CLINICAL REVIEW

Application Type	NDA
Application Number(s)	020-639 SE5-045, SE5-046
Priority or Standard	P (pediatric)
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Division	Division of Psychiatry Products
Reviewer Name(s)	Cara Alfaro, Clinical Analyst
Review Completion Date	5/11/2009
Established Name	Quetiapine fumarate
Trade Name	Seroquel
Therapeutic Class	Antipsychotic
Applicant	AstraZeneca
Formulation(s)	Oral tablet
Dosing Regimen	Titration to 400 – 800 mg/day for schizophrenia Titration to 400 – 600 mg/day for bipolar I mania
Indication(s)	Schizophrenia, Bipolar I Mania
Intended Population(s)	Adolescents (13 to 17 years) for schizophrenia Children (10 to 17 years) for bipolar I mania

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Sponsor has submitted two pivotal trials to support the following pediatric indications "treatment of schizophrenia in adolescents (13 to 17 years of age)" and "treatment of bipolar I mania in children and adolescents (10 to 17 years of age)".
Related to this submission, and at the request of the Division of Psychiatry Products, the Sponsor submitted data for the effect of quetiapine on several metabolic parameters for adult and pediatric/adolescent subjects in their clinical trials database. The review of the adult metabolic data has been recently completed and the pediatric metabolic data is currently under review.
The Sponsor has also submitted a Changes Being Effected labeling supplement that has incorporated some of the pediatric/adolescent safety data; this labeling supplement is under review.
The efficacy and safety data from the two pivotal trials in the current submission will be presented at a Psychopharmacological Drugs Advisory Committee (PDAC) meeting scheduled for June 9 and 10, 2009.

Recommendations for regulatory action will be made when all reviews have been completed and all pending requests for additional data and analyses from the Sponsor have been received and reviewed. An addendum to this clinical review is therefore expected and will also include a comprehensive review of proposed product labeling.

1.2 Risk Benefit Assessment

At the PDAC meeting, the efficacy and safety data for quetiapine (along with other atypical antipsychotics) will be presented and the risks/benefits discussed. Further evaluation of the risk/benefit profile of quetiapine in the treatment of schizophrenia in adolescents and the treatment of bipolar I mania in children and adolescents will occur after this meeting.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Further evaluation of postmarket risk evaluation and mitigation strategies for quetiapine in the treatment of schizophrenia in adolescents and the treatment of bipolar I mania in children and adolescents will occur after the scheduled PDAC meeting.

2 Introduction and Regulatory Background

2.1 Product Information

Quetiapine (Seroquel®) 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 adults (see the summary table below).

Table 1. Indication and Date(s) of Approval of Quetiapine Fumarate immediate release (Seroquel) [NDA 20-639]

Indication in Adults	Date of Approval
Schizophrenia (acute treatment)	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

2.2 Currently Available Treatments for Proposed Indications

Two atypical antipsychotic agents, Risperdal (risperidone) and Abilify (aripiprazole) are approved for use in the pediatric population for the treatment of schizophrenia (in adolescents) and bipolar mania (age 10-17 yrs). Lithium is also approved in the treatment of bipolar disorder (age >12 yrs).

2.3 Availability of Proposed Active Ingredient 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 200, 300 and 400 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, clinical worsening and suicidality, neuroleptic malignant syndrome, tardive dyskinesia (TD), orthostatic hypotension, hyperglycemia, weight gain and diabetes mellitus.

The sponsors of atypical antipsychotics have been asked to provide additional data and pooled analyses for the metabolic profile safety signals. This includes AstraZeneca who have been asked to provide data and analyses for quetiapine IR and quetiapine XR for effects on lipids (cholesterol, HDL, LDL, triglycerides), glucose (glucose, HbA1c, UA glucose), and weight for both adults and pediatric subjects (see Division letter January 8, 2008). The Sponsor recently provided these data on 6/26/08. The adult metabolic data review was completed in 03/2009 and

was part of the discussion at the PDAC meeting on 4/8/2009. The pediatric metabolic data are currently under review.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

February 11, 2003	FDA issued a pediatric written request
August 4, 2003	Sponsor requests a meeting with the Division to discuss the pediatric development program. Briefing document submitted which included a request for modifications to the Written Request and clinical study protocols 130, 112, 149 and 150.
November 4, 2003	Meeting between Sponsor and Division regarding pediatric development program. Concurrence on major protocol design issues including dosing and primary endpoints.
May 25, 2004	Protocols for Studies 112, 149 and 150 submitted to IND 32,132
February 3, 2005	The time for submission of reports was extended to 7 years from date of the Written Request letter.
March 29, 2006	Sponsor submitted statistical analysis plan for Study 149
June 19, 2007	Sponsor submitted statistical analysis plan for Studies 112 and 150

2.6 Other Relevant Background Information

Neither quetiapine or quetiapine XR have been approved for the treatment of schizophrenia in adolescents or bipolar mania in children and adolescents in any other country. The sponsor did not report any withdrawal of this product in other countries.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

See Sections 3.2 (Compliance with Good Clinical Practices) for other comments regarding data quality and integrity.
This reviewer completed a brief audit of adverse event safety data by comparing case report forms, narratives and line listings for consistency on reporting. Overall, there was good consistency of adverse event information across these sources of data. Adverse event coding (verbatim to preferred terms) appeared to be appropriate. No significant deficiencies were noted.
This reviewer did note that the narratives for serious adverse events and discontinuations due to adverse events were not comprehensive and additional data were requested from the Sponsor. Additionally, line listings (e.g. vital signs) did not include assessments obtained at times coordinating with adverse event reports (e.g. hypertensive crisis) – these discrepancies required further data from the Sponsor.

3.2 Compliance with Good Clinical Practices

In order to assess good clinical practice (GCP) compliance, a Division of Scientific Investigations (DSI) inspection for the following clinical investigator sites were requested: Site 240 (Clinical Investigator Kozlova in Russia) and Site 024 (Dr. Wamboldt from Denver, CO) for Study 112; and Site 019 (Dr. Rease from Riverside, CA) and Site 024 for Study 149. The Russian site was selected because if any significant deficiencies were found, removal of data from this site would yield negative efficacy results for the low dose group and marginally positive results for the high dose group in Study 112. The other sites inspected were chosen because they were large enrolling sites. Despite some inspection deficiencies noted at site 024, the DSI inspection summary report dated 4/27/09 concludes that data from all of these sites appear acceptable for use in support of the proposed indications.

The Sponsor received a letter from the FDA on 6/23/08 regarding allegations of research misconduct by John Gilliam, M.D., a clinical investigator who participated in the clinical development programs involving quetiapine and quetiapine XR. The FDA requested that pivotal efficacy trials be reanalyzed excluding patients from Dr. Gilliam's site and to compare this reanalysis to the original analysis. A total of 32 patients were randomized into the two pivotal trials from Dr. Gilliam's site: 6 patients (6/222 = 2.7%) were randomized in pivotal Study 112 and 28 patients (26/284 = 9.2%) were randomized into pivotal Study 149. A reanalysis excluding patients from this site was performed for each pivotal trial and the results were similar to the original analyses (see Section 6.1.1 and 6.2.1).

3.3 Financial Disclosures

Form 3455 (version 4/2006) "Disclosure – Financial Interests and Arrangements for Clinical Investigators" was available for the majority of investigators. Only two investigators were identified as having received "significant payments" of $\geq$ $25,000 for research funding, consulting fees or honoraria. These investigators included (b) (6) a subinvestigator at center (b) (6) for Study (b) (6) and (b) (6), a primary investigator at center (b) (6) for Studies (b) (6). No patients were enrolled in Study (b) at Dr (b) (6) center. Dr. (b) (6) center enrolled and (b) (6) The number of patients enrolled and randomized into the (b) (6) pivotal trials at Dr. (b) (6) center are < 5% of the efficacy populations in each study and is unlikely to significantly impact the overall study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Julia Pinto, Ph.D., is the CMC reviewer for this set of NDA supplements. All CMC information is cross-referenced to the original NDA. No environmental assessment is provided in this submission. As noted by Dr. Pinto in her review dated 04/16/2009, the EA recommended as FONSI (no significant impact) by Ranan Bloom, Ph.D. dated December 11, 2007 is valid through 2011. From the CMC standpoint, these NDA supplements are recommended for approval.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No new pharm/tox information in this submission.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) reviewer is Kofi Kumi, Ph.D. The OCP review dated 03/12/09 reviewed the data from the pediatric PK study (Study 28). In addition, the OCP-Pharmacometric Team, Hao Zhu, Ph.D., and Christine Garnette, Pharm.D., provided their assessment of QT data from the two pediatric pivotal studies in the same review. They also provided some labeling comments for the clinical pharmacology section.

4.4.1 Mechanism of Action

The mechanism of action of quetiapine is unknown, but its higher 5HT2/D2 binding ratio may contribute to its antipsychotic and mood stabilizing properties.

4.4.2 Pharmacodynamics

Quetiapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses. The potential for QTc prolongation was evaluated by the quetiapine concentration – QTcF relationship modeling derived from data from a thorough QT study in healthy adults. Based on the assumption that the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-adjusted baseline corrected QTc intervals are less than 10 ms following the highest dose tested in the two pivotal pediatric studies (Study 112 and 149). In addition, the largest observed mean QTcF interval change from baseline observed in the clinical trial was around 2 ms (i.e., approximately 4 ms difference in study 112 and no difference between the quetiapine and placebo in study 149). No patients had QTcF values above 500 ms or mean change from baseline in QTcF greater than 60 ms in both pediatric studies.

4.4.3 Pharmacokinetics

The OCP review of pediatric PK data is summarized. There was a tendency for children (10 -12 years of age) to have higher exposure of quetiapine (AUC 36% – 55% and Cmax 54% - 71% higher) than the levels observed in adolescents (13 to 17 years). Dose normalized exposures were generally lower (AUC = 12% lower and Cmax = 8% lower) in pediatric patients than adults. Dose normalized, weight-normalized AUC and Cmax decreased by about 40% in pediatric population (10 to 17 yrs) when compared to adults. These differences are not expected to be clinically relevant.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Clinical Trials Submitted

Protocol	Study Design*	Patients and Diagnosis	Treatment Arms	Duration of Treatment
D1441C00028 "Study 028" **PK Study** Region(s): United States	MC, OL, inpatient	Children and adolescents (10-17 years) with schizophrenia, schizoaffective disorder or bipolar disorder	Quetiapine IR titrated from 50 mg (day 1) up to 800 mg/day over 11 days administered BID. N = 28 enrolled (n = 27 in safety eval, N = 24 in PK eval)	13 days
D1441C00112 "Study 112" **Pivotal Study** Region(s): United States, Poland, Russia, Serbia, Ukraine, India, Malaysia, Philippines, South Africa, Germany	MC, R (1:1:1), DB, PC parallel group study	Adolescent (13-17 years) patients with schizophrenia	Quetiapine IR fixed doses of 400 mg/day and 800 mg/day administered BID or TID; placebo N = 268 enrolled ITT population: N = 220 Safety population: N = 222	42 days
D1441C00149 "Study 149" **Pivotal Study** Region(s): United States	MC, R (1:1:1), DB, PC, parallel group study	Child and adolescent (10 – 17 years) with bipolar mania	Quetiapine IR fixed doses of 400 mg/day and 600 mg/day administered BID or TID; placebo N = 393 enrolled ITT population: N = 277 Safety population: N = 283	21 days
D1441C00150 "Study 150" **Safety Study** Region(s): United States, Poland, Russia, Serbia, Ukraine, India, Malaysia, Philippines, South Africa, Germany	MC, OL, flexible dose study	Patients enrolled from studies 112 and 149	Quetiapine IR flexible dosing target of 400 mg/day to 800 mg/day administered BID or TID (could lower to 200 mg/day based on tolerability) N = 381 enrolled Safety population: N = 380	26 weeks

*PK = pharmacokinetics, MC = multicenter, OL = open-label, R = randomized, PC = placebo-controlled

6 Review of Efficacy

Efficacy Summary

The sponsor has provided sufficient evidence to support efficacy claims for acute treatment for quetiapine in both schizophrenia in adolescents (13-17 yrs of age) and bipolar mania in children and adolescents (10-17 yrs of age).

The primary efficacy endpoint for the schizophrenia study (Study 112) was the change from baseline to endpoint in the PANSS total score (MMRM analysis). The overall study results were statistically significant for quetiapine 400 mg/day versus placebo (LS Mean Diff = -8.16, p = 0.043) and quetiapine 800 mg/day versus placebo (LS Mean Diff = -9.29, p = 0.009). The LOCF analysis showed similar results for both quetiapine groups compared to placebo.

The primary efficacy endpoint for the bipolar I mania study (Study 149) was the change from baseline to endpoint in the YMRS total score (MMRM analysis). The overall study results were statistically significant for quetiapine 400 mg/day versus placebo (LS Mean Diff = -5.21, p < 0.001) and quetiapine 600 mg/day versus placebo (LS Mean Diff = -6.56, p < 0.001). The LOCF analysis showed similar results for both quetiapine groups compared to placebo.

6.1 Studies Pertinent to Schizophrenia Claim

Rationale for Selection of Studies for Review

The efficacy review was focused on data collected in a single study D1448C00112 (Study 112), which was a 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 800 mg compared with placebo in the treatment of adolescents (13 to 17 yrs of age) with schizophrenia.

6.1.1 Study 112

Clinical Trial

Study 112 [Protocol D1441C00112] “A 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase IIIb study of the efficacy and safety of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 800 mg compared with placebo in the treatment of adolescents with schizophrenia”.

This international study was conducted in 46 sites enrolling 268 patients: 23 sites in the United States (n = 88 enrolled), 2 sites in Poland (n = 9 enrolled), 4 sites in Russia (n = 40 enrolled), 4 sites in Serbia (n = 31 enrolled), 3 sites in Ukraine (n = 28 enrolled), 2 sites in India (n = 11 enrolled), 2 sites in Malaysia (n = 8 enrolled), 4 sites in Philippines (n = 46 enrolled), 1 site in South Africa (n = 6 enrolled), 1 site in Germany (n = 1 enrolled).

First patient enrolled 10/1/2004, last patient completed 6/20/2007.

Methods/Study Design/Analysis Plan

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 6-week trial in male and female inpatient and outpatient adolescents (age 13 – 17 years) with DSM-IV diagnosis of schizophrenia (confirmed by the K-SADS-PL). Following a medication washout period of 1 to 28 days, patients were

randomized (1:1:1) to one of three treatment groups: quetiapine 400 mg/day, quetiapine 800 mg/day or placebo. Study medication was administered twice or three times daily per the judgment of the investigator. Quetiapine was titrated to the target fixed dose according to the following regimen:

Table 3. Quetiapine treatment regimens (mg/day) for administration

		Study day										
Dose group	**Time**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11-42**
400 mg	AM	NA	50	100	100	200	200	200	200	200	200	200
	PM	50	50	100	200	200	200	200	200	200	200	200
800 mg	AM	NA	50	100	100	200	200	300	300	400	400	400
	PM	50	50	100	200	200	300	300	400	400	400	400

AM Morning. NA Not Applicable. PM Evening.

From Sponsor's Table 5 in Clinical Study Report

According to this titration regimen, target fixed doses were reached by Day 5 (400 mg/day) and Day 9 (800 mg/day). Based on tolerability issues, investigators could administer study drug three times daily. No more than 400 mg was to be administered as a single dose.

For inclusion into the study, patients had to have a PANSS total score $\geq$ 60 at screening and baseline and a score of $\geq$ 4 on at least one of the following items: delusions, conceptual disorganization, or hallucinations (see all inclusion/exclusion criteria in Appendix 9.3).

Allowable concomitant medications included benztropine for the treatment of emergent EPS, diphenhydramine (up to 50 mg/day) for "sleeplessness", lorazepam (up to 4 mg/day – not to exceed 4 days in any study week) orally or IM for the treatment of agitation or anxiety, propranolol for the treatment of akathisia. The following antidepressants were allowable if ongoing if needed in the clinical judgment of the investigator and if the dose had been stable > 30 days before screening (no adjustments were permitted): bupropion, citalopram, escitalopram, sertraline, or venlafaxine. Psychostimulants were not allowable concomitant medications.

Discontinuation criteria, included discontinuation due to adverse events but also included severe non-compliance to protocol or safety reasons as judged by the investigator or Sponsor; CGI-I score of 6 (much worse) or more at Day 14 or later (patient was to be withdrawn or hospitalized); CGI-I score of 5 (minimally worse) or more at 2 consecutive visits, starting with Day 14 (patient to be withdrawn or hospitalized); a patient who was hospitalized for meeting either CGI-I criteria (as listed previously) and who did not show improvement in the CGI-I score after one week of hospitalization; and patient unable to tolerate the assigned dose of study medication.

Patients completing this study, or were discontinued due to worsening of their symptoms, or were discontinued due to an AE not related to quetiapine were given the option to enter a 26-week, open-label quetiapine study (D1441C00150).

Efficacy assessments – also refer to Study Assessments Flow Chart in Appendix 9.4
The primary efficacy assessment was the PANSS total score. Secondary efficacy assessments included Clinical Global Impression (CGI) severity of illness and global improvement items, and Children's Depression Rating Scale-Revised (CDRS-R). No secondary assessments were identified as key secondaries for purposes of inclusion in product labeling.

Safety assessments
Safety assessments and variables included:
Physical examination, vital signs, weight, BMI, ECG, laboratory assessments (hematology, chemistry, prolactin).

EPS – Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movement Scale (AIMS)
The incidence of anticholinergic medication use to treat treatment emergent EPS

Statistics

The primary outcome variable was the change from baseline to Day 42 in the PANSS total score. The primary analysis was MMRM (unstructured covariance pattern). Baseline PANSS total score was used as a covariate, other variables in the model included treatment, region, visit, and visit-by-treatment interaction. All statistical comparisons used 2-sided tests with a significance level of 0.050, unless otherwise specified. The two contrasts of interest were the 400 mg/day and the 800 mg/day quetiapine groups versus placebo and the Simes-Hommel step-up procedure was used for adjustment of the 2 primary comparisons.
An additional analysis using ANCOVA model with missing values imputed by the LOCF method was conducted to further assess robustness of the primary analysis.
Centers were pooled into three geographically based regions: USA, Central and Eastern Europe including South Africa (Serbia, Russia, Ukraine, Germany, Poland, South Africa), and Asia (India, Malaysia, Philippines).

Sample size determination: A total of 66 evaluable patients per treatment group (N = 198) would provide at least 85% power to detect a difference of 15 points between either the 400 mg/day or 800 mg/day quetiapine treatment group and the placebo group for the mean change from baseline in PANSS total score. A Bonferroni correction using alpha = 0.025 for each dose was used as a conservative approach for obtaining the sample size estimate. The sample size calculation assumed a SD of 26 and a 2-tailed test at an overall type I error rate of 0.05. An additional 51 (20%) patients were added to provide an estimate of 249 patients needed for screening. These additional patients were added to account for those patients who may be screened but who may not become evaluable.

No interim analyses were planned or performed.

Definitions of the ITT and safety populations were standard. ITT population: all randomized patients who were given study treatment and who had baseline and at least one post-baseline PANSS assessment.
Safety population: all randomized patients who were given study treatment.

Results

Demographics

The mean age (15.4 yrs) was similar across the treatment groups. There were more males enrolled (58.6% of the overall study population) with similar proportion in each treatment group. The majority of patients were Caucasian (61%).

Table 4. Patient Demographics

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 73
Gender n (%)			
Male	43 (58.9)	44 (59.5)	42 (57.5)
Female	30 (41.1)	30 (40.5)	31 (42.5)
Age (years)			
Mean	15.45 (1.25)	15.45 (1.34)	15.34 (1.39)
Median	16	16	16
Range	13 - 17	13 - 17	13 - 17
Race n(%)			
Caucasian	45 (61.6)	44 (59.5)	46 (63)
Black	7 (9.6)	9 (12.2)	11 (15.1)
Oriental	15 (20.5)	13 (17.6)	12 (16.4)
Other	6 (8.2)	8 (10.8)	4 (5.5)
Ethnic Group n (%)			
African	1 (1.4)	1 (1.4)	2 (2.7)
African-American	6 (8.2)	8 (10.8)	9 (12.3)
Asian	15 (20.5)	14 (18.9)	10 (13.7)
Chinese	1 (1.4)	1 (1.4)	1 (1.4)
Hispanic	4 (5.5)	5 (6.8)	5 (6.8)
Native American	0	0	1 (1.4)
Not applicable	36 (49.3)	34 (45.9)	32 (43.8)
Other	10 (13.7)	11 (14.9)	13 (17.8)

From Sponsor Table 22 in Clinical Study Report

Baseline Characteristics

Select baseline characteristics are listed in Table 5. The treatment groups were well matched with regard to baseline characteristics of diagnosis and severity of illness. Approximately 10% of patients in each treatment group had a comorbid ADHD diagnosis. Baseline body weight and BMI were similar among the groups.

Table 5. Baseline Characteristics

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 73
DSM-IV diagnosis n (%)			
Schizophrenia, disorganized	6 (8.2)	5 (6.8)	5 (6.8)
Schizophrenia, paranoid	53 (72.6)	50 (67.6)	52 (71.2)
Schizophrenia, residual	0	1 (1.4)	0
Schizophrenia, undifferentiated	14 (19.2)	18 (24.3)	16 (21.9)
Comorbid ADHD diagnosis n (%)	7 (9.6)	8 (10.8)	7 (9.6)
Baseline CGI-Severity Score			
Mean (SD)	4.7 (0.77)	4.6 (0.76)	4.7 (0.67)
Range	4 – 7	3 – 6	4 – 6
Baseline PANSS Total Score			
Mean (SD)	96.2 (17.7)	96.9 (15.3)	96.7 (18.0)
Range	46 – 135	69 – 137	60 – 165.5
Years since first known diagnosis of schizophrenia			
Mean (SD)	2.3 (2.3)	2.5 (2.5)	2.2 (1.5)
Total number of schizophrenia hospitalizations [mean (SD)]	1.3 (1.6)	1.1 (1.3)	1.6 (1.9)
Has the subject been hospitalized for a suicide attempt?			
Yes n (%)	2 (2.7)	0	1 (1.4)
Current or prior exposure to quetiapine?			
Yes, n (%)	8 (11)	6 (8.1)	9 (12.3)
Quetiapine average daily dose in mg			
n	8	6	8
Mean (SD)	200 (157.5)	183.3 (132.9)	271.9 (167.7)
Weight (kg)			
Mean (SD)	60.95 (19.1)	61.73 (14.67)	62.78 (14.35)
Range	34-128	36-103	35-113
BMI (kg/m2)			
Mean (SD)	21.82 (5.57)	22.46 (4.75)	22.67 (4.72)
Range	14.5-41.3	13.5-37.2	15.4-40

From Sponsor Table 23 in Clinical Study Report, baseline PANSS scores obtained from Table 11.2.1.1.1

Patient Disposition

A total of 268 patients were enrolled into the clinical trial. Forty-six were screening failures, primarily due to not fulfilling eligibility criteria. A total of 222 patients were randomized and received study drug. One hundred and sixty-four subjects (74%) completed the study. The main reasons for subject discontinuation from the study were adverse events, study-specific discontinuation criteria and patients not willing to continue. Quetiapine groups had higher completion rates (i.e., 76.7% and 82.4% in the 400 mg, 800 mg quetiapine vs. 62.7% in placebo). There were more subjects listed for dropout due to adverse events in the quetiapine treatment groups compared to the placebo group.

Table 6. Patient Disposition

	Quetiapine 400 mg/day	Quetiapine 800 mg/day	Placebo
Randomized	73	74	75
Discontinued Study	**17 (23.3%)**	**13 (18.6%)**	**28 (37.7%)**
Adverse Event	5 (6.8%)	7 (9.5%)	2 (2.7%)
Met discontinuation criteria*	6 (8.2%)	2 (2.7%)	15 (20%)
Patient not willing to continue	3 (4.1%)	3 (4.1%)	8 (10.7%)
Lost to follow-up	0	0	2 (2.7%)
Other**	3 (4.1%)	1 (1.4%)	1 (1.3%)
Completed Study	**56 (76.7%)**	**61 (82.4%)**	**47 (62.7%)**
Enrolled in OL study 150	56 (76.7%)	58 (78.4%)	61 (81.3%)

From Sponsor Figure 1 in Clinical Study Report
*the majority of these discontinuations were due to lack of efficacy as defined by CGI-I scores per discontinuation criteria. [from Disposition of Each Subject document in submission]
**examples of "other" discontinuations included noncompliance, family withdrew consent, moving out of state, lack of efficacy, "according to agreement with sponsor" [from Disposition of Each Subject document in submission]

Table 7. Sample Sizes for ITT and Safety Populations

	Total	Quetiapine 400 mg/day	Quetiapine 800 mg/day	Placebo
ITT Population	220	73	73	74
Safety Population	222	73	74	75

Concomitant Medication Use

Allowable concomitant medications but with restrictions included benztropine for EPS, propranolol for akathesia, lorazepam for anxiety/agitation, and diphenhydramine for "sleeplessness".

Select antidepressants were allowed if the dose had been stable for > 30 days prior to screening. Allowable antidepressants included bupropion, citalopram, escitalopram, sertraline and venlafaxine. No dose adjustment was permitted.

Approximately 10% of patients in each treatment group had a comorbid diagnosis of ADHD. The incidence of antidepressant and psychostimulant use during the study is presented. The use of anticholinergic medications for EPS and the use of sleep medication are also presented.

Table 8: Concomitant Medication Use

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 73
"Sleep medication"	19 (26%)	16 (21.6%)	23 (30.7%)
Antidepressants	5 (6.8%)	1 (1.4%)	2 (2.7%)
Psychostimulants	0	0	0
Benzodiazepines			
Alprazolam	2 (2.7%)	0	0
Clonazepam	2 (2.7%)	5 (6.8%)	1 (1.3%)
Diazepam	1 (1.4%)	0	3 (4%)
Lorazepam	13 (17.8%)	8 (10.8%)	15 (20%)
Midazolam	2 (2.7%)	0	0
Diphenhydramine	7 (9.6%)	8 (10.8%)	9 (12%)
Anticholinergics	4 (5.5%)	1 (1.4%)	0

From Sponsor' Tables 11.1.7.4, 11.3.15.1, 11.3.20.1, 11.3.13.1

Important Protocol Violations

The majority of major protocol violations were patients using anxiolytics/hypnotics not specifically permitted or other concomitant medication violations. Concomitant medication use is discussed in the previous section. No other major protocol violations were noted that would impact the overall interpretation of the study results.
Of note, though major protocol violations were included in subject discontinuation criteria in the protocol, it does not appear that any patients were discontinued from the study based on this criterion.

Dosing

The study used two fixed doses of quetiapine, 400 mg/day and 800 mg/day, vs. placebo.

Efficacy Findings

Primary Efficacy Analysis

The MMRM analysis showed both quetiapine 400 mg/day and quetiapine 800 mg/day were statistically significantly superior to placebo.

Table 9. Primary Efficacy Variable (MMRM): PANSS Total Score Change from Baseline to Endpoint (week 6)

		Baseline		Endpoint		LSMean Change	LSMean Difference	P-value
	N	Mean	SD	Mean	SD			
Quetiapine 400 mg	54	96.9	16.41	72.5	20.35	-27.31	-8.16	0.043
Quetiapine 800 mg	55	98.4	15.73	70.3	17.28	-28.44	-9.29	0.009
Placebo	43	97.5	16.4	78	23.32	-19.15		

Modified from Sponsor Table 25 and 11.2.1.1.4 in Clinical Study Report

Based on a request from the FDA, the Sponsor also performed a separate analysis excluding Dr. Gilliam's site (site #10) [see Section 3.2, Compliance with Good Clinical Practices].

Table 10. Primary Efficacy Variable (MMRM): PANSS Total Score Change from Baseline to Endpoint (Week 6) – *Excluding Site #10*

	LSMean Difference	P-value
Quetiapine 400 mg (N = 53)	-8.37	0.042
Quetiapine 800 mg (N = 54)	-9.15	0.012
Placebo (N = 43)		

From Sponsor Table 2 in Response Document – Gilliam site

Other Analyses

Sensitivity Analysis

The LOCF showed similar statistically significant results for both quetiapine groups as compared to placebo.

Table 11. Primary Efficacy Variable: PANSS Total Score Change from Baseline (LOCF)

Treatment Groups	N	LSMean Change	LSMean Difference	P-value(vs. placebo)
Quetiapine 400 mg	74	-25.76	-7.24	0.036
Quetiapine 800 mg	73	-27.23	-8.71	0.012
Placebo	73	-18.52		

Modified from Sponsor Table 11.2.1.2.3 in Clinical Study Report

Analysis of Primary Endpoint over Time

The following table summarizes the treatment effect over time based on the MMRM analysis.

Table 12. Change from randomization in the PANSS total score (MMRM) over time

	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
Visit	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 07	72	-6.65	73	-8.23	72	-8.80	-1.58	0.410	-2.16	0.214
Day 14	72	-10.09	70	-14.24	71	-16.09	-4.15	0.098	-6.00	0.012
Day 21	65	-12.14	67	-20.37	68	-19.42	-8.23	0.006	-7.28	0.011
Day 28	57	-15.00	59	-22.72	65	-22.38	-7.72	0.023	-7.39	0.018
Day 35	51	-18.00	59	-24.68	62	-26.14	-6.68	0.085	-8.14	0.019
Day 42	43	-19.15	54	-27.31	55	-28.44	-8.16	0.043	-9.29	0.009

Note: extracted from Dr. Dinh's FDA statistical review; data from Sponsor's Study Report; Table 11.2.1.2.1
* p-values not adjusted for multiplicity

Secondary Efficacy Variables

The CGI-S was statistically significant in favor of quetiapine 800 mg compared to placebo, but did not reach a statistically significant level for the quetiapine 400 mg group (Table 13). Both quetiapine treatment arms were statistically significantly different from placebo on the PANSS positive symptom subscale score at endpoint (Table 14). Neither quetiapine treatment arm demonstrated efficacy on the variable % responders at endpoint (Table 15).

Table 13. Secondary Efficacy Variable: CGI-S Change from Baseline to Endpoint (MMRM)

Treatment Groups	N	LSMean Change	LSMean Difference	P-value(vs. placebo)
Quetiapine 400 mg	55	-1.15	-0.34	0.1
Quetiapine 800 mg	55	-1.28	-0.47	0.018
Placebo	43	-0.081		

Modified from Sponsor Table 11.2.3.2.1.3 in Clinical Study Report

Table 14. Secondary Efficacy Variable: PANSS Positive Symptom Subscale Score Change from Baseline to Endpoint (MMRM)

Treatment Groups	N	LSMean Change	LSMean Difference	P-value(vs. placebo)
Quetiapine 400 mg	55	-8.56	-2.05	0.075
Quetiapine 800 mg	55	-9.34	-2.83	0.008
Placebo	43	-6.51		

From Sponsor Table 31 in Clinical Study Report (Study 112)

Table 15. Secondary Efficacy Variable: Percent of Responders (≥ 30% reduction from baseline in PANSS total score at endpoint)

	OC			LOCF		
Treatment Groups	N	Responders N (%)	p-value	N	Responders N (%)	p-value
Quetiapine 400 mg	55	28 (51.9)	0.125	73	28 (38.4)	0.109
Quetiapine 800 mg	55	22 (40.0)	0.675	74	27 (36.5)	0.194
Placebo	43	17 (39.5)		73	19 (26.0)	

From Sponsor Table 27 in Clinical Study Report (Study 112)

Conclusions

The efficacy of quetiapine in the acute treatment of schizophrenia in adolescents was demonstrated in this pivotal trial.

6.1.2 Subgroup Analyses

Our statistics team conducted exploratory subgroup analyses based on age (≤15 yrs; >15 yrs), gender (M,F), race (Caucasian, others), and geographic regions (US vs. non-US). As noted in detail by Dr. Dinh in the FDA statistical review, the results trended in the same direction in favor of quetiapine in both the race or gender subgroups. Quetiapine appeared to show a significantly greater treatment effect in the ≤15 yrs age group. For the >15 yrs group, there seemed a larger placebo effect. Quetiapine appeared to show a greater improvement of treatment effect among the US patients than non-US patients.

6.1.3 Dose Response

The treatment response was numerically greater in the 800 mg group (i.e., the placebo-substracted LS mean difference of -8.16 in the 400 mg; -9.29 in the 800 mg quetiapine groups), but not statistically significantly different between the two doses.

6.1.4 Key Secondary Endpoints

No key secondary endpoint was pre-specified in this study.

6.1.5 Effect Size

The treatment effect size (change from baseline to endpoint in PANSS total scores around 8 to 9 points) observed in this study seems similar to the effect size observed in other schizophrenia trials.

6.1.6 Long-term Efficacy

No adequate and well controlled data to address the question of long-term efficacy in this submission.

6.1.7 Pediatric Development

This study was conducted in response to the Pediatric Written Request letter issued under pediatric exclusivity.

Efficacy Conclusions

The sponsor has provided positive efficacy data for quetiapine in support of the claim for the acute treatment of schizophrenia in adolescents.

6.2 Studies Pertinent to Bipolar Mania Claim

Rationale for Selection of Studies for Review

Our efficacy review was focused on data collected in a single study D1448C00149 (Study 149), which was a 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 600 mg compared with placebo in the treatment of children and adolescents (10 to 17 yrs of age) with bipolar mania.

6.2.1 Study 149

Clinical Trial

Study 149 [Protocol D1441C00149] "A 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase IIIb study of the efficacy and safety of quetiapine fumarate (Seroquel) immediate-release tablets in daily doses of 400 mg and 600 mg compared with placebo in the treatment of children and adolescents with bipolar I mania".
This study was conducted in 34 centers in the United States.

First patient enrolled 8/5/2004, last patient completed 7/10/2006.

Methods/Study Design/Analysis Plan

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group 3-week trial in male and female inpatient and outpatient children and adolescents (age 10 – 17 years) with DSM-IV diagnosis of Bipolar I mania (confirmed by the K-SADS-PL). Following a medication washout period of 1 to 28 days, patients were randomized (1:1:1) to one of three treatment groups: quetiapine 400 mg/day, quetiapine 600 mg/day or placebo. Randomization was stratified by age (10 – 12 years, 13 – 17 years). Study medication was administered twice or three times daily per the judgment of the investigator. Quetiapine was titrated to the target fixed dose according to the following regimen:

Table 16. Quetiapine treatment regimens (mg/day) for administration

Table 5 Quetiapine treatment regimens (mg/day) for administration twice daily

		Study day										
Dose group	Time	1	2	3	4	5	6	7	8	9	10	11-21
400mg	AM	NA	50	100	100	200	200	200	200	200	200	200
	PM	50	50	100	200	200	200	200	200	200	200	200
600mg	AM	NA	50	100	100	200	200	300	300	300	300	300
	PM	50	50	100	200	200	300	300	300	300	300	300

AM Morning. NA Not Applicable. PM Evening.

According to this titration regimen, target fixed doses were reached by Day 5 (400 mg/day) and Day 7 (600 mg/day). Based on tolerability issues, investigators could administer study drug three times daily. No more than 400 mg was to be administered as a single dose.

For inclusion into the study, patients had to have a YMRS total score $\geq$ 20 at both screening and baseline. Patients with rapid cycling or who experienced a first manic episode were included. Patients could also have a secondary diagnosis of ADHD (see all inclusion/exclusion criteria in Appendix 9.5).

Allowable concomitant medications included benztropine for the treatment of emergent EPS, diphenhydramine (up to 50 mg/day) for "sleeplessness", hydroxyzine (up to 100 mg/day not to exceed 4 days in any study week) for agitation or anxiety, lorazepam (up to 4 mg/day – not to exceed 4 days in any study week) orally or IM for the treatment of agitation or anxiety, propranolol for the treatment of akathisia. Ongoing treatment with select psychostimulants (methylphenidate, dextroamphetamine, mixed amphetamine salts, dexmethylphenidate) were allowed if the dose had been stable for $\geq$ 30 days before screening (no dose adjustments were allowed).

Discontinuation criteria were similar to Study 112.

Patients completing this study, or were discontinued due to worsening of their symptoms, or were discontinued due to an AE not related to quetiapine were given the option to enter a 26-week, open-label quetiapine study (D1441C00150).

Efficacy assessments
The primary efficacy assessment was the YMRS total score. Secondary efficacy assessments included the Clinical Global Impression-Bipolar Severity of Illness, Clinical Global Impression-Bipolar Global Improvement, Children's Global Assessment Scale, Children's Depression Rating Scale-Revised, Overt Aggression Scale-Modified and Caregiver Strain Questionnaire.
No secondary assessments were identified as key secondaries for purposes of inclusion in product labeling.

Safety assessments
Essentially the same as Study 112.

Statistics
The primary outcome variable was the change from baseline to Day 21 in the YMRS total score. The primary analysis was MMRM (unstructured covariance pattern). Baseline YMRS total score was used as a covariate, other variables in the model included age stratum, treatment, visit, and visit-by-treatment interaction. All statistical comparisons used 2-sided tests with a significance level of 0.050, unless otherwise specified. The two contrasts of interest were the 400 mg/day and the 600 mg/day quetiapine groups versus placebo and the Simes-Hommel step-up procedure was used for adjustment of the 2 primary comparisons.
An additional analysis using ANCOVA model with missing values imputed by the LOCF method was conducted to further assess robustness of the primary analysis.

Sample size determination: A total of 88 evaluable patients per treatment group (N = 264) would provide at least 85% power to detect a difference of 6 points between either the 400 mg/day or 600 mg/day quetiapine treatment group and the placebo group for the mean change from baseline in YMRS total score. A Bonferroni correction using an alpha = 0.025 for each dose comparison to placebo was used as a conservative approach for obtaining the sample size estimate. This sample size calculation assumed a standard deviation of 12 and a 2-tailed test at an overall experimental type I error rate of 0.05. An additional 66 (20%) patients were added to provide an estimate of 330 patients needed for screening. These additional patients were added to account for those patients who may be screened but who may not become evaluable.

No interim analyses were planned or performed.

Definitions of the ITT and safety populations were standard. ITT population: All randomized patients who were given study treatment and who had baseline and at least one post-baseline efficacy assessment for the YMRS. Safety population: All randomized patients who were given study treatment.

Results

Demographics

The mean age (~13 years) was similar across the treatment groups and the distribution between children (10 – 12 years) and adolescents (13 – 17 years) was similar between groups. More males were enrolled in the quetiapine 600 mg/day and placebo groups. The majority of patients were Caucasian.

Table 17. Patient Demographics

	Quetiapine 400 mg/day N = 93	Quetiapine 600 mg/day N = 95	Placebo N = 89
Sex n (%)			
Male	47 (50.5)	55 (57.9)	54 (60.7)
Female	46 (49.5)	40 (42.1)	35 (39.3)
Age (years)			
Mean	13.1 (2.2)	13.2 (2.2)	13.3 (2.1)
Median	13	13	13
Range	10 - 17	9* - 17	10 - 17
Age distribution n (%)			
10 – 12 years	43 (46.2)	42 (44.2)	36 (40.4)
13 – 17 years	50 (53.8)	53 (55.8)	53 (59.6)
Race n(%)			
Caucasian	73 (78.5)	73 (76.8)	66 (74.2)
Black	12 (12.9)	14 (14.7)	12 (13.5)
Oriental	0	0	1 (1.1)
Other	8 (8.6)	8 (8.4)	10 (11.2)
Ethnic Group n (%)			
African-American	10 (10.8)	14 (14.7)	12 (13.5)
African-Caribbean	2 (2.2)	0	0
Hispanic	8 (8.6)	7 (7.4)	11 (12.4)
Native American	2 (2.2)	3 (3.2)	1 (1.1)
Not applicable	69 (74.2)	70 (73.7)	61 (68.5)
Other	2 (2.2)	1 (1.1)	2 (2.2)
Native Hawaiian/Pacific Islander	0	0	2 (2.2)

*This patient was consented at 9 years old and was 10 years old by the start of study drug
From Sponsor Table 21 in Clinical Study Report

Baseline Characteristics

Select baseline characteristics are listed in Table 18. The treatment groups were well matched with regard to baseline characteristics of diagnosis and severity of illness. More patients in the quetiapine 400 mg/day group had comorbid ADHD. There was variability between the groups with regard to the number of manic/mixed episodes experienced in the past year.

Table 18. Baseline Characteristics

	Quetiapine 400 mg/day N = 93	Quetiapine 600 mg/day N = 95	Placebo N = 89
DSM-IV diagnosis n (%) Most recent episode manic Most recent episode manic, severe, without psychotic features Most recent episode manic, severe with psychotic features Most recent episode mixed Most recent episode mixed, severe without psychotic features Most recent episode mixed, severe with psychotic features	 73 (78.5) 14 (15.1) 5 (5.4) 0 0 1 (1.1)	 72 (75.8) 14 (14.7) 5 (5.3) 1 (1.1) 2 (2.1) 1 (1.1)	 68 (76.4) 14 (15.7) 7 (7.9) 0 0 0
Comorbid ADHD diagnosis n(%)	49 (52.7)	40 (42.1)	35 (39.3)
Baseline CGI-BP-Severity Score Mean (SD) Range	 4.7 (0.75) 3-7	 4.6 (0.71) 3-7	 4.6 (0.64) 4-7
Baseline YMRS score	29.4 (5.9)	29.6 (6.4)	30.7 (5.9)
Years since first known manic or mixed episode Mean (SD)	4.3 (3.1)	4.1 (3.0)	4.5 (2.9)
Total number of prior manic or mixed episodes over past year Mean (SD)	7.3 (38.7)	3.5 (11.2)	5.3 (21.9)
Years since first known depressed episode Mean (SD)	4.6 (3.0)	5.0 (2.8)	4.7 (2.5)
Total number of prior depressed episodes over past year Mean (SD)	1.1 (1.8)	3.7 (16)	2.4 (11.5)
Total number of bipolar hospitalizations over lifetime Mean (SD)	1.1 (1.8)	1.1 (2.5)	0.7 (1.5)
Years since last inpatient psychiatric hospitalization Mean (SD)	1.8 (1.5)	2.8 (2.5)	3.3 (3.3)
Has the subject been hospitalized for a suicide attempt? Yes n (%)	5 (5.4)	4 (4.2)	1 (1.1)
Current or prior exposure to quetiapine? Yes, n (%)	25 (26.9)	16 (16.8)	15 (16.9%)
Quetiapine average daily dose Mean (SD)	152 (124.1)	209 (187.1)	225 (203.1)

From Sponsor Table 22 in Clinical Study Report, baseline YMRS scores obtained from Table 11.2.1.2.3.

Patient Disposition

A total of 393 patients were enrolled into the clinical trial. One hundred nine were screening failures, primarily due to not fulfilling eligibility criteria. A total of 284 patients were randomized.

Table 19. Patient Disposition

	Quetiapine 400 mg/day	Quetiapine 600 mg/day	Placebo
Randomized	95	98	91
Received Drug	95	98	90
Discontinued Study	19 (20.0%)	18 (18.4%)	25 (27.5%)
Adverse Event	15 (15.8%)	7 (7.1%)	4 (4.4%)
Met discontinuation criteria*	1 (1.1%)	2 (2.0%)	4 (4.4%)
Patient not willing to continue	1 (1.1%)	5 (5.1%)	5 (5.5%)
Lost to follow-up	0	1 (1.0%)	2 (2.2%)
Other**	2 (2.1%)	3 (3.1%)	10 (11.0%)
Completed Study	**76 (80%)**	**80 (81.6%)**	**66 (72.5%)**
Enrolled in OL study 150	73 (76.8%)	67 (68.4%)	68 (75.6%)

From Sponsor Figure 1 in Clinical Study Report
*the majority of these discontinuations were due to lack of efficacy as defined by CGI-I scores per discontinuation criteria. [from Disposition of Each Subject document insubmission].
**examples of "other" discontinuations included noncompliance, family withdrew consent, moving out of state, lack of efficacy [from Disposition of Each Subject document in submission]

Table 20. Sample Sizes for ITT and Safety Populations

	Total	Quetiapine 400 mg/day	Quetiapine 600 mg/day	Placebo
ITT Population	277	93	95	89
Safety Population	283	95	98	90

Concomitant Medications

Allowable concomitant medications included benztropine for the treatment of emergent EPS, diphenhydramine (up to 50 mg/day) for "sleeplessness", hydroxyzine (up to 100 mg/day not to exceed 4 days in any study week) for agitation or anxiety, lorazepam (up to 4 mg/day – not to exceed 4 days in any study week) orally or IM for the treatment of agitation or anxiety, propranolol for the treatment of akathisia. Ongoing treatment with select psychostimulants (methylphenidate, dextroamphetamine, mixed amphetamine salts, dexmethylphenidate) were allowed if the dose had been stable for $\geq$ 30 days before screening (no dose adjustments were allowed).

The use of psychostimulants was 19.4% in the quetiapine 400 mg/day group, 11.6% in the quetiapine 600 mg/day group and 11.2% in the placebo group. The use of psychostimulants was less than the overall diagnosis of comorbid ADHD in each treatment group (~40-50%), with the quetiapine 400 mg/day group having a higher proportion of patients with comorbid ADHD than the other two treatment groups (see Table 18).
Not unexpectedly, the use of antihistamines and lorazepam was higher in the placebo group.

Table 21. Concomitant Medication Use

	Quetiapine 400 mg/day N = 93	Quetiapine 600 mg/day N = 95	Placebo N = 89
Antidepressants			
Sertraline	1 (1.1%)	0	0
Mood Stabilizers			
Valproate	0	0	1 (1.1%)
Lithium	1 (1.1%)	0	0
Psychostimulants			
Atomoxetine	1 (1.1%)	0	0
Dexamphetamine	6 (6.5%)	2 (2.1%)	3 (3.4%)
Methylphenidate	11 (11.8%)	9 (9.5%)	7 (7.9%)
Antihistamines*			
Diphenhydramine	5 (5.4%)	4 (4.2%)	9 (10.1%)
Hydroxyzine	4 (4.3%)	1 (1.1%)	4 (4.5%)
Benzodiazepines			
Lorazepam	8 (8.6%)	5 (5.3%)	10 (11.2%)

From Sponsor table 11.1.7.5 in Clinical Study Report
*Used for sedation or treatment of agitation

Important Protocol Violations

As with Study 112, the majority of major protocol violations were patients using anxiolytics/hypnotics not specifically permitted or other concomitant medication violations. Concomitant medication use is discussed in the previous section. No other major protocol violations were noted that would impact the overall interpretation of the study results.
Of note, though major protocol violations were included in subject discontinuation criteria in the protocol, it does not appear that any patients were discontinued from the study based on this criterion.

Dosing

The study used two fixed doses of quetiapine, 400 mg/day and 600 mg/day, vs. placebo.

Efficacy Findings

Primary Efficacy Analysis

The MMRM analysis showed both quetiapine 400 mg/day and quetiapine 600 mg/day were statistically significantly superior to placebo.

Table 22. Primary Efficacy Variable (MMRM): YMRS Total Score Change from Baseline to Endpoint (week 6) in the MITT Patient Population

		Baseline		Mean change from baseline to endpoint		LSMean Change	LSMean Difference	P-value vs. placebo
	N	Mean	SD	Mean	SD			
Quetiapine 400 mg	76	29.2	5.9	-15.3	8.45	-14.25	-5.21	<0.001
Quetiapine 600 mg	81	29.2	5.96	-15.8	9.32	-15.06	-6.56	<0.001
Placebo	67	30	5.45	-10.1	10.28	-9.04		

Modified from Sponsor Table 24 and 11.2.1.2.1 in Clinical Study Report

Based on a request from the FDA, the Sponsor also performed a separate analysis excluding Dr. Gilliam's site (site #10) [see Section 3.2, Compliance with Good Clinical Practices].

Table 23. Primary Efficacy Variable (MMRM): YMRS Total Score Change from Baseline to Endpoint (Week 3) – *Excluding Site #10*

	LSMean Difference	P-value
Quetiapine 400 mg (N = 67)	-5.56	< 0.001
Quetiapine 600 mg (N = 73)	-6.92	< 0.001
Placebo (N = 59)		

From Sponsor Table 2 in Response Document – Gilliam site

Sensitivity Analysis

The primary analysis model was repeated using the per-protocol population. This analysis corroborated with the primary analysis as noted by Dr. Dinh in his statistical review (table 14).

In addition, an ANOVA model with missing data imputed by the LOCF method in the MITT population showed similar statistically significant results for both quetiapine groups as compared to placebo.

Table 24. Primary Efficacy Variable: YMRS Total Score Change from Baseline (LOCF)

Treatment Groups	N	LSMean Change	LSMean Difference	P-value(vs. placebo)
Quetiapine 400 mg	93	-13.42	-5.15	<0.001
Quetiapine 600 mg	95	-15.18	-6.9	<0.001
Placebo	89	-8.28		

Modified from Sponsor Table 11.2.1.2.3 in Clinical Study Report

Analysis of Primary Endpoint over Time

The following table summarizes the treatment effect over time based on the MMRM analysis.

Table 25. Change from Randomization in the YMRS total score (MMRM) Over Time

	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
Visit	N	Mean	N	Mean	N	Mean	Diff	P-value*	Diff	P-value*
Day 04	64	-5.01	81	-8.05	75	-6.84	-3.05	0.015	-1.83	0.120
Day 07	84	-6.78	88	-11.88	90	-11.83	-5.10	<0.001	-5.05	<0.001
Day 14	73	-8.47	79	-13.26	82	-14.76	-4.79	0.001	-6.29	<0.001
Day 21	67	-9.04	76	-14.25	81	-15.60	-5.21	<0.001	-6.56	<0.001

Note: extracted from Dr. Dinh's FDA statistical review, table 16; data from Sponsor's Study Report; Table 11.2.1.2.1
* p-values not adjusted for multiplicity

Secondary Efficacy Variables

The sponsor claims that improvement of manic symptoms in this patient population treated by quetiapine, as assessed by the YMRS total score change from baseline at Day 4 and Day 7 for 400 mg quetiapine, and Day 7 fro 600 mg quetiapine (see table above).

The sponsor also claims that quetiapine 400 mg and 600 mg were superior to placebo in improving a broad range of mania symptoms in this patient population assessed by CGI-BP severity of illness at Day 7 and 21, GCI-BP Global Improvement (Overall Bipolar Illness) scale at Day 21, percentage of patients with remission (defined as a YMRS-total score <12 at Day 21), and percentage of patients with response (defined as a >50% reduction from baseline in the YMRS total score) at Day 7 and 21. None of these secondary variables were pre-specified as a key secondary variable. For details, refer to Sponsor's Appendix Tables in section 11.2 of the NDA submission regarding supporting data for these secondary variables

Table 26. Secondary Efficacy Variable: Percent of Responders (≥ 50% reduction from baseline in YMRS total score at endpoint)

	OC			LOCF		
Treatment Groups	N	Responders N (%)	p-value	N	Responders N (%)	p-value
Quetiapine 400 mg	76	49 (64%)	0.001	93	51 (55%)	< 0.001
Quetiapine 600 mg	81	47 (58%)	0.005	95	53 (56%)	< 0.001
Placebo	67	25 (37%)		89	25 (28%)	

From Sponsor Tables 26 and 11.2.1.6.2 in Clinical Study Report (Study 149)

Table 27. Secondary Efficacy Variable: Percent of Remitters (≤ 12 on YMRS total score at endpoint)

	OC			LOCF		
Treatment Groups	N	Remitters N (%)	p-value	N	Remitters N (%)	p-value
Quetiapine 400 mg	76	40 (53%)	0.010	93	42 (45%)	0.003
Quetiapine 600 mg	81	44 (54%)	0.003	95	49 (52%)	< 0.001
Placebo	67	20 (30%)		89	20 (22%)	

From Sponsor Tables 27 and 11.2.1.8.2 in Clinical Study Report (Study 149)

Conclusions

The efficacy of quetiapine in the acute treatment of bipolar mania in children and adolescents (ages 10 to 17 yrs) was demonstrated in this pivotal trial.

6.2.2 Subgroup Analyses

Our statistics team conducted exploratory subgroup analyses based on age (10-12 yrs; 13-17 yrs), gender (M,F), and race (Caucasian, others). As noted in detail by Dr. Dinh in the FDA statistical review (tables 26, 27 and 28), the results trended in the same direction in favor of quetiapine in all these subgroup analyses.

Table 28. Study D1448C00149: Sponsor's primary efficacy results by age: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Age 10-12			
Sample size at Week 3	26	32	37
LS Means	-8.68	-13.49	-17.06
Difference from placebo		-4.81	-8.38
(95% confidence interval)		(-9.73, 0.12)	(-13.05, -3.71)
Age 13 - 17			
Sample size at Week 3	41	44	44
LS Means	-9.35	-14.92	-14.39
Difference from placebo		-5.57	-5.04
(95% confidence interval)		(-9.18, -1.96)	(-8.83, -1.24)

From Statistician's review, Table 28

Inclusion criteria indicated that patients with rapid-cycling bipolar disorder could be enrolled into the study. The Sponsor did not indicate whether any patients with rapid-cycling disorder were enrolled nor, if enrolled, if there was any differential efficacy based on a subgroup analysis. The Sponsor has been asked to provide this information to the Division.

6.2.3 Dose Response

The treatment response was numerically greater in the higher dose 600 mg quetiapine group (i.e., the placebo-subtracted LS mean difference of -5.2 in the 400 mg; -6.6 in the 600 mg quetiapine group), though not statistically significantly different.

6.2.4 Key Secondary Endpoints

No key secondary endpoint was pre-specified in this study.

6.2.5 Effect Size

The treatment effect size (change from baseline to endpoint in YMRS total scores around 5 points) observed in this study seems similar to the effect size observed in other mania trials.

6.2.6 Long-term Efficacy

No adequate and well controlled data to address the question of long-term efficacy in this submission.

6.2.7 Pediatric Development

This study was conducted in response to the Pediatric Written Request letter issued on 2/11/2003 under pediatric exclusivity.

Efficacy Conclusions

The sponsor has provided positive efficacy data for quetiapine in support of the claim for the acute treatment of bipolar mania in children adolescents.

7 Review of Safety

Safety Summary

Note: a comprehensive review of the effects of quetiapine on weight, BMI, glucose and lipids in children/adolescents is ongoing (per the Division's separate request for these data in January 2008). This review will also include dose-related effects of quetiapine on these metabolic parameters (per the Division's additional request in February 2009).
Several additional requests for information regarding specific safety signals have been submitted to the Sponsor. When all of these data have been reviewed, the Sponsor's proposed product labeling will also be reviewed in a separate addendum to this clinical review.

No deaths occurred in the clinical trials included in this submission. Similar percentages of patients had serious adverse events in the quetiapine and placebo groups [Study 112: 6.1% in the quetiapine groups combined vs. 5.3% in the placebo group; Study 149: 4.7% in the quetiapine groups combined vs. 3.3% in the placebo group]. The majority of serious adverse events were potentially related to the underlying psychiatric diagnosis. Similarly, many of the discontinuations due to adverse events included events that were potentially related to the underlying psychiatric diagnoses, however, the majority of discontinuations due to adverse events included somnolence, sedation, lethargy and fatigue.

In both Studies 112 and 149, the common adverse events were similar to that already established for quetiapine in the adult clinical trials programs. Sedation/somnolence was the most common adverse event [Study 112: 33% quetiapine 400 mg/day, 35% quetiapine 800 mg/day, 11% placebo; Study 149: 49% quetiapine 400 mg/day, 57% quetiapine 600 mg/day, 14% placebo). In both studies, tachycardia occurred in ~5% of patient in the quetiapine 400 mg/day groups, ~8% in the quetiapine 600 – 800 mg/day groups and 0 patients in the placebo groups.

In Study 112, the rates of EPS were greater in the quetiapine groups compared to placebo (12.3% in the quetiapine 400 mg/day group, 13.5% in the quetiapine 800 mg/day group and 5.3% in the placebo group). Rates of EPS were lower in Study 149, but were greater in the quetiapine groups compared to placebo (4.2% in the quetiapine 400 mg/day group, 3.1% in the quetiapine 600 mg/day group and 1.1% in the placebo group).

The clinical chemistry findings for Studies 112 and 149 were similar to that already established for quetiapine in the adult clinical trials programs. Mean increases in quetiapine groups occurred for AST, ALT, alkaline phosphatase, total cholesterol, LDL and triglycerides. A mean decrease in glucose was noted in Study 112 while Study 149 showed a mean increase in the quetiapine groups (+3.5 mg/dL for quetiapine 400 mg/day, +3.7 mg/dL for quetiapine 600 mg/day vs. -1.2 mg/dL for placebo). Mean change in TSH concentrations were variable within and between studies while the overall effect on free T4 and total T4 was a mean decrease. Mean prolactin concentrations decreased in Study 112 and increased in Study 149 (+2.8 for quetiapine 400 mg/day, +1.9 for quetiapine 600 mg/day vs. -1.1 for placebo). The findings for hematology included the known effect of decreases in neutrophils in the quetiapine groups [Study 112: -0.07 10^9/L for quetiapine 400 mg/day, -0.12 10^9/L quetiapine

800 mg/day vs. +0.36 10^9/L for placebo group], decrements occurred in all treatment groups (including placebo) in Study 149.

A new signal that emerged in the children/adolescent population that was not present in the adult clinical trials programs was a significant increase in pulse, systolic blood pressure and diastolic blood pressure.

Vital Signs: Mean Change from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day	Quetiapine 800 mg/day	Placebo
Supine pulse (bpm)	6	3.9	-1.4
Supine Systolic BP (mmHg)	2	1	-1.6
Supine Diastolic BP (mmHg)	1.3	0.2	0.1
Standing Pulse (bpm)	6.3	2.2	-2.5
Standing Systolic BP (mmHg)	2.3	-0.4	-1.7
Standing Diastolic BP (mmHg)	2.1	1.1	-1.2

Vital Signs: Mean (SD) Change from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg/day	Quetiapine 600 mg/day	Placebo
Supine pulse (bpm)	8.8	10.6	-0.8
Supine Systolic BP (mmHg)	0.4	2.4	-2.7
Supine Diastolic BP (mmHg)	1.3	3.1	1.0
Standing Pulse (bpm)	9.6	11.3	0.1
Standing Systolic BP (mmHg)	1.0	1.3	-0.8
Standing Diastolic BP (mmHg)	1.	1.7	0.2

Clinically important shifts in vital signs at any time also indicated higher percentages of patients with increases in supine pulse, systolic and diastolic blood pressures in the quetiapine groups compared to placebo (Sponsor has been asked to provide these data for standing vital signs). When comparing the clinically important shifts to high in vital signs between patients 10 - 12 years of age and patients 13 to 17 years of age, a greater percentage of patients experienced these shifts for most categories in the 10 - 12 years cohort (see review).

Clinically Important Shifts (Select) in Vital Signs At Any Time (Studies 112 and 149 Pooled)

	Shift	Quetiapine N = 340	Placebo N = 165
Supine Pulse (bpm)	> 120	8.1%	0
	≥ 15 increase	50.7%	18.4%
Supine Systolic BP (mmHg)	> 121*	14.2	5.9%
	≥ 20 increase	15.2	5.5%
Supine Diastolic BP (mmHg)	≥ 78*	16.8%	7.3%
	≥ 10 increase	40.6%	24.5%
	≥ 30 increase	1.5%	1.8%

*Definitions used for cut-offs differed by gender and age, see review

In Study 112 (6-week study), mean increases in weight occurred in the quetiapine groups (+1.9 kg in 400 mg, +1.5 kg in 800 mg) compared to a mean decrease (-0.1 kg) in the placebo group. In Study 112, 23.2% of patients in the quetiapine 400 mg/day group, 18.2% of patients in the quetiapine 800 mg/day group and 6.8% of patients in the placebo group had a ≥ 7% weight gain.

In Study 149 (3-week study) mean increases in weight also occurred in the quetiapine groups (+1.7 kg in 400 mg, +1.7 kg in 600 mg) compared to a mean increase of 0.4 kg in the placebo group. In Study 149, 14.5% of patients in the quetiapine 400 mg/day group, 9.9% of patients in the quetiapine 600 mg/day group and 0% patients in the placebo group had a ≥ 7% weight gain. In a pooled analysis (Studies 112 and 149), the percent of patients who gained ≥ 7% weight was 14.1% for quetiapine-treated patients 10 to 12 years old (compared to 0% in the placebo groups) and 18% for quetiapine-treated patients 13 to 17 years old (compared to 3.1% in the placebo groups). In the 26-week open label study, similar percentages of patients in the quetiapine groups and placebo groups had shifts of ≥ 0.5 BMI z-score from baseline at anytime, end of treatment and final visit.

Other than effects on heart rate, which were consistent with vital signs data, there were no significant findings with regard to ECG data. Study 150, the open-label 26-week extension study, obtained slit-lamp examinations at baseline and end of study. Three patients (< 1%) had a shift from normal to abnormal – the Sponsor has been asked to provide more clinical information on these abnormal readings.

A suicidality assessment (similar to the Columbia-type assessment) was included in these clinical trials. Five (1.5%) patients in the pooled analysis of Studies 112 and 149 had suicidal behavior/ideation compared to 0 in the placebo groups. The calculated relative risk for quetiapine compared to placebo did not reach statistical significance.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The trials primarily reviewed for safety data include the two pivotal acute trials, Study 112 (schizophrenia) and Study 149 (bipolar I mania) and the 26-week open-label extension to these two acute trials, Study 150. Study 028, a small open-label pharmacokinetic study, was reviewed for occurrences of serious adverse events and discontinuations due to adverse events. No events in these categories occurred in Study 028.

The safety population for Study 112 included 73 patients in the quetiapine 400 mg/day group, 74 patients in the quetiapine 800 mg/day group and 90 patients in the placebo group.
The safety population for Study 149 included 95 patients in the quetiapine 400 mg/day group, 98 patients in the quetiapine 600 mg/day group and 75 patients in the placebo group.
The safety population for Study 150 included 381 patients treated with open-label quetiapine [mean daily dose 599 (256.8) mg over a median of 181 days on study medication].

Three hundred eighty one patients were enrolled into Study 150, 237 (62.2%) completed the study. Disposition of patients is in Table 29. Approximately 75% of patients in studies 112 and 149 entered the open-label extension Study 150. Since the dose and drug assignments from the acute studies were not known, all patients began treatment with quetiapine on Day 1 with a dose of 50 mg followed by dose escalation to 400 mg by Day 5. On Day 5 and thereafter, the target dose of 400 mg was maintained or increased, by no more than 100 mg/day, up to 800 mg according to clinical response and investigator discretion. Dose could be reduced to 200 mg/day based on tolerability.

Table 29. Patient Disposition (Study 150)

	Quetiapine Open-Label
Enrolled	**381**
Discontinued Study	144 (37.8%)
Adverse Event	40 (10.5%)
Met discontinuation criteria	13 (3.4%)
Patient not willing to continue	42 (11%)
Lost to follow-up	33 (8.7%)
Other**	16 (4.2%)
Completed Study	**237 (62.2%)**

From Sponsor Figure 1 in Clinical Study report for Study 150

7.1.2 Categorization of Adverse Events

An audit of adverse event categorization and the use of MedDRA preferred terms was performed by reviewing a small sample of case report forms and comparing them to the corresponding narrative summary and the MedDRA line listing. No major deficiencies were found.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Sponsor provided some pooled safety analyses for the two pivotal trials that were provided in a clinical summary of safety document. These two pivotal trials differed in doses used (400 and 800 mg/day quetiapine in Study 112 and 400 and 600 mg/day quetiapine in Study 149) and study duration (6 weeks in Study 112 and 3 weeks in Study 149); and most of the safety data were provided separately in the respective clinical study reports.

7.2 Adequacy of Safety Assessments

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

The mean daily dose and mean duration of exposure for patients treated with quetiapine are provided in Table 30. Though these were fixed dose trials, the mean daily dose is lower than the target fixed dose due to the titration period.

Table 30. Mean Daily Dose and Mean Duration of Exposure (Studies 112, 149 and 150)

	Quetiapine 400	Quetiapine 800
Study 112 N Mean daily dose (mg/day) Mean duration of exposure (days)	Quetiapine 400 73 308 (56) 40	Quetiapine 800 74 568 (130) 40
Study 149 N Mean daily dose (mg/day) Mean duration of exposure (days)	Quetiapine 400 mg 95 287 (81) 21	Quetiapine 600 98 404 (115) 20
Study 150 N Mean daily dose (mg/day) Mean duration of exposure (days)	Quetiapine 380 599 146	

From Summary of Clinical Safety and Clinical Study Report documents (112, 149 and 150)

The Sponsor did not provide summary data for patient years of exposure or an exposure by subject age cohort.

In the pooled analysis for Studies 112 and 149, most patients remained on the BID dosing schedule and 18.8% were switched to a TID dosing schedule based on tolerability issues as per the clinical judgment of the investigator.

7.2.2 Explorations for Dose Response

Dose response relationships could be explored in each of the two individual pivotal studies as they employed fixed-dose study designs. In general, the higher doses were associated with some additional numerical improvement in efficacy rating scale scores compared to the lower doses, but not statistically significantly different.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Given the known adverse event profile in the adult clinical trials programs, the type and frequency of vital sign, clinical laboratory, and ECG parameters measured and reported seems adequate. The schedule of safety assessments for Studies 112, 149 and 150 are in Appendices 9.4, 9.6 and 9.10.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new issues were identified.

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

Atypical antipsychotics have been associated with several safety issues. Among the major safety issues are increased mortality in elderly patients with dementia-related psychosis, suicidality in children and adolescents, clinical worsening and suicidality, neuroleptic malignant syndrome, tardive dyskinesia (TD), orthostatic hypotension, hyperglycemia and diabetes mellitus.

The sponsors of atypical antipsychotics have been asked to provide additional data and pooled analyses for the metabolic profile safety signals. This includes AstraZeneca who have been asked to provide data and analyses for quetiapine IR and quetiapine XR for effects on lipids (cholesterol, HDL, LDL, triglycerides), glucose (glucose, HbA1c, UA glucose), and weight for both adults and pediatric subjects (see Division letter January 8, 2008). The Sponsor recently provided these data on 6/26/08 with an analysis of dose-related effects on metabolic parameters provided in February 2009 by Division request. The adult metabolic data review was completed in 03/2009; and was part of the discussion at the PDAC meeting on 4/8/2009. The pediatric metabolic data are currently under review.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in acute studies 112 or 149 or the open-label extension study 150.

7.3.2 Nonfatal Serious Adverse Events

Most of the serious adverse events were potentially related to the underlying psychiatric disorder (e.g. schizophrenia, psychotic disorder, irritability, aggression, delusion, bipolar disorder, mania). Two patients experienced syncope (one in Study 149, one in Study 150), one patient experienced a serious drug rash (Study 149), one patient experienced neutropenia (Study 150) and one patient experienced hypertensive crisis (Study 150). Some comments regarding these cases appear after the tables of serious adverse events.

Table 31. Serious Adverse Events – Study 112

	Patient	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)	Action taken with Study Drug
Quetiapine 400	E0024102	M, 15	Schizophrenia	3	Moderate	17	None
	E0320101	M, 17	Hallucination (visual)	26	Severe	13	None
	E0342115	F, 16	Hypersensitivity*	35	Mild	7	Temporarily stopped
	E0343103	F, 14	Psychotic disorder	30	Severe	4	Stopped
Quetiapine 800	E0024106	M, 14	Schizophrenia	26	Moderate	6	None
	E0341103	M, 14	Aggression	2	Severe	11	None
	E0341108	F, 17	Agitation	12	Severe	10	None
			Restlessness	12	Severe	10	None
			Verbal Abuse	12	Severe	13	None
			Irritability	12	Severe	20	None
	E0342010	F, 15	Wound abscess*	23	Moderate	16	None
	E0342016	M, 17	Amoebiasis	7	Mild	7	Temporarily stopped
Placebo	E0004102	M, 16	Delusion	5	Severe	8	Stopped
	E0024101	M, 15	Schizophrenia	14	Severe	6	None
	E0342102	F, 15	Aggression	19	Moderate	6	None
			Insomnia	24	Moderate	24	None
	E0342117	M, 14	Pharyngotonsillitis	19	Moderate	11	None

From Sponsor Table 46 in Clinical Study Report
*Investigator terms: Hypersensitivity: hypersensitivity reaction probably secondary to food, Wound abscess: infected wound/abscess formation on plantar aspect of right foot

Table 32. Serious Adverse Events – Study 149

	Patient	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)	Action taken with Study Drug
Quetiapine 400 mg	E0017205	F, 15	Bipolar disorder	8	Severe	13	No
	E0019206	M, 12	Bipolar disorder	8	Severe	7	Stopped
			Suicidal ideation	8	Severe	7	Stopped
	E0026205	F, 12	Bipolar disorder	6	Moderate	Unknown	Stopped
	E0030202	M, 15	Aggression	2	Severe	5	Stopped
			Mania	2	Severe	5	Stopped
	E0038203	M, 12	Syncope	8	Moderate	1	Stopped
Quetiapine 600 mg	E0010208	M, 14	Staphylococcal infection	16	Severe	Unknown	None
	E0016204	F, 9	Drug rash with eosinophilia and systemic symptoms	11	Mild	12	Stopped
	E0016210	M, 15	Aggression	25	Moderate	8	None
	E0019220	F, 15	Bipolar disorder	21	Severe	12	Stopped
Placebo	E0017201	M, 13	Bipolar disorder	3	Severe	20	None
	E0019224	M, 17	Bipolar disorder	10	Severe	4	Stopped
	E0024213	M, 14	Bipolar disorder	14	Severe	2	None

From Sponsor Table 48 in Clinical Study Report

Table 33. Serious Adverse Events – Study 150 (open-label quetiapine)

Prior DB Trial/Treatment	Patient	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)	Action taken with Study Drug
112/PC	E0003104	M, 13	Abnormal behavior	61	Severe	8	Stopped
			Schizophrenia	61	Severe	8	
149/PC	E0009211	M, 14	Aggression	35	Severe	4	Temporarily stopped
149/PC	E0017201	M, 13	Bipolar disorder	31	Severe	3	None
149/PC	E0017201	M, 13	Bipolar disorder	48	Severe	9	None
112/ PC	E0024104	F, 15	Constipation	128	Severe	3	None
149/PC	E0024202	F, 13	Bipolar disorder	167	Moderate	15	None
149/PC	E0028206	F, 12	Bipolar disorder	151	Severe	9	Stopped
112/PC	E0041101	F, 16	Physical assault	90	Severe	19	Stopped
149/PC	E0046201	M, 16	Mania	192	Moderate	8	None
149/PC	E0047211	F, 16	Syncope	34	Severe	1	Stopped
112/PC	E0261101	F, 17	Schizophrenia	19	Severe	2	Temporarily stopped
112/PC	E0341101	M, 18	Delusion	115	Severe	16	None
			Hostility	115	Severe	16	
			Irritability	115	Severe	16	
112/PC	E0342113	M, 17	Urinary Tract Infection	13	Mild	10	None
112/PC	E0342117	M, 15	Upper Respiratory Tract Infection	38	Severe	5	None
149/Q 400	E0003207	M, 10	Disinhibition	20	Severe	15	None
149/Q 400	E0008202	M, 12	Bipolar disorder	127	Severe	8	Dose Change
112/Q 400	E0017102	F, 17	Schizophrenia	56	Severe	7	Dose Change
			Schizophrenia	90	Severe	22	None
112/Q 400	E0017102	F, 17	Schizophrenia	158	Severe	12	None
			Hyperglycemia	213	Severe	8	None
			Schizophrenia	213	Severe	51	None
149/Q 400	E0017203	M, 15	Overdose	19	Severe	8	Temporarily stopped
149/Q 400	E0017203	M, 15	Bipolar disorder	101	Severe	20	None
149/Q 400	E0017205	F, 15	Bipolar disorder	22	Severe	21	None
112/Q 400	E0024102	M, 15	Paroxysmal perceptual alteration	74	Severe	10	Stopped
			Bacterial infection	108	Severe	Unknown	None
112/Q 400	E0024107	M, 17	Schizophrenia	29	Severe	9	None
149/Q 400	E0024201	F, 12	Bipolar disorder	3	Moderate	11	None
149/Q 400	E0026202	F, 13	Appendicitis	3	Severe	2	Temporarily stopped
149/Q 400	E0026205	F, 12	Bipolar disorder	46	Moderate	3	Stopped
112/Q 400	E0240103	M, 14	Hypertensive crises	129	Severe	1	None
			Schizophrenia	129	Mild	84	None
112/Q 400	E0262101	F, 15	Suicide attempt	159	Severe	5	Stopped
			Psychotic disorder	159	Severe	36	Stopped
112/Q 400	E0282105	M, 17	Schizophrenia	9	Severe	34	None
112/Q 400	E0343103	F, 14	Pulmonary hypertension	84	Mild	40	Stopped
112/Q 400	E0362106	M, 17	Aggression	43	Severe	7	None
			Aggression	78	Moderate	9	None
149/Q 600	E0002217	M, 12	Bipolar disorder	98	Severe	7	Stopped
112/Q 800	E0017101	M, 16	Schizophrenia	204	Severe	9	None
149/Q 600	E0017202	M, 15	Bipolar disorder	5	Moderate	6	None
			Cellulitis Staph	161	Moderate	13	None
			Bipolar disorder	202	Severe	10	None
149/Q 600	E0017204	F, 16	Bipolar disorder	5	Severe	13	None
149/Q 600	E0024203	M, 14	Overdose	181	Severe	1	Stopped
149/Q 600	E0026221	M, 11	Appendicitis	66	Severe	4	Temporarily stopped
149/Q 600	E0030203	M, 10	Neutropenia	28	Severe	29	Stopped
112/Q 800	E0240101	M, 14	Schizophrenia	162	Severe	Unknown	Stopped
			Schizophrenia	183	Severe	12	Stopped
112/Q 800	E0262102	M, 17	Psychotic disorder	84	Severe	Unknown	None
112/Q 800	E0340101	M, 16	Aggression	59	Severe	29	None
112/Q 800	E0341103	M, 15	Decreased appetite	28	Severe	4	None
			Hallucination, auditory	29	Severe	Unknown	None
112/Q 800	E0342101	F, 16	Pyrexia	14	Mild	7	None

			Typhoid fever	27	Mild	7	None
112/Q 800	E0342116	M, 17	Agitation	6	Moderate	13	None
			Restlessness	6	Moderate	13	None
			Amoebiasis	66	Moderate	10	Dose changed
112/Q 800	E0342119	F, 17	Drug toxicity (benzo)	52	Mild	4	Temporarily stopped
112/Q 800	E0343101	M, 17	Myocarditis post infection	98	Mild	30	Dose changed

From Sponsor Table 11.3.4.2 in Study 150 Clinical Study Report

Comments from narratives:
Hypersensitivity (E0342115, Study 112) – patient experienced sudden appearance of maculopapular rash over upper and lower extremities and the cervical area, afebrile. Study medication was stopped. Patient recovered with treatment (hydroxyzine, prednisone). No comments regarding food allergies.

Syncope (E0038203, Study 149) – patient walking to school when stopped by a security guard for suspicion of substance abuse. Patient was asked to perform a maneuver involving tilting his head back and placing his index finger to his nose. During the procedure, he fainted and remained unconscious for approximately 10 minutes. He was lethargic and sleepy for several hours after the event (no chest pain, no SOB, no seizure activity reported). Event resolved on the same day without hospitalization.

Drug rash (E0016204, Study 149) – On day 11, rash of small papules on face and torso, no fever. Day 13, presented to ER with erythematous, blanching, pruiritic rash on the face, arms, palms of both hands, abdomen, back, buttocks, legs and feet. During ER stay temperature increased to 102.3 degrees F with swelling of eyes and face. Narrative noted that eosinophils were high, but value not available. Study medication was stopped on Day 13. Patient was treated (oral and IV diphenhydramine, oral hydroxyzine prn, and topical steroid cream) and discharged on Day 22. Impression was allergy to quetiapine.

Hypertensive crises (E0240103, Study 150) - BP 150/95, resolved same day, narrative does not indicate that treatment was administered. There was no interruption or change in quetiapine dose. More information has been requested from the Sponsor.

Suicide attempt (E0262101, Study 150)– more information has been requested from Sponsor. Of note, the patient also experienced neutropenia with an ANC of 0.46 on Day 85. The next WBCs were performed on days 89 and 96 but without a differential. The next available ANC was on Day 169, the event had resolved with ANC = 2.82.

Neutropenia (E0030203, Study 150) – Day 28 ANC = 1.40 x 10^9/L. Dose of study medication reduced, ANC continued to fall reaching 1.22 x 10^9/L on Day 49, patient was discontinued. Recovery on Day 56 with ANC = 2.33 x 10^9/L.

7.3.3 Dropouts and/or Discontinuations

Many of the discontinuations due to adverse events were potentially related to the underlying psychiatric disorder (e.g. schizophrenia, delusion, bipolar disorder). The majority of the other adverse events leading to discontinuation were somnolence, sedation, lethargy and fatigue. There were also a number of discontinuations due to syncope and orthostatic hypotension.

Table 34. Discontinuations due to Adverse Events – Study 112

	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)
Quetiapine 400	M, 15	Somnolence	2	Moderate	26
	M, 14	Neutropenia	42	Mild	Unk
	F, 13	Schizophrenia	15	Severe	8
	F, 15	Anxiety	1	Moderate	Unk
	M, 17	Elevated Mood	10	Moderate	Unk
Quetiapine 800	M, 17	Somnolence	2	Moderate	3
	M, 13	Dysarthria	10	Severe	3
		Fatigue	10	Severe	3
	F, 14	Rubella	44	Mild	15
	F, 13	Depression	16	Severe	Unk
		Suicidal ideation	27	Mild	Unk
	F, 15	Dyspnoea	15	Moderate	Unk
	M, 16	Nausea	9	Moderate	8
		Somnolence	9	Moderate	8
	M, 15	Sedation	2	Moderate	Unk
Placebo	M, 16**	Delusion	5	Severe	8
	F, 16	Schizophrenia	22	Moderate	Unk

From Sponsor Table 48 in Clinical Study Report
**Same patient as listed in Table 31

Table 35. Discontinuations due to Adverse Events – Study 149

	Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)
Quetiapine 400	M, 17	Fatigue	7	Mild	23
	F, 17	Somnolence	1	Mild	Unknown
	M, 12**	Bipolar disorder	8	Severe	7
		Suicidal ideation	8	Severe	7
	F, 10	Sedation	2	Moderate	Unknown
	M, 12	Irritability	11	Moderate	Unknown
		Hostility	13	Severe	Unknown
	F, 13	Sedation	1	Severe	3
	F, 12	Syncope	5	Moderate	1
	F, 12**	Bipolar disorder	6	Moderate	Unknown
	F, 16	Bradyphrenia*	2	Moderate	3
		Clumsiness	2	Mild	3
		Irritability	2	Moderate	3
		Sedation	2	Moderate	9
	M, 15**	Aggression	2	Severe	5
		Mania	2	Severe	5
	F, 12	Somnolence	2	Mild	Unknown
	M, 13	Sedation	1	Mild	6
	M, 13	Sedation	2	Severe	2
	M, 12**	Tympanic membrane perforation	8	Moderate	Unknown
		Syncope	8	Moderate	1
	F, 17	Fatigue	1	Severe	Unknown
		Hypotension	1	Moderate	Unknown
		Somnolence	1	Severe	Unknown
Quetiapine 600 mg	F, 15	Fatigue	1	Moderate	4
		Lethargy	1	Moderate	4
		Muscular weakness	1	Moderate	4
		Irritability	2	Moderate	3
	F, 13	Fatigue	1	Severe	3
	F, 9**	Drug rash	11	Mild	12
	F, 15**	Bipolar disorder	21	Severe	12
	M, 15	Stomach discomfort	4	Severe	6
	M, 13	Orthostatic	4	Severe	1

	M, 15	hypotension Blood pressure increased Tachycardia	5 5	Severe Severe	2 2
Placebo	F, 16 F, 15 M, 17** M, 10	Bipolar disorder Sedation Bipolar disorder Hostility	5 11 10 4	Moderate Moderate Severe Severe	Unknown 12 4 Unknown

From Sponsor Table 50 in Clinical Study Report
*investigator term = slowed thinking
**Same patient as listed in Table 32

In Study 150, Forty subjects (10.5%) discontinued due to adverse events. These 40 patients experienced 62 adverse events. Approximately 40% (25/62) of these adverse events (were potentially related to the underlying disorder (aggression, agitation, bipolar disorder, delusion, hallucination, irritability, psychotic disorder, schizophrenia).

Table 36. Discontinuations due to Adverse Events *of Interest* – Study 150

Sex, Age	AE Preferred Term	Time from start of treatment to onset (days)	Intensity	Duration of AE (days)
M, 13	Tachycardia	21	Moderate	15
	Angina pectoris	29	Mild	4
	Hyperhydrosis	29	Moderate	7
F, 16	Syncope	34	Severe	1
M, 17	Blood glucose incr.	96	Severe	Unknown
	HbA1c incr.	96	Severe	Unknown
M, 13	Extrasystoles	21	Severe	Unknown
	Angina pectoris	21	Severe	1
M, 13	Dyspnea	21	Severe	1
	Tachycardia	21	Severe	1
F, 14	Pulmonary hypertension	84	Mild	40
M, 10	Hypertension	81	Moderate	Unknown
M, 14	Overdose	181	Severe	1
M, 10	Neutropenia	28	Severe	29
F, 12	Tachycardia	3	Severe	7
M, 17	Petit mal epilepsy	142	Moderate	Unknown
M, 16	Sinus tachycardia	91	Mild	29
	Tachycardia paroxysmal	112	Moderate	Unknown

From Sponsor Table 11.3.5.2 in Clinical Study Report for Study 150
**Same patient as listed in Table 33

7.3.4 Significant Adverse Events

A review of the adverse events in Studies 112, 149 and 150 did not reveal any significant events not included under deaths, serious adverse events or discontinuations due to adverse events.

7.3.5 Submission Specific Primary Safety Concerns

Several safety concerns have been identified in the adult clinical trials programs for quetiapine as well as for atypical antipsychotics in general, many of which are covered in the respective sections of this clinical review. Known potential safety signals include neutropenia, orthostatic hypotension, weight gain, hyperlipidemia, hyperglycemia, hypothyroidism, EPS and tardive dyskinesia, development of cataracts and suicidality (class effect associated with antidepressants in certain age groups).

Cataracts
A slit-lamp examination by an ophthalmologist was to be performed at entry into the open-label extension study (Study 150) and at the end of this 26-week study. The Sponsor provided these data only as categorical shifts in eye examination (normal to abnormal) in the submission. For patients who received placebo in Studies 112 and 149 and then received open-label quetiapine in Study 150, 2/129 (6.3%) had a shift from normal to abnormal eye examination (5 patients had abnormal eye exam at baseline that remained in this category). For patients who received quetiapine in Studies 112 and 149 and then received open-label quetiapine in Study 150, 1/251 (1%) had a shift from normal to abnormal eye examination (15 patients had abnormal eye exams at baseline that remained in this category). The Sponsor has been asked to provide more detailed clinical information regarding the shifts from normal to abnormal eye exams as well as the abnormal eye exams at baseline and end of study (same abnormalities noted?).

Extrapyramidal Side Effects and Tardive Dyskinesia
Though the Barnes Akathisia Scale and the Simpson Angus Scale were used to assess extrapyramidal side effects, adverse effects associated with EPS can also be noted in adverse event reporting. The following table summarizes the incidence of adverse events potentially associated with EPS. In Study 112, EPS occurred at > twice the rate in the quetiapine groups compared to placebo. In Study 149, rates of EPS were low and slightly greater than placebo.

Table 37. Adverse Event Terms Potentially Related to EPS – Studies 112 and 149

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 75
Study 112			
Total*	**9 (12.3%)***	**10 (13.5%)***	**4 (5.3%)***
Akathisia	3 (4.1%)	3 (4.1%)	2 (2.7%)
Dykinesia	2 (2.7%)	0	0
Extrapyramidal disorder	1 (1.4%)	1 (1.4%)	0
Hypokinesia	1 (1.4%)	1 (1.4%)	0
Muscle rigidity	2 (2.7%)	0	0
Musculoskeletal stiffness	1 (1.4%)	0	0
Psychomotor hyperactivity	0	1 (1.4%)	1 (1.3%)
Restlessness	1 (1.4%)	1 (1.4%)	0
Salivary hypersecretion	2 (2.7%)	2 (2.7%)	2 (2.7%)
Tremor	3 (4.1%)	3 (4.1%)	2 (2.7%)
	Quetiapine 400 mg/day N = 95	Quetiapine 600 mg/day N = 98	Placebo N = 90
Study 149			
Total*	**4 (4.2%)**	**3 (3.1%)**	**1 (1.1%)**
Akathisia	1 (1.1%)	1 (1%)	0
Dykinesia	0	0	0
Extrapyramidal disorder	0	0	0
Hypokinesia	0	0	0
Muscle rigidity	0	0	0
Musculoskeletal stiffness	1 (1.1%)	3 (3.1%)	1 (1.1%)
Psychomotor hyperactivity	0	0	0
Restlessness	1 (1.1%)	1 (1%)	0
Salivary hypersecretion	0	0	0
Tremor	2 (2.1%)	1 (1%)	1 (1.1%)

Modified from Sponsor table 49 (Study 112) and Table 51 (Study 149), added AE terms salivary hypersecretion and musculoskeletal stiffness from Table 11.3.2.4.1 (Study 112) and Table 11.3.2.4 (Study 149) in Clinical Study Reports

*Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Since this reviewer added the AEs salivary hypersecretion and musculoskeletal stiffness, it is not known if these occurred in patients not already counted in the total tally by Sponsor, the overall incidence may be slightly higher if these occurred in unique patients.

Table 38. Categorical Change from Baseline to End of Study in Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BAS) and AIMS*

	Improved	No Change	Worsened
Study 112 SAS			
Quetiapine 400	21.8%	65.5%	12.7%
Quetiapine 800	21.8%	61.8%	16.4%
Placebo	23.8%	69.0%	7.1%
Study 149 SAS			
Quetiapine 400	12%	81.3%	6.7%
Quetiapine 800	7.4%	77.8%	14.8%
Placebo	19.4%	70.1%	10.4%
Study 112 BAS			
Quetiapine 400	9.1%	85.5%	5.5%
Quetiapine 800	3.6%	94.5%	1.8%
Placebo	9.5%	85.7%	4.8%
Study 149 BAS			
Quetiapine 400	8.0%	86.7%	5.3%
Quetiapine 800	6.2%	87.7%	6.2%
Placebo	9.0%	86.6%	4.5%
Study 112 AIMS			
Quetiapine 400	7.3%	85.5%	7.3%
Quetiapine 800	18.2%	80.0%	1.8%
Placebo	9.5%	88.1%	2.4%
Study 149 AIMS			
Quetiapine 400	13.3%	86.7%	0
Quetiapine 800	12.3%	85.2%	2.5%
Placebo	10.4%	89.6%	0

From Sponsor Tables 62, 63, 65 and X in Clinical Study Report (Study 112) and Tables 65, 66, 67 in Clinical Study Report (Study 149).
*improved: < 1 change in total score, worsened: $\geq$ 1 change in total score

For the AIMS-7 analysis In Study 150, 20/380 (5.3%) of patients had improvements, 332/380 (88.8%) had no change and 22/380 (5.9%) had worsening.

Suicidality Assessment
The Sponsor conducted an in-house review of suicidal behavior and ideation in Studies 112, 149 and 150 following the process developed by the group at Columbia University. A group of Sponsor certified physicians who were not associated with these studies reviewed the identified events from the 3 studies. All study data were blinded to the reviewers except as provided in the narratives used for patient classification.
No patients committed suicide during any of the clinical studies.

Table 39 (Sponsor's Table). Incidence of Patients with Suicidal Behavior/Ideation in Studies 112 and 149, Columbia-type Analysis

	All patients		Age ≤12 years		Age 13 to 17 years	
	PLA (N=165)	QTP (N=340)	PLA (N=36)	QTP (N=85)	PLA (N=129)	QTP (N=255)
Classification (codes)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Suicidal behavior/ideation (1, 2, 3, 4)	0	5 (1.5)	0	3 (3.5)	0	2 (0.8)
-- Suicidal behavior (1, 2, 3)	0	2 (0.6)	0	2 (2.4)	0	0
-- Suicidal ideation (4)	0	3 (0.9)	0	1 (1.2)	0	2 (0.8)
Possible suicidal behavior/ideation (5, 6, 9)[a]	2 (1.2)	6 (1.8)	0	2 (2.4)	2 (1.6)	4 (1.6)

From Sponsor Table SU3 in Suicidality Report document
Category 5 = self-injurious behavior, intent unknown; category 6 = not enough information, death; category 9 = not enough information, non-death

The relative risk for suicidal behavior/ideation was calculated and is presented in Table 40. Each of the confidence interval comparisons between quetiapine and placebo included 1 and therefore not considered statistically significant.

Table 40 (Sponsor Table). Suicidal Behavior/ideation Relative Risk for Quetiapine Compared to Placebo in Studies 112 and 149 (pooled), Columbia-type Analysis

	All patients		Age ≤12 years		Age 13 to 17 years	
Classification (codes)	RR	95% CI	RR	95% CI	RR	95% CI
Suicidal behavior/ideation (1, 2, 3, 4)	2.91[a]	0.352 – 24.080	3.01[a]	0.160 – 56.855	2.57[a]	0.125 – 52.810
Suicidal behavior/ideation (1, 2, 3, 4) + possible suicidal behavior/ideation (5, 6, 9)[a]	1.67	0.395 – 7.093	4.73[a]	0.269 – 83.410	1.26	0.292 – 5.460

From Sponsor Table SU4 in Suicidality Report document

In Study 150 (open-label study), 14 patients with events possibly related to suicidality were identified: 5 patients with suicidal behavior/ideation and 9 patients with possibly suicidal events.

Emergent Depression (Study 149)
The incidence of emergent depression was assessed in Study 149 and defined as a CDRS-R (Children's Depression Rating Scale-Revised) total score ≥ 40 at Day 21 for patients whose baseline CDRS-R score was < 40. The incidence of emergent depression was 2.1% in the quetiapine 400 mg/day group, 1.0% in the quetiapine 600 mg/day group and 3.3% in the placebo group.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported adverse events (> 5% in either quetiapine dose group) for Study 112 are listed in Table 41. The Sponsor was asked to calculate the frequency of occurrence of somnolence + sedation since these are very similar adverse events. The Sponsor indicated that somnolence/sedation occurred in 32.9% (24/73) patients in the quetiapine 400 mg/day group, 35.1% (26/74) patients in the quetiapine 800 mg/day group and 10.7% (8/75) patients in the placebo group.
A dose-related signal for frequency of common adverse events appears likely for dizziness, dry mouth, and tachycardia.

Table 41. (Sponsor Table 45) Most Commonly Reported Adverse Events (> 5% in either quetiapine group) – Study 112

Preferred term	Quetiapine 400 mg/day (N=73)		Quetiapine 800 mg/day (N=74)		Placebo (N=75)	
	n	%	n	%	n	%
Somnolence	20	27.4	22	29.7	5	6.7
Headache	6	8.2	16	21.6	14	18.7
Dizziness	6	8.2	11	14.9	4	5.3
Dry mouth	3	4.1	7	9.5	1	1.3
Insomnia	9	12.3	7	9.5	17	22.7
Agitation	6	8.2	6	8.1	10	13.3
Tachycardia	4	5.5	6	8.1	0	
Increased appetite	3	4.1	5	6.8	3	4.0
Fatigue	4	5.5	4	5.4	3	4.0
Irritability	2	2.7	4	5.4	0	
Nausea	3	4.1	4	5.4	13	17.3
Sedation	4	5.5	4	5.4	3	4.0
Vomiting	3	4.1	4	5.4	6	8.0
Anxiety	4	5.5	3	4.1	5	6.7
Diarrhea	4	5.5	1	1.4	4	5.3

Sponsor Table 45 from Clinical Study Report

The most commonly reported adverse events (> 5% in either quetiapine dose group) for Study 149 are listed in Table 42. The Sponsor was asked to calculate the frequency of occurrence of somnolence + sedation since these are very similar adverse events. The Sponsor indicated that somnolence/sedation occurred in 49.5% (47/95) patients in the quetiapine 400 mg/day group, 57.1% (56/98) patients in the quetiapine 800 mg/day group and 14.4% (13/90) patients in the placebo group.
A dose-related signal for frequency of common adverse events appears likely for somnolence/sedation, nausea, and tachycardia.

Table 42. (Sponsor Table 46) Most Commonly Reported Adverse Events (> 5% in either quetiapine group) – Study 149

Preferred term	Quetiapine 400 mg (N=95)		Quetiapine 600 mg (N=98)		Placebo (N=90)	
	n	%	n	%	n	%
Somnolence	27	28.4	31	31.6	9	10.0
Sedation	22	23.2	25	25.5	4	4.4
Dizziness	18	18.9	17	17.3	2	2.2
Headache	15	15.8	13	13.3	14	15.6
Nausea	6	6.3	10	10.2	4	4.4
Fatigue	13	13.7	9	9.2	4	4.4
Increased appetite	9	9.5	9	9.2	1	1.1
Tachycardia	5	5.3	8	8.2	0	
Vomiting	8	8.4	7	7.1	3	3.3
Dry mouth	7	7.4	7	7.1	0	
Weight increased	6	6.3	6	6.1	0	
Nasal congestion	3	3.2	6	6.1	2	2.2
Irritability	3	3.2	5	5.1	1	1.1

The most commonly reported adverse events were tabulated by age cohort (Study 112 did not enroll patients < 13 years). For patients 10 - 12 years, adverse events of increased appetite, dry mouth, tachycardia, weight increased and nasal congestion occurred more commonly compared to patients 13 to 17 years of age.

Table 43. Most Commonly Reported Adverse Events (> 5% in either quetiapine group) By Age Cohort – Studies 112 and 149 pooled

	10 - 12 Years		13 – 17 Years	
	Quetiapine N = 85	Placebo N = 36	Quetiapine N = 255	Placebo N = 129
Somnolence	24 (28.2)	2 (5.6)	76 (29.8)	12 (9.3)
Sedation	19 (22.4)	0	36 (14.1)	7 (5.4)
Dizziness	15 (17.6)	2 (5.6)	37 (14.5)	4 (3.1)
Headache	16 (18.8)	6 (16.7)	34 (13.3)	22 (17.1)
Fatigue	8 (9.4)	2 (5.6)	22 (8.6)	5 (3.9)
Increased appetite	12 (14.1)	0	14 (5.5)	4 (3.1)
Dry mouth	8 (9.4)	0	16 (6.3)	1 (0.8)
Insomnia	3 (3.5)	5 (13.9)	20 (7.8)	19 (14.7)
Nausea	6 (7.1)	1 (2.8)	17 (6.7)	16 (12.4)
Tachycardia	8 (9.4)	0	15 (5.9)	0
Vomiting	8 (9.4)	0	14 (5.5)	9 (7.0)
Agitation	4 (4.7)	5 (13.9)	15 (5.9)	11 (8.5)
Weight increased	6 (7.1)	0	11 (4.3)	2 (1.6)
Nasal congestion	5 (5.9)	1 (2.8)	4 (1.6)	2 (1.6)

From Sponsor Table SA01 from Summary-Clin-Safety document

7.4.2 Laboratory Findings

7.4.2.1 Clinical Chemistry

Per request of the Division, the Sponsor provided a separate submission addressing the metabolic effects of quetiapine on adult and pediatric/adolescent patients in their clinical trials database. These data, while also summarized briefly in this review, will be more extensively evaluated in a separate review document and will also evaluate the dose-response relationship to these metabolic effects.

Mean Change Analyses

The mean change analyses in the quetiapine treated patients for Studies 112 and 149 did not reveal any new findings. Mean increases were noted for AST, ALT, alkaline phosphatase, total cholesterol, LDL, and triglycerides. Interestingly, mean change in glucose was a decrease in Study 112 and an increase in Study 149, presumably related to prior antipsychotics with effects on glucose that may have elevated baseline values in Study 112. Similarly, prolactin concentrations decreased in Study 112 and increased in Study 149. The effects on TSH were variable within and between the two studies while the overall effect on free T4 and total T4 was a mean decrease.

Table 44. Clinical Chemistry Changes from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day (N=73)			Quetiapine 800 mg/day (N=74)			Placebo (N=75)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
AST (IU/L)	61	3.2459	11.33822	59	-0.8136	14.21082	63	-1.8889	9.80637
ALT (IU/L)	61	4.2787	18.15868	59	1.2373	25.38214	63	-1.4444	18.23925
Alkaline phosphatase (IU/L)	62	3.9194	20.51493	60	7.3500	21.37068	63	0.2857	26.07955
Total bilirubin (mg/dL)	62	-0.0871	0.21231	59	-0.1034	0.36998	63	0.0492	0.23201
Creatinine (mg/dL)	62	-0.0026	0.08402	59	0.0083	0.09952	63	0.0048	0.10690
BUN (mg/dL)	62	0.1129	3.50692	60	-0.1500	2.95058	63	0.0159	3.20026
Glucose (fasting)[a] (mg/dL)	68	-0.0735	12.07602	70	-1.4000	9.08000	67	-1.7015	10.82368
HOMA-R	56	1.1112	5.56351	57	0.0897	3.97753	56	-0.4368	6.11830
Insulin (µIU/mL)	62	4.2742	19.25938	59	1.2203	17.29567	60	-1.0333	19.05742
HbA1c (%)	62	0.0210	0.22480	62	0.0645	0.22477	61	-0.0049	0.25194
QUICKI	56	-0.0075	0.04560	57	-0.0056	0.03690	56	0.0062	0.04255
Bicarbonate (mEq/L)	58	0.4138	2.38441	56	-0.2857	3.20632	61	-0.4754	3.36950
Chloride (mEq/L)	62	0.4677	2.75632	60	0.1500	2.93907	63	1.1111	2.89109
Potassium (mEq/L)	62	-0.0113	0.41136	59	0.0458	0.47282	63	-0.0524	0.48422
Sodium (mEq/L)	62	0.5161	2.85003	60	-0.1167	2.89998	63	0.6984	3.14507
Total cholesterol (mg/dL)	62	7.8226	28.82310	59	7.4237	24.65710	63	-8.0635	25.74745
HDL (mg/dL)	62	-2.8226	9.24267	60	-0.9667	9.90115	63	-2.4603	8.95297
LDL (mg/dL)	62	8.6613	22.73579	60	4.8167	21.78515	63	-3.8889	20.50500
Triglycerides (mg/dL)	62	9.6613	64.77172	60	15.5833	47.94357	63	-8.1587	59.39730
TSH (µIU/mL)	62	0.3734	1.35773	59	-0.0966	0.93745	62	-0.0395	1.08274
Free T4 (ng/dL)	62	-0.1510	0.18939	60	-0.2790	0.23064	63	0.0097	0.21324
Total T4 (µg/dL)	62	-1.4419	1.29508	60	-2.5083	1.90897	63	0.1063	1.21667
Triiodothyronine resin uptake (%)	62	-0.9032	3.60650	60	0.7333	4.36421	63	-0.1746	4.45964
Prolactin (ng/mL)	63	-10.5476	16.12225	60	-7.8333	26.47357	63	-18.2467	28.74950

From Sponsor Table 53 from Clinical Study Report (Study 112)

Table 45. Clinical Chemistry Mean Changes from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg (N=95)			Quetiapine 600 mg (N=98)			Placebo (N=90)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
AST (IU/L)	90	1.8111	7.94771	87	2.5977	11.65937	79	1.1519	5.54952
ALT (IU/L)	90	3.0444	11.67049	87	6.6322	21.31225	79	0.4051	9.78424
Alkaline phosphatase (IU/L)	90	1.8111	26.24298	87	-4.0000	27.09758	79	-10.3038	36.42180
Total bilirubin (mg/dL)	90	-0.0700	0.17639	87	-0.1195	0.22968	79	0.0051	0.28189
Creatinine (mg/dL)	90	0.0133	0.08506	87	0.0195	0.15238	79	0.0139	0.09836
BUN (mg/dL)	90	-0.2111	3.35366	87	-0.8736	3.04541	79	0.7215	3.38525
Glucose (fasting)[a] (mg/dL)	87	3.4828	11.49708	83	3.7590	13.10240	81	-1.1728	11.03040
HOMA-R	67	1.9501	12.35612	73	2.8898	7.02099	67	-0.0210	3.77324
Insulin (µIU/mL)	76	6.7500	46.00409	83	10.5060	26.58093	76	-1.3816	23.88750
HbA1c (%)	88	-0.0011	0.25708	85	0.0494	0.23023	81	0.0123	0.16154
QUICKI	67	-0.0115	0.03723	73	-0.0197	0.04365	67	0.0006	0.04381
Bicarbonate (mEq/L)	90	-0.0667	3.12223	85	-0.6706	3.08756	76	-0.5132	2.99107
Chloride (mEq/L)	90	0.7778	2.69322	87	1.0460	2.90512	79	0.2405	2.47664
Potassium (mEq/L)	90	-0.0200	0.40090	87	-0.0460	0.48412	79	-0.1215	0.45083
Sodium (mEq/L)	90	0.7444	2.77857	87	0.3103	3.55459	79	-0.4557	2.78640
Total cholesterol (mg/dL)	90	7.8111	23.84166	87	7.6092	22.60806	79	-3.3291	23.88633
HDL (mg/dL)	90	-0.0556	7.72907	87	-1.4253	7.56773	79	-1.0380	7.95733
LDL (mg/dL)	90	5.6444	21.29109	87	2.8851	19.02106	79	-0.4810	18.51878
Triglycerides (mg/dL)	90	11.1667	58.53900	87	30.5747	64.59023	79	-8.7342	60.11095
TSH (µIU/mL)	81	-0.1063	1.18757	85	0.1973	1.11985	80	-0.1070	1.10592
Free T4 (ng/dL)	82	-0.1646	0.15178	86	-0.1659	0.17034	82	-0.0033	0.15101
Total T4 (µg/dL)	82	-1.4317	1.32338	86	-1.7733	1.57042	82	0.0207	1.20756
Triiodothyronine resin uptake (%)	82	-0.2805	3.11616	86	0.7558	3.64590	82	0.3171	3.59999
Prolactin (ng/mL)	82	2.8378	13.28464	86	1.8640	11.25527	82	-1.1451	9.17482

From Sponsor Table 57 from Clinical Study Report (Study 149)

Table 46. Clinical Chemistry Mean Changes from Baseline to Final Visit (Study 150)

	Bipolar I Disorder (N=205)			Schizophrenia (N=175)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Total									
AST (IU/L)	172	-2.4477	18.8705	160	1.7175	24.6534	332	-0.4404	21.9151
ALT (IU/L)	172	-2.6047	17.2113	160	-2.7681	24.2469	332	-2.6834	20.8676
Alkaline phosphatase (IU/L)	172	2.6628	50.0356	161	-1.0168	44.1889	333	0.8838	47.2643
Total bilirubin (mg/dL)	172	0.0081	0.2047	161	-0.0197	0.4025	333	-0.0053	0.3160
Creatinine (mg/dL)	172	0.0301	0.1033	161	0.0395	0.1200	333	0.0347	0.1117
BUN (mg/dL)	172	-0.1163	3.7570	160	0.2500	3.2852	332	0.0602	3.5369
Glucose (fasting)[a] (mg/dL)	173	0.0925	13.1464	161	5.2931	25.1642	334	2.5994	20.0075
HOMA-R	146	-0.4460	9.4470	156	0.9910	8.8029	302	0.2963	9.1331
Insulin (µIU/mL)	159	-1.8302	36.6648	158	1.9620	25.1355	317	0.0599	31.4588
HbA1c (%)	172	0.0262	0.2395	160	0.0936	0.6796	332	0.0586	0.5026
QUICKI	146	-0.0004	0.0414	156	-0.0012	0.0422	302	-0.0008	0.0417
Bicarbonate (mEq/L)	170	-0.4000	3.3413	156	-1.1923	3.2211	326	-0.7791	3.3032
Chloride (mEq/L)	172	-0.3023	3.2103	159	0.2013	2.9312	331	-0.0604	3.0851
Potassium (mEq/L)	172	-0.0349	0.4853	160	-0.0526	0.4319	332	-0.0434	0.4597
Sodium (mEq/L)	172	-0.6279	3.5212	160	-0.1825	2.9583	332	-0.4133	3.2648
Total cholesterol (mg/dL)	173	-4.4104	23.0744	161	-0.4850	28.1526	334	-2.5182	25.6842
HDL (mg/dL)	173	-2.7110	8.2249	161	-0.5940	8.6012	334	-1.6905	8.4623
LDL (mg/dL)	173	-2.4220	21.1419	160	-0.1750	23.5883	333	-1.3423	22.3451
Triglycerides (mg/dL)	173	3.6185	70.1192	161	-0.1148	68.0005	334	1.8189	69.0277
TSH (µIU/mL)	170	0.0339	1.3367	157	0.3223	1.2095	327	0.1724	1.2834
Free T4 (ng/dL)	173	0.0254	0.1870	160	0.0071	0.2116	333	0.0166	0.1991
Total T4 (µg/dL)	173	-0.0225	1.5781	160	-0.0988	1.7341	333	-0.0592	1.6528
Triiodothyronine resin uptake (%)	173	0.3295	3.5374	160	0.2454	3.4681	333	0.2891	3.4992
Prolactin (ng/mL)	173	-2.2439	10.8011	161	0.4516	13.8392	334	-0.9446	12.4138

From Sponsor Table 45 in Clinical Study Report (Study 150)

Prolactin

The effect of quetiapine on prolactin was evaluated by gender and by age cohort for Study 149 (since Study 112 had decrements in prolactin at endpoint). Overall, male patients had a greater elevation in prolactin compared to females. Analysis by age revealed similar elevations in prolactin across 3 different cohorts – the 16 to 17 year cohort had variable effects between quetiapine doses.

Table 47. Mean Change from Baseline in Prolactin By Gender (Study 149)

	Quetiapine 400	Quetiapine 600	Placebo
Male			
N	39	51	50
Mean Change	3.8	2.8	0.49
Female			
N	43	35	32
Mean Change	1.9	0.53	-3.7

From Sponsor Table 11.3.7.3.6.3.2 in Clinical Study Report (149)

Table 48. Mean Change from Baseline in Prolactin By Age (Study 149)

	Quetiapine 400	Quetiapine 600	Placebo
10 - 12 years			
N	37	38	32
Baseline	7.8	7.4	7.5
End of Study	10.9	9.3	5.9
Mean Change	2.7	1.9	-1.9
13 to 15 years			
N	33	35	30
Baseline	11.3	7.8	10.7
End of Study	14.5	10.7	9.9
Mean Change	2.3	3.6	-1.3
16 to 17 years			
N	12	13	20
Baseline	9.5	14.1	9.3
End of Study	14.8	12.7	9.2
Mean Change	4.7	-3.1	0.26

From Sponsor Table 11.3.7.3.6.3.1 in Clinical Study Report (149)

Outlier Analyses

A table of Sponsor-defined potentially clinically important values is included in Appendix 9.7. The most significant shifts to high occurred with triglycerides (Studies 112 and 149) and prolactin (Study149).

Table 49. Clinically Important Shifts from Baseline to the Final Visit (Study 112)*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 73	QTP 800 N = 74	PC N = 75	QTP 400 N = 73	QTP 800 N = 74	PC N = 75
Glucose (fasting) [mg/dL]	0	0	0	1 (1.5)	0	0
Bicarbonate (mEq/L)	0	1 (1.9)	4 (6.7)	0	0	0
Potassium (mEq/L)	0	0	1 (1.6)	0	0	1 (1.6)
Total cholesterol (mg/dL)	NA	NA	NA	2 (3.3)	0	1 (1.6)
HDL (mg/dL)	8 (14.8)	8 (16)	9 (16.7)	NA	NA	NA
LDL (mg/dL)	NA	NA	NA	1 (1.7)	1 (1.7)	1 (1.6)
Triglycerides (mg/dL)	NA	NA	NA	5 (8.9)	1 (1.8)	1 (1.7)
TSH (µIU/ml)	NA	NA	NA	3 (4.9)	0	0
Free T4 (ng/dL)	0	2 (3.3)	0	0	0	0
Total T4 (ng/dL)	2 (3.2)	3 (5.0)	0	0	0	0
Prolactin (ng/mL)	NA	NA	NA	1 (2.4)	3 (7.5)	1 (2.8)

From Sponsor Table 56 in Clinical Study Report (Study 112)
*There were no shifts to low or high for AST, ALT, alkaline phosphatase, total bilirubin, creatinine, HbA1c, chloride, sodium, T3 uptake.
NA = not applicable, no clinically important values were defined

Table 50. Clinically Important Shifts from Baseline to the Final Visit (Study 149)*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 95	QTP 600 N = 98	PC N = 90	QTP 400 N = 95	QTP 600 N = 98	PC N = 90
Creatinine (mg/dL)	NA	NA	NA	0	1 (1.2)	0
Glucose (fasting) [mg/dL]	0	0	0	1 (1.1)	1 (1.2)	0
Bicarbonate (mEq/L)	6 (6.7)	4 (4.9)	5 (6.8)	0	2 (2.4)	0
Potassium (mEq/L)	0	0	0	1 (1.1)	1 (1.2)	1 (1.3)
Sodium (mEq/L)	0	1 (1.2)	0	0	0	0
Total cholesterol (mg/dL)	NA	NA	NA	0	3 (3.5)	1 (1.3)
HDL (mg/dL)	2 (2.6)	13 (16.9)	4 (6.6)	NA	NA	NA
LDL (mg/dL)	NA	NA	NA	0	1 (1.2)	0
Triglycerides (mg/dL)	NA	NA	NA	6 (7.5)	12 (14.3)	4 (5.7)
TSH (µIU/ml)	NA	NA	NA	2 (2.6)	2 (2.4)	1 (1.3)
Free T4 (ng/dL)	1 (1.2)	0	0	0	0	0
Total T4 (ng/dL)	0	3 (3.5)	0	0	0	0
Prolactin (ng/mL)	NA	NA	NA	12 (15.8)	10 (12.3)	2 (2.6)

From Sponsor Table 59 in Clinical Study Report (Study 149)
*There were no shifts to low or high for AST, ALT, alkaline phosphatase, total bilirubin (one shift to high in PC group), BUN (2 shifts to high in PC group), insulin, HbA1c, chloride, T3 uptake.
NA = not applicable, no clinically important values were defined

Table 51. Clinically Important Shifts from Baseline to the Final Visit (Study 150)*

	Shift to Low, n (%)			Shift to High, n (%)		
	Bipolar Disorder (N = 205)	Schizophrenia (N = 175)	Total (N = 380)	Bipolar Disorder (N = 205)	Schizophrenia (N = 175)	Total (N = 380)
AST	NA	NA	NA	0	1 (0.6)	1 (0.3)
ALT	NA	NA	NA	0	1 (0.6)	1 (0.3)
Total bilirubin	NA	NA	NA	0	1 (0.6)	1 (0.3)
BUN	0	0	0	3 (1.8)	2 (1.3)	5 (1.5)
Glucose (fasting) [mg/dL]	0	0	0	1 (0.6)	6 (3.8)	7 (2.1)
HbA1c	NA	NA	NA	0	2 (1.3)	2 (0.6)
Bicarbonate (mEq/L)	7 (4.4)	9 (5.9)	16 (5.1)	1 (0.6)	2 (1.3)	3 (1.0)
Potassium (mEq/L)	0	0	0	1 (0.6)	1 (0.6)	2 (0.6)
Sodium (mEq/L)	0	0	0	1 (0.6)	0	1 (0.3)
Total cholesterol (mg/dL)	NA	NA	NA	0	1 (0.6)	1 (0.3)
HDL (mg/dL)	19 (13.4)	21 (16.5)	40 (14.9)	NA	NA	NA
LDL (mg/dL)	NA	NA	NA	1 (0.6)	0	1 (0.3)
Triglycerides (mg/dL)	NA	NA	NA	18 (11.9)	13 (8.4)	31 (10.2)
TSH (µIU/ml)	NA	NA	NA	5 (3.0)	4 (2.6)	9 (2.8)
Free T4 (ng/dL)	0	1 (0.6)	1 (0.3)	0	0	0
Total T4 (ng/dL)	2 (1.2)	6 (3.8)	8 (2.5)	0	0	0
Prolactin (ng/mL)	NA	NA	NA	6 (3.9)	13 (8.7)	19 (6.3)

From Sponsor Table 47 from Clinical Study Report (Study 150)
*There were no shifts to low or high for a kaline phosphatase, creatinine, chloride.
NA = not applicable, no clinically important values were defined

Prolactin

Potentially clinically significant increases in prolactin concentration were defined as > 26 ng/ml for males and > 20 ng/ml for females.
For Study 149, 8 female patients had increased prolactin in the quetiapine groups compared to 0 patients in the placebo group.

Table 52. Distribution of Potentially Clinically Significant Shifts in Prolactin Concentration

	Female		Male	
	Quetiapine	Placebo	Quetiapine	Placebo
Study 149				
N	8	0	15	2
> 20 – 25 ng/ml	NA	NA	7 (47%)	1 (50%)
> 25 – 30 ng/ml	2 (25%)	0	3 (20%)	1 (50%)
> 30 – 35 ng/ml	4 (50%)	0	3 (20%)	0
> 35 – 40 ng/ml	1 (12.5%)	0	1 (7%)	0
> 40 – 45 ng/ml	1 (12.5%)	0	0	0
> 45 – 50 ng/ml	0	0	1 (7%)	0
Study 150				
N	9	NA	10	NA

For Study 112, only one female patient in the quetiapine group had a potentially clinically significant shift in prolactin to 131.5 ng/ml. Three male patients had shifts to high prolactin, the highest shift was to 40.9 ng/ml. One male patient in the placebo group had a shift to 50.8 ng/ml.

For Study 150, 19 patients had clinically important shifts to high prolactin. In the clinical study report, the Sponsor provided the prolactin data in mIU/L units and has been asked to resubmit the data in ng/ml so that the results can be compared across trials.

7.4.2.2 Hematology

Mean Change Analyses

The mean change analyses did not reveal any new significant findings. Consistent with adult clinical data, a decrease in neutrophils was noted in both studies, though Study 149 findings were similar to placebo.

Table 53. Hematology Changes from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day (N=73)			Quetiapine 800 mg/day (N=74)			Placebo (N=75)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Hematocrit (%	65	-0.4652	2.63873	66	-1.0227	2.48118	67	-0.2075	2.56079
Total RBC (10^6/µL)	64	-0.0844	0.27673	65	-0.1077	0.26179	67	-0.0328	0.31449
Hemoglobin (g/dL)	64	-0.2734	0.74456	66	-0.3561	0.73634	67	-0.0627	0.86407
Platelet count (10^3/µL)	63	7.0794	39.25159	65	-0.2308	52.12958	65	-1.9692	45.35415
Total WBC (10^3/µL)	64	0.1359	1.86483	65	-0.1754	1.93092	67	0.2433	2.50752
Basophils (10^3/µL)	65	0.0042	0.02030	64	0.0022	0.01647	66	-0.0055	0.02328
Eosinophils (10^3/µL)	65	0.0398	0.38102	65	0.0143	0.18580	66	-0.0073	0.18085
Lymphocytes (10^3/µL)	65	0.1445	0.58748	64	-0.0159	0.57026	66	0.0498	0.54092
Monocytes (10^3/µL)	64	0.0055	0.18085	64	-0.0141	0.21880	66	-0.0032	0.21826
Neutrophils (10^3/µL)	63	-0.0690	1.87248	64	-0.1167	1.93323	66	0.3550	2.53009

From Sponsor Table 50 in Clinical Study Report (Study 112)

Table 54. Hematology Changes from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg (N=95)			Quetiapine 600 mg (N=98)			Placebo (N=90)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Hematocrit (volume fraction)	87	-1.1149	2.14999	83	-1.3193	2.42670	78	-0.2269	2.31890
Total RBC count (10^6/μL)	88	-0.1205	0.23933	85	-0.1341	0.26572	81	-0.0494	0.26178
Hemoglobin (g/dL)	88	-0.3341	0.71998	85	-0.3871	0.74014	80	-0.1688	0.72314
Platelet count (10^3/μL)	88	-8.3523	39.08289	85	6.5176	41.95962	81	0.1728	47.08338
Total WBC count (10^3/μL)	88	-0.2727	1.86318	85	-0.1224	1.51715	81	-0.0444	1.94885
Basophils (10^3/μL)	88	-0.0003	0.02996	83	0.0014	0.02405	80	0.0039	0.02844
Eosinophils (10^3/μL)	88	0.0269	0.16036	83	0.0370	0.11892	80	0.0151	0.09917
Lymphocytes (10^3/μL)	88	-0.1931	0.51573	83	-0.1683	0.52391	80	0.0469	0.44298
Monocytes (10^3/μL)	88	0.0194	0.15260	83	0.0101	0.16217	80	0.0000	0.15929
Neutrophils (10^3/μL)	88	-0.1242	1.64769	83	-0.0192	1.26954	80	-0.1013	1.77366

From Sponsor Table 54 in Clinical Study Report (Study 149)

Table 55. Hematology Changes from Baseline to Final Visit (Study 150)

	Bipolar I Disorder (N=205)			Schizophrenia (N=175)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Total									
Hematocrit (%)	187	-0.0925	2.4192	158	0.1001	2.9079	345	-0.0043	2.6520
Total RBC (10^6/μL)	188	0.0043	0.3006	163	0.2050	0.3132	351	0.0139	0.3062
Hemoglobin (g/dL)	188	-0.0495	0.7843	163	0.0542	0.9650	351	-0.0013	0.8731
Platelet count (10^3/μL)	188	-3.8298	36.2726	159	5.5836	52.3841	347	0.4836	44.5672
Total WBC (10^3/μL)	188	-0.0441	1.4754	163	-0.0471	2.2804	351	-0.0455	1.8894
Basophils (10^3/μL)	186	-0.0034	0.0254	161	0.0043	0.0243	347	0.0002	0.0252
Eosinophils (10^3/μL)	186	-0.0446	0.1839	159	-0.0487	0.2140	345	-0.0465	0.1981
Lymphocytes (10^3/μL)	186	-0.0054	0.4574	161	0.0761	0.4993	347	0.0324	0.4784
Monocytes (10^3/μL)	186	-0.0267	0.1473	161	-0.0176	0.1786	347	-0.0225	0.1624
Neutrophils (10^3/μL)	186	0.0331	1.2954	161	-0.0302	2.1440	347	0.0037	1.7389

From Sponsor Table 43 from Clinical Study Report (Study 150)

Outlier Analyses

Clinically important shifts from baseline to the final visit show similar % shifts to low ANC in the quetiapine and placebo groups. Clinically important shifts at any time in the study were available for Study 112 (Study 149 was a 3-week study with assessments at baseline and end of study), show similar % shifts to low ANC in the quetiapine and placebo groups. A table providing ANC values for these cases is in Appendix 9.8.

For the pooled analysis for studies 112 and 149, 3.5% (5/144) of patients in the placebo group had a shift in ANC to $\leq$ 1.5 x10^9/L at any time compared to 4.8% (14/294) of patients in the quetiapine group. In the placebo group, 3.1% and 3.6% of patients had a shift to low ANC in the 10 - 12 years and 13 to 17 year age groups respectively. In the quetiapine group, 8.2% and 3.6% of patients had a shift to low ANC in these age cohorts (data from Sponsor Table SA04 in summary-clin-safety document).

Table 56. Clinically Important Shifts from Baseline to the Final Visit (Study 112)*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 73	QTP 800 N = 74	PC N = 75	QTP 400 N = 73	QTP 800 N = 74	PC N = 75
Hematocrit (%)	6 (10)	2 (3.4)	0	0	1 (1.7)	1 (1.6)
Hemoglobin (g/dL)	2 (3.2)	0	1 (1.5)	0	0	0
Total WBC (10^9/L)	0	0	0	1 (1.6)	1 (1.5)	1 (1.5)
Neutrophils (10^9/L)	2 (3.3)	1 (1.6)	2 (3.2)	1 (1.6)	1 (1.6)	3 (4.8)
Eosinophils (10^9/L)	NA	NA	NA	2 (3.3)	0	0

From Sponsor Table 52 from Clinical Study Report (Study112)
*There were no shifts to low or high for total RBC, platelet count, basophils, lymphocytes, monocytes.
NA = not applicable, no clinically important values were defined

Table 57. Clinically Important Shifts At Any Time During the Study (Study 112)*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 73	QTP 800 N = 74	PC N = 75	QTP 400 N = 73	QTP 800 N = 74	PC N = 75
Hematocrit (%)	6 (8.2)	4 (5.4)	3 (4%)	0	2 (2.7)	1 (1.3)
Hemoglobin (g/dL)	3 (4.1)	1 (1.3)	1 (1.3)	-	-	-
Neutrophils (10^9/L)	5 (6.8)	2 (2.7)	6 (8%)	-	-	-

Sponsor provided data in text format
No shifts noted for RBC, platelets, WBC (low)

Table 58. Clinically Important Shifts from Baseline to the *Final Visit* (Study 149)*

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 95	QTP 600 N = 98	PC N = 90	QTP 400 N = 95	QTP 600 N = 98	PC N = 90
Hematocrit (%)	0	7 (8.9)	1 (1.4)	1 (1.2)	0	2 (2.8)
Hemoglobin (g/dL)	2 (2.3)	2 (2.4)	0	0	0	0
Neutrophils (10^9/L)	3 (3.6)	4 (4.9)	2 (2.5)	0	0	0
Eosinophils (10^9/L)	NA	NA	NA	2 (2.3)	0	0

From Sponsor Table 56 in Clinical Study Report (Study 149)
*There were no shifts to low or high for total RBC (one shift in PC group), WBC (one shift in PC group), basophils, lymphocytes, monocytes.
NA = not applicable, no clinically important values were defined

Table 59. Clinically Important Shifts from Baseline to the Final Visit (Study 150)*

	Shift to Low, n (%)			Shift to High, n (%)		
	Bipolar Disorder N = 205	Schizophrenia N = 175	Total N = 380	Bipolar Disorder N = 205	Schizophrenia N = 175	Total N = 380
Hematocrit (%)	8 (4.7)	2 (1.4)	10 (3.1)	1 (0.6)	3 (2.1)	4 (1.3)
Hemoglobin (g/dL)	2 (1.1)	1 (0.6)	3 (0.9)	1 (0.6)	3 (1.9)	4 (1.2)
Platelet count	0	0	0	0	1 (0.6)	1 (0.3)
Total WBC	0	0	0	0	1 (0.6)	1 (0.3)
Neutrophils (10^9/L)	6 (3.4)	2 (1.3)	8 (2.4)	0	2 (1.3)	2 (0.6)
Eosinophils (10^9/L)	NA	NA	NA	2 (1.1)	1 (0.6)	3 (0.9)

From Sponsor Table 44 in Clinical Study Report (Study 150)
*There were no shifts to low or high for total RBC, basophils, lymphocytes, or monocytes.
NA = not applicable, no clinically important values were defined

A total of 27 (8.3%) of patients shifted to potentially clinically important low ANC at *any time* in the Study 150.

7.4.3 Vital Signs

Approximately 11-19% of patients took concomitant psychostimulants in Study 149 (comorbid ADHD). The Sponsor has been asked to provide additional vital signs analyses for the patients with and without concomitant psychostimulant use to further evaluate the safety signal. However, it should be noted that psychostimulants were not allowed in Study 112 and there were similar findings between the two studies with regard to vital sign changes.

Mean Change Analyses

The mean change analyses for blood pressure and pulse revealed an increase in supine and standing pulse and systolic and diastolic blood pressure in the quetiapine groups compared to placebo. No overall effect consistent with orthostatic hypotension was noted in these trials (see Appendix 9.9).

Table 60. Vital Signs: Mean (SD) Change from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 75
Supine pulse (bpm)	6 (12.3)	3.9 (12.2)	-1.4 (11.3)
Supine Systolic BP (mmHg)	2 (10.3)	1 (9.7)	-1.6 (7.4)
Supine Diastolic BP (mmHg)	1.3 (8.4)	0.2 (12.4)	0.1 (8.5)
Standing Pulse (bpm)	6.3 (13.1)	2.2 (17.1)	-2.5 (13.1)
Standing Systolic BP (mmHg)	2.3 (10.8)	-0.4 (10.3)	-1.7 (9.1)
Standing Diastolic BP (mmHg)	2.1 (8.6)	1.1 (10.2)	-1.2 (7.7)

From Sponsor Table 59 in Clinical Study Report (Study 112)

Table 61. Vital Signs: Mean (SD) Change from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg/day n = 76*	Quetiapine 600 mg/day n = 81*	Placebo n = 68*
Supine pulse (bpm)	8.8 (13.6)	10.6 (16.3)	-0.8 (10.9)
Supine Systolic BP (mmHg)	0.4 (9.8)	2.4 (10.3)	-2.7 (8.9)
Supine Diastolic BP (mmHg)	1.3 (7.6)	3.1 (10.1)	1.0 (10.4)
Standing Pulse (bpm)	9.6 (15.2)	11.3 (18.9)	0.1 (12.7)
Standing Systolic BP (mmHg)	1.0 (11.5)	1.3 (9.6)	-0.8 (9.4)
Standing Diastolic BP (mmHg)	1.4 (11.6)	1.7 (10.1)	0.2 (9.3)

From Sponsor Table 63 in Clinical Study Report (Study 149)
*Vital signs data available for this number of patients; safety population included n = 95, 98 and 90 for quetiapine 400, 600 and placebo groups

Outlier Analyses

Shifts from Baseline to Final Visit

A table of Sponsor-defined potentially clinically important values is included in Appendix 9.7. Significantly greater percentages of patients exhibited shifts to high pulse and systolic blood pressure in the quetiapine groups compared to placebo.

Table 62. Clinically Important Shifts in Vital Signs From Baseline to Final Visit (Study 112)

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 73	QTP 800 N = 74	PC N = 75	QTP 400 N = 73	QTP 800 N = 74	PC N = 75
Supine Pulse	0	0	0	1 (1.4)	2 (2.7)	0
Supine Systolic BP	3 (4.5)	3 (4.4)	2 (2.9)	5 (7.6)	3 (4.4)	1 (1.4)
Supine Diastolic BP	3 (4.3)	0	1 (1.4)	1 (1.4)	2 (2.9)	2 (2.9)
Standing Pulse	0	0	0	6 (8.7)	5 (7.4)	0
Standing Systolic BP	2 (3.1)	5 (7.9)	5 (7.5)	4 (6.2)	3 (4.8)	1 (1.5)
Standing Diastolic BP	0	1 (1.5)	1 (1.4)	7 (10)	5 (7.6)	6 (8.7)

From Sponsor Table 60 in Clinical Study Report (Study 112)

Table 63. Clinically Important Shifts in Vital Signs From Baseline to Final Visit (Study 149)

	Shift to Low, n (%)			Shift to High, n (%)		
	QTP 400 N = 95	QTP600 N = 98	PC N = 90	QTP 400 N = 95	QTP 600 N = 98	PC N = 90
Supine Pulse	0	0	0	1 (1.1)	2 (2.2)	0
Supine Systolic BP	2 (2.4)	2 (2.3)	0	6 (7.1)	4 (4.5)	1 (1.3)
Supine Diastolic BP	0	0	2 (2.7)	1 (1.2)	4 (5.1)	3 (4.1)
Standing Pulse	0	0	0	13 (14.3)	10 (11.1)	1 (1.2)
Standing Systolic BP	3 (3.6)	6 (6.7)	2 (2.4)	9 (10.7)	2 (2.2)	4 (4.8)
Standing Diastolic BP	2 (2.6)	0	2 (2.7)	9 (11.5)	10 (12.0)	14 (18.7)

From Sponsor Table 64 in Clinical Study Report (Study 149)

Shifts at Any Time

The Sponsor did not provide a similar summary table for standing vital signs and has been requested to provide these data. Consistent with Tables 62 and 63 above, the quetiapine groups were associated with significantly greater percentages of patients with elevations in supine pulse, systolic BP and diastolic BP.

Table 64. Clinically Important Shifts in Vital Signs At Any Time (Studies 112 and 149 Pooled)

	Shift	QTP N = 340			PC N = 165		
		N	n	%	N	n	%
Supine Pulse (bpm)	> 120	333	27	8.1	161	0	0
	≥ 15 increase	335	170	50.7	163	30	18.4
	< 50	334	1	0.3	161	2	1.2
	≥ 15 decrease	335	41	12.2	163	33	20.2
Supine Systolic BP (mmHg)	> 121*	317	45	14.2	153	9	5.9
	≥ 20 increase	335	51	15.2	163	9	5.5
	< 89*	325	29	8.9	157	10	6.4
	≥ 20 decrease	335	27	8.1	163	13	8.0
Supine Diastolic BP (mmHg)	≥ 78*	315	53	16.8	151	11	7.3
	≥ 10 increase	335	136	40.6	163	40	24.5
	≥ 30 increase	335	5	1.5	163	3	1.8
	≤ 52*	321	36	11.2	154	21	13.6
	> 20 decrease	335	32	9.6	163	9	5.5

*Supine systolic BP: 10 to 12 years: boys > 123, girls > 121; 13-17 years: boys > 136, girls > 128; 10 to 12 years: ≤ 89; 13 to 17 years: ≤ 99
Supine diastolic BP: 10 to 12 years: ≥ 78; 13 to 17 years: boys ≥ 85, girls ≥ 82; 10 to 12 years ≤ 52, 13 to 17 years ≤ 56.
From Sponsor Table SA14 in Summary Clin Safety document

An analysis for clinically important shifts in vital signs at any time by age cohort was performed. Patients 10 - 12 years of age have a greater frequency of clinically important shifts in vital signs except for supine pulse > 120 bpm (1.2% in patients < 12, 10.5% in patients 13-17 years of age). It is noteworthy that 60% of patients in the 10 - 12 years cohort have an increase in supine pulse of > 15 bpm compared to 0 patients in the placebo group for this same cohort.

Table 65. Clinically Important Shifts in Vital Signs At Any Time – By Age Cohort (Studies 112 and 149 Pooled)

	Shift	Quetiapine			PC		
		N	n	%	N	n	%
10 - 12 Years							
Supine Pulse (bpm)	> 120	85	1	1.2	36	0	0
	≥ 15 increase	85	51	60	36	0	0
Supine Systolic BP (mmHg)	> 121*	80	16	20	32	3	9.4
	≥ 20 increase	85	15	17.6	36	1	2.8
Supine Diastolic BP (mmHg)	≥ 78*	74	22	29.7	29	6	20.7
	≥ 10 increase	85	40	47.1	36	8	22.2
	≥ 30 increase	85	2	2.4	36	1	2.8
13 – 17 Years							
Supine Pulse (bpm)	> 120	248	26	10.5	125	0	0
	≥ 15 increase	250	119	47.6	127	30	23.6
Supine Systolic BP (mmHg)	> 128*	237	29	12.2	121	6	5
	≥ 20 increase	250	36	14.4	127	8	6.3
Supine Diastolic BP (mmHg)	≥ 82*	241	31	12.9	122	5	4.1
	≥ 10 increase	250	96	38.4	127	32	25.2
	≥ 30 increase	250	3	1.2	127	2	1.6

*Supine systolic BP: 10 to 12 years: boys > 123, girls > 121; 13-17 years: boys > 136, girls > 128;
Supine diastolic BP: 10 to 12 years: ≥ 78; 13 to 17 years: boys ≥ 85, girls ≥ 82
From Sponsor Table SA14 in Summary Clin Safety document

Height and Weight

Per request of the Division, the Sponsor provided a separate submission addressing the metabolic effects of quetiapine on adult and pediatric/adolescent patients in their clinical trials database. These data, while also summarized briefly in this review, will be more extensively evaluated in a separate review document and will also evaluate the dose-response relationship to these metabolic effects.

Of note, for Study 112, only ~5.5% of patients in the quetiapine 400 and 800 mg/day group had been taking olanzapine prior to enrollment into the study compared to 13.3% of patients in the placebo group. Therefore, changes from baseline in the quetiapine group are unlikely to include substantial numbers of patients who are having weight decreases due to discontinuation of prior olanzapine therapy.

Mean Change Analyses

In Studies 112 and 149, quetiapine was associated with a significantly greater mean increase in weight compared to placebo.

Study 112 was an international trial. The Sponsor did provide a separate summary table for mean change in weight for the different pooled geographic locations. For the USA sites, the change from baseline to final visit was +2.7 kg (quetiapine 400 mg, n = 20), +2.0 kg (quetiapine 800 mg, n = 22) and -0.2 kg (placebo, n = 25).

Table 66. Height and Weight: Mean (SD) Change from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day N = 73	Quetiapine 800 mg/day N = 74	Placebo N = 75
Weight (kg)	1.9 (2.5)	1.5 (2.6)	-0.1 (2.8)
Height (cm)	0.3 (0.81)	0.3 (0.88)	0.2 (0.69)

From Sponsor Table 59 in Clinical Study Report (Study 112)

Table 67. Height and Weight: Mean (SD) Change from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg/day N = 95	Quetiapine 600 mg/day N = 98	Placebo N = 90
Weight (kg)	1.7 (2.0)	1.7 (2.3)	0.4 (1.7)
Height (cm)	0.5 (0.96)	0.5 (0.89)	0.3 (0.76)

From Sponsor Table 59 in Clinical Study Report (Study 112)

Outlier Analyses

In Study 112, 23.2% of patients in the quetiapine 400 mg/day group, 18.2% of patients in the quetiapine 800 mg/day group and 6.8% of patients in the placebo group had a ≥ 7% weight gain at Day 42.

In Study 149, 14.5% of patients in the quetiapine 400 mg/day group, 9.9% of patients in the quetiapine 600 mg/day group and 0% patients in the placebo group had a ≥ 7% weight gain at Day 21.

The pooled analysis for Studies 112 and 149 showed 17% (57/335) of patients in the quetiapine group gained > 7% weight compared to 2.5% (4/163) of patients in the placebo group. A pooled analysis by age cohort (Table 68) show that, in the quetiapine group, 14.1% of patients 10 - 12 years of age and 18% of patients 13 to 17 years of age gained > 7% weight (compared to 0% and 3.1% of patients in the respective placebo age cohorts).

Table 68. Weight: Clinically Important Shifts (≥ 7% Increase) at Any Time by Age Cohort – Pooled Analysis for Studies 112 and 149

	10 – 12 Years						13 – 17 Years					
	Quetiapine N = 85			Placebo N = 36			Quetiapine N = 255			Placebo N = 129		
	N	n	%	N	n	%	N	n	%	N	n	%
BMI Group												
< 18.5	21	5	23.8	7	0	0	44	15	34.1	14	2	14.3
18.5 - < 25	43	7	16.3	17	0	0	134	26	19.4	72	2	2.8
25 - < 30	16	0	0	9	0	0	42	3	7.1	27	0	0
30 - < 40	4	0	0	2	0	0	23	0	0	12	0	0
≥ 40	0	0	0	0	0	0	2	0	0	2	0	0
Total	**85**	**12**	**14.1**	**36**	**0**	**0**	**250**	**45**	**18.0**	**127**	**4**	**3.1**

From Sponsor Table SA15 from Summary Clin Safety document

7.4.4 Electrocardiograms (ECGs)

Due to the effect of quetiapine on heart rate, the Sponsor focused primarily on the QTcF as the main correction factor for the QT interval. The reviewer agrees that this approach was appropriate.

Mean Change Analyses

In general, minimal effect on ECG was noted in Studies 112 and 149. Mean changes in QTcF were inconsistent between doses and studies and all < 5 msec, so not considered to be clinically relevant. The mean increase in heart rate was a consistent finding and potentially related to dose in Study 112. The quetiapine 400 mg/day dose was associated with a greater mean increase in heart rate in Study 149 compared to Study 112.

Table 69. ECG: Mean (SD) Change from Baseline to Final Visit (Study 112)

	Quetiapine 400 mg/day N = 73 n = 64	Quetiapine 800 mg/day N = 74 n = 64	Placebo N = 75 n = 65
Heart rate (bpm)	3.8 (16.5)	11.2 (14.9)	-3.3 (12.0)
RR interval (msec)	-42.1 (148.3)	-101.1 (127.6)	33.2 (128.3)
PR interval (msec)	-2.0 (32.1)	2.8 (13.0)	1.1 (12.5)
QRS interval (msec)	0.3 (8.5)	-0.09 (6.1)	-0.25 (6.4)
QT interval (msec)	-4.9 (26.4)	-13.0 (28.5)	2.6 (26.5)
QTcF interval (msec)	1.4 (16.5)	3.1 (17.5)	-2.6 (18.4)
QTcB interval (msec)	5.1 (22.4)	12.2 (18.9)	-5.6 (20.9)

From Sponsor Table 59 in Clinical Study Report (Study 112)

Table 70. ECG: Mean (SD) Change from Baseline to Final Visit (Study 149)

	Quetiapine 400 mg/day N = 95 n = 90	Quetiapine 600 mg/day N = 98 n = 87	Placebo N = 90 n = 79
Heart rate (bpm)	12.8 (12.4)	13.4 (15.5)	-1.7 (11.6)
RR interval (msec)	-121.2 (123.4)	-136.1 (165.1)	18.2 (138.0)
PR interval (msec)	0.62 (14.1)	-0.76 (13.7)	-0.23 (13.9)
QRS interval (msec)	-0.98 (6.3)	-0.32 (6.0)	1.3 (6.3)
QT interval (msec)	-19.8 (23.6)	-22.8 (24.7)	1.4 (27.6)
QTcF interval (msec)	-0.80 (15.9)	-2.4 (16.4)	-1.7 (17.6)
QTcB interval (msec)	10.2 (20.0)	9.2 (24.3)	-3.4 (19.7)

From Sponsor Table 63 in Clinical Study Report (Study 149)

Outlier Analyses

In Study 112, 5.2% of patients in the quetiapine 400 mg/day group and 8.5% of patients in the quetiapine 800 mg/day group had shifts to high heart rate on ECG compared to 0 patients in the placebo group. No other shifts (from low or high) were noted in PR interval, QRS interval, QT interval or QTcF interval (QTcB shift data not provided by Sponsor). The definition for potentially clinically significant findings for QTcF = $\geq$ 450 msec or increase of 15% msec of baseline.

In Study 149, 1.1% of patients in the quetiapine 400 mg/day group and 2.4% of patients in the quetiapine 600 mg/day group had shifts to high heart rate on ECG compared to 0 patients in the placebo group. No other shifts (from low or high) were noted in PR interval, QRS interval, QT interval or QTcF interval (QTcB shift data not provided by Sponsor).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A dose-related signal was noted for some adverse events as noted in the respective sections.
A dose-dependent analysis for metabolic adverse events (hyperlipidemia, weight gain and hyperglycemia) is currently under review as the Sponsor provided these data under separate request pertaining to the original request for metabolic data issued in January 2008.

7.5.2 Time Dependency for Adverse Events

No analysis looking at the time dependency of adverse events, in particular tolerance to events and late onset events, is available.

7.5.3 Drug-Demographic Interactions

The only demographic factors that were analyzed were gender and age cohort (10 to 12 years and 13 to 17 years); the latter applicable only to Study 149.

Gender

Prolactin and weight changes were evaluated by gender since there are known differences between males and females on these safety parameters. No gender differences were noted for either mean change in prolactin value or shifts to potentially clinically important values in Study 112. Mean changes from baseline in prolactin concentration were higher in quetiapine-treated patients than in placebo-treated patients among males and females in Study 149 (see Section 7.4.2.1, Table 47). Shifts to clinically important high prolactin concentrations occurred at a higher incidence in the quetiapine groups than in the placebo group for both males (19.4% quetiapine 400 mg/day, 14.9% quetiapine 600 mg/day, 4.1% placebo) and females (12.5% quetiapine 400 mg/day, 8.8% quetiapine 600 mg/day, 0% placebo).

Females in both quetiapine groups in Study 112 had a greater mean change from baseline in weight and BMI (quetiapine 400 mg/day: +1.7 kg and + 0.6 kg/m2; quetiapine 800 mg/day: +1.1 kg, +0.3 kg/m2) compared to females in the placebo group (0.0 kg, -0.1 kg/m2). Similarly, males in both quetiapine groups in Study 112 had a greater mean change from baseline in weight and BMI (quetiapine 400 mg/day: +2.1 kg, +0.6 kg/m2; quetiapine 800 mg/day: +1.8 kg, +0.5 kg/m2) compared to males in the placebo group (-0.2 kg, -0.1 kg/m2). For females, incidence of $\geq$ 7% weight gain was 25% for quetiapine 400 mg/day, 10.5% for quetiapine 800 mg/day and 6.3% for placebo. For males, the incidence of $\geq$ 7% weight gain was 22.2% for quetiapine 400 mg/day, 22.2% for quetiapine 800 mg/day and 7.1% for placebo. Similar findings were noted for Study 149 (not included in this review).

Age Cohort

General comment:
Some differences in safety signals were noted when comparing the different age cohorts of 10 - 12 years of age and 13 to 17 years of age. However, it should be noted that patients 10 - 12 years of age were only recruited in Study 149, therefore, pooled comparisons for Studies 112 and 149 versus placebo also include the confound of time on drug since Study 149 was a 3-week study compared to Study 112 which was a 6-week study. For patients 10 - 12 years of age, there are only placebo-comparator data for exposure of $\leq$ 3 weeks.

The table of common adverse events (see Section 7.4.1, Table 43) provides a listing of the most common adverse events by age cohort. The Sponsor indicated that among the 7 quetiapine-treated patients with suicidal behavior, suicidal ideation, or possibly suicidal events, 5 were in the younger age group, including all 3 patients with suicidal behavior/ideation. Among the 4 quetiapine-treated patients with syncope, 3 were in the younger age group including both patients withdrawn from the study because of syncope. A table of clinically important shifts in vital signs at any time (Section 7.4.3, Table 65) provides an analysis by age cohort. In their safety summary document, the Sponsor highlights the changes in supine and standing pulse rate by age cohort. At day 21, patients 10 - 12 years had mean increases from baseline in supine pulse (quetiapine 400 mg/day: +12.2 bpm, quetiapine 600 mg/day: +12.9 bpm) that were greater than increases in supine pulse (quetiapine 400 mg/day: +6.0 bpm, quetiapine 600 mg/day: +8.6 bpm) in the 13 to 17 year old cohort. Similar findings were noted for standing pulse rate.

7.5.4 Drug-Disease Interactions

No new data are available on drug-disease interactions.

7.5.5 Drug-Drug Interactions

No new data are available on drug-drug interactions. In Study 149, adverse events were examined by concomitant psychostimulant use. In patients using psychostimulants (15.2% of the total population), the most common adverse events were similar to those in the overall population; however, the incidence of these individual adverse events was generally higher in concomitant psychostimulant users in the quetiapine 600 mg/day group. The Sponsor indicated that no other differences in safety parameters were observed to suggest an increased risk related to use of quetiapine in patients treated concurrently with psychostimulants. The Sponsor has been asked to provide an analysis of vital sign changes in patients with and without concomitant use of psychostimulants.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new data are available on human carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

No new data are available on human reproduction and pregnancy data

7.6.3 Pediatrics and Assessment of Effects on Growth

See section 7.4.3 (vital signs) of review for data on weight and height mean changes and categorical weight increases for Studies 112 and 149.

For Study 150, the open-label 26-week study, the Sponsor provided a summary of patients with a shift of $\geq$ 0.5 BMI z-score from baseline at anytime, end of treatment and final visit. For patients who received placebo in Studies 112 and 149, 30% had a shift at anytime, 22% had a shift at end of treatment and 31% had a shift at

week 26. For patients who received quetiapine in Studies 112 and 149, 22% had a shift at anytime, 15% had a shift at end of treatment and 18% had a shift at week 26.

For Study 150, the Sponsor provided a summary of change from open-label baseline to final visit in weight and BMI by BMI percentile CDC category. Approximately 53% of patients were in the healthy weight category, 20% in the at risk of overweight category and 22% in the overweight category.

Table 71 (Sponsor's Table). Change from Open-Label Baseline to Final Visit by Percentile CDC Category.

BMI percentile CDC category	Bipolar I Disorder (N=205)			Schizophrenia (N=175)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
0 to <5th percentile (underweight)									
Weight (kg)	2	4.5	4.95	8	7.6	6.19	10	7.0	5.85
BMI (kg/m^2)	2	2.3	2.97	8	2.7	2.29	10	2.6	2.25
5th to <85th percentile (healthy weight)									
Weight (kg)	83	3.6	4.86	120	3.2	9.48	203	3.4	7.91
BMI (kg/m^2)	81	1.0	1.81	120	1.0	3.53	201	1.0	2.96
85th to <95th percentile (at risk of overweight)									
Weight (kg)	53	4.6	5.23	23	4.3	7.90	76	4.5	6.11
BMI (kg/m^2)	53	1.1	1.89	23	1.1	2.69	76	1.1	2.14
95th percentile (overweight)									
Weight (kg)	61	4.0	5.71	24	1.5	8.76	85	3.3	6.75
BMI (kg/m^2)	60	0.7	2.53	24	-0.9	7.51	84	0.2	4.55

From Sponsor Table 51 in Clinical Study Report (Study 150)

Most patients in Study 150, the open-label 26-week study, did not change Tanner stage during the study and the majority of female patients had normal menstrual cycles. Of the 373 patients with Tanner staging data, 63 patients shifted 1 point, 6 patients shifted up 2 points and 1 patient shifted up 3 points.

In Study 112 (6 week study), 3 patients shifted up one point in the quetiapine groups (n = 124) and 2 patients shifted 1 point in the placebo group (n = 66).

In Study 149 (3 week study), 5 patients shifted up one point and 1 patient shifted up 2 points in the quetiapine groups (n = 175); 1 patient shifted 1 point in the placebo group (n = 81).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
There were a total of 10 cases of overdose (defined as a dose of study medication in excess of that prescribed) identified in Studies 112, 149 and 150. The maximum overdose was 2000 mg (2 unknown amounts) and this was the only case associated with adverse events (nausea, sedation). Only 3 of these cases were deemed intentional and all 3 occurred in Study 149 (bipolar mania) (see Section 7.3.5, suicidality assessment)

Drug Abuse
There were no reports of patients abusing quetiapine in Studies 112, 149 or 150.

Withdrawal or Rebound
Studies 112, 149 and 150 were not designed to assess withdrawal or rebound. Though quetiapine was titrated to the target fixed dose in Studies 112 and 149, there was no taper strategy at the end of the study nor an adequate assessment of adverse events after drug discontinuation to assess withdrawal symptoms.

7.7 Additional Submissions / Safety Issues

The Sponsor has supplied additional data requested during the review of this submission. Several requests were outstanding at the time this review was completed and these will be reviewed as an addendum to this review.

8 Postmarket Experience

Seroquel was first approved for marketing in the United Kingdom on July 31, 1997. By July 31, 2007, Seroquel had been approved (for use in adults) in 88 countries for schizophrenia and in 77 countries for mania.
All relevant safety issues from the periodic safety update report (PSUR) covering the reporting period of August 1, 2007 to July 31, 2008 were taken into consideration for this submission. Per the Sponsor, the PSUR did not identify any new significant safety issues bearing on the established overall safety profile of quetiapine.
Of note, this reviewer is not the primary reviewer for Seroquel, and therefore did not personally review any PSUR submissions for this drug.
Information on the Sponsor's literature review is included in Appendix 9.1.

9 Appendices

9.1 Literature Review and References

The Sponsor indicated that they utilize both in-house facilities as well as external providers to perform searches of the published literature. The worldwide published literature is searched for all Sponsor products with no restrictions made on product formulation or route of administration. Any report of an adverse drug reaction that is a valid case published in a local journal and identified by a marketing company is translated into English and forwarded for entry onto the Patient Safety database. In addition, a comprehensive search of published medical literature regarding quetiapine use in the pediatric population was conducted on October 9, 2007, utilizing the Sponsor's inhouse database. This search yielded 1,050 clinical article abstracts and 310 review article abstracts. All abstracts were reviewed and full-text articles requested for those deemed to be relevant and then reviewed by the Patient Safety staff (health care professionals including physicians, registered nurses and pharmacists).

The search strings for pediatric patients included the following terms: infant%, neonat%, child, children, pediatric%, fetal, fetus, foet%, adolescent, juvenile%.
The findings of the literature review were consistent with the known safety of Seroquel in adults and the safety profile discussed in the proposed labeling and clinical summary of safety in the supplements.

9.2 Requests for Information from Sponsor

1. For Studies 112 and 149, please combine the somnolence and sedation adverse events into one term "somnolence" and recalculate the frequencies for this combined adverse event.

2. In one of the lists of principal investigators tables, there are 6 sites in Germany that participated in study 112 (sites 380, 381, 382, 383, 384, 386). However, only one site (386) enrolled 1 subject in study 112. Was there difficulty in recruiting subjects for this trial in Germany, or is there another reason for the lack of enrollment?

3. Please provide some rationale for the increases in blood pressure (systolic and diastolic) observed in the child/adolescent populations in studies 112 and 149 - this is in contrast to the orthostatic signal present in the adult population.

4. In the recent CBE submission, data for increases in blood pressure were summarized for the bipolar and schizophrenia studies in children and adolescents. It appears that these data were pooled across all doses and studies 112 and 149. Please provide a table similar to Table 64 of the clinical study report for study 149 for these data and clarify whether the systolic and diastolic blood pressure changes in labeling refer to supine or standing measurements. Were the data in labeling based on the type of data presented in Table 64? Please provide these data by age group as well (10 - 12, 13-17 yrs.) for study 149.

5. Please provide more details regarding the following serious adverse events and adverse events leading to discontinuation:

   Study 149: Patient E0035208 - Tachycardia, Blood Pressure Increased
   The narrative indicates that the patient experienced these adverse events on Day 5 - however, the vital signs listing does not provide vitals obtained on Day 5. Please provide these data and any other additional vital sign readings obtained for this patient.

Study 150: Patient E0343103 - Pulmonary Hypertension
The narrative indicates that the patient was referred to a pediatric cardiologist. Please provide the consult and pertinent follow-up for this adverse event. Did the event resolve spontaneously after quetiapine was discontinued, did the patient receive any medical treatment for the condition?

Study 150: Patient E0240103 - Hypertensive Crisis
It appears that this patient had high blood pressure during the trial (narrative indicates from day 32 - 212) and enalapril is noted as a concomitant medication. Was enalapril initiated during the trial for high blood pressure? Listing 12.2.9.1 does not indicate high blood pressures for the visits included in the listing and the hypertensive crisis value (150/95) is not included in the listing. Please provide all blood pressures obtained for this patient. Did the patient receive any additional treatment for the 150/95 reading?
Please provide more clinical details regarding the hemorrhagic rash experienced by this patient.

Study 150: Patient E0262101 - Suicide attempt
Please provide details regarding the suicide attempt - there is no information provided in the narrative.
It is noted that this patient also experienced neutropenia with an ANC = 0.46 on Day 85. WBCs were obtained on Days 89 and 96 but, remarkably, no ANCs were obtained for these days. The next available ANC is at Day 169 (resolution). If the value of 0.46 is correct, why was this patient not discontinued? Please comment.

Study 150: Patient E0047211 - Syncope
The narrative notes that the patient also experienced the non-serious event "fall (mild intensity and considered related to study medication) Day 1 Day 20". Does this mean that the patient experienced falls from Day 1 to Day 20? Please clarify and provide additional information.

6. Please clarify the absolute neutrophil counts that are sporadically listed in Listing 12.2.8.2.2 (Study 150). On page 919, patient E0026202 had a WBC count of 5.9 with 25% neutrophils which should be an ANC of 1.47. However, it appears that the ANC listed in the appropriate column indicates a value of 0.18. Please clarify.

7. Please provide a table similar to SA14 (summary-clin-safety) for standing vital sign shifts.

8. For Study 149, the inclusion criteria indicate that patients with rapid cycling bipolar disorder could be enrolled. How many patients with rapid cycling bipolar disorder were enrolled? If sufficient numbers were randomized, please perform a separate efficacy analysis for patients with and without rapid cycling bipolar disorder.

9. What % of patients received BID and TID dosing in studies 112 and 149? Was any analysis performed regarding overall tolerability (AE incidence, etc.) between these two dosing regimens?

10. For Study 150, please provide a table similar to Table 62 (patients with potentially clinically important high shifts in prolactin) in the clinical study report for Study 149. For this table, please include prolactin concentrations in ng/ml units; table 11.3.7.3.11.2 in the clinical study report for Study 150 provides the prolactin concentrations in mIU/L units.

11. In the clinical study report for Study 150, Table 11.3.8.1.14 includes the categorical shifts in eye examinations from OL baseline. Please provide more detailed information for these cases. Please provide clinical details describing the cases that shifted from normal to abnormal. Please also provide clinical details describing the cases that were categorized as abnormal at OL baseline and that remained abnormal (e.g. were the same/similar abnormalities noted).

12. For Study 149, please provide an analysis of mean change in vital signs from baseline to final visit (supine and standing pulse, systolic BP and diastolic BP) for patients on concurrent psychostimulants and those not on concurrent psychostimulants. Please also provide an analysis of clinically important shifts at any time in vital signs for these same groups of patients. For patients with the clinically important shifts at anytime, please provide a line listing of all vital signs.

13. In the clinical study report for Study 150, Table 11.3.8.1.14 includes the categorical shifts in eye examinations from OL baseline. Please provide more detailed information for these cases. Please provide clinical details describing the cases that shifted from normal to abnormal. Please also provide clinical details describing the cases that were categorized as abnormal at OL baseline and that remained abnormal (e.g. were the same/similar abnormalities noted).

14. For Study 149, please provide an analysis of mean change in vital signs from baseline to final visit (supine and standing pulse, systolic BP and diastolic BP) for patients on concurrent psychostimulants and those not on concurrent psychostimulants. Please also provide an analysis of clinically important shifts at any time in vital signs for these same groups of patients. For patients with the clinically important shifts at anytime, please provide a line listing of all vital signs.

15. For Studies 112 and 149, please provide the subject identifiers for subjects with shifts to high in vital sign parameters (pulse, blood pressure) and provide listings for all study vital sign readings (including unscheduled visits) for these subjects including vital signs obtained in Study 150 for those subjects who continued in the open-label extension study. Did any subjects require treatment with antihypertensive medications?

16. Please provide mean change in prolactin concentration for studies 112 and 149 only for the subset of patients with normal prolactin at baseline.

9.3 Inclusion and Exclusion Criteria for Study 112

Inclusion Criteria

1. Provision of written informed consent by one or both parents or by legal guardian prior to any study procedure.
2. Provision of written assent by the patient prior to any study procedure.
3. Male or female, aged 13 to 17 years at randomization, hospitalized or outpatient.
4. If female and of childbearing potential, must have used a reliable method of contraception. Reliable methods included abstinence, hormonal contraceptives (e.g. oral contraceptive or long-term injectable or implantable hormonal contraceptive), double-barrier methods (e.g. condom and diaphragm, condom and foam, condom and sponge), intrauterine devices, and tubal ligation.
5. All female patients needed to have the absence of pregnancy confirmed by a negative β-human chorionic gonadotropin before randomization.
6. DSM-IV criteria for schizophrenia confirmed by the K-SADS-PL.
7. The Social Communication Questionnaire (SCQ) was administered to assess for pervasive developmental disorders. Patients with an SCQ score of $\geq$ 15 and who otherwise met entrance criteria must have had a documented history of delusions or hallucinations.
8. Patients with a secondary diagnosis of depression may have continued treatment with an antidepressant if clinically advised by the investigator, providing the antidepressant was permitted and the dose was stable for $\geq$ 30 days preceding randomization.
9. PANSS score > 60 and a score of $\geq$ 4 on at least one of the following items: delusions, conceptual disorganization or hallucinations at both screening and randomization.
10. Willingness to agree not to harm self

11. Had a parent or legal guardian accompany the patient at each scheduled study visit, provided reliable information, and was responsible for receiving and dispensing study medication.
12. Willingness to adhere to the schedule of assessments.

Exclusion Criteria

1. Secondary DSM-IV Axis I diagnoses of Bipolar Disorders including Cyclothymia, Schizophreniform Disorder, Schizoaffective Disorder, Psychotic Disorder Not Otherwise Specified, and acute (< 3 months) Post-traumatic Stress Disorder.
2. Premorbid IQ < 70 or diagnosis of mental retardation.
3. Psychosis judged to be the direct physiological consequence of a medical condition or treatment. These conditions included degenerative neurological conditions (e.g. Parkinson's disease, Huntington's disease), cerebrovascular disease (e.g. stroke), metabolic conditions (e.g. vitamin B12 deficiency), autoimmune conditions (e.g. systemic lupus erythematosis), viral or other infections (e.g. hepatitis, mononucleosis, HIV), and cancers.
4. Psychosis judged to be the direct physiological effect (e.g. intoxication, withdrawal) of an abused medication or substance.
5. History of any serious suicide attempt that required medical intervention or current suicidal risk that could not be safety managed as determined by the clinical judgment of the investigator.
6. Serious homicidal risk or homicidal behaviors within the past 3 months that resulted in adjudication.
7. Known intolerance for or lack of response to quetiapine, as judged by the investigator.
8. Contraindications as detailed in country-specific prescribing information for quetiapine.
9. For female patients, pregnancy or lactation.
10. Substance abuse or dependence including alcohol (except for caffeine or nicotine dependence) as defined in DSM-IV, within 1 month prior to screening.
11. Inability to discontinue psychoactive medications prior to randomization.
12. Use of haloperidol decanoate, fluphenazine decanoate, or risperidone microspheres
13. ECT within 30 days prior to screening.
14. Use of potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, saquinavir) in the 14 days preceding randomization.
15. Use of potent CYP3A4 inducers (e.g. phenytoin, carbamazepine, barbiturates, rifampin, glucocorticoids, Saint John's Wort) in the 14 days preceding randomization.
16. TSH hormone concentration more than 10% above the upper limit of the normal range.
17. Laboratory test results outside the reference range and considered by the investigator to be clinically significant.
18. Baseline QTcF $\geq$ 450 ms at baseline.
19. Renal, cardiovascular, hepatic, hematologic, endocrinologic, ophthalmologic, or other disease or clinical finding that was unstable or that in the opinion of the investigator would be negatively affected by study medication or that would affect study medication.
20. Unstable diabetes mellitus with a baseline HbA1c $\geq$ 8.5.
21. Patients admitted to a hospital for treatment of diabetes or diabetes-related illness in past 12 weeks.
22. Not under the care of a physician responsible for the patient's diabetes care.
23. Diabetes mellitus clinically unstable in the opinion of the physician responsible for the patient's diabetes management at the time of baseline.
24. The physician responsible for the patient's diabetes care had not approved the patient's participation in the study.
25. The patient had not been on the same dose of the oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones) this period should not have been less than 8 weeks.
26. A patient taking insulin whose daily dose on one occasion in the past 4 weeks was was more than 10% above or below their mean dose in the preceding 4 weeks.

27. If the patient's CBC with WBC differential showed an ANC < 1.0 x 10^9/L, the test was repeated within 24 hours. If the value remained < 1.0 x 10^9/L, the patient was excluded.
28. Medical condition that would affect the absorption, distribution, metabolism, or excretion of study medication.
29. History of seizure disorder, except febrile convulsions.
30. Use of experimental drug within 30 days of randomization.
31. Previous participation in this study.
32. Significant medical illness which could prevent patient from completing double-blind treatment.

9.4 Study Assessments Flow Chart – Study 112

Study plan	Screening	Washout period	Randomization[a]	Double-blind treatment					
Visit[b]	1	Up to 28 days	2	3	4	5	6	7	8[c]/Final
Day	Screening		1	7	14	21	28	35	42
Informed consent, assent, demography, history	√								
Inclusion/exclusion criteria	√		√						
Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL) and Social Communication Questionnaire (SCQ)	√								
Urine drug screen and urinalysis	√								√
Physical examination[d]	√								√
Tanner staging[e]	√								√
Vital signs[f], height, weight, temperature	√[g]		√	√	√	√	√	√	√
12-lead electrocardiogram	√[g]								√
Laboratory tests to include all of the following: Clinical chemistry[g] including lipid panel Insulin level and HbA1c Thyroid function and prolactin concentration β-hCG[j]	√[g]						√[h]		√
Hematology[k, l]	√						√		√
Genetic sampling[m]	√								
Positive and Negative Syndrome Scale (PANSS)	√		√	√	√	√	√	√	√
Clinical Global Impression (CGI) Severity of Illness and Global Improvement items[n]			√	√	√	√	√	√	√
Children's Global Assessment Scale (CGAS)			√						√
Caregiver Strain Questionnaire[o] (CGSQ)			√						√

Study plan	Screening	Washout period	Randomization[a]	Double-blind treatment					
Visit[b]	1	Up to 28 days	2	3	4	5	6	7	8[c]/Final
Day	Screening		1	7	14	21	28	35	42
Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS)			√	√	√	√	√	√	√
Children's Depression Rating Scale – Revised (CDRS-R)[p]			√	√	√	√	√	√	√
Adverse event recording	√		√	√	√	√	√	√	√
Prior and concomitant medication recording	√		√	√	√	√	√	√	√
Study drug dispensing			√[q]	√	√	√	√	√	
Drug accountability and treatment compliance				√	√	√	√	√	√

[a] Study drug was titrated up starting at Day 1 (see Table 5).
[b] Visit window: ± 3 days of scheduled visit date.
[c] End of double-blind treatment.
[d] Physical exam included routine ophthalmologic assessment at Screening and on Day 42 or final visit.
[e] Was completed by a physician or designated medical staff. A self-report or family-report assessment was not allowed.
[f] Blood pressure and pulse rate were obtained in supine and standing positions.
[g] Assessment was repeated if washout period was ≥14 days.
[h] Only fasting plasma glucose was obtained. Other clinical chemistry, insulin level, HbA_{1c}, thyroid function and prolactin concentration, and β-hCG were not required at this visit.
[i] Blood samples collected for clinical chemistry were obtained under fasting conditions. Fasting was defined as not having ingested food or liquids other than water for ≥8 hours. Fasting blood sample was drawn between 8:00 AM and 10:00 AM.
[j] For female patients only at Visits 1 and 8. Could be completed at additional visits if clinically indicated.
[k] If the patient presented with a fever, pharyngitis, or other signs and symptoms of infection at any time, a CBC with differential was completed.
[l] If the patient's CBC with WBC differential showed an ANC <1.0 x 10^9/L, the test was repeated within 24 hours. If it remained <1.0 x 10^9/L, the patient was discontinued.
[m] Genetic sampling was optional for both sites and patients at any time during the study.
[n] The CGI Global Improvement item, which assessed changes from baseline, was not recorded at randomization.
[o] Was completed by parent or legal guardian during the visit.
[p] New patients started at Visit 2, ongoing patients started at the next scheduled visit. Did not go back and complete prior visits.
[q] The first dose of study medication was taken on the evening of Day 1, which must have occurred no more than 14 days after baseline safety assessments were obtained.

9.5 Inclusion and Exclusion Criteria for Study 149

Inclusion Criteria

1. Provision of written informed consent by one of both parents or by legal guardian prior to any study procedure.
2. Provision of written assent by the patient prior to any study procedure.
3. Male or female, aged 10 to 17 years at randomization, hospitalized or outpatient
4. If female and of childbearing potential, must have used a reliable method of contraception. Reliable methods included abstinence, hormonal contraceptives (e.g. oral contraceptive or long-term injectable or implantable hormonal contraceptive), double-barrier methods (e.g. condom and diaphragm, condom and foam, condom and sponge), intrauterine devices, and tubal ligation.
5. All female patients needed to have the absence of pregnancy confirmed by a negative serum β-hCG) before randomization
6. DSM-IV criteria for Bipolar I mania confirmed by the K-SADS-PL. Patients with rapid cycling or who experienced a first manic episode were included. Patients could also have had a secondary diagnosis of ADHD. Patients with ADHD could, if judged necessary by the investigator, have continued the psychostimulant treatment if the prescribed dose had been stable for ≥ 30 days preceding randomization.
7. Willingness to agree not to harm self.
8. YMRS score ≥ 20 at both screening and randomization.
9. Had a parent or legal guardian accompany the patient at each scheduled study visit, provided reliable information, and was responsible for receiving and dispensing study medication.
10. Willingness to adhere to the schedule of assessments.

Exclusion

1. Diagnosis of a current DSM-IV Axis I disorder with the exception of those noted in the inclusion criteria. Excluded diagnoses included Tourette's disorder, OCD, acute (< 3 months) PTSD, panic disorder, pervasive developmental disorders.
2. Premorbid IQ < 70 or diagnosis of mental retardation.
3. Psychosis judged to be the direct physiological consequence of a medical condition or treatment. These conditions include degenerative neurological conditions (e.g. Parkinson's disease, Huntington's disease), cerebrovascular disease (e.g. stroke), metabolic conditions (e.g. vitamin B12 deficiency), autoimmune conditions (e.g. SLE), viral or other infections (e.g. hepatitis, mononucleosis, HIV), and cancers.
4. Psychosis judged to be the direct physiological effect of an abused medication or substance (e.g. intoxication, withdrawal).
5. Current manic episode judged to be the direct physiological effect of psychostimulant or antidepressant medication.

6. History of any serious suicide attempt that required medical intervention or current suicidal risk that cannot be safely managed as determined by the clinical judgment of the investigator.
7. Serious homicidal risk or homicidal behaviors within the past 3 months that resulted in adjudication
8. Known intolerance for or lack of response to quetiapine, as judged by the investigator
9. For female patients, pregnancy or lactation
10. Substance abuse or dependence including alcohol (except for caffeine or nicotine dependence), as defined in DSM-IV, within 1 month prior to screening.
11. Inability to discontinue psychoactive medications prior to randomization
12. Use of haloperidol decanoate, fluphenazine decanoate or risperidone microspheres within 1 dosing interval prior to randomization
13. ECT within 30 days prior to screening
14. Use of potent CYP3A4 inhibitors in the 14 days preceding randomization
15. Use of potent CYP3A4 inducers in the 14 days preceding randomization
16. TSH hormone concentration > 10% above the upper limit of normal range
17. Laboratory test results outside the reference range and considered by the investigator to be clinically significant
18. Baseline QTcF interval > 450 msec at baseline
19. Renal, cardiovascular, hepatic, hematologic, endocrinologic, ophthalmologic, or other disease or clinical finding that was unstable or that in the opinion of the investigator would be negatively affected by study medication or that would affect study medication
20. Unstable diabetes mellitus with a baseline HbA1c $\geq$ 8.5.
21. Patients admitted to a hospital for treatment of diabetes or diabetes related illness in past 12 weeks.
22. Not under the care of a physician responsible for the patient's diabetes care.
23. Diabetes clinically unstable in the opinion of the physician responsible for the patient's participation in the study.
24. The patient had not been on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones) this period should not have been less than 8 weeks.
25. A patient taking insulin whose daily dose on one occasion in the past 4 weeks was more than 10% above or below their mean dose in the preceding 4 weeks.
26. If the patient's CBC and WBC differential showed an ANC < 1.0 x 10^9/L, the test was repeated within 24 hours. If the value remained < 1.0 x 10^9/L, the patient was excluded.
27. Medical condition that would affect absorption, distribution, metabolism, or excretion of study medication
28. History of seizure disorder, except febrile convulsions
29. Use of experimental drug within 30 days of randomization
30. Previous participation in this study
31. Significant medical illness which could prevent patient from completing double-blind treatment
32. Patients with asthma treated with oral steroids within 3 months prior to randomization
33. Concurrent cognitive-behavior therapy initiated within 6 weeks prior to randomization

9.6 Study Assessments Flow Chart for Study 149

Study plan	Screening	Washout period	Randomization[b]	Double-blind treatment			
Visit[a]	1	Up to 28 days	2	3	4	5	6[c]/Final
Day	Screening		1	4	7	14	21
General events/assessments							
Informed consent, assent, and demography, history	√						
Inclusion/exclusion criteria	√		√				
Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL)	√						
Physical examination[d]	√						√
Tanner Staging	√						√
Vital signs[f], height, weight, temperature	√[e]		√	√	√	√	√
12-lead electrocardiogram	√[e]						√
Laboratory tests to include all of the following: Clinical chemistry[g] including lipid panel HbA1c Thyroid function and prolactin concentration Hematology[h] β-human chorionic gonadotropin (β hCG)[i]	√[e]						√
Genetic Sampling[j]	√						
Urine drug screen and urinalysis	√						√
Young Mania Rating Scale (YMRS)	√		√	√	√	√	√
Clinical Global Impression – Bipolar (CGI-BP) Severity of Illness and Global Improvement items[k]			√	√	√	√	√
Children's Depression Rating Scale – Revised (CDRS-R)			√	√	√	√	√
Overt Aggression Scale – Modified (OAS-M)			√	√	√	√	√
Children's Global Assessment Scale (CGAS)			√				√

Study plan	Screening	Washout period	Randomization[b]	Double-blind treatment			
Visit[a]	1	Up to 28 days	2	3	4	5	6[c]/Final
Day	Screening		1	4	7	14	21
Caregiver Strain Questionnaire (CGSQ)[l]			√				√
Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS)			√		√	√	√
Adverse event recording	√		√	√	√	√	√
Prior and concomitant medication recording	√		√	√	√	√	√
Study drug dispensing			√[m]	√	√	√	
Drug accountability and treatment compliance				√	√	√	√

[a] Visit window: ± 3 days of scheduled visit date.
[b] Study drug was titrated up starting at Day 1 (see Table 5).
[c] End of double-blind treatment.
[d] Physical exam included routine ophthalmologic assessment at Screening and on Day 21 or final visit.
[e] Assessment was repeated only if washout period is ≥14 days.
[f] Blood pressure and pulse rate were obtained in supine and standing positions.
[g] Blood samples collected for clinical chemistry were obtained under fasting conditions. Fasting was defined as not having ingested food or liquids other than water for ≥8 hours. Fasting blood sample was drawn between 8:00 AM and 10:00 AM.
[h] If the patient presented with a fever, pharyngitis, or other signs and symptoms of infection at any time, a CBC with differential was completed.
[i] For female patients only and was completed at any visit based on discussion with the patient.
[j] Genetic sampling was optional for both sites and patients at any time during the study.
[k] The CGI-BP Global Improvement item which assessed change from baseline was not recorded at randomization.
[l] Was completed by parent and legal guardian during visit.
[m] The first dose of study medication was taken on the evening of Day 1, which must have occurred no more than 10 days after baseline safety assessments were obtained.

9.7 Potentially Clinically Important Definitions for Hematology, Chemistry and ECG Values

	Low	High
Hematocrit	≤ 0.35	
Hemoglobin (g/dL)	≤ 11.5	≥ 17.2 g/dL
RBC (cells/L)	≤ $3x10^{12}$	≥ $6x10^{12}$
Platelet count (cells/L)	≤ $100x10^9$	≥ $600x10^9$
WBC		
Neutrophils	≤ 15%	
Absolute (calculated) (cells/L)	≤ $1.5x10^9$	≥ $10x10^9$
Eosinophils	≥ 10%	
Absolute (calculated) (cells/L)	≥ $1x10^9$	
Basophils	≥ $0.5x10^9$	
Lymphocytes	≤ $0.5x10^9$	> $6x10^9$
Monocytes	≥ $1.4x10^9$	
Chemistry		
ALT		≥ 3xULN
AST		≥ 3xULN
Alkaline phosphatase		≥ 3xULN
Total bilirubin		≥ 1.5xULN
HbA1c (%)		> 7.5%
Sodium (mmol/L)	≤ 132	≥ 152
Glucose (mg/dL)		
Fasting	≤ 45	≥ 126
Random	≤ 45	≥ 200
BUN (mg/dL)		≥ 21
Creatinine (mg/dL)		≥ 1.357
Potassium (mmol/L)	≤ 3.0	≥ 5.5
Chloride (mmol/L)	≤ 90	≥ 120
CO2 (mmol/L)	≤ 18	≥ 30
Total cholesterol (mg/dL)		≥ 240
HDL (mg/dL)	≤ 40	
LDL (mg/dL)		≥ 160
Triglycerides (mg/dL)		≥ 200
Total T4 and Free T4	≤ 0.8xLLN	≥ 1.2xULN
TSH (mIU/L)		> 5
Prolactin (ng/ml)		> 26 (females) > 20 (males)

ECG Parameter	Criterion Value	Change from Baseline
Heart rate (bpm)	> 110, < 50	Increase ≥ 15, decrease ≥ 15
PR (msec)	≥ 200	
QRS (msec)	≤ 50, ≥ 100	
QT (msec)	≥ 500, ≤ 200	Increase ≥ 60 msec
QTcF (msec)	≥ 450	Increase 15% msec of baseline

9.8 Potentially Clinically Significant Low ANCs

Study	Treatment	Gender/Age	Baseline ANC (10^9/L)	Lowest Value/Day	Final Visit	Comments
112	QTP 400	M, 15	2.3	1.46 (Day 46)	1.46 (Day 46)	
		M, 14	4.22	1.44 (Day 31)	2.20 (Day 45)	Discontinued
				1.19 (Day 38)		
		M, 16	1.30	0.99 (Day 30)		
				1.52 (Day 34)	1.01 (Day 43)	
		F, 17	1.61	1.33 (Day 48)	2.25 (Day 33)	1.40 (Day -9)
		F, 17	4.45	1.50 (Day 38)	1.50 (Day 38)	
	QTP 800	M, 13	1.73	1.14 (Day 33)	1.15 (Day 41)	
		M, 15	1.62	1.35 (Day 28)	2.40 (Day 46)	
	Placebo	M, 13	3.39	1.29 (Day 30)	1.33 (Day 43)	
		M, 13	1.99	1.41 (Day 27)	1.64 (Day 41)	
		M, 17	2.25	1.04 (Day 41)	1.04 (Day 41)	
		M, 14	NA	1.28 (Day 28)	0.75 (Day 48)	
		M, 14	1.44	1.63 (Day 31)	1.3 (Day 43)	
		F, 16	1.28	-	-	
149	QTP 400	F, 12	1.8		1.4 (Day 19)	
		M, 14	3.7		1.4 (Day 19)	1.4 (Day -2)
		F, 13	2.3		1.5 (Day 22)	
		F, 12	3.3	1.5 (Day 11)	2.7 (Day 14)	
		M, 10	2.4	1.2 (Day 20)	2.8 (Day 29)	
		M, 13	1.5		1.3 (Day 19)	
	QTP 600	M, 12	2.8		1.5 (Day 22)	
		M, 12	2.4		1.5 (Day 19)	
		F, 12	2.1		1.5 (Day 20)	1.6 (Day -7)
		M, 13	2.5		1.1 (Day 24)	
		M, 14	1.3		1.3 (Day 20)	
	Placebo	M, 12	1.6		1.0 (Day 23)	
		M, 13	1.7	1.2 (Day 22)	3.0 (Day 33)	1.5 (Day -4)

9.9 Mean Orthostatic Changes in Pulse and Blood Pressure

Mean Orthostatic Changes in Pulse and Blood Pressure – Study 112

		Quetiapine 400 N = 73		Quetiapine 800 N = 74		Placebo N = 75	
		n	Mean	n	Mean	n	Mean
Pulse (bpm)	Screen	73	7.4	71	7.8	74	7.1
	Day 1	70	6.7	71	6.2	73	5.7
	Day 7	73	9.3	72	7.3	72	7.3
	Day 14	70	7.5	70	6.3	72	4.8
	Day 21	67	8.4	67	5.3	65	4.8
	Day 28	61	6.6	64	5.9	57	5.6
	Day 35	58	9.1	62	5.6	51	5.5
	Day 42	55	6.4	55	3.9	44	4.4
	Final	73	6.8	74	4.7	73	4.9
Systolic BP (mmHg)	Screen	73	0.4	71	-0.4	74	-0.6
	Day 1	70	-1.3	71	0.7	73	-1.3
	Day 7	73	-1.7	72	-1.4	72	-2.0
	Day 14	70	-3.0	70	-0.5	72	-1.1
	Day 21	67	-1.5	67	-1.6	65	-0.6
	Day 28	61	-0.7	63	-1.0	57	-1.7
	Day 35	58	-0.1	62	-0.4	51	0.2
	Day 42	55	-1.1	55	-1.2	44	-0.6
	Final	73	-0.9	74	-0.4	73	-1.1
Diastolic BP (mmHg)	Screen	73	2.1	71	2.6	74	3.3
	Day 1	70	2.1	71	1.9	73	3.3
	Day 7	73	2.3	72	1.9	72	2.2
	Day 14	70	1.9	70	2.7	72	4.0
	Day 21	67	2.1	67	2.9	65	2.2
	Day 28	61	3.5	63	1.8	57	3.4
	Day 35	58	3.4	62	1.9	51	2.0
	Day 42	55	3.4	55	2.4	44	1.6
	Final	73	2.8	74	2.8	73	2.1

From Sponsor Table 11.3.8.2.3.1, 11.3.8.2.3.2, 11.3.8.2.3.3 in Clinical Study Report (Study 112)

Mean Orthostatic Changes in Pulse and Blood Pressure – Study 149

		Quetiapine 400 N = 95		Quetiapine 600 N = 98		Placebo N = 90	
		n	Mean	n	Mean	n	Mean
Pulse (bpm)	Screen	93	9.4	98	8.8	89	8.8
	Day 1	88	8.3	93	8.1	87	8.4
	Day 4	80	9.7	73	10.3	64	9.8
	Day 7	88	8.9	90	10.2	85	9.0
	Day 14	78	8.5	82	7.7	73	9.7
	Day 21	76	9.5	81	9.2	68	10.1
Systolic BP (mmHg)	Screen	93	-1.1	98	-1.4	89	-0.7
	Day 1	88	-0.3	93	0.3	87	-1.6
	Day 4	79	-0.7	72	-3.3	64	-0.8
	Day 7	88	-1.3	90	-1.7	85	0.1
	Day 14	78	-0.1	82	-1.1	73	0.6
	Day 21	76	0.2	81	-1.3	68	0.6
Diastolic BP (mmHg)	Screen	93	3.3	98	2.5	89	2.8
	Day 1	88	3.3	93	3.2	87	3.8
	Day 4	79	4.0	72	0.6	64	3.9
	Day 7	88	3.4	90	1.0	85	5.0
	Day 14	78	2.7	82	1.7	73	3.4
	Day 21	76	3.9	81	2.1	68	3.4

From Sponsor Table 11.3.8.2.3.1, 11.3.8.2.3.2, 11.3.8.2.3.3 in Clinical Study Report (Study 149)

9.10 Study Assessments Flow Chart – Study 150

Study plan	Open-label baseline		Open-label treatment								
Visit[a]	1 Baseline/Screen End of DB study[b]		2	3	4	5	6	7	8	9	10[d]/Final
Day	0	1[p]	7	14	21	28					
Week	1–7 days after end of DB study[c]		1	2	3	4	8	12	16	20	26
Informed consent and assent	√										
Inclusion/exclusion criteria	√										
Physical examination[e]	√										√
Ophthalmological slit-lamp examination[f]	√										√
Tanner staging[g]	√										√
Vital signs[h]/height/weight/oral temperature	√		√	√	√	√	√	√	√	√	√
12-lead electrocardiogram	√							√[h]			√
Laboratory tests to include all of the following: Clinical chemistry[i] including lipid panel Insulin level and HbA1c Thyroid function and prolactin concentration β-hCG[j]	√							√			√
Hematology[k,l]	√					√	√	√			√
Urine drug screen and urinalysis	√										√
Young Mania Rating Scale (YMRS)[m]	√					√	√		√		√
Clinical Global Impression-Bipolar (CGI-BP) Severity of Illness and Global Improvement items[m]	√		√	√	√	√	√	√	√	√	√
Positive and Negative Syndrome Scale (PANSS)[n]	√					√	√		√		√

Clinical Global Impression (CGI) Severity of Illness and Global Improvement items[h]	√		√	√	√	√	√	√	√	√	√
Clinical Global Assessment Scale (CGAS)	√										√
Caregiver Strain Questionnaire (CGSQ)[i]	√										√
Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS)	√		√	√	√	√	√	√	√	√	√
Children's Depression Rating Scale – Revised (CDRS-R)[g]	√		√	√	√	√	√	√	√	√	√
Adverse events recording	√		√	√	√	√	√	√	√	√	√
Prior and concomitant medication recording	√		√	√	√	√	√	√	√	√	√
Study drug dispensing		√[d]	√	√	√	√	√	√	√	√	
Drug accountability and treatment compliance			√	√	√	√	√	√	√	√	√

[a] Visit window: ± 3 days of scheduled visit date for Visits 1 to 4, ± 7 days for Visits 5 to 10 (early withdrawal).
[b] End-of-study assessments from Study 149 or Study 112 were carried forward as baseline assessments for OL study.
[c] Baseline/Screening visit was to be completed no more than 7 days from the end of the preceding double-blind study (Study 149 or Study 112).
[d] End of OL treatment. Please note that there is a 6-week period between Visits 9 and 10.
[e] Physical examination included routine ophthalmologic assessment
[f] Ophthalmologic slit-lamp examination was to be completed within 14 days from baseline visit and no greater than 14 days after end of study treatment. This was completed by an ophthalmologist.
[g] Blood pressure was obtained in the supine and standing positions.
[h] An ECG resulting in a QTc (Fridericia) ≥450 milliseconds was to be repeated. If QTc (Fridericia) remained ≥450 milliseconds the pediatric cardiologist was to be consulted regarding continuation in study.
[i] Blood samples collected for clinical chemistry were to be obtained under fasting conditions. Fasting was defined as not having ingested food or liquids other than water for ≥8 hours. Fasting blood samples were to be drawn between 8:00 – 10:00 AM.

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/s/

Cara Alfaro
5/11/2009 10:43:25 AM
PHARMACIST

Ni Aye Khin
5/11/2009 12:58:38 PM
MEDICAL OFFICER
This set of NDA supplements will be presented at the PDAC meeting scheduled for 6/9/09 and 6/10/09; a memo to file to be followed after discussion at the PDAC meeting.