U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA Serial Number:	22-047/ S-029; 20-639/S-057
Drug Name:	Quetiapine (SEROQUEL) XR
Indication(s):	Bipolar Depression
Applicant:	Astra-Zeneca
Date(s):	Submission date October 28, 2011
Review Priority:	Standard (under Pediatric Research Equity Act)
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1. EXECUTIVE SUMMARY

Under the Pediatric Research Equity Act (PREA), the sponsor conducted Study D144AC00001 to evaluate the efficacy and safety of quetiapine XR formulation at a dose of 150 to 300 mg/day in children and adolescents 10 to 17 years of age with bipolar depression. The primary objective was to determine whether quetiapine XR demonstrates superior efficacy versus placebo after 8 weeks of treatment.

In the primary analysis (MMRM) of CDRS-R Total score, the Quetiapine XR treatment group was not statistically significantly different from the placebo arm. Based on the MMRM analysis, the observed LS mean treatment effect was 2.29 units with p-value of 0.252.

In sample size estimation, the assumed treatment difference was larger than the observed one and the assumed standard deviation was smaller than the observed one. However, had the sample size estimation been based on more realistic assumptions, the required sample size would be too large to be practical.

2. INTRODUCTION

2.1 Overview

The sponsor submitted clinical study report of Trial D144AC00001 for the use of quetiapine as monotherapy in the treatment of bipolar depression The study was conducted to fulfill the post-marketing commitment under the Pediatric Research Equity Act requested by the FDA.

The study D144AC00001 had 42 study centers in 7 countries (United States 29, India 3, Colombia 3, Serbia 3, Mexico 2, South Africa 1, and Taiwan 1). This was an 8-week, double-blind, randomized, parallel-group, placebo-controlled study evaluating the efficacy and safety of quetiapine XR 150 to 300 mg/day in the treatment of children and adolescents with bipolar disorder.

The study consisted of an up to 35-day enrollment period (including washout and baseline periods), an 8-week treatment period with 1 of 2 treatment regimens (quetiapine XR 150 to 300 mg/day or placebo), a 1-week safety follow-up period, 2- to 4-week safety follow-up period for patients with a blood pressure (BP) >95th percentile at the study completion or discontinuation visit.

Eligible patients (male or female children and adolescents aged 10 to 17 years, inclusive), with a clinically established diagnosis of bipolar I or bipolar II disorder (current or most recent episode depressed) were enrolled. A Children's Depression Rating Scale-Revised (CDRS-R) total score of ≥45 and Young Mania Rating Scale (YMRS) total score ≤16 were required at both Visit 1 (screening) and Visit 2 (randomization) after washout of current medications.

There were 262 patients enrolled and 193 patients randomized from 42 study centers in 7 countries. Of the 193 patients randomized to the study, 99.5% (192/193 patients) received treatment, 74.6% (144/193 patients) completed the study, and 25.4% (49/193 patients) discontinued from the study.

2.2 Data Sources

The clinical study report for study D144AC00001 and data sets are submitted electronically. The network path for the submission is: \\Cdsesub1\evsprod\NDA022047\0108 .
Primary analysis data set r-cdrs.xpt is located at \\Cdsesub1\evsprod\NDA022047\0108\m5\datasets\d144ac00001\analysis\legacy\datasets .

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The sponsor conducted Study D144AC00001 to evaluate the efficacy and safety of quetiapine XR 150 to 300 mg/day in the treatment of children and adolescents (aged 10 to 17 years) with bipolar disorder.

Study Design and Endpoints

Study D144AC00001 was an 8-week, multicenter, double-blind, randomized, parallel-group, placebo- controlled study.

The study consisted of an up to 35-day enrollment period (including washout and baseline periods), an 8-week treatment period with 1 of 2 treatment regimens (quetiapine XR 150 to 300 mg/day or placebo), and a safety follow-up period.

Eligible patients (male or female children and adolescents aged 10 to 17 years, inclusive), with a clinically established diagnosis of bipolar I or bipolar II disorder (current or most recent episode depressed) were enrolled. A CDRS-R total score of ≥45 and Young Mania Rating Scale (YMRS) total score ≤16 were required at both Visit 1 (screening) and Visit 2 (randomization) after washout of current medications.

Patients were randomly assigned to blinded study medication in a 1:1 ratio within age strata (10-12 years and 13-17 years) and treated as outpatients.

Quetiapine XR or placebo was administered orally, once daily in the evening. Doses of study medication (ie, quetiapine XR or placebo) were titrated up in 50 mg increments to reach the expected therapeutic dose of 150 mg over 3 days, starting on Day 1 with 50 mg, on Day 2 with 100 mg, and on Day 3 with 150 mg.

The primary efficacy outcome variable was the change from baseline to Day 57 in CDRS-R total score. Higher CDRS-R scores indicate more severe depression, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in depression severity.

Patient Disposition, Demographic and Baseline Characteristics

This multicenter study was conducted in 42 study centers in 7 countries (United States 29, India 3, Colombia 3, Serbia 3, Mexico 2, South Africa 1, and Taiwan 1). The study was conducted between 27 January 2009 and 1 November 2010, which included the recall visit.

A total of 193 patients were randomized to the study as shown in Table 1. Of these, 99.5% (192/193 patients) received treatment, 74.6% (144/193 patients) completed the study, and 25.4% (49/193 patients) discontinued from the study. Overall, the most common reason for study discontinuation was AEs (7.8%, 15/193 patients). The number and percentage of subjects who discontinued due to AEs was higher in the placebo group (12.0%, 12/100 patients) than in the quetiapine group (3.2%, 3/93 patients).

Table 1. Patient Disposition

Study Population	**Quetiapine XR**	**Placebo**	**Total**
Patients Randomized	93 (100%)	100 (100%)	193 (100%)
Patients included in mITT analysis set	92 (98.9%)	100 (100%)	192 (99.5%)
Patients who completed the study	**70 (75.3%)**	**74 (74%)**	**144 (74.6%)**
Patients who discontinued the study	23 (24.7%)	26 (26%)	49 (25.4%)
Adverse Event	3 (3.2%)	12 (12%)	15 (7.8%)
Patient lost to follow-up	5 (5.4%)	1 (1.0%)	6 (3.1%)
Voluntary Discontinuation	2 (2.2%)	4 (4.0%)	6 (3.1%)
Severe non-compliance to protocol	2 (2.2%)	4 (4.0%)	6 (3.1%)
Lack of therapeutic response	4 (4.3%)	1 (1.0%)	5 (2.6%)
Other	4 (4.3%)	1 (1.0%)	5 (2.6%)
Conditions under investigation worsened	1 (1.1%)	3 (3.0%)	4 (2.1%)
Incorrect enrollment	1 (1.1%)	0 (0%)	1 (0.5%)
Safety Reason	1 (1.1%)	0	1 (0.5%)

Source: Clinical Study Report Table 6 (pg. 53), Table 8 (pg. 56)

In general, baseline demographic data were similar in both treatment groups (see Table 2). Most patients enrolled in this study were White (65.1%), with a higher percentage of patients in the 13-17 year age group (72.4%). The mean weight and body mass index (BMI) at baseline were similar in both treatment groups.

Table 2. Demographic and Baseline characteristics

Demographic Characteristic	Quetiapine XR N=92	Placebo N=100	Total N=192
Age (years)			
Mean (SD)	13.9 (2.18)	14.0 (2.05)	14.0 (2.11)
Min, Max	10,17	10,17	10,17
Age Group (years), n (%)			
10-12 years old	25 (27.2%)	28 (28.0%)	53 (27.6%)
13-17 years old	67 (72.8%)	72 (72.0%)	139 (72.4%)
Sex, n (%)			
Male	45 (48.9%)	52 (52.0%)	97 (50.5%)
Female	47 (51.1%)	48 (48.0%)	95 (49.5%)
Race, n (%)			
White	65 (70.7%)	60 (60%)	125 (65.1%)
Black	14 (15.2%)	21 (21%)	35 (18.2%)
Other	13 (14.1%)	19 (19%)	32 (16.7%)
Weight (kg)			
Mean (SD)	65.4 (24.6)	63.6 (23.2)	64.5 (23.9)
Min, Max	28, 177	27, 151	27, 177
BMI (kg/m^2)			
Mean (SD)	24.5 (7.4)	24.2 (7.2)	24.4 (7.3)
Min, Max	15, 55	13, 50	13, 55

Source: Clinical Study Report Table 9 (pg. 57)

Statistical Methodologies

The sponsor estimated that ninety-two evaluable patients per treatment arm (i.e. a total of 184 evaluable patients) would provide at least 85% power to detect a difference of 4 points between quetiapine XR 150 to 300 mg/day treatment arm and the placebo treatment arm with respect to mean change from baseline to final assessment (Day 57) in CDRS-R total score. This sample size calculation assumed a pooled Standard Deviation (SD) of 9 and a 2-sided test at an overall experiment type I error rate of 0.050. The planned sample size was 194 randomized subjects to yield 184 evaluable subjects (92 per treatment arm).

The primary efficacy variable, the change from baseline to Day 57 in the CDRS-R total score, was analyzed using the mITT analysis set. The mITT analysis set included all randomized patients who received at least one dose of study medication (ie, quetiapine XR or placebo) and who had baseline assessments and at least one post-baseline CDRS-R assessment.

Mean changes from baseline in CDRS-R total score were analyzed using a mixed-model for repeated measures (MMRM) approach. Restricted Maximum Likelihood (ReML) estimation was used. The MMRM model included the baseline CDRS-R total score as covariate; age stratum, treatment group, time point, and treatment group-by-time point interaction as fixed effects; and centers and patients within treatment group as random effects. An unstructured covariance structure was used to model the within-patient error and the Kenward-Roger approximation was used to estimate the degrees of freedom.

Primary and Exploratory Efficacy Results and Conclusions

In the mITT analysis set, the mean CDRS-R total scores decreased from baseline to Day 57 for both quetiapine XR and placebo, indicating a reduction in depression severity in both groups (see Table 3). Treatment comparisons were tested using a MMRM with baseline CDRS-R total score as covariate, age stratum, treatment group, time point, and treatment group-by-time point interaction as fixed effects; and center and patients within treatment group as random effects. The LS mean reduction in CDRS-R total scores was -29.6 for quetiapine XR and -27.3 for placebo. The difference between the treatment groups was not statistically significant (p=0.252). This reviewer confirmed sponsor's results.

Table 3. CDRS-R Total score change from baseline to Day 57 (MMRM analysis)

Variable	Statistics	Quetiapine XR	Placebo
Baseline Score	Mean (SD)	61.6 (9.93)	60.1 (9.01)
Change from Baseline at Day 57	Mean (SD)	-31.9 (14.86)	-28.8 (14.76)
	LS Mean (SE)	-29.6 (1.65)	-27.3 (1.60)
Difference between Quetiapine XR and Placebo	LS Mean (SE)	-2.29 (1.99)	
	95% CI	(-6.22, 1.65)	
	p-value	0.252	

Source: Clinical Study Report Table 11 (pg. 62)

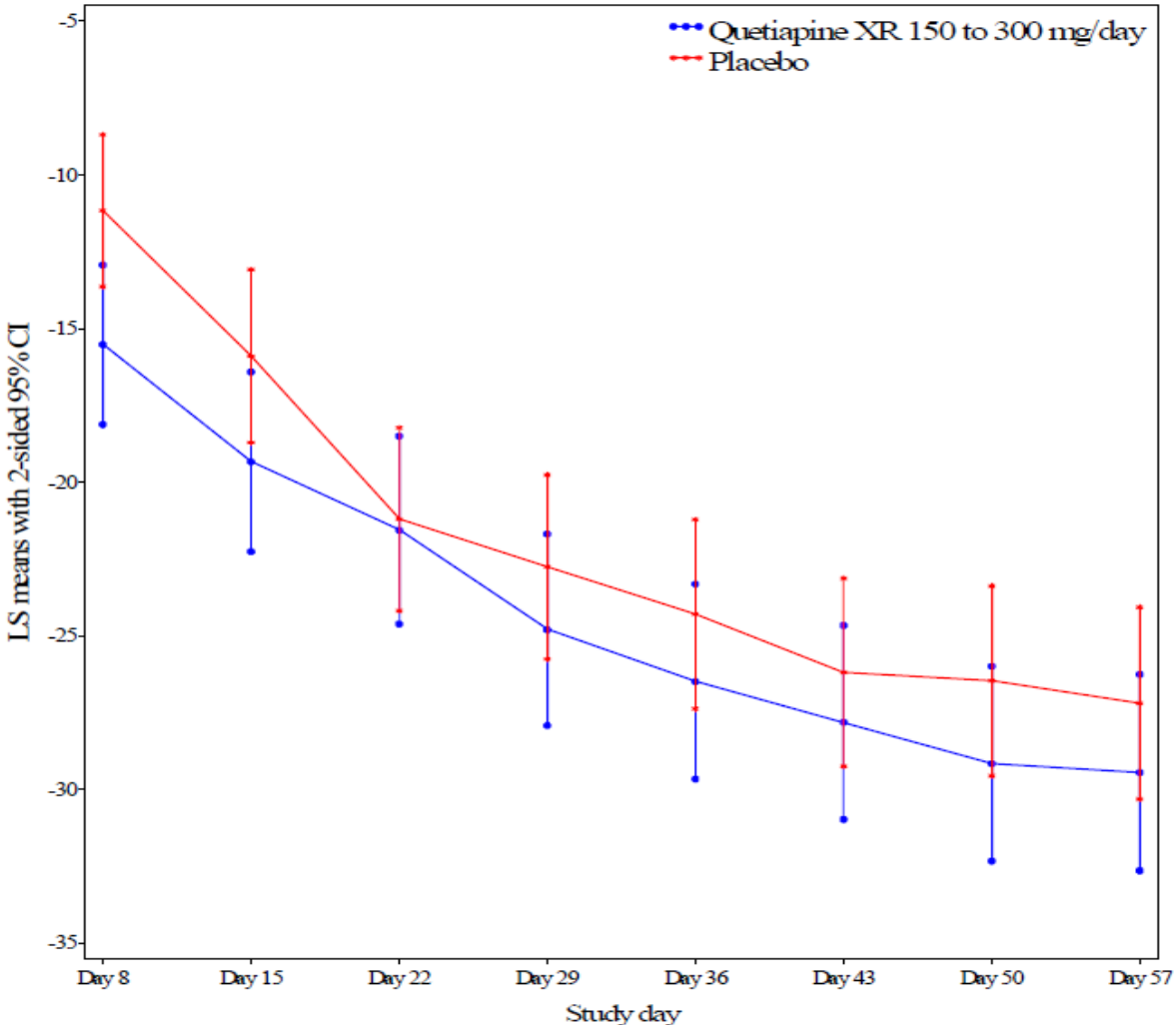
This reviewer also conducted exploratory MMRM analysis by visit (see Table 4) in the mITT analysis set. Numerically, quetiapine XR treatment arm was better than placebo at all visits. The maximal absolute difference was observed at the beginning of the double-blind phase (Days 8 and 15). Figure 1 illustrates the change from baseline to each time point in CDRS-R total score by treatment group.

Table 4. CDRS-R Total Score LS Mean Change from Baseline by Visit (MMRM analysis)

Day	Quetiapine XR	Placebo	Quetiapine XR -Placebo
8	-15.7 (1.36)	-11.3 (1.28)	-4.4 (1.46)
15	-19.5 (1.52)	-16.0 (1.46)	-3.5 (1.76)
22	-21.7 (1.59)	-21.3 (1.53)	-0.4 (1.88)
29	-24.9 (1.62)	-22.9 (1.55)	-2.1 (1.91)
36	-26.6 (1.65)	-24.4 (1.58)	-2.2 (1.96)
43	-27.9 (1.64)	-26.3 (1.570	-1.7 (1.95)
50	-29.3 (1.64)	-26.6 (1.59)	-2.7 (1.96)
57	-29.6 (1.65)	-27.3 (1.60)	-2.3 (1.99)

Source: Reviewer's Results

Figure 1. Change from Baseline to each time point in CDRS-R total score by treatment group-OC data using MMRM analysis



Source: Clinical Study Report Figure 2 (pg. 63)

The results of the ANCOVA analysis with LOCF data of the primary efficacy variable (change from baseline to Day 57 in CDRS-R total score) in the mITT analysis set are summarized in Table 5. Results were consistent with the primary efficacy analysis (p=0.178).

Table 5. Change from Baseline to Day 57 in CDRS-R total score LOCF data (ANCOVA analysis)

Variable	**Statistics**	**Quetiapine XR N=92**	**Placebo N=100**
Baseline Score	Mean (SD)	61.6 (9.93)	60.1 (9.01)
Change from Baseline	Mean (SD)	-27.9 (17.11)	-23.7 (16.90)
	LS Mean (SE)	-27.7 (1.62)	-24.8 (1.54)
Difference between Quetiapine XR and Placebo	LS Mean (SE)	-2.85 (2.11)	
	95% CI	(-7.00, 1.30)	
	p-value	0.178	

Source: Clinical Study Report Table 11.2.1.5.1 (pg. 220) and Table 11.2.1.5.2 (pg. 221)

3.2 Evaluation of Safety

Not evaluated by this reviewer.

3.3 Benefit:Risk Assessment (Optional)

Not evaluated by this reviewer.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The sponsor performed exploratory subgroup analyses on the primary efficacy variable (change from baseline in CDRS-R Total score at Week 8). The subgroup analyses by Region (US, Non-US) and Age-stratum (10-12years old, 13-17 years old) are presented in Table 7. The regional subgroups (US, Non US) were analyzed by the primary efficacy model- MMRM model including the baseline CDRS-R total score as covariate; age stratum, treatment group, time point, and treatment group-by-time point interaction as fixed effects; and centers and patients within treatment group as random effects. For the age subgroups, the sponsor used an MMRM model that did not include fixed effect of age stratum.

This reviewer also conducted exploratory subgroup analysis by gender and race using the primary efficacy model (see Table 7). For all subgroups presented in Table 7, except "Other" racial subgroup, the treatment effect appeared to be numerically in favor quetiapine when compared with placebo.

Table 6. Subgroup Analysis (Change from Baseline in CDRS-R Total Score)

Subgroup	Quetiapine XR		Placebo	
Gender	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**
Male	45	-30.0 (2.08)	52	-28.4 (1.90)
Female	47	-29.5 (2.54)	48	-25.8 (2.68)
Race				
White	65	-29.1 (1.88)	60	-27.3 (1.95)
Black	14	-24.9 (4.71)	21	-24.0 (3.88)
Other	13	Did not converge	19	Did not converge
Age Stratum				
10- 12 years old	24	-30.4 (2.80)	29	-26.5 (2.51)
13-17 years old	68	-29.4 (1.88)	71	-27.0 (1.90)
Region				
US	78	-28.8 (1.76)	82	-25.8 (1.73)
Outside US	14	-34.9 (5.11)	18	-34.2 (4.69)

Source: Reviewer's Results

4.2 Other Special/Subgroup Populations

Not evaluated by this reviewer.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In the primary analysis (MMRM) of CDRS-R Total score, the Quetiapine XR treatment group was not statistically significantly different from the placebo arm. Based on the MMRM analysis, the observed LS mean treatment effect (relative to placebo) was 2.29 units with p-value of 0.252.

In estimating sample size, the sponsor assumed treatment difference of 4 and pooled standard deviation of 9. Using a two-sample t-test for difference of means, 92 evaluable patients per treatment arm would be sufficient to provide a study power of at least 85%.

At Day 57 the observed standard deviation within each treatment arm was approximately 14.8 for OC data and 17 for the LOCF data. Had these observed standard deviations been used at the planning stage, the sample size per arm would need to be in the range 250 to 325 to achieve at least 85% power, which is much larger than the sample size typically used in a psychiatric trial. Furthermore, in this trial the observed treatment difference was at least one unit smaller than the one assumed in sample size estimation (<3 whether based on LOCF or MMRM analysis versus 4). Had a more conservative treatment difference been used in sample size estimation, it would require an unrealistically large sample size.

5.2 Conclusions and Recommendations

The primary results of this study did not show a statistically significant difference between quetiapine XR and placebo in decreasing depression symptoms in children and adolescents with bipolar disorder. In sample size estimation, the assumed treatment difference was larger than the observed one and the assumed standard deviation was smaller than the observed ones. However, had the sample size estimation been based on more realistic assumptions, the required sample size would be too large to be practical.

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/s/

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05/04/2012

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