AstraZeneca

Drug product:	SEROQUEL™ tablets	**SYNOPSIS**	
Drug substance(s):	quetiapine fumarate		
Study code:	D1446L00002/5077US0046		
Date:	22 August 2005		

A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) and Placebo in the Treatment of Agitation Associated with Dementia

Coordinating investigator

Not applicable.

Study center(s)

This study was conducted at 53 centers in the US.

Publications

Katz I, Zhong K, Minkwitz M, Devine N. Quetiapine does not increase the risk of falls in elderly institutionalized patients with dementia. Poster presented at 18th American Association for Geriatric Psychiatry Annual Meeting; March 3-6, 2004; San Diego, CA.
Zhong K, Tariot P, Minkwitz MC, Devine NA, Mintzer J. Quetiapine for the treatment of agitation in elderly institutionalized patients with dementia: a randomized, double-blind trial. Poster presented at the 18th American Association for Geriatric Psychiatry Annual Meeting; March 3-6, 2004; San Diego, CA. (Note: Poster was also presented at the 9th International Conference of Alzheimer's Disease and Related Disorders; July 17-22, 2004; Philadelphia, PA; the 56th Institute on Psychiatric Services Annual Meeting; October 6-10, 2004; Atlanta, GA; and the Florida Directors Association Annual Meeting; October 6-10, 2004; Orlando, FL).
Zhong K, Tariot P, Minkwitz MC, Devine NA, Mintzer J. Quetiapine treatment of behavioral disturbance in patients with Alzheimer's disease. Poster presented at the 18th American Association for Geriatric Psychiatry Annual Meeting; March 3-6, 2004; San Diego, CA.

Study dates		Phase of development
First patient enrolled	30 September 2002	Therapeutic confirmatory (III)
Last patient completed	1 December 2003	

Objectives

The primary objective of the study was to assess the efficacy of 2 fixed doses of quetiapine compared with placebo in the treatment of agitation associated with dementia (Alzheimer's disease [AD] or vascular dementia [VD]) in patients residing in long-term care facilities using the mean change from baseline (randomization) to Day 70 or day of withdrawal on the Positive and Negative Syndrome Scale-Excitement Component (PANSS-EC).

The secondary objectives were to evaluate the following:

1) To assess the efficacy of quetiapine compared with placebo in treating patients with agitation associated with dementia by comparing:
    a. The percentage of patients who had a reduction of ≥40% and ≥30% from baseline to endpoint in PANSS-EC score
    b. The mean change from baseline to endpoint on the Neuropsychiatric Inventory-Nursing Home version (NPI-NH) Agitation/Aggression item
    c. The mean change from baseline to endpoint on the Cohen-Mansfield Agitation Inventory (CMAI) total score and subscales
2) To assess the effect of quetiapine compared with placebo on the overall psychopathology by comparing:
    a. The mean change from baseline to endpoint on the NPI-NH total score
    b. The mean change from baseline to endpoint on the NPI-NH depression subscale
    c. The mean change from baseline to endpoint on the NPI-NH psychosis subscale
3) To assess the effect of quetiapine compared with placebo on global/functional status by comparing the mean change on the Clinical Global Impression of Change (CGI-C) scale
4) To assess the safety and tolerability of quetiapine compared with placebo by evaluation of:
    a. The mean change from baseline to endpoint on the Simpson-Angus Scale (SAS) total score and the Abnormal Involuntary Movement Scale (AIMS) total score
    b. The incidence of treatment-emergent adverse events (AEs) and potentially clinically important changes in laboratory test results, electrocardiogram (ECG) results, and vital signs
    c. The effects on cognition, measured by the mean change from baseline to endpoint on Mini Mental State Examination (MMSE)

5) To assess the effect on quetiapine compared with placebo on treatment-related outcome measures by comparing caregiver impact/occupational distress, measured by the Occupational Disruptiveness Scale of the NPI-NH

Study design

This was a 10-week, multicenter, double-blind, randomized study to compare the efficacy, safety, and tolerability of 2 fixed doses of quetiapine with placebo in the treatment of agitation associated with dementia in patients residing in long-term care facilities.

Target patient population and sample size

Male or female patients aged ≥55 years of age with documented symptoms of agitation associated with dementia and a diagnosis of probable or possible AD or VD according to the Diagnostic and Statistical Manual of Mental disorder, 4th edition, text revision (DSM-IV) or National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) Guidelines, could participate. The patients were required to be residents of a long-term care facility for at least 14 days and reside in the same facility for the duration of the study. Further, they had to score at least 14 on the PANSS-EC, with a score of 4 on at least 1 of the 5 items at both screening (Visit 1) and randomization (Visit 2).
A total of approximately 308 patients were to be randomized into this study to obtain 280 evaluable patients, defined as those who had a baseline visit and at least 1 post-baseline assessment. A sample size of 105 patients per quetiapine dose group and 70 patients in the placebo dose group would provide 80% power for a 2-sided pairwise comparison with placebo at α=0.025 to preserve the experiment wise error rate of α=0.05.

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

Study medication was administered orally twice daily. All patients randomized to treatment with quetiapine began their treatment on Day 1 with a 25-mg evening dose. The dose was then titrated upward by 25-mg increments every day to reach 100 mg/day on Day 4 for both quetiapine treatment groups. Patients randomized to treatment with 200 mg/day continued dose titration in 25-mg increments every day to reach 200 mg/day on Day 8. Patients who were randomized to placebo treatment had their daily tablet allotments titrated upward in a similar fashion to maintain the treatment blind. After the target dose was achieved, randomized treatment continued until Day 70 (or withdrawal).
AstraZeneca supplied the study medications as follows: tablet strength (formulation, batch number):

- Quetiapine 25-mg tablets (F12804, 7527F)
- Quetiapine 100-mg/day tablets (F12689, 7513F)
- Placebo to match 25-mg quetiapine tablets (F12636, 7553F)
- Placebo to match 100-mg/day quetiapine tablets (F12637, 7550F)

Duration of treatment

Seventy days (10 weeks)

Criteria for evaluation (main variables)

Efficacy

Primary variable: The primary variable was the change from baseline assessment to final assessment (Day 70) or the last observation carried forward (LOCF) in the PANSS-EC total score.

Secondary variables:

- Change from baseline to each assessment using the observed cases (OC) in PANSS-EC total score
- PANSS-EC total score at each assessment
- Responder classification based on percent change from baseline in PANSS-EC
- Change from baseline to each assessment and final assessment on NPI-NH (1) agitation domain (agitation/aggression item), (2) total score, (3) depression domain (depression/dysphoria item), and (4) psychosis domain (sum of delusions and hallucinations items)
- Change from baseline to each visit and final assessment on CMAI total score and subscale scores (Factor 1 – physically aggressive behavior, Factor 2 – physically non-aggressive behavior, Factor 3 – verbally aggressive behavior)
- CGI-C score and CGI-C improvement score (The proportion of patients rated as having "moderate or marked improvement" in their CGI-C scores) at each assessment subsequent to baseline and final assessment
- Outcome measure: Change from baseline to each assessment and final assessment in NPI-NH occupational disruptiveness scale

Safety and tolerability

- AEs (reported from randomization to last dose + 30 days), coded using the Medical Dictionary for Regulatory Activities (MedDRA) system of nomenclature, AEs leading to withdrawal, serious AEs (SAEs), and deaths
- Value and change from baseline to final assessment for clinical laboratory tests and potentially clinically important changes in clinical laboratory tests (hematology and chemistry)
- Value and change from baseline to final assessment in vital signs (supine and standing blood pressure and heart rate) measured daily from Day 1 to Day 10, and at each subsequent visit

- Value and change from baseline to final assessment in ECG results and potentially clinically important changes in ECG data
- Physical examinations, including measurement of weight
- Mean change from baseline to each assessment in the SAS and AIMS total scores
- Mean change from baseline to each assessment in the MMSE scores
- Characterization of and outcome of falls

Statistical methods

The efficacy variables of change from baseline to final assessment in PANSS-EC total score, NPI-NH, and CMAI were analyzed using analysis of covariance (ANCOVA) with baseline scores (Visit 2) as the covariate and including treatment, region, and dementia diagnosis as fixed effects. Binary variables (eg, analysis of differences between quetiapine and placebo in the proportion of PANSS-EC responders at each visit and final assessment and CGI-C global improvement scores) were analyzed using Cochran-Mantel-Haenszel techniques or logistic regression (to incorporate continuous baseline covariates).

Approaches for analyses used to handle missing data due to early patient discontinuation included LOCF and OC. With the LOCF analysis, all randomized patients with at least 1 post-baseline assessment contributed data for analysis whereby the last assessment for an early termination patient was carried forward and used as the Day 70 assessment. With the OC analysis, only data collected within a window around the scheduled assessment visit were evaluated for that assessment. With the OC approach, the Day 70 assessment included any data for a patient after Day 66 (considered to have sufficient duration in the study to be a completer patient, approximately10 weeks of treatment).

Populations for analyses were as follows:

1. The safety population – all randomized patients who took at least 1 dose of study medication
2. The intention-to-treat (ITT) population – all randomized patients who took study medication and who had a valid baseline PANSS-EC assessment and at least 1 valid post-baseline PANSS-EC assessment
3. The per-protocol (PP) population – excluded patients with significant protocol violations or deviations

Patient population

Of 435 patients screened, 333 were randomly assigned to study treatment, and all 333 patients were included in the safety population. With the exclusion of 7 patients who had no baseline or post-baseline PANSS-EC assessment scores, 326 patients were included in the ITT population.

Table S1 summarizes demographic and patient characteristics for the safety analysis set. The treatment groups were similar at baseline with respect to most demographic and patient characteristics.

AstraZeneca

Table S1 Demographic and patient characteristics - Safety population

	Treatment group			
	Quetiapine 200 mg/day (N=117)	Quetiapine 100 mg/day (N=124)	Placebo (N=92)	Total (N=333)
Demographic characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Sex				
Female	92 (78.6)	90 (72.6)	65 (70.7)	247 (74.2)
Male	25 (21.4)	34 (27.4)	27 (29.3)	86 (25.8)
Age (years)				
Mean (SD)	83.5 (8.0)	83.0 (7.2)	83.2 (7.2)	83.2 (7.5)
Range	56 to 97	56 to 96	58 to 98	56 to 98
Race				
Caucasian	95 (81.2)	107 (86.3)	78 (84.8)	280 (84.1)
Black	14 (12.0)	9 (7.3)	4 (4.3)	27 (8.1)
Hispanic	7 (6.0)	7 (5.6)	8 (8.7)	22 (6.6)
Oriental	1 (0.9)	1 (0.8)	1 (1.1)	3 (0.9)
Other	0	0	1 (1.1)	1 (0.3)
Baseline characteristics				
Weight (kg)	(N=114)	(N=121)	(N=90)	(N=325)
Mean (SD)	63.4 (14.8)	62.1 (13.1)	62.5 (12.3)	62.7 (13.5)
BMI (kg/m^2)	(N=111)	(N=118)	(N=89)	(N=318)
Mean (SD)	24.5 (4.4)	23.9 (4.5)	23.3 (3.3)	24.0 (4.2)
Duration of disease, Mean (SD)	(N=117)	(N=124)	(N=90)	(N=331)
Years since the first onset of dementia	5.4 (3.3)	5.1 (2.8)	6.0 (3.8)	5.5 (3.3)
	(N=117)	(N=124)	(N=91)	(N=332)
Years since the first onset of agitation	2.7 (1.8)	2.4 (1.6)	2.8 (2.3)	2.6 (1.9)

Note: The total "N" for the characteristics weight, BMI and duration of disease is variable based on the number of patients for whom data was available.
SD standard deviation.

Efficacy results

ITT population, LOCF analysis

Results of the analysis of the efficacy variables ITT population for the LOCF analysis set are summarized in Table S2. A summary of results is as follows:

- **PANSS-EC total score (primary efficacy variable):** The quetiapine 200-mg/day group had a greater reduction in PANSS-EC total score from baseline to Day 70 than the placebo group, with the difference approaching statistical significance (p=0.065). The quetiapine 100-mg/day group had a greater reduction in PANSS-EC total score from baseline to end of treatment compared to the placebo group, but the difference was not statistically significant.

- **PANSS-EC response rate (≥40% reduction) (secondary efficacy variable):** There was no statistically significant difference between the quetiapine 200-mg/day or 100-mg/day groups and placebo in the percentage of patients who had ≥40% reduction in PANSS-EC score from baseline to Day 70.

- **PANSS-EC response rate (≥30% reduction) (secondary efficacy variable):** A statistically significantly higher percentage of patients in the quetiapine 200-mg/day group had ≥30% reduction in this score from baseline to Day 70 relative to the placebo group (51% vs. 34%, p=0.014). The difference between the quetiapine 100-mg/day and placebo in the percentage of patients who had ≥30% reduction in PANSS-EC total score from baseline to final assessment was not statistically significant.

- **NPI-NH total score or subscale scores (secondary efficacy variable):** No statistically significant differences were evident between the quetiapine 200-mg/day group and placebo group in the reduction from baseline to Day 70 in NPI-NH total score or in the NPI-NH subscale scores for agitation, depression, or psychosis. Although the quetiapine 100-mg/day group did not differentiate from placebo with respect to the reduction from baseline to Day 70 in NPI-NH total score or in the subscale scores for agitation or psychosis, this group did have a statistically significantly greater reduction on the depression/dysphoria subscale score compared to placebo (p=0.009).

- **CMAI total score or subscale scores (secondary efficacy variable):** No statistically significant differences were evident between the quetiapine 200-mg/day or 100-mg/day groups and the placebo group in the reduction from baseline to Day 70 in CMAI total score or in the analyses of the subscale scores (physically aggressive, physically non-aggressive, and verbally aggressive behavior factor scores).

- **CGI-C score (secondary efficacy variable):** The quetiapine 200-mg/day group had a significantly improved CGI-C score compared with the placebo group at Day 70 (p=0.017), but the difference between the quetiapine 100-mg/day group and the placebo group was not statistically significant.

- **CGI-C response rate (secondary efficacy variable):** A significantly higher percentage of patients in the quetiapine 200-mg/day group was rated

"moderately improved" or "markedly improved" in CGI-C score compared with the placebo group ($p<0.001$). Although a higher percentage of patients in the quetiapine 100-mg/day group was rated "moderately improved" or "markedly improved" in CGI-C score compared with the placebo group, the difference was not statistically significant.

- **Caregiver impact/occupational distress (secondary efficacy variable):** No statistically significant differences were evident between quetiapine at either dose and placebo in the assessment of treatment-related outcome measures for caregiver impact/occupational distress.

Table S2 Summary of efficacy results at Day 70 (ITT, LOCF)

	Treatment group		
Efficacy variable	**Quetiapine 200 mg/day (N=114)**	**Quetiapine 100 mg/day (N=120)**	**Placebo (N=92)**
Primary variable			
PANSS-EC total score			
LS mean change from baseline (SE)	-5.68 (0.86)	-4.88 (0.82)	-3.91 (0.92)
p-value vs. placebo	0.065	0.306	
Secondary variables			
PANSS-EC responder rate			
≥40% reduction from baseline (% of patients)	38	33	29
p-value vs. placebo	0.214	0.620	
≥30% reduction from baseline (% of patients)	51	44	34
p-value vs. placebo	0.014	0.111	
NPI-NH total score			
LS mean change from baseline (SE)	-9.71 (2.20)	-8.88 (2.10)	-8.24 (2.35)
p-value vs. placebo	0.546	0.791	
NPI-NH agitation subscale score			
LS mean change from baseline (SE)	-1.06 (0.47)	-0.85 (0.45)	-1.23 (0.51)
p-value vs. placebo	0.745	0.467	
NPI-NH depression subscale score			
LS mean change from baseline (SE)	-0.42 (0.49)	-1.08 (0.49)	0.55 (0.53)
p-value vs. placebo	0.108	0.009	
NPI-NH psychosis subscale score			
LS mean change from baseline (SE)	-2.51 (0.90)	-1.81 (0.81)	-2.50 (0.94)

Table S2 Summary of efficacy results at Day 70 (ITT, LOCF)

Efficacy variable	Treatment group: Quetiapine 200 mg/day (N=114)	Quetiapine 100 mg/day (N=120)	Placebo (N=92)
p-value vs. placebo	0.985	0.464	
CMAI total score			
LS mean change from baseline (SE)	-11.04 (2.13)	-9.20 (2.04)	-2.50 (0.94)
p-value vs. placebo	0.352	0.877	
CMAI physical aggressive score			
LS mean change from baseline (SE)	-3.40 (0.90)	-3.12 (0.86)	-3.37 (0.97)
p-value vs. placebo	0.716	0.677	
CMAI physical non-aggressive score			
LS mean change from baseline (SE)	-2.46 (0.74)	-2.85 (0.70)	-1.37 (0.79)
p-value vs. placebo	0.182	0.067	
CMAI physical verbal aggressive score			
LS mean change from baseline (SE)	-3.94 (0.78)	-2.49 (0.75)	-2.55 (0.84)
p-value vs. placebo	0.111	0.942	
CGI-C score			
LS mean change from baseline (SE)	3.04 (0.20)	3.31 (0.19)	3.58 (0.22)
p-value vs. placebo	0.017	0.228	
CGI-C responder rate			
Moderate or marked improvement, % of patients	52	38	30
p-value vs. placebo	0.002	0.274	
NPI-NH Occupational Disruptiveness Score			
LS mean change from baseline (SE)	-3.65 (0.77)	-2.85 (0.74)	-3.02 (0.82)
p-value vs. placebo	0.460	0.839	

CGI-C Clinical Global Impression – Change, CMAI Cohen-Mansfield Agitation Inventory, ITT intention to treat, LOCF last observation carried forward, NPI-NH Neuropsychiatric Inventory - Nursing Home, PANSS-EC Positive and Negative Syndrome Scale - Excitement Component.

In the OC analysis, treatment with quetiapine 200 mg/day resulted in a significantly greater reduction in PANSS-EC compared with placebo (p=0.014) at Day 70, with an estimated mean difference between treatments of -2.66 (95% CI -4.78 to 0.54). The reduction from baseline in PANSS-EC score was numerically greater in the quetiapine

100-mg/day group compared with the placebo group, but the difference did not reach statistical significance.

Results for the OC analyses for the secondary variables were consistent with those for the LOCF analyses except that the difference between quetiapine 100 mg/day and placebo was statistically significant (p=0.033) in the analysis of CMAI physical non-aggressive score in the OC analysis.

The efficacy of quetiapine 200 mg/day and 100 mg/day was determined in the subgroup of patients with a diagnosis of AD only (approximately 78% of patients in the study were part of this subgroup) for 4 measures (LOCF/ITT). Results from of the analysis are shown in Table S3.

Table S3 Summary of efficacy results in subgroup of patients with AD only at Day 70 (ITT, LOCF)

	Treatment group		
Efficacy variable	**Quetiapine 200 mg/day (N=93)**	**Quetiapine 100 mg/day (N=89)**	**Placebo (N=73)**
Primary variable			
PANSS-EC total score			
LS mean change from baseline (SE)	-6.5 (0.76)	-5.3 (0.85)	-3.5 (0.85)
p-value vs. placebo	0.005	0.086	
Secondary variables			
PANSS-EC responder rate			
≥40% reduction from baseline (% of patients)	40	34	23
p-value vs. placebo	0.025	0.147	
≥30% reduction from baseline (% of patients)	56	47	27
p-value vs. placebo	<0.001	0.010	
CGI-C score			
LS mean change from baseline (SE)	3.08 (0.18)	3.29 (0.17)	3.76 (0.19)
p-value vs. placebo	0.006	0.056	
CGI-C responder rate			
Moderate or marked improvement, % of patients	54	42	26
p-value vs. placebo	<0.001	0.039	

CGI-C Clinical Global Impression – Change, ITT intention to treat, LOCF last observation carried forward, PANSS-EC Positive and Negative Syndrome Scale - Excitement Component, SE standard error.

Key findings were as follows:

- Quetiapine 200 mg/day treatment resulted in a statistically significantly greater reduction in PANSS-EC score from baseline to final assessment compared to

placebo (p=0.005). The result of the same comparison between the quetiapine 100-mg/day and placebo groups was not statistically significant.

- Quetiapine 200 mg/day achieved statistical significance compared to placebo when the PANS-EC response rate criterion was 40% (p=0.025) and also when it was 30% (p<0.001). Quetiapine 100 mg/day was numerically greater than placebo in the percentage of patients who met the responder criterion at 40% and 30%, but the difference from placebo was statistically significant only for the 30% criterion (p=0.010).

- Quetiapine 200 mg/day significantly improved the CGI-C score compared with placebo (p<0.05). Quetiapine 100 mg/day improved the CGI-C score compared with placebo with the difference approaching statistical significance at final assessment (p=0.056).

- Quetiapine 200 mg/day had a significantly higher percentage of patients with "moderate or marked improvement" on CGI-C score than placebo (54% vs. 26%, p<0.001). Quetiapine 100 mg/day had a significantly higher percentage of patients with "moderate or marked improvement" CGI-C score compared with placebo (42% vs. 26%, p<0.039).

Safety and tolerability results

The safety population consisted of 333 patients who were exposed to at least 1 dose of study medication. The mean (53 days in the quetiapine 200-mg/day group, and 55 days for the other 2 groups) and median days of exposure (approximately 68 days) were similar across the treatment groups. The size of the study population and the duration of overall study drug exposure were adequate to draw safety conclusions.

As shown in Table S4, the percentage of patients with at least 1 AE was similar in the 3 treatment groups. There was no dose-related increase in the percentage of patients who had SAEs in the quetiapine 200-mg/day group compared to the quetiapine 100-mg/day and placebo groups. The percentage of patients who had SAEs leading to death was higher in each of the quetiapine groups than in the placebo groups.

A total of 24 deaths occurred during the study: 5 during the screening period (before patients began receiving drug treatment), 9 during the treatment period, and 10 during the 30-day post-treatment follow-up period. Among the 19 deaths that occurred during treatment or during the 30-day post-treatment follow-up period, 7 (6.0%) deaths occurred among patients in the quetiapine 200-mg/day group, 9 (7.3%) deaths occurred among the patients in the quetiapine 100-mg/day group, and 3 (3.3%) deaths occurred among patients in the placebo group. Of these same 19 deaths, 17 were due to AEs that occurred either during or after treatment, and 2 (1 in the quetiapine 200-mg/d group and 1 in the placebo group) had no AEs associated with them.

Patients died from a variety of causes that were consistent with expectations for an elderly population, and there was no specific pattern as to the cause of death in any treatment group. The cases were confounded with medical histories, concurrent illnesses, trauma, or risk factors that may have contributed to death. There was no evidence to

demonstrate a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Table S4 Overview of AEs during treatment (safety population)

	Treatment group		
	Quetiapine 200 mg/day (N=117)	Quetiapine 100 mg/day (N=124)	Placebo (N=92)
Category[a] of AE	n (%)	n (%)	n (%)
Any AE	99 (84.6)	100 (80.6)	74 (80.4)
SAEs	8 (6.8)	14 (11.3)	9 (9.8)
SAEs leading to death[b]	3 (2.6)	5 (4.0)	1 (1.1)
SAEs not leading to death	6[c] (5.1)	9 (7.3)	8 (8.7)
Discontinuations of study treatment due to AEs	14 (12.0)	9 (7.3)	7 (7.6)

[a] Events in more than 1 category are counted once in each of those categories.
[b] Represents patients who had SAEs that during treatment that lead to death regardless of time of death.
[c] Patient E0049003 in the quetiapine 200-mg/day group had a SAE that led to death, as well as a different SAE that did not lead to death.
AE Adverse event, SAE Serious adverse event.

The most common AEs (incidence of ≥5% in any treatment group), summarized by preferred term, are shown in Table S5.

Table S5 Most common AEs (≥5% of patients in any treatment group) by preferred term in decreasing order of frequency in the quetiapine 200-mg/day group during the treatment period (safety population)

	Treatment group, n (%) of patients					
	Quetiapine 200 mg/day (N=117)		Quetiapine 100 mg/day (N=124)		Placebo (N=92)	
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lethargy	13	(11.1)	8	(6.5)	3	(3.3)
Skin laceration	13	(11.1)	19	(15.3)	13	(14.1)
Somnolence	11	(9.4)	10	(8.1)	2	(2.2)
Vomiting	11	(9.4)	7	(5.6)	3	(3.3)
Sedation	9	(7.7)	4	(3.2)	3	(3.3)
UTI	9	(7.7)	20	(16.1)	7	(7.6)
Cough	8	(6.8)	4	(3.2)	4	(4.3)
Constipation	7	(6.0)	7	(5.6)	1	(1.1)

Table S5 **Most common AEs (≥5% of patients in any treatment group) by preferred term in decreasing order of frequency in the quetiapine 200-mg/day group during the treatment period (safety population)**

	Treatment group, n (%) of patients		
	Quetiapine 200 mg/day (N=117)	**Quetiapine 100 mg/day (N=124)**	**Placebo (N=92)**
Decreased appetite	7 (6.0)	2 (1.6)	3 (3.3)
Arthralgia	6 (5.1)	7 (5.6)	3 (3.3)
Contusion[a]	6 (5.1)	12 (9.7)	6 (6.5)
Gait abnormal	6 (5.1)	6 (4.8)	0
Edema peripheral	6 (5.1)	9 (7.3)	6 (6.5)
Pain in extremity	6 (5.1)	5 (4.0)	4 (4.3)
Upper respiratory tract infection	6 (5.1)	6 (4.8)	4 (4.3)
Excoriation	5 (4.3)	7 (5.6)	4 (4.3}
Nausea	5 (4.3)	7 (5.6)	2 (2.2)
Rash	5 (4.3)	8 (6.5)	7 (7.6)
Headache	4 (3.4)	7 (5.6)	3 (3.3)
Weight decreased	4 (3.4)	5 (4.0)	5 (5.4)

[a] Reports of "contusions" were bruises in 90% of the cases.
UTI urinary tract infection.
Note: This table includes AEs that occurred from start of study treatment to last dose (treatment period) only.

There were dose-related increases in lethargy, somnolence, sedation, vomiting, constipation, decreased appetite, and gait abnormal in patients treated with quetiapine 200 mg/day relative to 100 mg/day.

During the treatment period, 14 patients (12.0%) in the quetiapine 200-mg/day group, 9 patients (7.3%) in the quetiapine 100-mg/day group, and 7 (7.6%) in the placebo group withdrew due to an AE. Fewer than 5% of patients were withdrawn for AEs within any specific SOC. There was no specific pattern of distribution of AEs leading to withdrawal among the 3 treatment groups.

Somnolence was reported for 11 (9.4%) of patients in the quetiapine 200-mg/day group, 10 (8.1%) in the quetiapine 100-mg/day group and 2 (2.2%) in the placebo group. Most episodes of somnolence in all 3 groups began during the titration period. Sedation was reported for 9 (7.7%) of patients in the quetiapine 200-mg/day group, 4 (3.2%) in the quetiapine 100-mg/day group and 3 (3.3%) in the placebo group. The onset of sedation was equally distributed between the titration and the post-titration period. Lethargy was reported for 13 (11.1%) patients in the quetiapine 200-mg/day group, 8 (6.5%) patients in the quetiapine 100-mg/day group and 3 (3.3%) patients in the placebo group. The

duration of the events of lethargy was comparable across treatments in general. Only 1 patient withdrew from the study due to lethargy.

The number of patients reporting orthostatic hypotension as an AE was low and did not indicate any safety concern for quetiapine: 3 (2.6%) in the quetiapine 200-mg/day group, 1 (0.8%) in the quetiapine 100-mg/day group, and 1 (1.1%) in the placebo group.

The AE "gait abnormal" was reported in 6 (5.1%) of patients in the quetiapine 200-mg/day group, 6 (4.8%) in the quetiapine 100-mg/day group, and none in the placebo group. In all cases, these were reported as "unsteady gait" or "worsening of unsteady gait" and were not associated with extrapyramidal symptoms (EPS) as assessed by the investigator.
Cardiac disorders occurred in 6 (5.1%) patients in the quetiapine 200-mg/day group, 2 (1.6%) patients in the quetiapine 100-mg/day group, and 4 (4.3%) patients in the placebo group.
There were 3 occurrences of cerebrovascular AEs in the study, 1 per treatment group.
Six patients had glucose-related AEs, and 1 of these events was a SAE.
The incidence of EPS, including akathisia, was similar in the 2 quetiapine groups and the placebo group. Overall, treatment with quetiapine was not associated with EPS.
In the category of blood dyscrasias, anemia was reported as an AE for 2 patients (1.6%) in the quetiapine 100-mg day group and 2 patients (2.2%) in the placebo group. Neither event with quetiapine was considered by the investigator to be related to study treatment.
There were no clinically important differences between the quetiapine and placebo groups with respect to mean changes in hematology and clinical chemistry parameters.
There were no apparent clinically significant systematic differences between the quetiapine and placebo groups with respect to changes in vital signs. There were no clinically important systematic differences between quetiapine and placebo in mean change from baseline in PR interval, QRS interval, QTc, or in categorical shifts in ECG parameters over the course of the study.
The proportions of patients in the quetiapine and placebo groups with significant (7% or greater) weight gain were similar. There were no clinically important changes in the results of physical examinations.
No important differences were seen between the quetiapine and placebo groups in change from baseline in SAS scores. There were improvements in EPS in patients treated with quetiapine, but these were not statistically different from placebo.
Compared with placebo, there was no statistically significant difference in the change in the AIMS score (which assesses dyskinesia and akathisia) in either quetiapine group relative to placebo.
The effects on cognition were measured by the mean change from baseline to endpoint on MMSE. Quetiapine was similar to placebo in not affecting MMSE scores.
There was a slightly higher incidence of falls in the quetiapine groups (7.7% and 7.3%) during the titration period compared to the placebo group (4.3%). Over the 70-day trial period the rate was between 4.6 and 4.7 falls per week across the 3 treatment groups
The proportion of patient reporting a fall was during treatment was similar among treatment groups (25.8% to 26.5% for the 3 groups). The rates across the 3 treatment groups were relatively similar for head injuries (1.7% to 4.8%) and fractures (0 to 0.9%).

The most common outcome of fall reported was redness, scraping, or bruising (11.1% to 15.2%).

A total of 26.4% of patients in the quetiapine 200-mg/day group, 40.0 % of patients in the quetiapine 100-mg/day group, and 37.5% of patients in the placebo group had a visible injury associated with a fall. The most common visible injury was a slight redness, reported in 24.5% to 35.0% of patients in the 3 groups.