SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: SEROQUEL™

ACTIVE INGREDIENT: Quetiapine fumarate

Trial title (number): A Multicenter, Double-blind Comparison of Efficacy and Safety of SEROQUEL (Quetiapine Fumarate), Haloperidol, and Placebo in the Treatment of Elderly Subjects Residing in Nursing Homes or Assisted Care Facilities and Presenting with Alzheimer's Dementia and Psychoses or Other Selected Psychoses (5077IL/0039)

Clinical phase: IIIb

First Patient recruited: 16 March 1998
Last Patient completed: 3 February 2000
AstraZeneca approval date:

Principal investigator and location: Pierre Tariot, MD, Monroe Community Hospital, Rochester, New York (Center 36)

Publications: Tariot PN, Schneider L, Katz IR, Mintzer JE, Street J, Copenhaver M, Williams-Hughes C. Quetiapine treatment of psychosis associated with dementia: A double-blind randomized placebo-controlled clinical trial. Am J Geriatr Psychiatry 2006;14:767-76.

OBJECTIVES

Primary—double-blind treatment phase: To evaluate the efficacy of quetiapine, haloperidol, and placebo with regard to psychotic symptoms in the treatment of elderly patients residing in nursing homes or assisted care facilities and who had Alzheimer's dementia and psychoses (ALZ-P) or other selected psychoses (OP)

Secondary—double-blind treatment phase: To compare the safety and tolerability of quetiapine, haloperidol, and placebo with regard to extrapyramidal symptoms (EPS), including dystonia, akathisia and parkinsonism, in geriatric residents of nursing homes or assisted care facilities; to compare the functional status (Activities of Daily Living) of patients treated with quetiapine with that of patients treated with haloperidol or placebo using the Multi-observational Scale for Elderly Patients (MOSES)—social activities subscale, the Activity Participation Frequency Rating (APFR) scale, and the Physical Self-maintenance Scale (PSMS); and to compare the caregiver burden for patients treated with quetiapine with that for patients treated with haloperidol or placebo

Open-label extension treatment phase: To provide patients an opportunity to be treated with quetiapine and to obtain (additional) efficacy, tolerability, and safety data

METHODS

Design: The trial design comprised a screening phase (Week –2 to Week 0), a 10-week, double-blind, randomized, flexible-dosage treatment phase, and a 12-week open-label extension (OLE) phase for patients who qualified from the double-blind treatment phase.

Population: Patients had either ALZ-P or OP per criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) or met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for possible Alzheimer's disease not captured by DSM-IV and for which treatment with an antipsychotic was indicated. Diagnosis was established via chart review and clinician interviews. Eligible patients resided in a nursing home or assisted care facility for the 2 weeks that preceded trial entry and were required to remain in the primary facility for the duration of the trial. Patients could not have a concurrent diagnosis of mental retardation, drug or alcohol dependence, or any DSM-IV Axis I diagnosis other than that specifically allowed by protocol.

Key inclusion criteria: At both screening and baseline, key inclusion criteria included the presence of psychotic symptoms and a total score of ≥24 on the 18 item Brief Psychiatric Rating Scale (BPRS) (0- to 6-point scale), with scores of ≥3 on two or more of the following positive symptom items: conceptual disorganization (Item 4), suspiciousness (Item 11), hallucinatory behavior (Item 12), and unusual thought content (Item 15); a score of at least 4 (moderately ill) on the Clinical Global Impression (CGI) Severity of Illness item; a frequency score of at least 3 on either the delusions or hallucinations item of the Neuropsychiatric Inventory-Nursing Home version (NPI-NH); and a score of at least 5 on the Mini-Mental State Exam (MMSE).

Key exclusion criteria: Any significant clinical disorder or laboratory finding, including a clinically significant electrocardiogram (ECG), that made the patient unsuitable to receive an investigational new drug; history of drug-induced agranulocytosis or acute orthostasis; ongoing corticosteroid therapy; previous participation in an investigational drug trial involving quetiapine or in any investigational drug trial within 30 days of entering the screening segment of the trial; and known allergy to haloperidol.

Dosage: Patients assigned to treatment with quetiapine received 25 mg on Day 1; 50 mg on Days 2 through 5; 75 mg on Days 6 through 9; and 100 mg on Days 10 through 14. Daily dose could then be flexibly increased or decreased in increments of 25 mg, up to 600 mg daily. Patients assigned to treatment with haloperidol received nominally matched doses, starting at 0.5 mg. The dose was subsequently increased to 1.0 mg, then 1.5 mg, and then 2.0 mg on the same schedule used to increase quetiapine dose (using a tablet configuration designed to maintain the blind). After Day 14, haloperidol could be flexibly increased or decreased, up to 12 mg/day. Patients assigned to treatment with placebo received matching tablets and had tablet counts increased to match that of quetiapine and haloperidol. At OLE entry, the recommended quetiapine starting dose was 25 mg/day, which could be increased by 25 or 50 mg every 2 to 4 days (investigator discretion) up to a maximum of 800 mg/day.

Batch (and formulation) numbers: Quetiapine 25 mg: ST70141-023-FA04, ST70141-023-FA03, and ST70141-023-FA02 (F12153); matching placebo: ST70142-004-FA08 and ST70142-004-FA07 (F7142); quetiapine 100 mg: 9008Y and 9013A (F12154); matching placebo, ST70142-008-FA03 and

ST70142-008-FA02 (F7207); haloperidol 0.5 mg: 808410 (F10106); matching placebo, 690610 (F10107); haloperidol 2.0 mg, 808420 (F10108); and matching placebo, 692350 (F10109).

Key assessments:

Efficacy assessments—double-blind treatment phase

Primary—Changes from baseline (Week 0) to Week 10 (or final assessment) in BPRS total and CGI Severity of Illness scores.

Secondary—Changes from baseline to Weeks 2, 4, and 6 in BPRS total and CGI Severity of Illness item scores; changes from baseline to Weeks 2, 4, 6, and 10 in values for the following psychiatric assessments: BPRS Positive Symptom Cluster score, BPRS Negative Symptom Cluster score, BPRS factor scores, NPI-NH total and select subscale scores, MOSES social activities subscale total score, APFR scores, PSMS total score, and MMSE total score; BPRS response, defined as a decrease of at least 30% in BPRS total score from baseline to Week 10 or final assessment; CGI Global Improvement score at Weeks 2, 4, 6, and 10 (or final assessment).

Efficacy assessments—OLE

Changes from baseline (Week 0 of the double-blind phase) to OLE Week 12 (or final assessment) in BPRS total, Positive Symptom Cluster, Negative Symptom Cluster, and factor scores; NPI-NH total and select subscale scores; MOSES social activities subscale total score; APFR scores; and MMSE total score; changes from baseline to OLE Weeks 4, 8, and 12 (or final assessment) in CGI Severity of Illness and PSMS scores; BPRS response at OLE Week 12 (or final assessment); and CGI Global Improvement score at OLE Weeks 4, 8, and 12 (or final assessment).

Safety assessments—double-blind and OLE treatment phases

Frequency of adverse events (AEs), serious AEs (SAEs), and AEs leading to withdrawal; hematology and clinical chemistry test results, ECG findings, vital sign measurements, physical examination results including weight and temperature, and neurological assessment scores including Simpson-Angus Scale and abnormal involuntary movement scale (AIMS) scores.

Statistical considerations:

In the double-blind treatment phase, the primary population for efficacy analyses was the intent-to-treat (ITT) population, defined as all randomized patients with ALZ-P who took trial treatment and had at least 1 postbaseline efficacy measurement (ie, at least 2 weeks of trial treatment). The secondary population was the subset of patients from the ITT population who were ruled protocol adherent.

A sample size of 90 patients per treatment group (ALZ-P patients only) provided 90% power to detect a difference of 4.5 between quetiapine and placebo treatment groups in the mean change from baseline BPRS total score, using a 2-sided test at a significance level of 0.05. The sample size calculation was based on a standard deviation of approximately 9. The targeted sample size was also sufficient to detect a difference of 0.5 units between the quetiapine and placebo treatment groups in mean change from baseline CGI Severity of Illness score with 90% power, based on a standard deviation of 1.

The primary time point for analysis was Week 10. If a patient withdrew before Week 10, data from the patient's final visit were carried forward for endpoint analysis (last observation carried forward [LOCF]). Secondary analyses evaluated data at each visit before Week 10. Each analysis was performed using LOCF data, as well as observed data.

Changes from baseline in BPRS total and CGI Severity of Illness item scores were analyzed using an analysis of covariance (ANCOVA) model that included terms for center, baseline score, and treatment. Pairwise differences between least-squares means were calculated for quetiapine versus placebo and quetiapine versus haloperidol, and 95% confidence intervals were constructed. (In post hoc analyses using the same ANCOVA model, differences were also calculated for haloperidol versus placebo to evaluate assay sensitivity.)

Secondary efficacy endpoints, with exception for CGI Global Improvement score, APFR response, and BPRS response, were analyzed using the same ANCOVA model developed for the primary endpoint. CGI Global Improvement scores were analyzed using an analysis of variance (ANOVA) model that included terms for center and treatment. APFR results were evaluated by tabulating the distribution of responses by trial week, treatment, and patient group. Rates of response based on a 30% decrease in BPRS total score were compared among treatment groups using Mantel-Haenszel chi-square tests.

Because all patients received quetiapine in the OLE, the primary focus was safety and tolerability, regardless of diagnosis. Without an OLE control group, statistical analyses were based on data from nominal patient subgroups defined by original double-blind treatment. The same statistical models used to analyze data from the double-blind treatment phase were used for OLE data. However, for reporting purposes, descriptive statistics for OLE efficacy and safety variables were considered key results, and thus, p-values from OLE analyses are not included in the main body of the report. Baseline values for OLE efficacy and safety assessments were those from double-blind Week 0.

RESULTS

Patients: In all, 501 patients from 47 centers were screened for eligibility; 378 qualified to enter the trial and were assigned to double-blind treatment as follows: 124 to quetiapine (91 ALZ-P, 33 OP), 128 to haloperidol (94 ALZ-P, 34 OP), and 126 to placebo (99 ALZ-P, 27 OP).

Disposition patterns were similar regardless of diagnosis (Table S1). For each diagnosis-based subgroup, withdrawal rates for quetiapine-treated and placebo-treated patients were similar and were slightly lower than withdrawal rates for haloperidol-treated patients.

Table S1 Disposition of randomized patients, by diagnosis subset and treatment

Diagnosis	Disposition	Quetiapine		Haloperidol		Placebo		Total	
		N	(%)	N	(%)	N	(%)	N	(%)
ALZ-P	Randomized	91	(100)	94	(100)	99[a]	(100)	284[a]	(100)
	Completed trial	62	(68)	55	(59)	63	(64)	180	(63)
	Withdrawn	29	(32)	39	(42)	36	(36)	104	(37)
	Entered OLE[b]	68	(75)	61	(65)	72	(73)	201	(71)
OP	Randomized	33	(100)	34	(100)	27	(100)	94	(100)
	Completed trial	21	(64)	20	(59)	17	(63)	58	(62)
	Withdrawn	12	(36)	14	(41)	10	(37)	36	(38)
	Entered OLE[b]	27	(82)	26	(77)	20	(74)	73	(78)

[a] The total number of patients assigned to placebo includes 1 patient withdrawn from the trial before treatment began.
[b] Patients were eligible to enter the OLE and continue/begin quetiapine treatment for up to 3 months if they completed the 10-week double-blind treatment segment or if they had adverse events (with any treatment) that led to withdrawal after Week 4 (of double-blind treatment).
ALZ-P Alzheimer's dementia with psychosis. OLE Open-label extension. OP Other psychoses.

Demographic characteristics were similar among the 3 treatment groups. Most patients were white (84% to 90%) and female (66% to 75%). Mean age was approximately 82 years (range, 66 to 99 years), and mean weight was approximately 136 lb, with the widest range seen among haloperidol-treated patients (60 to 289 lb). The overall distribution of patients by diagnosis was consistent with the protocol-specified 3:1 ratio for ALZ-P to OP. Among patients with ALZ-P, the most frequent diagnosis per treatment group was late-onset dementia with delusions (68% to 73%). Among patients with OP, the greatest proportion in each treatment group had vascular dementia (47% to 74%).

The ITT population comprised 265 patients with ALZ-P: 85 treated with quetiapine, 86 treated with haloperidol, and 94 treated with placebo. The safety population included 377 patients (all diagnoses): 124 treated with quetiapine, 128 treated with haloperidol, and 125 treated with placebo.

Baseline psychiatric rating scale scores (ITT population) are summarized in Table S2.

Table S2 Baseline psychiatric rating scale scores (ITT population)

Rating scale	Baseline score, by double-blind treatment for patients with ALZ-P[a]								
	Quetiapine			Haloperidol			Placebo		
	n	Mean	SD	n	Mean	SD	N	Mean	SD
BPRS total score	85	40.0	10.37	86	39.4	9.61	94	39.1	9.82
CGI Severity of Illness	85	4.8	0.75	86	4.6	0.69	94	4.7	0.66
NPI-NH total score	86	38.8	19.79	86	40.2	19.37	94	35.6	17.57
MOSES total score	81	21.1	5.16	78	21.4	4.98	91	21.0	5.55
PSMS total score	86	17.7	5.51	85	17.8	4.63	94	17.3	5.64
MMSE total score	72	12.4	5.09	66	12.7	5.60	75	13.2	5.44

ALZ-P Alzheimer's dementia with psychoses. BPRS Brief Psychiatric Rating Scale.
CGI Clinical Global Impression. ITT Intent to treat. MMSE Mini Mental State Exam.
MOSES Multi-observational Scale for Elderly Subjects.
NPI-NH Neuropsychiatric Inventory- Nursing Home Version. PSMS Physical Self-maintenance Scale.

Of 274 patients who entered the OLE, 219 did so after completing the double-blind portion of the study. Demographics for this population remained reflective of the overall population in the double-blind portion of the study. That is, the majority of patients were women (75%) and white (88%). Mean age and mean weight were 82 years (range, 66 to 98 years) and 137 lb (range, 75 to 267 lb), respectively. The overall rate of withdrawal was similar to rates of withdrawal by diagnostic subgroup (overall, 24%; ALZ-P, 24%; and OP, 25%). Most withdrawals were due to adverse events.

Efficacy—double-blind treatment phase:

BPRS total and CGI Severity of Illness scores improved overall from baseline to Week 10; the quetiapine-treated group showed greater improvement than the haloperidol-treated and placebo-treated groups, but the differences between groups at Week 10 were not significant. BPRS Positive Symptom Cluster scores showed similar, nonsignificant degrees of improvement from baseline to Week 10 in each of the 3 groups. In contrast, BPRS Negative Symptom Cluster scores improved slightly in the quetiapine and placebo treatment groups but worsened in haloperidol-treated patients; the difference between quetiapine and haloperidol was statistically significant (p=0.001). See Table S3 for a summary of LSmean changes from baseline and results from ANCOVA for other applicable psychiatric rating scale scores.

For the secondary efficacy endpoints of BPRS response and CGI Global Improvement, significant differences between quetiapine and haloperidol or placebo were not seen.

Efficacy—OLE treatment phase:

Mean BPRS total and CGI Severity of Illness scores improved from double-blind baseline (Week 0) to OLE Week 12; no significant differences were seen when patients were grouped by previous double-blind treatment. (For BPRS total score, LSmean change from baseline was –13.1, –11.7, and –12.2 for those previously treated with quetiapine, haloperidol, and placebo, respectively.) Similar patterns of additional improvement from baseline were noted in BPRS subscale (Positive and Negative Symptom Cluster) scores.

At OLE end, LSmean values for CGI Global improvement were 2.69, 3.05, and 3.01 for patients previously treated with quetiapine, haloperidol, and placebo, respectively (indicating small levels of improvement [2=moderately improved; 3=minimally improved]).

Table S3 Psychiatric assessments: change from double-blind baseline to Week 10: ITT population (ANCOVA)

Psychiatric rating scale score assessed	Change from baseline (LOCF)						P-value for comparison with quetiapine (ANCOVA)	
	Quetiapine (n=85)		Haloperidol (n=86)		Placebo (n=94)		Haloperidol	Placebo
	LSmean	SE	LSmean	SE	LSmean	SE		
BPRS total[a]	–7.53	1.29	–6.09	1.25	–5.63	1.16	0.354	0.217[c]
CGI Severity of Illness[a]	–0.46	0.11	–0.44	0.11	–0.38	0.10	0.887	0.577[c]
BPRS Positive Symptom Cluster total[b]	–0.74	0.11	–0.78	0.11	–0.62	0.10	0.751	0.355
BPRS Negative Symptom Cluster total[b]	–0.10	0.12	0.41	0.12	–0.20	0.11	**0.001**	0.507
NPI-NH total[b]	–12.70	2.15	–12.24	2.09	–9.42	1.96	0.859	0.203
Agitation item[b]	–2.34	0.53	–1.95	0.52	–1.49	0.49	0.544	0.187
Delusions item[b]	–3.28	0.44	–3.70	0.42	–2.75	0.39	0.425	0.311
Hallucinations item[b]	–1.23	0.34	–1.36	0.32	–1.09	0.30	0.743	0.733
Delusions + hallucinations items[b]	–4.52	0.63	–5.07	0.60	–3.82	0.57	0.470	0.352
Agitation + delusions + hallucinations items[b]	–6.68	0.94	–7.08	0.90	–5.04	0.85	0.719	0.145
NPI-NH disruption total[b]	–5.64	0.83	–4.25	0.81	–3.80	0.76	0.167	0.065
Agitation disruption[b]	–0.91	0.17	–0.77	0.17	–0.46	0.16	0.503	**0.032**
Delusions disruption[b]	–1.30	0.17	–1.24	0.16	–0.97	0.15	0.759	0.099
Hallucinations disruption[b]	–0.61	0.12	–0.56	0.12	–0.48	0.11	0.735	0.349
Delusions + hallucinations disruption[b]	–1.92	0.23	–1.80	0.22	–1.45	0.21	0.676	0.086
Agitation + delusions + hallucinations disruption[b]	–2.83	0.35	–2.55	0.34	–1.88	0.32	0.506	**0.024**
MOSES total[b]	–0.32	0.47	1.33	0.46	–0.04	0.41	**0.004**	0.612
PSMS total[b]	0.09	0.35	1.67	0.34	0.63	0.31	**<0.001**	0.198
MMSE total[b]	–2.11	0.52	–1.47	0.53	–1.04	0.48	0.336	0.098

[a] Primary endpoint.
[b] Secondary endpoint.
[c] In a post hoc ANCOVA comparing haloperidol with placebo, differences between treatments (LOCF) were not significant (BPRS, p=0.766; CGI, p=0.679).

ANCOVA Analysis of covariance. BPRS Brief Psychiatric Rating Scale. CGI Clinical Global Impression. ITT Intent-to-treat. LOCF Last observation carried forward. LSmean Least-squares mean. MOSES Multi-Observational Scale for Elderly Patients (Social activities subscale). MMSE Mini Mental State Examination. NPI-NH Neuropsychiatric Inventory - Nursing Home Version. PSMS Physical Self-maintenance Scale. SE Standard error.

Safety:

In both the double-blind and OLE treatment phases, quetiapine was generally well tolerated. Exposure was relatively low (mean daily dose: 113 mg, double-blind phase; 110 mg, OLE) although consistent with quetiapine exposure in previous trials in elderly patients. A categorical overview of AEs and related withdrawals is provided in Table S4 for both treatment phases.

Table S4 Categorical overview of adverse events

Category[a]	Patients by double-blind treatment		
Double-blind treatment phase, n (%)	Quetiapine (N=124)	Haloperidol (N=128)	Placebo (N=125)
Patients with at least 1 adverse event (AE)	114 (92)	117 (91)	111 (89)
Patients with serious adverse events[b] (SAE)	17 (14)	19 (15)	19 (15)
Patients with AEs that led to withdrawal[b]	16 (13)[c]	24 (19)[d,e]	18 (14)[f]
Deaths	4 (3)	9 (7)[g]	4 (3)

	All OLE patients	OLE patients by previous double-blind treatment		
OLE treatment phase, n (%)	Quetiapine (N=274)	Quetiapine (N=95)	Haloperidol (N=87)	Placebo (N=92)
Patients with at least 1 AE	245 (89.4)	85 (89.5)	77 (88.5)	83 (90.2)
Patients with SAEs	53 (19.3)[h]	19 (20.0)	18 (20.7)[h]	16 (17.4)
Patients with AEs that led to withdrawals	40 (14.6)[i]	12 (12.6)[i]	16 (18.4)	12 (13.0)
Deaths	15 (5.5)	6 (6.3)	4 (4.6)	5 (5.4)

[a] Patients may be included in more than 1 category. For patients who entered the open-label extension, deaths and SAEs that occurred during the 30 days following double-blind treatment are included in the OLE counts.

[b] Not all SAEs led to withdrawal and not all AEs that led to withdrawal were serious.

[c] One additional patient (Patient 0027/2704) withdrew from double-blind treatment because of an AE, but the day of withdrawal was also the first day of OLE treatment. By programming rules, the AE was assigned to the OLE AE count even though the patient completed OLE treatment.

[d] Includes Patient 0038/3809, who had an AE of psychosis, which led to withdrawal. Note, however, that the trial-completion case report form (CRF) indicates that the patient was withdrawn because of lack of efficacy.

[e] One additional patient (Patient 0039/3905) withdrew from double-blind treatment because of AEs, but the day of withdrawal was also the first day of OLE treatment. By programming rules, the AEs were assigned to the OLE AE count even though the patient completed OLE treatment.

[f] Includes Patient 0043/4301 whose AE occurred on the next to last day of double-blind treatment but who was not withdrawn because of this AE until after OLE treatment was started.

[g] Includes 3 patients with causative AEs that started more than 1 day after trial treatment ended and 1 patient (0041/4106) who, on Day 1, had numerous AEs and was withdrawn at the investigator's discretion and who subsequently died more than 30 days after trial treatment ended.

[h] Includes Patient 0013/1305 who completed the trial but who then died 106 days after onset of treatment due to heart arrest.

[i] One additional patient (Patient 0030/3008) was hospitalized for a serious urinary tract infection and subsequently withdrawn (per the disposition CRF) because of this event. However, due to an error in the database, this AE was not listed as having led to withdrawal in the AE tables. Overall, then, 41 (15.0%) patients withdrew because of AEs.

In the double-blind treatment phase, incidence of death was slightly higher for patients treated with haloperidol (7%), compared with that for patients treated with quetiapine (3%) or placebo (3%). The incidence of death during the OLE was 5.5%. Overall, the AEs that resulted in death were consistent with the known leading causes of death in patients ≥65 years of age, and included heart disease, cerebrovascular disease, pneumonia, and sepsis. Among patients who died (any treatment phase),

causative AEs were assessed as treatment related in only 2 patients: pneumonia in a patient treated with double-blind quetiapine and dementia in a patient treated with placebo. Incidences of SAEs were similar among double-blind treatment groups (14% to 15%). The overall incidence of SAEs during the OLE (19%) was slightly greater than the incidences seen during double-blind treatment. While AEs were the most common reasons for withdrawal, the types of AEs that led to withdrawal were varied and occurred with no obvious pattern or time to onset. Adverse events that occurred in 5% of patients treated with quetiapine during double-blind treatment are summarized in Table S5.

Table S5 Adverse events with reported incidences of ≥5% among quetiapine-treated patients: double-blind treatment phase

Body system and adverse event[a]	Number (%) of patients		
	Quetiapine (N=124)	Haloperidol (N=128)	Placebo (N=125)
Any adverse event	114 (92)	117 (91)	111 (89)
Body as a whole			
Accidental injury	52 (42)	55 (43)	55 (44)
Headache	11 (9)	10 (8)	7 (6)
Infection	14 (11)	8 (6)	6 (5)
Pain	17 (14)	12 (9)	17 (14)
Cardiovascular system			
Postural hypotension	7 (6)	6 (5)	5 (4)
Digestive system			
Vomiting	16 (13)	6 (5)	6 (5)
Metabolic and nutritional disorders			
Peripheral edema	10 (8)	5 (4)	5 (4)
Weight gain	7 (6)	6 (5)	2 (2)
Weight loss	6 (5)	9 (7)	5 (4)
Nervous system			
Agitation	12 (10)	15 (12)	23 (18)
Dizziness	9 (7)	6 (5)	8 (6)
Somnolence	32 (26)	41 (32)	7 (6)
Respiratory system			
Cough increased	8 (6)	11 (9)	6 (5)
Skin and appendages			
Rash	19 (15)	15 (12)	15 (12)
Skin ulcer	8 (6)	5 (4)	8 (6)
Special senses			
Conjunctivitis	8 (6)	6 (5)	3 (2)
Urogenital system			
Urinary tract infection	15 (12)	13 (10)	8 (6)

During double-blind treatment, accidental injuries were the most frequently reported adverse events overall, with events occurring at similar rates in the 3 treatment groups: in 42%, 43%, and 44% of patients treated with quetiapine, haloperidol, and placebo, respectively. Somnolence was the second most frequently reported event among patients treated with quetiapine (26%) and patients treated with haloperidol (32%) but was relatively infrequent among patients treated with placebo (6%).

A similar pattern of AEs was seen during the OLE, ie, accidental injuries (50%) and somnolence (20%) were the most frequently reported AEs overall. Somnolence was reported more frequently in patients not previously treated with quetiapine.

In both treatment phases, accidental injuries were predominantly falls, were not often associated with orthostatic effects, and were predominantly assessed as not drug related.

During double-blind treatment, rates of EPS-related AEs were similar between quetiapine- and placebo-treated patients (11% and 10%, respectively) and lower than that for haloperidol-treated patients (31%). The overall rate of EPS-related AEs (11%) did not increase with up to 12 additional weeks of quetiapine treatment in the OLE. In both treatment phases, results of neurological assessments reflected the placebo-like levels of EPS seen with quetiapine.

There were no AE reports of agranulocytosis or neutropenia and no evidence of treatment-emergent diabetes mellitus or hypothyroidism. Vital sign profiles (for blood pressure and pulse rate) were consistent with the known effects of quetiapine. Through up to 10 weeks of blinded treatment with quetiapine and up to an additional 12 weeks of open-label treatment, changes in QTc to ≥500 msec in patients with normal baseline values were uncommon. Changes in vital signs were rarely causes for withdrawal.

Overall, no new safety concerns were identified.