AstraZeneca

Clinical Study Report

Drug substance: Quetiapine fumarate

Study code: 5077IL/0041

Date: 02 March 2006

A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Sustained-release Formulation Quetiapine Fumarate (SEROQUEL™) and Placebo in the Treatment of Patients With Schizophrenia

Study dates: First patient enrolled: 7 March 2001
Last patient completed: 16 May 2002

Phase of development: Phase III

International coordinating investigator: None assigned

Sponsor's Responsible Medical Officer: Martin Brecher, MD, DMSc

This study was performed in compliance with Good Clinical Practice.

Drug product: Drug substance: Study code: Date:	SEROQUEL SR™ Quetiapine fumarate 5077IL/0041 02 March 2006	**SYNOPSIS**	

A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Sustained-release Formulation Quetiapine Fumarate (SEROQUEL™) and Placebo in the Treatment of Patients With Schizophrenia

International coordinating investigator

None assigned.

Study centers

This study was conducted at 49 centers in the United States (45) and Canada (4).

Publications

None at report time.

Study dates		**Phase of development**
First patient enrolled	7 March 2001	Phase III (Therapeutic confirmatory)
Last patient completed	16 May 2002	

Objectives

Primary: To demonstrate superior efficacy of quetiapine sustained-release (SR) tablets compared with placebo in the treatment of patients with schizophrenia.

Secondary: To assess the tolerability and safety of quetiapine SR tablets administered once daily as compared with placebo in patients with schizophrenia; to assess the tolerability and safety of quetiapine SR therapy initiated at a dose of 300 mg; and to assess the similarity of the safety and efficacy profiles of quetiapine SR tablets and marketed quetiapine immediate-release (IR) tablets.

Study design

This 6-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comprised a screening visit and a 42-day treatment period, which began within 7 days of screening.

All patients were hospitalized for the first 10 days of treatment. After baseline assessments on Day 1, patients were assigned to 1 of 6 possible treatments: quetiapine SR at 300, 600, or 800 mg daily, quetiapine IR at 300 or 600 mg daily (in 2 divided doses), or placebo. Prohibited psychoactive medications were discontinued at least 48 hours before baseline assessments, with depot and long-acting antipsychotics discontinued at least 1 dosing interval before baseline assessments. After a patient started treatment, efficacy and safety assessments were made on Days 4, 8 (Week 1), 15 (Week 2), 28 (Week 4), and 42 (Week 6) or last visit.

Target patient population and sample size

Patients, aged 18 to 65 years and hospitalized for ≤1 month with symptoms of schizophrenia,[1] were eligible for enrollment if they had a Positive and Negative Syndrome Scale (PANSS) total score of ≥60 on screening and Day 1, a score of ≥4 on at least one of the predesignated PANSS individual items (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution) on Day 1, and a score of ≥4 on the Clinical Global Impression (CGI) Severity of Illness item, with evidence of worsening in the 3 weeks before enrollment. Outpatients who otherwise qualified were eligible for enrollment as long as they agreed to be hospitalized for the first 10 days of treatment.

Eighty evaluable patients per treatment group were sufficient for 90% power over all 3 quetiapine SR treatment groups (adjusted for multiple comparisons), assuming a mean (SD) difference of 15.5 (25.8) points between active treatment and placebo for change from baseline PANSS total score at Day 42.

Investigational product and control groups: dosage, mode of administration and batch numbers

Patients assigned to quetiapine SR began treatment at 300 mg/day on Day 1; patients assigned to higher doses had their doses increased according to the provided dose-administration scheme to reach either 600 mg on Day 5 or 800 mg on Day 8. For quetiapine SR doses, 200- and 300-mg oral tablets were provided (Batch/Formulation Nos. 9077C/F12840 and 9052C/F12527, respectively). Patients assigned to quetiapine IR began treatment at 50 mg/day on Day 1; daily doses were increased according to the provided dose-administration scheme (which matched current labeling instructions) to reach either 300 mg/day on Day 4 or 600 mg/day on Day 6. For quetiapine IR doses, 25-, 100-, and 200-mg oral tablets (Batch/Formulation Nos. 7501B/F12864, 6081C/F12689, and 6082C and 6083C/F12690, respectively) were provided. SR-treated patients took active tablets in the morning and placebo tablets in the evening; IR-treated patients took active tablets in the morning and evening, with placebo tablets per packaging configuration. Placebo tablets were available to match the 200- and 300-mg quetiapine SR tablets (Batch/Formulation Nos. ST73043-001-FA03/F12422 and ST73042-001-FB02 to FB06/F12416) and the 25-, 100- and 200-mg quetiapine IR tablets (Batch/Formulation Nos. 8021B/F12636, 8022B/F12637, and 1012C and 7552F/F12638).

[1] In accord with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revised (DSM-IV 1994), for 1 of the 4 accepted subtypes of schizophrenia: catatonic, disorganized, paranoid, or undifferentiated.

Duration of treatment

Study medication was administered up to a maximum of 42 days, less if patients withdrew from the study early.

Criteria for evaluation: efficacy variables

- Primary variable: change in PANSS total score from baseline to Day 42

- Secondary variables: PANSS total score; Positive, Negative, and General Psychopathology subscale scores; activation factor score; and depression item score at each visit and changes from baseline at each postbaseline visit; change in PANSS total score from baseline to Day 4 (data for quetiapine-treatment groups pooled across doses within formulation); PANSS response at Day 42, ie, ≥30% decrease in PANSS total score from baseline (and alternative PANSS response at the ≥40% and ≥50% levels); CGI Severity of Illness score and change from baseline at each visit; and CGI Global Improvement score at each visit after baseline

Criteria for evaluation: safety variables

- Overall adverse events (AEs), serious adverse events (SAEs), and AEs leading to withdrawal; special-interest AEs (and onset), including somnolence, tachycardia, and postural hypotension (and related AEs), dizziness, and syncope; special safety-area AEs, including AEs related to EPS, QT prolongation, diabetes mellitus, neutropenia/agranulocytosis, and suicidality; clinical laboratory test results, vital signs and electrocardiogram (ECG) results, and weight and body mass index—changes from baseline and clinically important results; metabolic syndrome risk factors; Simpson-Angus Scale and Abnormal Involuntary Movement Scale (AIMS) total scores per visit and changes from baseline; Barnes Akathisia Rating Scale Clinical Global Assessment score; and use of anticholinergic medications

Statistical methods

All variables were summarized using descriptive statistics, as appropriate. The analysis establishing the primary objective tested for differences between each of the SR groups versus the placebo group in change from baseline in PANSS total score, using an analysis of covariance (ANCOVA) that included terms for center, treatment, and baseline score. The Hochberg (1988) method was used to adjust for multiplicity in testing quetiapine SR treatments to ensure that the overall statistical significance of the trial was 0.05. P-values were calculated as pairwise differences between least-squares means of groups, and 95% confidence intervals (95% CIs) for each difference were constructed. Statistical tests for secondary efficacy endpoints and testing of either quetiapine IR group were not adjusted for multiplicity. Other secondary variables were analyzed with the same ANCOVA methods used in the primary analysis (without correcting for multiplicity). Categorical endpoints such as PANSS response or CGI Global Improvement scores were analyzed using the Cochran-Mantel-Haenszel chi-square test. All statistical analyses used last-observation-carried-forward (LOCF) values for patients who withdrew early or had missing data.

Patient population

The randomized study population comprised 532 patients enrolled from 49 centers. Treatment-group sizes were as follows: placebo, n=84; quetiapine SR 300 mg, n=91; quetiapine SR 600 mg, n=92; quetiapine SR 800 mg, n=89; quetiapine IR 300 mg, n=90; and quetiapine IR 600 mg, n=86. At least 50% of patients in each treatment group withdrew early (placebo, 66%; quetiapine SR 300 mg, 62%; quetiapine SR 600 mg, 57%; quetiapine SR 800 mg, 51%; quetiapine IR 300 mg, 54%; and quetiapine IR 600 mg, 62%). Early withdrawal was most commonly due to lack of efficacy or withdrawn consent and not AEs. In all, 222 patients completed treatment (placebo, 35%; quetiapine SR 300 mg, n=39%; quetiapine SR 600 mg, 44%; quetiapine SR 800 mg, 49%; quetiapine IR 300 mg, 46%; and quetiapine IR 600 mg, 38%). All 532 enrolled patients were included in the safety population, and 498 were included in the primary analysis data set (modified intent to treat [MITT]).

The study population comprised primarily white and black patients (49.2% and 37.2%, respectively); Hispanic patients and patients of other races comprised 11.1% and 2.4%, respectively. Mean age was 39 years (range: 18 to 64), with approximately 50% of the population between 18 and 39 years old and 50% between 40 and 65 years old. Mean weight and BMI were 87.2 kg and 29.4 kg/m^2, respectively, with similar proportions of patients having BMI values in each of the following ranges: 18.5 to <25 kg/m^2 (30.6%), 25 to <30 kg/m^2 (31.9%), and 30 to <40 kg/m^2 (27.2%). Median age at first treatment for illness was 22 years. Approximately 91% of patients entered the study with previous positive responses to antipsychotic medications (full response, 29%; partial response, 62%). Overall, treatment groups were similar with respect to demographic characteristics and baseline disease characteristics, with the majority of patients per treatment group having paranoid schizophrenia (75.6% to 88.0%).

Efficacy results

Table S1 Overview of efficacy results at Day 42 (LOCF, MITT population)

Summary statistic	Placebo (n=78)	QTP SR 300 mg (n=83)	QTP SR 600 mg (n=87)	QTP SR 800 mg (n=85)	QTP IR 300 mg (n=85)	QTP IR 600 mg (n=80)
PANSS total score, LSmean change from BL[a]	-5.19	-5.01	-13.01[b]	-11.17	-9.42	-6.97
PANSS response, % patients with ≥30% improvement[c]	14.1	12.0	24.1	23.5	18.8	13.8
CGI Severity of Illness score, LSmean change from BL	–0.42	–0.50	–0.66	–0.68	–0.59	–0.51
CGI Global Improvement, % patients with improvement[d]	48.7	50.6	64.4	55.3	57.6	53.8
% much/very much improved	19.2	30.1	33.3	35.3[e]	42.3[e]	26.3

[a] Mean baseline PANSS total scores across treatment groups were 91.1, 91.5, 92.4, 89.0, 89.5, and 88.6, respectively.
[b] Significantly different from placebo (analysis of covariance adjusted for multiplicity, p=0.033).
[c] In PANSS total score.
[d] Includes patients improved, much improved and minimally improved per CGI Global Improvement rating.
[e] Significantly different from placebo (Cochran-Mantel-Haenszel analysis, p=0.015 for SR 800 mg and 0.005 for IR 300 mg).

BL Baseline. CGI Clinical Global Impression. LOCF Last observation carried forward. LSmean Least-squares mean. MITT Modified intent-to-treat. PANSS Positive and Negative Syndrome Scale.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.

The primary efficacy objective was met for the quetiapine SR 600-mg dose. At the final visit, the estimated mean difference between SR 600 mg and placebo (–7.82) for change from baseline in PANSS total score (primary efficacy variable) was significant in favor of SR 600 mg (p=0.033, ANCOVA, adjusted for multiplicity). In the same ANCOVA, the estimated mean differences between SR 300 mg and placebo and between SR 800 mg and placebo were not statistically significant; however, a numerical advantage in symptom improvement was seen with SR 800 mg compared with placebo. In secondary analyses, a significant difference between quetiapine SR 600 mg and placebo was seen as early as Day 15 and was sustained from Day 28 through to Day 42 (LOCF).

Treatment with quetiapine SR 600 and SR 800 mg provided meaningful clinical improvement (≥30% decrease in PANSS total score) in numerically greater proportions of patients (24% each), compared with placebo (14%); however, differences were not statistically significant. On other secondary endpoints, quetiapine SR 600 and SR 800 mg also provided consistent numerical advantages, compared with placebo, but the only statistically significant difference was seen between SR 800 mg and placebo for proportions of patients much or very much improved per CGI Global Improvement score (p=0.015, Cochran-Mantel-Haenszel analysis).

The effects of quetiapine IR 300 and IR 600 mg on the endpoints selected to address the secondary efficacy objective[2] were not consistently different from those of placebo, although a statistically significant difference was seen for the proportion of patients much or very much improved per CGI Global Improvement at the IR 300-mg dose. Conclusions relative to the study's secondary efficacy objective were as follows: In reducing the symptoms of schizophrenia, quetiapine SR 600 mg achieved efficacy versus placebo, while quetiapine IR 600 mg—a dose with known efficacy in the treatment of schizophrenia—did not; neither quetiapine formulation differed from placebo at the 300-mg dose.

Safety results

Quetiapine SR was generally safe and well tolerated across the dose range of 300 to 800 mg. No deaths were reported and few SAEs occurred (Table S2).

Table S2 Number (%) of patients with AEs in any category (safety population)

Category	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP SR Total	QTP IR 300 mg	QTP IR 600 mg	QTP IR Total
	(n=84)	(n=91)	(n=92)	(n=89)	(n=272)	(n=90)	(n=86)	(n=176)
Patients, number (%)[a]								
With any AE	64 (76.2)	78 (85.7)	83 (90.2)	75 (84.3)	236 (86.8)	75 (83.3)	73 (84.9)	148 (84.1)
With SAEs	3 (3.6)	2 (2.2)	4 (4.3)	0	6 (2.2)	1 (1.1)	2 (2.3)	3 (1.7)
SAEs leading to death	0	0	0	0	0	0	0	0
With DAEs	8 (9.5)	5 (5.5)	9 (9.8)	1 (1.1)	15 (5.5)	6 (6.7)	7 (8.1)	13 (7.4)
With drug-related AEs	40 (47.6)	53 (58.2)	60 (65.2)	48 (53.9)	161 (59.2)	47 (52.2)	54 (62.8)	101 (57.4)

[a] Patients with multiple events in the same category are counted only once per category. Patients with events in more than 1 category are counted once in each of those categories.

AE Adverse event. DAE AE leading to discontinuation. QTP IR Quetiapine immediate release.
QTP SR Quetiapine sustained release. SAE Serious AE.

[2]To assess the similarity of the efficacy profiles of quetiapine SR and marketed quetiapine IR tablets.

The most common AEs across all SR-treatment groups were those of the nervous, gastrointestinal, and vascular systems and included orthostatic hypotension, sedation or somnolence, headache, dry mouth, dizziness, and increased heart rate or tachycardia (Table S3). AEs were generally characterized as mild or moderate. A quetiapine SR 300-mg starting dose and the dose-administration schedule used to increase daily dose to 800 mg were well tolerated. Dose initiation at the SR 300-mg dose did not result in increased incidences of early withdrawal or increased rates of AEs assessed as drug-related, compared with IR 300 mg (Table S2). Increasing the SR dose to reach target doses of 600 and 800 mg daily (and treatment at those doses) did not produce consistent dose-related changes in safety indices.

There were no instances of agranulocytosis with any quetiapine treatment. The expected mean increases in pulse rate seen with quetiapine SR were also seen with quetiapine IR. Small mean and median weight gains of about 2 kg were seen for patients who completed 42 days of quetiapine treatment (SR or IR). Findings of clinically important laboratory, vital signs, or ECG findings were infrequent, with clinically important vital signs most commonly seen as increases in heart rate (≥15 bpm) in all treatment groups.

Incidences of extrapyramidal disorder (MedDRA preferred term) were low: 2.4%, 2.2%, and 0% among patients treated with placebo, quetiapine SR, and quetiapine IR, respectively. Individual AEs predesignated as potentially related to EPS were infrequent, rarely led to withdrawal, and were rated either mild or moderate. When these AEs were aggregated, overall rates for SR- and IR-treated patients were similar and somewhat greater than that with placebo; however, anticholinergic use for EPS was greatest among placebo-treated patients, compared with SR- and IR-treated patients. Anticholinergic use did not increase over time in any treatment group, and this was consistent with results of neurological assessments (Simpson Angus Scale, AIMS, and BARS global assessment scores), which showed that the majority of patients (all treatment groups) either improved or did not change relative to EPS, abnormal involuntary movements, or akathisia. Additionally, on each of the scales, slightly greater proportions of placebo-treated patients worsened, compared with quetiapine-treated patients (SR and IR), supporting a conclusion of little or no treatment-emergent EPS with quetiapine SR.

Overall, the safety profile of quetiapine SR was similar to that of quetiapine IR.

Table S3 Number (%) of patients with commonly reported AEs (incidence ≥5% in any quetiapine treatment group) (safety population)

MedDRA preferred term[a]	Number (%) of patients[b]														
	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP SR Total		QTP IR 300 mg		QTP IR 600 mg		QTP IR Total	
	(n=84)		(n=91)		(n=92)		(n=89)		(n=272)		(n=90)		(n=86)		(n=176)	
Orthostatic hypotension	15	(17.9)	21	(23.1)	21	(22.8)	24	(27.0)	66	(24.3)	16	(17.8)	19	(22.1)	35	(19.9)
Headache	21	(25.0)	15	(16.5)	18	(19.6)	14	(15.7)	47	(17.3)	17	(18.9)	13	(15.1)	30	(17.0)
Sedation	10	(11.9)	14	(15.4)	22	(23.9)	24	(27.0)	60	(22.1)	17	(18.9)	22	(25.6)	39	(22.2)
Dry mouth	1	(1.2)	12	(13.2)	18	(19.6)	13	(14.6)	43	(15.8)	8	(8.9)	9	(10.5)	17	(9.7)
Somnolence	7	(8.3)	11	(12.1)	15	(16.3)	12	(13.5)	38	(14.0)	18	(20.0)	11	(12.8)	29	(16.5)
Constipation	1	(1.2)	10	(11.0)	8	(8.7)	7	(7.9)	25	(9.2)	3	(3.3)	12	(14.0)	15	(8.5)
Dizziness	3	(3.6)	9	(9.9)	17	(18.5)	11	(12.4)	37	(13.6)	9	(10.0)	10	(11.6)	19	(10.8)
Hypotension	2	(2.4)	9	(9.9)	5	(5.4)	4	(4.5)	18	(6.6)	6	(6.7)	9	(10.5)	15	(8.5)
Tachycardia	2	(2.4)	7	(7.7)	8	(8.7)	6	(6.7)	21	(7.7)	10	(11.1)	13	(15.1)	23	(13.1)
BP diastolic decreased	2	(2.4)	7	(7.7)	2	(2.2)	4	(4.5)	13	(4.8)	3	(3.3)	7	(8.1)	10	(5.7)
Fatigue	5	(6.0)	7	(7.7)	4	(4.3)	2	(2.2)	13	(4.8)	3	(3.3)	5	(5.8)	8	(4.5)
Heart rate increased	4	(4.8)	6	(6.6)	11	(12.0)	12	(13.5)	29	(10.7)	5	(5.6)	10	(11.6)	15	(8.5)
Insomnia	11	(13.1)	6	(6.6)	11	(12.0)	10	(11.2)	27	(9.9)	8	(8.9)	6	(7.0)	14	(8.0)
Nausea	10	(11.9)	5	(5.5)	10	(10.9)	6	(6.7)	21	(7.7)	4	(4.4)	8	(9.3)	12	(6.8)
Dyspepsia	5	(6.0)	5	(5.5)	6	(6.5)	5	(5.6)	16	(5.9)	2	(2.2)	8	(9.3)	10	(5.7)
Agitation	6	(7.1)	5	(5.5)	6	(6.5)	2	(2.2)	13	(4.8)	2	(2.2)	3	(3.5)	5	(2.8)
BP systolic decreased	3	(3.6)	4	(4.4)	1	(1.1)	5	(5.6)	10	(3.7)	3	(3.3)	5	(5.8)	8	(4.5)
Back pain	3	(3.6)	4	(4.4)	2	(2.2)	1	(1.1)	7	(2.6)	3	(3.3)	4	(4.7)	7	(4.0)
Weight increased	2	(2.4)	4	(4.4)	5	(5.4)	8	(9.0)	17	(6.3)	8	(8.9)	8	(9.3)	16	(9.1)
Postural dizziness	2	(2.4)	3	(3.3)	4	(4.3)	4	(4.5)	11	(4.0)	1	(1.1)	4	(4.7)	5	(2.8)
Anxiety	0		3	(3.3)	4	(4.3)	4	(4.5)	11	(4.0)	2	(2.2)	3	(3.5)	5	(2.8)
Vomiting	7	(8.3)	2	(2.2)	9	(9.8)	2	(2.2)	13	(4.8)	3	(3.3)	1	(1.2)	4	(2.3)
Restlessness	1	(1.2)	2	(2.2)	1	(1.1)	4	(4.5)	7	(2.6)	0		0		0	
Akathisia	1	(1.2)	0		4	(4.3)	1	(1.1)	5	(1.8)	3	(3.3)	4	(4.7)	7	(4.0)
Tremor	0		1	(1.1)	4	(4.3)	1	(1.1)	6	(2.2)	1	(1.1)	4	(4.7)	5	(2.8)
Vision blurred	0		1	(1.1)	6	(6.5)	2	(2.2)	9	(3.3)	1	(1.1)	1	(1.2)	2	(1.1)
Lethargy	0		1	(1.1)	1	(1.1)	0		2	(0.7)	1	(1.1)	5	(5.8)	6	(3.4)

[a] Sorted by decreasing order of frequency as summarized for the QTP SR 300-mg treatment group. AEs with incidence rates that rounded up to 5% (any QTP group) are included.
[b] Patients with multiple occurences of the same event are counted only once in that AE category.
AEs Adverse events. MedDRA Medical dictionary for regulatory activities. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.

Conclusions

- Quetiapine SR 600 mg, when given once daily, was more effective than placebo in improving the symptoms of schizophrenia, as shown by a statistically significant difference between treatments in decrease from baseline in PANSS total score through 42 days of treatment.

- Quetiapine SR 800 mg produced a numerically greater, though not statistically significant, improvement in disease symptoms, compared with placebo, as shown by a 2-fold greater decrease from baseline in PANSS total score through 42 days of treatment.

- The effects of quetiapine SR 300 mg and quetiapine IR 300 and 600 mg (commercial tablets) on psychotic symptoms at Day 42 were not significantly different from those of placebo, although a numerical advantage was seen with IR 300 mg compared with placebo.

- Quetiapine SR was safe and well tolerated in the treatment of schizophrenia across the dose range of 300 to 800 mg. The AEs most commonly seen with quetiapine SR were also commonly seen with quetiapine IR and included orthostatic hypotension, sedation or somnolence, headache, dry mouth, dizziness, and increased heart rate or tachycardia. Incidence rates of EPS-related AEs were similar between SR and IR-treated patients, with neurological assessments suggesting little or no treatment-emergent EPS.

- The overall safety profile for quetiapine SR was similar to the safety profile seen for quetiapine IR.

- A quetiapine SR 300-mg starting dose and the dose-administration schedule used to increase daily dose to 800 mg were well tolerated.

Date of the report

02 March 2006

TABLE OF CONTENTS PAGE

LIST OF TABLES PAGE

LIST OF FIGURES PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study report.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 5.5.7.2).
AIDS	Acquired immunodeficiency syndrome
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CGI	Clinical Global Impression
CRF	Case report form
DAE	Adverse event leading to discontinuation of study treatment and the patient's participation in the study
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised 1994
ECG	Electrocardiogram
Endpoint	A point marking the completion of a process or stage of a process, typically in clinical studies, a patient-based predefined or outcome of interest
EPS	Extrapyramidal symptoms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
International coordinating investigator	The investigator who coordinates the investigators and study activities internationally when a study is conducted in several countries.
IR	Immediate release
IRB	Institutional review board
Measurement	An observation made on a variable using a measurement device
OAE	Other significant adverse event (ie, an adverse event of special interest in the clinical development of the reference study drug; see Section 5.5.7.2 for additional explanation). The classification of an AE as an OAE was made by the AstraZeneca drug safety physician after study completion.
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective.

Abbreviation or special term	Explanation
PANSS	Positive and Negative Syndrome Scale
Parameter	A quantity (usually unknown) that characterizes the distribution of a variable in a population of patients.
Principal investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator.
SAE	Serious adverse event (see definition in Section 5.5.7.2)
SAS	Simpson-Angus Scale
SR	Sustained release
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
Variable	A characteristic or a property of a patient that can vary across time or between patients

1. ETHICS

1.1 Ethics review

The institutional review board (IRB), or independent ethics committee (IEC), affiliated with each center approved the final study protocol and written-informed-consent form before any patient was enrolled in the study. The principal investigators were responsible for informing their IRBs of all amendments to the protocol in accordance with local requirements and for reporting to their IRBs any serious adverse events (SAEs). Study progress at individual centers was reported to the IRB by either the principal investigator or sponsor as appropriate. A list of the study IRBs is provided in Appendix 12.1.3.

1.2 Ethical conduct of study

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference of Harmonization (ICH) and Good Clinical Practice guidelines, applicable regulatory requirements, and AstraZeneca's policy on Bioethics.

1.3 Patient information and consent

Written, informed consent was obtained from each patient at the screening visit (Visit 1). Patients deemed incapable of providing informed consent were permitted to enter the study if written, witnessed, informed consent was obtained from the patient's legal guardian or representative.

The master version of the patient information and consent forms (in English) are provided in Appendix 12.1.3. Copies of the French translations of these documents, which were provided for Canadian patients if needed, are available upon request.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1 Staff at investigational sites

The study was conducted at 49 centers in the United States (45) and Canada (4). See Appendix 12.1.4.1 for a list of study investigators, subinvestigators, and other study personnel involved in patient assessments.

2.2 AstraZeneca study personnel

See Appendix 12.1.4.2.

2.3 Other participants

2.3.1 Nonsponsor organizations or individuals

This study was conducted by the clinical research organization Parexel (200 West Street, Waltham, Massachusetts) under the supervision of AstraZeneca personnel.

Electrocardiograms were reviewed and interpreted by personnel at eResearch Technology (30 South 17th Street, Philadelphia, Pennsylvania).

Clinical laboratory tests were conducted by Quest Diagnostics (7600 Tyrone Avenue, Van Nuys, California).

A list of study personnel from Parexel, eResearch Technology, and Quest Diagnostics is provided in Appendix 12.1.4.4.

Key Word Associates Inc (Bishopville, Maryland; not listed in Appendix 12.1.4.4) assisted in the production of this clinical study report.

2.3.2 Study committees

No external study committees were formed to assist in the conduct of this study.

3. INTRODUCTION

The purpose of this study was to investigate the efficacy of a sustained-release (SR) formulation of quetiapine fumarate (SEROQUEL™, quetiapine), a dibenzothiazepine derivative marketed by AstraZeneca Pharmaceuticals for the treatment of schizophrenia and acute mania associated with bipolar disorder. This study was also designed to evaluate the safety and tolerability of quetiapine SR at doses of up to 800 mg/day.

The marketed formulation of quetiapine is an immediate-release (IR) tablet with a recommended dose range of 150 to 750 mg per day. The IR formulation is administered 2 or 3 times daily and requires dose escalation over 4 to 5 days to reach the target therapeutic dose. AstraZeneca developed an SR formulation to deliver gradual and then sustained drug levels of quetiapine with once-a-day administration. In theory, the SR formulation would permit patient exposure to therapeutic doses earlier in the course of treatment without increasing the rates of AEs relative to that seen with the IR formulation.

In patients with psychotic disorders, treatment compliance is especially important and problematic; noncompliance often leads to relapse and other serious consequences, including suicide. While the reasons for noncompliance are varied, there is evidence that treatment complexity is a contributing factor (Osterberg and Blaschke 2005). Thus, there is a strong rationale for reducing the frequency of quetiapine administration and simplifying the dose-administration regimen.

This study compared quetiapine SR, administered once daily at doses of 300, 600, or 800 mg, with placebo to establish the efficacy and tolerability profile of the SR formulation in the treatment of patients with acute exacerbation of schizophrenia. All patients randomized to treatment with quetiapine SR began treatment at a dose of 300 mg; doses were then increased over the next 5 to 8 days to reach the assigned fixed dose. An earlier clinical pharmacology study (5077IL/0087) indicated that initiating treatment with quetiapine SR 300 mg is as well tolerated in terms of adverse events and changes in vital signs as is the dose-administration regimen typically used for quetiapine IR. A subsequent study (5077IL/00109) provided data on the safety and tolerability of increasing the dose of quetiapine SR from 300 mg per day up to 800 mg per day over a period of 9 days. Although these clinical pharmacology studies demonstrated the safety of quetiapine SR as administered in this study (5077IL/0041), patients in this study were carefully monitored for unexpected effects during the first 10 days of treatment.

The study design included the use of placebo as a control medication, which was randomly assigned to 1 of every 6 patients enrolled. To safeguard the well-being of all patients, criteria for deterioration of a patient's psychiatric condition were established a priori; any patient who met these criteria had to be withdrawn from the study and given appropriate treatment. The study also included treatment with 2 different doses of conventional quetiapine IR as an internal standard, with treatment initiated and dose increased and administered according to current prescribing information. This study feature was included for purposes of assessing similarities between the SR and IR formulations.

4. STUDY OBJECTIVES

4.1 Primary objectives

The study's primary objective was to demonstrate superior efficacy of quetiapine SR tablets compared with placebo in the treatment of patients with schizophrenia.

4.2 Secondary objectives

The study's secondary objectives were as follows:

- To assess the tolerability and safety of quetiapine SR tablets administered once daily as compared with placebo in patients with schizophrenia
- To assess the tolerability and safety of quetiapine SR therapy initiated at a dose of 300 mg
- To assess the similarity of the safety and efficacy profiles of quetiapine SR tablets and marketed quetiapine IR tablets

5. STUDY PLAN AND PROCEDURES

The overall study design and plan are presented and discussed in Section 5.1 and Section 5.2, respectively. The study population and its relationship to the intended target population are defined in Section 5.3. Study treatments and dosing regimens are described in Section 5.4. Study measurements and variables are described and justified in Section 5.5, and measures taken to ensure the quality of study data are described in Section 5.6. Statistical methods and presentation of the data are detailed in Section 5.7. Any changes to the planned conduct of the study, or planned statistical analyses, are presented in Section 5.8.

5.1 Overall study design and flow chart

This was a 6-week (42-day), multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy of quetiapine SR with placebo in the treatment of patients hospitalized with acute exacerbation of schizophrenia. The primary study endpoint was the change from baseline (Day 1) to the final assessment (Day 42 or withdrawal) in the Positive and Negative Syndrome Scale (PANSS) total score (Kay et al 1987). To be eligible for the study, a patient had to have a PANSS total score of at least 60 at screening and on Day 1 and a score of at least 4 on one or more of the following PANSS individual items on Day 1: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), and suspiciousness/persecution (P6). Patients also had to have a score of at least 4 on the Clinical Global Impression (CGI) Severity of Illness item, with evidence of worsening in the 3 weeks before enrollment, indicating acute exacerbation.

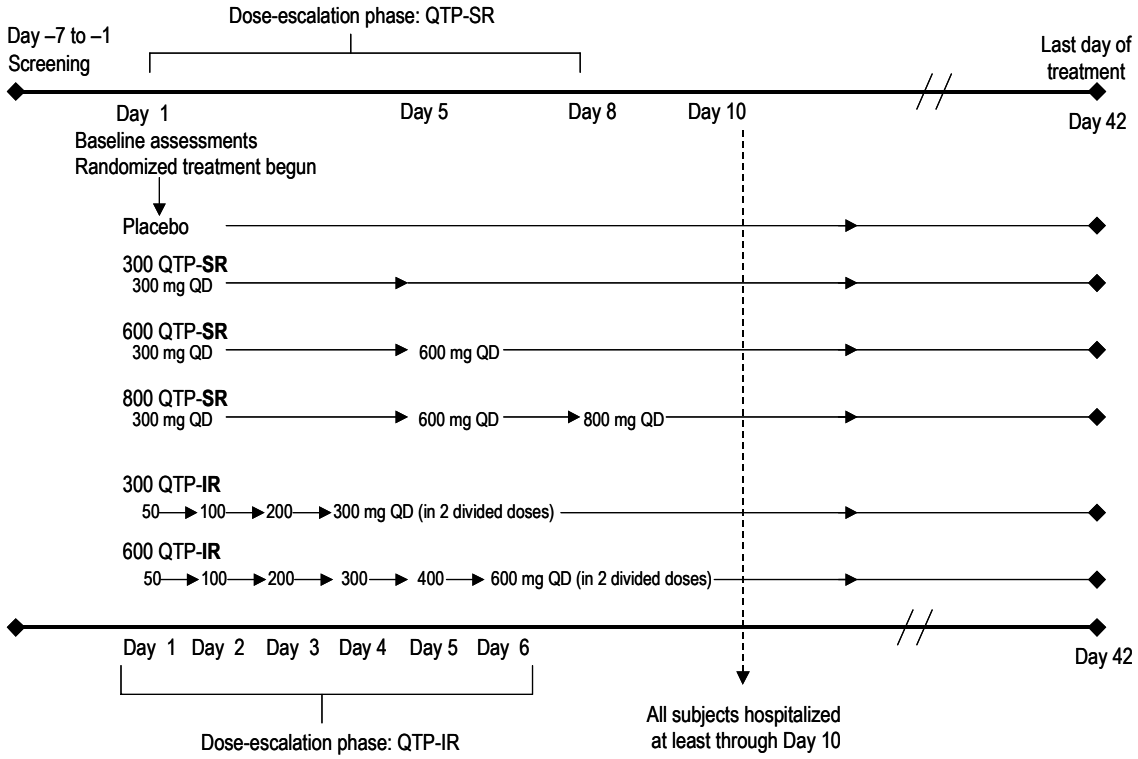
Patients provided informed consent and were screened for eligibility (at Visit 1) up to 7 days before randomized treatment was assigned. Patients who were screened as outpatients were hospitalized when enrolled. Patients could be discharged from the hospital on Day 10 at the investigator's discretion. On Day 1 (Visit 2), baseline assessments were performed, and patients were assigned to 1 of 6 possible randomized double-blind treatments: quetiapine SR at 300, 600, or 800 mg daily, quetiapine IR at 300 or 600 mg daily (in 2 divided doses), or placebo. Oral antipsychotic medications and other prohibited psychoactive medications (see Section 5.4.5) had to be discontinued at least 48 hours before baseline assessments were performed. Depot and long-acting antipsychotic treatments had to be discontinued at least 1 dosing interval before baseline assessments were performed.

For all patients assigned to treatment with quetiapine SR, treatment began at a dose of 300 mg/day on Day 1; patients assigned to higher doses had their doses increased according to the provided dose-escalation scheme to reach either the target dose of 600 mg on Day 5 or 800 mg on Day 8. For all patients assigned to treatment with quetiapine IR, treatment began at a total dose of 50 mg/day on Day 1; doses were then increased, according to the provided dose-administration scheme (which matched current label instructions) to reach the target dose of 300 mg/day on Day 4 or 600 mg/day on Day 6. Administration of study medication continued through Day 42. Patients treated with quetiapine SR took active tablets in the morning and placebo tablets in the evening; patients treated with quetiapine IR took active tablets in the morning and evening, with placebo tablets as directed per packaging configuration to maintain the blind (see Section 5.4.2).

The primary efficacy assessment was based on PANSS total score, determined on Day 1 (baseline) before the first dose of study medication was given and on Days 4, 8 (Week 1), 15 (Week 2), 28 (Week 4), and 42 (Week 6). Secondary efficacy assessments were based on PANSS total and subscale scores as well as on Clinical Global Impression (CGI) Severity of Illness scores, which were assessed along with PANSS scores. Safety was assessed throughout the study in terms of adverse events, laboratory assessments, physical assessments, and neurological findings.

Study design and flow are presented graphically in Figure 1. Study procedures and assessments, as conducted at each timepoint, are summarized in Table 1.

Figure 1 Study flow chart



QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.

Table 1 Study plan

		Screening	Randomization	Double-blind treatment				
	Visit	1[a]	2	3	4	5	6	7[b]
	Day	<–7	1	4	8	15	28	42
General events/assessments								
Informed consent		√						
Inclusion/exclusion criteria		√						
Prior and concurrent medication		√	√	√	√	√	√	√
Demographic data, medical and psychiatric history		√						
Urine toxicology test for substance abuse		√						
Blood sample for genetic testing (optional)		√						
Drug dispensing and accountability			√----------	----------	----------√[c]	√	√	√
Efficacy assessments								
Positive and Negative Syndrome Scale		√	√	√	√	√	√	√
Clinical Global Impression – Severity of Illness[d]			√	√	√	√	√	√
Safety assessments								
Adverse events		√	√[e]	√	√	√	√	√[f]
Clinical laboratory tests[g]		√						√
Vital signs[h] and weight		√	√	√	√	√	√	√
Physical examination, 12-lead electrocardiogram, ophthalmoscopic examination		√						√
Neurological assessments[i]			√	√	√	√	√	√

[a] Screening assessments had to be performed within 7 days before randomization.
[b] Assessments scheduled for Day 42 had to be conducted at the end of treatment for patients who withdrew early.
[c] Study drug was dispensed daily until patients were discharged from the hospital.
[d] Global Improvement was assessed on Days 4, 8, 15, 28, and 42.
[e] Adverse events were recorded from screening to randomization.
[f] Adverse events had to be followed until resolved or for up to 30 days.
[g] Clinical laboratory tests included hematology, hepatic chemistry, thyroid function, prolactin, fasting glucose, and lipid analysis.
[h] Routine vital sign assessments were performed on Day –1 and at every visit thereafter. On Days 1, 2, 5, 6, 8, 9, and 15, more extensive assessments were performed relative to the time of treatment administration.
[i] Using the modified Simpson-Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale.

Data derived from the study protocol (Table I).

5.2 Rationale for study design, doses, and control groups

The efficacy of quetiapine IR in the treatment of patients with acute exacerbation of schizophrenia was established in earlier clinical trials, with consistent benefit seen at doses of 300 mg and higher (Arvanitis et al 1997, Small et al 1997). Trends toward usage at the higher doses have been reported (Citrome et al 2005). Earlier studies (clinical pharmacology) demonstrated the safety and tolerability of quetiapine SR when administered as fixed doses up to 300 mg and when the SR dose was increased from 300 to 800 mg over a 9-day interval (Studies 0087 and 0109, respectively). Consideration of these factors led to the dose regimens incorporated in the design of this early Phase III efficacy trial. The inclusion of a placebo group to establish the absolute efficacy of quetiapine SR in reducing clinical symptoms was consistent with accepted scientific and regulatory standards. The use of 2 different doses of quetiapine IR provided an opportunity to compare the relative efficacy of quetiapine SR and quetiapine IR across a range of doses.

5.3 Selection of study population

Patients eligible for the study were those with acute exacerbation of schizophrenia who had been hospitalized (for no more than 1 month) in either psychiatric hospitals or psychiatric units of general hospitals for treatment of symptoms. Patients who were screened as outpatients and satisfied the inclusion and exclusion criteria were also eligible for the study; however, these patients had to be hospitalized upon enrollment for at least the first 10 days of treatment.

5.3.1 Inclusion criteria

For inclusion in the study, patients had to fulfill all of the following criteria:

1. be 18 to 65 years old. Age was restricted to specifically investigate treatment of the general adult population with schizophrenia; older and younger patients frequently require special dose adjustments

2. have a documented ability to provide written, informed consent. Patients who were deemed incapable of providing informed consent could enter the study if written, witnessed, informed consent was obtained from the patient's legal guardian. Written, informed consent was required to comply with ethical standards of Good Clinical Practice for clinical studies.

3. have a documented diagnosis that satisfied the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, revised 1994 (DSM-IV) for 1 of the following accepted subtypes of schizophrenia:

   - catatonic subtype 295.20
   - disorganized subtype 295.10
   - paranoid subtype 295.30

– undifferentiated type 295.90

These diagnostic criteria were specified for consistency with the approved indications for quetiapine IR.

4. have a PANSS total score of at least 60 at both screening and baseline (Day 1). PANSS criteria were included to insure that patients had a minimum severity of disease before treatment began.

5. have a score of at least 4 on one or more of the following PANSS individual items at baseline (Day 1):

   – P1 – delusions

   – P2 – conceptual disorganization

   – P3 – hallucinatory behavior

   – P6 – suspiciousness/persecution

6. have a Clinical Global Impression (CGI) Severity of Illness score (Guy and Bonato, 1970) of at least 4 (moderately ill) at baseline (Day 1), with evidence of worsening of the patient's condition during the 3 weeks immediately preceding the baseline CGI assessment. This criterion was intended to identify patients with acute exacerbation of schizophrenia.

5.3.2 Exclusion criteria

In general, and unless otherwise noted, exclusion criteria were used to exclude patients with conditions that could either adversely affect a patient's well-being if the patient were allowed to participate in the study or interfere with the evaluation of treatment efficacy. Any of the following was regarded as a criterion for exclusion from the study:

1. risk (in the investigator's opinion) of transmitting human immunodeficiency virus (HIV) or hepatitis B via blood or other body fluids. Excluding patients who met this criterion prevented enrollment of patients with increased safety risks and helped protect the safety of study personnel who handled blood samples.

2. being pregnant or lactating (with intentions to breast-feed). Additionally, female patients could not be at risk of becoming pregnant and were required to use a reliable method of birth control, ie, barrier method, oral contraceptive, implant, long-term injectable contraceptive, intrauterine device, or tubal ligation. These criteria were included because no studies have been performed to assess the safety of quetiapine when taken during pregnancy.

3. known intolerance or lack of response to previous treatment with quetiapine.

4. hospitalization for the treatment of symptoms of schizophrenia for a period of more than 1 month at the patient's current inpatient unit immediately before the baseline visit (Day 1), which could indicate possible treatment resistance.

5. satisfying criteria for an Axis I DSM-IV diagnosis, such as alcohol or psychoactive substance abuse or dependence not in full remission, or mental retardation, because such conditions could confound the effects of study treatment.

6. known lack of response to clozapine treatment, known requirement for clozapine treatment for symptom control, treatment with clozapine within 1 month of the baseline visit (Day 1), or, in the opinion of the investigator, lack of response to antipsychotic medications. These conditions could indicate treatment resistance.

7. use of antipsychotics, mood stabilizers, antidepressants, anxiolytics, hypnotics, or other psychoactive drugs within 48 hours before randomization to study treatment (Day 1) or throughout the randomized treatment period (except those medications specified in Section 5.4.5) because such medications could interfere with the efficacy of study treatment.

8. use of depot or long-acting injectable antipsychotic drugs within 1 injection cycle before randomization or during the study period because such medications could interfere with the efficacy of study treatment.

9. use of potent cytochrome P450 inhibitors or inducers within 14 days before the baseline visit (Day 1) or during randomized treatment. Quetiapine is metabolized by the cytochrome P450 enzyme system, and drugs that induce or inhibit this system could potentially affect plasma quetiapine concentrations.

10. history of recent uncontrolled blood pressure or use of antihypertensive medications if dosages used were not stable for at least 1 month before the baseline visit (Day 1).

11. history of idiopathic orthostatic hypotension or known sensitivity to the hypotensive or anaphylactic effects of antipsychotic or antidepressant medications.

12. transient ischemic attack, angina pectoris, or myocardial infarction in the 2 months before screening.

13. persistent standing heart rate of more than 120 beats per minute (bpm) or supine tachycardia (heart rate of more than 100 bpm). An exception was made for transient, nonpersistent tachycardia at the discretion of the investigator.

14. evidence of clinically relevant disease (eg, renal or hepatic impairment, significant coronary artery disease, cerebrovascular disease, viral hepatitis B or C, acquired immunodeficiency syndrome [AIDS] or serological evidence of HIV infection or cancer) or a clinical finding that was unstable or that, in the opinion of the

investigator, would be negatively affected by study medication or that would affect study medication.

15. a clinically significant electrocardiogram (ECG) abnormality as determined by a centralized, experienced cardiologist. Such a result was communicated to the investigator who made the final eligibility decision with the patient.

16. in the opinion of the investigator, demeanor suggesting an imminent risk of suicide or danger to oneself or others.

17. a thyroid-stimulating hormone (TSH) concentration more than 10% above the upper limit of the reference normal range, whether or not the patient was being treated for hypothyroidism.

18. history of idiopathic or drug-induced agranulocytosis.

19. participation in any drug study or compassionate-use program within 1 month of the baseline visit (Day 1).

20. risk of noncompliance with study procedures and requirements for any reason, including but not limited to any additional comorbid psychiatric diagnosis or symptoms that would be likely to result in such noncompliance.

5.3.3 Restrictions

Patients were asked to comply with the following restrictions during the study:

1. Patients who were blood donors were asked not to donate blood during the study or during the 3 months following administration of the last dose of study treatment. This restriction was placed on patients because blood donation during therapy could affect systemic exposure to quetiapine and hence the effects of treatment. This restriction also helped ensure that blood recipients were not inadvertently exposed to quetiapine.

2. Per protocol, patients had to be hospitalized at Visit 1 and remain hospitalized for treatment of symptoms following randomization until Day 10. Patients could then be discharged from the hospital at the discretion of the investigator, provided close supervision of the patient was arranged. Patients who were discharged from the hospital had to agree, and be able, to return to the hospital for further study visits and assessments. In addition, patients were contacted by telephone during the interval between scheduled study visits as required (but at least weekly) to reduce the possibility of an unobserved deterioration in the patient's condition.

3. Concurrent use of any antipsychotic medication other than study therapy was prohibited throughout the randomized treatment period (see Section 5.4.5) because such medication could confound assessment of the efficacy of the study therapy

4. Use of other prescription or nonprescription medications other than those specifically allowed by the protocol (see Section 5.4.5) that could alter or mask the effect of study medication was prohibited.

5.3.4 Discontinuation of patients from treatment or assessment

5.3.4.1 Criteria for discontinuation

Study treatment and assessments could be discontinued at any time at the discretion of the investigator. Specific reasons for discontinuing treatment and patient participation in the study included the following:

1. The study drug was not effective (alternative treatment was required).

2. An adverse event occurred.

3. The patient was lost to follow-up (ie, dropped out).

4. The patient was noncompliant with the protocol (resulting in protocol violations or deviations).

5. The patient withdrew consent.

Patients who had any assessments after Day 8 and whose CGI Severity of Illness scores had worsened by at least 2 units or who had at least a 1-unit worsening in their CGI Severity of Illness scores on 2 consecutive study visits had to be withdrawn from the study.

Any patient at imminent risk for suicide had to be withdrawn from the study.

5.3.4.2 Voluntary discontinuation by a patient

Patients were free to discontinue their participation in the study at any time, without prejudice to further treatment. Patients who did so were asked about their reasons and if any adverse events were present. If possible, patients were seen and assessed by an investigator. Adverse events were followed up, and patients were asked to return any investigational products and study materials.

5.3.4.3 Incorrectly enrolled or randomized patients

Incorrectly enrolled or randomized patients were permitted to continue in the study. Data for these patients would be handled as described in Section 5.7.1.3.

5.3.4.4 Procedures for discontinuation

Beginning September 2001, investigators were asked to call the study team physician or the clinical research manager before withdrawing a patient.

Once a patient was withdrawn, the reason for the withdrawal was documented on the appropriate case report form (CRF). Additionally, all assessments that were specified for the end of the study period were required at the time of withdrawal to the extent possible. All

adverse events were reported; adverse events resulting in patient withdrawal from the study were noted as such. All withdrawals due to SAEs had to be reported to AstraZeneca within 1 day. Withdrawals due to nonserious adverse events had to be reported to AstraZeneca within 15 days. If the reason for withdrawal was death, the event could be reported as either due to disease progression or due to an adverse event, and the cause of death was reported on the appropriate CRF.

Any patient who withdrew from the study and had clinically important or abnormal findings on any safety assessment was required to return for a follow-up visit within 1 week and at appropriate intervals thereafter until the abnormality resolved. When possible, patients were followed for 30 days after the last dose of study drug was given. All deaths and SAEs had to be reported to AstraZeneca; SAEs required follow up until resolution or for up to 30 days.

5.4 Treatments

5.4.1 Investigational products

Details of the investigational product (quetiapine SR) and other study treatments (quetiapine IR and placebo) are given in Table 2. All study treatments were manufactured and supplied by AstraZeneca.

Table 2 Supply details of the investigational product and other study treatments

Study treatment	Dosage form and strength	Formulation number	Batch number
Quetiapine SR	200-mg tablet	F12840	9077C
	300-mg tablet	F12527	9052C
Quetiapine IR	25-mg tablet	F12804	7501B
	100-mg tablet	F12689	6083C
	200-mg tablet	F12690	6081C and 6082C
Placebo	To match quetiapine SR 200 mg	F12422	ST73043-001-FA03
	To match quetiapine SR 300 mg	F12416	ST73042-001-FB05 ST73042-001-FB03 ST73042-001-FB04 ST73042-001-FB02 ST73042-001-FB06
	To match quetiapine IR 25 mg	F12636	8021B
	To match quetiapine IR 100 mg	F12637	8022B
	To match quetiapine IR 200 mg	F12638	1012C and 7552F

IR Immediate release. SR Sustained release.

Investigators were required to keep all investigational products in a secure place under appropriate storage conditions, ie, at controlled room temperature (20 to 25°C or 68 to 77°F) and protected from moisture.

5.4.2 Doses and treatment regimens

Blinded study treatment (quetiapine SR, quetiapine IR, or placebo) was administered orally, twice a day (morning and evening), throughout the 6-week randomized treatment period. Placebo tablets were combined with quetiapine tablets to ensure that the tablets given to patients in all treatment groups for a given dose were identical in number and appearance. The tablets were packaged in blister cards (see Section 5.4.4.1) designed so that patients assigned to treatment with quetiapine SR took active tablets in the morning and placebo only in the evening, while patients assigned to treatment with quetiapine IR took active tablets in the morning and in the evening.

The first dose of study treatment was given on the morning of Day 1, after baseline assessments were performed (see Table 1). Treatment with quetiapine SR began at a dose of 300 mg/day, with dose increases thereafter to reach the assigned fixed dose (600 mg on Day 5, 800 mg on Day 8). Treatment with quetiapine IR began at a dose of 50 mg/day; the daily dose was then increased, according to label instructions, to reach the fixed dose (300 mg/day on Day 4 or 600 mg/day on Day 6). Administration of study medication continued through Day 42.

The details of the dose-escalation schemes for quetiapine SR and quetiapine IR are shown in Table 3 and Table 4, respectively.

Table 3 Dose-escalation schemes for sustained-release quetiapine

Target dose	Total daily quetiapine dose (mg)		
	Days 1 through 4	Days 5 through 7	Days 8 through 42
300 mg	300	300	300
600 mg	300	600	600
800 mg	300	600	800

Table 4 Dose-escalation schemes for immediate-release quetiapine

Target dose	Total daily quetiapine dose (mg)					
	Day 1	Day 2	Day 3	Day 4	Day 5	Days 6 through 42
300 mg	50	100	200	300	300	300
600 mg	50	100	200	300	400	600

5.4.3 Method of assigning patients to treatment groups

At each site, the investigator established patient eligibility before any treatment was allocated. The actual treatment given to individual patients was determined by a randomization schedule prepared by the Clinical Information Sciences Department, Biostatics Group, at AstraZeneca. At each site, patient numbers were to be allocated in strict sequence as patients entered the study. Once a number was assigned to a patient, no attempt was to be made to use that number again if, for example, a patient withdrew or was withdrawn from the study. A patient could enter the study only once.

5.4.4 Blinding and procedures for unblinding the study

5.4.4.1 Methods for ensuring blinding

Study treatment was packaged in blister cards, with a separate card for each week of study treatment. The cards for Week 1 contained 32 tablets each. The cards for Weeks 2 through 6 contained 70 tablets each. Placebo tablets that matched the various strengths of SR and quetiapine IR tablets were used to maintain the treatment blind by ensuring that the tablet combinations in the blister card for all treatments for a given study week appeared identical. Each blister card was inserted into a wallet labeled with the study number, patient number, contents (number of tablets), instructions for use, and storage conditions. The label contained a space for entry of the patient's initials.

The treatment supplies for each patient were packed in a carton labeled with the study number, patient number, blinded contents, administration instructions, and storage conditions. The carton labels were perforated so that 1 portion of the label could be peeled off and applied to the drug-accountability CRF when the medication was dispensed. The peel-off portion of the carton label included a blinded disclosure panel that concealed the treatment regimen assigned to the patient.

5.4.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each patient, were available to the investigator or pharmacists at the study center. The investigator could break the treatment code only after deciding to withdraw a patient from the study and if immediate knowledge of the study medication was needed to make specific medical decisions regarding optimal clinical management of the patient. The investigator was responsible for documenting and reporting (to AstraZeneca) any breaking of the treatment code. AstraZeneca retained the right to break the code for SAEs that were causally related to treatment and potentially required expedited reporting to regulatory authorities, and in exceptional circumstances, for other safety reasons. Treatment codes were not to be broken for the planned analyses of data until all decisions on the evaluability of the data from each patient were made and documented.

5.4.5 Prestudy, concomitant, and poststudy treatments

The protocol required that all previously administered antipsychotic or psychoactive medications, including benzodiazepines, anxiolytics, antidepressants, hypnotics, sedatives,

and mood-stabilizing medication (except as specifically allowed by the protocol and described herein), be discontinued at least 48 hours before baseline assessments were performed on Day 1, regardless of the indication for which they had been prescribed. Depot antipsychotic medications were to be discontinued at least 1 dosing interval before Day 1. Thereafter, no antipsychotic or psychoactive medications other than study medication were permitted for the treatment of schizophrenia or other psychotic symptoms.

The use of concomitant medication during the study was restricted as follows:

- Use of antidepressants, anxiolytics, and mood-stabilizing medication, with the exception of lorazepam treatment for agitation, was not permitted during the screening period or during the randomized treatment period. Lorazepam for the treatment of agitation was allowed only as follows: up to 6 mg/day from screening to the day before randomization; up to 4 mg/day on Days 1 through 3; and up to 2 mg/day on Days 4 through 6. Lorazepam was not allowed for the treatment of agitation after Day 6 so as to minimize any impact of this medication on the efficacy of study therapy.

- Patients taking medication for sleep could continue to do so provided these medications were taken only at bedtime for sleep. Sleep medications that could be initiated after baseline (Day 1) were as follows: zolpidem 5 to 10 mg, zaleplon 10 mg, or flurazepam 15 to 30 mg. Lorazepam was not permitted for sleep so as to minimize any impact of this medication on the efficacy of study therapy.

- All anticholinergic medication had to be discontinued at least 48 hours before baseline assessments were performed on Day 1. Thereafter, anticholinergic medication could be used to treat extrapyramidal symptoms (EPS) but could not be used prophylactically. This restriction was intended to allow the assessment of extrapyramidal side effects while allowing for treatment of those effects when observed.

- Use of potent cytochrome P450 inducers and inhibitors was not permitted within 14 days of baseline (Day 1) or during the randomized treatment period. Inducers included, but were not limited to, carbamazepine, phenobarbital, and phenytoin. Inhibitors included, but were not limited to ketoconazole, azole antifungals, erythromycin, macrolide antibiotics, and protease inhibitors. Quetiapine is metabolized by the cytochrome P450 enzyme system, and drugs that induce or inhibit this system could potentially affect plasma quetiapine concentrations.

- Antihypertensive medication could be used during the screening period or randomized treatment period only if the dosage had been stable for at least 1 month before baseline (Day 1) so as to minimize the effects of these medications on vital-sign assessments.

- Women who entered the study with an intrauterine device in place, using oral contraceptives, or using injectable or implantable hormonal agents designed to

prevent pregnancy could continue these treatments throughout the study. Reliable contraception was required because no studies have been performed to assess the safety of quetiapine when taken during pregnancy.

- With minor exceptions, patients could not use other prescription or nonprescription medications unless agreed upon with AstraZeneca before the patients were enrolled. Acetaminophen preparations without caffeine were the only medications allowed for analgesia without consultation with AstraZeneca. Topical medications for treatment of local skin conditions, antacids, and laxatives could be used without AstraZeneca approval if the patient had been using the medication for at least 1 month before study entry and if the medications were not used within 4 hours of a dose of study medication.

During the study, the use of any other medication (except for medications used to treat emergencies) was not permitted unless agreed upon with AstraZeneca before administration.

Each concomitant medication, the indication for which it was prescribed, and the dates of usage were recorded on the appropriate CRF. Any condition that arose after study entry and required treatment was considered an adverse event and recorded on the adverse event CRF (see Section 5.5.7.2).

5.4.6 Treatment compliance

The investigator was required to maintain accurate records accounting for the receipt and disposition of the investigational materials (AstraZeneca provided an Investigational Product Shipping Order for tracking receipt). At a minimum, record keeping consisted of a dispensing record that included identification of the person to whom the drug was dispensed, the quantity and the date dispensed, and documentation of any unused drug returned to the investigator. This record keeping was in addition to any drug-accountability information recorded on the CRFs. Patients were required to return all unused drug to the investigator. At the termination of the study or at the request of AstraZeneca, the responsible clinical research associate returned any unused supplies to Universal Solutions Inc (2084-900 Lake Industrial Court, Conyers, Georgia, USA) for destruction. This return was documented on an Investigational Product Return Invoice supplied by AstraZeneca.

Treatment compliance was determined by comparing the number of tablets dispensed according to the preprinted prescription record form with the number of tablets returned. The study coordinators at the study sites counted and recorded the numbers of tablets remaining in returned blister cards. Returned tablets for morning and evening doses were recorded separately.

Once assigned to treatment, patients were considered noncompliant if they took fewer than 60% of the tablets that comprised randomized treatment or if they missed more than 5 consecutive doses of randomized treatment. This definition of treatment compliance was modified from the protocol-specified definition to improve accuracy.

5.5 Measurement of study variables and definitions of outcome variables

5.5.1 Primary variable

The primary variable was the change in PANSS total score from baseline (Day 1) to Day 42 or to time of withdrawal. The choice of this primary variable is explained in Section 5.2.

5.5.2 Screening and demographic measurements

The following patient data were collected at Visit 1 to determine patient eligibility and assess baseline status: demographic statistics, medical history, psychiatric history including documentation of DSM IV clinical diagnosis, current medication usage, and PANSS score. Blood samples were collected to establish baseline hematological and clinical chemistry profiles, including thyroid function, prolactin level, and fasting glucose and lipid levels. Urine was collected for toxicology screening to rule out substance abuse and, as applicable (all women), to determine human chorionic gonadotropin (HCG) levels to rule out pregnancy. A physical examination was performed, with measurements taken for weight and height, supine and standing blood pressure, and heart rate (vital signs measured on both Day –1 and Day 1 before administration of study drug); eyes were examined by ophthalmoscopy. Additionally, a 12-lead ECG was obtained for each patient.

If the interval between screening (Visit 1) and randomization (Day 1) exceeded 7 days, vital sign measurements, clinical laboratory tests, and electrocardiographic measurements had to be repeated to ensure that screening results were available for the 7-day period immediately preceding initiation of study treatment on Day 1.

In addition to the screening assessments described, the following baseline assessments or procedures were required on the day of randomization (Day 1), before assignment of patient number and initiation of study treatment:

- Supine and standing blood pressure, heart rate, and weight measurements
- PANSS score
- CGI Severity of Illness item score (Guy and Bonato 1970)
- Modified Simpson-Angus Scale (SAS) score (Simpson and Angus 1970)
- Abnormal Involuntary Movement Scale (AIMS) score (Guy 1976)
- Barnes Akathisia Rating Scale (BARS) score (Barnes 1989)
- Presence of adverse events
- Blood sampling (9 ml) for genetic analysis. This procedure was optional, and analysis of samples would be limited to genetic testing related to schizophrenia and

pharmacogenetics in an effort to identify markers for the disease and to identify those genetic traits that are the best predictors of response to study drug. The details of sample collection, coding to protect confidentiality, and testing are included in the study protocol (see Appendix 12.1.1).

5.5.3 Efficacy and pharmacodynamic measurements and variables

5.5.3.1 Summary of efficacy objectives and variables

Table 5 summarizes the efficacy variables of this study in relationship to the study objectives.

Table 5 Efficacy objectives and outcome variables relating to each objective

Objective	Summary outcome variables for analysis
Primary	**Primary**
To demonstrate superior efficacy of quetiapine SR tablets compared with placebo in the treatment of patients with schizophrenia	Change in PANSS total score from baseline (Day 1) to Day 42 or final visit (MITT population, LOCF)
	Secondary
	Change in PANSS total score from baseline (Day 1) to Day 4; data for quetiapine-treated groups pooled across doses within formulation (MITT population, LOCF)
	PANSS response, ie, ≥30% decrease in PANSS total score from baseline to Day 42 (MITT population, LOCF)
Secondary	
To assess the similarity of the efficacy profiles of quetiapine SR tablets and marketed quetiapine IR tablets	PANSS total score; Positive, Negative, and General Psychopathology Scale score; activation factor score; and depression item score at each visit and changes from baseline (Day 1) to each postbaseline visit (MITT population, LOCF and OC)
	PANSS response: alternative response criteria of ≥40% and ≥50% decreases in PANSS total score from baseline to Day 42 (MITT population, LOCF)
	CGI Severity of Illness score at each visit and changes from baseline (Day 1) to each postbaseline visit (MITT population, LOCF and OC)
	CGI Global Improvement score at each visit after baseline (Day 1) (MITT population, LOCF and OC)

CGI Clinical Global Impression. IR Immediate release. LOCF Last observation carried forward.
MITT Modified intention-to-treat (MITT population defined as all treated patients who had a baseline (Day 1) PANSS assessment and at least 1 postbaseline PANSS assessment. OC Observed case.
PANSS Positive and Negative Syndrome Scale. SR Sustained release.

The timings of efficacy assessments were presented in the study plan (Table 1). The methods used to collect efficacy data are presented in the sections that follows.

5.5.3.2 Primary variable: change in PANSS total score from Day 1 (baseline) to Day 42 or final visit

(a) Methods of assessment

The PANSS is a 30-item rating instrument that assesses the positive and negative symptoms of schizophrenia as well as symptoms of general psychopathology.

PANSS items are grouped into 3 subscales: the Positive Scale (7 items), the Negative Scale (7 items), and the General Psychopathology Scale (16 items). Positive (P) Scale items include delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), excitement (P4), grandiosity (P5), suspiciousness/persecution (P6), and hostility (P7). Negative (N) Scale items include blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), difficulty with abstract thinking (N5), lack of spontaneity and flow of conversation (N6), and stereotyped thinking (N7). General (G) Psychopathology Scale items range from somatic concerns (G1) to active social avoidance (G16).[3] Individual items are rated on a 7-point scale (1=absent, 7=extreme).

PANSS scores were determined at screening, at randomization (Day 1), and on Days 4, 8, 15, 28, and 42 (or withdrawal). On Days 4 and 8, the PANSS rater assessed the patient from the time of first study drug administration to the time of assessment. At all other visits, the patient was rated for the preceding 1-week period. The purpose of the screening assessment was to verify that the patient had acute symptoms of schizophrenia as specified in the inclusion criteria (see Section 5.3.1).

At each center, one individual was responsible for all PANSS assessments (across visits) to reduce variability in scoring. This individual was certified as a PANSS rater by participating in an inter-rater reliability program approved by AstraZeneca. PANSS raters were recertified annually.

(b) Calculation or derivation of outcome variable

The PANSS total score for each visit, including Day 42, was calculated as the sum of all 30 individual-item scores. Change from baseline to Day 42 (or withdrawal) was calculated as the difference between scores at Day 42 (or withdrawal) and baseline.

If exactly 1, 2, or 3 item scores were missing for a given visit, then the total score was calculated as the sum of all nonmissing item scores x (30/29), (30/28), or 30/27), respectively. If more than 3 items were missing, then the total score was considered missing for that visit.

---

[3] The full range of items comprises somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

5.5.3.3 Secondary variable: change in PANSS total score from Day 1 (baseline) to Day 4

(a) Methods of assessment

PANSS total scores were determined on Days 1 and 4 as described for the primary efficacy variable.

(b) Calculation or derivation of outcome variable

PANSS total scores at Day 1 were combined for all patients treated with quetiapine SR, regardless of dose, and for all patients treated with quetiapine IR, regardless of dose. PANSS total scores at Day 4 were similarly combined. Change from baseline to Day 4 was calculated as the difference between the 2 composite scores for each of the 3 treatment subgroups.

5.5.3.4 Secondary variable: change in PANSS total score from baseline to each postbaseline visit

(a) Methods of assessment

PANSS total scores were determined at each visit as described for the primary efficacy variable.

(b) Calculation or derivation of outcome variable

The PANSS total score at each visit was calculated as previously described. Change from baseline at each postbaseline visit was calculated as the difference between the postbaseline visit score and baseline score.

5.5.3.5 Secondary variables: PANSS subscale and factor scores

(a) Methods of assessment

PANSS total scores were determined at each visit as described for the primary efficacy variable. Scores for individual PANSS items (previously described) were combined to form composite scores for the positive and negative subscale scores, the General Psychopathology Scale score, and the activation-factor score; see subheading (b).

(b) Calculation or derivation of outcome variable

For each visit, the PANSS Positive and Negative subscale scores were calculated, respectively, as the sum of scores for items P1 through P7 and items N1 through N7 (see Section 5.5.3.2). The PANSS General Psychopathology Scale score for each visit was calculated as the sum of the scores for items G1 through G16 (see Section 5.5.3.2).

In the calculation of Positive and Negative subscale scores, if any item score was missing for a given visit, then the total score for that visit was considered missing. In the calculation of the General Psychopathology Scale score, if exactly 1 item score was missing for a given visit,

then the total score was calculated as the sum of all nonmissing item scores x (16/15). If more than 1 item score were missing, then the total score was considered missing for that visit.

For each visit, the PANSS activation factor score (White et al 1997) was calculated as the sum of the following 6 individual-item scores: excitement (P4), hostility (P7), poor rapport (N3), tension (G4), uncooperativeness (G8), and poor impulse control (G14). If any item had a missing score for a given visit, then the activation factor score was considered missing for that visit.

5.5.3.6 Secondary variable: PANSS response

(a) Methods of assessment

PANSS total scores were determined at each visit as described for the primary efficacy variable.

(b) Calculation or derivation of outcome variable

PANSS response was defined as a decrease from baseline in PANSS total score of at least 30% at Day 42 or the final visit. Alternative criteria, ie, decreases from baseline of at least 40% and at least 50%, were also used to define PANSS response.

5.5.3.7 Secondary variables: change in CGI Severity of Illness item score from baseline to postbaseline visits and CGI Global Improvement scores across visits

(a) Method of assessment

The CGI Severity of Illness item was assessed at randomization (Day 1), and on Days 4, 8, 15, 28, and 42 (or withdrawal). This item is rated on a 7-point scale (1=normal, 7=among the most extremely ill patients).

The CGI Global Improvement item, which describes change from baseline, was assessed on Days 4, 8, 15, 28, and 42 (or withdrawal). This item is rated on a 7-point scale (1=very much improved, 7=very much worse).

At each center from visit to visit, CGI assessments were made by a single individual to reduce variability in scoring.

(b) Calculation or derivation of variable

The change from baseline (Day 1) in the CGI Severity of Illness score was calculated as the difference between the score at a given postbaseline visit and the baseline score.

CGI Global Improvement was considered in terms of the proportion of patients who were rated as *much* or *very much improved*.

5.5.4 Patient-Reported Outcomes (PRO) measurements and variables (not applicable)

5.5.5 Health Economics measurements and variables (not applicable)

5.5.6 Pharmacokinetics measurements and variables (not applicable)

5.5.7 Safety measurements and variables

5.5.7.1 Summary of safety objectives and variables

Table 6 summarizes study safety variables and their relationship to study safety objectives.

Table 6 Safety variables relating to study objectives

Objective	Summary variables for analysis: safety population
To assess the following:	Adverse events (AEs) in the following categories:
The tolerability and safety of quetiapine SR tablets administered once daily as compared with placebo in patients with schizophrenia	• All AEs; drug-related AEs; serious AEs (SAEs); AEs leading to withdrawal (DAEs) • Special-interest AEs, including somnolence, tachycardia, and postural hypotension (and related AEs), dizziness, and syncope • Special safety-area AEs, including AEs related to EPS, QT prolongation, diabetes mellitus, neutropenia/agranulocytosis, and suicidality
The similarity of the safety profiles of quetiapine SR tablets and marketed quetiapine IR tablets	Clinical laboratory test results (hematology, clinical chemistry) at baseline (Day 1) and Day 42 or final visit, changes from baseline, and results categorized as clinically important per predefined criteria
The tolerability and safety of quetiapine SR therapy initiated at a dose of 300 mg	Vital signs (pulse rate and blood pressure), weight, and body mass index: results at baseline (Day 1) and each postbaseline visit, changes from baseline, and results categorized as clinically important per predefined criteria (including orthostatic changes); metabolic syndrome risk factors: change at end of treatment
	Electrocardiogram results at baseline (Day 1) and Day 42 or final visit; changes from baseline, and results categorized as clinically important per predefined criteria
	Simpson-Angus Scale total scores at baseline (Day 1) and each postbaseline visit; changes from baseline
	AIMS total scores at baseline (Day 1) and each postbaseline visit; changes from baseline to each postbaseline visit; proportion of patients whose scores exceed the baseline score at any time during study treatment
	Barnes Akathisia Rating Scale Clinical Global Assessment score
	Use of anticholinergic medications

AIMS Abnormal Involuntary Movement Scale. EPS Extrapyramidal symptoms.
IR Immediate release. SR Sustained release.

Timings for safety assessments were presented in the study plan (Table 1). The methods for collecting safety data are described below.

5.5.7.2 Adverse events

The definitions of AEs, SAEs, and other significant adverse events (OAEs) were provided in the protocol; study personnel were required to familiarize themselves with the terms, their definitions (provided herein), and any reporting requirements.

(a) Adverse events in general

An AE is the development of an undesirable medical condition or the deterioration of a preexisting medical condition during or following exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be a symptom (such as nausea or chest pain), a sign (such as rash or enlarged liver), or an abnormal result of an investigation (including blood tests, x-rays, electrocardiography, or scans of various types). In clinical studies, an AE can occur at any time, including the screening or run-in period, even if no study treatment has been administered.

Pregnancy itself would not to be regarded as an adverse event unless there was suspicion that the investigational product interfered with the effectiveness of a contraceptive medication. However, the protocol required that the outcome of any pregnancy (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) be documented and followed up even if the patient withdrew from the study. All reports of congenital abnormalities, birth defects, and spontaneous miscarriages would be recorded as SAEs. An elective abortion without complications would not be considered an AE. As applicable, all pregnancy outcomes would be reported to AstraZeneca on the pregnancy outcomes CRF.

(b) Serious adverse events

An SAE is an AE that occurs during any study phase and at any dose of the investigational product, active control agent, or placebo that fulfills one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalization or prolongs existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect as seen in the off-spring of a study patient
- is an important medical event that could jeopardize the patient or require medical intervention to prevent one of the outcomes listed above

Additional guidance on interpreting these criteria was provided in the protocol.

(c) Other significant adverse events

After data were unblinded, safety data were evaluated by the Drug Safety Physician and also by the Clinical Study Team Physician to determine if any OAEs occurred. Significant AEs of particular clinical importance, other than SAEs and AEs leading to discontinuation of study treatment (DAEs), are classified as OAEs. Examples of these are marked hematological and other laboratory abnormalities and AEs that require intervention (other than those already classified as serious), dose reduction, or significant additional treatment. Had OAEs been identified, narratives would have been included in this clinical study report.

(d) Recording of adverse events

Once patients were given enrollment numbers, all adverse events that occurred before treatment, during treatment, or within 30 days after treatment ended were recorded on the appropriate CRF, whether or not the events were considered related to study drug. If a diagnosis of the patient's condition were made in conjunction with an AE or group of AEs, then this diagnosis would be recorded as an adverse event in instances of well-recognized syndromes (eg, fever, runny nose, and cough could be recorded as *flu*). However, if a diagnosis of the patient's condition were not made, or if the individual symptoms were not well recognized, then the individual symptoms would be recorded separately.

For each AE, a description of the event, its intensity, its duration, the action taken (eg, treatment and follow-up tests), and outcome were noted, along with the investigator's assessment of causality, ie, the relationship between event and study drug, if any. To guide the investigator in the assignment of causality, the CRF asked the following question: *In your medical judgment, is there a reasonable possibility that the event may have been caused by the trial therapy?* If there were a valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the adverse event, then this question would be answered *yes*; otherwise, if no valid reason existed for suggesting a possible relationship, then the question would be answered *no*.

Patients were interviewed for subjective symptomatology throughout the study. After an initial inquiry, patients were asked the following standard question: *Has anything bothered you since the last visit (or last assessment)?* Patients were also instructed to volunteer adverse events noted at any time during the study. All positive responses were recorded on the AE CRF as previously described.

Patients were also asked to assess intensity for each reported AE according to the following scale:

1 = mild (awareness of sign or symptom but easily tolerated)

2 = moderate (discomfort sufficient to cause interference with normal activities)

3 = severe (incapacitating, with inability to perform normal activities)

In the handling of AEs, distinction was made between AEs that were severe and AEs that were serious. Severity is considered a measure of intensity, whereas seriousness is based on predefined criteria.

Lack of efficacy

Any detrimental change in the patient's condition after the patient entered the study was brought to the investigator's attention. Detrimental changes that constituted progression or relapse of schizophrenia or lack of drug efficacy, as assessed by the investigator, were not reported as adverse events even if the events necessitated or prolonged hospitalization. When there was uncertainty as to whether deterioration was due to a lack of efficacy or an adverse event, the deterioration was considered a lack of efficacy unless AstraZeneca or the reporting physician believed that the study drug contributed to the deterioration. In such a case, the deterioration was treated as an adverse event and reported on the appropriate CRF.

Overdose

For the purpose of this study, all overdoses, with or without associated symptoms, had to be reported as adverse events. When an overdose was associated with sequela that met SAE criteria, the overdose had to be reported immediately (within 1 day) to designated monitoring personnel. In all instances, the overdose substance was noted, and the overdose was assessed as being accidental or intentional. If an overdose was a suicide attempt, this fact was clearly stated. Any AE that occurred as a result of an overdose was recorded on the CRF as *sequela to overdose* (eg, nausea as sequela to overdose).

Drug abuse or misuse

Study drug abuse was considered and reported as an SAE, even when there were no symptoms or additional adverse events. Study drug misuse was considered an AE but not an SAE unless it was accompanied by serious sequelae.

Suicide and attempted suicide

Suicide and attempted suicide, irrespective of the method but occurring in connection with the use of study drug, was reported as an adverse event. The event was identified as suicide or attempted suicide, and the method of the suicide or attempt was also recorded. If an attempted suicide met SAE criteria, then it was reported as an SAE.

(e) Reporting of serious adverse events including deaths

All SAEs had to be reported, whether or not they were considered causally related to the investigational product. SAEs that occurred during the study period or within 30 days after administration of the last dose of study drug had to be reported to the local monitor or other AZ representative within 1 day of the investigator becoming aware of the event. Any fatal or

life-threatening adverse event had to be reported immediately, and no more than 1 day from the time the investigator became aware of the event. A statement of causality was provided for all SAEs. Follow-up information on SAEs was provided as soon as it became available, but no more than 1 day from the time the investigator became aware of the information.

If an SAE was reported to an investigator at any time after a patient completed or withdrew from the study (including any required post-treatment follow-up) and the investigator felt the event was related to study drug, the investigator was obligated to report that event to AstraZeneca.

All deaths that occurred within the study period or within 30 days after study drug was discontinued had to be reported to AstraZeneca or its designee within 1 day.

If death was the reason for a patient's withdrawal from the study, the withdrawal could be reported as either due to disease progression or due to an adverse event. If death was due to a combination of disease progression and any other condition, the investigator was required to decide on the primary cause of death and assign the withdrawal to the appropriate category. The cause of death was documented on the appropriate CRF. If an autopsy was performed, the autopsy results were to be obtained and forwarded to AstraZeneca, along with any available toxicology reports. Death from any cause except objective disease progression was considered an SAE and was recorded on the AE CRF. Deaths were subject to the same reporting criteria used for SAEs.

(f) AEs related to specific safety areas

The examination of safety data in the quetiapine SR clinical trial program also included evaluation of certain composite data for purposes of fully defining risk and providing overall conclusions relative to the following (also referred to as specific safety areas): EPS, diabetes mellitus, QT prolongation, clinically important weight gain, metabolic syndrome, blood dyscrasias (neutropenia or agranulocytosis), and suicidality. In assessing prevalence of these clinical conditions, AstraZeneca examined the safety database for certain MedDRA terms; these terms are summarized in Table 7, by specific safety area as applicable.

Table 7 Adverse events (MedDRA terms) defined for specific safety areas

Specific safety area	Related AEs (MedDRA preferred terms)
EPS	Akathisia * akinesia * athetosis * bradykinesia * buccoglossal syndrome * cervical spasm * chorea * choreoathetosis * cogwheel rigidity * drooling * dyskinesia * dystonia * esophageal dyskinesia * extrapyramidal disorder * freezing phenomenon * gait festinating * grimacing * hyperkinesia * hypertonia * hypokinesia * masked facies * micrographia * movement disorder * muscle contractions * involuntary * muscle rigidity * nuchal rigidity * oculogyration * opisthotonus * parkinsonian gait * parkinsonism * posturing * psychomotor hyperactivity * restlessness * tardive dyskinesia * torticollis * tremor
Diabetes mellitus	Anti-insulin antibody increased * anti-insulin antibody positive * blood glucose abnormal * blood glucose fluctuation * blood glucose increased * blood insulin abnormal * blood insulin decreased * blood insulin increased * blood insulin C-peptide abnormal * blood insulin C-peptide decreased * blood insulin C-peptide increased * blood proinsulin abnormal * blood proinsulin decreased * blood proinsulin increased * dawn phenomenon * diabetes mellitus * diabetes mellitus inadequate control * diabetes mellitus insulin dependent * diabetes mellitus non-insulin dependent * diabetes with hyperosmolarity * diabetic coma * diabetic complication * diabetic hyperglycemic coma * diabetic hyperosmolar coma * diabetic hyperosmolar non-ketoacidosis * diabetic ketoacidosis * diabetic ketoacidotic hyperglycemic coma * glucose tolerance decreased * glucose tolerance impaired * glucose tolerance test abnormal * glucose urine present * glycosylated hemoglobin increased * hyperglycemia * hyperinsulinemia * hyperinsulinism * impaired fasting glucose * impaired insulin secretion * increased insulin requirement * insulin resistance * insulin resistance syndrome * insulin resistant diabetes * insulin-requiring type II diabetes mellitus * insulin tolerance test abnormal * metabolic disorder * somogyi phenomenon * polydipsia * polyuria * thirst * blood ketone body present * blood ketone body increased * neonatal diabetes mellitus * glycosuria during pregnancy * gestational diabetes * glucose tolerance impaired in pregnancy * diabetes complicating pregnancy
QT prolongation	Long QT syndrome * electrocardiogram QT corrected interval prolonged * electrocardiogram QT prolonged * long QT syndrome congenital * torsades de pointes * cardiac arrest * cardiorespiratory arrest * cardiac death * electromechanical dissociation * sinus arrest
Neutropenia or agranulocytosis	Band neutrophil count decreased * band neutrophil percentage decreased * febrile neutropenia * neutropenia * neutropenic infection * neutropenic sepsis * neutrophil count decreased * neutrophil percentage decreased * granulocyte count decreased * granulocytopenia * idiopathic neutropenia * neutrophil count abnormal * neutrophil percentage abnormal * and agranulocytosis
Suicidality	Completed suicide * suicide attempt * suicidal ideation * intentional self-injury * self injurious behavior * self-injurious ideation

EPS Extrapyramidal syndrome. MedDRA Medical dictionary for regulatory activities.

5.5.7.3 Laboratory safety measurements and variables

The laboratory safety variables assessed in this study are summarized in Table 8.

Table 8 Laboratory safety variables

Type of assessment	Variables
Hematology	Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count (total and differential), and platelet count
Clinical chemistry	
Hepatic function	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase
Renal function	Urea nitrogen and creatinine
Serum electrolytes	Sodium and potassium
Thyroid function	Free thyroxine (T_4), thyroid-stimulating hormone (TSH), and triiodothyronine (T_3)
Lipid analysis	High-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides
Other	Albumin, prolactin, and glucose (assumed fasting)

(a) Collection of biological samples and methods of assessment

Blood samples for analysis of laboratory safety variables were collected on the day of screening (Day 1) and Day 42 (or upon withdrawal). Blood samples were analyzed by Quest Diagnostics (see Section 2.3.1) according to their standard operating procedures.

(b) Calculation or derivation of outcome variables

Changes from baseline were calculated as the differences between the test results at Day 42 (or final visit) and the baseline result.

Individual laboratory test results were assessed for clinical importance using the criteria listed in Table 9. Laboratory test results from periods outside of the accepted time windows were not used in programmed calculations.

Table 9 Criteria for clinically important clinical laboratory test results

Laboratory test category	Laboratory test	Criteria for clinically important
Hematology	Hematocrit	≤0.37 or ≥0.50 volume fraction (men)
		≤0.32 or ≥0.55 volume fraction (women)
	Hemoglobin	≤11.5 or ≥18.5 g/dL (men)
		≤10.5 or ≥16.5 g/dL (women)
	RBC count	≤3 or ≥6 x 10^{12} cells/L
	Total WBC count	≤3 or ≥16 x 10^{9} cells/L
	Absolute neutrophils	≤1.5 or ≥10 x 10^{9} cells/L
	Absolute neutrophils/agranulocytosis	<0.5 x 10^{9} cells/L
	Eosinophils	≥1 x 10^{9} cells/L
	Basophils	≥0.5 x 10^{9} cells/L
	Lymphocytes	≤0.5 or ≥6 x 10^{9} cells/L
	Monocytes	≥1.4 x 10^{9} cells/L
	Platelet count	≤100 or ≥600 x 10^{9} cells/L
Clinical chemistry		
Hepatic function	Alanine aminotransferase	≥3 x ULN (U/L)
	Aspartate aminotransferase	≥3 x ULN (U/L)
	Alkaline phosphatase	≥3 x ULN (U/L)
	Total bilirubin	≥1.5 x ULN (μmol/L)
Renal function	Blood urea nitrogen	≥30 mg/dL
	Creatinine	≥1.58 mg/dL
Serum electrolytes	Sodium	≤132 or ≥152 mmol/L
	Potassium	<3.0 or >5.5 mmol/L
Thyroid function	Free thyroxine	<0.8 x LLN or >1.2 x ULN
	Thyroid-stimulating hormone	>5 mIU/L
	Triiodothyronine	<0.8 x LLN or >1.2 x ULN
Lipid analysis	High-density lipoprotein cholesterol	≤40 mg/dL
	Low-density lipoprotein cholesterol	≥160 mg/dL
	Total cholesterol	>240 mg/dL
	Triglycerides	>200 mg/dL
Other	Albumin	<26 or ≥70 g/L
	Prolactin	>20 μg/L (men); >30 μg/L (women)
	Glucose	≤45 or ≥126 mg/dL (fasting)
		≤45 or ≥200 mg/dL (random)

LLN Lower limit of normal. RBC Red blood cell. ULN Upper limit of normal. WBC White blood cell.

The results of hepatic-function tests were also considered relative to Hy's Law, ie, whether patients had a modestly elevated ALT concentration (3 times the upper limit of normal) and a total bilirubin concentration of at least 1.5 times the upper limit of normal without a markedly elevated alkaline phosphatase concentration (1.5 times the upper limit of normal).

Glucose and lipid variables were evaluated for the general safety population with the assumption that all blood samples were taken under fasting conditions as required by the protocol (assumed fasting condition). Glucose data would also be evaluated separately, as applicable, for patients with a documented fasting status (ie, the investigator confirmed fasting on the CRF and the patient confirmed not eating in the 8-hour interval before blood sampling). If documented fasting status could not be confirmed, then glucose data were also evaluated as if blood samples were taken at random (assumed random condition). This is reflected in Table 9 by the application of 2 criteria in determining clinically important glucose values.

Glucose data were also evaluated for 3 patient subgroups: (1) patients known to be diabetic, (2) patients at risk for diabetes (at-risk) and (3) patients neither diabetic nor at risk for diabetes (nondiabetic). Subgroup definitions varied depending on assumed conditions, as follows:

- Under assumed fasting condition
  - Diabetic patients were those with either baseline glucose levels ≥126 mg/dL or a medical history that included any of the following key or partial key words: *diabetes, DDM, melli, insulin, hypergly, elevated blood sugar, or diabetic.*
  - At-risk patients were those with baseline glucose levels ≥100 but <126 mg/dL, a baseline BMI ≥35, or a medical history that included the key word *gestational*.
- Under assumed random condition
  - Diabetic patients were those with either baseline glucose levels ≥200 mg/dL or a medical history that included any of the following key or partial key words: *diabetes, DDM, melli, insulin, hypergly, elevated blood sugar, or diabetic*
  - At-risk patients were those with a baseline BMI ≥35 or a medical history that included the key word *gestational*.

Nondiabetic patients were those who did not meet diabetic or at-risk criteria per condition.

5.5.7.4 Other safety measurements and variables: vital signs, weight, and body mass index

(a) Methods of assessment

At each scheduled assessment, blood pressure and pulse rate were recorded after the patient had been supine for 5 minutes and then after the patient had been standing for 30 seconds or less. On Days 1, 2, 5, 6, 8, and 9, patients had supine and standing vital signs recorded within

15 minutes before and 1, 6, and 12 hours after study drug administration. On Day 15, all patients had supine and standing vital signs recorded before, and 1 and 6 hours after, study drug administration. Patients who were hospitalized on Day 15 were also required to have these assessments performed 12 hours after study drug administration. Those patients who were not hospitalized on Day 15 were required to take their study medication while at the study center so that predose and postdose assessments could be performed. Outpatients who did not take their study medication at the study center on Day 15 did not have timed assessments performed. The timing of vital-sign assessments relative to administration of study treatment was planned so that patients could be closely monitored for changes in their blood pressures and pulse rates as the doses of quetiapine SR were increased over the first 2 weeks of randomized treatment.

Weight was measured at each visit using a standard scale.

(b) Calculation or derivation of variables

Individual vital-sign measurements, including orthostatic changes, were assessed for clinical importance using the criteria listed in Table 10. After discussion with regulatory authorities, some of these criteria were modified from those specified in the protocol to more accurately identify important changes in vital signs.

Table 10 Criteria for clinically important vital signs and weight

Variable	Criteria for clinically important	
	Absolute value	**Change from baseline**
Pulse rate[a]	>120 bpm	Increase ≥15 bpm
	<50 bpm	Decrease ≥15 bpm
Systolic blood pressure[a]	≥180 mmHg	Increase ≥20 mmHg
	≤90 mmHg	Decrease ≥20 mmHg
Diastolic blood pressure[a]	≥105 mmHg	Increase ≥30 mmHg
	≤50 mmHg	Decrease ≥20 mmHg
Orthostatic change	**Change from supine to standing after 1 minute**	
Pulse rate	Increase ≥20 bpm	
Systolic blood pressure	Decrease ≥20 mmHg	
Diastolic blood pressure	Decrease ≥20 mmHg	
Combined pulse rate and blood pressure	Decrease ≥20 mmHg in systolic blood pressure and increase ≥20 bpm in pulse rate	

[a] Supine or standing.
bpm Beats per minute. mmHg Milliliters of mercury. NA Not applicable.

Body mass index (BMI) was defined as follows: BMI = (weight [kg])/(height [m^2]).

Changes from baseline (Day 1) in vital signs, weight, and BMI were calculated as the difference between a measurement at a given postbaseline visit and the corresponding baseline measurement.

Orthostatic change was the value difference between the supine value and the 1-minute standing value. Criteria for clinical importance were applied to the change in that difference from baseline to final visit.

A change in weight of ≥7% (whether an increase or decrease) was predefined as clinically important.

5.5.7.5 Other safety measurements and variables: ECG results

(a) Methods of assessment

Twelve-lead ECGs were acquired at the study center using an approved machine, with results transmitted to the central ECG laboratory, eResearch Technology (see Section 2.3.1). An operator at the central laboratory performed quality assurance of the ECG waveform and recorded patient demographics. The ECGs were processed through a computer interpretation program and were then reviewed, first by an ECG analyst and then by a board-certified cardiologist. The ECG results were immediately reported to the study center via fax.

When the ECG was performed on Day 42, the previous dose of study medication and the time of drug administration were recorded on the CRF; the time of ECG acquisition was recorded in the database at the central ECG laboratory.

(b) Calculation or derivation of variables

Individual ECG results were assessed for clinical importance using the criteria listed in Table 11.

Table 11 Criteria for clinically important electrocardiogram findings

Variable	Criteria for clinically important	
	Absolute value	**Change from baseline**
Heart rate	<50 bpm or >120 bpm	An increase ≥15 bpm or decrease ≥15 bpm
PR interval	≥210 ms	N/A
QRS interval	≤50 ms or ≥120 ms	N/A
QT interval	≤200 ms or ≥500 ms	An increase ≥60 ms
QTc interval (Fridericia correction)	≥450 ms	An increase ≥60 ms

bpm Beats per minute. ms Milliseconds. N/A Not applicable.
QTc interval. QT interval corrected for heart rate.

The QT interval was corrected for heart rate using the Fridericia correction:

QTc_F interval = QT interval/$RR^{0.33}$

Changes from baseline (Day 1) in ECG measurements were calculated as the difference between the measurement at Day 42 (or final visit) and the baseline measurement.

5.5.7.6 Other safety measurements and variables: physical examination results

(a) Methods of assessment

Physical examinations, including ophthalmologic examination, were conducted at screening and Day 42 (or at withdrawal). Ophthalmologic examination included an assessment of the lenses by methods adequate to detect cataract formation.

(b) Calculation or derivation of variables

Significant medical conditions and findings upon examination were listed as past conditions or current ongoing conditions.

5.5.7.7 Other safety measurements and variables: metabolic syndrome risk factors

(a) Methods of assessment

Metabolic risk factors were evaluated by determining which patients had relevant medical history at baseline or who exhibited combinations of the following findings:

- BMI ≥30 kg/m^2
- Supine systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mm Hg averaged over last 2 assessments
- Triglycerides ≥150 mg/dL
- High-density lipoprotein (HDL) <40 mg/dL for men or <50 mg/dL for women
- Fasting glucose ≥100 mg/dL

Patients who had at least 3 of the 5 findings were considered at risk for metabolic syndrome.

(b) Calculation or derivation of variables

Values for each variable were taken from data recorded on the relevant CRFs, except for BMI, which was calculated as described in Section 5.5.7.4.

5.5.7.8 Other safety measurements and variables: Modified Simpson-Angus Scale AIMS, and Barnes Akathisia Rating Scale scores

(a) Methods of assessment

The modified Simpson-Angus Scale (SAS) comprises 10 items that assess drug-induced extrapyramidal symptoms, including akathisia. Each item is rated on a 5-point scale (0=normal or condition absent; 4=condition present in extreme form).

The AIMS comprises 10 items that assess abnormal involuntary movements including facial expressions, ticks, and oral movements, movements in the extremities, and trunk movements. Additionally, the AIMS also provides for overall global assessments using 3 global-rating items. Each item is rated on a 5-point scale (0=none, 4=severe).

The Barnes Akathisia Rating Scale (BARS) comprises 4 items used to assess drug-induced akathisia. These items include objective assessment of motor restlessness, subjective patient awareness of restlessness and associated distress, and a global clinical assessment of akathisia. The objective and subjective items are rated a 4-point scale (0=condition absent, 3=condition present in extreme form). The global clinical assessment is rated on a 6-point scale (0= no akathisia, 6=severe akathisia). Only the global clinical assessment score was analyzed.

Scores on each of these 3 scales were determined at each visit starting on Day 1 (Visit 2).

(b) Calculation or derivation of variables

Modified SAS and AIMS total scores were calculated per visit as the sum of their 10 individual-item scores, respectively. Changes from baseline (Day 1) were calculated as the difference between the total score at a given postbaseline visit and the baseline score.

In the calculation of SAS total score, if exactly 1 item score was missing for a given visit, then the total score was calculated as the sum of all nonmissing values x (10/9). If scores for more than 1 individual item were missing or rated 9 (not ratable), then the total score for that visit was considered missing. Additionally, descriptive statistics for individual items did not include scores for items rated 9 (not ratable).

In the calculation of AIMS total score, if exactly 1 item score was missing for a given visit, then the total score was calculated as the sum of all nonmissing values x (10/9). If scores for more than 1 individual item were missing, then the total score for that visit was considered missing.

5.5.8 Pharmacogenetic measurements and variables

5.5.8.1 Collection of samples for genetic analysis

Each 9-ml blood sample collected and designated for genetic testing was sent to Quest Diagnostics (Van Nuys, California) for storage until the time of analysis. Maximum storage time was designated as 15 years, after which time samples will be destroyed.

5.5.8.2 Pharmacogenetic variables

No objectives were defined relative to pharmacogenetic parameters and, hence, no variables were identified. Results of pharmacogenetic blood testing were not expected prior to the conclusion of the study and no results are included in this report.

5.6 Data management and quality assurance

The quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in the sections that follow.

AstraZeneca's quality assurance and internal quality control procedures provide reassurance that the clinical study program was carried out in accordance with GCP guidelines. AstraZeneca undertakes a GCP audit program to ensure compliance with its procedures and to assess the adequacy of its quality control measures. Audits, by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures, are directed towards all aspects of the clinical study process and its associated documentation.

5.6.1 Monitoring

Parexel (200 West St, Waltham, Massachusetts, USA) provided monitoring services for this study. Before a study site was initiated, Parexel personnel visited the site to assure adequacy of the facilities for protocol implementation and to discuss with the investigator general obligations regarding clinical studies with investigational new drugs.

During the study, Parexel monitors had regular contact with study personnel at the investigational sites, at intervals of approximately every 6 weeks, with at least 2 phone contacts between monitoring visits. If a site had no active patients, the monitor would contact the site at least every 2 weeks to obtain a screening update. During onsite visits, monitors reviewed CRFs for completeness and adherence to the protocol. One hundred percent (100%) source data verification (a direct comparison of CRF data with the patient's clinical records) was performed. The monitor also performed drug-accountability checks and periodically asked to review the investigator's study file to assure completeness of documentation for all aspects of the study and its conduct.

As part of the data audit, source documents (eg, hospital and office records) had to be made available for the monitor's review. Investigators were made aware of their responsibilities for receiving monitors during onsite visits, for cooperating in providing documents for review, for responding to inquiries that might arise during the review, and for permitting study file inspection by the Food and Drug Administration or other national regulatory authorities as relevant.

Upon completion of the study, the monitor arranged for a final review of the study files, which were then made secure for 1 of the following 2 periods: (1) at least 2 years after the date on which the FDA approves quetiapine SR for marketing relative to the indications studied in the

investigational program or (2) at least 2 years after the date on which the entire investigational program (all clinical studies) is terminated and the FDA is notified.

5.6.2 Training

Principal investigators maintained records of all individuals involved in the study (medical, nursing, and other staff) and ensured that this staff was given appropriate training necessary for the conduct of the study. Additionally, any new information relevant to the performance of the study was communicated to these individuals.

5.6.3 Data management

Paper-based, carbonless CRFs (in triplicate) were provided for the recording of data not captured electronically. Guidelines for entering data and completing the CRFs were provided. The first copy (original) of the completed CRF was sent to AstraZeneca, the second copy was kept by Parexel as a working copy, and the third copy was retained by the investigator at the study site.

Data from CRFs were double-entered into the database management system. Queries were sent to study personnel to clarify any missing, impossible, or inconsistent entries in the CRF, and the database was amended accordingly. All coding, editing, and validation of data, including logic checks between records in the database, were performed on blinded data. AEs were coded for preferred terms and body system using an in-house dictionary based on the FDA's coding symbols for a thesaurus of adverse reaction terms (COSTART) dictionary.

To maintain consistency with other clinical studies in the quetiapine SR clinical study program, AEs were also coded using the Medical Dictionary for Regulatory Activities (MedDRA) and reported according to system-organ class and preferred term. Adverse event rates relative to MedDRA coding are included in the main body of this report. Adverse event rates relative to COSTART coding are included in Appendix 12.2 (12.2.7.1.1, 12.2.7.2.1, 12.2.7.3.1, 12.2.7.4.1, and 12.2.7.5.1).

Quality-control procedures were performed by both Parexel and AstraZeneca. All data for key variables (eg, PANSS scores, demographic characteristics, adverse events, medications, and trial completion) were checked. In addition, 10% of patients were selected at random for quality control of 100% of their data. Before *clean file* was declared, quality-control checks of the data were completed and all decisions on the evaluability of the data for each patient were made and documented. The randomization code was broken after clean file was declared.

Data received electronically by Parexel from a validated source (eg, ECG data from eResearch Technology and clinical laboratory data from Quest Diagnostics) were loaded directly into the study database for analysis.

5.7 Statistical methods and determination of sample size

5.7.1 Statistical evaluation

The Clinical Information Sciences group of AstraZeneca performed the complete statistical analyses of study data using SAS, version 8.2.

5.7.2 Description of outcome variables in relation to objectives and hypotheses

To demonstrate the superior efficacy of quetiapine SR tablets compared with placebo in the treatment of patients with schizophrenia (the primary objective), a reliable and well-accepted assessment tool was needed. The PANSS, which examines 30 aspects of schizophrenia including both positive and negative symptoms, as well as general psychopathology, was selected. Its reliable use in the evaluation of patients with schizophrenia is well documented in the literature. Assessing change in PANSS total score from baseline to Day 42 was consistent with an earlier quetiapine study that showed significant differences between quetiapine IR and placebo at 6 weeks for change from baseline in BPRS total scores. Secondary efficacy variables (outcomes) were considered supportive variables and hence were expected to provide additional data for consideration when the primary analysis results were interpreted. Additionally, secondary outcomes were expected to demonstrate similar efficacy between quetiapine SR and quetiapine IR.

To characterize the safety profile of quetiapine SR, standard and drug-class-specific safety assessments were incorporated into the study design. Laboratory variables and measurements of specific interest in the assessment of atypical antipsychotics included fasting glucose levels, thyroid function, lipid levels, prolactin levels, weight, heart rate and cardioelectrical activity, and eye health. Tools used specifically for assessing potential neurological effects included the modified SAS, the AIMS, and the BARS.

Efficacy and safety variables as they relate to study objectives were summarized previously in Table 5 and Table 6, respectively.

5.7.3 Description of analysis sets

The statistical analysis plan identified 3 populations or data analysis sets: the safety population, the modified intent-to-treat (MITT) population, and the per-protocol (PP) population or analysis set.

5.7.3.1 Safety population

The safety population included all patients who took at least 1 dose of study treatment. Data from this population were used for safety analyses.

5.7.3.2 MITT population

The MITT population included all evaluable patients in the safety population, ie, all patients who took study treatment and who had a PANSS assessment before taking study treatment (baseline) and at least 1 PANSS assessment after taking study treatment. Data from this population were used for the primary and secondary efficacy analyses.

5.7.3.3 PP analysis set

The PP analysis set, a subset of the MITT population, included only those patients who did not have significant protocol violations or deviations affecting efficacy. Data from this population were used to test for homogeneity of treatment effects in the primary efficacy analysis.

A protocol violation was defined as a failure to meet all inclusion and exclusion criteria. A protocol deviation was defined as noncompliance with protocol-specified procedures once the patient entered the study. In general, protocol violations and deviations with potential to significantly affect efficacy led to a patient's exclusion from the PP population. Data from patients with protocol deviations were included in the analyses in a way that would minimize any potential bias. However, if a deviation were considered serious enough, the patient's data would be excluded from analysis.

After all patients completed or withdrew from the study, but before any data were unblinded, the project physician and statistician reviewed all actual protocol violations and deviations to confirm exclusion of data from the PP analyses. Major protocol violations and deviations are defined in the statistical analysis plan and summarized in Table 12.

Table 12 Protocol deviations that excluded patients from the PP analysis set

Deviation	Data excluded from analysis
Violated inclusion criteria	All data
Violated exclusion criteria	All data
Treatment noncompliance	
Patient returned >60% of dispensed tablets	All data
Patient missed more than 5 consecutive doses of study treatment	Data collected after 5th dose was missed
Patient used prohibited concomitant medication	Data collected at the point of violation and any data collected thereafter

In the event that patients were incorrectly randomized, were randomized but did not take any study treatment, or did not comply with the protocol-specified visit schedule, data for these patients would be handled as follows:

- If the wrong treatment was given to a patient because of misrandomization, efficacy data included in the MITT and PP analyses would be analyzed according to the treatment assigned in the original randomization scheme. Safety data would be analyzed according to the patient's actual treatment if the patient took the wrong treatment throughout the entire study. If the patient took the wrong treatment

during part of the study only, safety data would be analyzed according to assigned treatment, and the incorrect treatment would be noted (if applicable) in this report.

- If a patient was randomized, but did not take any study treatment, data from these patients would be excluded from safety and efficacy (MITT and PP) analyses but would be included in data listings and enrollment summaries.

- Windows were defined for all protocol-specified visits, as detailed in the SAP (see Appendix 12.1.9). Rules for the inclusion of data, whether observed case (OC) data or last observation carried forward (LOCF), were also defined in the SAP. All such data were included in the data listings. Data excluded from analysis because they were not contained within the defined visit windows are indicated as such.

5.7.4 Methods of statistical analysis

All variables were summarized using descriptive statistics, as appropriate to the data. Statistics for continuous values included number of patients, minimum, maximum, mean, median, and standard deviation, while those for binary values included incidence and percentage of patients. All statistical analyses used the last-observation-carried-forward (LOCF) value for patients who withdrew early or who had missing data. Observed case (OC) data (other than at day 4) were not analyzed statistically. Descriptive statistics were presented for both LOCF and OC data. Analysis of covariance (ANCOVA) was used to analyze continuous valued outcomes (eg, PANSS total score), while binary data (eg, PANSS response) were analyzed using Cochran-Mantel-Haenszel chi-square tests.

Statistical analyses were adjusted for multiplicity among the three primary endpoints to control the experiment-wise error rate, using the Hochberg (1988) method. Consequently, it may be misleading to compare any of the adjusted p-values with unadjusted p-values. For example, an unadjusted p-value of p=0.02 cannot be considered more statistically significant than an adjusted p-value of p=0.04. Secondary analyses were not adjusted for multiplicity; therefore, the corresponding p-values cannot be regarded with equal certainty relative to the adjusted p-values.

All statistical tests were 2 sided, with a significance level of 0.05 (except as adjusted for multiplicity by the Hochberg method). Each test was a comparison of a quetiapine dose versus placebo, with the null hypothesis that the mean difference between quetiapine and placebo equaled zero, versus the alternative hypothesis that the mean difference was not equal to zero.

5.7.4.1 Statistical analysis methods for efficacy variables

(a) Primary variable

Change in PANSS total score from baseline to Day 42 (or final visit) was tested for treatment effect using an ANCOVA model that included terms for center, treatment, and baseline score. All pairwise differences between least-squares means for the quetiapine treatment groups and the placebo treatment group were calculated, and 95% confidence intervals for these

differences were constructed. The p-values from the pairwise comparisons of the 3 quetiapine SR treatment groups with the placebo group were rank ordered, and the Hochberg (1988) method was used to adjust for multiplicity. The p-values from the pairwise comparisons of the 2 quetiapine IR dose groups with the placebo group were not adjusted for multiplicity.

(b) Secondary variables

Change in PANSS total score from baseline to each visit and changes in PANSS Positive and Negative Symptom subscale scores from baseline to each visit and at final visit were analyzed using the same ANCOVA model described for the primary efficacy variable but without adjustment for multiplicity.

PANSS total scores for Days 1 and 4 were combined across doses within each quetiapine formulation, and the changes from baseline (Day 1) to Day 4 were tested for differences between each quetiapine formulation and placebo using the same ANCOVA model and pairwise comparisons as described for the primary efficacy variable (without adjustment). This analysis, which was not specified in the protocol, was added to the SAP because there was no difference in treatment regimens for those treated with quetiapine SR through Day 4 and those treated with quetiapine IR formulation through Day 4.

PANSS response rates based on a 30% decrease from baseline in PANSS total score were tested for treatment differences at Day 42 or final visit using the Cochran-Mantel-Haenszel chi-square test. Response rates based on alternative criteria (40% and 50%) were summarized using frequency statistics but were not subjected to formal statistical analysis.

Changes from baseline in CGI Severity of Illness scores were tested for treatment effects using the ANCOVA described for changes from baseline in PANSS scores, with baseline Severity of Illness score as the covariate.

CGI Global Improvement scores were tested for treatment differences at Day 42 (or final visit) in the proportions of patients rated as *much improved* or *very much improved* using the Cochran-Mantel-Haenszel chi-square test.

5.7.4.2 Statistical analysis methods for safety variables

(a) Adverse events

All categories of AEs—AEs in general, SAEs, and DAEs—were summarized for the safety population (ie, the safety analysis set).

Numbers of adverse events and incidence rates for adverse events were summarized by MedDRA system-organ class and preferred term (and by COSTART body system and preferred term) using frequency statistics. Data were summarized for individual treatment groups, for the 3 SR treatment groups combined, and for the 2 IR treatment groups combined.

An event that occurred 1 or more times on the date of, or subsequent to, randomization contributed 1 observation to the numerator of the incidence rate; the denominator comprised

all patients exposed. The highest intensity and highest degree of relatedness (to study treatment) were also tabulated for each adverse event by treatment group.

Onset of certain AEs during the first 14 days of study treatment was investigated by calculating incidence rates by day. The events of interest during this period (MedDRA terms) included sedation, somnolence, lethargy, and sluggishness (individual terms and terms aggregated under the major term of somnolence); tachycardia and sinus tachycardia (individual terms and terms aggregated under the major term of tachycardia), orthostatic hypotension, dizziness postural, and postural orthostatic tachycardia syndrome (individual terms and terms aggregated under the major term of postural hypotension); dizziness, and syncope.

Overall incidence rates for AEs related to EPS, diabetes, QT prolongation, neutropenia/agranulocytosis, and suicidality were examined (see Table 7 for a definition of these AEs) and tabulated if present.

(b) Laboratory assessments

Clinical laboratory test results and changes from baseline were summarized using descriptive statistics. The numbers of patients with clinically important results, as defined in Section 5.5.7.3, were summarized using frequency statistics and shift tables to show changes from baseline. The frequency and percentage of patients in each treatment group who had clinically important free thyroxine and TSH concentrations were calculated; this analysis was repeated for patients who had clinically important triiodothyronine and TSH concentrations. Liver function was assessed by calculating the frequency and percentage of patients in each treatment group who had liver function test results that met the criteria for Hy's Law (as defined in Section 5.5.7.3). The protocol-specified regression analysis to detect time-related trends in laboratory test results was not done because laboratory tests were performed at screening and at the final visit only.

(c) Vital signs, weight, and BMI

For vital signs, weight, and BMI, values and changes from baseline were summarized by visit using descriptive statistics. The numbers of patients with clinically important results and the numbers of patients with orthostatic changes in pulse rate and blood pressure, as defined in Section 5.5.7.4, were summarized by visit using frequency statistics and shift tables to show changes from baseline.

(d) Electrocardiograms

Electrocardiogram measurements and changes from baseline were summarized using descriptive statistics. The numbers of patients with clinically important results, as defined in Section 5.5.7.5, were summarized by visit using frequency statistics and shift tables to show changes from baseline. The frequencies of patients with clinically important overall ECG results were tested for treatment effects using a Cochran-Mantel-Haenszel chi-square test.

(e) Physical examination results

Physical examination results were listed. No statistical analyses were planned.

(f) Metabolic syndrome risk factors

Patients were classified as meeting or not meeting each risk criterion at baseline and at the final assessment. The number and proportions of patients who shifted from meeting 0, 1, or 2 criteria to meeting either fewer than 3 versus 3 or more criteria at the final assessment were tabulated. The contribution of each factor toward meeting 3 or more criteria was evaluated within the population meeting aggregate risk criteria by determining the proportion of patients who shifted from not meeting to fulfilling each individual criterion. The incidence of patients with at least 3 metabolic syndrome risk factors excluding the triglyceride risk criterion was also presented.

(g) Neurological assessments

The results of neurological assessments (SAS total score, AIMS total score, and BARS Clinical Global Assessment score) and changes from baseline were summarized by visit using descriptive statistics. Changes from baseline in AIMS total score were tested for treatment differences using ANCOVA techniques as described for the efficacy analyses. The number of patients in each treatment group whose AIMS total score exceeded the baseline value at any time during randomized treatment was summarized using frequency statistics. Additionally, response in terms of relative change from baseline at the final visit—improved, no change, or worsened—was summarized in frequency tables for each assessment.

(h) Exposure to study treatment and other medications

Exposure to study treatment, prior medication use, and concomitant medication use were summarized using descriptive and frequency statistics as appropriate. The use of anticholinergic medications (for the treatment of EPS) was summarized using frequency statistics. The following drugs were categorized as anticholinergic agents: amantadine, benztropine, benzhexol, biperiden, diphenhydramine, ethopropazine, hyoscyamine sulfate (sulphate), orphenadrine, procyclidine, and trihexyphenidyl.

(i) Withdrawals

All withdrawals and reasons for withdrawal were summarized by day and by week using frequency statistics.

5.7.5 Determination of sample size

To obtain 480 evaluable patients (80 per treatment group), the study had a randomization goal of 504 patients; this goal assumed that 5% of randomized patients would not be evaluable.

The sample size of 80 patients per treatment group was based upon detection of an anticipated difference of 15.5 points in change from baseline (Day 1) PANSS total score at Day 42 or the

final visit (LOCF) between pairwise comparisons of the 3 quetiapine SR-treatment groups and the placebo-treatment group. This sample size provided 96.5% power for each 2-sided test, at an alpha level of 5%, to demonstrate superior efficacy of quetiapine SR compared with placebo. The sample size also provided an overall study power of 90% for all 3 quetiapine SR treatment groups to demonstrate superior efficacy compared with placebo.

The power calculations were based on information from previous quetiapine studies (Trials 5077IL/0014, 5077IL/0052, and 5077IL/0053) as well as published data from Marder and Meibach (1994), Chouinard et al (1993), and Peuskens (1995). The within-patient variability of the change from baseline in PANSS total score was assumed to be 25.8, which is the largest within-group standard deviation seen in a placebo-controlled study (Marder and Meibach 1994). As noted earlier, the mean difference in change from baseline PANSS total score between placebo and quetiapine SR was assumed to be –15.5 points.

5.7.6 Interim analyses (not applicable)

5.7.7 Data and safety monitoring board (not applicable)

5.8 Clinical study protocol amendments and other changes in the conduct of the study or planned analyses

5.8.1 Changes in the conduct of the study

The original protocol was dated 13 October 2000. There were 6 subsequent amendments to the protocol, 2 of which were implemented before any patients were enrolled in the study and 4 of which were implemented after the study began.

Amendments to the study protocol are shown in Table 13, which also indicates when amendments came into force with respect to the recruitment of patients.

Table 13 Protocol amendments

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated amendment[a]
Amendments made before the start of patient recruitment			
1 (5 January 2001)	The number of patients to be exposed to study drugs and procedures was revised from 480 to 504 to obtain a total of 480 patients who were evaluable for efficacy (Synopsis, Section 5.7.5).	Clarification of the numbers of enrolled and evaluable patients for consistency with sample size calculations	AstraZeneca clinical study team
	The required duration of hospitalization after randomization for all patients was increased from 7 days to 9 days (Section 5.1).	To facilitate monitoring of vital signs as the dose of quetiapine was increased	AstraZeneca clinical study team
	Serum glucose and lipid concentrations, measured under fasting conditions, were added to the clinical laboratory tests to be conducted before randomization on Day 1 and on Day 42 (or final visit) (Sections 5.5.7.3 and 8.5.2.5).	Further assessment of safety	AstraZeneca clinical study team
	The exclusion of patients with an Axis I DSM-IV diagnosis such as alcohol or psychoactive substance dependence not in full remission, concomitant organic mental disorder, or mental retardation was moved from the list of inclusion criteria to the list of exclusion criteria (Section 5.3.2).	Logic	AstraZeneca clinical study team
	The restriction on use of potent cytochrome P450 inhibitors and inducers before the baseline visit (Day 1) was reduced from 1 month to 14 days (Section 5.3.2).	Unnecessarily long washout	AstraZeneca clinical study team

Table 13 Protocol amendments

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated amendment[a]
	The following exclusion criteria were added: 11) history of idiopathic orthostatic hypotension, known sensitivity to the hypotensive or anaphylactic effects of antipsychotic or antidepressant medication; 12) transient ischemic attack, or angina pectoris, or myocardial infarction in the 2 months before screening; 13) persistent standing heart rate of more than 120 beats per minute (bpm) or supine tachycardia (heart rate of more than 100 bpm); an exclusion was provided for transient, nonpersisting tachycardia at the discretion of the investigator (Section 5.3.2).	Addition of clinically relevant preexisting conditions with the potential to impact safety	AstraZeneca clinical study team
	Exclusion criterion 14 was expanded to exclude patients with significant coronary artery disease, cerebrovascular disease (Section 5.3.2).	Addition of clinically relevant preexisting conditions with the potential to impact safety	AstraZeneca clinical study team
	The exclusion of patients with a QT_c interval longer than 500 msec, as calculated using the Fridericia correction, was removed (not applicable).	Unnecessary exclusion, per recent clinical data	AstraZeneca clinical study team
	The criteria for provision of informed consent were modified to specify that competence to provide consent was to be judged by the investigator (not applicable).	Consistency with standard clinical practice	AstraZeneca clinical study team
	A Positive and Negative Syndrome Scale assessment was added to the list of procedures to be performed at screening (Synopsis, Section 5.1).	Additional criterion for eligibility	AstraZeneca clinical study team
	Use of lorazepam up to Day 3, within limits, was added (Section 5.4.5).	Control of baseline agitation	AstraZeneca clinical study team
	Additional vital sign assessments were added on Days 1, 2, 5, 6, 8, and 9 (Section 5.5.7.4)	Further assessment of safety	AstraZeneca clinical study team

Table 13 Protocol amendments

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated amendment[a]
	The text of Section 8 was revised to clarify definitions and reporting of adverse events (Section 5.5.7.2).	Consistency with updated AstraZeneca procedures	AstraZeneca clinical study team
	The criteria for patient withdrawal were expanded to include "investigator discretion" as a reason for withdrawing a patient (Section 5.3.4.1).	To allow for the exercise of clinical judgment, apart from assessment scores	AstraZeneca clinical study team
	The criteria for postural changes in vital signs were modified (Section 5.5.7.4).	To permit better discrimination of potentially treatment-related changes in vital signs	AstraZeneca clinical study team
2 (18 January 2001)	The schedule for escalating doses of immediate-release quetiapine was modified to specify an increase from 400 mg/day to 600 mg/day on Day 6 rather than on Day 8 (Section 5.4.2).	Consistency with the dose-escalation schedule allowed by the quetiapine label and with the protocol-specified dose escalation schedule for sustained-release quetiapine	AstraZeneca clinical study team
Amendments made after the start of patient recruitment			
3 (9 March 2001)	Exclusion criterion 5 was revised to delete the term "organic mental disorder" and to exclude patients with psychoactive substance abuse in addition to those with psychoactive substance dependence not in full remission (Section 5.3.2).	The term *organic mental disorder* is outdated. Psychoactive substance abuse was added as an exclusion criterion to make the screening criteria more objective, as substance dependence may require longer assessment than does abuse.	AstraZeneca clinical study team
	Exclusion criterion 11 was modified to exclude patients with a history of anaphylactic reaction to antipsychotic or antidepressant medication (Section 5.3.2).	To exclude patients who might have an unexpected allergic reaction to study therapy.	AstraZeneca clinical study team
	Exclusion criterion 16 was added to exclude patients who, in the opinion of the investigator, posed an imminent risk of suicide (Section 5.3.2).	Consistency with standard practice for clinical studies.	AstraZeneca clinical study team
	The study restrictions were expanded to specify that any patient who posed an imminent risk of suicide should be withdrawn from the study (Section 5.3.4.1).	Consistency with standard practice for clinical studies.	AstraZeneca clinical study team

Table 13 Protocol amendments

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated amendment[a]
	Criteria for substance abuse were appended to the protocol (not applicable)	Consistency with revised exclusion criteria.	AstraZeneca clinical study team
	The methods for recording vital signs were modified to specify that standing vital sign measurements should be recorded after the patient had been standing for 30 seconds or less instead of 1 minute (Section 5.5.7.4).	To allow more accurate assessment of orthostatic changes in pulse rate and blood pressure.	AstraZeneca clinical study team
4 (2 April 2001)	Optional collection of a blood sample for genetic analysis was added to the procedures to be conducted at screening (Section 5.5.2).	Consistency with newly implemented AstraZeneca policy	AstraZeneca clinical study team
5 (1 August 2001)	The use of lorazepam after randomization was clarified to allow up to 4 mg/day on Days 1 through 3 and up to 2 mg/day on Days 4 through 6. Lorazepam was not to be used to treat agitation after Day 6 (Section 5.4.5).	Consistency with standard clinical practice	AstraZeneca clinical study team
6 (19 February 2001)	Exclusion criterion 16 was revised to exclude patients who, in the opinion of the investigator, posed a danger to self or others (Section 5.3.2).	Request of Quorum Investigational Review Board	Quorum Investigational Review Board
	Exclusion criterion 20 was added to exclude any patient who was unlikely to comply with study procedures and requirements for any reason, including but not limited to any additional comorbid psychiatric diagnosis or symptoms that would be likely to result in such noncompliance (Section 5.3.2).	Consistency with standard practice for clinical studies	AstraZeneca clinical study team

[a] All protocol amendments were approved within AstraZeneca before being implemented.

5.8.2 Changes to planned analyses

Changes to the planned statistical analyses are shown in Table 14. This table indicates when changes were made in relationship to the unblinding of study data.

Table 14 Changes to planned statistical analyses

Key details of change (section of this report affected)	Reason for change	Persons who initiated change
Changes before study data were unblinded		
Definition of noncompliance was modified (Sections 5.4.6 and 6.6.1).	Improved accuracy	AstraZeneca clinical study team
Analysis of PANSS total scores at Day 4 using data pooled across doses within quetiapine formulation was added (Sections 5.5.3.3 and 7.2.2.1).	To provide a more complete assessment of efficacy	AstraZeneca clinical study team
Analyses of PANSS Positive, Negative, and general Psychopathology Scale, activation factor, and depression item scores were added (Sections 5.5.3.5, 7.2.2.3, and 7.2.2.4); PANSS response was determined at the 40% and 50% levels (Sections 5.5.3.6 and 7.2.2.2).	To provide a more complete assessment of efficacy	AstraZeneca clinical study team
Analyses of CGI Severity of Illness and Global Improvement scores were added (Sections 5.7.4.1 and 7.2.2.5).	To correct an oversight in the protocol	AstraZeneca clinical study team
Regression analysis to detect trends in changes from baseline laboratory test results over time was not performed (Section 5.7.4.2).	Laboratory tests were performed only at screening and at the final visit	AstraZeneca clinical study team
Changes after study data were unblinded		
Exposure to treatment was tabulated in terms of days only and not in terms of mg/day (Section 5.7.4.2).	Level of detail not required in a fixed dose trial with defined dose-escalation phase	Study team physician
Definition of clinically important vital signs changed (Sections 5.5.7.4 and 8.6.1.2).	To provide consistency across program documents	AstraZeneca SR submission team
Expanded search terms for AEs related to EPS and diabetes mellitus; specified search terms for AEs related to QT prolongation, neutropenia or agranulocytosis, and suicidality (Sections 5.5.7.2 and 8.4.5).	To provide consistency across program documents	AstraZeneca SR submission team
AEs tabulated by MedDRA preferred terms; special interest AEs tabulated by aggregated preferred-terms (Sections 5.6.3, 5.7.4.2 and 8.3).	To provide consistency across program documents; to determine overall incidence rates for special interest AEs	AstraZeneca SR submission team
Evaluated glucose data by additional patient subsets (diabetic, at-risk for being diabetic, and nondiabetic); applied criteria for clinical importance under the assumed condition of random sampling versus sampling under fasting conditions (Sections 5.5.7.3 and 8.5.2.4).	To provide consistency across program documents	AstraZeneca SR submission team

AEs Adverse events. CGI Clinical Global Impression. EPS Extrapyramidal symptoms.
MedDRA Medical dictionary for regulatory activities. PANSS Positive and Negative Syndrome Scale.

6. STUDY PATIENTS

A summary of the patient population is given in Section 6.1. Thereafter, the following aspects of the study population are considered: disposition (Section 6.2), adherence to the study protocol (Section 6.3), populations analyzed (Section 6.4), demography and other baseline characteristics (Section 6.5), and treatment compliance and use of concomitant medication (Section 6.6). Conclusions on the suitability of the patient population with respect to the overall purpose of the study are given in Section 6.7.

When data for individual patients are provided in the text, patients are referred to by a composite number that incorporates both center number and patient number, eg, Patient 0005/0183 was enrolled at Center 0005 and was assigned the unique patient number of 0183.

6.1 Summary of patients

The randomized study population comprised 532 patients enrolled from 49 centers. More patients were recruited than originally planned (ie, 504 patients) because of a time lag in site reporting of screened patients to the CRO. Treatment-group sizes ranged from 84 to 92 patients (placebo, n=84; quetiapine SR 300 mg, n=91; quetiapine SR 600 mg, n=92; quetiapine SR 800 mg, n=89; quetiapine IR 300 mg, n=90; and quetiapine IR 600 mg, n=86). At least 50% of patients in each treatment group withdrew early (placebo, 66%; quetiapine SR 300 mg, 62%; quetiapine SR 600 mg, 57%; quetiapine SR 800 mg, 51%; quetiapine IR 300 mg, 54%; and quetiapine IR 600 mg, 62%). Early withdrawal was most commonly due to lack of efficacy or withdrawn consent and not AEs. In all, 222 patients completed treatment (placebo, n=29 [35%]; quetiapine SR 300 mg, n=35 [39%]; quetiapine SR 600 mg, n=40 [44%]; quetiapine SR 800 mg, n=44 [49%]; quetiapine IR 300 mg, n=41 [46%]; and quetiapine IR 600 mg, n=33 [38%]).

Of the 532 patients assigned to treatment and included in the safety analyses, 34 were excluded from the MITT population: 12 because postbaseline PANSS scores were missing and 22 because all data from Center 43 were excluded in response to apparent investigator misrepresentation. Of the 498 patients included in the MITT analyses, 57 were fully excluded from the PP analysis set, with little differences among treatment groups in reasons for exclusion. In addition to those patients, another 76 patients were partially excluded from PP analyses (reflecting in large part the use of disallowed medications at various times during the treatment period). The study population included more men than women (3:1 ratio), similar percentages of patients in the age ranges of 18 to 39 and 40 to 65 years (approximately 50% each), slightly greater proportions of white patients relative to black patients, and more patients with history of partial response to treatment (versus full or poor response). Overall, the treatment groups were similar with respect to demographic characteristics and baseline disease characteristics.

Table 15 shows where supportive data for this section are presented.

Table 15 Location of supporting data on study patients

Data	Location	
	Summary tables (Section 11.1)	**Individual patient data (Appendix 12.2)**
Patient enrollment, distribution by center	Tables 11.1.1.1, 11.1.1.2	Appendixes 12.2.1.1, 12.2.1.2
Patient completions and withdrawals	Tables 11.1.3.2 to 11.1.3.5; see also individual patient data	Appendix 12.2.1.2
Study dates	See individual patient data	Appendix 12.2.1.3
Patients by study population	Table 11.1.3.1	Appendix 12.2.1.4
Major protocol violations and deviations leading to exclusion from analyses	Tables 11.1.2.1, 11.1.2.2, see also individual patient data	Appendix 12.2.2
Demographic and baseline characteristics	Tables 11.1.4.1 to 11.1.4.6, 11.1.4.7.1 to 11.1.4.7.6	Appendixes 12.2.4.1 and 12.2.4.2
Concomitant medication use	Tables 11.1.5.2.1 to 11.1.5.3.8; see also individual patient data	Appendix 12.2.10.8
Treatment compliance	Table 11.1.5.1	Appendix 12.2.5

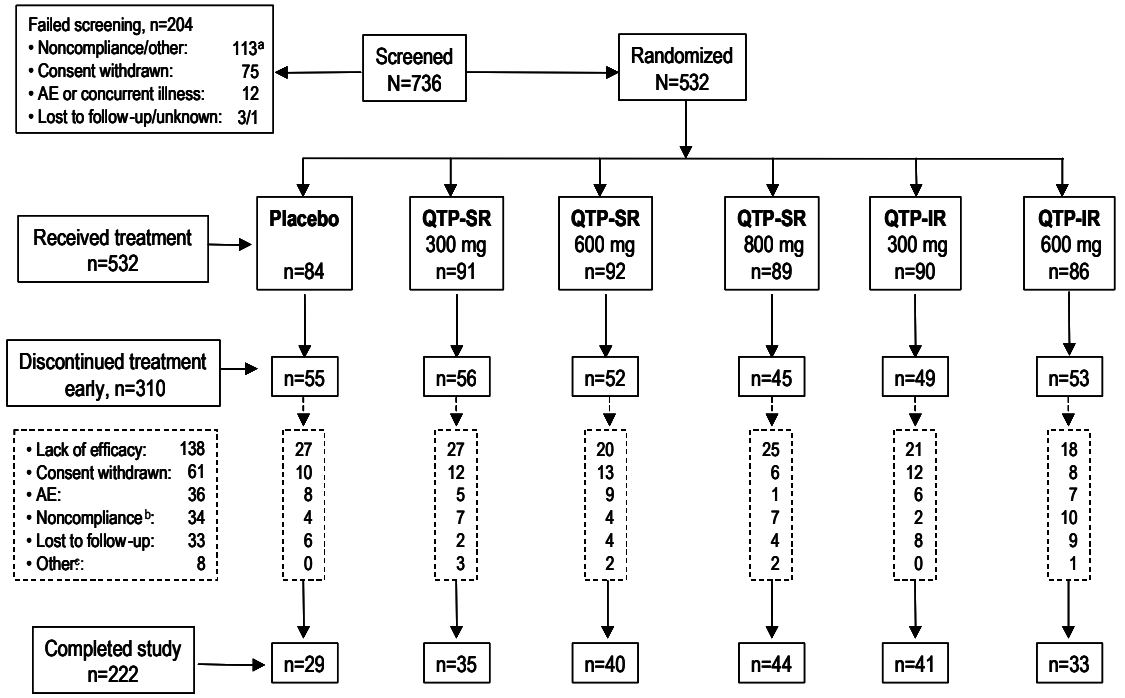
6.2 Disposition

In total, 736 patients were screened for possible study participation. Of those, 532 qualified and were assigned to randomized treatment on Day 1. Of the 204 patients who did not qualify, 37% (75 patients) were not eligible to receive treatment because they withdrew consent. Of the remaining patients, more patients were disqualified because of various exclusion criteria violations rather than inclusion criteria violations. Those who did not fully meet the inclusion criteria—at least 14 patients per investigator comments—generally had PANSS total scores that were too low, disease not severe enough for study participation, or no confirmed diagnoses of schizophrenia per DSM-IV.

Patients who qualified for study entry were assigned to randomized treatment as follows: 84 to placebo, 91 to quetiapine SR 300 mg, 92 to quetiapine SR 600 mg, 89 to quetiapine SR 800 mg, 90 to quetiapine IR 300 mg, and 86 to quetiapine IR 600 mg. All patients assigned to treatment received study drug, and all patients received the study drug to which they were assigned.

The disposition of patients relative to study completion is summarized in Figure 2.

Figure 2 Patient disposition (completion or discontinuation)



[a] Reasons provided under the heading of *Other* (n=32) were, in many cases, similar to reasons listed for *Noncompliance with the protocol* (n=81); hence, the 2 categories are considered together.
[b] Noncompliance with protocol requirements.
[c] Other reasons included patient incarceration (SR 300 and SR 800 mg, n=1 each); patient terminated by the IRB (SR 300 and SR 600 mg, n=1 each); patient worsening, more agitated (not in patient's best interest to continue) (SR 300 mg, n=1); CGI score decreased by 2 (discontinued per protocol) (SR 600 mg, n=1); patient required treatment for depression (SR 800 mg, n=1); and per sponsor request (IR 600 mg, n=1).
AE Adverse event. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.1.1.1 and 11.1.3.2, Section 11.1 and Listings 12.2.1.1 and 12.2.1.2, Section 12.2.

At least 50% of patients in each treatment group withdrew early (placebo, 66%; quetiapine SR 300 mg, 62%; quetiapine SR 600 mg, 57%; quetiapine SR 800 mg, 51%; quetiapine IR 300 mg, 54%; and quetiapine IR 600 mg, 62%). At the end of the first treatment week, 19% of placebo-treated patients, 26%, 14%, and 8% of patients in the SR treatment groups (low to high dose, respectively), and 26% and 9% of patients in the IR treatment groups (low to high dose, respectively) had been withdrawn. At the end of the second treatment week, another 19% of placebo-treated patients, 15%, 15%, and 18% of patients in the SR treatment groups (low to high dose, respectively), and 9% and 28% of patients in the IR treatment groups (low to high dose, respectively) had been withdrawn.

Early withdrawal was most commonly due to lack of efficacy or withdrawn consent and not AEs (see Table 35 for incidence of AE-related withdrawals). For 2 patients each treated with placebo, quetiapine SR 600 mg, quetiapine IR 300 mg, and quetiapine IR 600mg, AEs leading

to withdrawal may have reflected a lack of therapeutic response to treatment (see Table 42).[4] In all, 222 patients completed treatment (placebo, 35%; quetiapine SR 300 mg, 39%; quetiapine SR 600 mg, 44%; quetiapine SR 800 mg, 49%; quetiapine IR 300 mg, 46%; and quetiapine IR 600 mg, 38%).

Of the 49 centers that enrolled patients, Centers 0021 and 0005 enrolled the greatest percentages of patients at 7.9% and 7.0%, respectively. Nine additional centers enrolled between approximately 4.0% and 6.4% of patients, with the remaining centers enrolling between 0.2% and 3.2% of patients.

6.3 Protocol deviations

Protocol deviations were tabulated for the purpose of identifying which patients would be excluded from the MITT and PP population data sets (see Section 6.4 and Figure 3). Thus, protocol deviations that did not lead to exclusion from these sets were not summarized.

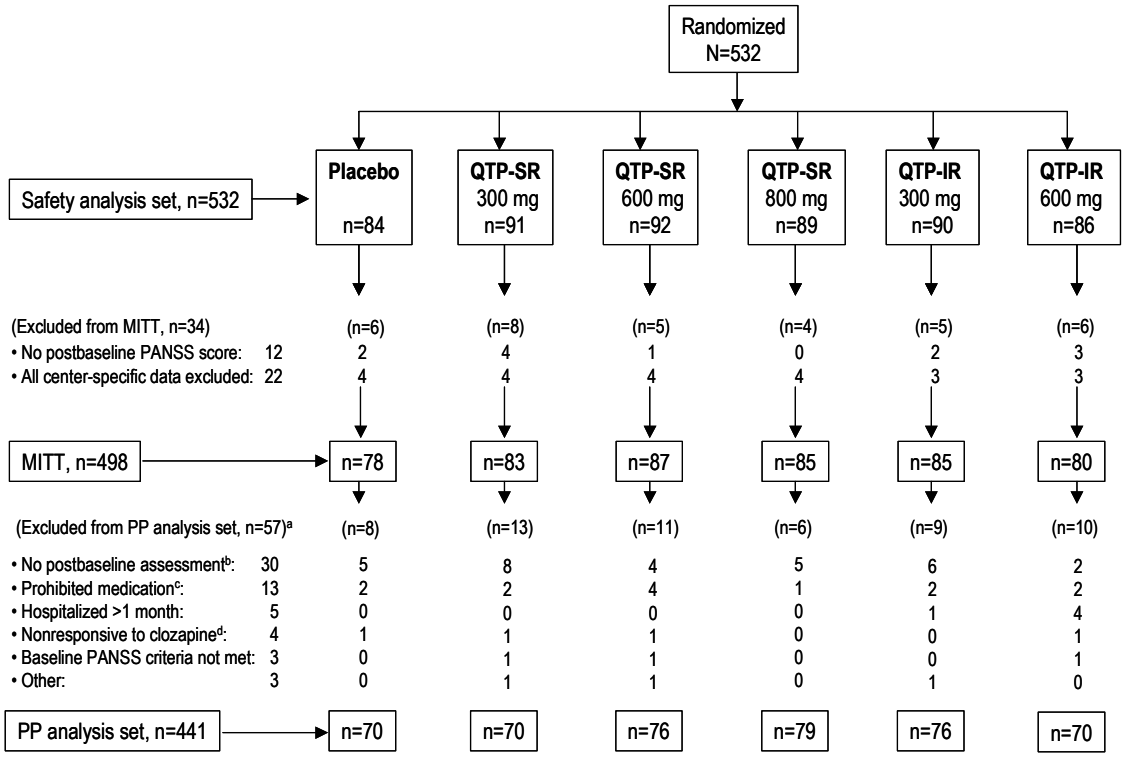
6.4 Patient populations analyzed (analysis sets)

The population size for each analysis set was as follows: 532 patients in the safety analysis set, 498 patients in the MITT analysis set, and 441 patients in the PP analysis set.

Analysis sets by treatment group are summarized in Figure 3, along with reasons for exclusion from the MITT and PP analysis sets. (See Section 5.7.3 for analysis-set definitions and Section 5.7.3.3 for the criteria used to define the PP analysis set.)

[4] These AEs included delusion, hallucination, auditory hallucination, psychotic disorder, catatonia, and schizophrenia (catatonic type).

Figure 3 Analysis sets



[a] Patients may have multiple reasons listed. These patients were fully excluded from the PP analysis set.
[b] After data exclusions.
[c] Specifically, psychoactive medications within 2 days before randomization.
[d] Or required or used clozapine within 1 month of Day 1 or lacked response to other antipsychotic medications.

MITT Modified intent-to-treat analysis set. PP Per protocol.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.1.2.1, 11.1.2.2, and 11.1.3.1, Section 11.1.

Data from all patients assigned treatment codes at Center 0043 (n=22) were excluded from the MITT population. This action was taken because the center's IRB discovered that the investigator had supplied false information about his licensure history, which resulted in the termination of the investigator's study participation. However, an additional analysis of the primary efficacy endpoint, as described in Section 5.7.4.1, was performed using the MITT analysis set supplemented with the data from patients enrolled at Center 0043 (hereafter referred to as the MITT+Center 43 analysis set) to test for homogeneity of treatment effects.

In addition to the 57 patients who had data fully excluded from the PP analysis set, another 76 patients had data partially excluded, ie, data were excluded after the point of protocol deviation. Data from these patients were most often excluded because patients used prohibited concomitant medications, including other psychoactive medications, or doses of concomitant medications that exceeded allowable limits, or they used lorazepam beyond the

time permitted by the protocol. Patients excluded from the various data analysis sets are identified in Table 16, by treatment group and reason.

Table 16 Patients excluded or partially excluded from analyses

Analysis set & treatment	Dose (mg)	Primary reason for exclusion	Extent of exclusion	Patients
MITT[a,b]				
Placebo	0	No postbaseline PANSS assessment	Full	0009/0199, 0021/0603
QTP SR	300	No postbaseline PANSS assessment	Full	0012/0031, 0015/0161, 0045/0212, 0046/0052
	600	No postbaseline PANSS assessment	Full	0028/0513
QTP IR	300	No postbaseline PANSS assessment	Full	0005/0183, 0010/1111
	600	No postbaseline PANSS assessment	Full	0014/0060, 0032/0499, 0049/0289
Per protocol[a]				
Placebo	0	Prohibited medication or dose	Full	0021/0380, 0021/0481
		Prohibited medication or dose	Partial	0005/0181 (Day 4); 0020/0193 (Day 5); 0025/0273, 0032/0119, and 0040/0284 (Day 7); 0016/0156, 0026/0451, and 0028/0514 (Day 8); 0010/0176 (Day 9); 0060/1085 (Day 10); 0017/0259 (Day 11); 0047/0037 (Day 20); 0005/0438 (Day 40) and 0026/0596 (Day 42)
QTP SR	300	Prohibited medication or dose	Full	0008/0067, 0010/1029
		Prohibited medication or dose	Partial	0021/0606 (Day 8); 0013/0266 (Day 9); 0025/0276 (Day 21); and 0026/0558 and 0026/0598 (Day 42)
	600	Prohibited medication or dose	Full	0014/0055, 0040/0286, 0046/0086, 0060/1117
		Prohibited medication or dose	Partial	0003/0134, 0008/0254, 0010/0661, and 0060/1082 (Day 5); 0025/0271 (Day 6); 0004/0011 and 0010/0180 (Day 7), 0009/0237 and 0038/0150 (Day 9); 0021/0280 and 0027/0632 (Day 10); 0016/0155 (Day 11); 0026/0599 (Day 12); 0024/0164 (Day 15); 0025/0607 and 0032/0630 (Day 18); 0026/0553 (Day 26); and 0026/0670 (Day 39)
	800	Prohibited medication or dose	Full	0008/0071
		Prohibited medication or dose	Partial	0013/0488 (Day 1); 0047/0567 and 0009/0200 (Day 7); 0005/0343 (Day 8); 0021/0485 (Day 9); 0062/0673 (Day 12); 0024/0167 (Day 13); 0025/0610 (Day 15); 0059/0295 (Day 18); 0026/0452 (Day 42); and 0026/0669 (Day 43)
QTP IR	300	Prohibited medication or dose	Full	0052/1210, 0060/1083
		Prohibited medication or dose	Partial	0025/0608 (Day 6); 0012/0547, 0036/0495, and 0064/1100 (Day 7); 0012/0036 (Day 8); 0021/0638 and 0062/1094 (Day 10); 0038/0145 (Day 11); 0005/0230 (Day 15); 0026/0668 (Day 17); 0025/0275 (Day 18); 0009/0420 (Day 42); and 0026/0557 (Day 43)
	600	Prohibited medication or dose	Full	0010/0664, 0027/0385
		Prohibited medication or dose	Partial	0025/0609, 0013/0265, and 0036/0498 (Day 7), 0026/0667 and 0062/0677 (Day 8); 0005/0182 (Day 9); 0060/1086 (Day 10); 0025/0274 (Day 14); 0005/0440 (Day 26); 0005/0234 (Day 38); 0033/0301 (Day 41); and 0026/0455 (Day 42)

Table 16 Patients excluded or partially excluded from analyses

Analysis set & treatment	Dose (mg)	Primary reason for exclusion	Extent of exclusion	Patients
Placebo	0	No postbaseline assessment[c]	Full	0026/0355, 0035/0449, 0035/0537, 0036/0497, 0047/1072
QTP SR	300	No postbaseline assessment[c]	Full	0005/0345, 0016/0154, 0021/0278, 0023/0109, 0026/0357, 0036/0631, 0038/0148, 0039/0527
	600	No postbaseline assessment[c]	Full	0008/0069, 0016/0475, 0026/0360, 0035/0446
	800	No postbaseline assessment[c]	Full	0018/0205, 0023/0541, 0025/0272, 0033/0461, 0049/0291
QTP IR	300	No postbaseline assessment[c]	Full	0008/0255, 0032/0504, 0032/0629, 0039/0122, 0047/0570, 0057/1214
	600	No postbaseline assessment[c]	Full	0021/0482, 0032/0374
Placebo	0	Nonresponsive to clozapine	Full	0026/0554
QTP SR	300	Nonresponsive to clozapine	Full	0057/1216
QTP SR	600	Nonresponsive to clozapine	Full	0009/0103
QTP IR	600	Nonresponsive to clozapine	Full	0024/0163
QTP SR	300	Baseline PANSS score <60[d]	Full	0033/0302
	600	Baseline PANSS score <60[d]	Full	0021/0616
QTP SR	300	Noncompliance with study drug	Full	0052/1209
	600	Noncompliance with study drug	Partial	0046/0050 (Day 32)
	800	Noncompliance with study drug	Partial	0031/0144 (Day 24); 0010/0029 (Day 28)
QTP IR	300	Hospitalization >1 month	Full	0028/0512
	600	Hospitalization >1 month	Full	0007/0350, 0033/0460, 0046/0053, 0047/1069
QTP IR	600	Baseline PANSS scores <4 on items P1, P2, P3, or P6	Full	0026/0600
QTP SR	600	Alcohol abuse	Full	0052/1208

[a] All patients excluded from the MITT analysis set were also fully excluded from the per-protocol analysis set.
[b] All 22 patients from Center 0043 were excluded per sponsor directive; of those patients, 4 were treated with placebo, 4 with QTP SR 300 mg, 4 with QTP SR 600 mg, 4 with QTP SR 800 mg, 3 with QTP IR 300 mg and 3 with QTP IR 600 mg.
[c] After data exclusions.
[d] PANSS total score missing on Day 1 for Patient 0033/0302 and was 56 at the screening visit for Patient 0021/0616.

MITT Modified intent-to-treat. PANSS Positive and Negative Syndrome Scale.
Data derived from Tables 11.1.2.1 and 11.1.2.2, Section 11.1 and Listings 12.2.1.4 and 12.2.2, Section 12.2.

6.5 Demographic and other patient characteristics

Of the 532 patients assigned to randomized treatment, 402 (75.6%) were men and 130 (24.4%) were women. White and black patients (49.2% and 37.2%, respectively) made up the largest part of the population, with Hispanic patients comprising 11.1% and Asian patients and patients of other races comprising the remaining 2.4%. Mean age was 39 years (range: 18 to 64), with similar proportions of patients between the ages of 18 and 39 years and 40 and 65 years (approximately 50% each). Mean weight and BMI were 87.2 kg and 29.4 kg/m^2, respectively, with similar proportions of patients having BMI values in each of the following ranges: 18.5 to <25 kg/m^2 (30.6%), 25 to <30 kg/m^2 (31.9%), and 30 to <40 kg/m^2 (27.2%). Median age at the time of first treatment was 22 years. Approximately 91% of patients entered the study with previous positive responses to antipsychotic medications (full response 29% [31% MITT] and partial response 62% [61% MITT]).

Additional demographic characteristics (safety population) are summarized in Table 17, and additional psychiatric history and baseline disease characteristics (MITT population) are summarized in Table 18, by treatment group. Overall, treatment groups were well balanced with respect to demographics and disease-related characteristics.

Table 17 Demographic and other baseline characteristics: safety population

Characteristic	Parameter	Placebo (n=84)		QTP SR 300 mg (n=91)		QTP SR 600 mg (n=92)		QTP SR 800 mg (n=89)		QTP IR 300 mg (n=90)		QTP IR 600 mg (n=86)	
Sex, No. (%) of patients	Male	65	(77)	67	(74)	66	(72)	73	(82)	68	(76)	63	(73)
	Female	19	(23)	24	(26)	26	(28)	16	(18)	22	(24)	23	(27)
Age, years	Mean (SD)	38.2	(10.4)	38.9	(11.0)	39.1	(9.2)	38.2	(10.4)	39.2	(10.7)	40.4	(9.5)
	Median	37.5		39.0		40.0		39.0		40.0		40.0	
	Min to max	19 to 64		18 to 64		19 to 61		20 to 59		19 to 62		21 to 60	
Age distribution, No. (%) of patients	<18 years	0		0		0		0		0		0	
	18 to 39 years	48	(57)	46	(51)	44	(48)	45	(51)	43	(48)	42	(49)
	40 to 65 years	36	(43)	45	(50)	48	(52)	44	(49)	47	(52)	44	(51)
	>65 years	0		0		0		0		0		0	
Race, No. (%) of patient	White	37	(44)	47	(52)	47	(51)	50	(56)	43	(48)	38	(44)
	Black	32	(38)	33	(36)	36	(39)	30	(34)	35	(39)	32	(37)
	Hispanic	11	(13)	7	(8)	8	(9)	9	(10)	11	(12)	13	(15)
	Asian	1	(1)	3	(3)	0		0		1	(1)	2	(2)
	Other	3	(4)	1	(1)	1	(1)	0		0		1	(1)
Weight, kg	N	83		90		92		88		89		86	
	Mean (SD)	85.6	(20.4)	82.7	(20.0)	91.6	(26.1)	89.3	(20.5)	86.7	(20.3)	87.0	(20.3)
	Median	81.8		81.7		86.2		85.5		83.5		82.7	
	Min to max	50 to 163		49 to 165		55 to 180		57 to 167		50 to 180		50 to 131	
Body mass index, kg/m^2	N	83		90		91		87		89		86	
	Mean (SD)	29.2	(7.49)	28.2	(7.44)	30.9	(9.24)	29.8	(7.51)	28.9	(6.58)	29.4	(6.31)
	Median	27.4		26.3		28.8		28.3		28.2		28.0	
	Min to max	19 to 52		17 to 55		18 to 58		19 to 54		18 to54		19 to 44	

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release. SD Standard deviation.
Data derived from Tables 11.1.4.1 and 11.1.4.4, Section 11.1.

Table 18 Psychiatric history and disease characteristics at baseline: MITT population

Characteristic	Parameter	Placebo (n=78)		QTP SR 300 mg (n=83)		QTP SR 600 mg (n=87)		QTP SR 800 mg (n=85)		QTP IR 300 mg (n=85)		QTP IR 600 mg (n=80)	
Disease subtype, No. (%) of patients	Catatonic	0		0		1	(1.1)	0		1	(1.2)	0	
	Disorganized	2	(2.6)	3	(3.6)	1	(1.1)	1	(1.2)	3	(3.5)	0	
	Paranoid	59	(75.6)	73	(88.0)	66	(75.9)	71	(83.5)	68	(80.0)	64	(80.0)
	Undifferentiated	17	(21.8)	7	(8.4)	19	(21.8)	13	(15.3)	13	(15.3)	16	(20.0)
Age at 1st treatment, years	N	76		82		86		85		83		79	
	Mean (SD)	23.7	(9.4)	22.9	(6.7)	22.8	(6.5)	22.7	(7.0)	23.0	(9.7)	25.9	(8.7)
	Median	21.0		21.0		21.5		22.0		21.0		25.0	
	Min to max	10 to 54		10 to 46		11to 46		7 to 40		5 to 57		7 to 47	
Hospitalizations, No. (%) of patients	0 or unknown	13	(16.7)	9	(10.8)	9	(10.3)	11	(12.9)	15	(17.6)	11	(13.8)
	1 to 5	26	(33.3)	35	(42.2)	34	(39.1)	32	(37.6)	31	(36.5)	32	(40.0)
	6 to 10	22	(28.2)	19	(22.9)	21	(24.1)	18	(21.2)	20	(23.5)	20	(25.0)
	≥11	17	(21.8))	20	(24.1)	23	(26.4)	24	(28.2)	19	(22.4)	17	(21.3)
Previous response,[a] No. (%) of patients	Full	19	(24.4)	24	(28.9)	28	(32.2)	32	(37.6)	26	(30.6)	23	(28.8)
	Partial	49	(62.8)	53	(63.9)	55	(63.2)	47	(55.3)	49	(57.6)	50	(62.5)
	Poor	3	(3.8)	5	(6.0)	2	(2.3)	2	(2.4)	3	(3.5)	3	(3.8)
	None/Unknown	7	(9.0)	1	(1.2)	2	(2.3)	4	(4.7)	7	(8.2)	4	(5.0)
PANSS total score (observed values)	N	76		81		86		83		85		79	
	Mean (SD)	91.3	(16.4)	91.8	(19.4)	92.5	(17.3)	89.2	(15.1)	89.5	(15.7)	88.6	(17.4)
	Median	89.5		90.0		89.0		89.0		88.0		85.0	
	Min to max	60 to 149		60 to 149		60 to 149		60 to 129		60 to 150		60 to 142	
CGI Severity of Illness score	N	78		83		87		85		85		80	
(observed values)	Mean (SD)	4.7	(0.7)	4.8	(0.7)	4.7	(0.8)	4.7	(0.7)	4.8	(0.7)	4.7	(0.7)
	Median	5.0		5.0		5.0		5.0		5.0		5.0	
	Min to max	4 to 7		4 to 7		4 to 7		4 to 7		4 to 6		4 to 6	

[a] To antipsychotic medication.

CGI Clinical global improvement. PANSS Positive and Negative Syndrome Scale. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release. SD Standard deviation.

Data derived from Tables 11.1.4.7.2, 11.1.4.7.3, 11.1.4.7.5, 11.1.4.7.6, 11.2.1.1.2, and 11.2.2.3.1.2, Sections 11.1 and 11.2.

6.6 Treatment compliance and use of concomitant medication

6.6.1 Treatment compliance

Among treatment groups, compliance with study-drug regimens was good. Of the 498 patients who comprised the MITT population, only 4 met the criteria for treatment noncompliance: 1 with a calculated compliance of <60% (QTP SR 300 mg, fully excluded from PP analyses) and 3 with >5 consecutive missed doses (1 treated with QTP SR 600 mg and 2 treated with QTP SR 800 mg, each partially excluded from PP analyses, see Table 16).

6.6.2 Concomitant medication

6.6.2.1 Use of medications prior to study entry

In total, 506 (95%) patients reported using some type of medication prior to study entry. Most common among those medications was lorazepam, reported by 320 (60%) patients overall (across treatment groups: 52% to 68%, safety population; 52% to 69%, MITT population).

Common prestudy antipsychotics (safety/MITT) included olanzapine (205/188 patients), risperidone (169/161 patients), haloperidol (88/87 patients), and quetiapine (63/56 patients). Table 19 shows frequency of use by treatment group in the month prior to study entry (for the MITT population). In that time period, atypical antipsychotics were used in similar proportions of patients per treatment group (71% to 76%), with some differences in use of individual drugs. Fewer patients used typical antipsychotics, with incidence by treatment group more variable (16.5% to 33.7%). Nonetheless, data show that patients were being managed therapeutically for their disease prior to study entry.

Sleep aids were also commonly used prior to enrollment, including predominantly, benzodiazepine hypnotics (118 patients) and zolpidem (126 patients) (MITT). Across treatment groups, the incidence of benzodiazepine use was similar (21.2% to 27.7%), while the incidence of zolpidem use was more variable (16.1% to 32.5%) (MITT).

Patients reported using a variety of antidepressants and other mood elevators prior to enrollment, including selective serotonin reuptake inhibitors (Table 19, MITT). Anticholinergic use for the treatment of EPS (most commonly benztropine) was reported in 33.3% of placebo-treated patients; 39.8%, 35.6%, and 35.3% of SR-treated patients (low to high dose); and 31.8% and 38.8% of IR-treated patients (low to high dose) (MITT).

Psychoactive medications taken in the month prior to study entry are summarized for the safety population in Table 11.1.5.2.5 (Section 11.1).

Table 19 Use of psychoactive treatments in the month prior to study entry (MITT population)

Medication	Number (%) of patients[a]											
	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP IR 300 mg		QTP IR 600 mg	
	(n=78)		(n=83)		(n=87)		(n=85)		(n=85)		(n=80)	
Any psychoactive medication	69	(88.5)	76	(91.6)	79	(90.8)	78	(91.8)	78	(91.8)	74	(92.5)
Antipsychotics	62	(79.5)	72	(86.7)	73	(83.9)	68	(80.0)	69	(81.2)	67	(83.8)
Typical[b]	18	(23.1)	28	(33.7)	19	(21.8)	18	(21.2)	14	(16.5)	20	(25.0)
Atypical	55	(70.5)	59	(71.1)	65	(74.7)	64	(75.3)	62	(72.9)	61	(76.3)
Olanzapine	32	(41.0)	29	(34.9)	21	(24.1)	28	(32.9)	36	(42.4)	34	(42.5)
Quetiapine	6	(7.7)	6	(7.2)	14	(16.1)	10	(11.8)	8	(9.4)	9	(11.3)
Risperidone	20	(25.6)	27	(32.5)	30	(34.5)	31	(36.5)	24	(28.2)	20	(25.0)
Other	5	(6.4)	7	(8.4)	7	(8.0)	7	(8.2)	4	(4.7)	5	(6.3)
>1 Antipsychotic	18	(23.1)	24	(28.9)	18	(20.7)	23	(27.1)	17	(20.0)	19	(23.8)
Antipsychotic + mood stabilizer	10	(12.8)	14	(16.9)	21	(24.1)	17	(20.0)	15	(17.6)	13	(16.3)
Mood stabilizer	10	(12.8)	14	(16.9)	22	(25.3)	19	(22.4)	15	(17.6)	14	(17.5)
Lithium	2	(2.6)	3	(3.6)	5	(5.7)	5	(5.9)	3	(3.5)	2	(2.5)
Lamotrigine	0		0		1	(1.1)	1	(1.2)	0		0	
Valproate	7	(9.0)	10	(12.0)	13	(14.9)	8	(9.4)	9	(10.6)	10	(12.5)
Other	2	(2.6)	2	(2.4)	5	(5.7)	3	(3.5)	3	(3.5)	3	(3.8)
Antidepressants	19	(24.4)	20	(24.1)	31	(35.6)	31	(36.5)	22	(25.9)	24	(30.0)
SSRI	14	(17.9)	14	(16.9)	17	(19.5)	16	(18.8)	13	(15.3)	12	(15.0)
SNRI	2	(2.6)	1	(1.2)	1	(1.1)	0		2	(2.4)	4	(5.0)
Other	6	(7.7)	8	(9.6)	16	(18.4)	16	(18.8)	9	(10.6)	14	(17.5)
Anxiolytics/ hypnotics	52	(66.7)	64	(77.1)	61	(70.1)	56	(65.9)	65	(76.5)	57	(71.3)
No psychoactive medication	9	(11.5)	7	(8.4)	8	(9.2)	7	(8.2)	7	(8.2)	6	(7.5)

[a] Patients who took multiple medications within a given medication subcategory were counted only once.
[b] Includes haloperidol.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
SNRIs Selective norepinephrine reuptake inhibitor. SSRI Selective serotonin reuptake inhibitor.
Data derived from Table 11.1.5.2.6, Section 11.1.

6.6.2.2 Use of concomitant medication after randomization

More than 80% of patients in each treatment group used concomitant medications during the treatment period (range: 81% [placebo] to 87% [quetiapine SR 800 mg]). After randomization, the concomitant medications most frequently used across treatment groups

were lorazepam (40% to 50%), zolpidem (27% to 33%), flurazepam (18% to 27%), and acetaminophen (27% to 38%). Specific rates of use per treatment group are shown in Table 20 for lorazepam (protocol compliant and noncompliant use) and the sleep aids (MITT population). Patients who received lorazepam in violation of the protocol were excluded from PP analyses.

Table 20 Concomitant use of lorazepam or sleep aids (MITT population)

Medication	Number (%) of patients who used concomitant lorazepam or sleep aids											
	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP IR 300 mg		QTP IR 600 mg	
	(n=78)		(n=83)		(n=87)		(n=85)		(n=85)		(n=80)	
Lorazepam[a]	36	(46.2)	40	(48.2)	42	(48.3)	36	(42.4)	42	(49.4)	31	(38.8)
Sleep aids												
Zolpidem	24	(30.8)	22	(26.5)	22	(25.3)	22	(25.9)	28	(32.9)	26	(32.5)
Flurazepam	23	(29.5)	24	(28.9)	21	(24.1)	16	(18.8)	22	(25.9)	18	(22.5)
Zaleplon	2	(2.6)	0		0		0		0		0	
Chloral hydrate	1	(1.3)	0		1	(1.1)	0		0		0	
Other[b]	0		0		1	(1.1)	0		0		3	(3.8)

[a] Any use regardless of time.
[b] Other sleep aids started before study entry were permitted during the study as long as patients took them only at bedtime for sleep. (Included in this category are temazepam, triazolam, and midazolam.)
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.1.5.3.2, Section 11.1.

Use of lorazepam over time is shown in Table 21 (MITT). Use of any sleep aid over time is shown in Table 22 (MITT). Use of individual sleep aids over time is shown in Tables 11.1.5.3.7 (safety) and 11.1.5.3.8 (MITT) (Section 11.1).

Table 21 Incidence of lorazepam use over time, by treatment group (MITT population)

Week	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP IR 300 mg			QTP IR 600 mg		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
1	78	35	(44.9)	83	39	(47.0)	87	40	(46.0)	85	36	(42.4)	85	40	(47.1)	80	29	(36.3)
2	61	5	(8.2)	62	1	(1.6)	71	8	(11.3)	73	5	(6.8)	63	6	(9.5)	68	4	(5.9)
3	43	1	(2.3)	50	0		59	2	(3.4)	59	3	(5.1)	52	1	(1.9)	49	1	(2.0)
4	34	0		44	0		47	2	(4.3)	53	2	(3.8)	46	0		43	0	
5	29	0		39	0		40	1	(2.5)	47	1	(2.1)	43	0		38	0	
6	28	0		34	0		40	0		42	1	(2.4)	40	0		37	0	
7	6	0		4	0		6	0		8	0		6	0		3	0	

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.1.5.3.8, Section 11.1.

Table 22 Incidence of sleep-aid use over time, by treatment group (MITT population)

Week	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP IR 300 mg			QTP IR 600 mg		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
1	78	47	(60.3)	83	57	(68.7)	87	55	(63.2)	85	49	(57.6)	85	48	(56.5)	80	50	(62.5)
2	61	30	(49.2)	62	23	(37.1)	71	26	(36.6)	73	28	(38.4)	63	28	(44.4)	68	23	(33.8)
3	43	11	(25.6)	50	13	(26.0)	59	10	(16.9)	59	12	(20.3)	52	10	(19.2)	49	9	(18.4)
4	34	7	(20.6)	44	10	(22.7)	47	8	(17.0)	53	9	(17.0)	46	8	(17.4)	43	7	(16.3)
5	29	7	(24.1)	39	8	(20.5)	40	6	(15.0)	47	7	(14.9)	43	8	(18.6)	38	6	(15.8)
6	28	5	(17.9)	34	5	(14.7)	40	5	(12.5)	42	5	(11.9)	40	9	(22.5)	37	6	(16.2)
7	6	2	(33.3)	4	0		6	0		8	2	(25.0)	6	2	(33.3)	3	0	

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.1.5.3.8, Section 11.1.

The overall use of concomitant anticholinergics in the treatment of EPS symptoms is summarized in Table 23 (MITT and safety population), and use over time is summarized in Table 24 (MITT population). Specific EPS symptoms are discussed later in Section 8.4.5.1.

Table 23 Concomitant use of anticholinergics for symptoms of EPS

Medication	Number (%) of patients who used anticholinergic concomitant medication											
	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP IR 300 mg		QTP IR 600 mg	
	(n=78)		(n=83)		(n=87)		(n=85)		(n=85)		(n=80)	
MITT population												
Any anticholinergic	11	(14.1)	6	(7.2)	10	(11.5)	4	(4.7)	6	(7.1)	3	(3.8)
Amantadine	0		0		0		0		1	(1.2)	0	
Benztropine	9	(11.5)	3	(3.6)	7	(8.0)	4	(4.7)	3	(3.5)	3	(3.8)
Diphenhydramine	3	(3.8)	2	(2.4)	4	(4.6)	1	(1.2)	2	(2.4)	0	
Trihexyphenidyl	0		1	(1.2)	0		0		1	(1.2)	0	
Safety population	**(n=84)**		**(n=91)**		**(n=92)**		**(n=89)**		**(n=90)**		**(n=86)**	
Any anticholinergic	12	(14.3)	7	(7.7)	10	(10.9)	4	(4.5)	6	(6.7)	3	(3.5)
Amantadine	0		0		0		0		1	(1.1)	0	
Benztropine	9	(10.7)	4	(4.4)	7	(7.6)	4	(4.5)	3	(3.3)	3	(3.5)
Diphenhydramine	4	(4.8)	2	(2.2)	4	(4.3)	1	(1.1)	2	(2.2)	0	
Trihexyphenidyl	0		1	(1.1)	0		0		1	(1.1)	0	

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.1.5.3.3 and 11.1.5.3.4, Section 11.1.

A greater proportion of placebo-treated patients (14.3% [safety population]) used anticholinergics, compared with SR or IR-treated patients, with the greatest differences seen between placebo and SR 800 mg (4.5% incidence) and placebo and IR 600 mg (3.5% incidence). Importantly, use did not increase over time as exposure to quetiapine (SR or IR) increased.

Table 24 Incidence of anticholinergic use over time, by treatment group (MITT population)

Week	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP IR 300 mg			QTP IR 600 mg		
	N	N	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
1	78	9	(11.5)	83	5	(6.0)	87	8	(9.2)	85	4	(4.7)	85	5	(5.9)	80	2	(2.5)
2	61	4	(6.6)	62	2	(3.2)	71	5	(7.0)	73	3	(4.1)	63	3	(4.8)	68	1	(1.5)
3	43	2	(4.7)	50	0		59	2	(3.4)	59	1	(1.7)	52	1	(1.9)	49	1	(2.0)
4	34	1	(2.9)	44	0		47	2	(4.3)	53	1	(1.9)	46	1	(2.2)	43	1	(2.3)
5	29	1	(3.4)	39	0		40	1	(2.5)	47	1	(2.1)	43	1	(2.3)	38	1	(2.6)
6	28	1	(3.6)	34	0		40	1	(2.5)	42	1	(2.4)	40	1	(2.5)	37	0	
7	6	0		4	0		6	0		8	0		6	0		3	0	

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.1.5.3.6, Section 11. 1.

6.7 Conclusions on study patients

The study population was shaped using both standard and study-focused inclusion and exclusion criteria. In wide overview, the typical patient was a 39-year-old man who weighed approximately 87 kg, was first treated for schizophrenia at 23 years of age, and had a history of full or partial response to treatment and up to 10 previous hospitalizations.

Enrollment relative to inclusion criteria was good in that all patients were between the ages of 18 and 65 years, all but 2 patients had baseline total PANSS scores of at least 60, and all had minimum baseline CGI scores of 4, thus establishing the disease severity and exacerbation required for the study. This population—predominantly with paranoid schizophrenia—had a good history of response to previous antipsychotics (31% full response; 61% partial response), with 80% to 87% on at least 1 antipsychotic in the month prior to enrollment. Across treatment groups, patients were well matched in terms of baseline demographics and disease characteristics.

Use of lorazepam (in 39% to 49% across treatment groups, MITT) occurred predominantly during the first week of study drug as required by the protocol. Use of anticholinergics for symptoms of EPS was greatest among placebo-treated patients (14.1%), with rates lower and variable among SR-treated patients (4.7% to 11.5%) and IR-treated patients (3.8% to 7.1%).

Lack of compliance with certain protocol requirements led to full exclusion of 57 patients from the PP population (see Figure 3). For each treatment group, the difference between the MITT and PP populations was largely a result of excluding patients who did not have adequate postbaseline assessments after data exclusions or patients who used prohibited medications just before randomization (placebo: 7 patients; quetiapine SR: 10, 8, and 6 patients [low to high dose]; and quetiapine IR: 8 and 4 patients [low to high dose]). Such differences between the MITT and PP populations were not unexpected given the population studied and the recognized problem of noncompliance in patients with schizophrenia.

Overall then, the study population comprised patients with acute exacerbation of schizophrenia representative of patients typically included in clinical studies evaluating the efficacy and safety of antipsychotic medications.

7. EFFICACY AND PHARMACOKINETIC RESULTS

A summary of efficacy results is given in Section 7.1. Full results are given in the sections that follow, and any issues potentially affecting these results are discussed in Section 7.6. Efficacy conclusions are given in Section 7.7. This study did not explore pharmacokinetic objectives; hence, there are no pharmacokinetics results to report.

7.1 Summary of efficacy results

An overview of efficacy results is presented in Table 25.

Table 25 Overview of efficacy results at Day 42 (LOCF, MITT population)

Summary statistic	Placebo (n=78)	QTP SR 300 mg (n=83)	QTP SR 600 mg (n=87)	QTP SR 800 mg (n=85)	QTP IR 300 mg (n=85)	QTP IR 600 mg (n=80)
PANSS total score, LSmean change from BL[a]	-5.19	-5.01	-13.01[b]	-11.17	-9.42	-6.97
PANSS response, % patients with ≥30% improvement[c]	14.1	12.0	24.1	23.5	18.8	13.8
CGI Severity of Illness score, LSmean change from BL	–0.42	–0.50	–0.66	–0.68	–0.59	–0.51
CGI Global Improvement, % patients with improvement[d]	48.7	50.6	64.4	55.3	57.6	53.8
% much/very much improved	19.2	30.1	33.3	35.3[e]	42.3[e]	26.3

[a] Mean baseline PANSS total scores across treatment groups were 91.1, 91.5, 92.4, 89.0, 89.5, and 88.6, respectively.
[b] Significantly different versus placebo (analysis of covariance adjusted for multiplicity, p=0.033)
[c] In PANSS total score.
[d] Includes patients improved, much improved and minimally improved per CGI Global Improvement rating.
[e] Significantly different from placebo (Cochran-Mantel-Haenszel analysis, p=0.015 for SR 800 mg and 0.005 for IR 300 mg).

BL Baseline. CGI Clinical Global Impression. LOCF Last observation carried forward. LSmean Least-squares mean.
MITT Modified intent-to-treat. PANSS Positive and Negative Syndrome Scale.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.2.1.1.1, 11.2.1.2.7, 11.2.2.1.5, 11.2.2.2.1, 11.2.2.3.3, 11.2.2.3.5.3, and 11.2.2.3.6, Section 11.2.

The primary objective—to demonstrate superior efficacy of quetiapine SR compared with placebo in the treatment of patients with schizophrenia—was met for the quetiapine SR 600-mg dose. At the final visit, the estimated mean difference between SR 600 mg and placebo (–7.82) for change from baseline in PANSS total score (primary efficacy variable) was significant in favor of SR 600 mg (p=0.033, ANCOVA, adjusted for multiplicity). In the same ANCOVA, the estimated mean differences between SR 300 mg and placebo and between SR 800 mg and placebo were not statistically significant; however, a numerical advantage in symptom improvement was seen with SR 800 mg compared with placebo. In secondary analyses, a significant difference between quetiapine SR 600 mg and placebo was seen as early as Day 15 and was sustained from Day 28 through to Day 42 (LOCF).

Treatment with quetiapine SR 600 and SR 800 mg provided meaningful clinical improvement (≥30% decrease in PANSS total score) in numerically greater proportions of patients (24% each), compared with placebo (14%); however, differences were not statistically significant. On other secondary endpoints, quetiapine SR 600 and SR 800 mg also provided consistent numerical advantages, compared with placebo, but the only statistically significant difference was seen between SR 800 mg and placebo for proportions of patients much or very much improved per CGI global assessment (p=0.015, Cochran-Mantel-Haenszel analysis).

The effects of quetiapine IR 300 and IR 600 mg on the endpoints selected to address the secondary efficacy objective were not consistently different from those of placebo, although a

statistically significant difference was seen for the proportion of patients much or very much improved per CGI global assessment at IR 300-mg dose. In this study, conclusions relative to the secondary efficacy objective—to assess the similarity of the efficacy profiles of quetiapine SR tablets and marketed quetiapine IR tablets—are limited, as follows: In reducing the symptoms of schizophrenia, quetiapine SR 600 mg achieved efficacy versus placebo, while quetiapine IR 600 mg—a dose with known efficacy in the treatment of schizophrenia—did not.

Table 26 shows where supportive data for this section are located.

Table 26 Location of supporting data on efficacy and pharmacokinetics

Data	Location	
	Summary tables (Section 11.2)	**Individual patient data (Appendix 12.2)**
Primary variable		
PANSS total score; change from baseline at Day 42 or final visit	Tables 11.2.1.1.1 to 11.2.1.1.6, 11.2.1.1.8, 11.2.1.1.9, 11.2.1.2.1 to 11.2.1.2.9, 11.2.2.1.2, 11.2.2.1.3, 11.2.2.1.5; Figures 11.2.3.1.1 to 11.2.3.1.3	Appendix 12.2.6.1
Secondary variables		
PANSS total score; change from baseline at each visit	Tables 11.2.1.1.1 to 11.2.1.1.6, 11.2.1.1.8, 11.2.1.1.9, 11.2.1.2.1 to 11.2.1.2.7, 11.2.2.1.2, 11.2.2.1.3; Figures 11.2.3.1.1 to 11.2.3.1.3	Appendix 12.2.6.1
PANSS total score; change from baseline at Day 4 (by quetiapine formulation)	Tables 11.2.1.1.7, 11.2.2.1.1, and 11.2.2.1.4	Appendix 12.2.6.1
PANSS response	Tables 11.2.2.2.1 to 11.2.2.2.3, Figure 11.2.3.1.7	Appendix 12.2.6.1
PANSS subscale and activation factor scores; change from baseline	Tables 11.2.1.1.1, 11.2.1.1.2, 11.2.1.1.8, 11.2.1.1.9, 11.2.1.2.1, 11.2.1.2.2, 11.2.2.1.2, 11.2.2.1.3; Figures 11.2.3.1.4 to 11.2.3.1.6	Appendix 12.2.6.1
PANS depression item score; change from baseline	Tables 11.2.2.4.1 to 11.2.2.4.4	Appendix 12.2.6.1
CGI Severity of Illness item; change from baseline	Tables 11.2.2.3.1.1 to 11.2.2.3.4.2; Figures 11.2.3.2.1 and 11.2.3.2.2	Appendix 12.2.6.2
CGI Global Improvement	Tables 11.2.2.3.5.1 to 11.2.2.3.5.4, 11.2.2.3.6; Figure 11.2.3.2.3	Appendix 12.2.6.2

CGI Clinical Global Impression. PANSS Positive and negative syndrome scale.

7.2 Efficacy results

7.2.1 Primary variable: Change in PANSS total score from baseline to Day 42 or final visit

Mean change from baseline in PANSS total score at Day 42 (LOCF) and analysis results are summarized by treatment group in Table 27.

Table 27 PANSS total score, change from baseline at Day 42, by treatment group: MITT population (LOCF)

Summary statistic	Placebo (n=78)	QTP SR 300 mg (n=83)	QTP SR 600 mg (n=87)	QTP SR 800 mg (n=85)	QTP IR 300 mg (n=85)	QTP IR 600 mg (n=80)
Within treatment group						
Baseline, mean (SD)	91.1 (16.3)	91.5 (19.2)	92.4 (17.2)	89.0 (14.9)	89.5 (15.7)	88.6 (17.3)
Day 42, mean (SD)	85.5 (23.4)	86.1 (25.0)	78.7 (23.8)	77.8 (22.1)	80.1 (23.3)	81.7 (25.3)
Change from baseline	-5.6 (18.6)	-5.5 (19.1)	-13.7 (22.1)	-11.1 (19.0)	-9.4 (22.8)	-6.9 (19.2)
Least-squares mean (SE)	-5.19 (2.34)	-5.01 (2.28)	-13.01 (2.23)	-11.17 (2.25)	-9.42 (2.24)	-6.97 (2.32)
95% CI	-9.78, -0.60	-9.49, -0.52	-17.39, -8.63	-15.60, -6.75	-13.83, -5.01	-11.54, -2.41
Difference from placebo[a]						
Estimated mean (SE)	N/A	0.19 (3.09)	-7.82 (3.06)	-5.98 (3.08)	-4.23 (3.07)	-1.78 (3.12)
95% CI	N/A	-5.88, 6.26	-13.83, –1.81	-12.03, 0.06	-10.27, 1.81	-7.92, 4.36
p-value (unadjusted)	N/A	0.952	0.011	0.052	0.169	0.569
p-value (adjusted)[b]	N/A	0.952	0.033	0.105	N/D	N/D

[a] From analysis of covariance.
[b] Interpretation of analysis after adjustment for multiplicity (Hochberg method).
CI Confidence interval. LOCF Last observation carried forward. MITT Modified intent-to-treat population.
N/A Not applicable. N/D Not done. NS Not statistically significant. QTP IR Quetiapine immediate release.
QTP SR Quetiapine sustained release. SD Standard deviation. SE Standard error of the mean.
Data derived from Table 11.2.1.1.1, 11.2.1.2.1, 11.2.1.2.7, and 11.2.2.1.5, Section 11.2.

For each treatment group, mean PANSS total score decreased from baseline to Day 42 (or final visit). The greatest mean change (–13.7) was seen with quetiapine SR 600 mg, although change at the quetiapine SR 800-mg dose (–11.4) was only slightly smaller. Each of these changes was greater than the change seen with placebo (–5.6). Mean change from baseline at the SR 300-mg dose (–5.5), however, was similar to that seen with placebo.

Mean change with quetiapine IR 300 mg (–9.4) was slightly greater than that seen with quetiapine IR 600 mg or placebo (by 2.5 and 3.8 points, respectively).

The difference between treatment groups in LSmean change from baseline at Day 42 (LOCF) was significant (p=0.033, analysis adjusted for multiplicity) for quetiapine SR 600 mg versus placebo (see Table 11.2.2.1.5, Section 11.2), but not between SR 300 or SR 800 mg and placebo.

In the PP analysis, greater LSmean changes from baseline were seen for patients treated with quetiapine SR 600, SR 800, and IR 300 mg (–12.8, –11.0, and –10.3, respectively), compared with changes for patients treated with placebo (–7.4), quetiapine SR 300 mg (–7.7), and quetiapine IR 600 mg (–7.8). Differences between placebo and each quetiapine group were not significant (ANCOVA, LOCF) (see Table 11.2.1.2.8, Section 11.2).

As described in Section 6.4, data from Center 43 were excluded from the MITT population and thus were excluded from the primary analysis. In a secondary analysis testing for consistency, the inclusion of Center 43 data in the ANCOVA (MITT+Center 43, LOCF) for change from baseline in PANSS total score at Day 42 (or last visit) did not change the study conclusion. The difference in statistical significances for the quetiapine SR 600 mg and placebo comparisons was within a round-off error, and the comparison of quetiapine SR 800 mg versus placebo remained statistically insignificant (see Table 11.2.1.2.9, Section 11.2).

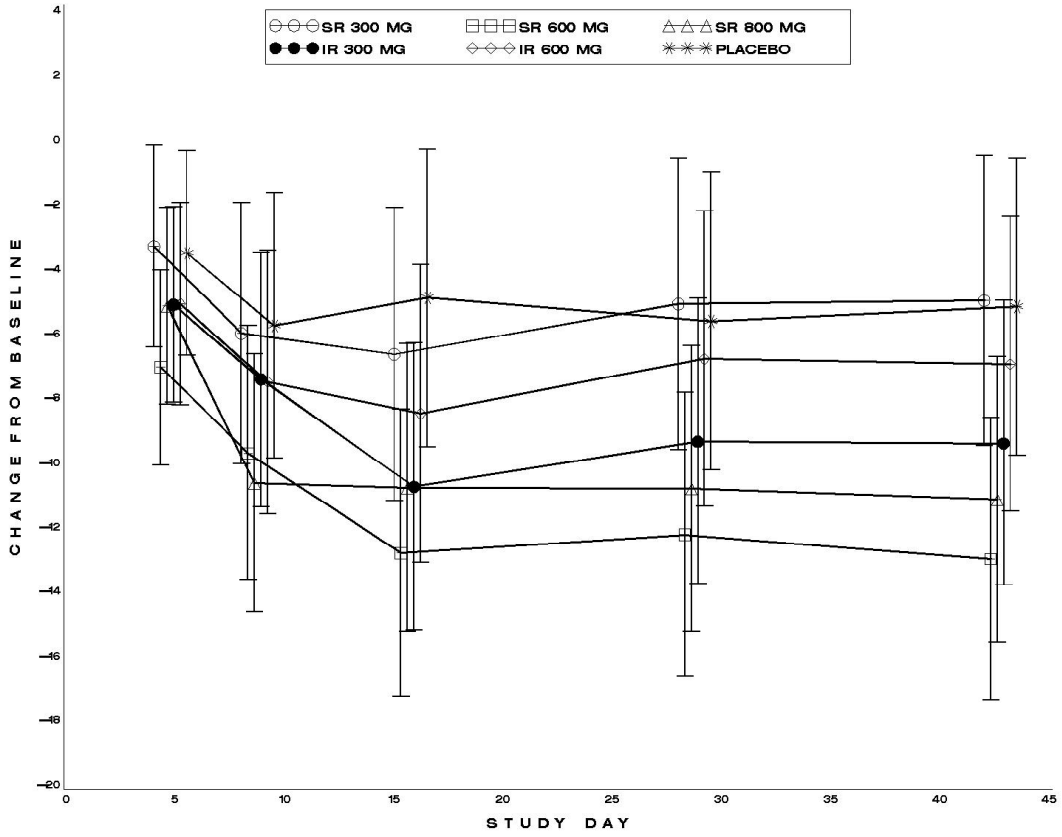
When only patients who completed the study were considered (OC data), a pattern of change similar to that seen with LOCF data was observed, with the greatest mean change from baseline also achieved with SR 600 mg (–25.0). Differences in change from baseline between placebo and the other treatment groups were marginal (within ±2.8 points), reflecting a strong placebo effect (–19.2 point change). Additional OC data for change in PANSS total score are provided in Tables 11.2.1.2.2 and 11.2.2.1.3.

7.2.2 Secondary variables

7.2.2.1 Change in PANSS total score from baseline to each visit

LSmean change in PANSS total score from baseline to each postbaseline visit (LOCF) is presented graphically in Figure 4. Supportive statistics are summarized in Table 11.2.1.2.7, (Section 11.2).

Figure 4 **LSmean change (95% CI) in PANSS total score from baseline (Day 1) to each visit (LOCF, MITT)**



CI Confidence interval. IR Quetiapine immediate release. SR Quetiapine sustained release.
LOCF Last observation carried forward. MITT Modified intent to treat analysis population.
Data from Figure 11.2.3.1.3, Section 11.2.

For all treatment groups, mean PANSS total scores at each visit were less than their respective total scores at baseline, indicating various degrees of symptom improvement over time. For subjects treated with quetiapine SR 600 or SR 800 mg, the magnitude of change increased over time through Day 42, ie, the smallest changes from baseline were seen on Day 4 (–7.3 and –5.0, respectively) and the largest changes were seen on Day 42 (LOCF, -13.7 and –11.1, respectively). For patients treated with placebo, the largest mean decrease (–6.2) occurred on Day 28. For patients treated at the other quetiapine doses, the largest mean decreases from baseline were seen on Day 15: –6.8 with SR 300 mg; –10.7 with IR 300 mg; and –8.2 with IR 600 mg.

In secondary analyses, differences between quetiapine SR 600 mg and placebo in LSmean change from baseline (ANCOVA, LOCF) were significant as early as Day 15 (p=0.003) and remained significant at Day 28 (p=0.026) and Day 42 (p=0.011). For other quetiapine treatments, significant differences between quetiapine and placebo were seen on Days 8 and

15 for quetiapine SR 800 mg (p=0.037 and p=0.030) and on Day 15 for quetiapine IR 300 mg (p=0.030).

Differentiation of early treatment effects among placebo, quetiapine SR-, and quetiapine IR-treated patients was slight, with mean changes from baseline to Day 4 in PANSS total score of –3.5, –5.2, and –4.9, respectively. Estimated differences in least-squares means between quetiapine (either formulation) and placebo were not significant. Data are summarized in Tables 11.2.1.1.7, 11.2.2.1.1, and 11.2.2.1.4 (Section 11.2).

7.2.2.2 PANSS response rates

The proportions of PANSS responders (MITT population) at the 30% level (ie, a decrease from baseline of ≥30% in PANSS total score) at the final visit were greatest among patients treated with quetiapine SR 600 and SR 800 mg (24% per treatment group). Response rate at the SR 300-mg dose (12.1%) was similar to that seen with placebo (14.1%). Differences between placebo and each quetiapine SR treatment group were not significant (Table 28).

The response rate with quetiapine IR 300 mg (19%) was slightly lower than the response rates seen for patients treated at the 2 higher SR doses, while the response rate with quetiapine IR 600 mg was similar to that seen with quetiapine SR 300 mg (and placebo). Differences between placebo and each quetiapine IR treatment group were not significant (Table 28).

Table 28 PANSS response rates: subjects with ≥30% decrease from baseline at final visit in PANSS total score: MITT

Treatment	N	Responders, n (%)	p-value[a]
Placebo	78	11 (14.1)	
QTP SR 300 mg	83	10 (12.1)	0.733
QTP SR 600 mg	87	21 (24.1)	0.091
QTP SR 800 mg	85	20 (23.5)	0.115
QTP IR 300 mg	85	16 (18.8)	0.543
QTP IR 600 mg	80	11 (13.8)	0.797

[a] Cochran-Mantel-Haenszel analysis response at final visit.
MITT Modified intent-to-treat population. QTP IR Quetiapine immediate release.
QTP SR Quetiapine sustained release.
Data derived from Tables 11.2.2.2.1 and 11.2.2.2.3, Section 11.2.

Response rates by treatment visit are presented graphically in Figure 11.2.3.1.7 (Section 11.2).

When observed data were considered (with denominators based on the numbers of patients remaining in the trial for each treatment group at Day 42), greater percentages of patients per treatment group (between 25% and 43% inclusive) met the 30% response criteria at Day 42. The pattern of relative magnitude among treatments was similar to that seen for LOCF data (ie, greatest percentage seen with quetiapine SR 600 mg and smallest percentage seen with

quetiapine SR 300 mg and IR 600 mg). (See Table T11.2.2.2.2 [Section 11.2] for details [all response levels]).

When response was considered at the 40% level, the proportion of responders (LOCF, MITT population) decreased by more than half for patients treated with quetiapine SR 300, SR 800, IR 300, and IR 600 mg. For patients treated with placebo and SR 600 mg, the proportion of responders decreased by less than half (from 14.1% to 10.3% with placebo and from 24.1% to 16.1% with SR 600 mg. The proportions of responders were still greatest overall for patients treated with quetiapine SR 600 mg and smallest for patients treated with quetiapine SR 300 mg (4.8%). Differences between placebo and each quetiapine treatment group were not significant.

With a minor exception, only 1 or 2 patients per treatment group met the response criteria at the 50% level; an exception of 4 patients was seen with quetiapine IR 300 mg. Differences between placebo and each active treatment were not significant.

Data for responders at the 40% and 50% levels (MITT population) can be found in Tables 11.2.2.2.1, 11.2.2.2.2, and 11.2.2.2.3 (Section 11.2).

7.2.2.3 PANSS Positive Symptom, Negative Symptom, and General Psychopathology subscale and activation scores

(a) PANSS Positive Symptom subscale score: change from baseline

Among patients treated with quetiapine SR, LSmean changes from baseline in PANSS positive symptom subscale score at Day 42 ranged from –2.15 (SR 300 mg) to –3.42 (SR 600 mg); these values were slightly greater than the LSmean change from baseline for patients treated with placebo (–1.76). LSmean changes in positive symptom subscale scores among patients treated at the 300- or 600-mg IR dose of quetiapine (–2.62 and –2.34, respectively) were similar to changes seen at the SR 300-mg dose. At the final visit, differences between quetiapine (any dose or formulation) and placebo were not statistically significant (all p-values ≥0.083). Complete analysis results are provided in Table 11.2.1.2.7 (Section 11.2).

Full descriptive statistics for positive symptom subscale scores at each visit and change from baseline at each visit are provided Tables 11.2.1.1.1, 11.2.1.1.2, 11.2.1.2.1, and 11.2.1.2.2 (Section 11.2).

(b) PANSS Negative Symptom subscale score: change from baseline

Among patients treated with quetiapine SR, LSmean changes from baseline in PANSS negative symptom subscale score at Day 42 (LOCF) ranged from –1.03 (SR 300 mg) to –2.87 (SR 600 mg); the latter value and the value at the SR 800-mg dose (–2.77) were slightly greater than the LSmean change from baseline for patients treated with placebo (–1.28). The LSmean change in negative symptom subscale score for patients treated with quetiapine IR 300 mg (–2.05) was most similar to that seen for patients treated with quetiapine SR 600 mg, while the LSmean change in negative symptom subscale score for patients treated with quetiapine IR 600 mg (–1.25) was similar to that for patients treated with placebo. At the final

visit, differences between quetiapine (any dose or formulation) and placebo were not statistically significant (all p-values ≥0.070). Complete analysis results are provided in Table 11.2.1.2.7 (Section 11.2).

Full descriptive statistics for negative symptom subscale scores at each visit and change from baseline at each visit are provided Tables 11.2.1.1.1, 11.2.1.1.2, 11.2.1.2.1, and 11.2.1.2.2 (Section 11.2).

(c) PANSS General Psychopathology subscale score: change from baseline

At Day 42 (LOCF), the greatest improvements in general psychopathology subscale scores were seen among patients treated with quetiapine SR 600 and SR 800 mg (–6.9 and –5.0, respectively). Change in mean score at the SR 300-mg dose (–2.2) was similar to that seen with placebo (–2.0). Changes in mean scores at the IR 300- and 600-mg doses (–4.7 and –3.4, respectively) were greater than that with placebo or SR 300 mg but less than those seen at the 600- or 800-mg SR doses. No statistical analyses were performed on these data.

Full descriptive statistics for subscale scores at each visit and change from baseline at each visit are provided Tables 11.2.1.1.1, 11.2.1.1.2, 11.2.1.2.1, and 11.2.1.2.2 (Section 11.2).

(d) PANSS activation factor score: change from baseline

At Day 42 (LOCF), small improvement in activation factor scores were seen at the quetiapine SR doses of 600 and 800 mg (mean change, –1.5 and –0.9, respectively). In contrast, mean scores with placebo and quetiapine SR 300 mg were increased slightly (+0.4 and +1.0, respectively), indicating a small degree of disease worsening.[5] For patients treated at the quetiapine IR 300- and 600-mg doses, decreases from baseline were marginal (–0.5 and –0.1, respectively) and less than those seen at the SR 600- and 800-mg doses. No statistical analyses were performed on these data.

Full descriptive statistics for activation factor scores at each visit and change from baseline at each visit are provided Tables 11.2.1.1.1, 11.2.1.1.2, 11.2.1.2.1, and 11.2.1.2.2 (Section 11.2).

7.2.2.4 PANSS depression item score: change from baseline

In all treatment groups, mean PANSS depression item scores were close to 3 at baseline, with small mean decreases seen at Day 42 (LOCF). The greatest mean change of –0.6 was seen with SR 600 mg, and the smallest mean change of –0.2 was seen with placebo. Mean changes at the SR 300- and SR 800-mg doses were –0.3 and –0.4, respectively. Change with quetiapine SR 600 mg was most closely similar to that seen with quetiapine IR 300 and 600 mg (–0.5 for both). Descriptive statistics, including baseline values and changes from baseline by visit (LOCF, MITT), are provided in Tables 11.2.2.4.1 and 11.2.2.4.3 (Section 11.2) for this and all other individual PANSS items. Observed case data are similarly

[5]In behaviors related to excitement, hostility, poor rapport, tension, uncooperativeness, and poor impulse control.

provided in Tables 11.2.2.4.2 and 11.2.2.4.4 (Section 11.2). No statistical analyses were performed on these data.

7.2.2.5 CGI Severity of Illness and Global Improvement scores

Mean change from baseline in CGI Severity of Illness score at Day 42 and analysis results are summarized by treatment group in Table 29.

Table 29 CGI Severity of Illness score: change from baseline at Day 42 and analysis results: MITT population (LOCF)

Summary statistic	Placebo (n=78)	QTP SR 300 mg (n=83)	QTP SR 600 mg (n=87)	QTP SR 800 mg (n=85)	QTP IR 300 mg (n=85)	QTP IR 600 mg (n=80)
Within treatment group						
Baseline, mean (SD)	4.7 (0.68)	4.8 (0.73)	4.7 (0.77)	4.7 (0.68)	4.8 (0.71)	4.7 (0.67)
Day 42, mean (SD)	4.3 (1.27)	4.3 (1.25)	4.1 (1.01)	4.0 (1.14)	4.2 (1.23)	4.2 (1.08)
Change from baseline	–0.4	–0.5	–0.7	–0.7	–0.6	–0.5
LSmean (SE) change	–0.42 (0.13)	–0.50 (0.12)	–0.66 (0.12)	–0.68 (0.12)	–0.59 (0.12)	–0.51 (0.13)
95% CI	–0.67, –0.17	–0.74, –0.26	–0.90, –0.43	–0.92, –0.44	–0.83, –0.35	–0.76, –0.27
Difference from placebo						
Estimated mean (SE)	N/A	–0.08 (0.17)	–0.24 (0.17)	–0.26 (0.17)	–0.17 (0.17)	–0.09 (0.18)
95% CI	N/A	–0.42, 0.26	–0.58, 0.09	–0.60, 0.08	–0.51, 0.17	–0.44, 0.25
p-value	N/A	0.647	0.156	0.133	0.322	0.597

CI Confidence interval. LOCF Last observation carried forward. MITT Modified intent-to-treat population.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
SD Standard deviation. SE Standard error of the mean.
Data derived from Tables 11.2.2.3.1.1, 11.2.2.3.2.1 and 11.2.2.3.3, Section 11.2.

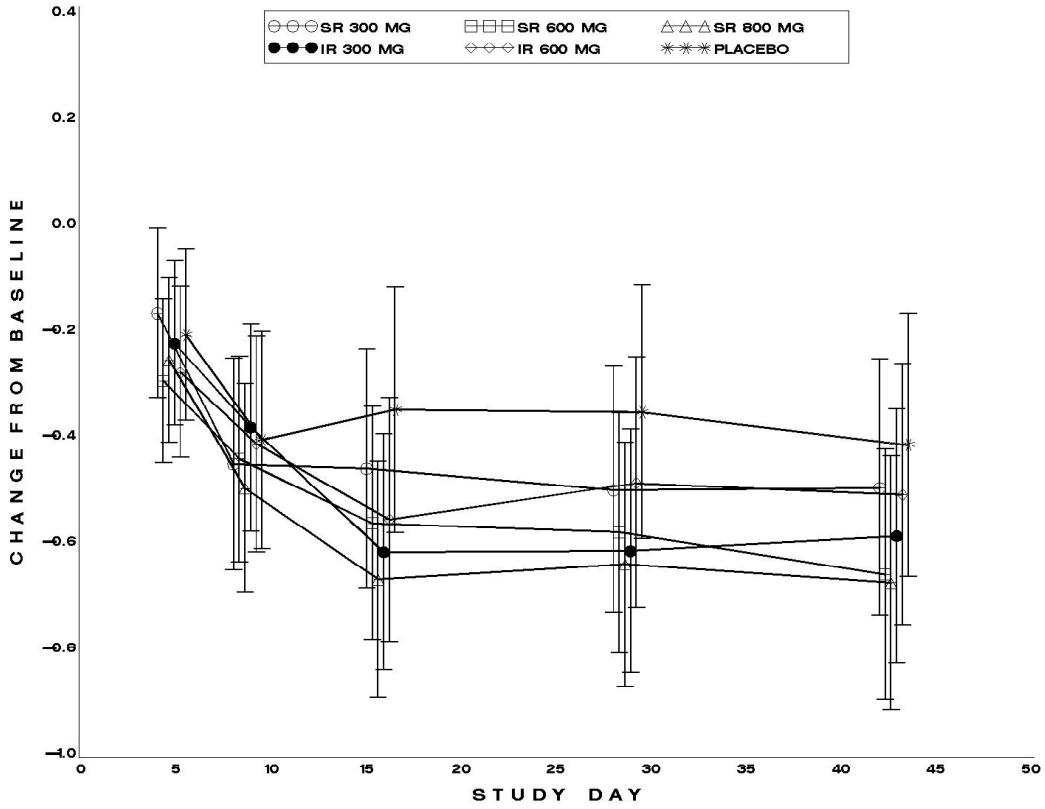
In each treatment group, decreases from baseline in mean CGI Severity of Illness scores at Day 42 (LOCF) indicated improvement in disease severity. The greatest changes were seen with quetiapine SR at doses of 600 and 800 mg (–0.7 each) and with quetiapine IR at the 300-mg dose (–0.6). The smallest change was seen with placebo (–0.4), with slightly greater changes seen with quetiapine SR 300 mg and IR 600 mg (–0.5).

Median changes showed a slightly different pattern in that greater decreases of –1.0 (greater improvement) were seen with SR 600 mg, SR 800 mg, and IR 300 mg and changes of zero (less improvement) were seen with placebo, SR 300 mg, and IR 600 mg.

Differences between quetiapine (any dose or formulation) and placebo were not statistically significant (all p-values ≥0.1326). Complete results are provided in Table 11.2.2.3.3 (Appendix 11.2).

Mean change in CGI Severity of Illness score from baseline to each postbaseline visit (MITT, LOCF) is shown in Figure 5.

Figure 5 **LSmean change (95% CI) in CGI Severity of Illness score from baseline to each visit (LOCF, MITT)**



CI Confidence interval. IR Quetiapine immediate release. SR Quetiapine sustained release.
LOCF Last observation carried forward. MITT Modified intent to treat analysis population.
Data from Figure 11.2.3.2.2, Section 11.2.

Throughout the study, disease improvement per CGI Global Improvement score was seen in each treatment group. Table 30 summarizes the proportions of patients much or very much improved per treatment group.

Table 30 Patients much or very much improved per CGI Global Improvement assessment at Day 42: MITT population (LOCF)

Summary statistic	Placebo (n=78)	QTP SR 300 mg (n=83)	QTP SR 600 mg (n=87)	QTP SR 800 mg (n=85)	QTP IR 300 mg (n=85)	QTP IR 600 mg (n=80)
Much/very much improved						
Number (%) of patients	15 (19.2)	25 (30.1)	29 (33.3)	30 (35.3)	36 (42.4)	21 (26.3)
Difference from placebo						
p-value[a]	N/A	0.114	0.097	0.015	0.005	0.291

[a] From Cochran-Mantel-Haenszel analysis.
CI Confidence interval. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.2.2.3.6, Section 11.2.

Among patients treated with quetiapine SR (any dose), the proportions of patients much or very much improved (30.1% to 35.3%) at Day 42 (LOCF) were greater than that achieved with placebo (19.2%).

Overall, more patients were much or very much improved at Day 42 (LOCF) after treatment with quetiapine IR 300 mg (42.4%) than after any of the other treatments (Table 30). The proportion of patients much or very much improved at the quetiapine IR 600-mg dose (26.3%) was slightly lower than that seen at the SR 300-mg dose (30.1%).

At Day 42 (LOCF), the proportion of patients much or very much improved at the quetiapine SR 800-mg dose was significantly greater (p=0.015) that than seen with placebo (Table 30). For these patients, a significant difference (p=0.017) was seen as early as Day 8. Differences between either quetiapine SR 300 mg or SR 600 mg and placebo were not significant.

At Day 42 (LOCF), the proportion of patients much or very much improved at the quetiapine IR 300-mg dose was significantly greater (p=0.005) that than seen with placebo (Table 30). For these patients, a significant difference (p=0.010) was seen as early as Day 15. A significant difference (p=0.032) in the proportions of patients much or very much improved was seen between patients treated with quetiapine IR 600 mg (32.5%) and placebo (16.7%) at Day 15 only.

When patients with any level of improvement (minimal, much, or very much) were considered, a greater proportion of patients treated with quetiapine SR 600 mg, 64.4%, were improved, compared with that in the other treatment groups: placebo, 48.7%; SR 300 mg, 50.6%; SR 800 mg, 55.3%; IR 300 mg, 57.6%; and IR 600 mg, 53.8%.

7.3 Patient Reported Outcomes (not applicable)

7.4 Health Economics results (not applicable)

7.5 Pharmacokinetic results (not applicable)

7.6 Potential issues affecting efficacy and pharmacokinetic results

7.6.1 Statistical and analytical issues

High rates of withdrawal early into treatment meant that affected patients withdrew before having a chance to improve and, thus, PANSS total and CGI Severity of Illness scores more closely reflective of baseline status were brought forward in LOCF analyses for fairly high proportions of patients. At the end of the first treatment week, 19.0% of placebo-treated patients, 26.4%, 14.1%, and 7.9% of patients in the SR treatment groups (low to high dose, respectively), and 25.6% and 9.3% of patients in the IR treatment groups (low to high dose, respectively) had been withdrawn. Through Day 7, patients in the SR 800-mg treatment group had not yet reached their target treatment dose, and patients in the IR 600-mg treatment group had been at their target dose for only 3 days. At the end of the second treatment week, another 19.0% of placebo-treated patients, 15.4%, 15.2%, and 18.0% of patients in the SR treatment groups (low to high dose, respectively), and 8.9% and 27.9% of patients in the IR treatment groups (low to high dose, respectively) had been withdrawn. Thus, the unexpected high rates of early withdrawal, overall withdrawal rates of >50% in each treatment group, and consequently, reduced time on treatment made it more difficult to show that quetiapine SR was superior to placebo in reducing the symptoms of schizophrenia.

When high-enrollment and low-enrollment centers were considered for possible center effects on efficacy trends, no differences from overall findings were seen. The inclusion or exclusion of data from Center 43 (see Section 6.4 for rationale) did not change the finding of a significant difference between SR 600 mg and placebo in change from baseline in PANSS total score (MITT population).

Findings based on the PP analysis set for the primary efficacy variable supported findings of an overall greater numerical advantage with SR 600 mg and slightly greater numerical advantages with SR 800 mg and IR 300 mg, compared with placebo.

7.6.2 Drug-dose or drug-concentration relationships (not applicable)

7.6.3 Drug-drug and drug-disease interactions

Use of lorazepam was fairly consistent with protocol requirements, which limited its use for agitation to the first 6 days of study-drug treatment. Between 36% and 48% across treatments used lorazepam during Week 1, after which use dropped dramatically in all treatment groups. By Week 3, use was rare—in zero to 3 patients per treatment group. Thus, lorazepam use was not considered a differentiating factor with regard to efficacy results.

7.6.4 Pharmacogenetic-drug concentration and drug-disease relationships

Blood samples taken for genetic analysis had not been evaluated at the time of this report.

7.7 Conclusions on efficacy and pharmacokinetic results

Efficacy conclusions are summarized it Table 31, relative to specific efficacy objectives and the variables selected to address each objective.

Table 31 Efficacy objectives, variables, and conclusions

Objective	Variables	Conclusions
Primary: To demonstrate superior efficacy of quetiapine SR tablets compared with placebo in the treatment of patients with schizophrenia	**Primary:** Change in PANSS total score from baseline (Day 1) to Day 42 or final visit (MITT population, LOCF)	QTP SR 600 mg was significantly more effective in improving the symptoms of schizophrenia, compared with placebo. QTP SR 800 mg was numerically more effective in improving the symptoms of schizophrenia, compared with placebo, but the difference between treatments was not statistically significant. QTP SR 300 mg and placebo produced similar numerical reductions in disease symptoms, and thus QTP SR 300 mg did not distinguish itself from placebo.
	Secondary: Change in PANSS total score over time	QTP SR 600 and SR 800 mg produced increasing symptom improvement over time (with up to 42 days of treatment). Differential treatment effects were evident as early as Day 15 (both doses) with statistically significant differentiation between SR 600 mg and placebo seen on Days 15, 28, and 42 (LOCF). Differences in treatment effects among SR-placebo- and IR-treated patients through the first 4 days of treatment, when all SR-treated patients were receiving SR 300 mg daily, were small and not statistically significant.
	PANSS response, ie, ≥30% decrease in PANSS total score from baseline to Day 42 (MITT population, LOCF)	Treatment with QTP SR 600 and SR 800 mg provided meaningful clinical improvement in numerically greater proportions of patients (24% each), compared with placebo (14%); however, differences were not statistically significant.

Table 31 Efficacy objectives, variables, and conclusions

Objective	Variables	Conclusions
Secondary: To assess the similarity of the efficacy profiles of quetiapine SR tablets and marketed quetiapine IR tablets	PANSS total score; Positive, Negative, and General Psychopathology subscale scores; activation factor score; and depression item score at each visit and changes from baseline (Day 1) to each postbaseline visit (MITT population, LOCF and OC)	The effects of QTP IR 300 and 600 mg on the endpoints selected to address the secondary efficacy objective were not consistently different from those of placebo, with the only statistically significant difference seen for the proportion of patients much or very much improved per CGI Global Improvement at the IR 300-mg dose. Comparative conclusions were as follows: In reducing the symptoms of schizophrenia, QTP SR 600 mg achieved efficacy versus placebo, while QTP IR 600 mg—a dose with known efficacy in the treatment of schizophrenia—did not; neither formulation differed from placebo at the 300-mg dose.
	PANSS response including alternative response criteria of ≥40% and ≥50% decreases in PANSS total score from baseline to Day 42 (MITT population, LOCF)	(See conclusion paragraph in preceding cell.)
	CGI Severity of Illness score at each visit and changes from baseline (Day 1) to each postbaseline visit (MITT population, LOCF and OC)	
	CGI Global Improvement score at each visit after baseline (Day 1) (MITT population, LOCF and OC)	

8. SAFETY RESULTS

Safety data in this report are presented under the following headings:

- Summary of safety (Section 8.1)
- Exposure (Section 8.2)
- Adverse events (Section 8.3)
- Deaths, serious adverse events, discontinuations due to adverse events, and other significant adverse events (Section 8.4)
- Clinical laboratory evaluation (Section 8.5)
- Vital signs, ECG results, physical findings, and other observations related to safety (Section 8.6)

8.1 Summary of safety

Quetiapine SR was generally safe and well tolerated across the dose range of 300 to 800 mg in the treatment of patients with acute exacerbation of schizophrenia. The most common AEs across all SR-treatment groups were those of the nervous, gastrointestinal, and vascular systems and included orthostatic hypotension, sedation or somnolence, headache, dry mouth, dizziness, and increased heart rate or tachycardia. AEs in general were predominantly characterized as mild or moderate. No deaths were reported and few SAEs occurred.

A quetiapine SR 300-mg starting dose and the dose-administration schedule used to increase daily dose to 800 mg were well tolerated. Dose initiation at the SR 300-mg dose did not result in increased incidences of early withdrawal or increased rates of AEs assessed as drug-related, compared with IR 300 mg. Increases in SR dose did not produce consistent dose-related changes in safety indices.

There were no instances of agranulocytosis with any quetiapine treatment. The expected mean increases in pulse rate seen with quetiapine SR were also seen with quetiapine IR. Small mean and median weight gains of about 2 kg were seen for patients who completed 42 days of quetiapine treatment (SR or IR). Findings of clinically important laboratory, vital signs, or ECG findings were infrequent, with clinically important vital signs most commonly seen as increases in heart rate (≥15 bpm) in all treatment groups.

Incidences of extrapyramidal disorder (MedDRA preferred term) were low: 2.4%, 2.2%, and 0% among patients treated with placebo, quetiapine SR, and quetiapine IR, respectively. Individual AEs predesignated as potentially related to EPS were infrequent, rarely led to withdrawal, and were either rated mild or moderate. When these AEs were aggregated, overall rates for SR- and IR-treated patients were similar and somewhat greater than that with placebo; however, anticholinergic use for EPS was greatest among placebo-treated patients,

compared with SR and IR-treated patients. Anticholinergic use did not increase over time in any treatment group, and this was consistent with results of neurological assessments (Simpson Angus Scale, AIMS, and BARS global assessment scores), which showed that the majority of patients (all treatment groups) either improved or did not change relative to EPS, abnormal involuntary movements, or akathisia. Additionally, on each of the scales, slightly greater proportions of placebo-treated patients worsened, compared with quetiapine-treated patients (SR and IR), supporting a conclusion of little or no treatment-emergent EPS with quetiapine SR.

Overall, the safety profile of quetiapine SR was similar to that of quetiapine IR.

Table 32 shows where supportive data for this section are presented.

Table 32 Location of supporting data on safety

Data	Location	
	Summary tables (Section 11.3)	**Individual patient data (Appendix 12.2)**
Treatment compliance (extent of exposure)	Tables 11.3.1.1 to 11.3.1.5, 11.1.5.1	Appendix 12.2.5
Adverse events	Tables 11.3.2.1, 11.3.2.2.1, 11.3.2.2.2, 11.3.2.2.3.1 to 11.3.2.2.4.2, 11.3.2.6.1 to 11.3.2.6.2	Appendix 12.2.7
Deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events	Tables 11.3.2.3.1 to 11.3.2.5.2, 11.3.2.7.1 to 11.3.2.7.8	Appendix 12.2.7.
Clinical laboratory evaluations	Tables 11.3.3.1.1.1 to 11.3.3.1.1.6, 11.3.3.2.1.1 to 11.3.3.2.1.19; Figures 11.3.3.1.2.1.1 to 11.3.3.1.2.3.2, 11.3.3.2.2.1.1 to 11.3.3.2.2.11.2, 11.3.3.2.2.12 to 11.3.3.2.2.17	Appendix 12.2.8
Vital signs, ECG results, physical findings and other observations related to safety, including weight, AIMS, SAS, and BARS scores	Table 11.3.4.1.1 to 11.3.4.1.8, 11.3.5.1.1 to 11.3.5.1.5, 11.3.6.1.1.1 to 11.3.6.1.1.5, 11.3.6.3.1.1.1 to 11.3.6.3.1.1.7, 11.3.6.3.2.1.1 to 11.3.6.3.2.1.5, 11.3.6.3.3.1.1 to 11.3.6.3.3.1.5; Figures 11.3.4.2.1.1 to 11.3.4.2.5.2, 11.3.5.2.1.1, 11.3.5.2.2.2, 11.3.6.1.2.1, 11.3.6.1.2.2, 11.3.6.3.1.2.1 to 11.3.6.3.1.2.3, 11.3.6.3.2.2.1 to 11.3.6.3.2.2.3, 11.3.6.3.3.2.1 to 11.3.6.3.3.2.3	Appendix 12.2.9 (vital signs, weight, BMI, height), Appendix 12.2.10 (ECG data, AIMS, SAS, and BARS)

8.2 Extent of exposure

An overview of exposure, in terms of duration of treatment and doses received, is presented in Table 33. This table also provides supporting data on the numbers of patients who completed or discontinued the study. An overview of exposure for patients who withdrew early is provided in Table 34.

Across treatment groups, mean duration of treatment was lower than expected. On average SR-treated patients received about 3 more days of treatment (25.6 d) compared with placebo-treated patients (22.5 d) and about 1 more day compared with IR-treated patients (24.4 d).

Less than 50% of patients in each treatment group completed the study. Patients treated with quetiapine SR had a better completion rate (43.8%) compared with placebo-treated patients (34.5%) and a completion rate similar to that seen with quetiapine IR (42.0%). On a treatment group basis, higher completion rates were seen for patients treated with SR 600 mg (43.5%), SR 800 mg (49.4%), and IR 300 mg (45.6%).

Table 33 Overview of exposure: safety population

Parameter	Placebo (n=84)	QTP SR 300 mg (n=91)	QTP SR 600 mg (n=92)	QTP SR 800 mg (n=89)	QTP SR Total (n=272)	QTP IR 300 mg (n=90)	QTP IR 600 mg (n=86)	QTP IR Total (n=176)
No. of patients evaluable for safety	84	91	92	89	272	90	86	176
Male	65	67	66	73	206	68	63	131
Female	19	24	26	16	66	22	23	45
Days exposed to treatment: all subjects								
Mean	22.5	23.3	25.6	27.9	25.6	24.4	24.5	24.4
SD	16.1	16.7	15.8	15.3	16.0	17.1	15.8	16.4
Median	15.0	22.0	24.0	33.0	27.0	26.5	23.0	25.0
Min to max	1 to 44	1 to 46	1 to 45	2 to 46	1 to 46	1 to 46	1 to 46	1 to 46
No. (%) of patients by relative exposure/study completion								
Partial exposure; withdrew b/c of AEs	8 (9.5)	5 (5.5)	9 (9.8)	1 (1.1)	15 (5.5)	6 (6.7)	7 (8.1)	13 (7.4)
Partial exposure; withdrew b/c of other reasons	47 (56.0)	51 (56.0)	43 (46.7)	44 (49.4)	138 (50.7)	43 (47.8)	46 (53.5)	89 (50.6)
Full exposure; completed study	29 (34.5)	35 (38.5)	40 (43.5)	44 (49.4)	119 (43.8)	41 (45.6)	33 (38.4)	74 (42.0)

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.1.3.2 and 11.1.4.1, Section 11.1 and Tables 11.3.1.1 and 11.3.1.2, Section 11.3.

Table 34 Overview of exposure for patients who withdrew early: safety population

Exposure parameter	Placebo (n=55)	QTP SR 300 mg (n=56)	QTP SR 600 mg (n=52)	QTP SR 800 mg (n=45)	QTP SR Total (n=153)	QTP IR 300 mg (n=49)	QTP IR 600 mg (n=53)	QTP IR Total (n=102)
Days exposed to treatment								
Mean	12.2	11.5	13.0	14.2	12.8	9.8	13.6	11.8
SD	9.2	9.5	8.6	8.6	9.0	7.9	9.8	9.1
Median	10.0	8.0	12.0	12.0	10.0	7.0	10.0	8.0
Min to max	1 to 41	1 to 33	1 to 42	2 to 33	1 to 42	1 to 30	1 to 38	1 to 38

Min Minimum. Max Maximum.
Data derived from Table 11.3.1.2, Section 11.3.

8.3 Adverse events

This section gives an overview of reported AEs by treatment group, summarizing overall AE frequency and seriousness (Section 8.3.1) and types of AEs categorized according to both MedDRA system-organ class (SOC) and preferred term (Section 8.3.2).[6] AE intensity and drug-relatedness are described in Sections 8.3.2.3 and 8.3.2.4, respectively. An overview of AEs related to somnolence, tachycardia, postural hypotension, dizziness, and syncope, as well as event onset, is provided in Section 8.3.2.5.

8.3.1 Categories of adverse events

More than 75% of patients in each treatment group reported at least 1 AE (placebo, 76.2%; quetiapine SR, 85.7%, 90.2%, and 84.3% [low to high dose]; and quetiapine IR, 83.3% and 84.9% [low to high dose]). Importantly, SAEs were infrequent (≤4 patients per treatment group) (see Section 8.4.2) and did not occur in patients treated with quetiapine SR 800 mg. No patients died as a result of their AEs. Rates of AE-related withdrawals were generally in the range of 6% to 10% per treatment group, with the lowest rate (1%) seen among patients treated with SR 800 mg (see Section 8.4.3). A categorical overview of AEs is provided by treatment group in Table 35.

[6] Adverse events tabulated by COSTART body system and preferred terms, in accord with the original statistical analysis plan, are provided in Appendix 12.2. MedDRA terms were incorporated into this report to be consistent with high-level summary documents.

Table 35 Patients with AEs in any category (safety population)

Category	PLA		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP SR Total		QTP IR 300 mg		QTP IR 600 mg		QTP IR Total	
	(n=84)		(n=91)		(n=92)		(n=89)		(n=272)		(n=90)		(n=86)		(n=176)	
Patients, number (%)[a]																
With any adverse event (AE)	64	(76.2)	78	(85.7)	83	(90.2)	75	(84.3)	236	(86.8)	75	(83.3)	73	(84.9)	148	(84.1)
With serious AEs (SAEs)	3	(3.6)	2	(2.2)	4	(4.3)	0		6	(2.2)	1	(1.1)	2	(2.3)	3	(1.7)
SAEs leading to death	0		0		0		0		0		0		0		0	
With AEs that led to withdrawal (DAEs)	8	(9.5)	5	(5.5)	9	(9.8)	1	(1.1)	15	(5.5)	6	(6.7)	7	(8.1)	13	(7.4)
With other significant AEs (OAES)	0		0		0		0		0		0		0		0	
With study-drug related AEs	40	(47.6)	53	(58.2)	60	(65.2)	48	(53.9)	161	(59.2)	47	(52.2)	54	(62.8)	101	(57.4)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

PLA Placebo. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.2.1, Section 11.3.

8.3.2 Most common adverse events

8.3.2.1 AEs by MedDRA SOC

(a) Nervous system AEs

Among patients treated with quetiapine SR (n=272), the most common types of AEs were those of the nervous system, reported in 145 (53.3%) patients. The AEs contributing to this finding were sedation (in 22.1%), headache (17.3%), somnolence (14.0%), and dizziness (13.6%). A slightly lower rate of nervous system AEs was seen for placebo-treated patients (46.4%, 39 patients), a finding that was driven, comparatively, by greater incidences of headache (25.0%) but lower incidences of sedation (11.9%), somnolence (8.3%), and dizziness (3.6%).

The incidence of nervous system AEs at the SR 600- and SR 800-mg doses (59.8% and 52.8%, respectively) were greater than the incidence at the 300-mg SR dose (47.3%). Despite this, rates did not consistently increase as doses increased across the full dose range (ie, the rate at the SR 800-mg dose was lower than the rate at the SR 600-mg dose). The incidence of nervous system AEs at the SR 300-mg dose was similar to that with placebo and lower than that with IR 300 mg (53.3%)

Nervous system AEs were also the most common types of AEs in patients treated with quetiapine IR, with events reported in 109 (61.9%) of 176 patients; this rate was greater than the overall rate reported for patients treated with quetiapine SR.

(b) Gastrointestinal AEs

In patients treated with quetiapine SR, gastrointestinal AEs were also commonly reported—in 106 (39.0%) patients. This rate was approximately 15% greater than that seen for placebo-treated patients (23.8%). Rate differences between quetiapine SR and placebo were in large part attributed to differences in incidences of dry mouth (SR, 15.8%; placebo, 1.2%) and constipation (SR, 9.2%; placebo, 1.2%). For patients treated with quetiapine SR, increases in dose did not consistently result in increases in the incidence of gastrointestinal AEs (ie, rates increased as the SR dose increased from 300 to 600 mg, but not when the SR dose increased from 300 to 800 mg or from 600 to 800 mg [Table 36]).

Patients treated with quetiapine IR also commonly reported gastrointestinal AEs, with the overall rate (32.4%) slightly less than that seen for patients treated with quetiapine SR. Rates of gastrointestinal AEs at the SR and IR 300-mg doses were similar.

(c) Vascular AEs

The third most common types of AEs seen among patients treated with quetiapine SR were vascular disorder AEs, reported in 84 (30.9%) patients. This rate was approximately 10% greater than that seen for placebo-treated patients (21.4%). Rate differences were attributed primarily to different incidences of hypotension (SR, 6.6%; placebo 2.4%) and orthostatic hypotension (SR, 24.3%; placebo, 17.9%). For SR-treated patients, the overall rate of

hypotension was largely influenced by the rate at the SR 300-mg dose (9.9%), while the overall rate of orthostatic hypotension was largely influenced by the rate at the SR 800-mg dose (27.0%). Overall, the incidence of vascular disorder AEs increased very little with increasing dose of quetiapine SR (from low to high: 29.7% to 31.5%). Consequently, rates of vascular AEs among SR treatment groups were similar to the overall SR rate (30.9%), which in turn was similar to that seen with quetiapine IR (26.7%). Rates of vascular disorder AEs at the SR and IR 300-mg doses were also similar.

(d) Investigation-related AEs and other AEs by SOC

Rates of AEs grouped by other SOCs were generally similar between patients treated with quetiapine SR and placebo.

One exception was a greater than 5% difference between placebo and quetiapine SR for investigation-related AEs (quetiapine SR, 22.1%; placebo, 14.3%). This finding primarily reflected the difference in incidence rates for increased heart rate (quetiapine SR, 10.7%; placebo, 4.8%).

For patients treated with quetiapine SR, investigation-related AEs were the only type of AEs with overall incidence rates that increased as the SR dose increased across the full dose range, ie, from 18.7% to 21.7% to 25.8% (low to high dose). Of the individual AEs comprising this SOC, the only ones to show somewhat similar trends were increased heart rate (from 6.6% to 12.0% to 13.5%) and increased weight (from 4.4% to 5.4% to 9.0%).

Patients treated with quetiapine IR reported investigational AEs at an overall rate (23.3%) similar to the overall rate reported for patients treated with quetiapine SR (22.1%). Rates of investigational AEs at the SR and IR 300-mg doses were similar.

Another exception was seen for eye-disorder AEs in that the incidence among patients treated with quetiapine SR (5.9%, 16 patients) was more than 2 times greater than that seen for placebo-treated patients (1.2%, 1 patient). This difference was attributed primarily to different incidences of blurred vision: 3.3% (9 patients) for overall quetiapine SR (8 of whom were treated with SR 600 mg) and 0% with placebo. Of the 9 SR-treated patients with blurred vision, 2 were being treated with benztropine.[7]

The rate of eye disorder AEs among SR-treated patients was similar to the overall rate for IR-treated patients (4.5%, 8 patients), although for IR-treated patients, no single AE type was predominant.

---

[7] For Patient 0052/1231 (SR 600 mg), mild blurred vision began on the 4th day of benztropine therapy (1 to 2 mg); the event was considered not drug-related. For Patient 0035/0450 (SR 800 mg), moderate blurred vision began on the same day that benztropine 4 mg was started; the event was considered drug-related. See Table 38 for a summary of drug-related blurred vision by treatment group.

(e) Other dose-related observations for AEs by SOC

For patients treated with quetiapine SR, incidence rates for a limited number of SOC-grouped AEs increased by greater than 5% as the dose increased from SR 300 to SR 600 mg: specifically, nervous system and gastrointestinal AEs (as discussed earlier), cardiac AEs (from 8.8% to 16.3%), and psychiatric AEs (from 24.2% to 29.3%). Corresponding increases in AE rates were not seen as the dose increased from SR 600 to SR 800 mg. For cardiac AEs, the greater incidence rate at the SR 600-mg dose was related to slightly greater incidences of tachycardia/sinus tachycardia, postural orthostatic tachycardia syndrome, palpitations, and bradycardia. For psychiatric AEs, the greater incidence rate at the SR 600-mg dose was related to a greater incidence of insomnia.

The dose-response pattern for nervous system and gastrointestinal AEs described for SR-treated patients was not evident for IR-treated patients in that incidence rates changed little at the higher IR dose (600 mg). For cardiac AEs, though, the increase in IR dose resulted in a small 4.2% increase in incidence rate, which followed the pattern seen when the SR dose was increased to 600 mg (7.5% increase). Similarly, for psychiatric AEs, the increase in IR dose resulted in a small 4.3% increase in incidence rate, which also closely followed the pattern seen when the SR dose was increased to 600 mg (5.1% increase).

Incidences of AEs by MedDRA SOC are shown in Table 36, by treatment group. Specific events are discussed in Section 8.3.2.2. All AEs by MedDRA SOC are summarized in Table 11.3.2.2.2 (Section 11.3).

Table 36 Patients with at least 1 AE in any MedDRA system-organ class (safety population)

MedDRA system-organ class (SOC) (disorder type)[a]	Number (%) of patients[b]															
	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP SR Total		QTP IR 300 mg		QTP IR 600 mg		QTP IR Total	
	(n=84)		(n=91)		(n=92)		(n=89)		(n=272)		(n=90)		(n=86)		(n=176)	
Nervous system	39	(46.4)	43	(47.3)	55	(59.8)	47	(52.8)	145	(53.3)	56	(62.2)	53	(61.6)	109	(61.9)
Gastrointestinal	20	(23.8)	31	(34.1)	44	(47.8)	31	(34.8)	106	(39.0)	28	(31.1)	29	(33.7)	57	(32.4)
Vascular	18	(21.4)	27	(29.7)	29	(31.5)	28	(31.5)	84	(30.9)	23	(25.6)	24	(27.9)	47	(26.7)
Psychiatric	24	(28.6)	22	(24.2)	27	(29.3)	18	(20.2)	67	(24.6)	16	(17.8)	19	(22.1)	35	(19.9)
Investigations	12	(14.3)	17	(18.7)	20	(21.7)	23	(25.8)	60	(22.1)	17	(18.9)	24	(27.9)	41	(23.3)
Musculoskeletal & connective tissue	7	(8.3)	13	(14.3)	13	(14.1)	5	(5.6)	31	(11.4)	12	(13.3)	12	(14.0)	24	(13.6)
General & admin site conditions	6	(7.1)	11	(12.1)	10	(10.9)	6	(6.7)	27	(9.9)	4	(4.4)	8	(9.3)	12	(6.8)
Cardiac	6	(7.1)	8	(8.8)	15	(16.3)	8	(9.0)	31	(11.4)	13	(14.4)	16	(18.6)	29	(16.5)
Respiratory, thoracic & mediastinal	8	(9.5)	6	(6.6)	6	(6.5)	4	(4.5)	16	(5.9)	7	(7.8)	6	(7.0)	13	(7.4)
Infections & infestations	6	(7.1)	5	(5.5)	6	(6.5)	6	(6.7)	17	(6.3)	6	(6.7)	6	(7.0)	12	(6.8)
Skin/subcutaneous tissue	7	(8.3)	4	(4.4)	4	(4.3)	4	(4.5)	12	(4.4)	4	(4.4)	3	(3.5)	7	(4.0)
Metabolism and nutrition	2	(2.4)	4	(4.4)	3	(3.3)	2	(2.2)	9	(3.3)	5	(5.6)	1	(1.2)	6	(3.4)
Eye disorders	1	(1.2)	4	(4.4)	8	(8.7)	4	(4.5)	16	(5.9)	2	(2.2)	6	(7.0)	8	(4.5)
Reproductive system & breast	1	(1.2)	2	(2.2)	1	(1.1)	1	(1.1)	4	(1.5)	1	(1.1)	1	(1.2)	2	(1.1)
Injury, poisoning, & procedural complications	3	(3.6)	1	(1.1)	3	(3.3)	3	(3.4)	7	(2.6)	3	(3.3)	4	(4.7)	7	(4.0)
Renal & urinary	3	(3.6)	1	(1.1)	4	(4.3)	1	(1.1)	6	(2.2)	0		0		0	
Ear & labyrinth	1	(1.2)	1	(1.1)	1	(1.1)	1	(1.1)	3	(1.1)	1	(1.1)	0		1	(0.6)
Hepatobiliary	0		0		1	(1.1)	0		1	(0.4)	0		0		0	
Neoplasms benign, malignant, & unspecified	0		0		0		1	(1.1)	1	(0.4)	0		0		0	

[a] Sorted by decreasing order of frequency as summarized for the QTP SR 300-mg treatment group.
[b] Patients with multiple events in the same SOC are counted only once in that SOC. Patients with events in more than 1 SOC are counted once in each of those categories.
MedDRA Medical dictionary for regulatory activities. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.2.2.2, Section 11.3.

8.3.2.2 Common AEs by MedDRA preferred term

Patients reported AEs with each treatment. For the 272 patients treated with quetiapine SR, the most commonly reported AEs were—by decreasing incidence rate—orthostatic hypotension, sedation, headache, dry mouth, somnolence, and dizziness.

Except for headache, each of these AEs was more common in patients treated with quetiapine SR than in patients treated with placebo. Differences in rates were greater by more than 5% for each AE, with incidence rates for dry mouth and dizziness also more than twice as great as the incidences seen with placebo: orthostatic hypotension (SR, 24.3%; placebo, 17.9%); sedation (SR, 22.1%; placebo, 11.9%); dry mouth (SR, 15.8%; placebo 1.2%); somnolence (SR, 14.0%; placebo, 8.3%); and dizziness (13.6% vs 3.6%).

Other AEs that occurred more than twice as often with quetiapine SR compared with placebo included constipation (9.2% vs 1.2%), hypotension (6.6% vs 2.4%), tachycardia (7.7% vs 2.4%), heart rate increased (10.7% vs 4.8%), weight gain (6.3% vs 2.4%), anxiety (4.0% vs 0%), vision blurred (3.3% vs 0%), restlessness (2.6% vs 1.2%), and tremor (2.2% vs 0%).

For 3 of the most commonly reported AEs, incidence rates increased as the dose of quetiapine SR increased over the full dose range (SR 300 to SR 800 mg): sedation (15.4% to 23.9% to 27.0%), heart rate increased (6.6% to 12.0% to 13.5%), and weight gain (4.4% to 5.4% to 9.0%).

Incidences of commonly reported AEs were similar between quetiapine SR and quetiapine IR treatment groups, with differences typically less than 5% (per event). Minor exceptions were seen for dry mouth (SR, 15.8%; IR 9.7%) and tachycardia (SR 7.7%; IR 13.1%).

AEs reported by at least 5% of patients in any treatment group are summarized by preferred term in Table 37. All AEs (MedDRA preferred terms) are summarized in Table 11.3.2.2.3.2 (Section 11.3).

Table 37 Number (%) of patients with commonly reported AEs (incidence ≥5%, any quetiapine treatment group) (safety population)

MedDRA preferred term[a]	Number (%) of patients[b]															
	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP SR Total		QTP IR 300 mg		QTP IR 600 mg		QTP IR Total	
	(n=84)		(n=91)		(n=92)		(n=89)		(n=272)		(n=90)		(n=86)		(n=176)	
Orthostatic hypotension	15	(17.9)	21	(23.1)	21	(22.8)	24	(27.0)	66	(24.3)	16	(17.8)	19	(22.1)	35	(19.9)
Headache	21	(25.0)	15	(16.5)	18	(19.6)	14	(15.7)	47	(17.3)	17	(18.9)	13	(15.1)	30	(17.0)
Sedation	10	(11.9)	14	(15.4)	22	(23.9)	24	(27.0)	60	(22.1)	17	(18.9)	22	(25.6)	39	(22.2)
Dry mouth	1	(1.2)	12	(13.2)	18	(19.6)	13	(14.6)	43	(15.8)	8	(8.9)	9	(10.5)	17	(9.7)
Somnolence	7	(8.3)	11	(12.1)	15	(16.3)	12	(13.5)	38	(14.0)	18	(20.0)	11	(12.8)	29	(16.5)
Constipation	1	(1.2)	10	(11.0)	8	(8.7)	7	(7.9)	25	(9.2)	3	(3.3)	12	(14.0)	15	(8.5)
Dizziness	3	(3.6)	9	(9.9)	17	(18.5)	11	(12.4)	37	(13.6)	9	(10.0)	10	(11.6)	19	(10.8)
Hypotension	2	(2.4)	9	(9.9)	5	(5.4)	4	(4.5)	18	(6.6)	6	(6.7)	9	(10.5)	15	(8.5)
Tachycardia	2	(2.4)	7	(7.7)	8	(8.7)	6	(6.7)	21	(7.7)	10	(11.1)	13	(15.1)	23	(13.1)
BP diastolic decreased	2	(2.4)	7	(7.7)	2	(2.2)	4	(4.5)	13	(4.8)	3	(3.3)	7	(8.1)	10	(5.7)
Fatigue	5	(6.0)	7	(7.7)	4	(4.3)	2	(2.2)	13	(4.8)	3	(3.3)	5	(5.8)	8	(4.5)
Heart rate increased	4	(4.8)	6	(6.6)	11	(12.0)	12	(13.5)	29	(10.7)	5	(5.6)	10	(11.6)	15	(8.5)
Insomnia	11	(13.1)	6	(6.6)	11	(12.0)	10	(11.2)	27	(9.9)	8	(8.9)	6	(7.0)	14	(8.0)
Nausea	10	(11.9)	5	(5.5)	10	(10.9)	6	(6.7)	21	(7.7)	4	(4.4)	8	(9.3)	12	(6.8)
Dyspepsia	5	(6.0)	5	(5.5)	6	(6.5)	5	(5.6)	16	(5.9)	2	(2.2)	8	(9.3)	10	(5.7)
Agitation	6	(7.1)	5	(5.5)	6	(6.5)	2	(2.2)	13	(4.8)	2	(2.2)	3	(3.5)	5	(2.8)
BP systolic decreased	3	(3.6)	4	(4.4)	1	(1.1)	5	(5.6)	10	(3.7)	3	(3.3)	5	(5.8)	8	(4.5)
Back pain	3	(3.6)	4	(4.4)	2	(2.2)	1	(1.1)	7	(2.6)	3	(3.3)	4	(4.7)	7	(4.0)
Weight increased	2	(2.4)	4	(4.4)	5	(5.4)	8	(9.0)	17	(6.3)	8	(8.9)	8	(9.3)	16	(9.1)
Postural dizziness	2	(2.4)	3	(3.3)	4	(4.3)	4	(4.5)	11	(4.0)	1	(1.1)	4	(4.7)	5	(2.8)
Anxiety	0		3	(3.3)	4	(4.3)	4	(4.5)	11	(4.0)	2	(2.2)	3	(3.5)	5	(2.8)

Table 37 Number (%) of patients with commonly reported AEs (incidence ≥5%, any quetiapine treatment group) (safety population)

MedDRA preferred term[a]	Number (%) of patients[b]							
	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP SR Total	QTP IR 300 mg	QTP IR 600 mg	QTP IR Total
	(n=84)	(n=91)	(n=92)	(n=89)	(n=272)	(n=90)	(n=86)	(n=176)
Vomiting	7 (8.3)	2 (2.2)	9 (9.8)	2 (2.2)	13 (4.8)	3 (3.3)	1 (1.2)	4 (2.3)
Restlessness	1 (1.2)	2 (2.2)	1 (1.1)	4 (4.5)	7 (2.6)	0	0	0
Akathisia	1 (1.2)	0	4 (4.3)	1 (1.1)	5 (1.8)	3 (3.3)	4 (4.7)	7 (4.0)
Tremor	0	1 (1.1)	4 (4.3)	1 (1.1)	6 (2.2)	1 (1.1)	4 (4.7)	5 (2.8)
Vision blurred	0	1 (1.1)	6 (6.5)	2 (2.2)	9 (3.3)	1 (1.1)	1 (1.2)	2 (1.1)
Lethargy	0	1 (1.1)	1 (1.1)	0	2 (0.7)	1 (1.1)	5 (5.8)	6 (3.4)

[a] Sorted by decreasing order of frequency as summarized for the QTP SR 300-mg treatment group.
[b] Patients with multiple occurences of the same event are counted only once in that category. Patients with more than 1 type of AE are counted once in each of the relevant AE categories. AEs with incidence rates that rounded up to 5% are included under the heading of commonly reported AEs.

AEs Adverse events. MedDRA Medical dictionary for regulatory activities. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.2.2.3.2, Section 11.3.

8.3.2.3 AEs by intensity

All but 47 AEs were characterized as mild or moderate. Of the 47 AEs rated severe, 13 were also considered SAEs. By treatment group, severe events were as follows:

- Placebo—6 events: agitation, auditory hallucination, insomnia, intentional overdose (SAE), myocardial infarct (SAE), and grand mal convulsion (SAE)
- Quetiapine SR 300 mg—6 events: aggression (SAE), convulsion (SAE), insomnia, intentional self-injury, intervertebral disc protrusion, and sedation
- Quetiapine SR 600 mg—17 events: agitation (x2), alcoholism (SAE), aggression, catatonia, dysarthria, head injury (SAE), hypoesthesia, hypotension, orthostatic hypotension x2 (SAE x1), paresthesia, sedation, sensory disturbance, somnolence, thrombosis (SAE), and toxic hepatitis (SAE)
- Quetiapine SR 800 mg—6 events: joint sprain, hypertension, hypotension, alcohol poisoning, dizziness, and somnolence
- Quetiapine IR 300 mg—4 events: tooth abscess, psychotic disorder, somnolence, and schizophrenia—catatonic type (SAE)
- Quetiapine IR 600 mg—8 events: panic attack, suicidal ideation, grand mal convulsion (SAE), insomnia, psychotic disorder (x2) (SAE x1), somnolence, and nasal congestion

Details on SAEs are provided in Table 41. A summary of all AEs by intensity (MedDRA preferred terms) is provided in Table 11.3.2.2.4.2 (Section 11.3).

8.3.2.4 Drug-related AEs as assessed by the investigator

Patients in each treatment group had AEs that were designated as drug-related. In all instances of drug-relatedness, such assessments were that of the investigator.

Incidence rates for patients treated with quetiapine SR were 58.2%, 65.2%, and 53.9% (from low to high dose), with the latter rate (for the SR 800-mg dose) most similar to the rate seen for placebo-treated patients (47.6%). For patients treated with quetiapine IR, incidence rates were 52.2% (IR 300 mg) and 62.8% (IR 600 mg) and were similar to those seen with quetiapine SR. Adverse events that occurred in any SR treatment group at a rate greater than 2 times that seen with placebo are summarized in Table 38. A tabulation of all drug-related AEs (MedDRA preferred terms) is presented by treatment group in Table 11.3.2.6.2 (Section 11.3).

Table 38 Investigator-assessed drug-related adverse events that occurred in any SR treatment group at a rate greater than 2 times that seen with placebo

MedDRA preferred term[a]	Number (%) of patients															
	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP SR Total		QTP IR 300 mg		QTP IR 600 mg		QTP IR Total	
	(n=84)		(n=91)		(n=92)		(n=89)		(n=272)		(n=90)		(n=86)		(n=176)	
Sedation	8	(9.5)	12	(13.2)	19	(20.7)	21	(23.6)	52	(19.1)	14	(15.6)	19	(22.1)	33	(18.8)
Somnolence	6	(7.1)	7	(7.7)	14	(15.2)	8	(9.0)	29	(10.7)	12	(13.3)	9	(10.5)	21	(11.9)
Dry mouth	1	(1.2)	11	(12.1)	13	(14.1)	11	(12.4)	35	(12.9)	8	(8.9)	7	(8.1)	15	(8.5)
Hypotension	1	(1.2)	8	(8.8)	4	(4.3)	3	(3.4)	15	(5.5)	4	(4.4)	6	(7.0)	10	(5.7)
Dizziness	2	(2.4)	7	(7.7)	12	(13.0)	8	(9.0)	27	(9.9)	6	(6.7)	7	(8.1)	13	(7.4)
Constipation	0		7	(7.7)	7	(7.6)	3	(3.4)	17	(6.3)	0		3	(3.5)	3	(1.7)
BP diastolic decreased	2	(2.4)	7	(7.7)	2	(2.2)	3	(3.4)	12	(4.4)	3	(3.3)	5	(5.8)	8	(4.5)
Tachycardia	2	(2.4)	5	(5.5)	8	(8.7)	5	(5.6)	18	(6.6)	8	(8.9)	10	(11.6)	18	(10.2)
Heart rate increased	4	(4.8)	3	(3.3)	10	(10.9)	9	(10.1)	22	(8.1)	4	(4.4)	9	(10.5)	13	(7.4)
Blood pressure decreased	0		2	(2.2)	0		1	(1.1)	3	(1.1)	0		0		0	
Weight increased	2	(2.4)	2	(2.2)	4	(4.3)	5	(5.6)	11	(4.0)	6	(6.7)	4	(4.7)	10	(5.7)
Dystonia	0		2	(2.2)	1	(1.1)	0		3	(1.1)	1	(1.1)	0		1	(0.6)
Anxiety	0		1	(1.1)	2	(2.2)	1	(1.1)	4	(1.5)	0		1	(1.2)	1	(0.6)
Pain	0		1	(1.1)	2	(2.2)	0		3	(1.1)	0		0		0	
Postural orthostatic tachycardia syndrome	1	(1.2)	1	(1.1)	3	(3.3)	0		4	(1.5)	0		1	(1.2)	1	(0.6)
Blurred vision	0		0		5	(5.4)	1	(1.1)	6	(2.2)	1	(1.1)	0		1	(0.6)
Tremor	0		1	(1.1)	4	(4.3)	1	(1.1)	6	(2.2)	0		2	(2.3)	2	(1.1)
Coordination abnormal	0		0		2	(2.2)	0		2	(0.7)	0		0		0	
Hypoesthesia	0		0		2	(2.2)	0		2	(0.7)	0		1	(1.2)	1	(0.6)
Paresthesia	0		0		2	(2.2)	0		2	(0.7)	0		1	(1.2)	1	(0.6)

[a] Sorted by decreasing order of frequency as summarized for the QTP SR 300-mg treatment group (except for somnolence which follows sedation for overview purposes).
BP Blood pressure. MedDRA Medical dictionary for regulatory activities. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.2.6.2, Section 11.3.

8.3.2.5 Special-interest AEs and their onset

(a) AEs associated with somnolence

To gain an overall view of the sedative effects of quetiapine SR, the following AEs (MedDRA preferred terms) were grouped under the major term of somnolence, and an overall incidence rate was tabulated: somnolence, sedation, lethargy, and sluggishness (Table 39).

When all terms were combined, the rate of somnolence for patients treated with quetiapine SR (36.0%) was almost twice that seen for patients treated with placebo (20.2%). This finding reflected higher rates of somnolence at the SR 600- and 800-mg doses (40.2% and 39.3%, respectively), compared with that at the SR 300-mg dose (28.6%). Overall rates of somnolence were similar among patients treated with quetiapine SR (36.0%) and IR (40.9%);

Most patients with AEs related to somnolence had AE onset during the first 2 weeks of treatment, with onset predominantly seen during Days 1 through 7. The overall 7-day incidence was similar between SR and IR treatments groups (SR, 33.1%; IR, 35.8%), with incidence for the SR 300-mg group (26.4%) slightly lower than that for the IR 300-mg group (34.4%). The 7-day incidence rate for somnolence was lowest with placebo (20.2%).

First onset of somnolence is summarized on a daily basis for Days 1 through 14 in Table 11.3.2.7.8 (Section 11.3).

Table 39 Adverse events associated with somnolence (safety population)

Preferred-term group / MedDRA preferred term	Number (%) of patients							
	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP SR Total	QTP IR 300 mg	QTP IR 600 mg	QTP IR Total
	(n=84)	(n=91)	(n=92)	(n=89)	(n=272)	(n=90)	(n=86)	(n=176)
Somnolence group	17 (20.2)	26 (28.6)	37 (40.2)	35 (39.3)	98 (36.0)	35 (38.9)	37 (43.0)	72 (40.9)
Somnolence	7 (8.3)	11 (12.1)	15 (16.3)	12 (13.5)	38 (14.0)	18 (20.0)	11 (12.8)	29 (16.5)
Sedation	10 (11.9)	14 (15.4)	22 (23.9)	24 (27.0)	60 (22.1)	17 (18.9)	22 (25.6)	39 (22.2)
Lethargy	0	1 (1.1)	1 (1.1)	0	2 (0.7)	1 (1.1)	5 (5.8)	6 (3.4)
Sluggishness	0	0	0	0	0	0	2 (2.3)	2 (1.1)

MedDRA Medical dictionary for regulatory activities. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.2.7.4, Section 11.3.

(b) AEs associated with tachycardia

To gain an overall view of the effects of quetiapine SR on heart rate, the AEs of tachycardia and sinus tachycardia (MedDRA preferred terms) were grouped under the major term of tachycardia, and an overall rate was tabulated (SR, 8.1%; placebo, 3.6%; and IR, 13.1%). However, given that there were only 2 events of sinus tachycardia (in 1 placebo-treated patient and 1 patient treated with quetiapine SR 600 mg), the overall picture for tachycardia essentially did not change from that presented earlier for tachycardia alone (SR, 7.7%; placebo, 2.4%; and IR, 13.1%; see Table 37). Specifically, the incidence of tachycardia among patients treated with quetiapine SR was (a) slightly more than 2-fold greater than that seen for placebo-treated patients and (b) still less than that for patients treated with quetiapine IR (by 5%).

All SR-treated patients with tachycardia events (n=22) and most IR-treated patients with tachycardia events (21 of 23) had onset during the first 2 weeks of treatment, with onset through Day 7 seen in similar proportions of SR- and IR-treated patients overall (SR, 7.4%; IR, 8.5%). Day 7 incidence rates were also similar among patients in the SR 300- and IR 300-mg treatment groups (6.6%, and 7.8%, respectively).

Of 3 placebo-treated patients with tachycardia events, 2 had first onset during the first 14 days of treatment (on Days 2 and 8).

First onset of tachycardia is summarized on a daily basis for Days 1 through 14 in Table 11.3.2.7.8 (Section 11.3).

(c) AEs associated with postural hypotension

To gain an overall view of the postural hypotensive effects of quetiapine SR, the following AEs (MedDRA preferred terms) were grouped under the major term of postural hypotension, and an overall rate was tabulated: orthostatic hypotension, postural dizziness, and postural orthostatic tachycardia syndrome (Table 40).

When all terms were combined, the rate of postural hypotension for patients treated with quetiapine SR (27.2%) was about 6% greater than that seen for patients treated with placebo (21.4%). This finding reflected slightly higher rates of postural hypotension at the SR 600- and 800-mg doses (28.3% and 29.2%, respectively), compared with that at the SR 300-mg dose (24.2%). The rate of postural hypotension among patients treated with quetiapine IR (21.6%) was less than that seen with quetiapine SR (by about 6%) and similar to that seen with placebo (21.4%).

In each treatment group, most patients with AEs related to postural hypotension had AE onset during the first 2 weeks of treatment, with onset predominantly seen during Days 1 through 7. The overall 7-day incidence rate was slightly greater with quetiapine SR (25.7%) compared

with quetiapine IR (16.5%) or placebo (20.2%), with rate at the SR 300-mg dose (22.0%) similar to that with placebo and slightly greater than that with IR 300 mg (15.6%).[8]

Among those with postural hypotension events that only occurred after Day 14 were 1 patient treated with quetiapine SR 600 mg, 2 patients treated with quetiapine IR 300 mg, and 2 patients treated with quetiapine IR 600 mg (orthostatic hypotension in each case). First onset of postural hypotension is summarized on a daily basis for Days 1 through 14 in Table 11.3.2.7.8 (Section 11.3).

[8] The first 7 days of treatment with quetiapine SR included the day of dose increase from SR 300 mg to SR 600 mg (Day 5), while the first 7 days of treatment with quetiapine IR included daily dose increases by increments of 50 mg on Day 2, 100 mg on Days 3 and 4 for the IR 300-mg group, and, for patients assigned to treatment with IR 600 mg, increments of 100 and 200 mg on Days 5 and 6, respectively.

Table 40 Adverse events associated with postural hypotension (safety population)

Preferred-term group / MedDRA preferred term	Number (%) of patients							
	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP SR Total	QTP IR 300 mg	QTP IR 600 mg	QTP IR Total
	(n=84)	(n=91)	(n=92)	(n=89)	(n=272)	(n=90)	(n=86)	(n=176)
Postural hypotension group	18 (21.4)	22 (24.2)	26 (28.3)	26 (29.2)	74 (27.2)	17 (18.9)	21 (24.4)	38 (21.6)
Orthostatic hypotension	15 (17.9)	21 (23.1)	21 (22.8)	24 (27.0)	66 (24.3)	16 (17.8)	19 (22.1)	35 (19.9)
Postural dizziness	2 (2.4)	3 (3.3)	4 (4.3)	4 (4.5)	11 (4.0)	1 (1.1)	4 (4.7)	5 (2.8)
Postural orthostatic tachycardia syndrome	2 (2.4)	1 (1.1)	3 (3.3)	0	4 (1.5)	0	1 (1.2)	1 (0.6)

MedDRA Medical dictionary for regulatory activities. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.2.7.6, Section 11.3.

(d) Dizziness

The incidence of dizziness was presented earlier in Table 37. There was a higher incidence of dizziness among quetiapine SR-treated patients (13.6%) than among placebo-treated patients (3.6%). The incidence of dizziness was similar between patients treated with quetiapine SR and quetiapine IR (10.8%). With 1 exception, dizziness was mild or moderate (see Table 11.3.2.2.4.2); the exception was Patient 0021/0605 (quetiapine SR 800 mg), who was withdrawn because of severe dizziness considered treatment related.

Except for 4 patients in the SR 600-mg treatment group, 1 patient in the SR 800-mg treatment group, and 1 patient in the IR 600-mg treatment group, all patients had first onset of dizziness within the first 2 weeks of treatment. In all treatment groups except the SR 800-mg group, onset was predominantly seen earlier during Days 1 through 7, rather than later. In the SR 800-mg treatment group, similar numbers of patients had dizziness onset during Week 1 and Week 2 of treatment (5 per week).

The 7-day onset rate for dizziness was similar between SR and IR treatments groups overall (SR, 8.8%; IR, 8.5%) and between the SR 300-mg group (8.8%) and the IR 300-mg group (8.9%).

For 3 (3.6%) placebo-treated patients with dizziness, onset occurred on Days 1, 2, and 9 respectively.

First onset of dizziness is summarized on a daily basis for Days 1 through 14 in Table 11.3.2.7.8 (Section 11.3).

(e) Syncope

Only 1 patient (quetiapine SR 800 mg) had syncope reported as an AE (Patient 0009/0235). This event, which began on Day 7 of treatment, was not serious, did not lead to withdrawal, and was classified as moderately intense and drug related.

8.4 Deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events

8.4.1 Deaths

No patients died during the course of this study.

8.4.2 Serious adverse events other than deaths

A total of 12 patients had 14 SAEs while on study treatment: 6 (2.2%) treated with quetiapine SR; 3 (3.6%) treated with placebo; and 3 (1.7%) treated with quetiapine IR; these patients are listed in Table 41. Among these patients, 1 (SR 600 mg) had 3 different SAEs (schizophrenia, alcoholism, and toxic hepatitis). Thirteen of the 14 SAEs were rated severe in intensity. Details on patients with SAEs are also provided in narrative format in Section 11.3.4.3 (Section 11.3).

Four SAEs were assessed as drug related by the investigator and each led to patient withdrawal:

- grand mal convulsion in 1 patient treated with placebo
- orthostatic hypotension in 1 patient treated with quetiapine SR 600 mg
- grand mal convulsion and psychotic disorder in 1 patient each treated with quetiapine IR 600 mg

Three other SAEs, each assessed as not drug-related, also led to premature patient withdrawal: myocardial infarction in 1 patient treated with placebo, convulsion in 1 patient treated with quetiapine SR 300 mg, and schizophrenia catatonic subtype (investigator term, psychological reaction) in 1 patient treated with IR 300 mg.

Of the 12 patients with SAEs, 6 were treated with either quetiapine SR 600 mg (n=4) or IR 600 mg (n=2). Despite this, no clear pattern of events was evident either at this dose or across treatments.

Table 41 Listing of all patients who had SAEs: safety population

Treatment and dose regimen	Center/Patient	Sex/Age/Race (age in years)	SAE: MedDRA preferred term[a]	SAE: Investigator text	Days from start of treatment to onset of SAE	Duration of SAE (if resolved)	Action taken with respect to study drug	Causality[b] (drug-related or not?)
Placebo	0005/0181	M/42/Hispanic	Grand mal convulsion	Grand mal seizures	12	1	Withdrawn	Yes
Placebo	0010/0025	M/64/Hispanic	Myocardial infarction	Heart attack	25	6	Withdrawn	No
Placebo	0026/0451	F/47/White	Intentional overdose	Deliberate overdose	21	4	Not withdrawn	No
QTP SR 300 mg	0008/0067	F/38/White	Convulsion	Generalized seizure	5	1	Withdrawn	No
QTP SR 300 mg	0010/0030	M/25/Hispanic	Aggression	Homicidal aggression	54	Unknown	Not withdrawn	No
QTP SR 600 mg	0010/1028	M/41/White	Thrombosis	Left leg blood clot	57	Unknown	Not withdrawn	No
QTP SR 600 mg	0016/0475	M/55/White	Orthostatic hypotension	Orthostatic hypotension	7	2	Withdrawn	Yes
QTP SR 600 mg	0036/0308	M/21/Hispanic	Head injury	Blunt head trauma	64	68	Not withdrawn	No
QTP SR 600 mg	0052/1208	M/52/White	Schizophrenia	Worsening schizophrenic symptoms	12	3	Not withdrawn	No
			Alcoholism	Alcoholism relapse	40	27	Not withdrawn	No
			Hepatitis toxic	Toxic hepatitis, possibly related to diet and alcoholism	66	8	Not withdrawn	No
QTP IR 300 mg	0025/0275	M/49/White	Schizophrenia, catatonic type	Psychological reaction (catatonic schizophrenia)	18	1	Withdrawn	No
QTP IR 600 mg	0004/0012	M/31/White	Grand mal convulsion	Grand mal seizure	13	1	Withdrawn	Yes
QTP IR 600 mg	0023/0621	M/59/White	Psychotic disorder	Psychotic decompensation	36	27	Withdrawn	Yes

[a] With 1 exception, all SAEs were rated severe; the exception was schizophrenia, which was rated mild.
[b] As assessed by the investigator.
MedDRA Medical dictionary for regulatory activities. QTP SR Quetiapine sustained release. QTP IR Quetiapine immediate release.
SAE Serious adverse event.
Data derived from Listing 12.2.7.2.2, Appendix 12.2.

8.4.3 Discontinuations due to AEs

A total of 36 patients were withdrawn from study treatment because of AEs (DAEs), as follows:

- 8 (9.5%) patients treated with placebo (13 events—4 severe and 10 drug related)
- 15 (5.5%) patients treated with quetiapine SR
  - 5 in the SR 300-mg treatment group (6 events—2 severe and 4 drug related)
  - 9 in the SR 600-mg treatment group (13 events—5 severe and 10 drug related)
  - 1 in the SR 800-mg treatment group (1 event—severe and drug related)
- 13 (7.4%) patients treated with quetiapine IR
  - 6 in the IR 300-mg treatment group (6 events—3 severe and 4 drug related)
  - 7 in the IR 600-mg treatment group (8 events—4 severe and 6 drug related)

The lowest incidence of DAEs was seen for patients treated with quetiapine SR; however, rates for placebo-treated patients and patients treated with quetiapine IR were only slightly greater (≤4% difference). AEs that led to the withdrawal of more than 1 SR-treated patient but not placebo-treated patients included orthostatic hypotension (n=3), somnolence or sedation (n=3), and dizziness (n=2). AEs that led to the withdrawal of more than 1 SR-treated patient but not IR-treated patients included orthostatic hypotension (n=3), dizziness (n=2), and agitation (n=2).

Onset of DAEs was variable. Some DAEs occurred during the dose-escalation phase; therefore, affected patients were withdrawn before they reached at their target doses (Table 42). Among SR-treated patients, onset was not consistently associated with either the start of treatment or with a dose increase. Of the 20 AEs that lead to withdrawal of SR-treated patients, only 1 incident each of orthostatic hypotension, sedation, dizziness, and anxiety had onset on the first treatment day. Among IR-treated patients, only 1 incident each of anxiety, somnolence, and upper abdominal pain had onset on the first treatment day (Table 42).

All patients withdrawn because of AEs and all relevant AEs are listed in Table 42. (See Table 11.3.2.5.2 [Section 11.3]) for a tabulation of these DAEs by SOC.)

Of the 47 DAEs, 19 were psychiatric disorder AEs and 13 were nervous system AEs. Compared with placebo- and IR-treated patients, a slightly smaller proportion of SR-treated patients (SR, 1.8%; placebo, 3.6%; IR 4.0%) were withdrawn because of psychiatric disorders, reflecting no DAEs of this type among patients treated at the SR 300- or SR 800-mg doses. On a treatment group basis, though, the rate of DAEs for psychiatric disorder AEs was similar among patients treated with SR 600 mg (5.4%), placebo (3.6%), and each of the IR doses (3.3% and 4.7%). In several instances, 2 occurrences of the same type of AE led to

withdrawal within a given treatment group: hallucinations in 2 patients treated with placebo; agitation in 2 patients treated with quetiapine SR 600 mg, and psychotic disorder AEs in 2 patients treated with quetiapine IR 600 mg.

Rates of nervous system DAEs were low and similar across individual treatment groups.

Three patients in 3 different treatment groups (placebo, quetiapine SR 300 mg, and quetiapine IR 600 mg) withdrew because of severe convulsions. Convulsions in 2 patients were assessed as drug related (in one instance to placebo, in another to quetiapine IR 600 mg). Convulsions in the third patient were considered serious but were assessed as not drug related.

Vascular disorder AEs led to the withdrawal of 4 patients treated with quetiapine SR: 3 treated with SR 300 mg (hypotension or orthostatic hypotension); and 1 treated with SR 600 mg (orthostatic hypotension). All instances of hypotension or orthostatic hypotension that led to withdrawal were assessed as drug related, with 1 episode considered severe.

Details on these patients are provided in narrative format in Section 11.3.5.3 (Section 11.3). Patients with AEs that led to withdrawal and were assessed as serious (ie, SAEs) were presented in Table 41.

Table 42 Listing of all patients who had study treatment discontinued because of AEs: safety population

Treatment group	Center/ Patient	Sex/Age/Race (age in years)	Adverse event: MedDRA preferred term	Adverse event: investigator text	Day of AE onset[a]	Daily QTP dose at onset day	Duration of AE (if resolved)	Reported as an SAE (yes/no)	Causality[b] (drug-related?)
Placebo	0005/0181	M/42/Hispanic	Grand mal convulsion	Grand mal seizures[c]	12	N/A	1	Yes	Yes
Placebo	0009/0417	M/38/White	Rash	Rash	1	N/A	5	No	Yes
Placebo	0010/0025	M/64/Hispanic	Myocardial infarction	Heart attack[c]	25	N/A	6	Yes	No
Placebo	0035/0102	M/36/White	Insomnia	Insomnia	4	N/A	10	No	No
			Nausea	Nausea	12	N/A	3	No	Yes
			Vomiting	Vomiting	13	N/A	1	No	Yes
Placebo	0035/0449	M/33/Hispanic	Agitation	Agitation[c]	3	N/A	1	No	Yes
			Hallucination auditory	Auditory hallucinations[c]	3	N/A	1	No	Yes
Placebo	0043/0077	M/52/White	Nausea	Nausea	2	N/A	3	No	Yes
Placebo	0049/0518	M/33/White	Blood TSH increase	Elevated TSH	1	N/A	Unknown	No	No
Placebo	0058/1202	M/32/White	Delusion	Worsening of delusions	8	N/A	Unknown	No	Yes
			Depression	Feelings of depression	8	N/A	Unknown	No	Yes
			Hallucination	Worsening of hallucinations	8	N/A	Unknown	No	Yes
QTP SR 300 mg	0008/0067	F/38/White	Convulsion	Generalized seizure[c]	5	300 mg	1	Yes	No
QTP SR 300 mg	0015/0324	M/41/White	Sedation	Sedation[c]	12	300 mg	10	No	Yes
QTP SR 300 mg	0040/0285	F/64/Black	Dehydration	Dehydration	8	300 mg	2	No	No
			Hypotension	Hypotension	8	300 mg	2	No	Yes
QTP SR 300 mg	0050/0559	M/53/Black	Orthostatic hypotension	Postural hypotension	1	300 mg	3	No	Yes
QTP SR 300 mg	0061/1088	M/34/Black	Orthostatic hypotension	Orthostatic hypotension	5	300 mg	2	No	Yes
QTP SR 600 mg	0008/0254	M/49/White	Psychotic disorder	Increased psychosis	5	600 mg	34	No	Yes
QTP SR 600 mg	0009/0415	M/45/Black	Sedation	Sedation	1	300 mg	2	No	Yes
QTP SR 600 mg	0016/0475	M/55/White	Orthostatic hypotension	Orthostatic hypotension[c]	7	600 mg	2	Yes	Yes
QTP SR 600 mg	0024/0164	M/49/White	Agitation	Agitation[c]	15	600 mg	Unknown	No	No

Table 42 Listing of all patients who had study treatment discontinued because of AEs: safety population

Treatment group	Center/ Patient	Sex/Age/Race (age in years)	Adverse event: MedDRA preferred term	Adverse event: investigator text	Day of AE onset[a]	Daily QTP dose at onset day	Duration of AE (if resolved)	Reported as an SAE (yes/no)	Causality[b] (drug-related?)
QTP SR 600 mg	0028/0513	M/38/Black	Agitation	Agitation[c]	3	300 mg	1	No	Yes
			Aggression	Threatening behavior toward study staff[c]	3	300 mg	1	No	Yes
QTP SR 600 mg	0032/0376	M/35/Black	Dizziness	Dizziness not due to postural hypotension	1	300 mg	17	No	Yes
			Nausea	Nausea	2	300 mg	16	No	No
QTP SR 600 mg	0032/0501	F/38/White	Dry mouth	Dry mouth	8	600 mg	9	No	Yes
			Somnolence	Drowsiness	8	600 mg	9	No	Yes
			Tremor	Tremors not due to EPS	8	600 mg	9	No	Yes
QTP SR 600 mg	0035/0446	M/40/White	Anxiety	Increased anxiety	1	300 mg	4	No	Yes
QTP SR 600 mg	0038/0150	M/39/White	Catatonia	Catatonia[c]	13	600 mg	1	No	No
QTP SR 800 mg	0021/0605	M/30/Black	Dizziness	Dizziness not due to postural hypotension[c]	4	300 mg	7	No	Yes
QTP IR 300 mg	0010/0657	F/44/White	Nausea	Nausea	3	200 mg	2	No	Yes
QTP IR 300 mg	0013/0487	F/39/Hispanic	Sedation	Sedation	12	300 mg	1	No	Yes
QTP IR 300 mg	0021/0602	F/42/White	Anxiety	Increased anxiety	1	50 mg	2	No	No
QTP IR 300 mg	0025/0275	M/49/White	Schizophrenia, catatonic type	Psychological reaction (catatonic schizophrenia)[c]	18	300 mg	1	Yes	No
QTP IR 300 mg	0038/0145	F/61/Black	Somnolence	Drowsiness[c]	1	50 mg	11	No	Yes
QTP IR 300 mg	0046/0049	M/56/White	Psychotic disorder	Increased psychosis[c]	2	100 mg	5	No	Yes
QTP IR 600 mg	0004/0012	M/31/White	Grand mal convulsion	Grand mal seizure[c]	13	600 mg	1	Yes	Yes
QTP IR 600 mg	0005/0440	F/37/Black	Akathisia	Worsening EPS (akathisia)	4	300 mg	1	No	Yes
			Dyskinesia	Worsening EPS (dyskinesia)	4	300 mg	1	No	Yes
QTP IR 600 mg	0009/0239	M/38/White	Insomnia	Insomnia[c]	3	200 mg	5	No	Yes

Table 42 Listing of all patients who had study treatment discontinued because of AEs: safety population

Treatment group	Center/ Patient	Sex/Age/Race (age in years)	Adverse event: MedDRA preferred term	Adverse event: investigator text	Day of AE onset[a]	Daily QTP dose at onset day	Duration of AE (if resolved)	Reported as an SAE (yes/no)	Causality[b] (drug-related?)
QTP IR 600 mg	0021/0482	F/43/White	Anxiety	Increased anxiety	2	100 mg	4	No	No
QTP IR 600 mg	0023/0621	M/59/White	Psychotic disorder	Psychotic decompensation[c]	36	600 mg	27	Yes	Yes
QTP IR 600 mg	0039/1063	F/26/White	Psychotic disorder	Increased psychosis[c]	24	600 mg	5	No	Yes
QTP IR 600 mg	0047/0569	M/49/White	Upper abdominal pain	Stomach ache	1	50 mg	2	No	No

[a] Relative to start of treatment (ie, days from start of treatment to onset of AE).
[b] As assessed by the investigator.
[c] Assessed as severe (in intensity).
AE Adverse event. EPS Extrapyramidal symptoms. MedDRA Medical dictionary for regulatory activities. N/A Not applicable. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release. SAE Serious adverse event. TSH Thyroid stimulating hormone. Tx Treatment.
Data derived from Listing 12.2.7.3.2, Appendix 12.2.

8.4.4 Other significant adverse events (OAEs)

There were no OAEs identified in this study.

8.4.5 Analysis of AEs by organ system or syndrome

The primary purpose of this section is to present data on adverse events for specific safety areas, which were defined by a collection of MedDRA terms. AEs associated with EPS (Section 8.4.5.1), AEs associated with QT prolongation (Section 8.4.5.2), AEs associated with diabetes mellitus (Section 8.4.5.3), AEs associated with neutropenia and agranulocytosis (Section 8.4.5.4), and AEs associated with suicidality (Section 8.4.5.5) are presented. Safety information from other types of assessments are referred to and cross-referenced where relevant. See Section 8.6.5 for an integrated discussion of results related to the specific safety areas.

8.4.5.1 AEs associated with EPS

EPS-related AEs were reported each treatment group. Among patients treated with quetiapine SR, the rate was 11.0% (30 of 272), which was greater than the rate seen with placebo (4.8%, 4 of 84). The overall rate for SR patients reflected similar rates in each of the 3 SR treatment groups: (from low to high dose) 9.9% (9 patients), 10.9% (10 patients), and 12.4% (11 patients); this overall rate was also similar to the overall rate seen for patients treated with quetiapine IR: 9.7% (17 of 176).

For patients treated with quetiapine SR, the most common EPS-related AEs, occurring in 5 to 7 (<3%) patients, were restlessness, extrapyramidal disorder, tremor, and akathisia. When SR treatment groups were considered individually, restlessness (4 patients) and extrapyramidal disorder (3 patients) were more frequent at the 800-mg dose, while tremor and akathisia (4 patients each) were more common at the 600-mg dose. With 1 exception, rates of individual EPS-related AEs did not increase as the dose of quetiapine SR increased across the dose range. The exception was extrapyramidal disorder, which occurred in 1 (1.1%) patient at the SR 300-mg dose, 2 patients at the SR 600-mg dose, and 3 patients at the SR 800-mg dose. However, the overall SR event rate (2.2%) for this AE was similar to that seen with placebo (2.4%).

Only 2 types of EPS-related AEs occurred among SR-treated patients at rates greater than twice that seen among placebo-treated patients: restlessness (2.6% SR vs 1.2% placebo) and tremor (2.2% SR vs 0% placebo).

Incidence rates for most EPS-related AEs were similar when compared between patients treated with quetiapine SR and quetiapine IR. Exceptions were seen for restlessness and extrapyramidal disorder, which occurred with a slightly greater incidence among SR-treated patients (2.6% vs 0% IR and 2.2% vs 0% IR, respectively) and for dyskinesia and akathisia, which occurred with a slightly lower incidence among SR-treated patients (0.7% vs 2.3% IR and 1.8% vs 4.0% IR, respectively).

None of the EPS-related AEs were categorized as severe, and none met the criteria for being an SAE. Two EPS-related AEs—dyskinesia and akathisia in a single patient treated at the quetiapine IR 600-mg dose—led to patient withdrawal (with both events assessed as treatment related, see Table 42).

All EPS-related AEs are summarized by treatment group in Table 43.

Table 43 Number (%) of patients who had AEs related to extrapyramidal symptoms: safety population

MedDRA preferred term[a]	Number (%) of patients[b]							
	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP SR Total	QTP IR 300 mg	QTP IR 600 mg	QTP IR Total
	(n=84)	(n=91)	(n=92)	(n=89)	(n=272)	(n=90)	(n=86)	(n=176)
Any AE related to EPS	4 (4.8)	9 (9.9)	10 (10.9)	11 (12.4)	30 (11.0)	8 (8.9)	9 (10.5)	17 (9.7)
Dystonia	0	2 (2.2)	2 (2.2)	0	4 (1.5)	2 (2.2)	0	2 (1.1)
Restlessness	1 (1.2)	2 (2.2)	1 (1.1)	4 (4.5)	7 (2.6)	0	0	0
Dyskinesia	1 (1.2)	1 (1.1)	1 (1.1)	0	2 (0.7)	2 (2.2)	2 (2.3)	4 (2.3)
Extrapyramidal disorder	2 (2.4)	1 (1.1)	2 (2.2)	3 (3.4)	6 (2.2)	0	0	0
Hypertonia	0	1 (1.1)	0	0	1 (0.4)	0	0	0
Tremor	0	1 (1.1)	4 (4.3)	1 (1.1)	6 (2.2)	1 (1.1)	4 (4.7)	5 (2.8)
Tardive dyskinesia	0	1 (1.1)	0	1 (1.1)	2 (0.7)	0	1 (1.2)	1 (0.6)
Akathisia	1 (1.2)	0	4 (4.3)	1 (1.1)	5 (1.8)	3 (3.3)	4 (4.7)	7 (4.0)
Drooling	0	0	0	1 (.1)	1 (0.4)	0	0	0
Parkinsonism	0	0	0	1 (1.1)	1 (0.4)	0	1 (1.2)	1 (0.6)

[a] Sorted by decreasing order of frequency as summarized for the QTP SR 300-mg treatment group.
[b] Patients with multiple occurences of the same event are counted only once for that AE. Patients with more than 1 type of EPS-related AE are counted once in each of the relevant AE categories.

AE Adverse event. MedDRA Medical dictionary for regulatory activities.
EPS Extrapyramidal symptoms. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.2.7.3, Section 11.3.

8.4.5.2 AEs associated with QT prolongation

No AEs associated with QT prolongation were reported. Single isolated increases in QT interval of ≥60 ms from baseline to final visit were seen in 3 patients treated with quetiapine SR (1 SR 300 mg; 2 SR 800 mg); however, final values remained below 500 ms (see Section 8.6.2.2).

8.4.5.3 AEs potentially associated with diabetes mellitus

AEs potentially associated with diabetes were infrequent. Individually, the AEs of hyperglycemia, increased blood glucose, polyuria, and thirst occurred in no more than 1 patient in any treatment group (Table 44).

Across treatment groups, the AEs of blood glucose increased or hyperglycemia were reported for 4 patients: Patient 0021/0637 (quetiapine SR 600 mg), Patient 0059/0295 (quetiapine SR 800 mg), Patient 0026/0600 (quetiapine IR 600 mg), and Patient 0043/0077 (placebo). Three of these patients had diabetes mellitus and elevated blood glucose levels at study entry. Respective baseline and final values were as follows: 309 and 563 mg/dL for Patient 0021/0637 (SR 600 mg), 182 and 131 mg/dL for Patient 0026/0600 (IR 600 mg), and 228 and 83 mg/dL for Patient 0043/0077 (placebo). Patient 0059/0295 had a history of obesity, increased triglycerides, and hyperlipidemia. Glucose values for this patient were 85 mg/dL at baseline, 155 mg/dL at the final visit, and 92 mg/dL at follow-up. These AEs were characterized as mild or moderate, were not considered drug related, and did not lead to patient withdrawal.

Polyuria in 1 patient treated with quetiapine SR 300 mg (Patient 0015/0397) and thirst in 1 patient treated with quetiapine IR 600 mg (Patient 0007/0350) were each characterized as mild and drug related. The patient with polyuria had no history of diabetes and normal blood glucose values at baseline and the final visit (94 and 58 mg/dL, respectively). Polyuria lasted 22 days and did not lead to withdrawal. The patient with thirst had no history of diabetes but had high blood glucose levels (per normal reference range) both at baseline and the final visit (122 and 128 mg/dL, respectively). Thirst was ongoing at the time of withdrawal.

Table 44 Number (%) of patients with AEs potentially associated with diabetes: safety population

MedDRA preferred term[a]	Number (%) of patients[b]							
	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP SR Total	QTP IR 300 mg	QTP IR 600 mg	QTP IR Total
	(n=84)	(n=91)	(n=92)	(n=89)	(n=272)	(n=90)	(n=86)	(n=176)
Any AE potentially related to diabetes	1 (1.2)	1 (1.1)	1 (1.1)	1 (1.1)	3 (1.1)	0	2 (2.3)	2 (1.1)
Polyuria	0	1 (1.1)	0	0	1 (0.4)	0	0	0
Blood glucose increased	1 (1.2)	0	0	1 (1.1)	1 (0.4)	0	1 (1.2)	1 (0.6)
Hyperglycemia	0	0	1 (1.1)	0	1 (0.4)	0	0	0
Thirst	0	0	0	0	0	0	1 (1.2)	1 (0.6)

[a] Sorted by decreasing order of frequency as summarized for the QTP SR 300-mg treatment group.
[b] A patient with multiple occurences of the same event is counted only once for that AE. Patients with more than 1 type of AE are counted once in each of the relevant AE categories.

AE Adverse event. MedDRA Medical dictionary for regulatory activities.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.2.7.3, Section 11.3.

8.4.5.4 AEs associated with neutropenia and agranulocytosis

No AEs potentially related to neutropenia or agranulocytosis were identified. Low clinically important neutrophil counts were identified for 2 patients from blood sample analysis (see Section 8.5.1.3).

8.4.5.5 AEs associated with suicidality

No patients committed suicide. Two patients (Patient 0021/0278, SR 300 mg and Patient 0035/0098, SR 800 mg) had intentional self-injuries. In the former case, the patient's puncture wounds were considered severe, but the patient recovered. In the latter case, the self-inflicted abrasions on the patient's nose and forehead were mild and ongoing at the time of study completion.

Suicidal ideation was reported for 1 patient treated with placebo (Patient 0026/0451) and 2 patients treated with quetiapine IR 600 mg (Patients 0043/0078 and 0052/1212). For Patient 0043/0078, the event was considered severe; for the other 2 patients, the events were considered mild. Each patient recovered.

None of the events met the criteria for being serious and none resulted in treatment withdrawal.

8.4.6 Discussion of deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events

No patients died during the course of this study. Few SAEs were reported (14 SAEs in 12 patients), with all but 1 severe.

Overall SAE incidence rates for placebo-, SR-, and IR-treated patients were similar (3.6%; 2.2%, and IR 1.7%), with small numbers of events assessed as drug related (placebo, grand mal convulsion; SR 600 mg, orthostatic hypotension, and IR 600 mg, grand mal convulsion and psychotic disorder). When SAE incidence rates for individual treatment groups were considered—3.6% for placebo; 2.2%, 4.3%, and 0% for SR (low to high dose); and 1.1% and 2.3% for IR (low to high dose), SAE incidence rates for patients treated with SR 600 mg and placebo were more closely similar.

The types of SAEs reported in more than 1 SR-treated patient but not in placebo-treated patients were psychiatric disorder AEs and vascular system AEs (MedDRA SOC); however, these types of SAEs do not represent unexpected findings given the population studied and the known pharmacology of quetiapine.

Overall, 36 (6.8%) patients were withdrawn from study treatment because of AEs: 9.5% treated with placebo, 5.5% treated with quetiapine SR, and 7.4% treated with quetiapine IR. Among treatment groups, similarities in rates of AE-related withdrawals were seen between patients treated with placebo (9.5%), quetiapine SR 600 mg (9.8%), and quetiapine IR 600 mg (8.1%). Psychiatric disorders and nervous system AEs were the types of AEs that most commonly led to withdrawal, again, not unexpected for the population studied.

Three types of AEs led to withdrawal of 2 or more quetiapine SR-treated patients, but not placebo-treated patients: orthostatic hypotension, somnolence or sedation, and dizziness (n=3, 3, and 2, respectively). Given the known effects of quetiapine, however, treatment withdrawal for these types of AEs was not unexpected. Three types of AEs led to withdrawal of 2 or more quetiapine SR-treated patients, but not IR-treated patients: orthostatic hypotension (n=3), dizziness (n=2), and agitation (n=2). Among SR-treated patients, onset of DAEs was variable and not consistently associated with either the start of treatment or with a dose increase. Additionally, the rate of AE-related withdrawals did not consistently increase as the dose of quetiapine SR increased.

When aggregated, EPS-related AEs occurred in a greater proportion of quetiapine SR-treated patients (11.0%), compared with placebo-treated patients (4.8%); however, a greater proportion of placebo-treated patients took anticholinergics for EPS symptoms (14.3%, safety population), compared with patients treated with SR 300 and SR 800 mg (7.7% and 4.5%, respectively) and IR 300 and 600 mg (6.7% and 3.5%, respectively). On an individual event basis, only 2 types of EPS-related AEs occurred among SR-treated patients at a rate greater than twice that of placebo-treated patients: restlessness (2.6% SR vs 1.2% placebo) and tremor (2.2% SR vs 0% placebo). As expected, rates of EPS-related AEs were similar among patients treated with quetiapine SR and quetiapine IR.

AEs potentially related to diabetes were seen sporadically with each treatment, including placebo. With so few events, there were no patterns to suggest treatment-emergent diabetes with any treatment. Treatment with quetiapine did not result in AEs associated with QT prolongation nor in neutropenia or agranulocytosis. Treatment with quetiapine did not result in increased risk of suicide, compared with placebo.

8.5 Clinical laboratory evaluation

Clinical laboratory results are presented separately for hematology and clinical chemistry variables. Within each of these categories, results are examined in 3 ways: changes in mean values over time, changes in individual patients over time, and individual clinically important abnormalities. The results for all clinical laboratory evaluations are discussed collectively in Section 8.5.4.

8.5.1 Hematology

8.5.1.1 Changes in mean values over time: hematology variables

Mean and median changes in hematology values from baseline to final visit were small and often close to zero. Descriptive statistics showing baseline and final values and change from baseline are presented in Tables 11.3.3.1.1.2 and 11.3.3.1.1.3 (Section 11.3).

8.5.1.2 Changes in individual patients over time: hematology variables

Relative shift changes from baseline to final visit (normal to low, normal to high, high to low, etc) for all hematology variables are presented in 11.3.3.1.1.4 (Section 11.3). Changes from normal to low or high values were generally seen in fewer than 5 patients per treatment group (AZ normal laboratory reference ranges applied).

Shift changes that resulted in clinically important values (baseline to final visit) were seen in 2 or fewer patients per treatment group for any given hematology variable (Table 45). Thus, differences between SR treatment groups and placebo, and between SR and IR treatment groups, were minimal. With so few patients having treatment-emergent clinically important hematology abnormalities, no dose-related trends could be identified with quetiapine SR treatment.

For clinically important shifts in hematology variables by all baseline and final categories, (low, not clinically important, or high), see Table 11.3.3.1.1.5 (Section 11.3).

Table 45 Hematology results—incidence of clinically important shifts from baseline to final visit: treatment emergent (safety population)

Hematology variable[a]	Number (%) of patients																							
	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP SR Total			QTP IR 300 mg			QTP IR 600 mg			QTP IR Total		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Shift to low values																								
Hematocrit	63	1	(1.6)	78	0		77	0		71	2	(2.8)	226	2	(0.9)	74	2	(2.7)	70	0		144	2	(1.4)
Hemoglobin	65	2	(3.1)	79	0		78	0		72	1	(1.4)	229	1	(0.4)	74	1	(1.4)	69	0		143	1	(0.7)
Platelets	67	0		79	0		79	1	(1.3)	73	0		231	1	(0.4)	72	0		70	0		142	0	
Neutrophils[b]	67	0		78	0		79	0		72	1	(1.4)	229	1	(0.4)	74	0		68	1	(1.5)	142	1	(0.7)
Shift to high values																								
Total WBC count	67	0		79	0		79	0		73	1	(1.4)	231	1	(0.4)	75	0		69	1	(1.4)	144	1	(0.7)
Neutrophils	66	0		79	2	(2.5)	79	2	(2.5)	73	2	(2.7)	231	6	(2.6)	74	2	(2.7)	67	0		141	2	(1.4)

[a] Definition of clinically important is provided in Table 9. For hematology variables that do not appear in the table, shifts to clinically important values were not seen.
[b] To values ≤1.5 x 10^9 cells/L but >0.5 x 10^9 cells/L.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release. WBC White blood cell.
Data derived from Table 11.3.3.1.1.6, Section 11.3.

8.5.1.3 Individual clinically important abnormalities: hematology variables

Seven patients had treatment-emergent, abnormally low hematocrit, hemoglobin, or both: 2 each treated with placebo and SR 800 mg and 3 treated with IR 300 mg. Three other patients had treatment-emergent, abnormally low neutrophil or platelet counts: 1 each treated with SR 600, SR 800, and IR 600 mg. Nine more patients had abnormally high neutrophil or WBC counts: 2 each treated with SR 300, SR 600, SR 800, and IR 300 mg and 1 treated with IR 600 mg. For variables in which abnormalities were seen only in patients treated with quetiapine (platelets, neutrophils and WBCs), abnormal values are provided by patient in Table 46, along with additional patient data and concurrent values of associated tests.

Table 46 Individual treatment-emergent clinically important hematology abnormalities seen only in quetiapine-treated patients (safety population)

Treatment	Age (y)	Sex/ Race	Weight (kg)	Clinically important value[a] and concurrent values of associated tests (clinically important criteria)							
Center/ patient				Neutrophils ($x10^9$ cells/L) (≤1.5 or ≥10)		WBC ($x10^{12}$ cells/L) (≤3 or ≥16)		Lymphocytes ($x10^9$ cells/L) (≤0.5 or ≥6)		Platelets ($x10^9$ cells/L) (≤100 or ≥600)	
				Base	Final	Base	Final	Base	Final	Base	Final
SR 300 mg											
0016/0154	56	M/W	68.9	5.34	**10.23**	10.5	14.6	3.99	3.31	317	343
0026/0357[b]	33	M/B	102.7	4.88	**12.35**	7.8	15.4	2.36	2.14	304	433
SR 600 mg											
0036/0367	29	M/W	71.4	3.31	**10.65**	5.2	13.0	1.42	1.57	183	226
0047/0040	44	M/B	100.4	4.07	3.39	7.0	6.1	1.79	1.84	111	**90**
0047/1071	37	F/B	84.1	8.87	**10.77**	11.8	14.8	2.30	3.32	328	307
SR 800 mg											
0005/0065	34	M/B	118.8	1.52	**1.12**	4.7	3.6	2.50	2.30	244	205
0008/0071	43	M/W	75.3	4.76	**11.02**	7.9	15.1	2.22	2.84	323	295
0047/0039[b]	43	M/W	81.4	5.84	**14.03**	8.3	**16.7**	1.86	1.84	289	311
IR 300 mg											
0021/0602	42	F/W	75.0	4.41	**10.01**	7.8	12.0	2.75	1.67	344	364
0039/0524	36	M/W	73.4	8.0	**10.66**	11.5	15.1	2.58	3.29	204	247
IR 600 mg											
0027/0081	51	F/W	81.4	7.13	9.17	13.5	**16.0**	5.37	5.66	363	347
0045/0211	58	M/B	90.0	1.92	**1.04**	4.9	3.4	2.30	2.01	258	235

[a] Clinically important values are indicated in bold.
[b] Clinically important values reported as adverse events.
Base Baseline. F Female. IR Quetiapine immediate release. M Male.
SR Quetiapine sustained release. W White. WBC White blood cells.
Data derived from Listings 12.2.8.1.1, 12.2.8.1.2, and 12.2.4.1, Section 12.2.

In none of these patients did clinically important values lead to withdrawal.

For the 2 patients with low, clinically important treatment-emergent neutrophil counts, baseline values were low or at the low end of the normal range and did not fall to $<0.5 \times 10^9$ cells/L. For Patient 0045/0211, follow-up data showed a normal absolute neutrophil count (2.39×10^9 cells/L) 11 days after the final visit.

For 2 patients, clinically important values were reflected in reported AEs. Patient 0026/0357 (SR 300 mg) had AEs of increased neutrophil and WBC counts (rated moderate and not drug related), as well as AEs of strep throat, peritonsillar abscess, and sore throat (investigator terms). Patient 0047/0039 (SR 800 mg) had AEs of increased neutrophil count, increased percent neutrophils, and increased WBC counts (rated mild and not drug related). For 2 additional patients with abnormally high neutrophils, AEs were also suggestive of infection or inflammatory response: toothache and stomach upset in Patient 0039/0524 (IR 300 mg) and abdominal pain, nausea, vomiting, and hematemesis in Patient 0036/0367 (SR 600 mg).

Limited follow-up data showed that Patient 0008/0071 had a normal neutrophil count (4.82×10^9 cells/L) 13 days after the final visit, and Patient 0047/0040 had a platelet count that remained low 3 days after the final visit.

8.5.2 Clinical chemistry

Clinical chemistry test results are presented according to the following categories: hepatic function, renal function, electrolyte concentrations, glucose regulation, lipid results, thyroid function, and other (including prolactin concentrations).

8.5.2.1 Hepatic function results

(a) Changes in mean values over time

Mean and median changes in hepatic-function variables were small, with median changes ≤3 U/L for AST and ALT, ≤6 U/L for alkaline phosphatase, and close to zero for total bilirubin. Descriptive statistics showing baseline and final values and change from baseline are presented in Tables 11.3.3.2.1.2 and 11.3.3.2.1.3 (Section 11.3).

(b) Changes in individual patients over time

Relative shift changes from baseline to final visit (normal to low, normal to high, low to high, etc) for all hepatic function variable variables (AZ normal laboratory reference ranges applied) are presented in Table 11.3.3.2.1.4 (Section 11.3).

Changes in AST, ALT, and alkaline phosphatase from normal at baseline to high at any time during the trial were seen in each treatment group. For patients treated with quetiapine SR, numbers of patients with shift changes to high values did not increase consistently as dose of quetiapine increased: from low to high dose: 5, 2, and 2 patients for AST; 5, 6, and 3 patients for ALT; and 2, 2, and 4 patients for alkaline phosphatase. For each variable, numbers of affected placebo-treated patients were similar to those of SR-treated patients in at least 1 SR

treatment group: AST, 5 patients; ALT, 3 patients; and alkaline phosphatase, 1 patient. Numbers of affected IR-treated patients were similar to or marginally greater than those for SR-treated patients for each variable (low to high dose): AST, 5 and 8 patients; ALT, 8 and 6 patients; and alkaline phosphatase, 3 and 4 patients. Changes in total bilirubin from normal to high at any time were seen only with placebo (n=3) and SR 800 mg (n=1).

Shift changes that resulted in treatment-emergent clinically important values (baseline to final visit) were seen in ≤1 patient per treatment group for any given hepatic function variable (Table 47). Thus, differences between SR treatment groups and placebo, and between SR and IR treatment groups, were minimal. With so few patients having treatment-emergent clinically important hepatic abnormalities, no dose-related trends could be identified for treatment with quetiapine SR.

For clinically important shifts in hepatic function variables by all baseline and final categories, (low, not clinically important, or high), see Table 11.3.3.2.1.5 (Section 11.3).

Table 47 Hepatic laboratory data—incidence of clinically important values at final visit: treatment emergent (safety population)

Hepatic function variable	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP SR Total			QTP IR 300 mg			QTP IR 600 mg			QTP IR Total		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Shift to high values																								
AST[a]	68	1	(1.5)	79	0		79	1	(1.3)	73	0		231	1	(0.4)	75	1	(1.3)	70	0		145	1	(0.7)
ALT[a]	67	1	(1.5)	79	1	(1.3)	79	1	(1.3)	70	0		228	2	(0.9)	75	0		68	0		143	0	
Total bilirubin[a]	68	1	(1.5)	78	0		79	0		73	0		230	0		74	1	(1.3)	71	0		145	1	(0.7)

[a] Values ≥3 times the upper limit of normal were predefined as clinically important.
[b] Values ≥1.5 times the upper limit of normal were predefined as clinically important.
ALT Alanine aminotransferase. AST Aspartate aminotransferase. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.3.2.1.6, Section 11.3.

(c) Individual clinically important abnormalities in hepatic function variables

Treatment-emergent, clinically important abnormalities in AST, ALT, or total bilirubin (as defined in Section 5.5.7.3) were noted for 6 patients through the final visit: 2 patients treated with placebo; 1 patient treated with SR 300; 1 patient treated with SR 600; and 2 patients treated with IR 300 mg. Abnormal values are provided, by patient, in Table 48, along with additional patient data and concurrent values of associated tests.

Table 48 Individual clinically important laboratory abnormalities in hepatic function variables (treatment emergent, safety population)

Treatment	Visit	Age (y)	Sex/Race	Weight (kg)	Clinically important value[a] and concurrent values of associated tests (clinically important criteria)			
Center/ patient					ALT (U/L) (≥3x ULN)	AST (U/L) (≥3x ULN)	Bilirubin[b] (mg/dL) (≥1.5x ULN)	ALP (U/L) (≥3x ULN)
Placebo								
0010/0662	Baseline	41	M/W	97.7	79	40	0.7	52.0
	Final				**205**	**137**	1.3	61.0
	F/U				**171**	117	0.8	68.0
0047/0037	Baseline	25	M/His	57.7	10	14	1.1	79.0
	Final				12	16	**2.1**	78.0
	F/U				9	13	0.8	76.0
SR 300 mg								
0031/0141	Baseline	24	M/Asian	60.0	72	53	0.7	112.0
	Final				**152**	101	0.5	126.0
	F/U				61	41	NR	NR
SR 600 mg								
0035/0097	Baseline	35	M/W	96.4	137	79	0.4	90.0
	Final				**253**	**130**	0.6	85.0
	F/U				53	29	0.8	89.0
IR 300 mg								
0023/0110	Baseline	23	M/W	93.2	27	20	1.8	73.0
	Final				15	26	**3.7**	79.0
0036/0495	Baseline	26	M/W	94.1	39	22	1.6	111.0
	Final				53	**193**	1.6	108.0
	F/U				59	**128**	1.2	82.0
	F/U				26	15	0.8	115.0

[a] Clinically important values are indicated in bold.
[b] Total bilirubin.
ALP Alkaline phosphatase. ALT Alanine aminotransferase. AST Aspartate aminotransferase.
F/U Follow-up visit or visit outside of acceptable window. His Hispanic. IR Immediate release.
M Male. NR Not recorded. SR Sustained release. W White.
Data derived from Listings 12.2.4.1, 12.2.8.2.1, and 12.2.8.2.2, Section 12.2.

None of these patients was withdrawn because of their clinically important abnormalities.

Among patients with non-treatment-emergent hepatic abnormalities, one patient (Patient 0009/0418, IR 600 mg) was withdrawn following alcohol ingestion while on-pass from the hospital (protocol noncompliance, reason for withdrawal) and because of an associated elevated ALT value (167 U/L), which was increased from a high baseline ALT of 154 U/L. The patient withdrew after 6 days of study drug treatment.

No patients met the criteria used by Hy's Law to identify clinically important abnormal liver function, ie, ALT ≥3x ULN, total bilirubin ≥1.5x ULN, and alkaline phosphatase ≤1.5x ULN.

8.5.2.2 Renal function results

(a) Changes in mean values over time

Mean changes in creatinine and BUN from baseline to final visit were small and unremarkable. Descriptive statistics showing baseline and final values and change from baseline are presented in Tables 11.3.3.2.1.2 and 11.3.3.2.1.3 (Section 11.3).

(b) Changes in individual patients over time

Change in BUN from normal at baseline to high at any time during the trial was rare, seen in only 1 of 68 patients treated with quetiapine SR 800 mg. However, this shift did not result in a clinically important value. For 1 placebo-treated patient (Patient 0010/0025), a high baseline BUN (28 mg/dL, not clinically important) increased to a clinically important value of 35 mg/dL. However, this value was recorded 12 days after the patient had been withdrawn because of a severe myocardial infarction that began on Day 25 of treatment (see Table 42).

Changes in creatinine from normal at baseline to high at any time during the trial were rare and were only seen in 1 of 79 patients treated with SR 600 mg and 2 of 75 patients treated with IR 300 mg. None of these shifts resulted in values that were clinically important.

See Table 11.3.3.2.1.4 (Section 11.3) for relative shift changes from baseline to final visit (AZ normal laboratory reference ranges applied) and Tables 11.3.3.2.1.5 and 11.3.3.2.1.6 (Section 11.3) for shift changes that resulted in treatment-emergent clinically important values (baseline to final visit).

(c) Individual clinically important abnormalities in renal laboratory data

See subsection (b).

8.5.2.3 Electrolytes

(a) Changes in mean values over time

Mean changes in potassium and sodium from baseline to final visit were small and unremarkable. Descriptive statistics and change from baseline are provided in Tables 11.3.3.2.1.2 and 11.3.3.2.1.3 (Section 11.3).

(b) Changes in individual patients over time

Changes in potassium from normal at baseline to high or low at the final visit occurred infrequently: in 1 patient treated with placebo; in 3, 2, and 1 patients, respectively, treated with SR 300, SR 600, and SR 800 mg; and in 4 patients and 1 patient, respectively, treated with IR 300 and IR 600 mg.

Changes in sodium from normal at baseline to high or low at the final visit also occurred infrequently: in 1 patient treated with placebo; in 0, 4, and 2 patients, respectively, treated with SR 300, SR 600, and SR 800 mg; and in 3 patients each treated with IR 300 and IR 600 mg.

Dose-related effects were not evident. Full shift tables are provided in Table 11.3.3.2.1.4 (Section 11.3) (AZ normal laboratory reference ranges applied). Shift changes that resulted in clinically important values are summarized in Table 49.

Table 49 Electrolyte data—incidence of clinically important values at final visit: treatment emergent (safety population)

Electrolyte	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP SR Total			QTP IR 300 mg			QTP IR 600 mg			QTP IR Total		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Shift to high values																								
Potassium	67	0		77	3	(3.9)	78	1	(1.3)	71	1	(1.4)	226	5	(2.2)	74	3	(4.1)	71	0		145	3	(2.1)
Sodium	68	0		79	0		79	0		73	0		231	0		75	0		71	0		146	0	
Shift to low values																								
Potassium	68	1	(1.5)	79	0		79	0		73	0		231	0		75	0		71	0		146	0	
Sodium	68	0		79	0		79	2	(2.5)	72	0		230	2	(0.9)	75	2	(2.7)	70	1	(1.4)	145	3	(2.1)

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.3.2.1.6, Section 11.3.

(c) Individual clinically important abnormalities in electrolytes

Treatment-emergent, clinically important potassium or sodium values (as defined in Section 5.5.7.3) were noted for a total of 14 patients through the final visit (see Table 49).

At the final visit, no patient had concurrent, clinically important potassium and sodium levels.

One placebo-treated patient (Patient 0005/0181) had low, clinically important potassium levels on the day of withdrawal (which was AE-related [grand mal convulsions and vomiting]).

Two patients with high, clinically important potassium levels—Patient 0033/0304 (SR 800 mg) and Patient 0036/0495 (IR 300 mg)—also had clinically important increases in ventricular and atrial rates per ECG findings (+18 and +18 bpm and +40 and +39 bpm, respectively) at the final visit. The former patient completed the study. The latter patient was withdrawn on Day 8 for reasons related to lack of efficacy, not to electrolyte or heart rate abnormalities.

One quetiapine-treated patient (Patient 0023/0621, IR 600 mg) with abnormally low sodium at the final visit had hyponatremia (MedDRA preferred term, blood sodium decreased) reported as an AE.

Abnormal values for these patients are provided in Table 50, along with patient demographics and concurrent sodium or potassium values.

Table 50 Individual clinically important potassium or sodium abnormalities in patients with other concomitant safety findings (treatment emergent, safety population)

Treatment	Age (y)	Sex/Race	Weight (kg)	Clinically important potassium and sodium values[a] (clinically important criteria)			
Center/ patient				Potassium (<3 or >5.5 mmol/L)		Sodium (≤132 or ≥152 mmol/L)	
				Baseline	Final	Baseline	Final
Placebo							
0005/0181[b]	42	M/Hispanic	66.7	4	**3**	145	139
SR 800 mg							
0033/0304[c]	39	M/White	64.1	4.9	**5.5**	141	144
IR 300 mg							
0036/0495[c]	26	Male/White	94.1	5.1	**8**	142	137
IR 600 mg							
0023/0621	59	Male/White	63.5	4.2	3.1	140	**102**[d]

[a] Clinically important values are indicated in bold.
[b] Patient had concurrent grand mal seizures and vomiting and was withdrawn.
[c] Patients with clinically important ECG abnormalities (increases of ≥15 bpm in ventricular or atrial heart rates).
[d] Also reported as an adverse event.
IR Quetiapine immediate release. SR Quetiapine sustained release.
Data derived from Listings 12.2.4.1 and 12.2.8.2.2, Section 12.2.

8.5.2.4 Glucose regulation laboratory data

(a) Changes in mean values over time

Mean changes in fasting glucose from baseline to final visit were small, with changes of <9 mg/dL in each treatment group. Descriptive statistics are provided in Table 51.

In each group, 5 to 9 patients had diabetes. Mean changes in glucose from baseline to final visit for these patients were in the negative direction for all but the SR 600-mg treatment group (mean, 20.1 mg/dL; median, –19.0 mg/dL), and median changes were in the negative direction for all but the placebo treatment group (median, 5.0 mg/dL; mean, –9.57 mg/dL). Full descriptive statistics for this subset of patients is provided in Table 51.

Descriptive statistics for patients at risk for diabetes and for nondiabetic patients are provided in Table 11.3.3.2.1.7 (Section 11.3).

Note that although patients were expected to fast prior to blood sampling, several factors, including the ranges of glucose values reported (especially for the final visit) and the times noted for blood sampling, suggested that this condition was not consistently met across treatment groups. Because investigator-confirmation of fasting status was missing for most patients, glucose values were secondarily evaluated under the assumption that they represented random glucose levels. This finding is discussed in more detail later in Section 8.5.4.

Table 51 Glucose laboratory data: change from baseline to final visit (safety population, fasting condition)

Glucose (mg/dL)		Placebo (N=84)	QTP SR 300 mg (N=91)	QTP SR 600 mg (N=92)	QTP SR 800 mg (N=89)	QTP IR 300 mg (N=90)	QTP IR 600 mg (N=86)
All patients		n=68	n=78	n=79	n=73	n=75	n=71
Baseline	Mean (SD)	97.7 (23.4)	95.1 (20.3)	102.3 (33.6)	102.9 (37.3)	101.9 (30.4)	104.9 (45.2)
Final	Mean (SD)	101.1 (23.6)	99.3 (19.3)	111.2 (59.4)	110.4 (45.2)	101.2 (24.0)	111.0 (41.6)
Change	Mean (SD)	3.4 (26.1)	4.2 (22.6)	8.9 (37.9)	7.5 (49.1)	–0.7 (27.9)	6.1 (32.7)
	Median	0.0	2.0	3.0	1.0	1.0	6.0
	Min to max	–145 to 63	–95 to 92	–88 to 254	–177 to 283	–121 to 70	–104 to 148
Patients with diabetes		n=7	n=5	n=7	n=9	n=8	n=9
Baseline	Mean (SD)	142.1 (50.4)	129.4 (62.1)	187.1 (62.3)	165.9 (78.6)	165.5 (59.6)	172.8 (103.1)
Final	Mean (SD)	132.6 (43.9)	112.0 (24.9)	207.3 (169.8)	164.1 (101.6)	128.5 (38.4)	162.9 (90.7)
Change	Mean (SD)	–9.6 (65.5)	–17.4 (48.1)	20.1 (111.6)	–1.8 (131.0)	–37.0 (57.4)	–9.9 (72.6)
	Median	5.0	–10.0	–19.0	–26.0	–24.5	–18.0
	Min to max	–145 to 47	–95 to 38	–88 to 254	–177 to 283	–121 to 33	–104 to 148

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release. SD Standard deviation.
Data derived from Tables 11.3.3.2.1.7, Section 11.3.

(b) Changes in individual patients over time

Numbers of patients with relative changes in glucose from normal at baseline to high or low at any time during the trial are summarized in Table 11.3.3.2.1.4 (Section 11.3) (AZ normal laboratory reference ranges applied).

When criteria for clinically important shifts in glucose were considered, no patients had shifts to low, clinically important levels (fasting or random). In the opposite direction, similar proportions of placebo-, SR-, and IR-treated patients had shifts to high, clinically important glucose levels when fasting criteria were applied—11.1%, 11.5%, and 9.0%, respectively—with even fewer patients having shifts to high clinically important levels when criteria for random glucose were applied—0%, 1.8%, and 0.7%.

Frequency of clinically important glucose levels is presented by treatment group and diabetic status in Table 52.

For patients treated with quetiapine SR and quetiapine IR, the incidences of high clinically important glucose levels (fasting criteria) did not appear dose related given the similarities in incidence rates among patients treated with placebo (11.1%), SR 600 mg (12.5%), SR 800 mg (14.7%), and IR 600 mg (12.5%).

Under assumed fasting condition, a greater proportion of nondiabetic placebo-treated patients (16.2%) contributed to the incidence of high clinically important glucose levels at the final visit, compared with proportions of nondiabetic patients treated with quetiapine SR (6.0%, 14.6%, and 10.3% [low to high dose]) and IR (4.8% and 8.8% [low to high dose]).

Table 52 Glucose data—incidence of treatment-emergent clinically important values at final visit: (safety population)

Patient type	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP SR Total			QTP IR 300 mg			QTP IR 600 mg			QTP IR Total		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Fasting condition[a]																								
All	63	7	(11.1)	77	6	(7.8)	72	9	(12.5	68	10	(14.7)	217	25	(11.5)	69	4	(5.8)	64	8	(12.5)	133	12	(9.0)
Diabetic	2	0		4	1	(25.0)	0			4	2	(50.0)	8	3	(37.5)	2	0		2	0		4	0	
At-risk	24	1	(4.2)	23	2	(8.7)	31	3	(9.7)	25	4	(16.0)	79	9	(11.4)	25	2	(8.0)	28	5	(17.9)	53	7	(13.2)
Nondiabetic	37	6	(16.2)	50	3	(6.0)	41	6	(14.6)	39	4	(10.3)	130	13	(10.0)	42	2	(4.8)	34	3	(8.8)	76	5	(6.6)
Random condition[b]																								
All	67	0		77	0		77	1	(1.3)	71	3	(4.2)	225	4	(1.8)	73	0		70	1	(1.4)	143	1	(0.7)
Diabetic	6	0		4	0		5	1	(20.0)	7	2	(28.6)	16	3	(18.8)	6	0		8	1	(12.5)	14	1	(7.1)
At-risk	24	0		23	0		31	0		25	0		79	0		25	0		28	0		53	0	
Nondiabetic	37	0		50	0		41	0		39	1	(2.6)	130	1	(0.8)	42	0		34	0		76	0	

[a] Under assumed fasting conditions, clinically important criteria for glucose: ≤45 or ≥126 mg/dL (see Section 5.5.7.3).
[b] Under assumed random conditions, clinically important criteria for glucose: ≤45 or ≥200 mg/dL (see Section 5.5.7.3).
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.3.3.2.1.8 and 11.3.3.2.1.9, Section 11.3.

(c) Individual clinically important abnormalities in glucose

Of the 44 patients with treatment-emergent clinically important glucose levels (fasting conditions assumed) at the final visit (Table 52) (7 placebo-, 25 quetiapine SR- and 12 quetiapine IR-treated patients), only 1 patient (Patient 0059/0295, SR 800 mg) had elevated blood glucose listed as an AE. The event (blood glucose increased, MedDRA preferred term) was considered mild and the patient recovered. Values were 85 mg/dL at baseline, 155 mg/dL at the final visit, and 92 mg/dL at follow-up. No patients withdrew because of elevated blood glucose levels.

High clinically important glucose levels are provided for all patients with treatment-emergent findings in Listing 12.2.8.2.2 (Section 12.2).

8.5.2.5 Lipid laboratory data

(a) Changes in mean values over time

Mean cholesterol values through the final visit were similar and within the normal range among patients treated with placebo, quetiapine SR 300, and quetiapine SR 800: 196.5, 195.4, and 198.4 mg/dL, respectively. Mean values through the final visit among patients treated with quetiapine SR 600 mg, IR 300 mg and IR 600 mg were slightly greater than the upper end of normal (199 mg/dL): 206.4, 202.9, and 214.8 mg/dL, respectively. Overall, patients treated with placebo had the smallest mean and median increases from baseline in total cholesterol (+0.1 and +0.0 mg/dL, respectively). Mean and median increases from baseline were largest among patients treated with quetiapine SR 300 (+14.6 and +9.0 mg/dL, respectively) and SR 800 mg (+14.2 and +10.0 mg/dL, respectively), although increases at these doses were similar to those seen with quetiapine IR 600 mg (+12.8 and +8.0 mg/dL, respectively). Full descriptive statistics are provided in Table 11.3.3.2.1.2 (Section 11.3).

Mean HDL values were within normal limits for each treatment group at both baseline and the final visit. Mean and median changes were small and close to zero across treatment groups (mean, –2.0 to +2.0 mg/dL; median –2.0 to +3.0 mg/dL), with changes smallest among patients treated with quetiapine SR 800 mg (0.0 mg/dL, both mean and median) (see Table 11.3.3.2.1.3 (Section 11.3).

Mean LDL values were within normal limits for each treatment group at both baseline and the final visit. Mean changes from baseline were greater among patients treated with quetiapine SR (any dose) (+8.0 to +10.9 mg/dL) than among placebo-treated patients (+3.8 mg/dL), although median changes were similar (placebo, +4.0 mg/dL; quetiapine SR, +3.0 to +6.0 mg/dL). Mean changes with quetiapine IR were smaller (+3.4 to +4.1 mg/dL), than those seen with quetiapine SR, but similar to those seen with placebo (see Table 11.3.3.2.1.3 (Section 11.3).

At baseline and the final visit, mean values for triglycerides were within normal limits in each treatment group, with 1 exception. The exception was seen at the final visit for patients treated with quetiapine IR 600 mg, who had a mean value of 217.6 mg/dL, a value slightly

greater than the upper limit of normal (199 mg/dL). For patients treated with placebo, mean triglyceride levels decreased from baseline to the final visit (mean change, –4.0 mg/dL; median –0.5 mg/dL). For patients treated with quetiapine SR, mean and median triglyceride values increased from baseline to the final visit, with magnitude of change appearing to increase with increasing dose of quetiapine SR. A similar pattern was seen for patients treated with quetiapine IR 300 and 600 mg (see Table 11.3.3.2.1.3 [Section 11.3]).

(b) Changes in individual patients over time

Numbers of patients with relative changes in cholesterol, HDL, LDL, or triglycerides from normal at baseline to high or low at any time during the trial are summarized in Table 11.3.3.2.1.4 (Section 11.3) (AZ normal laboratory reference ranges applied).

Incidences of patients with shift changes that resulted in clinically important values are summarized in Table 53. Similar proportions of placebo-treated (12.5%) and SR-treated patients (11.0%) had clinically important cholesterol values through the final visit, with these proportions smaller than those seen for IR-treated patients (20.0%).

Compared with placebo-treated patients (10.0%), greater proportions of SR- and IR-treated patients (17.4% and 20.2%) had high clinically important triglycerides levels through the final visit. This was consistent with the known effects of quetiapine on triglyceride levels.

Dose-related increases in incidence of high clinically important cholesterol or triglyceride levels were not evident among patients treated with quetiapine SR. For IR-treated patients, possible dose-related increases were seen for triglycerides only.

Table 53 Lipid laboratory data—incidence of treatment-emergent clinically important values at final visit (safety population)

Lipid	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP SR Total			QTP IR 300 mg			QTP IR 600 mg			QTP IR Total		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Shift to high																								
Cholesterol	56	7	(12.5)	73	8	(11.0)	66	8	(12.1)	70	7	(10.0)	209	23	(11.0)	62	12	(19.4)	58	12	(20.7)	120	24	(20.0)
Triglycerides	50	5	(10.0)	63	11	(17.5)	60	9	(15.0)	55	11	(20.0)	178	31	(17.4)	58	10	(17.2)	51	12	(23.5)	109	22	(20.2)

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.3.2.1.6, Section 11.3.

(c) Individual clinically important lipid abnormalities

Individual patients are identified in Listing 12.2.8.2.2 (Section 12.2).

No patients were withdrawn for reasons related to lipid abnormalities.

8.5.2.6 Thyroid function results

(a) Changes in mean values over time

Mean changes in TSH, T_4, and T_3 from baseline to final visit were small and unremarkable. Descriptive statistics are provided in Tables 11.3.3.2.1.2 and 11.3.3.2.1.3 (Section 11.3).

(b) Changes in individual patients over time

Relative changes in thyroid hormones (TSH, T_4, and T_3) from baseline to final visit (eg, from normal to high, normal to low, high to low, etc) were uncommon; these shifts are shown in Table 11.3.3.2.1.4 (Section 11.3) (AZ normal laboratory reference ranges applied).

Changes from baseline that resulted in clinically important values are shown in Table 54. No patients with shifts to high, clinically important TSH levels had concurrent shifts to low, clinically important T_4 levels. No patients with shifts to low, clinically important T_4 levels had concurrent shifts to high, clinically important TSH levels. No patients had treatment-emergent clinically important increases or decreases in T_3 levels. Data are summarized in Tables 11.3.3.2.1.12 and 11.3.3.2.1.14 (Section 11.3).

Table 54 Thyroid hormone laboratory data—incidence of treatment-emergent clinically important values at final visit (safety population)

Thyroid hormone	Number (%) of patients							
	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP SR Total	QTP IR 300 mg	QTP IR 600 mg	QTP IR Total
Shift to high	**(n=64)**	**(n=76)**	**(n=76)**	**(n=69)**	**(n=223)**	**(n=72)**	**(n=68)**	**(n=140)**
TSH >5 mIU/L[a]	1 (1.6)	0	0	1 (1.4)	1 (0.4%)	3 (4.2)	1 (1.5)	4 (2.9)
Shift to low	**(n=68)**	**(n=78)**	**(n=79)**	**(n=72)**	**(n=229)**	**(n=75)**	**(n=70)**	**(n=145)**
T_4 <0.8 x LLN	0	0	0	0	0	2 (2.7)[b]	3 (4.3)[b]	5 (3.4)

[a] No patient with high, clinically important TSH values (which ranged between 5.3 and 8.6 mIU/L) had concurrent low, clinically important T_4 or T_3 values.
[b] Actual values recorded as 7.72 pmol/L.
LLN Lower limit of normal. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release. TSH Thyroid stimulating hormone. T_4 Free thyroxine.
Data derived from Tables 11.3.3.2.1.16, Section 11.3 and Listing 12.2.8.2.2, Section 12.2. See also Table 11.3.3.2.1.17 for a tabulation of patients with clinically important shifts in TSH by relative change in T_4.

(c) Individual clinically important abnormalities in thyroid hormones

None of the 11 patients with treatment-emergent clinically important TSH or T_4 levels at the final visit (Table 54) (1 placebo-, 1 quetiapine SR- and 9 quetiapine IR-treated patients) had these events reported as AEs. None of the 11 patients withdrew because of elevated TSH or decreased T_4 levels. Abnormal values are provided for individual patients in Listing 12.2.8.2.2 (Section 12.2).

8.5.2.7 Other results including change in prolactin concentrations

Wide ranges of prolactin levels were reported for each treatment group at baseline. Mean changes from baseline to the final visit were –6.6 µg/dL with placebo, –7.0 to –13.5 µg/dL with quetiapine SR, and –7.9 to –10.3 µg/dL with quetiapine IR. Median decreases were ≤5 µg/dL in all but the SR 300-mg treatment group, who had a median decrease of –9.0 µg/dL. Descriptive statistics and changes from baseline in prolactin concentration from baseline to final visit are presented in Tables 11.3.3.2.1.2 and 11.3.3.2.1.3 (Section 11.3). Shift tables for change in prolactin laboratory data are presented in Table 11.3.3.2.1.4 (Section 11.3).

A greater proportion of placebo-treated patients (14.9%, 7 of 47) had shifts to high, clinically important prolactin values through the final visit, compared with patients treated with quetiapine SR (4.1%, 6 of 145) or quetiapine IR (7.8%, 8 of 103). Shifts by treatment group are provided in Table 11.3.3.2.1.6 (Section 11.3).

8.5.3 Urinalysis (not applicable)

8.5.4 Discussion of clinical laboratory results

No patients had agranulocytosis. Decreases to low clinically important neutrophil levels were uncommon. Increases in neutrophil counts to high clinically important levels were seen in isolated instances and, for several patients, were associated with infection or inflammatory conditions. Very few patients had changes in hepatic enzyme levels to high clinically important values. No occurrences led to patient withdrawal, and when available, follow-up data for quetiapine-treated patients showed values returning to normal. Treatment effects on renal function and electrolytes were unremarkable.

Small mean increases in glucose were seen in each treatment group, except for the IR 300-mg treatment group, which had a marginal mean decrease. Incidences of high, clinically important glucose levels were similar among patients treated with placebo, quetiapine SR, and quetiapine IR. Rates of clinically important changes in glucose did not appear related to increasing dose of quetiapine SR. Overall conclusions on quetiapine treatment effects relative to glucose are confounded by the possibility that patients were not in good fasting condition when blood samples were drawn. Fasting glucose status was not investigator-confirmed for most patients, ie, the check box on the relevant CRF used to confirm fasting status was checked for only 15 patients. Additionally, when blood-sampling times at baseline were compared with sampling times at the final visit, a clear shift toward later sampling times

(toward late morning and after noon) was evident in each treatment group at the final visit (Figures 11.3.3.2.2.12 through 11.3.3.2.2.17 Section 11.3).

Treatment effects on lipid profiles were variable, with the most notable difference between quetiapine SR and placebo seen for triglycerides (mean decrease with placebo, mean increase with quetiapine SR [possibly dose related]). However, this was not unexpected given the known effects of quetiapine on triglyceride levels. Overall conclusions on treatment effects relative to lipids are also confounded by patients not being in good fasted conditions and by the fact that the study was not designed to assess the effects of quetiapine on lipids (eg, no screening criteria specific for lipid studies used, no stratification of patients by baseline lipid values, limited blood sampling times, etc).

Treatment effects on thyroid hormones were minimal. Treatment-emergent clinically important increases in TSH did not occur with concurrent treatment-emergent clinically important decreases in T_4; additionally, these changes were not accompanied by symptoms or reported as AEs. Trends for changes in prolactin were for mean and median decreases among all treatment groups (placebo, quetiapine SR, and quetiapine IR).

The results of clinical laboratory testing produced no unexpected findings with quetiapine SR and continue to show the safety of quetiapine regardless of formulation used.

8.6 Vital signs, ECG results, physical findings and other observations related to safety

8.6.1 Vital signs

8.6.1.1 Changes in vital signs over time

Descriptive statistics and changes from baseline in supine pulse and blood pressures are provided in Tables 11.3.4.1.1 and 11.3.4.1.2 (Section 11.3). Descriptive statistics and changes from baseline in orthostatic pulse and blood pressures are provided in Tables 11.3.4.1.5 and 11.3.4.1.6 (Section 11.3). Results were considered relative to the dose-escalation regimen used and to the fact that multiple vital sign measurements were made on certain study days.[9] Summaries of changes in supine pulse and blood pressures follow.

[9] During the first 4 days of treatment, all patients assigned to quetiapine SR received SR 300 mg daily. On Day 5, patients assigned to the higher SR doses had their doses increased to SR 600 mg and likewise on Day 8, patients assigned to SR 800 mg had their doses increased to 800 mg. Therefore, assessments (3 to 4 measurements taken) on Days 1 and 2, 5 and 6, and 8 and 9 were made to monitor effects on day of dose increase and second day at new dose. Assessment through Day 15 also provided an opportunity to check results opposite expected time to maximum concentration (T_{max}). On Days 28 and 42, vital signs were measured once. Patients assigned to treatment with quetiapine IR had their doses increased incrementally from 50 mg/day on Day 1 to 300 mg/day on Day 4 and then to 600 mg on Day 6 (if assigned to the higher dose).

(a) Supine pulse

On Day 1, there were no clear differences in mean changes in supine pulse rate between SR treatment groups and placebo, or between SR and IR treatment groups, with maximum increases of 3.4 bpm across all groups. On Day 2, there were slightly greater increases in pulse rates in the SR treatment groups (mean changes between +0.2 bpm and + 6.6 bpm), compared with those observed in the placebo group (mean changes between +1 and + 3.4 bpm). Similar increases were seen in the SR and IR treatment groups (mean changes between +0.7 and +4.7 bpm in the IR groups).

On Day 5 (first SR dose increase [to 600 mg]), SR treatment groups had small increases vs placebo with slightly greater increases in both the SR 600- and SR 800-mg groups compared with the SR 300 mg group. Changes (increases) in pulse in SR and IR treatments groups were of similar magnitude. Results on Day 6 were similar to those observed on Day 5.

On Day 8 (second SR dose increase [to 800 mg]), SR treatment groups had slightly higher increases in pulse vs placebo with no apparent effect (among SR treatment groups) from the dose increase to 800 mg/day. Overall changes in SR and IR treatments groups were similar. On Day 9, results were similar to those observed on Day 8. On Day 15, changes in pulse rate were similar to those seen previously on Days 8 and 9.

There was a tendency toward greater mean change in pulse at the expected formulation T_{max} for the SR treatment groups (approximately 6 hours) but not the IR treatment groups (approximately 1 to 2 hours).

On Day 42, the overall effect among SR-treated patients was a small increase in pulse (mean changes of -0.8, +5.6, and +3.0 bpm, respectively, in the SR 300-, SR 600- and SR 800-mg treatment groups) vs a small mean decrease of -3.7 bpm with placebo. Changes were similar between SR and IR treatments groups (mean changes of +2.2 and +8.1 bpm in the IR 300 and IR 600 treatments groups, respectively).

(b) Supine systolic pressure

On Day 1, there were primarily small decreases in mean supine systolic blood pressure (SBP) in the SR treatment groups (mean changes between + 0.1 and –5.4 mmHg) compared with mostly small increases in placebo group (mean changes between –0.2 to + 2.8 mmHg). The decreases seen in the SR treatment groups were similar overall to those seen in the IR treatment groups (mean changes between +1.0 to -3.3 mmHg). Changes on Day 2 were similar to those observed on Day 1.

On Day 5 (first SR dose increase [to 600 mg]), mean changes with SR treatments were small and variable (ie, both decreases and increases were seen), compared with consistent small increases in the placebo group. Overall, there were no apparent differences in the changes between SR and IR treatments groups. Results on Day 6 were similar to those observed on Day 5.

On Day 8 (second SR dose increase [to 800 mg]), SR treatment groups tended to have small decreases in SBP vs small increases in the placebo group, with little to no effect apparent when SR dose was increased to 800 mg/day. Changes in SR and IR treatment groups were similar. Results on Day 9 were similar to those observed on Day 8. On Day 15, SBP changes in the SR treatment groups were similar overall to those seen in placebo and IR treatment groups.

One Day 42, SBP changes in the SR treatment groups were not clearly different from that seen in the placebo group (mean changes of +0.8, –0.8, and +5.8 mmHg, respectively, in the SR 300-, SR 600- and SR 800-mg treatment groups vs a mean change of + 3.3 mmHg in the placebo group). Changes between SR and IR treatments groups were similar (mean change of + 3.7 and + 1.1 mmHg in the IR 300- and IR 600-mg treatments groups, respectively).

(c) Supine diastolic pressure

On Day 1, there were primarily small decreases in mean supine diastolic blood pressure (DBP) in the SR treatment groups (mean changes between + 0.7 and –4.6 mmHg), with decreases somewhat greater than those seen in placebo group (mean changes between 0 and –1.9 mmHg) and IR treatment groups (mean changes between +0.8 to –0.8 mmHg). Changes on Day 2 were similar to those observed on Day 1.

On Day 5 (first SR dose increase [to 600 mg]), mean changes in DBP among SR treatment groups were not clearly different from those seen in the placebo group, with no effect apparent when the SR dose was increased to 600 mg/day. Changes were similar between SR and IR treatments groups. Results on Day 6 were similar to those observed on Day 5.

On Day 8 (second SR dose increase [to 800 mg]), changes were variable across the SR treatment groups when compared with placebo. Mean changes were most similar between the SR 300-mg (changes between –0.8 and +2.1 mmHg) and the placebo (changes between –1.2 and +0.3 mmHg) treatment groups, with slightly greater decreases seen in the SR 600-mg treatment group (mean changes between –0.8 and –3.7 mmHg) and small increases in the SR 800-mg group (mean changes between +0.5 and +1.7 mmHg). Changes with SR 800 mg, IR 300 mg, and IR 600 mg were similar (mean changes between +0.2 and +2.2 mmHg in the IR 300-mg treatment group and between –0.7 and +4.0 mmHg in IR 600-mg treatments group. Results on Day 9 were similar to those observed on Day 8.

On Day 15, changes in DBP in the SR treatment groups tended toward slight increases compared with small decreases in placebo group. Mean changes in SR treatment groups and IR treatment groups were similar. On Day 42, SR treatment groups had slightly greater increases (mean changes of +4.3, +1.9, and +5.6 mmHg, respectively, in the SR 300-, SR 600- and SR 800-mg treatment groups), compared with the placebo group (mean change of +1.6 mmHg). Changes were similar between SR and IR treatments groups (mean change of +5.7 and +6.9 mmHg in the IR 300- and IR 600-mg treatments groups, respectively).

Overall, mean changes in vital signs with quetiapine SR were small when compared with those seen with placebo but similar to those seen with quetiapine IR. The consistent change

observed with quetiapine SR was an increase in pulse rate that was similar to that seen with quetiapine IR but with no clear effect apparent when SR dose was increased. Increased pulse rate with quetiapine SR is consistent with the known safety profile of quetiapine. Changes in supine blood pressure with quetiapine SR were small and tended to be variable. There was no clear effect apparent when SR dose was increased. The changes observed in vital signs did not raise any new safety concerns.

8.6.1.2 Individual patient changes in vital signs

Relative shifts in supine vital signs from baseline to final visit (eg, normal to low, normal to high, high to low, etc) were infrequent. Shifts in supine pulse from normal to high were seen in 1 patient treated with SR 800 mg. Shifts in supine SBP from normal to low were seen 1, 1, and 2 patients treated, respectively, with placebo, SR 800 mg, and IR 600 mg. Shifts in supine DBP from normal to low were seen 2 patients each treated with SR 800 and IR 600 mg. All relative shifts in supine vital signs are presented in Table 11.3.4.1.4 (Section 11.3) (AZ normal laboratory reference ranges applied).

Frequencies of patients with clinically important supine pulse rates or supine blood pressures at the final visit, or in at least 30% of postbaseline assessments (sustained clinically important values), are shown in Table 55. Proportions of patients with clinically important values were not largely different among placebo-, SR-, and IR-treated patients. The greatest difference between placebo- and SR-treated patients was seen for proportions of patients with ≥15 bpm increases in pulse (SR, 31.4%; placebo, 25.0%). Similar patterns were seen for frequencies of patients with clinically important standing vital signs, with somewhat greater proportions having pulse rate increases of ≥15 bpm or pulse rates of >120 bpm (see Table 11.3.4.1.3 [Section 11.3]).

There were little to no differences between SR and IR treatment groups in incidences of clinically important vital signs.

Table 55 Vital signs data—incidence of clinically important values at final visit or in at least 30% of postbaseline assessments (safety population)

Vital sign	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP SR Total			QTP IR 300 mg			QTP IR 600 mg			QTP IR Total		
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Supine shift to high																								
Pulse																								
>120 bpm	84	0		91	0		92	0		88	1	1.1	271	1	0.4	89	0		84	0		173	0	
≥15 bpm increase	84	21	25.0	91	23	25.3	92	32	34.8	88	30	34.1	271	85	31.4	89	26	29.2	84	24	28.6	173	50	28.9
SBP																								
≥180 mmHg	84	0		91	1	1.1	92	1	1.1	88	0		271	2	0.7	89	0		83	0		172	0	
≥20 mmHg increase	84	14	16.7	91	14	15.4	92	12	13.0	88	18	20.5	271	44	16.2	89	15	16.9	84	10	11.9	173	25	14.5
DBP																								
≥105 mmHg	84	0		91	0		92	0		88	0		271	0		89	2	2.2	84	1	1.2	173	3	1.7
≥30 mmHg increase	84	0		91	1	1.1	92	0		88	2	2.3	271	3	1.1	89	1	1.1	84	4	4.8	173	5	2.9
Supine shift to low																								
Pulse																								
<50 bpm	84	1	1.2	90	0		92	0		88	1	1.1	270	1	0.4	89	0		83	0		172	0	
≥15 bpm decrease	84	14	16.7	91	12	13.2	92	8	8.7	88	10	11.4	271	30	11.1	89	14	15.7	84	8	9.5	173	22	12.7
SBP																								
≤90 mmHg	84	2	2.4	90	0		91	0		88	1	1.1	269	1	0.4	89	0		84	2	2.4	173	2	1.2
≥20 mmHg decrease	84	9	10.7	91	10	11.0	92	19	20.7	88	7	8.0	271	36	13.3	89	6	6.7	84	14	16.7	173	20	11.6
DBP																								
≤50 mmHg	81	0		91	0		91	0		87	2	2.3	269	2	0.7	88	0		82	2	2.4	170	2	1.2
≥20 mmHg decrease	84	5	6.0	91	8	8.8	92	9	9.8	88	9	10.2	271	26	9.6	89	5	5.6	84	9	10.7	173	14	8.1
Orthostatic change[a]																								
Pulse ≥20 bpm inc	75	12	16.0	78	22	28.2	77	18	23.4	80	19	23.8	235	59	25.1	80	19	23.8	70	14	20.0	150	33	22.0
SBP ≥20 mmHg dec	83	7	8.4	89	2	2.2	87	5	5.7	86	9	10.5	262	16	6.1	83	4	4.8	77	7	9.1	160	11	6.9
DBP ≥20 mmHg dec	81	0		91	2	2.2	90	1	1.1	87	0		268	3	1.1	85	2	2.4	81	0		166	2	1.2
Combination increase pulse/decrease SBP	75	1	1.3	77	1	1.3	74	0		79	4	5.1	230	5	2.2	76	2	2.6	65	2	3.1	141	4	2.8

[a] From supine to standing after 1 minute.
DBP Diastolic blood pressure. Dec Decrease. Inc Increase. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release. SBP Systolic blood pressure.
Data derived from Tables 11.3.4.1.3 and 11.3.4.1.7, Section 11.3.

Orthostatic changes in pulse and systolic blood pressure from normal at baseline to clinically important at the final visit or in 30% of postbaseline visits were seen in each treatment group (see Table 11.3.4.1.8 [Section 11.3]). The proportion of SR-treated patients who met the criteria for pulse rate (25.1%) was somewhat greater than that seen with placebo (16.0%), with rates at the higher SR doses (SR 600 mg, 23.4%; SR 800 mg, 23.8%) lower than the rate seen with SR 300 mg (28.2%) (Table 55). While proportions of patients with clinically important or sustained orthostatic decreases in SBP appeared to increase with increasing dose of quetiapine SR or IR, the proportion of affected placebo-treated patients was high, making it difficult to distinguish whether the finding was one of chance or an actual treatment effect. Orthostatic changes in diastolic blood pressure from normal at baseline to clinically important at the final visit or in 30% of postbaseline visits were seen in only 1 or 2 patients each in the SR 300-, SR 600-, and IR 300-mg treatment groups.

Less than 5 patients per treatment group had combined clinically important orthostatic increases in pulse rate and decreases in systolic blood pressure at the final visit or in 30% of postbaseline assessments. Rates were lowest with placebo (1.3%), SR 300 mg (1.3%), and SR 600 mg (0%) and higher with SR 800 mg (5.1%) and IR 300 and 600 mg (2.6% and 3.1%). Overall rates for quetiapine SR and quetiapine IR were similar (2.2% vs 2.8%, respectively).

8.6.1.3 Individual clinically important vital sign abnormalities

Patients with clinically important vital signs are presented individually in Listing 12.2.9.4 (Section 12.2). In each treatment group, patients with clinically important vital signs also had concurrent vascular and cardiac AEs, including postural hypotension, tachycardia, increased heart rate, postural dizziness, and decreases in systolic and diastolic blood pressures. In overview, though, cardiac and vascular AEs were not consistently reported for patients with clinically important vital signs as some patients had no AEs reported.

8.6.2 ECG findings

8.6.2.1 Changes in ECG findings over time

Descriptive statistics for atrial and ventricular rates and PR, QRS, QT, and QTc_F intervals are provided in Tables 11.3.5.1.1 (Section 11.3). Changes from baseline to final visit are presented in Table 56.

At the final visit, mean and median changes in atrial and ventricular heart rates were ≤8 bpm in each quetiapine SR and IR treatment group. These changes were somewhat greater than those seen with placebo (mean, +1.1 bpm; median, 0.0 bpm, both variables). Ranges of change (minimum to maximum values) were wide in each treatment group.

Mean and median changes in PR interval among SR-treated patients were small and variable and similar to the changes seen for placebo- and IR-treated patients.

Mean changes in QRS interval were less than 1 millisecond in either direction in all treatment groups, with corresponding median changes of –1.0 millisecond or zero.

Small decreases in mean and median QT interval were seen in all treatment groups. Change in the SR 800-mg treatment group (–5.7 milliseconds) was similar to that seen with placebo group (–4.3 milliseconds). Decreases in the lower-dose SR treatment groups were slightly larger (–8.8 and –8.6 milliseconds) and similar to those seen in the IR treatment groups (–9.6 and –12.0 milliseconds).

Small increases in mean QTc_F interval (+1.1 to +3.9 milliseconds) were seen in the SR 600- and SR 800-mg treatment groups while small decreases in mean values were seen in each of the other treatment groups (–2.7 [placebo], –0.3 [SR 300 mg], and –1.0 [IR 300 and 600 mg]). Median change ranged from –4.0 milliseconds (placebo) to +7.0 milliseconds (SR 800 mg), with median changes for the other treatment groups similar and closer to zero (–2.5 to +2.0 milliseconds). Ranges of QTc_F interval changes were wide in all treatment groups.

Table 56 ECG findings: change from screening at the final visit (safety population)

ECG parameter	Statistic	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP IR 300 mg	QTP IR 600 mg
		N=66	N=75	N=76	N=71	N=74	N=66
Atrial rate							
Change	Mean (SD)	1.1 (13.8)	4.9 (14.0)	5.7 (14.8)	6.0 (13.9)	5.7 (15.0)	6.8 (14.4)
	Median	0.0	4.0	8.0	6.0	3.0	5.0
	Min to max	–41 to 40	–37 to 50	–31 to 40	–25 to 42	–25 to 48	–17 to 44
Ventricular rate							
Change	Mean (SD)	1.1 (13.9)	5.1 (14.1)	5.8 (14.7)	6.1 (14.0)	5.8 (15.1)	6.9 (14.3)
	Median	0.0	5.0	8.0	8.0	3.0	6.5
	Min to max	–42 to 40	–37 to 50	–31 to 40	–25 to 42	–24 to 47	–17 to 44
PR interval							
Change	Mean (SD)	–1.0 (16.6)	1.4 (18.5)	–2.0 (17.9)	3.3 (16.8)	0.7 (16.1)	2.2 (17.7)
	Median	–2.0	1.0	0.5	–1.0	2.0	2.0
	Min to max	–37 to 34	–49 to 47	–47 to 43	–30 to 68	–46 to 45	–49 to 49
QRS interval							
Change	Mean (SD)	0.6 (7.6)	–0.8 (6.5)	0.0 (6.5)	0.1 (9.7)	–0.2 (8.3)	0.9 (6.5)
	Median	1.0	–1.0	0.0	0.0	–1.0	1.0
	Min to max	–23 to 19	–15 to 20	–13 to 18	–33 to 30	–19 to 19	–14 to 24
QT interval							
Change	Mean (SD)	–4.3 (29.6)	–8.8 (25.6)	–8.6 (30.2)	–5.7 (32.0)	–9.6 (32.1)	–12.0 (26.9)
	Median	–5.0	–8.0	–12.0	–6.0	–8.5	–9.0
	Min to max	–76 to 49	–74 to 60	–80 to 56	–91 to 81	–124 to 47	–81 to 33
QTC_F interval							
Change	Mean (SD)	–2.7 (16.6)	–0.3 (19.9)	1.1 (22.3)	3.9 (20.6)	–1.0 (21.5)	–1.0 (17.4)
	Median	–4.0	2.0	1.0	7.0	1.5	–2.5
	Min to max	–40 to 51	–56 to 49	–59 to 65	–40 to 56	–88 to 41	–46 to 53

F Fridericia correction. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release. SD Standard deviation.
Data derived from Tables 11.3.5.1.2, Section 11.3.

8.6.2.2 Individual patient changes in ECG findings

Of patients with normal ECG results at baseline, almost 90% or more in each treatment had normal ECG results at the final visit. Changes in ECG results from baseline (normal/abnormal) to final visit (normal/abnormal) are shown in Table 57, by treatment group.

Incidences of treatment-emergent clinically important values are summarized in Table 58, by treatment group for applicable parameters.

In a Cochran-Mantel-Haenszel analysis of clinically important results in ECG rates and intervals, differences among treatment groups were not significant (p=0.837) (see Table 11.3.5.1.3 [Section 11.3]).

Table 57 ECG evaluation: shift table of change from baseline at final visit (safety population)

	Nmber of patients by ECG result at final visit											
	Placebo (n=69)		QTP SR 300 mg (n=76)		QTP SR 600 mg (n=78)		QTP SR 800 mg (n=71)		QTP IR 300 mg (n=73)		QTP IR 600 mg (n=66)	
Baseline ECG result	**Abn**	**Norm**	**Abn**	**Norm**	**Abn**	**Norm**	**Abn**	**Norm**	**Abn**	**Norm**	**Abn**	**Norm**
Abnormal	6	4	10	4	6	7	11	3	7	3	7	3
Normal	2	57	3	59	6	59	3	54	3	60	5	51
Total	8	61	13	63	12	66	14	57	10	63	12	54

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.5.1.4, Section 11.3.

Table 58 ECG data—incidence of treatment-emergent clinically important values at final visit (safety population)

ECG parameter	Number (%) of patients													
	Placebo (n=66)		QTP SR 300 mg (n=75)		QTP SR 600 mg (n=76)		QTP SR 800 mg (n=71)		QTP SR Total (n=222)		QTP IR 300 mg (n=74)		QTP IR 600 mg (n=66)		QTP IR Total (n=140)	
Shift to high																
Heart rate (≥15 bpm increase)[a]	11	(16.7)	15	(20.0)	19	(25.0)	17	(23.9)	51	(23.0)	21	(28.4)	20	(30.3)	41	(29.3)
PR interval (≥210 msec)	0		0		0		0		0		1	(1.4)[b]	1	(1.5)	2	(1.4)[b]
QRS interval (≥120 msec)	0		0		0		1	(1.4)	1	(0.5)	0		0		0	
QT interval (≥60 ms increase)[a]	0		1	(1.3)	0		2	(2.8)	3	(1.4)[c]	0		0		0	
QTc interval$_{(F)}$ (≥450 msec)	0		1	(1.3)[d]	0		0		1	(0.5)[d]	0		0		0	
QTc interval$_{(F)}$ (≥60 msec increase)[a]	0		0		1	(1.3)[e]	0		1	(0.5)[e]	0		0		0	
Shift to low																
Heart rate (<50 bpm)	1	(1.6)[f]	2	(2.8)[f]	0		0		2	(0.9)	0		0		0	
Heart rate (≥15 bpm decrease)[a]	9	(13.6)	4	(5.3)	8	(10.5)	5	(7.0)	17	(7.7)	5	(6.8)	2	(3.0)	7	(5.0)

[a] From baseline.
[b] N=73 for IR 300 mg and N=139 for IR total.
[c] Final values of 394, 410, and 426 ms (from 334, 329, and 359 ms at baseline, respectively, for SR 300-, SR 600-, and SR 600-mg treatment groups).
[d] Final value of 461 ms (from 438 ms at baseline).
[e] Final value of 404 ms (from 339 ms at baseline).
[f] N=64 for placebo, N=71 for SR 300 mg, and N=216 for SR total.
F Fridericia adjustment. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.5.1.5, Section 11.3.

8.6.2.3 Individual clinically important ECG abnormalities

In some cases, isolated shifts to high, clinically important QTc_F values or PR intervals or to low, clinically important heart rates were of particular interest given the known effects of quetiapine; these abnormalities are described in more detail in the subsections that follow.

(a) QTc_F abnormalities

One patient (Patient 0032/0373, SR 300 mg) had a shift from normal QTc_F interval at baseline (0.438 ms) to a high, clinically important value at the final value (0.461 ms). No concurrent cardiovascular AEs were noted, and all parameters on the final ECG report were normal. The patient had a history of asthma, dyspepsia, gastroesophageal reflux disease, high cholesterol and hypertension; prior medications reflected the treatment of these conditions. During the study, the patient did not use concomitant medications and reported only 1 AE (dry mouth). The patient completed the study.

One additional patient (Patient 0009/0103, SR 600 mg) had an increase in QTc_F of ≥60 ms, from 339 ms at baseline to 404 ms at the final visit (+65 ms). The patient entered the study with an overall abnormal ECG report due to ectopic atrial rhythm and flat T-wave. At the final visit, the overall ECG report was normal with sinus tachycardia noted. AEs during the study included mild bradycardia and hypertension, neither assessed as drug related. The patient had a history of anxiety, asthma, right eye blindness, menopause, obesity and headaches. Concomitant medications included risperidone, acetaminophen, antacids, and trimethobenzamide. The patient withdrew from the study after 5 days of treatment (4 days at SR 300 mg, 1 day at SR 600 mg) for lack of treatment efficacy.

(b) PR interval abnormalities

Two patients treated with quetiapine IR had clinically important PR intervals at the final visit. Both patients completed the study. Additional details follow:

Patient 0064/1100 (IR 300 mg) had a PR interval of 181 ms at baseline and 214 ms at the final visit. The final ECG report indicated normal parameters for all but conduction, which was evaluated as abnormal because of 1st degree block. No concurrent cardiovascular events were noted. The patient had a history of hypertension, insomnia, knee surgery, spine surgery for herniated disk, and milk allergy; prior medications reflected treatment of these conditions. During the study, the patient used metoprolol for hypertension, lorazepam for agitation, zolpidem for sleep, and acetaminophen and cyclobenzaprine for back pain.

Patient 0026/1046 (IR 600 mg) had a PR interval of 203 ms at baseline and 210 ms at the final visit. Both baseline and final ECG reports indicated a conduction abnormality of 1st degree block. Cardiovascular events during treatment included hypotension, tachycardia, and orthostatic hypotension—all of which were considered mild but drug-related. The patient's medical history was extensive and included 1st degree AV block, dizziness upon standing, and tardive dyskinesia; prior medications included treatment for psychosis, insomnia, and EPS,

not but for cardiac arrhythmia. During the study, the patient used zolpidem for sleep and docusate sodium and magnesium hydroxide for constipation.

(c) Low, clinically important heart rates

Three patients had low, clinically important heart rates at the final visit. The final ECG report for each patient indicated an overall normal ECG, but with sinus bradycardia noted as a rhythm abnormality. Despite changes to low, clinically important values at the final visit, changes were small, ranging between –3 and –7 bpm. Additional details follow:

Patient 0009/0236 (placebo) had heart rates of 52 bpm at baseline and 49 bpm at the final visit. During the study, the patient had 3 episodes each of postural orthostatic hypotension and hypertension reported as AEs (mild and not drug related). The patient recovered and completed the study, without the need for concomitant medication. The patient's medical history included depression, GI reflux, and headaches.

Patient 0015/0046 (SR 300 mg) had heart rates of 54 bpm at baseline and 48 bpm at the final visit. The patient had unremarkable medical and medication histories, no treatment-emergent AEs (cardiovascular or otherwise), and completed the study without the need for concomitant medication.

Patient 0043/0076 (SR 300 mg) had heart rates of 50 bpm at baseline and 43 bpm at the final visit. No concurrent cardiovascular AEs were noted. The patient had a history of EPS, migraine headaches, peptic ulcer, and thigh injury, with prior medications reflective of treatment for EPS and ongoing psychosis. The patient completed the study without the need for concomitant cardiac medication.

8.6.3 Physical findings and other observations related to safety

8.6.3.1 Physical examination

Confirmations of physical and ophthalmological examinations are provided in Listing 12.2.4.2 (Section 12.2). Confirmation of new or worsening findings at the final visit were uncommon.

8.6.3.2 Weight and BMI

(a) Changes from baseline at final visit

Descriptive statistics for weight and weight change at the final visit (LOCF) and at Day 42 (OC) are summarized in Table 59.

Table 59 Weight: change from baseline at final visit (LOCF) and Day 42 (OC) (safety population)

Weight (kg)		Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP IR 300 mg	QTP IR 600 mg
LOCF							
N (baseline, final)		78, 80	85, 88	83, 91	80, 86	83, 88	78, 81
Baseline	Mean (SD)	84.0 (20.0)	81.9 (19.5)	90.9 (26.2)	89.6 (21.3)	85.9 (20.3)	86.3 (20.0)
Final	Mean (SD)	85.2 (19.9)	84.5 (20.8)	92.7 (26.6)	90.4 (21.3)	87.7 (20.0)	89.4 (20.3)
Change	Mean (SD)	0.1 (2.8)	1.2 (3.0)	1.2 (6.2)	1.1 (3.2)	1.1 (3.3)	2.1 (4.0)
	Median	0.0	0.4	1.0	0.9	0.7	0.9
	Min to max	–6.4 to 10.8	–6.0 to 14.5	–40.5 to 25.5	–10.9 to 14.5	–9.6 to 12.3	–3.7 to 19.1
Observed case							
N		30	37[a]	41	44	43	34
Day 42	Mean (SD)	81.9 (17.5)	89.4 (24.4)	93.8 (28.3)	91.5 (23.4)	91.1 (23.6)	89.0 (21.1)
Change	Mean (SD)	0.5 (3.5)	2.3 (3.7)	2.0 (5.5)	1.8 (3.2)	1.9 (3.9)	3.4 (4.4)
	Median	0.3	1.8	1.3	1.4	1.9	3.2
	Min to max	–5.8 to 10.8	–6.0 to 14.5	–8.2 to 25.5	–3.7 to 14.5	–7.3 to 12.3	–3.7 to 19.1

[a] N=36 for change values.
LOCF Last observation carried forward. OC Observed case.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.3.6.1.1.1 and 11.3.6.1.1.2, Section 11.3.

At the final visit, patients treated with quetiapine SR had small increases in mean weight of just over 1 kg; changes did not increase with increasing SR dose. Patients treated with placebo had little to no change in mean weight (+0.1 kg). Mean changes with quetiapine SR were similar to that seen with quetiapine IR 300 mg (+1.1 kg) and slightly less than that seen with quetiapine IR 600 mg (+2.1 kg).

Patients treated with quetiapine SR who completed 42 days of treatment had small increases in mean weight of +2.3, +2.0 and +1.8 kg (low to high dose). These increases were marginally greater than corresponding LOCF values. For placebo-treated patients who completed 42 days of treatment, change in mean weight was smaller (+0.5 kg) overall. At Day 42, mean changes with quetiapine SR were similar to that seen with quetiapine IR 300 mg (+1.9 kg) and slightly less than that seen with quetiapine IR 600 mg (mean, +3.4 kg).

For patients treated with quetiapine SR, mean change in BMI at the final visit (LOCF) was approximately +0.4 kg/m^2 in each treatment group; this small increase was greater than that seen with placebo (0.02 $kg/m^{2)}$, similar to that seen with quetiapine IR 300 mg (+0.36 kg/m^2), and less than that seen with quetiapine IR 600 mg (+0.71 kg/m^2).

Full descriptive statistics for weight and BMI (all patients and patients by sex), change in weight and BMI (all patients and patients by sex), and change in weight and BMI, by BMI category, are summarized by visit and treatment group in Tables 11.3.6.1.1.1, 11.3.6.1.1.2, and 11.3.6.1.1.3, respectively (Section 11.3).

(b) Clinically important increases in weight

Clinically important weight gain (ie, an increase of ≥7%) at the final visit or Day 42 is summarized in Table 60 for all patients by treatment group and for all patients by treatment group and baseline BMI.

Table 60 Weight data: patients with ≥7% weight increase from baseline to final visit (LOCF) and Day 42 (OC), overall and by baseline BMI (safety population)

	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP SR Total		QTP IR 300 mg		QTP IR 600 mg		QTP IR Total	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Final visit	80	1 (1.3)	87	7 (8.0)	91	7 (7.7)	86	3 (3.5)	264	17 (6.4)	88	6 (6.8)	81	12 (14.8)	169	18 (10.7)
Day 42	30	1 (3.3)	36	4 (11.1)	41	5 (12.2)	44	3 (6.8)	121	12 (9.9)	43	6 (14.0)	34	9 (26.5)	77	15 (19.5)
Final visit, by baseline BMI (kg/m^2)																
Missing	0		0		1	0	1	0	2	0	0		0		0	
0 to <18.5	0		1	1 (100)	1	0	0		2	1 (50.0)	1	1 (100)	0		1	1 (100)
18.5 to <25	29	1 (3.4)	33	4 (12.1)	23	4 (17.4)	22	2 (9.1)	78	10 (12.8)	25	1 (4.0)	24	7 (29.2)	49	8 (16.3)
25 to <30	22	0	25	2 (8.0)	28	0	32	0	85	2 (2.4)	32	3 (9.4)	25	2 (8.0)	57	5 (8.8)
30 to <40	22	0	21	0	26	3 (11.5)	21	0	68	3 (4.4)	23	1 (4.3)	26	2 (7.7)	49	3 (6.1)
≥40	7	0	7	0	12	0	10	1 (10.0)	29	1 (3.4)	7	0	6	1 (16.7)	13	1 (7.7)
Day 42, by baseline BMI (kg/m^2)																
Missing	0		0		0		1	0	1	0	0		0		0	
0 to <18.5	0		0		1	0	0		1	0	1	1 (100)	0		1	1 (100)
18.5 to <25	15	1 (6.7)	11	2 (18.2)	12	3 (25.0)	12	2 (16.7)	35	7 (20.0)	11	1 (9.1)	11	5 (45.5)	22	6 (27.3)
25 to <30	6	0	13	2 (15.4)	12	0	15	0	40	2 (5.0)	18	3 (16.7)	10	2 (20.0)	28	5 (17.9)
30 to <40	6	0	8	0	11	2 (18.2)	10	0	29	2 (6.9)	7	1 (14.3)	11	1 (9.1)	18	2 (11.1)
≥40	3	0	4	0	5	0	6	1 (16.7)	15	1 (6.7)	6	0	2	1 (50.0)	8	1 (12.5)

BMI Body mass index. LOCF Last observation carried forward. OC Observed case.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.3.6.1.1.4 and 11.3.6.1.1.5, Section 11.3.

Through the final visit, a weight gain of ≥7% relative to screening weight was seen in 1 (1.3%) placebo-treated patient; in 3 to 7 (3.5% to 8.0%, high to low dose) patients treated with quetiapine SR (6.4% overall); and in 6 (6.8%) and 12 (14.8%) patients treated with quetiapine IR 300 and IR 600 mg, respectively (10.7% overall). Among patients completing 42 days of treatment, proportions of patients with ≥7% increases in weight increased slightly for each treatment group (Table 60).

Of quetiapine SR-treated patients with clinically important weight gain at the final visit, the greatest proportion per treatment group had baseline BMI values of 18.5 to <25 kg/m^2. This was consistent with patterns of weight gain typically seen with quetiapine, ie, greater weight gain in patients with lower BMI values. The 1 placebo-treated patient with clinically important weight gain also had a baseline BMI of 18 to <25 kg/m^2. Of quetiapine IR-treated patients with clinically important weight gain at the final visit, patients predominantly had baseline BMI values of 18 to <25 kg/m^2 or 25 to <30 kg/m^2.

Clinically important weight gains among patients with lowest or highest BMI values were infrequent, ie, in only 1 patient each treated with SR 300 mg and IR 300 mg (baseline BMI <18.5 kg/m^2) and in 1 patient each treated with SR 800 mg and IR 600 mg (baseline BMI >40 kg/m^2).

Patterns were similar when Day 42 (observed case) data were considered.

No patients were withdrawn because of changes in weight.

8.6.3.3 Metabolic syndrome risk factors

Among patients with 1 risk factor for metabolic syndrome at baseline, more than 70% in each treatment group had <3 risk factors at the end of treatment. Proportions of patients with ≥3 risk factors at the end of treatment were variable across treatment groups: 4.2% (1 of 24) and 5.6% (1 of 18) with SR 300 and IR 600 mg, respectively; 16.7% (3 of 18) and 15.8% (3 of 19) with placebo and SR 600 mg, respectively, and 23.5% (4 of 17) and 29.4% (5 of 17) with SR 800 and IR 300 mg, respectively.

Among patients with 2 risk factors for metabolic syndrome at baseline, slightly greater proportion of patients treated with placebo (47.4% [9 of 19]) and IR 600 mg (50.0% [8 of 16]) had ≥3 risk factors at the end of treatment (fasting criteria for glucose applied)—compared with proportions of patients in the other treatment groups (35.7% [5 of 14], SR 300 mg; 31.3% [5 of 16], SR 600 mg, 20.0% [4 of 20], SR 800 mg, and 27.3% [6 of 22], IR 300 mg).

One patient with zero risk factors at baseline had ≥3 metabolic risk factors at end of treatment (IR 300 mg, 8.3% [1 of 12]). Full shift tabulations are provided Table 11.3.6.2.1 (Section 11.3).

Incidence of treatment-emergent risk of metabolic syndrome is summarized in Table 61 for all patients regardless of their individual risk factors and for all patients with the triglyceride risk factor excluded (fasting criteria for glucose applied).

Table 61 **Incidence of treatment-emergent risk of metabolic syndrome with triglycerides included and excluded as a risk factor: fasting glucose criteria applied (safety population)**

Metabolic syndrome	Placebo			QTP SR 300 mg			QTP SR 600 mg			QTP SR 800 mg			QTP IR 300 mg			QTP IR 600 mg		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Shift to ≥3 risk factors																		
Triglycerides included	53	12	(22.6)	52	6	(11.5)	49	8	(16.3)	49	8	(16.3)	51	12	(23.5)	39	9	(23.1)
Triglycerides excluded	58	8	(13.8)	62	2	(3.2)	56	10	(17.9)	58	5	(8.6)	63	9	(14.3)	49	7	(14.3)

QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Table 11.3.6.2.2, Section 11.3.

Despite mean increases in triglyceride concentrations and small increases in mean BMI over time among quetiapine SR-treated patients, the risk of metabolic syndrome based on the presence of at least 3 risk factors did not appear to increase in these patients compared with that in placebo-treated patients.

When triglycerides were excluded as a risk factor (criteria for fasting glucose applied), the proportions of patients at risk for metabolic syndrome decreased in all but the SR 600-mg treatment group, and in that group, the proportion remained similar. This finding appears anomalous given that similar proportions of patients across treatment groups had shifts in triglycerides to values greater than 150 mg/dL; however, results may have been influenced, in part, by the use of fasting glucose criteria. When those criteria were replaced with random glucose criteria and triglycerides were excluded as a risk factor, the proportion of patients at risk for metabolic syndrome decreased in each treatment group. Although under these conditions, risk was slightly greater for SR 600- and SR 800-mg treated patients, compared with placebo and SR 300-mg treated patients. Risk for IR-treated patients was similar to that for patients treated with SR 600 and SR 800 mg.

Frequencies of patients at risk for metabolic syndrome and with individual risk factors are tabulated by treatment group in Table 11.3.6.2.2 (Section 11.3).

8.6.3.4 EPS rating scale assessments

(a) Simpson-Angus total score

At Day 42 (LOCF), patients treated with placebo had a mean Simpson-Angus Scale total score (11.4) similar to those of patients treated with quetiapine SR (11.2, 11.3, and 10.9 [low to high dose]), who had scores similar to patients treated with quetiapine IR (11.3 to 11.7). Mean changes from baseline (all in the negative direction) indicated small but similar degrees of improvement in each treatment group: –0.6 with placebo, –0.5 to –0.8 with quetiapine SR, and –0.4 to –0.6 with quetiapine IR.

Minimal differences between treatment groups in change from baseline at Day 42 (LOCF) suggest that magnitude of change was not dose dependent or alternately prohibit conclusions in terms of dose response.

Observed data show similar Simpson-Angus Scale total scores across treatment groups at Day 42. Some differences, compared with LOCF data, were seen for patterns of change from baseline: a greater decrease was observed for placebo (–1.6 vs –0.6 LOCF), a slightly smaller decrease was observed for SR 800 mg (–0.3 vs –0.5 LOCF), and a slightly greater decrease was observed for IR 300 mg (–1.0 vs –0.4 LOCF). Nonetheless, conclusions based on observed data are similar to those for LOCF data. For both data sets, consistently small changes from baseline point more to similarities among treatment groups than to differences.

Complete descriptive statistics are provided in Tables 11.3.6.3.2.1.1 through 11.3.6.3.2.1.4 (Section 11.3).

When EPS status was considered in relative terms (improved, no change, or worsened), patterns also showed that the majority of patients in each treatment group either improved or did not change relative to baseline: placebo, 76%; SR-treated patients, 83%, 79% and 82% (low to high dose, 81% overall); and IR-treated patients, 80% and 82% (low to high dose, 81% overall). The proportion of SR-treated patients with worsening status (19%) was smaller than that for placebo-treated patients (24%) and similar to that seen for IR-treated patients (19%). Among SR- and IR-treated patients, worsening status did not appear related to increasing dose of quetiapine (SR low to high dose, 17%, 21%, and 18%; IR low to high dose, 20% and 18%). Complete data are provided in Table 11.3.6.3.2.1.5 (Section 11.3).

(b) AIMS total scores

At Day 42 (LOCF), mean AIMS scores were lower than their corresponding baseline scores in each treatment group, with scores for patients treated with quetiapine SR (1.9, 1.5, and 1.4 [low to high dose]) lower than that for patients treated with placebo (2.2). Mean AIMS scores at Day 42 for patients treated with quetiapine IR were similar: 1.7 with IR 300 mg and 2.1 with IR 600 mg.

For each treatment group, magnitude of change was small: –0.2 with placebo, –0.2 to –0.4 with quetiapine SR, and –0.2 to –0.4 with quetiapine IR. Differences in change from baseline at Day 42 were not significant between placebo and each quetiapine SR treatment group ($p \geq 0.354$, ANCOVA, LOCF). A similar finding was seen in comparisons between placebo and each quetiapine IR treatment group. Statistical comparisons between quetiapine SR and IR treatment groups were not performed.

Observed data support LOCF data showing very small, mostly decreases from baseline in AIMS scores over time and across treatment groups, with median scores and median changes of zero at each study visit for all treatments.

Descriptive statistics by study day and ANCOVA results are provided in Tables 11.3.6.3.1.1.1 through 11.3.6.3.1.1.5 in Section 11.3.

When status for abnormal involuntary movement was considered in relative terms (improved, no change, or worsened), results showed that the majority of patients in each treatment group either improved or did not change relative to baseline: placebo, 81%; SR-treated patients, 77%, 80% and 87% (low to high dose, 82% overall); and IR-treated patients, 82% and 87% (low to high dose, 84% overall). The proportion of SR-treated patients with worsening status (18%) was similar to that for placebo-treated patients (20%) and IR-treated patients (16%). Among SR-treated patients, the proportion of patients with a worsened status decreased as the quetiapine dose increased across treatment groups (22.7%, 19.8%, and 12.5%, low to high dose). A similar, reverse dose-response was seen for IR-treated patients (17.8% with IR 300 mg; 13.3% with IR 600 mg). Complete data are provided in Tables 11.3.6.3.1.1.6 and 11.3.6.3.1.1.7 (Section 11.3).

(c) BARS Clinical Global Assessment scores

At Day 42 (LOCF), mean BARS global assessment scores remained close to zero (0.4 to 0.5), with median scores of zero for each treatment group. Mean changes from baseline were in the negative direction (–0.2 to –0.1), with a median change of 0.0 seen for each treatment group. Similarities among the placebo and quetiapine SR treatment groups, and among quetiapine SR and IR treatment groups, indicate no increased risk of akathisia with quetiapine treatment compared with placebo treatment. Observed data support this finding (see Tables 11.3.6.3.3.1.1 through 11.3.6.3.3.1.4, Section 11.3).

When akathisia status was considered in relative terms (improved, no change, or worsened), results showed that nearly 90% of quetiapine SR- and IR-treated patients, and 84% of placebo-treated patients, either improved or did not change relative to baseline. Thus, the proportion of SR-treated patients with worsening status (11%) was similar to that for IR-treated patients (11%) and less than that for placebo-treated patients (16%). Dose trends for worsening akathisia were not evident among patients treated with quetiapine SR. Complete data are provided in Table 11.3.6.3.3.1.5 (Section 11.3).

(d) Use of anticholinergic medications for treatment of EPS

The use of anticholinergic agents to treat EPS was limited, with a greater percentage of placebo-treated patients using anticholinergics in general (14.3%, safety population), compared with patients treated with quetiapine SR (4.5% to 10.9%) or quetiapine IR (3.5% to 6.7%). Increasing the dose of quetiapine SR across the dose range did not increase the use of EPS-related medication. A comparison between the placebo and quetiapine SR treatment groups shows that use of anticholinergics was most similar among placebo-treated patients and patients treated at the SR 600-mg dose: 14.3% and 10.9%, respectively, used anticholinergics in general; 10.7% and 7.6%, respectively, used benztropine mesylate; and 4.8% and 4.3%, respectively, used diphenhydramine (see Table 23).

These data reflect the findings of little or no treatment-emergent EPS as determined from Simpson-Angus Scale total scores, AIMS scores, and BARS scores for the global assessment of akathisia.

8.6.4 Discussion of vital signs, ECG, physical findings and other observations related to safety

Treatment with quetiapine SR produced predictable increases in pulse rate similar to changes seen with quetiapine IR. Changes in supine blood pressures were small and tended to be variable. Clinically important changes in supine vital signs were seen in all treatment groups including placebo, with clinically important increases in pulse rate (≥15 bpm) the most frequent event, occurring in similar proportions of placebo-, quetiapine SR-, and quetiapine IR-treated patients. Supine pulse rates greater than 120 bpm were rare, and in fact were seen in only 1 patient (SR 800 mg); standing pulse rates greater than 120 bpm were seen in all treatment groups, although in slightly greater proportions of patients treated with quetiapine SR and IR, compared with placebo. Clinically important increases in heart rate, as confirmed

by ECG, was also a consistent finding across treatment groups. While mean increases in QTc_F interval were seen at the SR 600 and 800-mg doses, clinically important changes from baseline were isolated (in 1 patient each treated with SR 300 mg and SR 600 mg). Patients who completed 42 days of quetiapine SR had small mean increases in weight of ≤2.3 kg across treatment groups, with the smallest mean increase seen at the SR 800-mg dose (+1.8 kg). For these patients, a clinically important weight gain (≥7% increase) was more commonly associated with a baseline BMI in the range of 18.5 to < 25 kg/m^2, an effect also seen with quetiapine IR. The risk of metabolic syndrome based on the presence of at least 3 risk factors did not appear to increase with quetiapine SR or quetiapine IR treatment, compared with placebo treatment. Results of neurological assessments (showing improvement or no change in the majority of patients treated), limited use of anticholinergics after the second week of treatment, and no EPS-related withdrawals suggest no pattern of treatment-emergent EPS for quetiapine SR.

8.6.5 Integrated discussion of specific safety areas

8.6.5.1 EPS

Incidences of extrapyramidal disorder (MedDRA preferred term) were low: 2.4%, 2.2%, and 0% among patients treated with placebo, quetiapine SR, and quetiapine IR, respectively.

The individual AEs that were predesignated as potentially related to EPS occurred infrequently, were not serious, rarely led to withdrawal, and were rated either mild or moderate. Those that did lead to withdrawal (1 episode each of dyskinesia and akathisia) occurred in 1 patient treated with quetiapine IR 600 mg. The events started on Day 4 of treatment (first day at 300 mg [150 mg morning and evening]), were of moderate intensity, and lasted 1 day. When AEs potentially related to EPS were aggregated, incidence rates were similar between quetiapine SR- and quetiapine IR-treated patients (11.0% and 9.7%), with these rates somewhat greater than placebo rates (4.8%).

On each neurological assessment scale (Simpson-Angus, AIMS, BARS clinical global assessment), small mean decreases from baseline were similar among treatment groups including placebo. The majority of patients overall were either improved or unchanged when EPS, abnormal involuntary movements, and akathisia were judged on a relative basis; furthermore, on each scale, slightly greater proportions of placebo-treated patients worsened, compared with quetiapine-treated patients (SR and IR).

During the study, anticholinergic use for the treatment of EPS was greatest among placebo-treated patients, which may have obscured true treatment-emergent EPS rates for that group of patients. In addition, anticholinergic use prior to study entry—in more than 33% of patients per treatment group—suggests that EPS issues were present before the start of study treatment. Importantly, the use of anticholinergics did not increase over time in any treatment group, a finding consistent with results of neurological assessments.

Thus, in overview, the data support conclusions of limited or no treatment-emergent EPS with quetiapine SR.

8.6.5.2 QT prolongation

No AEs associated with QT prolongation were reported. Small decreases in mean and median QT interval were seen in each treatment group. Single isolated increases in QT interval of ≥60 ms from baseline to final visit were seen in 3 patients treated with quetiapine SR (1 SR 300 mg; 2 SR 800 mg); however, final values remained below 500 ms.

Small increases in mean QTc_F interval were seen with SR 600 and SR 800 mg, while small decreases in mean values were seen in the other treatment groups. Clinically important changes from baseline in QTc_F were isolated, in 1 patient each treated with SR 300 mg and SR 600 mg; changes resulted in final values of 461 ms and 404 ms, respectively.

Patterns to suggest treatment-emergent QT prolongation with quetiapine SR were not evident.

8.6.5.3 Diabetes mellitus

Of the AEs predesignated as potentially related to diabetes mellitus (Table 7), only the AEs of polyuria, blood glucose increased, hyperglycemia, and thirst were reported. All occurred in ≤1 patient per treatment group, with no patterns to suggest dose-related trends among quetiapine-treated patients. Under assumed fasting conditions (all patients), mean changes in glucose from baseline to final visit were <9 mg/dL all treatment groups. Less than 10 patients per treatment group had diabetes at study entry. Mean and median changes in glucose for these patients were variable but predominantly in the negative direction. Under assumed fasting conditions, the proportions of patients with treatment-emergent clinically important glucose values were similar among placebo-, SR-, and IR-treated patients. The same pattern was seen when random blood sampling was assumed. Only 1 patient with a clinically important, elevated blood glucose had the event recorded as an AE (as noted previously). Overall, <3% of patients were confirmed as fasting at the time that blood samples were taken for glucose analysis. Sampling time data also show a trend toward mid to late day sampling at the final visit, making it more likely that patients were not in fasted condition. Therefore, conclusions regarding the affects of quetiapine SR on glucose regulation cannot be made with an acceptable degree of certainty.

8.6.5.4 Metabolic syndrome risk factors

The risk of metabolic syndrome based on the presence of at least 3 risk factors did not appear to increase with quetiapine SR or quetiapine IR treatment, compared with placebo treatment, this despite mean increases in triglycerides and small mean increases in BMI over time for patients treated with quetiapine SR.

8.6.5.5 Neutropenia and agranulocytosis

No AEs potentially related to neutropenia or agranulocytosis were identified. Low clinically important neutrophil counts were identified for 2 patients from blood sample analysis (1 each treated with SR 800 mg and IR 600 mg). For these patients, baseline values were either low or at the low end of normal (normal reference range) and did not fall to $<0.5 \times 10^9$ cells/L. For 1 patient with available follow-up, absolute neutrophil count (2.39×10^9 cells/L) had returned

to normal 11 days after the final visit. The results of this study suggest that quetiapine SR treatment is not associated with treatment-emergent neutropenia or agranulocytosis.

8.6.5.6 Safety of starting dose and dose escalation

The quetiapine SR dose-administration scheme, which included a starting dose of SR 300 mg on Day 1, a dose increase to SR 600 mg on Day 4, and another dose increase to SR 800 mg on Day 8 (for patients assigned to the higher 2 doses), was generally safe and well tolerated. This was evident in incidences of AE-related withdrawals and SAEs that were similar to or lower than those seen with placebo. For SR-treated patients who did withdraw because of AEs, onset was not consistently associated with either start of treatment or dose increase. No patients died.

The most commonly reported AEs with quetiapine SR were—by decreasing incidence rate—orthostatic hypotension, sedation, headache, dry mouth, somnolence, and dizziness, with incidence rates for all but headache greater when compared with rates in the placebo group. Rates for SR-treated patients were similar to those seen for IR-treated patients, with a slightly greater overall incidence of dry mouth among SR-treated patients. In SR and IR treatment groups, onset of AEs related to somnolence, tachycardia, postural hypotension, and dizziness was generally within the first 2 weeks of treatment and for somnolence, postural hypotension, and dizziness, onset was predominantly within the first 7 days. In general, increases in SR dose to reach target doses did not produce consistent dose-related changes in safety indices. The overall AE profile for quetiapine SR was similar to the AE profile seen with quetiapine IR.

8.7 Conclusions on safety results

Safety conclusions as they relate to specific safety objectives and the study variables selected to address these objectives are presented in Table 62.

Table 62 Safety objectives, variables, and conclusions

Objectives	Variables	Conclusions
To assess the following: The tolerability and safety of quetiapine SR tablets administered once daily as compared with placebo in patients with schizophrenia The similarity of the safety profiles of quetiapine SR tablets and marketed quetiapine IR tablets The tolerability and safety of quetiapine SR therapy initiated at a dose of 300 mg	Adverse events (AEs) in the following categories: • All AEs; drug-related AEs; serious AEs (SAEs); AEs leading to withdrawal (DAEs) • Special-interest AEs, including somnolence, tachycardia, and postural hypotension (and related AEs), dizziness, and syncope • Special safety-area AEs, including AEs related to EPS, QT prolongation, diabetes mellitus, neutropenia or agranulocytosis, and suicidality	Quetiapine SR was generally safe and well tolerated across the dose range of 300 to 800 mg in the treatment of patients with acute exacerbation of schizophrenia. Compared with placebo, treatment with quetiapine SR did not increase incidences of SAEs or AEs leading to treatment withdrawal. Incidences of AEs and drug-related AEs with quetiapine SR were about 10% greater compared with placebo, and similar to rates seen with quetiapine IR. AEs were generally characterized as mild or moderate. The types of AEs most commonly reported with quetiapine SR and IR were similar (orthostatic hypotension, headache, sedation or somnolence, tachycardia or increased heart rate, and dry mouth). Onset of special-interest AEs was most common during the first 14 days of SR or IR treatment, with trends toward first occurrence by Day 7. Incidence rates of EPS-related AEs were similar between SR and IR-treated patients, with rates somewhat greater than placebo rates; however, anticholinergic use for the treatment of EPS was greatest among placebo-treated patients, possibly obscuring true rates for EPS-related AEs. Treatment with quetiapine SR did not lead to increased incidences of other special safety-area AEs, compared with placebo or quetiapine IR. A quetiapine SR 300-mg starting dose and the dose-administration schedule used to escalate daily dose to 800 mg were well tolerated. Dose initiation at the SR 300-mg dose did not result in increased incidences of early withdrawal or increased rates of AEs assessed as drug-related, compared with IR 300 mg. Increases in SR dose did not produce consistent dose-related changes in safety indices. The overall AE profile for quetiapine SR was similar to the AE profile seen with quetiapine IR.

Table 62 Safety objectives, variables, and conclusions

Objectives	Variables	Conclusions
	Clinical laboratory test results (hematology, clinical chemistry) at baseline (Day 1) and Day 42 or final visit, changes from baseline, and results categorized as clinically important per predefined criteria	Treatment with quetiapine SR produced no unexpected clinical laboratory findings, compared with known treatment effects of quetiapine IR. Shifts to clinically important laboratory values were infrequent. No shift in neutrophil count resulted in agranulocytosis. There was no evidence for treatment emergent hypothyroidism or diabetes.
	Vital signs (pulse rate and blood pressure), weight, and body mass index: results at baseline (Day 1) and each postbaseline visit, changes from baseline, and results categorized as clinically important per predefined criteria (including orthostatic changes)	Changes in vital signs showed an expected trend for increase in heart rate with quetiapine SR, which was similar to that seen with quetiapine IR. Small mean and median weight gains of about 2 kg were seen for patients who completed 42 days of quetiapine treatment (SR or IR).
	Electrocardiogram results at baseline (Day 1) and Day 42 or final visit; changes from baseline, and results categorized as clinically important per predefined criteria.	Although isolated episodes of clinically important changes in PR, QT, and QTc_F intervals were seen with quetiapine SR, no clear increase in risk, compared with placebo or quetiapine IR was evident. Incidences of heart rate increases of ≥15 bpm were seen with both SR (23%) and IR (29%) quetiapine.
	Simpson-Angus Scale total scores at baseline (Day 1) and each postbaseline visit; changes from baseline	On each neurological assessment scale, mean changes from baseline were similar among treatment groups, including placebo.
	AIMS total scores at baseline (Day 1) and each postbaseline visit; changes from baseline to each postbaseline visit; proportion of patients whose scores exceed the baseline score at any time during study treatment	On each neurological assessment scale, the majority of patients were either improved or unchanged. Use of anticholinergic medications did not increase over time with increased exposure to quetiapine SR.
	Barnes Akathisia Rating Scale Clinical Global Assessment score	
	Use of anticholinergic medications	

AIMS Abnormal Involuntary Movement Scale. IR Immediate release. SR Sustained release.

9. DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

This 6-week, multicenter, randomized, double-blind, parallel-group study compared the efficacy and safety of 3 doses of quetiapine SR with that of placebo in patients with acute exacerbation of schizophrenia (as demonstrated by PANSS total scores of ≥60 and CGI Severity of Illness scores of ≥4). In addition, this study provided an opportunity to explore similarities in the efficacy and safety profiles of the SR and IR formulations of quetiapine at 2 doses.

The study incorporated well-established outcome measures commonly used in the evaluation of patients with acute psychosis; additionally, investigators were trained for consistency on PANSS rating applications. The inclusion and exclusion criteria reflected criteria specifically developed for use in evaluating antipsychotics in short-term clinical efficacy studies; the overall population demographics, which closely reflected these criteria, were similar across treatment groups. There was good compliance with assigned treatment regimens, a condition achieved in part by having patients hospitalized minimally through the first 10 days of treatment. Differences between the planned analyses described in the protocol and those described in the statistical analysis plan were minor or reflected changes to allow consistency of reporting across clinical program documents.

The study's primary objective—to demonstrate superior efficacy of quetiapine SR compared with placebo in the treatment of patients with schizophrenia—was met for the quetiapine SR 600-mg dose. SR 600 mg also achieved consistent numerical (though not statistical) advantages, compared with placebo, on all secondary efficacy endpoints. The primary objective was not met for the SR 300- and SR 800-mg dose, although at the SR 800-mg dose, numerical advantages were seen over placebo.

The unusually high rates of withdrawal during Week 1, as well as continued high rates through Week 2, resulted in a nonnegligible proportion of patients having PANSS total and CGI scores more reflective of baseline values carried forward in efficacy analyses. Withdrawal before Day 7 meant that patients in the SR 800-mg treatment group had not yet reached their target dose and patients in the SR 600-mg treatment group were at their target dose for less than 3 days. Thus, patients did not have time to improve at their assigned doses before withdrawal.

In this study, the expected differentiation between placebo and quetiapine IR 300 mg and IR 600 mg was not seen, despite the established efficacy of these doses in reducing the symptoms of schizophrenia. With respect to exploration of the comparative efficacy of the 2 formulations, quetiapine SR 600 mg achieved efficacy versus placebo, while quetiapine IR 600 mg did not; neither formulation differed from placebo at the 300-mg dose.

Quetiapine SR was well tolerated across the dose range of 300 to 800 mg. Common AEs were those of the nervous, gastrointestinal, and vascular systems and included orthostatic hypotension, sedation or somnolence, headache, dry mouth, dizziness, and increased heart rate

or tachycardia, with AEs overall most often characterized as mild or moderate. Starting quetiapine SR at a dose of 300 mg was also well tolerated and did not lead to increased early incidences of the AEs commonly reported with quetiapine IR (eg, somnolence, tachycardia, postural hypotension, and dizziness) or increased incidences of AE-related withdrawals. AE incidence rates between quetiapine SR and IR were similar, with the rate of constipation slightly greater at the SR 300-mg dose, compared with the IR 300-mg dose. Increases in SR dose did not produce consistent dose-related changes in safety indices. At the highest SR dose of 800 mg, there were no serious AEs and only 1 AE-related withdrawal.

Incidence rates of EPS-related AEs were similar between SR and IR-treated patients, with rates somewhat greater than placebo rates; however, during the study, anticholinergic use for the treatment of EPS was greatest among placebo-treated patients, which may have obscured true treatment-emergent EPS rates. Anticholinergic use prior to study entry in more than 33% of patients per treatment group suggests that EPS issues were present before the start of study treatment. Importantly, the use of anticholinergics did not increase over time in any treatment group, a finding consistent with results of neurological assessments, which showed that the majority of patients (all treatment groups) either improved or did not change (ie, did not worsen) relative to EPS, abnormal involuntary movements, or akathisia.

Findings relative to other safety parameters, including laboratory results, vital sign changes, ECG changes, and metabolic syndrome risk factors, consistently showed similarities between the safety profiles of quetiapine SR and quetiapine IR.

9.2 Overall conclusions

- Quetiapine SR 600 mg, when given once daily, was more effective than placebo in improving the symptoms of schizophrenia, as shown by a statistically significant difference between treatments in decrease from baseline in PANSS total score through 42 days of treatment.

- Quetiapine SR 800 mg produced a numerically greater, though not statistically significant, improvement in disease symptoms, compared with placebo, as shown by a 2-fold greater decrease from baseline in PANSS total score through 42 days of treatment.

- The effects of quetiapine SR 300 mg and quetiapine IR 300 and 600 mg (commercial tablets) on psychotic symptoms at Day 42 were not significantly different from those of placebo, although a numerical advantage was seen with IR 300 mg compared with placebo.

- Quetiapine SR was safe and well tolerated in the treatment of schizophrenia across the dose range of 300 to 800 mg. The AEs most commonly seen with quetiapine SR were also commonly seen with quetiapine IR and included orthostatic hypotension, sedation or somnolence, headache, dry mouth, dizziness, and increased heart rate or tachycardia. Incidence rates of EPS-related AEs were

similar between SR and IR-treated patients, with neurological assessments suggesting little or no treatment emergent EPS.

- The overall safety profile for quetiapine SR was similar to the safety profile seen for quetiapine IR.

- A quetiapine SR 300-mg starting dose and the dose-administration schedule used to increase daily dose to 800 mg were well tolerated.

10. REFERENCE LIST

Arvanitis LA, Miller BG, Seroquel Trial 13 Study Group. Multiple fixed doses of Seroquel (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997;42:233-46.

Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672-6.

Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, LaBelle A, Beuclair L, Arnott W. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenia. J Clin Psychopharmacol 1993;13:25-40.

Citrome L, Jaffe A, Levine J, Lindenmayer J-P. Dosing of quetiapine in schizophrenia: how clinical practice differs from registration studies. J Clin Psychiatry 2005;66:1512-16.

Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rev ed. Rockville, Maryland: National Institute of Mental Health, 1976:534-7.

Guy W, Bonato RR.12-CGI Clinical Global Impression. In: Manual for the ECDEU Assessment Battery. 2nd Rev. ed. Washington, DC: US Department of Health, Education and Welfare; 1970:12.1-12.6.

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75(4):800-2.

Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenia: reliability and discriminative ability. Psychol Med 1983;13:177-83.

Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-76.

Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry. 1994;151:825-35.

Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.

Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Br J Psychiatry 1995;166(6):712-26.

Simpson GN, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970;212 (Suppl 44):11-19.

Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CGG, Seroquel Study Group. Quetiapine in patients with schizophrenia, a high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997;54:549-57.

White L, Harvey PD, Opler L, Lindenmayer JP. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. Psychopathology 1997;30(5):263-74.