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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Study D144CC00002

In the primary analysis of the MADRS Total score, bipolar patients with an acute depressive episode on Quetiapine XR 300 mg QD given in the evening were observed to show statistically significant improvement over patients in the placebo treatment group.

Study D144CC00004

In the primary analysis of the YMRS Total score, patients with bipolar I disorder with an acute manic episode on Quetiapine XR flexible doses in the range of 400 to 800 mg QD given in the evening were observed to show statistically significant improvement over patients in the placebo treatment group.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The development program was designed to investigate quetiapine's efficacy in 3 different indications: treatment of bipolar patients with an acute depressive episode (Quetiapine XR), treatment of patients with bipolar I disorder with an acute manic episode (Quetiapine XR), and adjunct therapy to either lithium or divalproex of patients with bipolar I disorder with manic episodes (Quetiapine). This reviewer evaluated the bipolar depression and acute mania (monotherapy) indications of Quetiapine XR. One pivotal study for each indication (bipolar depression and acute mania) was submitted in support of efficacy of Quetiapine XR compared with placebo.

Study D144CC00002 was an 8-week multicenter, double-blind, randomized, parallel-group, placebo controlled, Phase III study of the efficacy and safety of Quetiapine XR 300 mg QD given in the evening as monotherapy in the treatment of bipolar patients with an acute depressive episode. A total of 280 patients was randomized, 140 in each treatment group, and 183 patients (65.4%) completed the study, 87 in Quetiapine XR group and 96 in placebo group.

Study D144CC00004 was a 3-week, multicenter, randomized, parallel-group, double-blind, placebo-controlled phase III study of the efficacy and safety of Quetiapine XR with flexible doses in the range of 400 to 800 mg or placebo given QD in the evening in the treatment of patients with bipolar I disorder with an acute manic episode. A total of 316 patients were randomized, 155 in the Quetiapine XR group and 161 in the placebo group, and 227 patients (71.8%) completed the study, 111 in Quetiapine XR group and 116 in placebo group.

1.3 STATISTICAL ISSUES AND FINDINGS

Study D144CC00002

Quetiapine XR treatment group (300 mg QD given in the evening) was statistically superior to placebo in mean change from baseline to the endpoint visit in MADRS Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with fixed effects of treatment and bipolar diagnosis, random effect of center, and baseline MADRS total score as a covariate was < 0.001 .

Study D144CC00004

Quetiapine XR treatment group (flexible dose in the range of 400-800mg QD given in the evening) was statistically superior to placebo in mean change from baseline to the endpoint visit in YMRS Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with fixed effect of treatment, random effect of center random and baseline YMRS total score as a covariate was < 0.001 .

In general, no statistical issues are identified in both studies.

2 INTRODUCTION

2.1 OVERVIEW

The development program was designed to investigate quetiapine's efficacy in 3 different indications: treatment of bipolar patients with an acute depressive episode (Quetiapine XR), treatment of patients with bipolar I disorder with an acute manic episode (Quetiapine XR), and adjunct therapy to either lithium or divalproex of patients with bipolar I disorder with manic episodes (Quetiapine). This reviewer evaluated the bipolar depression and acute mania (monotherapy) indications of Quetiapine XR. The sponsor submitted results of

- single pivotal study D144CC00002 in support of efficacy of Quetiapine XR in treatment of patients with bipolar depression;
- single pivotal study D144CC00004 in support of efficacy of Quetiapine XR in treatment of patients with acute bipolar mania.

2.2 DATA SOURCES

Data used for review are from the electronic submission received on December 19 and 20, 2007. The network paths are \\Cdsesub1\evsprod\NDA022047\0008 and \\Cdsesub1\evsprod\NDA022047\0009.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY D144CC00002

3.1.1.1 Objective

The primary objective of this study is to evaluate whether Quetiapine XR formulation at a dose of 300 mg once daily (QD) given in the evening demonstrates superior efficacy compared to placebo in patients with bipolar depression, after 8 weeks of treatment, as evidenced by the change from baseline (randomization [Visit 2]) in the Montgomery- Åsberg Depression Rating Scale (MADRS) total score to the final visit (Visit 10).

3.1.1.2 Study Design

This was an 8-week multicenter, double-blind, randomized, parallel-group, placebo controlled, Phase III study of the efficacy and safety of Quetiapine XR 300 mg QD as monotherapy in the treatment of bipolar patients (Bipolar I or II) with an acute depressive episode. The study design is summarized in Table 1. The study consisted of an up to 35-day enrollment period and 8-week treatment period with randomized treatment regimens (Quetiapine XR 300 mg or placebo).

Table 1. D144CC00002 Study Flow Chart

	Enrollment	Randomized Treatment								Final
		Randomize								
Visit	1	2	3	4	5	6	7	8	9	10
Study Day	-35 to -1	1	8	15	22	29	36	43	50	57

Source: Corresponds to Figure 1 (pg 31), Clinical Study Report D144CC00002.

The dose titration schedule for Quetiapine XR was as follows: 50 mg on Day 1, 100 mg on Day 2, 200mg on Day 3, and beginning on Day 4 through the remainder of the study, a fixed dose of 300 mg. Quetiapine XR was not down titrated at the end of the study.

For inclusion in the study, among other criteria, patients had to have HAM-D (17-item) total score of ≥ 20 and HAM-D item 1 (depressed mood) score ≥ 2 at enrollment (Visit 1) and randomization (Visit 2).

3.1.1.3 Patient Disposition, Demographic and Baseline Characteristics

This study was conducted at 64 study centers in the United States (US). Sixty-one (61) sites completed procedures and received drug; 3 sites did not enroll patients. A total of 418 patients were screened to achieve the planned sample size of 280 randomized patients; there were 138 screen failures. Table 2 presents patient disposition by treatment arm. Two hundred eighty patients with either bipolar I disorder or bipolar II disorder exhibiting moderate to severe depression were randomized, 140 in each treatment group. Similar percentages of randomized patients completed the study in each treatment group; 62.1% in the Quetiapine XR group, and 68.6% in the placebo group.

Table 2. D144CC00002 Study Patient Disposition

	Quetiapine XR 300 mg	Placebo
Patients		
Randomized	140 (100%)	140 (100%)
Received Study Drug	139 (99.3%)	138 (98.6%)
MITT Analysis Set	133 (95.0%)	137 (97.9%)
Discontinued Study	52 (37.1%)	42 (30.0%)
Adverse Event	17 (12.1%)	2 (1.4%)
Lost to Follow-up	12 (8.6%)	8 (5.7%)
Severe noncompliance to the protocol	4 (2.9%)	5 (3.6%)
Condition worsened	3 (2.1%)	4 (2.9%)
Lack of therapeutic response	2 (1.4%)	10 (7.1%)
Safety reasons	1 (0.7%)	0
Voluntary discontinuation by patient	12 (8.6%)	10 (7.1%)
Other	1 (0.7%)	1 (0.7%)
Incorrect enrollment	0	2 (1.4%)
Completed study	87 (62.1%)	96 (68.6%)

Source: Corresponds to Figure 2 (pg. 80), Clinical Study Report D144CC00002

Table 3 summarizes baseline physical characteristics (gender, ethnic origin, age, and weight) and MADRS score at randomization for MITT population. The two treatment groups were well-matched with respect to demographic characteristics and baseline disease characteristics. In the MITT population, a higher percentage of patients (64%) were female. Mean age was 39 years (range 18 to 64 years). In both groups, 80% had bipolar I diagnosis; approximately 27% in each group had rapid cycling. Mean baseline MADRS and HAM-D scores were approximately 30 and 25, respectively. Mean CGI-BP severity scores for bipolar illness were similar; 4.5 for the quetiapine group and 4.4 for the placebo group. Mean CGI-BP severity score for depression were 4.5 for both groups.

Table 3. Demographic and Baseline characteristics (MITT analysis set)

Variable	Placebo N=137	Quetiapine XR N=133
Gender, n (%)		
Male	51 (37.2%)	45 (33.8%)
Female	86 (62.8%)	88 (66.2%)
Race		
Caucasian	98 (71.5%)	96 (72.2%)
African American	31 (22.6%)	29 (21.8%)
Americ. Indian/ Alaskan Native	3 (2.2%)	3 (2.3%)
Asian	1 (0.7%)	2 (1.5%)
Native Hawaiian/Pacific Island.	1 (0.7%)	0
Other	3 (2.2%)	3 (2.3%)
Age (years)		
Mean (SD)	39.9 (12.8)	39.0 (11.3)
Min, Max	18, 64	19, 64
Age category, n (%)		
18 to 39	67 (48.9%)	69 (51.9%)
40 to 65	70 (51.1%)	64 (48.1%)
Weight (kg)		
Mean (SD)	88.9 (22.7)	88.7 (22.1)
Min to Max	49, 158	48, 142
MADRS Total Score		
Mean (SD)	30.1 (5.5)	29.8 (5.2)
Min, Max	15, 47	14, 47

Source: Table 19 (pg. 84), Clinical Study Report D144CC00002

3.1.1.4 Statistical Methodologies

The primary hypothesis is that Quetiapine XR formulation at a dose of 300 mg QD demonstrated superior efficacy compared to placebo in patients with bipolar depression, after 8 weeks of treatment. The primary outcome variable is the change from baseline (randomization) in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at final visit.

The primary and secondary efficacy analyses were performed on the modified intention to treat – to treat (MITT) set. The MITT analysis set (Full analysis set) included all randomized patients who received at least 1 dose of study treatment and who had a randomization (baseline) value and at least one post-randomized MADRS assessment, classified by the randomized treatment assignment. For the MITT population, missing data resulting from patient dropout were imputed using a Last Observation Carried Forward (LOCF) approach with post-baseline data.

The primary analysis of change from baseline to final assessment (LOCF) in MADRS total scores will test the superiority of Quetiapine XR using a mixed model ANCOVA (PROC MIXED in SAS) which includes fixed effects of treatment group and bipolar diagnosis, baseline MADRS as a covariate, and a random effect of center.

A supportive secondary analysis model in the MITT analysis set, using a mixed model repeated measures approach, will be employed to further characterize the treatment effects across 8 weeks of treatment. This approach assumes that missing observations are missing at random (MAR), and utilizes observed data.

3.1.1.5 Results of Efficacy Analysis

Primary Analysis

Table 4 presents the results of the primary efficacy analysis. For the MITT population, LOCF analysis, MADRS total scores decreased for both Quetiapine XR and placebo-treated patients. Based on the mixed ANCOVA model, Quetiapine XR 300 mg was statistically significantly better than placebo in reducing MADRS total score from baseline to Week 8 with treatment comparison p-value < 0.001. This reviewer also confirmed sponsor's analysis of the MADRS total score mean change from baseline by visit (see Table 5). Numerically, the treatment effect of Quetiapine XR compared with placebo was consistent across the visits.

Table 4. MADRS Total Score LS Mean Change from Baseline to Endpoint, (ITT Population)

		Placebo	Quetiapine XR
Number of patients	Total number=270	137	133
Baseline MADRS	Mean (SD)	30.1 (5.5)	29.8 (5.2)
Change from Baseline	LS Mean (SE)	-11.9 (1.18)	-17.4 (1.24)
Placebo-adjusted difference	LS Mean Change (SE)	NA	-5.5 (1.2)
	95% CI	NA	(-7.9, -3.2)
	P-value	NA	<0.001

Source: Table 11.2.1.1.1. (pg. 230) Clinical Study Report D144CC00002

Table 5. MADRS Total score mean change from baseline by visit with missing values imputed by LOCF method (ITT Population).

Week	Placebo	Quetiapine XR	Treatment Difference: Quetiapine XR - Placebo	
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	95% CI
1	-6.54 (0.87)	-10.16 (0.91)	-3.61 (0.84)	(-5.27, -1.96)
2	-8.17 (0.98)	-12.82 (1.04)	-4.65 (1.03)	(-6.68, -2.63)
3	-9.29 (1.03)	-14.17 (1.09)	-4.88 (1.07)	(-6.99, -2.76)
4	-10.65 (1.11)	-16.39 (1.17)	-5.74 (1.11)	(-7.94, -3.55)
5	-10.27 (1.14)	-15.85 (1.20)	-5.58 (1.21)	(-7.96, -3.20)
6	-11.04 (1.13)	-16.72 (1.19)	-5.67 (1.21)	(-8.06, -3.29)
7	-11.25 (1.18)	-17.19 (1.24)	-5.94 (1.22)	(-8.34, -3.54)
8	-11.92 (1.18)	-17.43 (1.24)	-5.51 (1.20)	(-7.88, -3.15)

Source: Table 11.2.1.1.2 (pg. 231-236), Clinical Study Report D144CC00002

Note: The reported 95% CIs are nominal and are not adjusted for multiplicity.

Sensitivity Analysis

The reviewer confirmed sponsor's sensitivity analysis on the primary endpoint. Change from baseline in MADRS Total score was analyzed by mixed effect repeated measures model. The model included variables treatment (fixed effect) and baseline MADRS total score (covariate). The model also included random effects of centers and patient with unstructured variance-covariance matrix. The findings support the primary analysis results (see Table 6).

Table 6. MADRS Total Score Change from Baseline Visitwise LS means, Mixed Effects Repeated Measures model (ITT Population).

Week	Study Treatment	Number of patients	LS Mean (SE)	Treatment difference : Quetiapine- Placebo	
				LS Mean (SE)	95 % CI
1	Placebo	136	-7.12 (0.84)		
1	Quetiapine XR	132	-10.76 (0.80)	-3.64 (0.83)	(-5.26, -2.02)
2	Placebo	125	-9.16 (1.02)		
2	Quetiapine XR	117	-14.13 (0.89)	-4.97 (1.26)	(-7.45, -2.50)
3	Placebo	120	-10.48 (0.95)		
3	Quetiapine XR	107	-15.55 (0.90)	-5.07 (1.04)	(-7.11, -3.03)
4	Placebo	112	-11.47 (1.08)		
4	Quetiapine XR	101	-17.70 (0.88)	-6.23 (1.05)	(-8.29, -4.18)
5	Placebo	105	-11.56 (1.10)		
5	Quetiapine XR	93	-17.87 (1.01)	-6.30 (1.16)	(-8.57, -4.03)
6	Placebo	100	-12.35 (1.13)		
6	Quetiapine XR	87	-18.79 (1.11)	-6.44 (1.26)	(-8.92, -3.96)
7	Placebo	100	-12.70 (1.16)		
7	Quetiapine XR	87	-19.30 (1.31)	-6.60 (1.27)	(-9.09 -4.10)
8	Placebo	98	-13.58 (1.17)		
8	Quetiapine XR	86	-19.71 (1.25)	-6.13 (1.11)	(-8.32, -3.95)

Source: Table 11.2.1.3.1. (pg. 249-251), Clinical Study Report D144CC00002

Note: The reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

3.1.1.6 Reviewer's Comments.

In patients with bipolar I and II disorder, Quetiapine XR at a dose of 300 mg QD given in the evening as monotherapy was significantly superior to placebo in reducing the level of depressive symptoms after 8 weeks of treatment, as assessed by the change from baseline in the total MADRS score.

3.1.2 STUDY D144CC00004

3.1.2.1 Objective

The primary objective of this study was to demonstrate superior efficacy of Quetiapine XR formulation administered QD as monotherapy at a dose of 400 to 800 mg per day compared to placebo in decreasing the manic symptoms in patients with bipolar manic or mixed episode, after 3 weeks of treatment.

3.1.2.2 Study Design

This was a 3-week, multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase III study of the efficacy and safety of Quetiapine XR with flexible doses in the range of 400 to 800 mg or placebo given QD in the evening in the treatment of patients with bipolar I disorder with an acute manic episode. The study design is summarized in Table 7. The study consisted of an enrollment period of up to 35 days and a 3-week treatment period with randomized treatment regimens (Quetiapine XR 400 to 800 mg QD or placebo). Quetiapine XR was not down-titrated at the end of the study.

Table 7. Study Flow Chart

Visit 1 Enrollment	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6
Day -35 to -1	Day 1	Day 4	Day 8	Day 15	Day 22

Source: Corresponds to Figure 1 (pg 34.), Clinical Study Report D144CC00004

For inclusion in the study, patients had to fulfill all of the following criteria:

1. Provision of written informed consent before initiation of any study-related procedures.
2. Male and female patients aged 18 to 65 years, inclusive.
3. Documented clinical diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR, APA 2000) criteria for bipolar I disorder, most recent episode manic (296.4x) or mixed (296.6x) confirmed by the amended version of the Structured Clinical Interview for DSM-IV (SCID).
4. Patients must have had YMRS total score ≥ 20 and ≥ 4 on 2 of 4 core items (irritability, speech, content, disruptive/aggressive behavior) at enrollment (Visit 1) and randomization (Visit 2).
5. Patients must have had a CGI-BP score ≥ 4 (moderately ill) at randomization (Visit 2).
6. Patients must have experienced ≥ 1 manic or mixed episode in the past 5 years.

Eligible patients had an up to 28-day washout period and an overall enrollment period of up to 35 days. Following the washout and enrollment period, patients were randomized and entered the 3-week treatment period. Patients had to be hospitalized for at least 4 days immediately after randomization on Day 1.

Quetiapine XR was given at a dose of 300 mg on Day 1 (one 300-mg tablet) and at 600 mg (three 200-mg tablets) on Day 2. Quetiapine XR was given in flexible doses of 400 to 800 mg (two to four 200-mg tablets) from Day 3 to Day 21. Quetiapine XR was orally administered QD, in the evening. Placebo matching Quetiapine XR 300-mg and 200-mg tablets was orally administered QD, in the evening. Placebo matching Quetiapine XR 300 mg was given on Day 1; placebo matching Quetiapine XR 600 mg was given on Day 2. Placebo tablets to match 400 to 800 mg Quetiapine XR were given from Day 3 to Day 21.

3.1.2.3 Patient Disposition, Demographic and Baseline Characteristic

This study was conducted at 50 study centers in the United States (US); 48 sites enrolled patients. A total of 459 patients were screened to achieve the planned sample size of 313 randomized patients; there were 143 screen failures.

Table 8 presents patient disposition by treatment arm. A total of 316 patients were randomized (155 in the Quetiapine XR group and 161 in the placebo group), and 71.8% of the patients completed the study (71.6% in the Quetiapine XR group and 72.0% in the placebo group). Withdrawal due to lack of therapeutic response was more frequent in the placebo group (9.3%) compared to Quetiapine XR (3.9%) and more placebo patients discontinued study treatment due to AEs (7.5%) compared to Quetiapine XR (2.6%). There was a higher frequency of patients being lost to follow-up in the Quetiapine XR group (7.7%) compared to placebo (2.5%).

Table 8. D144CC00004 Study Patient Disposition

	Placebo	Quetiapine XR
Patients		
Randomized	161 (100%)	155 (100%)
Received Study Drug	160 (99.4%)	151 (97.4%)
MITT Analysis Set	159 (98.8%)	149 (96.1%)
Discontinued Study	45 (28.0%)	44 (28.4%)
Adverse Event	12 (7.5%)	4 (2.6%)
Lost to Follow-up	4 (2.5%)	12 (7.7%)
Severe noncompliance to the protocol	2 (1.2%)	4 (2.6%)
Condition worsened	0	3 (1.9%)
Lack of therapeutic response	15 (9.3%)	6 (3.9%)
Voluntary discontinuation by patient	12 (7.5%)	13 (8.4%)
Other	0	1 (0.6%)
Incorrect enrollment	0	1 (0.6%)
Completed study	116 (72.0%)	111 (71.6%)

Source: Corresponds to Figure 2 (pg 89), Study Report D144CC00004

Table 9 summarizes baseline physical characteristics (gender, ethnic origin, age, and weight) and YMRS score at randomization for MITT population. The two treatment groups appeared comparable with respect to demographic characteristics and baseline disease characteristics. In the MITT population, a higher percentage of patients (60.1%) were male. Mean age was 41 years (range 19 to 64 years). The majority of patients in both treatment groups had only manic episodes (versus mixed) at baseline: 58% and 55% in the Quetiapine XR and placebo groups, respectively;

approximately 30% and 33% of patients in the Quetiapine XR and placebo groups, respectively, had rapid cycling. Mean baseline YMRS scores were 28.8 and 28.4 for the Quetiapine XR and placebo groups, respectively. Study patients in both treatment groups had greater severity of illness for mania in comparison with depression.

Table 9. Demographic and Baseline Characteristics (MITT Analysis Set)

Variable	Placebo N=159	Quetiapine XR N=149
Gender, n (%)		
Male	93 (58.5%)	92 (61.7%)
Female	66 (41.5%)	57 (38.3%)
Race		
Caucasian	73 (45.9%)	72 (48.3%)
African American	77 (48.4%)	70 (47.0%)
Americ. Indian/ Alaskan Native	0	3 (2.0%)
Asian	1 (0.6%)	1 (0.7%)
Native Hawaiian/Pacific Island.	1 (0.6%)	0
Other	7 (4.4%)	3 (2.0%)
Age (years)		
Mean (SD)	40.8 (10.7)	41.3 (10.3)
Min, Max	19, 63	19, 64
Age category, n (%)		
18 to 39	65 (40.9%)	61 (40.9%)
40 to 65	94 (59.1%)	88 (59.1%)
Weight (kg)		
Mean (SD)	91.0 (24.8)	91.8 (23.7)
Min to Max	44, 189	48, 207
YMRS Total Score		
Mean (SD)	28.4 (5.1)	28.8 (5.4)
Min, Max	20, 47	20, 47
Current Episode, n (%)		
Manic	88 (55.3%)	86 (57.7%)
Mixed	71 (44.7%)	63 (42.3%)

Source: Corresponds to Table 19 (pg. 92), Study Report D144CC00004

3.1.2.4 Statistical Methodologies and Endpoints

The primary outcome variable was the change from baseline (randomization [Visit 2]) in the YMRS total score at final visit (Visit 6). The modified intention-to-treat (MITT) analysis set (full analysis set) included all randomized patients who received at least 1 dose of study treatment and who had baseline values and at least 1 post-randomized YMRS assessment, classified by the randomized treatment assignment. Data from the MITT analysis set were used for the primary analysis of the efficacy objectives.

The primary analysis used ANCOVA model (PROC MIXED in SAS) on LOCF change from baseline to final visit in YMRS total score for the time period of interest (Day 22, Visit 6). The model included treatment as a fixed effect, and baseline YMRS total score as a covariate. The centers were considered as random effects.

As a supportive analysis, the primary analysis utilized a linear mixed-model with repeated measures (MMRM) for the change from baseline (randomization [Visit 2]) to final visit (Visit 6) in the YMRS total score. The model included variables treatment (fixed effect) and baseline YMRS total score (covariate). The model also included random effects of centers and patient with unstructured variance-covariance matrix.

3.1.2.5 Results of Efficacy Analysis

Table 10 presents the results of the primary efficacy analysis. For the MITT population, LOCF analysis, YMRS total scores decreased in both the Quetiapine XR and placebo groups; the decrease was statistically significantly greater for the Quetiapine XR group. At Week 3 (Day 22), patients in the Quetiapine XR group in the MITT population had a least square (LS) mean decrease of 3.83 points greater than patients in the placebo group ($p < 0.001$). This reviewer also confirmed sponsor's analysis of the MADRS total score mean change from baseline by visit summarized in Table 11. The difference was numerically in favor of Quetiapine XR for each post-baseline visit.

Table 10. YMRS Total Score LS Mean Change from Baseline to Endpoint, (ITT Population)

		Placebo	Quetiapine XR
No patients		159	149
Baseline	Mean (SD)	28.4 (5.1)	28.8 (5.4)
Change from Baseline	LS Mean (SE)	-10.52 (0.88)	-14.34 (0.91)
Placebo-adjusted difference	LS Mean Change (SE)	NA	-3.83 (0.93)
	95% CI	NA	(-5.66, -2.00)
	P-value	NA	<0.001

Source: Table 11.2.1.1.1. (pg. 255), Clinical Study Report D144CC00004

Table 11. YMRS Total score mean change from baseline by visit with missing values imputed by LOCF method (ITT Population).

Visit (Day)	Placebo	Quetiapine XR	Treatment Difference: Quetiapine XR - Placebo	
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	95% CI
3 (4)	-6.87 (0.77)	-9.89 (0.79)	-3.01 (0.67)	(-4.33, -1.69)
4 (8)	-8.69 (0.68)	-12.64 (0.71)	-3.95 (0.85)	(-5.63, -2.27)
5 (15)	-10.68 (0.76)	-13.34 (0.79)	-2.66 (0.90)	(-4.42, -0.89)
6 (22)	-10.52 (0.88)	-14.34 (0.91)	-3.83 (0.93)	(-5.66, -2.00)

Source: Table 11.2.1.1.2 (pg. 256-258), Clinical Study Report D144CC00004

Note: The reported 95% CIs are nominal and are not adjusted for multiplicity.

Sensitivity Analysis

The reviewer confirmed sponsor's sensitivity analysis on the primary endpoint. Change from baseline in YMRS Total score was analyzed by mixed effect repeated measures model. The model included variables treatment (fixed effect) and baseline YMRS total score (covariate). The model also included random effects of centers and patient with unstructured variance-covariance matrix. The findings support the primary analysis results (see Table 12).

Table 12. YMRS Total Score Change from Baseline Visitwise LS means, Mixed Effects Repeated Measures model (ITT Population).

Visit (Day)	Study Treatment	Number of patients	LS Mean (SE)	Treatment difference : Quetiapine- Placebo	
				LS Mean (SE)	95 % CI
3 (4)	Placebo	158	-6.90 (0.77)		
3 (4)	Quetiapine XR	146	-9.79 (0.70)	-2.89 (0.59)	(-4.06, -1.73)
4 (8)	Placebo	149	-9.15 (0.67)		
4 (8)	Quetiapine XR	138	-13.14 (0.68)	-3.98 (0.71)	(-5.38, -2.59)
5 (15)	Placebo	133	-11.60 (0.75)		
5 (15)	Quetiapine XR	122	-14.03 (0.78)	-2.44 (0.74)	(-3.90, -0.98)
6 (22)	Placebo	120	-11.37 (0.91)		
6 (22)	Quetiapine XR	120	-15.29 (0.83)	-3.91 (0.73)	(-5.36, -2.47)

Source: Table 11.2.1.3.1. (pg. 267-268), Clinical Study Report D144CC00004

Note: The reported 95% CIs are nominal and are not adjusted for multiplicity.

3.1.2.6 Reviewer's Comments

In patients with bipolar I disorder, Quetiapine XR at a dose of 400 to 800 mg given QD in the evening as monotherapy was significantly superior to placebo in reducing the level of mania symptoms after 3 weeks of treatment, as assessed by the change from baseline in the total YMRS score.

3.2 EVALUATION OF SAFETY

Not evaluated by this reviewer. Please refer to clinical review of this application for a detailed safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

4.1.1 STUDY D144CC00002

This reviewer confirmed sponsor's exploratory subgroup analysis on the primary efficacy variable, MADRS Total score, using ANCOVA models, including the includes fixed effects of treatment group and bipolar diagnosis, baseline MADRS as a covariate, and a random effect of study site. The subgroups of interest included age (dichotomized by age greater than or equal to 40 versus others), gender and race. For all subgroups, the treatment effect appeared to be numerically in favor of quetiapine when compared with placebo.

Table 13. Subgroup Analysis by Age: MADRS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	Quetiapine XR
Younger than 40 years (18-39)			
No patients		67	69
Change from Baseline	LS Mean (SE)	-12.90 (1.49)	-17.56 (1.53)
Placebo-adjusted difference	LS Mean (SE)	NA	-4.65 (1.68)
	95% CI	NA	(-7.99, -1.32)
40 years or older (40-65)			
No patients		70	64
Change from Baseline	LS Mean (SE)	-10.75 (1.73)	-17.44 (1.70)
Placebo adjusted difference	LS Mean (SE)	NA	-6.69 (1.79)
	95% CI	NA	(-10.26, -3.12)

Source: Table 11.2.1.3.4 (pg. 256), Clinical Study Report D144CC00002

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 14. Subgroup Analysis by Gender: MADRS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	Quetiapine XR
Female			
No patients		86	88
Change from Baseline	LS Mean (SE)	-12.23 (1.31)	-17.98 (1.39)
Placebo-adjusted difference	LS Mean (SE)	NA	-5.75 (1.49)
	95% CI	NA	(-8.70, -2.81)
Male			
No patients		51	45
Change from Baseline	LS Mean (SE)	-11.85 (2.23)	-15.86 (2.23)
Placebo adjusted difference	LS Mean (SE)	NA	-4.00 (2.20)
	95% CI	NA	(-8.42, 0.42)

Source: Table 11.2.1.3.5 (pg. 257), Clinical Study Report D144CC00002

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 15. Subgroup Analysis by Origin: MADRS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	Quetiapine XR
Black			
No patients		31	29
Change from Baseline	LS Mean (SE)	-15.18 (2.19)	-18.29 (2.24)
Placebo-adjusted difference	LS Mean (SE)	NA	-3.12 (2.40)
	95% CI	NA	(-8.03, 1.80)
White			
No patients		98	96
Change from Baseline	LS Mean (SE)	-11.46 (1.36)	-17.94 (1.41)
Placebo adjusted difference	LS Mean (SE)	NA	-6.48 (1.42)
	95% CI	NA	(-9.29, -3.67)
Other			
No patients		8	8
Change from Baseline	LS Mean (SE)	-6.48 (4.21)	-9.93 (4.39)
Placebo adjusted difference	LS Mean (SE)	NA	-3.45 (5.65)
	95% CI	NA	(-75.24, 68.33)

Source: Table 11.2.1.3.6 (pg. 258-259), Clinical Study Report D144CC00002

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.1.2 STUDY D144CC00004

This reviewer confirmed sponsor's exploratory subgroup analysis on the primary efficacy variable, YMRS Total score, using ANCOVA models, including fixed effect of treatment, random effect of investigator study site, and baseline YMRS score as a covariate. The subgroups of interest included age (dichotomized by age greater than or equal to 40 versus others), gender, and race. The treatment effect appeared to be numerically in favor of quetiapine for all subgroups except the ethnic subgroup that combines patients that are not Caucasian or African American.

Table 16. Subgroup Analysis by Age: YMRS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	Quetiapine XR
Younger than 40 years (18-39)			
No patients		65	61
Change from Baseline	LS Mean (SE)	-11.62 (1.10)	-15.40 (1.13)
Placebo-adjusted difference	LS Mean (SE)	NA	-3.79 (1.51)
	95% CI	NA	(-6.80, -0.78)
40 years or older (40-65)			
No patients		94	88
Change from Baseline	LS Mean (SE)	-9.87 (1.10)	-13.20 (1.12)
Placebo adjusted difference	LS Mean (SE)	NA	-3.33 (1.22)
	95% CI	NA	(-5.73, -0.93)

Source: Table 11.2.1.3.4 (pg. 273), Clinical Study Report D144CC00004

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 17. Subgroup Analysis by Gender: YMRS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	Quetiapine XR
Female			
No patients		66	57
Change from Baseline	LS Mean (SE)	-10.43 (1.06)	-15.30 (1.15)
Placebo-adjusted difference	LS Mean (SE)	NA	-4.87 (1.56)
	95% CI	NA	(-7.98, -1.76)
Male			
No patients		93	92
Change from Baseline	LS Mean (SE)	-10.71 (1.20)	-13.69 (1.19)
Placebo adjusted difference	LS Mean (SE)	NA	-2.98 (1.16)
	95% CI	NA	(-5.26, -0.70)

Source: Table 11.2.1.3.5 (pg. 274), Clinical Study Report D144CC00004

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 18. Subgroup Analysis by Origin: YMRS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	Quetiapine XR
Black			
No patients		77	70
Change from Baseline	LS Mean (SE)	-10.71 (1.16)	-14.16 (1.23)
Placebo-adjusted difference	LS Mean (SE)	NA	-3.46 (1.24)
	95% CI	NA	(-5.91, 1.01)
White			
No patients		73	72
Change from Baseline	LS Mean (SE)	-9.95 (1.08)	-14.64 (1.09)
Placebo adjusted difference	LS Mean (SE)	NA	-4.69 (1.52)
	95% CI	NA	(-7.70, -1.68)
Other			
No patients		9	7
Change from Baseline	LS Mean (SE)	-13.91 (3.09)	-11.69 (3.51)
Placebo adjusted difference	LS Mean (SE)	NA	2.22 (4.68)
	95% CI	NA	(-17.90, 22.35)

Source: Table 11.2.1.3.6 (pg. 275-276), Clinical Study Report D144CC00004

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

This reviewer conducted exploratory subgroup analysis of efficacy by region for both studies.

4.2.1 STUDY D144CC00002

The change from baseline in MADRS total score at Day 57 (Week 8) is summarized for bipolar type subgroups in Table 19. The treatment effect appeared to be numerically in favor of quetiapine (when compared with placebo) within both subgroups. This reviewer confirmed sponsor's results.

Table 19. Subgroup Analysis by Bipolar type: MADRS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	Quetiapine XR
Bipolar type I			
No patients		110	107
Change from Baseline	LS Mean (SE)	-11.70 (1.16)	-18.23 (1.20)
Placebo-adjusted difference	LS Mean (SE)	NA	-6.53 (1.39)
	95% CI	NA	(-9.27, -3.79)
Bipolar type II			
No patients		27	26
Change from Baseline	LS Mean (SE)	-11.84 (2.20)	-14.87 (2.26)
Placebo adjusted difference	LS Mean (SE)	NA	-3.02 (2.04)
	95% CI	NA	(-7.19, 1.15)

Source: Table 11.2.1.3.7 (pg. 260), Clinical Study Report D144CC00002

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2.2 STUDY D144CC00004

Change from baseline in YMRS score at Day 22 by mixed versus manic episode at baseline, in the MITT population, LOCF, is presented in Table 20. The treatment effect appeared to be numerically in favor of quetiapine (when compared with placebo) within both subgroups. This reviewer confirmed sponsor's results.

Table 20. Subgroup Analysis by Episode type: YMRS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	Quetiapine XR
Manic Episode			
No patients		88	86
Change from Baseline	LS Mean (SE)	-10.38 (1.05)	-15.29 (1.08)
Placebo-adjusted difference	LS Mean (SE)	NA	-4.91 (1.23)
	95% CI	NA	(-7.35, -2.47)
Mixed Episode			
No patients		71	63
Change from Baseline	LS Mean (SE)	-10.14 (1.22)	-12.61 (1.26)
Placebo adjusted difference	LS Mean (SE)	NA	-2.47 (1.46)
	95% CI	NA	(-5.36, 0.41)

Source: Table 11.2.1.3.7 (pg. 277), Clinical Study Report D144CC00004

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Study D144CC00002

Quetiapine XR treatment group (300 mg QD given in the evening) was statistically superior to placebo in mean change from baseline to the endpoint visit in MADRS Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with fixed effects of treatment and bipolar diagnosis, random effect of center, and baseline MADRS total score as a covariate was < 0.001.

Study D144CC00004

Quetiapine XR treatment group (flexible dose in the range of 400-800mg QD given in the evening) was statistically superior to placebo in mean change from baseline to the endpoint visit in YMRS Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with fixed effect of treatment, random effect of center random and baseline YMRS total score as a covariate was < 0.001.

In general, no statistical issues are identified in both studies.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Study D144CC00002

In the primary analysis of the MADRS Total score, bipolar patients with an acute depressive episode on Quetiapine XR 300 mg QD given in the evening were observed to show statistically significant improvement over patients in the placebo treatment group.

Study D144CC00004

In the primary analysis of the YMRS Total score, patients with bipolar I disorder with an acute manic episode on Quetiapine XR flexible doses in the range of 400 to 800 mg QD given in the evening were observed to show statistically significant improvement over patients in the placebo treatment group.

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