Drug substance(s):	Quetiapine fumarate	**SYNOPSIS**	
Study code:	D144AL00002		
Date:	17 March 2008		

A Multicenter, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind, Phase III Study to Compare the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) versus Placebo as Adjunct Therapy with Mood Stabilizers (Lithium or Divalproex) for the Treatment of Alcohol Dependence in Patients with Bipolar I Disorder

Study center(s)

This study was conducted in 43 centers in the United States.

Publications

There were no publications at the time of this report.

Study dates		**Phase of development**
First patient enrolled	31 January 2006	Therapeutic confirmatory (III)
Last patient completed	30 April 2007	

Objectives

The primary objective of this study was to evaluate the efficacy of quetiapine versus placebo when used as adjunct therapy with lithium or divalproex in reducing the proportion of heavy drinking days from baseline to Week 12 as derived from the Timeline Followback (TLFB) scale.

The secondary objectives were to evaluate quetiapine versus placebo when used as adjunct therapy with lithium or divalproex by assessing the following:

1. Change in the proportion of non-drinking days from baseline to Week 12 and to monthly intervals, as derived from the TLFB.

2. Change in the mean number of standardized drinks per day from baseline to Week 12 and to monthly intervals, as derived from the TLFB.

3. Time from randomization to first 14 consecutive days of abstinence from alcohol consumption, as derived from the TLFB.

4. Change in γ-glutamyl transferase (GGT) value from baseline to Week 12.

5. Change in alcohol craving as assessed by the change from baseline to Week 12 as in the Obsessive Compulsive Drinking Scale (OCDS) total score.

6. Changes in concomitant drug craving/use as assessed by the Brief Substance Craving Scale (BSCS) total score, the total amount of money spent on drugs, and the total number of drug use days from baseline to Week 12.

7. Change in manic symptoms as assessed by the change from baseline to each visit in the Young Mania Rating Scale (YMRS) total score.

8. Change in depressive symptoms as assessed by the change from baseline to each visit in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

9. Change in the Clinical Global Impression – Severity of Illness (CGI-S) score from baseline to Week 12 and Clinical Global Impression – Improvement (CGI-I) response at each visit.

10. Change in anxiety symptoms as assessed by the change in the Hamilton Rating Scale for Anxiety (HAM-A) total score from baseline to Week 12.

11. Change in Quality of Life as assessed by the change in the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) total score from baseline to Week 12.

12. Change in functional impairment with regard to work/school, social life, and family life/home responsibilities as assessed by the Sheehan Disability Scale (SDS) total score from baseline to Week 12.

13. Change in the number of lost days from baseline to Week 12 as measured by SDS.

14. Change in the number of underproductive days from baseline to Week 12 as measured by the SDS.

15. Change in nicotine consumption as assessed by the change in the mean number of cigarettes smoked per day from baseline to Week 12.

16. The safety and tolerability of quetiapine in patients with bipolar I disorder and alcohol dependence.

17. Explore the effects of genetic polymorphisms on response to quetiapine fumarate and on susceptibility to bipolar disease with alcohol dependence. (The

pharmacogenetic research was optional for individual patients and centers. Further details are provided in Appendix C of the study protocol.)

Study design

This was a multicenter, randomized, placebo-controlled, parallel-group, double-blind, Phase III study to compare the efficacy and safety of quetiapine (300 mg/day – 800 mg/day) versus placebo as adjunct therapy with lithium or divalproex for the treatment of alcohol dependence in patients with bipolar I disorder over a 12-week treatment course following a Screening Period of 5-28 days.

Target patient population and sample size

Outpatients between 21 and 60 years of age were enrolled if they met the Diagnostic and Statistical Manual of the American Psychiatric Association, 4th ed. (DSM-IV) Criteria for bipolar I disorder and alcohol dependence, as confirmed by the Structured Clinical Interview for DSM-IV (SCID). Eligible patients had to have a recent history of heavy drinking, ie minimum 4 standard drinks/day (females) or 5 standard drinks/day (males) for at least 10 days out of the past 28 days prior to the Screening Visit.

A total of 157 evaluable patients per treatment group with bipolar I disorder and alcohol dependence (ie, 314 total patients) were required for 80% power to detect an absolute difference over placebo of 10 percentage points in the mean change in proportion of heavy drinking days from baseline to Week 12.

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

During the Screening Period, lithium or divalproex was administered on a dose regimen determined by the investigator in order to achieve recommended trough serum concentrations within the target range of 0.7 – 1.0 mEq/L or 50 – 100 µg/mL, respectively.

During the Randomized Treatment Phase, eligible patients were randomized to 12 weeks of treatment with quetiapine or placebo (study drug). Study drug was administered orally twice a day (with or without food). Patients underwent a forced titration of 50 mg on the evening of Day 1, 100 mg on Day 2, 200 mg on Day 3, 300 mg on Day 4, and 400 mg from Day 5 through Day 7. The 400 mg dose of quetiapine could not be changed from Day 5 through Day 7. Patients assigned to placebo underwent the same mock titration. Patients were further titrated (300 mg/day – 800 mg/day) at the investigator's discretion based upon efficacy and tolerability. Quetiapine could be increased in increments not to exceed 200 mg/day, based on efficacy and tolerability. This dosage of quetiapine could be decreased by any amount, based on safety and tolerability provided the total daily dose did not go below 300 mg at any time after Day 3. With the exception of Day 1 of the Randomized Treatment Phase, quetiapine (or matching placebo) should have always been taken twice daily. After Day 7, the daily dose distribution could have been determined by the investigator.

AstraZeneca supplied the following study medication (batch numbers are provided in parentheses)

- Quetiapine: 25 mg tablet (6500J), 100 mg tablet (6515J, 6516J, 7530K, 7532K)
- Placebo (for quetiapine): 25 mg tablet (LC4618, 7553F), 100 mg tablet (ST70142-015-FA02, ST70142-015-FA06, 7500F)
- Lithium: 300 mg capsule (457529A, 564081A)
- Divalproex: 250 mg tablet (24429AA21)

Duration of treatment

12 weeks.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Change in the proportion of heavy drinking days from baseline to Week 12 as derived from the TLFB scale. Baseline proportion of heavy drinking days was derived from the 28 days prior to the Screening Visit.
- Secondary variables: Change from baseline to Week 12 in the following: proportion of non-drinking days, mean number of standardized drinks, time to first 14 consecutive days of abstinence from alcohol consumption, CGI-S, HAM-A, mean number of cigarettes smoked per day and GGT level; and change from baseline to each visit in the YMRS, MADRS, and proportion of patients showing response (as assessed by the CGI-I global score).

Patient reported outcomes

- Secondary variables: Change from baseline to Week 12 in the following: Q-LES-Q total score, OCDS total score, BSCS total score, BSCS number of drug use days, BSCS amount of money spent on concomitant drug use, SDS total score, SDS number of lost days, and SDS number of underproductive days.

Safety

Safety variables included the incidence of AEs, clinically significant changes from baseline in clinical laboratory test results, vital signs, physical examinations, electrocardiograms, withdrawals due to AEs, clinically significant changes in weight, clinically significant changes from normal in glucose, insulin, lipid levels, ALT, AEs related to extrapyramidal symptoms, and the change from baseline in the Simpson-Angus Scale (SAS) score and Barnes Akathisia Rating Scale (BARS) global score.

Statistical methods

All statistical comparisons of quetiapine versus placebo were performed based on a two-sided hypothesis with a significance level of 0.05. The primary comparison of interest was the difference between quetiapine and placebo in the change from baseline to Week 12 in the proportion of heavy drinking days, which was analyzed using an Analysis of Covariance (ANCOVA) model. The model included stratum and treatment as fixed factors, center as a random factor, and baseline proportion of heavy drinking days as a covariate. Change in the proportion of heavy drinking days from baseline to Week 12 was also analyzed using a mixed effects repeated measures model. For all efficacy measurements, missing data were handled using a last observation carried forward approach, as appropriate. Patients with post randomization data had their last study assessment carried forward as the final assessment for analyses.

ANCOVA methods similar to those described for the primary efficacy variable were used for the analysis of the following change from baseline variables: proportion of non-drinking days, mean number of standard drinks per day, OCDS total score, BSCS score, BSCS total amount of money spent on drugs, BSCS total number of drug use days, YMRS total score, CGI-S score, MADRS total score, HAM-A total score, Q-LES-Q total score, SDS total score, SDS number of lost days per week, SDS number of underproductive days per week, and mean number of cigarettes smoked per day. For each model, the comparison of interest was the difference between quetiapine and placebo at Week 12. Time from randomization to the first 14 consecutive days of abstinence was analyzed using a Cox proportional hazards model. CGI-I response was analyzed using a generalized estimating equation (GEE) model.

The Screening Period safety analysis data set included data from all patients who took at least 1 dose of mood stabilizer and patients were classified according to the actual mood stabilizer taken (ie, divalproex or lithium). No safety analyses were performed on the Screening Period safety analysis set. The safety analysis data set included data from all patients who took at least 1 dose of randomized study treatment, and was used for Randomized Treatment Period safety analyses. Patients were classified according to actual randomized treatment taken (ie, quetiapine or placebo). The full analysis data set (FADS) was defined according to a modified intention-to-treat (ITT) principle and included data from all randomized patients who took at least 1 dose of randomized treatment and had both baseline and at least 7 consecutive days of post-baseline TLFB data. Patients were classified according to randomized treatment. FADS was used for all efficacy analyses. The per protocol (PP) analysis data set was a subset of the FADS that excluded data from all patients with significant protocol violations or deviations, and was used for sensitivity analyses to examine the robustness of FADS results. Patients were classified according to actual randomized treatment taken.

Patient population

In total, 585 patients were screened and 362 patients with bipolar I disorder and alcohol dependence were randomly assigned to receive quetiapine or placebo. Of those screened, a total of 480 patients met eligibility requirements and were assigned to open-label mood

stabilizer (lithium or divalproex) using an interactive voice response system. Of the 480 patients assigned to mood stabilizer, 362 patients were randomized 1:1 to either quetiapine (dose-titrated) or placebo. A total of 177 patients stratified to divalproex and 185 patients stratified to lithium were randomized. Of the 362 randomized patients, 361 patients received treatment and were analyzed for safety (one patient did not receive study drug because he was not willing to continue the study; thus he was not included in the safety analysis set); 328 patients were included in the FADS; and 276 patients were included in the PP analysis data set. With 176 patients in the quetiapine group and 186 patients in the placebo group, the randomization goals were considered to be adequately satisfied.

Of all randomized patients, 42.0% of the quetiapine-treated patients and 43.0% of the placebo-treated patients completed the study. The most common reason for discontinuation was AE in the quetiapine group and patient lost to follow-up in the placebo group. The 2 treatment groups were well matched in number and demographic and baseline characteristics (Table S1). The mean patient age was approximately 39 years, approximately 63% of all patients were male, and nearly 88% of patients in both treatment groups were Caucasian. Nearly 70% of patients in both groups had a DSM-IV diagnosis of either bipolar I most recent depressed moderate or bipolar I most recent mixed moderate. Demographic and baseline disease characteristics were similar between the mood stabilizer strata.

Table S1 Patient population and disposition

Demographic or baseline disease characteristic		**Treatment group**	
Demographic characteristics		**Placebo (N=186)**	**Quetiapine (N=176)**
Sex (n and % of patients)	Male	118 (63.4)	111 (63.1)
	Female	68 (36.6)	65 (36.9)
Age (years)	Mean (SD)	38.3 (9.82)	39.0 (9.11)
	Range	21 to 60	21 to 60
Race (n and % of patients)	Caucasian	160 (86.0)	157 (89.2)
	Black	19 (10.2)	14 (8.0)
	Oriental	1 (0.5)	0
	Other	6 (3.2)	5 (2.8)
Baseline disease characteristics (OC, Full analysis data set)[a]		**Placebo (N=169)**	**Quetiapine (N=159)**
Baseline proportion of heavy drinking days		0.67 (0.23)	0.66 (0.24)
Baseline proportion of non-drinking days		0.25 (0.21)	0.26 (0.21)
Baseline mean number of standardized drinks per day		7.17 (4.92)	6.99 (3.76)
Baseline GGT level		3.62 (0.895)	3.65 (0.873)
Baseline YMRS score		10.6 (7.03)	11.6 (6.62)
Baseline MADRS score		17.2 (8.60)	19.0 (8.66)
Baseline CGI-S score		3.9 (0.72)	4.0 (0.69)

Table S1 Patient population and disposition

Demographic or baseline disease characteristic	Treatment group	
Baseline HAM-A score	13.1 (6.2)[n=168]	13.9 (6.2)
Baseline cigarettes smoked per day	12.0 (12.6)[n=166]	13.8 (13.4)[n=156]

[a] Mean (SD) presented for all baseline disease characteristics.

CGI-S Clinical Global Impression-Severity of Illness. GGT Gamma glutamyl transferase. HAM-A Hamilton Rating Scale for Anxiety. MADRS Montgomery-Åsberg Depression Rating Scale. OC Observed case. SD Standard deviation. YMRS Young Mania Rating Scale.

Efficacy results

Table S2 presents the results of the main efficacy analyses comparing quetiapine versus placebo.

Table S2 Summary of results of main efficacy analyses comparing quetiapine versus placebo (Full analysis data set)

Variable[a,b,c]	Placebo (N=169)	Quetiapine (N=159)	Quetiapine vs Placebo		
	LS Mean	LS Mean	LS Mean	95% CI	p-value
Change in proportion of heavy drinking days					
Week 4 (OC) (169, 159)	-0.30	-0.32	-0.01	-0.07, 0.04	0.650
Week 8 (OC) (121, 100)	-0.34	-0.38	-0.04	-0.11, 0.03	0.290
Week 12 (primary) (169, 159)	-0.36	-0.36	0.00	-0.05, 0.06	0.930
Change in proportion of non-drinking days					
Week 4 (OC) (169, 159)	0.19	0.21	0.02	-0.03, 0.08	0.400
Week 8 (OC) (121, 100)	0.24	0.27	0.03	-0.04, 0.11	0.400
Week 12 (169, 159)	0.26	0.25	-0.01	-0.07, 0.05	0.730
Change in number of standardized drinks per day					
Week 4 (OC) (169, 159)	-3.21	-3.44	-0.23	-0.82, 0.36	0.450
Week 8 (OC) (121, 100)	-3.57	-3.98	-0.41	-1.10, 0.28	0.240
Week 12 (169, 159)	-3.84	-3.85	-0.02	-0.60, 0.56	0.950
Time from randomization to first 14 days of abstinence (169, 159)[d]			0.97[d]	0.62, 1.53	0.899
Change in the mean YMRS total score (169, 158)	-4.00	-4.89	-0.89	-1.98, 0.19	0.110
Change in the mean MADRS total score (169, 158)	-6.22	-6.30	-0.08	-1.82, 1.67	0.930
Change in the mean CGI-S total score (169, 157)	-0.83	-1.04	-0.21	-0.43, 0.01	0.060
CGI-I response (75, 69), n (%)[e]	49 (65.33)	69 (63.77)	0.93[e]	0.47, 1.85	0.846
Change in the mean HAM-A total score (105, 109)	-4.17	-4.39	-0.21	-1.67, 1.24	0.770
Change in the mean number of cigarettes smoked per day (103, 102)	-0.93	-0.89	0.04	-1.31, 1.38	0.960
Change in the GGT level (142, 138)	-0.16	-0.05	0.10	-0.05, 0.26	0.190
Change in the mean Q-LES-Q total score (105, 108)	2.76	2.07	-0.69	-3.49, 2.11	0.630
Change in the mean SDS total score (104, 105)	-2.93	-2.57	0.36	-1.78, 2.50	0.740

Variable[a,b,c]	Placebo (N=169)	Quetiapine (N=159)	Quetiapine vs Placebo		
	LS Mean	LS Mean	LS Mean	95% CI	p-value
Change in the SDS mean number of lost days per week (94, 95)	-0.64	-0.36	0.28	-0.20, 0.76	0.250
Change in the SDS mean number of underproductive days (94, 97)	-0.43	-0.27	0.16	-0.47, 0.78	0.620
Change in the mean OCDS total score (165, 157)	-7.29	-6.66	0.63	-0.81, 2.08	0.390
Change in the mean BSCS total score (169, 155)	-1.84	-1.79	0.05	-1.02, 1.11	0.930
Change in the BSCS mean total amount of money spent on drugs (161, 141)	-31.46	-30.97	0.49	-10.93, 11.91	0.930
Change in the BSCS mean total number of drug use days (77, 71)	-0.18	-0.09	0.09	-0.62, 0.80	0.800

[a] Data presented are for change from baseline to Week 12 unless otherwise specified.
[b] The n for each outcome variable is presented as (n for placebo group, n for quetiapine group) immediately after the outcome variable or week specified.
[c] Data presented are LOCF and are the results of an ANCOVA analysis unless otherwise noted.
[d] Cox proportional hazard model was used to analyze time from randomization to first 14 consecutive days of abstinence from alcohol. Hazard ratio is presented.
[e] Generalized estimating equation analysis of CGI-I response. CGI-I response was defined as having a CGI-I rating of either "very much improved" or "much improved." Odds ratio is presented.

ANCOVA Analysis of covariance. BSCS Brief Substance Craving Scale. CGI-I Clinical Global Impression-Improvement. CGI-S Clinical Global Impression-Severity of Illness. CI Confidence interval. GGT Gamma glutamyl transferase. HAM-A Hamilton Rating Scale for Anxiety. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. OC Observed case. OCDS Obsessive Compulsive Drinking Scale. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. SDS Sheehan Disability Scale. YMRS Young Mania Rating Scale.

There was no significant difference between quetiapine and placebo in the primary efficacy variable, the change from baseline to Week 12 in the proportion of heavy drinking days, as derived from the TLFB scale (p=0.930). There were no significant differences at Week 12 between the 2 treatment groups for the secondary variables that utilized the TLFB scale (proportion of non-drinking days, number of standardized drinks, and time to first 14 consecutive days of abstinence from alcohol).

The quetiapine group showed a greater reduction in manic and depressive symptoms compared to the placebo group, as assessed by the mean change from baseline to each visit in the YMRS and MADRS total scores, respectively; however, the differences were not statistically significant at any timepoint. The quetiapine group experienced a greater reduction in the severity of illness (CGI-S) at Week 12 (p=0.060) and a higher percentage of quetiapine-treated patients achieved a response (as assessed by CGI-I) compared to the placebo group at Week 4 (p=0.043), Week 6 (p<0.001), Week 8 (p=0.013), and Week 10 (p=0.044), but not Week 12 (p=0.337).

There were no significant differences between the 2 treatment groups at Week 12 in reducing anxiety (as assessed by the HAM-A total score), nicotine consumption (as assessed by the mean number of cigarettes smoked per day), or the biological marker for alcohol intake (as assessed by GGT concentration). There were no significant differences between the 2 treatment groups at Week 12 in any of the patient reported outcomes (Q-LES-Q total score, SDS total score, SDS number of lost days, SDS number of underproductive days, OCDS total score, BSCS total score, BSCS total amount of money spent on drugs, and BSCS total number of drug use days).

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 strata), summarized by preferred term, are shown in Table S3 and Table S4, respectively.

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (Safety analysis set)

Category of AE	Patients who had any AE in each category, n (%)[a]					
	Placebo			Quetiapine		
	Lithium (N=92)	Divalproex (N=94)	Total (N=186)	Lithium (N=93)	Divalproex (N=82)	Total (N=175)
Any AE	66 (71.7)	64 (68.1)	130 (69.9)	77 (82.8)	66 (80.5)	143 (81.7)
Any AE leading to death	0 (0.0)	0 (0.0)	0 (0.0)[b]	0 (0.0)	1 (1.2)	1 (0.6)
Any SAE (including death)	4 (4.3)	7 (7.4)	11 (5.9)	5 (5.4)	2 (2.4)	7 (4.0)
Any AE leading to discontinuation of study drug	11 (12.0)	10 (10.6)	21 (11.3)	33 (35.5)	9 (11.0)	42 (24.0)
Any other significant AE[c]	9 (9.8)	4 (4.3)	13 (7.0)	25 (26.9)	12 (14.6)	37 (21.1)

[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.

[b] One placebo-treated patient died of myocardial ischemia more than 30 days after her last dose of study drug and is not represented in this table.

[c] Other significant AEs were AEs that were not classified as serious but which resulted in either the dose of investigational product being changed (ie, not increased/decreased as the protocol specified) or temporarily stopped.

AE Adverse event. SAE Serious adverse event.

The overall incidence of AEs was higher in the quetiapine group than the placebo group. Most AEs were mild or moderate in intensity. There were 2 deaths in patients who participated in this study; 1 occurred greater than 30 days after the last dose of study drug and both deaths were judged unrelated to study medication. The incidence of SAEs was low and similar between the 2 treatment groups. More quetiapine-treated patients discontinued study drug due to AEs than did placebo-treated patients. The most common reason for

discontinuation of study drug in the quetiapine group was sedation. The incidence of drug-related AEs was higher in the quetiapine group than the placebo group.

Table S4 Number (%) of patients with the most commonly reported AEs, sorted by decreasing order of frequency as summarized over all treatment groups (Safety analysis set)

Preferred term[a]	Placebo			Quetiapine		
	Lithium (N=92)	Divalproex (N=94)	Total (N=186)	Lithium (N=93)	Divalproex (N=82)	Total (N=175)
Any AE	66 (71.7)	64 (68.1)	130 (69.9)	77 (82.8)	66 (80.5)	143 (81.7)
Sedation	9 (9.8)	8 (8.5)	17 (9.1)	38 (40.9)	23 (28.0)	61 (34.9)
Somnolence	2 (2.2)	5 (5.3)	7 (3.8)	17 (18.3)	21 (25.6)	38 (21.7)
Dry mouth	4 (4.3)	4 (4.3)	8 (4.3)	19 (20.4)	14 (17.1)	33 (18.9)
Weight increased	1 (1.1)	2 (2.1)	3 (1.6)	9 (9.7)	12 (14.6)	21 (12.0)
Dizziness	4 (4.3)	4 (4.3)	8 (4.3)	7 (7.5)	7 (8.5)	14 (8.0)
Headache	13 (14.1)	5 (5.3)	18 (9.7)	7 (7.5)	7 (8.5)	14 (8.0)
Tremor	12 (13.0)	3 (3.2)	15 (8.1)	9 (9.7)	4 (4.9)	13 (7.4)
Constipation	1 (1.1)	1 (1.1)	2 (1.1)	9 (9.7)	3 (3.7)	12 (6.9)
Dyspepsia	0	1 (1.1)	1 (0.5)	6 (6.5)	5 (6.1)	11 (6.3)
Increased appetite	2 (2.2)	7 (7.4)	9 (4.8)	7 (7.5)	4 (4.9)	11 (6.3)
Diarrhea	10 (10.9)	0	10 (5.4)	5 (5.4)	5 (6.1)	10 (5.7)
Fatigue	8 (8.7)	4 (4.3)	12 (6.5)	6 (6.5)	3 (3.7)	9 (5.1)
Nausea	9 (9.8)	3 (3.2)	12 (6.5)	6 (6.5)	2 (2.4)	8 (4.6)
Upper respiratory tract infection	3 (3.3)	7 (7.4)	10 (5.4)	5 (5.4)	3 (3.7)	8 (4.6)
Vision blurred	4 (4.3)	4 (4.3)	8 (4.3)	5 (5.4)	2 (2.4)	7 (4.0)
Vomiting	8 (8.7)	2 (2.1)	10 (5.4)	3 (3.2)	3 (3.7)	6 (3.4)
Insomnia	4 (4.3)	4 (4.3)	8 (4.3)	5 (5.4)	0	5 (2.9)

[a] This table uses a cut-off of 5% in any strata and is presented by decreasing incidence in the total quetiapine group.

AE Adverse event.

Sedation, somnolence, dry mouth, and weight increased were the most common AEs in the quetiapine group, and these AEs occurred at a higher incidence compared to placebo. The majority of these AEs were mild or moderate in intensity. The AE profile was typical of that reported for quetiapine in other trials for other patient populations.

The incidence of AEs of special interest, including AEs potentially associated with nausea and vomiting, sexual dysfunction, and suicidality, were low and similar between the 2 treatment

groups. There was no clinical evidence to suggest a relationship between quetiapine and increased suicidality. No patient had an AE associated with QT prolongation and no quetiapine-treated patient had an AE of syncope. The incidence of AEs potentially associated with somnolence was higher in the quetiapine group than the placebo group; the most common AEs in the quetiapine group were sedation and somnolence. The majority of AEs potentially associated with somnolence were mild or moderate in intensity, did not result in discontinuation of study drug, and were considered by the investigator to be related to study medication. These sedative properties are consistent with the known profile of quetiapine.

The incidence of AEs potentially associated with EPS was similar between the 2 treatment groups (approximately 10%) and the use of anticholinergic medication during the study was low for both treatment groups (<3.5%). The most commonly reported individual AE potentially associated with EPS was tremor in both treatment groups, with more patients stratified to lithium in each treatment group reporting tremor compared to those taking divalproex. The majority of the AEs potentially associated with EPS were judged to be mild or moderate in intensity by the investigator. Overall, the assessment of parkinsonian and akathisia symptoms by SAS and BARS scores indicated that quetiapine treatment was similar to placebo; the majority of patients in each treatment group experienced no change in score at the end of treatment.

The laboratory observations in this trial were consistent with the clinical laboratory profile that has been well characterized in other trials of quetiapine for other patient populations. The higher incidence of liver function abnormalities in both the placebo and quetiapine groups of this trial is likely due to the alcohol-related liver damage expected in this alcohol-dependent population. No differences in mean or median changes from baseline or in incidence of clinically important changes were attributable to exposure to quetiapine.

Clinically important neutropenia was not observed in any quetiapine-treated patients at the end of treatment. One quetiapine-treated patient experienced an AE of neutropenia on Day 1 (1.16×10^9/L) that was judged by the investigator not to be related to study medication. One patient in the placebo group had an ANC value consistent with neutropenia at the end of treatment and no patients had an ANC value consistent with agranulocytosis. Mean changes in glucose and glucose regulation parameters were similar between the 2 treatment groups. The incidence of AEs potentially associated with diabetes mellitus was low and similar between the groups (<2.5%) and only occurred in patients stratified to lithium. These AEs potentially associated with diabetes mellitus included glycosylated hemoglobin increased (2 quetiapine patients), blood glucose increased and polyuria (1 quetiapine patient each), and thirst (3 placebo patients and 1 quetiapine patient). Clinically important elevations of glucose or HbA1c at the end of treatment occurred at a similar incidence between the 2 treatment groups (6 patients in the placebo group and 8 patients in the quetiapine group). The percentage of patients who shifted from <3 metabolic risk factors at randomization to ≥3 metabolic risk factors by the end of treatment were similar between the 2 treatment groups.

Small increases in mean heart rate were seen in quetiapine-treated patients, similar to observations in other trial populations exposed to quetiapine. Observations of BP, orthostatic

changes in pulse and BP, ECG values, and physical examination findings showed no trends suggesting an effect of treatment with quetiapine. Mean increases in weight, and the number of patients with ≥7% increase in weight, were higher in the quetiapine group than the placebo group, similar to observations in other trial populations exposed to quetiapine. Increases in body weight were higher in patients stratified to divalproex than lithium in both treatment groups.