

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-047 S-006, S-007, and S-008

MEDICAL REVIEW(S)

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 7, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Seroquel (quetiapine) XR tablets for the acute treatment of depressive episodes and the acute treatment of manic and mixed episodes associated with bipolar disorder

TO: File NDA 22-047S-006/007/008
[Note: This overview should be filed with the 12-19-07 original submission of these supplements.]

1.0 BACKGROUND

Seroquel (quetiapine immediate release) is an atypical antipsychotic that is approved (1) as monotherapy for the acute treatment of schizophrenia, (2) as monotherapy and as adjunctive therapy to lithium or (b) (4) for the acute treatment of manic episodes associated with bipolar disorder, (3) as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder, and (4) as adjunctive therapy to lithium or (b) (4) for the maintenance treatment of bipolar disorder. The extended release formulation of quetiapine (i.e., Seroquel XR) is approved (1) as monotherapy for the acute treatment of schizophrenia and (2) as monotherapy for the maintenance treatment of schizophrenia.

This supplement provides data in support of claims for Seroquel XR (1) as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder (based on 1 new trial), (2) as monotherapy for the acute treatment of depressive episodes associated with bipolar I or II disorder (based on 1 new trial), and (3) as adjunctive therapy to lithium or (b) (4) for the acute treatment of manic or mixed episodes associated with bipolar I disorder (based on extrapolation from the adjunctive trial with Seroquel).

The proposed dose of Seroquel for the acute treatment of manic episodes is 400-800 mg/day and for the acute treatment of depressive episodes is 300 mg/day. Seroquel XR is currently marketed in strengths of 150, 200, 300, and 400 mg. The sponsor is seeking to market an additional strength of 50 mg.

We did not meet with the sponsor to discuss their plans for this program. We did, however, communicate our requirements in an 11-6-06 letter, i.e., 1 acute study in each of bipolar mania and bipolar depression.

The primary review of the efficacy and safety data was done by Cara Alfaro, Ph.D., from the clinical group. George Kordzhakhia, Ph.D., from the biometrics group, also reviewed the efficacy data.

The studies supporting this supplement were conducted under IND 76,146, and this supplement was submitted on 12-19-07.

We decided not to take this application to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

Seroquel XR is an approved product, and there were no CMC issues that required review as part of this supplement, except for an environmental assessment for which a FONSI was recommended.

3.0 PHARMACOLOGY

Seroquel XR is an approved product. The only pharm/tox issues that required review as part of this supplement were changes in the pregnancy section proposed by the Maternal Health Team, and we have reached agreement on these changes.

4.0 BIOPHARMACEUTICS

Seroquel XR is an approved product, and there were no biopharmaceutics issues that required review as part of this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application considered 2 short-term trials, one in patients with depressive episodes associated with bipolar disorder (study D144CC00002) and one in patients with manic episodes associated with bipolar I disorder (study D144CC00004).

Study D144CC00002 was a randomized, multicenter (US), double-blind, parallel group, placebo-controlled, fixed dose, 8-week monotherapy study in adult outpatients with depressive episodes associated with bipolar I or II disorder (DSM-IV). The fixed Seroquel XR dose was 300 mg/day at hs. The primary endpoint was change from baseline to endpoint in MADRS (ANCOVA; LOCF). Seroquel XR was statistically significantly superior to placebo ($p < 0.001$). Recommended dosing will be 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, and 300 mg on day 4 and beyond.

Study D144CC00004 was a randomized, multicenter (US), double-blind, parallel group, placebo-controlled, flexible-dose, 3-week monotherapy study in adult outpatients with manic or mixed episodes associated with bipolar I disorder (DSM-IV). The flexible Seroquel XR dose was 400-800 mg/day at hs. The mean daily dose was 604 mg/day. The primary endpoint was change from baseline to endpoint in YMRS (ANCOVA; LOCF). Seroquel XR was statistically significantly superior to placebo ($p < 0.001$). Recommended dosing will be 300 mg on day 1, 600 mg on day 2, and dosing in a range of 400-800 mg/day for day 3 and beyond.

5.1.2 Comment on Other Important Clinical Issues Regarding Efficacy

Evidence Bearing on the Question of Dose/Response for Efficacy

There was no evidence in this program pertinent to dose response.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis age, gender, and race. There was no indication of any difference in effectiveness based on these analyses.

Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in change from baseline (about 5 units on the MADRS and 4 units on the YMRS) were similar to effect sizes seen in other positive trials.

Duration of Treatment

There is no information from this program pertinent to the question of longer-term efficacy for bipolar depression or mania. As noted, Seroquel already has a claim for maintenance treatment in bipolar disorder as adjunct to lithium or (b) (4) [REDACTED]

PREA Requirements

The sponsor will get a waiver for ages less than 10, and a deferral for ages 10-17 for both acute treatment of mania and acute treatment of bipolar depression. They have done a study of pediatric mania with the IR product, and this will satisfy the mania requirement. They are planning a peds study in bipolar depression to satisfy this requirement.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of efficacy for Seroquel XR in the acute treatment of depression associated with bipolar disorder and the acute treatment of mania associated with bipolar disorder. Both Drs. Khin and Alfaro feel that it would be reasonable to extrapolate the acute adjunctive claim in mania with Seroquel to Seroquel XR, and I agree.

5.2 Safety Data

The safety review for these supplements was based on data from the 2 acute studies (002 and 004). Overall, the safety findings for these supplements were consistent with the known adverse event profile for quetiapine and no important adverse events that could be considered causally related to quetiapine were discovered as a result of the safety review. We are currently reviewing a comprehensive submission from the sponsor regarding metabolic effects of quetiapine. Both Drs. Khin and Alfaro feel that the safety profile of Seroquel XR in bipolar disorder can be adequately characterized in labeling, and I agree.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling and reached agreement with them on final labeling as of 10-7-08.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they conducted an update to previous literature searches and found no relevant papers that would adversely affect conclusions about the safety of Seroquel in the treatment of patients with bipolar disorder.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Seroquel XR is approved in 5 countries for bipolar mania and 1 country for bipolar depression.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at one site that enrolled patients for both pivotal studies. The data from this site were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

As noted, we have reached agreement with the sponsor on final labeling.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted sufficient data to support the conclusion that Seroquel XR is effective and acceptably safe as monotherapy in the acute treatment of depression associated with bipolar disorder and as both monotherapy and adjunctive therapy in the acute treatment of mania associated with bipolar disorder. In addition, we have reached agreement with the sponsor on final labeling. Thus, we will issue an approval letter for these supplements.

cc:

Orig NDA 22-047S-006/007/008

HFD-130

HFD-130/TLaughren/MMathis/NKhin/CAlfaro/DBates

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/s/

Thomas Laughren
10/7/2008 02:28:48 PM
MEDICAL OFFICER

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: September 12, 2008

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 22-047/SE1-006/007/008
(This overview should be filed with the 12-19-2007 original submission)

SUBJECT: Recommendation of Approval Action for quetiapine fumarate extended release (Seroquel® XR) in the treatment of Bipolar Depression; and Bipolar I Disorder, Acute Mania (Monotherapy and Adjunctive Treatment)

1. BACKGROUND

Quetiapine fumarate (Seroquel®) is an atypical antipsychotic agent. In the U.S., the immediate release (IR) oral formulation of quetiapine (NDA 20-639) was first approved in September 1997 for the treatment of schizophrenia. It is also approved for the treatment of Bipolar I disorder, acute mania and depression. Quetiapine's efficacy in schizophrenia and bipolar disorder is thought to be mediated through a combination of dopamine D2 and serotonin 5-HT₂ antagonism. The extended release tablets (Seroquel XR) was approved on May 17, 2007 (NDA 22-047). The dose range of Seroquel XR in the treatment of schizophrenia is 400-800 mg/day, administered once daily. The Seroquel XR oral tablet formulation is available as 150, 200, 300, and 400 mg strength.

The sponsor conducted two pivotal studies for Seroquel XR for bipolar disorder under IND 76,146. On December 18, 2007, the sponsor has submitted supplemental new drug applications for marketing approval of Seroquel XR in treatment of Bipolar I Disorder, acute mania, and Bipolar Depression. Results from study D144CC00002 was included in support of the Bipolar Depression indication, and results from study D144CC00004 was submitted in support of the Bipolar I acute mania monotherapy indication. The Sponsor did not provide any clinical data to support the acute mania adjunctive therapy indication but they seek for this indication as well based on available data from quetiapine IR.

This NDA has been reviewed by Julia Pinto, Ph.D, CMC reviewer (review dated 7/7/08), George Kordzhakhia, Ph.D., Statistical Reviewer, the Office of Biostatistics (review dated 7/28/08), and Cara Alfaro, Pharm.D., Clinical Analyst, DPP (review dated 08/21/2008).

2.0 CHEMISTRY

There was no new CMC information required for review in this submission, except for environmental assessment (EA) issues. In the Chemistry review, Dr. Pinto noted that an

environmental assessment was conducted by Raanan Bloom, Ph.D., from the Office of New Drug Quality Assessment. The EA was found acceptable and categorical exclusion was granted.

In this submission, the sponsor is proposing to market the 50 mg strength tablets. As noted in the CMC review, this strength was recommended for approval as part of the original NDA review but the sponsor decided not to market it at that time. The CMC reviewer has recommended for approval of this set of NDA supplements from a CMC perspective including labeling changes for the 50 mg extended release tablet, are to be made in the Dosage, Description and How Supplied Sections, to reflect the addition of the 50mg strength.

3.0 PHARMACOLOGY/TOXICOLOGY

There is no new pharmacology/toxicology data presented in this submission. The sponsor proposed labeling changes to Section 12 (Clinical Pharmacology) in this submission. The FDA's Maternal Health Team also reviewed labeling as part of their pilot project. They have suggested changes to the Pregnancy and Nursing Mothers subsections – the suggested changes include addition of animal data. Dr. Barry Rosloff, Supervisory Pharmacologist, and Dr. Linda Fossom, Pharm/Tox Team Leader, would review these documents and provide some labeling modifications in Section 8, 12 and 13.

4.0 CLINICAL PHARMACOLOGY

No new PK/PD data in this submission which would require an OCP review.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Bipolar Depression

Our review of efficacy was mainly based on the result of Study D1444CC00002 which was a multicenter, double-blind, randomized, placebo controlled U.S. study to evaluate the efficacy and safety of quetiapine fumarate sustained-release (QTP XR) as monotherapy in adult patients with bipolar depression after 8 weeks of treatment.

The sponsor indicated that results of this study 002 demonstrated that QTP XR 300 mg/day was superior to placebo on the primary efficacy variable (i.e., change from baseline to final visit in MADRS total score).

Bipolar I Disorder, Acute Mania (Monotherapy)

Our review of efficacy was mainly based on the result of Study D1444CC00004 which was an international, multicenter, double-blind, randomized, placebo controlled, flexible dose (QTP XR 400-800 mg/day) study to evaluate the efficacy and safety of QTP XR as monotherapy in adult patients with bipolar I disorder, acute mania, after 3 weeks of treatment.

The sponsor indicated that results of this study 004 demonstrated that QTP XR was superior to placebo on the primary efficacy variable (i.e., change from baseline to final visit in YMRS total score).

I would briefly describe the results of each of these studies in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

5.1.2.1 Bipolar Depression - Study D1444CC00002

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, outpatient study comparing the effect of QTP XR and placebo in adults (aged 18 to 65 yrs) who met a DSM-IV diagnosis of bipolar I or II disorder, most recent episode depressed and confirmed by the structured clinical interview for DSM-IV. After screening, eligible patients who entered into a 8 week double-blind treatment were randomized to receive either QTP XR 300 mg or placebo, oral dose given once daily in the evening. The QTP XR dose was titrated to 300 mg/day within 4 days: 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3 and beginning on Day 4 through the remainder of the study, a fixed dose of 300 mg.

The study was conducted at 64 centers in the U.S. Out of a total of 418 patients screened for the study, 280 subjects randomized to the double-blind treatment, 140 in each treatment group. The MITT samples (N=270) for quetiapine XR (300 mg) and placebo were 133, and 137, respectively. The subjects enrolled were mostly white (72%), mean age was 39 yrs, and had approximately 64% female subjects. 80% were diagnosed with bipolar I; approximately 27% had rapid cycling. There seemed to be no significant differences in demographic characteristics between the two treatment groups. A total of 324 subjects (65.4%) completed the double-blind study; 87 (62.1%) in QTP XR group, and 96 (68.6%) in the placebo group. 94 subjects discontinued from the study; 52 in QTP XR and 42 in placebo. The most common reason for discontinuation from the study was adverse events (12.1%) in QTP XR group; and lack of therapeutic response (7.1%) and voluntary discontinuation by patient (7.1%) in the placebo group.

The efficacy assessment included the Montgomery-Asberg Depression Rating Scale (MADRS), and the CGI rating scales. The primary outcome variable was the change from baseline in the MADRS total score at final visit (Week 8). 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. The ANCOVA was the statistical model employed, with baseline MADRS as a covariate using the LOCF method. Both OC and MMRM analyses were also done as sensitivity analysis. Dr. Kordzadkhia confirmed the sponsor's efficacy results. The primary efficacy results can be seen in Table 1 below:

Table 1: Efficacy Results on Change from baseline in total MADRS Scores at endpoint (LOCF)

Treatment Groups (Number of subjects)	Mean Baseline total MADRS (SD)	LS mean Change from Baseline Mean at endpoint	Placebo adjusted difference; p- values (drug vs. placebo)
QTP XR 300 mg (N=133)	29.8 (5.2)	-17.4	-5.5 (1.2); p<0.001
Placebo (N=137)	30.1 (5.5)	-5.5	

Comment: Both Drs. Alfaro and Kordzakhia considered this a positive study for Seroquel XR, and I agree with them.

5.1.2.2 Bipolar Disorder, Acute Mania (Monotherapy) - Study D1444CC00004

This was a 3 week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, flexible dose (dose range 400 to 800 mg) study comparing the effect of QTP XR and placebo in adult (aged 18 to 65 yrs) patients who met a DSM-IV-TR diagnosis of bipolar I disorder, most recent episode manic or mixed, confirmed by the amended version of the structured clinical interview for DSM-IV (SCID). After screening/washout period, eligible patients who entered into a 3 week treatment period were randomized to receive either QTP XR or placebo, oral dose given once daily in the evening. Patients had to be hospitalized for at least 4 days immediately after randomization on Day 1. QTP 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. QTP XR was given in flexible doses of 400 to 800 mg (two to four 200-mg tablets) from Day 3 to Day 21. The mean daily dose was 603.8 mg.

The study was conducted at 50 centers in the U.S. Out of a total of 459 patients screened for the study, 313 subjects randomized to the double-blind treatment (155 in the QTP XR treatment group and 161 in the placebo group). The MITT samples (N=308) for quetiapine XR and placebo were 149, and 159, respectively. The majority of subjects enrolled were African American (48%) and Caucasian (47%). Approximately 60% were male subjects; mean age was 41 yrs. Approximately 56% had recent manic episodes and 31% had rapid cycling. There seemed to be no significant differences in these demographic and baseline disease characteristics between the two treatment groups. A total of 227 subjects (72%) completed the double-blind study; 111 in QTP XR group, and 117 in the placebo group. 89 subjects discontinued from the study; 44 in QTP XR and 45 in placebo. The common reason for discontinuation from the study included adverse events, lack of therapeutic response and voluntary discontinuation by patient.

The efficacy assessment included the Young Mania Rating Scale (YMRS), and the CGI rating scales. The primary outcome variable was the change from baseline in the YMRS total score at final visit (Week 3). The MITT 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 YMRS assessment, classified by the randomized treatment assignment. The ANCOVA was the statistical model employed, with baseline YMRS total score as a covariate using the LOCF method. Both OC and MMRM analyses were also done as sensitivity analysis. Dr. Kordzakhia confirmed the efficacy results. The primary efficacy results can be seen in Table 2 below:

Table 2: Efficacy Results on Change from baseline in total YMRS Scores at endpoint (LOCF)

Treatment Groups (Number of subjects)	Mean Baseline total YMRS (SD)	LS mean Change from Baseline Mean at endpoint (Day 22)	Placebo adjusted difference; p- values (drug vs. placebo)
Quetiapine XR (N=149)	28.8 (5.4)	-14.3	-3.83 (0.93); p<0.001
Placebo (N=159)	28.4 (5.1)	-10.5	

Comment: Both Drs. Alfaro and Kordzakhia considered this a positive study for quetiapine XR, and I agree with them.

5.1.3 Comments on Other Important Clinical Issues

5.1.3.1 Predictors of Treatment Response

Exploratory subgroup analyses were done to detect subgroup interactions on the basis of age (18-39; 40-65), ethnicity (Caucasian, African American and others) and gender (M, F). For all subgroups (except for other ethnic subgroup in study 004), the treatment effect appeared to be numerically in favor of QTP XR compared to placebo.

5.1.3.2 Duration of Treatment

Quetiapine IR is currently approved for the maintenance treatment of Bipolar I disorder, mania, as adjunct therapy to lithium or divalproex; no maintenance indication has been granted for quetiapine IR for monotherapy. Quetiapine IR is currently approved for the acute treatment of Bipolar Depression. (b) (4)

(b) (4) DPP has already determined that a Phase 4 commitment to require adult longer-term studies in Bipolar Disorder would not be necessary as part of the action taken on NDA 20-639/S-026.

5.1.3.3 Onset of Treatment Effect

The sponsor showed that the treatment effect of Seroquel XR in Bipolar Mania starting at Day 4 to end of study (YMRS efficacy ratings were done on Days 4, 8, 15 and 22). The sponsor intends to claim (b) (4)

(b) (4) We should not allow them to do so in the labeling. The pre-specified primary efficacy endpoint was the change from baseline to week 8 in total MADRS scores.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analysis of study 002 supported the efficacy claim of Seroquel XR for acute treatment of bipolar depression. The efficacy analysis of study 004 supported the efficacy claim of Seroquel XR for acute monotherapy treatment of bipolar I mania.

Although the sponsor did not provide any clinical data to support the acute adjunctive therapy indication, they seek marketing approval of use of Seroquel XR as adjunctive treatment in Bipolar I Disorder, Mania. Based on extrapolation of this indication for quetiapine IR and with data to support the effectiveness of Seroquel XR in acute mania as monotherapy, I agree with Dr. Alfaro that the adjunctive treatment claim in bipolar mania be granted for Seroquel XR.

5.2 Safety Data

5.2.1 Safety Database

The sponsor did not submit an integrated safety summary (ISS) and it was deemed appropriate as there was only one study for each indication and the doses and duration of study drug exposure were different between these studies. Dr. Alfaro's safety review of this set of NDA supplements

was based on the safety data from above two studies: D1444CC00002 and D1444CC00004. The study 002 was a fixed dose, 8 week study in bipolar depressed patients; the mean daily dose was 266.9 mg (median = 284.8 mg) and the mean duration of treatment was 42.6 days. For study 004, the 400 – 800 mg/day flexible dose study of 3 weeks duration in bipolar acute mania, the mean daily dose was 603.8 mg (median = 585.7 mg) and the mean duration of treatment was 18.7 days. The crude exposure estimate was 16 patient-years for D144CC00002 and 7.7 patient-years for D144CC00004.

No deaths reported in the quetiapine XR groups for both pivotal trials. Serious adverse events included asthma, depression, bipolar I disorder, suicide attempt, vestibular neuronitis, psychotic disorder and suicidal ideation. Most of these adverse events were consistent with the underlying disorder and also occurred with similar frequency in the placebo groups.

For Study D144CC00002, the most common adverse events associated with subject discontinuation were sedation and somnolence. For Study D144CC00004, the most common adverse events associated with subject discontinuation were symptoms related to bipolar disorder.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is approximately twice or more the placebo risk). The sponsor reported the following most common adverse events in the quetiapine XR group for D144CC00002 and D144CC00004: dry mouth (37% and 34%), somnolence (29% and 17%), sedation (23% and 34%), dizziness (13% and 10%) and increased appetite (12% and 4%). As noted by Dr. Alfaro in her review, the frequencies of dry mouth, sedation and somnolence were higher in these bipolar pivotal trials compared to the acute schizophrenia trials.

5.2.2.2 Metabolic Effects

The mean change from baseline for weight was greater in the QTP XR groups (+ 1.3 kg) compared to the placebo groups (-0.2 kg, + 0.1 kg) for both studies.

As can be seen in Table 3 below, QTP XR was associated with mean change from baseline to endpoint increases in glucose, triglycerides, and prolactin.

Table 3: Mean Changes from Baseline to Endpoint for Select Laboratory Tests

	Study D144CC00002		Study D144CC00004	
	Quetiapine XR	Placebo	Quetiapine XR	Placebo
Fasting glucose (mg/dL)	NA	NA	9.0	2.9
Glucose (mg/dL)	6.1	5.9	9.0	2.7
Triglycerides (mg/dL)	15.9	-2.7	28.3	-7.1
Prolactin (ng/ml)	25.9	18.4	14.91	-1.72

There was higher percentage of patients who were noted to have shifts from normal to important high in these parameters [glucose \geq 120 mg/dL; triglyceride \geq 200 mg/dL; prolactin >20 (M) or 30

ng/ml (F)] in the QTP XR treated patients as compared to placebo. The sponsor did not provide the magnitude of these shifts.

Comments: The Division requested that the sponsor conduct an analysis of all clinical trials to study the effects of QTP IR and XR on these safety signals. The sponsor has recently submitted these data. Further modifications to product labeling will be made upon completion of our review of these submitted data.

5.2.2.3 Neutropenia and Agranulocytosis

There were four subjects in the QTP XR groups and 2 subjects in the placebo groups had shifts from normal baseline ANC to values $< 1.5 \times 10^9/L$ and most (one lost to follow-up) resolved per follow-up labs obtained after the study was completed. It should be noted that the Division has recently revised Seroquel labeling language under Warnings/Precautions, a subsection entitled "Leukopenia, Neutropenia and Agranulocytosis."

5.2.2.4 Vital Sign Changes

Mean change from baseline for supine and standing pulse was greater in the quetiapine XR groups compared to placebo: +4.5 vs. 0.1 bpm (supine) and +3.4 vs. -0.3 bpm (standing) for D144CC00002; +1.3 vs. -2.9 bpm (supine) and +2 vs. -3.6 bpm (standing) for D144CC00004. Greater decreases were noted for supine and standing systolic blood pressure in the quetiapine XR groups compared to placebo: -2.1 vs. -0.7 mmHg (supine) and -1.6 vs. -0.5 mmHg (standing) for D144CC00002; -2.4 vs. +0.2 mmHg (supine) and -2.6 vs. +1.5 mmHg (standing). These findings are consistent with the known effects of quetiapine IR and XR on vital signs. The mean changes in orthostatic measurements did not seem to be clinically significant in QTP XR group.

5.2.2.5 Extrapyramidal Symptoms (EPS)

The incidence of adverse events consistent with EPS was higher in the quetiapine XR groups compared to placebo (4.4% vs. 0.7% in study D144CC00002 and 6.6% vs. 3.8% in study D144CC00004). However, mean ratings for EPS and akathisia were low in both treatment groups and mean scores for all groups decreased from baseline to end of study as measured by Simpson Angus Scale and Barnes Akathisia Scale Global Assessment.

5.2.2.6 Treatment-Emergent Mania/Depression

An analysis of treatment-emergent mania (for study D144CC00002) or treatment-emergent depression (for study D144CC00004) did not suggest a significant increase in these symptoms in subjects in the quetiapine XR groups.

5.2.3 Conclusion Regarding Safety Data

This submission revealed no findings which were attributable to Seroquel XR treatment and inconsistent with the previously observed safety profile of quetiapine IR and XR. Overall, there are no new safety concerns that would preclude an approval action.

6.0 WORLD LITERATURE

The sponsor has indicated that they conducted an update to previously submitted literature searches for published articles pertaining to the safety of quetiapine XR. They did not identify any additional issue affecting the safety of Seroquel XR.

7.0 FOREIGN REGULATORY ACTION

The sponsor reported that Seroquel XR is approved in 26 countries for schizophrenia and 5 countries for bipolar mania. It is approved for use in treatment of bipolar depression in Mexico.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Dr. Vikram Mehra's site in Houston, Texas was chosen to be inspected due to the high numbers of subjects enrolled as well as the investigator's involvement with both pivotal clinical trials (20 subjects for D144CC00002 and 33 subjects for D144CC00004). Based on our preliminary communication with DSI, the inspectional findings did not indicate any data integrity issues. DSI clinical inspection summary report is still pending.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified. We should be negotiating labeling changes with the sponsor prior to approval of the NDA supplements.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that Seroquel XR is effective and reasonably safe in the acute monotherapy treatment of bipolar depression and bipolar I disorder, mania. Although the sponsor did not provide any clinical data to support the acute adjunctive therapy indication, based on extrapolation of this indication for quetiapine IR and with data to support the effectiveness of Seroquel XR in acute mania as monotherapy, I concur with Dr. Alfaro that the adjunctive treatment in bipolar mania indication be granted for Seroquel XR. Therefore, I recommend the Division should consider approval of this set of NDA supplements (S006, 007 and 008) provided that an agreement is reached between the sponsor and the Agency regarding the language in the labeling.

I note in Dr. Alfaro's clinical review that she is reviewing additional information provided by the sponsor in response to her questions listed in section 9.4; and also that she will be writing an amendment. I do not anticipate that there will be any significant issues which would preclude approvability of this NDA. If my conclusion changes upon review of Dr. Alfaro's clinical review amendment, addendum to this memo will be generated.

Cc: HFD-130/Laughren/Mathis/Alfaro/Bates

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Ni Aye Khin
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Review and Evaluation of Clinical Data

NDA # 22047 SE1 0006, 0007 and 0008

Sponsor: AstraZeneca

Drug: Seroquel XR

Drug category: Antipsychotic

Material submitted: Sponsor's responses to questions during NDA review

Indication: Treatment of bipolar depression, treatment of acute mania (monotherapy and adjunctive therapy)

Correspondence Date: 8/20/08 [email; 8/28/08 as amendment to NDA], 9/5/08 [email; 9/12/08 as amendment to NDA]

Date Review Completed: 9/22/08

Clinical Reviewer: Cara Alfaro, Pharm.D.

Background

During the review of NDA 22047 SE1 0006, 0007 and 0008, several requests for information were sent to the Sponsor. The Sponsor provided responses on 8/20/08 and 9/5/08 via secure email – these responses were later submitted as formal amendments to the NDA. This document is a review of those responses.

Division Requests for Information and Sponsor Responses

Division Request for Information (1)

Please provide an update for the subject in the quetiapine XR group in protocol D144CC00004 who experienced the SAE "vestibular neuronitis".

Sponsor response:

"AstraZeneca reviewed the case report forms, as well as the clinical and safety database for additional information on subject E4052003. The study site has provided no additional information on this subject."

Reviewer comments:

It appears that there was a lack of follow-up on an adverse event for this 51 YOM subject (patient #41231, E-code E4052003). Per electronic CRF, the subject presented on 7/15/2007 (3 days after completing study) with dizziness starting 2 days prior and worsening. On 7/15/2007, patient was "so dizzy that he could not stand". Brain MRI was "stable" when compared to 8/26/05 with no acute infarcts. Asymmetric signal in the jugular bulbs with prominence of the left jugular bulb. Patient was admitted to telemetry. Klonopin (scheduled) and Phenergan (prn) were initiated. Diagnosis was vestibular neuronitis. CRF indicated "more records to follow". In the site monitor notes, it was stated that there was no room to record further information and that a discharge summary was faxed to the "clinical team" on July 31, 2008. There is no further information regarding this discharge summary provided by the Sponsor. This adverse event should be included in product labeling.

Division Request for Information (2)

In protocols D144CC00002 and D144CC00004, approximately 2-3% of subjects in both the quetiapine XR and placebo groups were discontinued from the studies for "severe non-compliance to protocol". Please specify which subjects were discontinued and what these protocol violations were.

Additionally, in both studies approximately 7-8% of subjects were discontinued in the category "voluntary discontinuation by subject". Is any additional data available (e.g. comments in CRFs) for these subjects regarding this discontinuation category (e.g. comments suggestive of adverse events, lack of efficacy, etc.)?

Sponsor response:

Severe noncompliance to protocol -

The protocol included criteria for discontinuation of subjects from the clinical trial. One of these criteria was "severe noncompliance to protocol" defined as "subjects who miss 5 or more (Study 002) or 3 or more (Study 004) consecutive days of investigational product". Per protocol, subjects meeting this criterion "must be discontinued". Other reasons for severe noncompliance to the protocol were left to the judgment of the investigator.

In the CRFs, there was no place for comments to document the precise reason why subjects were discontinued due to severe noncompliance to protocol. Some investigators did make comments in the "other" discontinuations field, since that was the only section where these comments could be made.

Severe noncompliance to protocol was similar across treatment groups in both studies:

Study D144CC00002, n = 4 (2.9%) for quetiapine XR and n = 5 (3.6%) for placebo.

Study D144CC00004, n = 4 (2.6%) for quetiapine XR and n = 2 (1.2%) for placebo.

Voluntary discontinuation by subject-

The Sponsor reviewed CRFs for each subject who discontinued based on this criterion (n = 25 in D144CC00004, n = 22 in D144CC00002). "There were no additional comments regarding voluntary discontinuation by subject provided on the Study Termination eCRFs for either Study D144CC00002 or Study D144CC00004". Three of 25 subjects in D144CC00004 had ongoing adverse events at the time of discontinuation: suicidal ideation (n = 1, placebo), fatigue (n = 1, quetiapine XR) and dizziness (n = 1, quetiapine XR). Six of the 22 subjects in D144CC00002 had ongoing adverse events at the time of discontinuation: dizziness (n = 1, placebo), increase triglycerides (n = 1, placebo), increased appetite (n = 1, quetiapine XR), dry mouth (n = 1, quetiapine XR), sedation (n = 1, quetiapine XR), intermittent enuresis (n = 1, quetiapine XR).

Voluntary discontinuation was similar across treatment groups in both studies:

Study D144CC00002, n = 12 (8.6%) for quetiapine XR and n = 10 (7.1%) for placebo.

Study D144CC00004, n = 13 (8.4%) for quetiapine XR and n = 12 (7.5%) for placebo.

Reviewer comments:

Severe noncompliance to protocol -

It was unclear from the review of these comments in the CRF (summarized in the Sponsor's response), how this criterion was met since most comments refer to drug accountability (how to determine consecutive missed doses versus sporadic missed doses). It is also unclear to this reviewer whether this should be an acceptable criterion on which to discontinue subjects – most Sponsor's perform additional analysis including a per-protocol analysis which would not

include these subjects (though the review division does not consider this analysis in efficacy determination). However, since the % of subjects discontinued based on this criterion is fairly small and similar between the two treatment groups, it is unlikely that it significantly impacted efficacy study results.

Voluntary discontinuation by subject-

No further comments were available in the CRFs for subjects who were discontinued due to "voluntary discontinuation by subject". A few of these subjects had adverse events that were ongoing at the time of study discontinuation, only one of these were suggestive of lack of therapeutic response – suicidal ideation in a subject receiving placebo.

No further analysis or determination of reasons for discontinuation could be performed.

Division Request for Information (3)

The current Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format (January 2006) document states that similar events such as somnolence and sedation should be one category rather than separated into two categories. For all tables in currently proposed labeling (including schizophrenia data), please indicate the frequency of somnolence/sedation.

Sponsor's response [1]:

Sponsor provided the data for the combined term. The Sponsor disagreed that these terms should be lumped together:

“According to the MedDRA dictionary 11.0, somnolence and sedation are two distinct preferred terms with different lower level terms mapping to them. Lower level terms mapped to the preferred term sedation include: dopiness, druggedness, dullness, oversedation, overtranquilization, sedation, sedation excessive, tranquilization excessive, sedation aggravated, and tranquilization excessive. Lower level terms mapped to the preferred term somnolence include: daytime sleepiness, drowsiness, drowsy on awakening, excessive daytime sleepiness, feeling of residual sleepiness, groggy, groggy and sluggish, groggy on awakening, hard to awaken, less alert on arising, sleepiness, sleepy, somnolence.

AstraZeneca believes that these two preferred terms represent different outcomes for patients and therefore it is more precise to keep somnolence and sedation as separate categories in the adverse events section of the label thus providing information for physicians that is useful in the management of their patients.”

Division Request for Information

Separate request sent after reviewing initial Sponsor response:

We received your response to our suggestion to combine the terms sedation and somnolence as one adverse event term in product labeling. While you correctly indicate that the lower level terms are different for each of these preferred terms, there is substantial overlap between these terms. Additionally, it is unlikely that a clinician can reliably distinguish between sedation and somnolence, and that splitting these terms actually serves to "dilute" a potentially significant adverse event. You did provide some recalculations combining these terms, however, you may need to recalculate the data. It appears that you may have just added the % of patients

experiencing these adverse events together - this would potentially overestimate the incidence in the combined term. If some subjects experienced both sedation and somnolence they would currently be counted in both categories but should only be counted once in a combined term. Please recalculate these numbers for the combined term "somnolence" - this would be consistent with what we have asked other Sponsors to do. You may indicate that this term combines both somnolence and sedation terms as a footnote to the adverse event tables.

Sponsor's response [2]:

The Sponsor indicated that very few patients had reports of both somnolence and sedation in the quetiapine XR groups in both studies. "Because of the non-overlap, AstraZeneca would prefer to maintain the categories separately in labeling, since sedation and somnolence represent different patient experiences and evaluations by treating physicians, but we will follow the FDA's guidance".

Reviewer Comments:

Adverse event terms sedation and somnolence were combined in product labeling into one term "somnolence" [per Sponsor proposal]. The proposed adverse event tables now include a footnote indicating that the somnolence term includes both event terms sedation and somnolence.

Division Request for Information (4)

For study D144CC00002, Table 11.3.7.3.3 lists mean change from baseline for chemistry variables but does not include fasting glucose. Since Table 11.3.7.3.4.1 lists change shifts for chemistry variables and includes fasting glucose, the mean change from baseline data should also be available for fasting glucose. Please submit these data.

Sponsor Response:

The Sponsor provided the requested data. The mean change at end of treatment was + 0.25 mmol/L (4.5 mg/dL) for placebo and +0.32 mmol/L (5.8 mg/dL) for quetiapine XR.

Reviewer Comments:

The Sponsor provided the requested data for fasting glucose for study D144CC00002. The mean changes from baseline are similar (see above) but less pronounced than that found for study D144CC00004 (mean change from baseline +9 mg/dL for quetiapine XR and +2.9 mg/dL for placebo).

Current labeling contains a section on Hyperglycemia/Dabetes Mellitus (Section 5.3) in Warnings and Precautions, but no specific data for changes in glucose in the subsection Laboratory Changes in Adverse Reactions: Clinical Studies Experience.

The Sponsor has recently submitted a comprehensive analysis of glucose changes across all clinical studies in response to a Division request for these analyses (along with other adverse events/laboratory change data) to address safety signals across all atypical antipsychotics. It is likely that product labeling will be updated to reflect these new data after a comprehensive review has been completed.

Division Request for Information (5)

In section 8.2 (Extent of Exposure) of the clinical study report for D144CC00004, it states that patient E4013003 intentionally took 4000 mg of quetiapine XR. There is a hyperlink for a patient narrative for this case. However, upon review of this narrative, there is no discussion of the clinical symptoms experienced after this overdose. Please provide this information.

Sponsor Response:

The Sponsor was unable to provide these data. The Sponsor stated “there was no indication within the eCRF data that there were any signs or symptoms associated with the overdose” and “the safety database indicated that the patient contacted the local emergency room to inform them of his overdose but no information regarding signs or symptoms was provided”.

Reviewer Comments:

No comments.

Division Request for Information (6)

Under section 8.5 (Use in specific populations: Geriatric use) of your proposed labeling, there is a brief mention of some pharmacokinetic data for the clearance of quetiapine and refers the reader to section 12.3 (pharmacokinetics). However, there is no data for geriatrics/elderly patients in the pharmacokinetics section. Please add these data to this section and any additional pharmacokinetic data relevant to this population for quetiapine or quetiapine XR.

Sponsor Response:

The Sponsor provided language for this subsection of the Pharmacokinetic (Section 12.3) section of labeling. These data are from the currently approved quetiapine IR label and pertain to clinical trials submitted with the original NDA for quetiapine IR:

Age

Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary [see Dosage and Administration (2)]

Reviewer Comments:

Proposed language added to labeling.

Division Request for Information (7)

The dosing for elderly patients and patients with hepatic impairment is to initiate with quetiapine 50 mg/day and increase the dose by 50 mg/day depending on response and tolerance of the patient. Since a 50 mg quetiapine XR tablet is not currently available, currently approved labeling indicates that quetiapine IR 25 mg should be initiated in these populations with dose

increases of 25-50 mg/day and, when an effective dose has been reached, the patient can be switched to quetiapine XR.

Please provide a comparison of pharmacokinetic data for the quetiapine IR 25 mg tablet and the quetiapine XR 50 mg tablet. Is there any tolerability data that you can provide regarding these populations and initiation of quetiapine XR 50 mg/day?

Sponsor Response:

“There are no cross-over comparative pharmacokinetic data for the quetiapine IR 25 mg tablet and the quetiapine XR 50 mg tablet available from clinical trials”.

The Sponsor did, however, provide data from the clinical trial 5077IL/0115 “An exploratory, multicentre, double-blind, double-dummy, randomized, parallel-group, controlled Phase 3 study to evaluate the safety and tolerability of sustained-release formulation quetiapine fumarate (Seroquel) in treatment of elderly subjects with Alzheimer’s disease with symptoms of psychosis and/or agitation compared to Seroquel immediate release formulation”. In this clinical trial, quetiapine XR was initiated at a dose of 50 mg/day and quetiapine IR was initiated at a dose of 25 mg/day. Both dosage forms were titrated up to 100 mg/day on day 4 (quetiapine IR increased to 50 mg/day on day 2); further dose adjustments could be made after day 8.

The mean daily dose was 144 mg for quetiapine XR and 142 mg for quetiapine IR. The Sponsor included the following tables summarizing adverse event data:

Table 1 Number (%) of patients who had at least 1 adverse event in any category (safety population), Study 5077IL/0115

Category of adverse event ^a	Treatment	
	Quetiapine XR (N=68) n (%)	Quetiapine IR (N=32) n (%)
Any adverse events	47 (69.1)	23 (71.9)
Serious adverse events		
Serious adverse events leading to death	1 (1.5)	0 (0.0)
Serious adverse events not leading to death	2 (2.9)	2 (6.3)
Discontinuation due to adverse events	1 (1.5)	0 (0.0)
Other significant adverse events ^b	0 (0.0)	0 (0.0)

^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

^b One patient was identified by an AstraZeneca expert during the evaluation of safety data after completion of the study. Note: Only 1 SAE occurred during treatment period. The remaining 4 SAEs occurred during the 30-day follow-up period.
XR, Extended Release. IR, Immediate Release.

Per Sponsor, the discontinuation due to AE in the quetiapine XR group was due to an AE that occurred prior to randomization.

Table 2 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency in the quetiapine XR treatment group (safety population), Study 5077IL/0115

MedDRA ^b preferred term	Treatment	
	Quetiapine XR (N=68) n (%)	Quetiapine IR (N=32) n (%)
Somnolence	10 (14.7)	6 (18.8)
Vomiting nos	7 (10.3)	2 (6.3)
Headache	6 (8.8)	3 (9.4)
Urinary tract infection nos	6 (8.8)	1 (3.1)
Sedation	5 (7.4)	4 (12.5)
Dry mouth	4 (5.9)	1 (3.1)
Fatigue	4 (5.9)	1 (3.1)
Nausea	4 (5.9)	3 (9.4)
Chest pain	1 (1.5)	2 (6.3)
Dizziness	1 (1.5)	3 (9.4)
Orthostatic hypotension	1 (1.5)	2 (6.3)
Haemorrhage nos	0 (0.0)	3 (9.4)

This table uses a cut-off of at 5% in at least one of the treatment groups.

^b Medical Dictionary for Regulatory Activities

XR, Sustained Release. IR, Immediate Release.

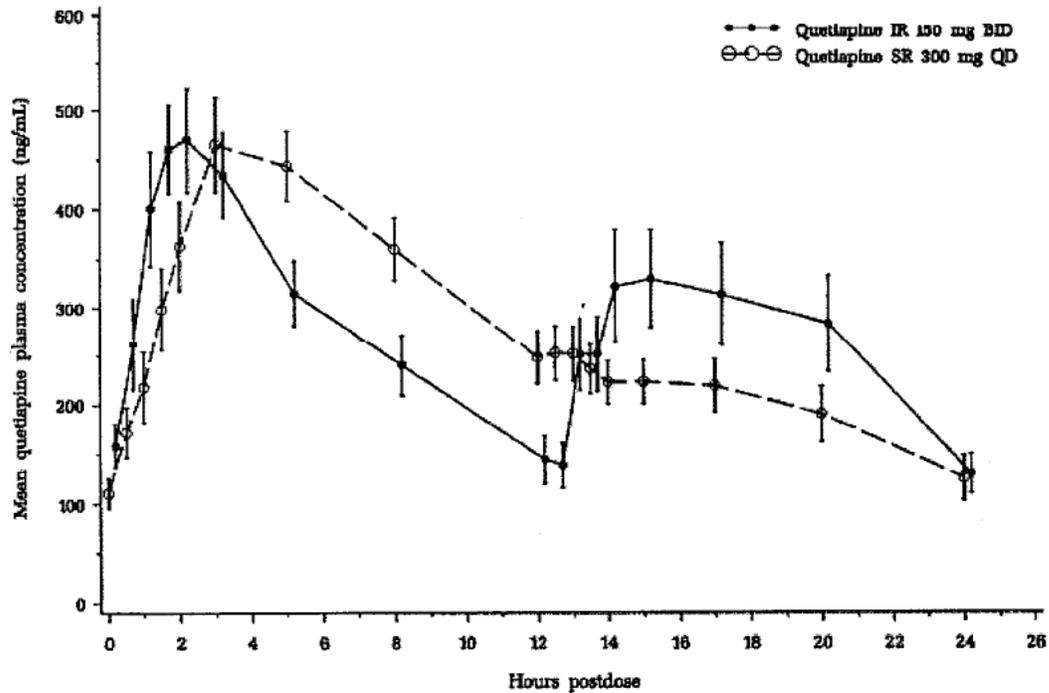
The Sponsor stated that specific studies (of quetiapine XR) in patients with hepatic or renal impairment have not been performed. “However, the similar bioavailability of quetiapine XR compared to quetiapine IR suggests that the recommended dosing modification for quetiapine IR would apply to quetiapine XR in this population.”

Reviewer Comments:

The Sponsor provided some data indicating that a starting dose of 50 mg/day for quetiapine XR is tolerated in an elderly population (in this case, patients with Alzheimer’s disease). In general, adverse events occurred with similar frequency in the quetiapine XR and quetiapine IR groups and the mean daily doses were similar between these groups. Although this does not directly address tolerability at dose initiation, it is suggestive of similarities in tolerability overall. The Sponsor has adequately addressed this issue and a starting dose of 50 mg for quetiapine XR in elderly subjects is acceptable to this reviewer.

No specific data were submitted by the Sponsor to support the dosing recommendations for quetiapine XR in subjects with hepatic impairment. The Sponsor indicates that the two dosage forms have similar bioavailability. This reviewer referred to the original biopharmaceutics review for quetiapine XR and looked at the PK data for the bioequivalence study comparing quetiapine IR 150 mg BID to quetiapine XR 300 mg QD. In evaluating the graphical display of AUCs for the two dosage forms and dosing regimens, the C_{max}’s after the first dose of the quetiapine IR 150 mg and the quetiapine XR 300 mg are very similar (see graph and table below

taken from the biopharmaceutics review). Based on these data, the suggested initial dosing for quetiapine XR in patients with hepatic impairment is acceptable.



IR: immediate-release quetiapine 150 mg twice daily
SR: sustained-release quetiapine 300 mg once daily

Figure taken from Biopharmaceutics review for Seroquel, XR (initial NDA 22047)

Table 1: Comparison of pharmacokinetic parameters for a 300-mg dose of quetiapine administered as SR tablets (300 mg once daily) or as IR tablets (150 mg twice daily)

Parameter (units) ^a	Immediate-release quetiapine (150 mg twice daily) (n=24)	Sustained-release quetiapine (300 mg once daily) (n=24)	Comparison of treatments: ratio of means ^b	
			Ratio (SR/IR)	90% CI ^c
Geometric mean (95% CI)				
AUC ₍₀₋₂₄₎ (ng·h/mL)	5882 (4729 to 7315)	6147 (5215 to 7246)	1.04	0.92 to 1.19
C _{max} (ng/mL)	568.1 (474.0 to 680.9)	495.3 (424.6 to 577.9)	0.87	0.77 to 0.99
C _{min} (ng/mL)	96.5 (66.2 to 140.4)	95.3 (69.4 to 130.8)	1.00	0.77 to 1.31
Median (range)				
t _{max}	2.0 (0.6 to 8.0)	5.0 (0.9 to 20.0)		
Degree of fluctuation (%)	171.8 (54.9 to 430.0)	155.7 (21.0 to 566.2)		

^a Parameters derived from data collected during the 24-hour interval following morning quetiapine administration on Day 4 of Periods 1 and 2.

^b Based on ratio (SR/IR) of least squares means from analysis of variance.

^c Based on log-transformed data.

Table taken from Biopharmaceutics review for Seroquel, XR (initial NDA 22047)

Division Request for Information (8)

In section 2.1 of labeling (Dosage and Administration: Bipolar depression- usual dose) you have included data for patients receiving (b) (4) mg of quetiapine XR. However, study D144CC00002 was a 300 mg fixed dose design. Please clarify and delete if this was included in error.

Sponsor Response:

The Sponsor indicated that these data are from the pivotal trial with quetiapine IR. The Sponsor wishes to keep this data in currently proposed labeling since:

(b) (4)

Reviewer Comments:

Since the pivotal quetiapine XR trial did not include a (b) (4) be removed from the Dosage and Administration

section of proposed labeling to reduce confusion to prescribers. It is acknowledged that the efficacy of quetiapine XR in bipolar disorder is, in part, extrapolated from data for quetiapine IR. However, the data regarding dosage and administration should, in this reviewer's opinion, reflect the clinical trials that were actually performed with that dosage form. The data for the (b) (4) is currently included in the Clinical Studies section of labeling.

Division Request for Information (9)

For the indication for adjunctive treatment of bipolar disorder with lithium or divalproex, we did not see anything in the proposed labeling discussing the dosing of quetiapine XR that should be used adjunctively. We assume that direct extrapolation from the IR data would give a recommended adjunctive dose between 400 and 800 mg/day. Please add the recommended dosing for adjunctive treatment using the XR into the proposed labeling, or, if the information has been included and we have failed to locate it, indicate where it can be found.

Sponsor Response:

The Sponsor included language for dosing and administration for adjunctive use of quetiapine XR:

2.1 Bipolar Disorder

Bipolar Mania-Usual Dose

When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL XR should be administered once daily in the evening starting with 300 mg on Day 1 and 600 mg on Day 2. SEROQUEL XR can be adjusted between 400 mg and 800 mg beginning on Day 3 depending on the response and tolerance of the individual patient.

Reviewer Comments:

No comments. Information incorporated into proposed labeling.

Division Request for Information (10)

For section 6.1 (Adverse Reactions: Clinical Studies Experience - Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials) of proposed labeling, the discontinuation rates due to AEs for SEROQUEL XR and placebo are given for the two bipolar studies. It is the understanding of this reviewer that these data came primarily from boxes checked on CRFs for reasons for discontinuations assessed by the investigators. The discontinuation rate due to AEs for D144CC00004 was interesting since 4.6% discontinued in the SEROQUEL XR group compared to 8.1% in the placebo group. However, upon review of the "adverse events", many do appear to be related to bipolar disorder (mania, etc.) and might be more reasonably categorized as lack of efficacy rather than an adverse event per se (this reviewer acknowledges that there is overlap with these terms). Please recalculate the discontinuations due to adverse events for both treatment groups in both clinical trials omitting adverse events that appear more related to lack of efficacy.

Sponsor Response:

The Sponsor recalculated adverse events leading to discontinuation using the following process:

1. A clinical review was performed of the investigator's verbatim terms for all adverse events leading to discontinuation as captured on the Adverse Event CRF.
2. These adverse events leading to discontinuation from study were then classified as either a bipolar disorder related adverse event or non bipolar disorder related event using the investigator's verbatim term.
3. If a patient had multiple adverse events and 1 event was a bipolar related adverse event, the patient was classified as discontinued due to a bipolar related adverse event.

Table 3 Summary of Adverse Events leading to discontinuation of investigational product for Study D144CC00002 and Study D144CC00004

Category	D144CC00002- Bipolar Depression				D144CC00004 – Bipolar Mania			
	Placebo N=140		Quetiapine XR N=137		Placebo N=160		Quetiapine XR N=151	
	N	%	N	%	N	%	N	%
Based on reported discontinuation (AE CRF page)								
Discontinuation for any AE	5	3.6	19	13.9	13	8.1	7	4.6
Discontinuation for only non –bipolar disorder AE	2	1.4	15	10.9	4	2.5	3	2.0
Discontinuation for any Bipolar disorder related AE	3	2.2	4	3.0	9	5.6	4	2.6

XR Extended Release. Adverse Event. CRF Case Report Form

Reviewer Comments:

The recalculation of discontinuations due to adverse events does demonstrate that for study D144CC00004, more patients discontinued due to bipolar-related adverse events in the placebo group compared to the quetiapine XR group – in the opinion of this reviewer, bipolar-related adverse events could also be considered “lack of efficacy”. It is also the opinion of this reviewer that clinicians who read the label would not be thinking that bipolar-related adverse events (e.g. mania) would be captured in the category “discontinuations due to adverse events”. The Division has not, to this reviewer's knowledge, parsed out discontinuations due to adverse events in this way and it may be premature to do so with this regulatory action. However, this issue does deserve some discussion within the Division.

Conclusions and Recommendations

The Sponsor has adequately addressed all requests for additional information. None of the data submitted alter the efficacy or safety conclusions for quetiapine XR in the treatment of bipolar

disorder. I recommend approval of quetiapine XR (Seroquel XR) for these three indications (bipolar depression, acute mania – monotherapy, acute mania – adjunct therapy). Labeling negotiations should continue with the Sponsor to address any outstanding issues.

This reviewer has suggested changes to product labeling. These changes were made to Sponsor's proposed labeling via track changes and submitted to the Team Leader (Dr. Khin) for further review. During review of labeling, it was noticed that the ECG summary data did not appear to be updated with data from these two pivotal bipolar disorder trials. In particular, 24% of patients in study D144CC00004 had evidence of tachycardia ($HR \geq 120$ bpm) on ECG and it is not known if these data were included in this summary section (the overall % of patients with this finding may not have changed). The Sponsor will be asked to clarify.

It is recommended that the Division discuss how to best provide information regarding discontinuations due to adverse events (see Division Request for Information [10]). In study D144CC00004, the placebo group had a greater % of subjects discontinuing due to adverse events compared to the quetiapine XR group. However, upon query and further analysis by the Sponsor, most of these adverse events were considered "bipolar-related" and may, in this reviewer's opinion, be better categorized as lack of efficacy. This issue is beyond the scope of this particular review but should be considered by the Division for future actions.

Cara Alfaro, Pharm.D.
Clinical Analyst
Division of Psychiatry Products

September 22, 2008

cc: Khin/Laughren/Bates/Alfaro

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/s/

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9/22/2008 02:06:09 PM
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CLINICAL REVIEW

Application Type	NDA
Submission Number	022047
Submission Code	SE1 0006/0007/0008
Letter Date	12/18/2007
PDUFA Goal Date	10/19/2008
Reviewer Name	Cara Alfaro, Pharm.D.
Review Completion Date	08/20/2008
Established Name	Quetiapine fumarate extended release tablets
Trade Name	Seroquel XR
Therapeutic Class	Antipsychotic
Applicant	AstraZeneca
Priority Designation	S
Formulation	Extended release tablets
Dosing Regimen	Bipolar depression: initiate at 50 mg/day and increase to 300 mg/day by day 4; Acute mania (monotherapy): initiate at 300 mg/day, 600 mg/day on Day 2 and adjust between 400 and 800 mg/day thereafter. Doses administered once daily in the evening.
Indications	Bipolar depression, Acute mania (monotherapy), Acute mania (adjunctive treatment)
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Sponsor has submitted supplemental NDAs SE1-006, SE1-007, and SE1-008 for quetiapine XR to the support indications:

- Depressive episodes associated with Bipolar I and II disorder with or without a rapid cycling course;
- Acute manic or mixed episodes associated with Bipolar I disorder as monotherapy;
- Acute manic or mixed episodes associated with Bipolar I disorder as adjunct to lithium or divalproex therapy

I recommend that the Division take an approval action for all of these indications.

The Sponsor submitted one pivotal trial for bipolar disorder, depressive episode and one pivotal trial for bipolar disorder, acute monotherapy. These pivotal trials support the efficacy of quetiapine XR for these indications. Since quetiapine IR is indicated in these populations, one clinical trial for each indication was sufficient for the quetiapine XR development program.

The Sponsor did not provide any clinical data to support the acute adjunctive therapy indication. However, based on extrapolation of this indication for quetiapine IR and with data to support the effectiveness of quetiapine XR in acute mania as monotherapy, it is recommended that the adjunctive indication be granted for quetiapine XR.

At the time this review was completed, several requests for information from the Sponsor were still pending. It is unlikely that responses to these requests will alter the recommendation of this reviewer (see Section 9.5 – Comments to Applicant). The Sponsor's responses to these requests will be reviewed in an addendum to this clinical review.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None are recommended by this reviewer.

1.2.2 Required Phase 4 Commitments

Quetiapine IR is currently approved for the maintenance treatment of Bipolar I disorder as adjunct therapy to lithium or divalproex; no maintenance indication has been granted for quetiapine IR for monotherapy. It is recommended that the Sponsor conduct a long-term (maintenance) trial of quetiapine XR in the treatment of Bipolar I disorder. Whether this will be considered a required Phase 4 commitment is at the discretion of the Division.

1.2.3 Other Phase 4 Requests

None are currently recommended by this reviewer. Pediatric waivers, deferrals and plans were under review at the time this review was completed. The Sponsor has plans to conduct at least one clinical trial in pediatric bipolar depression with quetiapine XR. The Sponsor has completed one clinical trial of quetiapine IR in acute mania associated with bipolar disorder in this population. See section 8.4 (Pediatrics) of this review.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Sponsor submitted one clinical trial to support the efficacy of quetiapine XR in bipolar depression. Study D144CC00002 was a multicenter, double-blind, randomized, parallel-group, placebo-controlled study of quetiapine XR as monotherapy in adult patients with bipolar I or II disorder, acute depressive episode. Subjects were randomized to quetiapine XR 300 mg/day fixed dose (n = 140) or placebo (n = 140) administered once daily in the evening for 8 weeks. Approximately 62% of subjects in the quetiapine XR group and 69% of subjects in the placebo group completed the clinical trial. The mean daily dose was 266.9 mg (median = 284.8 mg) and the mean duration of treatment was 42.6 days.

The Sponsor submitted one clinical trial to support the efficacy of quetiapine XR monotherapy in acute mania associated with bipolar disorder. Study D144CC00004 was a multicenter, double-blind, randomized, parallel-group, placebo-controlled study of quetiapine XR as monotherapy in adult patients with bipolar manic or mixed episode. Subjects were randomized to quetiapine XR 400 – 800 mg/day (flexible dose) administered once daily in the evening for 3 weeks. Approximately 72% of subjects in each treatment group completed the study. The mean daily dose was 603.8 mg (median = 585.7 mg) and the mean duration of treatment was 18.7 days.

1.3.2 Efficacy

Study D144CC00002 (Bipolar depression)

The primary efficacy endpoint for study D144CC00002 was change from baseline to endpoint in the MADRS total score (LOCF analysis). The overall study results were statistically significant for quetiapine XR versus placebo (LS Mean Diff = -5.51, $p < 0.001$). The supportive OC and MMRM analyses provided similar results. Secondary efficacy endpoints (% responders, % remitters, CGI rating scales) provided additional evidence of efficacy for quetiapine XR versus placebo.

Subgroup analyses were conducted for Bipolar I and Bipolar II disorder, rapid and nonrapid cycling, gender, age (18-39, 40-65 years) and origin. Several subgroups did not yield statistically significant results favoring quetiapine XR versus placebo: Bipolar II disorder, male subjects and African American/Black origin. Few subjects in this study had the diagnosis of Bipolar II disorder (n = 26, quetiapine XR; n = 27, placebo) and the LS Mean difference was -

3.02 (95% CI: -7.19, 1.15) compared to Bipolar I disorder with a LS Mean difference of -6.53 (95% CI: -9.27, -3.79). However, the LS Mean difference in the Bipolar II group was similar to the results for this same population in the pivotal trials for quetiapine IR where a larger sample size was noted for this population and statistical significance was demonstrated for quetiapine IR versus placebo. Though the male subgroup analysis did not show significance, the LS Mean difference for the female and male subgroups were similar (-5.75 and -4.0). Lack of significant findings for the African American/Black subgroup could be, in part, due to the small sample size (n = ~30 in both treatment groups).

Study D144CC00004 (Bipolar mania, acute monotherapy)

The primary efficacy endpoint for study D144CC00004 was change from baseline to endpoint in the YMRS total score (LOCF analysis). The overall study results were statistically significant for quetiapine XR versus placebo (LS Mean Diff = -3.83, p < 0.001). The supportive OC and MMRM analyses provided similar results. Secondary efficacy endpoints (% responders, % remitters, CGI rating scales) provided additional evidence of efficacy for quetiapine XR versus placebo.

Subgroup analyses were conducted for manic and mixed symptoms, rapid and nonrapid cycling, gender, age (18-39, 40-65 years) and origin. The only subgroup analyses that did not yield statistically significant results favoring quetiapine XR versus placebo was subjects with mixed symptoms. The LS Mean difference for the mixed subgroup was -2.47 (95% CI: -5.36, 0.41) compared to the LS Mean difference for the manic subgroup -4.91 (95% CI: -7.35, -2.47). Sample sizes were fairly similar between these subgroups (n = 174 for manic subgroup, n = 134 for mixed subgroup) and the LS Mean change in the placebo groups were similar between these subgroups.

1.3.3 Safety

The Sponsor did not submit an integrated summary of safety. Since there was only one study for each indication and the doses of quetiapine XR and the duration of exposure were very different between the two studies, analysis of safety data for each study is considered appropriate by this reviewer.

No deaths occurred in the quetiapine XR groups for either pivotal trial. Serious adverse events occurred in 2 (1.4%) subjects in study D144CC00002 and 6 (4%) subjects in study D144CC00004. These serious adverse events included asthma, depression, bipolar I disorder, suicide attempt, vestibular neuronitis, psychotic disorder and suicidal ideation. Most of these adverse events were consistent with the underlying bipolar disorder and also occurred with similar frequency in the placebo groups. An analysis of treatment-emergent mania (for D144CC00002) or treatment-emergent depression (for D144CC00004) did not suggest a significant increase in these symptoms in subjects in the quetiapine XR groups.

The common adverse events occurring in these clinical trials were similar to the adverse events included in current product labeling for quetiapine XR (for schizophrenia) and quetiapine IR. No new significant safety signals emerged during review of the safety data for these two acute

clinical trials. The most common adverse events in the quetiapine XR group for D144CC00002 and D144CC00004 were dry mouth (37% and 34%), somnolence (29% and 17%), sedation (23% and 34%), dizziness (13% and 10%) and increased appetite (12% and 4%). The Sponsor has been asked to recalculate the frequencies for somnolence and sedation as one adverse event term. The frequencies of dry mouth, sedation and somnolence were higher in these bipolar pivotal trials compared to the acute schizophrenia trials. The incidence of orthostatic hypotension in the bipolar pivotal trials was 1.5 – 2.6%. The incidence of adverse events consistent with EPS was higher in the quetiapine XR groups compared to placebo (4.4% vs. 0.7% in D144CC00002 and 6.6% vs. 3.8% in D144CC00004). Four subjects in the quetiapine XR groups and 2 subjects in the placebo groups had shifts from normal baseline ANC to values $< 1.5 \times 10^9/L$ and most resolved per follow-up labs obtained after the study was completed (one lost to follow-up).

Mean change from baseline for supine and standing pulse was greater in the quetiapine XR groups compared to placebo: +4.5 vs. 0.1 bpm (supine) and +3.4 vs. -0.3 bpm (standing) for D144CC00002; +1.3 vs. -2.9 bpm (supine) and +2 vs. -3.6 bpm (standing) for D144CC00004. Greater decreases were noted for supine and standing systolic blood pressure in the quetiapine XR groups compared to placebo: -2.1 vs. -0.7 mmHg (supine) and -1.6 vs. -0.5 mmHg (standing) for D144CC00002; -2.4 vs. +0.2 mmHg (supine) and -2.6 vs. +1.5 mmHg (standing). These findings are consistent with the known effects of quetiapine IR and XR on vital signs. The mean changes in orthostatic measurements were not as pronounced.

Quetiapine XR was associated with increases in glucose, total cholesterol, triglycerides, and weight. The Division requested that the Sponsor conduct an analysis of all clinical trials to study the effects of quetiapine IR and XR on these safety signals. The Sponsor recently submitted these data and they are under review. Further suggestions for modifications to product labeling with regard to these particular safety signals is likely and is beyond the scope of this particular review.

1.3.4 Dosing Regimen and Administration

The dosing regimens included in proposed labeling are the same as that used in the clinical trials:

Bipolar depression: Seroquel XR should be administered once daily in the evening to reach 300 mg/day by day 4. Recommended dosing schedule: day 1 = 50 mg, day 2 = 100 mg, day 3 = 200 mg, day 4 = 300 mg.

Bipolar mania (monotherapy): Seroquel XR should be administered once daily in the evening starting with 300 mg on day 1 and 600 mg on day 2. Seroquel XR can be adjusted between 400 and 800 mg beginning on day 3 depending on the response and tolerance of the individual patient.

Bipolar mania (adjunctive therapy): The Sponsor has not proposed dosing/administration information for this indication. They have been asked to modify labeling to include this information which will be extrapolated from the quetiapine IR data.

1.3.5 Drug-Drug Interactions

No drug interaction data was included in this submission.

1.3.6 Special Populations

The Sponsor has changed dosing recommendations for two populations – elderly and hepatic impairment. Since quetiapine XR has been available as 200, 300 and 400 mg tablets, currently approved labeling recommends initiating therapy in these populations with quetiapine IR 25 mg/day and increasing by 25-50 mg/day as tolerated. When an effective dose is reached, clinicians are advised to switch to quetiapine XR. In this submission, the Sponsor has indicated their interest to market a 50 mg extended-release dose (which was approved with the original NDA but never marketed). The dosing recommendations for these populations in proposed labeling is to initiate with the quetiapine XR 50 mg tablet and increase by 50 mg increments. The Sponsor has been asked for pharmacokinetic data comparing the quetiapine IR 25 mg and quetiapine XR 50 mg tablets as well as any tolerability data they may have with this proposed dosing regimen in these populations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

AstraZeneca submitted 3 supplemental NDAs for the following indications: SE1-006 for Bipolar Depression (acute), SE1-007 for Bipolar Mania (acute - monotherapy) and SE1-008 for Bipolar Mania (acute – adjunctive therapy to lithium or divalproex). Clinical protocols for assessment of safety and efficacy in bipolar disorder populations were submitted under IND 76,146 (originated 11/15/2006).

The following tables summarize the current approved indications for both Seroquel (quetiapine IR) and Seroquel XR (quetiapine XR):

Seroquel (quetiapine IR) [NDA 20-639]

Indication	Date of Approval
Schizophrenia (acute)	9/26/1997
Depressive Episodes associated with Bipolar Disorder	10/20/2006
Acute Manic Episodes associated with Bipolar I Disorder – monotherapy or adjunct therapy to lithium or valproex	1/12/2004
Maintenance Treatment of Bipolar I Disorder as adjunct therapy to lithium or divalproex	5/13/2008

Seroquel XR (quetiapine XR)

Indication	Date of Approval
Schizophrenia (acute)	5/17/2007
Schizophrenia (maintenance)	11/15/2007 [under NDA 22-172]

Supplemental NDAs for Seroquel XR currently under review in the Division: [REDACTED] (b) (4)

The Sponsor submitted one clinical study to support efficacy in the treatment of bipolar depression and one clinical study to support efficacy in the treatment of acute bipolar mania as monotherapy. The Sponsor is seeking an indication for the treatment of acute bipolar mania as adjunctive therapy to lithium and divalproex based on efficacy as monotherapy and extrapolation from the clinical trial to support efficacy as adjunctive therapy for quetiapine IR (Seroquel).

2.2 Currently Available Treatment for Indications

The following medications are currently approved for the treatment of acute mania associated with Bipolar Disorder:

As monotherapy: lithium, divalproex sodium, olanzapine, risperidone, aripiprazole, ziprasidone and quetiapine IR

As adjunctive therapy to lithium or valproate/divalproex: olanzapine (valproate), risperidone (valproate) and quetiapine IR (divalproex)

At the current time, only quetiapine IR is approved for the treatment of (acute) bipolar depression.

2.3 Availability of Proposed Active Ingredient in the United States

Quetiapine XR was first approved on 5/17/2007 for the acute treatment of schizophrenia. Quetiapine XR is currently available as 200, 300 and 400 mg extended-release tablets. A 150 mg extended-release tablet was approved in August 2008. A 50 mg extended-release tablet was previously approved but never marketed – the Sponsor is now seeking to market this new strength.

2.4 Important Issues With Pharmacologically Related Products

The atypical antipsychotics, of which quetiapine XR belongs, have been associated with a number of safety issues. Most recently these issues have included hyperglycemia, hyperlipidemia, and weight gain and Sponsors of these products have been asked to provide additional data and pooled analyses for these safety signals. The Sponsor of this submission has been asked to provide data and analyses for quetiapine IR and quetiapine XR for effects on lipids (cholesterol, HDL, LDL, triglycerides), glucose (glucose, HbA1c, UA glucose), and weight for both adults and pediatric subjects (see Division letter January 8, 2008). The Sponsor recently provided these data and they are currently under review.

2.5 Presubmission Regulatory Activity

July 24, 2006 The Sponsor requested an End of Phase II meeting to gain FDA's input and agreement on overall clinical trial programs and study designs pertaining to the use of Seroquel XR (was referred to as Seroquel SR) in bipolar disorder (under IND 45,456)

November 6, 2006 The Division submitted preliminary comments from the Division's internal meeting held on November 2, 2006. The Sponsor proposed that since Seroquel XR program in schizophrenia has been successful [NDA under review during this time], approval for 3 bipolar indications (mania, bipolar depression, and bipolar maintenance) for Seroquel XR (b) (4)

Alternatively, (b) (4)

(b) (4)

[Redacted text block]

The Sponsor asked if this justification is sufficient to support approval for Seroquel XR in the treatment of acute mania, bipolar maintenance and bipolar depression. The Division responded that “a single positive study with Seroquel XR would be needed for each of the indications bipolar mania and depression to support these claims. Once these claims have been established for Seroquel XR, and a claim for bipolar maintenance has been established for Seroquel IR, a claim for bipolar maintenance for Seroquel XR would also be considered established [Phase 4 commitment would not be required].”

The Sponsor was satisfied with the preliminary comments and canceled the EOP2 meeting request.

November 17, 2006 Division acknowledged receipt of Sponsor’s IND for Seroquel XR for bipolar disorder – IND 76, 146. This submission included both protocols D144CC00002 and D144CC00004. This reviewer did not find any specific comments provided to the Sponsor regarding the study design for these two pivotal trials.

2.6 Other Relevant Background Information

Seroquel XR is approved in 26 countries for schizophrenia, 5 countries for bipolar mania (first approved in Slovakia on 6/28/2007), and in 1 country for bipolar depression (Mexico, 11/2007).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

An environmental assessment was prepared by the Sponsor, but since the new indication does not increase the active moiety, a request was made for categorical exclusion under 21CFR25.31(a). The environmental assessments were reviewed by Raanan Bloom and the claim for categorical exclusion was concurred.

The reviewer for CMC was Julia Pinto, Ph.D. No new CMC was provided in these supplements. With this submission, the Sponsor is proposing to market a 50 mg strength of the extended release tablet. This strength was approved when the original NDA for quetiapine XR was submitted, but the Sponsor did not market it. There were no changes to the CMC for the drug substance or product. Chemistry has recommended approval of this supplement.

3.2 Animal Pharmacology/Toxicology

The Sponsor has proposed labeling changes to Section 12 (Clinical Pharmacology) that is being reviewed by pharmacology/toxicology. No new animal pharmacology/toxicology data was included in this submission.

3.3 Statistical Review and Evaluation

The statistical reviewer for this submission was George Kordzakhia, Ph.D. Dr. Kordzakhia was able to replicate the efficacy findings of the Sponsor and concluded that the clinical trials supported the efficacy of quetiapine XR in the treatment of bipolar depression and acute mania (monotherapy). No significant data issues were identified in his review.

3.4 DSI Clinical Site Inspections

Dr. Vikram Mehra's site in Houston, Texas was chosen to be inspected for this submission. Dr. Mehra enrolled subjects for both clinical trials, 20 subjects for D144CC00002 and 33 subjects for D144CC00004. This site was chosen primarily due to the high numbers of subjects enrolled as well as his involvement with both pivotal clinical trials. At the time this review was completed, the final report was still pending.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources for both efficacy and safety data are two clinical studies:

Protocol D144CC00002: A multicenter, double-blind, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine fumarate (Seroquel) sustained-release as monotherapy in adult patients with **acute bipolar depression**

Protocol D144CC00004: A multicenter, double-blind, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine fumarate (Seroquel) sustained-release as monotherapy in adult patients with **acute bipolar mania**. [monotherapy]

The Sponsor is also seeking an indication for the treatment of acute bipolar mania as adjunctive therapy to lithium and divalproex based on efficacy as monotherapy and extrapolation from the clinical trial to support efficacy as adjunctive therapy for quetiapine IR (Seroquel). The Sponsor did not submit a clinical trial evaluating the efficacy of quetiapine XR as adjunctive therapy to lithium or divalproex in the treatment of acute mania associated with bipolar disorder.

The safety data were submitted as part of the clinical study reports for these individual trials – no integrated summary of safety was submitted. Given the differences between these trials with

regard to study populations, doses of quetiapine XR administered and study duration, submission of the safety data for each separate study (rather than an integrated summary) is acceptable.

4.2 Data Quality and Integrity

See sections 3.3 (Statistical Review and Evaluation) and 3.4 (DSI Clinical Site Inspections) for other comments regarding data quality and integrity.

This reviewer completed a brief audit of adverse event safety data by comparing case report forms, narratives and line listings for consistency on reporting. Overall, there was good consistency of adverse event information across these sources of data. Adverse event coding (verbatim to preferred terms) appeared to be appropriate. No significant deficiencies were noted.

4.3 Compliance with Good Clinical Practices

Per study protocols, these clinical trials were “performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Committee on Harmonization/Good Clinical Practice and applicable regulatory requirements and the AstaZeneca policy on Bioethics”.

4.4 Financial Disclosures

The following investigators were noted to have received sums > \$25,000 from the Sponsor, primarily through consulting fees and honoraria:

(b) (6)

(b) (6) subjects were randomized at sites for (b) (6).
(b) (6) site randomized (b) (6) subjects and (b) (6) site randomized (b) (6) subjects

(b) (6) It is unlikely that the low numbers of subjects enrolled at these sites would significantly impact the overall study results.

5 CLINICAL PHARMACOLOGY

No issues were identified in this submission that required a review from clinical pharmacology.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication – Bipolar Depression

6.1.1 Methods

The Sponsor conducted one double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of quetiapine XR in the treatment of acute bipolar depression. One study was deemed sufficient by the Division since the efficacy of quetiapine IR (Seroquel) has been demonstrated for this indication (see Section 2.5 – Presubmission Regulatory Activity).

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for D144CC00002 was the change from baseline to endpoint in the MADRS total score. Both the MADRS and HAM-D total scores have been acceptable endpoints for the evaluation of efficacy in depression (primarily Major Depressive Disorder) and validity and reliability have been established for these rating scales.

6.1.3 Study Design

Protocol D144CC00002: A multicenter, double-blind, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine fumarate (Seroquel) sustained-release as monotherapy in adult patients with acute bipolar depression
First patient enrolled: 12/1/2006, Last patient enrolled: 4/4/2007

Investigators and sites: This study was conducted at 64 centers in the United States (see Appendix).

Study Objectives

Primary: To evaluate whether quetiapine fumarate sustained-release (quetiapine XR) formulation at a dose of 300 mg per day demonstrates superior efficacy compared to placebo in patients with bipolar depression, after 8 weeks of treatment.

Secondary (none identified as key secondary):

1. To evaluate the effectiveness of quetiapine XR in decreasing depressive symptoms in both rapid and non-rapid cyclers.
2. To evaluate the effectiveness of quetiapine XR compared to placebo in achieving remission in bipolar depression.
3. To evaluate the effectiveness of quetiapine XR compared to placebo in achieving response in bipolar depression.
4. To evaluate the effectiveness of quetiapine XR compared to placebo in the treatment of a broad range of symptoms of bipolar depression.

5. To evaluate the safety and tolerability of quetiapine XR once daily in patients with bipolar depression.

Study Population

Design: An 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled, study in the treatment of subjects with bipolar I or II disorder, acute depressive episode.

Following a washout period of 7 to 28 days, 280 subjects were randomized (1:1) to quetiapine XR 300 mg/day or placebo administered once daily in the evening. Randomization was done in balanced blocks within each stratum (bipolar I and bipolar II). Quetiapine XR was dosed 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3 and 300 mg Day 4 – end of study. Quetiapine XR was not down-titrated at the end of the study.

A list of inclusion and exclusion criteria are in the Appendix. Briefly, subjects were male or female, 18-65 years of age with a diagnosis of bipolar I or bipolar II (DSM-IV TR), most recent episode depressed (diagnosis confirmed by the SCID for DSM-IV). The proportion of bipolar II subjects randomized was restricted to $\leq 33\%$ of all randomized subjects. Subjects with rapid-cycling bipolar disorder (≥ 4 episodes of mood disturbance but ≤ 8 episodes in the previous 12 months) were not excluded. Subjects must have been outpatients, have a HAM-D17 total score ≥ 20 , a HAM-D Item 1 (depressed mood) score ≥ 2 at enrollment and randomization and have a YMRS ≤ 12 at enrollment and randomization.

Allowable Concomitant Medications

The following medications were allowed for the treatment of insomnia if treatment had been ongoing within 28 days prior to enrollment on a regular basis: zolpidem (10 mg), zaleplon (20 mg), zopiclone (7.5 mg), chloral hydrate (1 g). Lorazepam up to 2 mg/day could be used as a rescue medication for severe anxiety throughout the study. Anticholinergics were allowed for treatment of EPS.

Assessments

Efficacy: The primary outcome variable was change from baseline to final visit in MADRS total score. Other efficacy assessments included Clinical Global Impression-Bipolar-Severity of Illness (CGI-BP-S) and Clinical Global Impression-Bipolar-Change (CGI-BP-C).

Safety: Physical examination, vital signs, ECG, laboratory assessments (hematology, chemistry).

Treatment-emergent mania was defined as a YMRS total score ≥ 16 on 2 consecutive assessments or final assessment.

EPS – Simpson Angus Scale and Barnes Akathisia Scale

6.1.4 Efficacy Findings

Study Populations

Total randomized: quetiapine XR, n = 140; placebo, n = 140

Safety population: quetiapine XR, n = 139; placebo, n = 138

One subject in the quetiapine XR and two subjects in the placebo group did not receive investigational drug.

MITT population: quetiapine XR, n = 133 ; placebo, n = 137

Six subjects in the quetiapine XR and 1 subject in the placebo group did not have a MADRS at randomization or after.

Patient Disposition

Two hundred eighty patients were randomized, 140 to quetiapine XR 300 mg/day and 140 to placebo. Sixty-two percent of subjects in the quetiapine XR group completed the study and 69% of subjects in the placebo group completed the study. For purposes of this review, Sponsor categories “condition under investigation worsened” and “lack of therapeutic response” were collapsed into one category “lack of efficacy”. Not unexpectedly, more subjects in the placebo group discontinued due to lack of efficacy (10%) compared to the quetiapine XR group (3.6%). More subjects in the quetiapine XR group discontinued due to adverse events compared to the placebo group (12.1% vs. 1.4%). No details were provided for the discontinuation category “severe non-compliance to protocol” and this reviewer thought it odd to include this category since sponsors usually provide a per-protocol analysis. The Sponsor has been asked to provide more details about this discontinuation category. Similarly, it is unclear what the category “voluntary discontinuation by subject” means as it could indicate lack of efficacy – similar numbers of subjects in each treatment group discontinued under this category.

Table 6.1.4.1. Patient Disposition (All Randomized Subjects)

	Quetiapine XR (n = 140)	Placebo (n = 140)
Subjects who Received Treatment	139	138
Completers	87 (62.1%)	96 (68.6%)
Discontinuations	52 (37.1%)	42 (30.0%)
Incorrect Enrollment	0	2 (1.4%)
Severe Non-Compliance to Protocol	4 (2.9%)	5 (3.6%)
Safety Reasons	1 (0.7%)	0
Adverse Event	17 (12.1%)	2 (1.4%)
Lack of Efficacy*	5 (3.6%)	14 (10%)
Subject Lost to Follow-up	12 (8.6%)	8 (5.7%)
Voluntary Discontinuation by Subject	12 (8.6%)	10 (7.1%)
Other	1 (0.7%)	1 (0.7%)

Modified from Sponsor Table 11.1.1.2 in Clinical Study Report

*Combination of Sponsor terms “condition under investigation worsened” and “lack of therapeutic response”

Demographics and Baseline Disease Severity

The treatment groups appeared fairly well-balanced with regard to demographic and baseline characteristics. The majority of subjects were Caucasian, but Black/African Americans were fairly well represented. The baseline MADRS and HAM-D17 scores were similar between the two groups and indicated the presence of significant depressive symptoms.

The majority of subjects had a diagnosis of Bipolar I Disorder (80%) and the majority were not rapid cycling (72%).

Table 6.1.4.2. Demographic and Baseline Characteristics (MITT Population)

Demographic/Baseline Characteristic	Quetiapine XR (n = 133)	Placebo (n = 137)
Gender		
Male	45 (33.8%)	51 (37.2%)
Female	88 (66.2%)	86 (62.8%)
Age (years)		
Mean (SD)	39 (11.3)	39.9 (12.8)
Median	39	40
Min, Max	18, 64	18, 64
Race		
Caucasian	96 (72.2%)	98 (71.5%)
Black/African American	29 (21.8%)	31 (22.6%)
American Indian/Alaskan Native	3 (2.3%)	3 (2.2%)
Asian	2 (1.5%)	1 (0.7%)
Native Hawaiian/Pacific Islander	0	1 (0.7%)
Other	3 (2.3%)	3 (2.2%)
Weight (kg)		
Mean (SD)	88.7 (22.1)	88.9 (22.7)
Median	86.4	86.4
Min, Max	48, 142	49, 158
BMI (kg/cm²)		
Mean (SD)	31.6 (7.9)	30.8 (7.1)
Median	30	29.9
Min, Max	18, 55	17, 50

Modified from Sponsor Table S1 in Clinical Study Report

Table 6.1.4.3. Baseline Disease Characteristics and Psychiatric History (MITT Population)

Demographic/Baseline Characteristic	Quetiapine XR (n = 133)	Placebo (n = 137)
Baseline MADRS total score		
Mean (SD)	29.8 ± 5.2	30.1 ± 5.5
Min, Max	14 – 47	15 – 47
Baseline HAM-D17 total score		
Mean (SD)	24.8 (3.5)	24.6 (3.3)
Median	24	24
Min, Max	20-36	20 - 37
Baseline CGI-S depression score		
Mean (SD)	4.5 ± 0.6	4.5 ± 0.6
Min, Max	3 – 7	3 – 6
Baseline CGI-S mania score		
Mean (SD)	1.6 ± 0.7	1.5 ± 0.7
Min, Max	1 – 3	1 – 3
Baseline CGI score, overall bipolar illness		
Mean (SD)	4.5 ± 0.6	4.4 ± 0.7
Min, Max	3 – 6	1 – 6
YMRS total score		
Mean	7.4 (2.8)	6.5 (3.1)
Median	8.0	7.0
Min, Max	0 – 12	0 - 12
DSM-IV TR Diagnosis		
Bipolar I disorder	107 (80.5%)	110 (80.3%)
Bipolar II disorder	26 (19.5%)	27 (19.5%)
Rapid cycling		
No	97 (72.3%)	99 (72.3%)
Yes	36 (27.1%)	38 (27.7%)
Duration of present depressive episode (weeks)		
Mean (SD)	19.3 (12.8)	18.1 (11.2)
Median	14	14
Min, Max	0.6 – 57.6	4.3 – 52.1
Years since bipolar diagnosis		
Mean (SD)	18.8 (11.3)	19.7 (11.3)
Median	16	19
Min, Max	2 – 47	2 – 50
Attempted suicide		
No	91 (68.4%)	87 (63.5%)
Yes	42 (31.6%)	50 (36.5%)

Modified from Sponsor Tables 11.1.3.5.1, 11.1.3.5.2, 11.1.3.6 in Clinical Study Report

Concomitant Medications

Lorazepam 2 mg/day for severe anxiety was allowed per protocol. From week 1 through week 8, lorazepam was taken by approximately 9-10% of subjects in the quetiapine XR group and 10-11% of subjects in the placebo group. Slightly more subjects took sleep medications (zolpidem, zaleplon, zopiclone, chloral hydrate) in the placebo group compared to the quetiapine XR group. Few subjects in each group required medications for the treatment of EPS.

Table 6.1.4.4. Concomitant Medication Use

	Quetiapine XR (n = 131)	Placebo (n = 139)
Lorazepam		
Randomization to Week 1	6.9%	5.8%
Weeks 1-2	6.6%	6.0%
Weeks 2-3	6.1%	6.3%
Weeks 3-4	6.4%	8.3%
Weeks 4-5	7.2%	7.8%
Weeks 5-6	6.5%	9.1%
Weeks 6-7	6.7%	8.7%
Weeks 7-8	8.0%	9.0%
Sleep Medication		
Randomization to Week 1	8.4%	8.6%
Weeks 1-2	8.3%	8.2%
Weeks 2-3	7.8%	9.4%
Weeks 3-4	8.3%	12.4%
Weeks 4-5	9.3%	11.2%
Weeks 5-6	8.7%	12.7%
Weeks 6-7	9.0%	12.6%
Weeks 7-8	10.2%	12.0%
Anticholinergics		
Randomization to Week 1	1.5%	2.2%
Weeks 1-2	1.7%	2.2%
Weeks 2-3	0.9%	0.8%
Weeks 3-4	2.8%	1.7%
Weeks 4-5	2.1%	0
Weeks 5-6	3.3%	1.8%
Weeks 6-7	2.2%	1.0%
Weeks 7-8	1.1%	0

From Sponsor Tables 11.1.4.3.1, 11.1.4.3.2, 11.1.4.3.3 in Clinical Study Report
 Percentages are based on the number of patients in the study by week

Protocol Deviations

Thirty-five (13%) subjects in the MITT population had at least one “major protocol deviation”. The most common deviation was inadequate washout of prohibited medication that occurred in 9.8% (13/133) subjects in the quetiapine XR group and 8.8% (12/137) subjects in the placebo group.

Efficacy Analyses

Primary Efficacy Analysis:

The LOCF analysis by week showed statistical significance favoring quetiapine XR vs. placebo starting at week 1 and continuing to endpoint ($p < 0.001$ at all weeks).

Table 6.1.4.5. Primary efficacy variable: MADRS Total Score Change from Baseline to Endpoint (week 8) – *LOCF analysis*

	N	Baseline		Endpoint		LSMean Change	LSMean Difference	P-value
		Mean	SD	Mean	SD			
Quetiapine XR	133	29.8	5.2	12.1	9.4	-17.43	-5.51	< 0.001
Placebo	137	30.1	5.5	18	12.2	-11.92		

Modified from Sponsor Table 11.2.1.1.1 in Clinical Study Report

Secondary Analyses:

MADRS total score change from baseline to endpoint OC and MMRM analyses:

Similar to the LOCF analysis, the by week OC analysis showed statistical significance for quetiapine XR vs. placebo starting at week 1 and continuing to endpoint ($p < 0.001$ at all weeks) (Table 6.1.4.6).

Table 6.1.4.6. MADRS Total Score Change from Baseline to Endpoint (week 8) – *OC analysis*

	N	Baseline		Endpoint			LSMean Change	LSMean Difference	P-value
		Mean	SD	N	Mean	SD			
Quetiapine XR	133	29.8	5.2	86	10.4	8.4	-19.61	-4.96	< 0.001
Placebo	137	30.1	5.5	98	15.3	11.3	-14.65		

Modified from Sponsor Table 11.2.1.1.3 in Clinical Study Report

The results of the MMRM analysis were similar to the LOCF and OC analyses (Table 6.1.4.7)

Table 6.1.4.7. MADRS Total Score Change from Baseline to Endpoint (week 8) – *MMRM analysis*

	N	Baseline		Endpoint			LSMean Change	LSMean Difference	P-value
		Mean	SD	N	Mean	SD			
Quetiapine XR	133	29.8	5.2	86	10.4	8.4	-19.71	-6.13	< 0.001
Placebo	137	30.1	5.5	98	15.3	11.3	-13.58		

Modified from Sponsor Table 11.2.1.3.1 in Clinical Study Report

Proportion of responders ($\geq 50\%$ reduction in MADRS at endpoint), proportion of remitters (MADRS total score ≤ 12), CGI-BP-S overall, CGI-BP-C overall

The majority of the secondary efficacy variables were statistically significant in favor of quetiapine XR compared to placebo (Table 6.1.4.8).

Table 6.1.4.8. Summary of Select Secondary Efficacy Variables at Endpoint (Week 8) (LOCF)

	Quetiapine XR	Placebo	P-Value
% Responders	65.4%	43.1%	< 0.001
% Remitters	54.1%	39.4%	0.018
CGI-BP-S overall*	-1.82	-1.25	< 0.001
CGI-BP-S depression*	-1.96	-1.31	< 0.001
CGI-BP-S mania*	-0.11	-0.01	0.245
CGI-BP-C overall*	2.38	2.90	< 0.001
CGI-BP-C overall much improved or very much improved	63.2%	39.4%	< 0.001
CGI-BP-C depression*	2.28	2.81	< 0.001
CGI-BP-C mania*	3.57	3.74	0.074

Modified from Sponsor Tables 11.2.1.6.1, 11.2.1.7.1, 11.2.3.2.1, 11.2.3.2.2, 11.2.4.2.1, 11.2.4.2.2 in Clinical Study Report

*LS mean change from baseline

MADRS Individual Item Analysis

The MADRS item analyses are shown in Table 6.1.4.9. The mean (SD) scores on item 10 (suicidal thoughts) were 1.2 (1.0) for the quetiapine XR group and 1.0 (0.9) for the placebo group indicating no significant suicidal thoughts at baseline (per exclusion criteria). The mean change from baseline was -0.7 for the quetiapine XR group and -0.4 for the placebo group indicating a reduction in this item at endpoint for both treatment groups.

Table 6.1.4.9. Sponsor Table. MADRS Item Analysis

MADRS item	Quetiapine XR	
	LS mean difference from placebo	p-value
1. Apparent sadness	-0.62	<.001
2. Reported sadness	-0.65	<.001
3. Inner tension	-0.39	.014
4. Reduced sleep	-1.15	<.001
5. Reduced appetite	-0.62	<.001
6. Concentration difficulties	-0.57	.002
7. Lassitude	-0.16	.390
8. Inability to feel	-0.62	<.001
9. Pessimistic thoughts	-0.61	<.001
10. Suicidal thoughts	-0.18	.089

Subgroup analyses

The Sponsor provided the following analyses based on specific subgroups – confidence intervals were provided but not p-values.

Bipolar I vs. Bipolar II

The change from baseline to endpoint in the MADRS was statistically significant favoring quetiapine XR in the Bipolar I subgroup, but not the Bipolar II subgroup – though the numerical difference did favor quetiapine XR (Table 6.1.4.11). This reviewer compared these results with the quetiapine IR clinical trials for bipolar depression. In the pooled analysis of the two pivotal quetiapine IR trials, the LS mean difference from placebo was -6.45 (95% CI: -8.39, -4.50; p < 0.001) for the Bipolar I subgroup and -3.75 (95% CI: -6.47, -1.04; p = 0.007) for the Bipolar II subgroup for quetiapine IR 300 mg [n = 220 for Bipolar I, n = 107 for Bipolar II]. So, though the subgroup analysis for the Bipolar II subgroup in the quetiapine XR study is not statistically significant, it is numerically similar to findings from the subgroup analysis of the larger pooled sample from the quetiapine IR pivotal trials. It is therefore reasonable, in this reviewer’s opinion, to extrapolate these findings to quetiapine XR.

Table 6.1.4.10. Change from Baseline to Endpoint – MADRS: *Bipolar-I* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	107	30.2	5.1	-18.23	1.20	-6.53	-9.27, -3.79
Placebo	110	30.1	5.4	-11.70	1.16		

Modified from Sponsor Table 11.2.1.3.7 in Clinical Study Report

Table 6.1.4.11. Change from Baseline to Endpoint – MADRS: *Bipolar-II* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	26	28.1	5.6	-14.87	2.26	-3.02	-7.19, 1.15
Placebo	27	30.3	5.7	-11.84	2.20		

Modified from Sponsor Table 11.2.1.3.7 in Clinical Study Report

Rapid Cycling vs. Nonrapid Cycling

The change from baseline to endpoint in the MADRS was statistically significant favoring quetiapine XR in both the rapid and nonrapid cycling subgroups (Tables 6.1.4.12 and 6.1.4.13).

Table 6.1.4.12. Change from Baseline to Endpoint - MADRS: *Nonrapid Cycling* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	Mean Change from BL	SE		
Quetiapine XR	97	29.9	5.1	-16.46	1.49	-5.17	-7.93, -2.41
Placebo	99	30	5.7	-11.29	1.43		

Modified from Sponsor Table 11.2.1.3.8 in Clinical Study Report

Table 6.1.4.13. Change from Baseline to Endpoint – MADRS: *Rapid Cycling* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	Mean Change from BL	SE		
Quetiapine XR	36	29.5	5.6	-19.07	2.03	-6.76	-11.58, -1.94
Placebo	38	30.6	4.9	-12.31	1.91		

Modified from Sponsor Table 11.2.1.3.8 in Clinical Study Report

Age, Gender, Origin

Subgroup Analysis by Age

The change from baseline to endpoint in the MADRS was statistically significant favoring quetiapine XR in the two age groups analyzed – 18 to 39 years of age and 40 to 65 years of age.

Table 6.1.4.14. Change from Baseline to Endpoint – MADRS: *18 – 39 Years of Age* (LOCF)

	N	Baseline		Endpoint			LSMean Difference	95% CI
		Mean	SD	N	LSMean Change	SE		
Quetiapine XR	69	29.3	5.0	-	-17.56	1.63	-4.65	-7.99, -1.32
Placebo	67	30.0	5.7	-	-12.90	1.49		

Modified from Sponsor Table 11.2.1.3.4 in Clinical Study Report

Table 6.1.4.15. Change from Baseline to Endpoint – MADRS: *40 - 65 Years of Age* (LOCF)

	N	Baseline		Endpoint			LSMean Difference	95% CI
		Mean	SD	N	LSMean Change	SE		
Quetiapine XR	64	30.3	5.4	-	-17.44	1.70	-6.69	-10.26, -3.12
Placebo	70	30.2	5.3	-	-10.75	1.73		

Modified from Sponsor Table 11.2.1.3.4 in Clinical Study Report

Subgroup Analysis by Gender

The least square mean difference from placebo was similar between male and female subjects.

Table 6.1.4.16. Change from Baseline to Endpoint – MADRS: Female Subjects (LOCF)

	N	Baseline		Endpoint			LSMean Difference	95% CI
		Mean	SD	N	LSMean Change	SE		
Quetiapine XR	88	29.9	4.9	-	-17.98	1.39	-5.75	-8.70, -2.81
Placebo	86	30.3	5.3	-	-12.23	1.31		

Modified from Sponsor Table 11.2.1.3.5 in Clinical Study Report

Table 6.1.4.17. Change from Baseline to Endpoint – MADRS: Male Subjects (LOCF)

	N	Baseline		Endpoint			LSMean Difference	95% CI
		Mean	SD	N	LSMean Change	SE		
Quetiapine XR	45	29.7	5.9	-	-15.86	2.23	-4.0	-8.42, 0.42
Placebo	51	29.8	5.8	-	-11.85	2.23		

Modified from Sponsor Table 11.2.1.3.5 in Clinical Study Report

Subgroup Analysis by Origin

Statistically significant differences were noted for the quetiapine XR group for Caucasians and a numerical difference favoring quetiapine XR for the smaller African American/Black subgroup. Too few subjects were included in the “other” category for meaningful comparisons.

Table 6.1.4.18. Change from Baseline to Endpoint – MADRS: African American/Black (LOCF)

	N	Baseline		Endpoint			LSMean Difference	95% CI
		Mean	SD	N	LSMean Change	SE		
Quetiapine XR	29	30.2	5.0	-	-18.29	2.24	-3.12	-8.03, 1.80
Placebo	31	29.0	5.1	-	-15.18	2.19		

Modified from Sponsor Table 11.2.1.3.6 in Clinical Study Report

Table 6.1.4.19. Change from Baseline to Endpoint – MADRS: Caucasian/White (LOCF)

	N	Baseline		Endpoint			LSMean Difference	95% CI
		Mean	SD	N	LSMean Change	SE		
Quetiapine XR	96	29.6	5.4	-	-17.94	1.41	-6.48	-9.29, -3.67
Placebo	98	30.4	5.7	-	-11.46	1.36		

Modified from Sponsor Table 11.2.1.3.6 in Clinical Study Report

6.1.5 Efficacy Conclusions

The efficacy of quetiapine XR in the treatment of bipolar depression was demonstrated in pivotal trial D144CC00002.

6.2 Indication – Acute Mania, monotherapy

6.2.1 Methods

The Sponsor conducted one double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of quetiapine XR in the treatment of acute mania in Bipolar I Disorder (monotherapy). One study was deemed sufficient by the Division since the efficacy of quetiapine IR (Seroquel) has been demonstrated for this indication (see Section 2.5 – Presubmission Regulatory Activity).

6.2.2 General Discussion of Endpoints

The primary efficacy endpoint for D144CC00002 was the change from baseline to endpoint in the YMRS total score. The YMRS is the gold standard endpoint for the evaluation of efficacy in bipolar mania and validity and reliability have been established for this rating scale.

6.2.3 Study Design

Protocol D144CC00004: A multicenter, double-blind, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine fumarate (Seroquel) sustained-release as monotherapy in adult patients with acute bipolar mania.

First patient enrolled: 12/22/2006

Last patient enrolled: 6/14/2007

Investigators and sites: This study was conducted at 50 centers in the United States (see Appendix).

Study Objectives:

Primary: To evaluate the efficacy of quetiapine extended-release (XR) formulation administered once daily as monotherapy at a dose of 400 to 800 mg/day compared to placebo in decreasing the manic symptoms in patients with bipolar manic or mixed episode, after 3 weeks of treatment.

Secondary (none identified as key secondary):

1. To evaluate the efficacy and time course of quetiapine XR compared to placebo in decreasing the manic symptoms in patients with bipolar mania at each visit, including Day 4.
2. To evaluate the efficacy of quetiapine XR compared to placebo in decreasing agitation and aggression in patients with bipolar mania.
3. To evaluate the efficacy of quetiapine XR compared to placebo in decreasing psychotic symptoms in patients with bipolar mania.
4. To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in patients with bipolar mania.
5. To evaluate the safety and tolerability of quetiapine XR QD in patients with bipolar mania.

Study Population

Design: A 3-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study in the treatment of subjects with bipolar I disorder with an acute manic episode. Following a washout period of 7 to 28 days, subjects were randomized (1:1) to flexible dose quetiapine XR (400 – 800 mg/d) or placebo; both administered as one daily dose in the evening. Quetiapine XR was initiated at 300 mg on Day 1 and increased to 600 mg on Day 2; thereafter, quetiapine XR was administered in flexible doses of 400 to 800 mg/day. Quetiapine XR was not down-titrated at the end of the study.

A list of inclusion and exclusion criteria are in the Appendix. Briefly, subjects were male or female, 18-65 years of age with a diagnosis of bipolar I disorder (DSM-IV-TR), most recent episode manic or mixed and confirmed by the SCID for DSM-IV. Subjects with rapid-cycling bipolar disorder (≥ 4 episodes of mood disturbance but ≤ 8 episodes in the previous 12 months) were not excluded. Subjects must have had at least 1 bipolar manic or mixed episode in the prior 5 years, a YMRS total score at screening of ≥ 20 with a score of ≥ 4 on 2 of the 4 core YMRS items: irritability, speech, content and disruptive/aggressive behavior. Subjects must also have had a CGI-BP-S score of ≥ 4 on the overall bipolar illness item at randomization. Both hospitalized and non-hospitalized subjects were enrolled, subjects were then hospitalized at randomization and for at least the first 4 days of treatment.

Allowable Concomitant Medications:

Insomnia – one of the following could be used on any one study day for insomnia up to the specified dosage per night if treatment was ongoing since 28 days prior to enrollment on a regular basis as judged by investigator: zolpidem tartrate (10 mg), zolpidem tartrate CR (12.5 mg), zaleplon (20 mg), zopiclone (7.5 mg), chloral hydrate (2 g up to Day 7, 1 g Day 8-22)
Severe anxiety and agitation – lorazepam could be used as follows: up to 6 mg/day (enrollment – Day 4), up to 4 mg/day (Day 5-8), up to 2 mg/day (Day 8-10), up to 1 mg/day (Day 11-14).
Acute agitation – haloperidol (IM) up to 3 mg/day could be used from enrollment through the day prior to randomization
EPS – anticholinergics were allowed

Assessments

Efficacy: The primary outcome variable was change from baseline to final visit in the YMRS total score.

Other efficacy assessments included the Clinical Global Impression-Bipolar-Severity of Illness (CGI-BP-S), Clinical Global Impression-Bipolar-Change (CGI-BP-C).

Safety: Physical examination, vital signs, ECG, laboratory assessments (hematology, chemistry).

Treatment-emergent depression was defined as a MADRS ≥ 18 on 2 consecutive assessments or final assessment.

EPS – Simpson Angus Scale and Barnes Akathisia Scale

6.2.4 Efficacy Findings

Study Populations

Total randomized: quetiapine XR, n = 155; placebo, n = 161

Safety population: quetiapine XR, n = 151; placebo n = 160

Four subjects in the quetiapine XR and 1 subject in the placebo group did not receive investigational drug.

MITT population: quetiapine XR n = 149 ; placebo n = 159

Two subjects in the quetiapine XR and 1 subject in the placebo group did not have a valid YMRS assessment either at randomization or after.

Patient Disposition

Three hundred sixteen subjects were randomized, 155 to quetiapine XR and 161 to placebo. Seventy-two percent of subjects in each group completed the study. Discontinuation due to lack of efficacy was more common in the placebo group (9.3% vs. 5.8%). Interestingly, discontinuation due to adverse events was also more common in the placebo group; however, most of these “adverse events” could have better categorized as lack of efficacy (see Section 7.1.3.1 Adverse Events Associated with Dropouts).

Table 6.2.4.1. Patient Disposition (All Randomized Subjects)

	Quetiapine XR (n = 155)	Placebo (n = 161)
Subjects who Received Treatment	151	160
Completers	111 (71.6%)	116 (72%)
Discontinuations	44 (28.4%)	45 (28%)
Incorrect Enrollment	1 (0.6%)	0
Severe Non-Compliance to Protocol	4 (2.6%)	2 (1.2%)
Adverse Event	4 (2.6%)	12 (7.5%)
Lack of Efficacy*	9 (5.8%)	15 (9.3%)
Subject Lost to Follow-up	12 (7.7%)	4 (2.5%)
Voluntary Discontinuation by Subject	13 (8.4%)	12 (7.5%)
Other	1 (0.6%)	0

*Combination of Sponsor terms “condition worsened” and “lack of therapeutic response”

Demographics and Baseline Disease Severity

The treatment groups appeared fairly well-balanced with regard to demographic and baseline characteristics. The majority of subjects were Caucasian, but Black/African Americans were well represented. The baseline YMRS scores were similar between the two groups and indicated the presence of significant manic symptoms. The majority of subjects were not rapid cycling (70%).

Clinical Review
 Cara Alfaro, Pharm.D.
 NDA 022047 SE1 0006/0007/0008
 Seroquel XR (quetiapine fumarate) extended release tablets

Table 6.2.4.2. Demographic and Baseline Characteristics (MITT Population)

Demographic/Baseline Characteristic	Quetiapine XR (n = 149)	Placebo (n = 159)
Gender		
Male	92 (61.7%)	93 (58.5%)
Female	57 (38.3%)	66 (41.5%)
Age (years)		
Mean (SD)	41.3 (10.3)	40.8 (10.7)
Median	42	43
Min, Max	19, 64	19, 63
Race		
Caucasian	72 (48.3%)	73 (45.9%)
Black/African American	70 (47%)	77 (48.4%)
American Indian/Alaskan Native	3 (2%)	0
Asian	1 (0.7%)	1 (0.6%)
Native Hawaiian/Pacific Islander	0	1 (0.6%)
Other	3 (2%)	7 (4.4%)
Weight (kg)		
Mean (SD)	91.8 (23.7)	91 (24.8)
Median	90	86.5
Min, Max	48, 207	44, 189
BMI (kg/cm ²)		
Mean	31 (9)	30.9 (8.2)
Median	29.3	28.8
Min, Max	19, 78	17, 65

Modified from Sponsor Table 19 in Clinical Study Report

Table 6.2.4.3. Baseline Disease Characteristics and Psychiatric History (MITT Population)

Demographic/Baseline Characteristic	Quetiapine XR (n = 149)	Placebo (n = 159)
Baseline YMRS total score		
Mean (SD)	28.8 (5.4)	28.4 (5.1)
Min, Max	20, 47	20, 47
CGI-BP-S depression score		
Mean (SD)	2.4 (1.2)	2.4 (1.2)
Min, Max	1, 5	1, 5
CGI-BP-S mania score		
Mean (SD)	4.5 (0.7)	4.5 (0.7)
Min, Max	4, 7	4, 7
CGI-BP-S overall bipolar score		
Mean (SD)	4.5 (0.7)	4.5 (0.7)
Min, Max	4, 7	4, 7
MADRS total score		
Mean (SD)	14.3 (7.0)	14.6 (6.4)
Min, Max	0, 38	4, 34
Current episode		
Manic	86 (57.7%)	88 (55.3%)
Mixed	63 (42.3%)	71 (44.7%)
Psychiatric history		
Rapid cycling	45 (30.2%)	52 (32.7%)
Duration of present mania episode (weeks)		
Median	4	4
Min, Max	0.1, 29.7	0.1, 44.9
Years since bipolar diagnosis		
Median	18	17
Min, Max	1, 50	2, 45
Attempted suicide		
No	84 (56.4%)	91 (57.2%)
Yes	65 (43.6%)	68 (42.8%)

Modified from Sponsor Tables 11.1.3.4.2, 11.1.3.5 in Clinical Study Report

Concomitant Medications

Lithium and valproate were taken by a few patients during the randomized treatment period (protocol violation): lithium was taken by 1 subject in each treatment group and valproate was taken by 1 subject in the quetiapine XR group and 2 subjects in the placebo group.

Lorazepam was permitted for the treatment of severe anxiety and agitation (see study design) but not to be used after Day 14. Though the Sponsor did not provide dose data for the concomitant medications, the frequency of lorazepam and sleep medication use from randomization to week 3 was similar between the quetiapine XR and placebo groups with highest frequency during the first week of randomization (Table 6.2.4.4). The frequency of anticholinergic medication use was low in both treatment groups.

Table 6.2.4.4. Concomitant Medication Use

	Quetiapine XR (n = 149)	Placebo (n = 159)
Lorazepam		
Randomization to Week 1	43%	56.6%
Week 1 to Week 2	5.2%	7.9%
Week 2 to Week 3	4.1%	3.3%
Sleep Medication		
Randomization to Week 1	53%	64.2%
Week 1 to Week 2	14.1%	15%
Week 2 to Week 3	13.8%	10.6%
Anticholinergics		
Randomization to Week 1	4.7%	6.3%
Week 1 to Week 2	2.2%	2.1%
Week 2 to Week 3	1.6%	3.0%

From Sponsor Table 11.1.4.3.1, 11.1.4.3.2, 11.1.4.3.3 in Clinical Study Report
 Percentages are based on the number of patients in the study by week

Protocol Deviations

Fifty-five (18%) subjects in the MITT population had at least one “major protocol deviation”. The most common deviation was inadequate washout of prohibited medication that occurred in 16% (24/149) subjects in the quetiapine XR group and 14% (22/159) subjects in the placebo group.

Efficacy Analyses

Primary Efficacy Analysis:

The LOCF analysis by day showed statistical significance favoring quetiapine XR vs. placebo starting at Day 4 to end of study (ratings done on Days 4, 8, 15 and 22) [p 0.003 to < 0.001]

Table 6.2.4.5. Primary Efficacy Variable: YMRS Total Score Change from Baseline to Endpoint (week 3) – LOCF analysis

	N	Baseline		Endpoint		LSMean Change	LSMean Difference	P-value
		Mean	SD	Mean	SD			
Quetiapine XR	149	28.8	5.4	14.9	8.8	-14.34	-3.83	< 0.001
Placebo	159	28.4	5.1	18.4	9.6	-10.52		

Modified from Sponsor Table 11.2.1.1.1 in Clinical Study Report

Secondary Analyses:

YMRS total score change from baseline to endpoint OC and MMRM analyses:

Similar to the LOCF analysis, the by week OC analysis showed statistical significance for quetiapine XR vs. placebo starting at Day 4 and continuing to endpoint (p = 0.009 to < 0.001) (Table 6.2.4.6).

Table 6.2.4.6. Primary Efficacy Variable: YMRS Total Score Change from Baseline to Endpoint (week 3) – OC analysis

	Baseline			Endpoint			LSMean Change	LSMean Difference	P-value
	N	Mean	SD	N	Mean	SD			
Quetiapine XR	149	28.8	5.4	119	13.0	7.4	-16.03	-3.48	< 0.001
Placebo	159	28.4	5.1	120	16.4	8.6	-12.56		

Modified from Sponsor Table 11.2.1.1.3 in Clinical Study Report

The results of the MMRM analysis were similar to the LOCF and OC analyses (Table 6.2.4.7).

Table 6.2.4.7. Primary Efficacy Variable: YMRS Total Score Change from Baseline to Endpoint (week 3) – MMRM analysis

	Baseline			Endpoint			LSMean Change	LSMean Difference	P-value
	N	Mean	SD	N	Mean	SD			
Quetiapine XR	149	28.8	5.4	119	13.0	7.4	-15.29	-3.91	< 0.001
Placebo	159	28.4	5.1	120	16.4	8.6	-11.37		

Modified from Sponsor Table 11.2.1.1.3 in Clinical Study Report

Proportion of responders (≥ 50% reduction in YMRS at endpoint), proportion of remitters (YMRS total score ≤ 12), CGI-BP-S overall, CGI-BP-C overall

The majority of the secondary efficacy variables were statistically significant in favor of quetiapine XR compared to placebo (Table 6.2.4.8).

Table 6.2.4.8. Summary of Select Secondary Efficacy Variables at Endpoint (Week 3) (LOCF)

	Quetiapine XR	Placebo	P-Value
% Responders	55%	33.3%	< 0.001
% Remitters	41.6%	27.7%	0.006
CGI-BP-S overall	-1.51	-1.02	< 0.001
CGI-BP-S mania	-1.65	-1.14	< 0.001
CGI-BP-S depression	-0.41	-0.13	0.008
CGI-BP-C overall	2.58	3.18	< 0.001
CGI-BP-C overall much improved or very much improved	53.7%	32.7%	< 0.001
CGI-BP-C mania	2.41	3.01	< 0.001
CGI-BP-C depression	3.46	3.70	0.054

Modified from Sponsor Tables 11.2.1.6.1, 11.2.1.7.1, 11.2.2.2.1, 11.2.2.2.2, 11.2.2.2.3, 11.2.3.2.1, 11.2.3.2.2, 11.2.3.2.3

*LS mean change from baseline

YMRS Individual Item Analysis

The Sponsor provided YMRS item analysis for only the “four key YMRS individual items used for eligibility criteria” – irritability, speech, thought content and disruptive-aggressive behavior.

Table 6.2.4.9. Sponsor’s Table. YMRS Item Analysis for Irritability, Speech, Thought Content and Disruptive-Aggressive Behavior

Table 26 **YMRS item comparisons at Week 3 (LOCF, MITT population)**

YMRS item	Quetiapine XR	
	LS mean difference from placebo	p-value
5. Irritability	-0.53	0.008
6. Speech	-0.56	0.004
8 Thought content	-0.59	0.011
9 Disruptive- aggressive behavior	-0.35	0.063

Subgroup analyses

The Sponsor provided the following analyses based on specific subgroups – confidence intervals were provided but not p-values.

Manic vs. Mixed

The change from baseline to endpoint in the YMRS was statistically significant favoring quetiapine XR in the manic subgroup, but not the mixed subgroup – though the numerical difference did favor quetiapine XR (Table 6.2.4.10).

Table 6.2.4.10. Change from Baseline to Endpoint - YMRS Total Score: *Manic* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	86	28.7	5.2	-15.29	1.08	-4.91	-7.35, -2.47
Placebo	88	28.3	5.2	-10.38	1.05		

Modified from Sponsor Table 11.2.1.3.7 in Clinical Study Report

Table 6.2.4.11. Change from Baseline to Endpoint - YMRS Total Score: *Mixed* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	63	29	5.8	-12.61	1.26	-2.47	-5.36, 0.41
Placebo	71	28.5	5.1	-10.14	1.22		

Modified from Sponsor Table 11.2.1.3.7 in Clinical Study Report

Rapid vs. Nonrapid Cycling

The change from baseline to endpoint in the YMRS was statistically significant favoring quetiapine XR in both the rapid and nonrapid cycling subgroups (Tables 6.2.4.12 and 6.2.4.13).

Table 6.2.4.12. Change from Baseline to Endpoint - YMRS Total Score: *Nonrapid Cycling* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	104	28.5	5.6	-14.54	1.03	-3.88	-6.23, -1.53
Placebo	107	27.9	5.1	-10.66	1.01		

Modified from Sponsor Table 11.2.1.3.8 in Clinical Study Report

Table 6.2.4.13. Change from Baseline to Endpoint - YMRS Total Score: *Rapid Cycling* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	45	29.7	4.9	-13.18	1.54	-3.48	-6.38, -0.57
Placebo	52	29.4	5.0	-9.70	1.43		

Modified from Sponsor Table 11.2.1.3.8 in Clinical Study Report

Age, Gender, Origin

Subgroup Analysis by Age

The change from baseline to endpoint in the YMRS was statistically significant favoring quetiapine XR in the two age groups analyzed – 18 to 39 years of age and 40 to 65 years of age.

Table 6.2.4.14. Change from Baseline to Endpoint -YMRS Total Score: *18 – 39 Years of Age* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	61	30.2	6.7	-15.40	1.13	-3.79	-6.80, -0.78
Placebo	65	29.0	6.3	-11.62	1.10		

Modified from Sponsor Table 11.2.1.3.4 in Clinical Study Report

Table 6.2.4.15. Change from Baseline to Endpoint -YMRS Total Score: *40 to 65 Years of Age* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	88	27.9	4.1	-13.20	1.12	-3.33	-5.73, -0.93
Placebo	94	28.0	4.2	-9.87	1.10		

Modified from Sponsor Table 11.2.1.3.4 in Clinical Study Report

Subgroup Analysis by Gender

The change from baseline to endpoint in the YMRS was statistically significant favoring quetiapine XR in both males and females.

Table 6.2.4.16. Change from Baseline to Endpoint - YMRS Total Score: *Female* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	57	29.1	6.1	-15.30	1.15	-4.87	-7.98, -1.76
Placebo	66	28.7	5.6	-10.43	1.06		

Modified from Sponsor Table 11.2.1.3.5 in Clinical Study Report

Table 6.2.4.17. Change from Baseline to Endpoint - YMRS Total Score: *Male* (LOCF)

	N	Baseline		Endpoint		LSMean Difference	95% CI
		Mean	SD	LSMean Change	SE		
Quetiapine XR	92	28.7	5.0	-13.69	1.19	-2.98	-5.26, -0.70
Placebo	93	28.2	4.8	-10.71	1.20		

Modified from Sponsor Table 11.2.1.3.5 in Clinical Study Report

Subgroup Analysis by Origin

Statistically significant differences were noted for the quetiapine XR group for both Caucasians and African Americans/Black origins – there were significant numbers of subjects in both groups for meaningful comparisons. Too few subjects were included in the “other” category for meaningful comparisons.

Table 6.2.4.18. Change from Baseline to Endpoint – YMRS Total Score: *African American/Black* (LOCF)

	N	Baseline		Endpoint			LSMean Difference	95% CI
		Mean	SD	N	LSMean Change	SE		
Quetiapine XR	70	28.3	4.9		-14.16	1.23	-3.46	-5.91, -1.01
Placebo	77	27.9	4.6		-10.71	1.16		

Modified from Sponsor Table 11.2.1.3.6 in Clinical Study Report

Table 6.2.4.19. Change from Baseline to Endpoint – YMRS Total Score: *Caucasian/White* (LOCF)

	N	Baseline		Endpoint			LSMean Difference	95% CI
		Mean	SD	N	LSMean Change	SE		
Quetiapine XR	72	29.3	5.7		-14.64	1.09	-4.69	-7.70, -1.68
Placebo	73	29.0	5.4		-9.95	1.08		

Modified from Sponsor Table 11.2.1.3.6 in Clinical Study Report

Efficacy Analysis – Internal Review

The statistical reviewer for this supplement, George Kordzakhia, Ph.D., was able to replicate the efficacy findings of the Sponsor and concluded that the clinical trials supported the efficacy of quetiapine XR in the treatment of bipolar depression and acute mania (monotherapy). No significant data issues were identified in his review.

6.2.5 Efficacy Conclusions

The efficacy of quetiapine XR monotherapy in the treatment of acute mania associated with bipolar disorder was demonstrated in pivotal trial D144CC00004.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Sponsor did not submit an integrated summary of safety. Since there was only one study for each indication and the doses of quetiapine XR and the duration of exposure were very different between the two studies, analysis of safety data for each study is considered appropriate by this reviewer.

Both pivotal trials were acute studies. Study D144CC00002 was an 8-week study and D144CC00004 was a 3-week study. For D144CC00002, the 300 mg/day fixed dose study, the mean daily dose was 266.9 mg (median = 284.8 mg) and the mean duration of treatment was 42.6 days. For D144CC00004, the 400 – 800 mg/day flexible dose study, the mean daily dose was 603.8 mg (median = 585.7 mg) and the mean duration of treatment was 18.7 days. The distribution of quetiapine XR for final dose level for D144CC00004 was 0% at 200 mg/day, 2% at 300 mg/day, 21.9% at 400 mg/day, 47% at 600 mg/day and 29.1% at 800 mg/day. The Sponsor did not provide exposure data in patient-years. For a crude estimate, this reviewer multiplied the number of subjects in the quetiapine XR group with the mean exposure duration. This crude exposure estimate was 16 patient-years for D144CC00002 and 7.7 patient-years for D144CC00004.

Since quetiapine XR is currently approved for the treatment of schizophrenia (acute and maintenance), a significant amount of safety data is currently included in approved product labeling. Data corresponding to these indications consists of 951 subjects exposed to quetiapine XR in clinical trials corresponding to approximately 82.9 patient-years (data from currently approved product labeling).

7.1.1 Deaths

D144CC00002 (Acute Bipolar Depression) – no deaths

D144CC00004 (Acute Mania, Monotherapy) – one death occurred in a 57 YOM subject randomized to placebo; the event occurred 22 days after discontinuation of study treatment. The Sponsor stated that this death was unexplained and that no other information is available. Subject was found dead (presumably in home) by wife. The Sponsor included a brief narrative, but very little information was included (concomitant meds, labs, etc.).

7.1.2 Other Serious Adverse Events

D144CC00002 (Acute Bipolar Depression)

Four serious adverse events occurred in this clinical trial, two in the quetiapine XR group (1.4%) and 2 in the placebo group (1.4%) (see Table 7.1.2.1).

D144CC00004 (Acute Mania, Monotherapy)

Six (4%) subjects in the quetiapine XR group and 13 (8.1%) subjects in the placebo group had SAEs. Most of these SAEs appear to be related to bipolar disorder (suicidal ideation, suicide attempts, increased clinical symptoms related to bipolar disorder) and occurred with similar frequency in both treatment groups. The Sponsor has been asked to provide an update for the SAE “vestibular neuronitis” occurring in the quetiapine XR group (see Table 7.1.2.1).

In the extent of exposure section of the clinical study report for D144CC00004, the Sponsor indicated that subject 41253 (SAE = intentional overdose, suicide attempt) intentionally ingested 4000 mg of quetiapine XR. The narrative did not include any clinical symptoms resulting from this overdose, though the outcome was resolution. The Sponsor has been asked to provide details regarding the clinical symptoms experienced after this overdose.

Table 7.1.2.1. Serious Adverse Events in D144CC00002 and D144CC00004

Group	Subject #	Age/Gender	AE Preferred Term	AE Verbatim Term	Onset of AE* (days)	Last Dose to Onset of AE (days)	Outcome
D144CC00002							
Quetiapine XR	2110184	31 YOF	Asthma	Asthma	31	-10	Resolved
	2110174	33 YOF	Depression	Worsening of depression	23	2	Study drug stopped, AE ongoing
Placebo	2110105	41 YOF	Suicidal ideation	Suicidal ideations	82 (off treatment)	26	Resolved
	2110139	31 YOF	Suicidal ideation	Suicidal ideation	10	-46	Resolved
D144CC00004							
Quetiapine XR	41361	26 YOM	Bipolar I disorder	Worsening of bipolar I symptoms	13	1	Study drug stopped, AE resolved
	41253	27 YOM	Intentional overdose; Suicide attempt; Suicide attempt	Intentional overdose of study medication; intentional suicide attempt; suicide attempt	13	1	Study drug stopped, AE resolved
					13	1	
					17 (off treatment)	5	
	41231	51 YOM	Vestibular neuronitis	Vestibular neuronitis	46 (off treatment)	2	Continuing
	41384	44 YOM	Psychotic disorder	Worsening of psychotic symptoms	13	1	Study drug stopped, AE continuing
41333	33 YOM	Bipolar disorder; Suicidal ideation	Worsening of condition for bipolar mixed disorder;	12 (off treatment)	3	Study drug stopped, AE resolved	
				12	3		

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				Suicidal ideation			
	41180	26 YOM	Bipolar I disorder	Bipolar disorder in manic episode	31 (off treatment)	25	Resolved
Placebo	41290	44 YOF	COPD	Exacerbation of COPD	25 (off treatment)	2	Resolved
	41110	40 YOM	Bipolar disorder	Worsening of bipolar	22	-1	Study drug stopped, AE resolved
	41326	29 YOF	Depression; Suicidal ideation	Worsening of depression; Suicidal ideation	9 9	0 0	Study drug stopped, AE resolved
	41327	48 YOM	Agitation; Mania	Increased agitation; Exacerbation of mania	5 5	-3 -3	Study drug stopped, AE resolved
	41033	47 YOF	Agitation Anxiety	Worsening of agitation; Worsening of anxiety	5 5	0 0	Study drug stopped, AE continuing
	41010	39 YOF	Asthma; Pneumonia; URI	Exacerbation of asthma; Pneumonia in the right lobe; upper respiratory infection	29 29 29	15 15 15	Resolved Resolved Resolved
	41037	45 YOF	Suicide attempt; Ischemic hepatitis; Multiple drug overdose; Myocardia infarction; Pancreatitis; Renal failure acute	Suicide attempt; Ischemic hepatitis Polydrug overdose; Heart attack; Pancreatitis; Acute renal failure	20 (off tx) 20 20 20 20 21	9 9 9 9 9 10	Study drug stopped, all AE resolved except ischemic hepatitis which was ongoing
	41077	33 YOF	Intentional overdose; Suicide attempt	Overdose with Tylenol PM; Suicide attempt	46 (off treatment) 46	25 25	Resolved
	41063	31 YOM	Suicidal ideation	Suicidal ideation	16 (off treatment)	8	Study drug stopped, AE resolved
	41118	24 YOM	Mania	Worsening of manic symptoms	12	1	Study drug stopped, AE resolved
	41311	49 YOM	Mania	Worsening of mania with psychotic features	5	0	Study drug stopped, AE resolved
	41347	56 YOM	Mania	Exacerbation of manic symptoms	27	0	Study drug stopped, AE resolved

Modified from Sponsor Table 11.3.4.2 and narratives

*Time from start of treatment to onset of adverse event

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Adverse events associated with dropouts

For Study D144CC00002, the most common adverse events associated with subject discontinuation were sedation and somnolence. For Study D144CC00004, the most common adverse events associated with subject discontinuation were related to bipolar disorder.

Table 7.1.3.1.1. Sponsor's Table. Discontinuations Due to Adverse Events for D144CC00002

Table 38 Incidence of discontinuations of study treatment due to AEs by preferred term (safety population)

Preferred term	Number (%) of patients ^a	
	Quetiapine XR (N=137)	Placebo (N=140)
Patients with an SAE leading to discontinuation^b		
Depression	1 (0.7)	0
Patients with an AE leading to discontinuation^b		
Sedation	9 (6.6)	0
Somnolence	5 (3.6)	0
Irritability	1 (0.7)	1 (0.7)
Disorientation	1 (0.7)	0
Dizziness	1 (0.7)	0
Dysarthria	1 (0.7)	0
Fatigue	1 (0.7)	0
Hostility	1 (0.7)	0
Mental impairment	1 (0.7)	0
Sensation of heaviness	1 (0.7)	0
Aggression	0	1 (0.7)
Agitation	0	1 (0.7)
Gravitational edema	0	1 (0.7)
Migraine	0	1 (0.7)

Table 7.1.3.1.2. Sponsor's Table. Discontinuations Due to Adverse Events for D144CC00004

Table 41 Incidence of discontinuations of study treatment due to AEs by preferred term (safety population)

Preferred term	Number (%) of patients ^a	
	Quetiapine XR (N=151)	Placebo (N=160)
Patients with an AE leading to discontinuation^b	7 (4.6)	13 (8.1)
Suicidal ideation	1 (0.7)	2 (1.3)
Bipolar disorder	1 (0.7)	1 (0.6)
Dizziness	1 (0.7)	1 (0.6)
Suicide attempt	1 (0.7)	1 (0.6)
Bipolar I disorder	1 (0.7)	0
Coordination abnormal	1 (0.7)	0
Dermatitis allergic	1 (0.7)	0
Ear pain	1 (0.7)	0
Intentional overdose	1 (0.7)	0
Psychotic disorder	1 (0.7)	0
Mania	0	5 (3.1)
Abdominal pain lower	0	1 (0.6)
Agitation	0	1 (0.6)
Anxiety	0	1 (0.6)
Gastroesophageal reflux disease	0	1 (0.6)
Ischemic hepatitis	0	1 (0.6)
Lethargy	0	1 (0.6)
Multiple drug overdose	0	1 (0.6)
Myocardial infarction	0	1 (0.6)
Pancreatitis	0	1 (0.6)
Somnolence	0	1 (0.6)
Vision blurred	0	1 (0.6)

7.1.4 Common Adverse Events

7.1.4.1 Common adverse event tables

Because of the difficulty in distinguishing between “sedation” and “somnolence”, the Sponsor has been asked to provide frequency data for a combined term – the Sponsor has also been asked to do this for the adverse event tables already included in approved product labeling (e.g. schizophrenia indication).

The common adverse events occurring in these two clinical trials are similar to the common adverse events occurring in the pivotal schizophrenia trials.

Table 7.1.4.1.1. Sponsor’s Table. Most Common Adverse Events ($\geq 2\%$ Frequency): D144CC00002

Preferred term	Number (%) of patients ^a	
	Quetiapine XR (N=137)	Placebo (N=140)
Patients with any AE	121 (88.3)	96 (68.6)
Dry mouth	51 (37.2)	10 (7.1)
Somnolence	40 (29.2)	8 (5.7)
Sedation	32 (23.4)	10 (7.1)
Dizziness	18 (13.1)	15 (10.7)
Increased appetite	17 (12.4)	8 (5.7)
Headache	13 (9.5)	14 (10.0)
Constipation	11 (8.0)	9 (6.4)
Nausea	10 (7.3)	10 (7.1)
Weight increased	10 (7.3)	2 (1.4)
Dyspepsia	9 (6.6)	1 (0.7)
Fatigue	8 (5.8)	3 (2.1)
Arthralgia	6 (4.4)	2 (1.4)
Gastroenteritis viral	6 (4.4)	1 (0.7)
Irritability	6 (4.4)	4 (2.9)
Nasopharyngitis	6 (4.4)	8 (5.7)
Diarrhoea	5 (3.6)	5 (3.6)
Upper respiratory tract infection	5 (3.6)	6 (4.3)
Abnormal dreams	4 (2.9)	0
Back pain	4 (2.9)	1 (0.7)
Muscle spasms	4 (2.9)	1 (0.7)
Paresthesia	4 (2.9)	3 (2.1)
Toothache	4 (2.9)	0

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Anxiety	3 (2.2)	1 (0.7)
Cough	3 (2.2)	3 (2.1)
Decreased appetite	3 (2.2)	1 (0.7)
Disturbance in attention	3 (2.2)	1 (0.7)
Dysarthria	3 (2.2)	0
Hyperhidrosis	3 (2.2)	1 (0.7)
Influenza	3 (2.2)	3 (2.1)
Insomnia	3 (2.2)	7 (5.0)
Nasal congestion	3 (2.2)	4 (2.9)
Urinary tract infection	3 (2.2)	0
Vomiting	3 (2.2)	5 (3.6)
Pain in extremity	2 (1.5)	3 (2.1)

Table 7.1.4.1.2. Sponsor's Table. Most Common Adverse Events ($\geq 2\%$ Frequency):
 D144CC00004

Table 39 Adverse event incidence of $\geq 2\%$ by decreasing frequency sorted by the quetiapine XR group (safety population)

Preferred term	Number (%) of patients ^a	
	Quetiapine XR (N=151)	Placebo (N=160)
Patients with any AE	128 (84.8)	107 (66.9)
Sedation	52 (34.4)	12 (7.5)
Dry mouth	51 (33.8)	11 (6.9)
Somnolence	25 (16.6)	7 (4.4)
Headache	18 (11.9)	22 (13.8)
Constipation	15 (9.9)	5 (3.1)
Dizziness	15 (9.9)	7 (4.4)
Dyspepsia	10 (6.6)	6 (3.8)
Fatigue	10 (6.6)	6 (3.8)
Weight increased	10 (6.6)	1 (0.6)
Dysarthria	7 (4.6)	0
Nasal congestion	7 (4.6)	2 (1.3)
Increased appetite	6 (4.0)	3 (1.9)
Abnormal dreams	4 (2.6)	0
Back pain	4 (2.6)	3 (1.9)
Diarrhea	4 (2.6)	4 (2.5)
Heart rate increased	4 (2.6)	0
Orthostatic hypertension	4 (2.6)	0
Toothache	4 (2.6)	2 (1.3)
Insomnia	3 (2.0)	3 (1.9)
Lethargy	3 (2.0)	1 (0.6)
Nausea	3 (2.0)	4 (2.5)
Pharyngolaryngeal pain	3 (2.0)	4 (2.5)
Sluggishness	3 (2.0)	1 (0.6)
Tachycardia	3 (2.0)	1 (0.6)
Tremor	3 (2.0)	3 (1.9)
Vision blurred	3 (2.0)	2 (1.3)
Agitation	2 (1.3)	7 (4.4)
Decreased appetite	2 (1.3)	4 (2.5)

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Vomiting	2	(1.3)	6	(3.8)
Upper respiratory tract infection	1	(0.7)	5	(3.1)
Mania	0		5	(3.1)
Stomach discomfort	0		4	(2.5)

Though the common adverse events were similar between these bipolar populations and the schizophrenia population, the adverse events dry mouth, sedation and somnolence appeared to be more common in bipolar disorder subjects (Table 7.1.4.1.3). Interestingly, the rates for orthostatic hypotension were lower in the bipolar subjects compared to schizophrenia subjects.

Table 7.1.4.1.3. Most Common Adverse Events for Quetiapine XR in Clinical Trials for Schizophrenia*, Bipolar Depression (D144CC00002) and Bipolar Mania (D144CC00004)

	Schizophrenia (n = 951)	Bipolar Depression (n = 137)	Bipolar Mania (n = 151)
Trial Duration	6 weeks	8 weeks	3 weeks
Quetiapine XR Dose Range	300 – 800 mg/day	300 mg/day	400 – 800 mg/day
Adverse Event (%)			
Dry Mouth	12%	37.2%	33.8%
Sedation	13%	23.4%	34.4%
Somnolence	12%	29.2%	16.6%
Orthostatic hypotension	7%	1.5%	2.6%

*Data for schizophrenia acute trials from currently approved product labeling

For study D144CC00002, adverse events occurring in > 5% of subjects and twice as many subjects in the quetiapine XR group compared to the placebo group included dry mouth, somnolence, sedation, increased appetite, weight increased, dyspepsia and fatigue. For study D144CC00004, these adverse events included dry mouth, somnolence, sedation, constipation, dizziness and weight increased.

7.1.4.2 Additional analyses and explorations – adverse events of special interest

Extrapyramidal Symptoms

Study D144CC00002

Approximately 4% of subjects in the quetiapine XR group had adverse events consistent with EPS compared to < 1% in the placebo group.

Table 7.1.4.2.1. Sponsor's Table. Adverse Events Consistent with Extrapyramidal Symptoms (D144CC00002)

Table 40 AE assessed as potentially associated with EPS, by preferred term (safety analysis set)

Preferred term	Number (%) of patients	
	Quetiapine XR (n=137)	Placebo (n=140)
Patients with AE terms potentially associated with EPS	6 (4.4)	1 (0.7)
Akathisia	2 (1.5)	0
Dystonia	1 (0.7)	0
Extrapyramidal disorder	1 (0.7)	0
Hypertonia	1 (0.7)	0
Tremor	1 (0.7)	1 (0.7)

Study D144CC00004

Approximately 7% of subjects in the quetiapine XR group had adverse events consistent with EPS compared to 4% in the placebo group.

Table 7.1.4.2.2. Sponsor's Table. Adverse Events Consistent with Extrapyramidal Symptoms (D144CC00004)

Table 43 AE assessed as potentially related to EPS, by preferred term (safety population)

Preferred term	Number (%) of patients*	
	Quetiapine XR (N=151)	Placebo (N=160)
Patients with AE terms potentially related to EPS	10 (6.6)	6 (3.8)
Tremor	3 (2.0)	3 (1.9)
Akathisia	2 (1.3)	1 (0.6)
Restlessness	2 (1.3)	1 (0.6)
Cogwheel rigidity	1 (0.7)	0
Dystonia	1 (0.7)	0
Extrapyramidal disorder	1 (0.7)	1 (0.6)

Neutropenia/agranulocytosis

No adverse events were reported that were considered potentially related to neutropenia and agranulocytosis

See Section 7.1.5 - Laboratory Findings.

Treatment-emergent mania (in D144CC00002) or depression (in D144CC00004)

There were no adverse events of “mania” in either treatment group in study D144C00002.

Treatment-emergent mania was defined as YMRS \geq 16 at 2 consecutive visits or last visit. No subjects in either treatment group met the YMRS criteria.

One subject (0.6%) in the placebo group and no subjects in the quetiapine XR group had an adverse event of “depression” in D144CC00004. Treatment-emergent depression was defined as MADRS \geq 18 at 2 consecutive visits or last visit. The MADRS criteria was achieved in 9.3% (14/151) subjects in the quetiapine XR group and 15% (24/160) subjects in the placebo group.

Suicidality

D144CC00002

Suicidal ideation occurred in 1 (0.7%) subject in the quetiapine XR group and 2 (1.4%) subjects in the placebo group. There were no suicide attempts reported in this study.

An analysis similar to the Columbia-type of analysis was performed by the Sponsor – though few details were available in the study report about the process. These data are depicted in Table 7.1.4.2.3. The Sponsor did not provide further comments or information on the “possible” suicidality cases from this analysis.

Table 7.1.4.2.3. Adverse Events Associated with Suicidality and Columbia Analysis of Suicidality in Studies D144CC00002 and D144CC00004

	Study D144CC00002		Study D144CC00004	
	Quetiapine XR (N = 137)	Placebo (N = 140)	Quetiapine XR (N = 151)	Placebo (N = 160)
Suicidal ideation				
Adverse Event	1 (0.7%)	2 (1.4%)	1 (0.7%)	3 (1.9%)
Columbia Analysis	1 (0.7%)	1 (0.7%)	1 (0.7%)	4 (2.5%)
Suicide Attempts				
Adverse Event	0	0	1 (0.7%)	2 (1.3%)
Columbia Analysis	-	-	-	-
Suicidal Behavior				
Columbia Analysis	0	1 (0.7%)	1 (0.7%)	2 (1.3%)
Possible Suicidal behavior/ideation				
Columbia Analysis	4 (2.9%)	0	2 (1.3%)	1 (0.6%)

Adverse events potentially related to diabetes mellitus

Subjects with diabetes mellitus were not excluded from these trials, but had to meet specific criteria that their disease state was stable (see Inclusion/Exclusion criteria in Appendix). Very few subjects (≤ 7 per treatment group) with diabetes mellitus were enrolled in each study. It is not known in which subjects these adverse events occurred.

In study D144CC00002, 2 adverse events occurred in the placebo group – blood glucose increased (n = 1, 0.7%) and polyuria (n = 1, 0.7%). One adverse event occurred in the quetiapine XR group – thirst (0.7%).

In study D144CC00004, only one event occurred - diabetes mellitus non-insulin-dependent in the quetiapine XR group (0.7%). This 43-year-old obese black female did not have evidence of pre-existing DM but did have a positive family history. Her fasting blood glucose at enrollment was 91 mg/dL (HbA1c = 6.6%); on Day 22 (final visit) her weight had increased from 108 kg to 110 kg and her fasting blood glucose was 385 mg/dL (HbA1c = 8.1%). Labs were repeated one week later and blood glucose was 135 mg/dL (HbA1c = 8.2%). See Section 7.1.5 - Laboratory Results.

Subgroup Analyses for Adverse Events

Adverse events were summarized for various subgroups – the frequency of adverse events in the quetiapine XR-treated subjects is summarized here.

Study D144CC00002

Age Subgroups

The most common adverse events in both age subgroups (18 to 39 years of age and 40 to 65 years of age) were dry mouth (32.4% vs. 42.9%), somnolence (32.4% vs. 25.4%) and sedation (23% vs. 23.8%).

Other adverse events that occurred more frequently in the younger subgroup included increased appetite (14.9% vs. 9.5%) and headache (10.8% vs. 7.9%). Adverse events that occurred more frequently in the older subgroup included dizziness (17.5% vs. 9.5%).

Origin Subgroups

The most common adverse events in occurring in Caucasians and African Americans included dry mouth (34.7% vs. 42.9%), somnolence (29.7% vs. 28.6%), sedation (26.7% vs. 10.7%) and dizziness (11.9% vs. 17.9%).

Other adverse events that occurred more frequently in Caucasians included headache (12.9% vs. 0), increased appetite (11.9% vs. 7.1%), dyspepsia (8.9% vs. 0), and nausea (7.9% vs. 3.6%). Weight increased occurred in similar frequencies between both races (6.9% Caucasians vs. 7.1% African Americans). Too few subjects were in the race category “other” to make meaningful comparisons.

Gender Subgroups

The most common adverse events in both males and females were dry mouth (44.4% vs. 33.7%), somnolence (33.3% vs. 27.2%), sedation (22.2% vs. 23.9%) and dizziness (13.3% vs. 13%). Other adverse events that occurred more frequently in males were insomnia (6.7% vs. 0) and in females were increased appetite (15.2% vs. 6.7%) and weight increased (8.7% vs. 4.4%).

Study D144CC0004

Age Subgroups

The most common adverse events occurring in the subgroups 18-39 years of age and 40 to 65 years of age were sedation (37.1% vs. 32.6%), dry mouth (35.5% vs. 32.6%), headache (14.5% vs. 10.1%) and somnolence (14.5% vs. 18%).

Other adverse events that occurred more frequently in the younger subgroup included dizziness (12.9% vs. 7.9%), dysarthria (6.5% vs. 3.4%), tremor (4.8% vs. 0), hypotension (3.2% vs. 0),

Other adverse events that occurred more frequently in the older subgroup included constipation (11.2% vs. 8.1%), weight increased (9% vs. 3.2%), nasal congestion (6.7% vs. 1.6%), orthostatic hypotension (3.4% vs. 1.6%)

Origin Subgroups

The most common adverse events in occurring in Caucasians and African Americans included dry mouth (38.9% vs. 29.2%), somnolence (23.6% vs. 9.7%), sedation (33.3% vs. 34.7%) and constipation (15.3% vs. 4.2%). Other adverse events that occurred more frequently in Caucasians included dry mouth (38.9% vs. 29.2%), somnolence (23.6% vs. 9.7%), constipation (15.3% vs. 4.2%) and dizziness (11.1% vs. 6.9%). Adverse events occurring more frequently in African Americans included dyspepsia (8.3% vs. 5.6%) and fatigue (9.7% vs. 4.2%). Too few subjects were in the race category "other" to make meaningful comparisons.

Gender Subgroup

The most common adverse events in both males and females were dry mouth (39.1% vs. 25.4%), somnolence (16.3% vs. 16.9%) and sedation (35.9% vs. 32.2%).

Comparing other adverse event frequencies: constipation occurred more frequently in males (12% vs. 6.8%) and dizziness was reported more frequently in females (15.3% vs. 6.5%).

Increased appetite (3.3% vs. 5.1%) and weight increased (6.5% vs. 6.8%) occurred in similar frequencies between male and female subjects.

7.1.5 Laboratory Findings

7.1.5.1 Overview of laboratory testing in the development program

The following laboratory tests were performed in both pivotal studies at baseline and at end of study (week 8 for D144CC00002 and week 3 for D144CC00004):

Hematology – hemoglobin, leukocyte count, leukocyte differential count, platelet count, neutrophil count, red blood cells, hematocrit. Hematology panel was also performed at day 29 for D144CC00002.

Chemistry – creatinine, urea, bilirubin (total), albumin, alkaline phosphatase, ALT, AST, potassium, calcium, sodium, chloride, bicarbonates, glucose (fasting), insulin (fasting), hemoglobin A1C, lipids (fasting) including total cholesterol, triglycerides, HDL, LDL; thyroid function tests including free T3, free T4, TSH; prolactin; beta-HCG
 Urinalysis – urine toxicology (baseline only)

7.1.5.2 Standard analyses and explorations of laboratory data

7.1.5.2.1 Analyses focused on measures of central tendency

Significant mean increases in fasting glucose in the quetiapine XR group compared to the placebo group (+9 mg/dL vs. +2.9 mg/dL) were noted in study D144CC00004; data for fasting glucose was not included in the clinical study report for D144CC00002 and has been requested from the Sponsor. Significant mean increases in triglycerides and prolactin were also noted in both studies in the quetiapine XR group.

Table 7.1.5.2.1.1. Mean Changes from Baseline to Endpoint for Select Laboratory Indices*

	D144CC00002		D144CC00004	
	Quetiapine XR	Placebo	Quetiapine XR	Placebo
Leukocytes (x 10 ⁹ /L)	-0.30	0.04	-0.24	-0.20
Neutrophil count (x 10 ⁹ /L)	-0.18	0.06	-0.17	-0.13
ALT (IU/L)	2.26	1.96	3.48	4.66
AST (IU/L)	1.87	1.75	0.55	6.23**
Fasting glucose (mg/dL)	NA	NA	9.0	2.9
Glucose (mg/dL)	6.1	5.9	9.0	2.7
HbA1c (%)	0.08	0.01	0.13	0.03
LDL-C (mg/dL)	-4.6	-5.0	2.3	-0.77
Total cholesterol (mg/dL)	-3.5	-5.0	3.9	-3.1
Triglycerides (mg/dL)	15.9	-2.7	28.3	-7.1
Prolactin (ng/ml)	25.9	18.4	14.91	-1.72

*Samples sizes varied slightly for each analyte; conversion factors used for display of Sponsor data: glucose = 0.05551; LDL and cholesterol = 0.02586; triglycerides = 0.01129

**One outlier subject in the placebo group had an increase in AST to 473 IU/L, therefore the mean increase is fairly large. The median increase in the placebo group was 1 IU/L.

7.1.5.2.2 Analyses focused on outliers or shifts from normal to abnormal

Hematology and chemistry analytes were reviewed and the most significant “outliers” are noted in this section. Summary tables for all shift changes are in the Appendix.

Neutrophil Counts

“Important Low” defined as $< 1.5 \times 10^9$ L

Study D144CC00002

Two (1.8%) subjects in the quetiapine XR group and 2 (1.5%) subjects in the placebo group had shifts from normal to “important low”. [Hematology panels were performed at baseline, Day 29 and end of study]

Table 7.1.5.2.2.1. Shifts from Normal to Important Low Values – Neutrophil Count

	Patient Enrollment Number	Neutrophil Count			Comment
		Baseline Value	Low Value*	End of Study (Week 8) Value	
Quetiapine XR	E2001006	2.66×10^9 /L	1.35×10^9 /L (week 4)	1.78×10^9 /L	Repeat 2 weeks later: 1.78×10^9 /L
	E2061003	2.26×10^9 /L		1.17×10^9 /L	Repeat 2 weeks later: 3.48×10^9 /L
Placebo	E2002003	2.60×10^9 /L	1.19×10^9 /L (week 8)	-	Repeat 2 weeks later: 2.90×10^9 /L
	E2057003	2.07×10^9 /L	1.12×10^9 /L (week 4)	1.25×10^9 /L	Repeat 1 weeks later: 1.32×10^9 /L

From Sponsor table 11.3.7.2.6.2

Study D144CC00002

2 (1.5%) subjects in the quetiapine XR group had shift from normal to “important low” ($< 1.5 \times 10^9$ L) compared to no subjects in the placebo group. One of these subjects had a shift from 1.78×10^9 L to 0.99×10^9 L at week 3 (repeated 2 days later with result 2.69×10^9 L). The other subject had a shift from 2.03×10^9 L to 1.33×10^9 L at week 3; no follow-up labs provided.

Glucose

“Important high” defined as ≥ 126 mg/dL. The Sponsor did not provide specifics regarding the magnitude of these shifts.

D144CC00002

Fasting glucose shifts from normal to “important high” = 5.8% (5/86) in the quetiapine XR group compared to 2.1% (2/95) in the placebo group. The Sponsor did not provide any analysis based on different ranges for baseline glucose levels.

D144CC00004

Fasting glucose shifts from normal to “important high” = 6.9% (8/116) in the quetiapine XR group compared to 2.4% (3/126) in the placebo group. The Sponsor did not provide any analysis based on different ranges for baseline glucose levels.

Triglycerides and cholesterol

“Important high” defined as ≥ 200 mg/dL. The Sponsor did not provide specifics regarding the magnitude of these shifts.

D144CC00002

Approximately 7-8% of subjects in both quetiapine XR and placebo groups with normal triglycerides at baseline had a shift to “important high”. For cholesterol, 7.1% of subjects in the quetiapine XR group and 2.8% of subjects in the placebo group had a shift from normal to “important high”.

D144CC00004

Triglyceride shifts from normal to “important high” = 14.7% (15/102) in the quetiapine XR group compared to 6.4% (8/125) in the placebo group. For cholesterol, 7.0% of subjects in the quetiapine XR group and 3.7% of subjects in the placebo group had a shift from normal to “important high”. The Sponsor did not provide specifics regarding the magnitude of these shifts.

Prolactin

“Important high” defined as > 20 ng/ml for males and > 30 ng/ml for females. The Sponsor did not provide specifics regarding the magnitude of these shifts.

D144CC00002

No subjects in the quetiapine XR group had a shift from normal to “important high”.

D144CC00004

Shifts from normal to “important high” = 4.8% (6/126) in the quetiapine XR group and 1.4% (2/145) in the placebo group.

As mentioned elsewhere in this review, as part of an overall plan to evaluate specific safety signals for all atypical antipsychotics, the Sponsor of this submission has been asked to provide data and analyses for quetiapine IR and quetiapine XR for effects on lipids (cholesterol, HDL,

LDL, triglycerides), glucose (glucose, HbA1c, UA glucose), and weight for both adults and pediatric subjects (see Division letter January 8, 2008). The Sponsor recently provided these data and they are currently under review.

7.1.5.3 Special assessments

Simpson Angus Scale (SAS) and Barnes Akathisia Scale global assessment

Mean ratings for EPS and akathisia were low in both treatment groups and mean scores for all groups decreased from baseline to end of study.

Table 7.1.5.3.1. Mean (SD) Scores on SAS and BAS (global assessment)

	D144CC00002		D144CC00004	
	Quetiapine XR	Placebo	Quetiapine XR	Placebo
SAS				
Baseline	0.5 ± 1.5	0.5 ± 1.3	0.3 ± 1.0	0.3 ± 1.1
End of Study	0.3 ± 1.1	0.1 ± 0.7	0.2 ± 0.6	0.2 ± 0.8
BAS				
Baseline	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.5	0.2 ± 0.5
End of Study	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3

Subjects with diabetes risk factors

A separate analysis for mean change from baseline for glucose, HbA1c, HOMA-R, insulin and QUICKI for subjects with and without diabetes risk factors was performed by the Sponsor (it was not clear whether these were fasting or nonfasting glucose values). HOMA-R is a measure of insulin resistance, homeostasis model assessment-resistance, calculated as (insulin value x glucose value) divided by 22.5. QUICKI is a measure of insulin sensitivity, quantitative insulin sensitivity check index, calculated as 1 divided by the following value ($\log_{10}(\text{insulin value}) + \log_{10}(\text{glucose value})$). Diabetes risk factors included: fasting glucose ≥ 100 and < 126 mg/dL at randomization, history of diabetes or obesity or BMI > 35 kg/m².

Though the results for glucose are not consistent across the studies for all subgroups, there does appear to be a fairly consistent elevation in the quetiapine XR groups. The increase in insulin does appear to be fairly impressive and consistent.

Table 7.1.5.3.2. Mean Change from Baseline in Glucose, Hb1Ac, HOMA-R* and Insulin in Subjects with and without Diabetic Risk Factors

	C00002		C00004	
	Quetiapine XR (N = 137)	Placebo (N= 140)	Quetiapine XR	Placebo
No Diabetic risk factors**	n = 50	n = 57	n = 61	n = 76
Glucose (mg/dL)	4.3	5.9	5.9	4.9
HbA1c (%)	0.07	0.01	0.10	0.03
HOMA-R	2.25	1.27	1.83	0.51
Insulin (pmol/L)	46.3	28.6	41.2	9.8
QUICKI	-0.02	-0.02	-0.02	-0.01
Diabetic risk factors	n = 50	n = 58	n = 70	n = 70
Glucose (mg/dL)	7.9	5.6	12.1	0.72
HbA1c (%)	0.12	0.02	0.15	0.04
HOMA-R	3.41	1.66	2.86	1.30
Insulin (pmol/L)	67.7	31.8	38.7	28.2
QUICKI	-0.01	-0.01	-0.02	-0.01
Diabetics	N = 5	N = 6	n = 7	n = 4
Glucose (mg/dL)	7.6	11.7	3.1	-1.8
HbA1c (%)	-0.25	-0.10	0.24	0.03
HOMA-R	2.38	1.0	-3.91	-0.60
Insulin (pmol/L)	45.8	12.4	-68.3	5.5
QUICKI	-0.01	-0.01	-0.01	0.00

From Sponsor Tables 11.3.7.3.51

*HOMA-R = Homeostatic Model Assessment of insulin resistance

**Sample size given is for the analyte with the most subjects having baseline and postbaseline values as a guess as to the number of subjects with or without risk factors.

Conversion factor for glucose = 0.05551

7.1.6 Vital Signs

7.1.6.1 Overview of vital signs testing in the development program

Vital signs were obtained at each study visit for the 3-week bipolar mania study (D144CC00004) and the 8-week bipolar depression study (D144CC00002). Supine and standing blood pressure and pulse were measured at each visit.

7.1.6.2 Standard analyses and explorations of vital signs data

7.1.6.2.1 Analyses focused on measures of central tendencies

In both studies, subjects in the quetiapine XR groups had greater mean increases in supine and standing pulse, and greater decreases in supine systolic BP compared to subjects in the placebo group. However, the mean changes for orthostatic parameters were not that pronounced in the quetiapine XR group.

The mean change from baseline for weight was greater in the quetiapine XR groups (+ 1.3 kg) compared to the placebo groups (-0.2 kg, + 0.1 kg) for both studies. There was some variability between studies with regard to mean weight changes by baseline BMI for subjects in the quetiapine XR groups [see Tables 7.1.6.2.1.2 and 7.1.6.2.1.3]. Subjects with baseline BMI \geq 40 did not appear to gain as much weight.

Table 7.1.6.2.1.1. Mean Change from Baseline in Vital Signs

	D144CC00002				D144CC00004			
	Quetiapine XR (N = 137)		Placebo (N = 140)		Quetiapine XR (N = 151)		Placebo (N = 160)	
	Week 8	Final	Week 8	Final	Week 3	Final	Week 3	Final
Supine Pulse (beats/min)	4.3	4.5	-0.2	0.1	1.5	1.3	-4.8	-2.9
Supine Systolic BP (mmHg)	-2.4	-2.1	-0.2	-0.7	-1.9	-2.4	-0.2	0.2
Supine Diastolic BP (mm Hg)	0.7	-0.2	-1.6	-2.2	0.7	0.5	0.0	0.4
Standing Pulse (beats/min)	3.0	3.4	-1.1	-0.3	2.1	2	-4.9	-3.6
Standing Systolic BP (mm Hg)	-0.9	-1.6	-0.3	-0.5	-2.3	-2.6	0.8	1.5
Standing Diastolic BP (mm Hg)	-0.9	-1.6	-0.3	-0.5	-2.3	-2.6	0.8	1.5
Orthostatic Change Pulse (beats/min)	-1.3	-1.1	-1.0	-0.4	0.7	0.7	-0.2	-0.8
Orthostatic Change Systolic BP (mm Hg)	1.6	0.5	-0.1	0.2	-0.4	-0.2	0.9	1.2
Orthostatic Change Diastolic BP (mm Hg)	0.8	0.0	-0.3	0.9	-1.2	-1.1	0.3	0.3
Weight (kg)	-	1.3	-	-0.2	-	1.3	-	0.1
BMI (kg/m ²)	-	0.5	-	-0.1	-	0.5	-	0.1

From Sponsor Tables 11.3.8.1.1 and 11.3.8.2.1

Table 7.1.6.2.1.2. Sponsor's Table. Change in Weight from Baseline to End of Study by Baseline BMI Category: Study D144CC00002

Table 57 Change in weight (kg) from baseline to end-of-treatment by baseline BMI category (LOCF, safety population)

BMI (kg/m ²) at randomization		Quetiapine XR n=137	Placebo n=140
<18.5		n=1	n=1
Change	Mean	-0.9	1.3
18.5 to <25		n=18	n=24
Change	Mean (SD)	1.3 (2.5)	0.4 (1.9)
25 to <30		n=37	n=36
Change	Mean (SD)	1.2 (2.2)	0.1 (2.0)
30 to <40		n=37	n=50
Change	Mean (SD)	2.4 (3.3)	-0.6 (2.6)
≥40		n=18	n=13
Change	Mean (SD)	-0.5 (6.4)	-0.6 (1.7)

Table 7.1.6.2.1.3. Sponsor's Table. Change in Weight from Baseline to End of Study by Baseline BMI Category: Study D144CC00004

Table 59 Change in weight (kg) from baseline to end of treatment by baseline BMI category (safety population)

BMI (kg/m ²) at randomization		Quetiapine XR (N=151)	Placebo (N=160)
<18.5	n	0	2
Change	Mean change (SD)	NA	1.1 (0.3)
18.5 to <25	n	34	35
	Mean change (SD)	0.7 (2.3)	0.2 (1.7)
25 to <30	n	35	42
	Mean change (SD)	1.6 (2.5)	-0.1 (3.2)
30 to <40	n	51	47
	Mean change (SD)	1.9 (2.8)	0.1 (2.7)
≥40	n	18	23
	Mean change (SD)	0.5 (3.0)	0.6 (2.5)

7.1.6.2.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.1.6.2.2.1. Sponsor's Table. Definitions for Clinically Important Changes in Vital Signs

Table 11 Clinically-important vital signs vital signs and weight		
Vital sign	Criterion value	Change from baseline
Systolic blood pressure	≥180 mm Hg	Increase ≥20 mm Hg
	≤90 mm Hg	Decrease ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg	Increase ≥30 mm Hg
	≤50 mm Hg	Decrease ≥20 mm Hg
Pulse	>120 bpm	Increase ≥15 bpm
	<50 bpm	Decrease ≥15 bpm
Weight	-	Change ≥7% body weight
Orthostatic changes		
Systolic blood pressure or diastolic blood pressure	Decrease ≥20 mm Hg from supine to standing after ≥1 minute	
Pulse	Increase ≥20 bpm from supine to standing after ≥1 minute	
Combined	Decrease ≥20 mm Hg in systolic blood pressure and increase ≥20 bpm in pulse	

D144CC00002

For supine vital signs, virtually no shifts to clinically important values were noted for either treatment group. For orthostatic changes, 1.6% of subjects in the quetiapine XR group and 7.1% of subjects in the placebo group had shifts from normal to important high for orthostatic pulse. For orthostatic systolic blood pressure, 2.3% of subjects in the quetiapine XR group and 3.0% of subjects in the placebo group had shifts from normal to important low. No shift changes were noted for orthostatic diastolic blood pressure.

D144CC00004:

For supine pulse, 16.7% (20/120) of subjects with normal baseline values in the quetiapine XR group had a shift to important high compared to 3.3% (4/120) of subjects in the placebo group. The percentage of subjects with shifts from normal to "important low" values for supine systolic BP and supine diastolic BP were similar between treatment groups.

The orthostatic shift changes were similar between the treatment groups; ~8% in both groups had shift from normal baseline orthostatic pulse to "important high" and no subjects had shifts to "important low". Only one subject (0.7%) in the quetiapine XR group had a shift from normal to "important low" for orthostatic systolic blood pressure compared to 1.3% (2/155) in the placebo group.

Weight $\geq 7\%$ increase from baseline

In study D144CC00002, 8.2% (9/110) of subjects in the quetiapine XR group and 0.8% (1/125) of subjects in the placebo group had an increase in weight $\geq 7\%$ from baseline.

In study D144CC00004, 5.1% of subjects in the quetiapine XR group and no subjects in the placebo group had an increase in weight $\geq 7\%$ from baseline.

The percentage of subjects who gained $\geq 7\%$ weight varied by baseline BMI. No specific pattern was noted in study D144CC00002 since ~17% gained $\geq 7\%$ weight in the 18.5 to < 25 and 30 to < 40 kg/m² categories and no subjects gained $\geq 7\%$ weight in the 25 to < 30 kg/m² category. For both studies, no subjects in the ≥ 40 kg/m² category gained $\geq 7\%$.

Table 7.1.6.2.2.2. Percent of Subjects with Weight Gain > 7% by BMI Category at Randomization

	D144CC00002		D144CC00004	
	Quetiapine XR (N = 137)	Placebo (N = 140)	Quetiapine XR (N = 151)	Placebo (N = 160)
BMI Category				
0 - < 18.5	0 (0/1)	0 (0/1)	0 (0/0)	0 (0/2)
18.5 - < 25	16.7% (3/18)	0 (0/24)	8.8% (3/34)	0 (0/35)
25 - < 30	0 (0/36)	0 (0/37)	5.7% (2/35)	0 (0/42)
30 - < 40	16.2% (6/37)	2 (1/50)	3.9% (2/51)	0 (0/47)
≥ 40	0 (0/18)	0 (0/13)	0 (0/18)	0 (0/24)

From Sponsor Table 11.3.9.4

7.1.7 Electrocardiograms (ECGs)

7.1.7.1 Overview of ECG testing in the development program

ECGs were obtained at baseline and end of study using a unit supplied by the central ECG laboratory. ECGs for all subjects at all study sites were acquired at the site using an approved unit and were transmitted to eResearch Technology. ECGs were processed through a computer interpretation program and then reviewed first by an ECG analyst and then by a board-certified cardiologist. ECG results were reviewed by the investigator for clinical significance, in consultation with the cardiologist at the ECG laboratory if required.

7.1.7.2 Standard analyses and explorations of ECG data

7.1.7.2.1 Analyses focused on measures of central tendency

Similar to the vital signs data, increases in mean heart rate were noted in the quetiapine XR group compared to the placebo group.

Table 7.1.7.2.1.1. Mean Change from Baseline in ECG Parameters

	D144CC00002		D144CC00004	
	Quetiapine XR N = 107	Placebo N = 120	Quetiapine XR (N = 139)	Placebo (N = 149)
Heart Rate	6.7	2.1	7.9	1.4
PR interval (msec)	0.3	-2.9	-1.0	0.3
QRS (msec)	-0.6	-0.3	-0.4	-0.3
QT interval (msec)	-11.3	-6.5	-13.9	-1.7
QTcF (msec)	0.7	-2.7	0.9	1.0

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.1.7.2.2.1. Sponsor's Table. Definitions for Clinically Important Changes in ECG

Table 12 Definition of clinically-important ECG parameters

ECG parameter	Criterion value	Change from baseline
Heart rate	>120 bpm	increase \geq 15 bpm
	<50 bpm	decrease \geq 15 bpm
PR	\geq 210 msec	NA
QRS	\leq 50 msec	NA
	\geq 120 msec	NA
QT	\geq 500 msec	Increase \geq 60 msec
	\leq 200 msec	NA
QT _c (Fridenicia Correction)	\geq 450 msec	Increase \geq 60 msec

Study D144CC00002 – virtually no shift changes for any ECG variables. No subjects in either treatment group had a shift change from normal to important high in heart rate or QTcF interval.

Study D144CC00004: Shifts from normal to important high for heart rate occurred in 24.5% (34/139) of subjects in the quetiapine XR group compared to 12.1% (18/149) in the placebo group. For QTcF, 0.7% of subjects in each treatment group had shifts from normal to important high.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimens are consistent with the pivotal trials supporting efficacy for the following indications:

Bipolar depression – administer once daily in the evening starting with 50 mg per day and increasing doses to reach 300 mg per day by day 4. Proposed labeling includes a table for daily doses: day 1 = 50 mg, day 2 = 100 mg, day 3 = 200 mg and day 4 = 300 mg.

Bipolar mania – administer once daily in the evening – 300 mg on day 1, 600 mg on day 2 and thereafter between 400 – 800 mg depending on response and tolerance of the individual patient. Proposed labeling includes a table for daily doses.

8.2 Drug-Drug Interactions

No drug interaction data was included in this submission.

8.3 Special Populations

Dosing in elderly patients and patients with hepatic impairment require lower starting doses of quetiapine. In this supplement, the Sponsor is seeking to market the 50 mg quetiapine XR tablet – they had received approval in the past but never marketed this dosage strength. Currently, only the 200, 300, and 400 mg strengths are available and the 150 mg strength was recently approved (8/08). Therefore, since 200 mg was the lowest strength available for quetiapine XR, the dosing in these special populations was the following:

Elderly and Hepatic impairment populations

Patients “should be started on Seroquel immediate release formulation 25 mg/day and the dose can be increased in increments of 25 – 50 mg/day depending on the response and tolerance of the individual patient. When an effective dose has been reached, the patient may be switched to Seroquel XR at an equivalent total daily dose.”

The proposed labeling for these populations is now:

Patients “should be started on Seroquel XR 50 mg/day and the dose can be increased in increments of 50 mg/day depending on the response and tolerance of the individual patient.”

The Sponsor has been asked to provide comparison pharmacokinetic data for quetiapine IR 25 mg/day and quetiapine XR 50 mg/day. The Sponsor has also been asked if there is tolerability data for initiation of quetiapine XR 50 mg/day in these populations.

8.4 Pediatrics

In this submission, for the indications bipolar mania (monotherapy and adjunctive therapy) and bipolar depression, the Sponsor has asked for a waiver to study children < 10 years of age and a deferral for adolescents 10-17 years of age.

A Pediatric Review Committee (PeRC) meeting has been scheduled to review the pediatric deferrals, waivers and plans for clinical trials for pediatric bipolar populations with quetiapine XR. Currently, no written requests have been initiated for pediatric trials in bipolar populations for quetiapine XR.

The Sponsor has conducted pediatric clinical trials in schizophrenia and acute mania associated with Bipolar I disorder to fulfill written requests for quetiapine IR – the NDA is expected to be submitted in 2008. The results of the acute mania study may be able to be extrapolated to the quetiapine XR dosage form. The Sponsor currently does not have plans to study acute mania adjunctive therapy in the pediatric population.

The Sponsor has proposed a clinical trial with quetiapine XR to study bipolar depression in pediatric patients [5/7/2008 briefing packet to NDA 20-639]. The Sponsor has not submitted a final protocol at this time.

8.5 Advisory Committee Meeting

No advisory committee meeting was held to discuss this application.

8.6 Literature Review

The Sponsor included a literature review that contained the title, authors and abstract of published articles that mentioned quetiapine XR. The Sponsor did not provide any discussion of how the articles were identified or if, upon review, any new data (primarily safety) was identified for quetiapine XR.

8.7 Postmarketing Risk Management Plan

No risk management plan was submitted or is recommended by this reviewer.

9 OVERALL ASSESSMENT

9.1 Recommendation on Regulatory Action

The Sponsor has submitted supplemental NDAs SE1-006, SE1-007, and SE1-008 for quetiapine XR to the support indications:

- Depressive episodes associated with Bipolar I and II disorder with or without a rapid cycling course;
- Acute manic or mixed episodes associated with Bipolar I disorder as monotherapy;
- Acute manic or mixed episodes associated with Bipolar I disorder as adjunct to lithium or divalproex therapy

I recommend that the Division take an approval action for all of these indications.

The Sponsor submitted one pivotal trial for bipolar disorder, depressive episode and one pivotal trial for bipolar disorder, acute monotherapy. These pivotal trials support the efficacy of quetiapine XR for these indications. Since quetiapine IR is indicated in these populations, one clinical trial for each indication was sufficient for the quetiapine XR development program.

The Sponsor did not provide any clinical data to support the acute adjunctive therapy indication. However, based on extrapolation of this indication for quetiapine IR and with data to support the effectiveness of quetiapine XR in acute mania as monotherapy, it is recommended that the adjunctive indication be granted for quetiapine XR.

At the time this review was completed, several requests for information from the Sponsor were still pending. It is unlikely that responses to these requests will alter the recommendation of this reviewer (see Section 9.5 – Comments to Applicant). The Sponsor's responses to these requests will be reviewed in an addendum to this clinical review.

9.2 Recommendation on Postmarketing Actions

9.2.1 Risk Management Activity

None are recommended by this reviewer.

9.2.2 Required Phase 4 Commitments

Quetiapine IR is currently approved for the maintenance treatment of Bipolar I disorder as adjunct therapy to lithium or divalproex; no maintenance indication has been granted for quetiapine IR for monotherapy. It is recommended that the Sponsor conduct a long-term

(maintenance) trial of quetiapine XR in the treatment of Bipolar I disorder. Whether this will be considered a required Phase 4 commitment is at the discretion of the Division.

9.2.3 Other Phase 4 Requests

None are currently recommended by this reviewer. Pediatric waivers, deferrals and plans were under review at the time this review was completed. The Sponsor has plans to conduct at least one clinical trial in pediatric bipolar depression with quetiapine XR. The Sponsor has completed one clinical trial of quetiapine IR in acute mania associated with bipolar disorder in this population. See section 8.4 (Pediatrics) of this review.

9.3 Labeling Review

Comments regarding labeling changes are being made to the Sponsor's proposed labeling via track changes and forwarded as a separate document to the Team Leader for further editing. Significant modifications, per recommendations from the Division, were made to the Sponsor's labeling when it was first submitted in July 2006 (first approval of quetiapine XR in May 2007). The most significant additions with this submission are data related to the new indications (indications/usage; dosing/administration; adverse events etc.).

The Sponsor has also made changes to Section 12 (Clinical Pharmacology) that is being reviewed by pharmacology/toxicology.

Additionally, with the introduction of the 50 mg extended-release tablet (was approved with original NDA, but Sponsor did not market), the dosing recommendations for elderly patients and patients with hepatic impairment have also been modified (see Section 8.3 – Special Populations).

The Maternal Health Team also reviewed proposed labeling as part of a pilot project. They have suggested changes to the Pregnancy and Nursing Mothers subsections – the suggested changes include addition of animal and clinical data. Pharmacology/toxicology is reviewing the suggested changes which incorporate animal data.

9.4 Comments to Applicant

The following requests for information were sent to the Sponsor during the review process. Responses to these requests were still pending at the time this review was completed. A review of the responses will be performed as an addendum to this review.

1. Please provide an update for the subject in the quetiapine XR group in protocol D144CC00004 who experienced the SAE "vestibular neuronitis".
2. In protocols D144CC00002 and D144CC00004, approximately 2-3% of subjects in both the quetiapine XR and placebo groups were discontinued from the studies for "severe non-compliance to protocol". Please specify which subjects were discontinued and what these protocol violations were.
Additionally, in both studies approximately 7-8% of subjects were discontinued in the category "voluntary discontinuation by subject". Is any additional data available (e.g. comments in CRFs) for these subjects regarding this discontinuation category (e.g. comments suggestive of adverse events, lack of efficacy, etc.)?
3. The current Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format (January 2006) document states that similar events such as somnolence and sedation should be one category rather than separated into two categories. For all tables in currently proposed labeling (including schizophrenia data), please indicate the frequency of somnolence/sedation.
4. For study D144CC00002, Table 11.3.7.3.3 lists mean change from baseline for chemistry variables but does not include fasting glucose. Since Table 11.3.7.3.4.1 lists change shifts for chemistry variables and includes fasting glucose, the mean change from baseline data should also be available for fasting glucose. Please submit these data.
5. In section 8.2 (Extent of Exposure) of the clinical study report for D144CC00004, it states that patient E4013003 intentionally took 4000 mg of quetiapine XR. There is a hyperlink for a patient narrative for this case. However, upon review of this narrative, there is no discussion of the clinical symptoms experienced after this overdose. Please provide this information.
6. Under section 8.5 (Use in specific populations: Geriatric use) of your proposed labeling, there is a brief mention of some pharmacokinetic data for the clearance of quetiapine and refers the reader to section 12.3 (pharmacokinetics). However, there is no data for geriatrics/elderly patients in the pharmacokinetics section. Please add these data to this section and any additional pharmacokinetic data relevant to this population for quetiapine or quetiapine XR.
7. The dosing for elderly patients and patients with hepatic impairment is to initiate with quetiapine 50 mg/day and increase the dose by 50 mg/day depending on response and tolerance of the patient. Since a 50 mg quetiapine XR tablet is not currently available, currently approved labeling indicates that quetiapine IR 25 mg should be initiated in these populations with dose

increases of 25-50 mg/day and, when an effective dose has been reached, the patient can be switched to quetiapine XR.

Please provide a comparison of pharmacokinetic data for the quetiapine IR 25 mg tablet and the quetiapine XR 50 mg tablet. Is there any tolerability data that you can provide regarding these populations and initiation of quetiapine XR 50 mg/day?

8. We received your response to our suggestion to combine the terms sedation and somnolence as one adverse event term in product labeling. While you correctly indicate that the lower level terms are different for each of these preferred terms, there is substantial overlap between these terms. Additionally, it is unlikely that a clinician can reliably distinguish between sedation and somnolence, and that splitting these terms actually serves to "dilute" a potentially significant adverse event. You did provide some recalculations combining these terms, however, you may need to recalculate the data. It appears that you may have just added the % of patients experiencing these adverse events together - this would potentially overestimate the incidence in the combined term. If some subjects experienced both sedation and somnolence they would currently be counted in both categories but should only be counted once in a combined term. Please recalculate these numbers for the combined term "somnolence" - this would be consistent with what we have asked other Sponsors to do. You may indicate that this term combines both somnolence and sedation terms as a footnote to the adverse event tables.

9. In section 2.1 of labeling (Dosage and Administration: Bipolar depression- usual dose) you have included data for patients receiving ^{(b) (4)} mg of quetiapine XR. However, study D144CC00002 was a 300 mg fixed dose design. Please clarify and delete if this was included in error.

10 APPENDICES

10.1 Investigators and Sites

Site No. *	Principal Investigator	City	Protocol D144CC00002 Bipolar Depression		Protocol D144CC00004 Acute Mania (monotherapy)	
			# Pts Enrolled	# Pts Randomized	# Pts Enrolled	# Pts Randomized
2001	Charles Bailey	Orlando, FL	12	8	-	-
2002 4002	Roberta Ball	Philadelphia, PA	6	4	6	5
2003 4003	Jason D. Baron	Houston, TX	6	5	9	5
2005 4005	J Gary Booker	Shreveport, LA	11	7	9	9
4006	Jeffrey Borenstein	Holliswood, NY	-	-	4	3
4007	Guy Brannon	Shreveport, LA	-	-	2	1
2008	Neil S. Dubin	Cincinnati, OH	1	0	-	-
2009	Edward P. Burdick	North Miami, FL	5	2	-	-
4009	Alexander Pushka	North Miami, FL	-	-	16	10
2010 4010	Vicki E. Burdine	Greenwood, IN	2	2	4	2
2011	John S. Carman	Smyrna, GA	2	2	-	-
2012	Surendra Chaganti	St. Louis, MO	0	0	-	-
4013	Eduardo Cifuentes	Charleston, SC	-	-	7	5
2014 4014	Andrew J. Cutler	Bradenton, FL	7	4	4	1
2015	Kirk Denicoff	Rockville, MD	6	4	-	-
2016	Mark DiBuono	Staten Island, NY	16	10	-	-
2017	Dolores M. DiGaetano	Memphis, TN	14	10	-	-
2018 4018	Bradley C. Diner	Little Rock, AR	6	5	1	1
2019	Michael Downing	Dallas, TX	3	3	-	-
2020	Beal G. Essink	Portland, OR	1	0	-	-
4022	Donald Garcia	Austin, TX	-	-	18	13
2023	Thomas Gazda	Scottsdale, AZ	1	0	-	-
4024	John H. Gilliam	Richmond, VA	-	-	2	2
2025	Lawrence D. Ginsberg	Houston, TX	9	8	-	-
4026	Steven J. Glass	Willingboro, NJ	-	-	23	15
4028	Ramanath Gopalan	Arlington, VA	-	-	1	1
2029	Daniel E. Grosz	Encino, CA	3	2	-	-

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2030 4030	Barbara Harris	Phoenix, AZ	7	2	1	1
2032 4032	Willis Holloway Jr.	Oklahoma City, OK	9	4	5	1
2033 4034	Alexander E. Horwitz	Salem, OR	0	0	-	-
2035 4037	Naveed Iqbal	Elmsford, NY	-	-	7	5
2038 4038	John Mark Joyce	Jacksonville, FL	28	23	-	-
2039 4039	Justine M. Kent	Passaic, NJ	-	-	6	4
2040 4040	Arifulla Khan	Bellevue, WA	8	6	3	2
2041 4041	Richard D. Knapp	Leesburg, FL	0	0	11	7
2042 4042	Mary Ann Knesevich	Irving, TX	-	-	6	4
2043 4043	James Knutson	Kirkland, WA	7	5	-	-
2044 4044	David G. Krefetz	Clemont, NJ	10	8	-	-
2045 4045	Jelena Kunovac	Oceanside, CA	6	6	1	0
2046 4046	Mark Lerman	Hoffman Estates, IL	-	-	3	2
2047 4047	H. Edward Logue	Birmingham, AL	5	5	-	-
2048 4048	Adam F. Lowy	Washington DC	3	3	10	6
2049 4049	Cosme O. Lozano	Joliet, IL	7	5	-	-
2050 4050	R. Bruce Lydiard	Charleston, SC	1	1	-	-
2051 4051	Raymond A. Manning	Pico Rivera, CA	7	5	6	6
2052 4052	Morteza Marandi	Cerritos, CA	6	5	28	23
2053 4053	Denis Mee Lee	Honolulu, HI	2	1	3	3
2054 4054	Vikram Mehra	Houston, TX	20	13	33	12
2055 4055	Charles H. Merideth	San Diego, CA	10	9	7	5
2056 4056	Janice L. Miller	West Palm, FL	5	2	-	-
2057 4057	Eliot Moon	Wildomar, CA	7	4	-	-
2058 4058	Mark A. Novitsky	Philadelphia, PA	7	5	30	18
2059 4059	Nader Oskooilar	Newport Beach, CA	2	1	-	-
2060 4060	Michael Plopper	San Diego, VA	-	-	5	3
2061 4061	Jorge Porras	San Diego, CA	5	2	-	-
2062 4062	Neil L. Pugach	Virginia Beach, VA	3	2	-	-
2063 4063	Sohail Punjwani	North Miami, FL	5	3	16	14

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2063 4063	Rakesh Ranjan	Beachwood, OH	1	1	1	1
4064	Robert A. Riesenberg	Atlanta, GA	-	-	25	24
2065	Alfredo N. Rivera	Cincinnati, OH	22	4	-	-
4066	Joseph H. Rodd	Carson, CA	-	-	19	13
2067	Alan Rosenbaum	Farmington Hills, MI	1	0	-	-
2068	Leon I. Rosenberg	Cherry Hill, NJ	7	4	-	-
4070	Scott D. Segal	North Miami, FL	-	-	15	10
4072	Anantha Shekhar	Indianapolis, IN	-	-	3	1
2073	John Shemo	Charlottesville, VA	5	3	-	-
4074	Rajinder Shiwach	DeSoto, TX	-	-	15	12
2075 4075	Franco Sicuro	Bridgeton, MO	12	11	12	10
2076	Ward T. Smith	Portland, OR	3	3	-	-
2077 4077	Dwight St. Clair	Wichita, KS	5	3	0	0
2078	Mary L. Stedman	Tampa, FL	10	4	-	-
2079	Jerry C. Steiert	Seattle, WA	4	1	-	-
2080	Trisha Suppes	Dallas, TX	2	0	-	-
4081	Marshall Thomas	Denver, CO	-	-	1	0
2082 4082	Louise Beckett	Oklahoma City, OK	9	5	0	0
2083 4083	Tram K. Tran-Johnson	San Diego, CA	3	3	11	7
2084	Tanya Vapnik	Los Angeles, CA	5	3	-	-
2085	Nick G. Vatakis	New York, NY	9	5	-	-
2086 4086	Roger B. Vogelfanger	Memphis, TN	1	1	2	2
4087	David P. Walling	Garden Grove, CA	-	-	33	25
4088	Kashinath G. Yadalam	Lake Charles, LA	-	-	17	12
2089	Inna Yuryev Golger	Brooklyn, NY	5	5	-	-
2090	Jeffrey A. Danziger	Maitland, FL	10	7	-	-
2091 4091	Deborah Bergen	Newton, KS	0	0	2	0
2092	Bernadette B. D'Souza	Dayton, OH	20	18	-	-
4094	Michael J. Biunno	New Orleans, LA	-	-	0	0
4096	Robert E. Litman	Rockville, MD	-	-	4	2
4097	Sarah Benington	San Antonio, TX	-	-	3	0
2098 4098	Daniel Chueh	Santa Ana, CA	3	3	9	8
2099	Dennis J. Munjack	Beverly Hills, CA	0	0	-	-
Total			418	280	459	316

*2000s = bipolar depression study; 4000s = acute mania (monotherapy) study

10.2 Inclusion and Exclusion Criteria for D144CC00002 (bipolar depression)

Inclusion

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 DSM-IV-TR criteria for bipolar I disorder or bipolar II disorder, most recent episode depressed confirmed by the amended version of the SCID.
4. HAM-D (17 item) total score ≥ 20 and HAM-D item 1 (depressed mood) score ≥ 2 at enrollment and randomization.
5. Patients must be able to understand and comply with the requirements of the study, as judged by the investigator.
6. Outpatient status at enrollment.

Exclusion

1. Other than bipolar disorder under study, patients must not have another current, major DSM-IV Axis I disorder that is symptomatic or has required treatment within 6 months of enrollment.
2. Patients are excluded whose YMRS total > 12 at enrollment or randomization.
3. Patients with > 8 mood episodes during the past 12 months.
4. Patients whose current episode of depression exceeds 12 months or is less than 4 weeks from enrollment.
5. Patients with a history of nonresponse to an adequate treatment (6 weeks) with more than 2 classes of antidepressants during their current episode.
6. Alcohol or other substance dependence or abuse as defined by DSM-IV-TR criteria at enrollment that is not in sustained full or sustained partial remission (12 months or longer), except caffeine and nicotine dependence. Patients with a positive urine toxicology screen are not excluded unless they satisfy the DSM-IV-TR criteria for abuse or dependence, except that patients are excluded with a single urine toxicology screen positive for cocaine, heroin, or PCP.
7. Patients are excluded if they use or need to use, within the 2 weeks before randomization, drugs that strongly induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes.
8. Use of the following medication:
 - a. Antipsychotic, mood stabilizer, antidepressant, anxiolytic, hypnotic or other psychoactive drugs within 7 days before randomization
 - b. Fluoxetine within 28 days before randomization
 - c. Extended release risperidone within 14 days before randomization
 - d. A depot antipsychotic injection within one dosing interval (for the depot) before randomization
 - e. Lithium within 7 days before randomization and/or tapering off started less than 14 days before randomization
 - f. Irreversible MAOI within 14 days before randomization
9. Treatment with quetiapine IR at a dosage of at least 50 mg daily within 14 days before enrollment for any condition. Use of quetiapine IR in doses of at least 25 mg or more daily for insomnia within 7 days before randomization.
10. Receipt of ECT within 90 days before randomization.
11. Patients who in the investigator's opinion will require formalized psychotherapy during the study period, unless psychotherapy has been ongoing for a minimum of 3 months prior to randomization.
12. Patients who, in the investigator's judgment, pose a current serious suicidal or homicidal risk, have a HAM-D item 3 score of 3 or greater, or have made a suicide attempt within the past 6 months.
13. Pregnancy or if nursing, lactation. Female patients of childbearing potential must have a negative serum pregnancy test at enrollment and be willing to use a reliable method of birth control during the study. Acceptable methods of birth control include: double-barrier method, oral contraceptive, implant, dermal contraception, long-term injectable contraceptive, intrauterine device, or tubal ligation.
14. A patient with diabetes mellitus fulfilling one of the following criteria:
 - a. Unstable DM defined at enrollment as HbA1c $> 8.5\%$
 - b. Admitted to hospital for treatment of DM or DM related illness in past 12 weeks
 - c. Not under care of physician responsible for patient's DM care
 - d. Physician responsible for patient's DM care has not indicated that patient's DM is controlled

- e. Physician responsible for patient's DM care has not approved patient's participation in the study
 - f. Has not been on the same dose of oral hypoglycemic drug(s) and/or diet for the four weeks prior to randomization. For thiazolidinediones (glitazones) this period should be not less than 8 weeks
 - g. Taking insulin whose daily dose on one occasion in the past 4 weeks has been more than 10% above or below their mean dose in the preceding 4 weeks
15. Clinically significant deviation from the reference range in clinical laboratory test results at enrollment, judged by the investigator.
 16. Patients are excluded if they have conditions that could affect absorption or metabolism of study medication as judged by the investigator.
 17. Current or past diagnosis of stroke or medically-documented transient ischemic attacks.
 18. History of seizure disorder, except febrile convulsions.
 19. Evidence of a clinical disorder or clinical finding problematic to the study, as judged by the investigator, such as renal or hepatic impairment, significant coronary artery disease, cerebrovascular disease, active viral hepatitis B or chronic active hepatitis C, or AIDS.
 20. An ANC of $< 1.5 \times 10^9/L$
 21. A thyroid-stimulating hormone concentration more than 10% above the upper limit of the normal range of the laboratory used for sample analysis whether or not the patient is being treated for hypothyroidism.
 22. After the assessment by a centrally-located, experienced cardiologist interpreting the ECG obtained using centralized telephonically transmitted ECG methods, a patient will be excluded if this ECG result is considered to be clinically significant as determined by the investigator. In some rare clinical situations, the central reading cardiologist's interpretation will be exclusionary without the local investigator's interpretation, for example, recent massive myocardial infarction.
 23. An ECG QTC ≥ 500 msec
 24. Patients with a history of noncompliance as judged by the investigator.
 25. Patients are excluded if they have a history of episodic, idiopathic orthostatic hypotension, with or without near-syncope or syncope episodes, or conditions that would predispose them to episodic hypotension, such as dehydration or hypovolemia.
 26. Known history of intolerance or hypersensitivity to quetiapine or to any other component in the tablets.
 27. Known lack of response to quetiapine as judged by the investigator.
 28. Contraindications as detailed in country-specific prescribing information for quetiapine.
 29. Participation (receiving investigational product) in another clinical study or compassionate use program within 30 days of enrollment or as required by local regulations.
 30. Involvement in the planning and conduct of the study.
 31. Previous enrollment or randomization of treatment in the present study or 5077US/0049, D1447C00134 or D1447C00135.

10.3 Inclusion and Exclusion Criteria for D144CC00004 (acute bipolar mania)

Inclusion 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 DSM-IV TR criteria for bipolar I disorder, most recent episode manic or mixed confirmed by the amended version of the SCID for DSM-IV.
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.

7. Patients must have been able to understand and comply with the requirements of the study, as judged by the investigator.
8. Outpatients or inpatients at enrollment (visit 1), but all patients must have been inpatient upon randomization (visit 2) and remain inpatients until all procedures for visit 3 (day 4) had been completed.

Exclusion Criteria

1. Other than bipolar disorder under study, patients must not have had another current, major DSM-IV-TR Axis I disorder that was symptomatic or required treatment within 6 months of enrollment.
2. Patients with > 8 mood episodes during the past 12 months.
3. Patients were excluded if a mania-like syndrome was a physiological consequence of a medical condition, a medication, a treatment, substance abuse, or withdrawal.
4. Patients were excluded if continuously hospitalized for acute bipolar mania for > 3 weeks immediately before randomization (visit 2).
5. Alcohol or substance dependence or abuse as defined by DSM-IV-TR criteria at enrollment (visit 1) that was not in sustained full or sustained partial remission (12 months or longer), except caffeine and nicotine dependence. Patients with a positive urine toxicology screen result were not excluded unless they satisfy the DSM-IV-TR criteria for abuse or dependence, except that patients were excluded with a single urine toxicology screen result positive for cocaine, heroin, or PCP.
6. Patients were excluded if they used or needed to use, within the 2 weeks before randomization, drugs that strongly induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes.
7. Evidence of a clinical disorder or clinical finding problematic to the study, as judged by the investigator, such as renal (SCr \geq 1.5 mg/dL) or hepatic impairment (ALT/AST 3x ULN), significant coronary artery disease, cerebrovascular disease, active viral hepatitis B or chronic active hepatitis C, or acquired immunodeficiency syndrome.
8. Clinical findings that, in the opinion of the investigator, suggest unstable medical conditions, or that might be negatively affected by the investigational product or that would negatively affect the investigational product (e.g. poorly controlled hypertension, poorly controlled diabetes, unstable angina).
9. Patients were excluded if they have conditions that could affect absorption or metabolism of investigational product (e.g. malabsorption syndrome, severe liver disease) as judged by the investigator.
10. Current or past diagnosis of stroke or medically documented TIA.
11. History of seizure disorder, except febrile convulsions.
12. Use of any of the following medication:
 - a. antipsychotic, mood stabilizer, antidepressant, anxiolytic, hypnotic or other psychoactive drugs within 7 days before randomization (visit 2), unless as specified in protocol;
 - b. fluoxetine within 28 days before randomization (visit 2);
 - c. extended-release risperidone within 14 days before randomization;
 - d. a depot antipsychotic injection within one dosing interval (for the depot) before randomization;
 - e. lithium, unless specified in the protocol;
 - f. irreversible MAOIs within 14 days before randomization
13. Treatment with quetiapine IR at a dosage of \geq 50 mg QD within 14 days before enrollment (visit 1) for any condition. Use of quetiapine IR in doses of \geq 25 mg QD for insomnia within 7 days before randomization (visit 2).
14. Receipt of ECT within 90 days before randomization.
15. Patients who, in the investigator's opinion, would require formalized psychotherapy during the study period, unless psychotherapy has been ongoing for a minimum of 3 months prior to randomization (visit 2).
16. Patients, who, in the investigator's judgment, posed a current serious suicidal or homicidal risk or had made a suicide attempt within the past 6 months.
17. Pregnancy or, if nursing, lactation. Female patients of childbearing potential must have had a negative serum pregnancy test result at enrollment (visit 1) and be willing to use a reliable method of birth control during the study. Acceptable methods of birth control include: double-barrier method, oral contraceptive, implant, dermal contraception, long-term injectable contraceptive, IUD or tubal ligation.
18. A patient with diabetes mellitus fulfilling one of the following criteria:
 - a. unstable diabetes mellitus defined at enrollment (visit 1) as HbA1c > 8.5%
 - b. admitted to hospital for treatment of diabetes mellitus or related illness in past 12 weeks

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- c. not under care of physician responsible for patient's diabetes mellitus care
- d. physician responsible for patient's diabetes mellitus care has not indicated that patient's diabetes mellitus was controlled
- e. physician responsible for patient's diabetes mellitus care has not approved patient's participation in the study
- f. has not been on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones), this period should not be less than 8 weeks.
- g. taking insulin whose QD dose on one occasion in the past 4 weeks has been more than 10% above or below their mean dose in the preceding 4 weeks

(Note: if a diabetic patient met one of these criteria, the patient was to be excluded even if the treating physician believed that the patient was stable and could participate in the study)

- 19. Clinically significant deviation from the reference range in clinical laboratory test results at enrollment as judged by the investigator
- 20. An ANC $< 1.5 \times 10^9/L$
- 21. A TSH concentration $> 10\%$ above the upper limit of the normal range of the laboratory used for sample analysis whether or not the patient was being treated for hypothyroidism
- 22. After the assessment by a centrally located, experienced cardiologist interpreting the ECG obtained using centralized telephonically transmitted ECG methods, a patient was excluded if this ECG result was considered to be clinically significant as determined by the investigator. In some rare clinical situations, the central reading cardiologist's interpretation was exclusionary without the local investigator's interpretation, for example, recent massive MI.
- 23. An ECG QTc ≥ 500 msec.
- 24. Known history of intolerance or hypersensitivity to quetiapine or to any other component in the tablets.
- 25. Patients with a history of non-compliance as judged by the investigator
- 26. Patients were excluded if they had a history of episodic, idiopathic orthostatic hypotension, with or without near-syncopal or syncopal episodes, or conditions that would predispose them to episodic hypotension, such as dehydration or hypovolemia
- 27. Known lack of response to quetiapine as judged by the investigator
- 28. Contraindications as detailed in country-specific prescribing information for quetiapine
- 29. Participation (receiving investigational product) in another clinical study or compassionate use program within 30 days of enrollment (visit 1) or as required by local regulations.
- 30. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the investigational site)
- 31. Previous enrollment or randomization of treatment in the present study.

10.4 Hematology and Chemistry Shift Changes

Sponsor Table. Hematology and Chemistry Shift Changes: D144CC00002

Table 45 Hematology clinically-important change shift table comparing baseline to last observation (safety analysis set)

Laboratory safety variable	Group	Last observation n (%)			
		Baseline	Important low	Normal	Important high
Hematocrit	QTP	Low (n=2)	2 (100)	0	0
		Normal (n=111)	2 (1.8)	108 (97.3)	1 (0.9)
	PLA	Low (n=2)	1 (50.0)	1 (50.0)	0
		Normal (n=129)	2 (1.6)	127 (98.4)	0
Hemoglobin	QTP	Low (n=2)	2 (100)	0	0
		Normal (n=111)	1 (0.9)	109 (98.2)	1 (0.9)
	PLA	Low (n=1)	1 (100)	0	0
		Normal (n=130)	0	129 (99.2)	1 (0.8)
Platelets	QTP	Low (n=1)	1 (100)	0	0
		Normal (n=111)	0	111 (100)	0
	PLA	Normal (n=130)	0	130 (100)	0
		Red blood cell count	QTP	Normal (n=112)	1 (0.9)
High (n=1)	0			1 (100)	0
PLA	Normal (n=131)		0	130 (99.2)	1 (0.8)
	QTP		Normal (n=113)	0	113 (100)
Basophils, absolute		PLA	Normal (n=131)	0	131 (100)
	QTP		Normal (n=113)	0	113 (100)
Basophils, relative		QTP	Normal (n=113)	0	113 (100)

Laboratory safety variable	Group	Last observation n (%)			
		Baseline	Important low	Normal	Important high
Eosinophils, absolute	PLA	Normal (n=131)	0	131 (100)	0
	QTP	Normal (n=113)	0	113 (100)	0
Eosinophils, relative	PLA	Normal (n=131)	0	131 (100)	0
	QTP	Normal (n=113)	0	113 (100)	0
Leucocyte count	PLA	Normal (n=131)	0	131 (100)	0
	QTP	Normal (n=113)	0	113 (100)	0
Lymphocytes, absolute	PLA	Normal (n=131)	0	130 (99.2)	1 (0.8)
	QTP	Low (n=1)	0	1 (100)	0
Lymphocytes, relative	PLA	Normal (n=112)	0	112 (100)	0
	QTP	Normal (n=113)	0	113 (100)	0
Monocytes, absolute	PLA	Normal (n=131)	0	131 (100)	0
	QTP	Normal (n=112)	0	112 (100)	0
	PLA	High (n=1)	0	1 (100)	0
	QTP	Normal (n=131)	0	131 (100)	0

Laboratory safety variable	Group	Last observation n (%)			
		Baseline	Important low	Normal	Important high
Monocytes, relative	QTP	Normal (n=113)	0	113 (100)	0
	PLA	Normal (n=131)	0	131 (100)	0
Neutrophil Count (<0.5 x 10 ⁹ /L)	QTP	Normal (n=111)	0	111 (100)	0
	PLA	High (n=2)	0	2 (100)	0
Neutrophil Count (<1.5 x 10 ⁹ /L)	QTP	Normal (n=131)	0	129 (98.5)	2 (1.5)
	PLA	Normal (n=111)	2 (1.8)	109 (98.2)	0
Neutrophils, segmented	QTP	High (n=2)	0	2 (100)	0
	PLA	Normal (n=131)	2 (1.5)	127 (96.9)	2 (1.5)
	QTP	Normal (n=113)	0	113 (100)	0
	PLA	Normal (n=131)	0	131 (100)	0

Table 48 Laboratory chemistry clinically-important shift change table comparing baseline to last observation (safety analysis set)

Laboratory safety variable	Group	At last observation (%)			
		Baseline	Important low	Normal	Important high
Glucose, fasting ^a	Quetiapine XR	Normal (n=86)	0	81 (94.2)	5 (5.8)
		Important high (n=3)	0	2 (66.7)	1 (33.3)
	Placebo	Normal (n=95)	0	93 (97.9)	2 (2.1)
		High (n=5)	0	1 (20.0)	4 (80.0)
Glucose ^b	Quetiapine XR	Normal (n=100)	0	94 (94.0)	6 (6.0)
		Important high (n=3)	0	2 (66.7)	1 (33.3)
	Placebo	Normal (n=113)	0	109 (96.5)	4 (3.5)
		Important high (n=5)	0	1 (20.0)	4 (80.0)
HbA _{1c}	Quetiapine XR	Normal (n=103)	0	103 (100)	0
		Important high (n=1)	0	0	1 (100)
	Placebo	Normal (n=120)	0	120 (100)	0
		Important high (n=1)	0	0	1 (100)
Bicarbonate	Quetiapine XR	Important low (n=3)	0	3 (100)	0
		Normal (n=81)	3 (3.7)	77 (95.1)	1 (1.2)
		Important high (n=1)	0	1 (100)	0
	Placebo	Important low (n=3)	1 (33.3)	2 (66.7)	0
		Normal (n=98)	4 (4.1)	94 (95.9)	0
Calcium	Quetiapine XR	Normal (n=104)	0	104 (100)	0
	Placebo	Normal (n=120)	0	120 (100)	0
Chloride	Quetiapine XR	Normal (n=104)	0	104 (100)	0
	Placebo	Normal (n=120)	0	120 (100)	0
Potassium	Quetiapine XR	Normal (n=105)	0	105 (100)	0
	Placebo	Normal (n=121)	0	117 (96.7)	4 (3.3)
		Important high (n=1)	0	1 (100)	0
Sodium	Quetiapine XR	Important low (n=1)	0	1 (100)	0

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Laboratory safety variable	Group	At last observation (%)			
		Baseline	Important low	Normal	Important high
HDL-C		Normal (n=104)	0	104 (100)	0
	Placebo	Normal (n=122)	1 (0.8)	121 (99.2)	0
	Quetiapine XR	Important low (n=25)	18 (72.0)	7 (28.0)	0
LDL-C, Friedwald ^c		Normal (n=78)	7 (9.0)	71 (91.0)	0
	Placebo	Important low (n=38)	25 (65.8)	13 (34.2)	0
		Normal (n=83)	6 (7.2)	77 (92.8)	0
	Quetiapine XR	Normal (n=86)	0	83 (96.5)	3 (3.5)
		Important high (n=11)	0	5 (45.5)	6 (54.5)
Total cholesterol	Placebo	Normal (n=104)	0	102 (98.1)	2 (1.9)
		Important high (n=10)	0	4 (40.0)	6 (60.0)
	Quetiapine XR	Normal (n=85)	0	79 (92.9)	6 (7.1)
		Important high (n=18)	0	9 (50.0)	9 (50.0)
	Placebo	Normal (n=106)	0	103 (97.2)	3 (2.8)
Triglycerides		Important high (n=15)	0	7 (46.7)	8 (53.3)
	Quetiapine XR	Normal (n=84)	0	77 (91.7)	7 (8.3)
		Important high (n=19)	0	6 (31.6)	13 (68.4)
	Placebo	Normal (n=93)	0	86 (92.5)	7 (7.5)
		Important high (n=28)	0	16 (57.1)	12 (42.9)
ALT	Quetiapine XR	Normal (n=105)	0	105 (100)	0
	Placebo	Normal (n=122)	0	120 (98.4)	2 (1.6)
ALP	Quetiapine XR	Normal (n=105)	0	105 (100)	0
	Placebo	Normal (n=122)	0	122 (100)	0
AST	Quetiapine XR	Normal (n=105)	0	105 (100)	0
	Placebo	Normal (n=122)	0	121 (99.2)	1 (0.8)
Bilirubin (total)	Quetiapine XR	Normal (n=103)	0	103 (100)	0

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Laboratory safety variable	Group	At last observation (%)			
		Baseline	Important low	Normal	Important high
Albumin	Placebo	Normal (n=122)	0	122 (100)	0
	Quetiapine XR	Normal (n=104)	0	104 (100)	0
BUN	Placebo	Normal (n=120)	0	120 (100)	0
	Quetiapine XR	Normal (n=104)	0	104 (100)	0
Creatinine	Placebo	Normal (n=120)	0	120 (100)	0
	Quetiapine XR	Normal (n=105)	0	104 (99.0)	1 (1.0)
Free thyroxine	Placebo	Normal (n=122)	0	122 (100)	0
	Quetiapine XR	Normal (n=106)	0	106 (100)	0
TSH	Placebo	Normal (n=122)	0	122 (100)	0
	Quetiapine XR	Normal (n=106)	0	104 (98.1)	2 (1.9)
	Placebo	Normal (n=118)	0	116 (98.3)	2 (1.7)
		High (n=4)	0	3 (75.0)	1 (25.0)
Triiodothyronine, free	Quetiapine XR	Normal (n=105)	0	105 (100)	0
	Placebo	Normal (n=122)	0	122 (100)	0

Sponsor Table. Hematology and Chemistry Shift Changes: D144CC00004

Table 48 Hematology clinically-important change shift table comparing baseline to last observation on treatment (safety population)

Laboratory safety variable	Group	Baseline		Number (%) of patients at Week 3		
				Important low	Normal	Important high
Hematocrit	Quetiapine XR	Low	(n=7)	4 (57.1)	3 (42.9)	0
		Normal	(n=125)	7 (5.6)	118 (94.4)	0
	Placebo	Low	(n=7)	4 (57.1)	3 (42.9)	0
		Normal	(n=140)	1 (0.7)	139 (99.3)	0
Hemoglobin	Quetiapine XR	Low	(n=3)	2 (66.7)	1 (33.3)	0
		Normal	(n=129)	1 (0.8)	128 (99.2)	0
	Placebo	Low	(n=3)	2 (66.7)	1 (33.3)	0
		Normal	(n=146)	0	146 (100.0)	0
Platelets	Quetiapine XR	Normal	(n=128)	0	128 (100.0)	0
	Placebo	Normal	(n=146)	1 (0.7)	145 (99.3)	0
Red blood cell count	Quetiapine XR	Low	(n=1)	1 (100.0)	0	0
		Normal	(n=131)	0	131 (100.0)	0
	Placebo	Normal	(n=148)	0	147 (99.3)	1 (0.7)
		High	(n=1)	0	1 (100.0)	0
Basophils, absolute	Quetiapine XR	Normal	(n=132)	NA	132 (100.0)	0
	Placebo	Normal	(n=148)	NA	148 (100.0)	0
Basophils, relative	Quetiapine XR	Normal	(n=132)	NA	132 (100.0)	0
	Placebo	Normal	(n=148)	NA	148 (100.0)	0
Eosinophils, absolute	Quetiapine XR	Normal	(n=132)	NA	132 (100.0)	0
	Placebo	Normal	(n=148)	NA	148 (100.0)	0

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 Cara Alfaro, Pharm.D.
 NDA 022047 SE1 0006/0007/0008
 Seroquel XR (quetiapine fumarate) extended release tablets

Laboratory safety variable	Group	Baseline		Number (%) of patients at Week 3		
				Important low	Normal	Important high
Eosinophils, relative	Quetiapine XR	Normal	(n=132)	NA	132 (100.0)	0
	Placebo	Normal	(n=148)	NA	148 (100.0)	0
Leukocyte count	Quetiapine XR	Normal	(n=131)	0	131 (100.0)	0
		High	(n=1)	0	1 (100.0)	0
Lymphocytes, absolute	Placebo	Normal	(n=149)	0	148 (99.3)	1 (0.7)
		Normal	(n=132)	0	132 (100.0)	0
Lymphocytes, relative	Placebo	Normal	(n=148)	0	148 (100.0)	0
		Normal	(n=132)	0	132 (100.0)	0
Monocytes, absolute	Quetiapine XR	Normal	(n=131)	NA	131 (100.0)	0
		High	(n=1)	NA	1 (100.0)	0
Monocytes, relative	Placebo	Normal	(n=148)	NA	148 (100.0)	0
		Normal	(n=132)	NA	132 (100.0)	0
Neutrophil count (Agran) (<math><0.5 \times 10^3/L</math>)	Quetiapine XR	Normal	(n=131)	0	130 (99.2)	1 (0.8)
		High	(n=1)	0	1 (100.0)	0
Neutrophil count (<math><1.5 \times 10^3/L</math>)	Placebo	Normal	(n=148)	0	147 (99.3)	1 (0.7)
		Normal	(n=131)	2 (1.5)	128 (97.7)	1 (0.8)
	Quetiapine XR	Normal	(n=131)	2 (1.5)	128 (97.7)	1 (0.8)
		High	(n=1)	0	1 (100.0)	0

Laboratory safety variable	Group	Baseline		Number (%) of patients at Week 3		
				Important low	Normal	Important high
	Placebo	Low	(n=1)	0	1 (100.0)	0
		Normal	(n=147)	1 (0.7)	145 (98.6)	1 (0.7)
Neutrophils, segmented	Quetiapine XR	Normal	(n=132)	0	132 (100.0)	0
		Normal	(n=148)	0	148 (100.0)	0

Table 51 Chemistry clinically-important change shift table comparing baseline to last observation (safety population)

Laboratory safety variable	Group	Baseline		Number (%) of patients at Week 3		
				Important low	Normal	Important high
Fasting plasma glucose ^a	Quetiapine XR	Normal	(n=116)	0	108 (93.1)	8 (6.9)
		High	(n=3)	0	1 (33.3)	2 (66.7)
	Placebo	Normal	(n=126)	0	123 (97.6)	3 (2.4)
		High	(n=1)	0	0	1 (100.0)
Glucose ^b	Quetiapine XR	Normal	(n=131)	0	120 (91.6)	11 (8.4)
		High	(n=3)	0	1 (33.3)	2 (66.7)
	Placebo	Normal	(n=145)	0	140 (96.6)	5 (3.4)
		High	(n=1)	0	0	1 (100.0)
	HbA _{1c}	Quetiapine XR	Normal	(n=138)	0	135 (97.8)
Placebo		Normal	(n=149)	0	148 (99.3)	1 (0.7)
		High	(n=1)	0	0	1 (100.0)
Bicarbonate	Quetiapine XR	Low	(n=4)	0	4 (100.0)	0
		Normal	(n=130)	10 (7.7)	118 (90.8)	2 (1.5)
		High	(n=2)	0	2 (100.0)	0
	Placebo	Low	(n=3)	0	3 (100.0)	0
		Normal	(n=140)	3 (2.1)	134 (95.7)	3 (2.1)
		High	(n=7)	0	6 (85.7)	1 (14.3)
Calcium	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Normal	(n=150)	0	150 (100.0)	0

Table 51 Chemistry clinically-important change shift table comparing baseline to last observation (safety population)

Laboratory safety variable	Group	Baseline		Number (%) of patients at Week 3		
				Important low	Normal	Important high
Chloride	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Normal	(n=150)	0	150 (100.0)	0
Potassium	Quetiapine XR	Normal	(n=135)	0	134 (99.3)	1 (0.7)
		High	(n=2)	0	2 (100.0)	0
	Placebo	Normal	(n=147)	0	145 (98.6)	2 (1.4)
		High	(n=3)	0	3 (100.0)	0
Sodium	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Low	(n=1)	0	1 (100.0)	0
		Normal	(n=149)	0	149 (100.0)	0
HDL-C	Quetiapine XR	Low	(n=36)	24 (66.7)	12 (33.3)	0
		Normal	(n=100)	19 (19.0)	81 (81.0)	0
	Placebo	Low	(n=34)	26 (76.5)	8 (23.5)	0
		Normal	(n=115)	15 (13.0)	100 (87.0)	0
LDL-C, Friedwald	Quetiapine XR	Normal	(n=125)	0	120 (96.0)	5 (4.0)
		High	(n=5)	0	3 (60.0)	2 (40.0)
	Placebo	Normal	(n=135)	0	133 (98.5)	2 (1.5)
		High	(n=9)	0	4 (44.4)	5 (55.6)

Laboratory safety variable	Group	Baseline		Number (%) of patients at Week 3		
				Important low	Normal	Important high
Total cholesterol	Quetiapine XR	Normal	(n=128)	0	119 (93.0)	9 (7.0)
		High	(n=8)	0	5 (62.5)	3 (37.5)
	Placebo	Normal	(n=134)	0	129 (96.3)	5 (3.7)
		High	(n=15)	0	7 (46.7)	8 (53.3)
Triglycerides	Quetiapine XR	Normal	(n=102)	0	87 (85.3)	15 (14.7)
		High	(n=34)	0	13 (38.2)	21 (61.8)
	Placebo	Normal	(n=125)	0	117 (93.6)	8 (6.4)
		High	(n=24)	0	12 (50.0)	12 (50.0)
ALT	Quetiapine XR	Normal	(n=137)	0	134 (97.8)	3 (2.2)
	Placebo	Normal	(n=150)	0	147 (98.0)	3 (2.0)
Alkaline phosphatase	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Normal	(n=150)	0	150 (100.0)	0
AST	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Normal	(n=150)	0	147 (98.0)	3 (2.0)
Bilirubin	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Normal	(n=150)	0	149 (99.3)	1 (0.7)
Albumin	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Normal	(n=150)	0	150 (100.0)	0
Blood urea nitrogen	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Normal	(n=150)	0	150 (100.0)	0

Laboratory safety variable	Group	Baseline		Number (%) of patients at Week 3		
				Important low	Normal	Important high
Creatinine	Quetiapine XR	Normal	(n=137)	0	136 (99.3)	1 (0.7)
	Placebo	Normal	(n=150)	0	150 (100.0)	0
T3	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
		Placebo	Normal	(n=149)	0	149 (100.0)
		High	(n=1)	0	0	1 (100.0)
T4	Quetiapine XR	Normal	(n=137)	0	137 (100.0)	0
	Placebo	Normal	(n=150)	0	150 (100.0)	0
TSH	Quetiapine XR	Normal	(n=135)	0	131 (97.0)	4 (3.0)
		High	(n=2)	0	1 (50.0)	1 (50.0)
	Placebo	Normal	(n=149)	0	147 (98.7)	2 (1.3)
High		(n=1)	0	0	1 (100.0)	
Prolactin	Quetiapine XR	Normal	(n=126)	0	120 (95.2)	6 (4.8)
		High	(n=11)	0	9 (81.8)	2 (18.2)
	Placebo	Normal	(n=145)	0	143 (98.6)	2 (1.4)
		High	(n=5)	0	4 (80.0)	1 (20.0)

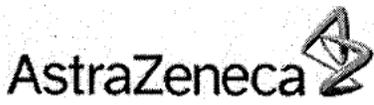
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Cara Alfaro
8/21/2008 11:00:09 AM
PHARMACIST

Ni Aye Khin
9/12/2008 10:43:41 AM
MEDICAL OFFICER

I concur with Dr. Alfaro's recommendation that the Division
take an approval action for this set of
NDA supplements. See memo to file for additional
comments.



Clinical Study Report	
Drug substance:	Quetiapine fumarate extended-release
Edition No.:	Final
Study code:	D144CC00004
Date:	20 November 2007

A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Sustained-release as Monotherapy in Adult Patients with Acute Bipolar Mania

Study dates:	First patient enrolled: 22 December 2006 Last patient enrolled: 14 June 2007
Phase of development:	Therapeutic confirmatory (III)
International Co-ordinating Investigator:	Andrew Cutler, MD Florida Research Center, LLC 3914 State Road 64 Bradenton, FL 34208

Sponsor's Responsible Medical Officer:	Arvid Nordenhem, MD, PhD
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This study was performed in compliance with Good Clinical Practice.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.



Drug product:	Seroquel XR	SYNOPSIS	
Drug substance(s):	Quetiapine fumarate extended-release		
Edition No.:	Final		
Study code:	D144CC00004		
Date:	20 November 2007		

A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Sustained-release as Monotherapy in Adult Patients with Acute Bipolar Mania

International co-ordinating investigator

Andrew Cutler, MD
Florida Research Center, LLC
3914 State Road
64 East
Bradenton, FL 34208

Study center(s)

This study was conducted at 50 centers in the United States; 48 sites actually enrolled patients.

Publications

None.

Study dates

First patient enrolled 22 December 2006

Last patient completed 31 July 2007

Phase of development

Therapeutic confirmatory (III)

Objectives

Primary objective

The primary objective was to demonstrate superior efficacy of quetiapine extended-release (XR)¹ formulation administered once daily (QD) as monotherapy at a dose of 400 to 800 mg

¹ Quetiapine XR was referred to as quetiapine sustained release (SR) in the protocol.

per day compared to placebo in decreasing the manic symptoms in patients with bipolar manic or mixed episode, after 3 weeks of treatment.

Secondary objectives

- To evaluate the efficacy and time course of quetiapine XR compared to placebo in decreasing the manic symptoms in patients with bipolar mania at each visit, including Day 4;
- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing agitation and aggression in patients with bipolar mania;
- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing psychotic symptoms in patients with bipolar mania;
- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in patients with bipolar mania;
- To evaluate the safety and tolerability of quetiapine XR QD in patients with bipolar mania.

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. This study consisted of an enrollment period of up to 35 days and a 3-week treatment period with 1 of 2 treatment regimens (quetiapine XR 400 to 800 mg QD or placebo). Quetiapine XR was not down-titrated at the end of the study.

Target patient population

The per-protocol plan was to enroll approximately 447 patients, with approximately 313 randomized to receive study treatment to obtain 288 evaluable patients (ie, patients receiving at least 1 dose of investigational product who had at least 1 post-baseline Young Mania Rating Scale [YMRS] assessment).

Patients were male or female, 18 to 65 years of age, inclusive with a diagnosis of bipolar I disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Text Revision 4th Edition (DSM-IV-TR 2000) criteria of 296.4x (Bipolar I Disorder, Most Recent Episode Manic) or 296.6x (Bipolar I Disorder, Most Recent Episode Mixed) confirmed by the amended version of the Structured Clinical Interview for DSM-IV (SCID). Patients who experienced rapid cycling as defined in DSM-IV-TR were eligible to participate in the study.

To be enrolled in the study, patients must have had at least 1 bipolar manic or mixed episode in the prior 5 years, a YMRS total score at screening of ≥ 20 with a score of ≥ 4 on 2 of 4 of the following core YMRS items: irritability, speech, content, and disruptive/aggressive behavior;

and must have a Clinical Global Impression – Bipolar – Severity of Illness (CGI-BP-S) score of ≥ 4 on the overall bipolar illness item at randomization (Visit 2).

Both hospitalized and non-hospitalized patients were enrolled in the study. Patients were hospitalized at randomization and for at least the first 4 days of treatment.

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

Quetiapine XR was given at a dose of 300 mg (one 300-mg tablet) on Day 1 and at 600 mg (three 200-mg tablets) on Day 2. From Day 3 to Day 21, quetiapine XR was given in flexible doses of 400 to 800 mg (two to four 200-mg tablets). Quetiapine XR was orally administered QD, in the evening. Batch numbers used in this study were LA4600 (200-mg tablets) and LH 4708 (300-mg tablets).

Comparator, dosage and mode of administration

Placebo matching quetiapine XR 300-mg and 200-mg tablets was orally administered QD, in the evening. Batch numbers used in this study were CE889X (placebo matching quetiapine XR 200-mg tablets) and CE891X (placebo matching quetiapine XR 300-mg tablets).

Duration of treatment

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.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

– **Primary outcome variable:**

- Change from baseline (randomization [Visit 2]) to final visit (Visit 6) in the YMRS total score.

– **Other variables supporting the primary objective:**

- Change from baseline (randomization [Visit 2]) to final visit in YMRS total score response (patients with $\geq 50\%$ reduction of YMRS);
- YMRS total score remission (patients with a YMRS total score ≤ 12 at final visit [Visit 6]);
- Change from baseline (randomization [Visit 2]) to final visit (Visit 6) Clinical Global Impression – Bipolar – Severity (CGI-BP-S);
- Final visit (Visit 6) assessment in Clinical Global Impression – Bipolar – Change (CGI-BP-C);

- Proportion of patients at final visit (Visit 6) with a CGI-BP-C of “much improved” or “very much improved” in overall assessment.
- **Secondary outcome variables:**
 - Change from baseline (randomization [Visit 2]) to each visit (including Day 4) in the YMRS total score;
 - Score change from baseline (randomization [Visit 2]) to final visit (Visit 6) of Items 5 Irritability, or 9 Disruptive – Aggressive Behavior, of the YMRS;
 - Score change from baseline (randomization [Visit 2]) to final visit (Visit 6) of Item 8, Content (Thought Content) of the YMRS;
 - Change from baseline (randomization [Visit 2]) to final visit (Visit 6) of the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Safety

- Change from baseline (defined as the sample/procedure taken closest to the randomization visit) in physical examinations, laboratory values (including glucose/lipids), vital signs, electrocardiogram (ECG);
- Adverse events (AEs), including somnolence, extrapyramidal symptoms (EPS) including akathisia, diabetes mellitus, QT prolongation, neutropenia/agranulocytosis, and suicidality;
- Serious adverse events (SAEs);
- Treatment-emergent EPS, as measured by the change in Simpson Angus Scale (SAS) total score and Barnes Akathisia Rating Scale (BARS) global assessment score from baseline (randomization [Visit 2]) to final visit (Visit 6) and AEs of EPS;
- Incidence of treatment-emergent depression (AE of depression or depressed mood, and or MADRS scores ≥ 18 on 2 consecutive assessments or on the final assessment);
- Proportion of patients withdrawing due to AEs;
- AEs leading to withdrawal;
- Change in weight from baseline (randomization [Visit 2]) to final visit (Visit 6);
- Proportion of patients with a $\geq 7\%$ increase in weight from baseline (randomization [Visit 2]) to final visit (Visit 6);

- Incidences of suicidality using a suicidality classification similar to the one established by Columbia University.

Statistical methods

The power was set at 90% for a 2-sided test at $\alpha=0.05$ for the comparison between quetiapine XR and placebo, using a 5-unit difference from placebo (YMRS total score) with a pooled standard deviation of 13.

Efficacy analyses were based on the following patient populations, which were finalized before unblinding of the data.

- 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 (randomization [Visit 2]) values and at least one post-randomized YMRS assessment, classified by the randomized treatment assignment. Data from the MITT analysis set were used for analysis of the efficacy objectives.
- The per protocol (PP) analysis set, a subset of the MITT analysis set, included patients who had no major protocol violations or deviations affecting efficacy. Data from this population were used for a consistency check only for the analysis of the primary objective.
- The safety analysis set included all randomized patients who took ≥ 1 dose of investigational product, classified according to the treatment actually received.

All statistical tests were 2-sided with a significance level of 5%, ie $\alpha=0.05$. Where appropriate, 95% confidence intervals are presented. Missing data resulting from patient withdrawal were imputed using a last observation carried forward (LOCF) approach. Patients with post-randomization data had their last study assessment carried forward as the final visit assessment for analysis. Also, descriptive statistics are provided for all variables.

Patient population

Baseline demographic and weight characteristics and patient disposition are shown in Table S1.

Table S1 Demographic and weight characteristics, and disposition (MITT population)

Demographic or Baseline Characteristic	Quetiapine XR (N=149)	Placebo (N=159)
Gender, n (%)		
Male	92 (61.7)	93 (58.5)
Female	57 (38.3)	66 (41.5)
Age (years)		
Mean \pm SD	41.3 (10.3)	40.8 (10.7)
Median	42.0	43.0
Min, Max	19, 64	19, 63
Age category (years), n (%)		
18 - 39	61 (40.9)	65 (40.9)
40 - 65	88 (59.1)	94 (59.1)
Race, n (%)		
Caucasian	72 (48.3)	73 (45.9)
Black/ African American	70 (47.0)	77 (48.4)
American Indian/ Alaskan Native	3 (2.0)	0
Asian	1 (0.7)	1 (0.6)
Native Hawaiian/ Pacific Islander	0	1 (0.6)
Other	3 (2.0)	7 (4.4)
Weight (kg)		
Mean (SD)	91.8 (23.7)	91.0 (24.8)
Median	90.0	86.5
Min, max	48, 207	44, 189
Waist circumference (cm)		
n	149	156
Mean (SD)	100.0 (19.8)	100.0 (20.7)
Median	98.0	97.0
Min, max	66, 183	64, 183

Table S1 Demographic and weight characteristics, and disposition (MITT population)

Demographic or Baseline Characteristic	Quetiapine XR (N=149)	Placebo (N=159)
BMI (kg/m²)		
n	149	159
Mean (SD)	31.0 (9.0)	30.9 (8.2)
Median	29.3	28.8
Min, max	19, 78	17, 65
BMI category, n (%)		
0 to <18.5	0	2 (1.3)
18.5 to <25	39 (26.2)	36 (22.6)
25 to <30	37 (24.8)	47 (29.6)
30 to <40	53 (35.6)	50 (31.4)
≥40	20 (13.4)	24 (15.1)
Disposition		
N (%) of patients who completed	111 (71.6)	116 (72.0)
N (%) of patients who withdrew	44 (28.4)	45 (28.0)
N analyzed for safety ^a	151 (97.4)	160 (99.4)
N analyzed for efficacy (MITT)	149 (96.1)	159 (98.8)
N analyzed for efficacy (PP)	124 (80.0)	129 (80.1)

BMI Body mass index. MITT Modified intention-to-treat. n Number of patients. N Number of patients in treatment group. PP Per Protocol. SD Standard deviation. XR Extended-release.

^a Number of patients who received at least 1 dose of study drug.

Note: Denominators are N in treatment group by gender and characteristic.

In the MITT population, the 2 treatment groups were well matched with respect to age, race, and weight. Overall, a higher percentage of patients were male (60.1%) and the mean age was 41 years. Median weight and BMI were slightly lower in the placebo group compared to the quetiapine XR group (90.0 kg and 29.3 kg/m² for the quetiapine XR group and 86.5 kg and 28.8 kg/m² for the placebo group, respectively). By BMI category, there were more patients in the 25 to <30 kg/m² category for placebo (29.6%) than quetiapine XR (24.8%). The 30 to <40 kg/m² category had slightly more quetiapine XR patients (35.6%) than placebo patients (31.4%).

Baseline disease characteristics and psychiatric history are presented in Table S2.

Table S2 Baseline disease characteristics and psychiatric history (MITT population)

Baseline disease characteristics	Quetiapine XR (N=149)	Placebo (N=159)
Baseline YMRS score		
Mean (SD)	28.8 (5.4)	28.4 (5.1)
Min, max	20, 47	20, 47
Baseline CGI-BP-S depression score		
n	148	159
Mean (SD)	2.4 (1.2)	2.4 (1.2)
Min, max	1, 5	1, 5
Baseline CGI-BP-S mania score		
n	148	159
Mean (SD)	4.5 (0.7)	4.5 (0.7)
Min, max	4, 7	4, 7
Baseline CGI-BP-S overall bipolar illness score		
n	148	159
Mean (SD)	4.5 (0.7)	4.5 (0.7)
Min, max	4, 7	4, 7
Baseline MADRS score		
n	148	159
Mean (SD)	14.3 (7.0)	14.6 (6.4)
Min, max	0, 38	4, 34
Current episode, n (%)		
Manic	86 (57.7)	88 (55.3)
Mixed	63 (42.3)	71 (44.7)
Psychiatric history		
Rapid cycling ^a , n (%)	45 (30.2)	52 (32.7)
Years since bipolar diagnosis		
Median	18	17
Min, max	1.0, 50.0	2.0, 45.0

Table S2 Baseline disease characteristics and psychiatric history (MITT population)

Baseline disease characteristics	Quetiapine XR (N=149)	Placebo (N=159)
Duration of present mania episode (weeks)		
n	146	154
Median	4	4
Min, max	0.1, 29.7	0.1, 44.9
Attempted suicide, n (%)		
Yes	84 (56.4)	91 (57.2)
No	65 (43.6)	68 (42.8)

CGI-BP-S Clinical Global Impression – Bipolar -Severity of illness. MADRS Montgomery-Åsberg Depression Rating Scale. n Number of patients. N Number of patients in treatment group. SD Standard deviation. XR Extended-release. YMRS Young Mania Rating Scale.

^a Defined as ≥ 4 and ≤ 8 mood episodes in the past year.

The 2 treatment groups were well-matched with respect to baseline disease characteristics. 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 similar (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. The mean baseline CGI-BP-S score for mania was 4.5 in each treatment group and the mean CGI-BP-S score for depression was 2.4 in each treatment group. Mean baseline MADRS scores were also low at 14.3 (range 0 to 38) and 14.6 (range 4 to 34) for the quetiapine XR and placebo groups, respectively.

Efficacy results

Key efficacy results are presented for the MITT population in Table S3.

Table S3 Key efficacy results (LOCF, MITT population)

Outcome variable	Quetiapine XR (N=149)		Placebo (N=159)		p-value at Day 4, Week 3
	Day 4	Week 3	Day 4	Week 3	
YMRS change, LS mean (SE)	-9.89 (0.79)	-14.34 (0.91)	-6.87 (0.77)	-10.52 (0.88)	<0.001, <0.001
Proportion with $\geq 50\%$ YMRS response, n (%)	33 (22.6)	82 (55.0)	24 (15.2)	53 (33.3)	0.086, <0.001

Table S3 Key efficacy results (LOCF, MITT population)

Outcome variable	Quetiapine XR (N=149)		Placebo (N=159)		p-value at Day 4, Week 3
	Day 4	Week 3	Day 4	Week 3	
Proportion with YMRS remission (total score ≤12), n (%)	27 (18.5)	62 (41.6)	20 (12.7)	44 (27.7)	0.112, 0.006
CGI-BP-S overall LS mean change from baseline (SE)	-0.81 (0.09)	-1.51 (0.11)	-0.56 (0.09)	-1.02 (0.11)	0.001, <0.001
CGI-BP-C overall, LS mean (SE)	2.86 (0.09)	2.58 (0.12)	3.32 (0.09)	3.18 (0.12)	<0.001, <0.001
CGI-BP-C “much improved” or “very much improved”, n (%)	44 (30.1)	80 (53.7)	23 (14.6)	52 (32.7)	0.001, <0.001

CGI-BP-S Clinical Global Impression - Bipolar - Severity of Illness. CGI-BP-C Clinical Global Impression - Bipolar - Change. LOCF Last observation carried forward. LS Least square. MITT Modified intention-to-treat. N Number of patients in treatment group. SE Standard error. XR Extended-release. YMRS Young Mania Rating Scale.

Quetiapine XR monotherapy at a dose of 400 to 800 mg QD for 3 weeks of treatment in patients with bipolar I mania (both manic and mixed at baseline) was superior to placebo in reducing the level of mania symptoms as measured by the change from baseline on the YMRS total score as early as Day 4 and continuing through the end of treatment ($p \leq 0.003$). The therapeutic effects of quetiapine XR were not restricted to any subgroup examined (gender, age group, race, manic/mixed episode, rapid/non-rapid cycling).

When analyzed by episode subgroup (patients with mixed versus only manic episodes at baseline), the MMRM results using OC data for the MITT population showed improvement in YMRS for both subgroups; the difference was statistically significant in favor of quetiapine XR over placebo for the manic subgroup ($p \leq 0.001$) but not for the mixed subgroup ($p = 0.107$) at Week 3. The analysis by rapid cycling subgroups also showed improvement in YMRS for both subgroups; the difference was statistically significant in favor of quetiapine XR over placebo for the non-rapid cycling subgroup ($p < 0.001$) but not for the rapid cycling subgroup ($p = 0.056$).

Analysis of other secondary outcome variables also supported the superiority of quetiapine XR 400 to 800 mg QD over placebo in the treatment of mania in patients with bipolar disorder. The proportions of patients showing $\geq 50\%$ reduction in YMRS total score (responders) and a YRMS total score ≤ 12 (remission) were statistically significantly higher for the quetiapine XR group compared to the placebo group by Day 8 (Week 1) and at the end of treatment ($p \leq 0.024$). The changes in CGI-BP-S and CGI-BP-C overall illness scores were statistically significant in favor of quetiapine XR beginning at Day 4 and continuing to the end of treatment ($p \leq 0.011$) with the exception of CGI-BP-C overall illness score at Day 15 ($p = 0.058$). Quetiapine XR patients were 2.44 times more likely to have CGI-BP-C for overall

bipolar illness score of “much improved” or “very much improved” as placebo patients beginning at Day 4 and continuing to the end of treatment ($p < 0.001$).

For the 4 key individual YMRS item scores used for eligibility criteria, including those related to secondary efficacy assessments (irritability, speech, thought content, and disruptive-aggressive behavior), all were reduced more by quetiapine XR treatment than by placebo treatment. Statistically significant separation from placebo was observed in the quetiapine XR group ($p \leq 0.011$) with the only exception being disruptive-aggressive behavior ($p = 0.063$).

Quetiapine XR monotherapy at a dose of 400 to 800 mg QD for 3 weeks was also superior to placebo in decreasing depressive symptoms in patients with bipolar I mania as measured by the change from baseline in MADRS total score beginning at Day 4 and continuing to the end of treatment ($p \leq 0.022$).

Safety results

For patients treated with quetiapine XR, the mean daily dose over the treatment period was 603.8 mg with 47% of patients having a final dose level of 600 mg/day; approximately 22% and 29% of patients had final dose levels of 400 and 800 mg/day, respectively.

A summary of AEs is presented in Table S4.

Table S4 Overview of adverse events (safety population)

AE category	Number (%) of patients ^a			
	Quetiapine XR (N=151)		Placebo (N=160)	
Any AE	128	(84.8)	107	(66.9)
Any AE with an outcome of death	0		1	(0.6)
Any SAE	6	(4.0)	13	(8.1)
Any SAE leading to discontinuation of treatment	4	(2.6)	9	(5.6)
Any non-serious AE leading to discontinuation of treatment	3	(2.0)	4	(2.5)
Any other significant AE ^b	0		1	(0.6)

AE Adverse event. N Number of patients in treatment group. SAE Serious adverse event. XR Extended-release.

^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 Any AE that led to dose of treatment being temporarily stopped, or deemed by the sponsor to be significant, excluding AEs reported as SAEs or led to discontinuation of treatment.

The percentage of patients with AEs was higher in the quetiapine XR (84.8%) than the placebo group (66.9%); however, the incidences of SAEs and discontinuations due to SAEs were higher in the placebo group (8.1% and 5.6%, respectively) compared with the quetiapine XR group (4.0% and 2.6%, respectively). The percentages of patients with discontinuation of

treatment due to non-serious AEs were comparable between the 2 treatment groups (2.0% in the quetiapine XR group and 2.5% in the placebo group). There was one “unexplained” death (placebo group).

The most common AEs were sedation, dry mouth, and somnolence, and all were reported more frequently in the quetiapine XR group (34.4%, 33.8%, and 16.6%, respectively) compared with placebo (7.5%, 6.9%, and 4.4%, respectively). Among AEs reported by >5% of patients in any group, AEs reported by at least twice as many patients in the quetiapine XR group compared to placebo included sedation, dry mouth, somnolence, constipation, dizziness, and weight increased.

Mean changes from baseline in glucose- and insulin-related laboratory variables were generally higher for the quetiapine XR-treated patients compared to placebo for patients both with and without diabetic risk factor(s) and for patients with diabetes mellitus; there was a large variability in results. For patients with diabetic risk factors at baseline, the incidence of clinically-important glucose values ≥ 100 and < 126 mg/dL at Week 3 was lower in the quetiapine XR than the placebo group (46.4% vs. 54.4%); however, a greater percentage of patients in the quetiapine XR group had clinically-important glucose values ≥ 126 mg/dL compared with patients in the placebo group (10.1% vs. 4.4%). The incidence of clinically-important HbA_{1c} values ($> 7.5\%$) was similar between the 2 treatments (4.3% and 2.9%). For patients with diabetes mellitus at baseline, the incidences of clinically-important glucose values ≥ 126 mg/dL and > 200 mg/dL were also higher in the quetiapine XR group compared to the placebo group (57.1% vs. 33.3% and 28.6% vs. 0, respectively); none of these patients had clinically-important HbA_{1c} values. A higher frequency of high glucose or HbA_{1c} was not observed in patients with no diabetic risk factors at baseline.

Patients treated with quetiapine XR showed a slight mean increase in body weight consistent with findings of this treatment in other patient populations (1.3 kg for quetiapine XR and 0.1 kg for placebo). Increases in weight $\geq 7\%$ were observed in 7 (5.1%) patients in the quetiapine XR group; no increases $\geq 7\%$ occurred in placebo patients. There was no differential shift to ≥ 3 metabolic risk factors at end-of-treatment with quetiapine XR.

An increase in the incidence in the composite of AEs potentially related to EPS was noted for the quetiapine XR group compared with the placebo group (6.6% vs. 3.8%). The incidences of individual AEs potentially related to EPS were low in both treatment groups. No AEs were encoded to QT prolongation. There were no AEs potentially related to neutropenia/agranulocytosis during the study; however, clinically laboratory assessments showed that 3 patients (2 quetiapine XR and 1 placebo) had shifts in neutrophil values from non-clinically significant at baseline to clinically-important low values ($< 1.5 \times 10^9/L$) at the end of treatment.

Treatment-emergent depression, as defined by criterion of MADRS and AEs relating to depression, was reported for 1 patient in the placebo group. Patients in the placebo group showed a slightly higher incidence of suicidal behavior/ideation and possible suicidal

behavior/ideation than patients treated with quetiapine XR (3.1% in the placebo group vs. 1.3% in the quetiapine XR group).

Conclusion(s)

- Quetiapine XR 400 to 800 mg given QD in the evening for 3 weeks, flexibly dosed, as monotherapy is superior to placebo in treatment of mania in patients with bipolar I diagnosis.
 - The effect of quetiapine XR (400 to 800 mg QD) treatment in decreasing manic symptoms was observed as early as Day 4 following treatment initiation and was maintained throughout the 3-week treatment course in patients with bipolar disorder.
 - Quetiapine XR 400 to 800 mg given QD was effective in decreasing manic symptoms in patients exhibiting either rapid or non-rapid cycling.
 - Quetiapine XR 400 to 800 mg given QD was superior to placebo in achieving response (defined as $\geq 50\%$ reduction of YMRS) and remission (defined as YMRS score ≤ 12) in patients with bipolar mania.
- Quetiapine XR, at a dose of 400 to 800 mg given QD, flexibly dosed, was generally safe and well-tolerated in patients with bipolar disorder who were experiencing a manic episode.

Date of the report

20 November 2007