	# receiving comp	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	Hemoglobin A1c. If no leave blank. If yes enter Y	Urine glucose. If no leave blank. If yes enter Y	If no leave blank. If yes enter Y	Duration controlled in weeks	Duration uncontrolled in weeks
D1441C00125	schizophrenia (Glucose-Tolerance)	168	400-800		Olanzapine Risperidone	169 173	NF	NF	NF	NF	F	Y	Y	Y	24 weeks	
D1441L00002	First Episode Psychosis	134	100-800 mg		Olanzapine, Risperidone	133 (Olanzapine), 133 (Risperidone)	F	F	F	F	F	Y		Y	up to 52 weeks	
5077IL/0053	Schizophrenia	200	50-800 mg		Risperidone	208								Y	9 weeks	1 week
5077US/0004	Schizophrenia or other selected psychotic disorders	550	25 mg - 200 mg		Risperidone	173								Y	16 weeks	
5077US/0043	Schizophrenia	338	50 mg - 800 mg		Risperidone	334	F	F	F	F	F			Y	8 weeks	
All Adult quetiapine-treated subjects, controlled and uncontrolled																
204636/0003	Healthy volunteers	5	25 mg	2			NF			NF	NF		NF	Y	2 weeks	
204636/0006	Schizophrenia	low dose = 94 high dose = 96	low dose = up to 250 high dose = 75-750 mg	96			NF			NF	NF			Y	6 weeks	
5077IL/0004	Schizophrenia	8	25 to 250	4			NF			NF	NF			Y	3 weeks	
5077IL/0005	Schizophrenia, BP with manic features, Delusional disorder, brief reactive psychosis, Schizophreniform, Schizoaffective, Induced Psychotic disorder, psychotic disorder NOS	118	50 to 500 mg				NF			NF				Y		4 weeks
5077IL/0006	Schizophrenia	54	75-750 mg	55			NF			NF	NF			Y	6 weeks	
5077IL/0008	Schizophrenia	13	50 - 450 mg								NF					2 weeks
5077IL/0012	Chronic/Sub-chronic Schizophrenia	618	50-450											Y		6 weeks
5077IL/0016	Schizophrenia	41	50-750								F			Y		2.5 weeks
5077IL/0020	schizophrenia, schizoaffective disorder, bipolar disorder	12 men (single center)	25-250 mg		Two 1-g doses on Days 10 and 21						F			Y		1.5 weeks
5077IL/0024a	schizophrenia, schizoaffective disorder, bipolar disorder	8 men (single center)	25-250 mg								F			Y		2.5 weeks
5077IL/0024b	schizophrenia, schizoaffective disorder, bipolar disorder	8 men (single center)	25-250 mg								F			Y		2.5 weeks
5077IL/0027	schizophrenia, schizoaffective disorder, bipolar disorder	10 subjects	25-250 mg	25 mg TID for Days 13-25							F			Y		2 weeks
5077IL/0029	Schizophrenia	8 subjects	25-150 mg											Y		4 weeks
5077IL/0033	Subchronic or chronic schizophrenia	10 male subjects	50-750 mg											Y		7 weeks
5077IL/0035	Subchronic or chronic schizophrenia, schizoaffective disorder, bipolar disorder	32 male subjects (11 withdrew)	25-200 mg								F			Y		3 weeks
5077IL/0036	schizophrenia, schizoaffective disorder, bipolar disorder	14 male subjects	25-300 mg											Y		3.5 weeks
5077IL/0037	schizophrenia, schizoaffective disorder, bipolar disorder	13	50-300 mg											Y		3 weeks
5077IL/0041	Schizophrenia	448	50-800 mg	84			NF	NF	NF	NF	F			Y	6 weeks	
5077IL/0044	schizophrenia or schizoaffective disorder	33	50-400 mg								NF			Y		2 weeks

Study	Indication	Quetiapine N	Quetiapine Dose Range	Placebo N	Comparator	Comparator N	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides	Glucose	HbA1c	UA glucose	Weight	Duration Controlled	Duration Uncont
Clinical Trial Name/Number	Trial Indication	# receiving QTP	Range of doses used	# receiving Pbo (if none leave blank)	Name all comp. used	# receiving comp	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	Hemoglobin A1c. If no leave blank. If yes enter Y	Urine glucose. If no leave blank. If yes enter Y	If no leave blank. If yes enter Y	Duration controlled in weeks	Duration uncontrolled in weeks
5077IL/0045	Schizophrenia, Schizoaffective, Bipolar Disorder	11	25-750 mg								NF			Y		3 weeks
5077IL/0047	Schizophrenia, Schizoaffective, Bipolar Disorder	13	25-150 mg								NF			Y		3 weeks
5077IL/0050	Schizophrenia	193	50-600 mg		Haloperidol	188								Y	51 weeks	1 week
5077IL/0058	schizophrenia or schizoaffective disorder	227	50-800 mg		Usual care	218								Y		53 weeks
5077IL/0061	schizophrenia, schizoaffective disorder or bipolar disorder	50 in drug-switching phase (period A), 30 in drug withdrawal phase (period C)	50-600 mg	26							NF		Y	Y		16 weeks
5077IL/0062	psychosis with parkinsonism	29	25-800 mg											Y		24 weeks
5077IL/0065	schizophrenia, schizoaffective disorder or bipolar disorder	39	50-600 mg	20 (Quetiapine+Placebo)	Haloperidol	19 (Quetiapine+Haloperidol)							Y	Y		2 weeks
5077IL/0066	schizophrenia, schizoaffective disorder or bipolar disorder	15	50-800 mg											Y		5 weeks
5077IL/0072	bi-polar/schizophrenia/schizo affective	25	25-100 mg											Y		2 weeks
5077IL/0084	healthy volunteers	33	25-150mg													4 weeks
5077IL/0056	schizophrenia	12	50-800mg											y		3 weeks
5077IL/0093	schizophrenia, bi-polar, schizoaffective	13	150-750mg											Y		10 days
5077IL/0097	bi-polar/schizophrenia/schizo affective	34	150-300mg											Y		1 week
5077IL/0107	schizophrenia	509	300-750mg											Y		12 weeks
5077IL/0109	bi-polar/schizophrenia/schizo affective	35	150-800 mg											Y		2 weeks
5077IL/0118	Schizaffective disorder and schizophrenia	30	SR - 50 mg - 400 mg IR - 300 mg											Y		2 weeks
D1448C00009	GAD	708	50, 150 or 300mg	234			F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00010	GAD		150 or 300 mg		Escitalopram (10 mg)		F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00011	GAD	438	50, 150 mg	217	Paroxetine 20 mg/day	215	F	F	F	F	F	Y	Y	Y	9 weeks	
D144CC00002	Acute Bipolar Depression	139	XR: 300	138			F	F	F	F	F	Y		Y	8 weeks	
D144CC00004	Acute Bipolar Mania	151	XR: 400-800	160			F	F	F	F	F	Y		Y	3 weeks	
20469900007	Schizophrenia	101	75 mg-750 mg		Chlorpromazine	100					NF			Y	6 weeks	
5077IL/0031	Treatment-resistant schizophrenia	18 subjects	5 segments: A)Placebo for 1 wk; B) 40 mg/day haloperidol for 4 wks; C) Placebo single blind for 1 wk; D) double-blind fixed dose 600-1200 mg/day for 6 wk; E) double-blind flexible dose; 75-1600 mg/day for 4 wks		Chlorpromazine		NF				NF			Y	16 weeks	
5077IL/0054	Schizophrenia	117	50-600 mg		Chlorpromazine	119								Y	8 weeks	2 weeks
5077IL/0013	Chronic/Sub-chronic Schizophrenia	258	75-750		Haloperidol	52					NF			Y		6 weeks
5077IL/0014	Chronic/Sub-chronic Schizophrenia	221	50-800		Haloperidol	227								Y		6 weeks
5077IL/0015	Chronic/Sub-chronic Schizophrenia	260	75-600		Haloperidol	41					NF			Y		up to 52 weeks
5077IL/0050	Schizophrenia	193	50-600 mg		Haloperidol	188								Y	51 weeks	1 week
5077IL/0052	Schizophrenia	143	50-600 mg		Haloperidol	145								Y	7 weeks	1 week
5077IL/0104	bi-polar	101	50-400mg	100	Haloperidol	98					NF			Y	12 weeks	
H-15-31	Schizophrenia	100	50 -600 mg	97	Haloperidol 1.5 -18 mg/day		NF							Y	8 weeks	
D1441C00125	schizophrenia (Glucose-Tolerance)	168	400-800		Olanzipine Risperidone	169 173	NF	NF	NF	NF	F	Y	Y	Y	24 weeks	

Study	Indication	Quetiapine N	Quetiapine Dose Range	Placebo N	Comparator	Comparator N	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides	Glucose	HbA1c	UA glucose	Weight	Duration Controlled	Duration Uncont
Clinical Trial Name/Number	Trial Indication	# receiving QTP	Range of doses used	# receiving Pbo (if none leave blank)	Name all comp. used	# receiving comp	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	Hemoglobin A1c. If no leave blank. If yes enter Y	Urine glucose. If no leave blank. If yes enter Y	If no leave blank. If yes enter Y	Duration controlled in weeks	Duration uncontrolled in weeks
D1441L00002	First Episode Psychosis	134	100-800 mg		Olanzapine, Risperidone	133 (Olanzapine) 133 (Risperidone)	F	F	F	F	F	Y		Y	up to 52 weeks	
5077IL/0053	Schizophrenia	200	50-600 mg		Risperidone	208								Y	9 weeks	1 week
5077US/0004	Schizophrenia or other selected psychotic disorders	550	25 mg - 200 mg		Risperidone	173								Y	16 weeks	
5077US/0043	Schizophrenia	338	50 mg - 800 mg		Risperidone	334	F	F	F	F	F			Y	8 weeks	
5077US/0049	Bipolar Depression	342	25 mg - 800 mg	169			F	F	F	F	F			Y	8 weeks	
D1441C00023	Schizophrenia or Schizoaffective disorder	165	100-1200 mg				F	F	F	F	F	Y	Y	Y	9.5 weeks	3.5 weeks
D1441C00130	PK(Schizophrenia,Schizoaffective disorder, Bipolar Mania)	29	100-800								NF		Y			5.2 weeks
D1444C00001	PK(Schizophrenia,Schizoaffective disorder, Bipolar Mania)	18	IR: 200-400 SR-F: 400 SR-S: 400 SR-T: 50, 400								F		Y	Y		3 weeks
D1444C00004	schizophrenia	327 (Open-label stabilization) 94 (Randomized)	XR: 400-800	103			F	F	F	F	F	Y	Y	Y		52 weeks
D1444C00132	acute schizophrenia	IR: 123 XR: 347	IR: 400 XR: 400-800	118			F	F	F	F	F	Y	Y	Y	6 weeks	
D1444C00133	acute schizophrenia	IR: 116 XR: 342	IR: 800 XR: 400-800	117			F	F	F	F	F	Y	Y	Y	6 weeks	
D1444C00145	Schizophrenia Schizoaffective disorder	52	XR: 300-800								F	Y		Y		1 week
D1444C00148	schizophrenia	IR(4 wk. OL run-in): 497 IR: 166 SR: 331	IR: 400-800 XR: 400-800				F	F	F	F	F	Y	Y	Y	6 weeks	4 weeks
D1444C00147	schizophrenia	XR:477	XR: 400-800				F	F	F	F	F	Y	Y	Y		12 weeks
D1447C00001	Bipolar Depression	518 in acute phase, 301(from the acute phase) in continuation phase	300-600 mg	129 in acute phase, 165 in continuation phase	Lithium	136 in acute phase, 74 in continuation phase	F	F	F	F	F	Y	Y	Y	8 weeks - Acute Phase; 26-52 weeks - Continuation Phase	
D1444C00001	PK(Schizophrenia,Schizoaffective disorder, Bipolar Mania)	18	IR: 200-400 SR-F: 400 SR-S: 400 SR-T: 50, 400								F		Y	Y		3 weeks
D1447C00134	Bipolar disorder	487 in acute phase, 237(from the acute phase) in continuation phase	50-600 mg	124 in acute phase, 129 (NOT from the placebo group in acute phase) in continuation phase	Paroxetine	121in acute phase	NF	NF	NF	NF	F	Y	Y	Y	48 weeks	3 weeks
D1447C00135	Bipolar disorder	339	50-600 mg	167			NF	NF	NF	NF	F	Y		Y	7 weeks	1 weeks
D1447C00144	Bipolar Maintenance	404	300-800 mg	404	Lithium	364	F	F	F	F	F	Y	Y	Y	Randomized - up to 104	OL - up to 24 wee
D1448C00001	MDD	536	50, 150 or 300mg	181			F	F	F	F	F	Y	Y	Y	6 weeks	
D1448C00002	MDD	304	150 or 300 mg	157	Duloxetine	149	F	F	F	F	F	Y	Y	Y	6 weeks	
D1448C00003	MDD	162	150 or 300 mg	166			F	F	F	F	F	Y	Y	Y	8 Weeks	
D1448C00004	MDD	157	150 or 300 mg	155	Escitalopram (10 mg)	156	F	F	F	F	F	Y	Y	Y	8 Weeks	
D1448C00008	Healthy volunteers	57	150 mg (SR)				NF	NF	NF	NF	F		Y	Y	2 weeks	0
D1448C00006	MDD	Open label only = 1078 Randomized QTP = 391	50, 150 & 300mg	386			F	F	F	F	F	Y	Y	Y		up to 78 weeks
D1448C00009	GAD	709	50, 150 or 300mg	234			F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00010	GAD		150 or 300 mg		Escitalopram (10 mg)		F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00011	GAD	438	50, 150 mg	217	Paroxetine 20 mg/day	219	F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00012	GAD	Open label only = 792 Randomized QTP = 216	50, 150 & 300mg	216			F	F	F	F	F	Y	Y	Y	12-18 Weeks	4 -8 Weeks
D1448C00017	Healthy volunteers	10	50-300 mg (XR)				NF	NF	NF	NF	F		Y	Y		1 week

Pediatric and Adolescent Subjects in Placebo-Controlled Trials																
D1441C00112	Pediatric Schizophrenia	147	400 or 800 mg	75			F	F	F	F	F	F		Y	6 weeks	
D1441C00149	Pediatric Bipolar Mania	193	400-600	91			F	F	F	F	F	Y	Y	Y	3 weeks	

Study	Indication	Quetiapine N	Quetiapine Dose Range	Placebo N	Comparator	Comparator N	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides	Glucose	HbA1c	UA glucose	Weight	Duration Controlled	Duration Uncont
Clinical Trial Name/Number	Trial Indication	# receiving QTP	Range of doses used	# receiving Pbo (if none leave blank)	Name all comp. used	# receiving comp	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	Hemoglobin A1c. If no leave blank. If yes enter Y	Urine glucose. If no leave blank. If yes enter Y	If no leave blank. If yes enter Y	Duration controlled in weeks	Duration uncontrolled in weeks
Pediatric and Adolescent Subjects in Comparator Trials	none															
All Pediatric and Adolescent Quetiapine-treated Subjects Controlled and Uncontrolled																
D1441C00150	Schizophrenia or Bipolar Mania	(Open label) 380	200-800				F	F	F	F	F	Y	Y	Y		26 weeks
20469/0007	Schizophrenia	101	75 mg-750 mg		Chlorpromazine	100					NF			Y	6 weeks	
5077IU/0038	schizophrenia, schizophreniform disorder, schizoaffective disorder, major depressive disorder, bipolar I and II disorder	10 subjects	50-800 mg											Y		3 weeks
5077IU/0107	schizophrenia	509	300-750mg											Y		12 weeks
D1441C00026	Schizophrenia	38	300 mg - 750 mg		Risperidone	34					F			Y		2 weeks
D1441C00112	Pediatric Schizophrenia	147	400 or 800 mg	75			F	F	F	F	F	F		Y	6 weeks	
D1441C00149	Pediatric Bipolar Mania	193	400-600	91			F	F	F	F	F	Y	Y	Y	3 weeks	
D1441L00002	First Episode Psychosis	134	100-800 mg		Olanzapine, Risperidone	133 (Olanzapine), 133 (Risperidone)	F	F	F	F	F	Y		Y	up to 52 weeks	
Subjects with first episode psychosis and antipsychotic-naive in placebo controlled trials																
D1441C00112	Pediatric Schizophrenia	147	400 or 800 mg	75			F	F	F	F	F	F		Y	6 weeks	
D1448C0001	MDD	536	50, 150 or 300mg	181			F	F	F	F	F	Y	Y	Y	6 weeks	
D1448C0002	MDD	304	150 or 300 mg	157	Duloxetine	149	F	F	F	F	F	Y	Y	Y	6 weeks	
D1448C0003	MDD	152	150 or 300 mg	155			F	F	F	F	F	Y	Y	Y	9 Weeks	
D1448C0004	MDD	157	150 or 300 mg	155	Escitalopram (10 mg)	156	F	F	F	F	F	Y	Y	Y	9 Weeks	
D1448C00008	Healthy volunteers	57	150 mg (SR)				NF	NF	NF	NF	F		Y	Y	2 weeks	0
D1448C00009	GAD	708	50, 150 or 300mg	234			F	F	F	F	F	Y	Y	Y	9 weeks	
Subjects with first episode psychosis and antipsychotic-naive in comparator controlled trials																
D1441L00002	First Episode Psychosis	134	100-800 mg		Olanzapine, Risperidone	133 (Olanzapine), 133 (Risperidone)	F	F	F	F	F	Y		Y	up to 52 weeks	
Subjects with first episode psychosis and antipsychotic-naive in controlled and uncontrolled trials																
D1441C00112	Pediatric Schizophrenia	147	400 or 800 mg	75			F	F	F	F	F	F		Y	6 weeks	
D1441L00002	First Episode Psychosis	134	100-800 mg		Olanzapine, Risperidone	133 (Olanzapine), 133 (Risperidone)	F	F	F	F	F	Y		Y	up to 52 weeks	
D1448C0001	MDD	536	50, 150 or 300mg	181			F	F	F	F	F	Y	Y	Y	6 weeks	
D1448C0002	MDD	304	150 or 300 mg	157	Duloxetine	149	F	F	F	F	F	Y	Y	Y	6 weeks	
D1448C0003	MDD	152	150 or 300 mg	155			F	F	F	F	F	Y	Y	Y	9 Weeks	
D1448C0004	MDD	157	150 or 300 mg	155	Escitalopram (10 mg)	156	F	F	F	F	F	Y	Y	Y	9 Weeks	

Study	Indication	Quetiapine N	Quetiapine Dose Range	Placebo N	Comparator	Comparator N	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides	Glucose	HbA1c	UA glucose	Weight	Duration Controlled	Duration Uncont
Clinical Trial Name/Number	Trial Indication	# receiving QTP	Range of doses used	# receiving Pbo (If none leave blank)	Name all comp. used	# receiving comp	If no leave blank, R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	If no leave blank. R (randomized) NF (non-fasting) F (fasting)	Hemoglobin A1c. If no leave blank. If yes enter Y	Urine glucose. If no leave blank. If yes enter Y	If no leave blank. If yes enter Y	Duration controlled in weeks	Duration uncontrolled in weeks
D1448C00005	MDD	Open label only = 1078 Randomized QTP = 391	50, 150 & 300mg	385			F	F	F	F	F	Y	Y	Y		up to 78 weeks
D1448C00008	Healthy volunteers	57	150 mg (SR)				NF	NF	NF	NF	F		Y	Y	2 weeks	0
D1448C00009	GAD	708	50, 150 or 300mg	234			F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00010	GAD		150 or 300 mg		Escitalopram (10 mg)		F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00011	GAD	438	50, 150 mg	217	Paroxetine 20 mg/day	215	F	F	F	F	F	Y	Y	Y	9 weeks	
D1448C00012	GAD	Open label only = 792 Randomized QTP = 216	50, 150 & 300mg	216			F	F	F	F	F	Y	Y	Y	12-18 Weeks	4 -8 Weeks
D1448C00017	Healthy volunteers	10	50-300 mg (XR)				NF	NF	NF	NF	F		Y	Y		1 week
5077IL/0051	Schizophrenia	450	50-800 mg											Y		up to 156 weeks

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/s/

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