CLINICAL REVIEW

Class 2 Resubmission

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Division/Office	Division of Psychiatry Products; ODE1
Reviewer Name	Cara Alfaro, Pharm.D. Clinical Analyst
Review Completion Date	03/22/2013
Established Name	Quetiapine
Trade Name	Seroquel, Seroquel XR
Therapeutic Class	Antipsychotic
Applicant	AstraZeneca Pharmaceuticals
Indication studied	Depressive episodes associated with bipolar disorder
Population	Children and adolescents (10 to 17 years of age)

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

This reviewer recommends that an approval action be taken on supplemental NDAs 22047 S-29 (Seroquel XR) and 20639 S-57 (Seroquel). These submissions included the results of one clinical trial investigating the efficacy and safety of quetiapine XR (150 to 300 mg/day) compared to placebo in the treatment of bipolar depression in children and adolescents (10 to 17 years of age). This clinical trial was a failed trial, there was no statistically significant difference between quetiapine XR and placebo groups on the primary endpoint, change from baseline in the Children's Depression Rating Scale – Revised. Safety data from this failed trial should be incorporated into product labeling and a summary of the failed trial should be included in the relevant section of labeling.

Product labeling for Seroquel XR and Seroquel are being extensively revised, based in part on input from SEALD. (b) (4) supplements will also be rolled into this efficacy supplement action (see Section 9.2). Additionally, the Division is extending the following indications for Seroquel to the Seroquel XR dosage form: treatment of schizophrenia (adolescents; 13 – 17 years of age) and treatment of bipolar mania (children and adolescents; 10 – 17 years of age).

1.2 Risk Benefit Assessment

Not applicable. The submitted study was a failed study, no new indications are being sought.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable. The submitted study was a failed study, no new indications are being sought.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable. The submitted study was a failed study, no new indications are being sought.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Quetiapine fumarate (Seroquel®, Seroquel XR®) is a dibenzothiazepine derivative which interacts with a broad range of neurotransmitter receptors including serotonin, dopamine and adrenergic receptors.

Quetiapine has been approved by the FDA for the treatment of schizophrenia, bipolar mania and bipolar depression in adult and pediatric patients (see the summary table below).

Table 1. Indication and Date(s) of Approval of Quetiapine Fumarate immediate release (Seroquel) [NDA 20639]

Indication in Adults	Date of Approval
Schizophrenia (acute)	9/26/1997
Acute Manic Episodes associated with Bipolar I Disorder monotherapy or adjunct therapy to lithium or valproex	1/12/2004
Depressive Episodes associated with Bipolar Disorder	10/20/2006
Maintenance Treatment of Bipolar I Disorder as adjunct therapy to lithium or divalproex	5/13/2008
Schizophrenia (adolescents; 13 to 17 years of age)	12/02/2009
Bipolar mania (children/adolescents; 10 to 17 years of age)	12/02/2009

Table 2. Indication and Date(s) of Approval of Quetiapine Fumarate extended release (Seroquel XR) [NDA 22047]

Indication in Adults	Date of Approval
Schizophrenia (acute)	5/17/2007
Schizophrenia (maintenance)	11/15/2007*
Acute Manic Episodes associated with Bipolar I Disorder monotherapy or adjunct therapy to lithium or valproex	10/08/2008
Depressive Episodes associated with Bipolar Disorder	10/08/2008
Major Depressive Disorder, adjunctive therapy	12/02/2009

(b) (4)

2.2 Tables of Currently Available Treatments (b) (4)

The Sponsor submitted the clinical study report for the evaluation of quetiapine (as Seroquel XR) in the treatment of depressive episodes associated with bipolar disorder in children and adolescents (10 to 17 years of age). This study did not demonstrate efficacy of quetiapine compared to placebo.

No psychotropic drugs are currently approved specifically for the treatment of depressive episodes associated with bipolar disorder. Lithium is approved for the treatment of bipolar disorder in patients > 12 years of age.

2.3 Availability of Proposed Active Ingredients in the United States

Quetiapine fumarate (immediate release tablets) was first approved for the acute treatment of schizophrenia in adults on September 26, 1997. Quetiapine is currently available as 25, 50, 100, 200, 300 and 400 mg immediate-release tablets.

Quetiapine extended release (Seroquel XR) was first approved on 5/17/2007 for the acute treatment of schizophrenia. Seroquel XR is currently available as 50, 150, 200, 300 and 400 mg extended-release tablets.

2.4 Important Safety Issues With Consideration to Related Drugs

Atypical antipsychotics have been associated with several safety issues. Among the major safety issues are increased mortality in elderly patients with dementia-related psychosis, increased cerebrovascular adverse events (stroke, transient ischemic attack) in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia (TD), orthostatic hypotension, and metabolic effects including hyperglycemia/diabetes mellitus, dyslipidemia and weight gain.

Quetiapine (immediate release) is approved for the treatment of schizophrenia in adolescents and bipolar mania in children and adolescents. In the clinical trials that supported those indications, an unexpected finding of increased blood pressure in this population was reported and described in approved product labeling.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

10/20/2006 Seroquel was approved for the treatment of depressive episodes associated with bipolar disorder in adults.

10/8/2008 Seroquel XR was approved for the treatment of depressive episodes associated with bipolar disorder in adults.

At the time of these approvals, pediatric studies under PREA for Seroquel/Seroquel XR were deferred. For Seroquel XR, the approval letter stipulated that the final clinical study report for a pediatric study for the use of Seroquel XR monotherapy in the treatment of bipolar depression be submitted by 6/1/2015.

11/20/2008 The clinical protocol for D144AC00001 “An 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy and safety of quetiapine fumarate extended-release (Seroquel XR) in children and adolescent subjects with bipolar depression” was submitted to IND 76146 (incorrectly submitted as new protocol for (b) (4) resubmitted under correct indication 1/15/2009).

6/22/2009 The Division sent an advice letter to the Sponsor with the following comments:

Statistical

In your statistical analysis plan, please include at least one sensitivity analysis to your primary analysis model. Please also include mock SAS codes for your primary analysis model. Enrolling a large number of subjects with co-morbid ADHD could complicate the interpretation of the results because these patients may stay on stimulants if deemed necessary by the investigator. Thus, your analysis plan should also address the consistency of the responses in

patients with and without co-morbid ADHD, and whether taking stimulants is an important factor in the treatment outcome.

Clinical
We note that the primary objective of the protocol (D144AC00001) is to evaluate whether quetiapine XR formulation at a dose of 150 to 300 mg/day demonstrates superior efficacy compared to placebo in children and adolescents 10 to 17 years of age with bipolar depression after 8 weeks of treatment, as assessed by change in Children's Depression Rating Scale-Revised total score from baseline to final assessment (Day 57). However, the protocol allows subjects with co-morbid ADHD to participate in the study. The protocol also permits subjects with ADHD to continue psychostimulant treatment if deemed necessary by the investigator, and provided the prescribed dose has been stable for $\geq$ 30 days prior to randomization. We recommend that you add an assessment to monitor ADHD symptomatology.

This reviewer was unable to find correspondence from the Sponsor addressing the Division's comments. The protocol was never amended to include any assessments for ADHD symptomatology.

10/28/2011 Supplemental NDA submitted to NDA 22047 S-29 (Seroquel XR) and NDA 20639 S-57 (Seroquel) to fulfill PREA requirements. Efficacy was not demonstrated, product labeling to include safety data from clinical trial in children/adolescent population.

8/6/2012 Complete response action taken by Division:
"During the review process, the Division posed a number of questions regarding additional information and clarication of discrepancies in the clinical study report (CSR). As part of your response to our information requests, you submitted an amendment to the NDA on May 4, 2012 that included a 252-page errata. On May 25, 2012, you communicated via email that, 'during the process of responding to [the Division's] requests for additional information, we have discovered additional errors in the analysis database which will result in additional corrections to several tables and listings in the CSR….Based on our latest findings, AstraZeneca has decided to conduct a new comprehensive quality control review of the study analysis database, tables and listings and issue a revised CSR as appropriate. Based on the breadth of the QC planned to ensure accuracy of the final report, we anticipate that a revised CSR will be submitted by October 2012'. Given that the revised CSR will not be submitted until October 2012, and the extent of additional revisions are unknown at this time, we are taking a complete response action."

10/29/2012 The Sponsor submitted the corrected CSR in a response to the complete response action.

2.6 Other Relevant Background Information

No other relevant background information was identified.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

A Division of Scientific Investigations consult was sent 11/28/2011. This reviewer evaluated a sample of CRFs, protocol violations, adverse events as well as financial disclosure forms. No information was found that would indicate cause for investigation of a particular site. However, during the filing meeting, it was noted that the efficacy findings were unusual. Though quetiapine was not statistically different from placebo on the primary variable (mean change from baseline in the Children's Depression Rating Scale-Revised), there were robust differences from baseline for both quetiapine (-31.9) and placebo (-28.8). This robust response, especially in the placebo group, is unexpected. DPP requested that DSI inspect 2 clinical sites with large numbers of randomized subjects with an emphasis on how subjects were recruited for this study as well as documentation of confirmed diagnosis. See Appendix 9.5 for details regarding enrolled and randomized subjects at the investigational sties.

The Office of Scientific Investigation's (OSI) clinical inspection summary was finalized on 6/24/12. The sites that were inspected were sites 1124 and 1125. Site 1124 is the Brighton Research Group, LLC in Virginia Beach, VA; David Spiegel, M.D. was the investigator. Site 1125 is the Wharton Research Center in Wharton, TX; Nilesh Patel, M.D. was the investigator. The preliminary outcome classification from DSI is "deviation from regulations" and is based on information on Form FDA 483 and communication with the field investigator. Final establishment inspection report (EIR) has not been received from the field office and OSI's complete review of the report remains pending as of the summary report. OSI states that an addendum to the clinical inspection summary will be forwarded to DPP if the final classification changes from the pending classification or if additional observations of clinical or regulatory significance are discovered after completing the EIR review.

Site 1124: 48 subjects were screened, 14 were enrolled and 11 completed the study; OSI reviewed records for the 14 enrolled subjects. The issues that were identified were primarily drug accountability issues (logs not completed). OSI concluded that these deficiencies are unlikely to impact data integrity or subject safety and that the data from this study site appear reliable.

Site 1125: 20 subjects were screened, 15 were enrolled and 10 completed the study; OSI reviewed records for 10 of the 15 enrolled subjects (6 of which had completed the study). The issues that were identified included failure to obtain adequate informed consent/assent and failure to maintain adequate source records. Upon reviewing the summary comments about failing to maintain adequate source records, one was potentially troubling "Subjects 1125007, 1125010, 1125011, 1125012, 1125016, 1125018, and 1125019: Parts of K-SADS-PL and C-SSRS appeared to have been completed and/or modified up to one year after the original assessment, typically without supporting documentation. This reviewer will review the EIR, once submitted, to obtain further details with respect to this item. OSI concluded that the observed deficiencies appear to reflect inadequate recordkeeping of otherwise adequate study conduct and the data from this study site appear reliable.

3.2 Compliance with Good Clinical Practices

The protocol was reviewed and approved by Institutional Review Boards and Independent Ethics Committees. In the United States, the Institutional Review Boards that reviewed the protocol were Sterling IRB, Atlanta GA; WIRB, Olympia WA; University of Cincinnati IRB; University of Minnesota IRB; and University Hospitals IRB, Cleveland OH. Informed consent and assent was obtained from participants in the clinical trial.

The Sponsor indicated that all studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

The Sponsor also stated that their quality assurance and internal quality control procedures provide reassurance that the clinical study program was carried out in accordance with GCP guidelines. The Sponsor undertakes a GCP audit program to ensure compliance with its procedures and to assess the adequacy of its quality control measures. Audits, by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures, are directed towards all aspects of the clinical study process and its associated documentation.

According to the study report, audits were conducted by the Sponsor at four sites in the United States: #1120 (Dr. Harshawat), #1121 (Dr. Handal), #1124 (Dr. Spiegel) and #1125 (Dr. Patel). Details regarding the outcome for these audits were not included in the NDA submission. The Sponsor did not identify any site-specific issues and no sites were excluded from Sponsor's analyses.

3.3 Financial Disclosures

The majority of investigators had no disclosable financial interests to report (see Appendix 9.5 for list of principal investigators/sites).
Form 3455 (version 10/2009) "Disclosure – Financial Interests and Arrangements for Clinical Investigators" was reviewed for the 6 investigators with financial interests to disclose: (b) (6)

Per form 3455, these investigators have participated in financial arrangements or holds financial interests that are required to be disclosed as follows: "any significant payments or other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria". Three investigators (b) (6)) received > $25,000 from the sponsor, the other three investigators (b) (6)) did not specify an amount received. (b) (6) was a subinvestigator who worked with (b) (6) site did not (b) (6) this research study. The numbers of subjects randomized at these sites (b) (6) were < (b) (6)
The overall study results were negative and did not support efficacy of quetiapine in the treatment of bipolar depression in pediatric patients.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls
No new information.

4.2 Clinical Microbiology
Not applicable

4.3 Preclinical Pharmacology/Toxicology
No issues were identified in this submission that required review from pharmacology/toxicology.

4.4 Clinical Pharmacology
No new information.

4.5 Other Review Disciplines
4.5.1 Pediatric and Maternal Health Staff
Pediatric and Maternal Health Staff were consulted to provide comments regarding the proposed labeling for the safety data generated from this clinical trial. PMHS staff provided some guidance with regard to the safety data to be incorporated into product labeling as well as the appropriate placement of the summary for the failed clinical trial.

4.5.2 Study Endpoints and Labeling Development (SEALD)
SEALD was involved in extensive evaluation of the product labeling for Seroquel and Seroquel XR as part of an OND initiative. SEALD provided significant input for streamlining product labeling.

4.5.3 Office of Surveillance and Epidemiology (OSE)
As part of the comprehensive review of product labeling, OSE was consulted to review cases of [redacted] (b) (4) This consult is pending.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials
This submission included only one clinical trial:
D144AC00001 An 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy and safety of quetiapine fumarate extended-release (Seroquel XR) in children and adolescent subjects with bipolar depression.

5.2 Review Strategy
One clinical study was included in this supplemental NDA: D144AC00001 "An 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy and safety of quetiapine fumarate (Seroquel XR) extended-release in children and adolescent subjects with bipolar depression". The efficacy and safety data from this one clinical study were reviewed.

Biometrics performed an assessment of efficacy for the pivotal studies from a statistical perspective with additional analyses as deemed necessary. Key analyses are included in the efficacy section of this review.

6 REVIEW OF EFFICACY

Efficacy Summary

As of the data submitted in the clinical study report, study D144AC00001 failed to establish the efficacy of quetiapine XR (150 – 300 mg/day) in the treatment of bipolar depression in children and adolescents 10 to 17 years of age.

The primary efficacy variable was the change from baseline to Day 57 in Children's Depression Rating Scale-Revised total score (MMRM analysis). The mean (SD) change from baseline was -31.9 (14.9) for the quetiapine XR group (n = 92) and -28.8 (14.8) for the placebo group (n = 100); LS mean difference (SE) was -2.29 (1.99) 95% CI (-6.22, 1.65), p = 0.252.

6.1 Studies Pertinent to Bipolar Depression

D144AC00001 "An 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy and safety of quetiapine fumarate (Seroquel XR) extended-release in children and adolescent subjects with bipolar depression"

6.1.1 Rationale for Selection of Studies for Review

The Sponsor conducted one clinical trial evaluating the safety and efficacy of quetiapine fumarate extended-release in children and adolescents (10 to 17 years of age) with bipolar depression.

6.1.2 Study Summaries

Clinical Trial

Study D144AC00001 "An 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy and safety of quetiapine fumarate (Seroquel XR) extended-release in children and adolescent subjects with bipolar depression". This trial included children and adolescents, 10 to 17 years of age.

This multicenter trial was conducted in 42 centers in 7 countries: United States (29 centers), Colombia (3 centers), India (3 centers), Mexico (2 centers), Serbia (3 centers), South Africa (1 center) and Taiwan (1 center). Approximately 83% (161/193) of subjects randomized were from the United States.

The first subject was enrolled on 1/27/2009, the last subject completed the study on 11/1/2010. The study had completed by February 23, 2010 when the Sponsor discovered that the central laboratory (b) (4) did not analyze the blood samples for prolactin and thyroid function tests. The Sponsor then submitted a protocol amendment for recall visits; the recall visits were scheduled from June 2010 to November 2010 (regardless of when the patients had completed the study) to obtain blood samples for prolactin and thyroid function tests.

Methods/Study Design/Analysis Plan

This study was an 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled outpatient study evaluating the efficacy and safety of quetiapine XR 150 to 300 mg/day in children and adolescents (10 to 17 years of age) with bipolar depression.

Eligible patients were evaluated using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL) at screening. Subjects who met the DSM-IV-TR diagnosis of bipolar I or bipolar II disorder with current episode depressed confirmed by K-SADS-PL were further screened for study entry. If the subject qualified for enrollment, the subject underwent a 7 to 28 day washout period (depending on prior

medications). Following washout, subjects were randomized (1:1) to quetiapine XR or placebo within age strata (10 to 12 years, 13 to 17 years). Study medication was administered orally, once daily in the evening. Quetiapine XR was administered as follows: 50 mg on day 1, 100 mg on day 2, 150 mg on day 3 and continued until week 2 or 3. If at 2 or 3 weeks, there was a deterioration defined as Clinical Global Impressions for Bipolar Disorder – Change from Preceding Phase (CGI-BP-C) $\geq$ 5, then the dose of quetiapine XR or placebo was increased to 300 mg/day: increase to 200 mg, then increase to 250 mg one day later, then increase to 300 mg one day later and maintain if subject's symptoms had stabilized. If the dose had not been increased from 150 to 300 at weeks 2 or 3, it was to be increased to 300 mg (following the same titration) at week 4 or later if the patient had a clinical deterioration or no improvement defined as Clinical Global Impressions for Bipolar Disorder – Severity of Illness (CGI-BP-S) $\geq$ 4. At any visit, the dose could be reduced to 150 mg/day if the higher dose was not tolerated. The randomized phase of the study was 8 weeks (days 1 – 56) followed by a telephone follow-up visit (day 57 – 63) and a visit for blood pressure measurement if elevations noted at study discontinuation (day 70 – 84).

Enrolled in this study were generally healthy male or female subjects, 10 to 17 years of age (inclusive), with a diagnosis of bipolar I or bipolar II disorder and current or most recent episode depressed. Diagnoses were confirmed by K-SADS-PL diagnostic interviews. The sponsor stated that, in order to ensure accurate diagnosis, the K-SADS-PL was conducted or reviewed by a board-certified or board-eligible child psychiatrist; exceptions were allowed where the availability of child psychiatrists was limited. Subjects had to have a Children's Depression Rating Scale – Revised (CDRS-R) total score of $\geq$ 45 and Young Mania Rating Scale (YMRS) total score $\leq$ 16 at screening and randomization; and current episode of depression $\geq$ 4 weeks.

Subjects with psychotic features could be enrolled in this study. Subjects who met criteria for rapid cycling were also permitted. Subjects with a secondary diagnosis of ADHD could also be enrolled, psychostimulants could be continued if the dose had been stable for $\geq$ 30 days before randomization. Informed consent was obtained from one or both parents or by legal guardian, written assent by the patient. Subjects were outpatients at enrollment and randomization and likely to remain outpatients for the duration of the study.

Exclusion criteria included diagnosis of another current DSM-IV-TR Axis I disorder with exceptions as noted above; YMRS > 16 (enrollment/randomization); subject met criteria for bipolar I or bipolar II, most recent episode mania, hypomania, or mixed; history of nonresponse to an adequate treatment with > 2 antidepressants during the current episode; subjects who, in the investigator's judgment, posed a current serious suicidal or homicidal risk, had a CDRS-R item 13 score > 3 (enrollment/randomization) or who had made a suicide attempt within the past 6 months; CDRS-R that decreased > 20% between enrollment and randomization. Concomitant medication exclusion criteria included: medications that induce or inhibit CYP3A4, antipsychotics, mood stabilizers, antidepressants, anxiolytics, hypnotics or other psychoactive medications.

Results

A total of 262 subjects were enrolled into the study, 193 subjects were randomized to receive either quetiapine XR (150 – 300 mg/day) or placebo. One subject randomized to the quetiapine XR group did not receive study medication and did not have a post-baseline CDRS-R assessment; therefore the intent-to-treat (ITT) population included 192 subjects (92 quetiapine XR, 100 placebo).

Demographics

The two treatment groups were similar with regard to major demographic characteristics.

Table 3. Demographic Characteristics

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
Age (years)		
Mean (SD)	13.9 (2.2)	14 (2.1)
Median	14	14
Minimum	10	10
Maximum	17	17
Age group (years), n (%)		
10 – 12 years old	25 (27.2)	28 (28)
13 – 17 years old	67 (72.8)	72 (72)
Gender, n (%)		
Male	45 (48.9)	52 (52)
Female	47 (51.1)	48 (48)
Race, n (%)		
White	65 (70.7)	60 (60)
Black/African American	14 (15.2)	21 (21)
Other	6 (6.5)	9 (9)
Asian	4 (4.3)	6 (6)
American Indian or Alaska Native	3 (3.3)	4 (4)
Ethnic group, n (%)		
Not applicable	43 (46.7)	38 (38)
African-American	14 (15.2)	21 (21)
Other	14 (15.2)	18 (18)
Hispanic or Latino	13 (14.1)	14 (14)
Native American	4 (4.3)	3 (3)
Asian (other than Chinese/Japanese)	3 (3.3)	3 (3)
Chinese	1 (1.1)	3 (3)
Weight (kg)		
Mean (SD)	65.4 (24.6)	63.6 (23.2)
Median	59.5	59
Minimum	28	27
Maximum	177	151
BMI (kg/m2)		
Mean (SD)	24.5 (7.4)	24.2 (7.2)
Median	22	22.9
Minimum	15	13
Maximum	55	50

Source: Table 9 of Clinical Study Report
Safety analysis dataset

Baseline Characteristics

The two treatment groups were similar with regard to psychiatric diagnosis and history. The majority of subjects had the diagnosis bipolar I disorder, most recent episode depressed with a severity of moderate. Approximately 40% of the subjects had comorbid ADHD and about 25% of subjects had rapid cycling bipolar disorder. Approximately 70% of subjects had not experienced a prior hospitalization for mental illness.

The CDRS-R and CGI-BP-S scores were similar between the two groups (Table 5).

Table 4. Psychiatric Diagnosis and History

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
Bipolar I disorder, most recent episode depressed	75 (81.5)	79 (79)
Unspecified	6 (8)	2 (2.5)
Mild	5 (6.7)	3 (3.8)
Moderate	55 (73.3)	62 (78.5)
Severe without psychotic features	7 (9.3)	11 (13.9)
Severe with psychotic features	2 (2.7)	1 (1.3)
Bipolar II disorder	17 (18.5)	21 (21)
Secondary diagnosis of ADHD		
No	54 (58.7)	54 (54)
Yes, *without* concomitant use of psychostimulants	18 (19.6)	19 (19)
Yes, *with* concomitant use of psychostimulants	20 (21.7)	27 (27)
Rapid cycler		
Yes	22 (23.9)	23 (23)
No	70 (76.1)	77 (77)
No. years since first diagnosis bipolar I or II		
Mean (SD)	1.9 (2.5)	1.9 (2.1)
Median	1	1
Minimum	0	0
Maximum	11	9
No. years since first manic, hypomanic, mixed episode		
Mean (SD)	3.1 (2.5)	2.9 (2.5)
Median	3	2
Minimum	0	0
Maximum	10	13
Total no. manic, hypomanic or mixed episodes in past year		
0	9 (10.1%)	8 (8.2%)
1	26 (29.2%)	40 (40.8%)
$\geq$ 2	54 (60.7%)	50 (51%)
No. years since first known depressed episode		
Mean (SD)	3.7 (2.7)	3.2 (2.7)
Median	3	3
Minimum	0	0
Maximum	10	13
Total no. depressed episodes in past year		
0	1 (1.1%)	3 (3.1%)
1	30 (32.6%)	33 (33.7%)
$\geq$ 2	61 (66.3%)	62 (63.3%)

Time since onset of present/most recent depressed episode (days)		
n	52	65
Mean (SD)	67.7 (50.8)	64.5 (62.6)
Median	49	46
Minimum	21	11
Maximum	233	427
Total no. hospitalizations for mental illness over lifetime		
0	69 (75%)	66 (66%)
1	18 (19.6%)	21 (21%)
≥ 2	5 (5.4%)	13 (13%)
Current/prior exposure to typical antipsychotic drugs		
No	77 (84.6%)	78 (78%)
Yes	14 (15.4%)	22 (22%)
Total no. suicide attempts over lifetime		
0	84 (91.3%)	90 (90%)
1	7 (7.6%)	6 (6%)
≥ 2	1 (1.1%)	4 (4%)

Source: Tables 11.1.4.5 , 11.1.4.6, 11.4.7 of Clinical Study Report.
Safety analysis dataset

Table 5. Baseline Psychiatric Rating Scale Ratings

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
CDRS-R total score Mean (SD)	61.6 (9.93)	60.1 (9.01)
CGI-BP-S Mean (SD)	4.4 (0.61)	4.3 (0.62)

Source: Tables 11 and 11.2.2.3.1 of Clinical Study Report

Patient Disposition

Over 70% of the subjects completed the clinical study. In the placebo group, the most frequent reason for discontinuing the study was "adverse event", though about half of those events appeared related to the underlying disorder (irritability, aggression, bipolar disorder, depressive symptom).

Table 6. Patient Disposition

	Number (%) of Patients	
	Quetiapine XR 150 – 300 mg/day N = 93	Placebo N = 100
Patients Randomized	93	100
Received Treatment	92	100
Completed Study	70 (75.3)	74 (74)
Discontinued Study*	23 (24.7)	26 (26)
Adverse Event	3 (3.2)	12 (12)
Lost to Follow-up	5 (5.4)	1 (1)
Withdrawal consent/assent	2 (2.2)	4 (4)
Lack of efficacy	5 (5.4)	4 (4)
Non-compliance	2 (2.2)	4 (4)

Other	4 (4.3)	1 (1)
Incorrect enrollment	1 (1.1)	0
Safety reasons	1 (1.1)	0

Source: Tables 6 in Clinical Study Report, Listing 12.2.1.2 (Subject disposition)
*Lack of efficacy included sponsor categories "lack of therapeutic response" and "condition under investigation worsened". Category "other" included: principal investigator resigned at study site, moving to another state, subject was out of study window and had to be discontinued, subject missed 3 consecutive study visits, subject improved > 20% from screening to baseline (should not have been randomized)
"Safety reasons": upon request, sponsor submitted CRFs. Subject endorsing suicidal ideation items on CSSRS, l kely reason for discontinuation.

Concomitant Medication Use

Very few patients took prohibited concomitant medications during the clinical trial; one patient in the quetiapine XR group took valproate (dose/duration not specified) and one patient in the placebo group took risperidone (dose/duration not specified).

Concomitant psychostimulants were allowed for subjects with comorbid ADHD as long as the dose was stable for $\geq$ 30 days prior to randomization. Twenty (22%) subjects in the quetiapine XR group and 28 (28%) subjects in the placebo group took concomitant psychostimulants during the trial (Table 7).

Table 7. Concomitant Psychostimulant Use

	Quetiapine XR 150 – 300 mg/day N = 92 n (%)	Placebo N = 100 n (%)
Methylphenidate	10 (10.9)	8 (8)
Amphetamine + dexamfetamine	4 (4.3)	10 (10)
Dexamfetamine	0	1
Dexmethylphenidate	3 (3.3)	1 (1)
Lisdexamfetamine	3 (3.3)	8 (8)

Source: Table 11.1.5.1.2 in Clinical Study Report

Important Protocol Violations

Major protocol violations included CDRS-R total score < 45 at screening/randomization (n = 2 quetiapine XR), duration of current episode of depression < 4 weeks at screening (n = 1 quetiapine XR, n = 1 placebo), diagnosis of another Axis I disorder (n = 2 quetiapine XR), CDRS-R decreased > 20% between screening and randomization (n = 2 quetiapine XR, n = 1 placebo). In general, the numbers of major protocol violations were low.

Efficacy Results

The primary efficacy analysis and secondary efficacy analyses failed to demonstrate a statistically significant difference between the quetiapine XR and placebo groups.

Primary Analysis

Change from baseline to day 57 in CDRS-R total score using MMRM.

Table 8. Change from Baseline to Day 57 in CDRS-R total score [MMRM analysis]

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
Baseline score (mean, SD)	61.6 (9.93)	60.1 (9.01)
Change from baseline		
Mean (SD)	-31.9 (14.86)	-28.8 (14.76)
LS mean (SE)	-29.6 (1.65)	-27.3 (1.60)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-2.29 (1.99)	
95% CI	(-6.22, 1.65)	
p-value	0.252	

Source: Table 11 in Clinical Study Report

Secondary Analyses

Change from baseline to day 57 in CDRS-R total score using ANCOVA with LOCF analysis

Table 9. Change from Baseline to Day 57 in CDRS-R total score [ANCOVA with LOCF analysis]

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
Baseline score (mean, SD)	61.6 (9.93)	60.1 (9.01)
Change from baseline		
Mean (SD)	-27.9 (17.11)	-23.7 (16.90)
LS mean (SE)	-27.7 (1.62)	-24.8 (1.54)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-2.85 (2.11)	
95% CI	(-7.00, 1.30)	
p-value	0.178	

Source: Tables 11.2.1.5.2 in Clinical Study Report

Additional secondary analyses results are in Table 10. Remission was defined as CDRS-R total score ≤ 28 from days 8 to 57. Response was defined as > 50% reduction from baseline in CDRS-R total score from days 8 to 57. The only secondary endpoint that approached significance favoring quetiapine XR was the mean change in CGI-BP-S score.

Table 10. Secondary Analyses*

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
Remission		
Day 57	42 (45.7%)	34 (34%)
Odds ratio	1.6	
95% CI	(0.84, 3.07)	
p-value	0.156	
Response		
Day 57	58 (63%)	55 (55%)
Odds ratio	1.20	
95% CI	(0.58, 2.45)	
p-value	0.625	
CGI-BP-S		
Baseline score (mean, SD)	4.4 (0.61)	4.3 (0.62)
Change from baseline		
Mean (SD)	-1.9 (1.41)	-1.5 (1.31)
LS mean (SE)	-1.72 (0.15)	-1.35 (0.14)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-0.38 (0.19)	
95% CI	(-0.76, 0.01)	
p-value	0.053	
CGI-BP-C		
Change from Day 8		
LS mean (SE)	2.4 (0.15)	2.6 (0.15)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-0.19 (0.19)	
95% CI	(-0.56, 0.19)	
p-value	0.331	

*Remission and response for OC data using Generalized Estimating Equations; CGI-BP-S and CGI-BP-C OC data using MMRM model
Source: Tables 11.2.2.1, 11.2.2.2, 11. from Clinical Study Report

6.1.3 Crosscutting Issues

Subgroup Analyses

Subgroup analyses included rapid versus non-rapid cycling, bipolar I vs. bipolar II disorder, age cohorts, with versus without comorbid ADHD (with/without psychostimulants) and United States versus nonUS sites. All analyses were conducted via MMRM. Similar to the primary and secondary analyses, these analyses also failed to demonstrate a statistically significant difference between the quetiapine XR and placebo groups.

Rapid cycler vs. non-rapid cycler

Table 11. Change from Baseline to Day 57 in CDRS-R total score: Rapid Cycler vs. Non-Rapid Cycler

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
Rapid cycler (n)	22	23
Baseline score (mean, SD)	63 (9.21)	61.1 (9.15)
Change from baseline		
Mean (SD)	-32.1 (17.48)	-25.8 (14.28)
LS mean (SE)	-30.2 (3.04)	-23.9 (3.10)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-6.35 (4.17)	
95% CI	(-14.84, 2.13)	
p-value	0.137	
Non-rapid cycler (n)	70	77
Baseline score (mean, SD)	61.1 (10.17)	59.9 (9.01)
Change from baseline		
Mean (SD)	-31.8 (14.08)	-29.7 (14.90)
LS mean (SE)	-29.8 (1.87)	-28.6 (1.80)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-1.20 (2.24)	
95% CI	(-5.65, 3.25)	
p-value	0.594	

Source: Tables 11.2.1.6.1 and 11.2.1.6.2 in Clinical Study Report

Bipolar I vs. Bipolar II diagnosis

Table 12. Change from Baseline to Day 57 in CDRS-R total score: Bipolar I vs. Bipolar II Diagnosis

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
Bipolar I (n)	75	79
Baseline score (mean, SD)	61.1 (9.76)	60.0 (9.29)
Change from baseline		
Mean (SD)	-30.6 (13.92)	-29.2 (15.09)
LS mean (SE)	-29.0 (1.88)	-27.8 (1.82)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-1.19 (2.21)	
95% CI	(-5.58, 3.20)	
p-value	0.592	
Bipolar II (n)	17	21
Baseline score (mean, SD)	63.7 (10.69)	60.6 (8.08)
Change from baseline		
Mean (SD)	-37.6 (18.13)	-27.4 (13.86)
LS mean (SE)	-33.1 (3.84)	-23.6(3.61)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-9.48 (5.23)	
95% CI	(-20.16, 1.20)	
p-value	0.080	

Source: Tables 11.2.1.7.1 and 11.2.1.7.2 in Clinical Study Report

Age Cohort: 10 to 12 vs. 13 to 17 years of age

Table 13. Change from Baseline to Day 57 in CDRS-R total score: 10 to 12 Years of Age vs. 13 to 17 Years of Age

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
10 to 12 years of age (n)	25	28
Baseline score (mean, SD)	60.7 (9.7)	60.4 (10.3)
Change from baseline		
Mean (SD)	-31.1 (13.92)	-25.9 (17.02)
LS mean (SE)	-29.2 (2.77)	-24.8 (2.58)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-4.47 (3.58)	
95% CI	(11.73, 2.79)	
p-value	0.220	
13 to 17 years of age (n)	67	72
Baseline score (mean, SD)	61.9 (10.06)	60.0 (8.54)
Change from baseline		
Mean (SD)	-32.2 (15.34)	-30.1 (13.66)
LS mean (SE)	-29.8 (1.88)	-27.7 (1.87)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	-2.12 (2.42)	
95% CI	(-6.95, 2.70)	
p-value	0.384	

Source: Table 11.2.1.8.1 and 11.2.1.8.2 from Clinical Study Report

Patients with comorbid ADHD (with and without concomitant psychostimulants) and patients without comorbid ADHD.

The only subgroup that approached significance for efficacy of quetiapine compared to placebo was the subgroup of patients with comorbid ADHD with concomitant psychostimulant use. No rating scales were included in this clinical trial to monitor symptoms of ADHD, so it is not known whether ADHD symptoms improved or worsened in the subgroup of patients with comorbid ADHD.

Table 14. Change from Baseline to Day 57 in CDRS-R total score: Patients With and Without Comorbid ADHD

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
No comorbid ADHD (n)	54	54
Baseline score (mean, SD)	62.4 (10.87)	61.1 (9.86)
Change from baseline		
Mean (SD)	-32.1 (16.53)	-31.2 (15.51)
LS mean (SE)	-30.0 (2.34)	-30.6 (2.33)
Difference (quetiapine XR vs. placebo)		
LS mean (SE)	0.59 (2.95)	
95% CI	(-5.31, 6.48)	
p-value	0.843	
Comorbid ADHD without psychostimulants	18	19

(n)*		
Baseline score (mean, SD)	60.6 (6.84)	60.5 (9.26)
Change from baseline Mean (SD) LS mean (SE)	 -30.4 (11.34) -29.3 (2.78)	 -29.6 (14.49) -26.5 (2.76
Difference (quetiapine XR vs. placebo) LS mean (SE) 95% CI p-value	 -2.79 (3.93) (-10.80, 5.23) 0.483	
Comorbid ADHD with psychostimulants (n)*	20	27
Baseline score (mean, SD)	60.3 (9.81)	57.9 (6.66)
Change from baseline Mean (SD) LS mean (SE)	 -32.8 (14.26) -29.5 (3.58)	 -23.2 (12.32) -20.7 (3.41)
Difference (quetiapine XR vs. placebo) LS mean (SE) 95% CI p-value	 -8.74 (4.56) (-18.01, 0.53) 0.064	

Source: Tables 11.2.1.9.1 and 11.2.1.9.2 from Clinical Study Report and revised Table 11.2.1.9.1 (errata) in 4/18 2012 submission
*Sponsor did not include LS mean change from baseline, LS mean difference, 95% CI or p-value for comorbid ADHD subgroups in the errata.

U.S. vs. Non U.S. sites

The majority of patients in the study were from sites in the U.S. (83%, 160/192). Though neither subgroup demonstrated efficacy of quetiapine vs. placebo, the nonUS sites had a larger LS mean change for both the quetiapine and placebo groups compared to the US sites.

Table 15. Change from Baseline to Day 57 in CDRS-R total score: U.S. and Non U.S. Sites

	Quetiapine XR 150 – 300 mg/day N = 92	Placebo N = 100
U.S. sites (n)	78	82
Change from baseline LS mean (SE)	 -28.8 (1.76)	 -25.8 (1.73)
Difference (quetiapine XR vs. placebo) LS mean (SE) 95% CI p-value	 -3.03 (2.07) (-7.13, 1.07) 0.146	
Non U.S. sites (n)	14	18
Change from baseline LS mean (SE)	 -34.9 (5.11)	 -34.2 (4.69)
Difference (quetiapine XR vs. placebo) LS mean (SE) 95% CI p-value	 -0.72 (6.11) (14.22, 12.78) 0.908	

Source: Tables 11.2.1.10.1 from Clinical Study Report
Baseline scores and mean change from baseline were not provided in CSR.

Dose Response

Quetiapine XR was dosed flexibly, from 150 mg to 300 mg/day, in this clinical trial. Therefore, no dose response analysis was performed.

Key Secondary Variables

No key secondary variables were identified in this study.

Effect Size

The primary efficacy analysis failed to demonstrate a statistically significant difference between quetiapine XR and placebo. The mean change from baseline on CDRS-R was -31.9 in the quetiapine XR group and -28.8 in the placebo group. Significant improvement in depression symptoms were demonstrated in both treatment groups.

Long-Term Efficacy

No long term studies have been performed in this population.

6.1.4 Efficacy Conclusions

Study D144AC00001 was a failed study. The primary efficacy analysis, change from baseline in CDRS-R total score, failed to demonstrate a statistically significant difference between the quetiapine XR (150 – 300 mg/day) and placebo groups. Both treatment groups had significant mean changes from baseline, -31.9 in the quetiapine XR group and -28.8 in the placebo group, indicating improvement in clinical symptoms in both groups. Due to this significant placebo effect, no differences could be detected between the two treatment groups.

Secondary analyses also failed to demonstrate a statistical difference between the two treatment arms. Subgroup analyses (see 6.1.3) also failed to demonstrate a statistical difference between the two treatment arms when analyzing specific relevant subgroups.

7 REVIEW OF SAFETY

Safety Summary

In general, the safety data from study D144AC00001 are consistent with prior clinical studies conducted with quetiapine. There were no new and significant safety findings in this trial that are not currently identified in approved product labeling. There were no deaths in this clinical trial.

Quetiapine is currently approved for the treatment of schizophrenia in adolescents (13 to 17 years of age) and bipolar mania in children and adolescents (10 to 17 years of age). In these clinical trials, rather than the expected finding of orthostatic hypotension that has been noted in clinical trials with adults, an unexpected finding of increased blood pressure was noted in this population. Increases in systolic and diastolic blood pressure were also noted in this clinical trial and appeared to be more frequent in the 10 to 12 year old age cohort.

A greater mean increase in weight was noted in the quetiapine XR group compared to placebo and this appeared to be solely driven by increases in the 10 to 12 year old age cohort. A similar pattern was noted for the numbers of patients with $\geq$ 7% increases in weight.

These weight change and blood pressure differences noted in the 10 to 12 year old cohort compared to the 13 to 17 year old cohort could be due to a higher mg/kg/day exposure to quetiapine XR in the younger cohort (3.6 mg/kg/day vs. 2.7 mg/kg/day) or an increased sensitivity in this younger population. Blood samples were not obtained in this clinical trial so comparisons of quetiapine and norquetiapine concentrations between the two populations cannot be performed.

Clinical laboratory findings were notable mainly for increases in cholesterol and triglycerides in the quetiapine XR group compared to the placebo group. Prolactin and thyroid function tests could not be evaluated since, due to an error, the blood samples were not analyzed during the clinical trial. Prolactin and TFTs were obtained at a recall visit after the study was completed, but these data are not interpretable with regard to determining changes secondary to quetiapine XR or placebo.

ECG findings were significant only for an increase in heart rate noted in the quetiapine XR group. No mean increases in QTcF were noted and no subjects experienced QTcF $\geq$ 450 msec.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data came from one clinical trial:
Study D144AC00001 "An 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy and safety of quetiapine fumarate (Seroquel XR) extended-release in children and adolescent subjects with bipolar depression". This trial included children and adolescents, 10 to 17 years of age.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA version 12.0. The JMP file for adverse events was reviewed with emphasis on the verbatim to preferred term coding. In general, it appeared that verbatim terms were appropriately coded to preferred terms.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The mean (SD) number of days of exposure for the 92 patients in the quetiapine group was 48.3 (14.8) equaling 12 patient-years of exposure. The mean (SD) number of days of exposure for the 100 patients in the placebo group was 50.6 (37.8) equaling 14 patient-years of exposure.

Seventy (76.1%) patients in the quetiapine XR group and 75 (75%) patients in the placebo group received study drug for $\geq$ 7 weeks. The mean modal dose was 204.9 mg/day in the quetiapine XR group (range 150 – 300 mg/day); the mean dose was 192 mg/day.

The Sponsor was asked to provide exposure data for the two age cohorts (Table 16). Though the 10 to 12 year old cohort did have a higher mean modal dose and mean dose of quetiapine XR compared to the 13 to 17 year old cohort, the differences were not large. On a mg/kg basis, using the baseline weight, the differences in mean dose (mg/kg/day) between the two cohorts appear larger. Blood samples were not obtained in this clinical trial so comparisons of quetiapine and norquetiapine concentrations between the two populations cannot be performed.

Table 16. Exposure Data by Age Cohort

	Age Cohort	Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
Duration of exposure (days) [Mean, SD]	10 to 12 years	49.4 (13.9)	52 (12)
	13 to 17 years	47.8 (15.2)	50 (44)
Mean modal dose (mg/day)	10 to 12 years	216	235.7
	13 to 17 years	200.7	215.3
Mean dose (mg/day)	10 to 12 years	196	212.3
	13 to 17 years	190.5	201.6
Mean dose (mg/kg/day)*	10 to 12 years	3.6	4.1
	13 to 17 years	2.7	3.0

* Rough calculation using mean weight at baseline
Source: Correspondence via email, 3/1/2013

7.2.2 Explorations for Dose Response

Quetiapine XR was dosed flexibly, from 150 mg to 300 mg/day, in this clinical trial. Therefore, no dose response explorations were performed.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The schedule of events is provided in Appendix 9.6.

The clinical trial included the usual routine clinical laboratory testing at screening/baseline, day 29 and end of study. The study had completed by February 23, 2010 when the Sponsor discovered that the central laboratory (b) (4) did not analyze the blood samples for prolactin and thyroid function tests. The Sponsor then submitted a protocol amendment for recall visits; the recall visits were scheduled from June 2010 to November 2010 (regardless of when the patients had completed the study) to obtain blood samples for prolactin and thyroid function tests [due to significant confounds, especially concomitant medications, these laboratory data were not analyzed or included in this review].
Overall, the types of assessments and frequency of assessments were acceptable for this clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Some of the relevant safety issues for the class of antipsychotics include extrapyramidal side effects (parkinsonism, dystonia, akathisia), tardive dyskinesia, neuroleptic malignant syndrome, QT prolongation, hyperprolactinemia, orthostatic hypotension, weight gain, diabetes mellitus, hyperglycemia, hyperlipidemia, and leukopenia/neutropenia/agranulocytosis. Additionally, increased blood pressure was noted in prior clinical trials in bipolar mania and schizophrenia in children/adolescents treated with quetiapine.
This clinical trial included appropriate assessments for these adverse events.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in this clinical trial.

7.3.2 Nonfatal Serious Adverse Events

Five patients experienced SAEs during this clinical trial, one patient was receiving quetiapine XR (300 mg) and four patients were receiving placebo. The patient receiving quetiapine XR was a 13 YOBF with comorbid ADHD who experienced agitation beginning on day 42 and continuing for 8 days, study drug was discontinued, the patient required hospitalization and the event resolved. The SAEs occurring in the patients receiving placebo included "social stay hospitalization", exacerbation of bipolar I symptoms, aggression and exacerbation of depressive symptoms; all patients required hospitalization and were discontinued from the study.

Two SAEs were reported at the recall visit, a visit that occurred 4 to 9 months after the study had completed (primarily to obtain some clinical labs, see Section 7.4.2). Both of these SAEs occurred in patients who had taken quetiapine during the study. Though these SAEs are difficult to interpret due to their occurrence months after study completion, they are included here for completeness. A 10 YOWF experienced a psychotic disorder occurring 4 months after she completed the study. This patient was hospitalized and diagnosed with paranoid schizophrenia. The event resolved after 10 days. She was not taking quetiapine at the time of the SAE. A 14 YOWF experienced suicidal ideation (no details provided) one month after she completed the study. She was hospitalized for approximately 1 month. She also experienced a "'non-suicidal'" overdose of methylphenidate nine months after she completed the study; she was taken to the emergency room but not admitted (no further details provided). This patient was taking quetiapine at the time of these SAEs.

7.3.3 Dropouts and/or Discontinuations

Three (3.3%) patients in the quetiapine XR group and 12 (12%) patients in the placebo group discontinued the study due to adverse events. One of the patients in the quetiapine group experienced three adverse events that led to discontinuation (headache, sedation, increased fatigue). Approximately half of the discontinuations due to adverse events in the placebo group appeared related to the underlying disorder (irritability, aggression, bipolar disorder, depressive symptom).

Table 17. Adverse Events (n, %) Leading to Study Discontinuation

	Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
Agitation	1 (1.1)	0
Fatigue	1 (1.1)	0
Headache	1 (1.1)	1 (1)
Sedation	1 (1.1)	1 (1)
Somnolence	1 (1.1)	2 (2)
Aggression	0	1 (1)
Bipolar disorder	0	1 (1)
Depressive symptom	0	1 (1)
Irritability	0	3 (3)
Neutropenia	0	1 (1)
Social stay hospitalization	0	1 (1)

Source: Table 18 from Clinical Study Report

7.3.4 Significant Adverse Events

No significant adverse events not otherwise covered elsewhere in the review were identified.

7.3.5 Submission Specific Primary Safety Concerns

Increased Blood Pressure

Quetiapine is currently approved for the treatment of schizophrenia in adolescents (13 to 17 years of age) and bipolar mania in children and adolescents (10 to 17 years of age). In these clinical trials, rather than the expected finding of orthostatic hypotension that has been noted in clinical trials with adults, an unexpected finding of increased blood pressure was noted in this population. Vital signs in this submission were reviewed with special emphasis on increases in systolic and diastolic blood pressure (see Section 7.4.3, Vital Signs).

Extrapyramidal symptoms

One subject in the quetiapine XR group had an adverse event "restlessness", no other EPS-related adverse events were reported. This reviewer reviewed the JMP file and did not note any adverse events (verbatim term) consistent with EPS. The protocol included the following EPS rating scales: Barnes Akathisia Rating Scale, Simpson-Angus Scale and the AIMS (dyskinesia). EPS ratings were conducted at baseline, day 29 and day 57/end of study. The mean changes from baseline were small and not different between the quetiapine and placebo groups (data not shown). The proportions of patients demonstrating a worsening of symptoms, no change in symptoms, or improved symptoms were also similar between the quetiapine and placebo groups for these scales (data not shown).

Suicidality

Subjects were excluded from this trial if they posed a current serious suicidal or homicidal risk, had a CDRS-R item 13 score of > 3 at enrollment/randomization, or who had made a suicide attempt within the past 6 months prior to enrollment.

The C-SSRS scale was used to assess suicidality in this clinical trial. The treatment groups were similar with regard to C-SSRS item ratings: occurrence of suicidality (6.5% quetiapine XR, 8% placebo), occurrence of suicidal ideation (6.5% quetiapine XR, 8% placebo), emergence of suicidal ideation (5.4% quetiapine XR, 6% placebo), worsening of ideation (0 quetiapine XR, 1% placebo). No subjects experienced occurrence of suicidal behavior, emergence of suicidal behavior or emergence of serious suicidal ideation.

One 15 YOWF in the quetiapine XR group had an adverse event of self-injurious behavior that occurred after receiving quetiapine for 29 days. The investigator considered the adverse event to be mild, no details regarding the incident were included in the narrative.

Treatment-emergent Mania

Treatment emergent mania was defined as the new onset of an adverse event of mania or hypomania and/or a YMRS score > 16 on two consecutive assessments or at day 57. The proportion of patients with mania at any time during treatment was 2 (2.2%) in the quetiapine XR group and 10 (10%) in the placebo group.

This reviewer reviewed the YMRS total scores in the JMP file to evaluate the occurrence of YMRS scores > 16 (not just consecutive scores > 16).
Four (4.3%) subjects in the quetiapine group had YMRS > 16 on $\geq$ 1 occasion compared to 8 (8%) subjects in the placebo group. The highest YMRS scores were 41 in the quetiapine XR group and 40 in the placebo group.

Cataracts
The only adverse events reported that related to disorders of the eye were astigmatism and blurred vision. One patient in the quetiapine group had the adverse event blurred vision and one patient in the placebo group had the adverse event blurred vision and astigmatism.

This protocol included a regular, hand-held ophthalmoscopic eye examination as part of the physical examination conducted screening and at the end of the study. Using this assessment, only three patients in the placebo group were found to have significant findings that were present at screening: cyst; myopia; orthophoria, congenital coloboma of iris and choroid. Four (< 1%) patients in the quetiapine group and 3 (< 1%) patients in the placebo group had a positive family history for congenital cataracts. This assessment was not specific for diagnosing cataract formation and no slit-lamp examinations were performed.

Neutropenia
Refer to Section 7.4.2 for hematology lab values.

QT Prolongation
Refer to Section 7.4.4 for ECG data. There was no signal for QT prolongation from this clinical trial.

Diabetes Mellitus
Three patients (3.3%) in the quetiapine group had adverse events potentially consistent with diabetes mellitus: thirst (n = 2) and diabetes mellitus (n = 1). The patient with diabetes mellitus was a 11 YOWF who had a baseline fasting glucose of 5.7 mmol/L (102.7 mg/dL) and day 31 fasting glucose of 7.4 mmol/L (133.3 mg/dL). Study medication was stopped on day 50 and a normal fasting glucose of 5.9 mmol (106.3 mg/dL) was obtained on day 91. Insulin levels also increased and normalized similar to fasting glucose levels. The patients with adverse events of thirst included a 15 YOWF who experienced the adverse event one day after receiving quetiapine and resolved the following day. Fasting glucose and insulin levels were obtained ~26 days after the onset of this adverse event and were within normal limits. The other patient with an adverse event of thirst was a 13 YOAM who complained of thirst 7 days after receiving quetiapine. The event resolved 30 days after the onset. Fasting glucose and insulin levels were within normal limits throughout the trial.
Refer to Section 7.4.2 for fasting glucose data.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Sixty-eight (73.9%) patients in the quetiapine XR group and 66 (66%) patients in the placebo group experienced adverse events in the clinical trial. In product labeling, the terms somnolence and sedation are combined into one term due to difficulties in discriminating between these two adverse events.

Table 18. Adverse Events (n, %) Occurring in ≥ 2% of Patients in the Quetiapine Treatment Group (in decreasing order of occurrence in quetiapine XR arm)

Preferred Term	Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
Headache	20 (21.7)	12 (12)
Sedation	7 (7.6)	6 (6)
Dizziness	6 (6.5)	2 (2)
Somnolence	6 (6.5)	4 (4)
Diarrhea	5 (5.4)	1 (1)
Fatigue	5 (5.4)	2 (2)
Nausea	5 (5.4)	1 (1)
Influenza	4 (4.3)	1 (1)
Nasopharyngitis	4 (4.3)	3 (3)
Appetite, increased	3 (3.3)	3 (3)
Epistaxis	3 (3.3)	0
Gastroenteritis	3 (3.3)	0
Increased appetite	3 (3.3)	3 (3)
Sinusitis	3 (3.3)	0
Urinary tract infection	3 (3.3)	0
Vomiting	3 (3.3)	3 (3)
Abdominal pain	2 (2.2)	3 (3)
Abdominal pain, upper	2 (2.2)	1 (1)
Appetite, decreased	2 (2.2)	2 (2)
Constipation	2 (2.2)	1 (1)
Dermatitis contact	2 (2.2)	1 (1)
Dysmenorrhea	2 (2.2)	2 (2)
Ear infection	2 (2.2)	0
Gastroesophageal reflux disease	2 (2.2)	0
Insomnia	2 (2.2)	0
Irritability	2 (2.2)	5 (5)

Nightmare	2 (2.2)	2 (2)
Pyrexia	2 (2.2)	1 (1)
Thirst	2 (2.2)	0

Source: Table 14 from Clinical Study Report

Common Adverse Events by Age Group

Approximately equal percentages of patients in each age group (10 to 12 years, 13 to 17 years) experienced adverse events in the quetiapine XR and placebo groups. In the quetiapine XR group, 18 (75%) patients 10 to 12 years of age and 50 (73.5%) patients 13 to 17 years of age experienced adverse events. In the placebo group, 18 (62.1%) patients 10 to 12 years of age and 48 (67.6%) patients 13 to 17 years of age experienced adverse events.

The overall pattern of common adverse events was similar between the two age cohorts (Table 18). Though there appeared to be some differences, e.g. sedation/somnolence appeared to be more frequent in the 10 to 12 year old cohort receiving quetiapine, there were also fewer patients in that cohort (3 patients = 12% incidence). Insomnia and nightmares occurred in the quetiapine-treated patients in the younger cohort and did not occur in the quetiapine-treated patients in the older cohort.

Table 19. Adverse Events (n, %) Occurring in $\geq$ 2 Patients in the Quetiapine Treatment Group (in decreasing order of occurrence in quetiapine XR arm) by Age Cohort

	10 to 12 years		13 to 17 years	
Preferred Term	Quetiapine XR 150 to 300 mg/day N = 25	Placebo N = 28	Quetiapine XR 150 to 300 mg/day N = 67	Placebo N = 72
Headache	4 (16)	2 (7.1)	16 (23.9)	10 (13.9)
Sedation	3 (12)	1 (3.6)	4 (6.0)	5 (6.9)
Somnolence	3 (12)	0	3 (4.5)	4 (5.6)
Diarrhea	2 (8)	0	3 (4.5)	1 (1.4)
Epistaxis	2	0	0	0
Insomnia	2 (8)	0	0	0
Nightmare	2 (8)	0	0	2 (2.8)
Dizziness	1 (4)	0	5 (7.5)	2 (2.8)
Fatigue	1 (4)	1 (3.6)	4 (6)	1 (1.4)
Nausea	1 (4)	0	4 (6)	1 (1.4)
Influenza	1 (4)	0	3 (4.5)	1 (1.4)
Nasopharyngitis	1 (4)	0	3 (4.5)	3 (4.2)

Vomiting	1 (4)	2 (7.1)	2 (3)	1 (1.4)
Abdominal pain	0	2 (7.1)	2 (3)	1 (1.4)
Abdominal pain, upper	0	0	2 (3)	1 (1.4)
Appetite, increased	1 (4)	1 (3.6)	2 (3)	2 (2.8)
Constipation	0	1 (3.6)	2 (3)	0
Dermatitis contact	0	0	2(3)	1 (1.4)
Dysmenorrhea	0	0	2 (3)	2 (2.8)
Gastroenteritis	1 (4)	0	2 (3)	0
Pyrexia	0	1 (3.6)	2 (3)	0
Sinusitis	1 (4)	0	2 (3)	0
Thirst	0	0	2 (3)	0
Urinary tract infection	1 (4)	0	2 (3)	0

Source: Table 15 from Clinical Study Report

7.4.2 Laboratory Findings

The study had completed by February 23, 2010 when the Sponsor discovered that the central laboratory (b) (4) did not analyze the blood samples for prolactin and thyroid function tests. The Sponsor then submitted a protocol amendment for recall visits; the recall visits were scheduled from June 2010 to November 2010 (regardless of when the subjects had completed the study) to obtain blood samples for prolactin and thyroid function tests. Since subjects could have completed the study months prior and were likely taking other psychotropics, these lab results were considered confounded and were not reviewed.

Hematology

Mean Change from Baseline

Mean change from baseline in hematology values is listed in Table 20 (only absolute values for differential included in this table). Mean changes were lower in the quetiapine XR group compared to placebo for hematocrit, hemoglobin, RBC and platelets. Of note, the mean changes in WBC and absolute neutrophil count were lower in the placebo group compared to the quetiapine XR group.

Table 20. Mean Change (SD) from Baseline to End of Study: Hematology

	Quetiapine XR 150 to 300 mg/day (N = 92)	Placebo (N = 100)
Hematocrit (proportion of 1)	-0.010 (0.02)	-0.005 (0.02)
Hemoglobin (g/L)	-3.4 (7.6)	-1.4 (7.0)
RBC (10E12/L)	-0.12 (0.27)	-0.05 (0.24)
Platelets (10E9/L)	-7.0 (43.7)	-4.8 (41.2)
WBC (10E9/L)	-0.08 (1.8)	-0.25 (1.6)

Basophils, Abs (10E9/L)	-0.002 (0.04)	-0.001 (0.03)
Eosinophils, Abs (10E9/L)	0.04 (0.19)	0.018 (0.13)
Lymphocytes, Abs (10E9/L)	-0.080 (0.60)	-0.090 (0.48)
Monocytes, Abs (10E9/L)	0.005 (0.13)	-0.024 (0.15)
Neutrophils, Abs (10E9/L)	-0.063 (1.6)	-0.14 (1.5)

Source: Table 11.3.7.1.1.1

Potentially Clinically Significant Shifts to Low/High

See Appendix 9.7 for the definition of potentially clinically significant laboratory values used by the Sponsor.

There were no shifts to low or high values in either treatment group for platelet count, basophils, lymphocytes, or monocytes. Interestingly, there were more shifts to low values for neutrophils in the placebo group compared to the quetiapine XR group. Neutropenia was defined as a baseline count $\geq 1.5 \times 10^9$ cells/L with a post-baseline count $< 1.5 \times 10^9$ cells/L; severe neutropenia was defined as a post-baseline count $< 0.5 \times 10^9$ cells/L. The 2 patients in the quetiapine XR group with a shift from normal baseline to low met criteria for neutropenia (lowest values 1.14×10^9 cells/L at day 57 and 1.12×10^9 cells/L at day 29); the 7 patients in the placebo group with a shift from normal baseline to low met criteria for neutropenia. One of the 7 patients in the placebo group met criteria for severe neutropenia (lowest vale 0.13×10^9 cells/L); no patients in the quetiapine XR group met criteria for severe neutropenia.

Table 21. Potentially Clinically Significant Shifts to Low/High at Any Time During Treatment

			Any Time During Treatment		
	Group*	Baseline	Low n (%)	Normal n (%)	High n (%)
Hematocrit	Quetiapine	Low Normal High	2 (2.2) 10 (11.1) 0	1 (1.1) 75 (83.3) 2 (2.2)	0 0 0
	Placebo	Low Normal High	3 (3.4) 3 (3.4) 0	1 (1.1) 80 (89.9) 1 (1.1)	0 1 (1.1) 0
Hemoglobin	Quetiapine	Low Normal High	0 3 (3.3) 0	0 85 (94.4) 2 (2.2)	0 0 0
	Placebo	Low Normal High	1 (1.1) 2 (2.2) 0	1 (1.1) 86 (94.5) 1 (1.1)	0 0 0
WBC	Quetiapine	Low Normal High	0 2 (2.2) 0	0 87 (97.8) 0	0 0 0
	Placebo	Low Normal High	0 1 (1.1) 0	0 90 (98.9) 0	0 0 0
Neutrophils, Abs	Quetiapine	Low Normal High	1 (1.2) 2 (2.3) 0	0 81 (94.2) 1 (1.2)	0 1 0
	Placebo	Low Normal High	0 7 (7.7) 0	0 83 (91.2) 0	0 1 (1.1) 0

Source: Table 11.3.7.1.1.2.4
*Safety analysis dataset: quetiapine XR N = 92, placebo N = 100; baseline and at least one post baseline lab value available for > 88% of patients

Clinical Chemistry

Mean Change from Baseline

The clinical chemistry analytes showing the greatest mean change from baseline between the two treatment groups were AST, insulin, cholesterol and triglycerides. Urea data was only obtained in 19 patients (n = 8 quetiapine, n = 11 placebo). The mean change from baseline for insulin in the quetiapine XR group was large primarily due to an outlier. Patient E110700, a 13 YOBF, had a baseline insulin of 194 pmol/L (fasting glucose = 4.6 mmol/L) that increased to 4688 pmol/L (fasting glucose = 5.5 mmol/L) by week 4 and 4980 pmol/L (random glucose = 6.9 mmol/L) by week 8. The Sponsor has been asked to clarify and interpret this finding. Due to this outlier, the mean and median changes from baseline for insulin are in Table 22.

Table 22. Mean Change (SD) from Baseline to Endpoint: Clinical Chemistry

	Quetiapine XR 150 to 300 mg/day (N = 92)	Placebo (N = 100)
ALT (IU/L)	2.2 (12.5)	-1.5 (9.6)
AST (IU/L)	1.5 (7.6)	-1.4 (5.6)
Alkaline Phosphatase (IU/L)	-3.9 (34.9)	-8.8 (36.7)
Total Bilirubin (µmol/L)	-0.7 (4.05)	-0.5 (3.50)
Sodium (mmol/L)	0.4 (2.9)	0.3 (2.7)
Glucose, Fasting (mmol/L) (mg/dL)	 0.06 (0.68) 1.1 (12.3)	 0.12 (0.63) 2.2 (11.3)
BUN (mmol/L)	-0.05 (1.3)	0.193 (1.27)
Creatinine (µmol/L)	-0.3 (8.4)	0.8 (8.6)
Potassium (mmol/L)	-0.11 (0.41)	0.03 (0.74)
Chloride (mmol/L)	0.9 (2.3)	0.7 (2.3)
Urea (mmol/L)	-0.50 (0.97)	-1.1 (1.6)
Albumin (g/L)	-1.1 (2.9)	-0.3 (2.9)
Calcium (mmol/L)	-0.01 (0.10)	-0.01 (0.11)
Bicarbonate (mmol/L)	-0.4 (2.5)	-0.3 (2.5)
Insulin (pmol/L) median	94.8 (531.4) 14	36.8 (152.6) 17
Total Cholesterol (mmol/L) (mg/dL)	 0.034 (0.55) 1.3 (21.2)	 -0.11 (0.56) -4.2 (21.6)
HDL		

(mmol/L)	-0.03 (0.21)	-0.02 (0.24)
(mg/dL)	-1.2 (8.1)	-0.77 (9.3)
LDL		
(mmol/L)	-0.04 (0.49)	-0.02 (0.50)
(mg/dL)	-1.5 (18.9)	-0.77 (19.3)
Triglycerides		
(mmol/L)	0.23 (0.62)	-0.12 (0.81)
(mg/dL)	20.3 (54.9)	-10.6 (71.7)

Source: Table 11.3.7.1.2.1 from Clinical Study Report
SI units converted to conventional units using conversion factors 0.0555 (glucose), 0.0259 (cholesterol, LDL, HDL), 0.0113 (triglycerides)

Potentially Clinically Significant Shifts to Low/High

See Appendix 9.7 for the definition of potentially clinically significant laboratory values used by the Sponsor. The original submission used PCS criteria for lipids that were relevant for adults and not children/adolescents. The Sponsor was asked to provide the shift data for the appropriate PCS values for this population: cholesterol $\geq$ 200 mg/dL, triglycerides $\geq$ 150 mg/dL, LDL $\geq$ 130 mg/dL and HDL $\leq$ 40 mg/dL.
Table 23 includes potentially clinically significant shifts for chemistry analytes where $\geq$ 1 patient exhibited a shift in the quetiapine XR group. For many analytes, no potentially clinically significant shifts were noted. The chemistry analytes that appeared to show more shifts in the quetiapine XR group compared to the placebo group were bicarbonates, HDL and triglycerides.

Table 23. Potentially Clinically Significant Shifts in Clinical Chemistry Indices at Any Time (n/N; %)

	PCS Criterion	Quetiapine XR 150 to 300 mg/day (N = 92)	Placebo (N = 100)
ALT*	$\geq$ 3x ULN	1/89 (1.1)	0
Total Bilirubin*	> 1.5x ULN	1/89 (1.1)	0
Sodium	$\leq$ 132 mmol/L	1/90 (1.1)	1/92 (1.1)
Glucose, fasting	$\geq$ 126 mg/dL	1/75 (1.3)	0
Bicarbonates	$\geq$ 30 mmol/L	7/89 (7.8)	3/89 (3.4)
Cholesterol	$\geq$ 200 mg/dL	7/83 (8.4)	5/84 (6)
HDL	< 40 mg/dL	13/65 (20)	11/74 (14.9)
LDL	$\geq$ 130 mg/dL	2/86 (2.3)	3/85 (3.5)
Triglycerides	$\geq$ 150 mg/dL	22/80 (27.5)	7/82 (8.5)

*The PCS shifts to high for ALT (n = 1) and total bilirubin (n = 1) are not the same patient.
Source: Table 11.3.7.1.2.2.7 from CSR and Tables 1 and 2 from 3/15/2013 email correspondence.

7.4.3 Vital Signs

Weight Change

The mean change from baseline for weight was 1.3 kg in the quetiapine XR group compared to 0.6 kg in the placebo group, similar patterns were noted for mean change in BMI and waist circumference. Interestingly, the 10 to 12 year old cohort was the cohort where the weight increase was most significant: 2.4 kg in the quetiapine XR group compared to no weight gain in the placebo group (Table 25). Similar findings were noted in the weight shift (> 7% gain) data (Table 26).

Table 24. Weight (kg), BMI, Waist Circumference: Mean Change (SD) from Baseline

		Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
Weight (kg)	Baseline	65.1 (24.4)	64.1 (23.1)
	End of Study	66.4 (24.1)	64.7 (23.7)
	Mean Change	1.3 (2.1)	0.6 (2.4)
BMI (kg/m2)	Baseline	24.4 (7.3)	24.4 (7.1)
	End of Study	24.8 (7.2)	24.4 (7.1)
	Mean Change	0.35 (0.84)	-0.03 (1.2)
Waist circumference (cm)	Baseline	81.5 (18.3)	81.3 (17.3)
	End of Study	82.7 (18.1)	81.7 (17.3)
	Mean Change	1.2 (3.62)	0.4 (3.7)

Source: Table 11.3.8.1.1.1 from Clinical Study Report

Table 25. Weight (kg): Mean Change (SD) from Baseline By Age Cohort

		Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
10 – 12 years	Weight (kg)		
	Baseline	53.9 (15.7)	53.3 (17.5)
	End of Study	56.3 (15.9)	53.3 (18.9)
	Mean Change	2.4 (2.2)	0.0 (2.1)
13 – 17 years	Weight (kg)		
	Baseline	69.1 (25.8)	68.5 (23.7)
	End of Study	70.3 (26.2)	69.4 (24.0)
	Mean Change	1.0 (2.1)	0.8 (2.5)

Source: Table 1 from 4/18/2012 submission

The Sponsor provided the $\geq$ 7% body weight increases by week. As noted above and in Table 26, the 10-12 year old cohort had the greatest increase in weight compared to placebo. Only 2 of the patients in this cohort had $\geq$ 7% increases in weight by Day 29. By Day 43, 4 patients met this criterion and by Day 50, 6 patients met this criterion.

Table 26. Weight Gain (≥ 7%)

	Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
End of Study (n/N, %)		
All patients	10/92 (10.9)	6/100 (6)
10 to 12 years	6/25 (24)	0/28
13 to 17 years	4/67 (6)	6/72 (8.3)
Day 57 (n/N, %)		
All patients	10/73 (13.7)	5/73 (6.8)
10 to 12 years	6/21 (28.6)	0/23
13 to 17 years	4/52 (7.7)	5/51 (9.8)

Source: Tables 11.3.8.1.1.3, 11.3.8.1.1.13, 11.3.8.1.1.14

Comparison of Quetiapine XR to Quetiapine (IR)
The data from the quetiapine IR studies are from one 6 week schizophrenia study in adolescents evaluating 400 and 800 mg/day (D1441C00112) and one 3-week bipolar mania study in children and adolescents evaluating 400 and 600 mg/day (D1441C00149). The mean change in weight was similar between these studies. The mean change in weight in the quetiapine (IR) studies were 1.5 to 1.9 kg increase in the quetiapine (IR) groups compared to -0.1 to 0.4 kg change in the placebo groups. The Sponsor did not provide a separate analysis for weight change by age cohort.

Blood Pressure

Vital signs were assessed at each study visit in the supine position (3 minutes) and in the standing position (within 3 minutes of standing). Sitting vital signs were obtained for very few patients (n = 13); sitting vital signs were added to the protocol via amendment a few months prior to the end of the study.

Orthostatic Assessments

In general, there was little evidence of orthostatic changes in vital signs in the quetiapine XR group. Though there was a mean decrease in SBP from supine to standing, it was small and consistent between the two age cohorts (Table 27). The increase in supine to standing pulse in the quetiapine XR group was similar to the increase in the placebo group and consistent between the two age cohorts.

The Sponsor was asked to provide PCS changes for diastolic BP defined as ≥ 10 mmHg increase (rather than the 20 mm Hg increase in the CSR). The PCS changes (Table 28) indicated a higher frequency of orthostatic changes in the placebo group compared to the quetiapine XR group in all but the DBP category.

Table 27. Supine to Standing Position – Mean (SD) Change from Baseline to End of Study

	Age	Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
Pulse (bpm)	All	7.7 (10.8)	8.6 (10.1)
	10 – 12 years	7.3 (8.1)	8.9 (10.3)
	13 – 17 years	8.2 (11.8)	7.9 (9.6)
SBP (mmHg)	All	-0.4 (6.2)	1.6 (7.3)
	10 – 12 years	-0.2 (5.5)	1.8 (6.2)

	13 – 17 years	-0.4 (6.6)	1.4 (7.3)
DBP (mmHg)	All 10 – 12 years 13 – 17 years	1.7 (6.2) 1.9 (5.8) 1.6 (6.3)	3.3 (7.6) 2.1 (9.7) 3.9 (6.5)

Source: Table 11.3.8.1.1.2 and Table 8 from 11/14/12 submission.

Table 28. Potentially Clinically Significant Orthostatic Changes (at any time)

			Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
	Age	Range	n/N,%	n/N,%
Supine to Standing Pulse	All 10 – 12 years 13 – 17 years	≥ 20 bpm increase	22/92 (23.9) 5/25 (20) 17/67 (25.4)	26/100 (26) 7/28 (25) 19/72 (26.4)
Supine to Standing SBP	All 10 – 12 years 13 – 17 years	≥ 20 mmHg decrease	1/92 (1.1) 0/25 1/67 (1.5)	10/100 (10) 3/28 (10.7) 7/72 (9.7)
Supine to Standing DBP	All 10 – 12 years 13 – 17 years	≥ 10 mmHg decrease	15/92 (16.3) 3/25 (12) 12/67 (17.9)	13/100 (13) 7/28 (25) 6/72 (8.3)
Supine to Standing Pulse + SBP	All 10 – 12 years 13 – 17 years	≥ 20 bpm increase *and* ≥ 20 mmHg decrease	0/92 0/25 0/67	5/100 (5) 0/28 5/72 (7)

Source: Table 11.3.8.1.1.4 and Tables 11.3.8.1.1.8 – 11.3.8.1.1.11
DBP data from Table 5 in 11/14/12 submission

Increases in Blood Pressure

There were greater mean increases in supine pulse, systolic blood pressure and diastolic blood pressure in the quetiapine XR group compared to the placebo group.

Table 29. Supine Vital Signs – Mean (SD) Change from Baseline to End of Study

	Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
Pulse (bpm)	3.4 (10.6)	-1.1 (10.8)
SBP (mmHg)	2.3 (9.4)	-1.3 (8.6)
DBP (mmHg)	1.7 (8.4)	-1.2 (9.1)

Source: Table 11.3.8.1.1.1

Potentially clinically significant increases in blood pressure was defined as ≥ 20 mmHg increase in supine SBP and ≥ 10 mmHg increase in supine DBP (Table 30). A greater percentage of subjects in the quetiapine XR group had increases ≥ 10 mmHg in supine DBP compared to placebo, this was especially evident in the 10 to 12 year old cohort. Blood pressure shifts to high for both SBP and DBP were more frequent in the younger cohort compared to the older cohort (Table 31).

Table 30. Potentially Clinically Important Increases in Blood Pressure (at any time)

		Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
Supine SBP ≥ 20 mmHg increase	All (n/N,%)	6/92 (6.5)	6/100 (6)
	10 – 12 years (n/N,%)	1/25 (4)	0/28
	13 – 17 years (n/N,%)	5/67 (7.5)	6/72 (8.3)
Supine DBP ≥ 10 mmHg increase	All (n/N,%)	43/92 (46.7)	36/100 (36)
	10 – 12 years (n/N,%)	14/25 (56)	10/28 (35.7)
	13 – 17 years (n/N,%)	29/67 (43.3)	26/72 (36.1)

Source: Table 30 from Clinical Study Report

Table 31. Potentially Clinically Important Blood Pressure Shifts (at any time)

			Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
	Age	Range	n/N,%	n/N,%
Supine SBP	All	All	10/92 (10.9)	12/100 (12)
	10 – 12 years	Boys ≥ 123 mmHg; Girls ≥ 121 mmHg	4/25 (16)	2/28 (7.1)
	13 – 17 years	Boys ≥ 136 mmHg; Girls ≥ 128 mmHg	6/67 (9)	10/72 (13.9)
Supine DBP	All	All	15/92 (16.3)	13/100 (13)
	10 – 12 years	Boys and Girls ≥ 78 mmHg	8/25 (32)	6/28 (21.4)
	13 – 17 years	Boys ≥ 85 mmHg; Girls ≥ 82 mmHg	7/67 (10.4)	7/72 (9.7)

Source: Table 31 from Clinical Study Report

Comparison of Quetiapine XR to Quetiapine (IR)

The data from the quetiapine IR studies are from one 6 week schizophrenia study in adolescents evaluating 400 and 800 mg/day (D1441C00112) and one 3-week bipolar mania study in children and adolescents evaluating 400 and 600 mg/day (D1441C00149). A greater percentage of patients in the quetiapine IR groups experienced potentially clinically important increases in blood pressure compared to patients in the quetiapine XR group (Table 30 vs. Table 32). It is important to note that the doses of quetiapine XR in the bipolar depression study were much lower than the doses of quetiapine (IR) in the schizophrenia and bipolar mania studies.

Table 32. Potentially Clinically Important Increases in Blood Pressure (at any time) – **Quetiapine IR**

		Quetiapine (IR) 400 – 800 mg/day N = 340	Placebo N = 165
Supine SBP ≥ 20 mmHg increase	All (n/N,%)	51/335 (15.2)	9/163 (5.5)
	10 – 12 years (n/N,%)	15/85 (17.6)	1/36 (2.8)
	13 – 17 years (n/N,%)	36/250 (14.4)	8/127 (6.3)
Supine DBP ≥ 10 mmHg increase	All (n/N,%)	136/335 (40.6)	40/163 (24.5)
	10 – 12 years (n/N,%)	40/85 (47.1)	8/36 (22.2)
	13 – 17 years (n/N,%)	96/250 (38.4)	32/127 (25.2)

Source: Clinical Review NDA 20-639 S-045, S-046

In general, the incidences of potentially clinically important blood pressure shifts are similar between the quetiapine XR and quetiapine IR studies. Interestingly, the rates of these shifts appeared higher in the placebo group for the quetiapine XR study compared to the placebo groups in the quetiapine (IR) studies (Table 31 vs. Table 33).

Table 33. Potentially Clinically Important Blood Pressure Shifts (at any time) – **Quetiapine (IR)**

			Quetiapine (IR) 400 – 800 mg/day N = 340	Placebo N = 165
	Age	Range	n/N,%	n/N,%
Supine SBP	All	All	45/317 (14.2)	9/153 (5.9)
	10 – 12 years	Boys ≥ 123 mmHg; Girls ≥ 121 mmHg	16/80 (20)	3/32 (9.4)
	13 – 17 years	Boys ≥ 136 mmHg; Girls ≥ 128 mmHg	29/237 (12.2)	6/121 (5)
Supine DBP	All	All	53/315 (16.8)	11/151 (7.3)
	10 – 12 years	Boys and Girls ≥ 78 mmHg	22/74 (29.7)	6/29 (20.7)
	13 – 17 years	Boys ≥ 85 mmHg; Girls ≥ 82 mmHg	31/241 (12.9)	5/122 (4.1)

Source: Clinical Review NDA 20-639 S-045, S-046

7.4.4 Electrocardiograms (ECG's)

The most notable finding on mean change from baseline in ECG parameters was heart rate, an increase of 3.4 bpm in the quetiapine XR group compared to an increase of 0.3 bpm in the placebo group. Consistent with this effect on heart rate, the mean change from baseline in QTcB was greater in the quetiapine XR group compared to placebo. The mean change from baseline in QTcF was similar between the two groups.

Table 34. ECG: Mean (SD) Change from Baseline to End of Study

	Quetiapine XR 150 to 300 mg/day N = 92	Placebo N = 100
Heart rate (bpm)	3.4 (12.6)	0.3 (13.6)
RR interval (msec)	-43.6 (140.8)	-6.7 (166.2)
PR interval (msec)	2.1 (11.4)	2.5 (12.8)
QRS interval (msec)	0.9 (5.7)	0.1 (5.8)
QT interval (msec)	-7.8 (26.4)	-2.0 (27.9)
QTcF interval (msec)	-1.6 (16.9)	-1.1 (16.6)
QTcB interval (msec)	1.7 (20.9)	-0.7 (22)

Source: Table 11.3.8.1.2.1 from Clinical Study Report

Potentially clinically significant changes in heart rate was defined as > 120 bpm and/or > 15 bpm increase from baseline in 10 – 12 year olds and > 110 bpm and/or > 15 bpm increase from

baseline in 13 – 17 year olds – no subjects met this criteria. No subjects experienced QTcF $\geq$ 450 msec and/or > 15% increase from baseline.

7.4.5 Special Safety Studies/Clinical Trials
Not applicable.

7.4.6 Immunogenicity
Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events
Quetiapine XR was dosed flexibly, from 150 mg to 300 mg/day, in this clinical trial. Therefore, no dose dependency was evaluated for adverse events.

7.5.2 Time Dependency for Adverse Events
This reviewer was unable to locate an analysis for time dependency of adverse events. Little data was available with respect to frequency of specific adverse events at discrete study visits.

7.5.3 Drug-Demographic Interactions
Some adverse events appeared to occur more frequently and/or to a greater extent in the 10 to 12 year old cohort compared to the 13 to 17 year old cohort – e.g. weight gain and increases in blood pressure (see Section 7.4.3, Vital Signs). This could be due to a higher mg/kg/day exposure to quetiapine XR in the younger cohort (3.6 mg/kg/day vs. 2.7 mg/kg/day) or an increased sensitivity in this younger population (see Section 7.2.1, Overall Exposure). Blood samples were not obtained in this clinical trial so comparisons of quetiapine and norquetiapine concentrations between the two populations cannot be performed.

7.5.4 Drug-Disease Interactions
No new information.

7.5.5 Drug-Drug Interactions
No new information.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity
No new information.

7.6.2 Human Reproduction and Pregnancy Data
No new information.

7.6.3 Pediatrics and Assessment of Effects on Growth
No new information.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound
No new information.

7.7 Additional Submissions/Safety Issues
No new information.

8 POSTMARKET EXPERIENCE
No new information was identified in the submission.
OSE was consulted to review cases of (b) (4) The consult is pending.

9 APPENDICES

9.1 Literature Review/References
The Sponsor provided references to support the submission. One of these references, DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine (immediate release) for depressed adolescents with bipolar disorder, Bipolar Disord 2009:11:483-493, was a failed study. This trial randomized 32 adolescents to quetiapine (300 – 600 mg/day) or placebo and the primary endpoint was the mean change from baseline to LOCF endpoint in the Children's Depression Rating Scale- Revised Version. Significant improvement in symptoms were noted for both the quetiapine and placebo groups with no statistically significant differences between the groups (mean difference = 0.8).

9.2 Labeling Recommendations
With the assistance of SEALD, Seroquel and Seroquel XR product labeling are being extensively revised to be more streamlined and to omit information that is redundant in labeling.

Along with the action that will be taken with this supplement (b) (4) . Among these are:

(b) (4)

The Division will also be extrapolating the data for the clinical trials for Seroquel in bipolar mania in children/adolescents and schizophrenia in adolescents to Seroquel XR; thereby granting those indications to the XR product. Available pharmacokinetic data has been reviewed by the Office of Clinical Pharmacology. Some safety data from these clinical trials with Seroquel are currently in Seroquel XR labeling (e.g. increased blood pressure); adverse event tables will also be added. A description of these clinical trials will be included in section 14, Clinical Studies. This was discussed with the Pediatric Review Committee (PeRC) in a meeting held March 20, 2013.

For the current submission, the Sponsor incorporated safety data from this clinical trial in bipolar depression throughout labeling. The Sponsor has proposed safety data to be incorporated into the following sections: WARNINGS and PRECAUTIONS: Metabolic Changes – hyperglycemia/diabetes mellitus, dyslipidemia and weight change subsections; Increases in Blood Pressure (Children and Adolescents); ADVERSE REACTIONS (b) (4) In the sections where safety data will be added from this clinical trial in bipolar depression, the following sentence will appear "In a placebo-controlled SEROQUEL XR monotherapy study (8 weeks duration) of children and adolescent patients (10 – 17 years of age) with bipolar depression, in which efficacy was not established, …."

The Sponsor proposed including the mean change in weight and the ≥ 7% increase in weight data in the relevant section. These data, however, were driven primarily by the younger cohort (10 – 12 years of age) and the Division is recommending that the data also be presented by cohort. The Sponsor also proposed to (b) (4) The Sponsor has proposed including a summary of the failed bipolar depression trial (D144AC00001) in the Pediatric Use (8.4) section of labeling.

9.3 Advisory Committee Meeting

The Division did not recommend that this NDA be reviewed by the Psychopharmacological Drugs Advisory Committee.

9.4 Questions to Sponsor

1. In your proposed labeling, you provide (b) (4)

2. An analysis of mean change in weight and PCS shifts in weight for each age cohort (10-12, 13-17) were requested and provided during the original sNDA review. Have these data changed with the revision of the CSR?

3. Patient E1107001 experienced a significant increase in insulin levels during the clinical trial (4980 pmol/L at day 57). Do you have any interpretation of these findings? Were there any errors in measurement or interfering substances?

4. Please provide extent of exposure data, as in Table 12 of the CSR, for each of the two age cohorts (10 to 12, 13 to 17).

9.5 List of Enrolled and Randomized Subjects at Investigational Sites

The following information was provided by the Sponsor upon request:

		Number of Subjects	
Center	Investigator	Enrolled	Randomized
United States			
1101 Cleveland OH	Robert Findling	3	1
1102 Rochester NY	Sarah Atkinson	16	15
1103 Oklahoma City OK	Willis Holloway	10	6
1105 Scottsdale AZ	Lydia Cohan	3	2
1106 Enid OK	Michael Feldman	9	6
1107 Atlanta GA	Robert Riesenberg	10	9
1108 North Miami FL	Segal Scott	7	3
1109 Houston TX	Lawrence Ginsberg	5	4
1110 Clinton Township MI	Sendi Ismail	2	1
1111 Hoffman Estates IL	Mark Lerman	2	2
1113 Gainesville FL	Elias Sarkis	4	0
1114 St. Louis MO	Mohammad Malik	11	9
1115 Eagle ID	Grant Belnap	7	7
1116 Smyrna GA	Ashraf Attalla	11	10
1117 Bradenton FL	Jose Zaglul	2	2
1118 Wichita KS	Deborah Bergen	1	0
1120 Terre Haute IN	Paras Harshawat	14	13
1121 Dothan AL	Nelson Handal	15	12
1122 Memphis TN	David Struble	6	4
1123 Bothell WA	Mustapha Syed	7	6
1124 Virginia Beach VA	David Spiegel	19	13
1125 Wharton TX	Patel Nilesh	20	15
1126 Overland Park KS	William Murphy	3	2

1127 Little Rock AR	Duong Nguyen	4	3
1128 Tampa FL	Michael Bengston	4	4
1130 Charleston SC	Steven Lopez	1	1
1131 Lincoln NE	Walter Duffy	5	0
1133 Minneapolis MN	Sanjiv Kumra	5	2
1134 Cincinnati OH	Melissa Delbello	3	3
1137 Flowood MS	Joseph Kwentus	1	0
1138 Mason OH	Susan McElroy	2	1
1139 West Allis WI	Kambiz Pahlavan	1	0
1140 Houston TX	Matthew Brams	4	3
1141 Escondido CA	Prakash Bhatia	6	2
Serbia			
1201	Aneta Lakic	1	1
1202	Smiljka Popovic-Deusic	3	2
1203	Dragan Mitrovic	2	2
South Africa			
1302	Juan Schronen	5	5
Mexico			
1502	Alfonso Ontiveros	1	1
1503	Juan Luis Vazquez Hernandez	4	4
Colombia			
1601	Rodrigo Cordoba	3	2
1603	Martha Alzate	1	1
1606	Hernan Dario Giraldo Castro	8	5
India			
1702	Indla Ramasubbareddy	2	2
1704	Hitendra Gandhi	2	2
1705	Venu Gopal Jhanwar	3	1
Taiwan			
1803	Chin-Bin Yeh	4	4
	Totals	262	193

9.6 Clinical Trial Schedule of Events

Schedule of Events (Sponsor's Table)

	Screening Enrollment Washout period	Double-blind treatment								Final Visit OR Study DC[g]	1-week safety follow-up (Phone)	If BP >95th percentile at Final Visit OR Study DC
		Randomization										
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Day	**D-35 to D-1**	**D1[a]**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D57 to D63**	**D70 to D84 (or 2-4 weeks after DC)**
Visit Window (days)	**Up to 35 days**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Informed consent	X											
Demography	X											
Psychiatric diagnosis	X											
Inclusion/exclusion criteria	X	X										
Medical & psychiatric history	X											
Physical examination[b]	X									X		
Height	X									X		
Weight & waist circumference	X	X	X	X	X	X	X	X	X	X		
Vital signs (pulse, BP and temperature)	X	X	X	X	X	X	X	X	X	X		
BP												X
12-lead ECG	(X)[c]									X		

	Screening Enrollment Washout period	Double-blind treatment								Final Visit OR Study DC[g]	1-week safety follow-up (Phone)	If BP >95th percentile at Final Visit OR Study DC
		Randomization										
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Day	**D-35 to D-1**	**D1[a]**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D57 to D63**	**D70 to D84 (or 2-4 weeks after DC)**
Visit Window (days)	**Up to 35 days**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Laboratory assessments												
Urine drug screen & urinalysis	(X)[c]											
Serum β-hCG pregnancy test	(X)[h]									(X)[h]		
Clinical chemistry	(X)[c]					X				X		
Hematology	(X)[c]					X				X		
Optional genetic sampling		X										
AE reporting		X	X	X	X	X	X	X	X	X	X	
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Rating scales												
K-SADS-PL	X											
CDRS-R[d]	X	X	X	X	X	X	X	X	X	X		
YMRS	X	X	X	X	X	X	X	X	X	X		

	Screening Enrollment Washout period	Double-blind treatment							Final Visit OR Study DC[g]	1-week safety follow-up (Phone)	If BP >95th percentile at Final Visit OR Study DC
		Randomization									
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Visit Day	D-35 to D-1	D1[a]	D8	D15	D22	D29	D36	D43	D50	D57	D57 to D63	D70 to D84 (or 2-4 weeks after DC)
Visit Window (days)	Up to 35 days	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	
CGI-BP-S[e]		X	X	X	X	X	X	X	X	X		
CGI-BP-C[f]			X	X	X	X	X	X	X	X		
C-SSRS	X	X	X	X	X	X	X	X	X	X		
SAS		X				X				X		
BARS		X				X				X		
AIMS		X				X				X		
Study medication												
Dispense study medication		X	X	X	X	X	X	X	X			
Drug accountability			X	X	X	X	X	X	X	X		

AIMS Abnormal Involuntary Movement Scale; BARS Barnes Akathisia Rating Scale; C-SSRS Columbia-Suicide Severity Rating Scale; ECG electrocardiogram; K-SADS-PL Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version; SAS Simpson-Angus Scale.

[a] Randomization was at least 7 days from the enrollment visit.
[b] Physical examination included a regular, hand-held ophthalmoscopic eye examination.
[c] Repeat tests were to be performed if more than 14 days had elapsed between screening/enrollment (Visit 1) AND/OR if results at screening/enrollment (Visit 1) were borderline abnormal after discussion with and approval from the Medical Monitor. If repeat laboratory tests and/or a repeat ECG were required, the patient was to come in for an unscheduled visit at least 72 hours (3 days) before randomization (Visit 2) to ensure test results were available and that the patient remained eligible for randomization.
[d] Patients were discontinued from the study if they had a CDRS-R item 13 score of >3.
[e] The CGI-BP-S was performed at each visit from Visit 2 (Day 1) through Visit 10 (Final Visit) or at time of study discontinuation.
[f] The CGI-BP-C was added from Visit 3 through Visit 10 (Final Visit) or at time of study discontinuation. Patients were to be discontinued from the study if they have a worsening of symptoms at Day 15 (Visit 4) or later, as indicated by a CGI-BP-C score of 6 (much worse) or more.
[g] DC is study discontinuation.
[h] Serum β-hCG pregnancy test was done for girls of childbearing potential only at Visit 1 (Day 1) and Visit 10 (Day 57) or study discontinuation. This might be completed at any additional visit if clinically indicated. Visit 1 assessment was to be repeated if washout period was ≥14 days.

NOTE: The screening/enrollment visit (Visit 1) might be conducted over more than one visit before randomization to minimize family burden. The interval between Visits 2 through 11 was 7±3 days such that the shortest interval between visits was no less than 4 days and no more than 10 days.

9.7 Definition of Potentially Clinically Significant Laboratory Values

Parameter (SI unit)	Criterion value	Criterion value (conventional unit)
Hematocrit	≤ 0.35, ≥ 0.50	
Hemoglobin (g/L)	≤ 115, ≥ 172	
RBC (cells/L)	$\leq 3 \times 10^{12}$, $\geq 6 \times 10^{12}$	
Platelet count (cells/L)	$\leq 100 \times 10^{9}$, $\geq 600 \times 10^{9}$	
WBC (cells/L)	$\leq 3 \times 10^{9}$, $\geq 16 \times 10^{9}$	
Neutrophils, relative (%)	≤ 15	
Neutrophils, absolute (cells/L)	$\leq 1.5 \times 10^{9}$, $\geq 10 \times 10^{9}$	
Eosinophils, relative (%)	≥ 10	
Eosinophils, absolute (cells/L)	$\geq 1.0 \times 10^{9}$	
Basophils, absolute (cells/L)	$\geq 0.5 \times 10^{9}$	
Lymphocytes, absolute (cells/L)	$\leq 0.5 \times 10^{9}$, $\geq 6.0 \times 10^{9}$	
Monocytes, absolute (cells/L)	$\geq 1.4 \times 10^{9}$	
ALT (U/L)	$\geq 3 \times$ ULN	
AST (U/L)	$\geq 3 \times$ ULN	
Alkaline phosphatase (U/L)	$\geq 3 \times$ ULN	
Total bilirubin (µmol/L)	$\geq 1.5 \times$ ULN	
Glucose, fasting (mmol/L)	≤ 2.5, ≥ 7.0	≤ 45, ≥ 126 mg/dL
Glucose, random (mmol/L)	≤ 2.5, ≥ 11.1	
HbA1c (%)	> 7.5	
Total cholesterol (mmol/L)	≥ 6.21	≥ 240 mg/dL
LDL (mmol/L)	≥ 4.2	≥ 162 mg/dL
HDL (mmol/L)	≤ 1.04	≤ 40 mg/dL
Triglycerides (mmol/L)	≥ 2.26	≥ 200 mg/dL
Creatinine (µmol/L)	≥ 120	
Sodium (mmol/L)	≤ 132, ≥ 152	
Potassium (mmol/L)	≤ 3.0, ≥ 5.5	
Chloride (mmol/L)	≤ 90, ≥ 120	
BUN (mmol/L)	≥ 70.03	
Bicarbonate (mmol/L)	≤ 18, ≥ 30	
Total T4 (nmol/L)	$< 0.8 \times$ LLN, $> 1.2 \times$ ULN	
Free T4 (pmol/L)	$< 0.8 \times$ LLN, $> 1.2 \times$ ULN	
TSH (mIU/L)	> 5	
Prolactin (µg/L)	males > 20 females > 26	

Source: Appendix C Statistical Analysis Plan
SI units converted to conventional units using conversion factors 0.0555 (glucose), 0.0259 (cholesterol, LDL, HDL), 0.0113 (triglycerides)

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/s/

CARA L ALFARO
03/22/2013

NI A KHIN
03/26/2013
See CDTL memo for additional comments.