Drug product:	Seroquel	**SYNOPSIS**	
Drug substance:	quetiapine fumarate		
Study code:	D1441C00112		
Date:	14 February 2008		

A 6-week, International, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

Study center(s)

This study was conducted at 43 international sites.

Publications

None at the time of this report.

Study dates		**Phase of development**
First patient enrolled	01 October 2004	IIIb (Therapeutic confirmatory)
Last patient completed	20 June 2007	

Objectives

The primary objective of this study was to compare the efficacy of 2 doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in the treatment of schizophrenia in adolescent patients as assessed by the change from baseline to Day 42 in the Positive and Negative Syndrome Scale (PANSS) total score (primary outcome variable). The primary hypotheses were as follows:

1. Quetiapine 400 mg/day is superior to placebo in reducing PANSS total score at Day 42 compared with baseline

2. Quetiapine 800 mg/day is superior to placebo in reducing PANSS total score at Day 42 compared with baseline

Secondary objectives were as follows:

1. To compare the effects of quetiapine 400 mg/day and quetiapine 800 mg/day with the effect of placebo on a broad range of schizophrenia symptoms, as assessed by the change from baseline to Day 42 in the Clinical Global Impression (CGI) Severity of Illness score, the CGI Global Improvement score at Day 42, the changes from baseline to Days 7 and 14 in the PANSS total score, the changes from baseline to Days 7, 14, and 42 in the PANSS positive symptom and negative symptom subscale scores, the changes from baseline to Days 7 and 14 in the CGI Severity of Illness score, and the percentage of patients with response, defined as a ≥30% reduction from baseline in the PANSS total score, at Day 42

2. To compare the effects of quetiapine 400 mg/day and quetiapine 800 mg/day with the effect of placebo on level of functioning, assessed by the change from baseline to Day 42 in the Children's Global Assessment Scale (CGAS) score

3. To compare the effects of quetiapine 400 mg/day and quetiapine 800 mg/day with the effect of placebo on agitation and aggression, as assessed by the changes from baseline to Days 7, 14, and 42 in the sum of scores for PANSS items S1, S2, and S3

4. To evaluate the safety and tolerability of quetiapine compared with placebo in the treatment of schizophrenia in adolescent patients, as assessed by the incidence and nature of adverse events (AEs), the changes from baseline to Day 42 in clinical laboratory test results (eg, prolactin concentration), vital signs, weight, body mass index (BMI), electrocardiogram (ECG) results, the Simpson-Angus Scale (SAS) total score, the Barnes Akathisia Rating Scale (BARS) global score, the Abnormal Involuntary Movement Scale (AIMS) total score, and the incidence of anticholinergic medication use for treatment of emergent extrapyramidal symptoms (EPS)

Exploratory objectives of this study were as follows:

1. To compare the effects of quetiapine 400 mg/day and quetiapine 800 mg/day with the effect of placebo on overall caregiver burden, as assessed by the change from baseline to Day 42 in the results of the Caregiver Strain Questionnaire (CGSQ)

2. To compare the efficacy of quetiapine 400 mg/day and quetiapine 800 mg/day with that of placebo, as assessed by the change from baseline to Day 42 in the PANSS-derived "BPRSd" total score (Brief Psychiatric Rating Scale (BPRS) score derived from the corresponding 18 items of the PANSS)

3. To establish a panel of DNA samples from those patients who provide separate consent, to enable future exploratory genetic research on potential associations with drug response (efficacy and safety/tolerability) and/or susceptibility to schizophrenia

Study design

This was a 6-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 800 mg/day) with placebo, given in divided doses (either twice daily [bid] or three times daily [tid], per the judgment of the investigator), in adolescent patients with schizophrenia. Patients were randomly assigned to blinded study treatment in a 1:1:1 ratio. Double-blind treatment was preceded by a medication washout period of 1 to 28 days (depending on the medications involved and at the discretion of the investigator) during which time the patient could have been hospitalized if deemed clinically necessary. The patient could have been treated as an inpatient or outpatient throughout the course of the study, according to the clinical judgment of the investigator.

Target patient population and sample size

Male and female inpatient and outpatient adolescents (aged 13 to 17 years), with a DSM-IV diagnosis of schizophrenia as confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version (K-SADS-PL) were recruited for the study. A PANSS total score of ≥60 and a score of 4 or greater on delusions (P1), conceptual disorganization, (P2), or hallucinations (P3) were required at both screening and randomization.

A total of 66 evaluable patients (ie, patients that are included in the intent-to-treat [ITT] analysis set) per treatment group (ie, a total of 198 patients) were required to provide 85% power (α=0.025 for each dose) to detect a difference of 15 points between either the 400 mg/day or 800 mg/day quetiapine treatment group and the placebo group with respect to mean change from PANSS total score.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Quetiapine tablets were administered orally in blinded fashion. Treatment began with a 50-mg dose on the evening of Day 1. The dose was escalated daily in increments of 100 mg thereafter, to reach a target fixed dose of 400 mg/day by Day 5 or 800 mg/day by Day 9, according to randomized treatment assignment. Placebo to match 25 mg and 100 mg quetiapine tablets was administered orally in blinded fashion, according to randomized treatment assignment. Study treatment was to be administered twice daily. However, in the event of tolerability issues, if deemed necessary in the clinical judgment of the investigator, study treatment could have been administered 3 times daily.

AstraZeneca supplied the study medication as follows (tablet strength, formulation, batch number):

- Quetiapine: 25 mg tablet (6500J, MC4601); 100 mg tablet (6510J, KT4604, LK460)

- Quetiapine placebo: 25 mg tablet (755eF, LC4618); 100 mg tablet (7550F, 7571K, LH4607)

Duration of treatment

42 days (6 weeks)

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Change in PANSS total score from baseline to Day 42
- Secondary variables: Change from baseline to each corresponding visit in the following assessment scores: PANSS total (Days 7 and 14), PANSS positive symptom and negative symptom subscale (Days 7, 14, and 42), CGI Severity of Illness (Days 7, 14, and 42), CGAS (Day 42), sum of PANSS items S1, S2, and S3 (Days 7, 14, and 42); sum of PANSS items P4, P7, G8, and G14 scores (aggression/hostility cluster) and depression cluster subscale scores at Day 42, percentage of patients with response, defined as a ≥30% reduction from baseline in the PANSS total score at Day 42; CGI Global Improvement Score at Day 42.

Patient reported outcomes

- Change from baseline to Day 42 in overall caregiver burden, as assessed by the CGSQ

Safety

Safety variables included the incidence and nature of AEs; changes from baseline to each visit, when measured, in clinical laboratory test results (eg, prolactin concentration) and ECG results; changes from baseline to each visit in vital signs, weight, and BMI; changes from baseline to each visit in SAS, BARS, and AIMS scores; and the incidence of anticholinergic medication use to treat emergent EPS.

Statistical methods

All statistical comparisons used 2-sided tests with a significance level of 0.050, unless otherwise specified. The primary analyses used observed case (OC) for the time period of interest. The changes from baseline PANSS total scores at Day 42 were analyzed using mixed model repeated measures (MMRM) analysis. Baseline PANSS total score was used as a covariate. Also included in the model were treatment, region, visit, and visit-by-treatment interaction, all of which were considered as fixed effects. An unstructured covariance pattern was used. Robust variance estimate for the fixed effects were used for testing the treatment differences. This analysis assumed that missing observations were missing at random (MAR) and utilized all available data. The two contrasts of interest were the 400 mg/day and 800 mg/day quetiapine groups versus the placebo group, and the Simes-Hommel step-up procedure was used for adjustment of the significance level for the 2 primary comparisons. If assumptions of normality did not hold for the secondary variables of CGI Severity of Illness

score and PANSS subscale scores, an ordinal logistic regression model (McCullagh 1980) was used at Day 42.

The safety population included all randomized patients who were given study treatment, and was used to assess safety and tolerability variables. The ITT population included all randomized patients who were given study treatment and who had baseline and at least 1 post-baseline efficacy assessment for the PANSS. The ITT population was used for the efficacy analyses. The per-protocol population (PP) excluded patients with significant protocol violations or deviations, as well as any data collected after a patient was withdrawn from the assigned treatment group, and all data from patients who were deemed to be non-compliant. The primary analysis was repeated on the PP population to test for homogeneity of treatment effects.

Patient population

Of the 268 patients enrolled in this study, 222 were randomly assigned to study treatment. The study design called for 198 patients, 66 in each of the 3 treatment groups. With 73 patients in the 400 mg/day quetiapine group, 74 patients in the 800 mg/day quetiapine group, and 75 patients in the placebo group, the randomization goals were considered to be adequately satisfied.

Baseline patient characteristics are shown in Table S1.

Table S1 Demographic and baseline characteristics of the ITT population

		Treatment group			
		Quetiapine 400 mg/day (N=73)	**Quetiapine 800 mg/day (N=74)**	**Placebo (N=73)**	**Total (N=220)**
Demographic characteristics					
Sex: n (%)	Male	43 (58.9)	44 (59.5)	42 (57.5)	129 (58.6)
	Female	30 (41.1)	30 (40.5)	31 (42.5)	91 (41.4)
Age (years)	Mean (SD)	15.45 (1.25)	15.45 (1.34)	15.34 (1.39)	15.41 (1.32)
	Median	16.0	16.0	16.0	16.0
	Range	13.0-17.0	13.0-17.0	13.0-17.0	13.0-17.0
Race: n (%)	Caucasian	45 (61.6)	44 (59.5)	46 (63.0)	135 (61.4)
	Black	7 (9.6)	9 (12.2)	11 (15.1)	27 (12.3)
	Oriental	15 (20.5)	13 (17.6)	12 (16.4)	40 (18.2)
	Other	6 (8.2)	8 (10.8)	4 (5.5)	18 (8.2)
Ethnic group: n (%)	African	1 (1.4)	1 (1.4)	2 (2.7)	4 (1.8)
	African-American	6 (8.2)	8 (10.8)	9 (12.3)	23 (10.5)
	Asian	15 (20.5)	14 (18.9)	10 (13.7)	39 (17.7)
	Chinese	1 (1.4)	1 (1.4)	1 (1.4)	3 (1.4)
	Hispanic	4 (5.5)	5 (6.8)	5 (6.8)	14 (6.4)
	Native American	0	0	1 (1.4)	1 (0.5)
	Not applicable	36 (49.3)	34 (45.9)	32 (43.8)	102 (46.4)
	Other	10 (13.7)	11 (14.9)	13 (17.8)	34 (15.5)
Baseline characteristics					
Weight (kg)	Mean (SD)	60.95 (19.10)	61.73 (14.67)	62.78 (14.35)	61.82 (16.12)
	Range	34.0-128.0	36.0-103.0	35.0-113.0	34.0-128.0
BMI (kg/m^2)	Mean (SD)	21.82 (5.57)	22.46 (4.75)	22.67 (4.72)	22.32 (5.02)
	Range	14.5-41.3	13.5-37.2	15.4-40.0	13.5-41.3

BMI Body mass index. ITT Intent to treat. SD Standard deviation.
Data derived from Table 11.1.5.2 and Table 11.1.5.5, Section 11.1.

The treatment groups in this study were generally well matched for demographic and baseline characteristics. The mean patient age was approximately 15 years. There was a slightly higher percentage of males than females, and approximately 61% of patients in all 3 treatment groups were Caucasian.

Baseline disease characteristics for the ITT population are presented in Table S2.

Table S2 Baseline disease characteristics of the ITT population

Outcome variable[a]	Treatment group Quetiapine 400 mg/day (N=73)	Quetiapine 800 mg/day (N=74)	Placebo (N=73)	Total (N=220)
DSM-IV diagnosis:				
Schizophrenia, disorganized, n (%)	6 (8.2)	5 (6.8)	5 (6.8)	16 (7.3)
Schizophrenia, paranoid, n (%)	53 (72.6)	50 (67.6)	52 (71.2)	155 (70.5)
Schizophrenia, residual, n (%)	0	1 (1.4)	0	1 (0.5)
Schizophrenia, undifferentiated, n (%)	14 (19.2)	18 (24.3)	16 (21.9)	48 (21.8)
Screening PANSS score, n	73	74	71	
Mean (SD)	98.1 (15.41)	97.7 (15.32)	97.2 (16.83)	NC
Range – minimum, maximum	69, 133	64, 133	61, 137	NC
Baseline CGI Severity of Illness score, n	73	74	72	
Mean (SD)	4.7 (0.77)	4.6 (0.76)	4.7 (0.67)	NC
Range – minimum, maximum	4, 7	3, 6	4, 6	NC
Baseline PANSS Positive Symptom Subscale score, n	73	74	72	
Mean (SD)	23.3 (5.80)	23.8 (4.84)	24.5 (5.57)	NC
Range – minimum, maximum	10, 39	13, 37	10, 43	NC
Baseline PANSS Negative Symptom Subscale score, n	73	74	72	
Mean (SD)	25.4 (5.65)	25.8 (5.43)	24.8 (5.85)	NC
Range – minimum, maximum	11, 41	13, 42	11, 44	NC
Baseline Sum of PANSS Items S1, S2, and S3 scores, n	73	74	72	
Mean (SD)	8.7 (3.86)	8.3 (3.74)	8.3 (3.98)	NC
Range – minimum, maximum	3, 21	3, 17	3, 21	NC
Baseline CGAS score, n	73	73	72	
Mean (SD)	43.4 (9.16)	42.6 (11.12)	41.8 (11.39)	NC
Range – minimum, maximum	20, 65	20, 69	10, 71	NC

Table S2 Baseline disease characteristics of the ITT population

Outcome variable[a]	Treatment group Quetiapine 400 mg/day (N=73)	Quetiapine 800 mg/day (N=74)	Placebo (N=73)	Total (N=220)
Baseline PANSS-derived BPRSd score, n	73	74	72	
Mean (SD)	53.6 (10.74)	53.8 (8.86)	54.1 (10.57)	NC
Range – minimum, maximum	25, 78	34, 75	36, 91	NC
Baseline CGSQ score, n	69	72	66	
Mean (SD)	2.3 (0.70)	2.2 (0.77)	2.2 (0.77)	NC
Range – minimum, maximum	0, 4	0, 4	0, 4	NC

[a] Baseline scores for the specified scales were not calculated (NC) for the total population.

ADHD Attention Deficit Hyperactivty Disorder. BPRSd Brief Psychiatric Rating Scale score derived from the corresponding 18 items of the PANSS. CGAS Children's Global Assessment Score. CGI Clinical Global Impression. CGSQ Caregiver Strain Questionnaire. DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition. ITT Intent to treat. NC Not calculated. PANSS Positive and Negative Syndrome Scale. SD Standard deviation.

Data derived from Table 11.1.6.1 and Table 11.1.8.1, Section 11.1, and Table 11.2.1.1.1, Table 11.2.1.3.1.1, Table 11.2.1.4.1, Table 11.2.1.7.1, Table 11.2.3.1.1.1, Table 11.2.3.2.1.1, Table 11.2.5.1.1, and Table 11.2.6.1.1.1, Section 11.2.

The 3 treatment groups were well matched with respect to baseline disease characteristics.

Efficacy results

A summary of the efficacy results for the quetiapine and placebo groups (ITT population) is shown in Table S3.

Table S3 Summary of efficacy results (ITT population)

Outcome Variable[a]	Treatment group				
	Quetiapine 400 mg/day (N=73)	Quetiapine 800 mg/day (N=74)	Placebo (N=75)	Quetiapine 400 mg/day vs Placebo	Quetiapine 800 mg/day vs Placebo
PANSS total score – LS mean change from baseline					
Day 7	-8.23	-8.80	-6.65	-1.58; p=0.410	-2.16; p=0.214
Day 14	-14.24	-16.09	-10.09	-4.15; p=0.098	-6.00; p=0.012
Day 42 (primary)	-27.31	-28.44	-19.15	-8.16; p=0.043	-9.29; p=0.009
PANSS response[b] (OC) - % of patients	51.9	40.0	39.5	1.86[c]; p=0.125	1.20[c]; p=0.675
PANSS response (LOCF) - % of patients	38.4	36.5	26.0	p=0.109	p=0.194
CGI-Severity of Illness – LS mean change from baseline					
Day 7	-0.32	-0.35	-0.18	-0.13; p=0.226	-0.17; p=0.061
Day 14	-0.56	-0.74	-0.40	-0.17; p=0.220	-0.34; p=0.006
Day 42	-1.15	-1.28	-0.81	-0.34; p=0.104	-0.47; p=0.018
CGI Global Improvement[b] – % of patients “with improvement"	60	56	42	2.81[c]; p=0.009	2.71[c]; p=0.014
PANSS positive symptom subscale score – LS mean change from baseline					
Day 7	-2.76	-3.31	-1.99	-0.77; p=0.260	-1.32; p=0.039
Day 14	-4.50	-6.03	-3.00	-1.50; p=0.055	-3.03; p<0.001
Day 42	-8.56	-9.34	-6.51	-2.05; p=0.075	-2.83; p=0.008
PANSS negative symptom subscale score – LS mean change from baseline					
Day 7	-1.83	-1.45	-1.77	-0.06; p=0.913	0.33; p=0.531
Day 14	-3.44	-2.90	-2.37	-1.07; p=0.124	-0.53; p=0.414
Day 42	-6.35	-6.21	-5.09	-1.27; p=0.239	-1.12; p=0.245
CGAS total score – LS mean change from baseline	13.04	14.94	9.89	3.14; p=0.139	5.05; p=0.019
Sum of PANSS items S1, S2, and S3 scores – LS mean change from baseline					
Day 7	-0.79	-1.12	-0.49	-0.30; p=0.463	-0.63; p=0.069
Day 14	-1.45	-1.55	-0.49	-0.96; p=0.020	-1.06; p=0.016
Day 42	-2.58	-2.39	-1.51	-1.07; p=0.059	-0.87; p=0.091

Table S3 Summary of efficacy results (ITT population)

Outcome Variable[a]	Treatment group				
	Quetiapine 400 mg/day (N=73)	Quetiapine 800 mg/day (N=74)	Placebo (N=75)	Quetiapine 400 mg/day vs Placebo	Quetiapine 800 mg/day vs Placebo
Sum of PANSS items P4, P7, G8, and G14 scores – LS mean change from baseline	-3.61	-3.83	-1.85	-1.76; p=0.018	-1.99; p=0.005
PANSS depression symptom subscale scores – LS mean change from baseline	-2.96	-3.16	-2.47	-0.49; p=0.319	-0.69; p=0.149
PANSS-derived BPRSd total score – LS mean change from baseline	-15.95	-17.05	-11.86	-4.09; p=0.067	-5.19; p=0.010
CGSQ global score – LS mean change from baseline	-0.47	-0.30	-0.17	-0.30; p=0.010	-0.13; p=0.253

[a] Data presented are for Day 42 unless otherwise specified.
[b] The PANSS and CGI response data (% of patients) represent the descriptive statistics for those patients with a value at Day 42.
[c] These data represent odds ratios.
CGI Clinical Global Impression. CGAS Children's Global Assessment Score. CGSQ Caregiver Strain Questionnaire. ITT Intent to treat. LS Least squares. OC Observed case. PANSS Positive and Negative Syndrome Scale.
Data derived from Table 11.2.1.2.1, Table 11.2.1.6.1, Table 11.2.3.2.1.3, Table 11.2.4.2.1, Table 11.2.1.3.1.3, Table 11.2.1.4.3, Table 11.2.5.2.1, Table 11.2.1.8.1, Table 11.2.3.1.1.3, and Table 11.2.6.2.1, Section 11.2.

Quetiapine 400 mg/day and 800 mg/day, given in divided daily doses (either bid or tid, per the judgment of the investigator), were statistically superior to placebo in the treatment of adolescents with schizophrenia, as assessed by the MMRM analysis of the PANSS total score change from baseline at Day 42 for the ITT population (p=0.043 for quetiapine 400 mg/day, p=0.009 for quetiapine 800 mg/day).

When 400 mg/day and 800 mg/day quetiapine were compared to placebo for treatment of a broad range of schizophrenia symptoms in adolescents:

- Quetiapine 800 mg/day was superior to placebo, as assessed by the PANSS total score change from baseline at Day 14, but not Day 7,
- Quetiapine 800 mg/day was superior to placebo, as assessed by the CGI Severity of Illness score change from baseline at Day 14 and Day 42, but not Day 7,
- Quetiapine 400 mg/day and 800 mg/day had superior rates of improvement compared to placebo, as assessed by the CGI Global Improvement scale at Day 42, and

- Quetiapine 800 mg/day was superior to placebo, as assessed by the PANSS positive symptom subscale scores change from baseline at Day 7, Day 14, and Day 42. Neither quetiapine 400 mg/day nor quetiapine 800 mg/day was superior to placebo in improving PANSS negative symptom subscale scores at Day 7, Day 14, or Day 42.

Neither 400 mg/day nor 800 mg/day quetiapine was superior to placebo in percentage of patients with response (defined as a ≥30% reduction from baseline in the PANSS total score) at Day 42.

Quetiapine 800 mg/day was superior to placebo in improving the level of functioning of adolescents with schizophrenia, as assessed by the CGAS total score change from baseline at Day 42.

Quetiapine 400 mg/day and 800 mg/day were superior to placebo in reducing levels of agitation and aggression in adolescents with schizophrenia, as assessed by the change from baseline in the sum of the PANSS items S1, S2, and S3, at Day 14, but not Day 7 or Day 42. Both doses were also superior to placebo in reducing levels of aggression/hostility in adolescents with schizophrenia, as assessed by the sum of PANSS items P4, P7, G8, and G14 scores change from baseline at Day 42.

Neither 400 mg/day nor 800 mg/day quetiapine were superior to placebo in reducing depression in adolescents with schizophrenia, as assessed by the PANSS depression symptom subscale total scores change from baseline at Day 42.

Quetiapine 400 mg/day was superior to placebo in relieving overall caregiver burden, as assessed by the CGSQ total score change from baseline at Day 42.

Quetiapine 800 mg/day was superior to placebo for the treatment of adolescents with schizophrenia, as assessed by the PANSS-derived BPRSd total score at Day 42.

Safety results

The number of patients who had an AE in any category, and the most common AEs (defined as incidence of 5% or more in either quetiapine group), summarized by preferred term, are shown in Table S4 and Table S5, respectively.

Table S4 Number (%) of patients who had an adverse event in any category (safety population)

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]							
	Quetiapine 400 mg/day (N=73)		Quetiapine 800 mg/day (N=74)		Placebo (N=75)		Total (N=220)	
	n	%	n	%	n	%	n	%
Any adverse events	58	79.5	55	74.3	45	60.0	158	71.2
Serious adverse events	4	5.5	5	6.8	4	5.3	13	5.9
Drug-related adverse events	41	56.2	34	46.0	17	22.7	92	41.4
Adverse events leading to death	0		0		0		0	
Withdrawal due to adverse event	5	6.9	7	9.5	2	2.7	14	6.3

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

Data derived from Table 11.3.2.1, Section 11.3.

The overall incidences of AEs reported in quetiapine-treated patients were higher (400 mg/day quetiapine, 79.5%; 800 mg/day quetiapine, 74.3%) than in the placebo group (60.0%). Larger proportions of patients in the 400 mg/day (6.9%) and 800 mg/day (9.5%) quetiapine dose groups discontinued due to an AE than did patients in the placebo group (2.7%). No deaths occurred in the study. The incidence of SAEs was similar in all 3 treatment groups (quetiapine 400 mg/day: 5.5%; quetiapine 800 mg/day: 6.8%; placebo: 5.3%).

Table S5 **Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized over all treatment groups (safety population)**

Preferred term	Quetiapine 400 mg/day (N=73)		Quetiapine 800 mg/day (N=74)		Placebo (N=75)	
	n	%	n	%	n	%
Somnolence	20	27.4	22	29.7	5	6.7
Headache	6	8.2	16	21.6	14	18.7
Dizziness	6	8.2	11	14.9	4	5.3
Dry mouth	3	4.1	7	9.5	1	1.3
Insomnia	9	12.3	7	9.5	17	22.7
Agitation	6	8.2	6	8.1	10	13.3
Tachycardia	4	5.5	6	8.1	0	
Increased appetite	3	4.1	5	6.8	3	4.0
Fatigue	4	5.5	4	5.4	3	4.0
Irritability	2	2.7	4	5.4	0	
Nausea	3	4.1	4	5.4	13	17.3
Sedation	4	5.5	4	5.4	3	4.0
Vomiting	3	4.1	4	5.4	6	8.0
Anxiety	4	5.5	3	4.1	5	6.7
Diarrhea	4	5.5	1	1.4	4	5.3

NOTE: This table uses a cutoff of 5% within either quetiapine treatment group. Data are ordered by descending incidence in the quetiapine 800 mg/day group.
Data derived from Table 11.3.2.4.1, Section 11.3.

A summary of AEs indicated that nervous system events predominated. Among the most common AEs (ie, those occurring at >5% in either quetiapine group and at twice the rate of the placebo group), somnolence, dizziness, dry mouth, tachycardia, and irritability occurred at higher rates in the quetiapine treatment groups compared to placebo. Most AEs were mild to moderate in intensity.

In the analysis of AEs by geographic region (Asia, Central and Eastern Europe [CEE], South Africa [SA], and the United States [US]), the overall incidences of AEs reported in the quetiapine treatment groups were higher than in the placebo group in all regions.

The incidences of AEs of special interest that were potentially associated with QTc prolongation, neutropenia, syncope, diabetes, and suicidality were less than 5% and similar to the incidence in placebo-treated patients in all categories. Likewise, the incidence of

clinically important shifts to low ANC levels, and to high glucose levels was similar between the quetiapine groups and the placebo group.

Adverse events potentially associated with EPS were reported for 9 (12.3%) 400 mg/day quetiapine-treated patients, 10 (13.5%) 800 mg/day quetiapine-treated patients, and 4 (5.3%) placebo patients. The majority of AEs potentially associated with EPS were mild or moderate in intensity; two patients experienced severe AEs potentially associated with EPS (1 in the 800 mg/day quetiapine group and 1 in the placebo group). Neither were judged to be related to study medication and neither resulted in discontinuation of study medication. Changes in EPS were also analyzed by several sensitive and objective scales. The majority of patients showed no change in EPS over the course of the study, as assessed by the SAS, AIMS, AIMS-7, and BARS scales. The odds of worsening were not significantly different between the quetiapine and placebo groups, as assessed by GEE analysis of the SAS, AIMS and AIMS-7 scores. The incidence of anticholinergic medication use for the treatment of emergent EPS during the study was 5.48% for the 400 mg/day quetiapine group, 1.35% for the 800 mg/day quetiapine group, and 0% for the placebo group.

Mean changes from baseline to final visit in clinical chemistry values showed differences between the quetiapine groups and the placebo group for the parameters listed below. In addition, laboratory values of potential clinical importance and laboratory-related AEs occurred as follows:

- Mean values for HDL cholesterol at final visit, and mean changes from baseline were similar for the 3 treatment groups. Mean values at final visit, and mean changes from baseline showed increases in the 2 quetiapine groups for total cholesterol (400 mg/day quetiapine: 7.8226 mg/dL; 800 mg/day quetiapine: 7.4237 mg/dL), LDL cholesterol (400 mg/day quetiapine: 8.6613 mg/dL; 800 mg/day quetiapine: 4.8167 mg/dL), and triglycerides (400 mg/day quetiapine: 9.6613 mg/dL; 800 mg/day quetiapine: 15.5833 mg/dL) that were not seen in the placebo group (total cholesterol: -8.0635 mg/dL; LDL cholesterol: -3.8889 mg/dL; triglycerides: -8.1587 mg/dL). Shifts to potentially clinically important high triglyceride levels at the final visit occurred more often in the quetiapine groups (400 mg/day quetiapine: 5 patients [8.9%]; 800 mg/day quetiapine: 1 patient [1.8%]; placebo: 1 patient [1.7%]). Adverse events related to lipid values were limited to two patients with elevated triglycerides at Day 42.

- Mean changes from baseline to final visit showed decreases in the 2 quetiapine treatment groups for free T4 (400 mg/day quetiapine: -0.1510 ng/dL; 800 mg/day quetiapine: -0.2790 ng/dL) and total T4 (400 mg/day quetiapine: -1.4419 µg/dL; 800 mg/day quetiapine: -2.5083 µg/dL) that differed from the changes seen in the placebo group (free T4: 0.0097 ng/dL; total T4: 0.1063 µg/dL). One quetiapine-treated patient had a potentially clinically important low total T4 or low free T4 (total T4 was 3.3 µg/dL) and a corresponding potentially clinically important high TSH (corresponding TSH was 5.23 µIU/mL); notably, her baseline total T4 was low at 4.2 µg/dL. One patient in the 400 mg/day quetiapine group experienced an

AE of elevated TSH of moderate intensity on Day 43 that was judged related to study medication. No AEs of hypothyroidism occurred in this study. Potentially clinically important shifts to low free T4 (400 mg/day quetiapine: 0 patients; 800 mg/day quetiapine: 2 patients [3.3%]; placebo: 0 patients) and low total T4 (400 mg/day quetiapine, 2 patients [3.2%]; 800 mg/day quetiapine, 3 patients [5.0%]; placebo, 0 patients) were seen along with a similar incidence of shifts to high TSH in the quetiapine groups (400 mg/day quetiapine: 3 patients [4.9%]; 800 mg/day quetiapine: 0 patients; placebo: 0 patients).

- Mean and median changes in prolactin from baseline to the final visit showed decreases for all 3 treatment groups. No AEs related to prolactin were reported. Potentially clinically important shifts to high prolactin concentration were seen in 1 patient (2.4%) in the 400 mg/day quetiapine group, 3 patients (7.5%) in the 800 mg/day quetiapine group, and 1 patient (2.8%) in the placebo group.

Mean pulse rates (supine pulse: 400 mg/day quetiapine: +6.0 bpm; 800 mg/day quetiapine: +3.9 bpm; placebo: -1.4 bpm) and heart rates as assessed by ECG (400 mg/day quetiapine: +3.78 bpm; 800 mg/day quetiapine: +11.16 bpm; placebo: -3.32 bpm) increased in the quetiapine groups but not the placebo group. Quetiapine-treated patients had a higher incidence of potentially clinically important shifts to high supine and standing systolic blood pressure, and a higher incidence of shifts to high supine and standing pulse than placebo-treated patients.

Increases in mean weight at Day 42 (400 mg/day quetiapine: 2.2 kg, 800 mg/day quetiapine: 1.8 kg, placebo: -0.4 kg) and reports of weight increases as AEs were similar in the quetiapine groups compared to the placebo group. A higher percentage of 400 mg/day (23.21%) and 800 mg/day (18.18%) quetiapine-treated patients had weight gain ≥7% at Day 42 compared to placebo-treated patients (6.82%).