Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 20-639/S-045/S-046, Seroquel (quetiapine fumarate) tablets, for the acute treatment of schizophrenia in adolescents from 13 to 17 years of age and the acute treatment of bipolar mania in children from 10 to 12 years of age and adolescents from 13 to 17 years of age, NDA 20-825/S-032, Geodon (ziprasidone hydrochloride) capsules for the acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features in children and adolescents from 10 to 17 years of age, and NDA 20-592/S-040/S-041, Zyprexa (olanzapine) tablets, for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adolescents from 13 to 17 years of age and the acute treatment of schizophrenia in adolescents from 13 to 17 years of age to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 8, 2009

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

SUBJECT: June 9-10, 2009 Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC)

TO: Members, PDAC

This two-day PDAC meeting will focus on safety and efficacy issues for the following supplemental new drug applications:
-sNDAs 20-639/S-045/S-046, quetiapine (Seroquel), Astra Zeneca, for the treatment of schizophrenia in pediatric patients (13-17 years of age) and bipolar mania in pediatric patients (10-17 years of age)
-sNDA 20-825/S-032, ziprasidone (Geodon), Pfizer, for the treatment of bipolar mania in pediatric patients (10-17 years of age)
-sNDA 20-592/S-040/S-041, olanzapine (Zyprexa), for the treatment of schizophrenia in pediatric patients (13-17 years of age) and bipolar mania in pediatric patients (13-17 years of age)

All of these drugs are approved for schizophrenia and bipolar disorder in adult patients. Each of these sponsors has conducted one acute, placebo-controlled efficacy and safety trial for each of the indications for which they are seeking claims in pediatric patients, and have also obtained pharmacokinetic data and some longer-term safety data in these populations. In FDA's background package, we have provided FDA's various review documents for these applications (primary medical officer reviews, team leader memos, and division director memos, and reviews on AERS reports and use data from the Office of Surveillance and Epidemiology). The sponsors' background packages will also provide data to support the safety and efficacy for these expanded claims. Although the Division has not yet reached a final conclusion for these applications, we generally are in agreement that the sponsors have provided adequate support to suggest effectiveness for these products for the claimed indications. In addition the safety profiles for these products in these pediatric populations studied appear to be qualitatively similar to those observed with these drugs in adult patients.

Schizophrenia and bipolar disorder are serious illnesses in pediatric patients and represent a substantial burden for both patients and their families. At the present time there are two antipsychotic drugs approved for the treatment of schizophrenia and bipolar mania in pediatric patients, i.e., risperidone (Risperdal) and aripiprazole (Abilify). Seroquel, Geodon, and Zyprexa,

if approved for these illnesses, would provide additional treatment options for these patients. It is important to note that all three of these drugs, although not yet approved for these disorders in pediatric patients, are, nevertheless, used in treating these patients.

All of these drugs also have significant risks that must be considered, both by FDA in deciding whether or not to approve these claims and also by clinicians in deciding whether or not to use these medications in treating these serious disorders. Adverse reactions that can occur with drugs in the class of atypical antipsychotic drugs include, among others, somnolence, weight gain, increases in blood lipids and glucose, acute extrapyramidal symptoms, and tardive dyskinesia. These risks are of particular concern in pediatric patients because of the life-long nature of these disorders and the fact that these patients are considered particularly vulnerable, in part because they may be exposed for many decades, and in part because of possible effects on growth and development.

Formal presentations of data at the meeting will include a summary of the safety and efficacy data for these expanded claims by the sponsors. FDA will not be making separate presentations, since we are in essential agreement with the data to be presented by the sponsors. We have, however, asked two members of the PDAC to provide formal comments on the seriousness of schizophrenia and bipolar disorder in pediatric patients, and the importance of having treatment options.

The Division of Psychiatry Products has not yet reached a final conclusion on these applications, and seeks the advice of the PDAC before reaching a conclusion.

After you have heard all the findings and arguments, we will ask you to discuss and vote on questions of risks and benefit for these products in the indications being sought. The questions for a vote are as follows:

1. Has Seroquel been shown to be effective for the treatment of schizophrenia in pediatric patients ages 13-17?

2. Has Seroquel been shown to be acceptably safe for the treatment of schizophrenia in pediatric patients ages 13-17?

3. Has Seroquel been shown to be effective for the treatment of bipolar mania in pediatric patients ages 10-17?

4. Has Seroquel been shown to be acceptably safe for the treatment of bipolar mania in pediatric patients ages 10-17?

5. Has Geodon been shown to be effective for the treatment of bipolar mania in pediatric patients ages 10-17?

6. Has Geodon been shown to be acceptably safe for the treatment of bipolar mania in pediatric patients ages 10-17?

7. Has Zyprexa been shown to be effective for the treatment of schizophrenia in pediatric patients ages 13-17?

8. Has Zyprexa been shown to be acceptably safe for the treatment of schizophrenia in pediatric patients ages 13-17?

9. Has Zyprexa been shown to be effective for the treatment of bipolar mania in pediatric patients ages 13-17?

10. Has Zyprexa been shown to be acceptably safe for the treatment of bipolar mania in pediatric patients ages 13-17?

cc:
HFD-130/TLaughren/MMathis/NKhin/RLevin/CAlfaro/MRitter/KUpdegraff

DOC: PDAC 060909 Memo 01.doc

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 17, 2009
To:	Mark Ritter, Medical Officer Division of Psychiatry Products Office of New Drugs
Through:	Laura Governale, PharmD, MBA Drug Use Data Analyst Team Leader Division of Epidemiology Office of Surveillance and Epidemiology
From:	Hina Mehta, PharmD Drug Use Data Analyst Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Total number of prescriptions and patients for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone)
Drug Name(s):	Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone)
Application Type/Number:	Various
Applicant/sponsor:	Various
OSE RCM #:	2009-439

1 INTRODUCTION

The Division of Psychiatry Products (DPP) is preparing for a presentation at the PDAC meeting. The committee will be asked to vote on whether or not Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) have been shown to be effective and acceptably safe for pediatric indications. In support of that presentation , the Division of Epidemiology (DEPI) has been requested to provide prescription and patient utilization data in the pediatric population for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone), for years 2004 through 2008.

2 METHODS AND MATERIAL

2.1 DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

The IMS Health, IMS National Sales Perspectives™ (see Appendix 1 for database descriptions) was used to determine the various retail and non-retail channels of distribution for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone).[i] The examination of wholesale sales data by eaches (packets, bottles, etc.) in year 2008 indicate that the majority of distribution for most of these products is toward outpatient pharmacy settings (56% or greater). Outpatient pharmacy settings include chain, independent, and food stores with pharmacies. Distribution towards non-retail pharmacy settings ranged from 29% to 37% during year 2008. The long term care setting within the non-retail channels received the majority of quetiapine and olanzapine sales. Mail order distribution ranged from 6% to 8% for the three agents analyzed. Thus, we examined outpatient utilization patterns. Mail order and long term care data are not included in this analysis.

2.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions by product using SDI, Vector One®: National (VONA) (see Appendix 1 for full description) for calendar years 2004 through 2008. We also examined the number of patients who received a prescription for quetiapine, olanzapine, or ziprasidone products using SDI, Vector One®: Total Patient Tracker (TPT) for calendar years 2004 through 2008. Diagnosis associated with the use of these products, as reported by office-based physicians, were determined using SDI's Physician Drug and Diagnosis Audit (PDDA) for calendar years 2002 through 2008.

3 DATA

3.1 OUTPATIENT DISPENSED PRESCRIPTIONS

Table 1 in Appendix 2 shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone). During year 2008, approximately 11.9 million prescriptions were dispensed for quetiapine followed by olanzapine and ziprasidone with 4 million and 2.3 million prescriptions, respectively. Both quetiapine and ziprasidone products realized an increase in the number of

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[i] IMS Health, IMS Nationals Sales Perspectives™, Years 2004-2008. Data extracted 4-1-09. File: 0904psyc.dvr

dispensed prescriptions in the past 5 years except for olanzapine which decreased by about a third during the time period. Prescriptions dispensed to pediatric patients aged 0-12 years accounted for less than 5% of the total dispensed prescriptions for all three agents. Adolescents aged 13-17 years accounted for approximately 7% of dispensed prescriptions of ziprasidone followed by 6% and 2% of quetiapine and olanzapine, respectively.

3.2 PATIENT COUNT

Trends for patient data were similar to that of prescription data (Appendix 2: Table 2). During year 2008, approximately 2.3 million patients received a prescription for quetiapine while 740,794 patients received a prescription for olanzapine and 445,934 received ziprasidone. Pediatric patients aged 0-12 years accounted for less than 5% of patients receiving a prescription for each of the agents studied. Adolescents aged 13-17 years accounted for approximately 8% of patients receiving a prescription for ziprasidone followed quetiapine and olanzapine with 6% and 3%, respectively.

3.3 DIAGNOSIS ASSOCIATED WITH USE

We also examined the most common diagnosis associated with the use of Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) as reported by office-based physician practices in the U.S. (Appendix 2: Tables 3a, 3b, and 3c). “Affective Psychoses” ICD-9 296 was the most common diagnosis associated with the use of quetiapine with approximately 46% of all uses in year 2008 followed by “Schizophrenic Disorders” ICD-9 295 with 21%. For olanzapine and ziprasidone the most common diagnosis was “Schizophrenic Disorders” ICD-9 295 with 42% and 40%, respectively, followed by “Affective Psychoses” with 33% and 35%, respectively.

3.4 PRESCRIBER SPECIALTY

Table 4 in Appendix 2 shows the total number of prescriptions dispensed for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) by physician specialty. The majority of prescriptions dispensed for all three were prescribed by Psychiatrists (52% for quetiapine, 49% for olanzapine, and 65% for ziprasidone) over the entire study period. Unspecified physicians prescribed approximately 6-7% of prescriptions dispensed for all three agents during year 2008. Approximately 14% of prescriptions dispensed were prescribed by General Practice/Family Medicine/Doctor of Osteopathy for both quetiapine and olanzapine and 7% for ziprasidone during year 2008.

4 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) are distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Indications for use were obtained using SDI’s PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for

the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

5 CONCLUSIONS

The majority of sales of Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) were to outpatient retail pharmacy settings. During year 2008, approximately 11.9 million prescriptions were dispensed for quetiapine followed by olanzapine and ziprasidone with 4 million and 2.3 million prescriptions, respectively. Prescriptions dispensed to pediatric patients aged 0-12 years accounted for less than 5% of the total dispensed prescriptions for all three agents. Adolescents aged 13-17 years accounted for approximately 7% of dispensed prescriptions of ziprasidone followed by 6% and 2% of quetiapine and olanzapine, respectively. The trends for patient data were similar to prescription data. The most common diagnosis associated with the use of the three agents is “Affective Psychoses” ICD-9 296 and “Schizophrenic Disorders” ICD-9 295. Psychiatrists were the most common prescribers for all three of the agents studied.

APPENDIX 1: DATABASE DESCRIPTIONS

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

6 APPENDIX 2: TABLES AND FIGURES

Table 1. Total Number of Dispensed Prescriptions for Selected Antipsychotic Agents by Patient Age Through U.S. Outpatient Retail Phamacies, 2004-2008

	2004		2005		2006		2007		2008	
	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*
TOTAL MARKET	**14,554,218**	***100.0%***	**14,792,835**	***100.0%***	**15,789,942**	***100.0%***	**17,325,053**	***100.0%***	**18,244,731**	***100.0%***
quetiapine fumarate	7,172,254	*49.3%*	8,419,610	*56.9%*	9,566,459	*60.6%*	11,035,967	*63.7%*	11,872,722	*65.1%*
Age 0-6	37,836	*0.5%*	37,984	*0.5%*	33,460	*0.3%*	31,163	*0.3%*	25,695	*0.2%*
Age 7-12	343,520	*4.8%*	377,005	*4.5%*	373,152	*3.9%*	383,639	*3.5%*	375,127	*3.2%*
Age 13-17	536,651	*7.5%*	602,560	*7.2%*	610,243	*6.4%*	673,230	*6.1%*	680,203	*5.7%*
Age 18+	6,054,350	*84.4%*	7,150,280	*84.9%*	8,425,490	*88.1%*	9,854,520	*89.3%*	10,711,958	*90.2%*
Age UNSPEC.	199,897	*2.8%*	251,781	*3.0%*	124,114	*1.3%*	93,415	*0.8%*	79,739	*0.7%*
olanzapine	6,026,964	*41.4%*	4,740,992	*32.0%*	4,260,125	*27.0%*	4,059,291	*23.4%*	4,049,512	*22.2%*
Age 0-6	23,412	*0.4%*	12,537	*0.3%*	7,416	*0.2%*	6,028	*0.1%*	6,092	*0.2%*
Age 7-12	153,592	*2.5%*	99,717	*2.1%*	74,441	*1.7%*	66,982	*1.7%*	66,788	*1.6%*
Age 13-17	208,958	*3.5%*	140,220	*3.0%*	110,167	*2.6%*	102,199	*2.5%*	96,339	*2.4%*
Age 18+	5,479,256	*90.9%*	4,345,932	*91.7%*	4,018,812	*94.3%*	3,850,138	*94.8%*	3,852,412	*95.1%*
Age UNSPEC.	161,746	*2.7%*	142,586	*3.0%*	49,289	*1.2%*	33,944	*0.8%*	27,881	*0.7%*
Ziprasidone	1,355,000	*9.3%*	1,632,233	*11.0%*	1,963,358	*12.4%*	2,229,795	*12.9%*	2,322,497	*12.7%*
Age 0-6	3,945	*0.3%*	3,849	*0.2%*	4,058	*0.2%*	3,450	*0.2%*	2,394	*0.1%*
Age 7-12	60,089	*4.4%*	69,054	*4.2%*	77,379	*3.9%*	82,219	*3.7%*	75,836	*3.3%*
Age 13-17	113,312	*8.4%*	131,311	*8.0%*	148,728	*7.6%*	165,404	*7.4%*	161,744	*7.0%*
Age 18+	1,137,178	*83.9%*	1,370,049	*83.9%*	1,705,061	*86.8%*	1,956,149	*87.7%*	2,063,606	*88.9%*
Age UNSPEC.	40,476	*3.0%*	57,970	*3.6%*	28,132	*1.4%*	22,573	*1.0%*	18,917	*0.8%*

Source: SDI. Vector One®: National. Extracted 4-1-09. File: VONA 2009-439 TRx by Age 4-1-09.qry

Table 2. Total Number of Unique Patients Receiving a Prescription for Selected Antipsychotic Agents by Patient Age Through U.S. Outpatient Retail Phamacies, 2004-2008

	2004		2005		2006		2007		2008	
	TRxs	***Share***	**TRxs**	***Share***	**TRxs**	***Share***	**TRxs**	***Share***	**TRxs**	***Share***
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
quetiapine fumarate	1,542,314	*100.00%*	1,744,179	*100.00%*	1,943,537	*100.00%*	2,173,053	*100.00%*	2,328,813	*100.00%*
Age 0-6	11,383	*0.74%*	11,402	*0.65%*	9,755	*0.50%*	8,543	*0.39%*	6,791	*0.29%*
Age 7-12	77,174	*5.00%*	80,094	*4.59%*	74,182	*3.82%*	73,534	*3.38%*	69,600	*2.99%*
Age 13-17	127,799	*8.29%*	136,274	*7.81%*	134,575	*6.92%*	143,089	*6.58%*	144,049	*6.19%*
Age 18+	1,286,368	*83.41%*	1,468,844	*84.21%*	1,707,151	*87.84%*	1,938,939	*89.23%*	2,101,066	*90.22%*
Age UNSPEC.	101,492	*6.58%*	124,134	*7.12%*	76,081	*3.91%*	65,269	*3.00%*	59,756	*2.57%*
olanzapine	1,254,933	*100.00%*	908,070	*100.00%*	787,437	*100.00%*	726,628	*100.00%*	740,794	*100.00%*
Age 0-6	7,388	*0.59%*	3,802	*0.42%*	2,419	*0.31%*	1,917	*0.26%*	1,862	*0.25%*
Age 7-12	39,070	*3.11%*	23,312	*2.57%*	17,006	*2.16%*	14,824	*2.04%*	14,878	*2.01%*
Age 13-17	56,719	*4.52%*	35,088	*3.86%*	26,246	*3.33%*	23,339	*3.21%*	22,677	*3.06%*
Age 18+	1,117,925	*89.08%*	817,910	*90.07%*	732,619	*93.04%*	681,079	*93.73%*	696,535	*94.03%*
Age UNSPEC.	85,310	*6.80%*	71,869	*7.91%*	33,561	*4.26%*	25,209	*3.47%*	21,353	*2.88%*
Ziprasidone	317,254	*100.00%*	351,940	*100.00%*	404,481	*100.00%*	433,897	*100.00%*	445,934	*100.00%*
Age 0-6	1,430	*0.45%*	1,324	*0.38%*	1,193	*0.30%*	1,025	*0.24%*	769	*0.17%*
Age 7-12	14,688	*4.63%*	15,761	*4.48%*	16,850	*4.17%*	16,872	*3.89%*	15,115	*3.39%*
Age 13-17	28,959	*9.13%*	30,812	*8.75%*	34,159	*8.45%*	34,997	*8.07%*	34,003	*7.63%*
Age 18+	263,996	*83.21%*	293,104	*83.28%*	349,429	*86.39%*	379,839	*87.54%*	395,440	*88.68%*
Age UNSPEC.	19,263	*6.07%*	24,084	*6.84%*	14,420	*3.57%*	10,540	*2.43%*	8,972	*2.01%*

Source: SDI. Vector One®: Total Patient Tracker. Extracted 4-1-09. File: TPT 2009-439 Geodon Patient Count 4-1-09.xls, TPT 2009-439 Seroquel Patient Count 4-1-09.xls and TPT 2009-439 Zyprexa Patient Count 4-1-09.xls

Table 3a. Most Common Indications by Age Associated With the Use of Quetiapine in Office-Based Practice Settings, 2004-2008

	2004		2005		2006		2007		2008	
	Uses (000)	*Share %*	Uses (000)	*Share %*	Uses (000)	*Share %*	Uses (000)	*Share %*	Uses (000)	*Share %*
Quetiapine, Olanzapine, and Ziprasidone Total	**10,717**	**100.0%**	**11,603**	**100.0%**	**10,597**	**100.0%**	**9,798**	**100.0%**	**8,864**	**100.0%**
quetiapine fumarate	4,414	*41.2%*	5,834	*50.3%*	5,894	*55.6%*	5,484	*56.0%*	4,717	*53.2%*
296 AFFECTIVE PSYCHOSES	1,671	*37.9%*	2,421	*41.5%*	2,191	*37.2%*	2,255	*41.1%*	2,174	*46.1%*
Age 0-6	5	*0.3%*	6	*0.2%*	--	--	7	*0.3%*	--	--
Age 7-12	25	*1.5%*	17	*0.7%*	64	*2.9%*	25	*1.1%*	15	*0.7%*
Age 13-17	52	*3.1%*	45	*1.9%*	64	*2.9%*	48	*2.1%*	55	*2.5%*
Age 18+	1,507	*90.2%*	2,251	*93.0%*	1,966	*89.7%*	2,114	*93.7%*	2,041	*93.9%*
Age UNSPEC.	82	*4.9%*	103	*4.2%*	98	*4.5%*	63	*2.8%*	62	*2.8%*
295 SCHIZOPHRENIC DISORDERS	938	*21.2%*	1,118	*19.2%*	1,289	*21.9%*	993	*18.1%*	981	*20.8%*
Age 13-17	6	*0.6%*	7	*0.6%*	8	*0.6%*	--	--	10	*1.0%*
Age 18+	900	*96.0%*	1,039	*92.9%*	1,235	*95.8%*	936	*94.3%*	955	*97.3%*
Age UNSPEC.	32	*3.4%*	73	*6.5%*	46	*3.6%*	56	*5.7%*	16	*1.7%*
311 DEPRESSIVE DISORDER NEC	274	*6.2%*	383	*6.6%*	313	*5.3%*	300	*5.5%*	268	*5.7%*
Age 7-12	6	*2.2%*	--	--	--	--	7	*2.5%*	6	*2.2%*
Age 13-17	--	--	--	--	6	*2.0%*	19	*6.3%*	4	*1.4%*
Age 18+	249	*90.8%*	351	*91.8%*	268	*85.7%*	274	*91.2%*	234	*87.1%*
Age UNSPEC.	19	*6.9%*	31	*8.2%*	38	*12.3%*	--	--	25	*9.2%*
309 ADJUSTMENT REACTION	128	*2.9%*	224	*3.8%*	194	*3.3%*	370	*6.7%*	222	*4.7%*
Age 7-12	--	--	6	*2.5%*	--	--	13	*3.4%*	5	*2.3%*
Age 13-17	--	--	11	*4.8%*	6	*3.2%*	--	--	7	*3.2%*
Age 18+	120	*93.9%*	208	*92.7%*	174	*89.8%*	352	*95.0%*	210	*94.4%*
Age UNSPEC.	8	*6.1%*	--	--	14	*7.0%*	6	*1.5%*	--	--
300 NEUROTIC DISORDERS	310	*7.0%*	486	*8.3%*	347	*5.9%*	307	*5.6%*	209	*4.4%*
Age 0-6	--	--	--	--	5	*1.5%*	--	--	--	--
Age 7-12	7	*2.2%*	6	*1.2%*	--	--	3	*1.1%*	--	--
Age 13-17	11	*3.7%*	20	*4.1%*	5	*1.4%*	6	*2.0%*	9	*4.2%*
Age 18+	244	*78.9%*	418	*86.2%*	331	*95.3%*	291	*94.8%*	200	*95.8%*
Age UNSPEC.	47	*15.2%*	42	*8.6%*	6	*1.8%*	7	*2.2%*	--	--
298 OTH NONORGANIC PSYCHOSES	237	*5.4%*	242	*4.1%*	234	*4.0%*	232	*4.2%*	172	*3.6%*
Age 7-12	--	--	--	--	5	*2.3%*	--	--	--	--
Age 13-17	6	*2.7%*	--	--	--	--	7	*3.2%*	3	*2.0%*
Age 18+	231	*97.3%*	235	*97.2%*	223	*95.0%*	224	*96.8%*	160	*93.4%*
Age UNSPEC.	--	--	7	*2.8%*	6	*2.7%*	--	--	8	*4.6%*
780 GENERAL SYMPTOMS	101	*2.3%*	142	*2.4%*	96	*1.6%*	40	*0.7%*	105	*2.2%*
Age 13-17	5	*5.3%*	14	*9.6%*	--	--	--	--	--	--
Age 18+	96	*94.7%*	128	*90.4%*	90	*93.8%*	40	*100.0%*	105	*100.0%*
Age UNSPEC.	--	--	--	--	6	*6.2%*	--	--	--	--
294 OTHER ORGANIC PSYCH COND	139	*3.1%*	95	*1.6%*	147	*2.5%*	166	*3.0%*	105	*2.2%*
Age 18+	134	*96.6%*	80	*83.8%*	142	*96.2%*	166	*100.0%*	97	*92.8%*
Age UNSPEC.	5	*3.4%*	15	*16.2%*	6	*3.8%*	--	--	8	*7.2%*
All Others	616	*14.0%*	723	*12.4%*	1,083	*18.4%*	820	*15.0%*	481	*10.2%*

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 4-1-09. File: PDDA 2009-439 TRx by Diagnosis 4-1-09.xls

Table 3b. Most Common Indications by Age Associated With the Use of Olanzapine in Office-Based Practice Settings, 2004-2008

Quetiapine, Olanzapine, and Ziprasidone Total	10,717	100.0%	11,603	100.0%	10,597	100.0%	9,798	100.0%	8,864	100.0%
olanzapine	4,450	*41.5%*	3,574	*30.8%*	2,809	*26.5%*	2,293	*23.4%*	2,104	*23.7%*
295 SCHIZOPHRENIC DISORDERS	1,682	*37.8%*	1,297	*36.3%*	1,011	*36.0%*	941	*41.0%*	880	*41.8%*
Age 7-12	--	--	--	--	6	*0.6%*	--	--	--	--
Age 13-17	26	*1.5%*	--	--	19	*1.9%*	8	*0.8%*	6	*0.7%*
Age 18+	1,583	*94.1%*	1,228	*94.6%*	927	*91.7%*	886	*94.2%*	860	*97.7%*
Age UNSPEC.	74	*4.4%*	70	*5.4%*	59	*5.8%*	47	*5.0%*	14	*1.6%*
296 AFFECTIVE PSYCHOSES	1,417	*31.8%*	1,144	*32.0%*	929	*33.1%*	827	*36.1%*	685	*32.6%*
Age 0-6	13	*0.9%*	5	*0.5%*	--	--	--	--	--	--
Age 7-12	14	*1.0%*	17	*1.5%*	--	--	--	--	4	*0.6%*
Age 13-17	48	*3.4%*	11	*0.9%*	6	*0.6%*	18	*2.1%*	19	*2.8%*
Age 18+	1,283	*90.5%*	1,049	*91.7%*	894	*96.3%*	779	*94.2%*	640	*93.4%*
Age UNSPEC.	59	*4.2%*	62	*5.4%*	29	*3.1%*	30	*3.6%*	22	*3.2%*
298 OTH NONORGANIC PSYCHOSES	339	*7.6%*	213	*6.0%*	151	*5.4%*	132	*5.7%*	140	*6.6%*
Age 13-17	--	--	11	*5.2%*	18	*12.1%*	--	--	18	*12.7%*
Age 18+	339	*100.0%*	202	*94.8%*	126	*83.6%*	119	*90.6%*	122	*87.3%*
Age UNSPEC.	--	--	--	--	6	*4.3%*	12	*9.4%*	--	--
294 OTHER ORGANIC PSYCH COND	87	*2.0%*	75	*2.1%*	48	*1.7%*	34	*1.5%*	70	*3.3%*
Age 13-17	--	--	6	*8.5%*	--	--	--	--	--	--
Age 18+	87	*100.0%*	69	*91.5%*	31	*64.7%*	34	*100.0%*	65	*93.0%*
Age UNSPEC.	--	--	--	--	17	*35.3%*	--	--	5	*7.0%*
309 ADJUSTMENT REACTION	45	*1.0%*	85	*2.4%*	42	*1.5%*	41	*1.8%*	66	*3.1%*
Age 0-6	--	--	--	--	--	--	--	--	6	*8.8%*
Age 7-12	--	--	--	--	--	--	--	--	5	*7.2%*
Age 13-17	5	*12.0%*	--	--	--	--	--	--	--	--
Age 18+	39	*88.0%*	73	*86.2%*	42	*100.0%*	35	*86.7%*	43	*65.9%*
Age UNSPEC.	--	--	12	*13.8%*	--	--	5	*13.3%*	12	*18.1%*
311 DEPRESSIVE DISORDER NEC	231	*5.2%*	193	*5.4%*	142	*5.1%*	55	*2.4%*	61	*2.9%*
Age 0-6	--	--	5	*2.7%*	--	--	--	--	--	--
Age 13-17	4	*1.8%*	5	*2.7%*	--	--	14	*24.9%*	6	*9.9%*
Age 18+	215	*93.4%*	172	*89.3%*	142	*100.0%*	42	*75.1%*	55	*90.1%*
Age UNSPEC.	11	*4.8%*	10	*5.2%*	--	--	--	--	--	--
300 NEUROTIC DISORDERS	102	*2.3%*	89	*2.5%*	84	*3.0%*	78	*3.4%*	51	*2.4%*
Age 7-12	--	--	--	--	--	--	6	*7.4%*	--	--
Age 13-17	--	--	--	--	6	*7.0%*	--	--	6	*11.8%*
Age 18+	95	*93.5%*	82	*92.2%*	72	*85.6%*	72	*92.6%*	41	*79.8%*
Age UNSPEC.	7	*6.5%*	7	*7.8%*	6	*7.3%*	--	--	4	*8.4%*
297 PARANOID STATES	44	*1.0%*	42	*1.2%*	79	*2.8%*	28	*1.2%*	26	*1.2%*
Age 13-17	--	--	--	--	--	--	8	*29.0%*	--	--
Age 18+	44	*100.0%*	36	*86.0%*	79	*100.0%*	20	*71.0%*	21	*81.5%*
Age UNSPEC.	--	--	6	*14.0%*	--	--	--	--	5	*18.5%*
780 GENERAL SYMPTOMS	71	*1.6%*	78	*2.2%*	43	*1.5%*	25	*1.1%*	22	*1.0%*
Age 18+	65	*91.6%*	72	*92.5%*	43	*100.0%*	25	*100.0%*	22	*100.0%*
Age UNSPEC.	6	*8.4%*	6	*7.5%*	--	--	--	--	--	--
All Others	434	*9.7%*	358	*10.0%*	281	*10.0%*	132	*5.8%*	103	*4.9%*

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 4-1-09. File: PDDA 2009-439 TRx by Diagnosis 4-1-09.xls

Table 3c. Most Common Indications by Age Associated With the Use of Ziprasidone in Office-Based Practice Settings, 2004-2008

Quetiapine, Olanzapine, and Ziprasidone Total	10,717	100.0%	11,603	100.0%	10,597	100.0%	9,798	100.0%	8,864	100.0%
Ziprasidone	1,853	17.3%	2,195	18.9%	1,894	17.9%	2,022	20.6%	2,043	23.0%
295 SCHIZOPHRENIC DISORDERS	875	47.2%	908	41.3%	775	40.9%	761	37.6%	817	40.0%
Age 0-6	--	--	--	--	15	1.9%	--	--	--	--
Age 13-17	12	1.4%	12	1.4%	--	--	--	--	6	0.7%
Age 18+	784	89.6%	878	96.8%	713	92.0%	743	97.7%	805	98.6%
Age UNSPEC.	79	9.0%	17	1.9%	47	6.0%	18	2.3%	5	0.7%
296 AFFECTIVE PSYCHOSES	549	29.6%	746	34.0%	717	37.9%	824	40.8%	708	34.6%
Age 7-12	5	1.0%	11	1.4%	19	2.6%	13	1.6%	9	1.3%
Age 13-17	7	1.3%	11	1.5%	30	4.1%	16	2.0%	9	1.3%
Age 18+	514	93.7%	715	95.8%	653	91.0%	732	88.8%	683	96.4%
Age UNSPEC.	22	4.1%	9	1.3%	16	2.3%	63	7.6%	7	1.0%
298 OTH NONORGANIC PSYCHOSES	89	4.8%	142	6.5%	92	4.9%	134	6.6%	171	8.4%
Age 13-17	6	6.3%	--	--	--	--	--	--	--	--
Age 18+	84	93.7%	130	91.6%	86	93.6%	125	93.4%	171	100.0%
Age UNSPEC.	--	--	12	8.4%	6	6.4%	9	6.6%	--	--
311 DEPRESSIVE DISORDER NEC	33	1.8%	60	2.7%	59	3.1%	34	1.7%	74	3.6%
Age 13-17	3	8.2%	--	--	--	--	--	--	--	--
Age 18+	30	91.8%	60	100.0%	59	100.0%	34	100.0%	74	100.0%
297 PARANOID STATES	6	0.3%	28	1.3%	31	1.6%	27	1.3%	39	1.9%
Age 18+	6	100.0%	28	100.0%	31	100.0%	27	100.0%	39	100.0%
300 NEUROTIC DISORDERS	105	5.7%	87	4.0%	30	1.6%	54	2.7%	36	1.8%
Age 7-12	--	--	--	--	6	19.6%	--	--	5	14.2%
Age 18+	105	100.0%	87	100.0%	24	80.4%	44	81.1%	31	85.8%
Age UNSPEC.	--	--	--	--	--	--	10	18.9%	--	--
299 PSYCHOSES OF CHILDHOOD	18	1.0%	15	0.7%	12	0.6%	--	--	27	1.3%
Age 7-12	--	--	--	--	6	49.9%	--	--	8	32.0%
Age 18+	18	100.0%	15	100.0%	6	50.1%	--	--	18	68.0%
307 SPECIAL SYMPTOM NEC	6	0.3%	18	0.8%	14	0.8%	13	0.6%	21	1.0%
Age 18+	6	100.0%	18	100.0%	14	100.0%	13	100.0%	21	100.0%
All Others	172	9.3%	192	8.7%	163	8.6%	175	8.6%	150	7.4%

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 4-1-09. File: PDDA 2009-439 TRx by Diagnosis 4-1-09.xls

Table 4. Estimated Number of Prescriptions Dispensed for Selected Antipsychotic Agents by Top 10 Physician Specialty, 2004-2008

	2004		2005		2006		2007		2008	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET	**14,554,272**	***100.0%***	**14,792,961**	***100.0%***	**15,790,005**	***100.0%***	**17,325,222**	***100.0%***	**18,245,005**	***100.0%***
quetiapine fumarate	7,172,316	*49.3%*	8,419,626	*56.9%*	9,566,473	*60.6%*	11,035,993	*63.7%*	11,872,829	*65.1%*
PSYCH	3,638,325	*50.7%*	4,232,063	*50.3%*	5,096,975	*53.3%*	5,702,603	*51.7%*	6,151,364	*51.8%*
UNSPEC	1,569,428	*21.9%*	1,555,090	*18.5%*	898,131	*9.4%*	959,047	*8.7%*	748,666	*6.3%*
GP/FM/DO	554,429	*7.7%*	812,752	*9.7%*	1,199,044	*12.5%*	1,522,391	*13.8%*	1,710,422	*14.4%*
IM	397,015	*5.5%*	561,404	*6.7%*	772,534	*8.1%*	951,115	*8.6%*	1,085,626	*9.1%*
NP	338,657	*4.7%*	426,521	*5.1%*	576,970	*6.0%*	722,685	*6.5%*	909,367	*7.7%*
NEURO	207,970	*2.9%*	242,937	*2.9%*	273,145	*2.9%*	298,535	*2.7%*	310,209	*2.6%*
HOSP	123,723	*1.7%*	139,644	*1.7%*	177,166	*1.9%*	179,702	*1.6%*	156,937	*1.3%*
PED	54,011	*0.8%*	73,787	*0.9%*	87,716	*0.9%*	103,213	*0.9%*	120,385	*1.0%*
OTHER	50,499	*0.7%*	62,187	*0.7%*	75,950	*0.8%*	102,067	*0.9%*	113,777	*1.0%*
PA	41,850	*0.6%*	59,262	*0.7%*	90,632	*0.9%*	126,883	*1.1%*	171,298	*1.4%*
All Others	196,409	*2.7%*	253,979	*3.0%*	318,210	*3.3%*	367,752	*3.3%*	394,778	*3.3%*
olanzapine	6,026,937	*41.4%*	4,741,112	*32.0%*	4,260,162	*27.0%*	4,059,436	*23.4%*	4,049,571	*22.2%*
PSYCH	2,574,494	*42.7%*	2,111,616	*44.5%*	2,221,388	*52.1%*	2,136,819	*52.6%*	2,224,289	*54.9%*
UNSPEC	1,401,593	*23.3%*	970,252	*20.5%*	388,831	*9.1%*	354,752	*8.7%*	248,939	*6.1%*
GP/FM/DO	810,599	*13.4%*	647,471	*13.7%*	644,872	*15.1%*	599,363	*14.8%*	578,796	*14.3%*
IM	540,329	*9.0%*	437,382	*9.2%*	407,504	*9.6%*	369,019	*9.1%*	353,215	*8.7%*
NP	219,998	*3.7%*	194,907	*4.1%*	227,071	*5.3%*	253,806	*6.3%*	300,815	*7.4%*
HOSP	101,333	*1.7%*	77,246	*1.6%*	80,134	*1.9%*	67,404	*1.7%*	58,964	*1.5%*
NEURO	67,349	*1.1%*	54,826	*1.2%*	53,250	*1.2%*	49,916	*1.2%*	48,399	*1.2%*
PED	43,422	*0.7%*	33,776	*0.7%*	30,876	*0.7%*	29,259	*0.7%*	31,066	*0.8%*
PA	35,819	*0.6%*	32,606	*0.7%*	37,437	*0.9%*	41,290	*1.0%*	52,853	*1.3%*
OTHER	34,791	*0.6%*	25,824	*0.5%*	25,104	*0.6%*	27,734	*0.7%*	29,619	*0.7%*
All Others	197,210	*3.3%*	155,206	*3.3%*	143,695	*3.4%*	130,074	*3.2%*	122,616	*3.0%*
Ziprasidone	1,355,019	*9.3%*	1,632,223	*11.0%*	1,963,370	*12.4%*	2,229,793	*12.9%*	2,322,605	*12.7%*
PSYCH	799,095	*59.0%*	996,869	*61.1%*	1,338,492	*68.2%*	1,488,687	*66.8%*	1,572,305	*67.7%*
UNSPEC	328,452	*24.2%*	337,186	*20.7%*	191,110	*9.7%*	201,178	*9.0%*	153,471	*6.6%*
GP/FM/DO	60,332	*4.5%*	84,900	*5.2%*	127,667	*6.5%*	159,769	*7.2%*	167,223	*7.2%*
NP	52,527	*3.9%*	73,151	*4.5%*	118,901	*6.1%*	159,782	*7.2%*	196,311	*8.5%*
IM	31,321	*2.3%*	43,008	*2.6%*	59,671	*3.0%*	72,358	*3.2%*	76,542	*3.3%*
HOSP	21,221	*1.6%*	23,781	*1.5%*	31,332	*1.6%*	30,936	*1.4%*	27,302	*1.2%*
NEURO	15,286	*1.1%*	16,199	*1.0%*	18,063	*0.9%*	21,083	*0.9%*	22,093	*1.0%*
OTHER	9,351	*0.7%*	10,911	*0.7%*	13,905	*0.7%*	17,550	*0.8%*	19,161	*0.8%*
PED	7,678	*0.6%*	9,341	*0.6%*	12,996	*0.7%*	15,693	*0.7%*	17,375	*0.7%*
PA	6,963	*0.5%*	9,401	*0.6%*	15,914	*0.8%*	24,070	*1.1%*	30,108	*1.3%*
All Others	22,793	*1.7%*	27,476	*1.7%*	35,319	*1.8%*	38,687	*1.7%*	40,714	*1.8%*

Source: SDI Vector One®: National Years 2004-2008 Extracted 4-1-09 File: VONA 2009-439 TRx by Physician Specialty 4-1-09 xls

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/s/

Hina S Mehta
5/11/2009 10:16:41 AM
DRUG SAFETY OFFICE REVIEWER

Laura Governale
5/11/2009 11:09:00 AM
DRUG SAFETY OFFICE REVIEWER

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	020-639 SE5-045, SE5-046
Priority or Standard	P (pediatric)
Submit Date(s)	10/28/2008
Received Date(s)	10/28/2008
PDUFA Goal Date	4/28/09
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 ≥ $25,000 for research funding, consulting fees or honoraria. These investigators included (b) (5) (b) (5), a subinvestigator at center #015 for Study 112 and Dr. Melissa DelBello, a primary investigator at center #08 for Studies 112, 149 and 150. No patients were enrolled in Study 112 at (b) (5) center. Dr. DelBello's center enrolled and randomized 1 patient in Study 112 and 12 patients in Study 149 and enrolled 8 patients in Study 150. The number of patients enrolled and randomized into the two pivotal trials at Dr. DelBello's 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 Schizophrenia, paranoid Schizophrenia, residual Schizophrenia, undifferentiated	 6 (8.2) 53 (72.6) 0 14 (19.2)	 5 (6.8) 50 (67.6) 1 (1.4) 18 (24.3)	 5 (6.8) 52 (71.2) 0 16 (21.9)
Comorbid ADHD diagnosis n (%)	7 (9.6)	8 (10.8)	7 (9.6)
Baseline CGI-Severity Score Mean (SD) Range	 4.7 (0.77) 4 – 7	 4.6 (0.76) 3 – 6	 4.7 (0.67) 4 – 6
Baseline PANSS Total Score Mean (SD) Range	 96.2 (17.7) 46 – 135	 96.9 (15.3) 69 – 137	 96.7 (18.0) 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 Mean (SD)	 8 200 (157.5)	 6 183.3 (132.9)	 8 271.9 (167.7)
Weight (kg) Mean (SD) Range	 60.95 (19.1) 34-128	 61.73 (14.67) 36-103	 62.78 (14.35) 35-113
BMI (kg/m2) Mean (SD) Range	 21.82 (5.57) 14.5-41.3	 22.46 (4.75) 13.5-37.2	 22.67 (4.72) 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 ≥ 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 ≥ 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	73 (78.5)	72 (75.8)	68 (76.4)
Most recent episode manic, severe, without psychotic features	14 (15.1)	14 (14.7)	14 (15.7)
Most recent episode manic, severe with psychotic features	5 (5.4)	5 (5.3)	7 (7.9)
Most recent episode mixed	0	1 (1.1)	0
Most recent episode mixed, severe without psychotic features	0	2 (2.1)	0
Most recent episode mixed, severe with psychotic features	1 (1.1)	1 (1.1)	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 ≥ 15 increase	8.1% 50.7%	0 18.4%
Supine Systolic BP (mmHg)	> 121* ≥ 20 increase	14.2 15.2	5.9% 5.5%
Supine Diastolic BP (mmHg)	≥ 78* ≥ 10 increase ≥ 30 increase	16.8% 40.6% 1.5%	7.3% 24.5% 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 Quetiapine 800 Placebo	 21.8% 21.8% 23.8%	 65.5% 61.8% 69.0%	 12.7% 16.4% 7.1%
Study 149 SAS Quetiapine 400 Quetiapine 800 Placebo	 12% 7.4% 19.4%	 81.3% 77.8% 70.1%	 6.7% 14.8% 10.4%
Study 112 BAS Quetiapine 400 Quetiapine 800 Placebo	 9.1% 3.6% 9.5%	 85.5% 94.5% 85.7%	 5.5% 1.8% 4.8%
Study 149 BAS Quetiapine 400 Quetiapine 800 Placebo	 8.0% 6.2% 9.0%	 86.7% 87.7% 86.6%	 5.3% 6.2% 4.5%
Study 112 AIMS Quetiapine 400 Quetiapine 800 Placebo	 7.3% 18.2% 9.5%	 85.5% 80.0% 88.1%	 7.3% 1.8% 2.4%
Study 149 AIMS Quetiapine 400 Quetiapine 800 Placebo	 13.3% 12.3% 10.4%	 86.7% 85.2% 89.6%	 0 2.5% 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: ≥ 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 ($10^6/\mu L$)	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 ($10^3/\mu L$)	88	-8.3523	39.08289	85	6.5176	41.95962	81	0.1728	47.08338
Total WBC count ($10^3/\mu L$)	88	-0.2727	1.86318	85	-0.1224	1.51715	81	-0.0444	1.94885
Basophils ($10^3/\mu L$)	88	-0.0003	0.02996	83	0.0014	0.02405	80	0.0039	0.02844
Eosinophils ($10^3/\mu L$)	88	0.0269	0.16036	83	0.0370	0.11892	80	0.0151	0.09917
Lymphocytes ($10^3/\mu L$)	88	-0.1931	0.51573	83	-0.1683	0.52391	80	0.0469	0.44298
Monocytes ($10^3/\mu L$)	88	0.0194	0.15260	83	0.0101	0.16217	80	0.0000	0.15929
Neutrophils ($10^3/\mu L$)	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 ($10^6/\mu L$)	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 ($10^3/\mu L$)	188	-3.8298	36.2726	159	5.5836	52.3841	347	0.4836	44.5672
Total WBC ($10^3/\mu L$)	188	-0.0441	1.4754	163	-0.0471	2.2804	351	-0.0455	1.8894
Basophils ($10^3/\mu L$)	186	-0.0034	0.0254	161	0.0043	0.0243	347	0.0002	0.0252
Eosinophils ($10^3/\mu L$)	186	-0.0446	0.1839	159	-0.0487	0.2140	345	-0.0465	0.1981
Lymphocytes ($10^3/\mu L$)	186	-0.0054	0.4574	161	0.0761	0.4993	347	0.0324	0.4784
Monocytes ($10^3/\mu L$)	186	-0.0267	0.1473	161	-0.0176	0.1786	347	-0.0225	0.1624
Neutrophils ($10^3/\mu L$)	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 <u>standing</u> 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[i] 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 $<1.0 \times 10^9$/L, the test was repeated within 24 hours. If it remained $<1.0 \times 10^9$/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 < 1.0×10^9/L, the test was repeated within 24 hours. If the value remained < 1.0×10^9/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[n]	√		√	√	√	√	√	√	√	√	√
Clinical Global Assessment Scale (CGAS)	√										√
Caregiver Strain Questionnaire (CGSQ)[o]	√										√
Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS)	√		√	√	√	√	√	√	√	√	√
Children's Depression Rating Scale – Revised (CDRS-R)[a]	√		√	√	√	√	√	√	√	√	√
Adverse events recording	√		√	√	√	√	√	√	√	√	√
Prior and concomitant medication recording	√		√	√	√	√	√	√	√	√	√
Study drug dispensing		√[q]	√	√	√	√	√	√	√	√	
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.

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-639 / S-045, S-046
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor submitted two short-term studies to seek claims for the efficacy and safety of quetiapine in the treatment of children and adolescent Bipolar I mania and adolescent schizophrenia. Efficacy in Bipolar I mania was demonstrated by the change from baseline to Week 3 in the Young Mania Rating Scale (YMRS) total score. Efficacy in schizophrenia was demonstrated by the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.
In both studies, the point estimate of the high dose was observed to be greater than the point estimate of the low dose; however, the difference between the high dose and the low dose was not statistically significant.

1.2 Brief Overview of Clinical Studies

Study D1441C00112 was a 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Quetiapine (400 mg/day and 800 mg/day) were investigated in adolescent schizophrenic patients aged between 13 and 17 years. The randomized sample consisted of 222 patients. The primary endpoint was the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.

Study D1441C00149 was a 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Bipolar I mania patients between the age of 10 and 17 years enrolled in the study. Two hundreds and eighty-four (284) patients were randomized to either quetiapine 400 mg/day, quetiapine 600 mg/day, or placebo in thirty-four United States centers. The primary endpoint was the change from baseline to Week 3 in the Young Mania Rating Scales (YMRS).

Subjects from studies D1441C00112 and D1441C00149 had an option to participate in an open-label, safety and tolerability extension study D1441C00150. Study D1441C00150 is not a subject of this review.

1.3 Statistical Issues and Findings

Both studies were positive on the primary endpoints. In the Bipolar I mania study, the effects appeared robust for both high dose and low dose. In the schizophrenia study, the effect for low dose appeared weaker and less robust than the high dose. However, in both studies, the difference between the low dose and the high dose was not statistically significant.

2. INTRODUCTION

2.1 Overview

This review provides a statistical evaluation of quetiapine as a treatment of adolescent schizophrenia and pediatric and adolescent Bipolar I mania.

According to the sponsor, schizophrenia is a neurodevelopmental disorder that affects many aspects of patient's life. Estimates of the lifetime prevalence of schizophrenia range from 0.5% to 1.5%. While onset of schizophrenia before the age of 13 years is rare, the incidence increases steadily during the adolescent years. Adolescents with schizophrenia have significant impairment, including deficits in cognition, affect, and social functioning.

According to the sponsor, Bipolar Disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive. Approximately 20% to 40% of adults with Bipolar Disorder report onset during childhood. The estimated prevalence among children and adolescents aged 9 to 17 years is 1.2%. Children and adolescents with bipolar mania have significant social impairment leading to conflict within the family, repeated hospitalization, and increased economic burden on the family. Adolescents with Bipolar Disorder have an increased risk of substance-abuse disorders.

Quetiapine (immediate release) was approved for the treatment of adult schizophrenia in 1997 and adult bipolar mania in 2004. The extended release formulation of quetiapine (quetiapine XR) was approved for the treatment of adult schizophrenia in 2007 and adult bipolar mania in 2008. In February 2003, The Food and Drug Administration (FDA) issued a Written Request (WR) asking AstraZeneca to conduct randomized, double-blind, parallel-group, placebo-controlled efficacy studies in schizophrenic patients aged 13 to 17 years and in Bipolar Disorder patients aged 10 to 17 years. Amendments to the WR were issued in May 2004 and February 2005. This submission contains two studies (one schizophrenia and one Bipolar I mania) to fulfill the Written Requests.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:
\\Cdsesub1\evsprod\NDA020639\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study D1448C00112

3.1.1.1 Objectives

Primary: The primary objective of this study was to compare the efficacy of 2 doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in the

treatment of schizophrenia in adolescent patients as assessed by the change from baseline to Day 42 in the PANSS total score.

3.1.1.2 Study Design

This was a 6-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in schizophrenic patients aged 13 to 17 years who were either hospitalized or were outpatients. The study consisted of three periods: a screening and washout period of up to 28 days; a randomized, double-blind treatment period of 42 days; and an optional entrance into a 6-month, open-label study of the safety and tolerability of quetiapine. Subjects were titrated to their assigned doses based on the schedule in Table 1.

Table 1. Study D1448C00112: 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.
(Source: d1448c00112 Study Report; Table 5, page 49)

Patients had to have a PANSS total score of at least 60 at screening and baseline; a score of 4 or greater on at least 1 of the following items: delusions, conceptual disorganization, or hallucinations; and a Diagnostic and Statistical Manual of Mental Disorder, 4th edition (DSM-IV) diagnosis of schizophrenia. The diagnosis was confirmed by the Schedule of Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (KSADS-PL).

The study was planned for 66 patients per arm to provide 85% power to detect a difference of 15 points change from baseline in the PANSS total score.

3.1.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from baseline to Day 42 in the PANSS total score. The primary analysis was a mixed effect model for repeated measures (MMRM) with baseline PANSS total score as a covariate, treatment, region, visit, and visit-by-treatment interaction. All effects were considered fixed. An unstructured covariance matrix was used. The Simes-Hommel's approach was used to control the type I error rate. The procedure ordered the p-values obtained from the pair-wise comparison as follows: $P(1) < P(2)$. If $P(2) < 0.05$, then reject null hypotheses associated with P(2) and P(1). Otherwise, if $P(1) < 0.025$, then reject the null hypothesis associated with P(1).

Sensitivity analyses on the primary efficacy variable included an ANCOVA model with missing data imputed by the Last Observation Carried Forward (LOCF) method, and an analysis on the per-protocol sample.

3.1.1.4 Efficacy Results

3.1.1.4.1 Study Population

The randomized sample consisted of 222 subjects. One hundred and sixty-four subjects (74%) completed the study. The main reasons for dropping out were adverse events, study-specific discontinuation criteria, and patients not willing to continue. Quetiapine groups had higher completion rates than placebo (76.7% and 82.4% compared to 62.7%). There were more subjects dropping out due to adverse events in quetiapine groups than in placebo arm.

Table 2. Study D1448C00112: Disposition of patients

	Placebo (N = 75)	QTP 400mg (N = 73)	QTP 800mg (N = 74)	Total (N = 222)
Discontinued study n (%)	**28 (37.3)**	**17 (23.3)**	**13 (17.6)**	**58 (26.1)**
Adverse event	2 (7.1)	5 (29.5)	7 (53.9)	14 (24.1)
Development of study-specific discontinuation criteria	15 (53.6)	6 (35.3)	2 (15.4)	23 (39.7)
Patient not willing to continue	8 (28.6)	3 (17.7)	3 (23.1)	14 (24.1)
Lost to follow-up	2 (7.1)			2 (3.5)
Other	1 (3.6)	3 (17.7)	1 (7.7)	5 (8.6)
Completed 6-week randomized treatment period	**47 (62.7)**	**56 (76.7)**	**61 (82.4)**	**164 (73.9)**

(Source: d1448c00112 Study Report; Figure 1, page 96)

The demographic and baseline disease characteristics of the modified intent-to-treat sample are presented in Table 3. The average age was 15.4 years. There were more males than females. Sixty-one percent of the subjects were Caucasians. Orientals and Blacks accounted for about 30% of the sample. The average baseline PANSS total score was 96 and ranged from 46 to 165.5. Across three arms, the demographic and baseline disease characteristics appeared balanced.

Table 3. Study D1448C00112: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 73	QTP 400 mg N = 73	QTP 800 mg N = 74	Total N = 220
Age at entry (yr) n				
Mean (SD)	15.3 (1.4)	15.5 (1.2)	15.4 (1.3)	15.4 (1.3)
Median	16	16	16	16
Min – Max	13 – 17	13 – 17	13 – 17	13 - 17
Sex – n (%)				
Male	42 (57.5)	43 (58.9)	44 (59.5)	129 (58.6)
Female	31 (42.5)	30 (41.1)	30 (40.5)	91 (41.4)
Race – n (%)				
Black	11 (15.1)	7 (9.6)	9 (12.2)	27 (12.3)
Caucasian	46 (63.0)	45 (61.6)	44 (59.5)	135 (61.4)
Oriental	12 (16.4)	15 (20.6)	13 (17.6)	40 (18.2)
Others	4 (5.5)	6 (8.2)	8 (10.8)	18 (8.2)
Baseline BMI (kg/m^2)				
Mean (SD)	22.7 (4.7)	21.8 (5.6)	22.5 (4.7)	22.3 (5.0)
Min – Max	15.4 – 40.0	14.5 – 41.3	13.5 – 37.2	13.5 – 41.3
Baseline PANSS-total score				
N	72	73	74	219
Mean (SD)	96.2 (17.7)	96.2 (17.7)	96.9 (15.3)	96.4 (16.8)
Median	94.5	93	93	94
Min – Max	60 – 165.5	46 – 135	69 – 137	46 – 165.5

(Source: d1448c00112 Study Report; Tables 22 & 11.2.1.1.1, pages 100 & 328)

3.1.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The sponsor's primary efficacy analysis is summarized in Table 4. Using the Simes-Hommel's adjustment for multiplicity, both quetiapine 400 mg/day and quetiapine 800 mg/day were statistically significantly superior to placebo.

Table 4. Study D1448C00112: Sponsor's primary efficacy results: change from randomization to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Sample size at Week 6	43	54	55
LS Means	-19.15	-27.31	-28.44
Difference from placebo		-8.16	-9.29
(95% confidence interval)		(-16.06, -0.26)	(-16.22, -2.36)
Unadjusted p-values		0.043	0.009

(Source: d1448c00112 Study Report; Table 25, page 110)

3.1.1.4.3 Sponsor's Other Efficacy Results

Primary sensitivity analyses: Table 5 summarizes the primary efficacy variable analyzed using an ANCOVA model with missing values imputed by the LOCF method. The results corroborated with the primary findings in Table 4.

Table 5. Study D1448C00112: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (LOCF) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Sample size	73	73	74
LS Means	-18.52	-25.76	-27.23
Difference from placebo		-7.24	-8.71
(95% confidence interval)		(-14.02, -0.47)	-15.45, -1.96)
Unadjusted p-values		0.036	0.012

(Source: d1448c00112 Study Report; Table 11.2.1.2.3, page 334)
*The sample sizes in Table 5 are larger than in Table 7 at Day 07 due to three subjects who didn't have visits Day 07 and Day 14 assessments (subjects E0004102 and ID0049101 did not have assessment visits Day 07 and Day 14, subject E0340108 did not have assessment visit Day 07).

The results in Table 4 were repeated for the per-protocol (PP) sample. Both quetiapine groups showed a numerical improvement over placebo. However, the differences between each quetiapine group and placebo were smaller and were not statistically significant.

Table 6. Study D1448C00112: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (MMRM) in the PP sample

	Placebo	QTP 400mg	QTP 800mg
Sample size at Week 6	32	44	46
LS Means	-21.28	-26.77	-27.99
Difference from placebo		-5.49	-6.72
(95% confidence interval)		(-14.15, 3.16)	(-14.48, 1.05)
Unadjusted p-values		0.212	0.090

(Source: d1448c00112 Study Report; Table 11.2.1.2.2, page 333)

<u>An analysis on the primary endpoint over time (MMRM)</u>:
Table 7 summarizes the treatment effect over time based on an MMRM analysis. The treatment effects appeared to be more consistent for quetiapine 800mg/day dose group than for the quetiapine 400mg/day dose group.

Table 7. Study D1448C00112: Sponsor's efficacy analysis: change from randomization in the PANSS total score (MMRM) over time in the MITT sample

	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

(Source: d1448c00112 Study Report; Table 11.2.1.2.1, page 332)
*p-values are not adjusted for multiplicity

Change from baseline in the CGI-Severity of Illness (MMRM):
The change from baseline over time in the CGI-Severity of Illness score was analyzed via an MMRM analysis similar to the primary analysis model. The model included the baseline CGI-S score, treatment, region, visit, and visit-by-treatment interactions. The model utilized an unstructured covariance matrix. The results are summarized in Table 8. The responses did not appear to be consistent for the 400 mg/day dose and did not reach a statistically significant level at the endpoint visit (Week 6). The high dose (800 mg/day) appeared more consistently superior to placebo over time and achieved the 0.05 significant level at Week 6.

Table 8. Study D1448C00112: Sponsor's secondary analysis: change from randomization in the CGI-S score (MMRM) in the MITT sample

	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	-0.18	73	-0.32	72	-0.35	-0.13	0.226	-0.17	0.061
Day 14	72	-0.40	70	-0.56	71	-0.74	-0.17	0.220	-0.34	0.006
Day 21	65	-0.52	66	-0.81	68	-0.78	-0.30	0.065	-0.26	0.060
Day 28	57	-0.64	60	-0.96	65	-0.99	-0.32	0.084	-0.35	0.039
Day 35	51	-0.88	59	-1.10	62	-1.16	-0.22	0.250	-0.28	0.113
Day 42	43	-0.81	55	-1.15	55	-1.28	-0.34	0.104	-0.47	0.018

(Source: d1448c00112 Study Report; Table 11.2.3.2.1.3, page 410)
*p-values are not adjusted for multiplicity

3.1.1.4.4 Reviewer's Results and Comments

This reviewer confirms the findings based on the primary efficacy variable as presented in Table 4. Both doses of quetiapine were statistically significantly better than placebo.

This reviewer performed an analysis based on an ANCOVA model with dropouts imputed by the LOCF method. The model included treatment, region, and baseline PANSS total score. The results were slightly different from those presented by the sponsor in Table 5, but did not affect the outcome of the trial.

Table 9. Study D1448C00112: Reviewer's primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (LOCF) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Sample size	73	73	74
LS Means	-18.53	-26.09	-27.23
Difference from placebo		-7.55	-8.70
(95% confidence interval)		(-14.26, -0.85)	(-15.37, -2.02)
Unadjusted p-values		0.027	0.011

(Source: Reviewer's results)

Two sensitivity analyses were pre-specified. One was based on the same analysis model as the primary analysis on the per-protocol population. This analysis showed that both doses of quetiapine were numerically better than placebo.

However, the numerical differences did not reach the statistically significant level. The other sensitivity analysis was an ANCOVA model with missing data imputed by the LOCF method. This analysis corroborated with the primary findings. An analysis on the CGI-Severity of Illness score showed superiority of the quetiapine 800mg/day dose group over placebo, but not on the 400 mg/day dose group.

One subject (ID # E0262103) did not appear to have the baseline evaluation or the baseline evaluation visit was miscoded. Removing this subject did not affect the outcome of the study.

Investigator John Gilliam (Site # 10) enrolled 6 subjects. The results of the primary analysis excluding Site # 10 remained statistically significant (p-value = 0.042 for the comparison between quetiapine 400 mg/day versus placebo and p-value = 0.012 for the comparison between quetiapine 800 mg/day versus placebo).

In summary, this study demonstrated the efficacy of quetiapine 400 mg/day and 800 mg/day over placebo on the change from baseline to Week 6 in the PANSS total score. The effect appeared more robust for the 800 mg/day dose group than the 400 mg/day dose group. The 800 mg/day dose group appeared numerically more efficacious than the 400 mg/day; however, the numerical difference was small and did not appear statistically meaningful.

3.1.2 Study D1448C00149

3.1.2.1 Objectives

Primary: The primary objective of this study was to compare the efficacy of 2 doses of quetiapine (400 mg/day and 600 mg/day) with that of placebo in the treatment of Bipolar mania in children and adolescent patients with Bipolar I Disorder, as assessed by the change from baseline to Day 21 in the Young Mania Rating Scale (YMRS) total score.

3.1.2.2 Study Design

This was a 3-week, randomized, double-blind, multi-center, parallel-group, placebo-controlled study. The study was to investigate the efficacy and safety of two fixed doses of quetiapine (400 mg/day and 600 mg/day) and placebo, in divided dosing (either twice daily or three times daily, per the judgment of the investigator). The study consisted of three periods: 1) a screening and washout period that lasted up to 28 days; 2) a randomized, double-blind period of 21 days; 3) an optional entrance into a 6-month, open-label study. Subjects were randomized in a 1:1:1 ratio to 1 of the 3 treatment groups. They could be treated as inpatient or outpatient. Patients initiated the treatment at a 50 mg/day and were titrated to their assigned dosages using the following schedule:

Table 10. Study D1448C00149: Quetiapine treatment regimens (mg/day) for administration twice daily

Dose group	Time	Study day 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.
(Source: d1448c00149 Study Report; Table 5, page 49)

Male and female patients between the age of 10 and 17 were eligible to participate in the study. Patients, diagnosed with a DSM-IV Bipolar I mania, had to have an YMRS score of ≥ 20 both at screening and at randomization to enroll. The diagnosis was confirmed by the K-SADS-PL.

The study was planned for 88 patients per arm to provide 85% power to detect a difference of 6 points change from baseline in the YMRS total score.

3.1.2.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from baseline to Day 21 in the YMRS total score. The primary analysis was a mixed model for repeated measures (MMRM). Covariates included age stratum, treatment, visit, visit-by-treatment interaction, and baseline YMRS total score. All of these effects were considered as fixed effects. An unstructured covariance pattern was used. Robust variance estimates for the fixed effects were used for testing the treatment differences. The Simes-Hommel's approach was used to control the type I error rate. The procedure ordered the p-values obtained from the pair-wise comparison as follows: $P(1) < P(2)$. If $P(2) < 0.05$ then reject null hypotheses associated with P(2) and P(1). Otherwise, if $P(1) < 0.025$, then reject the null hypothesis associated with P(1).

3.1.2.4 Efficacy Results

3.1.2.4.1 Study Population

The randomized sample consisted of 284 subjects. Seventy-eight percent of the subjects completed the study. The main reason for dropping out was adverse event. There were more adverse events in quetiapine arms than in placebo arm. There were more patients dropping out due to lack of efficacy in the placebo arm than in the quetiapine arms.

Table 11. Study D1448C00149: Disposition of Patients

	Placebo (N = 91)	QTP 400mg (N = 95)	QTP 600mg (N = 98)	Total (N = 284)
Discontinued study: n (%)	**25 (27.5)**	**19 (20.0)**	**18 (18.4)**	**62 (21.8)**
Adverse event	4 (16.0)	15 (79.0)	7 (38.9)	26 (41.9)
Development of study-specific discontinuation criteria	4 (16.0)	1 (5.3)	2 (11.1)	7 (11.3)
Patient not willing to continue	5 (20.0)	1 (5.3)	5 (27.8)	11 (17.7)
Lost to follow-up	2 (8.0)	0 (0.0)	1 (5.6)	3 (4.8)
Lack of efficacy	6 (24.0)	2 (10.5)	0 (0.0)	8 (12.9)
Other	4 (16.0)	0 (0.0)	3 (16.7)	7 (11.3)
Completed 3-week randomized treatment phase	**66 (72.5)**	**76 (80.0)**	**80 (81.6)**	**222 (78.2)**

(Source: d1448c00149 Study Report; Figure 1, page 95 and reviewer's results)

The demographic and baseline disease characteristics of the MITT sample are presented in Table 12. The average age was 13 years old. There were slightly more males than females. Caucasians accounted for about 77% of the sample and Blacks accounted for about 14% of the sample. The baseline YMRS total score was 30 on average and ranged from 12 to 48.

Table 12. Study D1448C00149: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 89	QTP 400 mg N = 93	QTP 600 mg N = 95	Total N = 277
Age at entry (yr) n				
Mean (SD)	13.31 (2.14)	13.11 (2.16)	13.15 (2.18)	13.19 (2.16)
Median	13	13	13	13
Min – Max	10 – 17	10 – 17	9 – 17	9 – 17
Sex – n (%)				
Male	54 (60.7)	47 (50.5)	55 (57.9)	156 (56.3)
Female	35 (39.3)	46 (49.5)	40 (42.1)	121 (43.7)
Race – n (%)				
Black	12 (13.5)	12 (12.9)	14 (14.7)	38 (13.7)
Caucasian	66 (74.2)	73 (78.5)	73 (76.8)	212 (76.5)
Oriental	1 (1.1)			1 (0.4)
Others	10 (11.2)	8 (8.6)	8 (8.4)	26 (9.4)
BMI at baseline (kg/m^2)				
Mean (SD)	24.14 (5.67)	23.50 (5.31)	23.38 (4.77)	23.67 (5.25)
Min – Max	14.3 – 41.1	12.2 – 38.6	16.2 – 35.2	12.2 – 41.1
*Baseline YMRS-total score**				
N	89	92	95	276
Mean (SD)	30.65 (5.89)	29.45 (5.84)	29.62 (6.35)	29.89 (6.03)
Median	30	29	29	29
Min – Max	21 – 48	12 – 44	20 – 46	12 – 48

(Source: d1448c00149 Study Report; Table 21, page 99)
* Reviewer's results

3.1.2.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary analysis model was a mixed model for repeated measures with model terms treatment, visit, treatment-by-visit interaction, baseline YMRS total score, and age stratum. Age at entry was dichotomized to two strata: 10-12 years

old and 13-17 years old. According to the statistical analysis plan, randomization numbers 3001-4500 were allocated to 10-12 years old group. Randomization numbers 4501-6000 were allocated to 13-17 years old group. If patients were randomized to a wrong stratum, the patients were analyzed as randomized. The sponsor's primary analysis is summarized in Table 13. Both doses of quetiapine were statistically significantly superior to placebo.

Table 13. Study D1448C00149: Sponsor's primary analysis: change from randomization to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	67	76	81
LS Means	-9.04	-14.25	-15.06
Difference from placebo		-5.21	-6.56
(95% confidence interval)		(-8.11, -2.31)	(-9.48, -3.65)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 24, page 111)

3.1.1.4.3 Sponsor's Other Efficacy Results

A primary sensitivity analysis (PP): The primary analysis model was repeated using the per-protocol population. The results are summarized in Table 14. This analysis corroborated with the primary analysis presented in Table 13.

Table 14. Study D1448C00149: Sponsor's sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (MMRM) in the PP sample

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	55	60	69
LS Means	-9.60	-15.50	-16.57
Difference from placebo		-5.90	-6.98
(95% confidence interval)		(-9.09, -2.72)	(-10.14, -3.81)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 11.2.1.2.2, page 368)

A primary sensitivity analysis (LOCF, MITT): An ANCOVA model with missing data imputed by the LOCF method is summarized in Table 15. This analysis also corroborated with the primary analysis presented in Table 13.

Table 15. Study D1448C00149: Sponsor's sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (LOCF) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Sample size	89	93	95
LS Means	-8.28	-13.42	-15.18
Difference from placebo		-5.15	-6.90
(95% confidence interval)		(-7.93, -2.36)	(-9.66, -4.13)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 11.2.1.2.3, page 369)

An analysis on the primary endpoint over time (MMRM): The treatment effects of quetiapine over the duration of the study are summarized in Table 16. The effects appeared consistent over the three weeks of the study. It is noted that many placebo patients did not have Visit Day 04 evaluated.

Table 16. Study D1448C00149: Sponsor's efficacy analysis: change from randomization in the YMRS total score (MMRM) over time in the MITT sample

	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - 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

(Source: d1448c00149 Study Report; Table 11.2.1.2.1, page 367)
*p-values are not adjusted for multiplicity

3.1.2.4.4 Reviewer's Results and Comments

This reviewer confirmed the results based on the primary endpoint as presented in Table 13. Quetiapine 400 mg/day and 600 mg/day were statistically superior to placebo in the change from baseline to Day 21 in the YMRS total score.

There were 5 patients who were randomized to a wrong age stratum. The primary analysis was re-analyzed using age group as defined by 10-12 years old versus 13-17 years old. Table 17 summarizes this analysis. Both doses of quetiapine were statistically significant based on this analysis.

Table 17. Study D1448C00149: Reviewer's analysis: change from randomization to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	67	76	81
LS Means	-9.03	-14.25	-15.60
Difference from placebo		-5.23	-6.57
(95% confidence interval)		(-8.13, -2.32)	(-9.49, -3.66)
Unadjusted p-values		0.001	<0.001

(Source: reviewer's results)

The reviewer's ANCOVA analysis with dropouts imputed by the LOCF method deviated slightly from the sponsor's results in Table 15. The deviations did not affect the outcome of the study.

Table 18. Study D1448C00149: Reviewer's sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (LOCF) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Sample size	89	93	95
LS Means	-8.39	-13.63	-15.16
Difference from placebo		-5.24	-6.77
(95% confidence interval)		(-8.01, -2.47)	(-9.53, -4.02)
Unadjusted p-values		<0.001	<0.001

(Source: Reviewer's results)

Investigator John Gilliam (Site # 10) randomized 26 subjects. The results of the primary analysis excluding Site # 10 remained statistically significant (p-values < 0.001 for both dose groups).

In summary, Study D1448C00149 demonstrated the efficacy of quetiapine at 400 mg/day and 600 mg/day in lowering the YMRS total score from baseline at Week 3. The 600 mg/day dose group showed a numerical greater benefit than the 400 mg/day dose group; however, the difference did not appear to be statistically meaningful.

3.2 Evaluation of Safety

Please refer to the clinical review for extensive safety evaluation and report. The following sections explore the effects of quetiapine on body weight and body mass.

3.2.1 Study D1448C00112

To explore the effects of quetiapine on body weight and body mass, this reviewer carried out two exploratory analyses. The first analysis was on the change from baseline in the body weight (in kg). The second analysis was on the change from baseline in the body mass index (BMI) (in kg/m^2). Repeated measures mixed effect models with baseline body weight or BMI, treatment, region, visit, sex, race, age at entry, and treatment-by-visit interaction as fixed factors were used. The models used unstructured covariance matrices. The results are summarized in Table 19 and Table 20. The results suggested that patients on quetiapine appeared to gain significantly more weights than patients on placebo.

Table 19. Study D1448C00112: Reviewer's exploratory analysis: change from randomization in the Body Weight (MMRM) in the Safety sample

	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	-0.22	73	0.31	72	0.33	0.53	0.014	0.55	0.012
Day 14	72	-0.11	70	1.06	71	0.63	1.17	<0.001	0.74	0.010
Day 21	65	-0.14	67	1.23	68	0.89	1.38	<0.001	1.03	0.003
Day 28	57	-0.35	61	1.40	65	1.05	1.76	<0.001	1.40	0.001
Day 35	51	-0.32	58	1.73	62	1.51	2.05	<0.001	1.83	<0.001
Day 42	44	-0.33	56	1.96	55	1.53	2.30	<0.001	1.86	0.001

(Source: Reviewer's results)
*p-values are not adjusted for multiplicity

Table 20. Study D1448C00112: Reviewer's exploratory analysis: change from randomization in the BMI (MMRM) in the Safety sample

	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	-0.06	73	0.13	72	0.14	0.19	0.014	0.20	0.017
Day 14	72	-0.03	70	0.38	71	0.22	0.41	<0.001	0.25	0.023
Day 21	65	-0.04	67	0.43	68	0.30	0.47	<0.001	0.34	0.010
Day 28	57	-0.13	61	0.48	65	0.33	0.60	<0.001	0.46	0.003
Day 35	51	-0.11	58	0.56	62	0.47	0.67	<0.001	0.57	0.001
Day 42	44	-0.15	56	0.63	55	0.45	0.78	<0.001	0.61	0.002

(Source: Reviewer's results)
*p-values are not adjusted for multiplicity

3.2.2 Study D1448C00149

To explore the effects of quetiapine on body weight and body mass, this reviewer carried out two exploratory analyses. The first analysis was on the change from baseline in the body weight (in kg). The second analysis was on the change from baseline in the body mass index (BMI) (in kg/m^2). The models utilized were similar to the primary analysis model with baseline body weight or BMI as fixed covariates, age group, sex, race, treatment, visit, and treatment-by-visit interaction as fixed factors. The models used unstructured covariance matrices. The results are summarized in Table 21 and Table 22. The results suggested that patients on quetiapine appeared to gain significantly more weights than patients on placebo.

Table 21. Study D1448C00149: Reviewer's exploratory analysis: change from randomization in the Body Weight (MMRM) in the Safety sample

	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - Pbo	
Visit	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**Diff**	**P-value***	**Diff**	**P-value***
Day 04	64	0.03	80	0.58	73	0.35	0.55	0.009	0.32	0.060
Day 07	85	0.16	88	0.86	90	0.88	0.69	<0.001	0.71	0.001
Day 14	73	0.13	78	1.31	82	1.29	1.18	<0.001	1.16	<0.001
Day 21	68	0.11	76	1.67	81	1.54	1.56	<0.001	1.43	<0.001

(Source: Reviewer's results)
*p-values are not adjusted for multiplicity

Table 22. Study D1448C00149: Reviewer's exploratory analysis: change from randomization in the BMI (MMRM) in the Safety sample

	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - Pbo	
Visit	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**Diff**	**P-value***	**Diff**	**P-value***
Day 04	64	0.03	80	0.24	73	0.14	0.21	0.012	0.11	0.128
Day 07	85	0.06	88	0.32	90	0.26	0.26	0.001	0.20	0.020
Day 14	73	0.01	78	0.48	82	0.43	0.47	<0.001	0.42	<0.001
Day 21	68	0.00	76	0.56	81	0.48	0.56	<0.001	0.48	<0.001

(Source: Reviewer's results)
*p-values are not adjusted for multiplicity

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study D1448C00112

4.1.1.1 Gender

The primary analysis stratified by gender is presented in Table 23. Quetiapine appeared to improve the PANSS total score for both males and females.

Table 23. Study D1448C00112: Sponsor's primary efficacy results by gender: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Females			
Sample size at Week 6	15	19	19
LS Means	-16.14	-26.05	-25.92
Difference from placebo		-9.91	-9.78
(95% confidence interval)		(-23.03, 3.20)	(-20.75, 1.19)
Males			
Sample size at Week 6	28	35	36
LS Means	-20.78	-27.99	-29.47
Difference from placebo		-7.21	-8.68
(95% confidence interval)		(-17.34, 2.92)	(-17.82, 0.46)

(Source: Reviewer's results)

4.1.1.2 Race

Due to small sample sizes, race was dichotomized to Caucasian versus other races. Quetiapine showed numerical improvements in the PANSS total score in both race groups.

Table 24. Study D1448C00112: Reviewer's primary efficacy results by race: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Caucasians			
Sample size at Week 6	24	33	31
LS Means	-16.79	-23.24	-24.79
Difference from placebo		-6.45	-8.01
(95% confidence interval)		(-16.94, 4.03)	(-17.45, 1.43)
Others			
Sample size at Week 6	19	21	24
LS Means	-25.04	-35.33	-34.99
Difference from placebo		-10.29	-9.95
(95% confidence interval)		(-22.50, 1.92)	(-20.54, 0.65)

(Source: Reviewer's results)

4.1.1.3 Age

Age at entry was dichotomized to ≤ 15 versus > 15 years old. The primary analysis stratified by age at entry is summarized in Table 25. Quetiapine appeared to be more efficacious for subjects under the age of 15 years. For subjects > 15 years old, the relative efficacy of quetiapine versus placebo appeared diminished by the large placebo effect.

Table 25. Study D1448C00112: Reviewer's primary efficacy results by age: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Age at entry ≤ 15			
Sample size at Week 6	20	23	23
LS Means	-12.18	-28.43	-28.71
Difference from placebo		-16.26	-16.53
(95% confidence interval)		(-28.27, -4.24)	(-26.19, -6.87)
Age at entry > 15			
Sample size at Week 6	23	31	32
LS Means	-25.72	-25.76	-27.91
Difference from placebo		-0.04	-2.18
(95% confidence interval)		(-10.40, 10.32)	(-12.07, 7.70)

(Source: Reviewer's results)

4.1.2 Study D1448C00149

4.1.2.1 Gender

Table 26 summarizes the primary analysis stratified by gender. Treatment benefits were observed in both males and females.

Table 26. Study D1448C00149: Sponsor's primary efficacy results by gender: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Females			
Sample size at Week 3	26	36	31
LS Means	-9.52	-15.27	-14.67
Difference from placebo		-5.75	-5.15
(95% confidence interval)		(-9.84, -1.67)	(-9.53, -0.76)
Males			
Sample size at Week 3	41	40	50
LS Means	-8.64	-13.46	-16.23
Difference from placebo		-4.82	-7.59
(95% confidence interval)		(-8.90, -0.74)	(-11.54, -3.65)

(Source: Reviewer's results)

4.1.2.2 Race

Table 27 summarizes the primary analysis by race. Due to small sample sizes, race was dichotomized into Caucasians versus other races. Treatment effects were observed in both groups.

Table 27. Study D1448C00149: Sponsor's primary efficacy results by race: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Caucasians			
Sample size at Week 3	50	60	60
LS Means	-8.61	-13.72	-15.95
Difference from placebo		-5.10	-7.34
(95% confidence interval)		(-8.42, -1.79)	(-10.74, -3.94)
Others			
Sample size at Week 3	17	16	21
LS Means	-10.82	-16.45	-14.66
Difference from placebo		-5.63	-3.84
(95% confidence interval)		(-11.48, 0.22)	(-9.38, 1.69)

(Source: Reviewer's results)

4.1.2.3 Age

Table 28 summarizes the primary analysis stratified by age groups. Treatment effects were observed in both quetiapine dose groups.

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)

(Source: Reviewer's results)

4.2 Other Subgroups

4.2.1 Study D1448C00112

4.2.1.1 U.S.A. versus non-U.S.A.

The primary efficacy analysis stratified by U.S.A. versus non-U.S.A. is presented in Table 29. Quetiapine appeared to show greater improvement among U.S.A patients than non-U.S.A. patients.

Table 29. Study D1448C00112: Sponsor's primary efficacy results by region: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
U.S.A.			
Sample size at Week 6	14	15	15
LS Means	-20.69	-38.50	-38.45
Difference from placebo		-17.81	-17.75
(95% confidence interval)		(-33.83, -1.78)	(-32.30, -3.20)
Non-U.S.A.			
Sample size at Week 6	29	39	40
LS Means	-19.33	-22.71	-23.89
Difference from placebo		-3.38	-4.56
(95% confidence interval)		(-11.91, 5.15)	(-11.81, 2.70)

(Source: Reviewer's results)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Both studies were positive on the primary endpoints. In the Bipolar I mania study, the effects appeared robust for both high dose and low dose. In the schizophrenia study, the effect for low dose appeared weaker and less robust than the high dose. However, in both studies, the difference between the low dose and the high dose was not statistically significant.

5.2 Conclusions and Recommendations

The sponsor submitted two short-term studies to seek claims for the efficacy and safety of quetiapine in the treatment of children and adolescent Bipolar I mania and adolescent schizophrenia. Efficacy in Bipolar I mania was demonstrated by the change from baseline to Week 3 in the Young Mania Rating Scale (YMRS) total score. Efficacy in schizophrenia was demonstrated by the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.

In both studies, the point estimate of the high dose was observed to be greater than the point estimate of the low dose; however, the difference between the high dose and the low dose was not statistically significant.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 7, 2009
To:	Thomas Laughren, M.D., Director Division of Psychiatry Products (DPP) Office of New Drugs (OND)
Through:	Mark Avigan, M.D., C.M., Director Division of Pharmacovigilance (DPV I)
From:	Ida-Lina Diak, Pharm.D., Safety Evaluator Acting Team Leader Division of Pharmacovigilance (DPV I)
Subject:	Pediatric overview
Drug Name(s):	Seroquel (quetiapine)
Application Type/Number:	NDA # 20639
Applicant/sponsor:	Astra Zeneca
OSE RCM #:	2009-439

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EXECUTIVE SUMMARY

The Division of Pharmacovigilance (DPV) conducted this review in response to a request from the Division of Psychiatry Products (DPP) to analyze the Adverse Event Reporting System (AERS) pediatric postmarketing data for quetiapine in patients aged 0-17 years of age since approval September 26, 1997. The focus of the review was all pediatric cases of death, metabolic effects (blood triglycerides increased, diabetes mellitus, hyperglycaemia, and weight increased), QT prolongation, and Torsade de pointes. The purpose of this review is to present post marketing pediatric adverse event data in an effort to assist the advisory committee in their decision of determining if quetiapine use in pediatric patients is acceptably safe.

The AERS database searched retrieved 890 post-marketing pediatric reports (crude count) associated with the use of quetiapine since approval through April 3, 2009 (see Appendix A for a graphical representation). Overall, the primary focus of this review included pediatric cases of death (39), metabolic-related events (58), and QT-related events (11). The adverse events that led up to the 39 pediatric deaths occurred in much the same manner as in adult patients. Suicide/overdose situations were associated with the highest number of deaths (17). Of the 58 metabolic-related cases, 43 reported dysglycemic events (diabetes mellitus, diabetic ketoacidosis, hyperglycemia, and hyperosmolar coma) either alone or in conjunction with another metabolic related event; and the remaining 15 cases reported weight increased alone (13), and blood triglycerides increased (2). Thirty-five were confounded by the use of concomitant medications also labeled for an association with metabolic-related events, which included 24 cases reporting the concomitant use of at least one atypical antipsychotic. Eleven cases reported QT prolongation and of these, four cases reported intentional overdoses, with one ultimately resulting in death. No cases of Torsade de pointes were reported.

The safety profile of the pediatric population is very similar compared to that of the adult population, and the adverse events occurred in much the same manner as well. No new safety signals emerged as part of this review; however, it has made us aware that the pediatric population is not spared from the adverse events caused by quetiapine therapy. The potential risks of quetiapine therapy should be weighed against the potential benefit when choosing to initiate therapy.

The current quetiapine label extensively describes the known pediatric safety data and concerns associated with the drug; therefore, at this time we do not recommend any further labeling enhancements specific to the pediatric population.

1 BACKGROUND

1.1 INTRODUCTION

DPV conducted this review in response to a request from DPP to analyze the AERS pediatric postmarketing data for quetiapine in patients aged 0-17 years of age since market approval. In addition, we were asked to focus on deaths, metabolic effects (blood triglycerides increased, diabetes mellitus, hyperglycaemia, and weight increased), QT prolongation, and Torsade de pointes. The purpose of this review is to present post marketing pediatric adverse event data in an effort to assist the advisory committee in their decision of determining if quetiapine use in pediatric patients is acceptably safe.

1.2 REGULATORY HISTORY

Quetiapine (SEROQUEL®) received FDA approval on September 26, 1997 for the treatment of the manifestations of psychotic disorders. Quetiapine is a psychotropic agent belonging to a chemical class,

the dibenzothiazepine derivatives, and is an antagonist at multiple neurotransmitter receptors in the brain including serotonergic, dopaminergic, histaminic, and adrenergic receptors.[1]

Table 1. Quetiapine approval history

Date	Indication
September 26, 1997	Approved for the treatment of the manifestations of psychotic disorders
January 12, 2004	As monotherapy in the treatment of acute manic episodes associated with Bipolar I disorder As adjunctive therapy with mood stabilizers (lithium or divalproex) in the treatment of acute manic episodes associated with Bipolar I disorder
October 20, 2006	The treatment of major depressive episodes associated with bipolar disorder
May 13, 2008	Maintenance treatment for Bipolar I Disorder, as adjunctive therapy to lithium or divalproex

Relevant previous OSE postmarketing reviews include:

- August 9, 2000. A review of *sudden death, Torsade de pointes, and other ventricular dysrhythmias* reported in association with thioridazine and other antipsychotics. The review concluded that among a selection of recently marketed atypical antipsychotics, clozapine appeared to stand apart in both the absolute numbers of cases and reporting rates in analyses using all cases and broad case definitions.[2]
- June 25, 2003. A literature review concerning the issue of *diabetes mellitus/hyperglycemia* associated with the atypical antipsychotic drugs. The findings of the review suggested that a risk management program be put in place for these drugs. [3]
- October 4, 2005. A class review of *galactorrhea* with atypical antipsychotic drugs in pediatric patients. The review supported further analysis of hyperprolactinemia and galactorrhea with atypical antipsychotics in order to update risperidone labeling to reflect the increased numbers of reports of hyperprolactinemia and galactorrhea associated with risperidone relative to other atypical antipsychotic drugs.[4]
- October 4, 2005. A class review of *pituitary tumors* with atypical antipsychotic drugs in pediatric patients. The review recommended further investigation, perhaps including reanalysis of the risperidone NDA, in order to update the risperidone label to include increased hyperprolactinemia compared to other atypical antipsychotic agents.[5]
- May 25, 2006. A review of cases of *myocarditis and cardiomyopathy* associated with the use of olanzapine and quetiapine. The review recommended that both cardiomyopathy and myocarditis be added to the Adverse Events section of both olanzapine and quetiapine labels as well as continued monitoring of cardiac adverse events associated with the two drug products. In

[1] Seroquel Product Label, January 2009, AstraZeneca Pharmaceuticals, http://www1.astrazeneca-us.com/pi/Seroquel.pdf.
[2] Brinker A. Review concerning sudden death, Torsade de pointes, and other ventricular dysrhythmias reported in association with thioridazine and other antipsychotics.
[3] Mosholder A. Literature review concerning the issue of diabetes mellitus/hyperglycemia associated with the atypical antipsychotic drugs. FDA Postmarketing Safety Review. June 25, 2003.
[4] Phelan K. A class review of galactorrhea with atypical antipsychotic drugs in pediatric patients. FDA Postmarketing Safety Review. October 4, 2005.
[5] Phelan K. A class review of pituitary tumors with atypical antipsychotic drugs. FDA Postmarketing Safety Review. October 4, 2005.

particular, pediatric cases and fatal cases with hypertrophic cardiomyopathy associated with these two drug products should undergo heightened monitoring.[6]

- January 25, 2008. A class review of selected antipsychotics and the occurrence of *agranulocytosis*. The review recommended the addition of agranulocytosis to the Precautions section of the olanzapine and risperidone label as well as elevating agranulocytosis to the Precautions section for chlorpromazine and haloperidol.[7]
- April 29, 2008- This review focused on cases of death in children 16 years old and younger. Quetiapine was associated with 25 death cases. This review concluded that the current safety profile in the labeling would not need revising to include any additional pediatric population specific adverse events.[8]

1.3 PEDIATRIC PRODUCT LABELING[1]

The current quetiapine label contains the following language regarding the pediatric population:

Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 years; however, pediatric data is extensively presented throughout the label in several sections. A complete listing of the pediatric labeling can be found in Appendix B.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

This section describes the AERS searches performed as well as the case series selection.

2.2 AERS SELECTION OF CASES

We conducted four separate searches as follows:

From Approval (September 26, 1997) to April 3, 2009 – Reports of pediatric patients aged 0-17 years

- All reports
- All reports coded with the outcome of DEATH
- All serious reports using the Preferred Terms (PTs) of blood triglycerides increased, diabetes mellitus, hyperglycaemia, and weight increased
- All serious reports using the narrow SMQ of Torsade de pointes/QT prolongation, which includes the PTs of electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, long QT syndrome, long QT syndrome congenital, Torsade de pointes, and ventricular tachycardia.

The search of all pediatric reports retrieved 890 reports (crude counts) and the report characteristics are summarized in table 2. Additionally, these reports are graphically represented based on the system organ class (SOC) associated with the adverse event as well as by the preferred term (PT) that have a reporting proportion of $\geq$ 2% (see Appendix A). The search of all pediatric reports coded with the outcome of death retrieved 56 reports. Of these 56 reports, 15 were duplicates; one report mistakenly reported quetiapine use and another report stated that the patient had discontinued quetiapine seven months prior to

[6] LaGrenade L. A review of cases of Myocarditis and Cardiomyopathy associated with the use of olanzapine and quetiapine. FDA Postmarketing Safety Review. May 25, 2006.
[7] Diak I. A mixed class review of antipsychotics and the occurrence of agranulocytosis. FDA Postmarketing Safety Review. January 25, 2008.
[8] Diak I. Postmarketing case coded with death in children 16 years old and younger. FDA Postmarketing Safety Review. April 29, 2008.

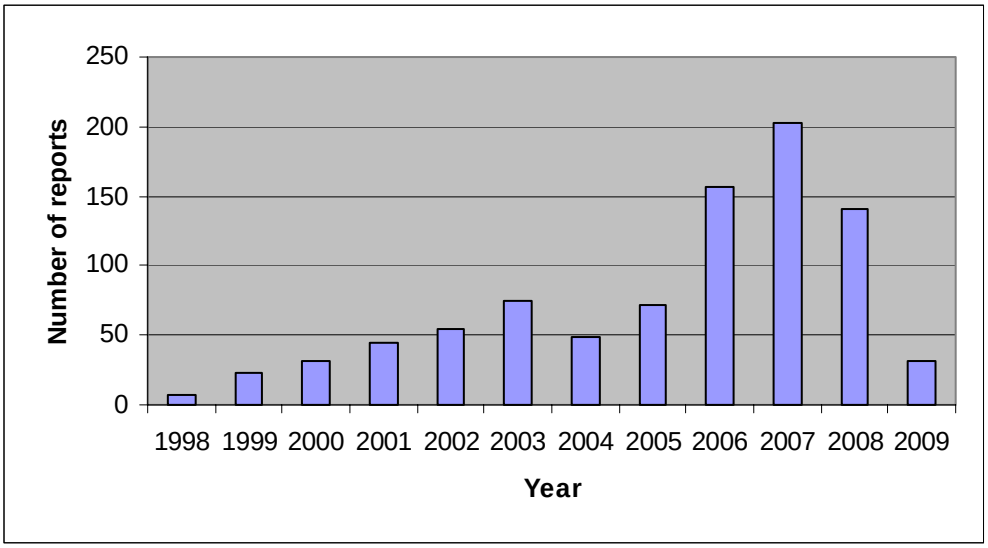
his death, therefore, we included 39 unique cases of death. The search of all serious reports using the PTs of blood triglycerides increased, diabetes mellitus, hyperglycaemia, and weight increased retrieved 73 reports, of which two were duplicates and 13 were not included for further discussion, therefore, we included 58 unique cases. The reasons for not including 13 cases for further discussion include, the adverse event occurred prior to the initiation of therapy with quetiapine (6), the adverse event occurred after the discontinuation (six months to one year and 4 months) of quetiapine (3), miscoded as a pediatric patient (3), the case outcome was downgraded to be non-serious (1).

The search of the narrow SMQ Torsade de pointes/QT prolongation retrieved 11 unique cases, which were all included for discussion in this review.

3 RESULTS

Table 2 : Characteristics of serious and non-serious pediatric reports associated with quetiapine reported from approval through April 3, 2009 n=890 (Crude counts)	
Gender [n=857]	Male: 487 Female: 370
Age [n=855]	0- <1 month (6) 1 month - <2 yrs (9) 2-5 yrs (27) 6-11 yrs (242) 12-17 yrs (569) Mean = 12.5 years, Median = 14 years, Range = 0 to 17 years
Origin [n=883]	US 719, Foreign 164
FDA reported date	1998 (7) 1999 (23) 2000 (31) 2001 (45) 2002 (55) 2003 (75) 2004 (49) 2005 (72) 2006 (157) 2007 (203) 2008 (141) 2009 (32)
Coded Outcomes, non-overlapping [n=740]	Death (56), Life-Threatening (55), Hospitalization (246), Required Intervention (110), Congenital Anomaly (10), Disability (17), and Other Serious (246)

Figure 1: Reporting trend for pediatric reports from approval (September 26, 1997) to April 3, 2009:



3.1 ADVERSE EVENTS CASES

Table 3. Summary of characteristics of death cases (n=39)

Origin	US (31), Foreign (8)
Gender	Male (19), Female (18), Unknown (2)
Age	Range 2 days to 17 years, Median 15 years
Daily Dose (n=20)	Range 25 to 800 mg , Median 200 mg
Adverse events (n=32)	Suicide (12), Overdose*(5), Diabetic Ketoacidosis (DKA) + Diabetes Mellitus (DM) (2), Pancreatitis (2), Neuroleptic Malignant Syndrome (2), Exposure during pregnancy/via breast milk (2), Cardiac arrest (1), Choking on food (1), Forced quetiapine administration and smothering by mother (1), Hyperosmolar coma (1), Hyponatremia (1), Multi-system organ failure + cardiac arrest (1), Respiratory failure + septicemia (1)
Time to death after initiation of quetiapine (n=19)	Range 1 to 382 days, Median 15 days
Concomitant medications labeled for an association with the cause of death (n=6)**	*Cardiac arrhythmia*- haloperidol, paroxetine, propranolol *Diabetic Ketoacidosis*- Olanzapine *Pancreatitis*- carbamazepine, fluvoxamine, minocycline, olanzapine, oxcarbazepine, ranitidine, risperidone, sertraline, valproic acid *Shock*- carbamazepine, ondansetron *Suicide*- escitalopram, fluvoxamine, sertraline

***** Both quetiapine alone and in combination with other drugs
** More than one drug may have been reported per case

3.1.1 TOTAL NUMBER OF CASES WITH AN OUTCOME OF DEATH (N=39)

Thirty- nine unique post-marketing cases of death associated with the use of quetiapine were reported to the AERS database from market approval (September 26, 1997) through April 3, 2009. Overall, for the 39 cases, 31 are US cases and eight are foreign cases, including 19 males, 18 females and 2 cases of unknown gender. The patients involved ranged in age from 2 days to 17 years with a median of 15 years. Nine cases reported an exact[9] onset of death relative to the initiation of drug therapy in the range of 1 to 382 days with a median of 15 days. Four cases had a confirmed cause of death based on autopsy findings and four additional cases reported toxicology results confirming the presence of quetiapine in the blood.

3.1.1.1 SUICIDE/OVERDOSE (N=17)

Suicides/overdoses accounted for 17 cases; 12 of these cases reported completed suicide as the cause of death and the remaining five cases described overdose situations that were not clearly reported as suicide. These overdose situations involved both excessive quantities of quetiapine alone and in combination with other drugs. In 10 of the 17 cases, the patient was currently prescribed quetiapine. Of note, the ages of the patients that committed suicide ranged from 14 to 16 years with a median of 16 years. Nine of the 12 suicide cases reported intentional overdoses as the cause of death and the remaining three cases reported two hangings and one case of setting herself on fire. Of the five cases of overdose, two were reported as accidental, an additional two cases reported overdose, however, they were not specifically coded as completed suicides, and the remaining case reported an overdose of medication caused by the parents.

3.1.1.2 METABOLIC EFFECTS (N=3)

In three cases, patients experienced metabolic effects described as diabetes mellitus, diabetic coma, or diabetic ketoacidosis (DKA) as contributing factors to their deaths. Two cases reported DKA along with diabetes mellitus as the cause of death and the remaining case reported non-ketotic hyperglycemic hyperosmolar coma. One of the cases reported a family history of diabetes mellitus.

3.1.1.3 MISCELLANEOUS/OTHER (N=19)

Of these nineteen cases, seven reported an unknown cause of death, and the remaining 12 reported a variety of adverse events contributing to the deaths. Two cases were reported for the following adverse events, *pancreatitis* (one acute and one hemorrhagic), *neuroleptic malignant syndrome* (NMS) or NMS-like symptoms (i.e. temperature elevation, muscle rigidity, and increased creatine kinase), and exposure to quetiapine either during pregnancy (exposed for 71 days) or via breast milk. One case each reported the following adverse events, choking on food, cardiac arrhythmia, hyponatremia, multi-system organ failure + cardiac arrest, and respiratory failure + septicemia. One additional case reported the death of a 2 year old that died because of forced administration of quetiapine and suffocation by smothering at the hand of his mother.

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[9] Three cases reported an approximate time to onset of death relative to the initiation of drug therapy; however, I did not include them in the median. They were 9, 10, and 28 months.

Table 4. Summary of non-fatal serious cases (n=69)

Adverse events (n=32)	DM only (17), Weight increased (13), DM + DKA (8), Electrocardiogram QT prolonged (8), Hyperglycemia (5), DM + weight increased (4), Hyperglycemia + weight increased (3), DM + DKA+ hyperosmolar coma (2), DM + blood triglycerides increased (2), Blood triglycerides increased (2), Ventricular tachycardia (2), DKA only (1), and DKA + weight increased (1), and Cardio-respiratory arrest (1)
Concomitant medications labeled for an association with the reported adverse event (n=36)*	*Diabetes Mellitus*- Aripiprazole, chlorpromazine, clozapine, fluoxetine, gabapentin, haloperidol, mirtazapine, olanzapine, oxcarbazepine, paroxetine, risperidone, topiramate, venlafaxine, ziprasidone, zolpidem *Diabetic Ketoacidosis*- Aripiprazole, clozapine, fluoxetine, gabapentin, paroxetine, risperidone *Hyperglycemia*- Haloperidol, lithium, risperidone, olanzapine, sertraline, ziprasidone *Electrocardiogram QT prolonged*- Fluoxetine *Weight increased*- Aripiprazole, buspirone, cetirizine, clonidine, clozapine, desmopressin, fluoxetine, gabapentin, lithium, mirtazapine, olanzapine, paroxetine, sertraline, risperidone, valproic acid, ziprasidone

*More than one drug may have been reported per case

3.1.2 TOTAL NON-FATAL SERIOUS ADVERSE EVENT REPORTS (N=69)

3.1.2.1 METABOLIC EFFECTS (N=58)

Fifty-eight unique post-marketing cases reported various metabolic effects associated with quetiapine therapy; including blood triglycerides increased, diabetes mellitus (DM), hyperosmolar coma, diabetic ketoacidosis (DKA), and weight increased. Overall, for the 58 cases, 51 are US cases and 7 are foreign cases, which includes 30 females and 28 males. The patients involved ranged in age from 6 to 17 years with a median of 14 years. The breakdown of the adverse events includes, DM only (17), weight increased (13), DM + DKA (8), hyperglycemia (5), DM + weight increased (4), hyperglycemia + weight increased (3), DM + DKA+ hyperosmolar coma (2), DM + blood triglycerides increased (2), blood triglycerides increased (2), DKA only (1), and DKA + weight increased (1).

Of the 58 cases, 19 reported a time to onset of the event that ranged from 42 to 855 days with a median of 299 days. Forty-two cases reported a daily dose, which ranged from 25 to 1000 mg with a median of 300 mg daily. Ten cases reported a weight increase in the range of 13 to 70 pounds with a median of 28 pounds; however, an exact duration of therapy with quetiapine was not reported during the period of weight gain. Five cases reported a past medical history of the following, hyperlipidemia including increased triglycerides (3), hyperglycemia (2), and obesity (2) (one case may have reported more than

one). Fifteen cases reported a positive family history of diabetes mellitus with six of those also reporting hyperlipidemia including triglycerides, and five reported obesity (one case may have reported more than one). A majority of the cases were coded with an outcome of other serious (26); followed by hospitalization (23), life threatening (4), death (3), and disability (2). Of note, 25 of the 58 cases were reported from a lawyer as part of a legal case.

3.1.2.2 QT RELATED EVENTS (N=11)

Eleven unique post-marketing cases were retrieved during the search of the AERS database using the narrow SMQ of Torsade de pointes/QT prolongation. Overall, for the 11 cases, eight are US cases; three are foreign cases, which include six males and five females. The patients involved ranged in age from 7 to 17 years with a median of 15 years. Only one case reported a time to onset of event, which was 122 days. Five cases reported a total daily dose, which ranged from 150 to 1200 mg with a median of 600 mg. Additionally, four cases reported intentional overdoses, of which one case resulted in death and only one of the remaining three cases reported QT prolongation. Only two cases reported a QTc value, which were 470 and 506 msec.

Eight of the 11 cases were coded with the PT of Electrocardiogram QT prolonged with the remaining three cases reporting ventricular tachycardia (2) and cardio-respiratory arrest (1) as the results of an intentional overdose. No cases of Torsade de pointes were reported in the pediatric population. The 11 cases were coded with the following outcomes (in order of significance), death (2), life threatening (2), hospitalization (5), and other serious (2). One case reported the involvement of fluoxetine as a concomitant medication, which is labeled for an association with QT interval prolongation.

The four cases that described intentional overdoses involved patients aged 15 and 16 years old who ingested unknown amounts of quetiapine. One death was reported because of the overdose; however, QT prolongation was not actually reported.

4 DISCUSSION

This review provides a post-marketing overview of the safety profile for the pediatric population being treated with quetiapine with a particular focus on deaths, metabolic events (blood triglycerides increased, diabetes mellitus, hyperglycaemia, and weight increased), and QT related events.

Overall, for the 39 deaths described, there was not a common underlying theme associating them. Seventeen deaths described a completed suicide or overdose situation. Quetiapine is labeled for an association with increased risk of suicidal thinking as well as stating, “the possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder and close supervision of high-risk patients should accompany drug therapy.” Additionally, quetiapine is also indicated for the treatment of depression and as such has a boxed warning for an increased risk of suicidal thinking and behavior in children, adolescents, and young adults. These cautions may lend to the thought that psychiatric illness is a confounding factor in many suicides. Thus, from AERS cases alone, it is not possible to distinguish events linked to the underlying condition from paradoxically heightened suicidality due to drug effect. Additionally, three cases reported DKA or diabetic coma, which are labeled events for quetiapine. The remaining 19 cases reported a variety of adverse events, of which three are labeled for an association with quetiapine (hyponatremia, NMS, and pancreatitis). Six of the 39 cases were confounded by the concomitant use of medications, which are labeled for an association with the adverse event reported (cardiac arrhythmia,

DKA, pancreatitis, shock, and suicide)[10]. The deaths in these seven cases did not appear to be the result of any drug-drug interactions with quetiapine and the concomitant medication reported.

Metabolic related adverse events accounted for 58 cases in this review. The common theme among these cases involved dysglycemic events; with a majority of the cases (33/58), reporting the occurrence of diabetes mellitus either alone or in conjunction with one of the other metabolic-related adverse events, two cases reported DKA alone, and an additional eight cases reported hyperglycemia without mention of diabetes mellitus. The remaining 15 cases reported weight increased alone (13) and blood triglycerides increased (2). The increase in appetite caused by quetiapine may result in an increased insulin demand, which ultimately can lead to increased insulin resistance, which may play a potential role in causing these metabolic related adverse events. Thirty-five cases were confounded by the use of concomitant medications, which are labeled for an association with one or more of the adverse events reported[11]. Twenty-four of these 35 cases reported the concomitant use of at least one atypical antipsychotic, which are all labeled for an association with diabetes mellitus, diabetic ketoacidosis, hyperosmolar coma, and weight gain. Therefore, the concomitant use of any of the medications reported may further increase the potential of developing these adverse events. The current quetiapine label contains language describing an association with hyperglycemia, diabetic ketoacidosis, diabetes mellitus, hyperosmolar coma, weight gain, and triglyceride elevations.

Eleven cases were retrieved during the search for reports of Torsade de pointes and QT prolongation; however, only eight were coded with the PT of Electrocardiogram QT prolonged. No cases of Torsade de pointes were reported among the 11 cases. Of these 11 cases, four cases reported intentional overdoses, with one ultimately resulting in death. Of these four cases, two patients had a current prescription for quetiapine and the remaining two were unknown. One case described a normalizing of the QT interval upon the discontinuation of quetiapine. One case reported the concomitant use of fluoxetine, which when used concurrently with antipsychotics might result in an increased risk of cardiotoxicity (QT prolongation, Torsade de pointes, and cardiac arrest). Fluoxetine is currently labeled for an association with QT prolongation. The adverse reactions section of the current quetiapine label lists QT interval prolonged as a possible adverse event associated with the use of quetiapine.

This review did not identify any necessary labeling revisions based on pediatric population specific adverse events different from what is currently labeled for children and adolescents.

5 CONCLUSION

The safety profile of the pediatric population is very similar compared to the adult population, and the adverse events occurred in much the same manner as well. No new safety signals emerged as part of this review; however, it has made us aware that the pediatric population is not spared from the adverse events caused by quetiapine therapy. The potential risks of quetiapine therapy should be weighed against the potential benefit when choosing to initiate therapy.

6 RECOMMENDATIONS

The current quetiapine label extensively describes the known pediatric safety data and concerns associated with the drug; therefore, at this time we do not recommend any further labeling enhancements specific to the pediatric population.

[10] Some of the adverse events were reported in more than one case

[11] Nineteen concomitant medications were included among those 35 cases.

7 APPENDIX A- GRAPHICAL REPRESENTATION OF ALL PEDIATRIC REPORTS

Figure 1. Adverse events by MedDRA SOC reported in pediatric patients

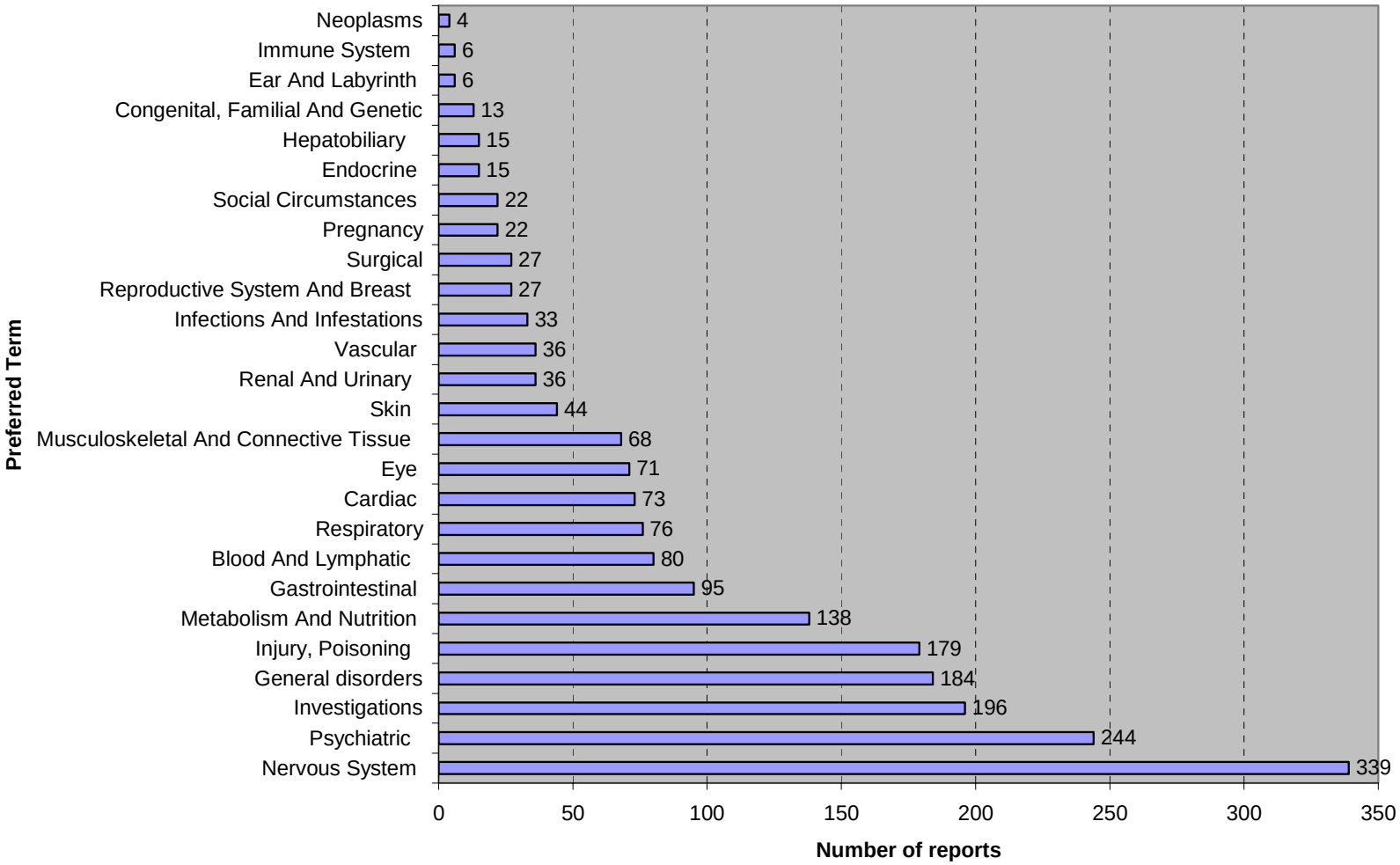
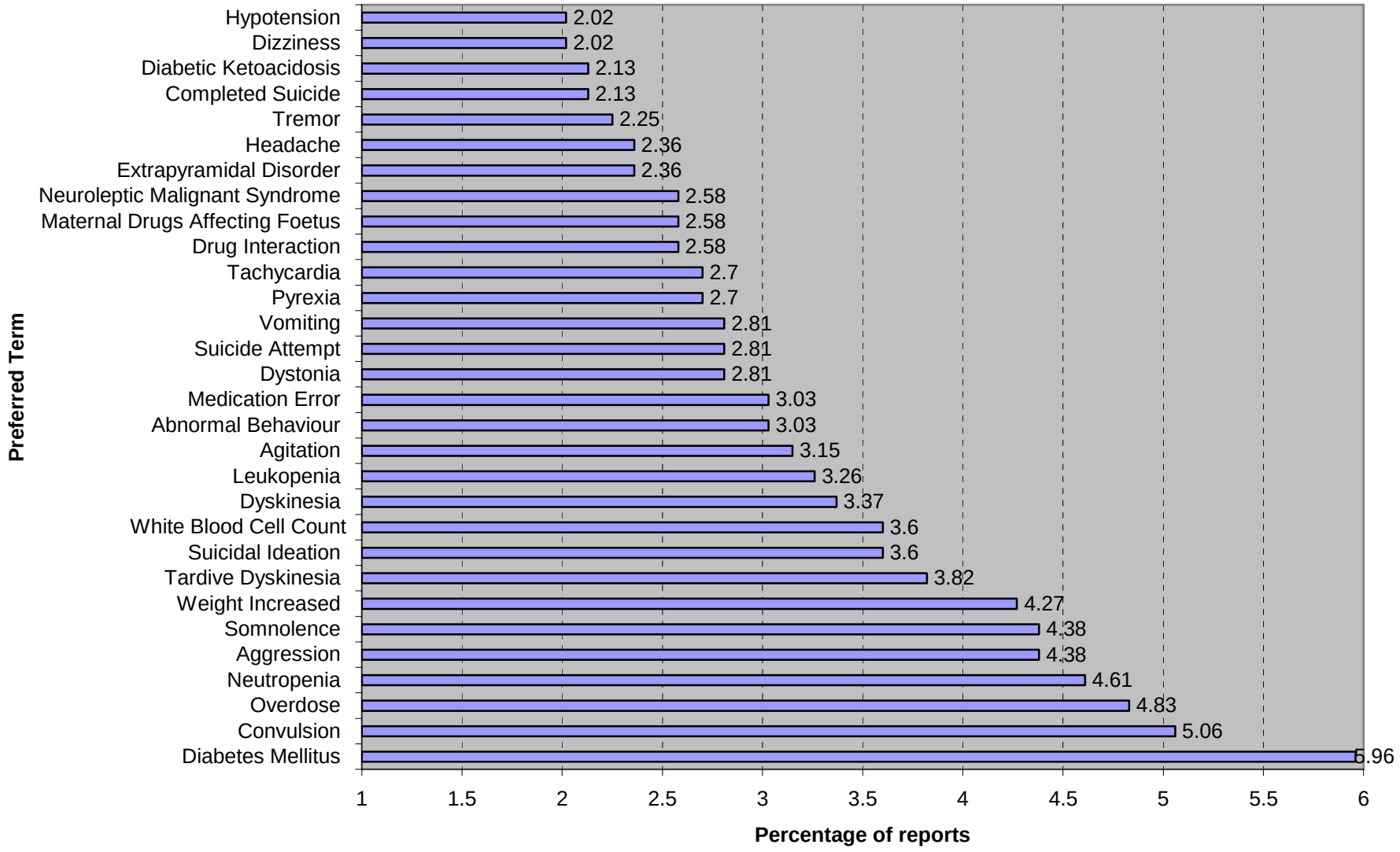


Figure 2. Preferred Terms with a reporting proportion ≥ 2%



8 APPENDIX B- RELEVANT PEDIATRIC LABELING

WARNINGS AND PRECAUTIONS Section:

Hyperglycemia and Diabetes Mellitus- Children and Adolescents: Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 years. In a placebo-controlled Seroquel monotherapy study of adolescent patients (13-17 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for Seroquel compared to placebo was -i.75 mg/dL versus -1.70 mg/dL. In a placebo-controlled Seroquel monotherapy, study of children and adolescent patients (10-17 years of age) with bipolar mania (3 weeks duration) the mean change in fasting glucose level for Seroquel compared to placebo was 3.62 mg/dL versus -1.17 mg/dL. No patient in either study with a baseline normal fasting glucose level (-:100 mg/dL) or a baseline borderline fasting glucose level (:2100 mg/dL and -:26 mg/dL) had a treatment-emergent blood glucose level of ≥126 mg/dL.

Clinical Worsening and Suicide Risk
Patients with major depressive disorder (MOD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. No suicides occurred in any of the pediatric trials.
The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric.

Hyperlipidemia
Children and Adolescents: Safety and effectiveness of Seroquel have not been established in pediatric patients and SEROQUEL is not approved for patients under the age of 18 years. In clinical trials with Seroquel, the percentage of patients with the following changes in cholesterol and triglycerides have been reported.

Weight Gain
Children and Adolescents: Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 years. In two clinical trials with Seroquel, one in bipolar mania and one in schizophrenia, reported increases in weight are included in the table below. When treating pediatric patients with Seroquel for any indication, weight gain should be assessed against that expected for normal growth. The mean change in body weight in the schizophrenia trial was 2.0 kg in the Seroquel group and -0.4 kg in the placebo group and in the bipolar mania trial, it was 1.7 kg in the Seroquel group and 0.4 kg in the placebo group.

In an open-label study that enrolled patients from the above two pediatric trials, 63% of patients (241/380) completed 26 weeks of therapy with Seroquel. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Fort-five percent of the patients gained ≥ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from

baseline in 8MI was used as a measure of a clinically significant change; 18.3% of patients on Seroquel met this criterion after 26 weeks of treatment.

Hypothyroidism
Children and Adolescents: Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts to potentially clinically important thyroid function values at any time for Seroquel treated patients and placebo-treated patients for elevated TSH was 2.9% vs 0.7%, respectively and for decreased total thyroxine was 2.8% vs 0%, respectively. Of the SEROQUEL treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

Hyperprolactinemia
Children and Adolescents: Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts in prolactin levels to a clinically significant value (>20 mcg/L males; >26 mcg/L females at any time) was 13.4% for Seroquel compared to 4% for placebo in males and 8.7% for Seroquel compared to 0% for placebo in females.

Increases in Blood Pressure
Children and Adolescents: Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 In acute placebo-controlled trials in children and adolescents with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increases at anytime in systolic blood pressure (20 mmHg) was 15.2% for Seroquel and 5.5% for placebo; the incidence of increases at any time in diastolic blood pressure (10 mmHg) was 40.6% for Seroquel and 24.5% for placebo

Adverse Reactions in clinical/trials with quetiapine and not listed elsewhere in the label section:

Extrapyramidal Symptoms
Children and Adolescents: Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 years. In a short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration), the aggregated incidence of extrapyramidal symptoms was 12.9% for Seroquel and 5.3% for placebo, though the incidence of the individual adverse events (eg, akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration), the aggregated incidence of extrapyramidal symptoms was 3.6% for Seroquel and 1.1 % for placebo.

Increased appetite
Children and Adolescents: Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or

bipolar mania (3-week duration), the incidence of increased appetite was 7.6% for Seroquel compared to 2.4% for placebo. In a 26- week open-label study that enrolled patients from the above two pediatric trials, the incidence of increased appetite was 10% for Seroquel.

Use in Specific Populations section:

Pediatric Use

Safety and effectiveness of Seroquel have not been established in pediatric patients and Seroquel is not approved for patients under the age of 18 years (see Warnings and Precautions (5) and Adverse Reactions (6)).

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/s/

Ida-Lina Diak
5/7/2009 01:18:42 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
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CLINICAL REVIEW

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Established Name	GEODON®
(Proposed) Trade Name	Ziprasidone HCl
Therapeutic Class	Antipsychotic
Applicant	Pfizer, inc.
Priority Designation	P
Formulation	Capsule
Dosing Regimen	Daily
Indication	Treatment of acute mania
Intended Population	Adolescents aged 10-17 years old.

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Regulatory action will be taken on this submission after recommendations from a scheduled June 2009 advisory committee have been received and analyzed.

1.2 Recommendation on Post marketing Actions

1.2.1 Risk Management Activity

Post marketing regulatory actions will be considered for this submission after recommendations have been received and analyzed from a scheduled June 2009 advisory committee.

1.2.2 Required Phase 4 Commitments

Any Phase 4 commitments will be considered for this submission after recommendations have been received and analyzed from a scheduled June 2009 advisory committee.

1.2.3 Other Phase 4 Requests

Additional phase 4 study requests will be considered for this submission after recommendations have been received and analyzed from a scheduled June 2009 advisory committee.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Pursuant to the Written Request, the sponsor conducted a single 4-week, outpatient, randomized (2:1 ziprasidone to placebo), double-blind, parallel-group, placebo controlled study of 238 pediatric patients aged 10-17 years of age with a diagnosis of bipolar I disorder, manic or mixed, as determined by a child psychiatrist using DSM-IV criteria via use of the K-SADS interview with symptoms for at least 7 days prior to screening. All patients were titrated off their current medication regimen during a 1 to 10 day screening/washout period. Flexible dosing was employed up to the first two weeks of the double-blind period with two *a priori* defined target dose ranges based on the patients weight at time of entry into study (patients weighing <45kg target dose 60-80mg/day; patients weighing ≥45kg, target dose 120-160mg/day).

The sponsor also conducted two (2) 6-month open-label studies to obtain additional data on the tolerability and safety of ziprasidone for use in pediatric bipolar disorder. A total of 201 bipolar

patients were enrolled in either the long term extension study to the double blind efficacy trial (N=162) or a dose titration study with a 6 month extension trial (N=39). The latter study also enrolled 17 pediatric patients with schizophrenia or schizoaffective disorder; however the primary focus of this review involved the review of the efficacy and safety data obtained from the 201 bipolar patients. Safety results from two double-blind studies of ziprasidone use in pediatric patients with Tourette's disorder were also reviewed. Pertinent safety data that has been submitted as part of this NDA for pediatric patients enrolled in schizophrenia trials were also reviewed and discussed within this review.

1.3.2 Efficacy

The sponsor conducted one 4-week outpatient, flexible dose, double blind, randomized (2:1 drug: placebo) study to demonstrate efficacy for the treatment of pediatric bipolar disorder. Patients were diagnosed by a child psychiatrist with pediatric bipolar disorder using the K-SADS interview and personal evaluation by study psychiatrists. All patients were aged 10-17 years of age. The primary efficacy endpoint was the mean change from baseline in the Young Mania Rating Scale (YMRS) at week 4 with a mixed model of repeated measures (MMRM) analysis employed for hypothesis testing.

The results clearly showed a statistically significant mean change decrease from baseline in the YMRS score at week 4 in ziprasidone treated subjects as compared to placebo.

Table 1: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the modified Intent to Treat population

STATISTIC	ZIPRASIDONE N=133*	PLACEBO N=85*
Least squares mean (SE)	-13.83 (0.96)	-8.61 (1.10)
Difference from placebo (SE)	-5.22 (1.48)	
95% Confidence interval for difference from placebo	(-8.12, -2.31)	
P-value	0.0005	

*modified Intent to treat (i.e. those patients with at least one post-dose efficacy measurement)

Even with the exclusion of all subject efficacy data obtained from two sites that were identified by the Division of Scientific Investigations (DSI) as having invalid data (sites 1013 and 1087) in addition to a sponsor-excluded site (site 1089), efficacy was still clearly demonstrated.

Table 1a: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the modified Intent to Treat population: Excluding subjects from sites 1013, 1087 and 1089

STATISTIC	ZIPRASIDONE N=118	PLACEBO N=76
Least squares mean (SE)	-14.08 (0.99)	-8.74 (1.19)
Difference from placebo (SE)	-5.34 (1.56)	
95% Confidence interval for difference from placebo	(-8.40, -2.27)	
P-value	0.0007	

Also, a statistically significant decrease in the key secondary endpoint, CGI-S score, was also seen at week 4, even after excluding all subjects from the three sites mentioned above in the key secondary efficacy analysis.

The employment of a flexible-dose study design for the double blind, placebo controlled study precluded the assessment of a dose-response relationship. In addition, the pediatric bipolar studies imposed maximum dose limits and titration schedules according to patient weight, where patients <45kg could receive a maximum dose of 80mg/day and all others potentially receiving a maximum dose of 160mg/day. These limits were identified as part of a dose titration phase in a previous study and were used to limit overall exposure of ziprasidone to smaller pediatric patients.

Overall this reviewer finds that the efficacy results demonstrate that ziprasidone is effective for the treatment of pediatric bipolar disorder.

1.3.3 Safety

Generally the adverse event profile for treatment of pediatric bipolar disorder was similar to the current labeling of the adult treatment of bipolar disorder. Sedation, dystonia and extrapyramidal symptoms appear to be frequently noted in the pediatric studies. A closer analysis of the adverse events by patient weight revealed that patients who weighed less than 45kg were most likely to report EPS, tremor and abdominal pain adverse events in the double-blind trials.

The sponsor also conducted a concentration-QTcF analysis from concentration-QTcF data points obtained from 4 pediatric trials and from 21 adult trials. The result showed a linear concentration-dependent increase in QTcF prolongation in the pediatric population. Of particular note is the pediatric population overall had a 58% increase in concentration dependant QTcF prolongation rates at any given concentration when compared to the adult population. This suggests that the pediatric population is at least as sensitive to the QT prolongation effects associated with ziprasidone use as adults and may potentially be at greater risk for developing torsades de pointes and other serious cardiac arrhythmias when administered ziprasidone when compared to the adult population.

A review of the post-marketing reports revealed eight (8) pediatric deaths from the sponsor's database, including one case of cardiac failure after receiving 160mg/day of ziprasidone for over 1 year. An Agency review of the FDA post-marketing database concluded that the safety profile of ziprasidone in the pediatric population is similar to the adult population, including QTc-related events. As a result of the FDA internal database review conducted by the Office of Surveillance and Epidemiology (OSE), the Office recommends enhancing the Warnings section of the current ziprasidone label to include the risk of QT prolongation for both adult and pediatric patients.

Although post marketing data is subject to many limitations from which to draw firm regulatory conclusions, reports of cardiovascular deaths in patients who received ziprasidone is of concern to this reviewer in light of the more prominent concentration dependant QTcF prolongation seen in pediatric patients as compared to the adult population. This reviewer therefore recommends that there is sufficient evidence to warrant a change in the current Warnings section of the QT prolongation to include children as being at risk for QT prolongation-related adverse events with ziprasidone use.

1.3.4 Dosing Regimen and Administration

Pediatric bipolar dosing recommendations for ziprasidone labeling were proposed by the sponsor to set maximum daily dosing limits based on a patients' weight as pharmacokinetic studies submitted within this submission. These proposed dosing recommendations are to limit maximum doses for patients who weigh less than 45kg are recommended to a maximum daily dose of 80mg/day, whereas patients who weigh 45kg or greater are recommended to receive up to the daily maximum dose of 160mg/day as currently labeled.

1.3.5 Drug-Drug Interactions

Drug interaction studies were not required under the Written Request. Please refer to the current product labeling and previous Agency reviews for details regarding drug-drug interactions. Include

1.3.6 Special Populations

The sponsor did not conduct any pharmacokinetic studies in patients with cardiovascular, hepatic or renal diseases.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ziprasidone hydrochloride, marketed under the brand name GEODON®, is pharmacologically classified as an antipsychotic medication. Although the *in vivo* mechanism of action is not well-

delineated, *in vitro* binding studies demonstrated that ziprasidone functioned as an antagonist at the dopamine 2 (D2), serotonin 2A ($5HT_{2A}$) and serotonin 1D ($5HT_{1D}$) receptors , and an agonist at the serotonin 1A ($5HT_{1A}$) receptor. ziprasidone is also noted for alpha-1 receptor and histamine-1 receptor antagonist properties as well, leading to potential side effects of orthostatic hypotension and sedation respectively.

2.2 Currently Available Treatment for Indications

Ziprasidone oral capsules are currently FDA approved for the treatment of adult schizophrenia and for the acute treatment of adult manic or mixed episodes associated with bipolar disorder. An intramuscular form (IM) of ziprasidone is available and approved for the treatment of acute agitation in schizophrenic patients for rapid control of agitation.

2.3 Availability of Proposed Active Ingredient in the United States

Ziprasidone HCl is available as a capsule in 20, 40, 60 and 80mg strengths, and as an IM formulation (with directions for reconstitution before use) with two strengths: 10mg and 20mg.

2.4 Important Issues with Pharmacologically Related Products

The Agency has recently mandated class labeling boxed warnings for all antipsychotic medications for an association of antipsychotic use and increased mortality in elderly patients with dementia-related psychosis. Agency action was taken after a review of placebo-controlled studies revealed a 1.6 to 1.7 times increased risk of death in elderly patients with dementia related psychosis who took antipsychotic medications compared to those who took placebo.

2.5 Presubmission Regulatory Activity

Ziprasidone hydrochloride capsules received initial Agency approval on February 5, 2001 for the treatment of adult schizophrenia. ziprasidone then received approval for the acute treatment of acute mania in adults on August 19, 2004. An oral suspension formulation of ziprasidone received Agency approval on March 29, 2006 for both indications.

Previous to the approval for the adult acute mania indication in August 2004, the Agency had issued a Written Request letter on February 11, 2003 to submit information from trials in pediatric patients with 1.) schizophrenia and 2.) acute mania as part of bipolar I disorder. At the request of the sponsor, the Written Request letter timeframe was amended on November 7, 2007 to extend the deadline for reporting data from the pediatric schizophrenia and bipolar studies to September 30, 2011. This was granted after review of recruitment data submitted by the sponsor in 2007 for the pediatric schizophrenia program demonstrated severe difficulties in recruitment and an inability to meet the original WR deadline for submission of reports. At the time of the extension, the sponsor clearly noted that studies for pediatric bipolar disorder were completed within the timeframe of the original WR and would be submitted in 2008.

On April 18, 2008, the sponsor and division met via teleconference as part of a pre-NDA meeting for submission of pediatric bipolar studies that were completed as part of the WR letter. It was re-iterated at the time of the pre-NDA meeting that the pediatric schizophrenia studies would still be conducted and that a Prior Approval Efficacy Supplement would be submitted to the Agency once the pediatric schizophrenia studies were completed.

On October 21, 2008, the sponsor submitted NDA supplement (#32) for the treatment of pediatric bipolar disorder. This document summarizes the review of this NDA application.

Post- Submission Regulatory Activity

Regarding the most recent status of the pediatric schizophrenia study, the Agency was informed on March 30, 2009 by the sponsor that "…based on the results of the interim analysis of the placebo-controlled pediatric schizophrenia efficacy study A1281134, Pfizer Inc has decided to stop the A1281134 and A1281135 (open-label extension) protocols." The sponsor stated that results of the interim analysis performed on March 23, 2009 was reviewed by the DSMB and recommended that "…the study be stopped per meeting the pre-defined stopping criteria for futility (lack of efficacy)."

2.6 Other Relevant Background Information

No other relevant pediatric background information is available for ziprasidone as this formulation has not received a pediatric mania indication in any other country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

At the time of this review there do not appear to be any major CMC issues pending. Please see the formal CMC review for further details and analysis.

3.2 Animal Pharmacology/Toxicology

Although the formal pharmacology/toxicology review is not available, no issues have been raised to this reviewer with regards to the approvability of ziprasidone from a pharmacology/toxicology perspective.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Pursuant to the Agency's Written Request, the efficacy of Geodon® for the treatment of mania in the child and adolescent population was determined after completion and analysis of a single phase 3 study (A1281132, a randomized double blind, placebo controlled flexible dose study).

The safety of Geodon® in adolescent mania was assessed from safety data submitted from study A1281132 with longer term safety data derived from a six-month open label extension study (A1281133) and an additional six month open label study (A1281123) whose initial objective was to determine the safety and tolerability of dosing regimens for use in both double-blind efficacy studies and 6-month safety studies. The safety data from studies A1281123 and A1281133 was summarized in an Integrated Safety Summary (ISS)

For completeness, additional safety data was submitted with this NDA supplement from several open-label Phase IIR studies including two studies of Geodon® use in patients with Tourette's (128-044 and 128-122) and bipolar disorder (20020501-8 weeks and 20030094); in patients with Autism (20010457- 6 weeks duration) and schizophrenia-spectrum disorders (20020012-one year study). Only pertinent positive or negative safety findings will be reviewed from each of these studies as part of the safety review.

4.2 Tables of Clinical Studies

Table 2: Geodon® Pediatric Bipolar Table of Studies

Phase 3 Studies	
A1281132 Flexible Dose	A four–week, outpatient, multicentered, double-blind, parallel-group, placebo controlled, randomized (2:1 drug: placebo), flexible dose study of 238 adolescent patients (ages 10-17 years of age) with a current clinical diagnosis of bipolar I disorder, manic or mixed (according to DSM-IV criteria using the K-SADS instrument) titrated with Geodon® according to weight to a target dose of 60-80mg/day (<45kg) or 120-160mg/day (≥45kg) for the first two weeks with stable dosing at weeks 3 and 4.
A1281133 Open label Safety	Six month multicentered, open label extension safety study of study A1281132 in 162 enrolled adolescent patients with mania.
A1281123 Open label Safety	24 week multicentered, two-period, open label safety study with an initial three week fixed-dose titration period followed with flexible dosing in period two for 56 treated adolescent patients with either mania (N=39) or schizophrenia/schizoaffective disorder (N=17).

4.3 Review Strategy

Table 3 below provides a listing of documents that were reviewed during the NDA review process.

Table 3: Items Utilized in this review

SUBMISSION DATE	ITEMS REVIEW
October 21, 2008	• Study reports: A1281132, A1281133 and A1281133 • Integrated Safety Summary • Review of pertinent SAEs and safety data from Tourette Syndrome and submitted phase IIR studies • Proposed labeling • Written Request • Financial Disclosure Certification • Application Summary • Case Report Tabulations (.xpt files) • Case Report Forms
February 17, 2009	• Response from sponsor with regards to additional analyses of the data requested by this reviewer
April 23, 2008	• Response from sponsor regarding re-analyses of primary and key secondary endpoint excluding all data from sites 1013, 1087 and 1089

4.4 Data Quality and Integrity

Routine NDA site investigations were performed by the Division of Scientific Investigations (DSI) at the following sites: Site 1040 (Dr Delbello), Site 1013 (Dr Punjwani) and Site 1087 (Dr Gazda). The sites were selected based on number of patients enrolled, as well as those sites with numerous protocol violations and dosing errors noted during the trial.

The inspection of these sites resulted in a recommendation of "No Action Indicated" for site 1040. However the review of sites 1013 and 1087 resulted in a FDA Form 483 being issued and an initial recommendation of official action indicated (OAI) for site 1013 and verbal action indicated (VAI) for site 1087. After further discussions within DSI, site 1013 (Dr Punjwani) was downgraded to verbal action indication as the site provided detailed corrective plan to the FDA Form 483.

After further consideration of the evidence from site 1087, DSI has concurred to upgrade the recommendation from a VAI to an OAI. In addition, a for-cause inspection was conducted for site 1089 (Dr. Summers) due to questions regarding inadequate sponsor monitoring and contract

research organization (CRO) monitoring. Additional audits of the sponsor and the CRO are being conducted at this time.

It is the recommendation of DSI that data from sites 1087 and 1013 are not considered valid to support this NDA. Consequently this reviewer requested that the sponsor re-analyze the primary efficacy and key secondary efficacy data excluding all data obtained from sites 1013, 1087 and additionally for site 1089 (Dr Tim Summers)-whose data was excluded by the sponsor from the per protocol analysis due to widespread good clinical practice violations. The results of the reanalyses are discussed in section 6.

4.5 Compliance with Good Clinical Practices

Studies A1281132, A1281123 and A1281133 were conducted in compliance with the ethical standards according to the Declaration of Helsinki and the International Conference on Harmonization guidelines of Good Clinical Practice. All subject information was documented and stored using Good Clinical Practices (GCP) as delineated in the Health Insurance Portability and Accountability Act (HIPAA) of 1997. The reader is directed to review the DSI inspection report for a full analysis of GCP variances and violations that occurred during the routine NDA DSI inspection process.

4.6 Financial Disclosures

There were eleven (11) financial disclosures filed from eight (8) investigators from five studies (A1281132, 1123, 1133, 128-044 and 128-122). These investigators indicated that they had significant payments from the sponsor requiring submission of FDA form 3454. Three investigators filed two disclosure forms as a result of participating in studies A1281132 and A1281133.

For the pivotal trial A1281132, approximately 18% (42/238) of the total patient population were randomized by the listed investigators below. Approximately 70% of these 42 patients (nearly 12% of the total study population 29/238) were randomized by Dr Delbello. Based upon results obtained from the DSI inspection for Dr Delbello, it is unlikely that financial payments were a significant bias in the efficacy results obtained from this site.

Table 4: Investigators with financial disclosure

NAME	SITE	AMOUNT (USD)
Study 1281123		
Jeffrey Lee Blumer	1004	[redacted]
Melissa DelBello	1002	[redacted]
Robert Findling	1004	[redacted]
Jean Frazier	1003	[redacted]
Floyd Randy Sallee	1002	[redacted]
Study 1281132 and 1281133		

Haisam Al-Khouri	1031		(b) (6)	
Melissa DelBello	1040		(b) (6)	
Arnold Mech	1132		(b) (6)	

5 CLINICAL PHARMACOLOGY

Note: Please see the biopharmacology/clinical pharmacology review for a more detailed pharmacokinetic review. This review is based upon information contained in the submitted Summary of Clinical Pharmacology Studies.

Pursuant to the Written Request, the sponsor obtained ziprasidone pediatric pharmacokinetic (PK) data from four (4) completed studies: A1281132, A1281123, 128-044 and 128-122 (the latter two were studies done in patients with Tourette's disorder). In addition to standard analyses of pharmacokinetic parameters, the sponsor evaluated the relationship of pediatric plasma drug levels to changes in QT intervals using statistical modeling for studies A1281123 and A11281132.

Of note, the sponsor also conducted a multistudy pooled analysis of population pharmacokinetic data to compare the ziprasidone concentration change in QTcF from data obtained from the two pediatric Tourette studies above plus the three submitted pediatric studies (N=180), as well as data obtained from 31 adult studies (N=1383). The purpose of this comparison was to conduct an analysis to characterize the relationship between ziprasidone concentration (and its' metabolites M9 and M10) to changes in QT/QTc intervals in children and adults. QTcF/concentration data primarily from study A1281132 was used for the majority of the pediatric analyses, though a pooled analysis of all pediatric and adult data was performed. The descriptive results showed a similar distribution pattern of data points between the two populations. At the request of this review, a linear regression analysis was performed to objectively compare the slopes of the linear regression lines obtained from the pediatric data vs. the adult data. The results showed that the pediatric dataset exhibited a steeper slope to the regression line as compared to the adult dataset, suggesting that the pediatric population is at least as sensitive to the concentration-dependant QTcF prolongation effects of ziprasidone administration as compared to adults or potentially may be at more at risk for QTc related cardiac arrhythmias. Despite the absence of reports or adverse events of torsades de pointes seen in the pediatric clinical trials and post-marketing reports thus far, this reviewer recommends that the QTc warning language be re-worded to include adults and children.

5.1 Pharmacokinetics

In general, ziprasidone appears to adhere to first-order, one compartmental model kinetics in both the adult and pediatric population. Clearance tended to be higher in adults (41-72L/hr vs. 27-75L/hr children) with body weight having the most influence over clearance (age had a small effect). Once body weight was corrected for in the analyses, pharmacokinetic exposure appeared to be similar between adults and children. Absorption tended to be higher in children as well.

Overall, the clearance of ziprasidone increases as body weight increases. Therefore a direct relationship exists between ziprasidone clearance and body weight.

Pharmacokinetic results from study A1281132 and 1281123

The QTcF/concentration effect will be discussed in greater detail in section 7.1.9.4.1. However ziprasidone was associated with a concentration dependant increase in QTcF in study A1281132. The rate of change increase to concentration for study A1281132 was estimated to be 0.0852 msec per ng/ml concentration of ziprasidone. For study A1281123, the rate of change increase in QTcF to concentration was 0.139 msec per ng/ml. A similar concentration dependant increase in QTcF was also observed with the M9 and M10 metabolite concentrations in children.

5.2 Pharmacodynamics

There is not expected to be a difference in the pharmacodynamic properties of ziprasidone in adults and children.

5.3 Exposure-Response Relationships

An analysis of ziprasidone exposure to changes in QT/QTcF intervals was performed and will be reviewed in depth in section 7.1.9.4 of this review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The submitted pediatric efficacy study (A1281132) was performed pursuant to the Written Request, for the treatment of mania or mixed episodes in children and adolescents aged 10-17 years old with a current bipolar I disorder diagnosis according to DSM-IV criteria.

6.1.1 Methods

Pursuant to the Written Request, a single randomized, double-blind, placebo controlled trial was performed to evaluate the efficacy of ziprasidone in the treatment of adolescent mania.

Study A1281132
This multicentered U.S. study was conducted at 36 sites from January 13, 2006 to July 26, 2007 with Paul Wang, MD as the coordinating investigator.

Protocol Amendments
There was one (1) Protocol amendment to this study on December 6, 2007 with numerous changes made to the protocol. Although a review of the pertinent changes are described below,

the changes do not appear to substantially alter the study design or objectives of the study and thus unlikely to have introduced bias into the study results.

- Change in the procedures for primary and secondary analyses of the ITT and PP populations
- Clarification of statistical methods to be used for analysis of the raw CGI-I score
- Reiterated that maximum dose for subjects weighing <45kg was 80mg/day
- Added the requirement to have a child psychiatrist determine diagnostic eligibility with K-SADS administration provided by qualified and experienced rater.
- Increased safety monitoring/DQ criteria for patients with clinically significant ECG abnormalities

6.1.2 General Discussion of Endpoints

The primary objective of this study was to establish the efficacy of oral ziprasidone compared with placebo in the treatment of children and adolescents with Bipolar I disorder (manic or mixed).

Primary efficacy was assessed by the change from baseline to week 4 on the YMRS total score between the ziprasidone treated groups compared to placebo for the intent to treat population (ITT). The YMRS has reported validity and reliability and has been previously accepted by the Agency as a standard measure for measuring mania symptom response in clinical trials. This measure also has wide acceptance and use within the pediatric population.

Although no key secondary efficacy variables were specified *a priori* in the protocol, the sponsor pre-specified that the change from baseline in the Clinical Global Impression of Severity scores (CGI-S) and the Clinical Global Impression of Improvement (CGI-I) scores between the ziprasidone group and placebo treatment as additional secondary efficacy endpoints in this study. It was noted by this reviewer that upon review of this application, the sponsor referred to the change from baseline in CGI-S score as a “Key” secondary endpoint in the statistical analysis plan. Therefore for purposes of this review, the CGI-S is noted throughout this review as a key secondary endpoint despite the lack of an *a priori* agreement between the sponsor and the Agency specifying a key secondary endpoint.

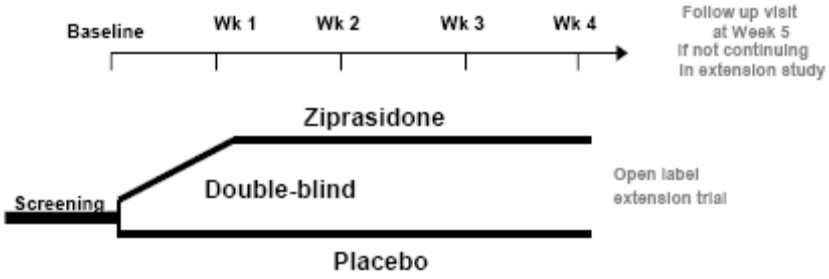
6.1.3 Study Design

Placebo Controlled Study (using ziprasidone Oral Capsules)

Study A1281132 was a 4-week outpatient, randomized (2:1 drug to placebo), double-blind, placebo-controlled, parallel group, flexible dose trial. Patients who met inclusion criteria at the end of a preceding one to ten (10) day wash-out period were then randomized at baseline to receive ziprasidone or placebo in a 2:1 ratio.

Over an initial two-week titration period, two (2) dosing arms for ziprasidone were pre-specified based upon the weight of the patient. Patients who weighed ≥ 45kg and tolerated 120mg/day were allowed to continue titration up to a target range of 120-160mg/day by the end of week two. Patients who weighed <45kg we allowed to achieve a maximum dose of 80mg/day by the end of week two.

In patients who did not require a rapid onset of action, treatment began with 20mg/day with dose increases of 20mg/day every second day. For those patients whose clinical symptoms required a more rapid titration schedule, the dose of ziprasidone could be increased 20mg daily in order to achieve the target dose as soon as possible. However a target dose of 160mg/day was not to be attained by day 8 for those patients who required a fast titration. Those patients who had an insufficient response to treatment one week after completing their titration and maximum tolerated dose were recommended to discontinue the study and consider enrolling in the open-label extension study A1281133, provided no safety concerns were seen.



During the first two weeks of the titration, the investigator or his/her staff would have daily contact (phone or in person) to ensure proper administration was obtained. Once the target dose was achieved, the dose of the medication could be reduced for concerns over tolerability or safety. Patients in the 160mg/day dosing group who could not tolerate 80mg/day (or those patients in the 80mg/day group not tolerating 40mg/day) were discontinued from the study. There were six (6) pre-specified in person weekly visits for all subjects in the study (baseline, Week 1-Week 4, 1 week post study Follow-up).

Open label Safety Studies

Study A1281123 (ziprasidone Oral suspension and capsules both administered)

Study A1281123 was organized into two (2) distinct dosing periods: A 3-week short-term, open label, fixed dose titration period (period 1) followed by a 27-week long term flexible dose period (Period 2) in patients aged 10-17 with bipolar I, schizophrenia and schizoaffective disorder. Adolescent patients with schizophrenia/schizoaffective disorder were included into this study to support the future NDA submission for adolescent schizophrenia as per the original Written Request. Since the sponsor has not completed studies for the schizophrenia indication under the Written Request at this time, this review will focus on the safety results obtained from only those patients in study A1281123 with a bipolar I diagnosis. However, serious and pertinent safety

findings obtained from patients with a diagnosis of schizophrenia and/or schizoaffective disorder were reviewed by this reviewer.

For period 1, 46 subjects with bipolar I disorder (17 subjects with schizophrenia/schizoaffective disorder) were screened with bipolar subjects scoring at least 17 or higher on the YMRS score being eligible for enrollment. Eligible subjects who continued to meet inclusion criteria were then randomized to one of two 10-day fixed titration dosing groups:

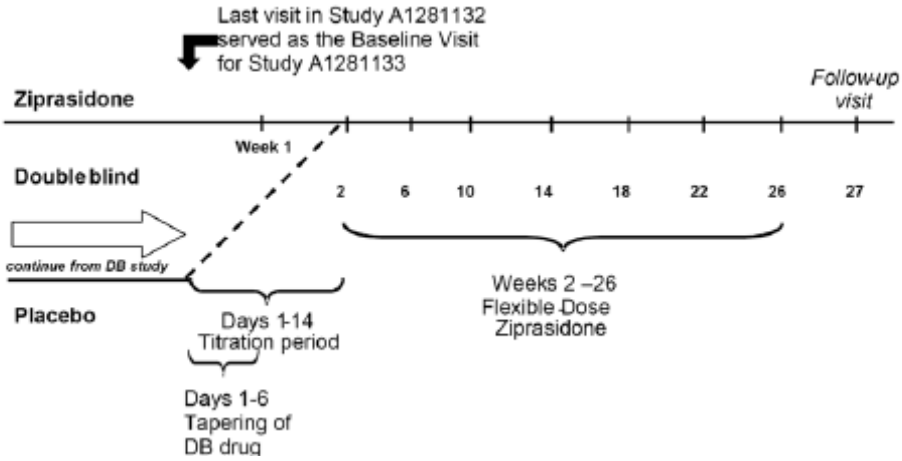
- Low dose group-patients began treatment at 10mg bid with sequential dose titration of 10mg bid increments to final dose of 40mg bid by day 10.
- High dose group- patients began treatment at 20mg bid with sequential dose titration of 20mg bid increments to final dose of 80 mg bid by day 10.

Patients who weighed <45 kg in body weight were to receive 50% of the stated mg strength associated with their respective Study Group Assignment for period 1. The rationale for administering 50% less medication to patients <45kg was to compensate for a possible increase in systemic exposure of ziprasidone in lower body weight subjects. All patients were prescribed ziprasidone oral suspension for period 1.

On August 4, 2004, the sponsor discontinued randomization into the low dose group in order to correct for low recruitment and poor completion rates for the high dose group. Sufficient data was obtained from the low dose group prior to discontinuation. Interim analyses showed that the low dose group showed better toleration as opposed to the high dose group over the initial 10 day dosing titration, but many low dosed patients needed additional medication in order to control symptoms. The results of these interim analyses were presented to the Agency on November 8, 2004 during a teleconference. It was agreed during the teleconference that the study results identified an allowable maximum tolerated dosing range and titration schedule to permit phase III studies.

For period 2 of the study, patients were allowed to take open label ziprasidone with concomitant medications (if required) for an additional 24 weeks after the completion of period 1 or early termination from period 1. In contrast to period 1 however, patients who weighed <45kg may receive doses up to 80mg BID, based upon symptomatology. The sponsor was to be notified for any patients <45kg who was titrated to doses above 40mg BID/day. Follow-up outpatient assessments were collected at weeks 4 (1 week after completion/ET from period 1), week 8, and weeks 12, 18 and 27. Patients were administered ziprasidone as either an oral capsule or oral suspension for period 2.

<u>Study A1281133 (ziprasidone capsules)</u>
This study was the open-label extension study to the placebo controlled study A1281132. Patients who completed at least three weeks of double-blind treatment under study A1281132 were eligible to enter this 26-week open label study. Patients were first tapered off their double blind medication for the first five days of the study and then re-titrated with active open label ziprasidone with flexible dosing to maintain optimal efficacy and tolerability. Patients who weighed less than 45kg were permitted to be titrated to a maximum dose of 80mg/day. The schematic below delineates the study design for study A1281133:



6.1.3.1 Patient Samples

Important inclusion criteria were:

- Patients aged 10-17 at time of study entry
- Had a primary diagnosis of bipolar I disorder, manic or mixed, as defined by DSM-IV through a K-SADS interview with symptoms for at least 7 days prior to screening.
    - "…as determined by a board-certified or board eligible child psychiatrist" was added as of the December 6, 2006 protocol amendment; original protocol issued September 22, 2005.
- Had both a screening and baseline YMRS score ≥17
- Patients were willing to discontinue all prohibited medications within 4.5 half lives or 10 days (whichever is less) prior to randomization.
- Female patients of childbearing potential are using appropriate birth control procedures.

Patients were excluded from participating for the following reasons:

Psychiatric Exclusions

- Patients who are stable on current regimen or have a substance abuse disorder
- Patients with rating of seven (7) on the single item suicidal ideation item #13 of the CDRS-R or thought to be at imminent risk of suicide or homicide.
- Patients with IQ <70 or with autism/PDD

Medical Exclusions

- Patients with any unstable serious medical condition
- Patients with a history of non-vasovagal syncope
- Abnormal liver function tests at screening (twice the upper limit of normal (ULN) or 1.5 X ULN for bilirubin), significant liver disease

- Clinically significant hypokalemia/hypomagnesaemia either not corrected or needing daily supplementation
- History of AIDS

Cardiovascular Exclusions

- History of significant cardiovascular disease requiring treatment and/or evaluation.
- History of cardiac arrhythmias, conduction abnormalities, QT prolongation or genetic risk for long QT prolongation
- Patients with clinically significant ECG abnormalities at baseline and screening, including a QTcF $\geq$460msec.

Medication Exclusions

- Patients who have taken Clozaril within 12 weeks of randomization or a depot antipsychotic within four weeks or an MAOI two weeks before baseline.
- Patients taking a concomitant medication known to prolong the QTc interval
- Patients who were non-responsive to a previously adequate trial of ziprasidone.

6.1.3.2 Concomitant medications

Patients were allowed to take the following medications during the study.

- Lorazepam for agitation and for insomnia
- Benadryl or Ambien for insomnia
- Anticholinerigcs or propranolol for EPS
- Non-sedating antihistamines, Tylenol, aspirin, pseudoephedrine
- Laxatives

6.1.3.3 Schedule of Assessments

The following table delineates the scheduled assessments that were performed for all subjects under study A1281132.

	Screening	Baseline	Treatment			EOT	FU[a]
Study Day	**-10 to –1**	**0**	**7**	**14**	**21**	**28**	**35**
Informed consent, assent	X						
Medical, psychiatric, family, suicidality history	X						
K-SADS	X						
Physical exam including body temperature	X					X	
Height/weight/BMI/waist circumference	X					X	
Electrocardiogram[b]	X	X[c]	X	X	X	X[d]	X[e]
Pharmacokinetic sample		X[f]				X[d]	
Blood pressure/pulse rate	X	X	X	X	X	X[d]	X[e]
Safety laboratory tests	X	X[e]		X		X	X[e]
Hormone assessment[g]	X	X[e]				X	X[e]
Fasting glucose, lipids, insulin, $HbA1_c$	X	X[e]				X	X[e]
Hepatitis serology	X						
Urine drug screen	X	X		X		X	
Serum pregnancy test	X	X		X		X	
Anonymized pharmacogenomics[h]		X					
Randomization		X					
Study drug dispensed		X	X	X	X		
Drug accountability			X	X	X	X	
YMRS	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	
CGI-I			X	X	X	X	
CGAS	X	X		X		X	
CHQ		X				X	
School placement		X		X		X	
CPBAQ	X	X	X	X	X	X	
CDRS-R	X	X	X	X	X	X	
CNS Vital Signs, including sedation item	X	X				X	
SARS, BAS, AIMS		X	X	X	X	X	X[e]
Tanner staging		X					
Adverse event assessments		X	X	X	X	X	X
Prior medications	X						
Concomitant medication		X	X	X	X	X	X

Source: Protocol (Appendix A1)
AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Rating Scale, BMI = body mass index, CDRS-R = Child Depression Rating Scale-Revised, CGAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression of Severity, CHQ = Child Health Questionnaire, CPBAQ = Children's Problem Behavior and Aggression Questionnaire, ECG = electrocardiogram, EOT = end-of-treatment, FU = follow up, $HbA1_c$ = glycosylated hemoglobin, IRB = institutional review board, K-SADS = Schedule for Affective Disorders and Schizophrenia for School Age Children, PK = pharmacokinetic, SARS = Simpson Angus Rating Scale, T4 = free thyroxine, TSH = thyroid-stimulating hormone, YMRS = Young Mania Rating Scale
[a]Subjects who did not enter the open extension returned for a post-treatment follow-up visit at Week 5.
[b]ECGs administered at least 3 hours after food intake.
[c]Triplicate ECGs after all assessments (except PK and before dosing).
[d]Obtained before and after dosing.
[e]Only if abnormalities present at the previous visit.
[f]Sample obtained twice after first dose of study medication.
[g]Free T_4 and TSH, prolactin, testosterone, IGF-1, IGFBP-3.
[h]Optional and subject to IRB approval

6.1.4 Efficacy Findings

Subject Disposition
Out of a total of 327 subjects screened, 238 were randomized to treatment, with 237 taking at least one dose of study medication (modified ITT population).

As seen below, the completion rates were 65% for ziprasidone vs. 58% for placebo.

TABLE 5: Study A1281132 Completion rates

	PLACEBO	**ZIPRASIDONE**
No. treated	88	149
Total No. of early discontinuations	37 (42%)	52 (35%)
Reason for Discontinuation		
Adverse event	13 (15%)	18 (12%)
Withdrew Consent	2 (2%)	9 (6%)
Lost to Follow up	1 (1%)	8 (5%)
Lab Abnormality	0	1 (1%)
Other*	21 (24%)	16 (11%)
Total	**37**	**52**

*Primarily included lack of efficacy or therapeutic response and insufficient response

In addition, the sponsor also characterized the discontinuation rates related to the fast (i.e. daily titration) vs. slow (every 2nd day) titration schedule. The results are seen below and indicate that slow titration was associated with more discontinuations due to adverse events compared to fast titration for both groups of patients and more overall discontinuations in the ziprasidone group when compared to fast titration:

TABLE 6: Patient Discontinuation by titration speed

	PLACEBO N=88		**ZIPRASIDONE N=149**	
	Fast (n=37)	**Slow (n=51)**	**Fast (n=56)**	**Slow (n=93)**
Adverse Event	2 (5%)	11 (22%)	3 (5%)	15 (16%)
Withdrew Consent		2 (4%)		9 (10%)
Lost to F/U		1 (1%)	2 (4%)	6 (6%)
Lab Abnl.			1 (2%)	
Other	15 (41%)	6 (12%)	6 (12%)	10 (11%)
Total	**17 (46%)**	**20 (39%)**	**12 (21%)**	**40 (43%)**

Protocol Deviations

There were a total of 113 protocol violations from 83 patients (ziprasidone 53; Placebo 25; not received any treatment 5). A listing of the top 6 protocol violations are seen below. The largest

number of protocol violations (40) occurred as a result of dosing/medication errors with study medication.

TABLE 7: Listing of Top 6 Protocol Deviations

PROTOCOL DEVIATION	NUMBER OF SUBJECTS
Dosing/medication errors*	40
Two or more positive UDS at any two visits	13
Subject not contacted daily during titration period	11
Week 4 visit more than 3 days outside of window	10
Informed Consent obtained by study coordinator	7
KID-SCID administered rather than K-SADS	5

*Defined as dosing errors from: 1) sites Punjwani, Lopez, Thebaud; 2) all subjects from site 1089 (Tim Summers MD) due to widespread protocol and GCP violations; 3) Exceeded maximum allowed dose for 6 or more doses (10 patients); 4) failure to reach target dose by day 14; 5) missed 20% of dose between first and last dose; 6) dosed below minimum allowed dose for 3 or more doses after reaching max dose.

At the request of this reviewer on January 30, 2009, the sponsor delineated the 40 dosing/medication errors, which included seven (7) patients who exceeded the maximum dose for greater than 6 doses and three (3) patients who misunderstood the dosing instructions. A further analysis performed by the sponsor to identify all patients who took at total daily dose of drug the exceeded the maximum dose on any occasion delineated a total of 26 patients (14 ziprasidone, 12 placebo) which includes nine (9) subjects from the previously described 10 patients. These additional 17 patients were not considered to be a protocol deviation as the number of overdoses was less than 6. Of the additional nine ziprasidone patients identified, five (5) subjects had adverse events during the period of overmedication. However there were no serious adverse events (SAEs) or patient's discontinuations noted for these additional patients. Adverse events for these patients included sedation, headache, somnolence, nausea, and vomiting.

Baseline Demographics

As seen in the table below, the majority of patients in this study were white adolescent males aged 13.6-13.7 years old.

Table 8: Demographic Characteristics of Study A1281132

DEMOGRAPHIC VARIABLE	PLACEBO N= 88	ZIPRASIDONE N= 149
Male (%)	47	84
White (%)	72 (82%)	121 (81%)
Black (%)	14 (16%)	21 (14%)
Mean Age (years)	13.7 ± 2.0	13.6 ± 2.2
Mean Weight (kg)	60.0 ± 16	57.2 ± 14.4

Baseline Psychiatric History

There appeared to be little difference in the duration length from initial diagnosis of bipolar disorder prior to screening between the ziprasidone and placebo treated subjects. The mean duration of illness ranged from 9.1 months (range 0-103.1 months) in the placebo group to 11.6 months (range 0-111.9 months) in the ziprasidone group. The majority of the patients had a primary diagnosis of bipolar I disorder, most recent episode mixed. Although the number of psychiatric hospitalizations (an indicator of severity of disease) was not reported in the study report, there were a greater proportion of patients with bipolar illness with psychotic features in the placebo group compared to ziprasidone (18% vs. 9% respectively).

Table 8a: Characteristics of the Presenting DSM-IV Bipolar Diagnosis

DSM-IV BIPOLAR I DISORDER DIAGNOSIS	PLACEBO N=88	ZIPRASIDONE N=149
Manic Episode	23 (26%)	45 (30%)
Mixed Episode	57 (60%)	90 (65%)
Single Manic Episode	8 (9%)	14 (9%)
Psychotic Features (all categories)	16 (18%)	13 (9%)

Concomitant medication use

Lorazepam use was permitted on an as needed basis during the double-blind treatment period up to maximum of 2mg/day, except within 6 hours prior to any assessments. In addition, 68% (101/149) of ziprasidone treated subjects received a concomitant medication during the study compared to 59% (52/88) of placebo treated subjects. The study allowed for lorazepam, diphenhydramine or zolpidem for treatment of insomnia. The top 6 concomitant medications used in ziprasidone treated patients are presented below:

TABLE 9: Concomitant Medication use In Study A1281132

CONCOMITANT MEDICATION	ZIPRASIDONE N=149	PLACEBO N=88
Benztropine Mesylate	26 (17%)	5 (6%)
Lorazepam	24 (16%)	15 (17%)
Paracetamol	19 (13%)	15 (17%)
Ibuprofen	16 (11%)	8 (9%)
Diphenhydramine	20 (13%)	12 (14%)
Zolpidem	10 (7%)	5 (6%)

Review of the database also showed that one patient each in the ziprasidone treatment groups received haloperidol and olanzapine vs. none in the placebo group. In addition three (3) ziprasidone treated patients vs. 0 placebo patients received quetiapine. For placebo treated subjects, two (2) patients were reported as taking ziprasidone.

The sponsor did not provide any data regarding the duration of concomitant medication use during the study. However since the percentage of concomitant medication use was generally similar between treatment groups, it is unlikely that concomitant medication significantly biased the efficacy results.

The nearly 3:1 increase in use of benztropine mesylate in the ziprasidone treatment group suggests that a significant proportion of patients taking ziprasidone likely experienced extrapyramidal symptoms with ziprasidone use. Extrapyramidal use is associated with atypical antipsychotic use. However the proportion of pediatric patients with likely EPS symptoms based on benztropine use (17%) is greater than the percentage of adult bipolar patients who reported EPS during clinical trials as per current approved labeling [11% (31/279) vs. 9% (12/136) ziprasidone to placebo].

Exposure Data

The mean duration of exposure for study A1281132 in the ziprasidone group was 22.0 days vs. 23.7 days in the placebo controlled group. The mean daily dose during weeks 3, 4 and early termination in patients ≥ 45kg was 118.8 mg, with a mean modal dose of 69.23 for patients <45kg.

Efficacy Results

Despite a moderate placebo effect on YMRS scores, the results from the primary statistical analysis demonstrated a statistically significant mean change decrease in YMRS scores from baseline at week 4 for the ziprasidone treated group as compared to placebo treated patients. The primary statistical model pre-specified the use of a mixed model of repeated measures analysis.

Table 10: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the modified Intent to Treat population

STATISTIC	ZIPRASIDONE N=133*	PLACEBO N=85*
Least squares mean (SE)	-13.83 (0.96)	-8.61 (1.10)
Difference from placebo (SE)	-5.22 (1.48)	
95% Confidence interval for difference from placebo	(-8.12, -2.31)	
P-value	0.0005	

*modified Intent to treat (i.e. those patients with at least on post-dose efficacy measurement)

Even after excluding subjects from sites 1013, 1087 and 1089 as a result of widespread GCP violations identified by the FDA DI and the sponsor, efficacy was still maintained.

Table 10a: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the modified Intent to Treat population: Excluding subjects from sites 1013, 1087 and 1089

STATISTIC	ZIPRASIDONE N=118	PLACEBO N=76
Least squares mean (SE)	-14.08 (0.99)	-8.74 (1.19)
Difference from placebo (SE)	-5.34 (1.56)	
95% Confidence interval for difference from placebo	(-8.40, -2.27)	
P-value	0.0007	

Efficacy was still seen for the primary efficacy endpoint in the per-protocol analysis even after sites 1013, 1087 and 1089 were excluded from the per-protocol analysis. The per-protocol analysis excluded ITT subjects from the analysis that did not violate any major inclusion/exclusion criteria or have major protocol violations and completed at least 1 week of study treatment post medication titration.

Table 10c: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the Per Protocol Population: Excluding subjects from sites 1013, 1087 and 1089

STATISTIC	ZIPRASIDONE N=90	PLACEBO N=62
Least squares mean (SE)	-14.47 (1.06)	-8.35 (1.36)
Difference from placebo (SE)	-6.13 (1.81)	
95% Confidence interval for difference from placebo	(-9.68, -2.58)	
P-value	0.0008	

Using the standard Last-Observation Carried Forward (LOCF) analysis of the primary endpoint, a similar statistically significant mean change reduction in the week 4 YRMS scores was also seen between the ziprasidone group as compared to placebo.

Table 11: Mean change from baseline analysis at week 4 in YMRS scores in the modified Intent to Treat population- LOCF Analysis

STATISTIC	ZIPRASIDONE N=133*	PLACEBO N=85*
Least squares mean (SE)	-13.23 (0.79)	-7-.14 (0.93)
Difference from placebo (SE)	-6.09 (1.08)	
95% Confidence interval for difference from placebo	(-8.23, -3.96)	
P-value	<0.0001	

*modified Intent to treat (i.e. those patients with at least one post-dose efficacy measurement)

Although formal statistical testing was not pre-specified for efficacy between the fast and slow titration sub-groups, a review of their respective week 4 mean change from baseline scores reveals overlapping 95% confidence intervals for the fast titration group as compared to placebo whereas patients with a slower titration schedule did not have overlapping confidence intervals as compared to placebo. This suggests that a slower speed of titration in adolescent patients may be associated with improved efficacy over a faster titration schedule.

Table 12: Descriptive Statistics for YMRS total score at baseline and change from baseline at week 4 by slow and fast titration sub-group-Modified ITT population

GROUP	$N_{BASELINE}$	MEAN BASELINE SCORE (SD)	$N_{WEEK\ 4}$	MEAN CHANGE WEEK 4 SCORE (SD)*	95% CI
Fast Titration					
ziprasidone	56	27.1 (7.2)	42	-11.7 (9.3)	(-14.25,-9.20)
Placebo	37	27.9 (6.6)	37	-7.0 (8.2)	(-9.76,-4.30)
Slow Titration					
ziprasidone	87	25.5 (6.2)	79	-13.6 (7.8)	(-15.32,-11.82)
Placebo	49	26.3 (6.6)	48	-7.1 (7.5)	(-9.28,-4.93)

*Last Observation Carried Forward (LOCF)

Key Secondary Endpoint
For the key secondary endpoint-change from baseline in the CGI-S score at week 4, patients in the ziprasidone group had a statistically significant reduction in severity scores as compared to placebo treated subjects at week 4. This additional analysis further supports the clinical efficacy of ziprasidone in the treatment of childhood and adolescent bipolar disorder.

Table 13: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in CGI-S scores in the modified Intent to Treat population

STATISTIC	ZIPRASIDONE N=133*	PLACEBO N=85*
Least squares mean (SE)	-1.43 (0.13)	-0.74 (0.13)
Difference from placebo (SE)	-0.69 (0.18)	
95% Confidence interval for difference from placebo	(-1.03, -0.34)	
P-value	0.0001	

*modified Intent to treat (i.e. those patients with at least on post-dose efficacy measurement)

As with the results from the primary efficacy reanalyses excluding subjects from three sites listed, ziprasidone patients continued to demonstrate less severe symptoms when compared to placebo subjects.

Table 13a: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in CGI-S scores in the modified Intent to Treat population Excluding subjects from sites 1013, 1087 and 1089

STATISTIC	ZIPRASIDONE N=118	PLACEBO N=76
Least squares mean (SE)	-1.44 (0.15)	-0.75 (0.14)
Difference from placebo (SE)	-0.69 (0.19)	
95% Confidence interval for difference from placebo	(-1.05, -0.33)	
P-value	0.0002	

Additional Secondary Endpoints
In addition, scores on the CGI-I instrument also indicates that patients taking ziprasidone had improvement in their clinical functioning from baseline to week 4 when compared to patients taking placebo.

Table 14: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in CGI-I scores in the modified Intent to Treat population

STATISTIC	ZIPRASIDONE N=132*	PLACEBO N=85*
Least squares mean (SE)	2.30 (0.13)	3.06 (0.16)
Difference from placebo (SE)	-0.76 (0.21)	
95% Confidence interval for difference from placebo	(-1.18, -0.34)	
P-value	0.0004	

*modified Intent to treat (i.e. those patients with at least on post-dose efficacy measurement)

Patients who were taking ziprasidone also had improved scores at week 4 on the Childhood-Global assessment of functioning [58.2 $\pm$ 12.4 vs. 51.5 $\pm$ 15.2 ziprasidone to placebo respectively). The proportion of patients whose CGAS scores indicated a return to normal functions (i.e. score $\geq$ 70) was higher in the ziprasidone group [21.6% (27/125)] as compared to placebo patients [12% (10/83)] by week 4 using an LOCF approach. The proportions of normal functioning subject reported to be in school were even higher fro ziprasidone treated patients [27% (14/52)] vs. placebo [3% (1/36)] at week 4.

Also mean change from baseline scores at week 4 between ziprasidone and placebo treated subjects on the Child Health Questionnaire form appeared to be similar across the different domains and subscales, though no formal statistical testing was performed.

6.1.4.1 Subgroup Efficacy Analysis of Primary Endpoint

At the request of this reviewer in January 2009, the sponsor conducted additional efficacy analyses for patients gender, race, age and weight for the primary endpoint YMRS. It should be

noted that the sponsor did not power the study to demonstrate statistical significant for subgroup efficacy analyses.

By Weight

The sponsor conducted a primary statistical analysis of the primary and secondary endpoints by subject weight. Using the ITT population, a treatment effect was demonstrated for patients weighing ≥45kg in ziprasidone treated subjects when compared to placebo. Although a trend towards improvement on the YMRS scores was noted for ziprasidone treated subjects vs. placebo who weighed less than 45kg, statistical significance was not achieved in this very small subgroup analysis.

TABLE 15: Change from baseline in YMRS at Week 4 repeated measures by weight

METRIC	≥45KG		<45KG	
	ziprasidone N=102	**Placebo N=71**	**ziprasidone N=31**	**Placebo N=14**
Least Squares Mean (SE)	-14.15 (0.90)	-8.21 (1.11)	-12.83 (1.86)	-10.97 (2.92)
Difference from placebo	-5.93		-1.86	
p-value	<0.0001		0.5643	

By Gender

Using a repeated measures ANCOVA analysis, both male and female patients demonstrated efficacy on the primary endpoint at week 4, though the treatment effect was greater for males than for females.

TABLE 16: Change from baseline in YMRS at Week 4 repeated measures by gender

METRIC	MALE		FEMALE	
	ziprasidone N=74	**Placebo N=44**	**ziprasidone N=59**	**Placebo N=41**
Least Squares Mean (SE)	-13.41 (1.12)	-6.50	-14.44 (1.15)	-10.70 (1.45)
Difference from placebo	-6.91		-3.74	
p-value	<0.0001		0.0445	

Age Group

Patients 14 years of age and older demonstrated efficacy with ziprasidone for bipolar symptoms whereas patients who were younger failed to demonstrate efficacy despite numerical

improvement in symptoms. Although both age groups receiving placebo achieved nearly identical response rates, a smaller treatment effect was seen.

TABLE 17: Change from baseline in YMRS at Week 4 repeated measures by age group

METRIC	AGE 10 TO <14 YEARS		AGE 14 YEAR TO <=18 YEARS	
	ziprasidone N=66	**Placebo N=35**	**ziprasidone N=67**	**Placebo N=50**
Least Squares Mean (SE)	-12.44 (1.12)	-8.57 (1.71)	-15.36 (1.15)	-8.33 (1.31)
Difference from placebo	-3.88		-7.03	
p-value	0.0510		<0.0001	

Race

White patients demonstrated efficacy as compared to other races. However generalization of this finding is not possible from this study as there were too few black and "other" races leading to a lack of statistical power to detect any treatment effects based on race alone.

TABLE 18: Change from baseline in YMRS at Week 4 repeated measures by Race

METRIC	WHITE		BLACK		OTHER	
	ziprasidone N=112	**Placebo N=69**	**ziprasidone N=15**	**Placebo N=14**	**ziprasidone N=5**	**Placebo N=2**
Least Squares Mean (SE)	-13.98 (0.95)	-7.68 (1.21)	-12.44 (2.30)	-11.38 (2.51)	-11.96 (2.62)	-17.54 (4.01)
Difference from placebo	-6.29 (1.37)		-1.06 (3.26)		5.59 (4.80)	
p-value	<0.0001		0.7461		0.2640	

6.1.4.2 Subgroup Efficacy Analysis of Secondary Endpoint

At the request of this reviewer in January 2009, the sponsor conducted additional efficacy analyses for patient's weight for the key secondary endpoint CGI-S. As with the primary efficacy subgroup analysis, only patients who weighed ≥45kg demonstrated efficacy on the key secondary endpoint.

Table 19: Mean change from baseline in CGI-S scores by subject weight

METRIC	≥45KG		<45KG	
	ziprasidone N=102	**Placebo N=71**	**ziprasidone N=31**	**Placebo N=14**
Least Squares Mean (SE)	-1.48 (0.12)	-0.70 (0.15)	-1.32 (0.20)	-1.03 (0.32)
Difference from placebo	-0.78		-0.28	
p-value	<0.0001		0.4122	

6.1.4.3 Per Protocol Analysis

A separate per-protocol analysis was performed by the sponsor that excluded the following subject data for the analysis:

1. Subjects affected by dosing errors
2. All subjects at site 1089 (Tim Summers) due to widespread protocol and GCP violations
3. Patients taking prohibited concomitant medications
4. Patients with a week 4 visit more than 5 days out-of-window
5. Patients that failed to reach target dose (based on weight) by day 14
6. Patients that missed more than 20% of doses
7. Patient dosed below the minimum for 3 or more days after reaching target dose
8. Patients with two or more positive drug screens

The results from this analysis again demonstrated that patients randomized to ziprasidone were statistically more likely to have improved YMRS scores as compared to placebo patients.

Table 20: Mean change from baseline analysis at week 4 repeated measures (MMRM analysis) in YMRS scores in the per-protocol population

STATISTIC	ZIPRASIDONE N=95	PLACEBO N=65
Least squares mean (SE)	-14.46 (1.01)	-8.16 (1.35)
Difference from placebo (SE)	-6.30 (1.70)	
95% Confidence interval for difference from placebo	(-9.77, -2.82)	
P-value	0.0004	

6.1.5 Clinical Microbiology

Clinical microbiology data is not applicable to this clinical study.

6.1.6 Efficacy Conclusions

The results from study A1281132 clearly demonstrates that patients with ziprasidone had significant improvements in acute bipolar symptoms and acute symptom severity when compared to placebo treated subjects. Taken together with the results from the adult bipolar trials, ziprasidone is effective for the acute treatment of pediatric bipolar symptoms.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This review is primarily focused on the safety data and analysis that took place during the pediatric bipolar studies. For purposes of analysis, two separate reviews will be performed on the safety data: one from the double-blind study and the other focused on the combined safety data from the two open-label studies. Pertinent safety data that has been submitted as part of this NDA for pediatric patients enrolled in schizophrenia trials were also reviewed and discussed within this review.

7.1.1 Deaths

No deaths occurred during any of the pediatric bipolar trials. However one reported death (completed suicide) did occur in a patient with schizophrenia enrolled in the long-term extension part of the pediatric schizophrenia double-blind, flexible dose study AS1281134 at the time of her death.

Subject 2007000210-a 17 year old female in Singapore with an approximate 2-year history of disorganized type schizophrenia (paranoid delusions, auditory hallucinations, psychosis with depressive symptoms), biochemical hyperthyroidism (not clinically significant by endocrinologist) and a past history of thyrotoxicosis 2 years prior, was enrolled into the flexible dose study A1281134 for schizophrenia. She then entered into the extension study A1281135 after reaching the maximum dose ziprasidone in study A1281134 (160mg).

The patient continued to have psychotic symptomatology during her inpatient stay, however the patient was granted home leave with her mother by the inpatient clinicians as the patient did not verbalize any suicidal ideations or display self-harm behavior to hospital staff. Her mother was planning to return her daughter to the hospital two days earlier due to worsening psychotic symptomatology with agitation but decided to let the patient rest at home after a successful visit to her grandmother's house. Upon arriving at home, the patient was left at home alone by the mother to rest as the mother determined that her son (the patient's brother) should see a doctor for abdominal pain. After the mother and brother completed the doctor's visit and returned home, both the mother and brother failed to locate the patient until the brother discovered that the patient had jumped out a window in the apartment to her death. No suicide note was written.

Based on the information presented in this case study, it is unlikely that ziprasidone use was causally related to the suicide of this patient, though the possibility of such an association (though remote) is still present. Suicidal behavior and completed suicides has been consistently associated with psychotic illnesses, particularly in an agitated psychotic state. The case report suggests that this patient continued to suffer from psychotic processes with increasing agitation while on home leave and fell to her death while home alone. It is this reviewer's opinion that the worsened psychotic state of this patient is more likely causal to this patient's death than is the use of ziprasidone.

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) were defined by the sponsor as those events that led to:

- Death
- were life threatening (immediate risk of death)
- led to a congenital anomaly/birth defect
- prolonged a pre-existing hospital stay
- led to a persistent or significant disability

Double-Blind Study A1281132

There were a total of 13 reported SAEs- six (6) in the ziprasidone group; seven (7) in the placebo group, that occurred during study A1281132 as listed below.

TABLE 21: Listing of Serious Adverse Events for study A1281132

SUBJECT NUMBER	WEIGHT GROUP	MEDDRA PREFERRED TERM	TOTAL DAILY DOSE	ACTION TAKEN	OUTCOME
ziprasidone N=6					
10261001	<45kg	Overdose Dystonia	100mg 100mg	Discontinued	Recovered
10281002	≥45kg	Viral Infection	20mg	Discontinued	Unknown
10401008	≥45kg	Suicidal Ideation	100mg	None	Recovered
10401022	≥45kg	LFTs abnormal	40mg	Discontinued	Recovered
10831001	≥45kg	Mania	80mg	Discontinued	Recovered
11241003	≥45kg	Aggression, physical aggression, verbal hyper sexuality	160mg	None	recovered
Placebo N=7					
10211004	<45kg	Bipolar I	0	None	Recovered
10331005	<45kg	Bipolar	-	Discontinued	Unknown

		Disorder			
10401015	≥45kg	Suicidal ideation	0	Discontinued	Recovered
10401023	<45kg	Suicidal ideation	0	Discontinued	Recovered
10891009	≥45kg	Suicidal ideation	0	Discontinued	Recovered
11241002	≥45kg	Aggression, hallucination, paranoia	0	Discontinued	Recovered
11241004	≥45kg	Aggression, verbal aggression, violence	0	None	recovered

Subject 10261001 was an 11 year old patient who incorrectly took her medication on the drug dispensing card. Instead of taking 20mg twice daily for the first two days of the trial, the subject took 80mg in the first evening, followed by 20mg in the morning and 80mg the second evening. The subjects went to the emergency room with an acute dystonic reaction, treated with anticholinergic medication and recovered without clinical sequealae.

Subject 10401022 was a 17 year old female who complained of abdominal and back pain 6 days after initiation of ziprasidone. Four days later laboratory tests indicated elevated liver enzymes. The investigator attributed the increase to mononucleosis. This patient was consequently discontinued from the study and recovered without sequelae.

Subject 10401008 was a 15 year old male who was reported to have had an altercation with his family 7 days after randomization. After the patient threatened to hurt himself and his stepfather once police were called, the subject was taken to the hospital, subsequently admitted and discharged one week later without clinical squealae.

Open Label Studies

From a total population of 201 patients, 35 patients reported 45 serious adverse events as delineated below. The vast majority of the SAEs that occurred in the open label trials were psychiatric SAEs, with bipolar disorder and suicidal ideation being the main two psychiatric SAEs of note. One additional SAE of “suicidal ideation” was reported in a patient with schizophrenia or schizoaffective disorder.

TABLE 22: SAEs from the Combined open-label studies

PREFFERED TERM	NUMBER OF EVENTS BIPOLAR PATIENTS ONLY N=201	NUMBER OF EVENTS BIPOLAR, SCHIZPHRENIA AND SCHIZOAFFECTIVE PATIENTS N=218
GI Disorders		
Constipation	1	1
General Disorders		
Drug Ineffective	2	2
Injury, Poisoning and procedural complications		
Overdose	1	1
Investigations		
ECG QT Prolonged	1	1
Nervous System Disorders		
Sedation	1	1
Psychiatric Disorders		
Aggression	3	3
Agitation	1	1
Bipolar/Bipolar I Disorder	13	13
Conversion Disorder	1	1
Delusion	1	1
Depressive Symptom	1	1
Hallucinations (auditory, visual, mixed)	3	3
Homicidal Ideation	2	2
Intentional Self injury-self injurious behavior	2	2
Mania	1	1
Negative Thoughts	1	1
Oppositional defiant disorder	2	2
Suicidal Ideation	8	9

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Placebo Controlled Trial

Please see table 5 in Section 6.1.4

Open Label Trials

Out of the 201 bipolar patients enrolled into the open label safety study, 188 received ziprasidone =<160mg/day. The remaining 13 patients received doses of ziprasidone above the maximum daily dose of 160mg/day. A total of 107 bipolar patients (57%) out of 188 discontinued from the trial early as seen below. Adverse events (24%) and subjects no longer willing to participate (18%) accounted for the majority of the reasons for subject discontinuation.

TABLE 23: Reason for Discontinuation by dose, combined open label studies

	≤40MG N=18	**<40 TO ≤80MG N=54**	**>80 TO ≤120MG N=29**	**>120 TO ≤160MG N=87**	**>160MG N=13**	**ALL SUBJECTS ≤160MG N=188**
Adverse Event	6 (33%)	15 (28%)	4 (14%)	20 (23%)	3 (23%)	45 (24%)
Insuff. Response	1 (6%)	3 (6%)	0	0	0	4 (2%)
Protocol Violations	1 (6%)	0	0	1 (1%)	0	2 (1%)
Subject no longer willing to participate	0	8 (15%)	9 (31%)	17 (20%)	1 (8%)	34 (18%)
Other*	1 (6%)	1 (2%)	3 (10%)	5 (6%)	1 (8%)	10 (5%)
Total Discontinued	**12 (67%)**	**30 (56%)**	**18 (62%)**	**47 (54%)**	**5 (38%)**	**107 (57%)**

*Includes long term care, investigator request, site closure, psychotherapy, scheduling conflicts, lack of efficacy (2) and withdrew consent (1).

7.1.3.2 Adverse events associated with dropouts

Placebo-Controlled study
Sedation, bipolar disorder/mania, dystonia and abnormal LFTs accounted for majority of the adverse event causes for patient dropouts assigned to ziprasidone in this study. Bipolar disorder/mania and suicidal ideation were associated with the majority of patient dropouts in the placebo group. Overall 13% (19/149) of ziprasidone patients compared to 15% (13/88) of placebo patients prematurely discontinued the study due to adverse events as seen below in table 24. Also the sponsor reported that the percentage of patients who discontinued due to an adverse event during fast vs. slow titration was 7.1% vs. 15.1% in the ziprasidone group and 5.4% vs. 17.6% in the placebo group.

Discontinuations due to adverse events were grouped by patient weight at the request of this reviewer in January 2009. The result of the subgroup analysis revealed a similar proportion of

patients stopping treatment in that 9% of patients weighing <45kg discontinued the study due to an all cause adverse event compared to 13% of patients weighing ≥45kg.

TABLE 24: Adverse Event DISCONTINUATION RATES FROM PLACEBO CONTROLLED TRIAL-Preferred Term

REASON FOR DISCONTINUATION	PLACEBO N=88	ZIPRASIDONE N=149
Sedation	---	4
Bipolar disorder/mania	5	2
Suicidal Ideation	4	---
Dystonia	1	2
QT Prolongation	---	1
LFT's increased/abnormal	---	2
Pregnancy	---	1
Extrapyramidal symptoms	---	1
Restlessness	---	1
Viral Infection	---	1
Syncope	---	1
Dysphagia	---	1
Nausea/Vomiting	---	1
Muscle Spasm	---	1
Self-Injurious behavior	1	---
Loss of Consciousness	1	---
Aggression	1	---
Total	**13**	**19**

Patient 11031004-a 15 year old female with a history of ADHD and allergic rhinitis assigned to placebo, experienced a loss of consciousness for 15 minutes with symptom resolution on the same day (day 7 of treatment with placebo). The causality or etiology of the event was not documented for this particular patient. No additional information regarding the event was provided within the submission. As a result of the event, the patient was discharged from the study.

Patient 10161008-a 13 year old male with history of asthma, excessive sweating, joint pain, seasonal rhinitis and frequent cough, was discontinued from the study on day 16 after experiencing an episode of moderate syncope. He was receiving 40mg/day of ziprasidone at the time of the syncopal event. It was noted that from day 3 to day 9, the patient exhibited tremor, sedation and poor balance leading to a temporary reduction in his dose. A review of his ECG reports indicate that the last ECG recording revealed a mean QTcF of 399 msec compared to his baseline mean QTcF value of 370msec (a 29 msec increase in QTcF over his baseline value). His mean baseline heart rate was 52bpm with a final mean heart rate of 61 bpm.

Open Label Studies

There were a total of 45 adverse events that led to subject discontinuation in the open label studies. However only 41 TEAEs led to discontinuation in patients given ziprasidone ≤ 160mg/day as described below. The four (4) TEAEs that led to discontinuation in those patients given doses above 160mg were reported as 'Overdose" and "Bipolar disorder" with two reports each respectively.

TABLE 25: Adverse Events associated with Dropouts, Studies A1281123 and 1133

MEDDRA TERM	N
Sedation	7
Bipolar I/Bipolar I disorder	5
Somnolence	4
Suicidal ideation	3
Fatigue, aggression, depression, mania	2 each
Chest pain, disease progression, AST increased, QT prolonged, Akatheisa, bradykinesia, headache, agitation, conversion disorder, delusion, hallucinations (mixed), homicidal ideation, negative thoughts, Oppositional defiant disorder, self injurious behavior, rash	1 each

7.1.3.3 Other significant adverse events

One patient-patient 10801001, who was randomized to ziprasidone and received a single dose of 20mg of ziprasidone became pregnant with subsequent study discontinuation. As of time of this submission, the patient has remained pregnant with no additional information noted at this time.

Open Label Studies

A review of the adverse events from the open label studies did not reveal any other significant adverse events.

7.1.4 Other Search Strategies

The sponsor assessed the suicidality risk during the double-blind, placebo controlled trial using the Columbia Classification system. All possible suicide-related adverse events (PSRAEs) were reviewed and categorized by a panel of experts, led by Dr Kelly Posner of Columbia University. In brief, the Columbia Classification system assigns a numerical value (1 through 8) to each PSRAE after review of the narrative for each PSRAE performed by the panel of experts. Though all possible suicide-related cases are classified using this scale, the Agency has previously focused suicidality analyses on cases classified 1 through 4 of the Columbia classification system, corresponding to the following definitions:

Table 26: Columbia Classification system definitions

COLUMBIA CLASSIFACTION	DEFINITION
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation

The results of PSRAEs analyses performed on the double-blind, placebo controlled trial data are listed below. There were no completed suicides in the trial, with two adjudicated suicide attempts (one each ziprasidone and placebo) that occurred in the trial. There were no cases of preparatory acts noted, however there were four (4) cases of suicidal ideation in the ziprasidone group and three (3) in the placebo group. In this reviewer's opinion, there was not an increased risk of suicidality observed in the placebo controlled trial between patients who took ziprasidone compared to placebo. However the small sample size of this trial limits the generalizability of this finding to the pediatric bipolar population. Thus more large scale double-blind, placebo controlled studies of ziprasidone in pediatric bipolar patients is required in order to appropriately examine the risk of suicidality with ziprasidone use in this population.

Subject Number	MedDRA Preferred Term	Total Daily Dose at Onset	Start Day/ Stop Day	Severity	Outcome	Columbia Classification
Ziprasidone						
10131007	Skin laceration	20 mg	1/11	Mild	Resolved	8
10171013	Accident	60 mg	11/17	Mild	Still present	8
	Joint sprain	60 mg	11/17	Mild	Still present	8
10401008	Self-injurious ideation[a]	100 mg	8/17	Severe	Resolved	4
	Suicidal ideation[a]	100 mg	8/17	Severe	Resolved	4
10401017	Skin laceration	60 mg	29/29	Mild	Resolved	2
11141004	Self mutilation	160 mg	21/21	Moderate	Resolved	7
	Self mutilation	80 mg	28/28	Moderate	Resolved	7
11141005	Suicidal ideation	40 mg	22/30	Mild	Resolved	4
11141008	Self-injurious ideation	160 mg	17/28	Mild	Resolved	4
11171006	Muscle strain	120 mg	16/[>29]	Moderate	Still present	8
Placebo						
10161013	Excoriation	0 mg	3/11	Moderate	Resolved	8
10401015	Suicidal ideation[a]	0 mg	8/13	Severe	Resolved	4
10401023	Suicidal ideation[a]	0 mg	14/[>14]	Severe	Still present	4
10861004	Self-injurious behavior	0 mg	13/[>15]	Mild	Still present	2
10891009	Suicidal ideation[a]	0 mg	15/[>16]	Severe	Unknown	4

MedDRA = Medical Dictionary for Regulatory Activities (Version 10.1)
[ ] imputed values from incomplete dates and times.
[a]SAE

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events are any untoward medical occurrences (or signs and/or symptoms of such) in subjects administered a pharmaceutical product with or without a causal relationship to the treatment as determined by the investigators through a review of clinical and laboratory assessments. Symptoms were collected during on-site visits and telephone contacts from both spontaneous patient reports and responses to queries. Direct observations of patients during on-site visits by site personnel were also used to collect adverse events.

Serious adverse events were collected from the time the subject signed the assent form until 28 days following discontinuation of the study drug administration had elapsed. For all other adverse events, adverse event reporting began at the time of study drug administration until 28 days following discontinuation of the study drug.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Standard adverse event dictionaries were used to categorize both documented and verbatim reports of all adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1. The investigators' terminology (i.e. the 'verbatim' report) was preserved and made available.

A review of the coding audit conducted revealed no discrepancies in categorization between database and adverse event reports.

7.1.5.3 Incidence of common adverse events

Table 27 in section 7.1.5.4 below enumerates the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with ziprasidone in the placebo controlled study. Upon visual inspection of the data, a greater proportion of ziprasidone patients tended to complain of more gastrointestinal symptoms, blurry vision, sedation/somnolence and extrapyramidal symptoms, insomnia, restlessness, musculoskeletal stiffness and hot flushes than those patients randomized to placebo.

7.1.5.4 Common adverse event tables

Table 27: Adverse events occurring in 2% or more in ziprasidone patients

SYSTEM ORGAN CLASS/PREFERRED TERM	PLACEBO N=88	ZIPRASIDONE N=149
Gastrointestinal disorders		
Abdominal Pain	4 (5%)	14 (9%)
Dysphagia	0	3 (2%)
Salivary Hypersecretion	0	3 (2%)
Nausea	6 (7%)	20 (13%)
Stomach Discomfort	2 (2%)	6 (4%)
Vomiting	1 (1%)	11 (7%)
Infections		
Upper Respiratory Infection	0	7 (5%)
Influenza	1 (1%)	3 (2%)
Sinusitis	0	4 (3%)
Eye Disorders		
Vision Blurred	1 (1%)	9 (6%)
Metabolism		
Decreased Appetite	2 (2%)	6 (4%)
Increased Appetite	3 (3%)	3 (2%)
Nervous System Disorders		
Akathesia	1 (1%)	7 (5%)
Dizziness	2 (2%)	16 (11%)
Drooling	0	4 (3%)
Dyskinesia	1 (1%)	3 (2%)
Dystonia	1 (1%)	6 (4%)
Extrapyramidal Disorder	1 (1%)	7 (5%)
Abnormal Glabellar Reflex	0	3 (2%)
Headache	19 (22%)	31 (21%)
Hypersomnia	0	3 (2%)
Sedation	4 (5%)	49 (33%)
Somnolence	7 (8%)	37 (25%)
Tremor	0	8 (5%)
Psychiatric Disorders		
Depression	0	3 (2%)
Insomnia	3 (3%)	13 (9%)
Restlessness	1 (1%)	8 (5%)
Reproductive System		
Dysmenorrhea	1 (1%)	3 (2%)
General Disorders		
Fatigue	6 (7%)	20 (13%)
Pain	0	3(2%)

Injury		
Medication/Drug Dispensing Error	1 (1%)	4 (3%)
Overdose	5 (6%)	7 (5%)
Musculoskeletal		
Joint Stiffness	1 (1%)	3 (2%)
Musculoskeletal stiffness	0	8 (5%)
Myalgia	4 (5%)	3 (2%)
Respiratory System		
Nasal Congestion/discomfort	1 (1)	3 (2%)
Pharyngolaryngeal pain	4 (5%)	5 (3%)
Vascular		
Hot Flush	0	4 (3%)

Open label Safety Studies
The following table represents those adverse events that occurred in at least 2% of patients during the 6 month open label safety trial.

Table 28: Adverse events occurring in 2% or more in Open Label Patients taking ziprasidone ≤160mg/day

SYSTEM ORGAN CLASS/PREFERRED TERM	BIPOLAR PATIENTS ≤160MG/DAY N=188	BIPOLAR, SCHIZOPHRENIA AND SCHIZOAFFECTIVE PATIENTS N=205
Gastrointestinal disorders		
Abdominal Pain	14 (7%)	15 (7%)
Toothache	6 (3%)	7 (3%)
Constipation	6 (3%)	6 (3%)
Nausea	17 (9%)	17 (9%)
Stomach Discomfort	10 (5%)	10 (5%)
Vomiting	12 (6%)	12 (6%)
Infections		
Upper Respiratory Infection	8 (4%)	9 (4%)
Streptococcal Pharyngitis	5 (3%)	5 (3%)
Nasopharyngitis	4 (2%)	4 (2%)
Viral Gastroenteritis	4 (2%)	4 (2%)
Eye Disorders		
Vision Blurred	7 (4%)	8 (4%)
Metabolism		
Decreased Appetite	5 (3%)	5 (2%)
Increased Appetite	5 (3%)	5 (2%)

Nervous System Disorders		
Akathesia	5 (3%)	6 (3%)
Dizziness	14 (7%)	15 (7%)
Drooling	4 (2%)	4 (2%)
Extrapyramidal Disorder	8 (4%)	8 (4%)
Headache	34 (18%)	34 (17%)
Sedation	54 (29%)	56 (27%)
Somnolence	40 (21%)	46 (22%)
Tremor	8 (4%)	8 (4%)
Dystonia	2 (1%)	5 (2%)
Psychiatric Disorders		
Depression	7 (4%)	8 (4%)
Anxiety	6 (3%)	6 (3%)
Bipolar/Bipolar I	9 (5%)	9 (5%)
Insomnia	22 (12%)	24 (12%)
Aggression	4 (2%)	4 (2%)
Suicidal Ideation	6 (3%)	8 (4%)
General Disorders		
Fatigue	16 (9%)	18 (9%)
Chest Pain	6 (3%)	7 (4%)
Irritability	7 (4%)	7 (3%)
Musculoskeletal		
Arthralgia	5 (3%)	5 (2%)
Muscle spasms	4 (2%)	4 (2%)
Pain in Extremity	4 (2%)	5 (2%)
Urinary System		
Enuresis	4 (2%)	4 (2%)
Respiratory Disorder		
Pharyngolaryngeal pain	7 (4%)	7 (4%)
Nasal Congestion	12 (6%)	12 (6%)
Skin and Subcutaneous Disorder		
Contact Dermatitis	4 (2%)	4 (2%)
Rash	7 (4%)	7 (4%)
Investigations		
Weight Increase	10 (5%)	11 (5%)

7.1.5.5 Identifying common and drug-related adverse events

Those events that were common (≥5% frequency) and drug related (frequency rate at least twice the rate of placebo) are summarized below in Table 29.

Table 29: Common, Drug-Related Adverse Experiences

ADVERSE EVENT-PREFERRED TERM	PLACEBO (N=88)	ZIPRASIDONE (N=149)
Sedation	4 (5%)	49 (33%)
Somnolence	7 (8%)	37 (25%)
Dizziness	2 (2%)	16 (11%)
Insomnia	3 (3%)	13 (9%)
Vomiting	1 (1%)	11 (7%)
Vision Blurred	1 (1%)	9 (6%)
Musculoskeletal stiffness	0	8 (5%)
Tremor	0	8 (5%)
Restlessness	1 (1%)	8 (5%)
Akathesia	1 (1%)	7 (5%)
Extrapyramidal Disorder	1 (1%)	7 (5%)
Upper Respiratory Infection	0	7 (5%)

This reviewer had also requested an analysis of treatment emergent adverse events categorized by weight. A review of those adverse events that are common and drug related are presented below:

Table 30: Treatment Adverse Events by Weight-placebo controlled study

ADVERSE EVENT-PREFERRED TERM	<45KG		≥45KG	
	Placebo N=15	ziprasidone N=34	Placebo N=73	ziprasidone N=115
Sedation	0	30%	6%	34%
Somnolence	0	21%	10%	26%
Dizziness	0	18%	3%	9%
Insomnia	0	12%	4%	8%
Vomiting	0	12%	1%	6%
Vision Blurred			1%	7%
Dystonia	0	12%		
Musculoskeletal Stiffness			0	6%
Tremor	0	12%		
Restlessness			1%	7%
Akathesia			1%	6%

Extrapyramidal Disorder	0	9%		
Upper Respiratory Infection	0	6%		
Abdominal Pain/stomach Discomfort	7%	21%		
Nausea	0	15%		
Fatigue	0	9%	8%	15%
Headache	7%	27%		

Reviewers Assessment of Common, Drug Related Adverse Events
Sedation, tremor, akathesia, and extrapyramidal symptoms were more common in ziprasidone treated patients. In particular, patients who weighed less than 45 kg were much more likely to report tremor, dystonia and extrapyramidal symptoms than heavier patients. However when compared to the common, treatment emergent adverse events seen in the adult bipolar trials, the side effect profile is similar (see table 29a below).

It is the opinion of this reviewer that the common, drug related adverse events table 29 be included into ziprasidone labeling. No additional labeling recommendations regarding adverse event warnings or precautions are indicated at this time based on this reviewers' analysis of the placebo controlled safety data contained in this NDA.

Table 29a: Common, Drug-Related Adverse Experiences between

Pediatric and Adult 3 week Bipolar Studies

	PEDIATRIC		**ADULT**	
Adverse event-preferred term	**Placebo (N=88)**	**ziprasidone (N=149)**	**Placebo (N=136)**	**ziprasidone (N=279)**
Sedation	5%	33%		
Somnolence	8%	25%	12%	31%
Dizziness	2%	11%	7%	16%
Insomnia	3%	9%		
Vomiting	1%	7%	2%	5%
Vision Blurred	1%	6%	3%	6%
Musculoskeletal stiffness	0	5%		
Tremor	0	5%		
Restlessness	1%	5%		
Akathesia	1%	5%	5%	10%
Extrapyramidal Disorder	1%	5%	12%	31%*

Upper Respiratory Infection	0	5%	3%	8%
Asthenia			2%	6%

* includes the preferred terms EPS, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching.

7.1.5.6 Additional analyses and explorations

The sponsor also explored the relationship of adverse events between fast and slow titrations in the placebo controlled trials. In general, placebo-corrected patients who were titrated fast reported more abdominal pain, nausea, vomiting, dizziness, dystonia, extrapyramidal symptoms, tremor and insomnia than slowly-titrated patients. Conversely, placebo corrected slow titrated patients exhibited more symptoms of blurry vision, appetite changes, restlessness and fatigue than patients titrated quickly in the placebo controlled study.

Table 31: Adverse events occurring in 2% or more in ziprasidone patients

SYSTEM ORGAN CLASS/PREFERRED TERM	FAST		SLOW	
	ziprasidone N=56	**Placebo N=37**	**ziprasidone N=93**	**Placebo N=51**
Gastrointestinal disorders				
Abdominal Pain	8 (14%)	1 (3%)	6 (6%)	2 (4%)
Dysphagia			2 (2%)	0
Salivary Hypersecretion			2(2%)	0
Nausea	7 (13%)	0	13 (14%)	6 (12%)
Stomach Discomfort	2 (4%)	1 (3%)	4 (4%)	1 (2%)
Vomiting	5 (9%)	0	6 (7%)	1 (2%)
Constipation			2 (2%)	0
Cardiac				
Tachycardia	2 (4%)	0		
Respiratory				
Epistaxis	2 (4%)	1 (3%)		
Pharyngolaryngeal pain	2 (4%)	1 (3%)	3 (3%)	3 (6%)
Infections				
Upper Respiratory Infection	3 (5%)	0	4 (4%)	0
Influenza	2 (4%)	0		
Sinusitis			3 (3%)	0
Gastroenteritis-viral			2 (2%)	1 (2%)
Eye Disorders				
Vision Blurred	2 (4%)	1 (3%)	7 (8%)	0
Digestive				
Decreased Appetite			5 (5%)	1 (2%)
Increased Appetite			2 (2%)	2 (4%)

Nervous System				
Akathesia			7 (8%)	0
Dizziness	7 (13%)	0	9 (10%)	2 (4%)
Drooling	2 (4%)	0	2 (2%)	0
Dyskinesia			2 (2%)	1 (2%)
Dystonia	4 (7%)	1 (3%)	2 (2%)	0
Extrapyramidal Disorder	5 (9%)	0	2 (2%)	1 (2%)
Abnormal Glabellar Reflex			2 (2%)	0
Headache	18 (32%)	5 (13%)	13 (14%)	14 (28%)
Hypersomnia			2 (2%)	0
Sedation	18 (32%)	0	31 (33%)	4 (8%)
Somnolence	12 (21%)	3 (8%)	25 (27%)	4 (8%)
Tremor	5 (9%)	0	3 (3%)	0
Musculoskeletal				
Musculoskeletal Stiffness	3 (5%)	0	5 (5%)	0
Jaw Pain	2 (4%)	0		
Myalgia			2 (2%)	4 (8%)
Psychiatric				
Depression			2 (2%)	0
Anxiety	2 (4%)	1 (3%)		
Insomnia	6 (11%)	0	7 (8%)	3 (6%)
Restlessness			8 (9%)	1 (2%)
Reproductive				
Dysmenorrhea			3 (3%)	0
Skin				
Hyperhidrosis	2 (4%)	0		
General Disorders				
Fatigue	5 (9%)	3 (8%)	15 (16%)	3 (6%)
Pain			2 (2%)	0
Irritability			2 (2%)	0
Injury				
Medication/Drug Dispensing Error	3 (5%)	1 (3%)		
Overdose	7 (13%)	5 (14%)		
Vascular				
Hot Flush	2 (4%)	0	2 (2%)	0

At the request of this reviewer, the sponsor performed a sub-group analysis of extrapyramidal adverse events based on weight. The results demonstrate that EPS symptoms are more prevalent in smaller children than in heavier children, suggesting more sensitivity to the adverse pharmacological properties of ziprasidone in smaller children.

TABLE 32: Adverse events associated with Extrapyramidal syndrome by body weight

ADVERSE EVENT (PREFERRED TERM)	<45KG		≥45KG	
	ziprasidone N=34	**Placebo N=15**	**ziprasidone N=115**	**Placebo N=73**
Gait Disturbance	0	0	1%	0
Muscle Spasms	3%	0	0	4%
Muscle Twitching	3%	0	1%	0
Musculoskeletal stiffness	3%	0	6%	0
Cogwheel Rigidity	0	0	1%	0
Drooling	0	0	4%	0
Dyskinesia	3%	0	2%	1%
Dystonia	12%	0	2%	1%
Extrapyramidal disorder	9%	0	4%	1%
Tremor	12%	0	4%	0
Tic	3%	0	0	0
TOTAL	**41%**	**0**	**19%**	**10%**

7.1.6 Less Common Adverse Events

A review of all of the adverse events from the open label data revealed one report each of syncope and vasovagal syncope. There were two (2) reports of tachycardia and one case of atrial fibrillation during the open label trials, however no reports of tachyarrhythmia's or other cardiovascular arrhythmia of clinical concern noted.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory assessments of all patients occurred at screening, baseline, day 14 of treatment, at day 28 (end of treatment) or day 35 for those patients who did not enter the open label extension study. Included in the laboratory assessments were the following tests: CBC with diff and platelet count; blood chemistry-including AST, ALT, LDH, total bilirubin, albumin and total protein; urinalysis; urine drug screen.

Also the sponsor collected fasting glucose, lipids, insulin, free T4 and TSH, prolactin, testosterone, IGF-1, IGFBP-3 and HbGA1c in all patients at screening, baseline, and at end of treatment day 28 (or day 35 follow-up for patients not entering into the open-label safety study). Urine drug screens and serum pregnancy tests on female patients were also performed at screening, baseline, day 14 and day 28-end of treatment.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The focus of this analysis is the single double-blind, placebo controlled study.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The mean change from baseline analysis is provided below. Overall there were minor mean changes from baseline differences noted between the two treatment groups. Of note, lower mean change from baseline serum testosterone levels were noted in ziprasidone treated subjects. This is most likely related to the increased mean change from baseline serum prolactin levels induced from ziprasidone administration and inhibitory changes in the hypothalamic-pituitary axis.

A mean change for baseline decrease in insulin-like growth factor 1 (IGF1) was more pronounced in ziprasidone treated patients compared to placebo patients. IGF1 is a polypeptide primarily secreted by the liver that acts to stimulate growth and development of various tissues via interactions with a receptor and tyrosine kinase in vivo.[1] Although it is premature to link the use of ziprasidone to a decrease in IGF-1 serum levels, the clinical significance of a decrease in IGF1-1 is not clearly delineated. Further studies are needed to determine if ziprasidone use is associated with a consistent decrease in IGF-1 and what, if any, long term effects may result from such an association.

Table 33: Mean Change from Baseline to Week 4/Early Termination in Laboratory Parameters For the Placebo Controlled Study

Parameter (units)	ziprasidone			Placebo		
	N	Baseline	Mean Change	N	Baseline	Mean Change
HEMATOLOGY						
RBC Count ($x10^6$/mm3)	114	4.8	-0.1	74	4.9	-0.1
Hemoglobin (G/L)	114	14.2	-0.2	75	14.3	-0.2
Hematocrit (%)	114	42.2	-0.7	74	43.2	-1.0
WBC Count ($x10^3$/mm3)	114	6.8	-0.3	74	6.8	-0.4
Neutrophils (%)	114	55.2	1.1	74	55.4	0.7

1 Laron Z " Insulin-like Growth factor 1: a growth hormone" *Molecular Pathology* 2001:54:311-316

Table 33: Mean Change from Baseline to Week 4/Early Termination in Laboratory Parameters For the Placebo Controlled Study

Parameter (units)	ziprasidone			Placebo		
	N	Baseline	Mean Change	N	Baseline	Mean Change
Lymphocytes (%)	114	35.7	-0.8	74	35.1	-1.5
Monocytes (%)	114	5.8	0.1	74	5.7	0.8
Eosinophils (%)	74	2.7	-0.5	53	3.0	0.2
Basophils (%)	114	1.0	0	74	1.0	0
Platelet Count ($x10^3$/mm3)	114	295.9	-4.7	74	302.6	-16.0
CLINICAL CHEMISTRY						
Potassium (MEq/L)	121	4.2	0	75	4.3	0
Sodium (MEQ/L)	119	141.2	-0.6	76	141.0	-0.4
Chloride (mEq/l)	121	103.3	-0.2	76	102.9	0.4
Bicarbonate (mEq/l)	121	22.4	-0.1	77	22.3	0.1
BUN (mg/dL)	122	12.2	-0.1	77	11.8	0.5
Creatinine (mg/dL)	80	0.7	0	54	0.7	0
Glucose-fasting(mg/dL)	99	87.2	-1.5	67	87.1	-0.2
Calcium (mg/dl)	122	9.9	0	76	9.9	-0.1
Phosphate (mg/dl)	80	4.6	-0.1	54	4.6	-0.1
Magnesium (mg/dl)	122	2.1	0	75	2.1	0
ALT (IU/L)	122	18.7	1.1	77	19	-0.7
AST (IU/L)	122	23.9	-0.5	77	22.6	-0.6
LDH (IU/L)	80	173.1	0.8	54	174.7	-1.8
Total Bilirubin (mg/dL)	122	0.4	0	77	0.4	0
Total Protein (g/L)	122	7.5	0	77	7.6	-0.1
Albumin (g/L)	122	4.7	0	77	4.7	-0.1
HORMONES						
Insulin (uu/dl)	79	11.5	1.4	49	13.2	
Free T4 (ng/dl)	123	1.1	0.0	78	1.1	0
Testosterone (ng/dl)	90	185.4	-5.2	59	192.3	16.1
Prolactin (ng/dl)	118	8.9	3.1	75	8.0	-0.2
TSH (UIU/ml)	123	2.0	-0.2	77	2.0	-0.2
Insulin-like growth factor-1 (ng/ml)	94	248.7	-6.7	61	261.6	1.4
Insulin-like growth factor binding protein 3 (mcg/ml)	94	5.4	-0.2	61	5.4	-0.1
LIPIDS						
LDL cholesterol (mg/dl)	122	87	-2.5	77	91.1	-1.4
HDL cholesterol (mg/dl)	122	52.4	0.3	77	53.2	-1.5
Cholesterol-fasting	122	158.6	-3.6	76	164.3	-4.3

Table 33: Mean Change from Baseline to Week 4/Early Termination in Laboratory Parameters For the Placebo Controlled Study

Parameter (units)	ziprasidone			Placebo		
	N	Baseline	Mean Change	N	Baseline	Mean Change
Triglycerides-fasting	122	96.8	-8.1	77	100.6	-7.8

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Placebo Controlled Study
The following table delineates ziprasidone patients who had at least one post-treatment abnormal laboratory value despite having a normal baseline status. In general patients who received ziprasidone had elevated prolactin levels (11% vs. 1%) and insulin levels (6% vs. 0) above threshold criteria compared to placebo patients respectively.

Table 34: Incidence of abnormal post dose laboratory parameter in ziprasidone patients who had normal baseline parameters.

PARAMETER (UNITS)	CRITERIA FOR ABNL	ZIPRASIDONE % (N/TOTAL)	Placebo % (n/total)
White Count (10*3/mm3)	>17.5	1% (1/118)	0
Lymphocyte (%)	<0.8 X LLN	2% (2/123)	1% (1/76)
Total Neutrophils (1000/mm3)	<0.8 X LLN	4 % (4/107)	4 % (3/74)
	>1,2 X ULN	4 % (4/107)	0
Neutrophils (%)	<0.8 X LLN	1% (1/117)	0
Basophils (5)	>1.2 X ULN	2 % (2/127)	5% (4/81)
Eosinophils (%)	>1.2 X ULN	1 % (1/79)	9 % (5/55)
Monocytes (5)	>1.2 X ULN	3% (4/124)	10 % (8/79)
AST (IU/L)	>3.0 X ULN	1% (1/127)	0
ALT (IU?L)	>3.0 X ULN	1 % (1/115)	0
HDL	<0.8 X LLN	1 %	1 %

Cholesterol (mg/dl)		(1/111)	(1/73)
Triglycerides (mg/dl)	>1.3 X ULN	3 % (3/110)	3 % (2/63)
Sodium (mEq/l)	>1.05 X ULN	1% (1/125)	0
Potassium (mEq/l)	>1.1 X ULN	1 % (1/131)	0
Magnesium (mg/l)	> 1.1 X ULN	2% (2/122)	0
Phosphate (mg/dl)	> 1.2 X ULN	4 % (2/55)	2 % (1/41)
Bicarbonate (mEq/l)	<0.9 X LLN	13% (12/90)	15% (8/53)
TSH (UIU/ml)	<0.8 X LLN	1% (1/122)	1% (1/77)
Prolactin (ng/ml)	>1.1 X ULN	11% (12/114)	1% (1/71)
Testosterone (ng/ml)	>1.2 X ULN	5% (4/75)	2% (1/48)
Insulin (UU/ml)	> 1.2 X ULN	6% (5/88)	0
Urine Ketones (qual)	≥1	16% (21/133)	24% (20/84)
Urine Blood (qual)	>1	26% (35/133)	24% (20/84)
Urine Specific Gravity	>1.030	5% (7/133)	10% (8/84)
Urine RBC (HPF)	≥6	6% (8/133)	6% (5/84)
Urine WBC (HPF)	≥6	5% (7/133)	5% (4/84)

Open Label Safety Data

The following table provides the proportion of patients who shifted above the pre-specified laboratory parameters who received ≤160 mg/day of ziprasidone from normal baselines. When compared to results from the placebo controlled study, a greater proportion of patients had exceeded threshold criteria for low bicarbonate levels (25% vs. 13%) and high testosterone levels (13% vs. 5%) respectively during the 6 months of open label treatment.

TABLE 35: Incidence of abnormal post dose laboratory parameter in ziprasidone patients who had normal baseline parameters, Open label studies

PARAMETER (UNITS)	CRITERIA FOR ABNL	ZIPRASIDONE % (N/TOTAL)
Lymphocyte (%)	>1.2 X ULN	3% (5/167)
Total Neutrophils (1000/mm3)	<0.8 X LLN	2% (3/142)
	>1,2 X ULN	4% (6/142)
Eosinophils (%)	>1.2 X ULN	3% (4/150)
Monocytes (5)	>1.2 X ULN	4% (6/149)
HDL Cholesterol (mg/dl)	<0.8 X LLN	2% (3/140)
Triglycerides (mg/dl)	>1.3 X ULN	5% (7/142)
Sodium (mEq/l)	>1.05 X ULN	3% (4/154)
Phosphate (mg/dl)	> 1.2 X ULN	2% (2/128)
Bicarbonate (mEq/l)	<0.9 X LLN	25% (21/85)
TSH (UIU/ml)	<0.8 X LLN	2% (3/124)
Prolactin (ng/ml)	>1.1 X ULN	9% (14/152)
Testosterone (ng/ml)	>1.2 X ULN	13% (17/133)
Insulin (UU/ml)	> 1.2 X ULN	6% (6/100)
Urine Ketones (qual)	≥1	22% (31/143)
Urine Specific Gravity	>1.030	8% (12/152)
Urine RBC (HPF)	≥6	8% (12/146)
Urine WBC (HPF)	≥6	6% (8/145)

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The sponsor notes that there was one case of a 'moderate' increase in testosterone and one case of 'severe' LFT abnormalities.

Subject 10401022 was a 17 year old female patient who received 40mg ziprasidone during the trial. On day 10, this patient had an AST of 202 u/l and an ALT of 242 u/l on day 11. She was discontinued from the study due to the event and her liver enzymes were not resolved at the time of termination.

Although only one patient was discontinued from the study for elevated liver enzymes, three (3) additional patients were noted by the sponsor to have some elevation of liver enzymes as follows:

- Subject 10171007-15 year old female with an ALT of 31 u/l (nl 5-20) while on 160mg/day with normal ALT by day 28.
- Subject 10171005- 16 year old male on placebo with elevated ALT at screening (35 u/l) and elevated total bilirubin levels (1.4 mg/dl).
- Subject 11221002-16 year old male taking ziprasidone 100mg/day had an AST of 89 u/l (nl 0-41) on day 16 which returned to WNL by day 23. However this patient had elevated ALT levels of 50, 147 and 56 u/l on days -5, 16 and 23 respectively that did not resolve at the time of termination.

Open Label Studies

There were no patients that were discontinued from the open label studies as a result of laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

No additional laboratory analyses were conducted by the sponsor.

7.1.7.5 Special assessments

Since ziprasidone has generally not been associated with laboratory abnormalities, special assessments of particular laboratory parameters are not indicated at this time.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

For the double blind study, ambulatory blood pressure and heart rate measurements were collected at all weekly visits. Additionally patient weight was obtained at screening, randomization and study completion with a physical examination performed at screening and at

day 28. The sponsor also obtained blood pressures at 5-7 hours (~around Tmax) post dose on day 28 only.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The focus of this analysis is the single double-blind, placebo controlled study. Pertinent vital sign abnormalities from the open label studies will be reviewed as well.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Below is the mean change from baseline in the blood pressure and pulse recordings at various times post dose in patients that were both supine and standing. It appears that ziprasidone treated patients were consistently noted to have slightly elevated parameters in blood pressure and pulse parameters 5-7 hours post dose while standing when compared to placebo treated subjects. Although a similar trend was seen in supine measurements, the magnitude of increase was smaller in ziprasidone treated subjects, with a larger increase in supine pulse rates seen in placebo patients taken 5-7 hours post dose.

In this reviewer's opinion, these slight elevations are unlikely to be clinically significant acutely. Larger studies of longer duration are recommended to confirm this trend and determine if clinically significant risks are evident.

Mean Change from Baseline on Supine Blood pressure and pulse

TABLE 36: MEAN CHANGE FROM BASELINE IN SUPINE VITAL SIGN PARAMETERS

VARIABLE	N_{ZIP}	ZIPRASIDONE	N_{PBO}	PLACEBO
Supine Systolic Blood Pressure (mmHg)				
Baseline mean (SD)	148	110.0 (11.1)	87	110.1 (10.3)
Mean Change from Week 4 - predose (SD)	95	0.2 (10.7)	50	-0.4 (10.8)
Mean Change from Week 4- 5 to 7 hrs post dose (SD)	85	1.4 (9.6)	48	0.1 (12.1)
Supine Diastolic Blood Pressure (mmHg)				
Baseline mean (SD)	148	67.6 (8.5)	87	67.4 (8.3)
Mean Change	95	-0.8 (9.3)	50	-0.5 (7.0)

from Week 4 - predose (SD)				
Mean Change from Week 4-5 to 7 hrs post dose (SD)	85	1.2 (9.0)	48	0.2 (8.3)
Supine Pulse Rate (bpm)				
Baseline mean (SD)	148	74.5 (11.8)	87	73.3 (8.7)
Mean Change from Week 4 - predose (SD)	95	-2.9 (12.1)	50	-1.4 (9.0)
Mean Change from Week 4-5 to 7 hrs post dose (SD)	85	2.5 (12.6)	48	3.1 (10.6)

Mean Change from Baseline on Standing Blood pressure and pulse

TABLE 37: MEAN CHANGE FROM BASELINE IN STANDING VITAL SIGN PARAMETERS

VARIABLE	N_{ZIP}	ZIPRASIDONE	N_{PBO}	PLACEBO
Standing Systolic Blood Pressure (mmHg)				
Baseline mean (SD)	147	109.7 (10.8)	87	111.2 (110.8)
Mean Change from Week 4 - predose (SD)	94	0.6 (10.8)	50	-0.5 (10.5)
Mean Change from Week 4-5 to 7 hrs post dose (SD)	84	2.4 (10.8)	48	-0.2 (11.3)
Standing Diastolic Blood Pressure (mmHg)				
Baseline mean (SD)	147	70.2 (8.8)	87	69-08 (7.7)
Mean Change from Week 4 - predose (SD)	94	1.6 (9.6)	50	0.9 (7.4)
Mean Change from Week 4-5 to 7 hrs post dose (SD)	84	2.3 (9.9)	48	0.9 (8.1)
Standing Pulse Rate (bpm)				

Baseline mean (SD)	147	80.7 (12.1)	87	80.4 (11.8)
Mean Change from Week 4 - predose (SD)	94	-0.5 (12.5)	50	-3.1 (12.6)
Mean Change from Week 4-5 to 7 hrs post dose (SD)	84	5.5 (15.6)	48	0.2 (12.3)

The sponsor did not examine the relationship between dosing group and vital sign changes

Mean Change from Baseline on Weight and BMI

The mean change from baseline at week 4 or early termination for weight and BMI were virtually identical regardless of the treatment a patient was randomized to.

TABLE 38: MEAN CHANGE FROM BASELINE IN Weight and BMI Z- Score PARAMETERS

VARIABLE	N_{ZIP}	ZIPRASIDONE	N_{PBO}	PLACEBO
Weight (Kg)				
Baseline mean (SD)	149	57.2 (14.4)	88	60.0 (16.0)
Mean Change from Week 4/ET (SD)	131	0.5 (2.2)	81	0.6 (2.3)
BMI Z-Scores				
Baseline mean (SD)	149	0.7 (0.9)	88	0.8 (0.9)
Mean Change from Week 4/ET (SD)	131	0	81	0

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following table delineates the proportion of patients who developed at least one post – randomization blood pressure or pulse recording that met or exceeded criteria thresholds for abnormal. Patients taking ziprasidone were more likely to experience clinically significant decreases of supine blood pressure parameters that met or exceeded threshold limits when compared to placebo treated subjects. This is likely as a result of the pharmacological alpha-1 antagonistic properties noted with ziprasidone and addressed in current approved labeling.

TABLE 39: Post-Baseline Vital sign outlier data

CRITERIA	ZIPRASIDONE N=144*	PLACEBO N=86
Standing Systolic BP		
<90 mmHg	2%	4%
≥30mmHg decrease	<1%	1%
≥30mmHg increase	3%	0
Standing Diastolic BP		
<50 mmHg	<1%	4%
≥20mmHg decrease	4%	6%
≥20mmHg increase	8%	11%
Supine Systolic BP		
<90 mmHg	6%	2%
≥30mmHg increase	3%	2%
Supine Diastolic BP		
<50 mmHg	3%	2%
≥20mmHg decrease	5%	2%
≥20mmHg increase	7%	6%
Supine Pulse Rate		
>120 bpm	<1%	0

* n=143 for Standing systolic and Standing diastolic measurements

Open Label Studies

The sponsor provided the mean change from baseline data for patients participating in the open label trial. Results from the open label studies revealed a dose-related increase in diastolic blood pressures in patients who took ziprasidone over a 26 week time period.

Table 40: Mean change from baseline parameters by dose in Open label Safety studies in patients with bipolar, schizophrenia and schizoaffective disorder

PARAMTER	≤ 40MG N=21	>40- ≤80MG N=68	>80- ≤120MG N=29	120- ≤160MG N=87	ALL SUBJECTS ≤160MG N=205
Mean Change Systolic BP (mmHg)	-6.4	0.5	-1.0	1.5	0
Mean Change Diastolic BP (mmHg)	-1.2	-0.3	0.8	1.6	0.6
Mean Change Heart Rate (BPM)	-1.5	0.6	1.7	0.2	0.4

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no reported marked outliers or dropouts as a result of vital sign abnormalities in the placebo controlled trial.

One subject, 11241005- a 10 year old male, who received ziprasidone 40mg had a week 4 weight gain of 4.99 kg compared to baseline weight which did not lead to study termination. In addition, subject 11001002 was an 11 year old male who received placebo during the study who had a weight gain of 9.8 kg from screening on day 29 of the study.

Subject 10311003 was a 14 year old male patient in the placebo group who had a 9.23 kg decrease in weight by day 29 of the study.

Open Label Studies

During the open label trials there were no patients who had a clinically significant increase or decrease in mean change from baseline systolic or diastolic blood pressure, or heart rate. In addition, there were no patients who were discontinued from the studies due to vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were performed by the sponsor with regards to vital sign abnormalities.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were performed in the placebo controlled study at baseline (performed in triplicate), every onsite visit and an ECG performed at the time to Tmax (5-7 hrs post dose) time point to analyze the effect of maximum ziprasidone concentrations on ECG parameters.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The placebo controlled study data results were used as the basis for the electrocardiogram analysis. Pertinent ECG abnormalities from the open label studies will be reviewed as well.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Due to the known QTc prolongation associated with ziprasidone, this review will primarily focus on the mean change from baseline on the QTcF parameters.

The table below delineates the QTc effect of ziprasidone at various time points throughout the study as compared to placebo treated subjects. Consistent with the adult data, ziprasidone is associated with a maximum, non-corrected 8-10msec increase in QTcF in pediatric subjects.

Table 41: Mean baseline and baseline change from baseline in QTcF at various time points

TIME	N_{ZIPR}	MEAN (SD)	N_{PBO}	MEAN (SD)
Mean baseline	147	396.1 (18.6)	87	399.6 (12.6)
Change from Baseline				
Week 1	131	7.1 (15.3)	83	-2.9 (14.0)
Week 2	112	10.1 (17)	69	-4.3 (16.2)
Week 3	99	6.7 (15.6)	54	-5.4 (15.8)
Week 4 predose	93	5.9 (16.9)	50	-0.9 (18)
Week 4/0.75 to 3 hrs post dose	90	5.1 (17.3)	50	-3.0 (16.8)
Week 4/5 to 7 hrs post dose	84	8.3 (15.0)	48	-2.9 (16.1)
End of Treatment/predose	27	4.7 (19.2)	4	-3.4 (16.9)
End of treatment/0.75 to 3 hrs post dose	16	10.3 (17.9)	19	-2.3 (12.2)
End of treatment/5 to 7 hrs post dose	17	10.8 (16.4)	21	-5.5 (12.5)
Combined week 4/ET pre-dose	120	5.6 (17.4)	77	-1.8 (17.6)
Combined week 4/ET/0.75 to 3 hrs post dose	106	5.9 (17.4)	69	-2.8 (15.6)
Combined week 4/ET/5 to 7 hrs post dose	101	8.7 (15.2)	69	-3.7 (15.1)

Open Label Studies

With the exception of the 120-160mg dosing group, there was a dose-dependant increase in the QTcF that was observed in the open label safety studies.

TABLE 42: Mean change from baseline ECG parameters by dose in Open label Safety studies in patients with bipolar, schizophrenia and schizoaffective disorder

PARAMTER	≤ 40MG N=21	>40- ≤80MG N=68	>80- ≤120MG N=29	120- ≤160MG N=87	ALL SUBJECTS ≤160MG N=205
Mean Baseline QTcF (msec)	391.5	394.4	401.1	396.1	395.8
Mean Change from Baseline in QTcF (msec)	0.3	4.4	6.9	3.5	3.9

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

A review of data from outliers demonstrates that treatment with ziprasidone is associated with a two-fold increase at least a 30 msec increase of QTcF over baseline as compared to placebo treated patients. Nearly 11 out of 50 patients treated with ziprasidone will experience at least s 30 msec increase in QTcF from baseline as compared to 11 out of 100 treated with placebo.

Table 43: Proportion of patients meeting QTcF outlier criteria in study A1281132

QTCF OUTLIER CRITERIA	ZIPRASIODNE N=140	PLACEBO N=85
≥ 450 msec	4%	1%
≥ 460 msec	1%	0
≥ 480 msec	0	0
≥ 500 msec	0	0
≥ 30 msec increase over baseline	22%	11%
≥ 60 msec over baseline	<1%	0

Open Label Study

No patients during the open label study had a recorded QTcF reading ≥450 msec. However 21% of bipolar-only patients who received ziprasidone ≤160mg had an increase of QTcF ≥30msec as compared to the recording from the pre-study drug ECG. Two (2) patients had a recorded increase of at least 60 msec in their QTcF. These cases will be described in section 7.1.1.3.3 below.

Table 44: QTcF outliers by dose: Open label studies

INCREASE FROM PRE-STUDY DRUG	≤ 40MG N=18	>40- ≤80MG N=54	>80- ≤120MG N=29	120- ≤160MG N=87	ALL SUBJECTS ≤160MG N=188
≥30 msec	1 (7%)	12 (22%)	4 (14%)	23 (26%)	40 (20%)
≥60 msec	0	0	1 (3%)	1 (1%)	2 (1%)

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Patient 10401007, a 16 year old female who received ziprasidone 60mg/day, was discontinued from the study on day 16 of the study due to an ECG finding of a QTcF greater than 460 msec before, 45 minutes after and 5 hours after dosing. Her previous ECG on day 8 showed a QTcF of 464 msec. Her follow-up ECGs on day 23 and 38 showed that here QTcF was returning to the screening measurement. Her maximum recorded QTcF was 478 msec.

An additional subject, patient 10671010, had a QTcF of 461 msec on day 29. However all other QTcF values were below 460 msec and the investigator did not consider this to be an adverse event.

Open Label Studies

Subject 11081003, a 14 year old female who participated in extension study 1281133, had a 59 msec increase in QTcF at week 10 (QTcF 438 msec) when compared to her baseline QTcF (QTcF 369 msec).Subsequent QTcF values were less than 45 msec and this subject had no associated adverse events.

Patient 10861006, a 12 year old female, had a 66 msec increase in QTcF at day 10 when compared to her baseline QTcF (baseline: 365msec; week 1: 431 msec) while receiving 80mg/day of ziprasidone. Repeated QTcF measurements over the next 55 days indicated a persistent prolonged QT interval and this subject was discontinued from the study on day 65 due to the prolonged QT interval.

One patient, patient 11081007- a 12 year old female-initially developed an increased heart rate (52 bpm to 72 bpm) on day 38 while receiving 80mg/day ziprasidone. The automated ECG interpretation stated that the patient had atrial fibrillation however central reading of the ECG was interpreted as an intermittent junctional rhythm. The patient continued in the study, with her last ECG being recorded on Week 18 (day 135).

7.1.9.4 Additional analyses and explorations

Although the proportion of female patients with ≥ 450 msec increases in QTcF from baseline was higher than for males, there appears to be no gender difference in the proportion of patients with ≥ 30msec increases from baseline ECGs on QTcF parameters:

Table 45: QTcF outliers by Gender

QTCF PARAMTER	ZIPRASIDONE	PLACEBO
Males	*N=79*	*N=44*
≥ 450 msec	1%	1%
≥ 460 msec	1%	0
≥ 30 msec increase	23%	9%
Females	*N=61*	*N=41*
≥ 450 msec	7%	0
≥ 460 msec	2%	0
≥ 30 msec increase	21%	12%
≥ 60 msec increase	<1%	0

7.1.9.4.1 Concentration Dependant QTc Effect analyses

As part of this submission, the sponsor performed two analyses within the pediatric development program to assess for a concentration/QTcF relationship with pediatric ziprasidone administration from data collected from studies A1281123 and A1281132.

Study A1281132 Concentration Dependant QTc Effect

For study A1281132, pharmacokinetic (PK) sampling was collected at baseline 0.5-1.5 hrs post dose and a 2nd PK sample 1.5-3hrs post dose. Baseline ECGs were administered in triplicate. At week 4, trough PK samples and ECG tracings were collected prior to morning dose administration, as well as a 2nd PK sample/ECG tracing 0.75-3 hrs post dose and a 3rd PK sample/ECG tracing 5-7 hrs post dose.

The concentration/QTcF (dose dependant) relationship results from the placebo controlled pediatric bipolar study A1281132 are described in the table below. Using linear regression, a positive relationship between increasing concentrations of ziprasidone and QTcF prolongation was seen. Using the population mean with a 90% confidence interval, ziprasidone administration to pediatric patients is associated with a 0.0852 msec/(ng/ml) increase in QTcF [90% CI 0.067-0.106 msec/(ng/ml)]. Using the predicted steady state Cmax data obtained from the population PK study of patients enrolled in study A1281132, patients would be predicted to have a mean 15 msec increase in QTcF at Cmax during at steady state if taking 160mg/day.

Table 33 Descriptive Statistics of the Predicted ΔQTcF (msec) Prolongation at Predicted Steady State Cmax based on Various Geodon™ Dosing Regimens

Dose	Minimum	1st.Quartile	Median	Mean	3rd.Quartile	Maximum
30 mg BID	1.497	4.112	5.205	5.794	7.086	17.59
40 mg BID	1.996	5.482	6.94	7.725	9.448	23.45
60 mg BID	2.995	8.223	10.41	11.59	14.17	35.18
80 mg BID	3.993	10.96	13.88	15.45	18.9	46.9

Study A1281123 Concentration Dependant QTc Effect

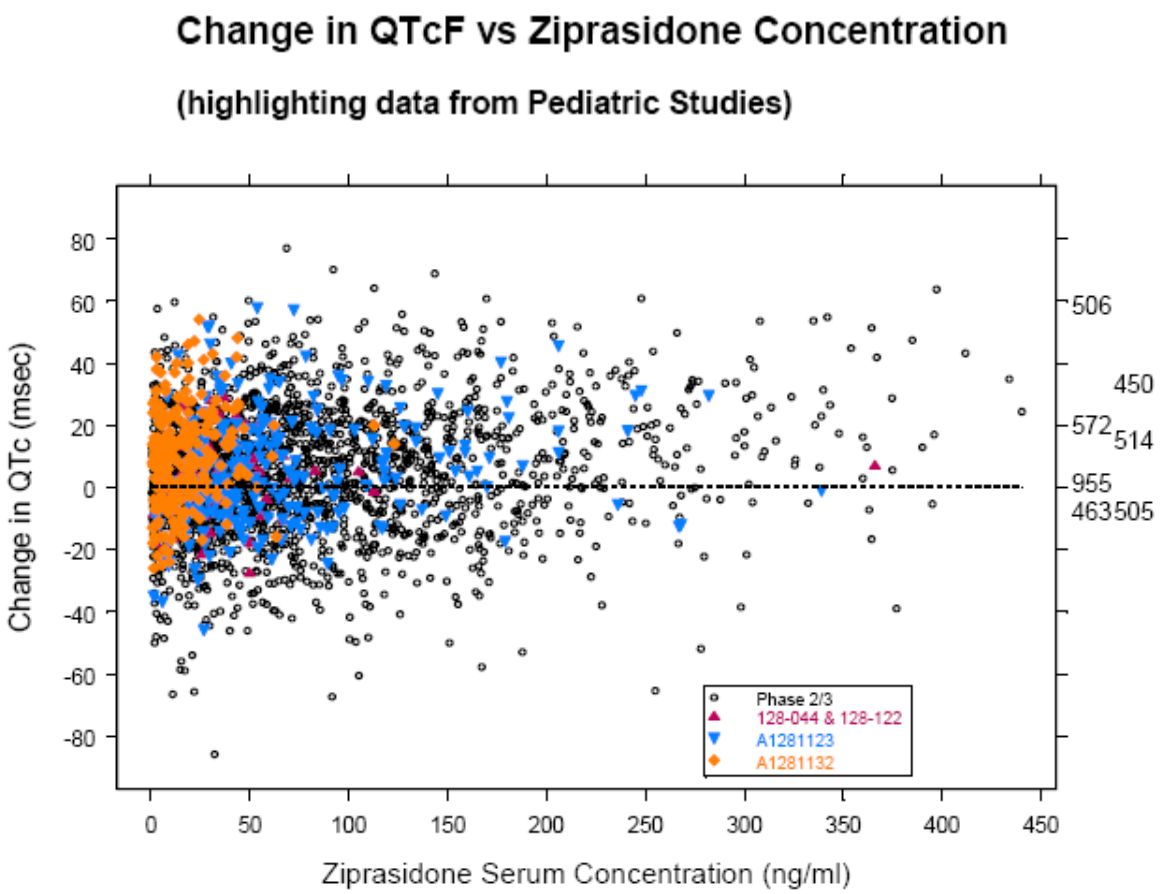
During the initial three week open label dose titration phase for this study, all patients received oral ziprasidone suspension. During the 27 week open label extension phase, patients could either take ziprasidone oral suspension or capsules. Pharmacokinetic measurements occurred at the following periods:

- Period 1 week 3-immediately prior to and 5-7 hours after the morning dose
- Period 2 week 1-random time
- Period 2 week 12- random time
- Period 2 week 27- random time

Again a positive linear relationship was seen between ziprasidone concentration and QTcF prolongation in this study. Using a 95 % confidence interval, ziprasidone administration to pediatric patients is in study A1281123 associated with a greater increase in QTcF prolongation of 0.139 msec/(ng/ml) increase in QTcF [95% CI -0.0132 to0.299 msec/(ng/ml)] as compared to the results seen in study A1281132.

Comparison of dose-dependant QTcF effects in pediatric and adult studies

The sponsor submitted a scatter plot diagram to compare ziprasidone concentration-change from baseline QTcF data pairs from QTcF/concentration data from 4 pediatric studies and 31 adult studies. The sponsor's conclusion was that "…the distribution of change from baseline QTcF values across the range of concentrations was similar between pediatric and adult subjects". The scatter plot is shown below for reference. The sponsor notes that subjects with a single change from baseline QTcF-ziprasidone concentration pair (i.e. those that did not also have a baseline QTcF/concentration data point) were included in the graph below.



At the request of this reviewer, the sponsor performed a regression analysis of the data points obtained in the pediatric studies and adult trials that were presented in the figure above. Of primary interest to this reviewer is the comparison of the slope of the regression lines between the pediatric and adult datasets as this data can be used to compare the rate of change in the QTcF- ziprasidone concentration relationship to see if differences exist between the two populations on this important variable. In the sponsor's analysis, only data from subjects with more than 1 data point were used to calculate the regression lines. In total, data (as reported by the sponsor in their correspondence to the Agency) from 21 studies (17 adult, 4 pediatric) were included in this analysis with a total of 2420 change in QTcF from baseline vs. concentration data pairs from 857 subjects (684 adult, 173 pediatric).

Of the 857 subjects, 419 (309 adult; 110 pediatric) had at least two or more concentration-QTcF data points but had no baseline concentration-QTcF data points. The remaining 438 patients did have baseline data points.

The results of the regression analysis indicate that the slope of the regression line for the pediatric dataset is 1.58 times steeper (i.e. a greater change in QTcF prolongation for a given concentration) as compared to the slope of the regression line from the adult dataset (0.0824 msec/ng/ml vs. 0.0521 msec/ng/ml). Of note, the slope of the pediatric regression line is

consistent with the data obtained from Pk-PD modeling from study A1281132 as described above.

TABLE 46: Summary of Regression of Change in QTcF vs. ziprasidone Concentration

PARAMETER (UNITS)	POPULATION MEAN (SE*)	STANDARD DEVIATION-INTER-INDIVIDUAL VARIANCE (SE*)
Intercept-Adult (msec)	0.744 (70.7)	9.04 (14.3)
Intercept-Pediatric (msec)	3.29 (28.5)	
Slope-Adult (msec/ng/ml)	**0.0521 (11.4)**	0.0601 (24.6)
Slope-Pediatric (msec/ng/ml)	**0.0824 (18.0)**	
Stand Deviation Additive Residual Error (msec)	13.0 (5.01)	

The result of the regression analysis suggests that the pediatric population is potentially more sensitive to the concentration dependant QTcF prolongation seen with ziprasidone use when compared to the adult population at any given concentration. For example, for a steady state Cmax of 150ng/ml, an adult patient could be predicted to experience an 8msec QTcF prolongation compared to baseline QTcF whereas a patient aged 0-17 years of age would experience a 12msec QTcF prolongation at the same concentration.

Although the regression analysis is limited by fewer pediatric data points and a large variance, the results of this data (given the limitations) is of particular clinical relevance since pediatric patients may be clinically exposed to higher concentrations of ziprasidone as a result of decreased clearance of ziprasidone with decreased weight. The results suggests that the pediatric population is at least as sensitive to the concentration-dependant QTcF prolongation effects of ziprasidone administration as compared to adults or potentially may be at more at risk for QTc related cardiac arrhythmias. Despite the absence of reports or adverse events of torsades de pointes seen in the pediatric clinical trials and post-marketing reports thus far, this reviewer recommends that the QTc warning language be re-worded to include children as being at risk to QTc prolongation associated with ziprasidone use.

7.1.10 Immunogenicity

Immunogenicity was not studied as part of the pediatric bipolar program.

7.1.11 Human Carcinogenicity

Although the studies performed under the pediatric bipolar development programs cannot fully address the potential carcinogenicity that may be associated with long term use, there is a low likelihood that ziprasidone use is associated with tumor growth.

Though there has been an association with some antipsychotics with D2 antagonistic properties and pituitary prolactinomas, a review of the Agency Post-marketing database using the terms

"GEODON®" and "PROLACTINOMA" revealed only one case of suspected prolactinoma suspected from only elevated prolactin levels. This patient was switched to a lower dose of ziprasidone with improvement in the prolactin levels.

7.1.12 Special Safety Studies

CNS Vital Signs test

The sponsor administered the CNS Vital Signs Computerized cognitive test battery to all patients in the double-blind placebo controlled study. The batter of tests included computerized tests to assess cognitive changes in verbal and visual memory, symbol digit coding, nonverbal reasoning, attention shifting, and reaction and recall times. There was no difference in the mean change from baseline index scores between ziprasidone and placebo treated patients (p=0.9571), however ziprasidone treated patient tended to have slower processing speeds at week 4 as compared to placebo treated patients [-3.5 (95% CI -6.01,-0.91) vs. 0.4 (95% CI -0.77,1.64)] drug to placebo respectively.

CDRS-R

Depression symptoms for both treatment groups, as measured by the CDRS-R, improved over baseline treatments, regardless of randomized treatment.

Table 47: Mean Change from baseline: CDRS-R scores, placebo controlled study

MEASURE	ZIPRASIDONE (95% CI)	PLACEBO (95% CI)
Mean Baseline	35.2 (33.45,36.86)	34.2 (31.84,36.63)
Mean Change from Baseline at Week 4	-8.0 (-10.23,-5.81)	-6.1 (-8.49,3.68)

Simpson Angus Rating Scale (SARS)
The SARS instrument is administered by clinicians to assess for Parkinsonian and extrapyramidal symptoms during the trial. Patients who were treated with ziprasidone were significantly more likely to have Parkinsonian symptoms/extrapyramidal side effects as compared to placebo controlled patients, as measured by the Simpson-Argus Rating Scale:

Table 48: Mean Change from baseline: Simpson Angus Rating Scale (SARS) scores placebo controlled study

VISIT	ZIPRASIDONE		PLACEBO		
	N	Mean Change from baseline (95% CI)	N	Mean Change from baseline (95% CI)	
Baseline	147	0.1	88	0.2	

		(0.06-0.22)		(0.08-0.33)	
Week 4-LOCF	133	0.5 (0.21-0.70)	85	-0.1 (-0.23-0.11)	

Barnes Akathesia Rating Scale (BARS)

ziprasidone treated patients were noted by clinicians to have a slight increase in Akathesia symptoms at week 1 as compared to placebo controlled patients [0.2 (95%CI 0.03,0.31) vs. -0.1 (95%CI -0.26,0.02)]. However no significant Akathesia symptoms were noted for the remaining visits in the ziprasidone treated group as compared to placebo.

Clinical Trial Suicidality Assessment

The sponsor assessed the suicidality risks associated with ziprasidone treatment through independent evaluation of cases that were identified in the double-blind placebo controlled study. Investigators, led by Dr Poser, reviewed the identified cases and classified each case according to the Columbia Classification scores. Please refer to section 7.1.4 for details.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No new information was presented as part of this submission that was relevant to the abuse potential of ziprasidone. Since ziprasidone is neither a controlled nor scheduled substance per the Drug Enforcement Agency (DEA), the abuse potential of ziprasidone is likely to be very low.

A review of the adverse events and cases does not suggest that withdrawal symptoms have been reported with the use of ziprasidone.

7.1.14 Human Reproduction and Pregnancy Data

The reader is referred to the current approved labeling and the original pharmacology/toxicology reviews completed with the original NDA submission for further details.

7.1.15 Assessment of Effect on Growth

During the placebo controlled trial, no significant differences were noted on height or weight parameters as measured by standard conventional units or through a derived z-score. A mean height increase of 0.9 cm was seen in the 6 month extension studies, in addition to a 1.4kg weight increase from baseline in all patients. The corresponding derived BMI only increased 0.3 units over the six month of observation with open label ziprasidone treatment. Increasingly

7.1.16 Overdose Experience

During the study, a total of 10 patients (6 in the ziprasidone group and 4 in the placebo group) received total daily doses of study medication that exceeded the maximum allowable dose in the protocol as a result of dosing errors. All ten of these cases occurred at three sites:

- site 1013 (Dr. Sohail S. Punjwani),
- site 1026 (Dr. Adly Thebaud) and
- site 1100 (Dr Steven Lopez)

These ten cases were identified in the study as an "overdose" adverse reaction. A table of these ten (10) cases is below.

Subject ID	Age (yrs) and Sex	Weight (kg)	Start Day/ Stop Day	Range of Overdosing (mg/day)	AE of Overdose	Other AEs	SAE	Disposition
Ziprasidone								
10131001	13 M	45.5	8/28	80-400	✓	Dizziness, headache, medication error, sedation	–	Completed
10131002	14 F	60.9	NA	80-120	–	EPS	–	Lost to follow-up
10131004	16 M	67.3	8/11	80-320	✓	Vomiting, sedation, drug dispensing error	–	DC due to AE (sedation)
10131006	13 M	35.5	9/30	80-400	✓	EPS, sedation, medication error	–	Completed
10131007	10 M	39.1	16/29	60-120	✓	Laceration, leg; medication error	–	Completed
10261001	11 F	34.1	2/2	80-100	✓	Dystonia	✓	DC due to SAEs (dystonia and overdose)
Placebo								
10131003	15 F	64.1	7/[>27]	0	✓	None	–	Completed
10131005	15 M	55.5	8/23	0	✓	Medication error	–	DC due to noncompliance
11001001	15 M	74.1	10/22	0	✓	Somnolence, fatigue, agitation	–	DC due to urine drug screen
11001002	11 M	42.0	8/29	0	✓	Weight increased	–	Completed

Source: Appendices B1.1, B2.1, B6
AE = adverse event, DC = discontinued, EPS = extrapyramidal symptoms, NA = not applicable, SAE = serious adverse event, ✓ = yes, - = no or none
Placebo subjects took 1 additional capsule.

These errors occurred as a result of incorrect understanding of the blinded study medication packaging by the personnel at the three investigative sites. Each dosing card had different columns representing 20,40, 60 and 80 mg of ziprasidone for each columns (distinguished by different sixe and color). The investigators at these sites incorrectly believed that all of the capsules were of the 20mg strength and thus instructed patients to ingest multiple capsules in order to achieve doses greater than 20mg. Once these errors were discovered, the information was immediately communicated to the DSMB, their IRBs and the patients and guardians.

The sponsor immediately suspended the three sites from additional patient enrollment. In addition, the sponsor re-trained all sites and study monitors on the use of the dosing cards, with 100% accountability requested from all sites. At the request of the DSMB, the sponsor reviewed the patient records for significant changes in QTc as delineated by the protocol. It was determined that none of the six patients who were overmedicated as a result of the dosing errors exhibited any significant QTc changes.

A sponsor review of all participating sites after the dosing errors occurred failed to detect any other instances of dosing errors or misunderstandings of dosing procedures.

7.1.17 Post marketing Experience

The sponsor provided an analysis of pediatric post-marketing use of ziprasidone for the three year time period between March 2005 to March 2008. The data based used for to collect exposure data was the IMS database which captures prescription retail data in 10 countries (Brazil, Canada, France, Germany, Italy, Japan, Mexico, Spain, UK and US). The Marketing Authorization Holder's (MAH) global safety database was used to search for pediatric adverse events associated with ziprasidone use, in addition to cases reported to health authorities and published cases in literature from 05 Feb 1998 to 30 Apr 2008.

During the three year period, there were approximately 631,000 pediatric patients (aged 0-17 years) exposed to ziprasidone. A review of the MAH database reported 2135 pediatric adverse events from 809 pediatric cases, which represented 6.7% of the total ziprasidone AE reports in the MAH database (total=12,073). Of these reports, 85% were reported by healthcare professionals. Approximately 83% of the pediatric AE cases were from US sources, followed by Germany (3%), Brazil (2%), Denmark and Norway (<2% respectively).

Although the majority of the pediatric AE cases occurred in patients with an unknown indication, pediatric AEs were reported most frequently in patients with a bipolar indication when compared to other psychiatric indications (13% vs. 12% for schizophrenia/psychotic disorders and schizoaffective combined).

Deaths
There were eight (8) reported pediatric deaths reported in the post marketing database during the time of reporting. The following table adapted from the sponsor's submission delineates these cases:

Case Number Age (yrs) /Gender Source	Daily Dose/Duration of Therapy	Indication/Relevant Medical History	Cause of Death	Adverse Events (Preferred Terms)	Comments
2004045603 8/Male Spontaneous non-Health professional	Unknown/Unknown	Autism/Unknown	Asphyxia	Asphyxia Drug toxicity	Death ruled a homicide by suffocation 'due to external chest compression' while being restrained; Medical examiner stated 'toxic blood levels' of brompheniramine and ziprasidone were present.
2005087572 13/Female Spontaneous Health professional	40mg/ < 1 month	Bipolar disorder/ Irritability, Oppositional defiant disorder, Weight increased	Gunshot wound	Completed suicide Belligerence Irritability Oppositional defiant disorder	Comcomitant medication includes risperidone; no history of active suicidal ideation or attempts; reporting physician stated subject was being tapered off risperidone and onto ziprasidone when patient became irritable and defiant (consistent with past behavior); patient shot herself in the head unexpectedly 2 days later.
2006086834 Child/Unknown Spontaneous Health professional	Unknown/Unknown	Unknown/Neuroleptic malignant syndrome	Neuroleptic malignant syndrome	Dystonia	Treated with methylphenidate prior to his or her death.
2006123196 Adolescent/Unknown Spontaneous Health professional	Unknown/Unknown	Unknown/Unknown	Unknown	Death	No other information.

Case Number Age (yrs) /Gender Source	Daily Dose/Duration of Therapy	Indication/Relevant Medical History	Cause of Death	Adverse Events (Preferred Terms)	Comments
2006127055 13/Male Spontaneous non-Health professional	Unknown/Unknown	Autism/Unknown	Unknown	Cerebrovascular accident Aggression Convulsion Decreased appetite Erection increased Haematoma Hydrocele Migraine Ocular hyperaemia Pain Testicular disorder Testicular swelling	Subject's mother reported that her son died of a 'stroke' in a local hospital; no other information available.
2007002612 16/Unknown Spontaneous Health professional	160 mg/1 year	Schizophrenia/Unknown	Cardiopulmonary failure	Cardiac failure Respiratory failure	Concomitant medications include quetiapine, sertraline, and topiramate; reporting physician did not suspect death related to ziprasidone.
A109864 17/Male Spontaneous Health professional	20 mg/ < 1 month	Autism, aggressive behavior/ seizures, mental retardation	Aspiration	Convulsion Loss of consciousness Nausea Vomiting	Following breakfast, became nauseous vomited and experienced a seizure; lost consciousness and never regained it.
A116732 17/Female Spontaneous Health professional	Unknown/Unknown	Ill-defined disorder/Unknown	Unknown	Death Mania	Concomitant medications include lorazepam and valproate; no cardiac history; subject was consuming alcohol and unknown drug (suspected to be marijuana and heroin) when she collapsed.

Adverse Events by System organ Classes

The top five system organ classes by number of pediatric adverse events were (in descending order): Nervous system, psychiatric, general disorders, investigations and gastrointestinal. There were no differences in rankings between the top five pediatric vs. non-pediatric AEs. In general, there were more nervous system adverse events reports in the pediatric population vs. non-pediatric patients.

Adverse Events by Preferred Term
For those adverse events that were reported in a proportion of ≥2% or greater, dystonia was noted to be reported at a rate of greater than 3 fold in the pediatric population (10.4% vs. 2.9% respectively) as compared to those in the non-pediatric population. Adverse events reports of somnolence were reported at a rate of greater than 2 fold in the pediatric group vs. non-pediatric patients (9.8% vs. 4.7%).

Of note, AE reports of convulsions were reported in 2.1% of pediatric patients. Extrapyramidal disorder AEs were reported more frequently in kids vs. non-pediatric patients, though less than a two-fold increase (5.9% vs. 3.5%). Adverse event reporting rates of Akathesia (2.6% vs. 3%), dyskinesia(3.8% vs. 2.4%), tardive dyskinesia (3% vs.3.1%) and tremor (4.8% vs. 3.7%) were generally similar between pediatric and non-pediatric populations.

Suicidality
Using a broad search strategy involving MedDRA preferred terms for suicide and suicide related events, the sponsor identified 27 cases (3% of total dataset) of suicidality-related adverse events. The vast majority (24) occurred in patients aged 13-17 years old taking ziprasidone for unknown

(10) or multiple indications (5). Most patients were receiving concomitant psychiatric medications as well.

There was one completed suicide (patient 2005087572) as seen in the table above. The remaining cases were classified as: suicidal ideation and suicide attempt (9 cases each respectively),intentional self-injury (2), and self-injurious ideation and suicidal behavior (1 case each). Four other cases were intentional overdoses. Compared to non-pediatric AE post marketing reports, the proportion of patients with suicidal ideation and attempts are generally similar between the groups.

Table 49: MedDRA classification of suicidality reports
Pediatric and non-pediatric reports

PREFERRED TERM	NO. OF EVENTS IN NON-PEDIATRIC CASES (N=11264)	NO. OF EVENTS REPORTED IN PEDIATRIC CASES (N=809)
Completed suicide	82 (<1%)	1 (<1%)
Intentional Self Injury	7 (<1%)	2 (<1%)
Self-injurious behavior	7 (<1%)	-
Self-injurious ideation	6 (<1%)	1(<1%)
Suicidal behavior	13(<1%)	1(<1%)
Suicidal ideation	114 (1%)	9 (1%)
Suicide attempt	90 (<1%)	9 (1%)
Total	319	23

QT related Events

There were 44 cases identified as QT prolongation AE, with 21 cases reported as syncope or loss of consciousness and considered not QT-related by the sponsor. Out of the 23 cases that were considered to be a QT-related event, 20 cases were reported as ECG prolonged. Of note, one patient (2007002612, AERS No 5259176), was a 16 yo male patient who was taking Geodon® 80mg BID X 1 year, in addition to Topomax, Zoloft and Aeroquip, when he collapsed and died. Autopsy results were inconclusive with cardiopulmonary failure noted as the cause of death and not related to death from any drug. This patient had no history of cardiac disease or suspicion of an arrhythmia.

There were no cases of torsades de pointes reported in the sponsor's database.

Nervous System events

There were 426 cases reporting nervous system disorder post marketing AEs. As stated before, dystonia was the only event with a post-marketing reporting proportion greater than 3 fold than that of non-pediatric patients, suggesting that the pediatric population may be more susceptible to dystonic reactions with ziprasidone use as compared to non-pediatric patients.

A total of 84 dystonic pediatric cases were reported, with 37 cases reported in children aged 2-11 years of age. Dystonic reactions were most commonly reported in patients with bipolar disorder (10) when an indication was reported, as well as with the 40mg dose (18 cases), when the dosing data was provided in the reports however 40mg was the most commonly reported dose in the database associated with nervous system AEs.

Pediatric Pregnancy use/Lactation

The sponsor identified 15 pediatric cases of in Utero exposure with ziprasidone. Out of the 15 cases, there were 11 live births, 1 spontaneous abortion and unknown information regarding the remaining three cases.

Of the 11 live births, seven (7) babies were reported as normal healthy infants, three were born with serious adverse events:

Case 2005079138 was reported in the literature (*Journal of Investigative Medicine Jan 2006*) and involved a congenital anomaly (46XY and 550 bands) of a 34 week gestational infant born to a 28 yo schizophrenic mother who continued treatment with ziprasidone. The infant was small for gestational age, phalange hypoplasia, nail deformity, dysmorphism, and nose deformity and finger hypoplasia.

Case 2006072812 involved a neonatal infection that occurred after birth to an uncomplicated delivery in a 33 yo mother for schizophrenic psychosis.

Case 2008034681 involved a case of neonatal pulmonary arterial hypertension in an infant whose mother received ziprasidone at some point during her pregnancy. No additional data is available for this case.

Drug Overdose

There were 17 cases of pediatric overdoses reported as AEs. For three of the cases, the patients received ziprasidone over the recommended amount for an unspecified period of time. One case developed parkinsonism, while a second of these three cases (200mg/day) developed tardive dyskinsia and serotonin syndrome. No AEs were reported for the third case.

In five cases where a single overdose was reported (200 to 2400mg), two cases were suicide attempts with three of the cases reporting prolonged QT intervals. All subjects recovered.

Drug abuse, misuse, dependence

There was one case of abuse reported (no information available) and eight (8) cases of misuse. One case of misuse, case 2004045603, involved the asphyxiation and death of an 8 year old boy who died during a “prayer session”. Toxicology results at autopsy revealed toxic levels of ziprasidone and another drug in the boy’s system.

Six (6) cases of intentional misuse were reported. One patient was described as snorting ziprasidone powder from his capsule, whereas another patient (17 yo with a record of homicide while "high" on lorazepam, committed homicide after skipping one of his daily doses of ziprasidone.

No cases of drug dependence were noted.

IM administration events

There were six cases reporting post marketing AEs associated with IM ziprasidone use, of which four (4) were considered serious. Aggression, circulatory collapse,dystonia, EPS, fatigue, hypersensitivity, orthostatic hypotension, resp. disorder, sedation, somnolence and syncope (1 case each respectively) were reported with IM use.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Pursuant to the Written Request for studies of bipolar in adolescent patients, 237 patients (149 ziprasidone vs. 88 placebo) in the placebo controlled study A1281132 were exposed to four weeks of study medication, with 162 patients participating in a 6-month open label extension safety study A1281133 [67 patients (41%) completed entire study]. For study A1281123, an initial 3 week, open-label, flexible dose titration study (46 patients, bipolar only) with a 6 month long term extension in patients with bipolar (39 patients) and schizophrenia or schizoaffective disorder (17 patients) with ziprasidone was performed. In total, 405 patients were exposed to flexible doses (maximum doses determined by weight of patients) vs. 88 placebo patients during the adolescent bipolar program. This is delineated below:

Table 50: Delineation of pediatric bipolar patients enrolled by study and treatment received

STUDY	ZIPRASIDONE PATIENTS TREATED	PLACEBO SUBJECTS TREATED	ALL SUBJECTS TREATED
A1281123 PERIOD 1 (3 week titration bipolar only)	46		46

A1281123 PERIOD 2 (6 month extension study of 1123-bipolar only	39		39
A1281132 (4 week, double blind, placebo controlled study)	149	88	237
A1281133 (6 month extension study of A1281132)	162		162
A1281123 + A1281133 (6 month studies combined-ISS)	201		201
Total Exposed	405	88	

For all bipolar patients enrolled in the 6 month open label studies, only 73 patients completed at least 5 months of ziprasidone treatment up to 160m/day out of 188 patient's total.

	Ziprasidone Dosage Group (mg/d)					
Days	≤40 n=18	>40–≤80 n=54	>80–≤120 n=29	>120-≤160 n=87	>160 n=13	All subjects ≤160 n=188
Mean Duration	72.5	103.7	101.7	116.5	111.5	106.3
Median Duration	39	98	82	135	148	102.5
Range	3-169	6-189	7-185	8-190	16-189	3-190
	No. of Subjects					
Duration Category (Days)						
1-<7	4	2	0	0	0	6
7-<14	5	3	2	3	0	13
14-<21	0	2	3	8	2	13
21-<30	0	2	1	2	0	5
30-<60	0	10	3	11	3	24
60-<90	2	7	6	11	1	26
90-<120	1	4	1	5	0	11
120-<150	1	2	2	6	1	11
150-<180	5	13	7	23	4	48
≥180	0	9	4	18	2	31

Source: Table 2.1.5
Note: The duration is defined as the total number of actual dosing days from first to and including last day of study treatment.

7.2.1.2 Demographics

Please refer to section 6.1.4 for a review of the demographics of patient's enrolled in the placebo controlled study. The review in this section will focus on the combined demographic characteristics of patients enrolled in the open label studies A1281123 and A1281133.

The following table delineates the demographic characteristics of patients exposed to 6 months of open label ziprasidone.

Table 51: Demographics of patients in open label pediatric bipolar trials by dose

METRIC	≤40MG/DAY N=18	>40 TO ≤80MG/DAY N=54	80 TO ≤120MG/DAY N=29	>120 TO ≤160MG/DAY N=87	160MG/DAY N=13
Male	50%	61%	45%	61%	62%
Age					
10-13 years	56%	59%	48%	48%	46%
Race					
White	89%	85%	97%	83%	77%
Black	11%	13%	3%	12%	8%
Weight (kg) ± SD	53.3 (13.3)	53.6 (17.3)	61.7 (14.9)	58.5 (14.3)	61.7 (11)
Height (cm) ± SD	156.2 (11.9)	155.4 (12.4)	162.2 (10.2)	159.7 (11.4)	160.6 (5.5)

Concomitant Medications and therapy

Excluding the 13 patients who received doses of ziprasidone >160mg/day, eighty percent (80%-151/188) of patients in the open label trials received at least one concomitant medication, with paracetamol (19%), ibuprofen (18%) and lorazepam (15%) being the top three concomitant medications taken. Approximately 10% of patients (18/188) also received psychotherapy during treatment in the open label trials.

7.2.1.3 Extent of exposure (dose/duration)

For the placebo controlled study, there was a total of 9.37 person-years exposure to ziprasidone during the trial. The mean duration of exposure during the double-blind trials was 22.9 days vs. 23.7 for placebo. The mean daily dose during weeks 3, 4 and early termination in patients ≥ 45kg was 118.8 mg, with a mean modal dose of 69.23 for patients <45kg.

The duration of exposure in the combined open label studies A1281123 and A1281133 for bipolar patients only was 58.73 person-years exposure. If the schizophrenia patients enrolled in study A1281123 were included, a total of 65.45 person-years exposure to ziprasidone.

Bipolar only patients enrolled in studies A1281123 and A1281133 had a mean duration of treatment of 106.3 days with a median of 102.5 days. Including the schizophrenia patients, the mean duration of treatment was 109.5 days with a median of 125 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The sponsor also submitted clinical data from the following pediatric studies. Pertinent safety findings are discussed below.

Table 52: Other pediatric ziprasidone studies submitted with this application

STUDY	ZIPRASIONE PATIENTS TREATED	PLACEBO PATIETNS TREATED	TOTAL PATEITNS TREATED
128-044- Phase 1 single dose pharmacokinetic study in patients with Tourettes Syndrome (TS)	24	0	24
128-122-phase II double-blind, placebo controlled 8 week study in patients with TS	16	12	28
IIR studies			
20010457-Autism-6 week open label	8	0	8
20020012- 1 year open label study in patients aged 8-18 with early onset schizophrenia	40	0	40
20020501-Pediatric Bipolar open label monotherapy 8 week study	21	0	21
20020516-Retrospective pediatric safety study with ziprasidone for various psychiatric disorders	36	0	36
20030094-Pediatr bipolar open label study	30	0	30

7.2.2.1.1 Studies 128-044 and 128-122

Both of these studies of ziprasidone use in patients with Tourette's Syndrome took place before the approval of the original NDA for ziprasidone. In the open label study 044, twenty four (24) patients aged 7-16 years of age with a diagnosis of TS or chronic tic disorder were given single oral doses of 20mg (>60kg), 10mg (31-60kg) or 5mg ziprasidone. At the conclusion of this study, no deaths or SAEs were noted. 71% of patients experienced an adverse event, with somnolence being the most often complaint. No significant changes in laboratory, vital signs or ECGs were recorded.

For the 56-day double-blind study 128-122, twenty eight (28) patients aged 7-16 years of age with a diagnosis of TS or chronic tic disorder were given flexible, escalating daily doses of ziprasidone (5mg/day initial) to a maximum dose of 20mg po BID or placebo. The primary efficacy endpoint was the change from baseline score using the global severity and total tic scores of the Yale Global Tic Severity Scale (YGTSS) and the CGI-S scale for Tourette's Syndrome. There were no deaths or serious adverse events noted in this study. Four (4) subjects were prematurely discontinued from the study (3-placebo, 1-ziprasidone, withdrew consent). Eleven (11) of 15 patients randomized to ziprasidone required dose reductions due to mild-moderate sedation. All patients randomized to ziprasidone experienced at least one nervous system adverse event, with the majority being somnolence. There were no sustained clinically significant changes in laboratory, vital signs or ECG recordings noted for this study.

Although the efficacy results from this study will not be fully reviewed at this time, it is worth noting that ziprasidone treated patients achieved a significant reduction in tic severity and total tic score as compared to placebo patients. However a statistically significant reduction on one of three co-primary endpoints (CGI-TS) was not achieved.

TABLE 53: Summary Efficacy results from Study 128-055, LOCF approach

EFFICACY VARIABLE	**ZIPRASIDONE N=16**		**PLACEBO N=11**		**P-VALUE**
	Baseline	*Mean change from Baseline*	*Baseline*	*Mean change from baseline*	
YGTSS Global severity (SD)	46.9 (13.8)	-18.25	46.9 (17.7)	-7.64	0.0155
YGTSS Total Tic score (SD)	24.7 (6.8)	-8.56	24.6 (9.6)	-1.73	0.0080
CGI-TS current score (SD)	4.6 (0.9)	-1.37	4.5 (1.0)	-0.73	0.1067

7.2.2.1.2 Phase IIR studies

Most of the submitted safety data from these studies were abstracts of study results. For the open label schizophrenia study 2002-0012, the sponsor noted that 27 of 40 patients completed at least 8 weeks of open label treatment. Only 10 subjects completed the entire 52 week course. The mean final dose was 117.8mg. From a safety standpoint, 17 patients had notable activation including 9 patients who developed frank mania or hypomania. A mean QTc prolongation of 5msec was also noted.

For the remaining studies listed above, very limited information was provided to full address the safety findings from these studies. However no deaths were noted from the information provided by the sponsor for these studies.

7.2.2.2 Post marketing experience

Please refer to the review in section 7.1.17 for a full review of the sponsor's post-marketing analysis of their global database.

7.2.2.3 Literature

The sponsor conducted a medical literature review from February 5, 1998 through April 30, 2008 as part of the sponsor's post marketing database review and analysis. The results of the medical literature search have been reviewed in section 7.1.17.

7.2.3 Adequacy of Overall Clinical Experience

Overall, the clinical development program for pediatric bipolar disorder is adequate to support the acute use of ziprasidone in the treatment of pediatric bipolar disorder. In this reviewer's opinion, there is sufficient efficacy and safety data from study A1281132 to adequately assess the acute efficacy and safety risks associated with pediatric ziprasidone use.

However, with only 73 pediatric patients (out of 188 total) completing a 5 month course of ziprasidone therapy, there is insufficient data from which to draw any long term safety risks or conclusions with pediatric use of ziprasidone at this time. A full assessment of the long term safety of pediatric ziprasidone use will take place once the long term studies of at least 6 months in duration that are currently underway in the pediatric schizophrenia program are completed and submitted to the agency.

7.2.4 Adequacy of Special Animal and/or *In vitro* Testing

No animal or *in vitro* testing studies were performed or required as part of the Written Request. In addition, the current labeling for ziprasidone has information from previous preclinical and *in vitro* testing of ziprasidone included.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No formal metabolic, clearance or drug interaction data or information was required or performed pursuant to the Written Request. In addition, this information is currently available as part of the current labeling for ziprasidone.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The pediatric studies conducted under this NDA were adequate to evaluate acute pediatric adverse events associated with ziprasidone use. The long term adverse events of pediatric ziprasidone use cannot be assessed at this time due to lack of long term safety data. ECG monitoring was adequate to detect acute changes in any QTc prolongation associated with ziprasidone use, although the long term QTc risks cannot be assessed at this due to lack of long term safety data.

7.2.8 Assessment of Quality and Completeness of Data

Review of case report forms, narrative and adverse event line listings for each of the patients listed below in Table 54 was conducted. Consistent reporting was noted in adverse events between all databases with no errors noted for studies A1281132, A1281123 and A1281133.

TABLE 54: GEODON® CRF AUDIT

PID (UNIQUE ID)	CASE REPORT FORM AE'S	SUMMARY
A1281132/10261001	Dystonia, Overdose	OK
A1281132/10401022	Liver Function Tests Abnormal	OK
A1281132/11241002	Hallucination, Paranoia, Aggression	OK
A1281123/10021008	Exacerbation of Bipolar Symptoms	OK
A1281123/10151012	Mania Aggravated	OK
A1281133/11011002	Hallucination, Conversion disorder, Self injurious behavior	OK
A1281133/10131002	Depressive Symptom, Drug Ineffective, Sedation	OK
A1281133/10401016	Suicidal ideation	OK

.

7.2.9 Additional Submissions, Including Safety Update

After discussions with the Agency, the sponsor was unable to submit the results of the pediatric schizophrenia studies at this time due to significant lack of recruitment for these studies. As a result, the Written Request was modified to allow the sponsor sufficient time (based on the sponsor's projected recruitment rates) to complete submit all pediatric schizophrenia studies as a separate amendment to this NDA by 2011.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Sedation, dystonia and extrapyramidal symptoms appear to be frequently noted in the pediatric population. A closer analysis of the adverse events by patient weight revealed that patients who weighed less than 45kg were most likely to report EPS, tremor and abdominal pain adverse events in the double-blind trials.

The sponsor also conducted a concentration-QTcF analysis from concentration-QTcF data points obtained from 4 pediatric trials and from 21 adult trials. The result showed a linear concentration-dependent increase in QTcF prolongation in both the pediatric and adult population. Of particular concern is that the pediatric population overall had a 58% increase in concentration dependant QTcF prolongation rates at any given concentration when compared to the adult population. The results showed that the pediatric dataset exhibited a steeper slope to the regression line as compared to the adult dataset, suggesting that the pediatric population is at least as sensitive to the concentration-dependant QTcF prolongation effects of ziprasidone administration as compared to adults or potentially may be at more at risk for QTc related cardiac arrhythmias. Despite the absence of reports or adverse events of torsades de pointes seen in the pediatric clinical trials and post-marketing reports thus far, this reviewer recommends that the QTc warning language be re-worded to include children as being potentially at risk for QTc related adverse events associated with ziprasidone use.

A review of the post-marketing reports revealed 8 pediatric deaths from the sponsor's database, including one case of cardiac failure after receiving 160mg/day of ziprasidone for over 1 year. A review of the Agency post-marketing database (please see section 8.8 for details) concluded that the safety profile of ziprasidone in the pediatric population is similar to the adult population, including QTc-related events. Thus the Office of Surveillance and Epidemiology recommends enhancing the Warnings section of the current ziprasidone label to include the risk of QT prolongation for both adult and pediatric patients.

Although post marketing data is subject to many limitations from which to draw firm regulatory conclusions, reports of cardiovascular deaths in patients who received ziprasidone is of concern to this reviewer in light of the more prominent concentration dependant QTcF prolongation seen in pediatric patients as compared to the adult population. This reviewer therefore recommends that there is sufficient evidence to warrant a change in the current Warnings section of the QT

prolongation to include children as being at risk for QT prolongation-related adverse events with ziprasidone use.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Safety data only from the placebo controlled study was reviewed to determine mean change from baseline differences in laboratory and vital sign data for ziprasidone. The safety data from the open label studies A1281123 and A1281133 were pooled and reviewed in response to the specific additional long term safety requirement as delineated in the Written Request.

Efficacy data was only reviewed from the placebo controlled, double blind study.

7.4.1.2 Combining data

Safety data from the two open label studies were combined with an analysis performed via a separate Integrated Safety Study. In addition, those patients with a diagnosis of schizophrenia and schizoaffective disorder who took part in study A1281123 were also pooled with study A1281133 to fully examine the long term safety of pediatric ziprasidone use.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Due to the flexible dose study design form the placebo controlled study, an analysis of dose related adverse events cannot be performed.

7.4.2.2 Explorations for time dependency for adverse findings

Time dependent studies were not performed as there were no long term controlled data that was collected during the clinical development program.

7.4.2.3 Explorations for drug-demographic interactions

Please see section 7.1.5.6 for review of adverse events as related to patient weight.

7.4.2.4 Explorations for drug-disease interactions

No additional studies were performed in patients with clinically significant medical illnesses.

7.4.2.5 Explorations for drug-drug interactions

There were no explorations done to examine drug-drug interactions in the clinical development program.

7.4.3 Causality Determination

In this review, causality was determined if an adverse event occurred in 5% or greater of patients taking ziprasidone compared to placebo AND that the adverse event reporting rate in patients taking drug was at least twice the rate in placebo patients.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Based on the three week dose titration results from study A1281123-period 1, the sponsor employed a maximum dose limit based on patient weight as to limit the maximum exposure of ziprasidone to patients who weighed <45kg.

8.2 Drug-Drug Interactions

There are no further recommendations at this time for dose adjustments for ziprasidone in pediatric patients taking concomitant medications. Discuss

8.3 Special Populations

Dosing for the pediatric studies utilized patient weight as a basis to limit overall exposure of ziprasidone in these trials. As a result, the sponsor has proposed language for labeling that is consistent with the dosing regimens used for dosing in the pediatric bipolar trials submitted under this NDA.

8.4 Pediatrics

The clinical development program was conducted pursuant to the Agency's Written Request.

8.5 Advisory Committee Meeting

An advisory committee meeting is scheduled for June 2009 to review the results of the clinical development program for pediatric bipolar disorder. The

8.6 Literature Review

Relevant reviews of the literature that are pertinent to this review have been cited throughout the review and in the references section of this NDA.

8.7 Post marketing Risk Management Plan

Not applicable at this time.

8.8 Other Relevant Materials

An FDA review of AERS post marketing data was completed by the Office of Surveillance and Epidemiology (OSE) on March 24, 2009 by Ida-Lina Diak, PharmD for the time period of initial market approval until January 14, 2009 for patients aged 0-17 years of age. For an in-depth review, the reader is referred to the March 24, 2009 review for details.

Ten (10) reports of death associated with ziprasidone in patients aged 3-17 years old were reviewed by OSE. Four of the deaths were of an unspecified cause, two were completed suicides and the remaining cases were deaths attributed to different causes. Overall the adverse events that led up to death in the pediatric cases were consistent with the pattern seen with the adult use of ziprasidone.

There were 24 suicide-related events associated with ziprasidone use, along with 24 cases describing QT-related events (3 cases as a result of intentional overdoses and two reports of accidental exposure). Again the cases that were reviewed occurred in a similar manner as reported in the adult population.

A comparison of adverse events reported with a proportion >= 2% by MedDRA system organ class (SOC) and by preferred term between adults and pediatric patients was also performed. For the system organ class comparison, the reports were generally similar between the two populations. However, for the preferred term, the top 5 adverse events reported by preferred term differed between the two populations. For the pediatric population, the top 5 adverse events (in descending order) were: Dystonia (11%), ECG QT prolonged (8%), Extrapyramidal disorder (8%), sedation (7%) and dyspnea (6%). For adults, ECG QT prolongation (7%), insomnia (6%), tremor (6%), agitation (5%) and anxiety (5%) were frequently reported.

9 OVERALL ASSESSMENT

9.1 Conclusions

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.2 Recommendation on Regulatory Action

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.3 Recommendation on Post marketing Actions

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.3.1 Risk Management Activity

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.3.2 Required Phase 4 Commitments

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.3.3 Other Phase 4 Requests

No formal regulatory conclusions are being made at this time for this application. Regulatory conclusions and recommendations will occur after this reviewer and division has fully reviewed the discussions and recommendations made by the Psychopharmacological Advisory Committee for this New Drug Application being presented on June 9 and 10th, 2009.

9.4 Labeling Review

A formal review of the submitted labeling for this application will occur after a full review of discussions and recommendations of advisory committee proceedings have been accomplished by this reviewer and division at the conclusion of the June 9-10th Advisory committee meeting.

However this reviewer recommends data table 29 of this review be included in final labeling as part of the pediatric trial safety results. Also, there appears to be sufficient evidence from both the post-marketing database reviews and the concentration dependant increase in QTcF seen with ziprasidone use in both adults and children to warrant a change in the Warnings section of final labeling to extend the risk of QT prolongation adverse events associated with ziprasidone use to children and adults.

9.5 Comments to Applicant

Comments to the applicant are being deferred until a full review of discussions and recommendations of advisory committee proceedings have been accomplished by this reviewer and division at the conclusion of the June 9-10th Advisory committee meeting.

10 APPENDICES

10.1 Review of Individual Study Reports

Please refer to section 6 for a full review of the protocol for the double-blind, placebo controlled study.

10.2 Line-by-Line Labeling Review

Deferred at this time.

REFERENCES

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/s/

Mark Ritter
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MEDICAL OFFICER

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

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	20-825 (SE5-032)
Drug Name:	GEODON® (ziprasidone HCl) Capsules
Indication:	Pediatric Bipolar Disorder
Applicant:	Pfizer Inc
Dates:	Date of Document: 10/21/2008
	PDUFA Due Date: 4/21/2009
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products, HFD-130
Clinical Team:	Clinical Reviewer: Mark Ritter, M.D.
	Clinical Team Leader: Robert Levin, M.D.
Project Manager:	Doris Bates, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The efficacy of ziprasidone in treating children and adolescents with Bipolar I disorder has been demonstrated. The patients with weight less than 45 kg appeared to show much less improvement numerically than the patients with weight at least 45 kg. Although the statistically insignificant results in the '< 45 kg' subgroup could be due to the lack of power and the patients in the two different weigh groups were dosed differently, it is unclear whether the weight effect is completely confounded with the dose effect.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Per the FDA's Pediatric Written Request (PWR) and also under the Pediatric Research Equity Act (PREA), the sponsor submitted a single efficacy study (Study A1281132) to demonstrate the efficacy of ziprasidone as a treatment of Bipolar I disorder with manic or mixed episodes in children and adolescents.

Study A1281132 was a 4-week, randomized, double-blind, placebo-controlled trial, where ziprasidone was titrated over the first 1-2 weeks of treatment and flexibly dosed through weeks 3 and 4. Ziprasidone was titrated from a starting dose of 20 mg/day with dose increases of 20 mg/day every other day up to a target dose of 120-160 mg/day for subjects weighing greater than or equal to 45 kg. For children weighing less than 45 kg, the target dose was only 60-80 mg/day. The primary efficacy endpoint of the study was change from baseline to Week 4 in YMRS total score. Based on the sponsor's analysis results, they concluded that oral ziprasidone was shown to be effective in the treatment of children and adolescents with Bipolar I disorder (manic or mixed).

1.3 STATISTICAL ISSUES AND FINDINGS

This statistical reviewer confirmed all of the sponsor's efficacy results and agreed that Ziprasidone's overall efficacy was demonstrated in both children and adolescents as a treatment of Bipolar I disorder with manic or mixed episodes. However, it was noted that the patients with weight less than 45 kg appeared to show much less improvement in comparison with the patients with weight at least 45 kg.

2. INTRODUCTION

2.1 OVERVIEW

The sponsor submitted this NDA to support a new indication, and associated prescribing information for the use of ziprasidone HCl in pediatric and adolescent patients aged 10-17 years with Bipolar I Disorder (manic or mixed episodes) in accordance with a commitment under the Pediatric Research Equity Act (PREA) per the 19 August 2004 approval letter for this indication in adults and per the development considerations contained in the 2003 Pediatric Written Request (PWR), and amended. In accordance

with the PWR, FDA agreed that a single positive study in pediatric patients aged 10-17 would support the bipolar indication in this new population.

The study drug, ziprasidone was initially approved in 2001. Oral formulations (capsule and oral suspension) are presently approved for treatment of schizophrenia and of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features, but only for adult population. FDA issued a PWR in February 2003 describing requirements for pediatric studies in both indications. In addition, there is a PREA Phase 4 commitment associated with the bipolar capsule approval for this indication. Studies proposed under the PREA requirement have been designed by Pfizer to meet the terms of the PWR.

The sponsor's clinical development program for ziprasidone consisted of three key studies (Studies A1281132, A1281123 and A1281133) in children and adolescents between the ages of 10 and 17 years. Study A1281132 was the only double-blind well-controlled study which supports the efficacy and safety of flexibly dosed ziprasidone in the treatment of Bipolar I disorder in pediatric patients. It was flexibly titrated over a 2-week period from a starting dose of 20 mg/day given in the evening with dose increases of 20 mg/day every 2nd day up to a target dose of 120-160 mg/day for subjects weighing ≥45 kg or 60-80 mg/day for subjects weighing <45 kg. The target dose was to be obtained by day 14. The dose was increased above 120 mg/day only in subjects who tolerated 120 mg/day. The study duration was 4 weeks. The primary endpoint was change from baseline to week 4 in YMRS total score. Per the FDA's requirement in the Written Request that at least 50% of subjects assigned to the active drug complete to the nominal endpoint for the study to be considered a completed trial, Study 1281132 was determined a completed study with 65.1% of total patients enrolled completed the 4 weeks of dosing. Based on statistically significant results in the primary endpoint and secondary endpoints for Study 1281132, the sponsor concluded that oral ziprasidone (120-160 mg/day) is efficacious in the treatment of manic or mixed episodes associated with Bipolar I Disorder in children and adolescents 10-17 years.

2.2 DATA SOURCES

The electronic submission for this NDA, including the clinical study report and the data sets, were stored in the following directory: **\\CDSESUB1\EVSPROD\NDA020825\0030** of the CDER electronic document room.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Description of Study A1281132

This study was titled "Four Week, Double-Blind, Placebo Controlled Phase III Trial Evaluating the Efficacy, Safety and Pharmacokinetics of Flexible Doses of Oral Ziprasidone in Children and Adolescents with Bipolar I Disorder (Manic or Mixed)." It

was conducted in 36 centers in the United States (US).

3.1.1.1 Study Objective

Primary Objectives:

1. To establish efficacy of oral ziprasidone compared with placebo in the treatment of children and adolescents with Bipolar I disorder (manic or mixed); as measured by the change from baseline to Week 4 in Young Mania Rating Scale (YMRS) total score.

2. To evaluate the safety and tolerability of oral ziprasidone over 4 weeks in the treatment of children and adolescents with Bipolar I disorder (manic or mixed).

Secondary Objectives:

1. To evaluate efficacy of oral ziprasidone as compared with placebo in the treatment Of children and adolescents with Bipolar I disorder (manic or mixed), as measured by

   • Change from baseline in Clinical Global Impression of Severity (CGI-S) score.
   • Clinical Global Impression of Improvement (CGI-I) score.

2. To characterize the population pharmacokinetics and pharmacokinetics/ pharmacodynamics (PK/PD) of oral ziprasidone in children and adolescents with Bipolar I disorder (manic or mixed), including PK/PD analysis for safety (corrected QT interval [QTc]) measurements.

3.1.1.2 Study Design

This was a 4-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and tolerability of flexibly dosed ziprasidone as compared with placebo for the treatment of Bipolar I disorder (manic or mixed) in children and adolescents. Ziprasidone was administered as oral capsules given twice daily (BID) with meals. Ziprasidone was titrated over the first 1-2 weeks of treatment, and flexibly dosed through Weeks 3 and 4.

Approximately 222 subjects (148 ziprasidone, 74 placebo) were to be recruited at approximately 70 US and Canadian sites. It was estimated that at least 318 subjects would be needed to be screened to account for a screen failure rate of approximately 30%. The completion rate of randomized subjects was 65.1%, which met the FDA's requirement.

Upon completion of the screening procedures, eligible subjects were allowed to begin a 1-10 day period to allow for washout of exclusionary medications. The qualified subjects were to be randomized in a 2:1 ratio at baseline to receive either double-blind oral ziprasidone or placebo, respectively.

During the 4 weeks of study, the first two weeks was the dose titration period. Following the titration, double-blind dosing continued to Week 4, during which time further dosing adjustments could be made if necessary within the range of 80-160 mg/day for subjects with a body weight of 45 kg or greater, or between 40-80 mg/day for subjects weighing less than 45 kg.

Subjects who demonstrated insufficient treatment response 1 week after completing their titration, and who reached their maximum tolerated dose, were to be discontinued from the study and could be eligible to enroll in the open-label extension trial (with active ziprasidone) provided there were no safety concerns. Subjects who could not tolerate the dose ranges cited above also were to be discontinued from the double-blind study and could be eligible to enter the extension trial. In addition, subjects requiring concomitant medications disallowed by the protocol could be discontinued and could enroll in the open-label extension if the concomitant medication(s) was/were allowed. Subjects who did not enter the open extension returned for a post-treatment follow-up clinic visit at Week 5.

Reviewer's Note: An interim analysis was originally planned to stop the trial for both efficacy and futility. Since this trial was conducted for seeking pediatric exclusivity, FDA recommended earlier that the sponsor forgo the interim analysis for futility. At the end, the interim analysis was not performed.

3.1.1.3 Efficacy Endpoint and Analysis

The primary efficacy endpoint was the change from baseline in the YMRS score. The primary time point was Week 4. All other collection time points were considered to be secondary.

The analysis of change from baseline in the YMRS score was performed using SAS PROC MIXED to fit a mixed model repeated measures analysis of covariance (ANCOVA) with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate. The estimation method used was restricted maximum likelihood. The covariance structure among repeated measures was assumed to be adequately modeled using a first order autoregressive structure. Other covariance structures could be examined if indicated by model diagnostics. The EMPIRICAL option was specified to compute the estimated variance-covariance matrix of the fixed-effects parameters. Type III sums of squares were used to test both main effects and interactions. The primary comparison was between ziprasidone and placebo at Week 4, conducted as a 2-sided test at 5% level of significance. Based on the specified model, the point estimate and 95% confidence interval (CI) for the difference in means between the 2 treatments were constructed using the least squares means and appropriate standard errors.

For change from baseline in the CGI-S score, analyses were conducted using SAS PROC MIXED to fit a mixed model repeated measures ANCOVA with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

For the raw CGI-I score, analyses were conducted using SAS PROC MIXED to fit a mixed model repeated measures analysis of variance (ANOVA) with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects.

For all the above analyses, the estimation method used was restricted maximum likelihood. The covariance structure among repeated measures was assumed to be adequately modeled using a first order autoregressive structure. Other covariance structures could be examined if indicated by model diagnostics. The EMPIRICAL option was specified to compute the estimated variance-covariance matrix of the fixed-effects parameters. Type III sums of squares were used to test both main effects and interactions. The point estimates and 95% CIs for the difference in means between the 2 treatments were constructed using the least squares means and appropriate standard errors.

3.1.2 Patient Disposition and Demography and Baseline Characteristics

Table 3.1 shows patient disposition and Table 3.2 summaries patient demographics. A total of 327 patients were screened and 238 were randomized to treatment. Of these patients, 237 took study medication. The percentage of patients who completed the study was 65% in the ziprasidone group and 58% in the placebo group. Nevertheless, the ITT population only included 229 patients where 143 patients were randomized to ziprasidone and 86 patients to placebo. As shown in Table 3.2, treatment groups were comparable with regard to demography and baseline characteristics. Patients ranged in age from 10 to 18 years with an overall mean age of 13.6 years in the ziprasidone group and 13.7 years in the placebo group. The majority of patients were white males of non-Hispanic/Latino ethnicity.

Table 3.1 Patient Disposition for Study A1281132

		Ziprasidone	Placebo
Number (%) of subjects:			
Screened:	N=327		
Assigned to study treatment:	N=238		
Treated		149	88
Completed		97 (65.1)	51 (58.0)
Discontinued		52 (34.9)	37 (42.0)
Reason for discontinuation:			
Related to study drug:		14 (9.4)	3 (3.4)
Adverse event		13 (8.7)	3 (3.4)
Laboratory abnormality		1 (0.7)	0 (0)
Not related to study drug:		38 (25.5)	34 (38.6)
Adverse event		5 (3.4)	10 (11.4)
Lost to follow-up		8 (5.4)	1 (1.1)
Other		16 (10.7)	21 (23.9)
Subject no longer willing to participate		9 (6.0)	2 (2.3)
Analyzed for efficacy:			
Intent-to-treat		143 (96.0)	86 (97.7)
Per protocol		103 (69.1)	66 (75.0)
Analyzed for safety:			
Adverse events		149 (100)	88 (100)
Laboratory data		134 (89.9)	84 (95.5)

Source: Table 4 of Sponsor's CSR.

Table 3.2 Patient Demographics for Study A1281132

	Ziprasidone			Placebo		
	Male N=84	**Female N=65**	**Total N=149**	**Male N=47**	**Female N=41**	**Total N=88**
Age (years)						
10-13	47 (56.0)	27 (41.5)	74 (49.7)	19 (40.4)	16 (39.0)	35 (39.8)
14-17	36 (42.9)	38 (58.5)	74 (49.7)	28 (59.6)	25 (61.0)	53 (60.2)
≥18	1 (1.2)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)
Mean	13.2	14.1	13.6	13.5	14.0	13.7
SD	2.4	2.0	2.2	2.0	1.9	2.0
Range	10-18	10-17	10-18	10-17	10-17	10-17
Race						
White	66 (78.6)	55 (84.6)	121 (81.2)	38 (80.9)	34 (82.9)	72 (81.8)
Black	15 (17.9)	6 (9.2)	21 (14.1)	8 (17.0)	6 (14.6)	14 (15.9)
Asian	0 (0)	1 (1.5)	1 (0.7)	0 (0)	0 (0)	0 (0)
Other	3 (3.6)	3 (4.6)	6 (4.0)	1 (2.1)	1 (2.4)	2 (2.3)
Ethnicity						
Hispanic/Latino	5 (6.0)	6 (9.2)	11 (7.4)	2 (4.3)	5 (12.2)	7 (8.0)
Not Hispanic/Latino	79 (94.0)	59 (90.8)	138 (92.6)	45 (95.7)	36 (87.8)	81 (92.0)
Weight (kg)						
Mean	55.9	58.8	57.2	61.3	58.5	60.0
SD	16.3	11.5	14.4	17.9	13.4	16.0
Range	28.0-88.0	34.1-94.4	28.0-94.4	29.0-109.4	32.1-87.1	29.0-109.4
Height (cm)						
Mean	160.3	158.1	159.3	163.4	157.1	160.5
SD	14.1	8.0	11.9	13.8	8.1	11.9
Range	128-188	134-174	128-188	137-193	133-170	133-193

Source: Table 7 of Sponsor's CSR.

3.1.3 Sponsor's Efficacy Analysis Results

3.1.3.1 Sponsor's Results for Primary Endpoint

Table 3.3 summarizes the sponsor's primary analysis results for change from baseline to Week 4 in the YMRS total score. As shown in the table, the estimated least square (LS) means for ziprasidone and placebo for the change from baseline to Week 4 in YMRS total score were -13.83 and -8.61, respectively. The estimated LS means and the 95% CI for placebo-adjusted scores for ziprasidone were -5.22 [-8.12, -2.31]. This difference in treatment effect was statistically significant (p=0.0005). The sponsor noted that results from the primary analysis using the PP analysis set also indicated a statistically significant treatment effect (p=0.0004) in favor of ziprasidone.

Table 3.3 Sponsor's Analysis Results for Change from Baseline in Young Mania Rating Scale (YMRS) at Week 4 Repeated Measures for ITT Population for Study A1281132

	Ziprasidone N=133	Placebo N=85
LS Mean (SE)	-13.83 (0.96)	-8.61 (1.10)
Difference from Placebo LS Mean (SE)	-5.22 (1.48)	
95% CI for the difference from Placebo	[-8.12, -2.31]	
P-value	0.0005	

Sponsor's Table 10 of CSR.

Table 3.4 presents descriptive statistics for YMRS total score at baseline and change from baseline to each visit for the ITT populations. Since the 95% confidence intervals ruled out zero from Week 1 to Week 4, the sponsor concluded that the active and placebo groups separated as early as at Week 1 for the change from baseline in YMRS total score. Nevertheless, we should note that this conclusion was drawn without any prospective analysis plan for adjusting the overall type I error rate due to multiple comparisons.

Table 3.4 Sponsor's Descriptive Statistics for YMRS Total Score at Baseline and Change from Baseline by Treatment Group and Visit for Study A1281132

	Ziprasidone			Placebo		
Visit	N	Mean (SD)	95% C.I.	N	Mean (SD)	95% C.I.
Baseline	143	26.2 (6.6)	(25.08, 27.26)	86	27.0 (6.6)	(25.59, 28.43)
Week 1	131	-9.3 (7.5)	(-10.63, -8.04)	85	-6.3 (7.1)	(-7.86, -4.80)
Week 2	120	-11.5 (8.7)	(-13.07, -9.92)	81	-8.1 (7.9)	(-9.88, -6.40)
Week 3	108	-13.0 (8.1)	(-14.51, -11.42)	65	-9.0 (7.3)	(-10.82, -7.21)
Week 4	97	-13.8 (7.8)	(-15.32, -12.18)	51	-9.9 (7.7)	(-12.03, -7.70)
Week 4-LOCF	133	-12.8 (8.4)	(-14.27, -11.37)	85	-7.1 (7.8)	(-8.74, -5.40)

Source: Sponsor's Table 13.4.2.1 of CSR.

3.1.3.2 Sponsor's Results for Secondary Endpoints

One secondary efficacy endpoint for this study was the change from baseline in CGI-S score. Table 3.5 summarizes the statistical analysis for change from baseline to Week 4 in CGI-S total score. The estimated LS means for ziprasidone and placebo for the change from baseline to Week 4 (repeated measures) in CGI-S score was -1.43 and -0.74, respectively. The estimated LS means and 95% CI for placebo-adjusted scores for ziprasidone were -0.69 [-1.03, -0.34]. The difference in treatment effect was statistically significant (p=0.0001). The sponsor noted that this secondary analysis further supports the efficacy of oral ziprasidone in children and adolescents with Bipolar I disorder (manic or mixed). Results from the statistical analysis using the PP analysis set also indicated a significant treatment effect (p=0.0003) in favor of ziprasidone.

Table 3.5 Sponsor's Analysis Results for Change from Baseline in CGI-S Total Score at Week 4 for ITT Population for Study A1281132

	Ziprasidone N=133	Placebo N=85
LS Mean (SE)	-1.43 (0.13)	-0.74 (0.13)
Difference from Placebo LS Mean (SE)	-0.69 (0.18)	
95% CI for the difference from Placebo	[-1.03, -0.34]	
P-value	0.0001	

Source: Sponsor's Table 11 of CSR.

CGI-I score was another secondary efficacy endpoint. Table 3.6 summarizes the statistical analysis for change from baseline to Week 4 in CGI-I score. The estimated LS means for ziprasidone and placebo for the change from baseline to Week 4 in CGI-I score were 2.30 and 3.06, respectively. The estimated LS mean and 95% CI for placebo-adjusted scores for ziprasidone were -0.76 [-1.18, -0.34]. The difference in treatment effect was statistically significant (p=0.0004).

Table 3.6 Sponsor's Analysis Results for Change from Baseline in CGI-I Score at Week 4 for ITT Population for Study A1281132

	Ziprasidone N=132	Placebo N=85
LS Mean (SE)	2.30 (0.13)	3.06 (0.16)
Difference from Placebo LS Mean (SE)	-0.76 (0.21)	
95% CI for the difference from Placebo	[-1.18, -0.34]	
P-value	0.0004	

Source: Sponsor's Table 12 of CSR.

3.1.4 Statistical Reviewer's Findings and Comments

1. This reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints. She agrees that the efficacy of ziprasidone has been demonstrated. However, she noted that ziprasidone seems to perform distinctly on two types of weight groups of patients. Patients with weights less than 45 kg showed much less improvement than patients with weight at least 45 kg. Since the dosing mechanism depends on weight of patients, it is unclear whether weight effect is completely confounded with the dose effect.

2. The change from baseline in CGI-S score was designated as a 'key' secondary efficacy endpoint in the clinical study report. In fact, none of secondary endpoints was pre-specified as a key secondary endpoint.

3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review. Please see the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

Tables 3.7 to 3.9 showed the sponsor's subgroup analysis for gender, race and age on the primary endpoint YMRS total score and the secondary endpoint, CGI-S respectively. Except the category of other in race subgroups, numerically, ziprasidone showed larger change from baseline values than placebo in all other subgroups. The statistical reviewer confirmed all of the sponsor's subgroup analysis results.

Table 3.7 Sponsor's Analysis Results for Gender Subgroups for Study A1281132

	Male		Female	
YMRS Total	Ziprasidone N=74	Placebo N=44	Ziprasidone N=59	Placebo N=41
LS Mean of Change (SE)	-13.41 (1.12)	-6.50 (1.48)	-14.44 (1.15)	-10.70(1.45)
Difference from placebo LS Mean (SE)	-6.91 (1.72)		-3.74 (1.85)	
95% CI for the difference from placebo	(-10.28, -3.53)		(-7.38, -0.09)	
P value	<0.0001		0.0445	

	Male		Female	
CGI-S Score	Ziprasidone N=74	Placebo N=44	Ziprasidone N=59	Placebo N=41
LS Mean (SE)	-1.36 (0.14)	-0.63 (0.18)	-1.54 (0.15)	-0.80 (0.18)
Difference from placebo LS Mean (SE)	-0.73 (0.21)		-0.74 (0.21)	
95% CI for the difference from placebo	(-1.14, -0.32)		(-1.16, -0.32)	
P value	0.0005		0.0006	

Source: Sponsor's Table 5 of Clinical-Overview and Table 13.4.3.3.1 of Email to FDA on 2/17/2009

Table 3.8 Sponsor's Analysis Results for Race Subgroups for Study A1281132

YMRS Total Score (Change from Baseline)

White	**Ziprasidone**	**Placebo**
N	112	69
LS Mean of Change (SE)	-13.98 (0.95)	-7.68 (1.21)
Difference from Placebo LS Mean (SE)	-6.29 (1.37)	
95% CI for the Difference from Placebo	(-8.98, -3.61)	
p-value	<0.0001	
Black	15	14
N	-12.44 (2.30)	-11.38 (2.51)
LS Mean of Change (SE)	-1.06 (3.26)	
Difference from Placebo LS Mean (SE)	(-7.55, 5.34)	
95% CI for the Difference from Placebo	0.7461	
p-value		
Other		
N	5	2
LS Mean of Change (SE)	-11.96 (2.62)	-17.54 (4.01)
Difference from Placebo LS Mean (SE)	5.59 (4.80)	
95% CI for the Difference from Placebo	(-4.71, 15.89)	
p-value	0.2640	

CGI-S Score (Change from Baseline)

White	**Ziprasidone**	**Placebo**
N	112	69
LS Mean of Change (SE)	-1.51 (0.12)	-0.68 (0.15)
Difference from Placebo LS Mean (SE)	-0.83 (0.17)	
95% CI for the Difference from Placebo	(-1.15, -0.50)	
p-value	<0.0001	
Black	15	14
N	-0.83 (0.23)	-0.71 (0.25)
LS Mean of Change (SE)	-0.12 (0.34)	
Difference from Placebo LS Mean (SE)	(-0.80, 0.55)	
95% CI for the Difference from Placebo	0.7156	
p-value		
Other		
N	5	2
LS Mean of Change(SE)	-1.53 (0.51)	-2.50 (0.73)
Difference from Placebo LS Mean (SE)	0.97 (0.89)	
95% CI for the Difference from Placebo	(-0.93, 2.86)	
p-value	0.2947	

Source: Sponsor's Table 7 of Clinical-Overview and Table 13.4.3.3.3 of Email to FDA on 2/17/2009

Table 3.9 Sponsor's Analysis Results for Age Subgroup for Study A1281132

	<14 years		≥14 years	
YMRS Total	Ziprasidone N=66	Placebo N=35	Ziprasidone N=67	Placebo N=50
LS Mean of Change (SE)	-12.44 (1.12)	-8.57 (1.17)	-15.36 (1.15)	-8.33(1.31)
Difference from placebo LS Mean (SE)	-3.88(1.98)		-7.03 (1.62)	
95% CI for the difference from placebo	(7.77, 0.02)		(-10.22, -3.84)	
P value	0.0510		<0.0001	
CGI-S Score	Ziprasidone N=66	Placebo N=35	Ziprasidone N=67	Placebo N=50
LS Mean of Change (SE)	-1.45 (0.14)	-0.77 (0.21)	-1.40 (0.15)	-0.69 (0.17)
Difference from placebo LS Mean (SE)	-0.68 (0.24)		-0.71 (0.19)	
95% CI for the difference from placebo	(-1.15, -0.21)		(-1.09, -0.33)	
P value	0.0045		0.0003	

Source: Sponsor's Table 6 of Clinical-Overview and Table 13.4.3.3.2 of Email to FDA on 2/17/2009

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Since patients were dosed according to their weight, we are interested in exploring whether treatment effects are different in two weight groups. Table 3.10 shows the sponsor's subgroup analysis results for the weight category. As seen in the tables, ziprasidone seems to show different effect for patients in two weight groups. The significant efficacy findings appear to be mainly from patients whose weights are greater than 45 kg although we should note that only about 20% of patients whose weights are less than 45 kg.

Table 3.10 Sponsor's Analysis Results for Weight Subgroups for Study A1281132

	Weight <45 kg		Weight ≥45 kg	
YMRS Total Score	Ziprasidone N=31	Placebo N=14	Ziprasidone N=101	Placebo N=71
LS Mean of Change (SE)	-12.83 (1.86)	-10.97 (2.92)	-14.15 (0.90)	-8.21 (1.11)
Difference from placebo LS Mean (SE)	-1.86 (3.22)		-5.93 (1.36)	
95% CI for the difference from placebo	(-8.24, 4.51)		(-8.61, -3.25)	
P value	0.56		<0.0001	
CGI-S Score	Ziprasidone N=31	Placebo N=14	Ziprasidone N=101	Placebo N=71
LS Mean of Change (SE)	-1.32 (0.20)	-1.03 (0.32)	-1.48 (0.12)	-0.70 (0.15)
Difference from placebo LS Mean (SE)	-0.28 (0.35)		-0.78 (0.17)	
95% CI for the difference from placebo	(-0.97, 0.40)		(-1.10, -0.45)	
P value	0.4122		<0.0001	

Source: Sponsor's Tables 13.4.2.23.1 and 13.4.3.3.4 from Sponsor's email to FDA on 2/28/2009

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

This statistical reviewer confirmed all of the sponsor's efficacy analysis results and agreed that Ziprasidone's overall efficacy was demonstrated in both children and adolescents as a treatment of Bipolar I disorder with manic or mixed episodes. However, it was noted that the patients with weight less than 45 kg appeared to show much less improvement in comparison with the patients with weight at least 45 kg.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The efficacy of ziprasidone in treating children and adolescents with Bipolar I disorder has been demonstrated. The patients with weight less than 45 kg appeared to show much less improvement numerically than the patients with weight at least 45 kg. Although the insignificant results in the < 45 kg subgroup could be due to the lack of power and the patients in the two different weigh groups were dosed differently, it is unclear whether the weight effect is completely confounded with the dose effect.

_____
Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 20-825
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Date:	March 24, 2009
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Through:	Mark Avigan, M.D., C.M., Director Division of Pharmacovigilance (DPV I) Office of Surveillance and Epidemiology (OSE)
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Subject:	Pediatric overview
Drug Name(s):	Geodon (ziprasidone)
Application Type/Number:	NDA # 20825
Applicant/sponsor:	Pfizer
OSE RCM #:	2009-76

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EXECUTIVE SUMMARY

The Division of Pharmacovigilance (DPV) conducted this review in response to a request from the Division of Psychiatry Products (DPP) to analyze the Adverse Event Reporting System (AERS) pediatric postmarketing data for ziprasidone in patients aged 0-17 years of age since market approval. The purpose of this analysis was for a comparison to the sponsor's submitted data.[1]

Overall, we analyzed the postmarketing pediatric safety profile for ziprasidone, with the primary focus on deaths (10), suicide-related events (24) and QT-related events (24). The adverse events that led up to the 10 pediatric deaths occurred in much the same manner as in adult patients. Of the 24 suicide-related cases, 13 were confounded by the use of concomitant medications also labeled for an association with suicide-related events and many of these medications were agents used to treat psychiatric illnesses. The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder. Based on the limitations of AERS data, it is not possible to distinguish events linked to the underlying condition from paradoxically heightened suicidality due to drug effect. Twenty-four cases reported QT prolongation with five of those cases reporting an overdose situation, both accidental (2) and intentional (3). The remaining 19 cases occurred in a similar manner as reported in the adult population. Seven of these 19 cases described a normalizing of the QT interval upon the discontinuation of ziprasidone. QT prolongation is a well-known adverse event associated with ziprasidone use. No cases of Torsade de pointes were reported.

The safety profile of the pediatric population is very similar compared to that of the adult population, and the adverse events occurred in much the same manner as well. No new safety signals emerged as part of this review; however, it has made us aware that the pediatric population is not spared from the adverse events caused by ziprasidone therapy. The potential risks of ziprasidone therapy should be weighed against the potential benefit when choosing to initiate therapy.

Although the safety and effectiveness of ziprasidone in pediatric patients have not been established, DPV recommends enhancing the Warnings section of the current ziprasidone label to include the risk of QT prolongation for both adult and pediatric patients.

1 BACKGROUND

1.1 INTRODUCTION

DPV conducted this review in response to a request from DPP to analyze the AERS pediatric postmarketing data for ziprasidone in patients aged 0-17 years of age since market approval. In addition, we were asked to focus on deaths, serious adverse events, the proportion of adverse event reporting for pediatric vs. non-pediatric groups, pediatric adverse events by system organ class, adverse events by preferred term with a reporting proportion $\geq$ 2% in both pediatric and non-pediatric cases, pediatric suicidality, and potentially QT-related events. The purpose of this analysis was for a comparison to the sponsor's submission[1], which included 10 years of pediatric postmarketing data.

1.2 REGULATORY HISTORY

Ziprasidone, an atypical antipsychotic agent (marketed as Geodon by Pfizer) received FDA approval February 5, 2001 for the treatment of schizophrenia in adults. On August 19, 2004, ziprasidone also

[1] Ziprasidone Pediatric Bipolar I Disorder Submission- Postmarketing Experience Ziprasidone and Pediatric cases, Submitted October 21, 2008 by Pfizer Inc. EDR location: **\\CDSESUB1\EVSPROD\NDA020825\0030**

received FDA approval for monotherapy in the treatment of acute manic or mixed episodes in Bipolar I Disorder, with or without psychotic features. The mechanism of action of atypical antipsychotics is not clearly understood. The presumed mechanism of action involves antagonism of both dopamine-2 and serotonin 5-HT2A receptors in the central nervous system. Increased affinity for the serotonin 5-HT2A receptor, a feature of "atypical" but not "conventional" antipsychotic agents, is believed to result in less extrapyramidal symptoms.

Relevant previous OSE postmarketing reviews include:

- June 25, 2003. A literature review concerning the issue of *diabetes mellitus/hyperglycemia* associated with the atypical antipsychotic drugs. The findings of the review suggested that a risk management program be put in place for these drugs. [2]
- September 9, 2004- This review focused on QT prolongation, ventricular arrhythmias including Torsade de pointes, cardiac arrest, syncope, overdose cases with associated QT prolongation or ventricular arrhythmias. The review concluded that the drug's possible role as an independent risk factor in these events could not be excluded. In addition, unlabeled use of the drug in elderly patients was identified as a potential risk. [3]
- October 4, 2005. A class review of *galactorrhea* with atypical antipsychotic drugs in pediatric patients. The review supported further analysis of hyperprolactinemia and galactorrhea with atypical antipsychotics in order to update risperidone labeling to reflect the increased numbers of reports of hyperprolactinemia and galactorrhea associated with risperidone relative to other atypical antipsychotic drugs.[4]
- October 4, 2005. A class review of *pituitary tumors* with atypical antipsychotic drugs. The review recommended further investigation, perhaps including reanalysis of the risperidone NDA, in order to update the risperidone label to include increased hyperprolactinemia compared to other atypical antipsychotic agents.[5]
- January 25, 2008. A class review of selected antipsychotics and the occurrence of *agranulocytosis*. The review recommended the addition of agranulocytosis to the Precautions section of the olanzapine and risperidone label as well as elevating agranulocytosis to the Precautions section for chlorpromazine and haloperidol.[6]
- April 29, 2008- This review focused cases of death in children 16 years old and younger. Ziprasidone was associated with four death cases. This review concluded that the current safety profile in the labeling would not need revising to include any additional pediatric population specific adverse events.[7]

1.3 PEDIATRIC PRODUCT LABELING[8]

The current ziprasidone contains the following language regarding the pediatric population.

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[2] Mosholder A. Literature review concerning the issue of diabetes mellitus/hyperglycemia associated with the atypical antipsychotic drugs. FDA Postmarketing Safety Review. June 25, 2003.

[3] Pratt B. A review of QT prolongation, ventricular arrhythmias including Torsade de pointes, cardiac arrest, syncope, overdose cases with associated QT prolongation or ventricular arrhythmias. FDA Postmarketing Safety Review. September 9, 2004.

[4] Phelan K. A class review of galactorrhea with atypical antipsychotic drugs in pediatric patients. FDA Postmarketing Safety Review. October 4, 2005.

[5] Phelan K. A class review of pituitary tumors with atypical antipsychotic drugs. FDA Postmarketing Safety Review. October 4, 2005.

[6] Diak I. A mixed class review of antipsychotics and the occurrence of agranulocytosis. FDA Postmarketing Safety Review. January 25, 2008.

[7] Diak I. Postmarketing cases coded with death in children 16 years old and younger. FDA Postmarketing Safety Review. April 29, 2008.

[8] Geodon Product Label, June 2008, Pfizer, U.S.A.; http://www.pfizer.com/files/products/uspi_geodon.pdf.

Information for patients:
Pediatric Use - The safety and effectiveness of ziprasidone in pediatric patients have not been established.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

This section describes the AERS searches performed as well as the case series selection.

2.2 AERS SELECTION OF CASES

We searched the AERS database on January 14, 2009 for all reports of pediatrics (age 0-17 years) and adults (18 years and greater) associated with ziprasidone use from market approval until January 14, 2009. We conducted separate searches as follows:

1. From Marketing to January 14, 2009 – Adults, 18 years old and older, (Section 3.1, Results, Table 1)
    - All adult reports
    - All adult reports coded serious
    - All adult reports coded 'death'
2. From Marketing to January 14, 2009 – Pediatrics aged 0 to 17 years old, (Section 3.1, Results, Table 1)
    - All pediatric reports
    - All pediatric reports coded serious
    - All pediatric reports coded 'death'
3. From Marketing to January 14, 2009 – Null ages (Section 3.1, Results, Table 1)
    - All reports
    - All reports coded serious
    - All reports coded death

The crude counts that resulted from the searches are included in section 3. For the cases that received a hands-on review, the search of all pediatric reports coded with the outcome of death retrieved nine cases. One additional case of pediatric death was discovered upon reviewing the nine reports not coded with an outcome. A total of 328 reports were associated with pediatric patients aged 0-17 years and 2731 reports were associated with adult patients aged $\geq$ 18 years old. These reports are graphically represented based on the system organ class (SOC) associated with the adverse event as well as by the preferred term (PT) with a reporting proportion of $\geq$ 2% (see Appendix 1).

We performed two additional searches of the AERS database; one for pediatric reports of suicide related events using the MedDRA SMQ Suicide/Self-Injury and the PT poisoning and the second for pediatric reports of potentially QT related events using the MedDRA SMQ Torsade de pointes/QT prolongation. The search of suicide related event retrieved 33 reports, of which four were duplicates and an additional five reports were not included for further discussion because the patient was not on ziprasidone at the time of the event; therefore, we included 24 unique cases in our discussion. The search of potentially QT related events retrieved 41 reports, of which three were duplicates and an additional 14 reports were not

included for further discussion because the report did not specifically describe the occurrence of QT prolongation; therefore, we included 24 unique cases in our discussion.

3 RESULTS

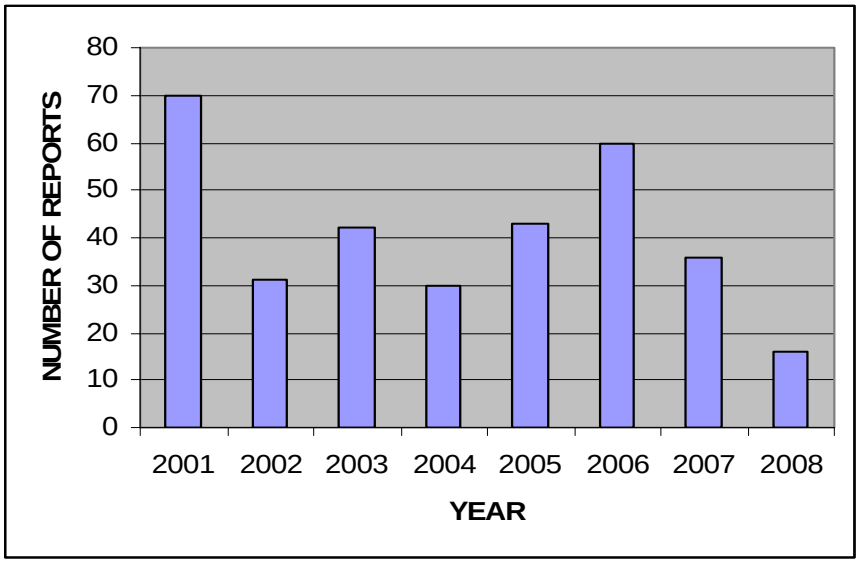
3.1 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM MARKETING APPROVAL (FEBRUARY 5, 2001) TO JANUARY 14, 2009 (TABLE 1)

Table 1: Crude counts[1] of AERS Reports for All Sources from Approval Date (February 5, 2001) through January 14, 2009

	All reports	Serious[2]	Death
Adults (≥ 18 yrs.)	2731	2558	421
Pediatrics (0-17 yrs.)	328	302	9
Age unknown (Null values)	1583	1503	182
Total	4642	4363	612

[1] May include duplicates
[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, other serious.

Figure 1: Reporting trend for pediatric reports from approval date (February 5, 2001) to December 31, 2008:



3.2 CASE CHARACTERISTICS (TABLE 2)

Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

Table 2: Characteristics of serious and non-serious pediatric cases associated with ziprasidone reported from approval through January 14, 2009 n=328 (Crude counts)	
Gender [n=322]	Male: 186 Female: 136
Age [n=327]	0- <1 month (0) 1 month - <2 yrs (3) 2-5 yrs (17) 6-11 yrs (76) 12-17 yrs (231) Mean = 12.9 years, Median = 14 years, Range = 0.6 to 17.8 years
Origin [n=322]	US 304, Foreign 18
FDA reported date	2001 (70) 2002 (31) 2003 (42) 2004 (30) 2005 (43) 2006 (60) 2007 (36) 2008 (16)
Indications [n=249]	Accidental ingestion (2), Acute Psychosis (1), Adjunctive therapy for ADD (1), Affective disorder (1), Aggression (1), Aggressive behavior (1), Agitation (5), Anti-psychotic (2), Asperger's disorder (3), ADHD (4), Auditory Hallucinations (1), Autism (6), Behavior disorder (3), Bipolar Disorder (58), Depression (11), Explosive behavior (1), Hallucinations (4), Ill-defined disorder (32), Impulse control disorder (3), Lennox-Gastaut Syndrome (1), Manic behavior (1), Manic depression (1), Migraine NOS (1), Mood disorder (7), Obesity (3), OCD(5), ODD (2), Paranoid schizophrenia (3), Personality disorder (1), PTSD (3), PMDD (2), Psychiatric/psychotic disorder (9), Psychosis (16), Reactive attachment disorder (1), Schizoaffective disorder (16), Schizophrenia (20), Social withdrawal (1), Seizures (2), Suicidal ideation (2), Temper tantrum (1), Tics (2), Tonsillitis (1), Tourette's syndrome (4), Traumatic brain injury (1), Violent behavior (3)
Coded Outcomes, non-overlapping [n=319]	Death (9), Life-Threatening (16), Hospitalization (111), Required Intervention (17), and Other Serious (166)

3.3 ADVERSE EVENTS CASES

3.3.1 Total reports with an outcome of death (n=10)

Ten unique post-marketing cases of death associated with the use of ziprasidone were reported to the AERS database from market approval (February 5, 2001) through January 14, 2009. Overall, for the 10 cases, nine are US cases and one is a foreign case, including six males and four females. The patients involved ranged in age from 3 to 17 years with a median of 16.5 years. Five cases reported an onset of death relative to the initiation of drug therapy in the range of 18 days to approximately one year with an

approximate median of 21 days. Three cases reported that an autopsy was performed; however, only one of these cases had a confirmed cause of death and one additional case reported toxicology results confirming the presence of ziprasidone in the blood.

ISR# 5009597; US, 2006. A 3-year old female died from an unspecified cause after an unknown duration of treatment with ziprasidone for bipolar disorder. At some point prior to her death, she experienced severe constipation and was hospitalized. Her concomitant medication included quetiapine.

ISR# 4404435; US, 2004. An 8-year old autistic male died from suffocation "due to external chest compression" during a "prayer session". The toxicology report revealed toxic levels of ziprasidone and brompheniramine in the patient's blood. The death was ruled a homicide by suffocation.

ISR# 4753938; US, 2005. A 13-year old female shot herself in the head with a gun and died during a taper off risperidone and a titration of ziprasidone for the treatment of bipolar disorder. She began to act irritable and defiant, which occurred in the past when she had stopped taking risperidone or decreased the dose. She had no history of suicide attempts.

ISR# 5277672; US, 2007. A 13-year old male experienced many unusual adverse events and "died of a stroke" (according to his mother) after initiating therapy with ziprasidone (dose and duration unknown) for the treatment of autism. Sometime prior to his death after the initiation of ziprasidone, he experienced a blood spot in his eye, enlarged testicles, a seizure, left hydrocele, aggressive behavior, prolonged erection, headache, migraine, and decreased appetite (adapted from the narrative).

ISR# 5259176; US, 2007. A 16-year old male died of cardiopulmonary failure within one year of initiating therapy with ziprasidone 160 mg daily for the treatment of schizophrenia. His concomitant medications included topiramate, sertraline, and quetiapine. The reporting physician stated, "he didn't think this patient's death was in any way related to Geodon." Autopsy results were inconclusive.

ISR# 5606100; US, 2008. A 17-year old male died from an unspecified cause after an unknown duration of treatment with ziprasidone for schizophrenia. The patient presented to the emergency room with abnormal laboratory values and became agitated at which time Geodon IM was administered for sedation. The patient was bradycardic, apneic and required oxygen and atropine. The patient experienced pulseless asystole at which time he was intubated and administered multiples doses of epinephrine with no response and was "pronounced". His concomitant medications included lithium and benztropine.

ISR# 5212670; Foreign, 2007. A 17-year old female committed suicide by jumping out of the window of her home 22 days after the initiation of ziprasidone for the treatment of schizophrenia. She had been treated with other antipsychotics prior to initiating ziprasidone. Her concomitant medication included lorazepam. Of note, she was a subject in a 26-week open-label extension study evaluating the safety and tolerability of flexible doses of oral ziprasidone in adolescent subjects with schizophrenia.

ISR# 3766636; US, 2001. A 17-year old female died from an unspecified cause within three weeks of initiating therapy with ziprasidone. The day she died, she was on a pass from the hospital and she left with friends and ingested an unknown amount of alcohol, marijuana and heroin. Within 5-10 minutes of ingestion, an ambulance was called and the patient expired an hour later. Her concomitant medications included divalproex sodium and lorazepam.

ISR# 3735792; US, 2001. A 17-year old male died from aspiration (suspected cause of death) 19 days after the initiation of ziprasidone 20 mg daily for the treatment of autism and aggressive behavior. Just prior to his death, he experienced a seizure, lost consciousness and never regained it. He had a history of a seizure disorder and mental retardation and was concomitantly being treated with clonidine.

ISR# 4197199; US, 2003. A 17-year old male died from an undetermined cause after an unknown duration of therapy with ziprasidone. In the week prior to his death, he complained of chest aching and burning. The autopsy found the heart minimally enlarged and some congestion and intra-alveolar hemorrhage in his lungs; however, the cause of death remained undetermined.

3.3.2 Suicide related events (n=24)

Twenty-four unique post-marketing cases of suicide related events associated with the use of ziprasidone were reported to the AERS database from market approval (February 5, 2001) through January 14, 2009. Overall, for the 24 cases, 15 are US cases, 7 are foreign cases, and 2 cases are of unknown origin, which includes 19 females and 5 males. The patients involved ranged in age from 10 to 17 years with a median of 15 years. Of the seven cases reporting a time to onset of the suicide-related event, the time ranged from 22 days to 9 months with a median of 41.5 days. A majority of the cases were coded with an outcome of hospitalization (13) followed by other serious (6), life-threatening (3), and death (2). The indication for use was reported in 15 of the cases; the most commonly reported indications were schizophrenia (4) and bipolar disorder (3), with the remaining eight cases being reported among several different indications.

Fifteen cases reported the involvement of concomitant or co-suspect medications; anti-depressant (9), anti-epileptic (5), anti-psychotic (3), anti-anxiety (2), and one each of cannabis, benztropine, and an unspecified herbal sleep aid (each case may report more than one concomitant medication). Based on the concomitant medications reported in the cases, we can infer that many of the patients most likely had a past medical history of psychiatric illness.

Twenty-two of the 24 cases reported suicidal and self-injurious behaviors, which includes two cases reporting a completed suicide. An additional two cases reported intentional overdose and they were not coded to be specifically suicide related. The reported PTs associated with the 23 cases included, suicide attempt (8), suicidal ideation (6), intentional self-injury/self-injurious ideation (5), completed suicide (2), intentional overdose (2), and 1 case reported suicidal behavior.

3.3.3 QT related events (n=24)

Twenty-four unique post-marketing cases of QT related events associated with the use of ziprasidone were reported to the AERS database from market approval (February 5, 2001) through January 14, 2009. Overall, for the 24 cases, 23 are US cases; one is a foreign case, which includes 16 males, 7 females, and one case of unknown gender. The patients involved ranged in age from 1.3 to 17 years with a median of 12 years. Only four cases reported a time to onset of event, which ranged from 7 to 24 days with a median of 16.5 days. Thirteen cases reported a total daily dose, which ranged from 20 to 160 mg with a median of 80 mg. Additionally, two cases reported accidental ingestion and three cases reported intentional overdoses, which all resulted in QT prolongation the day of the ingestion. Seventeen cases reported a QTc value, which ranged from 443 to 574 msec with a median of 480 msec. Nine cases reported a QT value, which ranged from 385 to 522 msec with a median of 480 msec (five of these cases also reported a QTc value).

Twenty-three of the 24 cases were coded with the PT of Electrocardiogram QT prolonged with the remaining case coded as dizziness and syncope. No cases of Torsade de pointes were reported in the pediatric population. A majority of the cases were coded with an outcome of hospitalization (11) followed by other serious (7), and life-threatening, required intervention and unknown (2). The indication for use was reported in 17 of the cases; the most commonly reported indication was bipolar disorder (5), with the remaining 12 cases being reported among several different indications. Six cases reported the involvement of concomitant or co-suspect medications that are labeled for an association with QT interval prolongation; atomoxetine, citalopram, escitalopram, quetiapine (2), and sertraline (2) (one case reported two medications).

Five cases reported an overdose [accidental (2) and intentional (3)] resulting in a prolongation of the QT interval. The two cases reporting accidental ingestion involved a 16 & 17 month old.

The first case described a 16 month old who ingested one 40mg ziprasidone tablet and five hours post-ingestion he experienced hypoactivity, progressive neurological deterioration and a QTc of 460 msec with a pulse of 120. He fully recovered the next day. The second case described a 17 month old who was suspected to have swallowed 20 tablets of ziprasidone 20mg. She was asleep upon admission and her EKG revealed a QTc of 480 msec with a pulse of 120 and was treated with activated charcoal. The patient was discharged the next day in good condition. The three cases that described intentional overdoses[9] involved patients aged 12, 16, and 17 years old who ingested 1600 mg, 2400 mg, and 2400 mg of ziprasidone, respectively. No deaths were reported as a result of the overdoses.

Representative cases:

ISR# 4767159; US, 2005. A 14-year old male patient experienced a QTc prolongation of 450 msec with first-degree heart block 24 days after the initiation of ziprasidone 20 mg daily. His baseline EKG reported a QTc of 438 msec. Ziprasidone was discontinued and the follow-up EKG showed normal sinus rhythm with early repolarization and a QTc of 416. The patient was not on any concomitant medications.

ISR# 5341364; US, 2007. A 14-year old female patient experienced QTc prolongation from 480–500 msec after an unknown duration of therapy with ziprasidone 160 mg daily for bipolar disorder. The patient did not have a past medical history of QTc prolongation and a baseline electrocardiogram was done prior to initiating therapy with ziprasidone and it was "presumed to be normal". The QTc normalized upon the discontinuation of ziprasidone therapy. The patient was concomitantly taking clozapine, lithium, metformin, and trazodone, which are not currently labeled for an association with QTc prolongation.

4 DISCUSSION

This review provides a post-marketing overview of the safety profile for the pediatric population being treated with ziprasidone with a particular focus on deaths, suicide-related events and QT related events.

Overall, for the 10 deaths described, there was not a common underlying theme associating them. Four deaths were of an unspecified cause, two were completed suicides and the remaining four cases were all from different causes (cardiopulmonary failure, possible stroke, suffocation, and suspected aspiration). Stroke (cerebrovascular event) and aspiration are both labeled for an association with ziprasidone therapy. After reviewing the 10 cases, it appears that the adverse events that led up to deaths of the pediatric patients occurred in much the same manner as in adult patients.

Suicide-related events were reported in 24 cases associated with ziprasidone use. Thirteen cases reported the concomitant use of medications also labeled for an association with suicide-related events. Ziprasidone as well as all other atypical antipsychotics have labeling describing an association with increased risk of suicidal thinking, "the possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder and close supervision of high-risk patients should accompany drug therapy." This caution may lend to the thought that psychiatric illness is a confounding factor in many suicides. Based on the concomitant medications (i.e. anti-anxiety, anti-depressants, anti-epileptics, anti-psychotics) reported in many of the cases, we can presume that psychiatric illness may have played in a role in the events. Only one case described a resolution of symptoms upon discontinuation of ziprasidone therapy along with the continuation of the co-suspect medication lamotrigine, which is labeled for an association with suicide-related events. Based on the limitations of AERS data, it is not possible to distinguish events linked to the underlying condition from paradoxically heightened suicidality due to drug effect.

[9] One case was coded as accidental, but it described an ingestion of 40 tablets of ziprasidone 40mg strength.

Twenty-four cases described QT-related events associated with ziprasidone use. Of these 24 cases, three cases reported intentional overdoses and an additional two cases reported accidental exposure. The remaining 19 cases occurred in a similar manner as reported in the adult population. Many sections of the current ziprasidone label (indications and usage, contraindications, warnings, and adverse reactions) describe the greater capacity of ziprasidone to prolong the QT/QTc interval compared to several other antipsychotic drugs. Six cases reported the use of concomitant medications that are also labeled for an association with QT prolongation. Seven cases described a normalizing of the QT interval upon the discontinuation of ziprasidone. One of these positive dechallenge cases also described idiopathic QTc prolongation. No cases of Torsade de pointes were reported among the 24 cases.

This review did not identify a necessary labeling revision based on pediatric population specific adverse events different from what is currently labeled in the adult population.

5 CONCLUSION

The safety profile of the pediatric population is very similar compared to the adult population, and the adverse events occurred in much the same manner as well. No new safety signals emerged as part of this review; however, it has made us aware that the pediatric population is not spared from the adverse events caused by ziprasidone therapy. The potential risks of ziprasidone therapy should be weighed against the potential benefit when choosing to initiate therapy.

6 RECOMMENDATIONS

Although the safety and effectiveness of ziprasidone in pediatric patients have not been established, DPV recommends enhancing the Warnings section of the current ziprasidone label to include the risk of QT prolongation for both adult and pediatric patients.

7 APPENDIX

Figure 1 - Adverse events by MedDRA SOC Reported in Pediatric Patients

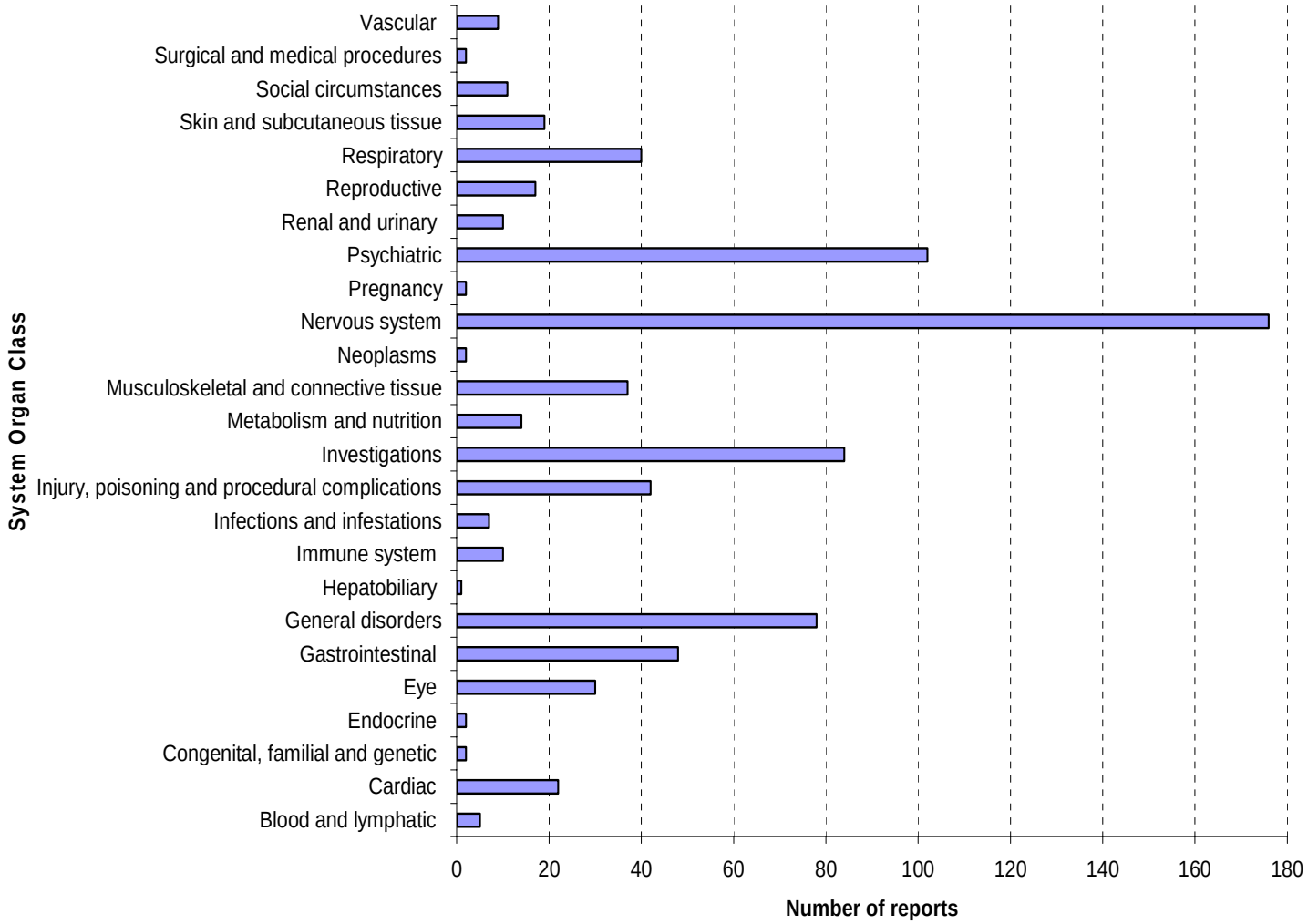


Figure 2 - Adverse events by MedDRA SOC Reported in Adults patients

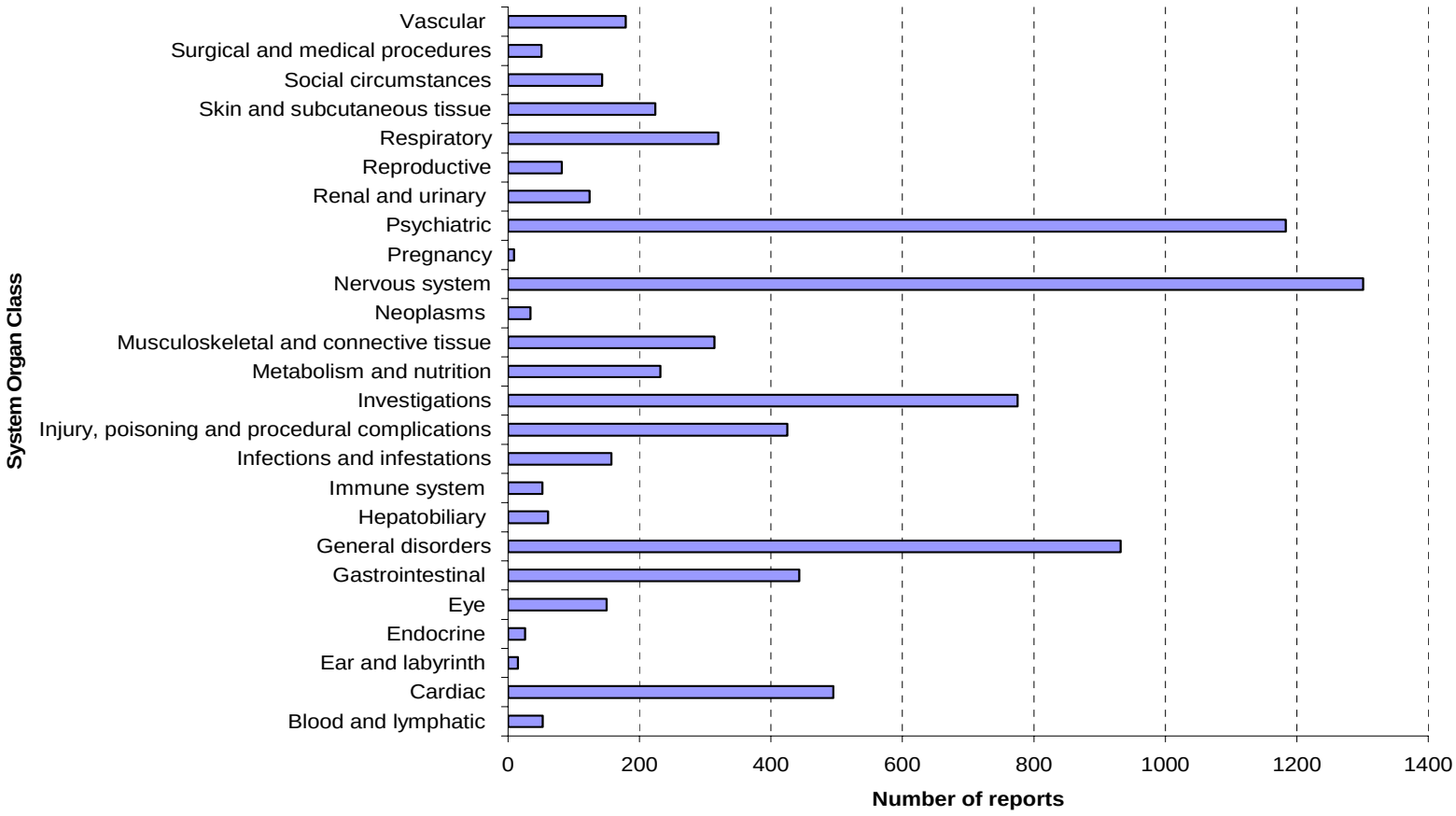


Figure 3 - Summary of Preferred Term with Reporting Proportion ≥ 2% in Pediatrics

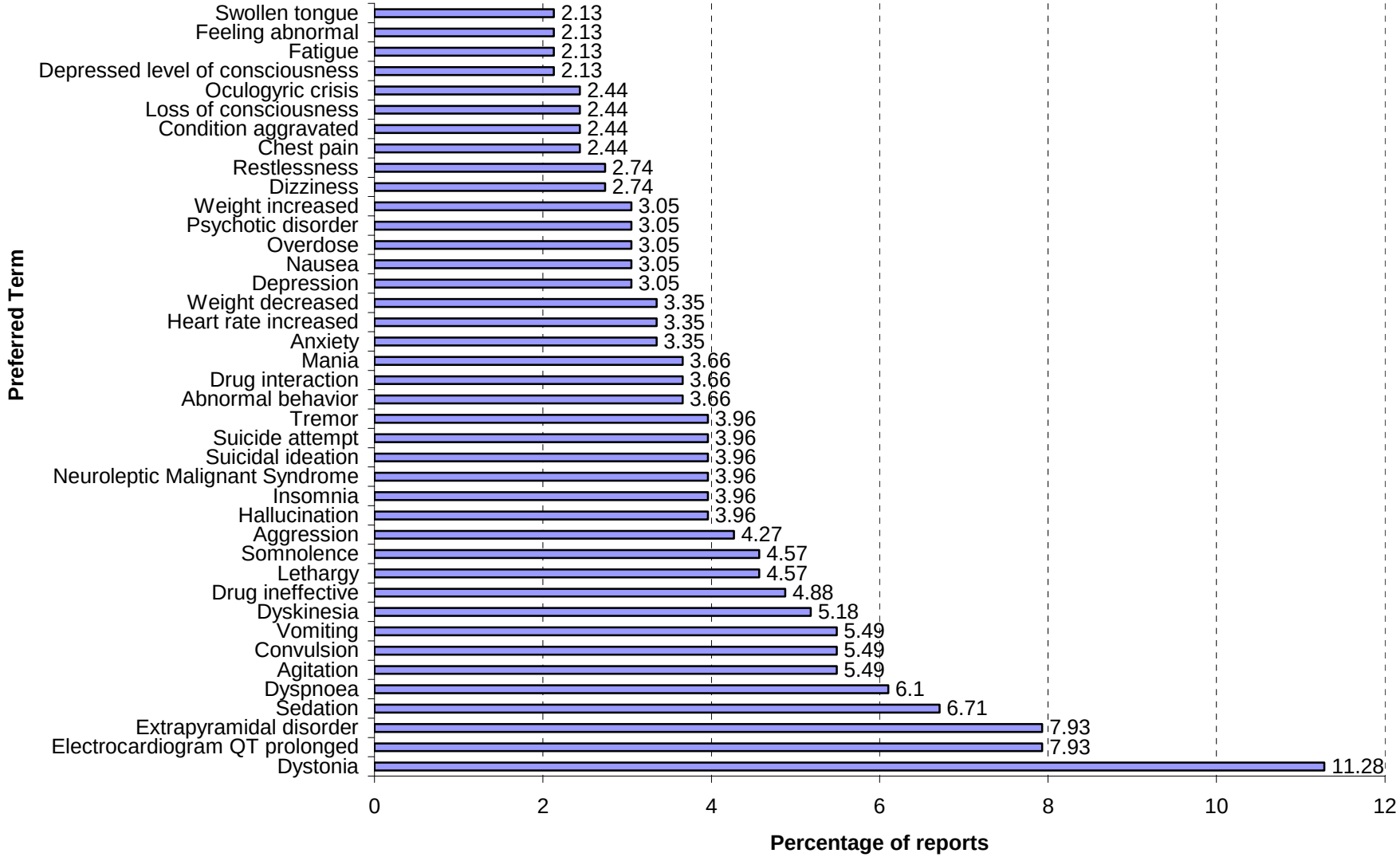
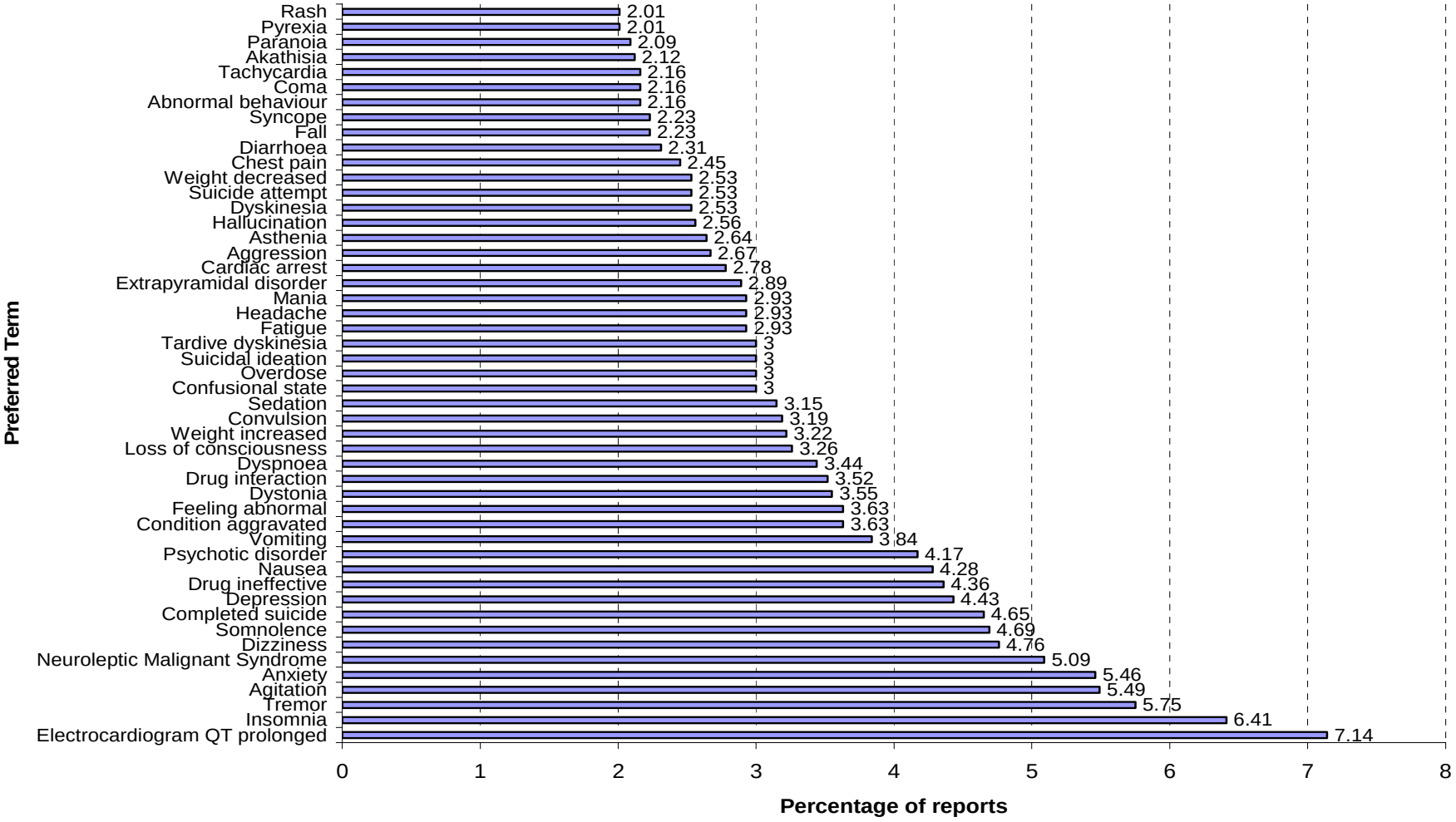


Figure 4 - Summary of Preferred Terms with Reporting Proportion ≥ 2% in Adults



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Ida-Lina Diak
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DRUG SAFETY OFFICE REVIEWER

M E M O R A N D U M

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

DATE: April 18, 2007

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

TO: NDA 20-592/SE5-040 (bipolar I disorder, acute mania)
NDA 20-592/SE5-041 (schizophrenia)
(This overview should be filed with the 10-30-2006 submission)

SUBJECT: Zyprexa (olanzapine)
Recommendation of 1) an approvable action - treatment of bipolar I disorder, acute mania in adolescents; and 2) a non-approvable action - treatment of schizophrenia in adolescents.

1. BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic agent, approved in the U.S. for treatment of schizophrenia and bipolar disorder, mania or mixed episodes, as monotherapy (both acute and maintenance) or combination therapy in adults. It is available as oral 2.5, 5, 10, 15, or 20 mg strength tablets; 5, 10, 15, or 20 mg oral disintegrating tablets (Zydis). The usual oral dose range is 10-20 mg/day. Zyprexa intramuscular injection is indicated for agitation associated with schizophrenia and Bipolar I Mania. The recommended dose in these patients is 10 mg injection. Currently, none of the available atypical antipsychotic drugs are approved for treatment of schizophrenia or bipolar disorder in adolescents.

The Agency has issued a written request on 11/30/2001 under 505A(c) [patent or exclusivity protection] that the sponsor to conduct clinical trials for two indications: schizophrenia and bipolar disorder in adolescents. It was further amended on 4/9/02 (timeframe to submit study reports by 11/30/2006), 7/3/02 [informing notification requirement to the FDA when pediatric studies be initiated or not agree to conduct the requested studies according to the BPCA provision new section 505(d)(4)(A)], 5/7/04 (to include ethnic and racial minorities in accordance to the BPCA) and 6/29/05 (conduct as acute inpatient or outpatient trial).

The sponsor submitted the above referenced supplemental NDAs for schizophrenia and bipolar claim in adolescents on 10/30/2006. The application included the efficacy and safety result from protocols F1D-MC-HGIN and F1D-MC-HGIU for schizophrenia and bipolar indications, respectively. In addition, the sponsor also included PK results from study F1D-MC-HGMF.

The data submitted was reviewed by Cara Alfaro, Pharm.D., Clinical Reviewer, DPP (review dated 4/6/2007), Andre Jackson, Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology (review dated 3/27/07) and Fanhui Kong, Ph.D., Statistics Reviewer, Office of Biostatistics (review dated

4/6/2007). An environmental assessment review (dated 1/17/2007) was performed by Janice Brown, Ph.D., Office of New Drug Quality Assessment.

2.0 CHEMISTRY

No new CMC information required for review in this submission except environmental assessment issues. A categorical exclusion was requested and granted.

3.0 PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues required for review in this submission.

4.0 CLINICAL PHARMACOLOGY

Based on results from study F1D-MC-HGMF (Study HGMF) and other existing adolescent pharmacokinetic data from studies F1D-MC-HGCS, F1DMCHGCR, F1D-MC-HGGC, and F1D-SB-LOAY, the sponsor submitted a study report in which olanzapine pharmacokinetics in adolescents was characterized. I would refer to Dr. Jackson's review for detail.

In brief, the sponsor reported that olanzapine pharmacokinetics was similar in adolescents and adults. The sponsor also claimed in their proposed labeling that Olanzapine exposure was approximately 27% higher in adolescents than in adults based upon simulations done with their model. However, Dr. Jackson noted that due to the poor quality of the prediction of the true steady-state values with the model, only the observed range of steady-state values was used. As Dr. Jackson pointed out in his review that in clinical studies, most adolescents had a lower average body weight compared to adults, resulting in an average range of olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients. Dr. Jackson provided labeling comments to reflect these findings.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the result of two short-term double-blind, placebo-controlled, randomized, efficacy and safety studies of olanzapine: one in the treatment of the adolescents (ages 13 to 17) with schizophrenia (Study HGIN); and the other study in the treatment of the adolescents with Bipolar I Disorder, Acute Mania or Mixed Episodes (Study HGIU).

The sponsor indicated that the result of each study supported for the treatment claim. Both Drs. Alfaro and Kong in their reviews indicated that only study HGIU support the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not seem to provide data to support the effectiveness claim of olanzapine in the treatment of schizophrenia in adolescents.

I would briefly describe the study design and then discuss the primary efficacy analysis results in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

5.1.2.1 Study F1D-MC-HGIN (Schizophrenia)

This study was a multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescent with schizophrenia, with a 6-week acute period. The primary objective of this study was to assess the efficacy and safety of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents with schizophrenia. After the screening and washout period (2-14 days), subjects were randomized to receive treatment with either olanzapine or placebo for up to 6 weeks of double-blind treatment.

The study was conducted in 20 U.S. centers which enrolled 53% of the study population; and in 5 Russian centers which enrolled 47% of the study population. One hundred and fifteen subjects entered the study. Of these, 107 (72 to olanzapine and 35 to placebo) were randomized and 64 subjects (49 to olanzapine and 15 to placebo) completed the acute phase of the study. Lack of efficacy was the most common reason for early termination in both groups: 18 (51%) patients for the placebo group; and 10 (14%) in the olanzapine group. 7.9% of study patients discontinued due to an adverse event.

Seventy two percent (N=77) of the patients were Caucasian; 22% were Africa-Americans; and 3% Hispanics. Seventy percent (N=75) were male and 30% (N=32) were female. 66% (N=71) were between 12 and 16 years and 33.6% (N=36) were 17 yrs of age; mean age of 16.1 yrs. There was no difference in demographic and baseline disease characteristics between the olanzapine and placebo groups.

The primary efficacy endpoint was the change from baseline to endpoint (up to 6 weeks double-blind treatment) in the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with covariate baseline scores, treatment and country factors. The protocol allowed interim analysis that the interim analysis result consistent with the final analysis results at α=.0294 level. According to the sponsor, there was no interim analysis conducted. Dr. Kong confirmed the primary efficacy results on LOCF dataset. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on BPRS Total Scores for Study HGIN in ITT population (LOCF):

	Mean Baseline BPRS (SD)	LS Mean Change from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=72	50.3	-19.3 (1.91)	-10.1 (-16.7, -3.5); p=0.003
Placebo N=35	50.1	-9.1 (2.73)	

Efficacy Results on BPRS Total Scores for Study HGIN (MMRM):

	Mean Baseline BPRS (SD)	LS MeanChange from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=72	50.3	-24.7 (1.70)	-1.25 (-8.11, 5.61); p=0.72
Placebo N=35	50.1	-23.5 (3.06)	

Efficacy Results on BPRS Total Scores for Study HGIN (OC):

	Mean Baseline BPRS (SD)	LS MeanChange from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=50	50.3	-24.4 (1.82)	-0.25 (-7.9, 7.4); p=0.95
Placebo N=15	50.1	-24.1 (3.35)	

According to Dr. Kong's assessments, there does not seem to have an advantage of olazapine over placebo. Both the OC and MMRM showed highly non-significant results. Although the LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. Given the high percentages of patient dropout as indicated in Drs. Kong and Alfaro's reviews, there seemed an impact on reliability of efficacy result in this study. Dr. Kong noted in his review that olanzapine reduced the BPRS-C total score in both the dropout group and the non-dropouts groups, while placebo reduced the score only in the non-dropouts group, not in the dropouts group. Although this phenomenon was observed in both US and Russia, the primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia (p = 0.003) but not the sites in the United States (p = 0.258). As Dr. Alfaro pointed out in her review, the sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia (see also section 5.1.3. Treatment Effect by Country).

Comment:

Both Drs. Alfaro and Kong did not consider this study as a positive study for olanzapine in treatment of schizophrenia in adolescents, and I agree with them.

5.1.2.2 Study F1D-MC-HGIU (Bipolar I Disorder)

This study was a multicenter, randomized, double-blind, placebo-controlled, flexible dose study of olanzapine (2.5 to 20mg/day) in adolescents with Bipolar I Disorder, acute mania or mixed episodes. After the screening and washout period (2-14 days), subjects were randomized to receive treatment with either olanzapine or placebo for 3 weeks of double blind treatment.

The study was conducted in 23 centers in the Unites States and 2 centers in Puerto Rico. Two hundred and three subjects entered the study. Of these, 161 (107 to olanzapine and 54 to placebo) were randomized and 120 subjects (85 in olanzapine and 35 in placebo) completed the acute phase of the study. The most common reason for the early withdrawal in both treatment groups was the lack of efficacy which had a total of 28 subjects (17.4%): 16 patients in the placebo group and 12. The difference between the two treatment groups is statistically significant (p=0.007). 14.5% of study patients discontinued due to an adverse event.

Seventy percent (N=112) of the patients were Caucasian, 16% (N=26) Hispanics and 9% (N=15) were Africa-Americans. More than half were male (N=85). 81% were between 12 and 16 years of age and 9.3% (N=15) were 17 yrs of age; mean age of 15.1 yrs. There was no difference in demographic characteristics between the olanzapine and placebo groups at baseline. The treatment groups, however, differed at baseline on measures of disease characteristics. Patients in the placebo group had greater numbers of previous manic, depressive, and mixed episodes. Patients in the olanzapine treatment group had much higher baseline scores on the CGI Severity for Depression;

more numbers reported in terms of history of psychiatric hospitalizations and paternal history of psychosis.

The primary efficacy endpoint was change from baseline to endpoint in the Adolescent Structured Young-Mania Rating Scale (YMRS) total score. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with covariate baseline scores, treatment and country factors. Dr. Kong confirmed the primary efficacy results on LOCF dataset. He also applied MMRM as a sensitivity analysis.

Efficacy Results on YMRS Total Scores for Study HGIU in ITT population (LOCF):

	Mean Baseline BPRS (SD)	LS Mean Change from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=105	33.1	-17.8 (0.87)	-7.7 (-10.7, -4.6); p<0.0001
Placebo N=54	32	-10 (1.53)	

Both MMRM and OC showed similar results, p=0.0004 and p=0.0013, respectively.

Comment:

Both Drs. Alfaro and Kong consider this study as a positive study for efficacy of olanzapine in treatment of bipolar I disorder, acute mania, in adolescents. I agree with them.

5.1.3 Comments on Other Important Efficacy Issues

Dose Response Relationship
Since both studies conducted were flexible dose (2.5 to 20 mg olanzapine) trials by design, there is no adequate data to address dose response for efficacy. The mean daily dose of olanzapine was 8.9 mg and in bipolar study and in schizophrenia study was 11.1 mg.

Treatment Effect by Country
The primary endpoint of schizophrenia study HGIN, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia (p = 0.003) but not the sites in the United States (p = 0.258). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Study HGIN	Placebo	Olanzapine
USA	N=19	N=38
Mean Change From Baseline of BPRS-C Total (SD)	-15.0 (18.3)	-21.2 (16.3)
Russia Mean Change From Baseline of BPRS-C Total (SD)	N=16 -2.6 (17.4)	N=34 -17.4 (14.5)

There were about 89% patients in US and only 11% patients in Puerto Rico in bipolar study HGIU.

Predictors of Efficacy in Subgroup Populations
Exploratory analyses in order to detect subgroup interactions on the basis of gender (M,F), age (<15 yrs, ≥15 yrs) and race (Caucasian, non-Caucasian). As stated in Dr. Kong's review, there were no

statistically significant effects in any of these subgroups in both studies although the effect was numerically larger in males compared to females; and in ≥15 yr age group than <15 yrs.

Duration of Treatment
The studies conducted were for short-term use of Olanzapine in the treatment of adolescent schizophrenia and bipolar disorder. There is no data pertinent to the long-term efficacy in this submission. Since these disorders are chronic illnesses, it would be good to have data from a longer term study. However, Olanzapine is approved for maintenance treatment in adults with schizophrenia or bipolar disorder. We could infer the efficacy data from adult maintenance trials to adolescent population. According to the 05-30-2002 meeting minute, we agreed to grant a waiver for bipolar maintenance studies in adolescents.

5.1.4 Conclusions Regarding Efficacy Data

I concur with both Drs. Kong and Alfaro's recommendation and conclusion that the data from study HGIN did not seem to support the schizophrenia claim; and that results from study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with acute mania in Bipolar I Disorder.

5.2 Safety Data

5.2.1 Safety Database

Dr. Alfaro's safety review was based on an integrated database covering Acute Database from both pivotal double-blind studies (HGIN - 6weeks; and HGIU – 3 weeks) ; and the Overall Combined Database from the 26 week open label extension phase of HGIN and HGIU, other open label studies (HGMF and LOAY). A total of 268 patients (179 olanzapine; 89 placebo) were enrolled in the Acute Placebo-Controlled Database and 454 patients were included in the Overall Combined Database. Total exposure of olanzapine in adolescents was 48,946 patient-days.

As requested in the Written Request letter, there were sufficient numbers of adolescents enrolled in the 26 week open label phase that followed the double blind trials. Eighty-two subjects from the bipolar study HGIU received olanzapine during this open-label phase for > 23 weeks (n = 30, 23-26 weeks; n = 52, > 26 weeks). Fifty-four subjects from the schizophrenia study HGIN received olanzapine during this open-label phase for > 23 weeks (n = 19, 23-26 weeks; n = 35, > 26 weeks).

There were no deaths reported in the olanzapine treatment group in the double-blind studies. A total of 7 SAE reported; 6 patients in the olanzapine treatment arm in the Acute Database for weight increased, migraine, arm fracture, worsening of bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the overall combined database. The majority of these SAEs, 19/35 patients, were listed as worsening of existing psychiatric disorder (schizophrenia, bipolar disorder).

The sponsor also reported data from the postmarketing safety database including 2359 case reports in patients 13 to 17 years of age. There were 27 deaths in the adolescent age group based on the post marketing spontaneous MedWatch reports and the published literature. Based on the limited information provided in these reports, 15 of the cases occurred in the US. Seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus,

diabetic coma or diabetic ketoacidosis. Based on the proportion of events (%) in patients 13-17 yrs potential safety signals reported by the sponsor included weight increased, overdose, fatigue, ALT increase, diabetes mellitus and increased appetite.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). In the double-blind studies, the most common AEs were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (24%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies HGIN and HGIU.

In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to < 5% of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

5.2.2.2 Weight Gain

The following table summarizes the significant mean weight changes by mean change in weight to endpoint, mean change in BMI to endpoint and % of patients with ≥ 7% increase in body weight based on the results obtained from the two double-blind studies. Similar results were obtained for OC.

	Olanzapine	Placebo	LS Mean Diff	P-value
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
BMI Mean Change to Endpoint (LOCF)	1.22	0.05	1.17	< 0.001
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001

A significant mean weight changes from baseline by mean change in weight to endpoint (7.35 Kg), mean change in BMI to endpoint (2.31) and % of patients with ≥ 7% increase in body weight (65%) based on the results from the overall combined database including the open label studies.

For each double-blind study, mean change in weight (kg) was evaluated between the subgroups gender and age. No statistical significant differences were noted between these subgroups. The change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for olanzapine group in study HGIN.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months.

5.2.2.3 Abnormal Laboratory Tests

Liver function tests

The percentage of adolescent patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute double blind studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009). The percentage was higher compared to the finding in adults (i.e., 2% in olanzapine group). Six patients discontinued HGIN and HGIU due to increases in liver transaminases (ALT). Four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and two in the placebo group. Six subjects in olanzapine group discontinued due to elevated liver enzymes. There were no subjects who had ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN.

Comment: The sponsor proposed these LFT abnormalities in adolescents as part of the transaminase elevations subsection under the Warnings/Precautions section of the labeling. I consider this as a reasonable proposal. In the adolescent section, I concur with Dr. Alfaro's recommendation to include the number of patients who discontinued due to elevations in LFTs in the labeling.

Lipid profile (Hypertriglyceridemia, Hypercholesterolemia)

The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, p < 0.001). There were 11 marked outliers noted for elevated triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) (p = 0.039).

The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, p < 0.001). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) (p = 0.023).

Comment: The sponsor proposed labeling changes in this submission, the finding on cholesterol and triglyceride was placed in the Adverse Reactions, laboratory changes subsections. I believe the finding on lipids should be placed more prominently in the labeling. Given other significant findings on weight, liver enzymes and glucose are part of the Warning/Precautions in the labeling, we should consider placing this topic in the same section.

Hyperglycemia

The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, p < 0.001). Regarding the percentage of patients with shifts from normal (< 100 mg/dL) to high fasting glucose, it was not significantly different between olanzapine (0/122) and placebo (1/51). Similarly, the percentage of patients with changes in fasting glucose from impaired glucose tolerance (≥ 100 mg/dL and < 126 mg/dL) to high (≥ 126 mg/dL) fasting glucose was not statistically different between olanzapine (2/13) and placebo (0/13).

In the Acute Database, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes). There was no change from baseline to endpoint in this parameter.

Comment: In this adolescent population, olanzapine did not appear to be associated with significant hyperglycemia. This finding could be attributable to initial development of insulin resistance in younger age group before actual increase in glucose level is observed. The finding on HbA1c was not unexpected either since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months.

Current Zyprexa labeling contains standard warning language on hyperglycemia and diabetes for atypical antipsychotics. The sponsor did not propose any changes to this warning section. Given the finding that the adolescent population experienced significant weight gain, it is important that sufficient information on these risks needs to be described in the labeling. Recently, the Division has asked the sponsor to provide more data on the glucose and lipid findings with Zyprexa in our March 28, 2007 approvable letter for Symbyax in treatment resistant depression and in our January 12, 2007 letter regarding the New York Times story. The sponsor has not adequately addressed to our concerns on these issues yet. We should reference these two letters in our action letter.

Hyperprolactinemia

Based on the acute database from the two double-blind studies, the mean change from baseline to endpoint in prolactin was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, $p < 0.001$). The washout period prior to baseline could be as short as 2 days. In study HGIN, 17% (11/64) of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The mean prolactin concentration at the end of study was 55.8 ± 15.8 ng/ml. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study.

It was noted that many patients had elevated prolactin at baseline. For those patients with normal baseline, it was found that 47.4% of patients in the olanzapine group had a treatment-emergent high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$). No significant treatment by gender interaction on prolactin level was found.

Gynecomastia occurred in 1 (0.9%) patient in the olanzapine group and no patients in the placebo group and amenorrhea occurred in no patients in the olanzapine group and 1 (2.4%) patient in the placebo group. As Dr. Alfaro stated in her review, the Overall Combined Database was evaluated since adverse events such as gynecomastia are not expected to occur with acute use but rather more long term use of antipsychotics. In the Overall Combined Database, gynecomastia occurred in 7 (4.3%) of patients (all from schizophrenia trials), galactorrhea occurred in 2 (3.1%) patients with schizophrenia and 1 (1%) patient with bipolar disorder and amenorrhea occurred in 1 (1.5%) patient with schizophrenia and 1 (1%) patient with bipolar disorder. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Comment: The proposed labeling contains the paragraph on hyperprolactinemia from the approved labeling in the Warning/Precaution section. The sponsor did not propose any labeling changes with adolescent data in the Warning section and the Pediatric Use section. We should ask the sponsor that more specific information be included in the Pediatric Use section.

I concur with Dr. Alfaro's recommendation that the sponsor should provide additional analyses on the subset of patients with baseline prolactin within the normal range and also, a subgroup analysis for gender and age. While I note Dr. Alfaro's request to obtain narratives on 8 cases of gynecomastia (1 case in the acute trials and 7 cases in the open trials) and two cases of high prolactin concentrations from study HGIN (1 in acute trial and 1 during the open label). It will be difficult to interpret such data if they came from the open-label phase, but we may be able to note any potential signal. It would be worthwhile to look at the individual narratives in this population, although it will be difficult to distinguish this AE from normal breast development in adolescent female. Given the fact that Dr. Alfaro was unable to identify gender in any of these cases, I have no objection to her request for more information from the sponsor.

Elevated CPK

In Dr. Alfaro's comments to the sponsor section, she recommends that we ask for narrative summaries for cases with CPK >500 U/L in our action letter. From her review, I am not able to identify which one of these CPK elevations were noted during the double-blind treatment. Upon follow up with Dr. Alfaro on this issue, we agree that we could just limit our request to one patient with a CK of 7289 U/L in the acute trial.

5.2.2.4 Vital signs and ECG changes

There was a mean increase in heart rate of 6.3 bpm in adolescents treated with olanzapine compared to a decrease of 5.1 bpm in the placebo group. The sponsor attributed this increase in heart rate to olanzapine's potential for inducing orthostasis. There were no significant changes in ECG parameters including QTc.

5.2.2.5 Extrapyrimidal Symptoms

For both HGIN and HGIU, change from baseline to endpoint in the EPS rating scales was similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups. I note Dr. Alfaro's request to the sponsor for case narratives regarding one case of opisthotonus and one case of oculogyration. Since these AEs occurred during the open-label phase, I do not think it is necessary to review these 2 case narratives. It may be difficult to ascertain causality in the open label trials. I also note as part of Dr. Alfaro's request for additional information on how was "treatment-emergent" parkinsonism, akathisia and dyskinesia defined by the respective rating scales, and an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database. It is doubtful that further assessment would give any significant result.

5.2.2.6 Suicidality

No completed suicides occurred in the clinical trials. In the acute double-blind studies, 2 events occurred in the olanzapine group (suicidal ideation/behavior – intent unknown and suicidal ideation) and 1 event occurred in the placebo group. These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in

bipolar disorder patients. I agree with Dr. Alfaro that suicidal behaviors or ideation is not uncommon in these patients and it is difficult to interpret any causality to olanzapine therapy in the absence of a placebo comparator. One of the exclusion criteria for HGIU was "patients who have been judged clinically to be at serious suicidal risk". However, Dr. Alfaro noted that three patients (012-1203, 012-1212, and 024-2402) who were rated the maximum score of "7" at baseline (has made a suicide attempt within the last month or is actively suicidal) of the CDRS-R individual item "suicidal ideation." She recommended that we ask the sponsor in the approvable letter to provide more information regarding inclusion of these patients in this study. Given the study results from the acute double-blind phase of the study, I do not think we need to convey this question to the sponsor.

5.2.2.7 Risk Management Plan

The sponsor's proposed risk management plan includes routine pharmacovigilance of spontaneous case reports with target AEs, a long term safety study and a pharmacoepidemiology study with retrospective cohort analysis of a large US health claims database to estimate the incidence and prevalence of diabetes mellitus and dyslipidemia among adolescent patients with schizophrenia or bipoloar disorder compared with the general adolescent population. The OSE was consulted on this proposed risk management plan. The OSE has stated that they would provide their input on the appropriateness of the RMP after the sponsor submits a complete response to the action letter.

5.2.3 Conclusion Regarding Safety Data

This submission revealed safety findings of Olanzapine in adolescent population in which most AEs consistent with the previously observed AE profile of olanzapine as described in current labeling. The sponsor has included all the percentages in the treatment emergent AE of ≥5% and ≥2% table as the commonly observed AEs in controlled adolescent clinical trials under the adverse events section of the labeling. I think this portion of their labeling proposal seems acceptable.

Significant safety signals that emerged in these adolescent clinical trial databases were weight gain, hypertriglyceridemia, hypercholesterolemia, hyperprolactinemia and transaminase elevations. Although there are some changes proposed in the labeling by the sponsor, we need to work on the labeling language so that all pertinent safety findings are adequately reflected in the labeling. We have already asked the sponsor for an extensive search for data to address the concerns regarding weight, glucose and lipid profiles in our 1/12/2007 letter and our 3/28/2007 approvable letter for symbyax (olanzapine/fluoxetine combination) in treatment of treatment resistant depression. In our action letter for this set of olanzapine pediatric supplements, we should reiterate related safety concerns and ask the sponsor to make relevant safety changes in the labeling.

6.0 WORLD LITERATURE

The sponsor has provided a literature update pertaining to the safety of Olanzapine. As Dr. Alfaro noted, the sponsor reported that none of the articles would change safety conclusion for olanzapine.

7.0 FOREIGN REGULATORY ACTION

I am not aware of any foreign regulatory action of this drug for adolescent claim.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take these supplemental NDAs to the PDAC.

9.0 DSI INSPECTIONS

DSI data audit inspections were requested for two domestic sites and two Russian sites. DSI did not indicate any major inspectional issues that would impact data integrity on efficacy and safety.

We also informed DSI of GCP non-compliance reported by the sponsor in one clinical trial site 021 for study HGIN (CI: Dr. A. Robb). DSI will decide if further investigation of this clinical investigator site is needed. The sponsor has excluded data from at this site (N=3) in their analysis and reported no impact on efficacy results.

10.0 LABELING AND ACTION LETTER

Since we are recommending a non-approval action on schizophrenia indication, we should delete the labeling language in reference to this efficacy claim. We have made modifications to the proposed labeling and should provide our labeling comments to the sponsor with respect to safety language in labeling, and related safety issues in our action letter. Our modified version of draft labeling in the new PLR format is attached in our action letter for bipolar indication.

11.0 CONCLUSION AND RECOMMENDATION

I concur with both Drs. Alfaro and Kong that the sponsor has not provided sufficient evidence to convince that olanzapine is effective for treatment of schizophrenia in adolescents. Therefore, I recommend the Division issue a non-approvable letter for this NDA supplement (SE5-041).

Regarding the NDA supplement (SE5-040), results from study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Although there are some changes in the labeling proposed by the sponsor in the submission, we will need more information in order to adequately address the safety findings regarding changes in weight, glucose and lipid profiles. We may need further modification in the labeling to reflect all significant findings. Therefore, I recommend that the Division issue an approvable action letter with our labeling comments.

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

Ni Aye Khin
4/19/2007 01:45:57 PM
MEDICAL OFFICER

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 29, 2007

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

SUBJECT: Recommendation for approvable actions for Zyprexa Pediatric Supplements for bipolar disorder (acute mania) and schizophrenia

TO: File NDA 20-592 (S-040 [bipolar] and S-041 [schizophrenia])
[Note: This overview should be filed with the 10-30-06 original submission of these supplements.]

1.0 BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic (5HT2 and D2 receptor antagonist) that is approved for both schizophrenia and bipolar disorder in adults, including maintenance claims for both. We issued a written request (WR) for both indications, and these supplements are a response to that WR. The 10-30-06 response includes the results from acute studies in mania (HGIU) and schizophrenia (HGIN), and also pediatric PK data from study HGMF.

2.0 CHEMISTRY

The only CMC issue requiring review was environmental assessment. The sponsor sought and was granted a categorical exclusion.

3.0 PHARMACOLOGY

There were no pharm/tox issues requiring review for these supplements.

4.0 BIOPHARMACEUTICS

The sponsor utilized pk data from a formal pk study (HGMF) and also from 3 other studies (HGCS, HGCR, and HGGC) to characterize olanzapine pk in adolescents. Based on these data,

they concluded that overall olanzapine pk was similar in adolescents and adults, and that the one observed difference was greater exposure (by 27%) due to lower weights. Dr. Jackson from OCP agreed, except that he felt that the increased exposure by 27% was an underestimate. He estimated that exposure was increased by about 30-63%. This difference has resulted in a slight modification to the labeling regarding exposure.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on 2 short-term, multicenter, double-blind, placebo-controlled, flexible-dose (2.5 to 20 mg/day), randomized, efficacy and safety studies in adolescents (ages 13-17). One of these studies was in patients with acute mania in bipolar I disorder (HGIU) and the other in schizophrenia (HGIN).

5.1.1 Study HGIU (Acute Mania in Bipolar I Disorder)

This was a 3-week study in bipolar I disorder patients with acute manic or mixed episodes. It was mostly conducted in the US (23 sites) but had 2 sites in Puerto Rico as well. N=161 patients were randomized, and the randomization was 2:1 for olanzapine vs placebo. The mean modal olanzapine dose was 10.7 mg, and the mean daily dose was 8.9 mg. The overall dropouts for this trial favored olanzapine (20% for olanzapine vs 35% for placebo). Of these, the dropouts were mostly for lack of efficacy (11% for olanzapine vs 30% for placebo). The primary endpoint was change from baseline to endpoint on an Adolescent Structured YMRS (total score) and the primary analysis was ANCOVA (LOCF). The results on this analysis were highly favorable to olanzapine ($p < 0.0001$), as were the results for the MMRM ($p=0.0004$) and the OC ($p=0.0013$). Drs. Alfaro, Kong, and Khin all considered this a positive study, and I agree.

5.1.2 Study HGIN (Acute Schizophrenia)

This was a 6-week study in adolescent patients with schizophrenia. It was conducted partly in the US (20 sites, comprising 53% of the total sample) and partly in Russia (5 sites, comprising 47% of the total sample). N=107 patients were randomized, and the randomization was 2:1 for olanzapine vs placebo. The mean modal olanzapine dose was 12.5 mg, and the mean daily dose was 11.1 mg. The overall dropouts for this trial again favored olanzapine (32% for olanzapine vs 57% for placebo). Of these, the efficacy dropouts were most striking, with a 51% loss due to lack of efficacy for placebo compared to only 14% for olanzapine. This finding by itself is almost enough, in my view, to convince one of the benefits of olanzapine in this condition. The primary endpoint was change from baseline to endpoint on a children's version of the BPRS (BPRS-C) total score, and the primary analysis was ANCOVA (LOCF). The overall results on this analysis were highly favorable to olanzapine ($p = 0.003$). However, there were 2 aspects to the data that the review team found troubling, resulting in conclusions by Drs. Alfaro, Kong, and Khin that this should be considered a negative study. Their concerns were as follows:

Highly Non-Significant Results on the MMRM and OC Analyses

Dr. Kong conducted an MMRM analysis as a sensitivity analysis, which yielded a p-value of 0.72. An OC analysis was also highly non-significant result (p=0.95).

> Comment: In my tertiary evaluation, I found this discrepancy between LOCF and MMRM quite unusual, in my experience, and asked for further exploration. As it turned out, Dr. Kong's MMRM analysis was quite discrepant with the sponsor's MMRM analysis (p=0.015). Upon further evaluation, Dr. Kong discovered that the program he had used to conduct the analysis included, as a default, a variance-covariance structure that required independence between the repeated observations for any subject. This is an unusual requirement, and not the variance-covariance structure that we generally recommend. In fact, we almost always recommend an unstructured variance-covariance structure, i.e., the same one used by the sponsor, and a goodness-of-fit exploration for different variance-covariance structures revealed the best fit for this structure. Thus the biometrics group has now recommended that we accept the sponsor's highly significant MMRM result (see addendum to original biometrics review).
>
> Regarding the OC analysis, this remains a discrepancy with the LOCF and the revised MMRM analyses. However, I am not as troubled by this outcome on the OC analysis. As noted, the dropouts on placebo were very substantial, and I'm inclined to view the patients completing a study such as this to 6 weeks on placebo as quite different than the remaining patients. I think the diagnosis of schizophrenia in this younger population is challenging, and likely results in the inclusion of some patients who improve spontaneously, and thus, are doing as well as drug-treated patients at 6 weeks simply because they represent a very different group of patients. This, I think the OC results for this trial can be largely discounted.

Treatment by Geographic Region Interaction

A second problem for the review team was a finding that the positive results were coming predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data from the Russian sites appeared to be driving the overall result:

-For the US patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -21 and -15, respectively (p=0.258).

-For the Russian patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -17 and -3, respectively (p=0.003).

-So the treatment effect in olanzapine patients was roughly the same in both regions, however, the placebo response was much larger in the US sites compared to the Russian sites.

Comment: In addition to the difference in outcome by region, Dr. Alfaro expressed concern that the Russian sites were far more successful in recruiting patients than the US sites. Implicit in such a concern is a suggestion of a problem in study conduct. It is important to note that we did have DSI inspect the Russian sites, and they found no evidence for fraud. It is also important to point out that there are alternative explanations for more successful recruitment at the Russian sites and also a more successful outcome. The sites may have been drawing patients from larger catchment areas than US sites, many of which were single investigators. There also may have been less competition for patients than is the case in the US. There are numerous studies ongoing in the US, and routine treatment is likely also more readily available in the US than in Russia. These same factors may also explain the different results. If difficulty in recruitment in the US sites led to enrollment of a more heterogeneous group of subjects, this could have led to a higher placebo response rate. It is possible that the Russian patients were the more representative schizophrenic patients who typically have very little response to placebo. There is also the expressed concern about relying primarily on non-US data for an approval action. Although I agree this is generally a concern, I think it is more a concern for an initial claim than it is in this case, where we already have a very strong prior belief that olanzapine is an effective treatment for schizophrenia, based on an abundance of positive data in adults. In summary, while I agree this geographic discrepancy is a concern, I do not think it is, by itself, a sufficient justification for a nonapproval action, when the trial is positive overall on the primary analysis and on the MMRM. Nevertheless, we will ask the sponsor to further address our concern about this discrepancy.

5.1.3 Summary of Efficacy

There is unanimous agreement within the review team on the positive outcome for study HGIU. For study HGIN, I disagree with the review team on the recommendation for a nonapproval action. One of the concerns, namely Dr. Kong's original finding on the MMRM, has now been addressed, and we are in agreement that an appropriate MMRM analysis yields a highly significant outcome. On the issue of geographic differences in outcome, I disagree that this is of sufficient concern to justify a nonapproval action. Nevertheless, we will ask the sponsor to further address this concern.

5.2 Safety Data

Safety data for these supplements were derived from the 2 pivotal controlled trials (HGIU and HGIN), and also from studies LOAY and HGMF. The combined total for these studies was n=454 patients, and this included 89 placebo patients from the 2 controlled trials. Thus, there were 365 olanzapine-exposed patients in this safety database. This included 136 patients who were treated with olanzapine for at least 23 weeks.

There were no deaths among the olanzapine-exposed patients. There were 44 serious adverse events, the majority of which represented a worsening of psychiatric symptoms. Overall, the profile of common and drug-related adverse events included events already well-recognized for olanzapine, i.e, increased appetite and weight gain, somnolence, sedation, fatigue, dizziness, and dry mouth. Other findings included the following:

-Weight Gain: For the 2 short-term trials (HGIU and HGIN), olanzapine patients gained almost 4 kg more than placebo patients ($p<0.001$). Almost 44% of olanzapine patients gained > 7% of their body weight compared to only 7% of placebo patients ($p<0.001$).

-Transaminase Increases: For the 2 short-term trials (HGIU and HGIN), 12% of olanzapine patients compared to only 2% of placebo patients had ALT increases to > 3xULN ($p=0.009$). None of these patients had bilirubin abnormalities, and transaminase elevation is a well-known finding for olanzapine.

-Hyperprolactinemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in prolactin of 11.44 mcg/L compared to a decrease of -0.16 mcg/L for placebo ($p<0.001$).

-Hyperlipidemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in triglycerides of 29.2 mg/dL compared to a decrease of -4.4 mg/dL for placebo ($p<0.001$). For total cholesterol, olanzapine patients had a mean increase from baseline of 13.1 mg/dL compared to a decrease of -1.2 mg/dL for placebo ($p<0.001$).

-Hyperglycemia: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in fasting glucose of 2.7 mg/dL compared to a decrease of -2.9 mg/dL for placebo ($p<0.001$).

-Heart Rate Increase: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in heart rate of 6.3 bpm compared to a decrease of 5.1 bpm for placebo. These changes were thought to be related to orthostatic changes seen with olanzapine, especially early in treatment.

Summary of Safety Experience with Olanzapine in Adolescents: Overall, the adverse event profile and other safety parameters for olanzapine in the adolescent population is similar to that seen in adult patients treated with this drug, however, with some differences in magnitude. These differences will need to be reflected in labeling. In addition, we have recently asked the sponsor to provide more complete information generally with regard to effects on weight, glucose regulation, and lipid levels so that labeling for olanzapine can be enhanced with regard to these risks.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would add important new information to the existing database regarding the safety of olanzapine in the treatment of schizophrenia or bipolar disorder in adolescents.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, olanzapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in adolescents.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 US sites and at 2 Russian sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included an extensively modified version of labeling with the approvable letter.

10.2 Foreign Labeling

Olanzapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in adolescents.

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for additional data.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that olanzapine is effective and acceptably safe in the treatment of adolescents with schizophrenia and acute mania/mixed episodes in bipolar disorder. However, before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling.

cc:
Orig NDA 20-592/S-040 and 041
HFD-130/TLaughren/MMathis/NKhin/CAlfaro/KKiedrow/DBates/SHardeman

DOC: Zyprexa_Peds_Laughren_AE_Memo.doc

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/s/

Thomas Laughren
4/29/2007 10:55:29 AM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: July 18, 2008

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

TO: NDA 20-592/SE5-040 (bipolar I disorder, acute mania)
NDA 20-592/SE5-041 (schizophrenia)
(This overview should be filed with the 02-05-2008 submission in response to the Agency's Approvable Letter dated 04-30-2007)

SUBJECT: Recommendation of an approvable action for use of Zyprexa (olanzapine) in the treatment of 1) Bipolar I disorder, Mania, and 2) schizophrenia in Adolescents.

1. BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic agent, approved in the U.S. for treatment of schizophrenia and bipolar disorder, mania or mixed episodes, as monotherapy (both acute and maintenance) or combination therapy in adults. It is available as oral 2.5, 5, 10, 15, or 20 mg strength tablets; 5, 10, 15, or 20 mg oral disintegrating tablets (Zydis). The target dose for adults with schizophrenia is 10 mg/day. Zyprexa intramuscular injection (10 mg) is indicated for agitation associated with schizophrenia and Bipolar I Mania.

Currently, two atypical antipsychotic drugs, Risperdal and Abilify, are approved for treatment of schizophrenia and bipolar disorder in the pediatric population.

In response to the Agency's written request (original 11/30/2001; amended 4/9/02, 7/3/02, 5/7/04, 6/29/05), the sponsor conducted clinical trials for two indications: schizophrenia (F1D-MC-HGIN) and bipolar disorder (F1D-MC-HGIU) in adolescents, and submitted the study results to the above referenced supplemental NDA on 10/30/2006.

The Agency issued an approvable letter (AE letter) on 4/30/07 asking the sponsor to provide additional safety data analysis regarding risks of weight gain, hyperglycemia and hyperlipidemia in patients taking Zyprexa. In the AE letter, we noted our intent to ensure that the Zyprexa label is enhanced with the updated information to characterize these risks. We also requested the sponsor to address the geographic discrepancy in the efficacy results between the US and Russia in adolescent schizophrenia trial, and other information pertaining to high prolactin levels in adolescents. In addition, we asked to provide the MedWatch reports for 4 fatalities.

The sponsor submitted their complete response to the AE letter on 02/05/2008. This submission was reviewed by Cara Alfaro, Pharm.D. Clinical Analyst, DPP (review dated 07/14/2008). Evelyn

Mentari, M.D., Safety Medical Officer (review dated 07/15/2008) reviewed the additional analyses provided by the sponsor regarding the metabolic data. Sally Yasuda, Pharm.D., Safety Team Leader, provided a secondary review of the metabolic data and the sponsor's proposed Risk Minimization Plan (memo dated 07/17/2008).

2.0 CHEMISTRY

No new CMC information required for review in this submission. Dr. Nallaperun Chidambarm, Chemistry Team Leader from the ONDQA, stated that there were no CMC comments regarding the PLR conversion of the Zyprexa labeling included in this submission.

3.0 PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues required for review in this submission. Dr. Barry Rosloff, Supervisory Pharmacologist, provided his PLR labeling comments for the pharm/tox sections.

4.0 CLINICAL PHARMACOLOGY

Dr. Andre Jackson has provided labeling comments to reflect the adolescent PK findings (F1D-MC-HGMF) and also, for the clinical pharmacology sections in the PLR labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

As noted by Dr. Alfaro in her prior review, the sites in Russia appeared to drive the entire efficacy signal for the adolescent schizophrenia clinical trial (HGIN), primarily due to the very low placebo response in the sites in Russia.

The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$).

Study HGIN	Placebo	Olanzapine
USA	N=19	N=38
Mean Change From Baseline of BPRS-C Total (SD)	-15.0 (18.3)	-21.2 (16.3)
Russia	N=16	N=34
Mean Change From Baseline of BPRS-C Total (SD)	-2.6 (17.4)	-17.4 (14.5)

In our 04/30/2007 approvable letter, we had asked the sponsor for additional analyses (e.g. baseline illness characteristics) to evaluate potential differences between subjects enrolled in the US and Russian sites. In the sponsor's 02/05/2008 response to the AE letter, the sponsor provided details for further exploratory analyses including:

1. Between-country comparisons, comparison of baseline characteristics, and inclusion of significant baseline characteristics into the ANCOVA model
2. Analyses by country for disposition, effect size, response rate, modal dose, concomitant medication use, and weight gain

3. Visit-wise LOCF and OC mean change for BPRS-C total score by country
4. Analysis of treatment-by-country interaction and within-country effect for secondary efficacy measures
5. Evaluation of data from placebo-treated patients with therapeutic improvements similar to the olanzapine treatment magnitude

As Dr. Alfaro commented in her review dated 07/14/2008, no significant differences that might account for the low placebo response rate at the Russian sites was identified during review of these additional analyses.

In the 02/05/2008 response, the sponsor reiterated that discontinuation due to lack of efficacy was significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US (15.8% in olazapine; 42.1% in placebo; $p = 0.049$) and Russia (11.8% in olazapine; 62.5% in placebo; $p < 0.001$). The effect sizes were 0.63 for all patients, 0.32 for the US and 0.96 for the Russian patients. The mean modal doses were 13.2 mg for the U.S. and 11.8 mg for Russia. The sponsor also reiterated that the treatment-by-country interaction was not significant ($p = 0.146$).

Dr. Alfaro mentioned in her review that she also looked at the data from two recently approved drugs in adolescent population in the treatment of schizophrenia [i.e., for the aripiprazole (NDA 21-436/SE5-017) and risperidone (NDA 20-272/SE5-046) adolescent schizophrenia programs]. By comparing Russian data from these programs, Dr. Alfaro's concerns are seemed satisfactorily addressed.

5.2 Safety Data

Metabolic Effects

As stated in Dr. Mentari's safety review, the sponsor's additional analysis results and their labeling proposals for the Weight Gain, Hyperglycemia and Hyperlipidemia sections seemed adequately addressed our concerns on the issue.

There was statistically significant treatment emergent increase in lipid profile, glucose and weight in both olanzapine treated adults and adolescents as compared to placebo. It should be noted that the magnitude of mean changes from baseline was greater in adolescents treated with olanzapine than changes for the adults in total cholesterol, LDL and triglycerides. In addition, adolescents were likely to gain more weight and have greater increases in prolactin and hepatic transaminase levels.

Dr. Mentari recommended some further modification in the labeling for weight gain (adding description of data on treatment emergent glycosuria) and hyperglycemia sections to more clearly communicate the information in both adult and adolescent subsections. She also recommended fasting blood glucose testing and lipid profile at the beginning of and periodically during olanzapine treatment be added as part of the laboratory tests.

Additionally, Dr. Mentari noted that a proposal for a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide to be requested from the sponsor. The same was reflected by Dr. Yasuda in her secondary safety review memo. I agree with their recommendations, and we should ask the sponsor to do so.

Response to Other Additional Data: Hyperprolactinemia, Hepatic Analytes, AIMS analysis and Case Narratives

In Dr. Alfaro's review dated 07/14/08, she provided her item-by-item evaluation of the sponsor's response to the clinical safety questions imposed in the 04/30/2007 approvable letter. She reviewed results from additional requested analysis on prolactin, hepatic analytes and AIMS scores.

The sponsor provided additional analyses on the subset of patients with baseline prolactin within the normal range and also, a subgroup analysis for gender and age. The sponsor was asked to include the frequency of hyperprolactinemia in adolescents in the hyperprolactinemia section and the information was now included in the proposed labeling. In clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168). Dr. Alfaro recommends that these adverse events (gynecomastia and galactorrhea) should also be noted in the Adverse Events section of labeling. I have no objection to add these events. A greater percentage of adolescent subjects had treatment emergent increases in AST, ALT and alkaline phosphatase compared to adult subjects. The hepatic results are reflected in the sponsor's proposed labeling. Dr. Alfaro recommends no further labeling changes based on results of AIMS analysis provided in this submission.

She also reviewed case narratives of 8 cases of gynecomastia, 2 cases with elevated prolactin, and one CPK elevation case. Most of these cases were from the open-label studies. Based on the limited information provided, Dr. Alfaro's review of the 4 additional requested fatalities narratives from the MedWatch reports revealed that these subjects were on multiple concomitant medications. Based on her review of these requested case narratives, no further labeling changes was recommended.

Safety Update

In this submission, the sponsor provided an analysis of their database (Lilly Safety System) for spontaneously reported adverse events occurring from the time of product launch to May 31, 2007. Based on Dr. Alfaro's review this safety update, no new safety signals emerged that would require additional changes to product labeling.

Risk Minimization Plan (RMP)

The sponsor's proposed RMP includes routine pharmacovigilance of spontaneous case reports with target AEs, a long term open-label safety study (study F1D-MC-HCMX) and a pharmacoepidemiology study with retrospective cohort analysis of a large US health claims database to estimate the incidence and prevalence of diabetes mellitus and dyslipidemia among adolescent patients with schizophrenia or bipoloar disorder compared with the general adolescent population. The sponsor also states that the RMP would include the labeling and the product website which would provide advice on weight management and nutrition, (b) (4) The sponsor has not submitted the full protocol for study HCMX yet. Dr. Yasuda noted in her safety memo that we should ask the sponsor to submit a full protocol for review. (b) (4) .

Given the metabolic safety profile observed with olanzapine, Drs. Alfaro, Mentari and Yasuda unanimously recommended the need to highlight to a larger extent of these metabolic risks in development of a Medication Guide for this product, and should ask the sponsor to do so. I am agreeing with them.

The OSE was consulted on this proposed risk management plan. The OSE would provide their input on the appropriateness of the RMP after the sponsor submits a complete response to the action letter.

5.3 Conclusion Regarding Overall Efficacy and Safety Data

I concur with Dr. Alfaro that the sponsor has adequately responded to our concern regarding the discrepancy in the efficacy data primarily driven by the differential placebo response between the United States and Russian sites in the schizophrenia study HGIN.

As mentioned before, significant safety signals that emerged in these adolescent clinical trial databases were a greater magnitude of weight gain, hypertriglyceridemia, hypercholesterolemia, hyperprolactinemia and transaminase elevations. These findings should be adequately described in the labeling.

The greater metabolic risks observed in the adolescent population should be considered in our overall risk benefit evaluation. I concur with Dr. Alfaro's recommendation of olanzapine as a second-line treatment in adolescent schizophrenia and bipolar disorder given the greater metabolic risks and the morbidity associated with potential chronic use of this product in the patient population once approved.

As a second-line treatment of olanzapine for the acute treatment in adolescent schizophrenia and bipolar disorder, I have no further objection to giving as a similar statement as in recently approved other atypical psychotics that maintenance treatment effect may be extrapolated from adult data in the clinical studies section of the labeling.

6.0 WORLD LITERATURE

The sponsor provided a comprehensive literature review pertaining to the safety of olanzapine for the time period August 25, 2006 through May 31, 2007. The sponsor reported that adverse events and changes in laboratory parameters described in the citations are consistent with the types of adverse events reported for adult patients receiving olanzapine.

7.0 FOREIGN REGULATORY ACTION

According to the information provided by the sponsor in this submission, as of August 21, 2007, olanzapine has not been approved for pediatric use in any country.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take these supplemental NDA to the PDAC.

9.0 DSI INSPECTIONS

No additional DSI inspection requested. Refer to the DSI Clinical Inspection Summary from the first review cycle.

10.0 LABELING AND ACTION LETTER

Although there are some improvements in the labeling language by the sponsor, we have made further modifications so that all pertinent safety findings are clearly reflected in the labeling. Our modified version of draft labeling in the PLR format should be attached in our action letter.

11.0 CONCLUSION AND RECOMMENDATION

In my opinion, the sponsor has adequately addressed the issues noted in our 04/30/2007 approvable letter. I have no doubt about effectiveness of olanzapine in the treatment of schizophrenia and bipolar disorder in both adults and adolescents. However, a greater safety risk observed in adolescents treated with olanzapine in terms of significant weight gain and metabolic effects should be accounted in our risk-benefit determination. I concur with Dr. Alfaro that we should make olanzapine as a second-line treatment in the adolescent population. I also concur with Drs. Alfaro, Mentari and Yasuda that we should ask the sponsor to provide a proposal for a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide. Therefore, I recommend the Division issue a second approvable letter for this set of NDA supplements.

Cc: HFD-130/Laughren/Mathis/Alfaro/Grewal
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/s/

Ni Aye Khin
7/18/2008 01:54:51 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 20-592
Submission Number	S-041
Submission Code	SE5
Letter Date	10/30/06
Stamp Date	10/31/06
PDUFA Goal Date	04/30/07
Reviewer Name	Cara Alfaro, Pharm.D.
Review Completion Date	04/06/07
Established Name	Olanzapine
Trade Name	Zyprexa
Therapeutic Class	Antipsychotic
Applicant	Eli Lilly
Priority Designation	P
Formulation	Oral tablets
Dosing Regimen	2.5 – 5 mg starting, maximum dose 20 mg/day
Indication	Treatment of Schizophrenia
Intended Population	Adolescents

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that the Division take a non approval action on NDA 20-592 SE5-041 that was filed to support the indication "treatment of schizophrenia in adolescents".

Fifty-three percent of randomized patients in pivotal trial HGIN were from sites in the United States and 47% of randomized patients were from sites in Russia. The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Though the LOCF analysis was the primary analysis, it is also concerning that the OC and MMRM analyses (the latter by recalculation by the reviewing statistician in the Division) are substantially different from the LOCF analysis and not statistically significant.

I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

1.2 Recommendation on Postmarketing Actions

Since non approval is recommended, there are no recommendations for postmarketing actions.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Study HGIN was the pivotal trial for establishing efficacy and safety for the indication "treatment of schizophrenia in adolescent patients". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 6-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day ($n = 72$), or placebo ($n = 35$).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

1.3.2 Efficacy

The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg. Seventy-five percent of patients in the olanzapine group and 56% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -10.12, p = 0.003).

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value
BPRS-C Total Score	Olanzapine	72	50.26	9.98	-19.42	15.51	-19.26	-10.12	.003
	Placebo	35	50.09	8.59	-9.31	18.70	-9.14		

The supportive OC analysis was discordant from the LOCF analysis (LS Mean Diff = -0.26, p = 0.947). The reviewing statistician recalculated the MMRM supportive analysis and found similar results to the OC analysis (LS Mean Diff = -1.25, p = 0.72) though the Sponsor's results for the MMRM analysis were statistically significant.

When evaluating the efficacy signal for the sites in the United States and the sites in Russia, only the latter were statistically significant in favor of olanzapine. The low placebo response in the sites in Russia appears to be driving these results.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

Efficacy Variable	Country	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy by Country)
BPRS-C Total Score	America	Olanzapine	38	53.18	10.10	-21.21	16.30	-20.89	-5.26	.258	.146
		Placebo	19	51.42	8.64	-15.00	18.28	-15.64			
	Russia	Olanzapine	34	47.00	8.88	-17.41	14.55	-17.44	-14.95	.003	
		Placebo	16	48.50	8.52	-2.56	17.38	-2.49			

Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a non approval action.

1.3.3 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar disorder) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events (≥ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with ≥ 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
HGIN + HGIU Acute Database				
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Weight (kg) Mean Change to Endpoint (OC)	3.6 (n = 154)	0.08 (n = 67)	3.57	< 0.001
BMI Mean Change to Endpoint (LOCF)	1.22	0.05	1.17	< 0.001
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001
Overall Combined Database				

Weight (kg) Mean Change to Endpoint (LOCF)	7.35	-	-	< 0.001 (compared to baseline)
Weight (kg) Mean Change to Endpoint (OC)	10.8	-	-	< 0.001 (compared to baseline)
BMI Mean Change to Endpoint (LOCF)	2.31	-	-	< 0.001 (compared to baseline)
≥ 7% increase in body weight (%)	65%	-	-	-

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits. In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin

elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).
For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

Hypertriglyceridemia
The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, $p < 0.001$). In reviewing the individual lab data, 11 marked outliers were noted for triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) ($p = 0.039$).

Hypercholesterolemia
The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, $p < 0.001$). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) ($p = 0.023$).

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were also similar between the

olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality

Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation is not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Olanzapine (Zyprexa) is an atypical antipsychotic. Olanzapine oral tablets were approved on 9/30/1996 for the treatment of schizophrenia in adults. Olanzapine is also available as Zyprexa Zydis, orally disintegrating tablets and Zyprexa IntraMuscular for injection.
Olanzapine oral tablets are currently approved for the following indications: treatment of schizophrenia, treatment of acute mixed or manic episodes associated with bipolar I disorder, maintenance monotherapy for bipolar I disorder, and combination therapy (with lithium or valproate) for the short-term treatment of acute mixed or manic episodes associated with bipolar I disorder.

Olanzapine is not currently indicated for use in child/adolescent populations.

2.2 Currently Available Treatment for Indications

Other currently available atypical antipsychotics include clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify), quetiapine (Seroquel), ziprasidone (Geodon).
Risperidone (Risperdal) was recently approved for the indication “treatment of irritability associated with autistic disorder in children and adolescents” (5 to 16 years of age).

None of the currently available atypical antipsychotics have an approved indication for the treatment of schizophrenia in children or adolescents.

2.3 Important Issues With Pharmacologically Related Products

Although the atypical antipsychotics have less extrapyramidal side effects compared to typical antipsychotics, the adverse event profile is notable for weight gain, hyperglycemia, and diabetes mellitus in adults. Little data is available with regard to the adverse event profile in other populations including children and adolescents.

2.4 Presubmission Regulatory Activity

This summary was taken from the note to reviewer document contained in the Sponsor’s submission.

On June 11, 1999, Eli Lilly and Company (Lilly) submitted a Proposed Pediatric Study Request to FDA related to the conduct of pediatric studies of Zyprexa.

In response to Lilly's proposed pediatric study request, the FDA issued to Lilly a Written Request for Pediatric Studies dated November 30, 2001 (reissued under the Best Pharmaceuticals for Children Act (BPCA) on July 3, 2002) and amended on April 9, 2002, May 7, 2004, and June 29, 2005. FDA's Written Request (WR) as amended, included a request for clinical data on the use of Zyprexa to treat adolescents with schizophrenia and adolescents with acute bipolar mania in order to make Zyprexa eligible for the pediatric exclusivity extension under Section 505A of the Federal Food, Drug, and Cosmetic Act. More details regarding FDA's WR, and Lilly's response, are provided in Item 20 of this submission.

FDA granted an indication for olanzapine for the treatment of bipolar mania in adults (NDA 20-592/S006) on March 17, 2000. As part of the approval, the FDA requested a study in pediatric patients with bipolar mania as a post-marketing commitment. Study F1D-MC-HGIU is included in this submission to fulfill this post-marketing commitment.

On January15, 2004, the FDA met with Lilly to discuss the PK package proposed by Lilly to fulfill FDA's Written Request for Pediatric Studies. At this meeting, Lilly provided an overview of the available PK data. FDA requested additional justification of

the utility of the data from Study LOAY in order to make a final decision on whether or not the data is acceptable to sufficiently meet the PK aspects of the Written Request.

On March 22, 2004 Lilly submitted to IND 28,705 additional information regarding study LOAY and requested a meeting to further discuss fulfillment of the PK aspects of the WR. In response to questions from FDA sent to Lilly on July 7, 2004, Lilly submitted additional information to IND 28,705 on July 13, 2004.

Lilly met with FDA on July 21, 2004 to again discuss the PK information needed to fulfill the WR. At that meeting, FDA agreed with Lilly's proposal to provide PK data in adolescents from Studies HGCS, HGCR, HGGC, and LOAY to address the PK requirements outlined in the Written Request.

In discussions with FDA, it was noted that information about the exact sampling time relative to the dose were not collected as part of the protocol in Study LOAY; however, extensive simulations showed that lack of data regarding timing of samples in Study LOAY should not adversely affect the ability to perform a meaningful population analysis. Nonetheless, to assure the robustness of the PK data, Lilly collected additional population PK data in adolescent patients with schizophrenia or bipolar disorder by conducting Study HGMF. Inclusion of data from Study HGMF in this submission was discussed at a pre-NDA meeting on March 17, 2006. At that meeting, FDA requested that Lilly conduct the population PK analysis both with and without the data from Study LOAY. Both analyses were conducted by Lilly and are included with this submission. The population PK analysis also includes a comparison of pediatric olanzapine PK data with the adult olanzapine PK data from Study HGAJ.

The format and content of the submission were also discussed and agreed to at the March 17, 2006 pre-sNDA meeting. The FDA indicated that, based on the pre-sNDA package and discussions, the proposed submission content appeared to be adequate to respond to FDA's Written Request and that Study HGIU appeared to be adequate to fulfill the post-marketing commitment which was part of the bipolar mania in adults approval.

In the 11/30/01 written request, the Division stated "We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug". The Division also recommended that a relapse prevention trial should follow the acute treatment trial. The Sponsor did not follow either recommendation and neither was required to fulfill the pediatric written request.

2.5 Other Relevant Background Information

The Pediatric Exclusivity Board met on January 10, 2007 to determine whether the Sponsor had fulfilled the requirements in the written request. It was determined that the requirements had been met and exclusivity was granted.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Statistics

The statistician (Fanhui Kong) reviewed the efficacy data from the pivotal trial, HGIN. Several significant statistical issues were identified in his review including differential efficacy in U.S. versus Russia sites and inconsistent statistical results based on LOCF, OC and MMRM analyses (see Statistical review). This reviewer has similar issues which are described in Section 6.1.3 (Efficacy Findings) of this review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Tables of Clinical Studies

The Sponsor included study reports for 9 pediatric studies in this submission. HGIN is the pivotal study for adolescent schizophrenia and HGIU is the pivotal study for adolescent bipolar I disorder. HGMF is the primary study for determining pharmacokinetic parameters in the adolescent population. The other studies are supportive and provide safety and pharmacokinetic data.

Table 4.1.1 Summary of Clinical Studies

Study	Description	Length	Age Range (years)	Number of Patients
HGIN	MC, DB, PC study in adolescent patients with schizophrenia. Flexible dose olanzapine (2.5 – 20 mg) U.S. and Russia sites	6 weeks DB 26 weeks OL extension	13 to 17	107 (n = 72 olanzapine, n = 35 placebo)
HGIU	MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder. Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico	3 weeks DB 26 weeks OL extension	13 – 17	161 (n = 107 olanzapine, n = 54 placebo)
LOAY	OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders Flexible dose olanzapine (5 – 20 mg) German sites	24 weeks	12 – 21	96 (n = 89, 13-17 years)
HGMF	OL study in adolescent patients with schizophrenia or bipolar I disorder Flexible dose olanzapine (2.5	4.5 weeks	13 – 17	107 (n = 37 schizophrenia, n = 70 bipolar)

	– 20 mg) U.S., Puerto Rico, Russia			
HGCS	OL study in adolescent patients with schizophrenia Dosing: 2.5 to 20 mg/day Single site	8 weeks	10 – 18	8
HGCR	DB study in adolescent patients with schizophrenia, haloperidol as active comparator Dosing: 2.5 qod – 20 mg/day Single site	8 weeks	12 – 16	2
HGGC	OL study in children and adolescents with bipolar disorder Dosing: 2.5 to 20 mg/day Single site (U.S.)	8 weeks	5 – 14	23

Modified from Sponsor Table 2.5.1.1 clinical-overview.
MC = multicenter, DB = double-blind, PC = placebo-controlled, OL = open-label

4.2 Data Quality and Integrity

The Division of Scientific Investigations was asked to inspect a number of sites for studies HGIN and HGIU – some sites enrolled patients for both studies. DSI was asked to audit one site in Georgia (n = 7 HGIU, n = 5 HGIN) and one site in Ohio (n = 15 HGIU, n = 6 HGIN).

For pivotal trial HGIN, DSI was also asked to inspect two sites in Russia. This request was made since the sites in Russia, that enrolled approximately 50% of patients in study HGIN, were driving the overall efficacy signal in that trial. The final DSI report was not available at the time this review was completed, but preliminary comments from the investigator did not indicate any major issues thought to effect efficacy.

4.3 Compliance with Good Clinical Practices

Per protocols, the studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Of note, one clinical trial site was omitted from the primary efficacy analyses due to significant GCP issues. This site enrolled patients in both HGIU (site 028) and HGIN (site 021). Details regarding the GCP issues is in Section 6.1.3 (Efficacy Findings) of this review.

4.4 Financial Disclosures

Financial disclosure information was provided for the study HGIN. No investigators were noted to have received significant monies from the Sponsor.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetics of oral olanzapine were evaluated primarily in study HGMF (see Table 4.1.1 in Section 4.1 Tables of Clinical Studies) via population pharmacokinetic analyses. These data have been extensively reviewed by the biopharmaceutical reviewer (see Biopharm review).

6 INTEGRATED REVIEW OF EFFICACY

One pivotal trial, F1D-MC-HGIN, was submitted to support the efficacy of olanzapine in the treatment of schizophrenia in adolescents.

6.1 Indication

The Sponsor proposes the following indication "indicated for the treatment of schizophrenia in adolescents".

6.1.1 General Discussion of Endpoints

The primary efficacy endpoint for the clinical trial was the change from baseline to endpoint on the Anchored version of the Brief Psychiatric Rating Scale for Children. The BPRS, in general, is a standard rating scale used to evaluate efficacy in adult schizophrenia populations and is appropriate for evaluating efficacy in this clinical trial. The BPRS-C is slightly different from the BPRS and has been validated in the adolescent population.

The scoring of the Anchored BPRS-C was determined by interviews with both the patient and the parent/legal guardian at all visits. Investigators were told to record the "reference score" on the CRF and that this score is the higher of the two scores. This reviewer asked if the ratings were recorded separately for the patient and parent/legal guardian so that disparate ratings might be reviewed. The Sponsor indicated that the investigators were instructed to collect both ratings and retain the sheets as source documentation but not to enter them on the CRF. Therefore, the separate ratings are not available.

The Sponsor also included the Clinical Global Impression-Severity and Clinical Global Impression-Improvement scales to rate overall symptomatology. These are standard rating scales in clinical trials for psychiatric illnesses, including schizophrenia.

6.1.2 Study Design

Protocol F1D-MC-HGIN is the pivotal study submitted to support the indication "for the treatment of adolescents with schizophrenia". The other studies submitted as supportive studies

in this population are open-label trials and are supportive primarily from a safety and not efficacy perspective. Therefore, only study HGIN is reviewed here.

Protocol HGIN
"Olanzapine versus placebo in the treatment of adolescents with schizophrenia"
First patient enrolled 11/26/02, last patient completed 4/29/05.

Investigators and sites
This study enrolled patients at 20 sites in the United States and 5 sites in Russia. It is noteworthy that 107 patients were randomized and 50 (47%) of those were randomized from the 5 sites in Russia. Investigator and site information (including numbers of patients randomized and completing the trial) are included in Appendix 10.1.

Study Objectives
Primary objective: To assess the efficacy of a flexible dose of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents (ages 13 – 17) with schizophrenia as measured by the difference between treatment groups in mean change from baseline to endpoint in the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

Secondary objectives:
To assess secondary efficacy measures 1) Clinical Global Impression: Improvement Scale, (CGI-I); 2) Clinical Global Impression: Severity Scale (CGI-S); 3) Positive and Negative Syndrome Scale (PANSS) total, positive subscale, and negative subscale scores; and 4) Overt Aggression Scale (OAS).

To assess the efficacy of olanzapine compared with placebo in improving clinical symptoms in terms of rate of response, with response defined as a reduction of 30% or more in the Anchored BPRS-C total score and a CGI Severity score of 3 or less.

To assess the safety of olanzapine compared with placebo for up to 6 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

To assess the health-related quality of life and cognition associated with olanzapine compared with placebo for up to 6 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

Study Population
The study population consisted of generally healthy adolescents, ages 13 to 17 inclusive, with a DSM-IV-TR diagnosis of schizophrenia. The diagnosis of schizophrenia was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime (K-SADS-PL). The inclusion and exclusion criteria are listed in Appendix 10.2. Patients must have obtained an Anchored BPRS-C total score $\geq$ 35 with a minimum score of 3 on at least one of the following items at Visit 1 and Visit 2: hallucinations, delusions or peculiar fantasies. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required

by local regulations. Exclusion criteria included patients who have been judged clinically to be at serious suicidal risk; patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment; patients currently meeting DSM-IV-TR criteria for delusional disorder, psychotic disorder, schizophreniform disorder, schizoaffective disorder, bipolar disorder, attention deficit/hyperactivity disorder, or major depressive disorder.

Design
This was a multicenter, randomized, double-blind, parallel, placebo-controlled trial consisting of three periods: screening/washout, 6-week double-blind trial, 26-week open-label olanzapine treatment. The screening/washout period was 2-14 days, patients who were on previous antipsychotic therapy had to undergo a taper allowing the patient to be free of antipsychotic therapy for at least 2 days prior to randomization. Patients were then randomized to olanzapine flexible dose (2.5 to 20 mg/day) or placebo treatment (2:1 randomization) for the 6-week acute double-blind trial. Olanzapine was initiated at 2.5 or 5 mg/day and the dose could be increased by 2.5 or 5 mg/day dose increments at the investigator's discretion. If no tolerability or safety issues were apparent, the dose had to be titrated to at least 10 mg/day by Visit 4 (end of first week). The investigator could continue to increase the dose by 2.5 or 5 mg/day to the maximum tolerable dose not to exceed 20 mg/day. The investigator could decrease the dose at any time and in any number of dose decrements if patients experienced an adverse event. The minimum allowable olanzapine dose was 2.5 mg/day. During this 6-week acute trial, 3 study visits occurred in the first week (including baseline visit) and then weekly thereafter.

Patients who did not respond after at least 3 weeks during the 6-week double-blind trial could participate in the optional 26-week open-label extension study and receive open-label olanzapine therapy (2.5 to 20 mg/day). Response was defined as having a $\geq$ 20% decrease in the Anchored version of the BPRS-C compared to baseline and a CGI-S score $\leq$ 3. Study visits occurred weekly x 1 visit, biweekly x 2 visits and then monthly until the end of the 26-week study.

Assessments (The Schedule of Events is in Appendix 10.3)
Rating scales – efficacy:
Primary efficacy endpoint: Anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C)
Secondary efficacy endpoints: Clinical Global Impression – Severity (CGI-S), Clinical Global Impression – Improvement (CGI-I), Positive and Negative Syndrome Scale (PANSS), Overt Aggression Scale (OAS), Child Health Questionnaire (CHQ), Brief Assessment of Cognition Scale (BACS)

Safety assessments:
Vital signs (blood pressure, pulse, weight, height, temperature) – including orthostatic assessments, ECG, Labs (hematology, clinical chemistry, urinalysis, lipid panel, hepatitis screen and panel, serum pregnancy test, prolactin, thyroid stimulating hormone, HgbA1c, urine drug screen.
Fasting glucose at baseline, end of 6-week study and end of 26-week open-label study.
HbA1c was only obtained for patients with diabetes.

Rating scales: Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Abnormal Involuntary Movement Scale (AIMS)
Spontaneous reporting of adverse events.

6.1.3 Efficacy Findings

One hundred seven patients were randomized, 72 to the olanzapine group and 35 to the placebo group. In the olanzapine group, 23 patients discontinued with lack of efficacy as the primary reason for discontinuation for 43.5% of drop-outs. In the placebo group, 20 patients discontinued with lack of efficacy as the primary reason for discontinuation for 90% of drop-outs. Drop-outs due to adverse events was the primary reason for discontinuation for 5 patients in the olanzapine group and no patients in the placebo group.

Table 6.1.3.1 Patient Disposition

	Olanzapine N = 72	Placebo N = 35	P-value
Completers	49 (68.1%)	15 (42.9%)	0.020
Drop Outs	23 (31.9%)	20 (57.1%)	
Adverse Event	5 (6.9%)	0	0.170
Lack of Efficacy	10 (13.9%)	18 (51.4%)	< 0.001
Lost to Follow-up	1 (1.4%)	0	1.00
Patient Decision	4 (5.6%)	1 (2.9%)	1.00
Criteria Not Met/Compliance	2 (2.8%)	1 (2.9%)	1.00
Sponsor Decision	1 (1.4%)	0	1.00

Modified from Sponsor table HGIN.10.1 in study report
*Percent - number of drop-outs is denominator

Demographics and Baseline Disease Severity

There were no statistically significant differences between the olanzapine and placebo groups with regard to baseline demographics or baseline disease severity. Information regarding the subtypes of schizophrenia was not included in the study report.

Table 6.1.3.2 Baseline Demographics and Severity of Disease

		Olanzapine N = 72	Placebo N = 35	P-value
Gender	Male	51 (70.8%)	24 (68.6%)	0.825
	Female	21 (29.2%)	11 (31.4%)	
Age (years)	Mean	16.14	16.30	0.536
	Median	16.31	17.00	
	St. Dev	1.25	1.55	
	Minimum	13.03	13.06	
	Maximum	17.99	18.00	
Origin	African descent	17 (23.6%)	7 (20.0%)	0.656
	Caucasian	52 (72.2%)	25 (71.4%)	
	Hispanic	2 (2.8%)	1 (2.9%)	
	Other	1 (1.4%)	2 (5.7%)	
Country	America	38 (52.8%)	19 (54.3%)	1.00

	Russia	34 (47.2%)	16 (45.7%)	
Age of onset of illness (years)*	Mean Median St. Dev. Minimum Maximum	12.54 13.00 3.18 5.0 17.0	13.40 13.00 2.79 5.0 17.0	0.175
No. of Prev. Schizophrenia episodes	Mean Median St. Dev. Minimum Maximum	2.53 2.00 4.18 0.00 30.00	2.25 2.00 1.80 0.00 6.00	0.672
Total hospitalization for the past year (months)	Mean Median St. Dev. Minimum Maximum	2.43 2.00 2.43 0.20 11.00	2.21 1.50 1.96 0.10 6.50	0.957
Length of current episode (days)	Mean Median St. Dev. Minimum Maximum	274.3 109.0 483.0 0.00** 2742	233.5 92.0 435.2 4.00 2139	0.675
Days since last hospitalization	Mean Median St. Dev. Minimum Maximum	335.4 88.0 618.4 1.00 2889	250.9 37.0 494.0 1.00 2045	0.678
Psychiatric hospitalization within the past year	Yes No	38 (52.78%) 34 (47.22%)	22 (62.86%) 13 (37.14%)	0.407
CGI-S	Mean Median St. Dev. Minimum Maximum	4.83 5.00 0.69 4.00 6.00	4.94 5.00 0.80 4.00 7.00	0.471
BPRS-C Thinking Disturbance	Mean Median St. Dev. Minimum Maximum	10.49 10.00 3.16 4.00 18.00	10.29 10.00 3.12 6.00 17.00	0.730
BPRS-C Total Score	Mean Median St. Dev. Minimum Maximum	50.26 49.50 9.98 36.00 79.00	50.09 49.00 8.59 35.00 68.00	0.894
PANSS Positive Score	Mean Median St. Dev. Minimum Maximum	22.75 22.50 5.22 11.00 36.00	22.66 22.00 4.17 17.00 32.00	0.885
PANSS Total Score	Mean Median St. Dev. Minimum	95.25 96.50 14.06 66.00	95.54 94.00 14.11 68.00	0.902

	Maximum	122.00	123.0	

Modified from Sponsor table HGIN.11.1 and HGIN.11.2 in study report
*The Sponsor was asked to provide a list of patients with age of onset < 10 along with CRFs. Seventeen patients had age of onset < 10 years of age, only two patients had age of onset = 5 years of age (both from U.S. sites).
**Only 1 patient had length of current episode = 0. This patient entered the study when he had just started his most recent episode – the month was in the CRF, the actual date was imputed.

Efficacy Analyses

Site Issues
In the efficacy analysis, the sponsor included analyses with and without site 021. Per the sponsor, site 021 had significant GCP issues and patients from this site were dropped from the primary analyses (efficacy analyses were similar with and without this site). The study report did not specify what the GCP issues were with this site. The sponsor was asked to provide details and indicated the following:

Lilly discontinued site 021 (Dr. Robb) from study HGIN, and also discontinued Dr Robb's site (site 028) from study HGIU. Lilly informed FDA of the discontinuation of Dr Robb's site from these studies in a submission to IND 28,705; serial number 953, dated May 21, 2004. In a letter dated May 2, 2004 sent to Dr Robb, Lilly listed the following GCP issues that occurred at this site related to studies HGIN and HGIU:

- Not following the randomization procedures outlined in the protocol
- Not submitting protocol amendment A, approved by Lilly on October 17, 2002, to the Institutional Review Board (IRB) for approval before use
- Not submitting revised informed consent documents to IRB
- Not communicating to patients about safety issues in risk profile of study drug. The risk profile was updated by Lilly on December 4, 2003 and faxed to the site on January 6, 2004 and a reminder fax was sent on January 28, 2004.
- Significant problems with drug accountability
- Not being able to reconstruct the regulatory document in the Clinical Trial Record Binder
- Violation of inter-active voice response system (IVRS) security personal identification number process.

Concomitant Medications
Interestingly, 29.2% (21/72) patients in the olanzapine group and 14.3% (5/35) patients in the placebo group did not have any previous medications for schizophrenia.

There were no statistically significant differences in the frequency of concomitant benzodiazepine use between the olanzapine and placebo groups. Concomitant lorazepam use occurred in 18.1% (13/72) patients in the olanzapine group and 34.3% (12/35) patients in the placebo group (p = 0.088). Concomitant diazepam use occurred in 12.5% (9/72) patients in the

olanzapine group and 8.6% (3/35) patients in the placebo group. A few patients in both groups had concomitant clonazepam, temazepam and phenazepam use. The mean number of days of benzodiazepine use did not differ between the treatment groups: 6.25 days in the olanzapine group and 7.39 days in the placebo group. The mean dose of benzodiazepines (using equivalent doses) did not differ between the treatment groups: 1.64 ± 0.80 mg in the olanzapine group and 1.80 ± 0.64 mg in the placebo group.

There were no statistically significant differences in the frequency of concomitant anticholinergic medication use between the olanzapine and placebo groups. Three patients had concomitant benztropine mesylate use – 2 in the olanzapine group and 1 in the placebo group. One patient in the olanzapine group had concomitant dimenhydrinate use. One patient in the placebo group had concomitant trihexyphenidyl use. There was a statistically significant difference in the number of days of concomitant anticholinergic use: 22.5 ± 0.7 days in the olanzapine group and 6.5 ± 6.4 days in the placebo group. The mean dose of anticholinergic medication did not differ between the treatment groups: 2.6 ± 2.0 mg in the olanzapine group and 2.0 ± 1.4 mg in the placebo group.

Primary Endpoint
Primary Analysis - LOCF
The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg.

The Sponsor was asked to provide statistical analysis for the weekly visits for the primary endpoint (BPRS-C total score). Statistical differences favoring the olanzapine group occurred beginning at visit 5 and were maintained to the end of study (visit 9). The analysis including site 021 was similar, least square mean difference was 10.38 favoring the olanzapine group (p = 0.003).

Table 6.1.3.3 Sponsor's Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Visit– LOCF. (without site 021)

Visit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value
3	Olanzapine	72	50.26	9.98	-5.39	6.88	-5.30	-2.25	.132
	Placebo	35	50.09	8.59	-3.17	8.30	-3.05		
4	Olanzapine	72	50.26	9.98	-10.13	9.56	-9.97	-1.80	.370
	Placebo	35	50.09	8.59	-8.37	11.50	-8.16		
5	Olanzapine	72	50.26	9.98	-14.33	10.78	-14.15	-5.50	.017
	Placebo	35	50.09	8.59	-8.89	13.43	-8.65		
6	Olanzapine	72	50.26	9.98	-16.65	15.27	-16.46	-9.14	.003
	Placebo	35	50.09	8.59	-7.54	15.55	-7.32		
7	Olanzapine	72	50.26	9.98	-17.46	15.64	-17.27	-8.52	.008
	Placebo	35	50.09	8.59	-8.97	16.63	-8.75		

8	Olanzapine	72	50.26	9.98	-18.81	16.06	-18.59	-9.91	.003
	Placebo	35	50.09	8.59	-8.94	18.05	-8.68		
9	Olanzapine	72	50.26	9.98	-19.42	15.51	-19.26	-10.12	.003
	Placebo	35	50.09	8.59	-9.31	18.70	-9.14		

Sponsor provided LOCF analyses by visit upon request

Supportive Analyses – OC and MMRM

By contrast, the OC analysis (Table 6.1.3.4) found statistically significant differences favoring olanzapine treatment only at visits 5 and 6. The MMRM analysis (Table 6.1.3.5) was also statistically significant, however, the statistician has also performed an MMRM analysis and the results from his analysis are very different from the Sponsor's analysis. The statistician calculated a p-value of 0.72 at endpoint for his MMRM analysis (see Statistician's review).

Table 6.1.3.4. Sponsor's Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Visit– OC.

Table HGIN.14.20. BPRS-C Total Score
Mean Change from Baseline to Each Visit (OC)
Double-Blind Period

Efficacy Variable	Visit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value
BPRS-C Total Score	3	Olanzapine	72	50.26	9.98	-5.39	6.88	-5.30	-2.25	.132
		Placebo	35	50.09	8.59	-3.17	8.30	-3.05		
	4	Olanzapine	70	50.07	9.94	-10.00	9.61	-9.83	-1.42	.490
		Placebo	34	49.74	8.46	-8.53	11.63	-8.41		
	5	Olanzapine	69	50.12	10.00	-14.77	10.31	-14.52	-4.92	.032
		Placebo	33	49.76	8.59	-9.64	13.37	-9.60		
	6	Olanzapine	66	50.24	10.16	-17.42	15.33	-17.17	-7.49	.021
		Placebo	30	49.50	8.84	-9.83	15.20	-9.68		
	7	Olanzapine	57	49.63	10.59	-20.19	14.74	-20.07	-4.08	.250
		Placebo	21	49.05	9.51	-16.38	15.30	-15.99		
	8	Olanzapine	52	50.23	10.56	-23.02	14.73	-23.08	-4.52	.253
		Placebo	18	49.11	9.51	-18.72	18.10	-18.55		
	9	Olanzapine	50	50.64	10.57	-24.52	13.47	-24.38	-0.26	.947
		Placebo	15	49.00	8.49	-23.73	14.62	-24.12		

Table 6.1.3.5 Sponsor's Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Visit– MMRM.

Table HGIN.14.23. BPRS-C Total Score Repeated Measures ANOVA Analysis
Mean Change from Baseline to Each Visit
Double-Blind Period

Efficacy Variable	Visit (Week)	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean StdErr	LSMean Difference	Diff StdErr	*P-value
BPRS-C Total Score	Combined	olanzapine						-15.17	1.36	-6.55	2.42	.008
		Placebo						-8.62	2.00			
	3 (0.5)	olanzapine	72	50.26	9.98	-5.39	6.88	-5.26	0.85	-2.26	1.48	.131
		Placebo	35	50.09	8.59	-3.17	8.30	-3.01	1.22			
	4 (1)	olanzapine	70	50.07	9.94	-10.00	9.61	-10.12	1.17	-1.76	2.05	.392
		Placebo	34	49.74	8.46	-8.53	11.63	-8.36	1.68			
	5 (2)	olanzapine	69	50.12	10.00	-14.77	10.31	-14.49	1.33	-5.50	2.33	.020
		Placebo	33	49.76	8.59	-9.64	13.37	-8.98	1.92			
	6 (3)	olanzapine	66	50.24	10.16	-17.42	15.33	-16.98	1.85	-9.79	3.27	.004
		Placebo	30	49.50	8.84	-9.83	15.20	-7.19	2.69			
	7 (4)	olanzapine	57	49.63	10.59	-20.19	14.74	-18.10	1.90	-7.90	3.42	.023
		Placebo	21	49.05	9.51	-16.38	15.30	-10.20	2.84			
	8 (5)	olanzapine	52	50.23	10.56	-23.02	14.73	-19.96	2.02	-9.76	3.69	.010
		Placebo	18	49.11	9.51	-18.72	18.10	-10.21	3.08			
	9 (6)	olanzapine	50	50.64	10.57	-24.52	13.47	-21.29	1.93	-8.90	3.58	.015
		Placebo	15	49.00	8.49	-23.73	14.62	-12.39	3.02			

U.S. vs. Russia sites

Since almost half of the patients were from sites in Russia, the Sponsor provided an analysis of mean change from baseline to endpoint (LOCF) on the BPRS-C total score between the two sites (Table 6.1.3.6). Interestingly, the overall efficacy signal comes entirely from the sites in Russia and is driven by the very low mean change from baseline to endpoint in the placebo group.

Table 6.1.3.6. Sponsor's Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Country– U.S. vs. Russian sites.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

Efficacy Variable	Country	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy by Country)
BPRS-C Total Score	America	Olanzapine	38	53.18	10.10	-21.21	16.30	-20.89	-5.26	.258	.146
		Placebo	19	51.42	8.64	-15.00	18.28	-15.64			
	Russia	Olanzapine	34	47.00	8.88	-17.41	14.55	-17.44	-14.95	.003	
		Placebo	16	48.50	8.52	-2.56	17.38	-2.49			

Because of these differences in efficacy, this reviewer asked the Sponsor to analyze the baseline psychiatric illness variables of patients between the U.S. and Russia sites. This analysis is in Appendix 10.4. In general, patients from the U.S. sites had fewer days since last hospitalization (149 vs. 477 days, p = 0.012) [other differences between the countries may account for this difference], higher baseline BPRS-C scores (52.6 vs. 47.5, p = 0.005) and higher baseline scores on several BPRS-C subscales including behavioral problems, depression, thinking disturbance

(11.04 vs. 9.72, p = 0.030), and psychomotor excitation. The PANSS total scores were not different between the sites though there were some inconsistent differences on the subscales. Although not statistically significant, the PANSS total scores were numerically higher in the Russia sites (97.6 vs. 93.3, p = 0.116). Therefore, it does not appear that there is a consistent signal indicating that the patients enrolled in the Russia sites are more severely ill compared to the patients enrolled in the U.S. sites.

Secondary Analyses

BPRS-C Individual Items and Composite Scores

When evaluating the BPRS-C individual items, statistical differences favoring olanzapine were found only for uncooperativeness (p = 0.003), hostility (p < 0.001), manipulativeness (p = 0.035), hyperactivity (p = 0.004) and sleep difficulties (p < 0.001) (see Appendix 10.5). Although there were statistical differences favoring olanzapine for the Thinking Disturbance composite (p = 0.050), the effect is only significant for peculiar fantasies (p = 0.014) but not delusions (p = 0.151) or hallucinations (p = 0.249) – despite the similar severity ratings at baseline for all three symptoms. Interestingly, the "peculiar fantasies" item is one that has been noted to have poor interrater reliability in psychometric testing.[1]

Subgroup Analyses

The Sponsor evaluated the following subgroups: gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian.

Statistically significant differences favoring olanzapine were found for all subgroups except females (p = 0.203), < 15 years of age (p = 0.302) and nonCaucasians – the greater change to endpoint in the placebo group in these subgroups may have contributed to these findings. However, the treatment-by-subgroup analyses were not significant.

Table 6.1.3.6. Sponsor's Table. BPRS-C Total Score - Subgroup Analyses

Efficacy Variable	Subgroup	Strata	N	Therapy	Baseline n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy*Subgroup)
BPRS-C Total Score	Gender	Female	32	Olanzapine	21	51.90	11.92	-18.67	12.77	-17.66	-8.08	.203	.682
				Placebo	11	53.36	7.58	-10.45	21.88	-9.58			
		Male	75	Olanzapine	51	49.59	9.10	-19.73	16.61	-20.03	-10.99	.009	
				Placebo	24	48.58	8.75	-8.79	17.55	-9.03			
	Age	< 15	22	Olanzapine	15	50.73	9.27	-17.27	17.80	-10.20	-8.01	.302	.561
				Placebo	7	54.71	8.88	-12.57	20.40	-2.19			
		>=15	85	Olanzapine	57	50.14	10.23	-19.98	14.97	-19.95	-11.07	.004	
				Placebo	28	48.93	8.27	-8.50	18.56	-8.88			

1 Lachar D, Randle SL, Harper RA et al. The Brief Psychiatric Rating Scale for Children (BPRS-C): validity and reliability of an anchored version. J Am Acad Child Adolesc Psychiatry 2001;40:333-340.

Efficacy Variable	Subgroup	Strata	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy*Subgroup)
BPRS-C Total Score	Origin	Caucasian	77	Olanzapine	52	50.02	10.08	-17.65	15.02	-18.22	-10.92	.007	.802
				Placebo	25	49.08	8.33	-6.72	18.42	-7.30			
		Non-Caucasian	30	Olanzapine	20	50.90	9.92	-24.00	16.21	-24.55	-9.85	.092	
				Placebo	10	52.60	9.16	-15.80	18.73	-14.70			

Efficacy issues

1. It is troubling to this reviewer that the efficacy signal appears to be coming entirely from the sites in Russia (p = 0.003), whereas the efficacy data is far from significant in the sites in the U.S. (p = 0.258). The mean change to endpoint in the BPRS-C total score in the olanzapine groups are similar between the sites and the difference in efficacy signal appears to be driven by the very low mean change in the placebo group in the Russia sites.
2. Because of this discrepancy in efficacy findings, DSI was sent to inspect two of the sites in Russia. Although a final report has not been issued, they did not find any major compliance issues.
3. It is interesting that all 5 of the sites in Russia randomized 10 patients each while most of the 20 U.S. sites (80%) randomized between 1 and 3 patients. Only one of the 20 U.S. sites randomized 10 patients (no sites randomized more than 10). It is not surprising that many U.S. sites did not enroll a high number of patients since adolescent schizophrenia is a rare disorder. It is surprising that the sites in Russia were able to randomize that many patients. This reviewer asked the Sponsor if enrollment was capped at 10 for the Russia sites – the Sponsor indicated that the "target number of patients for each site in Russia was 10 patients for a total of 50 patients".
4. The efficacy results from the clinical trial are not consistent among different analyses. While the LOCF analysis is significant (p = 0.003), the OC analysis is not (p = 0.947). Significant numbers of patients were still in the study at endpoint (50/72, 69% in the olanzapine group and 15/35, 43% in the placebo group). The least squares mean difference was -10.12 in the LOCF analysis, -8.90 in the MMRM analysis and -0.26 in the OC analysis.
5. The statistician reanalyzed the dataset per MMRM and obtained very different results compared to the Sponsor's MMRM analysis. The statistician calculated a LS Mean Difference of -1.25, p = 0.72 (see Statistician's review).

6.1.4 Efficacy Conclusions

The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg. Seventy-five percent of patients in the olanzapine group and 56% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -10.12, p = 0.003).

The supportive OC analysis was discordant from the LOCF analysis (LS Mean Diff = -0.26, p = 0.947). The reviewing statistician recalculated the MMRM supportive analysis and found similar results to the OC analysis (LS Mean Diff = -1.25, p = 0.72) though the Sponsor's results for the MMRM analysis were statistically significant.

When evaluating the efficacy signal for the sites in the United States and the sites in Russia, only the latter were statistically significant in favor of olanzapine. The LS Mean Diff for United States sites -5.26 (p = 0.258) and for Russia -14.95 (p = 0.003). The low placebo response in the sites in Russia appears to be driving these results. Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a non approval action.

7 INTEGRATED REVIEW OF SAFETY

The Sponsor used the following databases for assessment of safety (see Table 4.1.1 in Section 4.1 – Tables of Clinical Studies for more information on individual studies). For studies HGCS (n = 8), HGCR (n = 2), and HGGC (n = 23), the Sponsor included only information regarding deaths, serious adverse events and discontinuations due to adverse events.

Sponsor's Table. Databases for Summary of Clinical Safety

Table 2.7.4.1. Databases for Summary of Clinical Safety

Database	Indication	Studies Used	Number of Patients
Acute Placebo-Controlled Databases	Schizophrenia	HGIN	N=107 (Olz=72, Pla=35)
	Bipolar	HGIU	N=161 (Olz=107, Pla=54)
	Combined	HGIN, HGIU	N=268 (Olz=179, Pla=89)
Overall Olanzapine Exposure Databases	Schizophrenia	HGIN, LOAY, HGMF[a]	N=227
	Bipolar	HGIU, HGMF[a]	N=227
	Combined	HGIN, HGIU, LOAY, HGMF	N=454

a Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

The Sponsor also included information on serious adverse events and discontinuations due to adverse events for the 37 adolescent patients who participated in the olanzapine <u>adult</u> studies:

Study HGBG and HGCL were clinical trials for adult patients aged 18 or older – two adolescent patients were enrolled in those trials (17.9 and 17.8 years of age).
Study HGDH – acute and long-term efficacy of olanzapine in first-episode psychotic patients aged 16 – 40 years (n = 7 adolescents).
Study HGGF – delaying or preventing psychosis onset in persons aged 12 to 45 years prodromal to psychosis (n = 24 adolescents).

Study HGKL – clinical trial in patients aged 15 to 65 years with borderline personality disorder (n = 4 adolescents).

"Acute Placebo Controlled Database" hereafter called HGIN + HGIU Acute Database
A total of 268 patients were included in the HGIN + HGIU Acute Database**.** Eight (4.5%) patients discontinued due to adverse events in the olanzapine treatment group.

Patient Disposition (HGIN + HGIU)

	Olanzapine N = 179	Placebo N = 89	P-value
Completers	134 (74.9%)	50 (56.2%)	0.003
Drop Outs	45 (25%)	39 (44%)	
Adverse Event	8 (4.5%)	1 (1.1%)	0.279
Lack of Efficacy	22 (12.3%)	34 (38.2%)	< 0.001
Lost to Follow-up	1 (0.6%)	0	1.00
Patient Decision	8 (4.5%)	2 (2.2%)	0.504
Criteria Not Met/Compliance	2 (1.1%)	2 (2.2%)	0.602
Sponsor Decision	1 (0.6%)	0	1.00
Physician Decision	1 (0.6%)	0	1.00
Other	2 (1.1%)	0	1.00

Modified from Sponsor table 2.7.4.20 in summary-clin-safety document

Patient demographics (HGIN + HGIU): The majority of patients were male (60%), Caucasian (70%) with a mean age of ~ 15.6 years (see Appendix 10.6). For study HGIN, the majority of patients were 16 and 17 years of age at baseline (61%); for study HGIU, the majority of patients were 14 and 15 (55%). This is expected and consistent with the psychiatric diagnoses in these two trials. A table of age distribution at baseline is in Appendix 10.6.

"Overall Olanzapine Exposure Combined Database" hereafter called Overall Combined Database
A total of 454 patients were included in the Overall Combined Database. The patient disposition by diagnoses (bipolar vs. schizophrenia) is given in Table 6.1.4.2. Twice as many patients with bipolar disorder discontinued due to an adverse event compared to patients with schizophrenia (14.5% vs. 7.9%). More than twice as many patients with schizophrenia discontinued due to lack of efficacy compared to patients with bipolar disorder (16.3% vs. 5.7%).

Sponsor's Table. Patient Disposition (Overall Combined Database)

Table 2.7.4.23. Patient Disposition
All Patients with Olanzapine Exposure
Overall Olanzapine Exposure Combined Database

	Bipolar		Schizophrenia		Overall	
Patient Disposition	N	%	N	%	N	%
Reporting Interval Completed	130	57.3%	119	52.4%	249	54.8%
Adverse Event	33	14.5%	18	7.9%	51	11.2%
Lack of Efficacy	13	5.7%	37	16.3%	50	11.0%
Lost To Follow-Up	9	4.0%	4	1.8%	13	2.9%
Patient Decision	24	10.6%	10	4.4%	34	7.5%
Criteria Not Met/Compliance/Protocol Violation	2	0.9%	28	12.3%	30	6.6%
Sponsor Decision	3	1.3%	5	2.2%	8	1.8%
Physician Decision	10	4.4%	4	1.8%	14	3.1%
Other	3	1.3%	2	0.9%	5	1.1%
Total	227	100.0%	227	100.0%	454	100.0%

The patient demographics in the Overall Combined Database were fairly consistent with the demographics of the HGIU + HGIN Acute Database with the exception of country – 89 additional patients with schizophrenia from study LOAY (German sites) were included in the Overall Combined Database. Patient demographics for the Overall Combined Database are included in Appendix 10.6.

7.1 Methods and Findings

7.1.1 Deaths

No deaths occurred in the HGIU + HGIN Acute Database, Overall Combined Database, studies HGCS, HGCR, HGGC or in adolescent patients from the adult studies.

7.1.2 Other Serious Adverse Events

The following tables for serious adverse events were compiled from narratives provided by the Sponsor.

A total of 7 serious adverse events occurred in 6 patients in the olanzapine treatment arm in the HGIU + HGIN Acute Database (see Table 7.1.2.1).
One serious adverse event (schizophrenia) occurred in 1 patient in the placebo arm of study HGIN (no SAEs in the placebo group in study HGIU).

Table 7.1.2.1. Serious Adverse Events: HGIN + HGIU Acute Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGIN 025-2504	15 YOWF	Olanzapine DB phase	Migraine	Migraine	Severe Worsened from baseline; failed to restart study med and discontinued from study
HGIN 930-9301	15 YOWM	Olanzapine DB phase	Closed fracture of right forearm	Forearm fracture	Severe Fracture from fall, treated in hospital
HGIN 026-2603	14 YOWF	Olanzapine DB phase	Weight gain	Weight increased	Mild/moderate Onset of AE in DB phase, patient discontinued OL phase due to weight gain of 18.3 kg over 4 months
HGIU 012-1211	14 YOWF	Olanzapine DB phase	Exacerbation of bipolar symptoms	Bipolar disorder	Severe Discontinued during OL phase
HGIU 035-3501	14 YOWF	Olanzapine DB phase	Relapse of bipolar disorder	Bipolar disorder	Moderate Hospitalized, Discontinued due to weight gain
HGIU 031-3103	14 YOWM	Olanzapine DB phase	Decreased WBC count and decreased neutrophils	WBC count decreased, neutrophil count decreased	Moderate WBC 4.04 to 2.52; ANC 1.63 to 0.83; Discontinued in OL phase due to persistently low counts

A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database (see Table 7.1.2.2). The majority of these SAEs, 19/35 patients, were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

Table 7.1.2.2 Serious Adverse Events: Overall Combined Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGIN 007-0704	15 YOBM	Olanzapine OL phase	Exacerbation of schizophrenia	Schizophrenia	Severe Hospitalization, discontinuation from study
HGIN 013-1302	17 YOM	Olanzapine OL phase	Wosening of schizophrenia symptoms	Schizophrenia	Moderate
HGIN 019-1901	15 YOWF	Olanzapine OL phase	Depressive with psychotic features, weight gain	Major depression, weight increased	Severe Hospitalization, discontinuation from study
HGIN 021-2101	14 YOBM	Olanzapine OL phase	Worsening of schizophrenia	Schizophrenia	Severe
HGIN 026-2603	14 YOWF	Olanzapine OL phase	Exacerbation of schizophrenia,	Schizophrenia, weight	Severe (schiz) Moderate (weight)

			suicidal ideation, weight gain	increased	Hospitalization, weight gain of 18.3 kg over 4 months
HGIN 030-3001	17 YOWM	Olanzapine OL phase, 1st visit	Exacerbation of psychosis	Psychotic disorder	Severe Hospitalized
HGIN 910-9101	16 YOWF	Olanzapine OL phase	Worsening of Schizophrenia	Schizophrenia	Moderate Hospitalized
HGIN 930-9301	15 YOWM	Olanzapine OL phase	Closed fracture of right forearm	Forearm fracture	Severe Fracture from fall, treated in hospital
HGIN 930-9307	15 YOWF	Olanzapine OL phase	Attempted suicide	Suicide attempt	Severe Attempted overdose with Phenobarbital, hospitalized, discontinued from study
HGIU 001-0103	13 YOWM	Olanzapine OL phase	Increased agitation	Agitation	Severe Hospitalized, completed study
HGIU 001-0107	13 YOWM	Olanzapine OL phase	Agitation, aggression	Agitation, aggression	Severe Hospitalized, completed study
HGIU 001-0108	14 YOWF	Olanzapine OL phase	Alcohol intoxication, suicidal ideation	Alcohol poisoning, suicidal ideation	Severe (alcohol) Moderate (SI) Discontinued from study
HGIU 012-1202	15 YOWF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, completed study
HGIU 012-1211	14 YOWF	Olanzapine OL phase	Exacerbation of bipolar symptoms	Bipolar disorder	Severe Discontinued study
HGIU 012-1212	14 YOBF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, discontinued "patient decision"
HGIU 020-2016	14 YOWF	Olanzapine OL phase	Attempted suicide	Suicide attempt	Mild Overdose of Benadryl and ibuprofen, recovered without treatment; completed study
HGIU 026-2604	16 YOHM**	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, completed study
HGIU 026-2605	14 YOM	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized and discontinued study
HGIU 026-2608	13 YOWF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, discontinued study
HGIU 027-2705	15 YOBM	Olanzapine OL period	Worsening of bipolar disorder, self-inflicted superficial lacerations	Bipolar disorder, Intentional self-injury	Severe (BP) Moderate (SIB) Hospitalized, discontinued study (cut arms with fingernails)
HGIU	14 YOBF	Olanzapine	Worsening of	Bipolar disorder	Severe

027-2707		OL phase	bipolar disorder		Hospitalized, completed study
HGIU 028-2804	15 YOWF	Olanzapine OL phase	Recurrence of bipolar symptoms	Bipolar disorder	Severe Hospitalized, discontinued study "sponsor's decision" – GCP issues at site
HGIU 028-2805	14 YOWF	Olanzapine OL phase	Suicidal ideation	Suicidal ideation	Severe Hospitalized, discontinued – GCP issues at site
HGIU 028-2806	15 YOBF	Olanzapine OL phase	Bipolar mania	Bipolar disorder	Severe Hospitalized, discontinued study
HGIU 031-3103	14 YOWM	Olanzapine OL phase	Decreased WBC count and decreased neutrophils	WBC count decreased, neutrophil count decreased	See Table 7.1.2.1.
HGIU 033-3304	15 YOWF	Olanzapine OL phase	Intensifying aggressiveness and irritability	Aggression, irritability	Severe Hospitalized, discontinued study
HGIU 035-3519	14 YOWM	Olanzapine OL phase	Violent behavior	Aggression	Severe Hospitalized, discontinued study
HGIU 730-7302	13 YOHM	Olanzapine OL phase	Oppositional defiant behavior	Oppositional defiant disorder	Severe Hospitalized, discontinued due to noncompliance
HGMF 003-0303	17 YOWF	Olanzapine OL	Acute appendicitis	Appendicitis	Severe Hospitalized, completed study
HGMF 003-0304	16 YOWF	Olanzapine OL	Exacerbation of bipolar illness with positive suicidal ideation	Bipolar disorder	Severe Hospitalized, discontinued study
LOAY 407-4078	17 YOWM	Olanzapine OL	Recurrence of acute psychotic symptoms	Psychotic disorder	Severe Hospitalized
LOAY 407-4207	14 YOWM	Olanzapine OL	Borrelia infection	Borrelia infection	Mild Discontinued study
LOAY 413-4145	16 YOWM	Olanzapine OL	Worsening of underlying disease schizophrenia	Schizophrenia	Severe Hospitalized Discontinued study

Table 7.1.2.3 Serious Adverse Events: HGCR, HGCS, HGGC

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGCR 001-2001	12 YOWM	Olanzapine OL	Headache lumbar puncture	Headache	Moderate Completed study
HGCS 001-1001	14 YOHF	Olanzapine OL	Mallory Weiss tear, vomiting blood	Esophageal hemorrhage, hematemesis	Severe Completed study
HGGC 001-2023	14 YOWF	Olanzapine	Suicidality	Depression	Hospitalized and discontinued from study

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who experienced serious adverse events (Table 7.1.2.4).

Table 7.1.2.4 Serious Adverse Events: Adolescent Patients from Adult Studies (n = 37)

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGDH 007-1607	17 YOWM	Olanzapine	Overdose	Overdose	Ingested 175 mg olanzapine, completed the study
HGGF 001-0102	15 YOWM	Olanzapine	Worsening depression with suicidal ideation	Depression, affective disorder, suicidal ideation	Gained significant amount of weight- 14 kg in 17 weeks; patient discontinued
HGGF 001-113	16 YOWF	Olanzapine	Dysphoria, Superficial self-mutilation	Dysphoria, self mutilation	Cuts on upper arm made with piece of glass, discontinued from study
HGGF 004-405	17 YOWF	Olanzapine	Auditory perceptual abnormalities, depersonalization, depressed mood, suicidal ideation, worsening psychosis	Auditory hallucination, depersonalization, depressed mood, illusion, suicidal ideation, psychotic disorder	
HGGF 004-406	17 YOWF	Olanzapine	Depressed mood, suicidal ideation	Depressed mood, suicidal ideation	Discontinued study

Narratives were provided by Sponsor upon request

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Adverse events associated with dropouts

Table 7.1.3.1.1 Discontinuations Due to Adverse Events: HGIN + HGIU Acute Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGIN 007-703	13 YOBF	Olanzapine DB phase	Clinically significant increased ALT	ALT increased	ALT up to 231 (AST up to 142) Returned to WNL after discontinuation from study
HGIN 010-1001	17 YOWM	Olanzapine DB phase	Elevated liver function	Liver function test abnormal	ALT = up to 597 AST = up to 410 GGT = up to 129 Noted at randomization visit (was taking olanzapine prior to study) Discontinued study
HGIN 021-2103	17 YOBM	Olanzapine DB phase	Elevated transaminases	Transaminases increased	AST up to 136 ALT up to 396

					Returned to WNL after discontinuation from study
HGIN 910-9110	17 YOWM	Olanzapine DB phase	AST increased	AST increased	AST up to 190 (ALT up to 321) Returned to WNL after discontinuation from study
HGIN 920-9202	17 YOWM	Olanzapine DB phase	Rise ALT	ALT increased	ALT up to 393 (AST up to 179 GGT up to 82) ALT and GGT returned to WNL after discontinuation from study (AST N/A)
HGIU 035-3503	16 YOBF	Olanzapine DB phase	Heart rate increased	Elevated pulse	Holter noted sinus tachycardia Discontinued from study, pulse WNL at 4th follow-up visit
HGIU 012-1203	15 YOWF	Olanzapine DB phase	Hepatic enzyme increased	Elevated liver enzymes	AST up to 148 ALT up to 325 GGT up to 53 Returned to near WNL after discontinuation from study (ALT 48)
HGIU 035-3501	14 YOWF	Olanzapine DB phase	Weight increased	Weight gain	Weight increase of 4.5 kg in ~ 15 days

Table 7.1.3.1.2 Discontinuations Due to Adverse Events: Overall Combined Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGIN 003-0302	17 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.7 kg in 3 months
HGIN 019-1901	15 YOWF	Olanzapine OL	Weight increased	Weight gain	Gained 6.62 kg during DB phase, Gained 15.88 kg over 5.7 months
HGIN 020-2002	15 YOBM	Olanzapine OL	Sedation	Sedation	
HGIN 025-2502	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.2 kg over 183 days
HGIN 027-2701	17 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12 kg over 92 days
HGIN 027-2702	13 YOWF	Olanzapine OL	Weight increased	Weight gain	Gained 17.5 kg over 148 days
HGIN 030-3007	13 YOWF	Olanzapine OL	Increased appetite	Increased appetite	Gained 21.8 kg over 94 days
HGIN 900-9003	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.8 kg over 169 days
HGIN 930-9307	15 YOWF	Olanzapine OL	Suicide attempt	Suicide attempt	See Table 7.1.2.2.
HGIN 940-9403	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 13.4 kg over 152 days
HGIU	14 YOWF	Olanzapine	Alcohol	Alcohol	See Table 7.1.2.2.

001-108		OL	intoxication	poisoning	
HGIU 007-708	15 YOWM	Olanzapine OL	Drowsiness	Somnolence	
HGIU 009-902	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 14.2 kg over 78 days
HGIU 013-1303	17 YOWF	Olanzapine OL	Syncope	Syncope	100/60 mm Hg, 88 bpm supine, 98/62 mmHg, 100 bpm standing
HGIU 013-1308	14 YOHF	Olanzapine OL	Weight gain	Weight increased	Gained 9.1 kg over 103 days
HGIU 013-1310	16 YOWF	Olanzapine OL	Increased appetite	Increased appetite	Gained 9.5 kg over ~ 56 days (at time of weight patient had been off drug for 11 days)
HGIU 013-1311	13 YOHM	Olanzapine OL	Worsened aggressive behavior	Aggression	
HGIU 019-1901	16 YOBF	Olanzapine OL	Pregnancy	Pregnancy	
HGIU 019-1907	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 17.7 kg over 170 days
HGIU 020-2007	14 YOWF	Olanzapine OL	Elevated liver function test	Liver function test abnormal	AST up to 204, ALT up to 330 Resolved after discontinuation from study
HGIU 020-2008	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 9.3 kg over 58 days
HGIU 020-2019	16 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 9.5 kg over 81 days
HGIU 024-2404	13 YOWF	Olanzapine OL	Fear of more weight gain	Fear of weight gain	Gained 5.9 kg over 34 days
HGIU 026-2608	13 YOWF	Olanzapine OL	Exacerbation of bipolar disorder	Bipolar disorder	
HGIU 027-2701	15 YOWF	Olanzapine OL	Sedation	Sedation	
HGIU 027-2704	15 YOBM	Olanzapine OL	Weight gain	Weight increased	Gained 18.6 kg over 119 days
HGIU 027-2705	15 YOBM	Olanzapine OL	Worsening of bipolar disorder	Bipolar disorder	
HGIU 028-2806	15 YOBF	Olanzapine OL	Bipolar mania	Bipolar disorder	
HGIU 031-3103	14 YOWM	Olanzapine OL	Decreased WBC	WBC count decreased	See Table 7.1.2.1
HGIU 033-3304	15 YOWF	Olanzapine OL	Intensifying aggressiveness	Aggression	See Table 7.1.2.2.
HGIU 035-3510	15 YOWM	Olanzapine OL	Weight gain	Weight increased	Gained 5.4 kg over 89 days
HGIU 035-3517	13 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 5 kg over ~6 weeks
HGIU 720-7217	15 YOHM	Olanzapine OL	Hepatic enzymes increases	Hepatic enzyme increased	AST up to 103, ALT up to 125 (also had significant weight gain, 21 kg over ~ 5 months)

HGIU 720-7219	14 YOHF	Olanzapine OL	Pregnancy	Pregnancy	
HGMF 002-0211	17 YOWF	Olanzapine OL	Somnolence	Somnolence	
HGMF 003-0304	16 YOWF	Olanzapine OL	Exacerbation of bipolar illness with positive suicidal ideation	Bipolar disorder	See Table 7.1.2.2.
HGMF 008-0806	15 YOWM	Olanzapine OL	Increased depression	Depression	
HGMF 014-1400	17 YOBF	Olanzapine OL	Elevated CK level lab	Blood creatine phosphokinase	CK up to 690 U/L
HGMF 025-2501	15 YOWM	Olanzapine OL	Drowsiness	Somnolence	
HGMF 028-2801	18 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 8.9 kg over 27 days
LOAY 405-4057	13 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 10.1 kg over 42 days
LOAY 407-4207	14 YOWM	Olanzapine OL	Suspicion of neuroborreliosis	Neuroborreliosis	See Table 7.1.2.2.
LOAY 407-4218	15 YOWF	Olanzapine OL	Galactorrhea	Galactorrhea	Prolactin up to 35 mcg/L (ULN = 29)

There were no discontinuations due to adverse events for studies HGCS, HGCR and HGGC.

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who discontinued due to adverse events (Table 7.1.3.1.3).

Table 7.1.3.1.3 Discontinuations Due to Adverse Events: Adolescent Patients from Adult Studies

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGGF 001-127	13 YOWM	Olanzapine	Weight gain	Weight increased	Gained 23 kg in ~5 months (BMI from 32 to 39)
HGKL 014-1416	15 YOWM	Olanzapine	Weight gain	Weight increased	Gained 12.5 kg over 3 months; triglycerides also increased from 260 to 508 mg/dL

7.1.4 Common Adverse Events

7.1.4.1 Eliciting adverse events data in the development program

Adverse events were obtained by spontaneous reports, patient observation and investigator query at every study visit. Rating scales were included for evaluation of extrapyramidal symptoms (SAS), akathisia (BAS) and dyskinesias (AIMS). Vital signs, ECGs and laboratory tests were obtained at intervals throughout the study.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the MedDRA version 8.0 coding dictionary. A sample of patient narratives was reviewed and the coding of verbatim terms to preferred terms was appropriate.

7.1.4.3 Common adverse event tables

Adverse events occurring in ≥ 2% of patients in the HGIU + HGIN Acute Database is in Table 7.1.4.3.1. The majority of adverse events in this table occurred more than twice as frequently in the olanzapine group compared to the placebo group, that adverse events that were statistically more frequent in the olanzapine group were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%) and sedation (24% vs. 6%).

Table 7.1.4.3.1 Sponsor's Table. Adverse Events Occurring in ≥ 2% of Patients: HGIU + HGIN Acute Database

	Therapy						
	Olanzapine			Placebo			
Event Classification	N	n	%	N	n	%	*P-value
Patients with >=1 TESS	179	158	88.3%	89	54	60.7%	<.001
Weight increased	179	53	29.6%	89	5	5.6%	<.001
Somnolence	179	44	24.6%	89	3	3.4%	<.001
Increased appetite	179	43	24.0%	89	5	5.6%	<.001
Sedation	179	34	19.0%	89	5	5.6%	.003
Headache	179	30	16.8%	89	11	12.4%	.374
Fatigue	179	17	9.5%	89	4	4.5%	.227
Dizziness	179	13	7.3%	89	2	2.2%	.155
Dry mouth	179	11	6.1%	89	0	0.0%	.018
Dysmenorrhoea	67	4	6.0%	41	4	9.8%	.475
Pain in extremity	179	9	5.0%	89	1	1.1%	.173
Vomiting	179	9	5.0%	89	6	6.7%	.580
Constipation	179	8	4.5%	89	0	0.0%	.055
Nausea	179	8	4.5%	89	8	9.0%	.172
Nasopharyngitis	179	7	3.9%	89	2	2.2%	.722
Abdominal pain upper	179	6	3.4%	89	5	5.6%	.514
Diarrhoea	179	6	3.4%	89	0	0.0%	.183
Irritability	179	6	3.4%	89	4	4.5%	.735
Pharyngolaryngeal pain	179	6	3.4%	89	3	3.4%	1.00
Restlessness	179	6	3.4%	89	2	2.2%	1.00
Alanine aminotransferase increased	179	5	2.8%	89	0	0.0%	.174
Dyspepsia	179	5	2.8%	89	1	1.1%	.667
Epistaxis	179	5	2.8%	89	0	0.0%	.174
Hepatic enzyme increased	179	5	2.8%	89	0	0.0%	.174
Insomnia	179	5	2.8%	89	10	11.2%	.009
Sinusitis	179	5	2.8%	89	0	0.0%	.174

Sponsor's Table 2.7.4.27 from summary-clin-safety document

The common adverse events for the two trials are listed separately in Table 7.1.4.3.2 since the trials differed in duration (6 vs. 3 weeks) and study population. For study HGIN, the adverse events that were statistically different between olanzapine and placebo included weight increased ($p = 0.014$) and somnolence ($p = 0.0006$). For study HGIU, the adverse events that were statistically different between olanzapine and placebo included weight increased ($p < 0.001$), increased appetite ($p < 0.001$), somnolence ($p < 0.001$) and sedation ($p = 0.011$). The adverse events and frequencies occurring in the olanzapine group between the two clinical trials were fairly similar though more patients in HGIU exhibited somnolence (25% vs. 17%), increased

appetite (29% vs. 17%), sedation (22% vs. 15%), dry mouth (8% vs. 4%) and fatigue (14% vs. 3%)

Table 7.1.4.3.2 Adverse Events Occurring in > 2% of Patients with Olanzapine > 2x Placebo: HGIU and HGIN Clinical Trials

	Percentage of Patients Reporting Event			
	6 Week Trial % Schizophrenia Patients		3 Week Trial % Bipolar Patients	
Adverse Event	Olanzapine (N = 72)	Placebo (N = 35)	Olanzapine (N = 107)	Placebo (N = 54)
Weight increased	31%*	9%	29%*	4%
Somnolence	17%*	3%	25%*	4%
Headache	17%	6%	17%	17%
Increased appetite	17%	9%	29%*	4%
Sedation	15%	6%	22%*	6%
Dizziness	8%	3%	7%	2%
Pain in extremity	6%	3%	5%	0
Abdominal pain	4%	0	5%	7%
ALT increase	4%	0	-	-
AST increase	4%	1%	1%	0
Constipation	4%	0	5%	0
Dry mouth	4%	0	8%	0
Fatigue	3%	3%	14%	6%
Diarrhea	1%	0	5%	0
Dyspepsia	-	-	5%	0
Hepatic enzyme increased	1%	0	4%	0
Sinusitis	1%	0	4%	0

From Tables HGIN.12.4, HGIN.14.27 and HGIU.12.4 clinical study reports
*p < 0.05

7.1.4.4 Common adverse events – further analysis

Weight Gain

Weight gain was a significant adverse event occurring in these clinical trials and is further analyzed and discussed in this section along with the weight data.

HGIU + HGIN Acute Database

In the HGIU + HGIN Acute Database, patients in the olanzapine treatment group had significantly greater weight gain and increase in BMI compared to the placebo group (see Table 7.1.4.4.1).

Table 7.1.4.4.1 Weight and BMI Data (LOCF): HGIN + HGIU Database

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	177	66.03	17.93	3.90	2.72	3.68		
	Placebo	88	67.63	17.24	0.24	2.16	0.01	3.66	< 0.001
BMI	Olanzapine	177	23.91	6.01	1.22	1.01	1.11		

	Placebo	88	23.98	5.67	0.05	0.91	-0.07	1.17	< 0.001

From Table 2.7.4.43 in summary-clin-safety document

The visit wise weight change for observed cases was similar to the LOCF analysis. The mean change at visit 6 was + 3.63 kg for olanzapine (n = 154) and + 0.08 kg for placebo (n = 67) (LS Mean Diff = 3.57, p < 0.001).

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Seventy-seven (43.5%) patients in the olanzapine group and 6 (6.8%) of patients in the placebo group had a ≥ 7% increase in body weight (p < 0.001). Only 2 patients, both randomized to placebo, had a ≥ 7% decrease in body weight.

Since studies HGIN and HGIU were different with respect to types of patients and duration of the double-blind period (HGIN 6 weeks, HGIU 3 weeks), the weight and BMI data were also evaluated separately:

Table 7.1.4.4.2. Weight and BMI Data: Study HGIU

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	105	65.33	20.55	3.66	2.18	3.51		
	Placebo	54	66.83	17.55	0.30	1.67	0.16	3.36	< 0.001
BMI	Olanzapine	105	24.21	6.82	1.18	0.85	1.15		
	Placebo	54	24.05	5.44	0.02	0.62	0.00	1.15	< 0.001

From Table HGIU.12.44 in study report

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Forty-four (41.9%) patients in the olanzapine group and 1 (1.9%) patient in the placebo group had a ≥ 7% increase in body weight (p < 0.001). No patients in the study had a ≥ 7% decrease in body weight.

Table 7.1.4.4.3. Weight and BMI Data: Study HGIN

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	72	67.04	13.31	4.26	3.33	4.22		
	Placebo	34	68.91	16.93	0.13	2.80	0.08	4.13	< 0.001
BMI	Olanzapine	72	23.45	4.59	1.39	1.21	1.37		
	Placebo	34	24.02	6.12	-0.05	1.03	-0.07	1.44	< 0.001

From Table HGIN.12.42 in study report

The results for the OC analysis for change in weight and BMI were similar to the LOCF analysis. At end of study, patients in the olanzapine group (n = 50) gained 4.95 kg from baseline and patients in the placebo group (n = 15) gained 0.61 kg [LS mean diff = 4.65, p < 0.001]. BMI

increased by 1.56 in the olanzapine group and decreased by 0.04 in the placebo group [LS mean diff = 1.62, p < 0.001].

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Thirty-three (45%) patients in the olanzapine group and 5 (14.7%) of patients in the placebo group had a ≥ 7% increase in body weight (p = 0.002). Only 2 patients in the study, both randomized to placebo, had a ≥ 7% decrease in body weight.

Only 1 of the 8 discontinuations due to adverse events was due to weight gain in the HGIU + HGIN Acute Database (4.5 kg increase over ~15 days).
Unfortunately, insufficient data were collected during the follow-up visits to adequately address weight loss after patients completed the clinical trial (if they switched to a different antipsychotic). Though many of the investigators noted that the adverse event of "weight gain" had resolved at some of the follow-up visits, no actual weights were obtained for the majority of patients (or at least not recorded in the CRFs).

Overall Combined Database
Though no placebo comparison is available in this database, weight change over longer duration of time could be evaluated in general terms. Similar to the acute data, weight did appear to increase over time. This patient population (adolescents) are expected to increase in height and weight during this developmental period, however, the increases in weight are well above what would be considered expected (see Section 7.1.9 - Assessment of Effect on Growth).

Table 7.1.4.4.4. Weight and BMI Data (LOCF): Overall Combined Database

			Baseline		Change to Endpoint		
		N	Mean	Std	Mean	Std	P-value
Weight (kg)	Bipolar	224	68.58	21.21	7.63	6.62	< 0.001
	Schizophrenia	226	65.71	13.30	7.07	6.53	< 0.001
	Overall	450	67.13	17.72	7.35	6.58	< 0.001
BMI	Bipolar	216	24.92	7.34	2.37	2.39	< 0.001
	Schizophrenia	223	22.40	4.17	2.24	2.25	< 0.001
	Overall	439	23.64	6.07	2.31	2.31	< 0.001

From Table 2.7.4.45 in summary-clin-safety document

Sixty-five percent of patients in the Overall Combined Database gained ≥ 7% body weight.

The Sponsor provided a summary of weight change by visit for observed cases for the Overall Combined Database (see Appendix 10.7). For the 131 patients who completed visits > 25 and ≤ 32 weeks, the mean increase in weight was 10.8 kg (p < 0.001 compared to baseline).

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months. The patient who gained 21.8 kg did so over a period of 3 months.

For those patients in the Overall Combined Database who participated in HGIU or HGIN, the weight gain for the acute phase of these trials was also evaluated to determine whether they gained a greater amount of weight early in the trial. These data were readily available for only 10 patients (some of the patients had been randomized to placebo and are not included here). The mean weight gain at the end of the double-blind phase of the study (or early termination) was 4.8 ± 2.6 kg, similar to the overall mean weight gain of 3.9 ± 2.7 kg in the acute database (see Table 7.1.4.4.1).

Weight – Subgroup Analyses
Because of the different duration of dosing in the HGIN and HGIU acute phases, these data were reviewed separately for each study.
The Sponsor evaluated weight changes for the subgroups gender and age (< 15, ≥ 15 years) for the adverse event "weight increased". Approximately 30% of females and males had this adverse event in the olanzapine group in both HGIU and HGIN acute studies while this adverse event was ~4% for the placebo group (with the exception of females in HGIN). No significant differences were noted between the gender subgroups (see Appendix 10.7). For the age subgroups, 28-40% had the adverse event "weight increased" in the olanzapine group compared to 0 – 14% in the placebo group. No significant differences were noted between the age subgroups (see Appendix 10.7).

Mean change in weight (kg) was also evaluated between the subgroups gender and age. These data were not included in the study report for HGIU, the Sponsor has been asked to submit these data (per the study report, only those data where results were significant were included). Data from HGIN are included in Appendix 10.7. Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine.
The Sponsor also did not include mean change in weight for the age subgroup for the HGIN + HGIU Acute Database (per the study reports, only those data where results were significant were included). The Sponsor has been asked to provide these data. In the HGIN + HGIU Acute Database, significant treatment-by-gender differences were noted (see Table 7.1.4.4.5). However, these findings are likely due to the differences in the placebo group since the weight gain (mean change to endpoint) in the olanzapine group was similar between females and males.

Table 7.1.4.4.5 Sponsor's Table. Mean Change in Weight (kg) – Gender Subgroup Analysis: HGIU + HGIN Acute Database

By Subgroup: Gender

Vital Signs	Subgroup	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean	LSMean Diff.	*P-value	**P-value
Weight in Kg	Female	106	olz	66	61.79	16.68	3.66	2.65	3.63	3.05	<.001	.083
			Placebo	40	62.83	13.65	0.55	2.27	0.59			
	Male	159	olz	111	68.54	18.25	4.05	2.76	3.79	4.16	<.001	
			Placebo	48	71.64	18.97	-0.03	2.05	-0.36			

Table 2.7.4.70 in Summary-clin-safety

The Sponsor was asked to evaluate the relationship of weight gain to baseline BMI. The Sponsor evaluated 4 BMI subgroups: < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30. There was a similar magnitude of weight gain by patients in each of these categories (Table 7.1.4.4.6). The percentage of patients who had a ≥ 7% weight gain was greatest in the < 18 BMI group and least in the ≥ 30 BMI group (Table 7.1.4.4.7).

Table 7.1.4.4.6 Sponsor's Table. Mean Change in Weight by Baseline BMI: HGIN + HGIU Acute Database

Table 1. Mean Change in Weight (kg) from Baseline to Endpoint (LOCF) by Baseline BMI Acute Placebo-Controlled Combined Database

			Baseline		Change to Endpoint				
BMI(Baseline)	Therapy	N	Mean	Std	Mean	Std	LSMean Change	LSMean Difference	*P-value
BMI<18	Olz	15	45.68	5.62	4.21	2.29	4.39	3.51	.005
	Placebo	10	48.19	6.54	0.70	2.89	0.88		
18<=BMI<25	Olz	107	58.84	9.37	3.52	2.53	3.24	3.12	<.001
	Placebo	49	61.18	8.41	0.50	2.16	0.12		
25<=BMI<30	Olz	30	76.31	10.29	4.44	3.61	4.25	3.93	<.001
	Placebo	19	77.50	9.32	-0.09	1.41	0.32		
BMI>=30	Olz	25	96.66	15.02	4.71	2.33	3.93	5.59	<.001
	Placebo	10	99.93	16.42	-0.90	2.37	-1.66		

Table 7.1.4.4.7 Sponsor's Table. PCS Weight Changes by Baseline BMI: HGIN + HGIU Acute Database

Table 2. Potentially Clinically Significant Weight Changes (7% Weight Gain) By Baseline BMI Acute Placebo-Controlled Combined Database

Vital Signs	BMI(Baseline)	Direction	Therapy	N	n	%	*P-value
Weight in kg	BMI<18	Gain	Olz	15	12	80.0%	.005
			Placebo	10	2	20.0%	
	18<=BMI<25	Gain	Olz	107	49	45.8%	<.001
			Placebo	49	4	8.2%	
	25<=BMI<30	Gain	Olz	30	12	40.0%	.001
			Placebo	19	0	0.0%	
	BMI>=30	Gain	Olz	25	4	16.0%	.303
			Placebo	10	0	0.0%	

The Sponsor was also asked to provide data regarding the numbers of patients at baseline and endpoint who were obese (BMI > 30) and whether there were differences between the treatment groups. At baseline, 14% (25/177) of patients in the olanzapine group and 11.4% (10/88) patients in the placebo group had BMI > 30. At endpoint, 18.6% of patients in the olanzapine group and 11.4% of patients in the placebo group had BMI > 30 (p = 0.158, NS).

The Sponsor was also asked to provide an analysis of laboratory parameters for patients who gained > 3.9 kg (mean weight gain). The major differences between olanzapine and placebo in this subgroup are noted in Table in Appendix 10.7. The LS mean change appears to be fairly similar between this subgroup and the entire study population except for a larger increase in CPK (LS mean diff 39 vs. 16 U/L) and triglycerides (LS mean diff 54 vs. 34 mg/dL) in the subgroup with > 3.9 kg weight gain. Of course, the entire population includes this subgroup – the Sponsor was not asked to provide laboratory data for patients with ≤ 3.9 kg weight gain.

7.1.5 Less Common Adverse Events

Hyperprolactinemia
The summary of the prolactin laboratory data is included in Sections 7.1.6 (Laboratory Findings) and 7.1.6.3 (Special Assessments). The adverse event tables were reviewed for any terms that might be related to hyperprolactinemia. In the HGIU + HGIN Acute Database, gynecomastia occurred in 1 (0.9%) patient in the olanzapine group and no patients in the placebo group and amenorrhea occurred in no patients in the olanzapine group and 1 (2.4%) patient in the placebo group.

The Overall Combined Database was evaluated since adverse events such as gynecomastia are not expected to occur with acute use but rather more long term use of antipsychotics. In the Overall Combined Database, gynecomastia occurred in 7 (4.3%) of patients (all from schizophrenia trials), galactorrhea occurred in 2 (3.1%) patients with schizophrenia and 1 (1%) patient with bipolar disorder and amenorrhea occurred in 1 (1.5%) patient with schizophrenia and 1 (1%) patient with bipolar disorder. The Sponsor has been asked to provide narrative summaries for all cases of gynecomastia – it is unknown whether this adverse event occurred in both male and female patients. If cases of gynecomastia occurred exclusively in female patients, it would be important to differentiate this adverse event from usual adolescent female physical development. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Extrapyramidal Symptoms
Due to the difference in frequency of EPS occurring in patients with schizophrenia and bipolar disorder taking antipsychotics, these data are summarized separately for each diagnostic group from the individual study reports (HGIN and HGIU).

Data for EPS is from a number of sources including rating scales (primarily the BAS and SAS), use of anticholinergic medications (though benzodiazepines may be used to treat EPS, they are more commonly used for managing psychiatric symptoms) and adverse events.

<u>HGIN</u>
Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.1. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown). In both the olanzapine and placebo groups, the mean change to endpoint was a decrease in rating scale score. This is not necessarily surprising depending on which

antipsychotics patients may have been taking during screening and the length of the washout period prior to obtaining the baseline rating.

Table 7.1.5.1. Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIN

EPS Variables	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
AIMS Non-Global Total(1-7)	Olanzapine	72	0.38	0.94	-0.18	0.84	-0.18	0.02	.897
	Placebo	35	0.54	1.50	-0.20	0.72	-0.21		
BRNS 4:Global Assessment of Akathisia	Olanzapine	72	0.31	0.66	-0.15	0.69	-0.15	0.05	.747
	Placebo	35	0.31	0.63	-0.20	0.76	-0.20		
Simpson-Angus Total(1-10)	Olanzapine	72	0.81	1.87	-0.22	1.51	-0.24	0.33	.260
	Placebo	35	0.97	2.41	-0.54	1.34	-0.57		

The Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined. The Sponsor has been asked to provide an analysis for the individual items of these scales.

Only 5 patients in study HGIN (acute phase) had concomitant anticholinergic medication use: 4.2% (3/72) in the olanzapine group and 5.7% (2/35) in the placebo group (p = 0.661).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.2. Adverse Events Potentially Related to EPS: HGIN

	Olanzapine N = 72	Placebo N = 35
Akathisia	2 (2.8%)	2 (5.7%)
Drooling	2 (2.8%)	0
Restlessness	2 (2.8%)	0
Dyskinesia	1 (1.4%)	0
Muscle twitching	1 (1.4%)	0
Musculoskeletal stiffness	1 (1.4%)	0
Cogwheel rigidity	0	1 (2.9%)
Tremor	0	1 (2.9%)

From Sponsor Table HGINB.14.27 in study report

Open-Label Phase HGIN

Noteworthy EPS-related adverse events occurring in the open-label phase of HGIN included oculogyration (n = 1, 0.4%) and opisthotonus (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for these events.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIN. The mean change to endpoint on the AIMS was -0.12 ± 0.94. The incidence of "treatment emergent" dyskinesia was 2.6% - again, it is

unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

HGIU

Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.3. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown) – though the mean baseline scores were numerically higher in the olanzapine group.

Table 7.1.5.3 Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIU

EPS Variables	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
AIMS Non-Global Total(1-7)	Olanzapine	105	0.16	0.90	-0.10	0.71	-0.12	-0.10	.289
	Placebo	54	0.04	0.19	0.00	0.19	-0.02		
BRNS 4:Global Assessment of Akathisia	Olanzapine	105	0.20	0.49	-0.04	0.44	-0.06	-0.09	.264
	Placebo	54	0.09	0.35	0.06	0.60	0.03		
Simpson-Angus Total(1-10)	Olanzapine	105	0.24	0.89	0.02	0.93	0.02	0.04	.769
	Placebo	54	0.07	0.33	-0.02	0.14	-0.02		

As with study HGIN, the Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined.

Only 5 patients in study HGIU (acute phase) had concomitant anticholinergic medication use, all in the olanzapine group: 4.7% (5/107) in the olanzapine group and 0% (0/54) in the placebo group (p = 0.169).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.3. Adverse Events Potentially Related to EPS: HGIU

	Olanzapine N = 107	Placebo N = 54
Restlessness	4 (3.7%)	2 (3.7%)
Musculoskeletal stiffness	3 (2.8%)	0
Tremor	2 (1.9%)	0
Akathisia	1 (0.9%)	0
Drooling	1 (0.9%)	0
Dysarthria	1 (0.9%)	0
Dyskinesia	1 (0.9%)	0
Muscle tightness	1 (0.9%)	0
Muscle twitching	1 (0.9%)	0
Salivary hypersecretion	1 (0.9%)	0

From Sponsor's table HGIU.14.30 in study report

Open-Label Phase HGIU
Noteworthy EPS-related adverse events occurring in the open-label phase of HGIU included oculogyration (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for this event.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIU. The mean change to endpoint on the AIMS was -0.03 ± 0.30. The incidence of "treatment emergent" dyskinesia was 0.7% - again, it is unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

Suicidality

The Sponsor included an analysis of suicide-related events, specifically the incidence of possible suicidal behavior or ideation, in the HGIN + HGIU Acute Database. These data were summarized for the Overall Combined Database. The following suicide-related categories were included: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, self-injurious behavior (intent unknown), not enough information (fatal), not enough information (non-fatal).

The analysis for events included categorizing suicidal behaviors as follows: suicidal behavior or ideation (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation), suicidal behavior (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior), suicidal ideation (includes suicidal ideation) and possible suicidal behavior or ideation (includes all categories). The searches included the subsequent visit (if available) after stopping treatment.

To identify cases, all preferred AE term, verbatim AE terms and comments of clinical trial data were searched for the following: accident, attempt, burn, cut, drown, gas, gun, hang, hung, immolat, injur, jump, monoxide, mutilat, overdos, self-damag, self-harm, self-inflict, self-damage, self harm, shoot, slash, suic, poison, asphyxiation, suffocation, firearm. All blinded patient listings were independently reviewed by two members of the Sponsor's medical staff "trained to evaluate suicide-related events". If a discrepancy arose, the case was discussed between them and, if necessary, a third reviewer was consulted to achieve consensus.

HGIN + HGIU Acute Database
Three possible suicidal behaviors or ideation events were identified, all three occurred in study HGIU. Two events occurred in patients treated with olanzapine (self-injurious behavior [intent unknown] in a 14.2 YOWF, suicidal ideation in a 14.6 YOWF) and one occurred in a patient receiving placebo (self-injurious behavior [intent unknown] in a 13.9 YOWM). The Sponsor's brief description of the event (from the case narratives) are provided in Appendix 10.8. No statistical differences were noted between treatment groups. The risk ratio was calculated as 1.01 (95% CI [0.09, 10.88], p = 1.000). Additional analyses (Mantel-Haenszel risk diff) also did not show statistical differences between the olanzapine and placebo groups (data not shown).

Overall Combined Database
Twenty-four cases of possible suicidal behaviors or ideation were identified – two of these events occurred in olanzapine-treated patients during the acute phase of study HGIU. The events were as follows: completed suicide (n = 0), suicide attempt (n = 2), preparatory acts toward imminent suicidal behavior (n = 2), suicidal ideation (n = 13), self-injurious behavior (intent unknown) (n = 6), not enough information (fatal) (n = 0), not enough information (non-fatal) (n = 1). The number of days to the event ranged from 4 to 214 (mean/SD = 73.5 ± 57.4 days, median = 57 days). The cases occurred in the following trials: HGIN (4), HGIU (13), HGMF (2), LOAY (5).

It is more difficult to ascertain whether a medication is associated with this adverse event in this database due to lack of a comparison group as well as the presence of a psychiatric disorder that can be associated with suicidal behaviors (esp. bipolar disorder). Of the 24 cases of suicide-related behaviors, 15 (62%) occurred in bipolar patients.

This reviewer also evaluated the individual item "suicidal ideation" in the Children's Depression Rating Scale-Revised. Though rating scales may not capture this specific adverse event, these data were reviewed to see if any trends in worsening occurred on the suicide-related item. For the CDRS[2], most patients scored a "1" at baseline. For patients who scored > 1, most showed improvement (decrease in score). Two patients in the placebo group had worsening on this item; one patient had an increase from a 1 to a 3 and another from a 2 to a 3 severity rating. Two patients in the olanzapine group had worsening on this item; one patient had an increase from a 2 to a 3 and another from a 2 to a 4 severity rating. Of note, 3 patients had a severity rating of 7 at baseline (all were randomized to olanzapine). The Sponsor will be asked to provide details regarding inclusion of these patients in the clinical trial.

Hostility and Aggression Adverse Events
Similar to the strategy used to identify possible suicide-related behaviors, the Sponsor identified patient cases for hostility and aggression. The following categories were used for these cases: aggressive behavior with physical harm directed toward another person, aggressive behavior with physical harm directed toward animals, aggressive behavior with physical harm directed toward objects, aggressive behavior with nonspecific information, aggressive behavior with indirect or no potential for direct physical harm, hostility without aggression, anger without hostility or aggressive behavior, violent ideation with no anger, hostility or aggressive behavior, and does not meet case definition.

In the HGIN + HGIU Acute Database, 7 cases were identified (1 case in HGIN, 6 cases in HGIU). Four cases occurred in patients in the olanzapine treatment groups. The olanzapine

2 CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does ont understand the concept of suicide), usually when angry; 4 = intermediate rating, not anchored; 5 = has recurrent thoughts of suicide; 6 = intermediate rating, not anchored; 7 = has made a suicide attempt within the last month or is actively suicidal

cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, hostility without aggression and anger without hostility or aggressive behavior. The placebo cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, and hostility without aggression. Given the patient population, it is surprising that not more cases of hostility or aggression were identified. However, overtly hostile patients or patients with a strong history of hostility or aggression would be less likely to be enrolled in a clinical trial. No statistical differences were noted between treatment groups (data not shown).

In the Overall Combined Database, 23 cases of possible hostility or aggression-related events were identified: HGIN (5), HGIU (13), HGMF (1), LOAY (4). It is not unexpected for hostility or aggressive behaviors to be exhibited by patients with inadequately controlled symptoms of schizophrenia or bipolar disorder.

7.1.6 Laboratory Findings

The data from the HGIN + HGIU Acute Database was the primary source of data reviewed. When individual patient labs were being reviewed, it was noticed that many labs were missing from the study reports – most commonly the last (third) page of labs for many patients. Though all of the lab data appeared to be present in the JMP datasets, it was sometimes more difficult to look for trends or other signals using the dataset than the individual lab profile.

7.1.6.1 Overview of laboratory testing in the development program

During the acute 3 week trial labs were obtained as follows:
Clinical chemistry, electrolytes – baseline and weekly during trial
Lipids - baseline and weekly during trial; fasting glucose/lipids were obtained at baseline and end of study
Hematology - baseline and weekly during trial
Urinalysis – baseline and end of study
TSH – screening only
Prolactin – baseline and end of study
HbA1c – screening and end of study <u>for patients with known diabetes</u>
Hepatitis screen, urine drug screen, pregnancy test – screening only

7.1.6.2 Standard analyses and explorations of laboratory data

7.1.6.2.1 Analyses focused on measures of central tendency

The mean change from baseline to endpoint for the laboratory evaluations for HGIN + HGIU Acute Database is included in Appendix 10.9. Statistically significant decreases in lab parameters in the olanzapine group compared to placebo included hematocrit, hemoglobin, erythrocyte count, basophils, mean cell volume, albumin, total bilirubin and direct bilirubin – though these mean changes were small. Statistically significant increases in lab parameters in

the olanzapine group compared to placebo included ALT, AST, GGT, fasting glucose, cholesterol, LDL cholesterol, triglycerides, uric acid, prolactin, eosinophils and urea nitrogen.

The mean change from baseline to endpoint for selected laboratory parameters is in Table 7.1.6.2.1.1 below. For ALT and AST, the standard deviation at *baseline* in these laboratory parameters for the olanzapine group was very large (SD > mean) compared to the SD at baseline in the placebo group. For change to endpoint, the SD is still quite large in the olanzapine group compared to the placebo group indicating considerable variability and some significant increases in these parameters. The fasting glucose, triglyceride and cholesterol data were converted from SI units to the more conventional mg/dL units in this table.

It should be noted that there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. Elevated baseline prolactin was more common in study HGIN, as would be expected. A cursory review of the JMP dataset found that approximately 17% of patients in HGIN had a baseline prolactin > 30 ng/ml (maximum baseline prolactin = 65 ng/ml). The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range. Of note, the Sponsor did acknowledge this limitation and provided some additional analyses (see Section 7.1.2.3 – Special assessments).

Table 7.1.6.2.1.1. Select Laboratory Analytes of Interest: HGIN + HGIU Acute Database

			Baseline		**Change to Endpoint**				
		N	Mean	Std	**Mean**	Std	LS Mean Change	LS Mean Difference	P-value
Alkaline Phosp (U/L)	Olanzapine	175	152.3	82.3	**-1.3**	25.6	-2.7		
	Placebo	87	138.7	86.9	**-4.0**	16.6	-5.3	2.6	0.396
ALT (U/L)	Olanzapine	175	24.1	45.9	**19.95**	54.84	28.11		
	Placebo	87	20.4	13.0	**-3.08**	11.69	5.13	22.98	< 0.001
AST (U/L)	Olanzapine	175	24.5	29.9	**6.43**	26.41	9.89		
	Placebo	87	23.6	8.5	**-2.47**	7.51	0.98	8.91	0.002
GGT (U/L)	Olanzapine	175	19.0	12.3	**7.47**	20.02	7.73		
	Placebo	87	17.7	8.5	**-0.43**	5.96	-0.16	7.89	< 0.001
Glucose, fasting (mg/dL)*	Olanzapine	135	88.1	9.91	**2.70**	10.4	2.70		
	Placebo	64	89.7	10.27	**-2.88**	10.1	-3.06	5.59	< 0.001
Cholesterol (mg/dL)*	Olanzapine	175	161.0	32.0	**13.1**	22.78	12.74		
	Placebo	87	160.2	32.8	**-1.16**	24.32	-1.54	14.29	< 0.001
Triglycerides (mg/dL)*	Olanzapine	175	104.4	58.4	**29.2**	80.53	26.55		
	Placebo	87	110.6	64.6	**-4.42**	54.87	-6.19	33.63	< 0.001
Prolactin (mcg/L)	Olanzapine	163	14.06	9.92	**11.44**	14.52	10.51		
	Placebo	80	14.95	11.86	**-0.16**	10.69	-1.15	11.66	< 0.001

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113

Since urinalysis for ketones, glucose and protein is noted as 1+, 2+ etc., no mean change from baseline was provided for these parameters. It was noted, however, that there were no patients with PCS changes in these parameters (defined as increase $\geq$ 2) in either the olanzapine or placebo groups. Only 1 patient exhibited a PCS change in urinalysis – protein in the Overall Combined Database.

In the HGIN + HGIU Acute Database, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes). There was no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

7.1.6.2.2 Analyses focused on outliers or shifts from normal to abnormal

Percentage of patients with statistically significant treatment-emergent abnormal high laboratory values at any time (HGIN + HGIU Acute Database).
AST –27.6% of olanzapine and 3.8% of placebo-treated patients ($p < 0.001$)
ALT - 38.6% of olanzapine and 2.5% of placebo-treated patients ($p < 0.001$)
GGT – 10.1% of olanzapine and 1.2% of placebo-treated patients ($p = 0.008$)
Total bilirubin –0% of olanzapine and 7.1% of placebo-treated patients ($p = 0.001$)
Albumin –6.3% of olanzapine and 23.2% of placebo-treated patients ($p = 0.002$)
Fasting glucose – 3.7% of olanzapine and 3.2% of placebo-treated patients (p = NS)
Cholesterol –19.7% of olanzapine and 3.9% of placebo-treated patients ($p = 0.001$)
Triglycerides –54.7% of olanzapine and 19.6% of placebo-treated patients ($p < 0.001$)
HDL –9.7% of olanzapine and 1.2% of placebo-treated patients ($p = 0.014$) [shift to low were NS between groups]
Further analyses for shifts in fasting glucose, cholesterol, and triglycerides is included in Section 7.1.2.3 – Special Assessments.

7.1.6.2.3 Marked outliers and dropouts for laboratory abnormalities

In the HGIN + HGIU Acute Database, six patients discontinued due to elevations in ALT and/or AST. See Table 7.1.3.1.1 in Section 7.1.3.1 (Adverse events associated with dropouts).

The Sponsor did not provide a summary of marked outliers in the laboratory analysis. The individual patient labs and/or JMP datasets were reviewed from HGIN and HGIU study reports to identify marked outliers. It should be noted that the marked outliers in Table 7.1.6.2.3.1. may include lab values that were less than the potentially clinically significant (PCS) abnormalities defined by the Sponsor. For example, the cholesterol PCS was defined as > 15.516 mmol/L (> 599 mg/dL), whereas the values noted as marked outliers were usually lower than this PCS value. Of note, there was no defined PCS for triglycerides.

Table 7.1.6.2.3.1 includes the marked outlier (in bold font), other related analytes at the same timepoint, end of acute study value for the marked outlier (resolution?) and a column for comments which included any additional values for the marked outlier in the open-label phase.

Individual patient profiles were not readily available so it is not known if resolutions in marked outlier values were related to decreases in olanzapine dose.

Table 7.1.6.2.3.1. Marked Outliers for Laboratory Values – HGIN and HGIU

			Marked Outlier Related Analytes at Same Timepoint *(Italics = values > ULN)*			
Patient	Lab Analyte	Reference Range*	Baseline	Highest	End of Study	Comments
HGIU 005-501	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	102.6 125.9 68.7	**1237** (v.4) *220.8* NA	*389.4* *205.8* 90.0	TG = *160* at v.307 EOS
HGIU 012-1203	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	18 19 0.41 18	**325** (v.5) **148** 0.29 *53*	*230* (150 repeat) *92* (51 repeat) 0.29 (0.18 repeat) *48* (52 repeat)	ALT = *48*, AST = 24 at v. 501 (follow-up)
HGIU 012-1207	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	45 49 0.53 30	**147** (v.4) *60* 0.41 **163**	**147** 60 0.41 **163**	None
HGIU 013-1303	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	110.6 178.8 123.9	**261.9** (v.5) 179.5 *95.7*	**261.9** 179.5 95.7	TG = 111 at v.306
HGIU 019-1901	Creatine Phosphokinase	0 – 169 U/L	83	**256** (v.5)	*256*	CK = 168 at v. 301 (repeat 72)
HGIU 020-2007	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	67.2 149.8 98.8	**536.3** (v.4) 165.6 NA	*365.5* *231.7* 120.8	*TG = 103 at v. 307*
HGIU 020-2011	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	22 19 0.41 11	**124** (v.6) *87* 0.29 27	**124** *87* 0.29 27	ALT = 11 at v. 309
HGIU 026-2607	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	59.3 201.5 125.9	**324.8** (v.4) 171.8 62.9	179.6 164.9 84.9	TG = 72 at v. 310
HGIU 027-2704	Creatine Phosphokinase	0 – 363 U/L	326	**619** (v.6)	**619**	CK = 261 at v. 307
HGIU 031-3103	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	16 19 1 13	**135** (v.4) 35 0.82 **153**	*75* *62* 0.53 *87*	ALT = 33/25 at v. 302
HGIU 035-3503	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	62.8 164.9 120.8	**317.7** (v.4) 167.6 74.9	100 203.9 *141.7*	None
HGIU 035-3518	Creatine Phosphokinase	0 – 187 U/L	55	**257** (v.6)	**257**	CK = 56 at v. 310
HGIU 036-3607	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	43 27 0.71 36	**208** (v.6) *91* 0.29 *65*	**208** *91* 0.29 *65*	ALT = *99* at v. 307
HGIU	Creatine					CK = 70 at v.

720-7202	Phosphokinase	0 – 363 U/L	71	**650** (v.5)	**650**	310
HGIU 720-7203	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	11 15 0.41 21	**128** (v.6) *58* 0.29 *98*	**128** *58* 0.29 *98*	ALT = 15 at v. 310
HGIU 720-7210	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	108.8 172.6 109.6	**382.3** (v.4) 195.7 88.0	*171.7* 199.6 127.8	TG = *148* at v. 310
HGIU 720-7214	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	38 31 0.71 20	**448** (v.6) **164** 0.41 46	**448** **164** 0.41 46	ALT = *69* at v. 302
HGIU 720-7217	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	20 32 0.88 21	**125** (v.6) *103* 0.53 35	**125** *103* 0.53 35	ALT = *58* at v. 308
HGIU 720-7221	Glucose, fasting	70 – 115 mg/dL	86.5	**145.9 (v.4)**	72	Glucose = 77 at v. 306
HGIU 730-7302	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	22 29 0.29 13	**123** (v.5) *77* 0.18 27	41 28 0.18 22	ALT = 16 at v. 310
HGIN 003-302	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	19 17 0.29 10	**132** (v.9) 38 0.29 18	**132** 38 0.29 18	ALT = 27 at v. 305
HGIN 004-401	ALT AST TBili GGT	6 – 43 U/L 10 - 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	18 19 0.18 19	*39* **157** (v.4) 0.18 18	19 25 0.41 17	AST = 22 at v. 309
	Creatine Phosphokinase	0 – 363 U/L	289	**7289** (v.4)	*610*	CPK = *781* at v. 309 (was *1766* at v. 306)
HGIN 006-602	ALT AST TBili GGT	6 – 43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	22 27 0.88 44	**240** (v.8) **141** 0.29 **206**	*134* *60* 0.53 *216*	ALT = 32 AST = *49* GGT = 38 at v. 308
	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	136.3 171.8 96.9	**532.7** (v.7) *210.8* NA	*207.1* 185.7 102.7	TG = 93 at v. 308
HGIN 007-703	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	29 33 0.41 11	**231** (v.6) **142** 0.41 *34*	*199* *101* 0.29 *34*	ALT = *66*, AST = 33 at v. 501 (follow-up)
HGIN 007-705	Creatine Phosphokinase	0 – 408 U/L	115	**855** (v.8)	189	CK = 141 at v. 305
HGIN 016-1601	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	23 26 *1.41* 22	**159** (v.6) *67* 1.23 *64*	36 32 1.11 36	ALT = 43 at v. 309
HGIN 017-1703	ALT AST	6 – 43 U/L 10 – 40 U/L	*60* 40	**210** (v.5) *96*	*79* *50*	ALT = 15 at v. 309

	TBili GGT	0.18 – 1.23 mg/dL 0 – 33 U/L	0.18 23	0.18 29	0.29 18	
HGIN 020-2004	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	21 21 0.29 29	**163** (v.5) *87* 0.29 *81*	18 22 0.18 *43*	ALT = 9 at v. 309
HGIN 021-2102	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	8 19 0.29 12	**105** (v.9) *90* 0.41 23	**105** *90* 0.41 23	ALT = 13 at v. 307
	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	84.9 201.5 102.7	111.5 **289.6** (v.6) *165.6*	109.7 *237.4* 132.8	TG = *293* Chol = *240* at v. 307
HGIN 021-2103	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	16 20 0.41 18	**396** (v.7) **136** 0.41 *63*	**396** **136** 0.41 *63*	ALT = *154*, AST = 36 at v. 502 (follow-up)
HGIN 030-3002	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	11 19 0.71 23	**175** (v.7) *69* 0.29 *72*	*61* *60* 0.29 48	ALT = 39 at v. 309
HGIN 033-3301	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	87.6 *214.7* *139.8*	**426.5** (v.9) *214.7* *149.8*	**426.5** *214.7* *149.8*	None
HGIN 900-9003	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	85.8 118.1 82.6	**270.8** (v.8) 167.2 84.5	*195.6* 147.1 79.5	TG = 143 at v. 307
HGIN 900-9006	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	*231* 194.5 107.3	**363.7** (v.7) *241.3* 130.9	*170.8* *228.2* *147.9*	AST = 23 at v.309
HGIN 900-9010	ALT AST TBili GGT	6 – 43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	20 26 0.41 20	*68* **161** (v.8) 0.47 20	35 31 0.65 15	AST = 31/29 at v. 309
HGIN 910-9101	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	*65* 27 0.47 *36*	*51* 38 0.23 **95** (v.5)	16 24 0.18 26	GGT = *46* at v. 309
HGIN 910-9103	ALT AST TBili GGT	6 – 43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	29 30 0.35 22	**141** (v.6) *84* 0.76 29	36 38 0.53 20	ALT = 23 at v. 309
HGIN 910-9105	Glucose, Fasting	70 – 115 mg/dL	108	**127.9** (v.9)	*127.9*	Glucose, fasting = 92 at v. 309
HGIN 910-9107	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	132.7 190 128.2	**285.8** (v.4) *213.5* 118.9	*178.8* 197.7 127.0	TG = 107 at v. 309
HGIN 910-9108	ALT AST TBili GGT	6-43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	40 20 0.35 32	**117** (v.5) *52* 0.35 34	28 23 0.35 23	ALT = 28 at v. 309
HGIN	ALT	6-43 U/L	25	**321** (v.5)	*128*	ALT = 17,

910-9110	AST TBili GGT	10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	25 0.47 19	**190** 0.59 37	*53* 0.41 29	AST = 19 at v. 501 (follow-up)
HGIN 920-9202	ALT AST TBili GGT	6-43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	15 19 1 27	**393** (v.6) **177** 1 *78*	**393**(231 repeat) **177** (59 repeat) 1 (0.71 repeat) *78* (82 repeat)	ALT = 20 at v. 501 (follow-up), AST NA
HGIN 920-9207	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	123.9 *205.0* *135.1*	**336.3** (v.6) *233.2* 126.2	**336.3** *233.2* 126.2	None

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259, bilirubin = 17.1 (micromol/L to mg/dL)

Very few patients exhibited an increase in fasting glucose that might be considered a marked outlier in the HGIN + HGIU Acute Database. In reviewing the JMP dataset, 3 patients were noted with markedly elevated fasting glucose in the open-label phase of HGIN and HGIU:

Patient HGIN-900-9011 was randomized to placebo in the DB phase and had a baseline fasting glucose of 110 mg/dL. At visit 301, fasting glucose was 169 mg/dL on 7.5 mg olanzapine which normalized with continued dosing at 10 mg to 97 mg/dL at end of the study.

Patient HGIN 910-9108 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 95 mg/dL. At visit 7 of the acute phase, fasting glucose was 101 mg/dL, at visit 303 fasting glucose was 149 mg/dL on 20 mg olanzapine which normalized with continued dosing to 94 mg/dL at visit 309.

Patient HGIU 026-2602 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 104 mg/dL. At visit 6 of the acute phase, fasting glucose was 112 mg/dL, at visit 310 fasting glucose was 205 mg/dL on 12.5 mg olanzapine and at visit 501 (follow-up) fasting glucose was 113 mg/dL.

The Sponsor did not include prolactin in the list of analytes for definitions of potentially clinically significant changes. For purposes of this review, the laboratory data in the JMP database was reviewed and a PCS value of ≥ 40 ng/ml was arbitrarily chosen. Prolactin levels were obtained at screening, baseline, end of study in the double-blind acute phase of HGIN and HGIU and visit 305 (HGIN) and 307 (HGIU) (~8-10 weeks into OL) and end of OL phase.
The reference ranges used for prolactin were males 2.8 – 22 ng/ml and females 3.2 – 20 ng/ml. – per protocol amendment.
However, in the summary-clin-safe-app, the following Covance adolescent reference ranges were noted:

Gender	Age	Low (ug/L)	High (ug/L)
Male	12<=Age<14	2.84	24.0
	14<=Age<19	2.76	16.1
Female	12<=Age<14	2.52	16.9
	14<=Age<19	4.20	39.0

In the double-blind phase of HGIU, 13% (13/99) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 99/107 patients]. Only 3 of the 13 patients were male. The mean prolactin concentration at the end of study for this subgroup was 50.4 ± 8.3 ng/ml.

In the double-blind phase of HGIN, 17% (11/64) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 64/72 patients]. Only 4 of the 11 patients were male. The mean prolactin concentration at the end of study for this subgroup was 55.8 ± 15.8 ng/ml. One patient receiving placebo in the acute HGIN study had an increase from 18.2 ng/ml at baseline to 42.4 ng/ml at end of study. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

With the exception of one patient, it is not known whether these patients exhibited any clinical symptoms associated with hyperprolactinemia (narratives not available for these cases). Galactorrhea was not reported as an adverse event in the acute phases of HGIU or HGIN and one patient in the olanzapine group had the adverse event "gynecomastia" (see Section 7.1.4.3 Special Assessments). Patient HGIU 028-2804, who had an increase in prolactin concentration to 129.7 ng/ml, exhibited bilateral galactorrhea. Of note, one female patient in the LOAY study (data not included here) discontinued due to the adverse event galactorrhea – the narrative stated that her prolactin increased to 35 ng/ml. Therefore, clinical symptoms may have been associated with these prolactin elevations. It is possible that patients, especially adolescents, might be reluctant to report the types of adverse events associated with hyperprolactinemia.
Some patients who continued into the open-label phase had a decrease in their prolactin concentrations, others did not. Due to time constraints, this reviewer was unable to evaluate each case to determine whether decrease/resolution of hyperprolactinemia was related to a reduction in olanzapine dose.

Table 7.1.6.2.3.2. Prolactin Outliers: HGIN + HGIU Acute Database

		Prolactin (ng/ml)		
Patient	Age/Gender	Baseline	End of Double-Blind Phase	End of Open-Label Phase
HGIU 010-1005	14 YOM	23.4	60.7	17.6
HGIU 012-1216	16 YOM	18.9	51.1	51.6
HGIU 019-1901	16 YOF	9.2	43.8	35.0
HGIU 019-1905	14 YOF	18.8	44.5	32.6
HGIU 020-2007	14 YOF	16.5	57.6	14.5
HGIU 020-2011	13 YOF	8.1	57.5	10.9
HGIU 020-2020	16 YOF	12.7	44.4	40.3
HGIU 021-2103	17 YOF	20.6	45.1	13.5

HGIU 024-2403	15 YOF	31.1	49.8	31.5
HGIU 024-2405	13 YOM	15.2	40.3	24.3
HGIU 026-2602	13 YOF	20.2	50.3	49.5
HGIU 028-2803	15 YOF	31.6	68.1	11.7
HGIU 035-3517	13 YOF	13.8	42.3	17.4
HGIN 005-503	14 YOF	17.2	90.7	45.5
HGIN 013-1303	16 YOF	17.3	48.3	NA
HGIN 020-2003	17 YOF	26.3	79.9	NA
HGIN 021-2102	16 YOF	30.8	59.9	16.7
HGIN 026-2602	15 YOF	36	41.5	9.6
HGIN 026-2603	14 YOF	33	44.9	59.4
HGIN 030-3010	13 YOF	17.4	55	NA
HGIN 034-3401	16 YOM	22.7	43.8	30.4
HGIN 900-9006	17 YOM	28	55.5	40.1
HGIN 910-9107	16 YOM	45.8	48.2	43.2
HGIN 940-9408	15 YOM	12	45.8	21.7

Table 7.1.6.2.3.3. Prolactin Outliers: HGIN + HGIU Open Label Phase

Patient	Age/Gender	Treatment in DB Phase	Baseline	Visit #307(HGIU) #305 (HGIN)	End of Open-Label Phase Visit #310 (HGIU) Visit #309 (HGIN)
HGIU 007-704	15 YOM	Placebo	32.5	36.1	**47.3**
HGIU 019-1904	15 YOF	Placebo	5.5	28.5	**43.7**
HGIU 019-1907	15 YOF	Olanzapine	10.1	**40.6**	38.5 (v. 308)
HGIU 020-2003	13 YOF	Olanzapine	18.4	**41.8**	23.6
HGIU 021-2102	17 YOF	Olanzapine	25	**57.7**	10.6
HGIU 026-2608	13 YOF	Olanzapine	20.5	-	**57** (v. 304)
HGIU 028-2804	15 YOF	Placebo	11.8	**129.7** (v.302)	**49.8** (v. 307)

HGIU 035-3519	14 YOM	Olanzapine	28.3	-	**41.7** (v. 302)
HGIU 036-3606	16 YOF	Placebo	20.7	**59.5**	**44.0**
HGIN 900-9009	17 YOF	Olanzapine	17.5	17	**110**
HGIN 020-2005	14 YOM	Olanzapine	41.1	-	**64.7** (v. 305)

7.1.6.3 Special assessments

Hyperprolactinemia

A discussion of the adverse events potentially related to hyperprolactinemia are in Section 7.1.5 (Less Common Adverse Events). The mean change from baseline to endpoint in prolactin concentration is in Section 7.1.6.2.1 and marked outliers are in Section 7.1.6.2.3.
As was mentioned in Section 7.1.6.2.1, there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range (including treatment by gender and treatment by age analyses).

Elevations in prolactin due to antipsychotics occur more frequently in females compared to males. The Sponsor did include an analysis of these laboratory data by gender for the individual HGIU and HGIN studies. For each separate study, no significant treatment by gender interaction was found. However, there was a numerically greater mean change to endpoint in prolactin in females (16.2) compared to males (5.4) in study HGIN. Also, for the patients with an end of study prolactin > 40 ng/ml, the majority of these patients were female (see Section 7.1.6.2.3.). For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction (see Appendix 10.10), though there was a numerically greater mean change to endpoint in females (15.6) compared to males (8.8).

Table 7.1.6.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: Study HGIU

Laboratory Analyte	Gender	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean	LSMean Diff.	*P-value	**P-value
PROLACTIN	Female	70	Olanzapine	43	15.23	10.01	15.38	13.73	15.96	12.75	<.001	.590
			Placebo	27	14.99	8.00	2.67	8.60	3.21			
	Male	79	Olanzapine	56	11.36	5.46	11.50	9.50	11.91	10.83	<.001	
			Placebo	23	10.00	6.40	0.66	3.06	1.08			

Table HGIU.12.13 in study report

Table 7.1.6.3.2. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: Study HGIN

Laboratory Analyte	Gender	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean	LSMean Diff.	*P-value	**P-value
PROLACTIN	Female	30	olanzapine	20	17.24	10.31	16.17	22.59	14.25	17.99	.025	.258
			Placebo	10	15.95	6.67	-2.20	10.26	-3.73			
	Male	64	olanzapine	44	14.89	13.11	5.37	14.35	5.43	9.27	.028	
			Placebo	20	20.10	19.26	-3.91	16.86	-3.84			

This reviewer could not find an analysis of prolactin concentrations by the subgroup "age". The Sponsor will be asked to provide these data.

The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIU + HGIN Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$). No significant treatment-by-gender interactions were noted in this analysis, though a higher percentage of males (41/68, 60.3%) had a high prolactin concentration at any time compared to females (14/48, 29%).

The Sponsor did evaluate prolactin concentrations over time for the Overall Combined Database. In general, there is a decrease in mean prolactin concentration over the course of the 32 weeks which approaches baseline concentrations. There are still outliers in this analysis at the 19-32 week timepoint. The Sponsor will be asked to provide a similar summary for only those patients completing the 19-32 weeks.

Table 7.1.6.3.3. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database

Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points Overall Olanzapine Exposure Combined Database

Database	Olz Exposure	Summary N	Mean	Std	Median	Max
Bipolar	Baseline	217	15.35	12.58	11.28	110.30
	1-6 weeks	174	26.60	16.18	23.10	129.66
	7-18 weeks	122	19.24	11.89	16.71	59.49
	19-32 weeks	83	18.03	10.42	14.36	49.53
Schizophrenia	Baseline	214	18.84	19.97	11.87	131.57
	1-6 weeks	190	31.82	20.75	26.48	110.84
	7-18 weeks	88	22.75	16.24	18.62	112.00
	19-32 weeks	93	19.01	15.60	14.81	109.97
Overall	Baseline	431	17.08	16.74	11.60	131.57
	1-6 weeks	364	29.33	18.86	25.00	129.66
	7-18 weeks	210	20.71	13.95	17.13	112.00
	19-32 weeks	176	18.55	13.38	14.70	109.97

Metabolic Parameters
The Sponsor performed more detailed analyses on several adverse event profiles including "metabolic parameters".
The analyses included LOCF mean change from baseline to endpoint in fasting glucose and lipids; incidence of significant changes in fasting glucose and lipids, nonfasting glucose and lipids, weight gain-related adverse events, diabetes-related adverse events and dyslipidemia related adverse events; mean weight over time; correlations between mean changes in weight, glucose and lipids.

HGIN + HGIU Acute Database
LOCF mean change from baseline to endpoint:
There were statistically significant greater mean increases in fasting glucose levels (+ 2.7 mg/dL olanzapine vs. -2.9 mg/dL placebo, $p < 0.001$), total cholesterol (+ 12.7 mg/dL vs. +1.5 mg/dL, $p = 0.002$), and triglycerides (+27.4 mg/dL vs. -1.8 mg/dL, $p = 0.007$).

Significant changes in fasting glucose and lipids <u>at any time</u>:
There was a greater incidence of significant changes in patients treated with olanzapine than in patients treated with placebo for normal to borderline total cholesterol (15.7% vs. 3.6%, $p = 0.023$) and for normal to high fasting triglycerides (12.4% vs. 1.9%, $p = 0.039$).
The change from normal to borderline LDL cholesterol was approaching statistical significance (13.7% vs. 3.8%, $p = 0.064$).

The changes in fasting glucose were not statistically different:
Normal (< 100 mg/dL) to high ($\geq$ 126 mg/dL) = 0% (0/122) olanzapine, 2% (1/51) placebo
Impaired glucose tolerance ($\geq$ 100 mg/dL and < 126 mg/dL) to high ($\geq$ 126 mg/dL): 15.4% (2/13) olanzapine, 0% (0/13) placebo
Normal/impaired glucose tolerance (< 126 mg/dL) to high ($\geq$ 126 mg/dL): 1.5% (2/135) olanzapine, 1.6% (1/64) placebo.
The lack of a statistically significant difference in the change from impaired glucose tolerance to high fasting glucose levels (15.4% olanzapine vs. 0% placebo) is likely due to the low number of subjects enrolled with baseline impaired glucose tolerance (n = 13 each group).

Significant changes in fasting glucose and lipids <u>at endpoint</u>:
The only parameter that was statistically significant was normal to borderline cholesterol (14% olanzapine, 3.6% placebo, $p = 0.039$). The change from normal to high triglycerides was approaching statistical significance (10.6% olanzapine, 1.9% placebo, $p = 0.064$).

For the fasting glucose data, only 1 subject in the olanzapine treatment arm had a change from impaired glucose tolerance to high and 1 subject in the olanzapine treatment arm had a change from normal/impaired glucose tolerance to high.

In the Overall Combined Dataset, few patients had baseline impaired glucose (n = 47). Of those subjects, 6 (12.8%) had a shift from impaired glucose tolerance to high fasting glucose.
As mentioned in Section 7.1.6.2.1, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes) in the HGIN + HGIU Acute Database. There was

no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

The Sponsor provided correlation coefficients of change at endpoint between weight, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (it is unclear what correlation coefficient was used):
For the Overall Combined Dataset, there were statistically significant correlations between weight and total cholesterol (corr = 0.166, p = 0.005) and between weight and triglycerides (corr = 0.210, p < 0.001).
The Sponsor was asked to provide these correlations for the HGIN + HGIU Acute Database. In this database, there were statistically significant correlations between weight and total cholesterol (corr = 0.211, p = 0.003), between weight and triglycerides (corr = 0.223, p = 0.002) and between weight and fasting glucose (corr = 0.165, p = 0.021). Though these correlations are statistically significant, they are not particularly robust.

Hepatic-related Parameters
The Sponsor performed more detailed analyses on several adverse event profiles including "hepatic-related parameters".

For this analysis, a potentially clinically significant increase is defined as a change from a value less than or equal to the PCS high limit at all baseline visits to a value greater than the PCS high limit at endpoint or for two consecutive measures during therapy.

HGIN + HGIU Database
Mean change to endpoint in hepatic laboratory analytes in provided in Section 7.1.6 (Laboratory Findings).
The Sponsor analyzed treatment emergent high values at anytime (Table 7.1.6.3.4) and at endpoint (Table 7.1.6.3.5) for alkaline phosphatase, ALT, AST, GGT and total bilirubin. A higher percentage of patients in the olanzapine group had elevations in ALT, AST and GGT for both analyses.

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at Anytime: HGIN + HGIU Acute Database

Table APP.2.7.4.7.2.2. Hepatic Laboratory Analytes
Treatment-Emergent Abnormally High Values Anytime (>1 X ULN)
All Randomized Patients with Normal Baseline Values
Acute Placebo-Controlled Combined Database

Hepatic Analytes	Olanzapine N	Olanzapine n	Olanzapine %	Placebo N	Placebo n	Placebo %	p-value*
ALKPH	159	11	6.9%	77	2	2.6%	.231
ALT	153	59	38.6%	79	2	2.5%	<.001
AST	163	45	27.6%	79	3	3.8%	<.001
GGT	169	17	10.1%	83	1	1.2%	.008
T. Bili	170	0	0.0%	85	6	7.1%	.001

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at Endpoint: HGIN + HGIU Acute Database

Table APP.2.7.4.7.2.24. Hepatic Laboratory Analytes
Treatment-Emergent Abnormally High Values at Endpoint (>1 X ULN)
All Randomized Patients with Normal Baseline Values
Acute Placebo-Controlled Combined Database

Hepatic Analytes	Olanzapine N	Olanzapine n	Olanzapine %	Placebo N	Placebo n	Placebo %	p-value*
ALKPH	159	6	3.8%	77	1	1.3%	.432
ALT	153	32	20.9%	79	1	1.3%	<.001
AST	163	19	11.7%	79	1	1.3%	.005
GGT	169	14	8.3%	83	0	0.0%	.006
T. Bili	170	0	0.0%	85	5	5.9%	.004

Abnormal ALT values at anytime
> 3X ULN: olanzapine 11.1% (17/153) vs. placebo 1.3% (1/79) p = 0.008
> 5X ULN : olanzapine 3.9% (6/153) vs. placebo 0% p = 0.098
> 10X ULN : olanzapine 0.7% (1/153) vs. placebo 0% p = 1.00

> 3X ULN ALT anytime for patients with ALT baseline ≤ 3X ULN:olanzapine 12.1% (21/174) vs. 2.3% placebo (2/87) p = 0.009. [This analysis is the one that is included in proposed labeling for ALT elevations]

Only four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and two in the placebo group.

The Sponsor also used Hy's rule (ALT ≥ 3 times and TBili ≥ 1.5 times ULN) to identify any patients with potential severe hepatic injury. There were no patients who met Hy's rule criteria at any time in the clinical trials or at endpoint.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

Blood pressure and heart rate were taken at every visit during the acute study – supine for 5 minutes and after standing for 2 minutes
Weight and temperature were taken at every visit
Height was taken at screening, at multiple study visits and end of study.

7.1.7.2 Standard analyses and explorations of vital signs data

7.1.7.2.1 Analyses focused on measures of central tendencies

Mean change from baseline to endpoint (LOCF) for vital signs is included in Appendix 10.11. Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events). Statistically significant differences in mean change from baseline to endpoint between the olanzapine and placebo groups were noted for:
Supine SBP: olanzapine + 2.94 mmHg, placebo - 0.71 mm Hg ($p = 0.009$)
Standing DBP: olanzapine + 1.42 mmHg, placebo -1.28 mmHg ($p = 0.033$)
Supine pulse: olanzapine + 7.07 bpm, placebo - 0.60 bpm ($p < 0.001$)
Standing pulse: olanzapine +6.97 bpm, placebo - 0.89 bpm ($p < 0.001$)
Orthostatic SBP and pulse were not significantly different between olanzapine and placebo.
Weight: olanzapine +3.90 kg, placebo +0.24 kg ($p < 0.001$)
BMI: olanzapine + 1.22, placebo + 0.05 ($p < 0.001$)

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially clinically significant definitions for vital signs are in Appendix 10.12.
There were no statistically significant differences between olanzapine and placebo for percentages of patients with potentially clinically significant changes (high or low) with the exception of weight. Of note, 5.7% of olanzapine and 4.5% of placebo-treated patients exhibited orthostatic hypotension (p = NS).
The percentage of patients who gained ≥ 7% body weight was higher in the olanzapine group (43.5%) compared to the placebo group (6.8%) ($p < 0.001$). Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events).

7.1.7.2.3 Marked outliers and dropouts for vital sign abnormalities

Individual vital signs were reviewed from the JMP datasets. In general, few patients had markedly abnormal vital signs. Isolated systolic BP 150 – 155 mmHg was noted in both olanzapine and placebo groups, no diastolic BPs > 110 mmHg were noted and pulse rates > 130 bpm were noted in few patients but more olanzapine-treated patients than placebo-treated patients (highest pulse was 148 bpm in placebo patient).
Patient HGIU-035-3503 (16 YOBF) receiving olanzapine discontinued study HGIU due to an elevated pulse (standing pulse 140 bpm from baseline 96 bpm).

7.1.8 Electrocardiograms (ECGs)

7.1.8.1 Overview of ECG testing in the development program

The reviewer focused mainly on the two placebo-controlled acute trials, HGIN and HGIU, for evaluation of ECG data. Though the Sponsor states that differences from baseline were analyzed, it should be noted that ECGs were not obtained at baseline (visit 2), but were obtained during the screening period (visit 1):
"Twelve-lead ECGs were collected on each patient at baseline to determine the eligibility of the patient for entry into the study, and at the Final Visits of Study Period II and Study Period III to monitor the general safety of the patient during the course of the study".
Therefore, patients could be on other medications since this was the washout period prior to randomization.
Mean "baseline" ECG parameters appear fairly similar between the olanzapine and placebo groups such that any differences between the groups with regard to concomitant medications taken during screening might have been "equalized" by randomization.

7.1.8.2 Standard analyses and explorations of ECG data

7.1.8.2.1 Analyses focused on measures of central tendency

Statistically significant differences were found between olanzapine and placebo on all ECG parameters except QTcF (see Table 7.1.8.2.1.1). The most notable was the increase in heart rate in the olanzapine group (+6.3 bpm) compared to the placebo (-5.1 bpm) group ($p < 0.001$). Because of this effect on heart rate, the QTcB interval was also significantly longer in the olanzapine group compared to the placebo group.

Table 7.1.8.2.1.1. Sponsor's Table. ECG Intervals and Heart Rate: HGIN + HGIU Acute Database

ECG Intervals/ Heart Rate	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Heart Rate/Minute	Olz	158	72.291	13.183	6.266	14.039	4.335	11.624	<.001
	Placebo	80	72.788	12.553	-5.100	11.052	-7.289		
Intervals PR/Second	Olz	158	0.139	0.019	0.003	0.010	0.004	0.005	.003
	Placebo	78	0.146	0.031	-0.002	0.015	-0.001		
Intervals QRS/Second	Olz	158	0.088	0.011	-0.001	0.005	-0.001	-0.002	.039
	Placebo	80	0.087	0.010	0.001	0.006	0.001		
Intervals QT/Msec	Olz	158	380.532	30.825	-10.481	29.222	-7.948	-23.603	<.001
	Placebo	80	378.975	26.752	12.700	28.247	15.655		
Intervals QTc/Msec-Bazett formula	Olz	158	412.880	16.358	6.899	18.146	4.872	9.634	<.001
	Placebo	80	413.362	17.134	-2.475	16.543	-4.762		
Intervals QTc/Msec-Fridericia formula	Olz	158	401.763	15.537	0.743	15.165	0.404	-1.974	.345
	Placebo	80	401.596	14.722	2.732	15.219	2.378		

7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal

An analysis of the percent of patients with potentially clinically significant changes between the olanzapine and placebo groups is in Table 7.1.8.2.2.1. Though patients in the olanzapine group exhibited a mean increase in heart rate (see previous section), no PCS increases were noted for heart rate. Three patients had PCS increases in QTcB in the olanzapine group, no patients had PCS changes in QTcF. No patients had QTcB or QTcF increases $\geq$ 60 msec. No patients had QTcB or QTcF $\geq$ 500 msec.

Table 7.1.8.2.2.1. Sponsor's Table. ECG Intervals and Heart Rate – Potentially Clinically Significant Changes. HGIN + HGIU Acute Database.

ECG Intervals/ Heart Rate	Unit	Direction	Therapy	N	n	%	*P-value
Heart Rate <=40 bpm or >=120 bpm	bpm	High	Olz	158	0	0.0%	
			Placebo	80	0	0.0%	
		Low	Olz	158	0	0.0%	
			Placebo	80	0	0.0%	
Heart Rate < 50 bpm,Dec>=15 or >120 bpm,Inc>=15	bpm	High	Olz	158	0	0.0%	
			Placebo	80	0	0.0%	
		Low	Olz	157	0	0.0%	.038
			Placebo	80	3	3.8%	
Intervals PR >=200 ms	sec	High	Olz	158	0	0.0%	.322
			Placebo	75	1	1.3%	
Intervals QRS >=100 ms	sec	High	Olz	132	7	5.3%	.497
			Placebo	72	2	2.8%	
Intervals QT >=450 ms	ms	High	Olz	156	1	0.6%	.045
			Placebo	79	4	5.1%	
QTc Bazett's Male >=450 ms or Female >=470 ms	ms	High	Olz	156	3	1.9%	.553
			Placebo	79	0	0.0%	
QTc Fridericia's Male >=450 ms or Female >=470 ms	ms	High	Olz	158	0	0.0%	
			Placebo	80	0	0.0%	

7.1.8.2.3 Marked outliers and dropouts for ECG abnormalities

There were no dropouts due to ECG abnormalities.

7.1.9 Assessment of Effect on Growth

The Sponsor provided an analysis of the effect of olanzapine on growth that included data from the Overall Combined Database. Gender and age-adjusted growth in olanzapine-treated patients was compared with the expected growth seen in the general US population by using data provided by the National Center for Health Statistics. Standardized mean weight and BMI increased significantly for olanzapine-treated patients, regardless of gender, country, or disorder (schizophrenia or bipolar disorder). The changes in standardized mean height were closer to expected values based on the CDC reference population.

Table 7.1.9.1. Sponsor's Table.

Table APP.2.7.4.7.3.2. Standardized Growth (Z-Score)
LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint
Overall Olanzapine Exposure Combined Database

			Baseline		Endpoint		Change		P-value
Measure	Value	N	Mean	Std	Mean	Std	Mean	Std	*P-value
Weight	Actual	450	67.13	17.72	74.48	19.07	7.35	6.58	<.001
	Expected	450	67.13	17.72	68.17	17.90	1.03	1.01	<.001
	Z-Score	450	0.53	1.13	0.98	1.02	0.45	0.44	<.001
	Percentile	450	63.54	29.54	75.33	24.50	11.79	14.19	
Height	Actual	440	168.24	9.71	169.27	9.45	1.03	2.17	<.001
	Expected	440	168.24	9.71	168.92	9.60	0.67	0.91	<.001
	Z-Score	440	0.02	1.02	0.07	1.00	0.05	0.24	<.001
	Percentile	440	50.60	29.13	52.11	28.76	1.51	6.58	
BMI	Actual	439	23.64	6.07	25.95	6.21	2.31	2.31	<.001
	Expected	439	23.64	6.07	23.83	6.01	0.19	0.30	<.001
	Z-Score	439	0.50	1.14	0.99	0.95	0.49	0.53	<.001
	Percentile	439	63.51	29.85	76.77	23.48	13.26	16.47	

Table 7.1.9.2. Sponsor's Table.

Table APP.2.7.4.7.3.3. Standardized Growth (Z-Score)
LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint by Gender
Overall Olanzapine Exposure Combined Database

				Baseline		Endpoint		Change		P-value
Measure	Gender	Value	N	Mean	Std	Mean	Std	Mean	Std	*P-value
Weight	Female	Actual	167	64.41	18.15	70.94	19.34	6.53	6.08	<.001
		Expected	167	64.41	18.15	65.05	18.29	0.64	0.73	<.001
		Z-Score	167	0.64	1.12	1.05	0.97	0.40	0.45	<.001
		Percentile	167	67.26	28.90	77.62	23.18	10.36	14.04	
	Male	Actual	283	68.74	17.30	76.58	18.64	7.83	6.81	<.001
		Expected	283	68.74	17.30	70.01	17.43	1.27	1.08	<.001
		Z-Score	283	0.47	1.13	0.94	1.05	0.47	0.44	<.001
		Percentile	283	61.35	29.74	73.98	25.20	12.64	14.23	
Height	Female	Actual	163	162.07	7.82	162.78	7.63	0.71	1.45	<.001
		Expected	163	162.07	7.82	162.35	7.75	0.27	0.37	<.001
		Z-Score	163	0.04	1.15	0.10	1.13	0.07	0.20	<.001
		Percentile	163	51.74	30.32	53.86	29.83	2.12	6.40	
	Male	Actual	277	171.88	8.86	173.09	8.26	1.21	2.48	<.001
		Expected	277	171.88	8.86	172.78	8.42	0.90	1.05	<.001
		Z-Score	277	0.00	0.95	0.04	0.92	0.04	0.26	.012
		Percentile	277	49.94	28.44	51.09	28.11	1.15	6.68	
BMI	Female	Actual	162	24.46	6.76	26.78	7.12	2.32	2.30	<.001
		Expected	162	24.46	6.76	24.66	6.83	0.20	0.17	<.001
		Z-Score	162	0.66	1.07	1.08	0.88	0.42	0.48	<.001
		Percentile	162	67.73	28.52	79.04	21.25	11.31	15.25	
	Male	Actual	277	23.16	5.58	25.46	5.57	2.30	2.33	<.001
		Expected	277	23.16	5.58	23.35	5.42	0.19	0.36	<.001

The Sponsor noted a number of limitations in the evaluation of these data. Tanner Stage information was not collected during these studies, so the pubertal effects on individual standard deviation scores for height, weight or BMI are not known. The observational period of these studies (up to 8 months) did not allow for "meaningful evaluation" of the potential effect of olanzapine on height. Additionally, the CDC reference database is based on the US population and may not be representative of patients from Germany or Russia – both countries had significant numbers of patients in this combined database.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1.1 Extent of exposure (dose/duration)

Acute, placebo-controlled trials: Total exposure for olanzapine in adolescent patients was 4776 patient-days. The mean daily dose was 9.75 mg/day, the modal daily dose was 11.46 mg/day.

Overall olanzapine exposure combined database: Total exposure for olanzapine in adolescent patients was 48,946 patient-days. The mean daily dose was 10.56 mg/day, the modal daily dose was 11.36 mg/day.

The highest olanzapine dose allowed in trials HGIN and HGIU was 20 mg/day. The Sponsor provided exposure data regarding the numbers of patients taking olanzapine 20 mg at any time, who had a modal dose of 20 mg and who had a final dose of 20 mg.

Table 2.7.4.14. Anytime, Modal Dose, and Final Dose of 20 mg
All Randomized Patients
Acute Placebo-Controlled Combined Database

	HGIN (N= 72) n(%)	HGIU (N= 106) n(%)	Combined (N= 178) n(%)
20 mg Dose(Anytime)	21(29.17%)	13(12.26%)	34(19.10%)
20 mg Modal Dose	12(16.67%)	10(9.43%)	22(12.36%)
20 mg Final Dose	18(25.00%)	11(10.38%)	29(16.29%)

Table 2.7.4.19. Anytime, Modal Dose, and Final Dose of 20 mg
All Patients with Olanzapine Exposure
Overall Olanzapine Exposure Combined Database

Summary of Patients Who Took >= 20 mg OLZ at Any Time

	Schizophrenia			Bipolar			Combined		
Dose	N	n	%	N	n	%	N	n	%
20	227	81	35.7%	226	52	23.0%	453	133	29.4%
25	227	0	0.0%	226	2	0.9%	453	2	0.4%

Summary of Patients Who Had Modal Dose at 20 mg OLZ

	Schizophrenia			Bipolar			Combined		
Modal Dose	N	n	%	N	n	%	N	n	%
20	227	46	20.3%	226	26	11.5%	453	72	15.9%

Summary of Patients Who Had Final Dose at 20 mg OLZ

	Schizophrenia			Bipolar			Combined		
Final Dose	N	n	%	N	n	%	N	n	%
20	227	46	20.3%	226	30	13.3%	453	76	16.8%

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Postmarketing experience

The Lilly Safety System was searched for spontaneously reported adverse events involving patients younger than 18 years of age treated with olanzapine for the time period of product launch through May 31, 2006. The search identified 5,633 spontaneously reported adverse events (in 2,359 case reports) for patients ≤ 18 years of age out of 110,529 total events (age was unknown for 25,415 events).

The Sponsor analyzed these data by using a proportional reporting ratio (PRR) and Chi square value. The PRR was used to compare events between olanzapine treated patients aged 13 to 17 years and olanzapine-treated patients aged 18 to 64 years. The Sponsor indicated that some general guidelines for interpreting a drug-event combination as a potential signal include: at least 3 reports, a PRR > 2 and a Chi-square > 4. The spontaneously reported adverse events somnolence, aggression, galactorrhea, and sedation met the PRR and Chi-square criteria and had a proportion of the event of interest ≥ 1% of all events in patients aged 13 – 17 years (see Table 7.2.2.1.1).

Table 7.2.2.1.1 Sponsor's Table. Potential Safety Signals in Postmarketing Database for Patients 13 to 17 Years of Age – Proportion, PRR and Chi-Square Criteria Met

MedDRA Preferred Term (# of events in patients 13-17 years)	Proportion of Event in Patients 13-17 years (%) (N=3,288 events)	Proportion of Event in Patients 18-64 years (%) (N=68,450 events)	PRR[a]	Chi-Square Value
Somnolence (108)	3.28	1.60	2.06	53.39
Aggression (41)	1.25	0.33	3.76	70.36
Galactorrhoea (39)	1.19	0.32	3.67	64.51
Sedation (38)	1.16	0.46	2.50	30.41

From Sponsor table 2.7.4.79 in summary-clin-safety document

The Sponsor also included an additional table for adverse events reported with a proportion of the event of interest > 1% of all events in patients aged 13 to 17 years not meeting additional criteria (PRR and Chi-square) (see Table 7.2.1.1.2).

Table 7.2.2.1.2. Sponsor's Table. Potential Safety Signals in Postmarketing Database for Patients 13 to 17 Years of Age – Proportion Criteria Met

MedDRA Preferred Term (# of events in patients 13-17 years)	Proportion of Event in Patients 13-17 years (%) (N=3,288 events)	Proportion of Event in Patients 18-64 years (%) (N=68,450 events)	PRR[a]	Chi-Square Value
Weight increased (320)	9.73	7.74	1.26	15.98
Prescribed overdose (52)	1.58	1.84	0.86	1.15
Overdose (42)	1.28	1.23	1.04	0.05
Fatigue (40)	1.22	0.70	1.75	11.76
Alanine aminotransferase increased (38)	1.16	0.90	1.29	2.31
Diabetes mellitus (36)	1.09	4.75	0.23	91.49
Drug ineffective (36)	1.09	0.77	1.43	4.36
Increased appetite (36)	1.09	0.77	1.41	4.09
Convulsion (33)	1.00	0.55	1.82	11.26

Of the 2,359 case reports in patients 13 to 17 years of age, 27 had a fatal outcome (Sponsor indicated that 28 cases were fatal, upon review it was noted that one case was duplicated). These cases are from spontaneous reports or publications in the literature. The Sponsor included CIOMS line listings and MedWatch reports for each fatality. In the narrative summary for one of the fatality cases, a reference to 4 additional US fatalities was made.[3] These appear to be a cluster of deaths occurring in a county in Tennessee. Further investigation may be deemed necessary. It is not known if the reporter had contacted the FDA regarding these cases as was mentioned in the case narrative. MedWatch reports for these additional cases were not included in the submission. The Sponsor will be asked to provide these reports as well as to submit any new reports that may have occurred since this search was last completed.

The MedWatch reports were incomplete and many details regarding the deaths (autopsy reports, pertinent laboratory values, clinical description of death) were not available. In some cases, it appears that the Sponsor attempted to obtain more information, it is not known to what extent these attempts were made. Fifteen of the cases occurred in the United States, a number of these cases were reported by an attorney via the legal department – it is not known if litigation is ongoing in these cases.
Of note, seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus, diabetic coma or diabetic ketoacidosis. A brief summary of these cases is in Appendix 10.13.

7.3 Safety Conclusions

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar

3 In the narrative summary for US_010158510, the following statements were noted: "This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in Roane County, Tennessee. The reporter stated he has also notified the FDA."

disorder) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events (≥ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with > 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
HGIN + HGIU Acute Database				
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Weight (kg) Mean Change to Endpoint (OC)	3.6 (n = 154)	0.08 (n = 67)	3.57	< 0.001
BMI Mean Change to Endpoint (LOCF)	1.22	0.05	1.17	< 0.001
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001
Overall Combined Database				
Weight (kg) Mean Change to Endpoint (LOCF)	7.35	-	-	< 0.001 (compared to baseline)
Weight (kg) Mean Change to Endpoint (OC)	10.8	-	-	< 0.001 (compared to baseline)

BMI Mean Change to Endpoint (LOCF)	2.31	-	-	< 0.001 (compared to baseline)
≥ 7% increase in body weight (%)	65%	-	-	-

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits. In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN +

HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

Hypertriglyceridemia
The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, $p < 0.001$). In reviewing the individual lab data, 11 marked outliers were noted for triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) ($p = 0.039$).

Hypercholesterolemia
The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, $p < 0.001$). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) ($p = 0.023$).

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were also similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown

and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in bipolar disorder patients. Suicidal behaviors or ideation is not uncommon in these patients and, in the absence of a placebo comparator, it is difficult to interpret any causality to olanzapine therapy.

7.4 General Methodology

7.4.1.1 Explorations for dose dependency for adverse findings

All of the clinical trials, both placebo-controlled and open-label, included a flexible dosing paradigm for olanzapine. Therefore, it is not possible to evaluate the dose-dependency of adverse events.

7.4.1.2 Explorations for drug-demographic interactions

The drug – demographic interactions summarized here are the adverse events occurring in HGIN + HGIU Acute Database. Subgroup analyses, particularly for gender and age, for efficacy and some safety data (prolactin, weight gain, etc.) are summarized in those relevant sections of the review. Most of the patients enrolled in the pivotal clinical trials were Caucasian, therefore any analyses by race/ethnicity are of limited usefulness.

Treatment-by-gender interactions were significant for the following adverse events: myalgia, nasal congestion, sinus congestion and tremor (see Table 7.4.1.2.1); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.1.2.1. Sponsor's Table. Adverse Events – Treatment-by-Gender Interactions: HGIN + HGIU Acute Database

By Subgroup: Gender

		Therapy							
		Olanzapine			Placebo				
Event Classification	Gender	N	n	%	N	n	%	*P-value	**Homogeneity of Odds Ratio
Myalgia	Female	67	0	0.0%	41	1	2.4%	.380	.070
	Male	112	3	2.7%	48	0	0.0%	.555	
Nasal congestion	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	
Sinus congestion	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	
Tremor	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	

Treatment-by-age (< 15, ≥ 15 years) interactions were significant for ear pain and migraine (see Table 7.4.1.2.2); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.1.2.2. Sponsor's Table. Adverse Events – Treatment-by-Age Interactions: HGIN + HGIU Acute Database

By Subgroup: Age

		Therapy							
		Olanzapine			Placebo				
Event Classification	Age	N	n	%	N	n	%	*P-value	**Homogeneity of Odds Ratio
Ear pain	< 15	64	1	1.6%	27	0	0.0%	1.00	.100
	>=15	115	0	0.0%	62	2	3.2%	.121	
Migraine	< 15	64	0	0.0%	27	1	3.7%	.297	.062
	>=15	115	2	1.7%	62	0	0.0%	.542	

7.5 Comparing adolescent and adult data

The common adverse event tables for adults in current product labeling and the common adverse events occurring in HGIN and HGIU were compared. In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to < 5% of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

Table 7.5.1. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 6 Week Acute Trials in *Schizophrenia*

	Adults	
	Olanzapine N = 248	Placebo N = 118
Dizziness	11%	4%
Constipation	9%	3%
Personality disorder	8%	4%
Weight gain	6%	1%
Akathisia	5%	1%
Postural hypotension	5%	2%

	Adolescents	
	Olanzapine N = 72	Placebo N = 35
Weight increased	31%	9%
Somnolence	24%	3%
Headache	17%	6%
Increased appetite	17%	9%
Sedation	15%	6%
Dizziness	8%	3%
Pain in extremity	6%	3%

Table 7.5.2. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 3 Week Acute Trials in *Bipolar Disorder*

	Adults	
	Olanzapine N = 125	Placebo N = 129
Somnolence	35%	13%
Dry mouth	22%	7%
Dizziness	18%	6%

Adolescents		
	Olanzapine N = 107	Placebo N = 54
Weight increased	29%	4%
Increased appetite	29%	4%
Somnolence	25%	4%

Asthenia	15%	6%
Constipation	11%	5%
Dyspepsia	11%	5%
Increased appetite	6%	3%
Tremor	6%	3%

Sedation	22%	6%
Headache	17%	17%
Fatigue	14%	6%
Dry mouth	8%	0%
Pain in extremity	5%	0%

The Sponsor included an analysis of select adverse events occurring in the adult clinical trials databases and adolescent clinical trials databases. These analyses summarized all data including the open-label trials. The Sponsor was asked if a similar analysis could be done for the placebo-controlled studies only and they responded that none of the placebo-controlled studies included fasting glucose and lipid data so these analyses were not available.

Metabolic parameters (fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides):
Mean change from baseline to endpoint – the only statistically significant differences between populations was in fasting glucose and triglycerides. Mean change to endpoint for fasting glucose was 1.8 ± 13 mg/dL for adolescents and 4.9 ± 32.8 mg/dL for adults (p = 0.002), triglycerides was 23.0 ± 76 mg/dL for adolescents and 20.3 ± 124 mg/dL for adults (p = 0.007).

Treatment-emergent significant changes at any time: statistically significant differences were noted for most of the parameters with a higher percentage of adults having significant changes at any time (see Table 7.5.3).

Table 7.5.3. Treatment-Emergent Significant Changes at Any Time – Adults vs. Adolescents

Laboratory Analytes	Categories	Population	N	n	%	*P-value
Fasting Glucose	Normal to High (< 100 mg/dL to >=126 mg/dL)	Adolescent	251	3	1.2%	.033
		Adult	251	12	4.8%	
	Impaired Glucose Tolerance to High(>=100 & <126 mg/dL to >=126 mg/dL)	Adolescent	47	6	12.8%	.066
		Adult	121	32	26.4%	
	Normal/Impaired Glucose Tolerance to High(<126 mg/dL to >=126 mg/dL)	Adolescent	298	9	3.0%	<.001
		Adult	372	44	11.8%	
Total Cholesterol	Normal to Borderline(<200 mg/dL to >=200 mg/dL and <240 mg/dL)	Adolescent	262	54	20.6%	<.001
		Adult	216	82	38.0%	
	Normal to High(<200 mg/dL to >=240 mg/dL)	Adolescent	262	3	1.1%	.001
		Adult	216	15	6.9%	
LDL Cholesterol	Normal to Borderline(<130 mg/dL to >=130 mg/dL and <160 mg/dL)	Adolescent	270	48	17.8%	<.001
		Adult	241	75	31.1%	
	Normal to High(<130 mg/dL to >=160 mg/dL)	Adolescent	270	4	1.5%	.014
		Adult	241	14	5.8%	
HDL Cholesterol	Normal to Low(>=50 mg/dL to <40 mg/dL)	Adolescent	107	10	9.3%	.052
		Adult	155	28	18.1%	
Fasting Triglycerides	Normal to Borderline(<150 mg/dL to >=150 mg/dL and <200 mg/dL)	Adolescent	247	51	20.6%	<.001
		Adult	253	91	36.0%	
	Normal to High(<150 mg/dL to >=200 mg/dL)	Adolescent	247	43	17.4%	.030
		Adult	253	65	25.7%	
	Normal to Extremely High(<150 mg/dL to >=500 mg/dL)	Adolescent	247	1	0.4%	1.00
		Adult	253	1	0.4%	

Weight Gain
Mean change from baseline to endpoint – There was a statistically significant greater mean increase in body weight for adolescents compared to adults (see Table 7.5.4).

Table 7.5.4. Sponsor's Table. Mean Change from Baseline to Endpoint - Adolescents vs. Adults. Overall Combined Databases

Population	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Adolescent	450	67.13	17.72	7.35	6.58	6.97	3.71	<.001
Adult	7847	78.12	18.86	3.24	5.82	3.26		

From Sponsor's table APP.2.7.4.7.1.25 in summary-clin-safe-app document

In product labeling, it is stated that in the 6-week placebo-controlled studies in adults, olanzapine patients gained an average of 2.8 kg compared to a 0.4 kg weight loss in placebo patients. In study HGIN, adolescent patients receiving olanzapine gained an average of 4.26 kg compared to 0.13 kg weight gain in placebo patients.

PCS weight increase at any time– Significantly more adolescent patients had a $\geq$ 7% increase in weight (65.1%) compared to adult patients (35.6%) ($p < 0.001$).

In the 6-week placebo controlled trials in adults, 29% of olanzapine patients had a $\geq$ 7% increase in weight compared to 3% of placebo patients. In study HGIN, 45% of olanzapine patients had a $\geq$ 7% increase in weight compared to 14.7% of placebo patients.
The Sponsor did not provide an comparison of hepatic laboratory analytes between the two populations and will be asked to provide these data. Per product labeling, in placebo-controlled olanzapine monotherapy studies in adults, elevations in ALT $\geq$ 3 x ULN were observed in 2% (6/243) olanzapine patients compared to 0/115 placebo patients. In the placebo-controlled monotherapy studies in adolescents, elevations in ALT > 3 x ULN (from baseline $\leq$ 3 x ULN) were observed in 12% (21/174) of olanzapine patients compared to 2% (2/87) of placebo patients.

Prolactin
Because of differences in reference ranges between the populations, normalized units were used in the analysis of prolactin changes (% URL = % upper range limit).

Mean change from baseline to endpoint – statistically significant differences were noted between the populations with adolescents having a mean change to endpoint of 23.0 %URL compared to -4.19 %URL in adults ($p = 0.004$) (see Table 7.5.5).

Table 7.5.5. Sponsor's Table. Mean Change from Baseline to Endpoint in Prolactin (Normalized Units) – Adult vs. Adolescent Patients, Overall Combined Databases

Laboratory Evaluations	Unit	Population	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
PROLACTIN	%URL	Adolescent	431	78.73	76.47	23.01	83.69	9.70	12.62	.004
		Adult	4503	99.42	126.56	-4.19	125.57	-2.92		

From Sponsor's table APP.2.7.4.7.4.31 in summary-clin-app document

Treatment-emergent high prolactin concentrations at any time: a higher percentage of adolescent patients (55.5%) had high prolactin concentrations at any time compared to adult patients (29%) ($p < 0.001$). The Sponsor did not provide an analysis for adolescent vs. adult patients by gender.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

(b) (4)

(b) (4)

8.2 Advisory Committee Meeting

No advisory committee meeting was held for this submission.

8.3 Literature Review

The Sponsor submitted a literature review though there was no attempt to summarize key findings. The Sponsor stated that none of the reviewed articles presented safety data contradictory to the conclusions presented in the NDA. Due to time constraints for this priority application, a separate literature review was not conducted by this reviewer.

8.4 Postmarketing Risk Management Plan

The Sponsor submitted a Risk Management document outlining their proposed actions for risk minimization. The identified risks in this document included weight gain, sedation, hepatic changes, hyperprolactinemia, glucose dysregulation, dyslipidemia. For all of these safety issues, the Sponsor has proposed the following actions for pharmacovigilance: clinical trial surveillance, routine pharmacovigilance, targeted surveillance, long-term safety study and studies in pediatric patients with PDD. For glucose dysregulation and dyslipidemia, an additional action was to perform a retrospective cohort claims database study.

Routine pharmacovigilance was defined as periodic reporting per PSUR or as appropriate. Targeted surveillance was similar but targeted weight gain, hepatic changes, glucose dysregulation and dyslipidemia. The Sponsor has proposed a long-term safety study to evaluate the safety of olanzapine in adolescent patients with schizophrenia or bipolar disorder and to estimate the incidence and prevalence of identified and potential risks associated with olanzapine treatment. The study is still in the planning phase.

(b) (4)

The actions proposed for risk minimization include product labeling and prescriber education – no details were provided regarding the latter proposal.

9 OVERALL ASSESSMENT

9.1 Recommendation on Regulatory Action

I recommend that the Division take a non approval action on NDA 20-592 SE5-041 that was filed to support the indication “treatment of schizophrenia in adolescent patients”.

Fifty-three percent of randomized patients in pivotal trial HGIN were from sites in the United States and 47% of randomized patients were from sites in Russia. The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Though the LOCF analysis was the primary analysis, it is also concerning that the OC and MMRM analyses (the latter by recalculation by the reviewing statistician in the Division) are substantially different from the LOCF analysis and not statistically significant.

I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

9.2 Recommendation on Postmarketing Actions

Since non approval is recommended, there are no recommendations for postmarketing actions.

9.3 Labeling Review

Changes to proposed labeling are being made directly to the annotated labeling submitted by the Sponsor, this was the first PLR labeling so there were many changes from prior approved labeling. The project manager, Dr. Doris Bates, reviewed the PLR labeling against the prior approved labeling and noted any differences – especially differences that were not highlighted by the Sponsor.
In the proposed labeling, all of the "frequent" adverse events in the "Other Adverse Events Observed" section were removed and some of the adverse events in other categories (infrequent, rare) were also removed. The Sponsor has been asked to address this and had not responded at the time this review was finalized.

This section will briefly discuss some of the labeling that may require revision:
(b) (4)
.
WARNINGS AND PRECAUTIONS – The team will have to discuss the order of the items under this heading.

Weight Gain: should be placed earlier in this section

Transaminase Elevations: in the adult section, the number of patients with ALT $\geq$ 3 times ULN data is provided. In the adolescent section, the number of patients with ALT > 3 times ULN data is provided. These should be consistent (should both be $\geq$ 3 x ULN). In the adult section, use ALT rather than SGPT in the discussion of the larger premarketing database. In the adolescent section, I would recommend including the number of patients who discontinued due to elevations in LFTs.

Hyperprolactinemia: I would suggest including the % of patients with elevated prolactin levels for both adolescents and adults in the placebo-controlled acute trials.

Laboratory Tests: The information with regard to glucose monitoring should be included here.

ADVERSE REACTIONS
Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine
All of the adverse events in the category "frequent" have been removed in the proposed labeling. Other adverse events in the categories infrequent and rare have also been removed. The Sponsor has been asked to address this. Similar issues occur in this same section for IM olanzapine.

Clinical Trials in Adolescent Patients
ECG Changes – correct spelling of Frederica to Fredericia

Postmarketing Experience
When was the last time the Sponsor updated this section? There have been some postmarketing reports of death due to diabetic ketoacidosis occurring in adolescents – should this data be included in this section?

9.4 Comments to Applicant

Requests for information

<u>The Sponsor has responded to the following requests and the reviewer has reviewed the responses</u>

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.

2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.

3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the CRF, it does not appear that there is an area where the recorder could state the source of the ratings. Are both ratings, patient and parent/legal guardian, available for subjects in this study? If so, please provide these ratings and indicate the primary source for the ratings.

4. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF analysis (similar to table HGIN 14.20 for OC analysis) - with and without site 021.

5. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF and OC analysis for the US and Russia sites separately.

6. Provide patient baseline demographics and analysis for US vs. Russia sites (similar to HGIN.11.1 but comparing US vs. Russia).

7. It is noted that 50 patients were randomized at the 5 sites in Russia - 10 patients per site. Is it coincidental that 10 subjects were randomized at each of these sites? Were caps specified to the investigators such that each site could randomize no more than 10 patients?

8. Please provide patient baseline severity of illness and statistical analysis for US vs. Russia sites (similar to HGIN.11.2 but comparing US vs. Russia). Include the following variables: age of onset of illness, # of previous schizophrenia episodes, total hospitalization, length of current episode, days since last hospitalization, psychiatric hospitalization, CGI-S, BPRS-C subscales, BPRS-C total score, PANSS subscales, and PANSS total score

9. Do study reports for HGIN and HGIU include information regarding the adverse events associated with patient drop-outs? Please indicate where this information may be found.

10. In table HGIN.11.2, it is noted that the minimum value for age for Age of Illness Onset was 5 years old for each treatment group. Please provide the study numbers for all patients with an age of illness onset < 10 years old and CRFs for these patients.

11. In table HGIN.11.2, it is noted that the minimum value for the Length of Current Episode is "0" - please clarify.

12. For Psychiatric Hospitalization in table HGIN.11.2, please clarify whether this is past or current hospitalization.

13. Please provide # of prior psychiatric hospitalizations for both treatment groups with statistical analysis for this variable.

14. In the brief summary for study HGCS, it is noted that 2 patients experienced the adverse event "intentional injury". Please provide brief summaries for these two events.

15. For study HGGC, were there any serious adverse events? The synopsis states that no patients experienced serious adverse events associated with cardiac abnormalities or weight gain - but there is no mention of other SAEs that may have occurred in this trial.

16. For the adult studies HGDH and HGGF that included adolescent patients, please submit narratives for the serious adverse events (per Table 2.7.4.4 in the summary-clin-safety document).

17. For the adult studies HGGF and HGKL, please submit narratives for the discontinuations due to adverse event cases.

18. For patient HGIU-028-2804, the narrative indicates that she experienced bilateral galactorrhea while hospitalized for a recurrence of bipolar symptoms. Please provide the prolactin concentrations that were obtained by the hospital (pending at time patient was discharged).

19. Patient HGMF-003-0304 had the SAE "exacerbation of bipolar illness with positive suicidal ideation". However, it appears that this was coded to the preferred term "bipolar disorder". Why weren't both verbatim terms coded to preferred terms - i.e. bipolar disorder and suicidal ideation?

20. For the discontinuations due to the adverse event "weight gain" in the acute and combined databases, please provide weight data for the post-study follow-up visits. Some of the narratives have this information, but the majority indicate that the adverse event had resolved without providing weight data.

21. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.

22. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?

23. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

The following questions were submitted to the Sponsor via email on 3/19/07. The Sponsor attempted to send an email response on 3/26/07 but encountered technical difficulties. The Sponsor faxed the response on 3/27/07 and was asked to also fax the response to this reviewer (working in another location). The Sponsor did not fax the response to this reviewer. This reviewer received the response on 4/2/07 (working in office) and had insufficient time to review the responses to meet the internal NDA deadline. Of note, request #30 was not addressed in this response and the Sponsor indicated that the response will be provided at a later date.

24. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15, >= 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.

25. Please provide a subgroup analysis for age (< 15 and >=15) and gender for the variable "PCS weight change (> 7%)" for the Acute Placebo Controlled Combined Database.

26. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.

27. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.

28. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.

29. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?

30. In proposed labeling, some adverse events have been removed from the sections "other adverse events observed during the clinical trial evaluation of oral olanzapine" and "other adverse events observed during the clinical trial evaluation of intramuscular olanzapine for injection". In the former section, it appears that all of the frequently occurring AEs ("frequent") have been removed. In both sections, many adverse events that were included in the infrequent and rare categories have been removed. Please provide a justification for removal of these adverse events from proposed product labeling.

<u>Requests for additional information from the Sponsor – may be included in action letter:</u>

31. Please provide narrative summaries for the following: 8 cases of gynecomastia, 1 case of opisthotonus, 1 case of “oculogyration”, and two cases with high prolactin concentrations (HGIN 900-9009, HGIN 005-503) and the cases with CPK > 500 U/L.

32. Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had “DRAFT” at the top of the page and the date of the report was 7/27/06 - have all of these reports been previously filed with the Agency?

33. For MedWatch fatality case US_010158510, the narrative states “This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in Roane County, Tennessee. The reporter stated he has also notified the FDA...". The only MedWatch report included in this submission is

for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

34. Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed the 19-32 weeks in the study (n = 83 bipolar, n = 93 schizophrenia) - e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

35. One of the exclusion criteria for HGIU was "patients who have been judged clinically to be at serious suicidal risk". However, a review of the CDRS-R individual item "suicidal ideation" noted a number of patients who were rated the maximum score of "7" at baseline (has made a suicide attempt within the last month or is actively suicidal". These patients include 012-1203, 012-1212, and 024-2402. Please provide more information regarding inclusion of these patients in this study.

36. Please provide an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

37. For HGIU and HGIN, how was “treatment-emergent” parkinsonism, akathisia and dyskinesia defined by the respective rating scales?

38. For the acute phases of HGIU and HGIN, many patients had elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses on the subset of patients with baseline prolactin within the normal range - please provide a separate analysis for gender and age.

39. For study HGIN, it is noted that 21/72 patients in the olanzapine group and 5/35 patients in the placebo group did not have any previous medications for schizophrenia (Table HGIN.14.4). How many of these patients were from the sites in Russia? How many were first-break schizophrenic patients?

40. The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes.

41. Please provide an analysis of mean change to endpoint for prolactin by age (< 15, > 15) for HGIN + HGIU Acute Database, HGIN and HGIU.

10 APPENDICES

10.1 Investigators and Sites (HGIN)

Site #	Principal Investigator	Site & Address	# Pts Randomized	# Pts Completing DB; OL
3	Bastani, Bijan	Northcoast Clinical Trials 3733 Park East Drive, Suite 100 Beachwood, OH 44122 USA	2	2;1
4	Kaplan, Stuart Busner, Joan	Penn State University Milton S. Hershey Medical Center 500 University Drive Dept. of Psychiatry, HO73, Rm H1141 Hershey, PA 17033 USA	1	1;1
5	Childress, Ann	Nevada Behavioral Health, Inc. 2055 W. Charlestone Blvd, Ste B Las Vegas, NV 89102 USA	2	1;1
6	Cueva, Jeanette	Bioscience Research, Llc 222 W. 14th Street New York, NY 10011 USA	3	2;2
7	DelBello, Melissa	University of Cincinnati Medical Center 231 Albert B. Sabin Way Dept. of Psychiatry Cincinnati, OH 45267 USA	6	2;1
10	Gracious, Barbara	Strong Memorial Hospital 300 Crittenden Blvd Dept. of Psychiatry, Box PSYCH Rochester, NY 14642 USA	2	1;1
11	Kaczenski, Gregory	Summit Research Group, Llc 1014 Autumn Rd, Suite 3 Little Rock, AR 72211 USA	1	0;0
13	Knutson, James	Eastside Therapeutic Resources 512 6th Street, Suite 101 Kirkland, WA 98033 USA	2	2;0

14	Leventhal, Bennett	University of Chicago Pritzker School of Medicine 5841 S. Maryland Avenue Dept. of Child & Adolescent, MC 3077 Chicago, IL 60637 USA	3	1;1
16	Mintz, Mark	Bancroft Neurohealth 201 King's Highway South Cherry Hill, NJ 08034 USA	1	1 ;1
17	Plopper, Michael	Sharp Mesa Vist Hospital 7850 Vista Hill Avenue San Diego, CA 92123 USA	3	2;2
19	Krishnasastry, Chandra	Tennessee Christian Medical Center 320 Hospital Drive Madison, TN 37115 USA	1	1;0
20	Riesenberg, Robert	Atlanta Center of Medical Research 811 Juniper Street Atlanta, GA 30308 USA	5	3;3
21	Robb, Adelaide	Children's National Medical Center 111 Michigan Ave, NW Washington, DC 20010 USA	3	1; 0 [1]
25	Soni, Poonam	University of Utah School of Medicine Mood Disorder Clinic, Rm 5R218 Dept. of Psychiatry 30 N. 1900 East Salt Lake City, UT 84132 USA	4	1;0
26	White, Tonya	University of Minnesota Medical School 2450 Riverside Avenue Dept. of Psychiatry, F256/2B West Minneapolis, MN 55454 USA	2	2;0

27	Yadalam, Kashinath	Institute for Neuropsychiatry 2829 4th Avenue Lake Charles, LA 70601 USA	2	1;0
30	Punjwani, Sohail	Segal Institute for Clinical Research 1065 NE 125th Street, Suite 417 North Miami, FL 33161 USA	10	6;1
33	Valencerina, Madeleine	BHC Alhambra Hospital 4619 N. Rosemead Blvd. Rosemead, CA 91770 USA	1	0;0
34	Vogelfanger, Robert	Compass Intervention Center 7900 Lowrance Road Memphis, TN 38125 USA	3	2;2
900	Smulevich, Anatoly	Moscow Clinical Psychiatric Hospital #1 N.A. Alexeyev Zagorodnoye Shosse, 2 PKDO #2 Moscow, 117152 Russia	10	8;7
910	Bardenstein, Leonid	Moscow Medical University, N.A. Semashko Moskvorechye 7 City Psychiatric Hospital #15 Moscow, 115522 Russia	10	6;9
920	Alexandrovsky, Yuriy	Serbsky National Research Center 47 Volokolamskoye Shosse Psychiatric Hospital #12, korp5, Rm 27 Moscow, 123367 Russia	10	5;4
930	Morozova, Margarita	National Mental Health Research Centre Kashirskoye Shosse 34 Moscow, 115522 Russia	10	6;7
940	Krasnov, Valery	Moscow Research Institute of Psychiatry UL. Poteshnaya 3 Moscow, 107076 Russia	10	7;6

[1] Site was closed by sponsor due to protocol violations. Patients were discontinued.

10.2 Inclusion and Exclusion Criteria

Inclusion

1. Are male or female patients, 13 to 17 years of age, but must not yet have reached their 18th birthday prior to Visit 1, when informed consent is obtained.
2. Patient must have a diagnosis of schizophrenia according to DSM-IV-TR and confirmed by the K-SADS-PL. Patients must meet diagnostic criteria at Visit 1 and Visit 2.
3. Female patients of childbearing potential (not surgically sterilized) must test negative for pregnancy at the time of enrollment based on a serum pregnancy test. Furthermore, female patients must agree to abstain from sexual activity or to use a medically acceptable method of birth control during their participation in the study.
4. Each patient and the patient's parent/authorized legal representative must understand the nature of the study. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations.
5. Each patient and the patient's parent/authorized legal representative must have a level of understanding sufficient to perform all tests and examinations required by the protocol.
6. Patient must obtain an Anchored BPRS-C total score of > 35 with a minimum score of 3 on at least one of the following items at Visit 1 and Visit 2: hallucinations, delusions, peculiar fantasies.
7. Patients must be capable of swallowing study medication whole (without crushing, dissolving, etc.).

Exclusion criteria

1. Are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
2. Are employed by Lilly (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
3. Patients who have participated in a clinical trial of oral olanzapine or have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.
4. Patients who have a history of mental retardation, current comorbid autism or current comorbid pervasive developmental disorder.
5. Female patients who are either pregnant or nursing.
6. Patients with acute or unstable medical conditions, including (but not limited to) inadequately controlled diabetes, hepatic insufficiency (specifically any degree of jaundice), uncorrected hypothyroidism or hyperthyroidism, acute systemic infection, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic diseases (specifically current agranulocytosis with an absolute neutrophil count < 500 mm^3).

7. Patients with acute or unstable medical conditions, such that intensive care unit hospitalization for the disease is anticipated within 6 months.
8. Prolactin level at Visit 1 $\geq$ 200 ng/ml.
9. Patients who have been judged clinically to be at serious suicidal risk.
10. Patients who have experienced one or more seizures without a clear and resolved etiology.
11. Laboratory results, including serum chemistries, hematology, and urinalysis, must show no clinically significant abnormalities. In addition, there must be no clinical information that, in the judgment of a physician, should preclude a patient's participation at study entry.
12. Patients with a documented history of allergic reaction to olanzapine.
13. Patients who have undergone treatment with remoxipride within 6 months (180 days) prior to Visit 2.
14. Any concomitant medication with primarily central nervous system activity, including alternative medications, other than specified as permitted in Table HGIN.2 and HGIN.3 at Visit 2.
15. Use of any concomitant medication(s) at Visit 2 as specified in Section 5.7 or expected to need treatment with any medication during the study other than what is allowed.
16. Patients who have used monoamine oxidase inhibitors (MAOIs) within 14 days prior to Visit 2 or are expected to need treatment at any time during this study.
17. DSM-IV-TR substance (except nicotine and caffeine) dependence within the past 30 days.
18. Patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment.
19. Patients, who, in the opinion of the investigator, are unsuitable in any other way to participate in this study including being unable to comply with the requirements of the study for any reason.
20. Treatment with an injectable neuroleptic $\leq$ 14 days before Visit 2.
21. Patients currently meeting DSM-IV-TR criteria for delusional disorder, psychotic disorder NOS, schizophreniform disorder, schizoaffective disorder, bipolar disorder, attention deficit/hyperactivity disorder or major depressive disorder.

10.3. Sponsor's Table. Schedule of Events HGIN

Table HGIN.9.4. Schedule of Events for F1D-MC-HGIN (continued)

Description of the Data	V1	V2	V3	V4	V5	V6	V7	V8	V9	Final SPII Visit[i]	Visit501	V301	V302	V303	V304	V305	V306	V307	V308	V309	Final SPIII Visit[i]	Visit 501
AIMS, Barnes Akathisia Scale, Simpson-Angus Scale	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
LABORATORY TESTS[b]																						
Clinical chemistry[c]/ electrolytes/lipids[e]	X	X		X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	
Hematology	X	X		X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	
Urinalysis	X									X											X	
Hepatitis screen[c], urine drug screen[d], serum pregnancy test[d], and TSH	X																					
HbgA1$_c$[f]	X									X						X					X	
Prolactin[g]	X	X								X						X					X	
EFFICACY ASSESSMENTS/Measurements																						
Anchored BPRS-C[j]	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
CGI Severity		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
CGI-Improvement			X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
PANSS		X				X				X											X	
OAS		X				X				X											X	
Child Health Questionnaire (CHQ)[k]		X								X											X	
Brief Assessment of Cognition for Schizophrenia (BACS)[k]		X								X											X	

Table HGIN.9.4. Schedule of Events for F1D-MC-HGIN (continued)

Description of the Data	V1	V2	V3	V4	V5	V6	V7	V8	V9	Final SPII Visit[i]	Visit501	V301	V302	V303	V304	V305	V306	V307	V308	V309	Final SPIII Visit[i]	Visit 501
AIMS, Barnes Akathisia Scale, Simpson-Angus Scale	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
LABORATORY TESTS[b]																						
Clinical chemistry[c]/ electrolytes/lipids[e]	X	X		X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	
Hematology	X	X		X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	
Urinalysis	X									X											X	
Hepatitis screen[c], urine drug screen[d], serum pregnancy test[d], and TSH	X																					
HbgA1$_c$[f]	X									X						X					X	
Prolactin[g]	X	X								X						X					X	
EFFICACY ASSESSMENTS/Measurements																						
Anchored BPRS-C[j]	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
CGI Severity		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
CGI-Improvement			X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
PANSS		X				X				X											X	
OAS		X				X				X											X	
Child Health Questionnaire (CHQ)[k]		X								X											X	
Brief Assessment of Cognition for Schizophrenia (BACS)[k]		X								X											X	

10.4 Severity of Illness: Russia vs. U.S. Sites

Table 1. Illness Characteristics at Baseline by Country
All Randomized Patients
F1D-MC-HGIN, Acute Phase

Illness Characteristics	Statistics	Country: Russia (N=50)	Country: U.S. (N=57)	*P-value
Onset Age	No. of Patients	50	57	
	Mean	13.02	12.65	.536
	Median	14.00	13.00	
	Std. Dev.	2.64	3.43	
	Minimum	6.00	5.00	
	Maximum	17.00	17.00	
No. of Prev. Schizophrenia episode	No. of Patients	40	45	
	Mean	2.10	2.73	.416
	Median	2.00	2.00	
	Std. Dev.	1.45	4.71	
	Minimum	0.00	0.00	
	Maximum	6.00	30.00	
Total cum hospitalization in months	No. of Patients	26	34	
	Mean	2.96	1.88	.065
	Median	2.00	1.00	
	Std. Dev.	1.92	2.40	
	Minimum	1.00	0.10	
	Maximum	9.50	11.00	

* Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA): Model= Country

Illness Characteristics	Statistics	Country: Russia (N=50)	Country: U.S. (N=57)	*P-value
Length of current episode in days	No. of Patients	50	56	
	Mean	262.44	259.43	.974
	Median	125.50	80.00	
	Std. Dev.	396.21	524.28	
	Minimum	7.00	0.00	
	Maximum	2139.00	2742.00	
Days since the last hospitalization	No. of Patients	37	40	
	Mean	476.95	149.58	.012
	Median	163.00	7.00	
	Std. Dev.	632.51	477.26	
	Minimum	31.00	1.00	
	Maximum	2718.00	2889.00	

Illness Characteristics	Category	Country: Russia (N=50) n (%)	Country: U.S. (N=57) n (%)	*P-value
Psychiatric hospitalization	Yes	26(52.00)	34(59.65)	.442
	No	24(48.00)	23(40.35)	

Table 2. Severity of Illness at Baseline by Country
All Randomized Patients
F1D-MC-HGIN, Acute Phase

Illness Characteristics	Statistics	Country: Russia (N=50)	Country: U.S. (N=57)	*P-values
CGI Severity	No. of Patients	50	57	
	Mean	4.86	4.88	.904
	Median	5.00	5.00	
	Std. Dev.	0.70	0.76	
	Minimum	4.00	4.00	
	Maximum	6.00	7.00	
BPRS-C Behavioral Problem(Sum 1-3)	No. of Patients	50	57	
	Mean	5.46	7.77	<.001
	Median	6.00	8.00	
	Std. Dev.	2.54	3.70	
	Minimum	0.00	0.00	
	Maximum	9.00	14.00	
BPRS-C Depression(Sum 4-6)	No. of Patients	50	57	
	Mean	5.30	6.47	.044
	Median	5.50	6.00	
	Std. Dev.	2.61	3.25	
	Minimum	0.00	1.00	
	Maximum	11.00	16.00	

* Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA): Model= Country

Illness Characteristics	Statistics	Country: Russia (N=50)	Country: U.S. (N=57)	*P-values
PANSS Total Score	No. of Patients	50	57	
	Mean	97.62	93.35	.116
	Median	96.00	95.00	
	Std. Dev.	13.09	14.60	
	Minimum	74.00	66.00	
	Maximum	122.00	123.00	

Illness Characteristics	Statistics	Country: Russia (N=50)	Country: U.S. (N=57)	*P-values
BPRS-C Thinking Disturbance(Sum 7-9)	No. of Patients	50	57	
	Mean	9.72	11.04	.030
	Median	10.00	11.00	
	Std. Dev.	3.29	2.88	
	Minimum	4.00	5.00	
	Maximum	18.00	18.00	
BPRS-C Psychomotor Excitation Subtotal(Sum 10-12)	No. of Patients	50	57	
	Mean	6.08	7.32	.038
	Median	5.00	7.00	
	Std. Dev.	2.84	3.19	
	Minimum	2.00	2.00	
	Maximum	13.00	14.00	
BPRS-C Withdrawal Subtotal(Sum 13-15)	No. of Patients	50	57	
	Mean	9.54	7.98	.021
	Median	10.00	8.00	
	Std. Dev.	2.76	3.93	
	Minimum	4.00	1.00	
	Maximum	18.00	15.00	

Illness Characteristics	Statistics	Country: Russia (N=50)	Country: U.S. (N=57)	*P-values
BPRS-C Anxiety Subtotal(Sum 16-18)	No. of Patients	50	57	
	Mean	8.16	8.58	.467
	Median	9.00	9.00	
	Std. Dev.	2.76	3.13	
	Minimum	2.00	1.00	
	Maximum	15.00	14.00	
BPRS-C Organicity Subtotal(Sum 19-21)	No. of Patients	50	57	
	Mean	3.22	3.44	.708
	Median	2.50	3.00	
	Std. Dev.	3.29	2.74	
	Minimum	0.00	0.00	
	Maximum	12.00	10.00	
BPRS-C Total Score	No. of Patients	50	57	
	Mean	47.48	52.60	.005
	Median	46.50	52.00	
	Std. Dev.	8.71	9.60	
	Minimum	36.00	35.00	
	Maximum	68.00	79.00	

Illness Characteristics	Statistics	Country: Russia (N=50)	Country: U.S. (N=57)	*P-values
PANSS Positive Score	No. of Patients	50	57	
	Mean	21.08	24.16	<.001
	Median	21.00	25.00	
	Std. Dev.	4.29	4.95	
	Minimum	11.00	13.00	
	Maximum	32.00	36.00	
PANSS Negative Score	No. of Patients	50	57	
	Mean	26.92	23.02	<.001
	Median	27.00	23.00	
	Std. Dev.	4.78	6.02	
	Minimum	18.00	11.00	
	Maximum	39.00	35.00	
PANSS General Psychopathology Score	No. of Patients	50	57	
	Mean	49.62	46.18	.033
	Median	48.00	48.00	
	Std. Dev.	7.53	8.77	
	Minimum	36.00	25.00	
	Maximum	65.00	67.00	

10.5 BPRS-C Individual Items – Mean Change from Baseline to Endpoint

Table HGIN.14.24. BPRS-C Individual Items
LOCF Mean Change from Baseline to Endpoint
Double-Blind Period

Efficacy Variable	Therapy	N	Mean	Std	Mean	Std	LSMean Change	LSMean Difference	*P-value
Uncooperativeness	Olanzapine	72	2.51	1.42	-0.99	1.60	-1.05	-0.88	.003
	Placebo	35	2.89	1.49	-0.29	1.43	-0.16		
Hostility	Olanzapine	72	2.67	1.53	-1.25	1.57	-1.21	-1.16	<.001
	Placebo	35	2.43	1.48	0.03	1.74	-0.06		
Manipulativeness	Olanzapine	72	1.57	1.52	-0.54	1.40	-0.47	-0.55	.035
	Placebo	35	1.26	1.46	0.17	1.74	0.07		
Depressed Mood	Olanzapine	72	2.83	1.28	-1.00	1.42	-1.01	-0.20	.460
	Placebo	35	2.86	1.40	-0.80	1.39	-0.81		
Feelings of Inferiority	Olanzapine	72	2.46	1.46	-1.03	1.41	-1.05	-0.44	.104
	Placebo	35	2.60	1.58	-0.66	1.57	-0.61		
Suicidal Ideation	Olanzapine	72	0.67	1.26	-0.46	1.10	-0.39	-0.09	.479
	Placebo	35	0.40	0.74	-0.17	0.92	-0.30		
Peculiar Fantasies	Olanzapine	72	3.42	1.63	-1.65	1.87	-1.61	-0.78	.014
	Placebo	35	3.29	1.30	-0.80	1.59	-0.82		
Delusions	Olanzapine	72	3.86	1.05	-1.72	1.57	-1.73	-0.47	.151
	Placebo	35	4.06	1.30	-1.34	1.86	-1.26		
Hallucinations	Olanzapine	72	3.21	1.74	-1.61	1.98	-1.56	-0.41	.249

Hallucinations	Placebo	35	2.94	1.85	-1.06	1.95	-1.15		
Hyperactivity	Olanzapine	72	1.81	1.76	-0.78	1.59	-0.77	-0.82	.004
	Placebo	35	1.77	1.55	0.06	1.66	0.04		
Distractibility	Olanzapine	72	3.61	0.99	-0.93	1.40	-0.94	-0.45	.101
	Placebo	35	3.71	1.02	-0.54	1.42	-0.49		
Speech or Voice Pressure	Olanzapine	72	1.14	1.42	-0.53	1.20	-0.61	-0.42	.068
	Placebo	35	1.63	1.52	-0.37	1.59	-0.19		
Underproductive Speech	Olanzapine	72	2.39	1.47	-0.61	1.34	-0.56	-0.37	.164
	Placebo	35	2.03	1.81	-0.09	1.62	-0.20		
Emotional Withdrawal	Olanzapine	72	3.40	1.11	-0.86	1.59	-0.81	-0.17	.528
	Placebo	35	3.26	1.24	-0.57	1.72	-0.64		
Blunted Affect	Olanzapine	72	3.04	1.41	-0.51	1.29	-0.52	-0.04	.876
	Placebo	35	3.17	1.40	-0.54	1.36	-0.49		
Tension	Olanzapine	72	2.97	0.92	-1.07	1.33	-1.07	-0.44	.120
	Placebo	35	2.97	1.25	-0.63	1.63	-0.62		
Anxiety	Olanzapine	72	2.79	1.47	-0.89	1.63	-0.91	-0.49	.103
	Placebo	35	2.89	1.53	-0.46	1.69	-0.42		

Table HGIN.11.17. BPRS-C Composite Factor Scores Mean Change from Baseline to Endpoint (LOCF) Double-Blind Period

			Baseline		Change to Endpoint				
Efficacy Variable	Therapy	N	Mean	Std	Mean	Std	LSMean Change	LSMean Diff.	*P-value
BPRS-C Behavioral Problem(Sum 1-3)	Olanzapine	72	6.75	3.40	-2.78	3.72	-2.74	-2.63	<.001
	Placebo	35	6.57	3.45	-0.09	3.81	-0.11		
BPRS-C Depression(Sum 4-6)	Olanzapine	72	5.96	3.15	-2.49	2.85	-2.47	-0.81	.129
	Placebo	35	5.86	2.76	-1.63	2.95	-1.66		
BPRS-C Thinking Disturbance(Sum 7-9)	Olanzapine	72	10.49	3.16	-4.99	4.53	-4.91	-1.70	.050
	Placebo	35	10.29	3.12	-3.20	4.62	-3.21		
BPRS-C Psychomotor Excitation Subtotal(Sum 10-12)	Olanzapine	72	6.56	2.99	-2.24	3.15	-2.33	-1.68	.006
	Placebo	35	7.11	3.28	-0.86	3.63	-0.65		
BPRS-C Withdrawal Subtotal(Sum 13-15)	Olanzapine	72	8.83	3.39	-1.99	3.40	-1.91	-0.61	.357
	Placebo	35	8.46	3.76	-1.20	3.95	-1.30		
BPRS-C Anxiety Subtotal(Sum 16-18)	Olanzapine	72	8.25	3.02	-3.60	3.87	-3.65	-2.19	.004
	Placebo	35	8.66	2.85	-1.66	4.35	-1.46		
BPRS-C Organicity Subtotal(Sum 19-21)	Olanzapine	72	3.43	3.04	-1.35	2.26	-1.28	-0.54	.184
	Placebo	35	3.14	2.93	-0.69	2.75	-0.75		

10.6 Patient Baseline Demographics – HGIN + HGIU Acute Database and Overall Combined Database

Table 10.6.1 Sponsor's Table

Table 2.7.4.21. Patient Demographics at Baseline
All Randomized Patients
Acute Placebo-Controlled Combined Database

Demographic Variables	Statistics/ Category	Olanzapine (N=179) n (%)	Placebo (N=89) n (%)	*P-value
Gender	Male	112(62.57)	48(53.93)	.188
	Female	67(37.43)	41(46.07)	
Age	No. of Patients	179	89	
	Mean	15.54	15.74	.200
	Median	15.54	15.62	
	Std. Dev.	1.36	1.42	
	Minimum	13.02	13.06	
	Maximum	17.99	18.00	
Origin	African Descent	30(16.76)	9(10.11)	.359
	Caucasian	123(68.72)	66(74.16)	
	East/Southeast Asian	0(0.0)	1(1.12)	
	Hispanic	20(11.17)	9(10.11)	
	Other	6(3.35)	4(4.49)	
Country	United States	133(74.30)	67(75.28)	1.00
	Puerto Rico	12(6.70)	6(6.74)	
	Russia	34(18.99)	16(17.98)	

Table 10.6.2 Sponsor's Table. Age Distribution at Baseline (HGIN + HGIU)

Table 2.7.4.22. Age Distribution at Baseline
All Randomized Patients
Acute Placebo-Controlled Combined Database

	HGIN		HGIU		Combined	
Age Group	n	%	n	%	n	%
13	9	8.4%	31	19.3%	40	14.9%
14	13	12.1%	38	23.6%	51	19.0%
15	20	18.7%	50	31.1%	70	26.1%
16	29	27.1%	27	16.8%	56	20.9%
17	36	33.6%	15	9.3%	51	19.0%
Total	107	100.0%	161	100.0%	268	100.0%

Table 10.6.3 Sponsor's Table. Patient Demographics at Baseline – Overall Olanzapine Combined Database

Table 2.7.4.24. Patient Demographics at Baseline
All Patients with Olanzapine Exposure
Overall Olanzapine Exposure Combined Database

Demographic Variables	Statistics/ Category	Bipolar (N=227) n (%)	Schizophrenia (N=227) n (%)	Overall (N=454) n (%)
Gender	Male	124(54.63)	162(71.37)	286(63.00)
	Female	103(45.37)	65(28.63)	168(37.00)
Age	No. of Patients	227	227	454
	Mean	15.44	16.38	15.91
	Median	15.43	16.67	16.02
	Std. Dev.	1.33	1.27	1.38
	Minimum	13.02	13.03	13.02
	Maximum	18.00	18.00	18.00
Origin	African Descent	22(9.69)	28(12.33)	50(11.01)
	Caucasian	166(73.13)	189(83.26)	355(78.19)
	East/Southeast Asian	1(0.44)	0(0.0)	1(0.22)
	Hispanic	31(13.66)	6(2.64)	37(8.15)
	Other	7(3.08)	4(1.76)	11(2.42)
Country	United States	205(90.31)	58(25.55)	263(57.93)
	Puerto Rico	21(9.25)	1(0.44)	22(4.85)
	Russia	1(0.44)	79(34.80)	80(17.62)
	Germany	0(0.0)	89(39.21)	89(19.60)

10.7 Weight Gain – Additional Analyses

Table 10.7.1. Weight Change by Visit (OC): Overall Combined Database

				Change to Maximum		
		Visit Week	N	Mean	Std	P-value
Weight (kg)	Bipolar	≤ 1	224	1.27	1.55	< 0.001
	Schizophrenia		224	1.75	1.51	< 0.001
	Overall		448	1.51	1.55	< 0.001
	Bipolar	> 1 ≤ 2	221	2.29	2.04	< 0.001
	Schizophrenia		219	2.73	1.96	< 0.001
	Overall		440	2.51	2.01	< 0.001
	Bipolar	> 2 ≤ 3	183	3.07	2.62	< 0.001
	Schizophrenia		148	3.46	2.24	< 0.001
	Overall		331	3.25	2.46	< 0.001
	Bipolar	> 3 ≤ 4	199	3.74	2.84	< 0.001
	Schizophrenia		201	4.02	2.51	< 0.001
	Overall		400	3.88	2.68	< 0.001
	Bipolar	> 4 ≤ 5	167	4.05	3.31	< 0.001
	Schizophrenia		147	4.66	2.42	< 0.001
	Overall		314	4.34	2.94	< 0.001
	Bipolar	> 5 ≤ 9	157	6.03	3.80	< 0.001
	Schizophrenia		130	7.12	3.80	< 0.001
	Overall		287	6.52	3.83	< 0.001
	Bipolar	> 9 ≤ 13	121	7.59	4.95	< 0.001
	Schizophrenia		117	8.17	4.84	< 0.001
	Overall		238	7.87	4.89	< 0.001
	Bipolar	> 13 ≤ 17	114	8.84	5.87	< 0.001
	Schizophrenia		103	9.01	6.03	< 0.001
	Overall		217	8.92	5.93	< 0.001
	Bipolar	> 17 ≤ 21	102	9.69	6.43	< 0.001
	Schizophrenia		88	10.2	6.75	< 0.001
	Overall		190	9.93	6.56	< 0.001
	Bipolar	> 21 ≤ 25	93	10.19	6.98	< 0.001
	Schizophrenia		81	10.84	6.92	< 0.001
	Overall		174	10.49	6.94	< 0.001
	Bipolar	> 25 ≤ 32	53	9.60	7.12	< 0.001
	Schizophrenia		78	11.68	7.62	< 0.001
	Overall		131	10.84	7.46	< 0.001

From Sponsor table APP.2.7.4.7.1.18 in summary-clin-safe-app document

Table 10.7.2. Adverse Event "Weight Increased" Gender Analysis: HGIU and HGIN Acute Phases

			Olanzapine			Placebo			p-value	Homogeneity of Odds Ratio
		Gender	N	n	%	N	n	%		
Weight Increased	HGIU	Female	46	16	35%	30	1	3%	0.001	
		Male	61	15	25%	24	1	4%	0.033	0.628
	HGIN	Female	21	6	29%	11	2	18%	0.681	
		Male	51	16	31%	24	1	4%	0.008	0.186
Weight Increased	HGIU	< 15 yrs	49	14	29%	20	0	0	0.007	
		≥ 15 yrs	58	17	29%	34	2	6%	0.008	0.280
	HGIN	< 15 yrs	15	6	40%	7	1	14%	0.350	
		≥ 15 yrs	57	16	28%	28	2	7%	0.045	0.868

From Sponsor Tables HGIN.14.28 and HGIU.14.31

Table 10.7.3. Mean Change in Weight (kg) – Subgroup Analyses: HGIN

				Baseline		Change to Endpoint					
	Subgroup	Therapy	n	Mean	St.Dev	Mean	St. Dev	LS Mean	LSMean Diff	P-value	P-value
HGIN											
Weight (kg)	Female	Olanzapine	21	64.0	16.6	3.8	3.7	3.4			
		Placebo	10	61.0	12.5	0.8	3.5	0.7	2.73	0.063	
	Male	Olanzapine	51	68.3	11.6	4.5	3.2	4.6			
		Placebo	24	72.2	17.6	-0.2	2.5	-0.2	4.76	< 0.001	0.140
	< 15 yrs	Olanzapine	15	64.7	14.0	6.3	4.2	5.2			
		Placebo	7	62.5	9.6	1.1	4.1	-0.2	5.37	0.009	
	≥ 15 yrs	Olanzapine	57	67.7	13.2	3.7	2.9	3.8			
		Placebo	27	70.6	18.1	-0.1	2.4	-0.1	3.84	< 0.001	0.370

From Sponsor Tables HGIN.14.47

Table 10.7.4. Mean Change from Baseline to Endpoint in Laboratory Values – Patients Who Gained > 3.9 kg vs. Placebo

The LS Mean Change and p-value for the entire population is in parenthesis for comparison purposes

			Baseline	Change to Endpoint			
	Therapy	n	Mean	Mean	LS Mean Change	LSMean Diff	P-value
AST (U/L)	Olanzapine	84	21.9	9.5	11.3		
	Placebo	87	23.6	-2.5	-0.4	11.7	< 0.001
						(8.91)	(0.002)
ALT (U/L)	Olanzapine	84	20.8	25.8	29.6		
	Placebo	87	20.4	-3.1	1.0	28.5	< 0.001
						(23.0)	(< 0.001)
CPK (U/L)	Olanzapine	84	125	18.1	16.8		
	Placebo	87	164	-23.6	-21.9	38.7	0.037
						(16.1)	(0.38)
Glucose, fasting	Olanzapine	58	88.8	3.2	4.3		
(mg/dL)*	Placebo	64	89.7	-2.9	-2.0	6.3	0.001
						(5.6)	(< 0.001)
Cholesterol (mg/dL)*	Olanzapine	84	164.1	17.4	13.5		
	Placebo	87	160.2	-1.1	-4.6	18.5	< 0.001
						(14.3)	(< 0.001)
Triglycerides (mg/dL)*	Olanzapine	84	97.3	51.3	46.9		
	Placebo	87	110.6	-4.4	-7.1	54.0	< 0.001
						(33.6)	(<0.001)
LDL (mg/dL)*	Olanzapine	84	96.1	6.6	3.1		
	Placebo	87	91.5	-0.39	-3.5	6.6	0.038
						(6.6)	(0.016)
Prolactin (ng/ml)	Olanzapine	79	13.3	12.6	12.0		
	Placebo	80	14.9	-0.2	-0.9	12.91	< 0.001
						(11.7)	(< 0.001)

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259

10.8 Patients with Possible Suicidal Behavior or Ideation Events
HGIU + HGIN Acute Database

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Therapy	Days to Event	Fatal?
HGIU-001-0103	THE PATIENT HAS REPORTEDLY BEEN HAVING DIFFICULTIES WITH DYSPHORIC MOOD. IN MID TO LATE APRIL, 2003, HE TRIED TO TIE A BELT AROUND HIS NECK RESULTING IN A RASH.	5	Placebo	23	No
HGIU-012-1206	INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM	5	Olz	22	No
HGIU-012-1211	SUICIDAL IDEATION / SUICIDAL IDEATION	4	Olz	14	No

Overall Combined Database

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIN-019-1901	SUICIDAL IDEATION / SUICIDAL IDEATION	4	167	No
HGIN-026-2603	SUICIDAL IDEATION / SUICIDAL IDEATION	4	135	No
HGIN-030-3001	SUBJECT IS EXPERIENCING SYMPTOMS OF DELUSIONS, AUDITORY AND VISUAL HALLUCINATIONS, AND SUICIDAL IDEATIONS SUBJECT WILL BE HOSPITALIZED FOR STABILIZATION ON TRADITIONAL MEDICATION	4	51	No
HGIN-930-9307	SUICIDE ATTEMPT / SUICIDE ATTEMPT	2	59	No
HGIU-001-0108	ALCOHOL POISONING / ETOH INTOXICATION. LSS: ON (b) (6) NEARLY SIX MONTHS AFTER STARTING STUDY DRUG, THE PATIENT WAS ADMITTED TO THE HOSPITAL WITH ALCOHOL ("ETOH") POISONING. THE PATIENT WAS RECEIVING 15MG OLANZAPINE AT THE TIME OF THE EVENT. THIS WAS THE FIRST PSYCHIATRIC HOSPITALIZATION FOR THIS 14-YEAR OLD WHO WAS BROUGHT TO THE EMERGENCY ROOM (ER) BY POLICE AFTER THE PATIENT BECAME INTOXICATED, VOICED SUICIDAL IDEATION, AND PASSED OUT AT SCHOOL. APPROXIMATELY (b) (6) (A WEEK AND A HALF A GO), THE PATIENT TRIED TO JUMP OUT OF HER MOTHER'S MOVING VEHICLE AT 55 MILES PER HOUR, BUT THE MOTHER PREVENTED HER FROM FALLING OUT.	3	157	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIU-012-1206	INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM	5	22	No
HGIU-012-1211	SUICIDAL IDEATION / SUICIDAL IDEATION	4	14	No
HGIU-012-1212	THE PATIENT HAD BEEN DRAWING PICTURES OF HOW THE PATIENT COULD DIE . . . THE PATIENT COULD NOT ASSURE THE INVESTIGATOR THAT SHE WOULDN'T HARM HERSELF.	4	34	No
HGIU-013-1301	SUICIDAL IDEATION / OCCASIONAL SUICIDAL THOUGHTS	4	71	No
HGIU-013-1310	INTENTIONAL SELF-INJURY / SELF INJURY	5	64	No
HGIU-020-2016	SUICIDE ATTEMPT / ATTEMPTED SUICIDE	2	214	No
HGIU-026-2604	SELF INJURIOUS BEHAVIOUR / SELF-INJURIOUS BEHAVIOR. LSS: THE PATIENT REPORTED THAT HIS DEPRESSION WORSENED APPROXIMATELY ONE WEEK PRIOR (~05-NOV-2003). ADDITIONALLY HE BEGAN FEELING SUICIDAL (WITHOUT PLAN) APPROXIMATELY THREE DAYS PRIOR (~09-NOV-2003). THE PATIENT'S MOTHER CALLED THE SITE TO REPORT THAT THE PATIENT HAD CUT HIMSELF THE PRIOR EVENING AND DIDN'T FEEL SAFE. THE PATIENT WAS BROUGHT TO THE HOSPITAL FOR SAFETY AND STABILIZATION.	4	59	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIU-026-2605	THE PATIENT WAS BEHAVING INAPPROPRIATELY AND WAS ON THE ROOF OF HIS HOME REFUSING TO COME DOWN	9	53	No
HGIU-026-2606	SUICIDAL IDEATION / SUICIDAL IDEATION	4	35	No
HGIU-027-2705	INTENTIONAL SELF-INJURY / SELF-INFLICTED SUPERFICIAL LACERATIONS	5	76	No
HGIU-028-2805	SUICIDAL IDEATION / SUICIDAL IDEATION. LSS: THE PATIENT'S MOTHER CALLED THE INVESTIGATOR'S SITE ON 14-MAY-2004 TO STATE THAT HER DAUGHTER HAD BECOME SUICIDAL WITH A PLAN TO OVERDOSE ON LORAZEPAM (ATIVAN) DURING THE LAST WEEK OF MAY 2004, BUT ENDED UP TELLING HER PARENTS THE EVENING OF 09-MAY-2004.	3	108	No
HGIU-730-7302	SUICIDAL IDEATION / PASSIVE SUICIDAL IDEATION	4	177	No
HGMF-003-0304	EXACERBATION OF BIPOLAR ILLNESS WITH POSITIVE SUICIDAL IDEATION	4	29	No
HGMF-008-0805	INTENTIONAL SELF-INJURY, CUTTING LEFT ARM	5	93	No
LOAY-400-4001	PATIENT IS IN A DEPRESSIVE MOOD AROUND 10-11.05.99 AND EXPRESSES SUICIDALTHOUGHTS, SIGNIFICANTLY SLOWED MOVEMENT.	4	44	No
LOAY-401-4012	SELF-INJURIOUS BEHAVIOR, SELF-INJURY	5	16	No
LOAY-407-4077	SELF INJURIOUS BEHAVIOR, SELF-INFLICTING TENDENCIES	5	55	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
LOAY-407-4078	SUICIDAL IDEATION, ACUTE SUICIDAL TENDENCIES	4	4	No
LOAY-413-4150	SUICIDAL IDEATION, SUICIDAL TENDENCY	4	27	No

10.9 Laboratory Evaluations – Mean Change from Baseline to Endpoint

Table 10.9.1 Sponsor's Table. Mean Change from Baseline to Endpoint: HGIN + HGIU Acute Database

Table 2.7.4.33. Laboratory Evaluations
Mean Change from Baseline to Endpoint
Acute Placebo-Controlled Combined Database

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
HEMATOCRIT	1	Olz	174	0.43	0.03	-0.01	0.03	-0.01	-0.01	<.001
		Placebo	87	0.43	0.04	-0.00	0.03	-0.00		
HEMOGLOBIN	mml/L-F	Olz	174	8.93	0.78	-0.30	0.47	-0.30	-0.22	<.001
		Placebo	87	8.93	0.83	-0.08	0.41	-0.07		
ERYTHROCYTE COUNT	TI/L	Olz	174	5.00	0.39	-0.15	0.27	-0.15	-0.11	.002
		Placebo	87	4.99	0.49	-0.04	0.26	-0.04		
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mml/L-F	Olz	174	20.87	0.92	-0.00	0.76	0.02	0.16	.100
		Placebo	87	21.00	0.79	-0.17	0.73	-0.14		
LEUKOCYTE COUNT	GI/L	Olz	174	7.27	1.92	-0.19	1.86	-0.10	-0.32	.201
		Placebo	87	7.18	1.91	0.14	1.99	0.21		
NEUTROPHILS, SEGMENTED	GI/L	Olz	174	4.22	1.59	-0.13	1.67	-0.06	-0.29	.203
		Placebo	87	4.29	1.48	0.17	1.79	0.23		
LYMPHOCYTES	GI/L	Olz	174	2.38	0.66	-0.09	0.49	-0.06	-0.07	.297
		Placebo	87	2.24	0.60	-0.02	0.51	0.01		
MONOCYTES	GI/L	Olz	174	0.43	0.14	0.02	0.17	0.01	0.01	.544
		Placebo	87	0.41	0.16	0.01	0.17	0.00		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
EOSINOPHILS	GI/L	Olz	174	0.20	0.21	0.01	0.16	0.01	0.04	.042
		Placebo	87	0.19	0.14	-0.02	0.10	-0.03		
BASOPHILS	GI/L	Olz	174	0.05	0.03	-0.01	0.03	-0.01	-0.01	.008
		Placebo	87	0.05	0.03	0.00	0.03	0.00		
MEAN CELL VOLUME (MCV)	fL	Olz	174	85.96	4.66	-0.25	2.53	-0.02	-0.97	.005
		Placebo	87	85.76	4.59	0.72	2.78	0.95		
PLATELET COUNT	GI/L	Olz	173	291.08	68.65	1.26	46.42	2.44	6.09	.339
		Placebo	87	286.54	63.84	-4.68	52.18	-3.66		
LYMPHOCYTES, ATYPICAL	GI/L	Olz	1	0.06		0.03		0.03		
UA-SPECIFIC GRAVITY	NO UNIT	Olz	156	1.02	0.01	-0.00	0.01	-0.00	-0.00	.292
		Placebo	72	1.02	0.01	-0.00	0.01	-0.00		
AST/SGOT	U/L	Olz	175	24.53	29.87	6.43	26.41	9.89	8.91	.002
		Placebo	87	23.63	8.46	-2.47	7.51	0.98		
ALT/SGPT	U/L	Olz	175	24.13	45.95	19.95	54.84	28.11	22.98	<.001
		Placebo	87	20.39	13.05	-3.08	11.69	5.13		
CREATINE PHOSPHOKINASE	U/L	Olz	175	141.28	138.78	-7.31	131.11	2.81	16.06	.376
		Placebo	87	164.36	160.04	-23.62	152.22	-13.25		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
ALKALINE PHOSPHATASE	U/L	Olz	175	152.33	82.35	-1.35	25.61	-2.74	2.57	.396
		Placebo	87	138.67	86.92	-3.97	16.63	-5.31		
GGT (GGPT/SGGT/YGGT)	U/L	Olz	175	18.99	12.31	7.47	20.02	7.73	7.89	<.001
		Placebo	87	17.68	8.49	-0.43	5.96	-0.16		
THYROID STIMULATING HORMONE	mU/L	Olz	6	2.73	2.32	0.11	1.02	-0.12		
UREA NITROGEN	mmol/L	Olz	175	4.40	1.18	0.22	1.18	0.14	0.39	.010
		Placebo	87	4.37	1.06	-0.17	1.06	-0.25		
CREATININE	umol/L	Olz	175	93.29	14.47	-2.90	9.85	-2.07	-1.80	.147
		Placebo	87	95.83	12.43	-1.08	8.56	-0.27		
CALCIUM	mmol/L	Olz	175	2.48	0.08	-0.03	0.09	-0.03	-0.02	.215
		Placebo	87	2.50	0.12	-0.01	0.10	-0.02		
SODIUM	mmol/L	Olz	175	141.70	2.27	-0.05	2.83	-0.12	0.49	.190
		Placebo	87	141.78	2.44	-0.53	2.94	-0.61		
POTASSIUM	mmol/L	Olz	175	4.32	0.33	-0.04	0.36	-0.07	0.04	.462
		Placebo	87	4.41	0.42	-0.07	0.41	-0.10		
ALBUMIN	g/L	Olz	175	45.07	3.75	-2.01	3.20	-2.13	-1.70	<.001
		Placebo	87	45.39	3.03	-0.31	2.90	-0.43		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
GLUCOSE, FASTING	mmol/L	Olz	135	4.89	0.55	0.15	0.58	0.15	0.31	<.001
		Placebo	64	4.98	0.57	-0.16	0.56	-0.17		
GLUCOSE, NON-FASTING	mmol/L	Olz	141	5.04	0.83	0.17	1.13	0.12	0.15	.374
		Placebo	73	5.01	0.79	0.03	1.23	-0.03		
URIC ACID	umol/L	Olz	175	331.18	74.27	25.21	51.54	30.87	26.95	<.001
		Placebo	87	329.40	84.01	-1.86	53.02	3.92		
CHOLESTEROL	mmol/L	Olz	175	4.17	0.83	0.34	0.59	0.33	0.37	<.001
		Placebo	87	4.15	0.85	-0.03	0.63	-0.04		
TRIGLYCERIDES	mmol/L	Olz	175	1.18	0.66	0.33	0.91	0.30	0.38	<.001
		Placebo	87	1.25	0.73	-0.05	0.62	-0.07		
LDL CHOLESTEROL	mmol/L	Olz	175	2.42	0.74	0.16	0.52	0.14	0.17	.016
		Placebo	87	2.37	0.76	-0.01	0.53	-0.02		
BILIRUBIN, TOTAL	umol/L	Olz	175	7.84	5.27	-1.73	3.82	-2.21	-2.52	<.001
		Placebo	87	8.56	5.33	0.78	5.96	0.31		
BILIRUBIN, DIRECT	umol/L	Olz	175	1.84	1.07	-0.33	1.07	-0.36	-0.38	.005
		Placebo	87	2.01	1.08	0.05	0.93	0.02		
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Olz	175	1.22	0.31	0.03	0.23	0.02	0.03	.331

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Placebo	87	1.21	0.25	-0.00	0.25	-0.01		
PROLACTIN	ug/L	Olz	163	14.06	9.92	11.44	14.52	10.51	11.66	<.001
		Placebo	80	14.95	11.86	-0.16	10.69	-1.15		
HEMOGLOBIN A1C	1	Olz	6	0.05	0.00	-0.00	0.00	-0.00	0.00	.741
		Placebo	3	0.05	0.01	-0.00	0.00	-0.00		

10.10 Prolactin Analysis by Gender

Table 10.10.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: HGIU + HGIN Acute Database.

Laboratory Evaluations	Gender	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value	**P-value
PROLACTIN	Female	Olz	63	15.87	10.06	15.63	16.86	14.26	14.25	<.001	.236
		Placebo	37	15.25	7.59	1.35	9.20	0.00			
	Male	Olz	100	12.92	9.71	8.80	12.20	8.70	10.12	<.001	
		Placebo	43	14.70	14.67	-1.46	11.78	-1.42			

10.11 Vital Signs – Mean Change from Baseline to Endpoint

Table 10.11.1 Vital Signs, Weight, Height and BMI - Mean Change from Baseline to Endpoint (LOCF). HGIN + HGIU Acute Database

Vital Signs	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Systolic Blood Pressure - Supine	Olz	177	111.52	10.95	2.94	10.57	1.73	3.66	.009
	Placebo	89	112.79	13.18	-0.71	10.90	-1.93		
Systolic Blood Pressure - Standing	Olz	177	113.33	12.25	3.14	12.06	2.16	1.94	.225
	Placebo	89	112.18	13.25	1.22	12.51	0.23		
Systolic Blood Pressure - Orthostatic	Olz	177	-1.81	9.63	-0.20	11.68	-0.43	1.72	.262
	Placebo	89	0.61	8.33	-1.93	11.83	-2.15		
Diastolic Blood Pressure - Supine	Olz	177	67.71	9.27	1.24	9.74	1.56	2.17	.095
	Placebo	89	68.19	8.53	-0.92	10.27	-0.61		
Diastolic Blood Pressure - Standing	Olz	177	72.86	10.12	1.42	10.25	-0.24	2.73	.033
	Placebo	89	73.56	9.48	-1.28	9.14	-2.97		
Pulse - Supine	Olz	177	73.88	11.40	7.07	13.99	7.55	7.71	<.001
	Placebo	89	74.15	12.81	-0.60	12.04	-0.16		
Pulse - Standing	Olz	177	83.77	12.73	6.97	14.83	6.55	7.90	<.001
	Placebo	89	85.55	12.98	-0.89	14.69	-1.35		
Pulse - Orthostatic	Olz	177	9.89	11.23	-0.11	13.37	-1.01	0.19	.914
	Placebo	89	11.40	11.15	-0.29	13.09	-1.19		

Vital Signs	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Temperature in Centigrade	Olz	177	36.57	0.44	-0.03	0.49	-0.03	-0.03	.695
	Placebo	88	36.58	0.42	-0.00	0.49	-0.00		
Weight in Kg	Olz	177	66.03	17.93	3.90	2.72	3.68	3.66	<.001
	Placebo	88	67.63	17.24	0.24	2.16	0.01		
Height in cm	Olz	177	165.84	10.13	0.48	1.22	0.46	0.18	.235
	Placebo	88	167.59	9.67	0.31	1.01	0.28		
Body Mass Index	Olz	177	23.91	6.01	1.22	1.01	1.11	1.17	<.001
	Placebo	88	23.98	5.67	0.05	0.91	-0.07		

10.12 Potentially Clinically Significant Definitions for Safety Analyses

Table 2.7.4.6. Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs and Weight

Parameter	Low	High
Orthostatic hypotension (mm Hg)	≥20 mm Hg decrease in systolic BP (supine to standing) and ≥10 bpm increase in pulse (supine to standing)	--
Supine systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Standing systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Supine diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Standing diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Supine pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Standing pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Temperature (°F)[a]	--	≥101°F and increase ≥2
Weight (kg)	decrease ≥7%	increase ≥7%

10.13 Postmarketing Reports - Fatalities

Table 10.13.1. Postmarketing Reports – Fatalities

Patient Identifier	Date of Death	Dose/Duration	Event	Concom Rx	Comments
BR200605002130 16 YOM	(b) (6)	7.5 mg 10/05 – 4/06	Sudden death, cardiac arrest, prescribed overdose, suicide attempt, depression, psychosis	Alprazolam	Brazil Autopsy done, result will be available by June 2006 (per summary)
BE200602002031 17 YOF	(b) (6)	Unknown ~6 years	Bilateral pneumonia, gastric hemorrhagia, fever, coma	Not reported	Belgium (no autopsy)
US_0510123183 14 YO	(b) (6)	Unknown	Toxic exposure, completed suicide	Fluoxetine Risperidone	Literature
JP_051007889 17 YOM	(b) (6)	5 mg, 8/2005 – 10/05	Completed suicide, suicidal ideation, apathy	Lorazepam	Japan "Police told psychiatrist about patient's death, no details provided" [prior suicide attempt per hx]
CA_050708496 17 YOM	(b) (6)	15 mg 11/03 – 6/05	Completed suicide	Lorazepam Flupentixol decanoate	Canada 5 days after discontinuing olanzapine, committed suicide (method unknown) Not known whether autopsy performed.
US_0506118439 17 YOF	Unknown (b) (6) estimated	Unknown, 7/1999 - 2004	Death, weight increased, diabetes mellitus, hyperglycemia, multiple drug overdose, triglycerides increased, cholesterol abnormal, musculoskeletal chest pain		Reported by attorney via legal department
EWC050644285 17 YOF	(b) (6)	5 mg 3/5/05 – 3/6/05	Endotoxic shock, kidney infection, sepsis, acute abdomen, disseminated intravascular blood coagulation, myeloid hyperplasia of spleen, pancreatitis, gastric		Russian Federation

			ulcer perforation, peritoneal infection		
US_0506118189 15 YOM	Unknown (b) (6) estimated	~ May 2003 - unknown	Death		Reported by an attorney via the legal department Cause of death not provided
CA_050207717 16 YOM	(b) (6)	Unknown	Completed suicide	Isotretinoin mepha	Canada No details provided
US_0412108962 16 YOM	Unknown (b) (6) estimated	1-2002 – unknown	Death, diabetes mellitus		Reported by an attorney via the legal department Cause of death not provided, not known if autopsy performed
JP_041105122 17 YOF	(b) (6)	50 mg 11/10/2004 – 11/10/2004	Intentional overdose, completed suicide	Paroxetine, sulpiride, amoxapine, fluvoxamine, flunitrazepam	Japan "Coroner refused to provide any information"
USA040979162 US_0402100550 15 YOM	(b) (6)	10/29/2003?	Death, coma Accidental overdose, drug toxicity, intentional drug misuse	Metronidazole, topiramate, clonazepam	Reported by an attorney via the legal department Case reported in a newspaper "Patient was sold olanzapine by another individual, not prescribed" Olanzapine Cp = 490 ng/ml postmortem
US_0412109585 15 YOF		11/2000 - unk	Diabetic ketoacidosis, diabetic coma, diabetes mellitus, pain, anxiety, drug ineffective	Methylphenidate, sertraline	Reported to company by an attorney No details provided about the event, unknown if an autopsy was performed
EWC031237179 16 YOM		5 mg, 11/24/2003 – 11/25/2003	Death, pulmonary infarction		Greece Pulmonary infarction per autopsy
USA030742307 13 YOF		5 mg Unknown	Diabetic ketoacidosis, loss of consciousness, dizziness		Diabetic ketoacidosis per autopsy. No labs provided.
USA030741953 17 YOM		8/2002 – 11/2002	Convulsion, heart rate increased	Mixed amphetamine salts, trazodone	Cause of death listed as idiopathic seizure disorder, toxicology screen

					negative
GBS030413039 17 YOM	(b) (6)	12.5 mg 10/2002 – unk	Completed suicide, sedation, eczema	Risperidone, biperiden	United Kingdom Death by drowning, autopsy did not reveal other significant findings
US_020180581 15 YOM	(b) (6)	20 mg Unknown	Acute asthma		Patient had been in blinded study 3/01 – 9/01 prior [F1D-US-X090]; did not receive olanzapine; taking marketed olanzapine at time of event.
US_010973481 17 YOM	Unknown (received by Sponsor (b) (6)	30 mg Unknown	Prescribed overdose, drug toxicity		No details provided, unknown if autopsy performed
EWC010928155 15 YOM	(b) (6)	10 mg 8/1/2001 – 8/28/2001	Death	Dextro-amphetamine	Switzerland Asperger's syndrome Patient drowned while swimming in lake; autopsy unremarkable
CA_010603921 17 YOF	Unknown (received by Sponsor (b) (6)	Unknown	Death	Citalopram, valproate semisodium	Canada Patient "died suddenly", autopsy was completed but not available. "Several attempts at follow-up unsuccessful".
CA_010603802 16 YOM	Unknown (received by Sponsor (b) (6))	10 mg 90 days	Diabetic coma	Valproate sodium Topiramate	Canada No personal history of diabetes. Weight at time of event unknown, labs not provided. "Numerous attempts to obtain follow-up unsuccessful".
US_010566315 16 YOM	(b) (6)	5 mg 730 days	Drug interaction, death, hepatic steatosis	Mixed amphet-Amine salts	Patient found dead. Hepatic steatosis per autopsy, no cause of death provided. Autopsy never provided.
US_010158510 17 YOM	(b) (6)	2.5 mg Unknown	Accidental overdose	Citalopram, trazodone	Patient found dead by family member. Cause of death presumed

					overdose. Olanzapine Cp = 158 ng/ml.
US_000542556 15 YOM	(b) (6)	Unknown 1998 x 120 days	Necrotizing pancreatitis, diabetes mellitus, increased cholesterol	Carbamazepine, paroxetine	Follow-up in the literature
US_000236591 17 YOM	(b) (6)	22.5 mg Unknown	Overdose, death	Fluoxetine, valproate semisodium, nortriptyline, buspirone, haloperidol, thioridazine	Patient died while being restrained by staff in group home.
US97121702A 14 YOM	(b) (6)	12.5 mg 150 days	Asphyxia, agitation	Haloperidol, sertraline	Became agitated on school bus and was restrained and died. Per coroner, cause of death by mechanical asphyxia due to the restraining position.

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/s/

Cara Alfaro
4/6/2007 10:42:11 AM
PHARMACIST

Ni Aye Khin
4/18/2007 11:20:56 AM
MEDICAL OFFICER
I agree with Dr. Alfaro's recommendation that this application be considered for non-approval; see memo to file for additional comments.

CLINICAL REVIEW

Application Type	NDA 20-592
Submission Number	S-040
Submission Code	SE5
Letter Date	10/30/06
Stamp Date	10/31/06
PDUFA Goal Date	04/30/07
Reviewer Name	Cara Alfaro, Pharm.D.
Review Completion Date	04/06/07
Established Name	Olanzapine
Trade Name	Zyprexa
Therapeutic Class	Antipsychotic
Applicant	Eli Lilly
Priority Designation	P
Formulation	Oral tablets
Dosing Regimen	2.5 – 5 mg starting, maximum dose 20 mg/day
Indication	Treatment of Bipolar I Disorder
Intended Population	Adolescents

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1 EXECUTIVE SUMMARY

Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

Recommendation on Postmarketing Actions

1.1.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

1.1.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be adequately addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

Summary of Clinical Findings

1.1.3 Brief Overview of Clinical Program

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar I disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

1.1.4 Efficacy

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -7.66, p < 0.001).

			Baseline		Change to Endpoint				
Efficacy Variable	Therapy	N	Mean	Std	Mean	Std	LSMean Change	LSMean Difference	*P-value
YMRSTOT:Total(1-11)	Olanzapine	105	33.08	6.55	-15.90	10.03	-17.65	-7.66	<.001
	Placebo	54	32.04	6.23	-7.72	9.42	-9.99		

The supportive OC analysis was similar to the LOCF analysis (LS Mean Diff = -5.74, p = 0.001). The supportive MMRM analysis was similar to the LOCF analysis (LS Mean Diff = -6.95, p < 0.001). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

Subgroup analyses included gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds (p = 0.094), patients with psychotic features (p = 0.111) and rapid cyclers (p = 0.271) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found.

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

1.1.5 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIN is the pivotal trial for schizophrenia) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events (≥ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with ≥ 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
HGIN + HGIU Acute Database				
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Weight (kg) Mean Change to Endpoint (OC)	3.6 (n = 154)	0.08 (n = 67)	3.57	< 0.001
BMI	1.22	0.05	1.17	< 0.001

Mean Change to Endpoint (LOCF)				
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001
Overall Combined Database				
Weight (kg) Mean Change to Endpoint (LOCF)	7.35	-	-	< 0.001 (compared to baseline)
Weight (kg) Mean Change to Endpoint (OC)	10.8	-	-	< 0.001 (compared to baseline)
BMI Mean Change to Endpoint (LOCF)	2.31	-	-	< 0.001 (compared to baseline)
≥ 7% increase in body weight (%)	65%	-	-	-

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits.

In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

Hypertriglyceridemia
The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, $p < 0.001$). In reviewing the individual lab data, 11 marked outliers were noted for triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) ($p = 0.039$).

Hypercholesterolemia
The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, $p < 0.001$). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) ($p = 0.023$).

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these

types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation is not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

Although there are significant risks outlined in this review, there is also significant morbidity and mortality associated with untreated bipolar I disorder.

(b) (4)

(b) (4)

2 INTRODUCTION AND BACKGROUND

Product Information

Olanzapine (Zyprexa) is an atypical antipsychotic. Olanzapine oral tablets were approved on 9/30/1996 for the treatment of schizophrenia in adults. Olanzapine is also available as Zyprexa Zydis, orally disintegrating tablets and Zyprexa IntraMuscular for injection.
Olanzapine oral tablets are currently approved for the following indications: treatment of schizophrenia, treatment of acute mixed or manic episodes associated with bipolar I disorder, maintenance monotherapy for bipolar I disorder, and combination therapy (with lithium or valproate) for the short-term treatment of acute mixed or manic episodes associated with bipolar I disorder.

Olanzapine is not currently indicated for use in child/adolescent populations.

Currently Available Treatment for Indications

Other currently available atypical antipsychotics include clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify), quetiapine (Seroquel), ziprasidone (Geodon). Many of these atypical antipsychotics are approved for the indication treatment of acute mixed or manic episodes associated with bipolar I disorder, but none are approved for use in children/adolescents.

Risperidone (Risperdal) was recently approved for the indication “treatment of irritability associated with autistic disorder in children and adolescents” (5 to 16 years of age).

Lithium (various salts) and divalproex sodium are indicated in the treatment of manic episodes of bipolar I disorder in adults.

Important Issues With Pharmacologically Related Products

Although the atypical antipsychotics have less extrapyramidal side effects compared to typical antipsychotics, the adverse event profile is notable for weight gain, hyperglycemia, and diabetes mellitus in adults. Little data is available with regard to the adverse event profile in other populations including children and adolescents.

Presubmission Regulatory Activity

This summary was taken from the note to reviewer document contained in the Sponsor’s submission.

On June 11, 1999, Eli Lilly and Company (Lilly) submitted a Proposed Pediatric Study Request to FDA related to the conduct of pediatric studies of Zyprexa.

In response to Lilly's proposed pediatric study request, the FDA issued to Lilly a Written Request for Pediatric Studies dated November 30, 2001 (reissued under the Best Pharmaceuticals for Children Act (BPCA) on July 3, 2002) and amended on April 9, 2002, May 7, 2004, and June 29, 2005. FDA's Written Request (WR) as amended, included a request for clinical data on the use of Zyprexa to treat adolescents with schizophrenia and adolescents with acute bipolar mania in order to make Zyprexa eligible for the pediatric exclusivity extension under Section 505A of the Federal Food, Drug, and Cosmetic Act. More details regarding FDA's WR, and Lilly's response, are provided in Item 20 of this submission.

FDA granted an indication for olanzapine for the treatment of bipolar mania in adults (NDA 20-592/S006) on March 17, 2000. As part of the approval, the FDA requested a study in pediatric patients with bipolar mania as a post-marketing commitment. Study F1D-MC-HGIU is included in this submission to fulfill this post-marketing commitment.

On January15, 2004, the FDA met with Lilly to discuss the PK package proposed by Lilly to fulfill FDA's Written Request for Pediatric Studies. At this meeting, Lilly provided an overview of the available PK data. FDA requested additional justification of

the utility of the data from Study LOAY in order to make a final decision on whether or not the data is acceptable to sufficiently meet the PK aspects of the Written Request.

On March 22, 2004 Lilly submitted to IND 28,705 additional information regarding study LOAY and requested a meeting to further discuss fulfillment of the PK aspects of the WR. In response to questions from FDA sent to Lilly on July 7, 2004, Lilly submitted additional information to IND 28,705 on July 13, 2004.

Lilly met with FDA on July 21, 2004 to again discuss the PK information needed to fulfill the WR. At that meeting, FDA agreed with Lilly's proposal to provide PK data in adolescents from Studies HGCS, HGCR, HGGC, and LOAY to address the PK requirements outlined in the Written Request.

In discussions with FDA, it was noted that information about the exact sampling time relative to the dose were not collected as part of the protocol in Study LOAY; however, extensive simulations showed that lack of data regarding timing of samples in Study LOAY should not adversely affect the ability to perform a meaningful population analysis. Nonetheless, to assure the robustness of the PK data, Lilly collected additional population PK data in adolescent patients with schizophrenia or bipolar disorder by conducting Study HGMF. Inclusion of data from Study HGMF in this submission was discussed at a pre-NDA meeting on March 17, 2006. At that meeting, FDA requested that Lilly conduct the population PK analysis both with and without the data from Study LOAY. Both analyses were conducted by Lilly and are included with this submission. The population PK analysis also includes a comparison of pediatric olanzapine PK data with the adult olanzapine PK data from Study HGAJ.

The format and content of the submission were also discussed and agreed to at the March 17, 2006 pre-sNDA meeting. The FDA indicated that, based on the pre-sNDA package and discussions, the proposed submission content appeared to be adequate to respond to FDA's Written Request and that Study HGIU appeared to be adequate to fulfill the post-marketing commitment which was part of the bipolar mania in adults approval.

In the 11/30/01 written request, the Division stated "We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug". The Division also recommended that a relapse prevention trial should follow the acute treatment trial. The Sponsor did not follow either recommendation and neither was required in order to fulfill the pediatric written request.

Other Relevant Background Information

The Pediatric Exclusivity Board met on January 10, 2007 to determine whether the Sponsor had fulfilled the requirements in the written request. It was determined that the requirements had been met and exclusivity was granted.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Statistics

The statistician (Fanhui Kong) reviewed the efficacy data from the pivotal trial, HGIU. In general, the data submitted by the Sponsor provide evidence for efficacy per his review (see Statistical review).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Tables of Clinical Studies

The Sponsor included study reports for 9 pediatric studies in this submission. HGIN is the pivotal study for adolescent schizophrenia and HGIU is the pivotal study for adolescent bipolar I disorder. HGMF is the primary study for determining pharmacokinetic parameters in the adolescent population. The other studies are supportive and provide safety and pharmacokinetic data.

Table 4.1.1 Summary of Clinical Studies

Study	Description	Length	Age Range (years)	Number of Patients
HGIN	MC, DB, PC study in adolescent patients with schizophrenia. Flexible dose olanzapine (2.5 – 20 mg) U.S. and Russia sites	6 weeks DB 26 weeks OL extension	13 to 17	107 (n = 72 olanzapine, n = 35 placebo)
HGIU	MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder. Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico	3 weeks DB 26 weeks OL extension	13 – 17	161 (n = 107 olanzapine, n = 54 placebo)
LOAY	OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders Flexible dose olanzapine (5 – 20 mg) German sites	24 weeks	12 – 21	96 (n = 89, 13-17 years)
HGMF	OL study in adolescent patients with schizophrenia or bipolar I disorder Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico, Russia	4.5 weeks	13 – 17	107 (n = 37 schizophrenia, n = 70 bipolar)

HGCS	OL study in adolescent patients with schizophrenia Dosing: 2.5 to 20 mg/day Single site	8 weeks	10 – 18	8
HGCR	DB study in adolescent patients with schizophrenia, haloperidol as active comparator Dosing: 2.5 qod – 20 mg/day Single site	8 weeks	12 – 16	2
HGGC	OL study in children and adolescents with bipolar disorder Dosing: 2.5 to 20 mg/day Single site (U.S.)	8 weeks	5 – 14	23

Modified from Sponsor Table 2.5.1.1 clinical-overview.
MC = multicenter, DB = double-blind, PC = placebo-controlled, OL = open-label

Data Quality and Integrity

The Division of Scientific Investigations was asked to inspect a number of sites for studies HGIN and HGIU – some sites enrolled patients for both studies. DSI was asked to audit one site in Georgia (n = 7 HGIU, n = 5 HGIN) and one site in Ohio (n = 15 HGIU, n = 6 HGIN). The final DSI report was not available at the time this review was completed, but preliminary comments from the investigator did not indicate any major issues thought to effect efficacy.

Compliance with Good Clinical Practices

Per protocols, the studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Of note, one clinical trial site was omitted from the primary efficacy analyses due to significant GCP issues. This site enrolled patients in both HGIU (site 028) and HGIN (site 021). Details regarding the GCP issues are in Section 6.1.3 (Efficacy Findings) of this review.

Financial Disclosures

Financial disclosure information was provided for the study HGIU. Two investigators received ~$40,000 in honoraria or other grant monies (sites 033 and 024), a small number of patients were randomized from these sites (n = 8).

5 CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of oral olanzapine were evaluated primarily in study HGMF (see Table 4.1.1 in Section 4.1 Tables of Clinical Studies) via population pharmacokinetic analyses. These data have been extensively reviewed by the biopharmaceutical reviewer (see Biopharm review).

6 INTEGRATED REVIEW OF EFFICACY

One pivotal trial, F1D-MC-HGIU, was submitted to support the efficacy of olanzapine in the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents.

Indication

The Sponsor proposes the following indication "indicated for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents".

6.1.1 General Discussion of Endpoints

The primary efficacy endpoint for the clinical trial was the change from baseline to endpoint on the YMRS-adolescent structured rating scale total score. The YMRS is a standard rating scale used to evaluate efficacy in adult bipolar populations and is appropriate for evaluating efficacy in this clinical trial.
The Sponsor also included the Clinical Global Impression-Severity rating scale to rate severity of mania, depression and overall severity of bipolar disorder. The Children's Rating Scale for Depression was also included to assess depressive symptoms. Due to the presence of mania and depression in bipolar illness, inclusion of these endpoints was appropriate.

6.1.2 Study Design

Protocol F1D-MC-HGIU is the pivotal study submitted to support the indication "for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". The other studies submitted as supportive studies in this population are open-label trials and are supportive primarily from a safety and not efficacy perspective. Therefore, only study HGIU is reviewed here.

Protocol HGIN
"Olanzapine versus placebo in the treatment of mania in adolescents with bipolar I disorder"
First patient enrolled 11/18/02, last patient completed 5/9/05.

Investigators and sites
This study enrolled patients at 23 sites in the United States and 2 sites in Puerto Rico. Investigator and site information (including numbers of patients randomized and completing the trial) are included in Appendix 10.1.

Study Objectives
Primary objective: To assess the efficacy of a flexible dose of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of mania in bipolar I disorder (manic or mixed episode associated with bipolar I disorder, with or without psychotic features) in adolescents (ages 13 – 17) as measured by the difference between treatment groups in mean change from baseline to endpoint in the Adolescent Structured Young-Mania Rating Scale (YMRS) total score.

Secondary objectives:
To assess secondary efficacy measures 1) YMRS individual items; 2) Clinical Global Impression Scale – Bipolar Version Severity of Illness (Severity of Mania, Severity of Depression, Severity Overall); 3) Children's Depression Rating Scale-Revised; 4) Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (investigator administered and scored) and 5) Overt Aggression Scale.

To assess the safety of olanzapine compared with placebo for up to 3 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

To assess the health-related quality of life associated with olanzapine compared with placebo for up to 3 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

Compare the frequency of response during the double-blind treatment period (up to 3 weeks), as defined by a $\geq$ 50% reduction in YMRS total score from baseline to endpoint and a CGI-BP Severity of Mania score of $\leq$ 3 at endpoint for olanzapine vs. placebo treatment.

Study Population
The study population consisted of generally healthy adolescents, ages 13 to 17 inclusive, with a DSM-IV-TR diagnosis of bipolar I disorder and currently displaying an acute manic or mixed episode (with or without psychotic features). The diagnosis was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime (K-SADS-PL). The inclusion and exclusion criteria are listed in Appendix 10.2. Patients must have obtained an YMRS total score $\geq$ 20 at Visit 1 and 2. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations. Exclusion criteria included patients who have been judged clinically to be at serious suicidal risk; patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment; patients currently meeting DSM-IV-TR criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Design
This was a multicenter, randomized, double-blind, parallel, placebo-controlled trial consisting of three periods: screening/washout, 3-week double-blind trial, 26-week open-label olanzapine treatment. The screening/washout period was 2-14 days. Patients were then randomized to olanzapine flexible dose (2.5 to 20 mg/day) or placebo treatment (2:1 randomization) for the 3-week acute double-blind trial. Olanzapine was initiated at 2.5 or 5 mg/day and the dose could be increased by 2.5 or 5 mg/day dose increments at the investigator's discretion. If no tolerability or safety issues were apparent, the dose had to be titrated to at least 10 mg/day by Visit 4 (end of week 1). The investigator could continue to increase the dose by 2.5 or 5 mg/day to the maximum tolerable dose not to exceed 20 mg/day. The investigator could decrease the dose at any time and in any number of dose decrements if patients experienced an adverse event. The minimum allowable olanzapine dose was 2.5 mg/day. During this 3-week acute trial, 3 study visits occurred during the first week and then weekly thereafter.

Patients who did not respond after at least 10 days during the 3-week double-blind trial could participate in the optional 26-week open-label extension study and receive open-label olanzapine therapy (2.5 to 20 mg/day). Response was defined as having a $\geq$ 20% decrease in the YMRS total score compared to baseline and a CGI-BP Severity of Mania score $\leq$ 3. Study visits occurred weekly x 2 visits, biweekly x 4 visits and then monthly until the end of the 26-week study.

Assessments (The Schedule of Events is in Appendix 10.3)
Rating scales – efficacy:
Primary efficacy endpoint: Adolescent Structured Young-Mania Rating Scale (YMRS)
Secondary efficacy endpoints: Clinical Global Impression – Severity of Mania, Severity of Depression, Severity Overall; Children's Depression Rating Scale-Revised; Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version; Overt Aggression Scale (OAS); Child Health Questionnaire (CHQ)

Safety assessments:
Vital signs (blood pressure, pulse, weight, height, temperature) – including orthostatic assessments, ECG, Labs (hematology, clinical chemistry, urinalysis, lipid panel, hepatitis screen and panel, serum pregnancy test, prolactin, thyroid stimulating hormone, HgbA1c, urine drug screen.
Fasting glucose at baseline, end of 3-week study and end of 26-week open-label study.
HbA1c was only obtained for patients with diabetes.

Rating scales: Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Abnormal Involuntary Movement Scale (AIMS)
Spontaneous reporting of adverse events.

6.1.3 Efficacy Findings

One hundred sixty one patients were randomized, 107 to the olanzapine group and 54 to the placebo group. In the olanzapine group, 22 patients discontinued with lack of efficacy as the primary reason for discontinuation for 54.5% of drop-outs. In the placebo group, 19 patients discontinued with lack of efficacy as the primary reason for discontinuation for 84.2% of drop-outs. Drop-outs due to adverse events were the primary reason for discontinuation for 3 patients in the olanzapine group and 1 patient in the placebo group.

Table 6.1.3.1 Patient Disposition

	Olanzapine N = 107	Placebo N = 54	P-value
Completers	85 (79.4%)	35 (64.8%)	0.056
Drop Outs	22 (20.6%)	19 (35.2%)	
Adverse Event	3 (2.8%)	1 (1.9%)	1.00
Lack of Efficacy	12 (11.2%)	16 (29.6%)	0.007
Lost to Follow-up	0	0	-
Patient Decision	4 (3.7%)	1 (1.9%)	0.665
Criteria Not Met/Compliance	0	1 (1.9%)	0.335
Sponsor Decision	0	0	-
Physician Decision	1 (0.9%)	0	1.00
Other	2 (1.9%)	0	0.551

Modified from Sponsor table HGIU.10.1 in study report

Demographics and Baseline Disease Severity

There were no statistically significant differences between the olanzapine and placebo groups with regard to baseline demographics.

Statistically significant differences indicating a potential imbalance in severity of illness were found for several categories – most indicated that more ill patients were randomized into the olanzapine treatment group (although the YMRS baseline scores, the primary efficacy measure, were not statistically different between the groups). Statistical differences were found for the mean number of previous mania episodes (olanzapine = 2.07, placebo = 4.43), mean number of previous depressive episodes (olanzapine = 1.6, placebo = 3.98), mean number of previous mixed episodes (olanzapine = 1.19, placebo = 3.85), psychiatric hospitalization within the past year (olanzapine = 32.1%, placebo = 16.7%). Scores on most rating scales at baseline did not differ between the two treatment groups with the exception of the CGI-Severity Depression (olanzapine = 3.1, placebo = 2.6).

The groups did not differ with regard to the number of patients with psychotic features (olanzapine = 21%, placebo = 13%) or current episode, manic (olanzapine = 41%, placebo = 54%). The groups did differ with regard to the number of rapid cyclers (olanzapine = 23%, placebo = 9%).

Table 6.1.3.2 Baseline Demographics and Severity of Disease

		Olanzapine N = 107	Placebo N = 54	P-value
Gender	Male Female	61 (57.0%) 46 (43%)	24 (44.4%) 30 (55.6%)	0.137
Age (years)	Mean Median St. Dev Minimum Maximum	15.14 15.12 1.28 13.02 17.89	15.38 15.41 1.20 13.07 17.68	0.250
Origin	African descent Caucasian East/Southeast Asian Hispanic Other	13 (12.1%) 71 (66.4%) 0 18 (16.8%) 5 (4.7%)	2 (3.7%) 41 (75.9%) 1 (1.8%) 8 (14.8%) 2 (3.7%)	0.247
Country	America Puerto Rico	95 (88.8%) 12 (11.2%)	48 (88.9%) 6 (11.1%)	1.00
Age of onset of illness (years)	Mean Median St. Dev. Minimum Maximum	10.93 12.00 3.32 1.00* 17.00	11.46 12.00 3.13 4.00 17.00	0.331
No. of Prev. Mania episodes	Mean Median St. Dev. Minimum Maximum	2.07 1.00 4.97 0.00 35.00	4.43 1.00 8.95 0.00 42.00	0.048
No. of Prev. Depressive episodes	Mean Median St. Dev. Minimum Maximum	1.60 1.00 2.84 0.00 20.00	3.98 1.50 8.26 0.00 50.00	0.014
No. of Prev. mixed episodes	Mean Median St. Dev. Minimum Maximum	1.19 0.00 3.65 0.00 25.00	3.85 0.00 9.40 0.00 42.00	0.027
Total hospitalization for the past year (months)	Mean Median St. Dev. Minimum Maximum	0.85 0.50 1.23 0.13 6.00	1.43 0.50 2.53 0.10 8.00	0.327
Length of current episode (days)	Mean Median St. Dev. Minimum Maximum	309.8 45.50 749.1 2.00 4441	237.2 50.50 542.20 4.00 2902	0.521
Days since last hospitalization	Mean Median St. Dev. Minimum Maximum	145.4 8.00 310.3 0.00 1688	361.0 33.00 540.9 0.00 1651	0.072
Psychiatric	Yes	34 (32.08%)	9 (16.67%)	0.040

hospitalization within the past year	No	72 (67.92%)	45 (83.33%)	
Current episode has concurrent psychotic features	Yes No	22 (20.75%) 84 (79.25%)	7 (12.96%) 47 (87.04%)	0.281
Current episode, manic	Yes No	44 (41.1%) 63 (58.9%)	29 (53.7%) 25 (46.3%)	0.136
Rapid Cyclers	Yes No Unknown	25 (23.4%) 71 (66.4%) 11 (10.3%)	5 (9.3%) 43 (79.6%) 6 (11.1%)	0.031
CDRS Raw Total Score	Mean Median St. Dev. Minimum Maximum	40.2 39 15.3 17 82	36.2 33.5 15.5 17 101	0.096
CGI-Severity of depression	Mean Median St. Dev. Minimum Maximum	3.14 4.00 1.57 1.00 6.00	2.65 2.00 1.60 1.00 6.00	0.043
CGI-Severity of mania	Mean Median St. Dev. Minimum Maximum	4.79 5.00 0.70 4.00 6.00	4.81 5.00 0.75 3.00 6.00	0.852
CGI-Severity overall	Mean Median St. Dev. Minimum Maximum	4.79 5.00 0.71 4.00 6.00	4.83 5.00 0.75 3.00 6.00	0.727
YMRS Total score	Mean Median St. Dev. Minimum Maximum	33.05 33.00 6.53 20.00 48.00	32.04 32.00 6.23 21.00 43.00	0.347

Modified from Sponsor table HGIU.11.1, HGIU.11.2, HGIU.11.3, HGIU.11.4, HGIU.11.6 in study report
*An age of onset of 1 year old is highly suspect.

No statistically significant differences were noted between groups in baseline OAS verbal aggression total, OAS physical aggression toward self total, OAS physical aggression toward objects, OAS total, ADHD total, ADHD inattention subtotal. Baseline ADHD hyperactivity-impulsivity subtotal bordered on significance (olanzapine 13.68 vs. placebo 11.67; p = 0.051).

A diagnosis of comorbid ADHD was present in more patients in the olanzapine group compared to the placebo group (42% vs. 24%, p = 0.024). Though not common, a diagnosis of comorbid conduct disorder was present in more patients in the olanzapine group compared to the placebo group (n = 14, n = 1, p = 0.021).

Efficacy Analyses

Site Issues
In the efficacy analysis, the sponsor included analyses with and without site 028. Per the sponsor, site 028 had significant GCP issues and patients from this site were dropped from the primary analyses (efficacy analyses were similar with and without this site). The study report did not specify what the GCP issues were with this site. The sponsor was asked to provide details and indicated the following:

> Lilly discontinued site 021 (Dr. Robb) from study HGIN, and also discontinued Dr Robb's site (site 028) from study HGIU. Lilly informed FDA of the discontinuation of Dr Robb's site from these studies in a submission to IND 28,705; serial number 953, dated May 21, 2004. In a letter dated May 2, 2004 sent to Dr Robb, Lilly listed the following GCP issues that occurred at this site related to studies HGIN and HGIU:
>
> - Not following the randomization procedures outlined in the protocol
> - Not submitting protocol amendment A, approved by Lilly on October 17, 2002, to the Institutional Review Board (IRB) for approval before use
> - Not submitting revised informed consent documents to IRB
> - Not communicating to patients about safety issues in risk profile of study drug. The risk profile was updated by Lilly on December 4, 2003 and faxed to the site on January 6, 2004 and a reminder fax was sent on January 28, 2004.
> - Significant problems with drug accountability
> - Not being able to reconstruct the regulatory document in the Clinical Trial Record Binder
> - Violation of inter-active voice response system (IVRS) security personal identification number process.

Concomitant Medications
Interestingly, 39.3% (42/107) of patients in the olanzapine group and 46.3% (25/54) of patients in the placebo group had no previous medications for bipolar I disorder. It is not known whether these patients participated in nonpharmacological treatment of their disorder.

The most commonly used concomitant medications (> 5% of patients) included benzodiazepines (see next paragraph) and mixed amphetamine salts in 7.5% (8/107) of patients in the olanzapine group and 5.6% (3/54) patients in the placebo group.

There were no statistically significant differences in the frequency of concomitant benzodiazepine use between the olanzapine and placebo groups. Concomitant lorazepam use occurred in 9.3% (10/107) patients in the olanzapine group and 7.4% (4/54) patients in the placebo group. Concomitant temazepam use occurred in 3.7% (4/107) patients in the olanzapine

group and 1.9% (1/54) patients in the placebo group. A few patients in both groups had concomitant clonazepam, alprazolam and diazepam use. There was a statistically significant difference in the mean number of days of benzodiazepine use between the treatment groups: 2.8 ± 3.5 days in the olanzapine group and 10 ± 7.0 days in the placebo group (p = 0.019). The mean dose of benzodiazepines (using equivalent doses) did not differ between the treatment groups: 1.4 ± 0.5 mg in the olanzapine group and 2.0 ± 1.7 mg in the placebo group.

There were no statistically significant differences in the frequency of concomitant anticholinergic medication use between the olanzapine and placebo groups. However, only 5 patients in the study had concomitant use of anticholinergic medications and all 5 were in the olanzapine group: benztropine mesylate (n = 3), amantadine (n = 1), and diphenhydramine (n = 1). The mean number of days on anticholinergic medication was 3 ± 2.6 days. The mean dose of anticholinergic medication was 1.4 ± 0.5 mg.

Primary Endpoint
Primary Analysis - LOCF
The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg.

The primary efficacy analysis is in Table 6.1.3.3 below. The analysis including site 028 was similar, least square mean difference was 7.88 favoring the olanzapine group (p < 0.001).

Table 6.1.3.3 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint – *LOCF*. (Excluding site 028)

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
YMRSTOT:Total(1-11)	Olanzapine	105	33.08	6.55	-15.90	10.03	-17.65	-7.66	<.001
	Placebo	54	32.04	6.23	-7.72	9.42	-9.99		

Supportive Analyses – OC and MMRM
The findings for the OC analysis (Table 6.1.3.4) and MMRM analysis (Table 6.1.3.5) were similar to the LOCF analysis.

Table 6.1.3.4 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Visit– *OC*.

Efficacy Variable	Visit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
YMRSTOT:Total(1-11)	3	Olanzapine	105	33.08	6.55	-7.98	7.26	-6.37	-2.24	.048
		Placebo	54	32.04	6.23	-5.37	6.83	-4.13		
	4	Olanzapine	104	33.11	6.57	-12.62	9.01	-11.46	-3.97	.002
		Placebo	53	32.17	6.21	-8.06	7.38	-7.49		
	5	Olanzapine	103	33.03	6.56	-15.46	9.47	-16.16	-7.40	<.001
		Placebo	53	32.17	6.21	-7.49	10.56	-8.77		
	6	Olanzapine	88	33.23	6.48	-17.17	9.71	-19.14	-5.74	.001
		Placebo	37	32.41	6.19	-11.11	9.05	-13.40		

Sponsor's Table HGIU.14.21

Table 6.1.3.5 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Visit– *MMRM*

Efficacy Variable	Visit (Week)	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean StdErr	LSMean Difference	Diff StdErr	*P-value
YMRSTOT:Total(1-11)	Combined	Olanzapine						-12.41	0.85	-5.19	1.08	<.001
		Placebo						-7.23	1.05			
	3 (0.5)	Olanzapine	105	33.08	6.55	-7.98	7.26	-7.27	0.88	-2.14	1.14	.062
		Placebo	54	32.04	6.23	-5.37	6.83	-5.13	1.09			
	4 (1)	Olanzapine	104	33.11	6.57	-12.62	9.01	-11.84	0.94	-4.08	1.28	.002
		Placebo	53	32.17	6.21	-8.06	7.38	-7.76	1.19			
	5 (2)	Olanzapine	103	33.03	6.56	-15.46	9.47	-14.77	1.06	-7.58	1.53	<.001
		Placebo	53	32.17	6.21	-7.49	10.56	-7.19	1.37			
	6 (3)	Olanzapine	88	33.23	6.48	-17.17	9.71	-15.78	1.10	-6.95	1.68	<.001
		Placebo	37	32.41	6.19	-11.11	9.05	-8.83	1.50			

Sponsor's Table HGIU.14.27

U.S. vs. Puerto Rico Sites

The Sponsor did perform an analysis comparing the efficacy between U.S. and Puerto Rico sites. There were, however, very few subjects from the latter sites.

Table 6.1.3.6 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Country– U.S. vs. Puerto Rico sites.

Efficacy Variable	Country	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy*Country)
YMRSTOT:Total(1-11)	America	Olanzapine	93	32.80	6.65	-15.28	9.99	-15.09	-7.87	<.001	.668
		Placebo	48	31.71	6.38	-6.85	8.63	-7.22			
	Puerto Rico	Olanzapine	12	35.25	5.45	-20.75	9.38	-20.71	-5.97	.297	
		Placebo	6	34.67	4.37	-14.67	13.23	-14.74			

Secondary Analyses
Efficacy results from select secondary analyses were reviewed.

YMRS Individual Item Analyses
Mean change from baseline to endpoint (LOCF) for the individual items of the YMRS were analyzed. Statistically significant differences favoring olanzapine were evident for all YMRS items except sexual interest and insight (see Appendix 10.4).

CGI-BP (Severity)
Mean change from baseline to endpoint (LOCF) for CGI-BP Severity of Mania, Depression and Overall were analyzed. Statistically significant differences favoring olanzapine were found for CGI-BP Severity – Mania and CGI-BP Severity-Overall, but not for CGI-BP Severity-Depression (see Table 6.1.3.7). Patients enrolled in this clinical trial were exhibiting acute manic or mixed bipolar symptoms. In the olanzapine group, 42% (44/105) exhibited manic symptoms and 58% (61/105) exhibited mixed symptoms at baseline. In the placebo group, 54% (29/54) exhibited manic symptoms and 46% (25/54) exhibited mixed symptoms at baseline. The CGI-BP Depression mean scores at baseline indicated mildly ill severity while the CGI-BP Mania and Overall mean scores at baseline indicated moderate-markedly ill severity.

Table 6.1.3.7 Sponsor's Table. CGI-BP Severity for Mania, Depression and Overall

Table HGIU.11.23. CGI-BP Severity (Mania, Depression, Overall)
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

			Baseline		Change to Endpoint				
Efficacy Variable	Therapy	N	Mean	Std	Mean	Std	LSMean Change	LSMean Difference	*P-value
CGI Severity Depression	Olanzapine	105	3.12	1.59	-0.86	1.21	-0.89	-0.10	.533
	Placebo	54	2.65	1.60	-0.54	1.04	-0.80		
CGI Severity Mania	Olanzapine	105	4.81	0.69	-1.70	1.29	-1.73	-0.67	<.001
	Placebo	54	4.81	0.75	-1.04	1.12	-1.05		
CGI Severity Overall	Olanzapine	105	4.81	0.71	-1.60	1.30	-1.63	-0.64	<.001
	Placebo	54	4.83	0.75	-0.98	1.17	-0.99		

Children's Depression Rating Scale - Revised
No statistically significant differences were found between olanzapine and placebo for mean change from baseline to endpoint for CDRS-R Total Score (The CDRS-R contains 17 anchored items, most are rated from 1 to 7 for severity; maximum score = 113). Some statistical differences were found for individual items – one favored olanzapine (sleep disturbance) and three items favored placebo (appetite disturbance, excessive fatigue, and depressed facial affect) [See Appendix 10.5]. Most of these statistical differences on individual items could have been related more to the side effect profile of olanzapine. Of note, the baseline mean score for suicidal ideation[1] was 1.77 in the olanzapine group and 1.42 in the placebo group, mean change

1 CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to

to endpoint was -0.47 and -0.23 respectively (p = NS) [one of the exclusion criterion was "patients who have been judged clinically to be at serious suicidal risk"]. A further analysis and discussion of the suicidal ideation item is in Section 7.1.5 (Less Common Adverse Events).

Table 6.1.3.8 Sponsor's Table. CDRS-R Total Score

Table HGIU.11.24. CDRS-R Total Score
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
CDRS Raw Total Score	Olanzapine	100	40.43	15.60	-7.18	12.09	-8.37	1.14	.508
	Placebo	53	35.77	15.35	-5.85	13.27	-9.50		

Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHDRS) and Overt Aggression Scale (OAS)
Statistically significant differences favoring olanzapine were found for the mean change from baseline to endpoint in the ADHDRS hyperactivity-impulsivity subtotal (-4.96 vs. -1.62, p = 0.008) and the ADHDRS total score (-9.47 vs. -3.97, p = 0.048) [See Appendix 10.6]. It should be noted that at baseline, there were more patients with comorbid ADHD in the olanzapine group compared to the placebo group (42% vs. 24%, p = 0.024). The Sponsor did not provide changes in the ADHDRS separately for patients with and without comorbid ADHD.
Statistically significant differences favoring olanzapine were found for the mean change from baseline to endpoint for all subscales (except physical aggression towards self) and total score for the OAS. Comorbid conduct disorder was present in a small number of patients (olanzapine n = 14, placebo n = 1). See Appendix 10.6.

Subgroup Analyses
The Sponsor evaluated the following subgroups: gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features, rapid vs. nonrapid cycling.
Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds (p = 0.094), patients with psychotic features (p = 0.111) and rapid cyclers (p = 0.271). The mean change to endpoint was similar in both the patients with and without psychotic features; failure to show efficacy in patients with psychotic features may have been due to the small sample size (n = 20 olanzapine, n = 7 placebo). The mean change to endpoint was also similar in both rapid and nonrapid cyclers – again, the small sample size in the rapid cycler

himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does ont understand the concept of suicide), usually when angry; 4 = intermediate rating, not anchored; 5 = has recurrent thoughts of suicide; 6 = intermediate rating, not anchored; 7 = has made a suicide attempt within the last month or is actively suicidal

subgroup may have contributed to the negative findings. A significant treatment-by-age interaction was found.

Table 6.1.3.9 Sponsor's Table. YMRS Total Score - Subgroup Analyses

Efficacy Variable	Subgroup	Strata	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy* Subgroup)
YMRSTOT:Total(1-11)	Gender	Female	75	olanzapine	45	32.69	6.41	-14.73	10.06	-20.07	-5.98	.005	.213
				Placebo	30	33.17	6.38	-9.27	9.33	-14.10			
		Male	84	olanzapine	60	33.37	6.69	-16.78	10.01	-17.47	-9.87	<.001	
				Placebo	24	30.63	5.85	-5.79	9.35	-7.60			
	Age	< 15	69	olanzapine	49	32.78	6.96	-14.63	10.17	-16.61	-4.49	.094	.089
				Placebo	20	32.40	5.70	-9.45	10.96	-12.12			
		>=15	90	olanzapine	56	33.34	6.21	-17.02	9.87	-18.90	-9.86	<.001	
				Placebo	34	31.82	6.59	-6.71	8.39	-9.03			

Efficacy Variable	Subgroup	Strata	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy* Subgroup)
YMRSTOT:Total(1-11)	Origin	Caucasian	111	olanzapine	70	32.84	6.90	-14.17	9.58	-13.90	-6.95	<.001	.570
				Placebo	41	31.05	6.40	-6.49	8.85	-6.95			
		Non-Caucasian	48	olanzapine	35	33.54	5.85	-19.37	10.16	-20.00	-9.19	.005	
				Placebo	13	35.15	4.58	-11.62	10.44	-10.82			
	Mania Type	Manic	73	olanzapine	44	34.50	5.63	-16.43	10.67	-17.44	-5.59	.019	.160
				Placebo	29	33.10	5.20	-10.07	9.15	-11.85			
		Mixed	86	olanzapine	61	32.05	7.00	-15.52	9.62	-19.66	-9.70	<.001	
				Placebo	25	30.80	7.15	-5.00	9.16	-9.96			
	Psychotic features	N	132	olanzapine	85	32.53	6.49	-15.94	9.82	-18.07	-7.92	<.001	.739
				Placebo	47	31.72	6.09	-7.62	9.58	-10.15			
		Y	27	olanzapine	20	35.40	6.45	-15.75	11.17	-7.71	-7.24	.111	
				Placebo	7	34.14	7.24	-8.43	8.89	-0.46			

Subgroup	Strata	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy* Subgroup)
Rapid Cycling	N	114	olanzapine	71	32.97	6.48	-15.63	9.17	-18.75	-7.64	<.001	.885
			Placebo	43	32.51	6.56	-7.72	9.55	-11.11			
	Y	29	olanzapine	24	33.50	7.07	-16.79	12.70	-13.67	-6.35	.271	
			Placebo	5	30.60	4.22	-7.40	10.57	-7.32			

The Sponsor further evaluated the age subgroup in post hoc analyses since the findings suggested a differential effect. Three additional analyses were performed: age as a continuous variable, age subgroups defined as < 16 and $\geq$ 16 years of age and age subgroups defined by age at last birthday. The treatment-by-age interaction was not significant in the first two analyses, but the last analysis did not show a similar treatment effect (i.e. change to endpoint) for the 14 year olds compared to the 13, 15, 16 and 17 year olds. In this last analysis, neither the 14 year old subgroup nor the 17 year old subgroup showed a statistically significant treatment effect, the

smaller sample size in the 17 year old group could have contributed to those findings. See Appendix 10.7 for these additional analyses.

The Sponsor also evaluated the subgroups with or without past or current ADHD or ODD diagnoses. Statistically significant differences favoring olanzapine occurred within each subgroup with no differences between patients with and without a past or current ADHD diagnosis or between patients with and without a past or current ODD diagnosis (data not shown).

6.1.4 Efficacy Conclusions

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -7.66, $p < 0.001$).

The supportive OC analysis was similar to the LOCF analysis (LS Mean Diff = -5.74, $p = 0.001$). The supportive MMRM analysis was similar to the LOCF analysis (LS Mean Diff = -6.95, $p < 0.001$). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

Subgroup analyses included gender, age (< 15, $\geq$ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds ($p = 0.094$), patients with psychotic features ($p = 0.111$) and rapid cyclers ($p = 0.271$) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found.

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

7 INTEGRATED REVIEW OF SAFETY

The Sponsor used the following databases for assessment of safety (see Table 4.1.1 in Section 4.1 – Tables of Clinical Studies for more information on individual studies). For studies HGCS (n = 8), HGCR (n = 2), and HGGC (n = 23), the Sponsor included only information regarding deaths, serious adverse events and discontinuations due to adverse events.

Sponsor's Table. Databases for Summary of Clinical Safety

Table 2.7.4.1. Databases for Summary of Clinical Safety

Database	Indication	Studies Used	Number of Patients
Acute Placebo-Controlled Databases	Schizophrenia	HGIN	N=107 (Olz=72, Pla=35)
	Bipolar	HGIU	N=161 (Olz=107, Pla=54)
	Combined	HGIN, HGIU	N=268 (Olz=179, Pla=89)
Overall Olanzapine Exposure Databases	Schizophrenia	HGIN, LOAY, HGMF[a]	N=227
	Bipolar	HGIU, HGMF[a]	N=227
	Combined	HGIN, HGIU, LOAY, HGMF	N=454

a Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

The Sponsor also included information on serious adverse events and discontinuations due to adverse events for the 37 adolescent patients who participated in the olanzapine adult studies:

Study HGBG and HGCL were clinical trials for adult patients aged 18 or older – two adolescent patients were enrolled in those trials (17.9 and 17.8 years of age).
Study HGDH – acute and long-term efficacy of olanzapine in first-episode psychotic patients aged 16 – 40 years (n = 7 adolescents).
Study HGGF – delaying or preventing psychosis onset in persons aged 12 to 45 years prodromal to psychosis (n = 24 adolescents).
Study HGKL – clinical trial in patients aged 15 to 65 years with borderline personality disorder (n = 4 adolescents).

"Acute Placebo Controlled Database" hereafter called HGIN + HGIU Acute Database
A total of 268 patients were included in the HGIN + HGIU Acute Database**.** Eight (4.5%) patients discontinued due to adverse events in the olanzapine treatment group.

Patient Disposition (HGIN + HGIU)

	Olanzapine N = 179	Placebo N = 89	P-value
Completers	134 (74.9%)	50 (56.2%)	0.003
Drop Outs	45 (25%)	39 (44%)	
Adverse Event	8 (4.5%)	1 (1.1%)	0.279
Lack of Efficacy	22 (12.3%)	34 (38.2%)	< 0.001
Lost to Follow-up	1 (0.6%)	0	1.00
Patient Decision	8 (4.5%)	2 (2.2%)	0.504
Criteria Not Met/Compliance	2 (1.1%)	2 (2.2%)	0.602
Sponsor Decision	1 (0.6%)	0	1.00
Physician Decision	1 (0.6%)	0	1.00
Other	2 (1.1%)	0	1.00

Modified from Sponsor table 2.7.4.20 in summary-clin-safety document

Patient demographics (HGIN + HGIU): The majority of patients were male (60%), Caucasian (70%) with a mean age of ~ 15.6 years (see Appendix 10.8). For study HGIN, the majority of patients were 16 and 17 years of age at baseline (61%); for study HGIU, the majority of patients were 14 and 15 (55%). This is expected and consistent with the psychiatric diagnoses in these two trials. A table of age distribution at baseline is in Appendix 10.8.

"Overall Olanzapine Exposure Combined Database" hereafter called Overall Combined Database

A total of 454 patients were included in the Overall Combined Database. The patient disposition by diagnoses (bipolar vs. schizophrenia) is given in Table 6.1.4.2. Twice as many patients with bipolar disorder discontinued due to an adverse event compared to patients with schizophrenia (14.5% vs. 7.9%). More than twice as many patients with schizophrenia discontinued due to lack of efficacy compared to patients with bipolar disorder (16.3% vs. 5.7%).

Sponsor's Table. Patient Disposition (Overall Combined Database)

Table 2.7.4.23. Patient Disposition
All Patients with Olanzapine Exposure
Overall Olanzapine Exposure Combined Database

	Bipolar		Schizophrenia		Overall	
Patient Disposition	N	%	N	%	N	%
Reporting Interval Completed	130	57.3%	119	52.4%	249	54.8%
Adverse Event	33	14.5%	18	7.9%	51	11.2%
Lack of Efficacy	13	5.7%	37	16.3%	50	11.0%
Lost To Follow-Up	9	4.0%	4	1.8%	13	2.9%
Patient Decision	24	10.6%	10	4.4%	34	7.5%
Criteria Not Met/Compliance/Protocol Violation	2	0.9%	28	12.3%	30	6.6%
Sponsor Decision	3	1.3%	5	2.2%	8	1.8%
Physician Decision	10	4.4%	4	1.8%	14	3.1%
Other	3	1.3%	2	0.9%	5	1.1%
Total	227	100.0%	227	100.0%	454	100.0%

The patient demographics in the Overall Combined Database were fairly consistent with the demographics of the HGIU + HGIN Acute Database with the exception of country – 89 additional patients with schizophrenia from study LOAY (German sites) were included in the Overall Combined Database. Patient demographics for the Overall Combined Database are included in Appendix 10.8.

Methods and Findings

7.1.1 Deaths

No deaths occurred in the HGIU + HGIN Acute Database, Overall Combined Database, studies HGCS, HGCR, HGGC or in adolescent patients from the adult studies.

7.1.2 Other Serious Adverse Events

The following tables for serious adverse events were compiled from narratives provided by the Sponsor.

A total of 7 serious adverse events occurred in 6 patients in the olanzapine treatment arm in the HGIU + HGIN Acute Database (see Table 7.1.2.1).
One serious adverse event (schizophrenia) occurred in 1 patient in the placebo arm of study HGIN (no SAEs in the placebo group in study HGIU).

Table 7.1.2.1. Serious Adverse Events: HGIN + HGIU Acute Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGIN 025-2504	15 YOWF	Olanzapine DB phase	Migraine	Migraine	Severe Worsened from baseline; failed to restart study med and discontinued from study
HGIN 930-9301	15 YOWM	Olanzapine DB phase	Closed fracture of right forearm	Forearm fracture	Severe Fracture from fall, treated in hospital
HGIN 026-2603	14 YOWF	Olanzapine DB phase	Weight gain	Weight increased	Mild/moderate Onset of AE in DB phase, patient discontinued OL phase due to weight gain of 18.3 kg over 4 months
HGIU 012-1211	14 YOWF	Olanzapine DB phase	Exacerbation of bipolar symptoms	Bipolar disorder	Severe Discontinued during OL phase
HGIU 035-3501	14 YOWF	Olanzapine DB phase	Relapse of bipolar disorder	Bipolar disorder	Moderate Hospitalized, Discontinued due to weight gain
HGIU 031-3103	14 YOWM	Olanzapine DB phase	Decreased WBC count and decreased neutrophils	WBC count decreased, neutrophil count decreased	Moderate WBC 4.04 to 2.52; ANC 1.63 to 0.83; Discontinued in OL phase due to persistently low counts

A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database (see Table 7.1.2.2). The majority of these SAEs, 19/35 patients, were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

Table 7.1.2.2 Serious Adverse Events: Overall Combined Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGIN 007-0704	15 YOBM	Olanzapine OL phase	Exacerbation of schizophrenia	Schizophrenia	Severe Hospitalization, discontinuation from study
HGIN 013-1302	17 YOM	Olanzapine OL phase	Wosening of schizophrenia symptoms	Schizophrenia	Moderate
HGIN 019-1901	15 YOWF	Olanzapine OL phase	Depressive with psychotic features, weight gain	Major depression, weight increased	Severe Hospitalization, discontinuation from study
HGIN 021-2101	14 YOBM	Olanzapine OL phase	Worsening of schizophrenia	Schizophrenia	Severe
HGIN 026-2603	14 YOWF	Olanzapine OL phase	Exacerbation of schizophrenia, suicidal ideation, weight gain	Schizophrenia, weight increased	Severe (schiz) Moderate (weight) Hospitalization, weight gain of 18.3 kg over 4 months
HGIN 030-3001	17 YOWM	Olanzapine OL phase, 1st visit	Exacerbation of psychosis	Psychotic disorder	Severe Hospitalized
HGIN 910-9101	16 YOWF	Olanzapine OL phase	Worsening of Schizophrenia	Schizophrenia	Moderate Hospitalized
HGIN 930-9301	15 YOWM	Olanzapine OL phase	Closed fracture of right forearm	Forearm fracture	Severe Fracture from fall, treated in hospital
HGIN 930-9307	15 YOWF	Olanzapine OL phase	Attempted suicide	Suicide attempt	Severe Attempted overdose with Phenobarbital, hospitalized, discontinued from study
HGIU 001-0103	13 YOWM	Olanzapine OL phase	Increased agitation	Agitation	Severe Hospitalized, completed study
HGIU 001-0107	13 YOWM	Olanzapine OL phase	Agitation, aggression	Agitation, aggression	Severe Hospitalized, completed study
HGIU 001-0108	14 YOWF	Olanzapine OL phase	Alcohol intoxication, suicidal ideation	Alcohol poisoning, suicidal ideation	Severe (alcohol) Moderate (SI) Discontinued from study
HGIU 012-1202	15 YOWF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, completed study
HGIU 012-1211	14 YOWF	Olanzapine OL phase	Exacerbation of bipolar	Bipolar disorder	Severe Discontinued study

			symptoms		
HGIU 012-1212	14 YOBF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, discontinued "patient decision"
HGIU 020-2016	14 YOWF	Olanzapine OL phase	Attempted suicide	Suicide attempt	Mild Overdose of Benadryl and ibuprofen, recovered without treatment; completed study
HGIU 026-2604	16 YOHM**	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, completed study
HGIU 026-2605	14 YOM	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized and discontinued study
HGIU 026-2608	13 YOWF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, discontinued study
HGIU 027-2705	15 YOBM	Olanzapine OL period	Worsening of bipolar disorder, self-inflicted superficial lacerations	Bipolar disorder, Intentional self-injury	Severe (BP) Moderate (SIB) Hospitalized, discontinued study (cut arms with fingernails)
HGIU 027-2707	14 YOBF	Olanzapine OL phase	Worsening of bipolar disorder	Bipolar disorder	Severe Hospitalized, completed study
HGIU 028-2804	15 YOWF	Olanzapine OL phase	Recurrence of bipolar symptoms	Bipolar disorder	Severe Hospitalized, discontinued study "sponsor's decision" – GCP issues at site
HGIU 028-2805	14 YOWF	Olanzapine OL phase	Suicidal ideation	Suicidal ideation	Severe Hospitalized, discontinued – GCP issues at site
HGIU 028-2806	15 YOBF	Olanzapine OL phase	Bipolar mania	Bipolar disorder	Severe Hospitalized, discontinued study
HGIU 031-3103	14 YOWM	Olanzapine OL phase	Decreased WBC count and decreased neutrophils	WBC count decreased, neutrophil count decreased	See Table 7.1.2.1.
HGIU 033-3304	15 YOWF	Olanzapine OL phase	Intensifying aggressiveness and irritability	Aggression, irritability	Severe Hospitalized, discontinued study
HGIU 035-3519	14 YOWM	Olanzapine OL phase	Violent behavior	Aggression	Severe Hospitalized, discontinued study
HGIU 730-7302	13 YOHM	Olanzapine OL phase	Oppositional defiant behavior	Oppositional defiant disorder	Severe Hospitalized, discontinued due to noncompliance
HGMF 003-0303	17 YOWF	Olanzapine OL	Acute appendicitis	Appendicitis	Severe Hospitalized, completed study
HGMF	16 YOWF	Olanzapine	Exacerbation of	Bipolar disorder	Severe

003-0304		OL	bipolar illness with positive suicidal ideation		Hospitalized, discontinued study
LOAY 407-4078	17 YOWM	Olanzapine OL	Recurrence of acute psychotic symptoms	Psychotic disorder	Severe Hospitalized
LOAY 407-4207	14 YOWM	Olanzapine OL	Borrelia infection	Borrelia infection	Mild Discontinued study
LOAY 413-4145	16 YOWM	Olanzapine OL	Worsening of underlying disease schizophrenia	Schizophrenia	Severe Hospitalized Discontinued study

Table 7.1.2.3 Serious Adverse Events: HGCR, HGCS, HGGC

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGCR 001-2001	12 YOWM	Olanzapine OL	Headache lumbar puncture	Headache	Moderate Completed study
HGCS 001-1001	14 YOHF	Olanzapine OL	Mallory Weiss tear, vomiting blood	Esophageal hemorrhage, hematemesis	Severe Completed study
HGGC 001-2023	14 YOWF	Olanzapine	Suicidality	Depression	Hospitalized and discontinued from study

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who experienced serious adverse events (Table 7.1.2.4).

Table 7.1.2.4 Serious Adverse Events: Adolescent Patients from Adult Studies (n = 37)

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGDH 007-1607	17 YOWM	Olanzapine	Overdose	Overdose	Ingested 175 mg olanzapine, completed the study
HGGF 001-0102	15 YOWM	Olanzapine	Worsening depression with suicidal ideation	Depression, affective disorder, suicidal ideation	Gained significant amount of weight- 14 kg in 17 weeks; patient discontinued
HGGF 001-113	16 YOWF	Olanzapine	Dysphoria, Superficial self-mutilation	Dysphoria, self mutilation	Cuts on upper arm made with piece of glass, discontinued from study
HGGF 004-405	17 YOWF	Olanzapine	Auditory perceptual abnormalities, depersonalization, depressed mood, suicidal ideation, worsening psychosis	Auditory hallucination, depersonalization, depressed mood, illusion, suicidal ideation, psychotic disorder	
HGGF 004-406	17 YOWF	Olanzapine	Depressed mood, suicidal ideation	Depressed mood, suicidal ideation	Discontinued study

Narratives were provided by Sponsor upon request

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Adverse events associated with dropouts

Table 7.1.3.1.1 Discontinuations Due to Adverse Events: HGIN + HGIU Acute Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGIN 007-703	13 YOBF	Olanzapine DB phase	Clinically significant increased ALT	ALT increased	ALT up to 231 (AST up to 142) Returned to WNL after discontinuation from study
HGIN 010-1001	17 YOWM	Olanzapine DB phase	Elevated liver function	Liver function test abnormal	ALT = up to 597 AST = up to 410 GGT = up to 129 Noted at randomization visit (was taking olanzapine prior to study) Discontinued study
HGIN 021-2103	17 YOBM	Olanzapine DB phase	Elevated transaminases	Transaminases increased	AST up to 136 ALT up to 396 Returned to WNL after discontinuation from study
HGIN 910-9110	17 YOWM	Olanzapine DB phase	AST increased	AST increased	AST up to 190 (ALT up to 321) Returned to WNL after discontinuation from study
HGIN 920-9202	17 YOWM	Olanzapine DB phase	Rise ALT	ALT increased	ALT up to 393 (AST up to 179 GGT up to 82) ALT and GGT returned to WNL after discontinuation from study (AST N/A)
HGIU 035-3503	16 YOBF	Olanzapine DB phase	Heart rate increased	Elevated pulse	Holter noted sinus tachycardia Discontinued from study, pulse WNL at 4th follow-up visit
HGIU 012-1203	15 YOWF	Olanzapine DB phase	Hepatic enzyme increased	Elevated liver enzymes	AST up to 148 ALT up to 325 GGT up to 53 Returned to near WNL after discontinuation from study (ALT 48)
HGIU 035-3501	14 YOWF	Olanzapine DB phase	Weight increased	Weight gain	Weight increase of 4.5 kg in ~ 15 days

Table 7.1.3.1.2 Discontinuations Due to Adverse Events: Overall Combined Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGIN 003-0302	17 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.7 kg in 3 months
HGIN 019-1901	15 YOWF	Olanzapine OL	Weight increased	Weight gain	Gained 6.62 kg during DB phase, Gained 15.88 kg over 5.7 months
HGIN 020-2002	15 YOBM	Olanzapine OL	Sedation	Sedation	
HGIN 025-2502	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.2 kg over 183 days
HGIN 027-2701	17 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12 kg over 92 days
HGIN 027-2702	13 YOWF	Olanzapine OL	Weight increased	Weight gain	Gained 17.5 kg over 148 days
HGIN 030-3007	13 YOWF	Olanzapine OL	Increased appetite	Increased appetite	Gained 21.8 kg over 94 days
HGIN 900-9003	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.8 kg over 169 days
HGIN 930-9307	15 YOWF	Olanzapine OL	Suicide attempt	Suicide attempt	See Table 7.1.2.2
HGIN 940-9403	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 13.4 kg over 152 days
HGIU 001-108	14 YOWF	Olanzapine OL	Alcohol intoxication	Alcohol poisoning	See Table 7.1.2.2.
HGIU 007-708	15 YOWM	Olanzapine OL	Drowsiness	Somnolence	
HGIU 009-902	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 14.2 kg over 78 days
HGIU 013-1303	17 YOWF	Olanzapine OL	Syncope	Syncope	100/60 mm Hg, 88 bpm supine, 98/62 mmHg, 100 bpm standing
HGIU 013-1308	14 YOHF	Olanzapine OL	Weight gain	Weight increased	Gained 9.1 kg over 103 days
HGIU 013-1310	16 YOWF	Olanzapine OL	Increased appetite	Increased appetite	Gained 9.5 kg over ~ 56 days (at time of weight patient had been off drug for 11 days)
HGIU 013-1311	13 YOHM	Olanzapine OL	Worsened aggressive behavior	Aggression	
HGIU 019-1901	16 YOBF	Olanzapine OL	Pregnancy	Pregnancy	
HGIU 019-1907	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 17.7 kg over 170 days
HGIU 020-2007	14 YOWF	Olanzapine OL	Elevated liver function test	Liver function test abnormal	AST up to 204, ALT up to 330 Resolved after discontinuation from study
HGIU 020-2008	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 9.3 kg over 58 days

HGIU 020-2019	16 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 9.5 kg over 81 days
HGIU 024-2404	13 YOWF	Olanzapine OL	Fear of more weight gain	Fear of weight gain	Gained 5.9 kg over 34 days
HGIU 026-2608	13 YOWF	Olanzapine OL	Exacerbation of bipolar disorder	Bipolar disorder	
HGIU 027-2701	15 YOWF	Olanzapine OL	Sedation	Sedation	
HGIU 027-2704	15 YOBM	Olanzapine OL	Weight gain	Weight increased	Gained 18.6 kg over 119 days
HGIU 027-2705	15 YOBM	Olanzapine OL	Worsening of bipolar disorder	Bipolar disorder	
HGIU 028-2806	15 YOBF	Olanzapine OL	Bipolar mania	Bipolar disorder	
HGIU 031-3103	14 YOWM	Olanzapine OL	Decreased WBC	WBC count decreased	See Table 7.1.2.1.
HGIU 033-3304	15 YOWF	Olanzapine OL	Intensifying aggressiveness	Aggression	See Table 7.1.2.2
HGIU 035-3510	15 YOWM	Olanzapine OL	Weight gain	Weight increased	Gained 5.4 kg over 89 days
HGIU 035-3517	13 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 5 kg over ~6 weeks
HGIU 720-7217	15 YOHM	Olanzapine OL	Hepatic enzymes increases	Hepatic enzyme increased	AST up to 103, ALT up to 125 (also had significant weight gain, 21 kg over ~ 5 months)
HGIU 720-7219	14 YOHF	Olanzapine OL	Pregnancy	Pregnancy	
HGMF 002-0211	17 YOWF	Olanzapine OL	Somnolence	Somnolence	
HGMF 003-0304	16 YOWF	Olanzapine OL	Exacerbation of bipolar illness with positive suicidal ideation	Bipolar disorder	See Table 7.1.2.2.
HGMF 008-0806	15 YOWM	Olanzapine OL	Increased depression	Depression	
HGMF 014-1400	17 YOBF	Olanzapine OL	Elevated CK level lab	Blood creatine phosphokinase	CK up to 690 U/L
HGMF 025-2501	15 YOWM	Olanzapine OL	Drowsiness	Somnolence	
HGMF 028-2801	18 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 8.9 kg over 27 days
LOAY 405-4057	13 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 10.1 kg over 42 days
LOAY 407-4207	14 YOWM	Olanzapine OL	Suspicion of neuroborreliosis	Neuroborreliosis	See Table 7.1.2.2.
LOAY 407-4218	15 YOWF	Olanzapine OL	Galactorrhea	Galactorrhea	Prolactin up to 35 mcg/L (ULN = 29)

There were no discontinuations due to adverse events for studies HGCS, HGCR and HGGC.

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who discontinued due to adverse events (Table 7.1.3.1.3).

Table 7.1.3.1.3 Discontinuations Due to Adverse Events: Adolescent Patients from Adult Studies

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGGF 001-127	13 YOWM	Olanzapine	Weight gain	Weight increased	Gained 23 kg in ~5 months (BMI from 32 to 39)
HGKL 014-1416	15 YOWM	Olanzapine	Weight gain	Weight increased	Gained 12.5 kg over 3 months; triglycerides also increased from 260 to 508 mg/dL

7.1.4 Common Adverse Events

7.1.4.1 Eliciting adverse events data in the development program

Adverse events were obtained by spontaneous reports, patient observation and investigator query at every study visit. Rating scales were included for evaluation of extrapyramidal symptoms (SAS), akathisia (BAS) and dyskinesias (AIMS). Vital signs, ECGs and laboratory tests were obtained at intervals throughout the study.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the MedDRA version 8.0 coding dictionary. A sample of patient narratives was reviewed and the coding of verbatim terms to preferred terms was appropriate.

7.1.4.3 Common adverse event tables

Adverse events occurring in $\geq$ 2% of patients in the HGIU + HGIN Acute Database is in Table 7.1.4.3.1. The majority of adverse events in this table occurred more than twice as frequently in the olanzapine group compared to the placebo group, that adverse events that were statistically more frequent in the olanzapine group were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%) and sedation (24% vs. 6%).

Table 7.1.4.3.1 Sponsor's Table. Adverse Events Occurring in ≥ 2% of Patients: HGIN + HGIU Acute Database

	Therapy						
	Olanzapine			Placebo			
Event Classification	N	n	%	N	n	%	*P-value
Patients with >=1 TESS	179	158	88.3%	89	54	60.7%	<.001
Weight increased	179	53	29.6%	89	5	5.6%	<.001
Somnolence	179	44	24.6%	89	3	3.4%	<.001
Increased appetite	179	43	24.0%	89	5	5.6%	<.001
Sedation	179	34	19.0%	89	5	5.6%	.003
Headache	179	30	16.8%	89	11	12.4%	.374
Fatigue	179	17	9.5%	89	4	4.5%	.227
Dizziness	179	13	7.3%	89	2	2.2%	.155
Dry mouth	179	11	6.1%	89	0	0.0%	.018
Dysmenorrhoea	67	4	6.0%	41	4	9.8%	.475
Pain in extremity	179	9	5.0%	89	1	1.1%	.173
Vomiting	179	9	5.0%	89	6	6.7%	.580
Constipation	179	8	4.5%	89	0	0.0%	.055
Nausea	179	8	4.5%	89	8	9.0%	.172
Nasopharyngitis	179	7	3.9%	89	2	2.2%	.722
Abdominal pain upper	179	6	3.4%	89	5	5.6%	.514
Diarrhoea	179	6	3.4%	89	0	0.0%	.183
Irritability	179	6	3.4%	89	4	4.5%	.735
Pharyngolaryngeal pain	179	6	3.4%	89	3	3.4%	1.00
Restlessness	179	6	3.4%	89	2	2.2%	1.00
Alanine aminotransferase increased	179	5	2.8%	89	0	0.0%	.174
Dyspepsia	179	5	2.8%	89	1	1.1%	.667
Epistaxis	179	5	2.8%	89	0	0.0%	.174
Hepatic enzyme increased	179	5	2.8%	89	0	0.0%	.174
Insomnia	179	5	2.8%	89	10	11.2%	.009
Sinusitis	179	5	2.8%	89	0	0.0%	.174

Sponsor's Table 2.7.4.27 from summary-clin-safety document

The common adverse events for the two trials are listed separately in Table 7.1.4.3.2 since the trials differed in duration (6 vs. 3 weeks) and study population. For study HGIN, the adverse events that were statistically different between olanzapine and placebo included weight increased ($p = 0.014$) and somnolence ($p = 0.0006$). For study HGIU, the adverse events that were statistically different between olanzapine and placebo included weight increased ($p < 0.001$), increased appetite ($p < 0.001$), somnolence ($p < 0.001$) and sedation ($p = 0.011$). The adverse events and frequencies occurring in the olanzapine group between the two clinical trials were fairly similar though more patients in HGIU exhibited somnolence (25% vs. 17%), increased appetite (29% vs. 17%), sedation (22% vs. 15%), dry mouth (8% vs. 4%) and fatigue (14% vs. 3%)

Table 7.1.4.3.2 Adverse Events Occurring in > 2% of Patients with Olanzapine > 2x Placebo: HGIU and HGIN Clinical Trials

	Percentage of Patients Reporting Event			
	6 Week Trial % Schizophrenia Patients		3 Week Trial % Bipolar Patients	
Adverse Event	Olanzapine (N = 72)	Placebo (N = 35)	Olanzapine (N = 107)	Placebo (N = 54)
Weight increased	31%*	9%	29%*	4%
Somnolence	17%*	3%	25%*	4%
Headache	17%	6%	17%	17%
Increased appetite	17%	9%	29%*	4%
Sedation	15%	6%	22%*	6%
Dizziness	8%	3%	7%	2%
Pain in extremity	6%	3%	5%	0
Abdominal pain	4%	0	5%	7%
ALT increase	4%	0	-	-
AST increase	4%	1%	1%	0
Constipation	4%	0	5%	0
Dry mouth	4%	0	8%	0
Fatigue	3%	3%	14%	6%
Diarrhea	1%	0	5%	0
Dyspepsia	-	-	5%	0
Hepatic enzyme increased	1%	0	4%	0
Sinusitis	1%	0	4%	0

From Tables HGIN.12.4, HGIN.14.27 and HGIU.12.4 clinical study reports
*p < 0.05

7.1.4.4 Common adverse events – further analysis

Weight Gain

Weight gain was a significant adverse event occurring in these clinical trials and is further analyzed and discussed in this section along with the weight data.

HGIU + HGIN Acute Database

In the HGIU + HGIN Acute Database, patients in the olanzapine treatment group had significantly greater weight gain and increase in BMI compared to the placebo group (see Table 7.1.4.4.1).

Table 7.1.4.4.1 Weight and BMI Data (LOCF): HGIN + HGIU Database

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	177	66.03	17.93	3.90	2.72	3.68		
	Placebo	88	67.63	17.24	0.24	2.16	0.01	3.66	< 0.001
BMI	Olanzapine	177	23.91	6.01	1.22	1.01	1.11		
	Placebo	88	23.98	5.67	0.05	0.91	-0.07	1.17	< 0.001

From Table 2.7.4.43 in summary-clin-safety document

The visit wise weight change for observed cases was similar to the LOCF analysis. The mean change at visit 6 was + 3.63 kg for olanzapine (n = 154) and + 0.08 kg for placebo (n = 67) (LS Mean Diff = 3.57, p < 0.001).

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Seventy-seven (43.5%) patients in the olanzapine group and 6 (6.8%) of patients in the placebo group had a ≥ 7% increase in body weight (p < 0.001). Only 2 patients, both randomized to placebo, had a ≥ 7% decrease in body weight.

Since studies HGIN and HGIU were different with respect to types of patients and duration of the double-blind period (HGIN 6 weeks, HGIU 3 weeks), the weight and BMI data were also evaluated separately:

Table 7.1.4.4.2. Weight and BMI Data: Study HGIU

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	105	65.33	20.55	3.66	2.18	3.51		
	Placebo	54	66.83	17.55	0.30	1.67	0.16	3.36	< 0.001
BMI	Olanzapine	105	24.21	6.82	1.18	0.85	1.15		
	Placebo	54	24.05	5.44	0.02	0.62	0.00	1.15	< 0.001

From Table HGIU.12.44 in study report

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Forty-four (41.9%) patients in the olanzapine group and 1 (1.9%) patient in the placebo group had a ≥ 7% increase in body weight (p < 0.001). No patients in the study had a ≥ 7% decrease in body weight.

Table 7.1.4.4.3. Weight and BMI Data: Study HGIN

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	72	67.04	13.31	4.26	3.33	4.22		
	Placebo	34	68.91	16.93	0.13	2.80	0.08	4.13	< 0.001
BMI	Olanzapine	72	23.45	4.59	1.39	1.21	1.37		
	Placebo	34	24.02	6.12	-0.05	1.03	-0.07	1.44	< 0.001

From Table HGIN.12.42 in study report

The results for the OC analysis for change in weight and BMI were similar to the LOCF analysis. At end of study, patients in the olanzapine group (n = 50) gained 4.95 kg from baseline and patients in the placebo group (n = 15) gained 0.61 kg [LS mean diff = 4.65, p < 0.001]. BMI increased by 1.56 in the olanzapine group and decreased by 0.04 in the placebo group [LS mean diff = 1.62, p < 0.001].

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Thirty-three (45%) patients in the olanzapine group and 5 (14.7%) of patients in the placebo group had a ≥ 7% increase in body weight (p = 0.002). Only 2 patients in the study, both randomized to placebo, had a ≥ 7% decrease in body weight.

Only 1 of the 8 discontinuations due to adverse events was due to weight gain in the HGIU + HGIN Acute Database (4.5 kg increase over ~15 days).
Unfortunately, insufficient data were collected during the follow-up visits to adequately address weight loss after patients completed the clinical trial (if they switched to a different antipsychotic). Though many of the investigators noted that the adverse event of "weight gain" had resolved at some of the follow-up visits, no actual weights were obtained for the majority of patients (or at least not recorded in the CRFs).

Overall Combined Database
Though no placebo comparison is available in this database, weight change over longer duration of time could be evaluated in general terms. Similar to the acute data, weight did appear to increase over time. This patient population (adolescents) are expected to increase in height and weight during this developmental period, however, the increases in weight are well above what would be considered expected (see Section 7.1.9 – Assessment of Effect on Growth).

Table 7.1.4.4.4. Weight and BMI Data (LOCF): Overall Combined Database

			Baseline		Change to Endpoint		
		N	Mean	Std	Mean	Std	P-value
Weight (kg)	Bipolar	224	68.58	21.21	7.63	6.62	< 0.001
	Schizophrenia	226	65.71	13.30	7.07	6.53	< 0.001
	Overall	450	67.13	17.72	7.35	6.58	< 0.001
BMI	Bipolar	216	24.92	7.34	2.37	2.39	< 0.001
	Schizophrenia	223	22.40	4.17	2.24	2.25	< 0.001
	Overall	439	23.64	6.07	2.31	2.31	< 0.001

From Table 2.7.4.45 in summary-clin-safety document

Sixty-five percent of patients in the Overall Combined Database gained ≥ 7% body weight.

The Sponsor provided a summary of weight change by visit for observed cases for the Overall Combined Database (see Appendix 10.9). For the 131 patients who completed visits > 25 and ≤ 32 weeks, the mean increase in weight was 10.8 kg (p < 0.001 compared to baseline).

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months. The patient who gained 21.8 kg did so over a period of 3 months.

For those patients in the Overall Combined Database who participated in HGIU or HGIN, the weight gain for the acute phase of these trials was also evaluated to determine whether they

gained a greater amount of weight early in the trial. These data were readily available for only 10 patients (some of the patients had been randomized to placebo and are not included here). The mean weight gain at the end of the double-blind phase of the study (or early termination) was 4.8 ± 2.6 kg, similar to the overall mean weight gain of 3.9 ± 2.7 kg in the acute database (see Table 7.1.4.4.1).

Weight – Subgroup Analyses
Because of the different duration of dosing in the HGIN and HGIU acute phases, these data were reviewed separately for each study.
The Sponsor evaluated weight changes for the subgroups gender and age (< 15, ≥ 15 years) for the adverse event "weight increased". Approximately 30% of females and males had this adverse event in the olanzapine group in both HGIU and HGIN acute studies while this adverse event was ~4% for the placebo group (with the exception of females in HGIN). No significant differences were noted between the gender subgroups (see Appendix 10.9). For the age subgroups, 28-40% had the adverse event "weight increased" in the olanzapine group compared to 0 – 14% in the placebo group. No significant differences were noted between the age subgroups (see Appendix 10.9).

Mean change in weight (kg) was also evaluated between the subgroups gender and age. These data were not included in the study report for HGIU, the Sponsor has been asked to submit these data (per the study report, only those data where results were significant were included). Data from HGIN are included in Appendix 10.9. Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine.

The Sponsor also did not include mean change in weight for the age subgroup for the HGIN + HGIU Acute Database (per the study reports, only those data where results were significant were included). The Sponsor has been asked to provide these data. In the HGIN + HGIU Acute Database, significant treatment-by-gender differences were noted (see Table 7.1.4.4.5). However, these findings are likely due to the differences in the placebo group since the weight gain (mean change to endpoint) in the olanzapine group was similar between females and males.

Table 7.1.4.4.5 Sponsor's Table. Mean Change in Weight (kg) – Gender Subgroup Analysis: HGIU + HGIN Acute Database

By Subgroup: Gender

Vital Signs	Subgroup	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean	LSMean Diff.	*P-value	**P-value
Weight in Kg	Female	106	olz	66	61.79	16.68	3.66	2.65	3.63	3.05	<.001	.083
			Placebo	40	62.83	13.65	0.55	2.27	0.59			
	Male	159	olz	111	68.54	18.25	4.05	2.76	3.79	4.16	<.001	
			Placebo	48	71.64	18.97	-0.03	2.05	-0.36			

Table 2.7.4.70 in Summary-clin-safety

The Sponsor was asked to evaluate the relationship of weight gain to baseline BMI. The Sponsor evaluated 4 BMI subgroups: < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30. There was a similar magnitude of weight gain by patients in each of these categories (Table 7.1.4.4.6). The percentage of patients who had a ≥ 7% weight gain was greatest in the < 18 BMI group and least in the ≥ 30 BMI group (Table 7.1.4.4.7).

Table 7.1.4.4.6 Sponsor's Table. Mean Change in Weight by Baseline BMI: HGIN + HGIU Acute Database

Table 1. Mean Change in Weight (kg) from Baseline to Endpoint (LOCF) by Baseline BMI Acute Placebo-Controlled Combined Database

			Baseline		Change to Endpoint				
BMI(Baseline)	Therapy	N	Mean	Std	Mean	Std	LSMean Change	LSMean Difference	*P-value
BMI<18	Olz	15	45.68	5.62	4.21	2.29	4.39	3.51	.005
	Placebo	10	48.19	6.54	0.70	2.89	0.88		
18<=BMI<25	Olz	107	58.84	9.37	3.52	2.53	3.24	3.12	<.001
	Placebo	49	61.18	8.41	0.50	2.16	0.12		
25<=BMI<30	Olz	30	76.31	10.29	4.44	3.61	4.25	3.93	<.001
	Placebo	19	77.50	9.32	-0.09	1.41	0.32		
BMI>=30	Olz	25	96.66	15.02	4.71	2.33	3.93	5.59	<.001
	Placebo	10	99.93	16.42	-0.90	2.37	-1.66		

Table 7.1.4.4.7 Sponsor's Table. PCS Weight Changes by Baseline BMI: HGIN + HGIU Acute Database

Table 2. Potentially Clinically Significant Weight Changes (7% Weight Gain) By Baseline BMI Acute Placebo-Controlled Combined Database

Vital Signs	BMI(Baseline)	Direction	Therapy	N	n	%	*P-value
Weight in kg	BMI<18	Gain	Olz	15	12	80.0%	.005
			Placebo	10	2	20.0%	
	18<=BMI<25	Gain	Olz	107	49	45.8%	<.001
			Placebo	49	4	8.2%	
	25<=BMI<30	Gain	Olz	30	12	40.0%	.001
			Placebo	19	0	0.0%	
	BMI>=30	Gain	Olz	25	4	16.0%	.303
			Placebo	10	0	0.0%	

The Sponsor was also asked to provide data regarding the numbers of patients at baseline and endpoint who were obese (BMI > 30) and whether there were differences between the treatment groups. At baseline, 14% (25/177) of patients in the olanzapine group and 11.4% (10/88) patients in the placebo group had BMI > 30. At endpoint, 18.6% of patients in the olanzapine group and 11.4% of patients in the placebo group had BMI > 30 (p = 0.158, NS).

The Sponsor was also asked to provide an analysis of laboratory parameters for patients who gained > 3.9 kg (mean weight gain). The major differences between olanzapine and placebo in this subgroup are noted in Table in Appendix 10.9. The LS mean change appears to be fairly similar between this subgroup and the entire study population except for a larger increase in CPK (LS mean diff 39 vs. 16 U/L) and triglycerides (LS mean diff 54 vs. 34 mg/dL) in the subgroup with > 3.9 kg weight gain. Of course, the entire population includes this subgroup – the Sponsor was not asked to provide laboratory data for patients with ≤ 3.9 kg weight gain.

7.1.5 Less Common Adverse Events

Hyperprolactinemia
The summary of the prolactin laboratory data is included in Sections 7.1.6 (Laboratory Findings) and 7.1.6.3 (Special Assessments). The adverse event tables were reviewed for any terms that might be related to hyperprolactinemia. In the HGIU + HGIN Acute Database, gynecomastia occurred in 1 (0.9%) patient in the olanzapine group and no patients in the placebo group and amenorrhea occurred in no patients in the olanzapine group and 1 (2.4%) patient in the placebo group.

The Overall Combined Database was evaluated since adverse events such as gynecomastia are not expected to occur with acute use but rather more long term use of antipsychotics. In the Overall Combined Database, gynecomastia occurred in 7 (4.3%) of patients (all from schizophrenia trials), galactorrhea occurred in 2 (3.1%) patients with schizophrenia and 1 (1%) patient with bipolar disorder and amenorrhea occurred in 1 (1.5%) patient with schizophrenia and 1 (1%) patient with bipolar disorder. The Sponsor has been asked to provide narrative summaries for all cases of gynecomastia – it is unknown whether this adverse event occurred in both male and female patients. If cases of gynecomastia occurred exclusively in female patients, it would be important to differentiate this adverse event from usual adolescent female physical development. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Extrapyramidal Symptoms
Due to the difference in frequency of EPS occurring in patients with schizophrenia and bipolar disorder taking antipsychotics, these data are summarized separately for each diagnostic group from the individual study reports (HGIN and HGIU).

Data for EPS is from a number of sources including rating scales (primarily the BAS and SAS), use of anticholinergic medications (though benzodiazepines may be used to treat EPS, they are more commonly used for managing psychiatric symptoms) and adverse events.

<u>HGIN</u>
Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.1. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown). In both the olanzapine and placebo groups, the mean change to endpoint was a decrease in rating scale score. This is not necessarily surprising depending on which

antipsychotics patients may have been taking during screening and the length of the washout period prior to obtaining the baseline rating.

Table 7.1.5.1. Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIN

EPS Variables	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
AIMS Non-Global Total(1-7)	Olanzapine	72	0.38	0.94	-0.18	0.84	-0.18	0.02	.897
	Placebo	35	0.54	1.50	-0.20	0.72	-0.21		
BRNS 4:Global Assessment of Akathisia	Olanzapine	72	0.31	0.66	-0.15	0.69	-0.15	0.05	.747
	Placebo	35	0.31	0.63	-0.20	0.76	-0.20		
Simpson-Angus Total(1-10)	Olanzapine	72	0.81	1.87	-0.22	1.51	-0.24	0.33	.260
	Placebo	35	0.97	2.41	-0.54	1.34	-0.57		

The Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined. The Sponsor has been asked to provide an analysis for the individual items of these scales.

Only 5 patients in study HGIN (acute phase) had concomitant anticholinergic medication use: 4.2% (3/72) in the olanzapine group and 5.7% (2/35) in the placebo group (p = 0.661).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.2. Adverse Events Potentially Related to EPS: HGIN

	Olanzapine N = 72	Placebo N = 35
Akathisia	2 (2.8%)	2 (5.7%)
Drooling	2 (2.8%)	0
Restlessness	2 (2.8%)	0
Dyskinesia	1 (1.4%)	0
Muscle twitching	1 (1.4%)	0
Musculoskeletal stiffness	1 (1.4%)	0
Cogwheel rigidity	0	1 (2.9%)
Tremor	0	1 (2.9%)

From Sponsor Table HGINB.14.27 in study report

Open-Label Phase HGIN

Noteworthy EPS-related adverse events occurring in the open-label phase of HGIN included oculogyration (n = 1, 0.4%) and opisthotonus (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for these events.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIN. The mean change to endpoint on the AIMS was -0.12 ± 0.94. The incidence of "treatment emergent" dyskinesia was 2.6% - again, it is

unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

HGIU

Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.3. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown) – though the mean baseline scores were numerically higher in the olanzapine group.

Table 7.1.5.3 Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIU

EPS Variables	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
AIMS Non-Global Total(1-7)	Olanzapine	105	0.16	0.90	-0.10	0.71	-0.12	-0.10	.289
	Placebo	54	0.04	0.19	0.00	0.19	-0.02		
BRNS 4:Global Assessment of Akathisia	Olanzapine	105	0.20	0.49	-0.04	0.44	-0.06	-0.09	.264
	Placebo	54	0.09	0.35	0.06	0.60	0.03		
Simpson-Angus Total(1-10)	Olanzapine	105	0.24	0.89	0.02	0.93	0.02	0.04	.769
	Placebo	54	0.07	0.33	-0.02	0.14	-0.02		

As with study HGIN, the Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined.

Only 5 patients in study HGIU (acute phase) had concomitant anticholinergic medication use, all in the olanzapine group: 4.7% (5/107) in the olanzapine group and 0% (0/54) in the placebo group (p = 0.169).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.3. Adverse Events Potentially Related to EPS: HGIU

	Olanzapine N = 107	Placebo N = 54
Restlessness	4 (3.7%)	2 (3.7%)
Musculoskeletal stiffness	3 (2.8%)	0
Tremor	2 (1.9%)	0
Akathisia	1 (0.9%)	0
Drooling	1 (0.9%)	0
Dysarthria	1 (0.9%)	0
Dyskinesia	1 (0.9%)	0
Muscle tightness	1 (0.9%)	0
Muscle twitching	1 (0.9%)	0
Salivary hypersecretion	1 (0.9%)	0

From Sponsor's table HGIU.14.30 in study report

Open-Label Phase HGIU
Noteworthy EPS-related adverse events occurring in the open-label phase of HGIU included oculogyration (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for this event.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIU. The mean change to endpoint on the AIMS was -0.03 ± 0.30. The incidence of "treatment emergent" dyskinesia was 0.7% - again, it is unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

Suicidality

The Sponsor included an analysis of suicide-related events, specifically the incidence of possible suicidal behavior or ideation, in the HGIN + HGIU Acute Database. These data were summarized for the Overall Combined Database. The following suicide-related categories were included: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, self-injurious behavior (intent unknown), not enough information (fatal), not enough information (non-fatal).

The analysis for events included categorizing suicidal behaviors as follows: suicidal behavior or ideation (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation), suicidal behavior (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior), suicidal ideation (includes suicidal ideation) and possible suicidal behavior or ideation (includes all categories). The searches included the subsequent visit (if available) after stopping treatment.

To identify cases, all preferred AE term, verbatim AE terms and comments of clinical trial data were searched for the following: accident, attempt, burn, cut, drown, gas, gun, hang, hung, immolat, injur, jump, monoxide, mutilat, overdos, self-damag, self-harm, self-inflict, self-damage, self harm, shoot, slash, suic, poison, asphyxiation, suffocation, firearm. All blinded patient listings were independently reviewed by two members of the Sponsor's medical staff "trained to evaluate suicide-related events". If a discrepancy arose, the case was discussed between them and, if necessary, a third reviewer was consulted to achieve consensus.

HGIN + HGIU Acute Database
Three possible suicidal behaviors or ideation events were identified, all three occurred in study HGIU. Two events occurred in patients treated with olanzapine (self-injurious behavior [intent unknown] in a 14.2 YOWF, suicidal ideation in a 14.6 YOWF) and one occurred in a patient receiving placebo (self-injurious behavior [intent unknown] in a 13.9 YOWM). The Sponsor's brief description of the event (from the case narratives) are provided in Appendix 10.10. No statistical differences were noted between treatment groups. The risk ratio was calculated as 1.01 (95% CI [0.09, 10.88], p = 1.000). Additional analyses (Mantel-Haenszel risk diff) also did not show statistical differences between the olanzapine and placebo groups (data not shown).

Overall Combined Database
Twenty-four cases of possible suicidal behaviors or ideation were identified – two of these events occurred in olanzapine-treated patients during the acute phase of study HGIU. The events were as follows: completed suicide (n = 0), suicide attempt (n = 2), preparatory acts toward imminent suicidal behavior (n = 2), suicidal ideation (n = 13), self-injurious behavior (intent unknown) (n = 6), not enough information (fatal) (n = 0), not enough information (non-fatal) (n = 1). The number of days to the event ranged from 4 to 214 (mean/SD = 73.5 ± 57.4 days, median = 57 days). The cases occurred in the following trials: HGIN (4), HGIU (13), HGMF (2), LOAY (5).

It is more difficult to ascertain whether a medication is associated with this adverse event in this database due to lack of a comparison group as well as the presence of a psychiatric disorder that can be associated with suicidal behaviors (esp. bipolar disorder). Of the 24 cases of suicide-related behaviors, 15 (62%) occurred in bipolar patients.

This reviewer also evaluated the individual item "suicidal ideation" in the Children's Depression Rating Scale-Revised. Though rating scales may not capture this specific adverse event, these data were reviewed to see if any trends in worsening occurred on the suicide-related item. For the CDRS[2], most patients scored a "1" at baseline. For patients who scored > 1, most showed improvement (decrease in score). Two patients in the placebo group had worsening on this item; one patient had an increase from a 1 to a 3 and another from a 2 to a 3 severity rating. Two patients in the olanzapine group had worsening on this item; one patient had an increase from a 2 to a 3 and another from a 2 to a 4 severity rating. Of note, 3 patients had a severity rating of 7 at baseline (all were randomized to olanzapine). The Sponsor will be asked to provide details regarding inclusion of these patients in the clinical trial.

Hostility and Aggression Adverse Events
Similar to the strategy used to identify possible suicide-related behaviors, the Sponsor identified patient cases for hostility and aggression. The following categories were used for these cases: aggressive behavior with physical harm directed toward another person, aggressive behavior with physical harm directed toward animals, aggressive behavior with physical harm directed toward objects, aggressive behavior with nonspecific information, aggressive behavior with indirect or no potential for direct physical harm, hostility without aggression, anger without hostility or aggressive behavior, violent ideation with no anger, hostility or aggressive behavior, and does not meet case definition.

In the HGIN + HGIU Acute Database, 7 cases were identified (1 case in HGIN, 6 cases in HGIU). Four cases occurred in patients in the olanzapine treatment groups. The olanzapine

2 CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does ont understand the concept of suicide), usually when angry; 4 = intermediate rating, not anchored; 5 = has recurrent thoughts of suicide; 6 = intermediate rating, not anchored; 7 = has made a suicide attempt within the last month or is actively suicidal

cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, hostility without aggression and anger without hostility or aggressive behavior. The placebo cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, and hostility without aggression. Given the patient population, it is surprising that not more cases of hostility or aggression were identified. However, overtly hostile patients or patients with a strong history of hostility or aggression would be less likely to be enrolled in a clinical trial. No statistical differences were noted between treatment groups (data not shown).

In the Overall Combined Database, 23 cases of possible hostility or aggression-related events were identified: HGIN (5), HGIU (13), HGMF (1), LOAY (4). It is not unexpected for hostility or aggressive behaviors to be exhibited by patients with inadequately controlled symptoms of schizophrenia or bipolar disorder.

7.1.6 Laboratory Findings

The data from the HGIN + HGIU Acute Database was the primary source of data reviewed. When individual patient labs were being reviewed, it was noticed that many labs were missing from the study reports – most commonly the last (third) page of labs for many patients. Though all of the lab data appeared to be present in the JMP datasets, it was sometimes more difficult to look for trends or other signals using the dataset than the individual lab profile.

7.1.6.1 Overview of laboratory testing in the development program

During the acute 3 week trial labs were obtained as follows:
Clinical chemistry, electrolytes – baseline and weekly during trial
Lipids - baseline and weekly during trial; fasting glucose/lipids were obtained at baseline and end of study
Hematology - baseline and weekly during trial
Urinalysis – baseline and end of study
TSH – screening only
Prolactin – baseline and end of study
HbA1c – screening and end of study <u>for patients with known diabetes</u>
Hepatitis screen, urine drug screen, pregnancy test – screening only

7.1.6.2 Standard analyses and explorations of laboratory data

7.1.6.2.1 Analyses focused on measures of central tendency

The mean change from baseline to endpoint for the laboratory evaluations for HGIN + HGIU Acute Database is included in Appendix 10.11. Statistically significant decreases in lab parameters in the olanzapine group compared to placebo included hematocrit, hemoglobin, erythrocyte count, basophils, mean cell volume, albumin, total bilirubin and direct bilirubin – though these mean changes were small. Statistically significant increases in lab parameters in

the olanzapine group compared to placebo included ALT, AST, GGT, fasting glucose, cholesterol, LDL cholesterol, triglycerides, uric acid, prolactin, eosinophils and urea nitrogen.

The mean change from baseline to endpoint for selected laboratory parameters is in Table 7.1.6.2.1.1 below. For ALT and AST, the standard deviation at *baseline* in these laboratory parameters for the olanzapine group was very large (SD > mean) compared to the SD at baseline in the placebo group. For change to endpoint, the SD is still quite large in the olanzapine group compared to the placebo group indicating considerable variability and some significant increases in these parameters. The fasting glucose, triglyceride and cholesterol data were converted from SI units to the more conventional mg/dL units in this table.

It should be noted that there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. Elevated baseline prolactin was more common in study HGIN, as would be expected. A cursory review of the JMP dataset found that approximately 17% of patients in HGIN had a baseline prolactin > 30 ng/ml (maximum baseline prolactin = 65 ng/ml). The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range. Of note, the Sponsor did acknowledge this limitation and provided some additional analyses (see Section 7.1.6.3 – Special Assessments).

Table 7.1.6.2.1.1. Select Laboratory Analytes of Interest: HGIN + HGIU Acute Database

			Baseline		**Change to Endpoint**				
		N	Mean	Std	**Mean**	Std	LS Mean Change	LS Mean Difference	P-value
Alkaline Phosp (U/L)	Olanzapine	175	152.3	82.3	**-1.3**	25.6	-2.7		
	Placebo	87	138.7	86.9	**-4.0**	16.6	-5.3	2.6	0.396
ALT (U/L)	Olanzapine	175	24.1	45.9	**19.95**	54.84	28.11		
	Placebo	87	20.4	13.0	**-3.08**	11.69	5.13	22.98	< 0.001
AST (U/L)	Olanzapine	175	24.5	29.9	**6.43**	26.41	9.89		
	Placebo	87	23.6	8.5	**-2.47**	7.51	0.98	8.91	0.002
GGT (U/L)	Olanzapine	175	19.0	12.3	**7.47**	20.02	7.73		
	Placebo	87	17.7	8.5	**-0.43**	5.96	-0.16	7.89	< 0.001
Glucose, fasting (mg/dL)*	Olanzapine	135	88.1	9.91	**2.70**	10.4	2.70		
	Placebo	64	89.7	10.27	**-2.88**	10.1	-3.06	5.59	< 0.001
Cholesterol (mg/dL)*	Olanzapine	175	161.0	32.0	**13.1**	22.78	12.74		
	Placebo	87	160.2	32.8	**-1.16**	24.32	-1.54	14.29	< 0.001
Triglycerides (mg/dL)*	Olanzapine	175	104.4	58.4	**29.2**	80.53	26.55		
	Placebo	87	110.6	64.6	**-4.42**	54.87	-6.19	33.63	< 0.001
Prolactin (mcg/L)	Olanzapine	163	14.06	9.92	**11.44**	14.52	10.51		
	Placebo	80	14.95	11.86	**-0.16**	10.69	-1.15	11.66	< 0.001

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113

Since urinalysis for ketones, glucose and protein is noted as 1+, 2+ etc., no mean change from baseline was provided for these parameters. It was noted, however, that there were no patients with PCS changes in these parameters (defined as increase $\geq$ 2) in either the olanzapine or placebo groups. Only 1 patient exhibited a PCS change in urinalysis – protein in the Overall Combined Database.

In the HGIN + HGIU Acute Database, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes). There was no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

7.1.6.2.2 Analyses focused on outliers or shifts from normal to abnormal

Percentage of patients with statistically significant treatment-emergent abnormal high laboratory values at any time (HGIN + HGIU Acute Database).
AST –27.6% of olanzapine and 3.8% of placebo-treated patients ($p < 0.001$)
ALT - 38.6% of olanzapine and 2.5% of placebo-treated patients ($p < 0.001$)
GGT – 10.1% of olanzapine and 1.2% of placebo-treated patients ($p = 0.008$)
Total bilirubin –0% of olanzapine and 7.1% of placebo-treated patients ($p = 0.001$)
Albumin –6.3% of olanzapine and 23.2% of placebo-treated patients ($p = 0.002$)
Fasting glucose – 3.7% of olanzapine and 3.2% of placebo-treated patients (p = NS)
Cholesterol –19.7% of olanzapine and 3.9% of placebo-treated patients ($p = 0.001$)
Triglycerides –54.7% of olanzapine and 19.6% of placebo-treated patients ($p < 0.001$)
HDL –9.7% of olanzapine and 1.2% of placebo-treated patients ($p = 0.014$) [shift to low were NS between groups]
Further analyses for shifts in fasting glucose, cholesterol, and triglycerides is included in Section 7.1.6.3 – Special Assessments.

7.1.6.2.3 Marked outliers and dropouts for laboratory abnormalities

In the HGIN + HGIU Acute Database, six patients discontinued due to elevations in ALT and/or AST. See Table 7.1.3.1.1 in Section 7.1.3.1 (Adverse events associated with dropouts).

The Sponsor did not provide a summary of marked outliers in the laboratory analysis. The individual patient labs and/or JMP datasets were reviewed from HGIN and HGIU study reports to identify marked outliers. It should be noted that the marked outliers in Table 7.1.6.2.3.1. may include lab values that were less than the potentially clinically significant (PCS) abnormalities defined by the Sponsor. For example, the cholesterol PCS was defined as > 15.516 mmol/L (> 599 mg/dL), whereas the values noted as marked outliers were usually lower than this PCS value. Of note, there was no defined PCS for triglycerides.

Table 7.1.6.2.3.1 includes the marked outlier (in bold font), other related analytes at the same timepoint, end of acute study value for the marked outlier (resolution?) and a column for comments which included any additional values for the marked outlier in the open-label phase. Individual patient profiles were not readily available so it is not known if resolutions in marked outlier values were related to decreases in olanzapine dose.

Table 7.1.6.2.3.1. Marked Outliers for Laboratory Values – HGIN and HGIU

			Marked Outlier Related Analytes at Same Timepoint *(Italics = values > ULN)*			
Patient	Lab Analyte	Reference Range*	Baseline	Highest	End of Study	Comments
HGIU 005-501	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	102.6 125.9 68.7	**1237** (v.4) *220.8* NA	*389.4* *205.8* 90.0	TG = *160* at v.307 EOS
HGIU 012-1203	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	18 19 0.41 18	**325** (v.5) **148** 0.29 *53*	*230* (150 repeat) *92* (51 repeat) 0.29 (0.18 repeat) *48* (52 repeat)	ALT = *48*, AST = 24 at v. 501 (follow-up)
HGIU 012-1207	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	45 49 0.53 30	**147** (v.4) *60* 0.41 **163**	**147** 60 0.41 **163**	None
HGIU 013-1303	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	110.6 178.8 123.9	**261.9** (v.5) 179.5 *95.7*	**261.9** 179.5 95.7	TG = 111 at v.306
HGIU 019-1901	Creatine Phosphokinase	0 – 169 U/L	83	**256** (v.5)	*256*	CK = 168 at v. 301 (repeat 72)
HGIU 020-2007	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	67.2 149.8 98.8	**536.3** (v.4) 165.6 NA	*365.5* *231.7* 120.8	*TG = 103 at v. 307*
HGIU 020-2011	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	22 19 0.41 11	**124** (v.6) *87* 0.29 27	**124** *87* 0.29 27	ALT = 11 at v. 309
HGIU 026-2607	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	59.3 201.5 125.9	**324.8** (v.4) 171.8 62.9	179.6 164.9 84.9	TG = 72 at v. 310
HGIU 027-2704	Creatine Phosphokinase	0 – 363 U/L	326	**619** (v.6)	**619**	CK = 261 at v. 307
HGIU 031-3103	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	16 19 1 13	**135** (v.4) 35 0.82 **153**	*75* *62* 0.53 *87*	ALT = 33/25 at v. 302
HGIU 035-3503	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	62.8 164.9 120.8	**317.7** (v.4) 167.6 74.9	100 203.9 *141.7*	None
HGIU 035-3518	Creatine Phosphokinase	0 – 187 U/L	55	**257** (v.6)	**257**	CK = 56 at v. 310
HGIU	ALT	6 – 43 U/L	43	**208** (v.6)	**208**	ALT = *99* at

036-3607	AST TBili GGT	10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	27 0.71 36	*91* 0.29 *65*	*91* 0.29 *65*	v. 307
HGIU 720-7202	Creatine Phosphokinase	0 – 363 U/L	71	**650** (v.5)	**650**	CK = 70 at v. 310
HGIU 720-7203	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	11 15 0.41 21	**128** (v.6) *58* 0.29 *98*	**128** *58* 0.29 *98*	ALT = 15 at v. 310
HGIU 720-7210	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	108.8 172.6 109.6	**382.3** (v.4) 195.7 88.0	*171.7* 199.6 127.8	TG = *148* at v. 310
HGIU 720-7214	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	38 31 0.71 20	**448** (v.6) **164** 0.41 46	**448** **164** 0.41 46	ALT = *69* at v. 302
HGIU 720-7217	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	20 32 0.88 21	**125** (v.6) *103* 0.53 35	**125** *103* 0.53 35	ALT = *58* at v. 308
HGIU 720-7221	Glucose, fasting	70 – 115 mg/dL	86.5	**145.9 (v.4)**	72	Glucose = 77 at v. 306
HGIU 730-7302	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	22 29 0.29 13	**123** (v.5) *77* 0.18 27	41 28 0.18 22	ALT = 16 at v. 310
HGIN 003-302	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	19 17 0.29 10	**132** (v.9) 38 0.29 18	**132** 38 0.29 18	ALT = 27 at v. 305
HGIN 004-401	ALT AST TBili GGT	6 – 43 U/L 10 - 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	18 19 0.18 19	*39* **157** (v.4) 0.18 18	19 25 0.41 17	AST = 22 at v. 309
	Creatine Phosphokinase	0 – 363 U/L	289	**7289** (v.4)	*610*	CPK = *781* at v. 309 (was *1766* at v. 306)
HGIN 006-602	ALT AST TBili GGT	6 – 43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	22 27 0.88 44	**240** (v.8) **141** 0.29 **206**	*134* *60* 0.53 *216*	ALT = 32 AST = *49* GGT = 38 at v. 308
	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	136.3 171.8 96.9	**532.7** (v.7) *210.8* NA	*207.1* 185.7 102.7	TG = 93 at v. 308
HGIN 007-703	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	29 33 0.41 11	**231** (v.6) **142** 0.41 *34*	*199* *101* 0.29 *34*	ALT = *66*, AST = 33 at v. 501 (follow-up)
HGIN 007-705	Creatine Phosphokinase	0 – 408 U/L	115	**855** (v.8)	189	CK = 141 at v. 305
HGIN 016-1601	ALT AST	6 – 43 U/L 10 – 40 U/L	23 26	**159** (v.6) *67*	36 32	ALT = 43 at v. 309

	TBili GGT	0.18 – 1.23 mg/dL 0 – 51 U/L	*1.41* 22	1.23 *64*	1.11 36	
HGIN 017-1703	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	*60* 40 0.18 23	**210** (v.5) *96* 0.18 29	*79* *50* 0.29 18	ALT = 15 at v. 309
HGIN 020-2004	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	21 21 0.29 29	**163** (v.5) *87* 0.29 *81*	18 22 0.18 *43*	ALT = 9 at v. 309
HGIN 021-2102	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	8 19 0.29 12	**105** (v.9) *90* 0.41 23	**105** *90* 0.41 23	ALT = 13 at v. 307
	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	84.9 201.5 102.7	111.5 **289.6** (v.6) *165.6*	109.7 *237.4* 132.8	TG = *293* Chol = *240* at v. 307
HGIN 021-2103	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	16 20 0.41 18	**396** (v.7) **136** 0.41 *63*	**396** **136** 0.41 *63*	ALT = *154*, AST = 36 at v. 502 (follow-up)
HGIN 030-3002	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	11 19 0.71 23	**175** (v.7) *69* 0.29 *72*	*61* *60* 0.29 48	ALT = 39 at v. 309
HGIN 033-3301	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	87.6 *214.7* *139.8*	**426.5** (v.9) *214.7* *149.8*	**426.5** *214.7* *149.8*	None
HGIN 900-9003	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	85.8 118.1 82.6	**270.8** (v.8) 167.2 84.5	*195.6* 147.1 79.5	TG = 143 at v. 307
HGIN 900-9006	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	*231* 194.5 107.3	**363.7** (v.7) *241.3* 130.9	*170.8* *228.2* *147.9*	AST = 23 at v.309
HGIN 900-9010	ALT AST TBili GGT	6 – 43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	20 26 0.41 20	*68* **161** (v.8) 0.47 20	35 31 0.65 15	AST = 31/29 at v. 309
HGIN 910-9101	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	*65* 27 0.47 *36*	*51* 38 0.23 **95** (v.5)	16 24 0.18 26	GGT = *46* at v. 309
HGIN 910-9103	ALT AST TBili GGT	6 – 43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	29 30 0.35 22	**141** (v.6) *84* 0.76 29	36 38 0.53 20	ALT = 23 at v. 309
HGIN 910-9105	Glucose, Fasting	70 – 115 mg/dL	108	**127.9** (v.9)	*127.9*	Glucose, fasting = 92 at v. 309
HGIN 910-9107	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	132.7 190 128.2	**285.8** (v.4) *213.5* 118.9	*178.8* 197.7 127.0	TG = 107 at v. 309
HGIN	ALT	6-43 U/L	40	**117** (v.5)	28	ALT = 28 at

910-9108	AST TBili GGT	10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	20 0.35 32	*52* 0.35 34	23 0.35 23	v. 309
HGIN 910-9110	ALT AST TBili GGT	6-43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	25 25 0.47 19	**321** (v.5) **190** 0.59 37	*128* *53* 0.41 29	ALT = 17, AST = 19 at v. 501 (follow-up)
HGIN 920-9202	ALT AST TBili GGT	6-43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	15 19 1 27	**393** (v.6) **177** 1 *78*	**393**(231 repeat) **177** (59 repeat) 1 (0.71 repeat) *78* (82 repeat)	ALT = 20 at v. 501 (follow-up), AST NA
HGIN 920-9207	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	123.9 *205.0* *135.1*	**336.3** (v.6) *233.2* 126.2	**336.3** *233.2* 126.2	None

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259, bilirubin = 17.1 (micromol/L to mg/dL)

Very few patients exhibited an increase in fasting glucose that might be considered a marked outlier in the HGIN + HGIU Acute Database. In reviewing the JMP dataset, 3 patients were noted with markedly elevated fasting glucose in the open-label phase of HGIN and HGIU:

Patient HGIN-900-9011 was randomized to placebo in the DB phase and had a baseline fasting glucose of 110 mg/dL. At visit 301, fasting glucose was 169 mg/dL on 7.5 mg olanzapine which normalized with continued dosing at 10 mg to 97 mg/dL at end of the study.
Patient HGIN 910-9108 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 95 mg/dL. At visit 7 of the acute phase, fasting glucose was 101 mg/dL, at visit 303 fasting glucose was 149 mg/dL on 20 mg olanzapine which normalized with continued dosing to 94 mg/dL at visit 309.

Patient HGIU 026-2602 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 104 mg/dL. At visit 6 of the acute phase, fasting glucose was 112 mg/dL, at visit 310 fasting glucose was 205 mg/dL on 12.5 mg olanzapine and at visit 501 (follow-up) fasting glucose was 113 mg/dL.

The Sponsor did not include prolactin in the list of analytes for definitions of potentially clinically significant changes. For purposes of this review, the laboratory data in the JMP database was reviewed and a PCS value of $\geq$ 40 ng/ml was arbitrarily chosen. Prolactin levels were obtained at screening, baseline, end of study in the double-blind acute phase of HGIN and HGIU and visit 305 (HGIN) and 307 (HGIU) (~8-10 weeks into OL) and end of OL phase.
The reference ranges used for prolactin were males 2.8 – 22 ng/ml and females 3.2 – 20 ng/ml. – per protocol amendment.
However, in the summary-clin-safe-app, the following Covance adolescent reference ranges were noted:

Gender	Age	Low (ug/L)	High (ug/L)
Male	12<=Age<14	2.84	24.0
	14<=Age<19	2.76	16.1
Female	12<=Age<14	2.52	16.9
	14<=Age<19	4.20	39.0

In the double-blind phase of HGIU, 13% (13/99) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 99/107 patients]. Only 3 of the 13 patients were male. The mean prolactin concentration at the end of study for this subgroup was 50.4 ± 8.3 ng/ml.

In the double-blind phase of HGIN, 17% (11/64) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 64/72 patients]. Only 4 of the 11 patients were male. The mean prolactin concentration at the end of study for this subgroup was 55.8 ± 15.8 ng/ml. One patient receiving placebo in the acute HGIN study had an increase from 18.2 ng/ml at baseline to 42.4 ng/ml at end of study. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

With the exception of one patient, it is not known whether these patients exhibited any clinical symptoms associated with hyperprolactinemia (narratives not available for these cases). Galactorrhea was not reported as an adverse event in the acute phases of HGIU or HGIN and one patient in the olanzapine group had the adverse event “gynecomastia” (see Section 7.1.4.3 Special Assessments). Patient HGIU 028-2804, who had an increase in prolactin concentration to 129.7 ng/ml, exhibited bilateral galactorrhea. Of note, one female patient in the LOAY study (data not included here) discontinued due to the adverse event galactorrhea – the narrative stated that her prolactin increased to 35 ng/ml. Therefore, clinical symptoms may have been associated with these prolactin elevations. It is possible that patients, especially adolescents, might be reluctant to report the types of adverse events associated with hyperprolactinemia.
Some patients who continued into the open-label phase had a decrease in their prolactin concentrations, others did not. Due to time constraints, this reviewer was unable to evaluate each case to determine whether decrease/resolution of hyperprolactinemia was related to a reduction in olanzapine dose.

Table 7.1.6.2.3.2. Prolactin Outliers: HGIN + HGIU Acute Database

		Prolactin (ng/ml)		
Patient	Age/Gender	Baseline	End of Double-Blind Phase	End of Open-Label Phase
HGIU 010-1005	14 YOM	23.4	60.7	17.6
HGIU 012-1216	16 YOM	18.9	51.1	51.6
HGIU 019-1901	16 YOF	9.2	43.8	35.0
HGIU 019-1905	14 YOF	18.8	44.5	32.6
HGIU 020-2007	14 YOF	16.5	57.6	14.5
HGIU 020-2011	13 YOF	8.1	57.5	10.9
HGIU 020-2020	16 YOF	12.7	44.4	40.3
HGIU 021-2103	17 YOF	20.6	45.1	13.5
HGIU 024-2403	15 YOF	31.1	49.8	31.5
HGIU 024-2405	13 YOM	15.2	40.3	24.3
HGIU 026-2602	13 YOF	20.2	50.3	49.5
HGIU 028-2803	15 YOF	31.6	68.1	11.7
HGIU 035-3517	13 YOF	13.8	42.3	17.4
HGIN 005-503	14 YOF	17.2	90.7	45.5
HGIN 013-1303	16 YOF	17.3	48.3	NA
HGIN 020-2003	17 YOF	26.3	79.9	NA
HGIN 021-2102	16 YOF	30.8	59.9	16.7
HGIN 026-2602	15 YOF	36	41.5	9.6
HGIN 026-2603	14 YOF	33	44.9	59.4
HGIN 030-3010	13 YOF	17.4	55	NA
HGIN 034-3401	16 YOM	22.7	43.8	30.4
HGIN 900-9006	17 YOM	28	55.5	40.1
HGIN 910-9107	16 YOM	45.8	48.2	43.2
HGIN 940-9408	15 YOM	12	45.8	21.7

NA = not applicable, patient was not enrolled in open-label phase

Table 7.1.6.2.3.3. Prolactin Outliers: HGIN + HGIU Open Label Phase

Patient	Age/Gender	Treatment in DB Phase	Baseline	Visit #307(HGIU) #305 (HGIN)	End of Open-Label Phase Visit #310 (HGIU) Visit #309 (HGIN)
HGIU 007-704	15 YOM	Placebo	32.5	36.1	**47.3**
HGIU 019-1904	15 YOF	Placebo	5.5	28.5	**43.7**
HGIU 019-1907	15 YOF	Olanzapine	10.1	**40.6**	38.5 (v. 308)
HGIU 020-2003	13 YOF	Olanzapine	18.4	**41.8**	23.6
HGIU 021-2102	17 YOF	Olanzapine	25	**57.7**	10.6
HGIU 026-2608	13 YOF	Olanzapine	20.5	-	**57** (v. 304)
HGIU 028-2804	15 YOF	Placebo	11.8	**129.7** (v.302)	**49.8** (v. 307)
HGIU 035-3519	14 YOM	Olanzapine	28.3	-	**41.7** (v. 302)
HGIU 036-3606	16 YOF	Placebo	20.7	**59.5**	**44.0**
HGIN 900-9009	17 YOF	Olanzapine	17.5	17	**110**
HGIN 020-2005	14 YOM	Olanzapine	41.1	-	**64.7** (v. 305)

7.1.6.3 Special assessments

Hyperprolactinemia

A discussion of the adverse events potentially related to hyperprolactinemia are in Section 7.1.5 (Less Common Adverse Events). The mean change from baseline to endpoint in prolactin concentration is in Section 7.1.6.2.1 and marked outliers are in Section 7.1.6.2.3.

As was mentioned in Section 7.1.6.2.1, there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range (including treatment by gender and treatment by age analyses).

Elevations in prolactin due to antipsychotics occur more frequently in females compared to males. The Sponsor did include an analysis of these laboratory data by gender for the individual HGIU and HGIN studies. For each separate study, no significant treatment by gender interaction was found. However, there was a numerically greater mean change to endpoint in prolactin in females (16.2) compared to males (5.4) in study HGIN. Also, for the patients with an end of

study prolactin > 40 ng/ml, the majority of these patients were female (see Section 7.1.6.2.3.). For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction (see Appendix 10.12), though there was a numerically greater mean change to endpoint in females (15.6) compared to males (8.8).

Table 7.1.6.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: Study HGIU

Laboratory Analyte	Gender	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean	LSMean Diff.	*P-value	**P-value
PROLACTIN	Female	70	Olanzapine	43	15.23	10.01	15.38	13.73	15.96	12.75	<.001	.590
			Placebo	27	14.99	8.00	2.67	8.60	3.21			
	Male	79	Olanzapine	56	11.36	5.46	11.50	9.50	11.91	10.83	<.001	
			Placebo	23	10.00	6.40	0.66	3.06	1.08			

Table HGIU.12.13 in study report

Table 7.1.6.3.2. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: Study HGIN

Laboratory Analyte	Gender	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean	LSMean Diff.	*P-value	**P-value
PROLACTIN	Female	30	Olanzapine	20	17.24	10.31	16.17	22.59	14.25	17.99	.025	.258
			Placebo	10	15.95	6.67	-2.20	10.26	-3.73			
	Male	64	Olanzapine	44	14.89	13.11	5.37	14.35	5.43	9.27	.028	
			Placebo	20	20.10	19.26	-3.91	16.86	-3.84			

This reviewer could not find an analysis of prolactin concentrations by the subgroup "age". The Sponsor will be asked to provide these data.

The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIU + HGIN Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$). No significant treatment-by-gender interactions were noted in this analysis, though a higher percentage of males (41/68, 60.3%) had a high prolactin concentration at any time compared to females (14/48, 29%).

The Sponsor did evaluate prolactin concentrations over time for the Overall Combined Database. In general, there is a decrease in mean prolactin concentration over the course of the 32 weeks which approaches baseline concentrations. There are still outliers in this analysis at the 19-32 week timepoint. The Sponsor will be asked to provide a similar summary for only those patients completing the 19-32 weeks.

Table 7.1.6.3.3. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database

Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points Overall Olanzapine Exposure Combined Database

		Summary				
Database	Olz Exposure	N	Mean	Std	Median	Max
Bipolar	Baseline	217	15.35	12.58	11.28	110.30
	1-6 weeks	174	26.60	16.18	23.10	129.66
	7-18 weeks	122	19.24	11.89	16.71	59.49
	19-32 weeks	83	18.03	10.42	14.36	49.53
Schizophrenia	Baseline	214	18.84	19.97	11.87	131.57
	1-6 weeks	190	31.82	20.75	26.48	110.84
	7-18 weeks	88	22.75	16.24	18.62	112.00
	19-32 weeks	93	19.01	15.60	14.81	109.97
Overall	Baseline	431	17.08	16.74	11.60	131.57
	1-6 weeks	364	29.33	18.86	25.00	129.66
	7-18 weeks	210	20.71	13.95	17.13	112.00
	19-32 weeks	176	18.55	13.38	14.70	109.97

Metabolic Parameters

The Sponsor performed more detailed analyses on several adverse event profiles including "metabolic parameters".

The analyses included LOCF mean change from baseline to endpoint in fasting glucose and lipids; incidence of significant changes in fasting glucose and lipids, nonfasting glucose and lipids, weight gain-related adverse events, diabetes-related adverse events and dyslipidemia related adverse events; mean weight over time; correlations between mean changes in weight, glucose and lipids.

HGIN + HGIU Acute Database

LOCF mean change from baseline to endpoint:

There were statistically significant greater mean increases in fasting glucose levels (+ 2.7 mg/dL olanzapine vs. -2.9 mg/dL placebo, $p < 0.001$), total cholesterol (+ 12.7 mg/dL vs. +1.5 mg/dL, $p = 0.002$), and triglycerides (+27.4 mg/dL vs. -1.8 mg/dL, $p = 0.007$).

Significant changes in fasting glucose and lipids <u>at any time</u>:

There was a greater incidence of significant changes in patients treated with olanzapine than in patients treated with placebo for normal to borderline total cholesterol (15.7% vs. 3.6%, $p = 0.023$) and for normal to high fasting triglycerides (12.4% vs. 1.9%, $p = 0.039$).

The change from normal to borderline LDL cholesterol was approaching statistical significance (13.7% vs. 3.8%, $p = 0.064$).

The changes in fasting glucose were not statistically different:

Normal (< 100 mg/dL) to high (≥ 126 mg/dL) = 0% (0/122) olanzapine, 2% (1/51) placebo
Impaired glucose tolerance (≥ 100 mg/dL and < 126 mg/dL) to high (≥ 126 mg/dL): 15.4% (2/13) olanzapine, 0% (0/13) placebo
Normal/impaired glucose tolerance (< 126 mg/dL) to high (≥ 126 mg/dL): 1.5% (2/135) olanzapine, 1.6% (1/64) placebo.

The lack of a statistically significant difference in the change from impaired glucose tolerance to high fasting glucose levels (15.4% olanzapine vs. 0% placebo) is likely due to the low number of subjects enrolled with baseline impaired glucose tolerance (n = 13 each group).

Significant changes in fasting glucose and lipids at endpoint:
The only parameter that was statistically significant was normal to borderline cholesterol (14% olanzapine, 3.6% placebo, p = 0.039). The change from normal to high triglycerides was approaching statistical significance (10.6% olanzapine, 1.9% placebo, p = 0.064).

For the fasting glucose data, only 1 subject in the olanzapine treatment arm had a change from impaired glucose tolerance to high and 1 subject in the olanzapine treatment arm had a change from normal/impaired glucose tolerance to high.

In the Overall Combined Dataset, few patients had baseline impaired glucose (n = 47). Of those subjects, 6 (12.8%) had a shift from impaired glucose tolerance to high fasting glucose.
As mentioned in Section 7.1.6.2.1, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes) in the HGIN + HGIU Acute Database. There was no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

The Sponsor provided correlation coefficients of change at endpoint between weight, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (it is unclear what correlation coefficient was used):
For the Overall Combined Dataset, there were statistically significant correlations between weight and total cholesterol (corr = 0.166, p = 0.005) and between weight and triglycerides (corr = 0.210, p < 0.001).
The Sponsor was asked to provide these correlations for the HGIN + HGIU Acute Database. In this database, there were statistically significant correlations between weight and total cholesterol (corr = 0.211, p = 0.003), between weight and triglycerides (corr = 0.223, p = 0.002) and between weight and fasting glucose (corr = 0.165, p = 0.021). Though these correlations are statistically significant, they are not particularly robust.

Hepatic-related Parameters
The Sponsor performed more detailed analyses on several adverse event profiles including "hepatic-related parameters".

For this analysis, a potentially clinically significant increase is defined as a change from a value less than or equal to the PCS high limit at all baseline visits to a value greater than the PCS high limit at endpoint or for two consecutive measures during therapy.

HGIN + HGIU Database
Mean change to endpoint in hepatic laboratory analytes in provided in Section 7.1.6 (Laboratory Findings).

The Sponsor analyzed treatment emergent high values at anytime (Table 7.1.6.3.4) and at endpoint (Table 7.1.6.3.5) for alkaline phosphatase, ALT, AST, GGT and total bilirubin. A higher percentage of patients in the olanzapine group had elevations in ALT, AST and GGT for both analyses.

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at Anytime: HGIN + HGIU Acute Database

Table APP.2.7.4.7.2.2. Hepatic Laboratory Analytes
Treatment-Emergent Abnormally High Values Anytime (>1 X ULN)
All Randomized Patients with Normal Baseline Values
Acute Placebo-Controlled Combined Database

Hepatic Analytes	Olanzapine N	Olanzapine n	Olanzapine %	Placebo N	Placebo n	Placebo %	p-value*
ALKPH	159	11	6.9%	77	2	2.6%	.231
ALT	153	59	38.6%	79	2	2.5%	<.001
AST	163	45	27.6%	79	3	3.8%	<.001
GGT	169	17	10.1%	83	1	1.2%	.008
T. Bili	170	0	0.0%	85	6	7.1%	.001

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at Endpoint: HGIN + HGIU Acute Database

Table APP.2.7.4.7.2.24. Hepatic Laboratory Analytes
Treatment-Emergent Abnormally High Values at Endpoint (>1 X ULN)
All Randomized Patients with Normal Baseline Values
Acute Placebo-Controlled Combined Database

Hepatic Analytes	Olanzapine N	Olanzapine n	Olanzapine %	Placebo N	Placebo n	Placebo %	p-value*
ALKPH	159	6	3.8%	77	1	1.3%	.432
ALT	153	32	20.9%	79	1	1.3%	<.001
AST	163	19	11.7%	79	1	1.3%	.005
GGT	169	14	8.3%	83	0	0.0%	.006
T. Bili	170	0	0.0%	85	5	5.9%	.004

Abnormal ALT values at anytime
> 3X ULN: olanzapine 11.1% (17/153) vs. placebo 1.3% (1/79) p = 0.008
> 5X ULN : olanzapine 3.9% (6/153) vs. placebo 0% p = 0.098
> 10X ULN : olanzapine 0.7% (1/153) vs. placebo 0% p = 1.00

> 3X ULN ALT anytime for patients with ALT baseline ≤ 3X ULN:olanzapine 12.1% (21/174) vs. 2.3% placebo (2/87) p = 0.009. [This analysis is the one that is included in proposed labeling for ALT elevations]

Only four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and two in the placebo group.

The Sponsor also used Hy's rule (ALT ≥ 3 times and TBili ≥ 1.5 times ULN) to identify any patients with potential severe hepatic injury. There were no patients who met Hy's rule criteria at any time in the clinical trials or at endpoint.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

Blood pressure and heart rate were taken at every visit during the acute study – supine for 5 minutes and after standing for 2 minutes
Weight and temperature were taken at every visit
Height was taken at screening, at multiple study visits and end of study.

7.1.7.2 Standard analyses and explorations of vital signs data

7.1.7.2.1 Analyses focused on measures of central tendencies

Mean change from baseline to endpoint (LOCF) for vital signs is included in Appendix 10.13. Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events). Statistically significant differences in mean change from baseline to endpoint between the olanzapine and placebo groups were noted for:
Supine SBP: olanzapine + 2.94 mmHg, placebo - 0.71 mm Hg ($p = 0.009$)
Standing DBP: olanzapine + 1.42 mmHg, placebo -1.28 mmHg ($p = 0.033$)
Supine pulse: olanzapine + 7.07 bpm, placebo - 0.60 bpm ($p < 0.001$)
Standing pulse: olanzapine +6.97 bpm, placebo - 0.89 bpm ($p < 0.001$)
Orthostatic SBP and pulse were not significantly different between olanzapine and placebo.
Weight: olanzapine +3.90 kg, placebo +0.24 kg ($p < 0.001$)
BMI: olanzapine + 1.22, placebo + 0.05 ($p < 0.001$)

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially clinically significant definitions for vital signs are in Appendix 10.14.
There were no statistically significant differences between olanzapine and placebo for percentages of patients with potentially clinically significant changes (high or low) with the exception of weight. Of note, 5.7% of olanzapine and 4.5% of placebo-treated patients exhibited orthostatic hypotension (p = NS).
The percentage of patients who gained $\geq$ 7% body weight was higher in the olanzapine group (43.5%) compared to the placebo group (6.8%) ($p < 0.001$). Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events).

7.1.7.2.3 Marked outliers and dropouts for vital sign abnormalities

Individual vital signs were reviewed from the JMP datasets. In general, few patients had markedly abnormal vital signs. Isolated systolic BP 150 – 155 mmHg was noted in both olanzapine and placebo groups, no diastolic BPs > 110 mmHg were noted and pulse rates > 130 bpm were noted in few patients but more olanzapine-treated patients than placebo-treated patients (highest pulse was 148 bpm in placebo patient).
Patient HGIU-035-3503 (16 YOBF) receiving olanzapine discontinued study HGIU due to an elevated pulse (standing pulse 140 bpm from baseline 96 bpm).

7.1.8 Electrocardiograms (ECGs)

7.1.8.1 Overview of ECG testing in the development program

The reviewer focused mainly on the two placebo-controlled acute trials, HGIN and HGIU, for evaluation of ECG data. Though the Sponsor states that differences from baseline were analyzed, it should be noted that ECGs were not obtained at baseline (visit 2), but were obtained during the screening period (visit 1):

"Twelve-lead ECGs were collected on each patient at baseline to determine the eligibility of the patient for entry into the study, and at the Final Visits of Study Period II and Study Period III to monitor the general safety of the patient during the course of the study".
Therefore, patients could be on other medications since this was the washout period prior to randomization.
Mean "baseline" ECG parameters appear fairly similar between the olanzapine and placebo groups such that any differences between the groups with regard to concomitant medications taken during screening might have been "equalized" by randomization.

7.1.8.2 Standard analyses and explorations of ECG data

7.1.8.2.1 Analyses focused on measures of central tendency

Statistically significant differences were found between olanzapine and placebo on all ECG parameters except QTcF (see Table 7.1.1.2.1.1). The most notable was the increase in heart rate in the olanzapine group (+6.3 bpm) compared to the placebo (-5.1 bpm) group ($p < 0.001$). Because of this effect on heart rate, the QTcB interval was also significantly longer in the olanzapine group compared to the placebo group.

Table 7.1.8.2.1.1. Sponsor's Table. ECG Intervals and Heart Rate: HGIN + HGIU Acute Database

ECG Intervals/ Heart Rate	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Heart Rate/Minute	Olz	158	72.291	13.183	6.266	14.039	4.335	11.624	<.001
	Placebo	80	72.788	12.553	-5.100	11.052	-7.289		
Intervals PR/Second	Olz	158	0.139	0.019	0.003	0.010	0.004	0.005	.003
	Placebo	78	0.146	0.031	-0.002	0.015	-0.001		
Intervals QRS/Second	Olz	158	0.088	0.011	-0.001	0.005	-0.001	-0.002	.039
	Placebo	80	0.087	0.010	0.001	0.006	0.001		
Intervals QT/Msec	Olz	158	380.532	30.825	-10.481	29.222	-7.948	-23.603	<.001
	Placebo	80	378.975	26.752	12.700	28.247	15.655		
Intervals QTc/Msec-Bazett formula	Olz	158	412.880	16.358	6.899	18.146	4.872	9.634	<.001
	Placebo	80	413.362	17.134	-2.475	16.543	-4.762		
Intervals QTc/Msec-Fridericia formula	Olz	158	401.763	15.537	0.743	15.165	0.404	-1.974	.345
	Placebo	80	401.596	14.722	2.732	15.219	2.378		

7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal

An analysis of the percent of patients with potentially clinically significant changes between the olanzapine and placebo groups is in Table 7.1.8.2.2.1. Though patients in the olanzapine group exhibited a mean increase in heart rate (see previous section), no PCS increases were noted for heart rate. Three patients had PCS increases in QTcB in the olanzapine group, no patients had PCS changes in QTcF. No patients had QTcB or QTcF increases $\geq$ 60 msec. No patients had QTcB or QTcF $\geq$ 500 msec.

Table 7.1.8.2.2.1. Sponsor's Table. ECG Intervals and Heart Rate – Potentially Clinically Significant Changes. HGIN + HGIU Acute Database.

ECG Intervals/ Heart Rate	Unit	Direction	Therapy	N	n	%	*P-value
Heart Rate <=40 bpm or >=120 bpm	bpm	High	Olz	158	0	0.0%	
			Placebo	80	0	0.0%	
		Low	Olz	158	0	0.0%	
			Placebo	80	0	0.0%	
Heart Rate < 50 bpm,Dec>=15 or >120 bpm,Inc>=15	bpm	High	Olz	158	0	0.0%	
			Placebo	80	0	0.0%	
		Low	Olz	157	0	0.0%	.038
			Placebo	80	3	3.8%	
Intervals PR >=200 ms	sec	High	Olz	158	0	0.0%	.322
			Placebo	75	1	1.3%	
Intervals QRS >=100 ms	sec	High	Olz	132	7	5.3%	.497
			Placebo	72	2	2.8%	
Intervals QT >=450 ms	ms	High	Olz	156	1	0.6%	.045
			Placebo	79	4	5.1%	
QTc Bazett's Male >=450 ms or Female >=470 ms	ms	High	Olz	156	3	1.9%	.553
			Placebo	79	0	0.0%	
QTc Fridericia's Male >=450 ms or Female >=470 ms	ms	High	Olz	158	0	0.0%	
			Placebo	80	0	0.0%	

7.1.8.2.3 Marked outliers and dropouts for ECG abnormalities

There were no dropouts due to ECG abnormalities.

7.1.9 Assessment of Effect on Growth

The Sponsor provided an analysis of the effect of olanzapine on growth that included data from the Overall Combined Database. Gender and age-adjusted growth in olanzapine-treated patients was compared with the expected growth seen in the general US population by using data provided by the National Center for Health Statistics. Standardized mean weight and BMI increased significantly for olanzapine-treated patients, regardless of gender, country, or disorder (schizophrenia or bipolar disorder). The changes in standardized mean height were closer to expected values based on the CDC reference population.

Table 7.1.9.1. Sponsor's Table.

Table APP.2.7.4.7.3.2. Standardized Growth (Z-Score)
LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint
Overall Olanzapine Exposure Combined Database

			Baseline		Endpoint		Change		P-value
Measure	Value	N	Mean	Std	Mean	Std	Mean	Std	*P-value
Weight	Actual	450	67.13	17.72	74.48	19.07	7.35	6.58	<.001
	Expected	450	67.13	17.72	68.17	17.90	1.03	1.01	<.001
	Z-Score	450	0.53	1.13	0.98	1.02	0.45	0.44	<.001
	Percentile	450	63.54	29.54	75.33	24.50	11.79	14.19	
Height	Actual	440	168.24	9.71	169.27	9.45	1.03	2.17	<.001
	Expected	440	168.24	9.71	168.92	9.60	0.67	0.91	<.001
	Z-Score	440	0.02	1.02	0.07	1.00	0.05	0.24	<.001
	Percentile	440	50.60	29.13	52.11	28.76	1.51	6.58	
BMI	Actual	439	23.64	6.07	25.95	6.21	2.31	2.31	<.001
	Expected	439	23.64	6.07	23.83	6.01	0.19	0.30	<.001
	Z-Score	439	0.50	1.14	0.99	0.95	0.49	0.53	<.001
	Percentile	439	63.51	29.85	76.77	23.48	13.26	16.47	

Table 7.1.9.2. Sponsor's Table.

Table APP.2.7.4.7.3.3. Standardized Growth (Z-Score)
LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint by Gender
Overall Olanzapine Exposure Combined Database

				Baseline		Endpoint		Change		P-value
Measure	Gender	Value	N	Mean	Std	Mean	Std	Mean	Std	*P-value
Weight	Female	Actual	167	64.41	18.15	70.94	19.34	6.53	6.08	<.001
		Expected	167	64.41	18.15	65.05	18.29	0.64	0.73	<.001
		Z-Score	167	0.64	1.12	1.05	0.97	0.40	0.45	<.001
		Percentile	167	67.26	28.90	77.62	23.18	10.36	14.04	
	Male	Actual	283	68.74	17.30	76.58	18.64	7.83	6.81	<.001
		Expected	283	68.74	17.30	70.01	17.43	1.27	1.08	<.001
		Z-Score	283	0.47	1.13	0.94	1.05	0.47	0.44	<.001
		Percentile	283	61.35	29.74	73.98	25.20	12.64	14.23	
Height	Female	Actual	163	162.07	7.82	162.78	7.63	0.71	1.45	<.001
		Expected	163	162.07	7.82	162.35	7.75	0.27	0.37	<.001
		Z-Score	163	0.04	1.15	0.10	1.13	0.07	0.20	<.001
		Percentile	163	51.74	30.32	53.86	29.83	2.12	6.40	
	Male	Actual	277	171.88	8.86	173.09	8.26	1.21	2.48	<.001
		Expected	277	171.88	8.86	172.78	8.42	0.90	1.05	<.001
		Z-Score	277	0.00	0.95	0.04	0.92	0.04	0.26	.012
		Percentile	277	49.94	28.44	51.09	28.11	1.15	6.68	
BMI	Female	Actual	162	24.46	6.76	26.78	7.12	2.32	2.30	<.001
		Expected	162	24.46	6.76	24.66	6.83	0.20	0.17	<.001
		Z-Score	162	0.66	1.07	1.08	0.88	0.42	0.48	<.001
		Percentile	162	67.73	28.52	79.04	21.25	11.31	15.25	
	Male	Actual	277	23.16	5.58	25.46	5.57	2.30	2.33	<.001
		Expected	277	23.16	5.58	23.35	5.42	0.19	0.36	<.001

The Sponsor noted a number of limitations in the evaluation of these data. Tanner Stage information was not collected during these studies, so the pubertal effects on individual standard deviation scores for height, weight or BMI are not known. The observational period of these studies (up to 8 months) did not allow for "meaningful evaluation" of the potential effect of

olanzapine on height. Additionally, the CDC reference database is based on the US population and may not be representative of patients from Germany or Russia – both countries had significant numbers of patients in this combined database.

Adequacy of Patient Exposure and Safety Assessments

7.2.1 Extent of exposure (dose/duration)

Acute, placebo-controlled trials: Total exposure for olanzapine in adolescent patients was 4776 patient-days. The mean daily dose was 9.75 mg/day, the modal daily dose was 11.46 mg/day.

Overall olanzapine exposure combined database: Total exposure for olanzapine in adolescent patients was 48,946 patient-days. The mean daily dose was 10.56 mg/day, the modal daily dose was 11.36 mg/day.

The highest olanzapine dose allowed in trials HGIN and HGIU was 20 mg/day. The Sponsor provided exposure data regarding the numbers of patients taking olanzapine 20 mg at any time, who had a modal dose of 20 mg and who had a final dose of 20 mg.

Table 2.7.4.14. Anytime, Modal Dose, and Final Dose of 20 mg
All Randomized Patients
Acute Placebo-Controlled Combined Database

	HGIN (N= 72) n(%)	HGIU (N= 106) n(%)	Combined (N= 178) n(%)
20 mg Dose(Anytime)	21(29.17%)	13(12.26%)	34(19.10%)
20 mg Modal Dose	12(16.67%)	10(9.43%)	22(12.36%)
20 mg Final Dose	18(25.00%)	11(10.38%)	29(16.29%)

Table 2.7.4.19. Anytime, Modal Dose, and Final Dose of 20 mg All Patients with Olanzapine Exposure Overall Olanzapine Exposure Combined Database

Summary of Patients Who Took >= 20 mg OLZ at Any Time

	Schizophrenia			Bipolar			Combined		
Dose	N	n	%	N	n	%	N	n	%
20	227	81	35.7%	226	52	23.0%	453	133	29.4%
25	227	0	0.0%	226	2	0.9%	453	2	0.4%

Summary of Patients Who Had Modal Dose at 20 mg OLZ

	Schizophrenia			Bipolar			Combined		
Modal Dose	N	n	%	N	n	%	N	n	%
20	227	46	20.3%	226	26	11.5%	453	72	15.9%

Summary of Patients Who Had Final Dose at 20 mg OLZ

	Schizophrenia			Bipolar			Combined		
Final Dose	N	n	%	N	n	%	N	n	%
20	227	46	20.3%	226	30	13.3%	453	76	16.8%

7.2.3 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.3.1 Postmarketing experience

The Lilly Safety System was searched for spontaneously reported adverse events involving patients younger than 18 years of age treated with olanzapine for the time period of product launch through May 31, 2006. The search identified 5,633 spontaneously reported adverse events (in 2,359 case reports) for patients ≤ 18 years of age out of 110,529 total events (age was unknown for 25,415 events).

The Sponsor analyzed these data by using a proportional reporting ratio (PRR) and Chi square value. The PRR was used to compare events between olanzapine treated patients aged 13 to 17 years and olanzapine-treated patients aged 18 to 64 years. The Sponsor indicated that some general guidelines for interpreting a drug-event combination as a potential signal include: at least 3 reports, a PRR > 2 and a Chi-square > 4. The spontaneously reported adverse events somnolence, aggression, galactorrhea, and sedation met the PRR and Chi-square criteria and had a proportion of the event of interest ≥ 1% of all events in patients aged 13 – 17 years (see Table 7.2.3.1.1).

Table 7.2.3.1.1 Sponsor's Table. Potential Safety Signals in Postmarketing Database for Patients 13 to 17 Years of Age – Proportion, PRR and Chi-Square Criteria Met

MedDRA Preferred Term (# of events in patients 13-17 years)	Proportion of Event in Patients 13-17 years (%) (N=3,288 events)	Proportion of Event in Patients 18-64 years (%) (N=68,450 events)	PRR[a]	Chi-Square Value
Somnolence (108)	3.28	1.60	2.06	53.39
Aggression (41)	1.25	0.33	3.76	70.36
Galactorrhoea (39)	1.19	0.32	3.67	64.51
Sedation (38)	1.16	0.46	2.50	30.41

From Sponsor table 2.7.4.79 in summary-clin-safety document

The Sponsor also included an additional table for adverse events reported with a proportion of the event of interest > 1% of all events in patients aged 13 to 17 years not meeting additional criteria (PRR and Chi-square) (see Table 7.2.3.1.2).

Table 7.2.3.1.2. Sponsor's Table. . Potential Safety Signals in Postmarketing Database for Patients 13 to 17 Years of Age – Proportion Criteria Met

MedDRA Preferred Term (# of events in patients 13-17 years)	Proportion of Event in Patients 13-17 years (%) (N=3,288 events)	Proportion of Event in Patients 18-64 years (%) (N=68,450 events)	PRR[a]	Chi-Square Value
Weight increased (320)	9.73	7.74	1.26	15.98
Prescribed overdose (52)	1.58	1.84	0.86	1.15
Overdose (42)	1.28	1.23	1.04	0.05
Fatigue (40)	1.22	0.70	1.75	11.76
Alanine aminotransferase increased (38)	1.16	0.90	1.29	2.31
Diabetes mellitus (36)	1.09	4.75	0.23	91.49
Drug ineffective (36)	1.09	0.77	1.43	4.36
Increased appetite (36)	1.09	0.77	1.41	4.09
Convulsion (33)	1.00	0.55	1.82	11.26

Of the 2,359 case reports in patients 13 to 17 years of age, 27 had a fatal outcome (Sponsor indicated that 28 cases were fatal, upon review it was noted that one case was duplicated). These cases are from spontaneous reports or publications in the literature. The Sponsor included CIOMS line listings and MedWatch reports for each fatality. In the narrative summary for one of the fatality cases, a reference to 4 additional US fatalities was made.[3] These appear to be a cluster of deaths occurring in a county in Tennessee. Further investigation may be deemed necessary. It is not known if the reporter had contacted the FDA regarding these cases as was mentioned in the case narrative. MedWatch reports for these additional cases were not included

3 In the narrative summary for US_010158510, the following statements were noted: "This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in Roane County, Tennessee. The reporter stated he has also notified the FDA."

in the submission. The Sponsor will be asked to provide these reports as well as to submit any new reports that may have occurred since this search was last completed.

The MedWatch reports were incomplete and many details regarding the deaths (autopsy reports, pertinent laboratory values, clinical description of death) were not available. In some cases, it appears that the Sponsor attempted to obtain more information, it is not known to what extent these attempts were made. Fifteen of the cases occurred in the United States, a number of these cases were reported by an attorney via the legal department – it is not known if litigation is ongoing in these cases.
Of note, seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus, diabetic coma or diabetic ketoacidosis. A brief summary of these cases is in Appendix 10.15.

Safety Conclusions

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar disorder) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with > 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
HGIN + HGIU Acute Database				
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Weight (kg) Mean Change to Endpoint (OC)	3.6 (n = 154)	0.08 (n = 67)	3.57	< 0.001
BMI Mean Change to Endpoint (LOCF)	1.22	0.05	1.17	< 0.001
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001
Overall Combined Database				
Weight (kg) Mean Change to Endpoint (LOCF)	7.35	-	-	< 0.001 (compared to baseline)
Weight (kg) Mean Change to Endpoint (OC)	10.8	-	-	< 0.001 (compared to baseline)
BMI Mean Change to Endpoint (LOCF)	2.31	-	-	< 0.001 (compared to baseline)
≥ 7% increase in body weight (%)	65%	-	-	-

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, $p < 0.001$). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits. In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

Hypertriglyceridemia
The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, $p < 0.001$). In reviewing the individual lab data, 11 marked outliers were noted for triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) ($p = 0.039$).

Hypercholesterolemia
The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, $p < 0.001$). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) ($p = 0.023$).

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were also similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in bipolar disorder patients. Suicidal behaviors or ideation is not uncommon in these patients and, in the absence of a placebo comparator, it is difficult to interpret any causality to olanzapine therapy.

General Methodology

7.4.1 Explorations for dose dependency for adverse findings

All of the clinical trials, both placebo-controlled and open-label, included a flexible dosing paradigm for olanzapine. Therefore, it is not possible to evaluate the dose-dependency of adverse events.

7.4.2 Explorations for drug-demographic interactions

The drug – demographic interactions summarized here are the adverse events occurring in HGIN + HGIU Acute Database. Subgroup analyses, particularly for gender and age, for efficacy and some safety data (prolactin, weight gain, etc.) are summarized in those relevant sections of the review. Most of the patients enrolled in the pivotal clinical trials were Caucasian, therefore any analyses by race/ethnicity are of limited usefulness.

Treatment-by-gender interactions were significant for the following adverse events: myalgia, nasal congestion, sinus congestion and tremor (see Table 7.4.2.1); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.2.1. Sponsor's Table. Adverse Events – Treatment-by-Gender Interactions: HGIN + HGIU Acute Database

By Subgroup: Gender

		Therapy							
		Olanzapine			Placebo				
Event Classification	Gender	N	n	%	N	n	%	*P-value	**Homogeneity of Odds Ratio
Myalgia	Female	67	0	0.0%	41	1	2.4%	.380	.070
	Male	112	3	2.7%	48	0	0.0%	.555	
Nasal congestion	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	
Sinus congestion	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	
Tremor	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	

Treatment-by-age (< 15, ≥ 15 years) interactions were significant for ear pain and migraine (see Table 7.4.2.2); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.2.2. Sponsor's Table. Adverse Events – Treatment-by-Age Interactions: HGIN + HGIU Acute Database

By Subgroup: Age

		Therapy							
		Olanzapine			Placebo				
Event Classification	Age	N	n	%	N	n	%	*P-value	**Homogeneity of Odds Ratio
Ear pain	< 15	64	1	1.6%	27	0	0.0%	1.00	.100
	>=15	115	0	0.0%	62	2	3.2%	.121	
Migraine	< 15	64	0	0.0%	27	1	3.7%	.297	.062
	>=15	115	2	1.7%	62	0	0.0%	.542	

Comparing adolescent and adult data

The common adverse event tables for adults in current product labeling and the common adverse events occurring in HGIN and HGIU were compared. In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to < 5% of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

Table 7.5.1. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 6 Week Acute Trials in *Schizophrenia*

	Adults	
	Olanzapine N = 248	Placebo N = 118
Dizziness	11%	4%
Constipation	9%	3%
Personality disorder	8%	4%
Weight gain	6%	1%
Akathisia	5%	1%
Postural hypotension	5%	2%

	Adolescents	
	Olanzapine N = 72	Placebo N = 35
Weight increased	31%	9%
Somnolence	24%	3%
Headache	17%	6%
Increased appetite	17%	9%
Sedation	15%	6%
Dizziness	8%	3%
Pain in extremity	6%	3%

Table 7.5.2. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 3 Week Acute Trials in *Bipolar Disorder*

	Adults	
	Olanzapine N = 125	Placebo N = 129
Somnolence	35%	13%
Dry mouth	22%	7%
Dizziness	18%	6%
Asthenia	15%	6%
Constipation	11%	5%
Dyspepsia	11%	5%
Increased appetite	6%	3%
Tremor	6%	3%

Adolescents		
	Olanzapine N = 107	Placebo N = 54
Weight increased	29%	4%
Increased appetite	29%	4%
Somnolence	25%	4%
Sedation	22%	6%
Headache	17%	17%
Fatigue	14%	6%
Dry mouth	8%	0%
Pain in extremity	5%	0%

The Sponsor included an analysis of select adverse events occurring in the adult clinical trials databases and adolescent clinical trials databases. These analyses summarized all data including the open-label trials. The Sponsor was asked if a similar analysis could be done for the placebo-controlled studies only and they responded that none of the placebo-controlled studies included fasting glucose and lipid data so these analyses were not available.

Metabolic parameters (fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides):
Mean change from baseline to endpoint – the only statistically significant differences between populations was in fasting glucose and triglycerides. Mean change to endpoint for fasting glucose was 1.8 ± 13 mg/dL for adolescents and 4.9 ± 32.8 mg/dL for adults ($p = 0.002$), triglycerides was 23.0 ± 76 mg/dL for adolescents and 20.3 ± 124 mg/dL for adults ($p = 0.007$).

Treatment-emergent significant changes at any time: statistically significant differences were noted for most of the parameters with a higher percentage of adults having significant changes at any time (see Table 7.5.3).

Table 7.5.3. Treatment-Emergent Significant Changes at Any Time – Adults vs. Adolescents

Laboratory Analytes	Categories	Population	N	n	%	*P-value
Fasting Glucose	Normal to High (< 100 mg/dL to >=126 mg/dL)	Adolescent	251	3	1.2%	.033
		Adult	251	12	4.8%	
	Impaired Glucose Tolerance to High(>=100 & <126 mg/dL to >=126 mg/dL)	Adolescent	47	6	12.8%	.066
		Adult	121	32	26.4%	
	Normal/Impaired Glucose Tolerance to High(<126 mg/dL to >=126 mg/dL)	Adolescent	298	9	3.0%	<.001
		Adult	372	44	11.8%	
Total Cholesterol	Normal to Borderline(<200 mg/dL to >=200 mg/dL and <240 mg/dL)	Adolescent	262	54	20.6%	<.001
		Adult	216	82	38.0%	
	Normal to High(<200 mg/dL to >=240 mg/dL)	Adolescent	262	3	1.1%	.001
		Adult	216	15	6.9%	
LDL Cholesterol	Normal to Borderline(<130 mg/dL to >=130 mg/dL and <160 mg/dL)	Adolescent	270	48	17.8%	<.001
		Adult	241	75	31.1%	
	Normal to High(<130 mg/dL to >=160 mg/dL)	Adolescent	270	4	1.5%	.014
		Adult	241	14	5.8%	
HDL Cholesterol	Normal to Low(>=50 mg/dL to <40 mg/dL)	Adolescent	107	10	9.3%	.052
		Adult	155	28	18.1%	

Laboratory Analytes	Categories	Population	N	n	%	*P-value
Fasting Triglycerides	Normal to Borderline(<150 mg/dL to >=150 mg/dL and <200 mg/dL)	Adolescent	247	51	20.6%	<.001
		Adult	253	91	36.0%	
	Normal to High(<150 mg/dL to >=200 mg/dL)	Adolescent	247	43	17.4%	.030
		Adult	253	65	25.7%	
	Normal to Extremely High(<150 mg/dL to >=500 mg/dL)	Adolescent	247	1	0.4%	1.00
		Adult	253	1	0.4%	

From Sponsor table APP.2.7.4.7.1.24 in summary-clin-safe-app document

Weight Gain

Mean change from baseline to endpoint – There was a statistically significant greater mean increase in body weight for adolescents compared to adults (see Table 7.5.4).

Table 7.5.4. Sponsor's Table. Mean Change from Baseline to Endpoint - Adolescents vs. Adults. Overall Combined Databases

		Baseline		Change to Endpoint				
Population	N	Mean	Std	Mean	Std	LSMean Change	LSMean Difference	*P-value
Adolescent	450	67.13	17.72	7.35	6.58	6.97	3.71	<.001
Adult	7847	78.12	18.86	3.24	5.82	3.26		

From Sponsor's table APP.2.7.4.7.1.25 in summary-clin-safe-app document

In product labeling, it is stated that in the 6-week placebo-controlled studies in adults, olanzapine patients gained an average of 2.8 kg compared to a 0.4 kg weight loss in placebo patients. In study HGIN, adolescent patients receiving olanzapine gained an average of 4.26 kg compared to 0.13 kg weight gain in placebo patients.

PCS weight increase at any time– Significantly more adolescent patients had a $\geq$ 7% increase in weight (65.1%) compared to adult patients (35.6%) ($p < 0.001$).

In the 6-week placebo controlled trials in adults, 29% of olanzapine patients had a ≥ 7% increase in weight compared to 3% of placebo patients. In study HGIN, 45% of olanzapine patients had a ≥ 7% increase in weight compared to 14.7% of placebo patients.

The Sponsor did not provide an comparison of hepatic laboratory analytes between the two populations and will be asked to provide these data. Per product labeling, in placebo-controlled olanzapine monotherapy studies in adults, elevations in ALT ≥ 3 x ULN were observed in 2% (6/243) olanzapine patients compared to 0/115 placebo patients. In the placebo-controlled monotherapy studies in adolescents, elevations in ALT > 3 x ULN (from baseline ≤ 3 x ULN) were observed in 12% (21/174) of olanzapine patients compared to 2% (2/87) of placebo patients.

Prolactin
Because of differences in reference ranges between the populations, normalized units were used in the analysis of prolactin changes (% URL = % upper range limit).

Mean change from baseline to endpoint – statistically significant differences were noted between the populations with adolescents having a mean change to endpoint of 23.0 %URL compared to -4.19 %URL in adults (p = 0.004) (see Table 7.5.5).

Table 7.5.5. Sponsor's Table. Mean Change from Baseline to Endpoint in Prolactin (Normalized Units) – Adult vs. Adolescent Patients, Overall Combined Databases

Laboratory Evaluations	Unit	Population	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
PROLACTIN	%URL	Adolescent	431	78.73	76.47	23.01	83.69	9.70	12.62	.004
		Adult	4503	99.42	126.56	-4.19	125.57	-2.92		

From Sponsor's table APP.2.7.4.7.4.31 in summary-clin-app document

Treatment-emergent high prolactin concentrations at any time: a higher percentage of adolescent patients (55.5%) had high prolactin concentrations at any time compared to adult patients (29%) (p < 0.001). The Sponsor did not provide an analysis for adolescent vs. adult patients by gender.

8 ADDITIONAL CLINICAL ISSUES

(b) (4)

(b) (4)
(b) (4)

Advisory Committee Meeting

No advisory committee meeting was held for this submission.

Literature Review

The Sponsor submitted a literature review though there was no attempt to summarize key findings. The Sponsor stated that none of the reviewed articles presented safety data contradictory to the conclusions presented in the NDA. Due to time constraints for this priority application, a separate literature review was not conducted by this reviewer.

Postmarketing Risk Management Plan

The Sponsor submitted a Risk Management document outlining their proposed actions for risk minimization. The identified risks in this document included weight gain, sedation, hepatic changes, hyperprolactinemia, glucose dysregulation, dyslipidemia. For all of these safety issues, the Sponsor has proposed the following actions for pharmacovigilance: clinical trial surveillance, routine pharmacovigilance, targeted surveillance, long-term safety study (b) (4). For glucose dysregulation and dyslipidemia, an additional action was to perform a retrospective cohort claims database study.

Routine pharmacovigilance was defined as periodic reporting per PSUR or as appropriate. Targeted surveillance was similar but targeted weight gain, hepatic changes, glucose dysregulation and dyslipidemia. The Sponsor has proposed a long-term safety study to evaluate the safety of olanzapine in adolescent patients with schizophrenia or bipolar disorder and to estimate the incidence and prevalence of identified and potential risks associated with olanzapine treatment. The study is still in the planning phase.

(b) (4)
(b) (4)

The actions proposed for risk minimization include product labeling and prescriber education – no details were provided regarding the latter proposal.

9 OVERALL ASSESSMENT

Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

Recommendation on Postmarketing Actions

9.1.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

9.1.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts

to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

Labeling Review

Changes to proposed labeling are being made directly to the annotated labeling submitted by the Sponsor, this was the first PLR labeling so there were many changes from prior approved labeling. The project manager, Dr. Doris Bates, reviewed the PLR labeling against the prior approved labeling and noted any differences – especially differences that were not highlighted by the Sponsor.
In the proposed labeling, all of the "frequent" adverse events in the "Other Adverse Events Observed" section were removed and some of the adverse events in other categories (infrequent, rare) were also removed. The Sponsor has been asked to address this and had not responded at the time this review was finalized.

This section will briefly discuss some of the labeling that may require revision:

WARNINGS AND PRECAUTIONS – The team will have to discuss the order of the items under this heading.

Weight Gain: should be placed earlier in this section

Transaminase Elevations: in the adult section, the number of patients with ALT $\geq$ 3 times ULN data is provided. In the adolescent section, the number of patients with ALT > 3 times ULN data is provided. These should be consistent (should both be $\geq$ 3 x ULN). In the adult section, use ALT rather than SGPT in the discussion of the larger premarketing database. In the adolescent section, I would recommend including the number of patients who discontinued due to elevations in LFTs.

Hyperprolactinemia: I would suggest including the % of patients with elevated prolactin levels for both adolescents and adults in the placebo-controlled acute trials.

Laboratory Tests: The information with regard to glucose monitoring should be included here.

ADVERSE REACTIONS
Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine
All of the adverse events in the category "frequent" have been removed in the proposed labeling. Other adverse events in the categories infrequent and rare have also been removed. The Sponsor has been asked to address this. Similar issues occur in this same section for IM olanzapine.

Clinical Trials in Adolescent Patients
ECG Changes – correct spelling of Frederica to Fredericia

Postmarketing Experience
When was the last time the Sponsor updated this section? There have been some postmarketing reports of death due to diabetic ketoacidosis occurring in adolescents – should this data be included in this section?

Comments to Applicant

Requests for information

The Sponsor has responded to the following requests and the reviewer has reviewed the responses

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.

2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.

3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the CRF, it does not appear that there is an area where the recorder could state the source of the ratings. Are both ratings, patient and parent/legal guardian, available for subjects in this study? If so, please provide these ratings and indicate the primary source for the ratings.

4. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF analysis (similar to table HGIN 14.20 for OC analysis) - with and without site 021.

5. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF and OC analysis for the US and Russia sites separately.

6. Provide patient baseline demographics and analysis for US vs. Russia sites (similar to HGIN.11.1 but comparing US vs. Russia).

7. It is noted that 50 patients were randomized at the 5 sites in Russia - 10 patients per site. Is it coincidental that 10 subjects were randomized at each of these sites? Were caps specified to the investigators such that each site could randomize no more than 10 patients?

8. Please provide patient baseline severity of illness and statistical analysis for US vs. Russia sites (similar to HGIN.11.2 but comparing US vs. Russia). Include the following variables: age of onset of illness, # of previous schizophrenia episodes, total hospitalization, length of current

episode, days since last hospitalization, psychiatric hospitalization, CGI-S, BPRS-C subscales, BPRS-C total score, PANSS subscales, and PANSS total score

9. Do study reports for HGIN and HGIU include information regarding the adverse events associated with patient drop-outs? Please indicate where this information may be found.

10. In table HGIN.11.2, it is noted that the minimum value for age for Age of Illness Onset was 5 years old for each treatment group. Please provide the study numbers for all patients with an age of illness onset < 10 years old and CRFs for these patients.

11. In table HGIN.11.2, it is noted that the minimum value for the Length of Current Episode is "0" - please clarify.

12. For Psychiatric Hospitalization in table HGIN.11.2, please clarify whether this is past or current hospitalization.

13. Please provide # of prior psychiatric hospitalizations for both treatment groups with statistical analysis for this variable.

14. In the brief summary for study HGCS, it is noted that 2 patients experienced the adverse event "intentional injury". Please provide brief summaries for these two events.

15. For study HGGC, were there any serious adverse events? The synopsis states that no patients experienced serious adverse events associated with cardiac abnormalities or weight gain - but there is no mention of other SAEs that may have occurred in this trial.

16. For the adult studies HGDH and HGGF that included adolescent patients, please submit narratives for the serious adverse events (per Table 2.7.4.4 in the summary-clin-safety document).

17. For the adult studies HGGF and HGKL, please submit narratives for the discontinuations due to adverse event cases.

18. For patient HGIU-028-2804, the narrative indicates that she experienced bilateral galactorrhea while hospitalized for a recurrence of bipolar symptoms. Please provide the prolactin concentrations that were obtained by the hospital (pending at time patient was discharged).

19. Patient HGMF-003-0304 had the SAE "exacerbation of bipolar illness with positive suicidal ideation". However, it appears that this was coded to the preferred term "bipolar disorder". Why weren't both verbatim terms coded to preferred terms - i.e. bipolar disorder and suicidal ideation?

20. For the discontinuations due to the adverse event "weight gain" in the acute and combined databases, please provide weight data for the post-study follow-up visits. Some of the narratives

have this information, but the majority indicate that the adverse event had resolved without providing weight data.

21. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.

22. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?

23. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

The following questions were submitted to the Sponsor via email on 3/19/07. The Sponsor attempted to send an email response on 3/26/07 but encountered technical difficulties. The Sponsor faxed the response on 3/27/07 and was asked to also fax the response to this reviewer (working in another location). The Sponsor did not fax the response to this reviewer. This reviewer received the response on 4/2/07 (working in office) and had insufficient time to review the responses to meet the internal NDA deadline. Of note, request #30 was not addressed in this response and the Sponsor indicated that the response will be provided at a later date.

24. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15, >= 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.

25. Please provide a subgroup analysis for age (< 15 and >=15) and gender for the variable "PCS weight change (> 7%)" for the Acute Placebo Controlled Combined Database.

26. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.

27. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.

28. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.

29. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?

30. In proposed labeling, some adverse events have been removed from the sections "other adverse events observed during the clinical trial evaluation of oral olanzapine" and "other adverse events observed during the clinical trial evaluation of intramuscular olanzapine for injection". In the former section, it appears that all of the frequently occurring AEs ("frequent") have been removed. In both sections, many adverse events that were included in the infrequent and rare categories have been removed. Please provide a justification for removal of these adverse events from proposed product labeling.

<u>Requests for additional information from the Sponsor – may be included in action letter:</u>

31. Please provide narrative summaries for the following: 8 cases of gynecomastia, 1 case of opisthotonus, 1 case of “oculogyration”, and two cases with high prolactin concentrations (HGIN 900-9009, HGIN 005-503) and the cases with CPK > 500 U/L.

32. Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had “DRAFT” at the top of the page and the date of the report was 7/27/06 - have all of these reports been previously filed with the Agency?

33. For MedWatch fatality case US_010158510, the narrative states “This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in Roane County, Tennessee. The reporter stated he has also notified the FDA...". The only MedWatch report included in this submission is for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

34. Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed the 19-32 weeks in the study (n = 83 bipolar, n = 93 schizophrenia) - e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

35. One of the exclusion criteria for HGIU was "patients who have been judged clinically to be at serious suicidal risk". However, a review of the CDRS-R individual item "suicidal ideation" noted a number of patients who were rated the maximum score of "7" at baseline (has made a suicide attempt within the last month or is actively suicidal". These patients include 012-1203, 012-1212, and 024-2402. Please provide more information regarding inclusion of these patients in this study.

36. Please provide an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

37. For HGIU and HGIN, how was “treatment-emergent” parkinsonism, akathisia and dyskinesia defined by the respective rating scales?

38. For the acute phases of HGIU and HGIN, many patients had elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses on the subset of patients with baseline prolactin within the normal range - please provide a separate analysis for gender and age.

39. For study HGIN, it is noted that 21/72 patients in the olanzapine group and 5/35 patients in the placebo group did not have any previous medications for schizophrenia (Table HGIN.14.4). How many of these patients were from the sites in Russia? How many were first-break schizophrenic patients?

40. The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes.

41. Please provide an analysis of mean change to endpoint for prolactin by age (< 15, > 15) for HGIN + HGIU Acute Database, HGIN and HGIU.

10 APPENDICES

10.1 Investigators and Sites

Site #	Principal Investigator	Site & Address	# Pts Randomized	# Pts Completing DB; OL
1	Gupta, Sanjay	Global Research and Consulting 515 Main Street Olean, NY 14760 USA	9	6;7
5	Bastani, Bijan	Northcoast Clinical Trials 3733 Park East Drive, Suite 100 Beachwood, OH 44122 USA	3	1;1
7	Brams, Matthew	Bayou City Research Corp 550 Westcott, #310 Houston, TX 77007 USA	11	6;5
9	Childress, Ann	Nevada Behavioral Health, Inc. 2055 W. Charlestone Blvd, Ste B Las Vegas, NV 89102 USA	2	2;0
10	Cueva, Jeanette	Bioscience Research, Llc 222 W. 14th Street New York, NY 10011 USA	5	4;3
12	DelBello, Melissa	Univ of Cincinnati Med Center 231 Albert B. Sabin Way Dept. of Psychiatry Cincinnati, OH 45267 USA	15	6;6
13	Dempsey, G. Michael	Albuquerque Neurosciences 715 Dr. Martin Luther King Jr. Ave NE ; Suite 203 Albuquerque, NM 87102 USA	8	5;3
14	Duesenberg, David	Mercy Health Research 12680 Olive Blvd, Suite 200 St. Louis, MO 63141 USA	5	5;4
16	Gracious, Barbara	Strong Memorial Hospital 300 Crittenden Blvd Dept. of Psychiatry, Box PSYCH Rochester, NY 14642 USA	6	3;1

17	Gutierrez, Rosben	Psycare, Inc. 2120 Thibodo Court, #230 Vista, CA 92083 USA	1	0;0
19	Kaczenski, Gregory	Summit Research Group, Llc 1014 Autumn Rd, Suite 3 Little Rock, AR 72211 USA	7	4;4
20	Khan, Arifulla	NW Clinical Research Center 1900 116th Ave, NE Bellevue, WA 98004 USA	16	14;9
21	Krishnasastry, Chandra	Tennessee Christian Med Center 320 Hospital Drive Madison, TN 37115 USA	4	4;2
23	Mintz, Mark	Bancroft Neurohealth 201 King's Highway South Cherry Hill, NJ 08034 USA	2	2 ;2
24	Pathak, Anjali	AP Psychiatric & Counseling Service, Inc. 5251 Emerson St Jacksonville, FL 32207 USA	5	5;3
26	Plopper, Michael	Sharp Mesa Vist Hospital 7850 Vista Hill Avenue San Diego, CA 92123 USA	7	6;3
27	Riesenberg, Robert	Atlanta Center of Med Research 811 Juniper Street Atlanta, GA 30308 USA	7	7;3
28	Robb, Adelaide	Children's National Med Center 111 Michigan Ave, NW Washington, DC 20010 USA	4	3; 0 [1]
31	Soni, Poonam	Univ of Utah School of Medicine Mood Disorder Clinic, Rm 5R218 Dept. of Psychiatry 30 N. 1900 East Salt Lake City, UT 84132 USA	4	3;2

33	Wozniak, Janet	Massachusetts General Hospital 185 Alewife Brook Parkway, Suite 200 Cambridge, MA 02138 USA	3	3;1
34	Bhatia, Prakash	Synergy Clinical Research 5577 University Avenue San Diego, CA 92105 USA	1	1;0
35	Yadalam, Kashinath	Institute for Neuropsychiatry 2829 4th Avenue Lake Charles, LA 70601 USA	10	7;3
36	Terry, William	Mountain West Clinical Trials 1166 N. Cole Road, Suite D Boise, ID 89704 USA	8	7;5
720	Varela, Alberto	Instituto Psicoterapeutico de Puerto Rico Hostos Avenue 405 San Juan, 00918 Puerto Rico	17	15;10
730	Velez, Jesus	RCMI-Clinic Research Center University District Hospital 1st Floor Clinical Research Center Rio Piedras, 00936 Puerto Rico	1	1;0

[1] Site was closed by sponsor due to protocol violations. Patients were discontinued.

10.2 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Are male or female patients, 13 to 17 years of age, but must not yet have reached their 18th birthday prior to Visit 1, when informed consent is obtained.
2. Patient must have a diagnosis of bipolar I disorder and currently display an acute manic or mixed episode (with or without psychotic features) according to DSM-IV-TR and confirmed by the K-SADS-PL. Patients must meet diagnostic criteria at Visits 1 and 2.
3. Female patients of childbearing potential (not surgically sterilized) must test negative for pregnancy at the time of enrollment based on a serum pregnancy test. Furthermore, female patients must agree to abstain from sexual activity or to use a medically acceptable method of birth control during their participation in the study.
4. Each patient and the patient's parent/authorized legal representative must understand the nature of the study. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations.

5. Each patient and the patient's parent/authorized legal representative must have a level of understanding sufficient to perform all tests and examinations required by the protocol.
6. Patients must have a YMRS total score $\geq$ 20 at both Visits 1 and 2.
7. Patients must be capable of swallowing study medication whole (without crushing, dissolving, etc.).

Exclusion criteria

1. Are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
2. Are employed by Lilly (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
3. Patients who have participated in a clinical trial of oral olanzapine or have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.
4. Female patients who are either pregnant or nursing.
5. Patients, who, in the opinion of the investigator, are unsuitable in any other way to participate in this study including being unable to comply with the requirements of the study for any reason.
6. Patients with acute or unstable medical conditions, including (but not limited to) inadequately controlled diabetes, hepatic insufficiency (specifically any degree of jaundice), uncorrected hypothyroidism or hyperthyroidism, acute systemic infection, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic diseases (specifically current agranulocytosis with an absolute neutrophil count < 500 mm^3).
7. Patients with acute or unstable medical conditions, such that intensive care unit hospitalization for the disease is anticipated within 6 months.
8. DSM-IV-TR substance (except nicotine and caffeine) dependence within the past 30 days.
9. Patients who have undergone treatment with remoxipride within 6 months (180 days) prior to Visit 2.
10. Any concomitant medication with primarily central nervous system activity, including alternative medications, other than specified as permitted in Table HGIU.2 and HGIU.3 at Visit 2.
11. Patients who have been judged clinically to be at serious suicidal risk.
12. Patients who have experienced one or more seizures without a clear and resolved etiology.
13. Patients with a documented history of allergic reaction to olanzapine.
14. Treatment with an injectable neuroleptic $\leq$ 14 days before Visit 2.
15. Prolactin level at Visit 1 $\geq$ 200 ng/ml.
16. Patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment.

17. Laboratory results, including serum chemistries, hematology, and urinalysis, must show no clinically significant abnormalities. In addition, there must be no clinical information that, in the judgment of a physician, should preclude a patient's participation at study entry.
18. Use of any concomitant medication(s) at Visit 2 as specified in Section 5.7 or expected to need treatment with any medication during the study other than what is allowed.
19. Patients who have a history of mental retardation, current comorbid autism, or current comorbid pervasive developmental disorder.
20. Patients who have used monoamine oxidase inhibitors (MAOIs) within 14 days prior to Visit 2 or are expected to need treatment at any time during this study.
21. Patients having psychosis or bipolar symptoms related to an underlying medical condition.
22. Current diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder as defined in the DSM-IV-TR.

10.3 Sponsor's Table. Schedule of Events – HGIU

Table HGIU.9.4. Study Schedule, Protocol F1D-MC-HGIU

Description of Data	V1	V2	V3	V4	V5	V6	Sum. Visit SP II[i]	V301	V302	V303	V304	V305	V306	V307	V308	V309	V310	Sum. Visit SP III[i]	Follow-Up (V501)
Weeks until next visit	2-14 days	3 days	4 days	1	1	1		1	1	2	2	2	2	4	4	4			
Screening and Inclusion Measures																			
Informed Consent	X																		
K-SADS-PL	X																		
Study drug compliance			X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Study drug dispensed		X	X	X	X	X		X	X	X	X	X	X	X	X	X			
Safety Measures																			
Demographics	X																		
Weight and temperature	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Height	X		X			X	X		X		X	X	X	X	X	X	X	X	
Blood pressure[a] and heart rate	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Psychiatric examination	X																		
Physical examination	X																		
Electrocardiography[b]	X						X											X	
Preexisting conditions and adverse events	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
AIMS, Barnes Akathisia, Simpson-Angus	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Historical illnesses / Previous medications Family history	X																		

Description of the Data	V1	V2	V3	V4	V5	V6	Sum. Visit SP IIi	V301	V302	V303	V304	V305	V306	V307	V308	V309	V310	Sum. Visit SP IIIi	Follow-Up (V501)
Weeks until next visit	2-14 days	3 days	4 days	1	1	1		1	1	2	2	2	2	4	4	4			
Safety Measures, Cont.																			
Habits (tobacco, alcohol, drugs)	X																		
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
Visit comments	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
Patient summary including comments							X											X	
Adverse event follow-up, if necessary																			X
Laboratory Tests[c]																			
Clinical chemistry[d] / Electrolytes / Lipids[e]	X	X		X	X	X	X		X		X		X	X	X	X	X	X	
Hematology	X	X		X	X	X	X		X		X		X	X	X	X	X	X	
Urinalysis	X						X											X	
Hepatitis screen, urine drug screen[f], serum pregnancy test[f], and TSH	X																		
Prolactin[g]	X	X					X							X				X	
HgbA1c [h]	X						X							X				X	
Behavioral Intervention (optional)							X	X	X	X	X	X	X	X	X	X	X		

Description of the Data	V1	V2	V3	V4	V5	V6	Sum. Visit SP IIi	V301	V302	V303	V304	V305	V306	V307	V308	V309	V310	Sum. Visit SP IIIi	Follow-Up (V501)
Weeks until next visit	2-14 days	3 days	4 days	1	1	1		1	1	2	2	2	2	4	4	4			
Efficacy Measures																			
YMRS	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
CGI-BP Severity of Illness	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
OAS		X					X											X	
ADHDRS-IV-PI		X					X											X	
CDRS-R		X					X			X			X					X	
Health Outcome Measures																			
CHQ		X					X											X	
General																			
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
Visit comments	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
Patient summary including comments							X											X	
Adverse event follow-up, if necessary																			X

10.4 YMRS Individual Item Analyses

Table 10.4.1. Sponsor's Table. YMRS Individual Item Analyses

Table HGIU.11.22. YMRS Individual Items
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
YMRS1: Elevated Mood	Olanzapine	105	2.79	0.99	-1.50	1.19	-1.40	-0.71	<.001
	Placebo	54	2.74	0.78	-0.76	1.26	-0.69		
YMRS2: Increased Motor Activity-Energy	Olanzapine	105	2.95	0.90	-1.32	1.44	-1.21	-0.70	<.001
	Placebo	54	2.80	0.76	-0.52	1.13	-0.51		
YMRS3: Sexual Interest	Olanzapine	105	1.14	1.08	-0.63	0.95	-0.72	-0.14	.249
	Placebo	54	1.33	1.13	-0.59	0.94	-0.58		
YMRS4: Sleep	Olanzapine	105	2.42	1.08	-1.79	1.43	-1.98	-0.71	<.001
	Placebo	54	2.30	1.19	-0.98	1.30	-1.26		
YMRS5: Irritability	Olanzapine	105	5.48	1.32	-1.90	2.10	-2.32	-0.92	.004
	Placebo	54	5.28	1.37	-0.91	1.72	-1.40		
YMRS6: Speech(Rate and Amount)	Olanzapine	105	5.14	1.53	-2.93	2.01	-2.96	-1.59	<.001
	Placebo	54	4.69	1.66	-1.07	2.21	-1.37		
YMRS7: Language Thought Disorder	Olanzapine	105	2.24	0.58	-0.92	0.90	-1.18	-0.47	<.001
	Placebo	54	2.11	0.66	-0.37	0.90	-0.71		
YMRS8: Content	Olanzapine	105	3.41	2.29	-1.86	2.39	-2.08	-0.73	.019
	Placebo	54	3.11	2.13	-0.94	2.12	-1.35		
YMRS9: Disruptive-Aggressive Behavior	Olanzapine	105	4.84	1.37	-1.84	2.12	-2.10	-0.93	.006
	Placebo	54	4.74	1.58	-0.87	1.94	-1.18		
YMRS10: Appearance	Olanzapine	105	1.18	1.05	-0.52	0.94	-0.61	-0.47	<.001
	Placebo	54	1.24	1.10	-0.09	1.17	-0.14		
YMRS11: Insight	Olanzapine	105	1.49	1.39	-0.69	1.15	-0.96	-0.19	.268
	Placebo	54	1.70	1.37	-0.61	1.45	-0.77		

10.5 Children's Depression Rating Scale - Individual Items

Table 10.5.1. Sponsor's Table. CDRS-R Individual Items

Table HGIU.11.25. CDRS-R Individual Items
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
CDRS1: Impaired School Work	Olanzapine	100	3.64	1.83	-0.79	1.56	-1.06	-0.17	.482
	Placebo	53	3.23	1.94	-0.36	2.06	-0.89		
CDRS2: Difficulty Having Fun	Olanzapine	100	2.74	1.73	-0.33	1.54	-0.56	0.35	.103
	Placebo	53	2.49	1.85	-0.53	1.65	-0.91		
CDRS3: Social Withdrawal	Olanzapine	100	2.41	1.46	-0.37	1.34	-0.43	0.31	.098
	Placebo	53	1.98	1.65	-0.45	1.32	-0.74		
CDRS4: Sleep Disturbance	Olanzapine	100	3.36	1.67	-1.56	1.87	-1.59	-0.64	.009
	Placebo	53	2.87	1.65	-0.55	1.75	-0.96		
CDRS5: Appetite Disturbance	Olanzapine	100	1.92	1.29	0.51	1.54	0.33	1.00	<.001
	Placebo	53	1.87	1.23	-0.45	1.32	-0.66		
CDRS6: Excessive Fatigue	Olanzapine	100	2.66	2.06	-0.58	2.03	-0.75	0.56	.014
	Placebo	53	2.45	1.88	-0.98	1.78	-1.31		
CDRS7: Physical Complaints	Olanzapine	100	1.90	1.47	-0.35	1.42	-0.48	-0.02	.925
	Placebo	53	1.75	1.25	-0.23	1.38	-0.47		
CDRS8: Irritability	Olanzapine	100	4.60	1.44	-1.29	1.87	-1.29	-0.38	.124
	Placebo	53	4.45	1.53	-0.79	1.79	-0.90		

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
CDRS9: Excessive Guilt	Olanzapine	100	1.68	1.13	-0.31	0.83	-0.26	0.07	.515
	Placebo	53	1.45	0.87	-0.28	0.74	-0.33		
CDRS10: Low Self-Esteem	Olanzapine	100	2.76	1.75	-0.37	1.64	-0.49	-0.05	.824
	Placebo	53	2.23	1.35	-0.11	1.28	-0.44		
CDRS11: Depressed Feelings	Olanzapine	100	2.57	1.46	-0.45	1.33	-0.56	-0.02	.912
	Placebo	53	2.02	1.35	-0.13	1.37	-0.54		
CDRS12: Morbid Ideation	Olanzapine	100	1.81	1.35	-0.33	1.10	-0.37	-0.10	.530
	Placebo	53	1.62	1.21	-0.13	1.21	-0.27		
CDRS13: Suicidal Ideation	Olanzapine	100	1.77	1.32	-0.47	1.21	-0.44	0.03	.769
	Placebo	53	1.42	0.95	-0.23	0.91	-0.47		
CDRS14: Excessive Weeping	Olanzapine	100	1.87	1.32	-0.30	1.39	-0.39	0.04	.840
	Placebo	53	1.75	1.33	-0.26	1.60	-0.43		
CDRS15: Depressed Facial Affect	Olanzapine	100	1.90	1.17	-0.03	1.18	-0.18	0.32	.042
	Placebo	53	1.62	1.16	-0.15	1.18	-0.50		
CDRS16: Listless Speech	Olanzapine	100	1.35	0.59	-0.02	0.70	-0.09	0.13	.155
	Placebo	53	1.28	0.69	-0.09	0.77	-0.22		

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
CDRS17: Hypoactivity	Olanzapine	100	1.49	0.95	-0.14	0.89	-0.15	0.10	.334
	Placebo	53	1.28	0.86	-0.11	0.78	-0.26		

10.6 ADHDRS and OAS Analyses

Table 10.6.1 Sponsor's Table. Mean Change from Baseline to Endpoint: ADHDRS Total Score

Table HGIU.11.26. ADHDRS-IV-PI Total Score
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value
ADHDRS - hyperactivity-impulsivity subtotal	Olanzapine	100	13.84	6.81	-4.96	6.19	-5.29	-2.42	.008
	Placebo	50	11.56	5.39	-1.62	4.33	-2.87		
ADHDRS - Inattention subtotal	Olanzapine	99	15.21	8.02	-3.15	6.11	-4.43	-0.81	.388
	Placebo	51	13.67	7.49	-1.73	5.77	-3.62		
ADHDRS-IV inv. scored total	Olanzapine	99	73.46	16.45	-9.47	13.64	-11.36	-3.96	.048
	Placebo	50	69.72	13.86	-3.97	10.64	-7.40		

Table 10.6.2 Sponsor's Table. Mean Change from Baseline to Endpoint: Overt Aggression Scale

Table HGIU.11.27. OAS Total and Subtotal Scores
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Verbal Aggression Total	Olanzapine	100	2.74	1.31	-1.17	1.65	-1.43	-0.68	.004
	Placebo	52	2.73	1.21	-0.48	1.34	-0.75		
Physical Aggression Toward Self Total	Olanzapine	100	0.84	1.12	-0.58	1.03	-0.54	-0.18	.071
	Placebo	52	0.58	0.85	-0.19	0.91	-0.36		
Physical Aggression Towards Others Total	Olanzapine	100	1.18	1.20	-0.72	1.39	-0.65	-0.42	.010
	Placebo	52	1.00	1.12	-0.15	1.26	-0.23		
Physical Aggression Toward Objects	Olanzapine	100	1.58	1.14	-0.86	1.14	-0.99	-0.36	.026
	Placebo	52	1.42	1.02	-0.40	1.19	-0.63		
Total of OAS01-OAS16	Olanzapine	100	6.34	3.67	-3.33	3.92	-3.60	-1.70	<.001
	Placebo	52	5.73	2.94	-1.23	3.08	-1.90		

10.7 YMRS Total Score – Additional Age Subgroup Analyses

Table 10.7.1 Sponsor's Table.

Table HGIU.11.19. YMRS Total Score Age Subgroup Analysis Mean Change from Baseline to Endpoint (LOCF) Age as a Continuous Variable

		Baseline		Change to Endpoint					**P-value
N	Therapy	Mean	Std	Mean	Std	LSMean Change	LSMean Diff.	*P-value	Age*Therapy
105	Olanzapine	33.08	6.55	-15.90	10.03	-17.65	-7.66	<.001	.626
54	Placebo	32.04	6.23	-7.72	9.42	-9.99			

Table 10.7.2 Sponsor's Table

Table HGIU.11.20. YMRS Total Score Age Subgroup Analysis Mean Change from Baseline to Endpoint (LOCF) Alternative Age Subgroup Categorization

			Baseline		Change to Endpoint					**P-value
Strata	N	Therapy	n	Mean	Std	Mean	Std	LSMean Change	LSMean Diff.	*P-value	Therapy*Age
<16	118	Olanzapine	79	32.91	6.72	-15.80	10.23	-17.73	-7.13	<.001	.577
		Placebo	39	32.85	6.27	-8.31	9.64	-10.61			
>=16	41	Olanzapine	26	33.58	6.09	-16.23	9.59	-17.26	-8.37	.010	
		Placebo	15	29.93	5.79	-6.20	8.95	-8.88			

Table 10.7.3 Sponsor's Table.

Table HGIU.11.21. YMRS Total Score Age Subgroup Analysis
Mean Change from Baseline to Endpoint (LOCF)
Age Subgroups Based on Age at Last Birthday

Strata	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value Therapy*Age
13	31	Olanzapine	22	32.73	6.90	-16.50	8.94	-18.95	-10.49	.007	.068
		Placebo	9	31.89	7.52	-4.22	10.23	-8.46			
14	38	Olanzapine	27	32.81	7.15	-13.11	11.00	-13.58	0.64	.865	
		Placebo	11	32.82	4.00	-13.73	9.98	-14.22			
15	49	Olanzapine	30	33.13	6.41	-17.70	10.22	-19.73	-10.52	<.001	
		Placebo	19	33.32	6.94	-7.11	8.14	-9.21			
16	27	Olanzapine	17	34.00	6.06	-16.65	6.44	-20.18	-9.86	.008	
		Placebo	10	29.50	5.17	-6.60	9.05	-10.32			
17	14	Olanzapine	9	32.78	6.44	-15.44	14.27	-15.61	-8.35	.213	
		Placebo	5	30.80	7.46	-5.40	9.76	-7.27			

10.8 Patient Baseline Demographics – HGIN + HGIU Acute Database and Overall Combined Database

Table 10.8.1 Sponsor's Table

Table 2.7.4.21. Patient Demographics at Baseline
All Randomized Patients
Acute Placebo-Controlled Combined Database

Demographic Variables	Statistics/ Category	Olanzapine (N=179) n (%)	Placebo (N=89) n (%)	*P-value
Gender	Male	112(62.57)	48(53.93)	.188
	Female	67(37.43)	41(46.07)	
Age	No. of Patients	179	89	
	Mean	15.54	15.74	.200
	Median	15.54	15.62	
	Std. Dev.	1.36	1.42	
	Minimum	13.02	13.06	
	Maximum	17.99	18.00	
Origin	African Descent	30(16.76)	9(10.11)	.359
	Caucasian	123(68.72)	66(74.16)	
	East/Southeast Asian	0(0.0)	1(1.12)	
	Hispanic	20(11.17)	9(10.11)	
	Other	6(3.35)	4(4.49)	
Country	United States	133(74.30)	67(75.28)	1.00
	Puerto Rico	12(6.70)	6(6.74)	
	Russia	34(18.99)	16(17.98)	

Table 10.8.2 Sponsor's Table. Age Distribution at Baseline (HGIN + HGIU)

Table 2.7.4.22. Age Distribution at Baseline
All Randomized Patients
Acute Placebo-Controlled Combined Database

	HGIN		HGIU		Combined	
Age Group	n	%	n	%	n	%
13	9	8.4%	31	19.3%	40	14.9%
14	13	12.1%	38	23.6%	51	19.0%
15	20	18.7%	50	31.1%	70	26.1%
16	29	27.1%	27	16.8%	56	20.9%
17	36	33.6%	15	9.3%	51	19.0%
Total	107	100.0%	161	100.0%	268	100.0%

Table 10.8.3 Sponsor's Table. Patient Demographics at Baseline – Overall Olanzapine Combined Database

Table 2.7.4.24. Patient Demographics at Baseline
All Patients with Olanzapine Exposure
Overall Olanzapine Exposure Combined Database

Demographic Variables	Statistics/ Category	Bipolar (N=227) n (%)	Schizophrenia (N=227) n (%)	Overall (N=454) n (%)
Gender	Male	124(54.63)	162(71.37)	286(63.00)
	Female	103(45.37)	65(28.63)	168(37.00)
Age	No. of Patients	227	227	454
	Mean	15.44	16.38	15.91
	Median	15.43	16.67	16.02
	Std. Dev.	1.33	1.27	1.38
	Minimum	13.02	13.03	13.02
	Maximum	18.00	18.00	18.00
Origin	African Descent	22(9.69)	28(12.33)	50(11.01)
	Caucasian	166(73.13)	189(83.26)	355(78.19)
	East/Southeast Asian	1(0.44)	0(0.0)	1(0.22)
	Hispanic	31(13.66)	6(2.64)	37(8.15)
	Other	7(3.08)	4(1.76)	11(2.42)
Country	United States	205(90.31)	58(25.55)	263(57.93)
	Puerto Rico	21(9.25)	1(0.44)	22(4.85)
	Russia	1(0.44)	79(34.80)	80(17.62)
	Germany	0(0.0)	89(39.21)	89(19.60)

10.9 Weight Gain – Additional Analyses

Table 10.9.1. Weight Change by Visit (OC): Overall Combined Database

				Change to Maximum		
		Visit Week	N	Mean	Std	P-value
Weight (kg)	Bipolar	≤ 1	224	1.27	1.55	< 0.001
	Schizophrenia		224	1.75	1.51	< 0.001
	Overall		448	1.51	1.55	< 0.001
	Bipolar	> 1 ≤ 2	221	2.29	2.04	< 0.001
	Schizophrenia		219	2.73	1.96	< 0.001
	Overall		440	2.51	2.01	< 0.001
	Bipolar	> 2 ≤ 3	183	3.07	2.62	< 0.001
	Schizophrenia		148	3.46	2.24	< 0.001
	Overall		331	3.25	2.46	< 0.001
	Bipolar	> 3 ≤ 4	199	3.74	2.84	< 0.001
	Schizophrenia		201	4.02	2.51	< 0.001
	Overall		400	3.88	2.68	< 0.001
	Bipolar	> 4 ≤ 5	167	4.05	3.31	< 0.001
	Schizophrenia		147	4.66	2.42	< 0.001
	Overall		314	4.34	2.94	< 0.001
	Bipolar	> 5 ≤ 9	157	6.03	3.80	< 0.001
	Schizophrenia		130	7.12	3.80	< 0.001
	Overall		287	6.52	3.83	< 0.001
	Bipolar	> 9 ≤ 13	121	7.59	4.95	< 0.001
	Schizophrenia		117	8.17	4.84	< 0.001
	Overall		238	7.87	4.89	< 0.001
	Bipolar	> 13 ≤ 17	114	8.84	5.87	< 0.001
	Schizophrenia		103	9.01	6.03	< 0.001
	Overall		217	8.92	5.93	< 0.001
	Bipolar	> 17 ≤ 21	102	9.69	6.43	< 0.001
	Schizophrenia		88	10.2	6.75	< 0.001
	Overall		190	9.93	6.56	< 0.001
	Bipolar	> 21 ≤ 25	93	10.19	6.98	< 0.001
	Schizophrenia		81	10.84	6.92	< 0.001
	Overall		174	10.49	6.94	< 0.001
	Bipolar	> 25 ≤ 32	53	9.60	7.12	< 0.001
	Schizophrenia		78	11.68	7.62	< 0.001
	Overall		131	10.84	7.46	< 0.001

From Sponsor table APP.2.7.4.7.1.18 in summary-clin-safe-app document

Table 10.9.2. Adverse Event "Weight Increased" Gender Analysis: HGIU and HGIN Acute Phases

			Olanzapine			Placebo			p-value	Homogeneity of Odds Ratio
		Gender	N	n	%	N	n	%		
Weight Increased	HGIU	Female	46	16	35%	30	1	3%	0.001	
		Male	61	15	25%	24	1	4%	0.033	0.628
	HGIN	Female	21	6	29%	11	2	18%	0.681	
		Male	51	16	31%	24	1	4%	0.008	0.186
Weight Increased	HGIU	< 15 yrs	49	14	29%	20	0	0	0.007	
		≥ 15 yrs	58	17	29%	34	2	6%	0.008	0.280
	HGIN	< 15 yrs	15	6	40%	7	1	14%	0.350	
		≥ 15 yrs	57	16	28%	28	2	7%	0.045	0.868

From Sponsor Tables HGIN.14.28 and HGIU.14.31

Table 10.9.3. Mean Change in Weight (kg) – Subgroup Analyses: HGIN

				Baseline		Change to Endpoint					
	Subgroup	Therapy	n	Mean	St.Dev	Mean	St. Dev	LS Mean	LSMean Diff	P-value	P-value
HGIN											
Weight (kg)	Female	Olanzapine	21	64.0	16.6	3.8	3.7	3.4			
		Placebo	10	61.0	12.5	0.8	3.5	0.7	2.73	0.063	
	Male	Olanzapine	51	68.3	11.6	4.5	3.2	4.6			
		Placebo	24	72.2	17.6	-0.2	2.5	-0.2	4.76	< 0.001	0.140
	< 15 yrs	Olanzapine	15	64.7	14.0	6.3	4.2	5.2			
		Placebo	7	62.5	9.6	1.1	4.1	-0.2	5.37	0.009	
	≥ 15 yrs	Olanzapine	57	67.7	13.2	3.7	2.9	3.8			
		Placebo	27	70.6	18.1	-0.1	2.4	-0.1	3.84	< 0.001	0.370

From Sponsor Tables HGIN.14.47

Table 10.9.4. Mean Change from Baseline to Endpoint in Laboratory Values – Patients Who Gained > 3.9 kg vs. Placebo

The LS Mean Change and p-value for the entire population is in parenthesis for comparison purposes

			Baseline	Change to Endpoint			
	Therapy	n	Mean	Mean	LS Mean Change	LSMean Diff	P-value
AST (U/L)	Olanzapine	84	21.9	9.5	11.3		
	Placebo	87	23.6	-2.5	-0.4	11.7	< 0.001
						(8.91)	(0.002)
ALT (U/L)	Olanzapine	84	20.8	25.8	29.6		
	Placebo	87	20.4	-3.1	1.0	28.5	< 0.001
						(23.0)	(< 0.001)
CPK (U/L)	Olanzapine	84	125	18.1	16.8		
	Placebo	87	164	-23.6	-21.9	38.7	0.037
						(16.1)	(0.38)
Glucose, fasting	Olanzapine	58	88.8	3.2	4.3		
(mg/dL)*	Placebo	64	89.7	-2.9	-2.0	6.3	0.001
						(5.6)	(< 0.001)
Cholesterol (mg/dL)*	Olanzapine	84	164.1	17.4	13.5		
	Placebo	87	160.2	-1.1	-4.6	18.5	< 0.001
						(14.3)	(< 0.001)
Triglycerides (mg/dL)*	Olanzapine	84	97.3	51.3	46.9		
	Placebo	87	110.6	-4.4	-7.1	54.0	< 0.001
						(33.6)	(<0.001)
LDL (mg/dL)*	Olanzapine	84	96.1	6.6	3.1		
	Placebo	87	91.5	-0.39	-3.5	6.6	0.038
						(6.6)	(0.016)
Prolactin (ng/ml)	Olanzapine	79	13.3	12.6	12.0		
	Placebo	80	14.9	-0.2	-0.9	12.91	< 0.001
						(11.7)	(< 0.001)

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259

10.10 Patients with Possible Suicidal Behavior or Ideation Events
HGIU + HGIN Acute Database

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Therapy	Days to Event	Fatal?
HGIU-001-0103	THE PATIENT HAS REPORTEDLY BEEN HAVING DIFFICULTIES WITH DYSPHORIC MOOD. IN MID TO LATE APRIL, 2003, HE TRIED TO TIE A BELT AROUND HIS NECK RESULTING IN A RASH.	5	Placebo	23	No
HGIU-012-1206	INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM	5	Olz	22	No
HGIU-012-1211	SUICIDAL IDEATION / SUICIDAL IDEATION	4	Olz	14	No

Overall Combined Database

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIN-019-1901	SUICIDAL IDEATION / SUICIDAL IDEATION	4	167	No
HGIN-026-2603	SUICIDAL IDEATION / SUICIDAL IDEATION	4	135	No
HGIN-030-3001	SUBJECT IS EXPERIENCING SYMPTOMS OF DELUSIONS, AUDITORY AND VISUAL HALLUCINATIONS, AND SUICIDAL IDEATIONS SUBJECT WILL BE HOSPITALIZED FOR STABILIZATION ON TRADITIONAL MEDICATION	4	51	No
HGIN-930-9307	SUICIDE ATTEMPT / SUICIDE ATTEMPT	2	59	No
HGIU-001-0108	ALCOHOL POISONING / ETOH INTOXICATION. LSS: ON [redacted] NEARLY SIX MONTHS AFTER STARTING STUDY DRUG, THE PATIENT WAS ADMITTED TO THE HOSPITAL WITH ALCOHOL ("ETOH") POISONING. THE PATIENT WAS RECEIVING 15MG OLANZAPINE AT THE TIME OF THE EVENT. THIS WAS THE FIRST PSYCHIATRIC HOSPITALIZATION FOR THIS 14-YEAR OLD WHO WAS BROUGHT TO THE EMERGENCY ROOM (ER) BY POLICE AFTER THE PATIENT BECAME INTOXICATED, VOICED SUICIDAL IDEATION, AND PASSED OUT AT SCHOOL. APPROXIMATELY [redacted] (A WEEK AND A HALF A GO), THE PATIENT TRIED TO JUMP OUT OF HER MOTHER'S MOVING VEHICLE AT 55 MILES PER HOUR, BUT THE MOTHER PREVENTED HER FROM FALLING OUT.	3	157	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIU-012-1206	INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM	5	22	No
HGIU-012-1211	SUICIDAL IDEATION / SUICIDAL IDEATION	4	14	No
HGIU-012-1212	THE PATIENT HAD BEEN DRAWING PICTURES OF HOW THE PATIENT COULD DIE . . . THE PATIENT COULD NOT ASSURE THE INVESTIGATOR THAT SHE WOULDN'T HARM HERSELF.	4	34	No
HGIU-013-1301	SUICIDAL IDEATION / OCCASIONAL SUICIDAL THOUGHTS	4	71	No
HGIU-013-1310	INTENTIONAL SELF-INJURY / SELF INJURY	5	64	No
HGIU-020-2016	SUICIDE ATTEMPT / ATTEMPTED SUICIDE	2	214	No
HGIU-026-2604	SELF INJURIOUS BEHAVIOUR / SELF-INJURIOUS BEHAVIOR. LSS: THE PATIENT REPORTED THAT HIS DEPRESSION WORSENED APPROXIMATELY ONE WEEK PRIOR (~05-NOV-2003). ADDITIONALLY HE BEGAN FEELING SUICIDAL (WITHOUT PLAN) APPROXIMATELY THREE DAYS PRIOR (~09-NOV-2003). THE PATIENT'S MOTHER CALLED THE SITE TO REPORT THAT THE PATIENT HAD CUT HIMSELF THE PRIOR EVENING AND DIDN'T FEEL SAFE. THE PATIENT WAS BROUGHT TO THE HOSPITAL FOR SAFETY AND STABILIZATION.	4	59	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIU-026-2605	THE PATIENT WAS BEHAVING INAPPROPRIATELY AND WAS ON THE ROOF OF HIS HOME REFUSING TO COME DOWN	9	53	No
HGIU-026-2606	SUICIDAL IDEATION / SUICIDAL IDEATION	4	35	No
HGIU-027-2705	INTENTIONAL SELF-INJURY / SELF-INFLICTED SUPERFICIAL LACERATIONS	5	76	No
HGIU-028-2805	SUICIDAL IDEATION / SUICIDAL IDEATION. LSS: THE PATIENT'S MOTHER CALLED THE INVESTIGATOR'S SITE ON 14-MAY-2004 TO STATE THAT HER DAUGHTER HAD BECOME SUICIDAL WITH A PLAN TO OVERDOSE ON LORAZEPAM (ATIVAN) DURING THE LAST WEEK OF MAY 2004, BUT ENDED UP TELLING HER PARENTS THE EVENING OF 09-MAY-2004.	3	108	No
HGIU-730-7302	SUICIDAL IDEATION / PASSIVE SUICIDAL IDEATION	4	177	No
HGMF-003-0304	EXACERBATION OF BIPOLAR ILLNESS WITH POSITIVE SUICIDAL IDEATION	4	29	No
HGMF-008-0805	INTENTIONAL SELF-INJURY, CUTTING LEFT ARM	5	93	No
LOAY-400-4001	PATIENT IS IN A DEPRESSIVE MOOD AROUND 10-11.05.99 AND EXPRESSES SUICIDALTHOUGHTS, SIGNIFICANTLY SLOWED MOVEMENT.	4	44	No
LOAY-401-4012	SELF-INJURIOUS BEHAVIOR, SELF-INJURY	5	16	No
LOAY-407-4077	SELF INJURIOUS BEHAVIOR, SELF-INFLICTING TENDENCIES	5	55	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
LOAY-407-4078	SUICIDAL IDEATION, ACUTE SUICIDAL TENDENCIES	4	4	No
LOAY-413-4150	SUICIDAL IDEATION, SUICIDAL TENDENCY	4	27	No

10.11 Laboratory Evaluations – Mean Change from Baseline to Endpoint

Table 10.11.1 Sponsor's Table. Mean Change from Baseline to Endpoint: HGIN + HGIU Acute Database

Table 2.7.4.33. Laboratory Evaluations
Mean Change from Baseline to Endpoint
Acute Placebo-Controlled Combined Database

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
HEMATOCRIT	1	Olz	174	0.43	0.03	-0.01	0.03	-0.01	-0.01	<.001
		Placebo	87	0.43	0.04	-0.00	0.03	-0.00		
HEMOGLOBIN	mml/L-F	Olz	174	8.93	0.78	-0.30	0.47	-0.30	-0.22	<.001
		Placebo	87	8.93	0.83	-0.08	0.41	-0.07		
ERYTHROCYTE COUNT	TI/L	Olz	174	5.00	0.39	-0.15	0.27	-0.15	-0.11	.002
		Placebo	87	4.99	0.49	-0.04	0.26	-0.04		
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mml/L-F	Olz	174	20.87	0.92	-0.00	0.76	0.02	0.16	.100
		Placebo	87	21.00	0.79	-0.17	0.73	-0.14		
LEUKOCYTE COUNT	GI/L	Olz	174	7.27	1.92	-0.19	1.86	-0.10	-0.32	.201
		Placebo	87	7.18	1.91	0.14	1.99	0.21		
NEUTROPHILS, SEGMENTED	GI/L	Olz	174	4.22	1.59	-0.13	1.67	-0.06	-0.29	.203
		Placebo	87	4.29	1.48	0.17	1.79	0.23		
LYMPHOCYTES	GI/L	Olz	174	2.38	0.66	-0.09	0.49	-0.06	-0.07	.297
		Placebo	87	2.24	0.60	-0.02	0.51	0.01		
MONOCYTES	GI/L	Olz	174	0.43	0.14	0.02	0.17	0.01	0.01	.544
		Placebo	87	0.41	0.16	0.01	0.17	0.00		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
EOSINOPHILS	GI/L	Olz	174	0.20	0.21	0.01	0.16	0.01	0.04	.042
		Placebo	87	0.19	0.14	-0.02	0.10	-0.03		
BASOPHILS	GI/L	Olz	174	0.05	0.03	-0.01	0.03	-0.01	-0.01	.008
		Placebo	87	0.05	0.03	0.00	0.03	0.00		
MEAN CELL VOLUME (MCV)	fL	Olz	174	85.96	4.66	-0.25	2.53	-0.02	-0.97	.005
		Placebo	87	85.76	4.59	0.72	2.78	0.95		
PLATELET COUNT	GI/L	Olz	173	291.08	68.65	1.26	46.42	2.44	6.09	.339
		Placebo	87	286.54	63.84	-4.68	52.18	-3.66		
LYMPHOCYTES, ATYPICAL	GI/L	Olz	1	0.06		0.03		0.03		
UA-SPECIFIC GRAVITY	NO UNIT	Olz	156	1.02	0.01	-0.00	0.01	-0.00	-0.00	.292
		Placebo	72	1.02	0.01	-0.00	0.01	-0.00		
AST/SGOT	U/L	Olz	175	24.53	29.87	6.43	26.41	9.89	8.91	.002
		Placebo	87	23.63	8.46	-2.47	7.51	0.98		
ALT/SGPT	U/L	Olz	175	24.13	45.95	19.95	54.84	28.11	22.98	<.001
		Placebo	87	20.39	13.05	-3.08	11.69	5.13		
CREATINE PHOSPHOKINASE	U/L	Olz	175	141.28	138.78	-7.31	131.11	2.81	16.06	.376
		Placebo	87	164.36	160.04	-23.62	152.22	-13.25		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
ALKALINE PHOSPHATASE	U/L	Olz	175	152.33	82.35	-1.35	25.61	-2.74	2.57	.396
		Placebo	87	138.67	86.92	-3.97	16.63	-5.31		
GGT (GGPT/SGGT/YGGT)	U/L	Olz	175	18.99	12.31	7.47	20.02	7.73	7.89	<.001
		Placebo	87	17.68	8.49	-0.43	5.96	-0.16		
THYROID STIMULATING HORMONE	mU/L	Olz	6	2.73	2.32	0.11	1.02	-0.12		
UREA NITROGEN	mmol/L	Olz	175	4.40	1.18	0.22	1.18	0.14	0.39	.010
		Placebo	87	4.37	1.06	-0.17	1.06	-0.25		
CREATININE	umol/L	Olz	175	93.29	14.47	-2.90	9.85	-2.07	-1.80	.147
		Placebo	87	95.83	12.43	-1.08	8.56	-0.27		
CALCIUM	mmol/L	Olz	175	2.48	0.08	-0.03	0.09	-0.03	-0.02	.215
		Placebo	87	2.50	0.12	-0.01	0.10	-0.02		
SODIUM	mmol/L	Olz	175	141.70	2.27	-0.05	2.83	-0.12	0.49	.190
		Placebo	87	141.78	2.44	-0.53	2.94	-0.61		
POTASSIUM	mmol/L	Olz	175	4.32	0.33	-0.04	0.36	-0.07	0.04	.462
		Placebo	87	4.41	0.42	-0.07	0.41	-0.10		
ALBUMIN	g/L	Olz	175	45.07	3.75	-2.01	3.20	-2.13	-1.70	<.001
		Placebo	87	45.39	3.03	-0.31	2.90	-0.43		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
GLUCOSE, FASTING	mmol/L	Olz	135	4.89	0.55	0.15	0.58	0.15	0.31	<.001
		Placebo	64	4.98	0.57	-0.16	0.56	-0.17		
GLUCOSE, NON-FASTING	mmol/L	Olz	141	5.04	0.83	0.17	1.13	0.12	0.15	.374
		Placebo	73	5.01	0.79	0.03	1.23	-0.03		
URIC ACID	umol/L	Olz	175	331.18	74.27	25.21	51.54	30.87	26.95	<.001
		Placebo	87	329.40	84.01	-1.86	53.02	3.92		
CHOLESTEROL	mmol/L	Olz	175	4.17	0.83	0.34	0.59	0.33	0.37	<.001
		Placebo	87	4.15	0.85	-0.03	0.63	-0.04		
TRIGLYCERIDES	mmol/L	Olz	175	1.18	0.66	0.33	0.91	0.30	0.38	<.001
		Placebo	87	1.25	0.73	-0.05	0.62	-0.07		
LDL CHOLESTEROL	mmol/L	Olz	175	2.42	0.74	0.16	0.52	0.14	0.17	.016
		Placebo	87	2.37	0.76	-0.01	0.53	-0.02		
BILIRUBIN, TOTAL	umol/L	Olz	175	7.84	5.27	-1.73	3.82	-2.21	-2.52	<.001
		Placebo	87	8.56	5.33	0.78	5.96	0.31		
BILIRUBIN, DIRECT	umol/L	Olz	175	1.84	1.07	-0.33	1.07	-0.36	-0.38	.005
		Placebo	87	2.01	1.08	0.05	0.93	0.02		
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Olz	175	1.22	0.31	0.03	0.23	0.02	0.03	.331

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Placebo	87	1.21	0.25	-0.00	0.25	-0.01		
PROLACTIN	ug/L	Olz	163	14.06	9.92	11.44	14.52	10.51	11.66	<.001
		Placebo	80	14.95	11.86	-0.16	10.69	-1.15		
HEMOGLOBIN A1C	1	Olz	6	0.05	0.00	-0.00	0.00	-0.00	0.00	.741
		Placebo	3	0.05	0.01	-0.00	0.00	-0.00		

10.12 Prolactin Analysis by Gender

Table 10.12.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: HGIU + HGIN Acute Database.

Laboratory Evaluations	Gender	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value	**P-value
PROLACTIN	Female	Olz	63	15.87	10.06	15.63	16.86	14.26	14.25	<.001	.236
		Placebo	37	15.25	7.59	1.35	9.20	0.00			
	Male	Olz	100	12.92	9.71	8.80	12.20	8.70	10.12	<.001	
		Placebo	43	14.70	14.67	-1.46	11.78	-1.42			

10.13 Vital Signs – Mean Change from Baseline to Endpoint

Table 10.13.1 Vital Signs, Weight, Height and BMI - Mean Change from Baseline to Endpoint (LOCF). HGIN + HGIU Acute Database

Vital Signs	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Systolic Blood Pressure - Supine	Olz	177	111.52	10.95	2.94	10.57	1.73	3.66	.009
	Placebo	89	112.79	13.18	-0.71	10.90	-1.93		
Systolic Blood Pressure - Standing	Olz	177	113.33	12.25	3.14	12.06	2.16	1.94	.225
	Placebo	89	112.18	13.25	1.22	12.51	0.23		
Systolic Blood Pressure - Orthostatic	Olz	177	-1.81	9.63	-0.20	11.68	-0.43	1.72	.262
	Placebo	89	0.61	8.33	-1.93	11.83	-2.15		
Diastolic Blood Pressure - Supine	Olz	177	67.71	9.27	1.24	9.74	1.56	2.17	.095
	Placebo	89	68.19	8.53	-0.92	10.27	-0.61		
Diastolic Blood Pressure - Standing	Olz	177	72.86	10.12	1.42	10.25	-0.24	2.73	.033
	Placebo	89	73.56	9.48	-1.28	9.14	-2.97		
Pulse - Supine	Olz	177	73.88	11.40	7.07	13.99	7.55	7.71	<.001
	Placebo	89	74.15	12.81	-0.60	12.04	-0.16		
Pulse - Standing	Olz	177	83.77	12.73	6.97	14.83	6.55	7.90	<.001
	Placebo	89	85.55	12.98	-0.89	14.69	-1.35		
Pulse - Orthostatic	Olz	177	9.89	11.23	-0.11	13.37	-1.01	0.19	.914
	Placebo	89	11.40	11.15	-0.29	13.09	-1.19		

Vital Signs	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Temperature in Centigrade	Olz	177	36.57	0.44	-0.03	0.49	-0.03	-0.03	.695
	Placebo	88	36.58	0.42	-0.00	0.49	-0.00		
Weight in Kg	Olz	177	66.03	17.93	3.90	2.72	3.68	3.66	<.001
	Placebo	88	67.63	17.24	0.24	2.16	0.01		
Height in cm	Olz	177	165.84	10.13	0.48	1.22	0.46	0.18	.235
	Placebo	88	167.59	9.67	0.31	1.01	0.28		
Body Mass Index	Olz	177	23.91	6.01	1.22	1.01	1.11	1.17	<.001
	Placebo	88	23.98	5.67	0.05	0.91	-0.07		

10.14 Potentially Clinically Significant Definitions for Safety Analyses

Table 2.7.4.6. Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs and Weight

Parameter	Low	High
Orthostatic hypotension (mm Hg)	≥20 mm Hg decrease in systolic BP (supine to standing) and ≥10 bpm increase in pulse (supine to standing)	--
Supine systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Standing systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Supine diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Standing diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Supine pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Standing pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Temperature (°F)[a]	--	≥101°F and increase ≥2
Weight (kg)	decrease ≥7%	increase ≥7%

10.15 Postmarketing Reports - Fatalities

Table 10.15.1. Postmarketing Reports – Fatalities

Patient Identifier	Date of Death	Dose/Duration	Event	Concom Rx	Comments
BR200605002130 16 YOM	(b) (6)	7.5 mg 10/05 – 4/06	Sudden death, cardiac arrest, prescribed overdose, suicide attempt, depression, psychosis	Alprazolam	Brazil Autopsy done, result will be available by June 2006 (per summary)
BE200602002031 17 YOF	(b) (6)	Unknown ~6 years	Bilateral pneumonia, gastric hemorrhagia, fever, coma	Not reported	Belgium (no autopsy)
US_0510123183 14 YO	(b)	Unknown	Toxic exposure, completed suicide	Fluoxetine Risperidone	Literature
JP_051007889 17 YOM	(b) (6)	5 mg, 8/2005 – 10/05	Completed suicide, suicidal ideation, apathy	Lorazepam	Japan "Police told psychiatrist about patient's death, no details provided" [prior suicide attempt per hx]
CA_050708496 17 YOM	(b) (6)	15 mg 11/03 – 6/05	Completed suicide	Lorazepam Flupentixol decanoate	Canada 5 days after discontinuing olanzapine, committed suicide (method unknown) Not known whether

					autopsy performed.
US_0506118439 17 YOF	Unknown (b) (6) estimated	Unknown, 7/1999 - 2004	Death, weight increased, diabetes mellitus, hyperglycemia, multiple drug overdose, triglycerides increased, cholesterol abnormal, musculoskeletal chest pain		Reported by attorney via legal department
EWC050644285 17 YOF	(b) (6)	5 mg 3/5/05 – 3/6/05	Endotoxic shock, kidney infection, sepsis, acute abdomen, disseminated intravascular blood coagulation, myeloid hyperplasia of spleen, pancreatitis, gastric ulcer perforation, peritoneal infection		Russian Federation
US_0506118189 15 YOM	Unknown (b) (6) estimated	~ May 2003 - unknown	Death		Reported by an attorney via the legal department Cause of death not provided
CA_050207717 16 YOM	(b) (6)	Unknown	Completed suicide	Isotretinoin mepha	Canada No details provided
US_0412108962 16 YOM	Unknown (b) (6) estimated	1-2002 – unknown	Death, diabetes mellitus		Reported by an attorney via the legal department Cause of death not provided, not known if autopsy performed
JP_041105122 17 YOF	(b) (6)	50 mg 11/10/2004 – 11/10/2004	Intentional overdose, completed suicide	Paroxetine, sulpiride, amoxapine, fluvoxamine, flunitrazepam	Japan “Coroner refused to provide any information”
USA040979162 US_0402100550 15 YOM	(b) (6)	10/29/2003?	Death, coma Accidental overdose, drug toxicity, intentional drug misuse	Metronidazole, topiramate, clonazepam	Reported by an attorney via the legal department Case reported in a newspaper “Patient was sold olanzapine by another individual, not prescribed”

					Olanzapine Cp = 490 ng/ml postmortem
US_0412109585 15 YOF	(b) (6)	11/2000 - unk	Diabetic ketoacidosis, diabetic coma, diabetes mellitus, pain, anxiety, drug ineffective	Methylphenidate, sertraline	Reported to company by an attorney No details provided about the event, unknown if an autopsy was performed
EWC031237179 16 YOM	(b) (6)	5 mg, 11/24/2003 – 11/25/2003	Death, pulmonary infarction		Greece Pulmonary infarction per autopsy
USA030742307 13 YOF	(b) (6)	5 mg Unknown	Diabetic ketoacidosis, loss of consciousness, dizziness		Diabetic ketoacidosis per autopsy. No labs provided.
USA030741953 17 YOM	(b) (6)	8/2002 – 11/2002	Convulsion, heart rate increased	Mixed amphetamine salts, trazodone	Cause of death listed as idiopathic seizure disorder, toxicology screen negative
GBS030413039 17 YOM	(b) (6)	12.5 mg 10/2002 – unk	Completed suicide, sedation, eczema	Risperidone, biperiden	United Kingdom Death by drowning, autopsy did not reveal other significant findings
US_020180581 15 YOM		20 mg Unknown	Acute asthma		Patient had been in blinded study 3/01 – 9/01 prior [F1D-US-X090]; did not receive olanzapine; taking marketed olanzapine at time of event.
US_010973481 17 YOM	Unknown (received by Sponsor)	30 mg Unknown	Prescribed overdose, drug toxicity		No details provided, unknown if autopsy performed
EWC010928155 15 YOM		10 mg 8/1/2001 – 8/28/2001	Death	Dextro-amphetamine	Switzerland Asperger's syndrome Patient drowned while swimming in lake; autopsy unremarkable
CA_010603921 17 YOF	Unknown (received by Sponsor)	Unknown	Death	Citalopram, valproate semisodium	Canada Patient "died suddenly", autopsy was completed but not available.

					"Several attempts at follow-up unsuccessful".
CA_010603802 16 YOM	Unknown (received by Sponsor (b) (6))	10 mg 90 days	Diabetic coma	Valproate sodium Topiramate	Canada No personal history of diabetes. Weight at time of event unknown, labs not provided. "Numerous attempts to obtain follow-up unsuccessful".
US_010566315 16 YOM	(b) (6)	5 mg 730 days	Drug interaction, death, hepatic steatosis	Mixed amphet-Amine salts	Patient found dead. Hepatic steatosis per autopsy, no cause of death provided. Autopsy never provided.
US_010158510 17 YOM	(b) (6)	2.5 mg Unknown	Accidental overdose	Citalopram, trazodone	Patient found dead by family member. Cause of death presumed overdose. Olanzapine Cp = 158 ng/ml.
US_000542556 15 YOM	(b) (6)	Unknown 1998 x 120 days	Necrotizing pancreatitis, diabetes mellitus, increased cholesterol	Carbamazepine, paroxetine	Follow-up in the literature
US_000236591 17 YOM		22.5 mg Unknown	Overdose, death	Fluoxetine, valproate semisodium, nortriptyline, buspirone, haloperidol, thioridazine	Patient died while being restrained by staff in group home.
US97121702A 14 YOM	(b) (6)	12.5 mg 150 days	Asphyxia, agitation	Haloperidol, sertraline	Became agitated on school bus and was restrained and died. Per coroner, cause of death by mechanical asphyxia due to the restraining position.

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/s/

Cara Alfaro
4/12/2007 04:22:45 PM
PHARMACIST

Ni Aye Khin
4/18/2007 01:32:15 PM
MEDICAL OFFICER
I concur with Dr. Alfaro's recommendation that this application is approvable; see memo to file for additional comments.

Review and Evaluation of Clinical Data - **Addendum**

Application Type: NDA 20-592
Submission Number: S-041 SE5
Established Name: Olanzapine (Zyprexa)
Therapeutic Class: Antipsychotic
Indication: Treatment of schizophrenia in adolescent patients
Letter Date: 10/30/06
Stamp Date: 10/31/06
Priority Designation: P
PDUFA Goal Date: 4/30/07
Reviewer: Cara Alfaro, Pharm.D.
Date: 5/19/07

Background

This is an addendum to the Clinical Review of NDA 20-592 S-041 SE5 that was completed (signed off) on 4/18/07. Prior to the action date of this NDA, a conference call was held to discuss issues related to this NDA. During this discussion, it was mentioned that the MMRM analysis conducted by the statistical reviewer was not statistically significant (p = 0.72) while the MMRM analysis conducted by the Sponsor was statistically significant (p = 0.015). The statistical reviewer was not able to explain the discrepancy and was going to recheck his analysis.

This addendum describes the results of the statistician's reanalysis as well as an additional analysis requested by this reviewer. It is noteworthy that this new information did not alter the final recommendation of this reviewer for a not approvable action (though the Division did take a different action).

MMRM Analysis

The primary analysis for this submission was the LOCF analysis for the BPRS-C total score mean change from baseline at endpoint. The Sponsor included OC and MMRM as secondary analyses for this primary endpoint.

The results from the Sponsor's analyses are in the table below:

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
LOCF	Olanzapine	72	50.3	10.0	-19.4	15.5	-19.3		
	Placebo	35	50.1	8.6	-9.3	18.7	-9.1	-10.1	0.003
OC	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.4		
	Placebo	15	49.0	8.5	-23.7	14.6	-24.1	-0.26	0.947
MMRM	Olanzapine	50	50.6	10.6	-24.5	13.5	-21.3		
	Placebo	15	49.0	8.5	-23.7	14.6	-12.4	-8.90	0.015

The results from the MMRM analysis conducted by the statistician (Fanhui Kong) are as follows*:

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
MMRM	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.7		
	Placebo	15	49.0	8.5	-23.7	14.6	-23.5	-1.25	0.72

*In the addendum to Dr. Kong's review, a recalculation of this MMRM analysis provided a p-value of 0.90

In the addendum to Dr. Kong's review, he stated that the reason for the discrepancy between MMRM analyses was due to the different models/assumptions used for these calculations. In his investigation of the different models, Dr. Kong did indicate that the best fit for the data was the unstructured variance-covariance model which the Sponsor used and that yielded significant results. However, it is also noteworthy that the results of the various MMRM analyses are quite variable and not consistent yielding p-values from 0.015 to 0.90 and LS mean differences ranging from -0.43 to -8.9 (table from Dr. Kong's addendum):

Table 2.1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIN

Variance-covariance Structure	Placebo	Olanzapine	AIC
Variance Components			
LS Mean change from baseline (SE)	-24.1 (3.13)	-24.5 (1.73)	
Difference between LS Means and C.I.	-0.43 (-6.6,7.5)		
P-value	0.90		4691
Unstructured			
LS Mean change from baseline (SE)	-12.6 (2.99)	-21.5 (1.97)	
Difference between LS Means and C.I.	-8.9 (-16.0, -1.9)		
P-value	0.015		4055.2
Compound Symmetry			
LS Mean change from baseline (SE)	-17.8 (2.61)	-22.9 (1.60)	
Difference between LS Means and C.I.	-5.1 (-11.1, 0.9)		
P-value	0.10		4353.0
Toeplitz			
LS Mean change from baseline (SE)	-14.3 (2.68)	-21.9 (1.65)	
Difference between LS Means and C.I.	-7.67 (-13.8, -1.5)		
P-value	0.015		4129.0
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-21.7 (2.70)	-24.4 (1.53)	
Difference between LS Means and C.I.	-2.68 (-8.8, 3.4)		
P-value	0.39		4356.0
First Order Auto-regression			
LS Mean change from baseline (SE)	-15.4 (2.71)	-22.3 (1.64)	
Difference between LS Means and C.I.	-7.0 (-13.8, -0.8)		
P-value	0.029		4129.0

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

One of the reasons that this reviewer recommended a not approvable action was the disparity between results from the U.S. and Russia sites. The Sponsor included the LOCF analysis for evaluation of the primary endpoint between the two geographic regions, but did not include companion OC or MMRM analyses. This reviewer asked Dr. Kong to perform an MMRM analysis between the U.S. and Russia sites (table from Dr. Kong's addendum):

Table 2.2 Treatment Effect by Country by MMRM Analysis

Country	Placebo	Olanzapine
Russia		
N (Number of patients)	16	34
LS Mean change from baseline (SE)	-5.3 (4.46)	-19.0 (2.73)
Difference between LS Means and C.I.	-13.7 (-23.9,3.3)	
P-value	0.012	
US		
N (Number of patients)	19	35
LS Mean change from baseline (SE)	-18.7 (4.13)	-23.5 (2.89)
Difference between LS Means and C.I.	-4.8 (-14.7, -5.1)	
P-value	0.35	

While exploratory in nature, this analysis is consistent with the LOCF analysis – robust findings in the Russia sites and not the U.S. sites.

Due to the inconsistent findings in the various MMRM analyses performed by Dr. Kong for study HGIN, this reviewer asked him to perform similar MMRM analyses for the HGIU study (SE5-040, bipolar disorder in adolescent patients) since the LOCF, OC and MMRM analyses performed by the Sponsor were consistent and statistically significant. Dr. Kong provided the summary table below (this table is not included in Dr. Kong's addendum). It is noteworthy that the different MMRM analyses for HGIU were consistent and robustly positive – in contrast to the inconsistent findings for these same analyses for study HGIN.

Table 1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIU (Without Country in Model)

Variance-covariance Structure	Placebo	Olanzapine	AIC
Sample Size	54	105	
Variance Components (Default)			
LS Mean change from baseline (SE)	-11.3 (1.33)	-16.9 (0.86)	
Difference between LS Means and C.I.	-5.6 (-8.7,-2.5)		
P-value	0.0004		4171.5
Unstructured			
LS Mean change from baseline (SE)	-9.4 (1.37)	-16.4 (0.92)	
Difference between LS Means and C.I.	-6.9 (-10.2, -3.7)		
P-value	<0.0001		3994.6
Compound Symmetry			
LS Mean change from baseline (SE)	-10.3 (1.26)	-16.8 (0.84)	
Difference between LS Means and C.I.	-6.4 (-9.4, -3.5)		
P-value	<0.0001		4038.2
Toeplitz			
LS Mean change from baseline (SE)	-9.6 (1.26)	-16.4 (0.84)	
Difference between LS Means and C.I.	-6.8 (-9.8, -3.8)		
P-value	<0.0001		4005.7
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-9.9 (1.25)	-16.6 (0.82)	
Difference between LS Means and C.I.	-6.7 (-9.6, -3.7)		
P-value	<0.0001		4043.2
First Order Auto-regression			
LS Mean change from baseline (SE)	-9.6 (1.26)	-16.4 (0.84)	
Difference between LS Means and C.I.	-6.8 (-9.8, -3.9)		
P-value	<0.0001		4003.4

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Conclusions

This reviewer continues to be troubled by the disparity in the results of the statistical analyses between the U.S. and Russia sites. While the overall LOCF and MMRM were positive, these results are largely driven by the Russia sites. It is noteworthy that of the various MMRM analyses that were performed by the statistician, results range from a p-value of 0.015 to 0.90 and LS mean differences ranging from -0.43 to -8.9. However, when the statistician performed this same set of MMRM analyses on the data from HGIU (a study in which the LOCF, OC and MMRM analyses were significant), the results were consistent and robust.

It is unclear why there is such a disparity in the efficacy results between the U.S. and Russia sites. While the Sponsor did include the LOCF analysis evaluating the efficacy endpoint between the U.S. and Russia sites, there is no further discussion on the disparate findings. The Sponsor has been asked to address this issue in the action letter.

Cara Alfaro, Pharm.D.
Clinical Reviewer
May 19, 2007

Cc: Khin/Bates/Laughren/Alfaro

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/s/

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CLINICAL REVIEW

Application Type	NDA (Complete Response to Approvable Action)
Submission Number	020592
Submission Code	SE5 040/041
Letter Date	2/5/2008
Stamp Date	2/5/2008
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Reviewer Name	Cara Alfaro, Pharm.D.
Review Completion Date	7/14/2008
Established Name	Olanzapine
Trade Name	Zyprexa
Therapeutic Class	Antipsychotic
Applicant	Eli Lilly & Co
Priority Designation	S
Formulation	Oral tablets
Dosing Regimen	2.5 – 5 mg starting, maximum dose 20 mg/day
Indications	Treatment of Bipolar I Disorder (040) and Schizophrenia (041)
Intended Population	Adolescents

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and SE5-041 "treatment of schizophrenia in adolescents". It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents (b) (4) . Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Sponsor submitted a "risk management plan" document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

1.2.2 Required Phase 4 Commitments

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents). This study is being considered as a Phase 4 commitment. As of this time, the protocol for this study has not been submitted.
No additional Phase 4 commitments are recommended.

2 INTRODUCTION AND BACKGROUND

On 10/30/06, Eli Lilly and Company submitted NDA 20-592 SE5-040 and SE5-041 to support the indications "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and "treatment of schizophrenia in adolescents" respectively. An approvable action was taken 4/30/2007 and the Sponsor was asked to submit additional safety analyses as well as further exploration of the disparity in efficacy results between the US and Russian sites (largely driven by a very low placebo response in the Russian sites) in the pivotal adolescent schizophrenia trial (HGIN). The Sponsor was also asked to submit updated information on risks of weight gain, hyperglycemia and hyperlipidemia that would be reflected not only in Zyprexa labeling, but also in Symbyax labeling.

The Sponsor submitted a response on 8/30/2007, this response was considered incomplete (letter date 9/13/2007) since the submission did not include all requested data regarding the risks of weight gain, hyperglycemia and hyperlipidemia. The Sponsor submitted a response on 2/5/2008 and it was considered a complete response. For the purposes of this review, this reviewer is addressing the portions of the complete response pertaining to SE5-040 and SE5-041, specifically the questions posed to the Sponsor for issues relating to the pivotal trials for the bipolar and schizophrenia adolescent trials. Another clinical reviewer (Evelyn Mentari, M.D.) will be reviewing the requested safety information relating to risks of weight gain, hyperglycemia and hyperlipidemia for both adult and adolescent populations.

2.1 Brief Overview of Pivotal Trials HGIU and HGIN

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar I disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Study HGIN was the pivotal trial for establishing efficacy and safety for the indication "treatment of schizophrenia in adolescent patients". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 6-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 72), or placebo (n = 35).

2.2 Summary Table of Clinical Trials in Original Submission

This summary table is included in this review as some of the Sponsor's responses included additional data from some of the supportive trials.

Study	Description	Length	Age Range (years)	Number of Patients
HGIN	MC, DB, PC study in adolescent patients with schizophrenia. Flexible dose olanzapine (2.5 – 20 mg) U.S. and Russia sites	6 weeks DB 26 weeks OL extension	13 to 17	107 (n = 72 olanzapine, n = 35 placebo)
HGIU	MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder. Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico	3 weeks DB 26 weeks OL extension	13 – 17	161 (n = 107 olanzapine, n = 54 placebo)
LOAY	OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders Flexible dose olanzapine (5 – 20 mg) German sites	24 weeks	12 – 21	96 (n = 89, 13-17 years)
HGMF	OL study in adolescent patients with schizophrenia or bipolar I disorder Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico, Russia	4.5 weeks	13 – 17	107 (n = 37 schizophrenia, n = 70 bipolar)
HGCS	OL study in adolescent patients with schizophrenia Dosing: 2.5 to 20 mg/day Single site	8 weeks	10 – 18	8
HGCR	DB study in adolescent patients with schizophrenia, haloperidol as active comparator Dosing: 2.5 qod – 20 mg/day Single site	8 weeks	12 – 16	2
HGGC	OL study in children and adolescents with bipolar disorder Dosing: 2.5 to 20 mg/day Single site (U.S.)	8 weeks	5 – 14	23

3. REQUESTS FOR INFORMATION

This section includes the requests for information that were outlined in the 4/30/2007 approvable letter, the Sponsor's response and reviewer's comments.

Table 3.1, below, is from the original NDA submission and defines the different databases used to address various safety signals. Some of the requests for information asked for reanalysis in the Overall Olanzapine Exposure Database.

Table 3.1. Sponsor's Table – Databases for Summary of Clinical Safety

Table 2.7.4.1. Databases for Summary of Clinical Safety

Database	Indication	Studies Used	Number of Patients
Acute Placebo-Controlled Databases	Schizophrenia	HGIN	N=107 (Olz=72, Pla=35)
	Bipolar	HGIU	N=161 (Olz=107, Pla=54)
	Combined	HGIN, HGIU	N=268 (Olz=179, Pla=89)
Overall Olanzapine Exposure Databases	Schizophrenia	HGIN, LOAY, HGMF[a]	N=227
	Bipolar	HGIU, HGMF[a]	N=227
	Combined	HGIN, HGIU, LOAY, HGMF	N=454

a Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

3.1 Prolactin

Division Request #1

For the acute phases of HGIU and HGIN, many patients have elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses for the change from baseline to endpoint on the subset of patients with baseline prolactin within the normal range. Please also provide a separate analysis for gender and age.

Data Submitted in the Original Submission

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU[1]: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

In the original analysis of the HGIN + HGIU acute studies, the following change from baseline to endpoint in prolactin concentrations were provided (Table 3.1.1). However, this analysis included subjects with abnormal (usually elevated due to prior therapies) prolactin concentrations making a change from baseline difficult to interpret.

[1] Covance did not have pediatric reference ranges for prolactin. The Sponsor obtained these reference ranges from the Tietz Textbook of Clinical Chemistry (Burtis CA and Ashwood ER 1999).

Table 3.1.1. Prolactin: Change from Baseline To Endpoint, All Subjects (HGIN + HGIU)

			Baseline		**Change to Endpoint**				
		N	Mean	Std	**Mean**	Std	LS Mean Change	LS Mean Difference	P-value
Prolactin (mcg/L)	Olanzapine	163	14.06	9.92	**11.44**	14.52	10.51		
	Placebo	80	14.95	11.86	**-0.16**	10.69	-1.15	11.66	< 0.001

The Sponsor also included a prolactin analysis by gender since it is well established that females have a more pronounced elevation in prolactin concentration with antipsychotic therapy.

Table 3.1.2. Prolactin Analysis by Gender

Laboratory Evaluations	Gender	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value	**P-value
PROLACTIN	Female	Olz	63	15.87	10.06	15.63	16.86	14.26	14.25	<.001	.236
		Placebo	37	15.25	7.59	1.35	9.20	0.00			
	Male	Olz	100	12.92	9.71	8.80	12.20	8.70	10.12	<.001	
		Placebo	43	14.70	14.67	-1.46	11.78	-1.42			

In the original analysis, the Sponsor did not provide a prolactin analysis by age.

Sponsor's Response
Seventy percent of olanzapine-treated subjects (114/163) and 71% of placebo-treated subjects (57/80) had normal baseline prolactin concentrations. Table 3.1.3 provides the reanalysis by the Sponsor including only those subjects with normal baseline prolactin levels.

Table 3.1.3. Prolactin: Change from Baseline To Endpoint, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

			Baseline		**Change to Endpoint**				
		N	Mean	Std	**Mean**	Std	LS Mean Change	LS Mean Difference	P-value
Prolactin (mcg/L)	Olanzapine	114	11.72	6.63	**12.98**	11.93	12.24		
	Placebo	57	12.07	6.34	**2.32**	7.30	1.48	10.76	< 0.001

From Sponsor table APP.1.1 in Regulatory Response document

Table 3.1.4. Prolactin Analysis by Gender and Age, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

Laboratory Evaluations	Subgroup	Group	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value	**P-value
PROLACTIN	Gender	Female	Olz	47	14.65	8.68	15.14	15.25	12.66	11.96	<.001	.574
			Placebo	29	15.14	7.21	3.19	8.98	0.70			
		Male	Olz	67	9.67	3.53	11.47	8.72	11.57	10.01	<.001	
			Placebo	28	8.90	2.99	1.41	5.01	1.56			
	Age	<15	Olz	46	12.02	6.37	14.70	13.60	11.15	14.86	<.001	.080
			Placebo	18	10.97	2.98	-0.22	3.72	-3.71			
		>=15	Olz	68	11.52	6.84	11.82	10.61	11.76	8.53	<.001	
			Placebo	39	12.58	7.38	3.49	8.24	3.23			

Reviewer Comments
In the reanalysis including only those subjects with normal baseline prolactin (Table 3.1.3), the change from baseline to endpoint in olanzapine-treated subjects is slightly greater (12.98 mcg/L) compared to the original analysis (11.44 mcg/L). However, change from baseline to endpoint in placebo-treated subjects was also greater (2.32 mcg/L) compared to the original analysis (-0.16 mcg/L) such that the LS mean difference is lower in this analysis (10.76) compared to the original analysis (11.66). Both analyses found these differences between treatment groups to be statistically significant ($p < 0.001$).

For the gender analysis, the results from this reanalysis including only those subjects with normal baseline prolactin concentrations was similar to the original analysis; however, the change from baseline to endpoint in olanzapine-treated males was higher in this analysis (11.47 mcg/L) compared to the original analysis (8.80 mcg/L). The LS mean differences in this analysis were less than the original analysis primarily due to an increase in change from baseline to endpoint in placebo-treated subjects. The overall results are essentially the same – no differential gender effects were noted; olanzapine increases prolactin concentrations to the same degree in both male and female adolescents.

The Sponsor had not provided an age subgroup analysis in the original submission. This analysis (including only those subjects with normal baseline prolactin concentrations) found a statistically significant ($p = 0.08$) increase in prolactin concentrations in olanzapine-treated subjects < 15 years old compared to subjects $\geq$ 15 years old. Mean change from baseline to endpoint for olanzapine-treated subjects < 15 years old was 14.7 mcg/L compared to 11.82 mcg/L in subjects $\geq$ 15 years old. It does appear, however, that the statistical differences may have been driven by differences in the placebo-treated subjects: change in prolactin for subjects < 15 years old was -0.22 mcg/L compared to 3.49 mcg/L for subjects $\geq$ 15 years old.

Division Request #2
Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed 19-32

weeks in the study (n = 83 bipolar, n = 93 schizophrenia) – e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

Data Submitted in the Original Submission
In the original submission, the Sponsor had included prolactin concentrations for all subjects in the Overall Olanzapine Exposure Combined Database (see Table 3.1.5). However, it was difficult to evaluate patterns over time in subjects completing the trials since these data also included subjects who dropped out over the course of these trials. Therefore, the Sponsor was asked to provide these data only for subjects completing these trials in order to evaluate a potential pattern in prolactin concentration for subjects with exposures up to 6 -8 months.

Table 3.1.5 Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Olanzapine Exposure Combined Database

Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points Overall Olanzapine Exposure Combined Database

		Summary				
Database	Olz Exposure	N	Mean	Std	Median	Max
Bipolar	Baseline	217	15.35	12.58	11.28	110.30
	1-6 weeks	174	26.60	16.18	23.10	129.66
	7-18 weeks	122	19.24	11.89	16.71	59.49
	19-32 weeks	83	18.03	10.42	14.36	49.53
Schizophrenia	Baseline	214	18.84	19.97	11.87	131.57
	1-6 weeks	190	31.82	20.75	26.48	110.84
	7-18 weeks	88	22.75	16.24	18.62	112.00
	19-32 weeks	93	19.01	15.60	14.81	109.97
Overall	Baseline	431	17.08	16.74	11.60	131.57
	1-6 weeks	364	29.33	18.86	25.00	129.66
	7-18 weeks	210	20.71	13.95	17.13	112.00
	19-32 weeks	176	18.55	13.38	14.70	109.97

Sponsor's Response

Table 3.1.6. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database for Subjects Completing 19-32 weeks of Olanzapine Exposure

		Summary				
Database	Olz Exposure	N	Mean	Std	Median	Max
Bipolar	Baseline	83	12.91	8.04	10.36	37.41
	1-6 weeks	49	27.21	11.65	25.86	60.72
	7-18 weeks	83	18.88	10.78	17.11	59.49
	19-32 weeks	83	18.03	10.42	14.36	49.53
Schizophrenia	Baseline	93	18.03	17.37	11.98	100.00
	1-6 weeks	74	31.22	21.54	24.34	104.00
	7-18 weeks	55	20.03	11.60	16.83	54.11
	19-32 weeks	93	19.01	15.60	14.81	109.97
Overall	Baseline	176	15.62	13.98	11.17	100.00
	1-6 weeks	123	29.62	18.30	24.68	104.00
	7-18 weeks	138	19.34	11.09	16.87	59.49
	19-32 weeks	176	18.55	13.38	14.70	109.97

Reviewer Comments
For this reanalysis (as in the original analysis), sample sizes vary by timepoint likely due to differences in the various protocols. Similar to the original analysis, the increase in mean prolactin values appears to occur early (1-6 weeks) and decreases at subsequent timepoints; though still elevated compared to baseline concentrations. This analysis was requested so that data could be evaluated over time in the same group of subjects – however, obviously, if subjects dropped out of the study due to prolactin elevations (or other reasons but also had elevated prolactin concentrations), this analysis would not include those subjects and may underestimate the effect. However, the prior analysis did include all subjects and results between the analyses were very similar.

Proposed Language in Product Labeling re: Prolactin
The Sponsor was asked to include the frequency of hyperprolactinemia in adolescents in this section and also included this data for the adult populations.

Section 5 – WARNINGS AND PRECAUTIONS; 5.16 Hyperprolactinemia
"In clinical studies, plasma prolactin concentrations were elevated in 34% of adults treated with olanzapine. These elevations were mild and transient (end-point mean not above upper limits of normal and not statistically significantly different from placebo). Associated clinical manifestations (e.g. gynecomastia, galactorrhea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.
In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), elevated prolactin concentrations occurred in 47.4% of olanzapine-treated patients compared to 6.8% of patients in the placebo group."

This frequency data is also reflected in Section 6 ADVERSE REACTIONS, 6.2 Vital Signs and Laboratory Studies.
The frequency data do not indicate the magnitude of the elevations in prolactin, the adult data included in currently approved labeling also do not indicate the magnitude of prolactin elevation (only the frequency of occurrence). Unlike adverse events of weight gain or ALT increases, there is not a well recognized potentially clinically significant change in which to further categorize these increases. Therefore, it is reasonable to include only the frequencies of prolactin increases and then to note elsewhere in labeling adverse events that may be related to hyperprolactinemia.

Since the Sponsor has now included data about the frequency of potentially prolactin-related adverse events for adults, this data should also be included for adolescents – however, these effects are not rare in the latter population (refer to Sections 3.2 [Additional Narrative Summaries] and 4 [Safety Update] of review).
I would propose to add the following data which is from the original submission (Table 2.7.4.31 in summary-clin-safety document):
In clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168).

These adverse events (gynecomastia and galactorrhea) should also be noted in the section of labeling: 6 ADVERSE REACTIONS, 6.1 Clinical Trials Experience, Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine. These events would be considered frequent (based on the 1/100 definition).

3.2 Additional Narrative Summaries

Division Request #3
Please provide narrative summaries for the following: 8 cases of gynecomastia, 2 cases with high prolactin concentrations (HGIN 005-503, HGIN 900-9009) and the case with a CPK of 7289 U/L.

The Sponsor supplied the requested narratives. This reviewer compiled a table (Table 3.2.1) summarizing some of the relevant information for the cases of gynecomastia (7 cases, one subject experienced the adverse event twice).

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

Prolactin reference ranges for adolescents in study LOAY:
Males ≥ 12 but ≤ 13 years = 2.8 – 24 ng/ml; ≥ 14 but ≤ 16 years = 2.8 – 16.1 ng/ml; > 16 but ≤ 19 years = 2.1 – 17.7 ng/ml
Females ≥ 12 but ≤ 13 years = 2.5 – 16.9 ng/ml; ≥ 14 but ≤ 16 years = 4.2 – 29 ng/ml; > 16 but ≤ 19 years = 2.8 – 29.2 ng/ml

Table 3.2.1. Summary Table for Gynecomastia Cases

Patient ID	Demographics	Baseline Prolactin (mcg/L)	Prolactin During Study (mcg/L) *indicates prolactin at time of AE report	Clinical Description	Resolved?
HGIN-910-9103*	15 YOM	6.12	21.3 (~5 weeks)* 19.1 (3 months) 12.2 (7 months)	Left side gynecomastia (mild)	Ongoing at study completion
LOAY-400-4008	17 YOM	10.50	23.0 (~2 weeks)* 16.8 (1 month) 16.8 (2 months) 7.4 (6 months)	Gynecomastia (mild)	Ongoing at study completion
LOAY-400-4009	14 YOM	3.90	30 (2 weeks) 28 (3 weeks) 32 (5 weeks) NA* 41 (2 months)	Gynecomastia (moderate)	Noted at baseline visit. Severity changed to severe at 2 months. Ongoing at time of discontinuation.
LOAY-406-4063	17 YOM	5.50	25 (2 weeks) 36 (1 month) 34 (5 weeks) 30 (6 weeks)*	Gynecomastia (mild)	NA
LOAY-407-4074	17 YOM	9.50	23 (2 weeks) 24 (1 month) 20 (5 weeks) 12.80 (6 months)*	Gynecomastia (mild)	AE noted at last study visit
LOAY-407-4077	16 YOM	17.7	31 (2 weeks) 37 (1 month) 37 (6 weeks) 14.7 (7 months)*	Gynecomastia (mild)	AE noted at last study visit
LOAY-407-4201	16 YOM	17.3	27 (2 weeks) 24 (1 month)* 20 (6 weeks)* 28 (2 months)	Gynecomastia (mild)	Ongoing at study discontinuation.

* Sponsor indicates that 2 cases of gynecomastia occurred in this patient – the narrative indicates that the subject had these symptoms "periodically" since ~2 years prior to study participation. It is noteworthy that this subject had a prolactin concentration of 95.35 mcg/ml at Visit 1 (presumably screening visit).

Reviewer Comments

Seven subjects participating in the clinical trials for bipolar disorder and schizophrenia had an adverse event "gynecomastia". Interestingly, six of these subjects participated in the 24-week open label LOAY study conducted exclusively in Germany (these cases occurred at 3 different sites and 3 different investigators). These cases were associated with some elevations in prolactin concentration and most were considered by the investigators to be of mild severity. Though the narratives did not include vital sign data, this reviewer wanted to evaluate the weight gain in these subjects since fat deposition in the breast area, "pseudogynecomastia", might be mistaken as gynecomastia. Not surprisingly, these subjects gained a significant amount of weight over the course of these studies – from 9.1 to 24.6 kg over ~24 weeks (Table 3.2.2).

Table 3.2.2. Weight Changes in Subjects with the Adverse Event Gynecomastia

	Baseline		End of Study		Change from Baseline to Endpoint	
	Weight	BMI	Weight	BMI	Weight	BMI
HGIN-910-9103	58 kg	20.1	82 kg	28.4	24 kg	8.3
LOAY-400-4008	83.5 kg	24.7	108.1 kg	31.9	24.6 kg	7.2
LOAY-400-4009	66.6 kg	23.6	78.8 kg	27.9	12.2 kg	4.3
LOAY-406-4063	62.7 kg	20	71.8 kg	22.9	9.1 kg	2.9
LOAY-407-4074	65.9 kg	20.3	82.6 kg	25.5	16.7 kg	5.2
LOAY-407-4077	63.3 kg	19.8	82 kg	25.6	18.7 kg	5.8
LOAY-407-4201	65.5 kg	22.7	81.7 kg	28.3	16.2 kg	5.6

According to Harrison's medical textbook, gynecomastia is not uncommon in teenage boys with 65% of 14 year-old boys having gynecomastia that usually goes away on its own in 2 or 3 years (hormonally-related). However, the temporal association with olanzapine therapy may implicate the antipsychotic in this adverse event. These cases are not, however, associated with remarkably elevated prolactin concentrations (upper range of normal in males in this age range = 16 to 18 ng/ml for reference ranged used in LOAY) such that it is not clear that these were in fact cases of gynecomastia and may be cases of pseudogynecomastia secondary to significant weight gain. However, since the investigators used the term "gynecomastia" as an adverse event term for these cases, this reviewer will assume this to be correct (since it does not appear to have been queried by the Sponsor) and will recommend some labeling changes to reflect this information (see Section 3.1 [Prolactin] of review). It is not clear to this reviewer why the majority of these cases were from one clinical trial (LOAY).

Elevated Prolactin Cases

HGIN-005-0503 14 YOF. Baseline prolactin 17.2 mcg/L, increased to 90.68 mcg/L at ~6 weeks (no other labs available between these two values). Subsequent prolactin concentrations were 40.2 mcg/L at ~4.5 months and 45.5 mcg/L at ~7.5 months. The subject was receiving olanzapine 20 mg/day when the 90.68 and 45.5 mcg/L concentrations were obtained. No adverse events reported that were associated with elevated prolactin.

HGIN-900-9009 17 YOF. Baseline prolactin 17.5, elevation to 109.97 mcg/L noted at study completion (~8 months); prolactin concentration prior to this was 17.0 mcg/L at ~4 months. Subject was receiving olanzapine 10 mg/day when elevated concentration obtained. No adverse events associated with elevated prolactin were noted.

CPK Elevation Case

HGIN-004-0401 14 YOM. No baseline CPK available. Elevated CPK of 7289 U/L (reference range = 0 – 363 U/L noted one week after randomization – this was the highest CPK value obtained. CPKs were monitored weekly/monthly thereafter and ranged from 445 – 1766 U/L with no clear trend; last CPK noted as 781 U/L at ~8 months. CK-MB concentrations were obtained at some timepoints and most were elevated (5.2 – 10 ng/ml; reference range 0 – 4.9 ng/ml). Urine myoglobin obtained once (at ~2 months when CPK = 531 U/L) and was < 0.006.

Of note, the subject was receiving haloperidol decanoate prior to the study and, if narrative is correct, received his last dose approximately 9 days prior to randomization. No comments regarding extent of exercise or other potential contributing causes.

Reviewer Comments
This reviewer has recommended some labeling language to reflect the gynecomastia cases (see section 3.1 [Prolactin] of review).
The elevated prolactin cases appear to be related to olanzapine therapy and both occurred in female subjects who tend to have a more robust prolactin response to antipsychotics. These were the most significant elevations noted during the original review and appear to represent outliers. Per the Sponsor, there were no adverse events associated with the elevated prolactin, though it is not clear how this was determined (spontaneous reports vs. specific queries for prolactin-related adverse events).
The elevated CPK case was impressive and the highest value (7289 U/L0 was noted one week after randomization – it is possible that this could have been secondary to a haloperidol decanoate injection which appears to have been received 9 days prior to randomization (protocol violation). The CPK was consistently elevated over the course of the 8 month trial, though concentrations were quite variable.
No further labeling changes based on these additional cases (elevated prolactin and CPK) is recommended.

3.3 Hepatic Analytes

Division Request #4
The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes. Although it is stated in the submission that the hepatic laboratory analyte comparisons were not provided due to differences in reference ranges for adults and adolescents, these comparisons were provided for the prolactin data despite differences in reference ranges for these populations.

Sponsor's Response
The Sponsor provided the following data for mean change from baseline to endpoint in hepatic analytes using normalized units for comparing the adolescent and adult populations. Statistically significant, though small, changes were noted for alkaline phosphatase (adolescents > adults) and total bilirubin (decreases noted in both populations).

Table 3.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint in Hepatic Analytes (Normalized Units). Comparison of Adult Versus Adolescent Patients (Overall Exposure Database)

Laboratory Evaluations	Unit	Population	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
AST/SGOT	%URL	Adolescent	446	59.35	51.72	9.00	54.59	7.29	-0.81	.767
		Adult	7074	63.19	36.97	7.99	59.21	8.10		
ALT/SGPT	%URL	Adolescent	446	57.30	74.23	21.39	82.65	18.09	3.49	.520
		Adult	7084	66.00	57.78	14.39	115.43	14.60		
ALKALINE PHOSPHATASE	%URL	Adolescent	446	65.27	30.13	4.38	18.19	4.33	1.96	.019
		Adult	7132	65.59	20.42	2.37	17.36	2.37		
GGT (GGPT/SGGT/YGGT)	%URL	Adolescent	446	43.60	31.34	8.19	32.44	5.88	1.33	.582
		Adult	7051	54.40	52.99	4.40	51.93	4.54		
BILIRUBIN, TOTAL	umol/L	Adolescent	446	8.56	5.96	-1.12	4.60	-1.19	-0.94	<.001
		Adult	7182	8.71	5.22	-0.26	6.05	-0.25		

The Sponsor also provided an analysis for treatment-emergent abnormally high hepatic analyte values (> 1X ULN) at anytime for adolescent and adult populations – the Sponsor did not include these data for ALT $\geq$ 3x ULN. In general, a greater percentage of adolescent subjects had increases in AST, ALT and alkaline phosphatase compared to adult subjects.

Table 3.3.2. Sponsor's Table. Treatment-Emergent Abnormally High Hepatic Analyte Values (> 1X ULN) at Anytime, Adult versus Adolescents (Overall Exposure Database)

Laboratory Analyte	Direction	Population	N	n	(%)	*P-Value
AST/SGOT	High	Adolescent	418	127	30.4%	<.001
		Adult	6338	1459	23.0%	
ALT/SGPT	High	Adolescent	396	169	42.7%	<.001
		Adult	5891	1791	30.4%	
ALKALINE PHOSPHATASE	High	Adolescent	387	52	13.4%	<.001
		Adult	6655	469	7.0%	
GGT (GGPT/SGGT/YGGT)	High	Adolescent	432	34	7.9%	.136
		Adult	6292	642	10.2%	
BILIRUBIN, TOTAL	High	Adolescent	423	9	2.1%	.054
		Adult	7080	75	1.1%	

Reviewer Comments

The mean change from baseline to endpoint in hepatic analytes for adult versus adolescents (including the open-label trials) did not indicate significant differences between these populations. In contrast, the percentage of subjects experiencing an abnormally high hepatic analyte concentration was generally higher for adolescents compared to adults; especially for AST, ALT and alkaline phosphatase.

Proposed Language in Product Labeling re: Hepatic Analytes

The proposed labeling includes data from the placebo-controlled trials and indicates the increased incidence of elevations in ALT (≥ 3x ULN) in adolescents compared to adults. This reviewer has no additional recommendations for further labeling based on these additional analyses.

In Section 5 Warnings and Precautions (5.12 Transaminase Elevations)
"In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from < 3 times the upper limit of normal at baseline to > 3 times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine".

In Section 6.2 Vital Signs and Laboratory Studies
"In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (> 3x ULN in patients with ALT at baseline < 3 X ULN) (12.1% vs. 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%)…"

3.4 Fatalities

Division Request #5
Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had "DRAFT" at the top of the page and the date of the report was 7/27/06. Have all of these reports been previously filed with the Agency?

Sponsor's Response
The Sponsor indicated that because these MedWatch forms were generated for the purposes of a submission dossier, they all showed the date that they were generated (7/27/06) and were marked "draft". The Sponsor also stated that all of the MedWatch forms for fatalities had been previously filed to NDA 20-592 (submission dates 12/16/97 to 5/19/06).

Reviewer Comments
No further information is requested.

Division Request #6

For MedWatch fatality case US_010158510, the narrative states "this is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in Roane County, Tennessee. The reported stated he has also notified the FDA…". The only MedWatch report included in this submission

is for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

Sponsor's Response
The Sponsor stated that all these cases had been previously filed to NDA 20-592. The Sponsor included brief narrative summaries for these cases. This reviewer compiled a table summarizing data from these cases (Table 3.4.1). As with most MedWatch cases, these patients were taking numerous concomitant medications.

Table 3.4.1. Summary of Additional Requested Fatality Narratives

	Demographics	Olanzapine dose/duration	Diagnosis	Date of Death	Cause of Death
US_010158520	52 YOWF	20 mg ~1 year	MDD with psychotic features	(b) (6)	Unknown, found dead in home. No autopsy
US_010158524	29 YOWF	30 mg ~9 months	MDD with psychotic features	(b) (6)	Diabetic ketoacisosis
US_010158498	19 YOWM	5 mg ~7 weeks	Intermittent explosive disorder, antisocial PD	(b) (6)	Unknown
US_010158510	17 YOWM	2.5 mg not provided	Dysthymic disorder, schizophreniform disorder	(b) (6)	Accidental overdose vs. suicide
US_010158537	34 YOWF	30 mg ~9 months	Psychotic disorder	(b) (6)	Unknown, found dead in home. No autopsy. Coroner comments indicate possible narcotic overdose.

Reviewer Comments
It is difficult to interpret the relatedness of these fatalities to olanzapine therapy especially in light of the usual confounds inherent in MedWatch spontaneous reports. It is of interest that these cases were clustered in one geographic area with the majority occurring in 2000, but this could reflect reporting bias to some extent. It is troubling that there is very little data available for 3 of these cases – the narratives indicate that the Sponsor did attempt to obtain further information but was unable to do so.

3.5 AIMS Analysis

Division Request #7
Please provide an analysis of AIMS individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

This item was requested to evaluate potential emergent tardive dyskinesia for subjects who completed the long-term extension phases of the acute studies – since duration of antipsychotic use is a risk factor for development of this adverse event.

Sponsor's Response

Table 3.5.1. Sponsor's Table. Mean Change from Baseline to Endpoint in AIMS Scores. All Patients who Completed the Study – Overall Exposure Database.

EPS Variables	Database	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	*P-value
AIMS Non-Global Total(1-7)	Bipolar	129	0.06	0.35	-0.04	0.29	.132
	Schizophrenia	85	0.29	0.88	-0.22	0.88	.021
	Overall	214	0.15	0.63	-0.11	0.60	.007
AIMS Total(1-10)	Bipolar	129	0.10	0.50	-0.05	0.54	.332
	Schizophrenia	85	0.59	1.77	-0.51	1.76	.010
	Overall	214	0.29	1.20	-0.23	1.21	.006
AIMS Item 1 - Muscles of Facial Expression	Bipolar	129	0.00	0.00	0.01	0.09	.319
	Schizophrenia	85	0.11	0.44	-0.07	0.51	.203
	Overall	214	0.04	0.28	-0.02	0.33	.298
AIMS Item 2 - Lips and Perioral Area	Bipolar	129	0.00	0.00	0.00	0.00	
	Schizophrenia	85	0.04	0.19	-0.04	0.19	.083
	Overall	214	0.01	0.12	-0.01	0.12	.083
AIMS Item 3 - Jaw	Bipolar	129	0.01	0.09	-0.01	0.09	.319
	Schizophrenia	85	0.00	0.00	0.00	0.00	
	Overall	214	0.00	0.07	-0.00	0.07	.318
AIMS Item 4 - Tongue	Bipolar	129	0.02	0.12	-0.02	0.12	.158
	Schizophrenia	85	0.04	0.33	-0.04	0.33	.320
	Overall	214	0.02	0.23	-0.02	0.23	.132
AIMS Item 5 - Upper Extremity	Bipolar	129	0.01	0.09	0.00	0.12	1.00

EPS Variables	Database	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	*P-value
AIMS Item 5 - Upper Extremity	Schizophrenia	85	0.06	0.28	-0.05	0.30	.159
	Overall	214	0.03	0.19	-0.02	0.22	.207
AIMS Item 6 - Lower Extremity	Bipolar	129	0.02	0.12	-0.01	0.09	.319
	Schizophrenia	85	0.05	0.34	-0.04	0.36	.369
	Overall	214	0.03	0.24	-0.02	0.24	.249
AIMS Item 7 - Neck, Shoulders, Hips	Bipolar	129	0.02	0.12	-0.02	0.12	.158
	Schizophrenia	85	0.01	0.11	0.00	0.15	1.00
	Overall	214	0.01	0.12	-0.01	0.14	.318
AIMS Item 8 - Global Severity	Bipolar	129	0.00	0.00	0.01	0.09	.319
	Schizophrenia	85	0.13	0.48	-0.12	0.47	.024
	Overall	214	0.05	0.31	-0.04	0.31	.049
AIMS Item 9 - Global Incapacitation	Bipolar	129	0.00	0.00	0.00	0.00	
	Schizophrenia	85	0.05	0.21	-0.05	0.21	.045
	Overall	214	0.02	0.14	-0.02	0.14	.045
AIMS Item 10 - Patient's Awareness	Bipolar	129	0.04	0.19	-0.02	0.28	.529
	Schizophrenia	85	0.12	0.45	-0.12	0.45	.018
	Overall	214	0.07	0.32	-0.06	0.36	.023

Reviewer Comments

For the AIMS non-global (items 1-7), AIMS total (items 1-10) and most individual AIMS items, there was a decrease in score rating at endpoint compared to baseline for the bipolar, schizophrenia and overall (bipolar + schizophrenia) treatment groups. Based on this mean change analysis, there is no signal for increased risk of tardive dyskinesia in this dataset.

3.6 Disparity in Efficacy Results US vs. Russian Sites in HGIN

Division Request #8

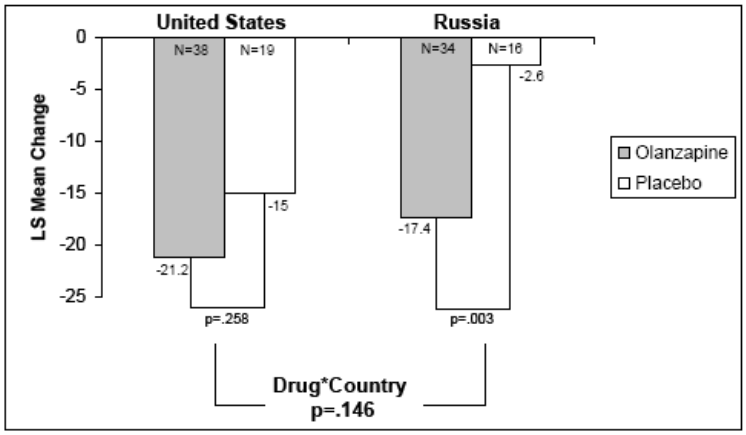
One concern we have for study HGIN is a finding that the positive results for this trial appeared to come predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data from the Russian sites appeared to be driving the overall result. For the US patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -21 and -15 respectively (p = 0.258). For the Russian patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -17 and -3, respectively (p = 0.003). So, the treatment effect in olanzapine patients was roughly the same in both regions, however, the placebo response was much larger in the US sites compared to the Russian sites. Please address this geographic discrepancy in the efficacy results.

Sponsor's Response

The Sponsor provided details for further exploratory analyses including:

1. Between-country comparisons, comparison of baseline characteristics, and inclusion of significant baseline characteristics into the ANCOVA model
2. Analyses by country for disposition, effect size, response rate, modal dose, concomitant medication use, and weight gain
3. Visit-wise LOCF and observed case (OC) mean change for BPRS-C total score by country
4. Analysis of treatment-by-country interaction and within-country effect for secondary efficacy measures
5. Evaluation of data from placebo-treated patients with therapeutic improvements similar to the olanzapine treatment magnitude

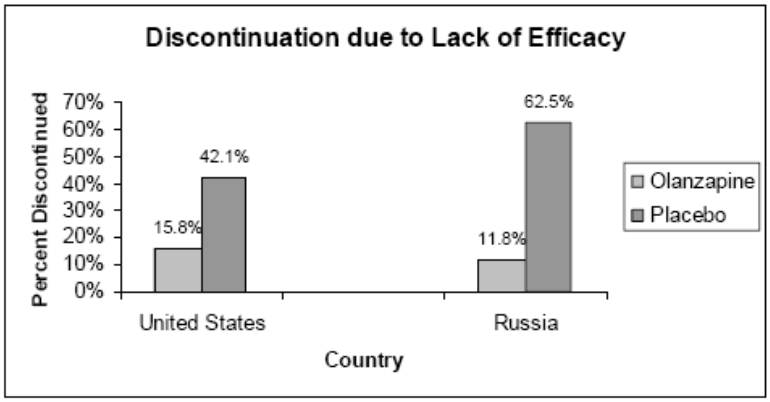
The Sponsor also reiterated in this response that the treatment-by-country interaction was not significant (p = 0.146):



Abbreviation: LS = least-squares.
Source: CLOBPRA1, CLOBPRA4.

Figure APP.4.1. Brief Psychiatric Rating Scale for Children Total score mean change by country.

The Sponsor reiterated that discontinuation due to lack of efficacy was significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US (p = 0.049) and Russia (p < 0.001). "This result is supportive of the efficacy demonstrated with olanzapine treatment compared with placebo treatment in both countries."



Source: INACMGA1.

Figure APP.4.2. Percentage of patients discontinuing due to lack of efficacy in the United States and Russia.

- The effect sizes were .63 for all patients, .32 for the US patients, and .96 for Russian patients.
- Protocol-defined response rate was not statistically different between the two treatment groups in either the United States (39.5% for olanzapine; 31.6% for placebo; p=.772) or in Russia (35.3% for olanzapine; 18.8% for placebo; p=.328).
- Use of concomitant benzodiazepine medication was not statistically significantly different in the United States (26.3% for olanzapine; 42.1% for placebo; p=.244) or in Russia (32.4% for olanzapine; 62.5 % for placebo; p=.066).
- The mean modal doses were calculated for patients in both countries. The mean modal doses were 13.2 mg for the United States and 11.8 for Russia.

Overall conclusion by Sponsor:

Despite numerous statistical and clinical evaluations, an explanation for the difference in placebo response between the United States and Russia remains unclear. It is possible that factors such as population heterogeneity or cultural availability of adjunct therapy may have influenced the placebo response, but this cannot be proven with the available data. Lilly believes that the lack of a clear explanation for the difference in placebo response in the two countries should be considered in light of the fact that a similar magnitude of efficacy response was observed for the olanzapine treatment group in both countries, and that the treatment-by-country interaction was not significant. Furthermore, the overall results of the trial are positive, and are consistent with the abundance of positive efficacy data for the use of olanzapine for the treatment of schizophrenia in adults.

Reviewer Comments
During the review of the original submission, this reviewer had asked the Sponsor for additional analyses (e.g. baseline illness characteristics) to evaluate potential differences between subjects enrolled in the US and Russian sites. No significant differences that might account for the low placebo response rate at the Russian sites was identified during review of these additional analyses.

<u>Discontinuations Due to Lack of Efficacy</u>
The Sponsor commented that the discontinuations due to lack of efficacy were significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US ($p = 0.049$) and Russia ($p < 0.001$) and that this result is supportive of the efficacy demonstrated with olanzapine treatment compared with placebo treatment in both countries. While this statement is true, the p-value for the US sites is marginally significant and could change depending on how you might categorize “lost to follow up” (1.4% in olanzapine group vs. 0% in placebo) and “patient decision” (5.6% in olanzapine group vs. 2.9% in placebo group). It bears mentioning that lack of efficacy, though different between the olanzapine and placebo groups, is the main reason for study discontinuation in both groups.

This reviewer also referred to the recent NDA submissions for the aripiprazole (NDA 21436 SE5-021) and risperidone (NDA 20272 SE5-046) adolescent schizophrenia programs (both recently granted approval actions). Though there are obvious limitations in comparing study HGIN to the pivotal trials for these other antipsychotics, there are certainly noteworthy differences with respect to several issues including discontinuations due to lack of efficacy:

Table 3.6.1. Subject Disposition: Adolescent Schizophrenia Pivotal Trials for Olanzapine, Aripiprazole, and Risperidone

	Sample Size	Discontinuation Rates	DC due to Lack of Efficacy	DC due to AE	Withdrew Consent/Patient Decision	Lost to Follow-up
Olanzapine	72	32%	13.9%	6.9%	5.6%	1.4%
Placebo	35	57%	51.4%	0	2.9%	0
Aripiprazole 10 mg	99	16%	5%	7%	4%	0
Aripiprazole 30 mg	97	18%	1%	3.9%	11.8%	0
Placebo	98	10%	1%	2%	5%	1%
Risperidone 1-3 mg	54	18%	5%	5%	5%	NA
Risperidone 4-6 mg	50	14%	2%	8%	2%	NA
Placebo	54	33%	24%	4%	4%	NA

Comparing across these trials, the overall discontinuation rates for the olanzapine study (HGIN) are much higher compared to the aripiprazole and risperidone pivotal trials. This disparity is also reflected in the discontinuations due to lack of efficacy across these trials including what appear to be significant differences between the olanzapine-treated subjects compared to aripiprazole or risperidone-treated subjects. However, the discontinuations due to lack of efficacy in the aripiprazole 30 mg group may be more similar to the olanzapine group depending on the definition of "withdrew consent".

<u>Evaluating the Low Placebo Response in Russian Sites Compared to US Sites.</u>

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

Efficacy Variable	Country	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy by Country)
BPRS-C Total Score	America	Olanzapine	38	53.18	10.10	-21.21	16.30	-20.89	-5.26	.258	.146
		Placebo	19	51.42	8.64	-15.00	18.28	-15.64			
	Russia	Olanzapine	34	47.00	8.88	-17.41	14.55	-17.44	-14.95	.003	
		Placebo	16	48.50	8.52	-2.56	17.38	-2.49			

Source: Original NDA submission

This reviewer again referred to the recent NDA submissions for the aripiprazole and risperidone adolescent schizophrenia programs to compare placebo response between the Russian sites in HGIN compared to the aripiprazole and risperidone pivotal schizophrenia trials. For these latter pivotal trials, the primary efficacy variable was the PANSS total score.

Approximately 32 % (93/294) of subjects in the aripiprazole pivotal trial were from US sites and 22% (64/294) from Russian sites (the remaining from Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Serbia, South Africa, south Korea and Ukraine). In the statistical analysis for this NDA, a separate subgroup analysis for the Russian sites was not performed by

the statistician. However, upon request from this reviewer, the statistician (Yeh Fong, Ph.D.) did provide an analysis of change from baseline for the Russian sites (Table 3.6.2). Contrary to the olanzapine pivotal trial (HGIN), the placebo response in the Russian sites was similar to the US sites (-17.8 vs. -23.7).

Table 3.6.2. Region Subgroup Analysis: Adolescent Schizophrenia Pivotal Trials for **Aripiprazole**

Table 7 Sponsor's Region Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
US			
Arip-10 mg (N=31)	Baseline	97.2 (16.5)	-31.4 (22.5)
	Last Visit (Week 6)	65.8 (21.8)	
Arip-30 mg (N=31)	Baseline	101.3 (15.1)	-30.7 (21.4)
	Last Visit (Week 6)	70.5 (24.1)	
Placebo (N=31)	Baseline	98.6 (17.0)	-23.7 (20.9)
	Last Visit (Week 6)	74.9 (26.8)	

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
Russia			
Arip-10 mg (N=21)	Baseline	91.14 (15.56)	-19.57 (21.70)
	Last Visit (Week 6)	71.57 (21.43)	
Arip-30 mg (N=25)	Baseline	88.28 (12.31)	-19.76 (16.77)
	Last Visit (Week 6)	68.52 (17.59)	
Placebo (N = 18)	Baseline	95.72 (13.46)	-17.83 (14.33)
	Last Visit (Week 6)	77.89 (11.67)	

Approximately 21 % (33/160) of subjects in the risperidone pivotal trial were from US sites and 23% (37/160) from Russian sites (the remaining from India and Ukraine). In the risperidone pivotal trial, the placebo response in the Russian sites is consistent with the olanzapine HGIN pivotal trial (Table 3.6.3). Interestingly, the risperidone change from baseline is also much lower in the Russian sites compared to the US sites.

Table 3.6.3. Region Subgroup Analysis: Adolescent Schizophrenia Pivotal Trials for **Risperidone**

Treatment	Change from Baseline to Endpoint LS Mean Change	P-value
Russia		
Risperidone 1-3 mg (N=12)	-9.29	0.23
Risperidone 4-6 mg (N=13)	-11.6	0.09
Placebo (N = 12)	-0.44	

Treatment	Change from Baseline to Endpoint LS Mean Change	P-value
United States		
Risperidone 1-3 mg (N= 12)	-29.2	0.030
Risperidone 4-6 mg (N= 11)	-27.7	0.046
Placebo (N = 10)	-11.1	

Overall, though the placebo response is quite low in the Russian sites in the olanzapine pivotal trial HGIN, a similarly low placebo response in Russian sites has been noted in similar studies in similar populations (risperidone) though not all (aripiprazole). This reviewer did not look at individual investigators or individual sites within Russia for any further comparisons.

<u>Evaluating the Change from Baseline to Endpoint in Olanzapine Groups (US vs. Russia)</u>
The Sponsor states that although the olanzapine vs. placebo comparisons were statistically significant for the Russian sites and not the US sites (primarily due to the low placebo response rate in the Russian sites), the change from baseline to endpoint in the olanzapine groups are similar between the these geographic sites. This reviewer agrees that the overall decrease from baseline to endpoint between the olanzapine groups in the US and Russian sites is similar. Again the overall statistically significant finding is largely driven by the low placebo response in the Russian sites and not due to disparities between the olanzapine groups. It is also entirely likely that, when the US sites are evaluated separately, there is insufficient power to detect a statistical difference. In efforts to further evaluate efficacy signals, this reviewer also looked at the adolescent schizophrenia pivotal trials for aripiprazole and risperidone. It should be noted that the primary efficacy variable in the pivotal trials for aripiprazole and risperidone was the PANSS total score. MMRM analyses were not available for the aripiprazole and risperidone pivotal trials.

In general, when comparing the change from baseline to endpoint in the olanzapine group in the US sites (-21.2), it is of a similar magnitude to changes from baseline in other antipsychotic clinical trials in similar populations (most of these clinical trials enrolled ~20% of subjects from

US sites). Since study HGIN used the BPRS as the primary endpoint whereas the aripiprazole and risperidone pivotal trials used the PANSS, a decrease of this magnitude in HGIN (-21.2) may be more significant given the higher baseline scores in the latter trials due to the differences in the BPRS and PANSS instruments.

It is noteworthy that, largely due to differences in subject discontinuation rates (see Table 3.6.1), the OC analyses for the aripiprazole and risperidone pivotal trials were statistically significant whereas the OC analysis for the olanzapine HGIN trial was not (Table 3.6.4). Due to the 2:1 randomization scheme in HGIN, only 35 subjects received placebo and 57% of subjects in the placebo group discontinued the study leaving 15 subjects for the OC analysis.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

Efficacy Variable	Country	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy by Country)
BPRS-C Total Score	America	Olanzapine	38	53.18	10.10	-21.21	16.30	-20.89	-5.26	.258	.146
		Placebo	19	51.42	8.64	-15.00	18.28	-15.64			
	Russia	Olanzapine	34	47.00	8.88	-17.41	14.55	-17.44	-14.95	.003	
		Placebo	16	48.50	8.52	-2.56	17.38	-2.49			

Table 3.6.4. LOCF and OC Analyses: Adolescent Schizophrenia Pivotal Trials for Olanzapine (US + Russian sites), Aripiprazole, and Risperidone

			Change from Baseline to Endpoint or LS Mean Change					
	Primary Endpoint	Baseline	LOCF analysis			OC analysis		
			Change	P-value	Sample Size	Change	P-value	Sample Size
Olanzapine	BPRS	50.3	-19.3	p = 0.003	72	-24.5	p = 0.947	50
Placebo		50.1	-9.1		35	-23.7		15
Aripiprazole 10 mg	PANSS	93.7	-26.7	p = 0.04	99	-30.6	p = 0.001	84
Aripiprazole 30 mg		94.9	-28.6	p = 0.006	97	-31.9	p = 0.0002	84
Placebo		95.0	-21.2		98	-22.3		90
Risperidone 1-3 mg	PANSS	95.4	-21.3	p < 0.001	54	-24.6	p < 0.001	44
Risperidone 4-6 mg		93	-21.2	p < 0.001	50	-24.5	p < 0.001	43
Placebo		93.2	-8.9		54	-13.6		35

<u>Discrepancies in MMRM analyses depending on model chosen</u>

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C total score by LOCF analysis with OC and MMRM as supportive analyses. The LOCF analysis was statistically significant favoring olanzapine (LS mean difference = -10.12; p = 0.003) as was the MMRM analysis (LS mean difference = -8.90; p = 0.015). The OC analysis was not statistically significant (LS mean difference = -0.26; p = 0.947).

In his original review, the statistician had indicated that the MMRM analysis was not statistically significant based on his analysis (not the Sponsor's). In an addendum to his review, he indicated that he had used a different model for the MMRM analysis (default variance-covariance structure model) than the Sponsor had used (unstructured model); however, he indicated that the unstructured model was the most appropriate to use based on the fit of the data.
However, it should be noted that, based on the MMRM model, the p-values are very different:

Variance-covariance Structure	Placebo	Olanzapine	AIC
Variance Components			
LS Mean change from baseline (SE)	-24.1 (3.13)	-24.5 (1.73)	
Difference between LS Means and C.I.	-0.43 (-6.6,7.5)		
P-value	0.90		4691
Unstructured			
LS Mean change from baseline (SE)	-12.6 (2.99)	-21.5 (1.97)	
Difference between LS Means and C.I.	-8.9 (-16.0, -1.9)		
P-value	0.015		4055.2
Compound Symmetry			
LS Mean change from baseline (SE)	-17.8 (2.61)	-22.9 (1.60)	
Difference between LS Means and C.I.	-5.1 (-11.1, 0.9)		
P-value	0.10		4353.0
Toeplitz			
LS Mean change from baseline (SE)	-14.3 (2.68)	-21.9 (1.65)	
Difference between LS Means and C.I.	-7.67 (-13.8, -1.5)		
P-value	0.015		4129.0
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-21.7 (2.70)	-24.4 (1.53)	
Difference between LS Means and C.I.	-2.68 (-8.8, 3.4)		
P-value	0.39		4356.0
First Order Auto-regression			
LS Mean change from baseline (SE)	-15.4 (2.71)	-22.3 (1.64)	
Difference between LS Means and C.I.	-7.0 (-13.8, -0.8)		
P-value	0.029		4129.0

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Statistician's review – addendum to review

Evaluating the different MMRM models for the data for study HGIU (bipolar study) yields very consistent results with p-values ranging from < 0.0001 to 0.0004 (see Appendix). It appears that the MMRM analyses are very unstable for the schizophrenia data (HGIN) and are quite dependent on the specific MMRM model used in contrast to the very stable results for the bipolar data (HGIU). It should also be noted that the drop-out rates in the two studies were different with more subjects remaining in study HGIU – how this impacts the various MMRM models is beyond the expertise of this clinical reviewer. The OC analysis for study HGIU was statistically significant.

Since the Sponsor prespecified the LOCF as the primary analysis and the statistician agrees that the unstructured MMRM model is the most appropriate, it would appear that the Sponsor's data support efficacy of olanzapine versus placebo in study HGIN.

DSI inspections for Russian sites

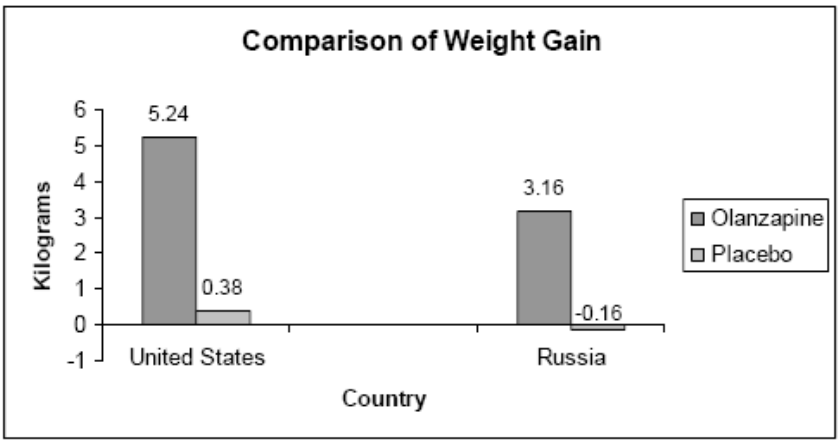
Fifty subjects were enrolled in Russian sites – 10 subjects in each of 5 sites in Moscow. Upon query, the Sponsor indicated that the maximum number of subjects any one site could enroll was 10. 20 US sites enrolled 57 subjects (only one US site enrolled 10 subjects).

Because of the discrepancy in efficacy findings between the US and Russian sites, the Division requested that The Division of Scientific Investigations (DSI) inspect 2 Russian sites. The Moscow Research Institute of Psychiatry, Moscow, Russia; Valery Kransov, M.D. (principle investigator) was inspected between February 26 – March 2, 2007. The Moscow Medical University, Moscow, Russia; Leonid Bardenstein, M.D. (principle investigator) was inspected between February 19 – 22, 2007.
An audit of all subjects' records at these two sites was conducted and revealed few protocol violations. The overall conclusions of the DSI medical officer was that the study appeared to have been conducted adequately and the data generated by these sites may be used.

3.7 Other Issues

In this complete response document, the Sponsor included data comparing weight gain between the US and Russian sites:

- Comparison of weight gain in the 2 countries is illustrated in Figure APP.4.3. The significant differences between countries in weight do not explain the placebo effect difference seen within countries, but do suggest potential cultural differences in the two countries that may impact weight gain.



Source: INACMGA6.

Figure APP.4.3. Comparison of weight gain in the United States and Russia.

For the HGIN study (US + Russian sites), the increase in weight was 4.26 kg in the olanzapine group and 0.13 kg in the placebo group. The Sponsor did not include additional weight analyses between these geographic sites such as % of subjects having $\geq$ 7% weight gain. However, these

data do indicate a difference in the magnitude of weight gain in the US and Russian populations. The currently proposed labeling with regard to weight gain does not differentiate between these populations and the Sponsor was not asked to perform separate analyses for differences in geographic sites for the adult data either. However, the important issue of weight gain is being evaluated by another clinical reviewer and significant changes to proposed labeling are being made to further highlight this issue for both the adult and adolescent populations - though these data may underestimate the weight gain in the US population.

4. SAFETY UPDATE

The Sponsor provided an analysis of their database (Lilly Safety System) for spontaneously reported adverse events occurring from the time of product launch to May 31, 2007. The purpose of the review was to identify differences in the safety information between adolescent and adult patients treated with olanzapine.

As in the original submission, a proportional reporting ratio (PRR) and Chi-square value were calculated to compare the frequency of adverse event reports between the adolescent and adult populations. The Sponsor indicated the following general guidelines that may indicate an adverse event signal: at least 3 reports, a PRR > 2 and a Chi-square > 4.

The following table includes adverse events that indicate an increased frequency in the adolescent compared to the adult populations, again, based on spontaneous reports. It is noteworthy that galactorrhea occurs more frequently in the adolescent population and is further evidence that this adverse event should be included in product labeling (as recommended in section 3.1 of review).
The Sponsor commented that when evaluated the cases of aggression, some reported a history of the event, some reported use of concomitant medications, some of the events were considered to be disease-related, and some cases lacked sufficient information for an evaluation.

Table 6. Adverse Events Reported with a PRR ≥2 in Olanzapine-Treated Patients Aged 13-17 Years Compared with Events Reported in Patients Aged 18-64 Years, with a Proportion of the Event of Interest ≥1.0% of All Events Reported in Patients Aged 13-17 Years, and with a Chi-Square Value ≥4

MedDRA Preferred Term (# of events in patients 13-17 years)	Proportion of Event in Patients 13-17 years (%) (N=3,754 events)	Proportion of Event in Patients 18-64 years (%) (N=85,420 events)	PRR[a]	Chi-Square Value
Somnolence (118)	3.14	1.40	2.24	73.69
Aggression (47)	1.25	0.29	4.38	102.90
Galactorrhoea (43)	1.15	0.31	3.72	73.51
Sedation (40)	1. 07	0.41	2.62	35.80

[a] Ratio of event proportion in patients aged 13-17 years to event proportion in patients aged 18-64 years.

Based on this safety update, no new safety signals emerged that would require additional changes to product labeling.

5. LITERATURE UPDATE

A worldwide literature search was conducted for the time period August 25, 2006 through May 31, 2007 using Ovid Embase and Ovid Medline. Per the Sponsor, all resulting articles were reviewed by a Lilly clinical research physician. The Sponsor indicated that the adverse events and changes in laboratory parameters described in the citations are consistent with the types of adverse events reported for adult patients receiving olanzapine.

6. FOREIGN REGULATORY UPDATE

As of August 21, 2007, olanzapine has not been approved for pediatric use in any country.

7. STUDIES TO BE CONDUCTED IN ADOLESCENTS

In the Risk Management Plan document, the Sponsor indicated that they would be conducting a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects.

The Sponsor provided a very brief synopsis of this safety study. The primary objective of this study is to evaluate the long-term safety of oral olanzapine in these adolescent populations. The study will enroll (b) (4) patients recruited at sites in the US and possibly other countries. Measurements to be included in the protocol are assessment of body weight, reported adverse events, vital signs, ECG parameters, and clinical laboratory tests including hepatic enzymes, insulin, fasting glucose, fasting lipids (total cholesterol, LDL and HDL cholesterol, triglycerides), and prolactin. The secondary objectives are to evaluate efficacy of olanzapine in these adolescent populations as well as the effect of an intervention program on weight gain.

The protocol for this study has not yet been submitted to the Division for review.

8. OVERALL ASSESSMENT

8.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 “treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents” and SE5-041 “treatment of schizophrenia in adolescents”. It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and

reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents (b) (4) . Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

8.2 Recommendation on Postmarketing Actions

8.2.1 Risk Management Activity

The Sponsor submitted a “risk management plan” document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

8.2.2 Required Phase 4 Commitments

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents). This study is being considered as a Phase 4 commitment. As of this time, the protocols for this study has not been submitted.
No additional Phase 4 commitments are recommended.

9 APPENDICES

9.1 MMRM Analyses for HGIU (Bipolar Study)

Table 1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIU (Without Country in Model)

Variance-covariance Structure	Placebo	Olanzapine	AIC
Sample Size	54	105	
Variance Components (Default)			
LS Mean change from baseline (SE)	-11.3 (1.33)	-16.9 (0.86)	
Difference between LS Means and C.I.	-5.6 (-8.7,-2.5)		
P-value	0.0004		4171.5
Unstructured			
LS Mean change from baseline (SE)	-9.4 (1.37)	-16.4 (0.92)	
Difference between LS Means and C.I.	-6.9 (-10.2, -3.7)		
P-value	<0.0001		3994.6
Compound Symmetry			
LS Mean change from baseline (SE)	-10.3 (1.26)	-16.8 (0.84)	
Difference between LS Means and C.I.	-6.4 (-9.4, -3.5)		
P-value	<0.0001		4038.2
Toeplitz			
LS Mean change from baseline (SE)	-9.6 (1.26)	-16.4 (0.84)	
Difference between LS Means and C.I.	-6.8 (-9.8, -3.8)		
P-value	<0.0001		4005.7
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-9.9 (1.25)	-16.6 (0.82)	
Difference between LS Means and C.I.	-6.7 (-9.6, -3.7)		
P-value	<0.0001		4043.2
First Order Auto-regression			
LS Mean change from baseline (SE)	-9.6 (1.26)	-16.4 (0.84)	
Difference between LS Means and C.I.	-6.8 (-9.8, -3.9)		
P-value	<0.0001		4003.4

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Statistician, upon request

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/s/

Cara Alfaro
7/14/2008 12:33:38 PM
PHARMACIST

Ni Aye Khin
7/18/2008 09:57:26 AM
MEDICAL OFFICER
I concur with Dr. Alfaro's recommendations; see memo to file for additional comments.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-592
Drug Name:	Olanzapine
Indication(s):	Schizophrenia for Adolescents
Applicant:	Eli Lilly and Company
Date(s):	December 29, 2006
Review Priority:	Priority
Biometrics Division:	Biometrics I (HFD-710)
Statistical Reviewer:	Fanhui Kong
Concurring Reviewers:	Peiling Yang, H. M. James Hung
Medical Division:	Division of Psychiatry Products
Clinical Team:	Cara Alfaro, Mitchell Mathis, Thomas Laughrem
Project Manager:	Doris J. Bates

Keywords: Olanzapine, Adolescent, Schizophrenia, ANCOVA, LOCF, MMRM

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies between November 2002 and May 2005 in the United States, Russia and Puerto Rico. The primary objectives of the studies were to evaluate the efficacy and safety of olanzapine compared with placebo in the treatment of the adolescents (ages 13 to 17) with schizophrenia (Study HGIN) and in the treatment of the adolescents with Mania in Bipolar I Disorder (Study HGIU). The primary efficacy measures were the change from baseline to Endpoint of the BPRS-C total score (Study HGIN) and the change from baseline to Endpoint of the YMRS total score (Study HGIU).

In the two studies, only Study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. Indeed, the difference between treatment groups only occurred in the patients who dropped out of Period II of the study.

1.2 Brief Overview of Clinical Studies

Two pivotal studies were submitted for the evaluation of the efficacy of olanzapine (2.5 to 20mg/day) in the treatment of adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU). The studies were conducted between November 2002 and May 2005 (26 November 2002 to 29 April 2005 for Study HGIN and 18 November 2002 to 9 May 2005 for Study HGIU) in the United States, Russia and Puerto Rico.

Study HGIN was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescent with schizophrenia, with a 6-week acute period conducted in the Unites States and Russia. The primary objective of this study was to assess the efficacy of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents (ages 13 to 17) with schizophrenia. The primary efficacy measure was the change from baseline to endpoint (up to 6 weeks double-blind treatment) in the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

Study HGIU was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescents with Mania in Bipolar I Disorder, with an acute double-blind treatment period of 3 weeks in the Unites States and Puerto Rico. The primary objective was to evaluate the efficacy and safety of olanzapine (2.5 to 20mg/day) compared with placebo in adolescents with Mania in Bipolar I Disorder. The primary efficacy measure was the change from baseline to Endpoint of the Adolescent Structured Young-Mania Rating Scale (YMRS) total score.

In Study HGIN, 99 subjects were planned in a 2:1 ratio to have 80% power at the Type I error rate of 0.05 to test a treatment group difference of 7.93, a common standard deviation estimate of 12.15. One hundred and fifteen subjects entered the study. Of these, 107 (72 to olanzapine and 35 to placebo) were randomized and 64 subjects (49 to olanzapine and 15 to placebo) completed the acute phase of the study. Seventy two percent (72%) of the patients were Caucasian and 22% were Africa-Americans. Seventy percent (70%) were male and 30% were female. All the patients were between 13 and 17 years of age (inclusive).

In Study HGIU, 130 to 200 subjects were planned in a 2:1 ratio to have 80% power at the Type I error rate of 0.05 to detect an anticipated treatment group difference of 7.00, a common standard deviation estimate of 12.50. Two hundred and three subjects entered the study. Of these, 161 (107 to olanzapine and 54 to placebo) were randomized and 120 subjects (85 in olanzapine and 35 in placebo) completed the acute phase of the study. Seventy percent (70%) of the patients were Caucasian, 16% Hispanics and 9% were Africa-Americans. More than half were male. All the patients were between 13 and 17 years of age (inclusive).

After the screening and washout period (2 days to 2 weeks for screening and washout), subjects in Study HGIN were treated for 6 weeks, and subjects in Study HGIU were treated for 3 weeks, during a double-blind phase.

1.3 Statistical Issues and Findings

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies. In Study HGIN, the primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. In Study HGIU, the primary efficacy measure was the change from baseline to Endpoint of the YMRS total score. The treatment efficacy was analyzed using ANCOVA with LOCF data.

In Study HGIU, the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder is supported by both the primary efficacy results using LOCF, and the results using OC and MMRM. In Study HGIN, however, the efficacy results using OC and MMRM strongly contradict that of the LOCF result. Both the OC and MMRM results are highly nonsignificant. Although LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. This is not the case in this study. On the other hand, MMRM yields quite reliable result if patient dropout mechanism depends only on the observed data, not on unobserved ones. This seems to be a more reasonable assumption. Indeed, the individual outcome profile plots indicate that most dropouts happened when there were no obvious improvements. On the other hand, both the population mean profile plot and individual profile plot suggest that the difference between treatment groups only occurred in the patients who dropped out before the Endpoint. Together, Study HGIN does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents (ages 13 to 17) with schizophrenia.

2. INTRODUCTION

2.1 Overview

In this submission, two efficacy studies were submitted for the evaluation of the efficacy and safety of olanzapine in doses from 2.5 to 20 mg/day in the treatment of adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU) (Table 2.1). In the pooled pivotal Studies HGIN and HGIU, a total of 268 subjects were randomized. Of those, 179 subjects were in the olanzapine group (2.5 to 20mg/day) and 89 subjects were in the placebo group. The numbers of subjects in these studies are given in Table 2.1.

Table 2.1: Studies Supporting the Efficacy of Olanzapine

Protocol	Study Description	Study Treatment	No. of Subjects[a]
Study HGIN	6-week, randomized, double-blind, placebo-controlled, multicenter, flexible dose study	Placebo	35
		Olanzapine (flexible doses)	72
Study HGIU	3-week, randomized, double-blind, placebo-controlled, multicenter, flexible dose study	Placebo	54
		Olanzapine (flexible dose)	107

a: Includes all subjects who were randomized.
Source: FDA analysis.

2.2 Data Sources

The Clinical Study Reports and SAS transport data sets for the studies were provided in electronic form in \\CDSESUB1\N20592\S_040\2006-10-30.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Efficacy studies were designed to evaluate the efficacy and safety of olanzapine compared with placebo in adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU). In both studies, eligible subjects were randomly assigned to receive olanzapine or placebo in a 2:1 ratio (Table 2.1). The subjects received a screening or washout period of 2 to 14 days before randomization. Following randomization, all subjects went through a 6-week (3-week for Study HGIU) double-blind acute period starting with 2.5 or 5mg/day of olanzapine or placebo given once daily. The dose was increased by 2.5 or 5 mg/day dose increments at the investigator's discretion to the maximum tolerable dose, not to exceed 20 mg/day.

In Study HGIN, the primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. The secondary measures included CGI-I, CGI-S, PANSS total score and Overt Aggressive Scale (OAS), ECGs, AIMS, CHQ and BACS. In Study HGIU, the primary efficacy measure was the change from baseline to Endpoint of the Y-MRS total score. The secondary measures included Y-MRS individual scores, CGI scale Bipolar Version Severity of Illness, CDRS-R, OAS, EPS, AIMS, CHQ and CGI-S.

Eligible subjects were from 13 to 17 years of age. Patient must have a diagnosis of schizophrenia according to DSM-IV-TR and confirmed by the K-SADS-PL in Study HGIN. Patients were diagnosed as bipolar I disorder and currently displayed an acute manic or mixed episode according to DSM-IV-TR in Study HGIU.

3.1.1 Baseline Demographic Characteristics

The patient baseline demographic characteristics are summarized in Tables 3.1 to 3.2 for these two studies. In Study HGIN, the majority of patients were male, Caucasian, and from the United States. The mean age of patients in the study was 16.1 years in the olanzapine treatment group and 16.3 years in the placebo group. There were 71% males and 29% females in the olanzapine group, 69% males and 31% females in the placebo group. In Study HGIU, the majority of patients were Caucasian and from the United States, with a mean age of 15.1 years in the olanzapine group and 15.4 years in the placebo group. There were 57% males and 43% females in the olanzapine group, 44% males and 56% females in the placebo group. Patient demographic characteristics were not significantly different between treatment groups at baseline.

Table 3.1 Demographic Characteristics for Study HGIN at Baseline of Period II

		Therapy		
		Olanzapine (N=72)	Placebo (N=35)	
Demographic Variables	Statistics/ Category	n (%)	n (%)	*P-value
Gender	Male	51(70.83)	24(68.57)	.825
	Female	21(29.17)	11(31.43)	
Age	No. of Patients	72	35	
	Mean	16.14	16.30	.536
	Median	16.31	17.00	
	Std. Dev.	1.25	1.55	
	Minimum	13.03	13.06	
	Maximum	17.99	18.00	
Origin	African Descent	17(23.61)	7(20.00)	.656
	Caucasian	52(72.22)	25(71.43)	
	Hispanic	2(2.78)	1(2.86)	
	Other	1(1.39)	2(5.71)	
Country	America	38(52.78)	19(54.29)	1.00
	Russia	34(47.22)	16(45.71)	

* Frequencies are analyzed using the Fisher's Exact Test

Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA): Model= Country Therapy

Source: Table HGIN.11.1 of sponsor's HGIN Study Report.

Table 3.2 Demographic Characteristics for Study HGIU at Baseline Period II

Demographic Variables	Statistics/ Category	Olanzapine (N=107) n (%)	Placebo (N=54) n (%)	*P-value
Gender	Male	61(57.01)	24(44.44)	.137
	Female	46(42.99)	30(55.56)	
Age	No. of Patients	107	54	
	Mean	15.14	15.38	.250
	Median	15.12	15.41	
	Std. Dev.	1.28	1.20	
	Minimum	13.02	13.07	
	Maximum	17.89	17.68	
Origin	African Descent	13(12.15)	2(3.70)	.247
	Caucasian	71(66.36)	41(75.93)	
	East/Southeast Asian	0(0.0)	1(1.85)	
	Hispanic	18(16.82)	8(14.81)	
	Other	5(4.67)	2(3.70)	
Country	America	95(88.79)	48(88.89)	1.00
	Puerto Rico	12(11.21)	6(11.11)	

* Frequencies are analyzed using a Fisher's Exact Test

Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA): Model= Country Therapy

Source: Table HGIU.11.1 of sponsor's HGIN Study Report.

3.1.2 Baseline Disease Characteristics

Across the individual studies, the baseline disease characteristics between the treatment and placebo groups were compared.

In Study HGIN, there were no statistically significant differences between the two treatment groups on the age of onset, the number of previous schizophrenia episode, the total cumulative hospitalization in months, the length of current episode in days, the BPRS-C total score and corresponding subtotal scores.

In Study HGIU, The treatment groups differed considerably at baseline on several illness characteristics. Patients in the placebo group had greater numbers of previous manic, depressive, and mixed episodes. Patients in the olanzapine treatment group had much higher baseline scores on the CGI Severity of Depression scale. In addition, the treatment groups differed on several subscales of the CHQ at baseline. Finally, considerably more patients in the olanzapine treatment group reported a paternal history of psychosis and a history of psychiatric hospitalization at baseline. These are depicted in Table 3.3. The different Quality-of-Life scores at baseline in CHQ are given by the sponsor in Table HGIU.11.9 in the Clinical Study Report. A more specific assessment of these differences will be made by the medical officer.

Table 3.3 Patient Differences in Illness Characteristics and Family History at Baseline in Study HGIU

Illness Characteristics	Placebo	Olanzapine	P-value
	(N=54)	(N=106)	
No. Prev. Mania Episode	4.43 (8.95)*	2.07 (4.97)	0.048
	(N=46)	(N=92)	
No. Prev. Depression Episodes	3.98 (8.26)	1.60 (2.84)	0.014
	(N=50)	(N=92)	
No. of Prev. Mixed Episodes	3.85 (9.40)	1.19 (3.65)	0.027
	(N=46)	(N=81)	
CGI Severity Depression	2.65 (1.60)	3.14 (1.57)	0.043
	N=54	(N=107)	
Paternal History of Psychosis-Fahter	0/51/3†	8/78/20	0.025
	(N=54)	(N=106)	
Paternal History of Hospitalization	9/45‡	34/72	0.040
	(N=54)	(N=106)	

*Standard Deviation. †Yes/No/Unknown. ‡Yes/No.

Source: Tables HGIU.11.2, HGIU.11.6 in Clinical Study Report.

3.1.3 Patient Discontinuation

In Study HGIN, 107 subjects were randomized and 63 (60%) subjects completed the 3-week double-blind phase of the study (Table 3.4), including 49 (32%) subjects from the olanzapine group and 15 (43%) from the placebo group. Lack of efficacy was the most common reason for early termination in both groups. But there was a dramatic difference, which was also statistically significant in nominal sense, between the two treatment groups. In the placebo group, eighteen (51%) patients dropped because of lack of efficacy and the corresponding number for the olanzapine group was 10 (14%).

In Study HGIU, 161 subjects were randomized and 120 (74.5%) completed the 3-week double-blind phase, as shown in Table 3.4. The most common reason for the early withdrawal in both treatment groups was the Lack of Efficacy which had a total of 28 subjects (17.4%). Sixteen (30%) patients dropped out of study because of lack of efficacy in the placebo group and the corresponding number in the olanzapine group was 12 (12%). The difference between the two treatment groups is highly statistically significant in nominal sense (p-value = 0.007).

Table 3.4 Number (%) of Subjects Who Discontinued Treatment During the Double-Blind Period by Primary Reason for Withdrawal in Studies HGIN and HGIU

	Placebo	Olanzapine	Overall
Study HGIN	(N=35)	(N=72)	(N=107)
Total withdrawal	20 (57.1%)	23 (31.9%)	43 (40.2%)
Reason for Withdrawal			
Adverse event	0	5 (6.9)	5 (4.7)
Lack of efficacy	18 (51.4)	10 (13.9)	28 (26.2)
Patient decision/ Personal conflict	1 (2.9)	4 (5.6)	5 (4.7)
Noncompliance	1 (2.9)	2 (2.8)	3 (2.8)
Sponsor decision	0	1 (1.4)	1 (0.9)
Lost to follow-up	0	1 (1.4)	1 (0.9)
Study HGIU	(N=54)	(N=107)	(N=161)
Total withdrawal	19 (35.2%)	22 (20.1%)	41 (25.5%)
Reason for Withdrawal			
Adverse event	1 (1.9)	3 (2.8)	4 (2.5)
Lack of efficacy	16 (29.6)	12 (11.2)	28 (17.4)
Patient decision/Personal conflict	1 (1.9)	4 (3.7)	5 (3.1)
Non-compliance	1 (1.9)	0	1 (0.6)
Physician decision	0	1 (0.9)	1 (0.6)
Other	0	2 (1.9)	2 (1.2)

Source: Tables HGIN.10.1 and HGIU.10.1 – Results in Clinical Study Report.

3.1.4 Statistical Issues and Results

According to the protocol, efficacy analyses were performed on an intent-to-treat (ITT) basis. An ITT analysis defines the treatment groups as those to which patients were assigned by random allocation, even if a patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. For each efficacy variable, the analysis included all randomized patients with baseline and post baseline observations. Using LOCF for missing observations, only patients with a baseline and a post baseline measure were to be included in the analysis. All total scores from rating scales and subscales were derived from individual items. If any of the individual items were missing, the total score was treated as missing.

According to the protocol, the null hypothesis for primary analysis was that there was no difference between treatment groups in the mean change from baseline to Endpoint in the BPRS-C total score for Study HGIN (the YMRS total score for Study HGIU). For efficacy analyses, baseline was defined as the

last observation prior to the end of Study Period II of the study (the period for efficacy study) and Endpoint was defined as the last observation within the period. This was analyzed using the ANCOVA model which included baseline score as covariate, treatment and country as factors.

Interim Analyses: According to the protocol, an interim analysis might be conducted after approximately half of the required patients finished the double-blind acute therapy phase of the study, regardless of whether they completed the 6-week double-blind therapy or discontinued from the double-blind therapy. This interim analysis was planned with the intent to terminate the double-blind phase if overwhelming efficacy of olanzapine was shown. If enrollment was faster than initially anticipated, the sponsor might elect not to conduct the interim analysis. Statistical evidence of overwhelming efficacy was defined to be a statistically significant difference between the placebo and olanzapine group in the change from baseline to Endpoint of the BPRS-C total score, consistent with the primary efficacy analysis, at the α=.0294 level. In the final analysis, the treatment comparison on the BPRS-C total score would also be tested at α=.0294 level. This adjustment followed the methodology described in Pocock (1977).

STUDY HGIN

The protocol for this study was approved by the sponsor on 15 July 2002 and was amended on: 17 October 2002; 03 February 2004; and 08 July 2004. According to the sponsor, the statistical analysis plan (SAP), which supersedes the statistical plans described in the protocol, was approved on 10 June 2005, the same day the reporting database was validated and subsequently locked for analysis. The sponsor made substantial changes on Version C of the protocol. The SAP was not submitted to FDA for review until 21 March 2006, upon the request of the agency. Some changes were made to the planned analyses outlined in the Final SAP after the unblinding of the database. These additional analyses did not alter the interpretation of the primary efficacy analysis of this study (See 9.8.2.2.1 of the Clinical Study Report).

Based on the data set of Study HGIN, the normality test for the primary endpoint gives a p-value of 0.76 using the Shapiro-Wilk test, density plot also shows a symmetric and single mode distribution so the normality assumption is not seriously violated in my opinion. Therefore, no nonparametric method is used on the efficacy test. The analysis results are presented in Table 3.7.

According to the sponsor, the interim analysis was not conducted.

Using the data sets provided by the sponsor, the reviewer confirmed the efficacy results on LOCF data set. The ANCOVA with the primary efficacy measure gave similar significance results as reported in the Clinical Study Report. The homoscedasticity was assessed through the plot of residuals against the predicted values from ANCOVA model on the primary efficacy measure. No heteroscedasticity was found from the plots.

Given the high percentages of patient dropout as indicated in Table 3.4, the reliability and interpretability of the efficacy results becomes an issue. In general, LOCF procedure is reliable only when the mean outcome measure is stable over the whole study period. This is obviously not the case as the mean BPRS-C total score decreased 24.5 points from a baseline mean of 56 for those stayed to the Endpoint of Study Period II. Alternatively, the MMRM method gives reliable efficacy results if the patient dropouts were non-informative, with dropouts only depending on the observed outcome values, not on the unobserved values. This seems to be a reasonable assumption in this study.

Table 3.7: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Studies HGIN --- ITT Population

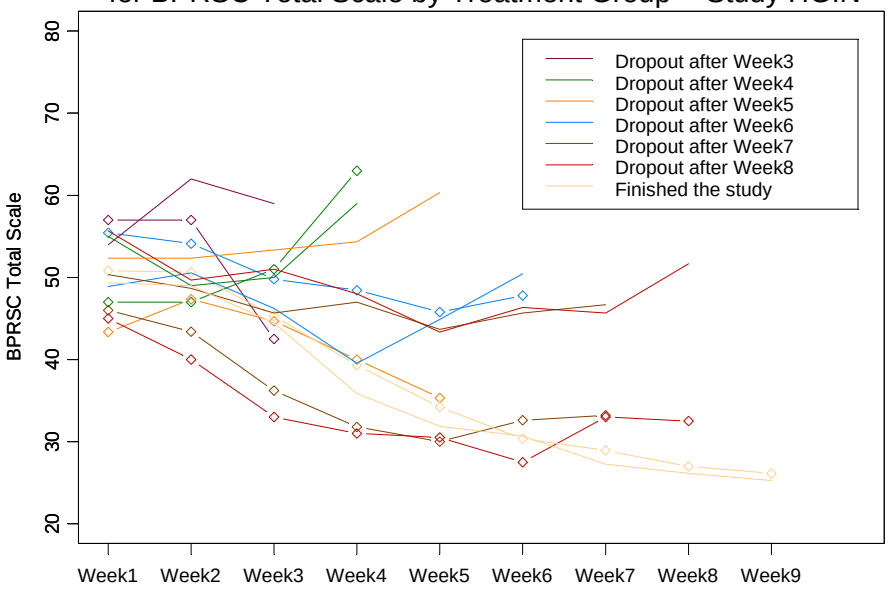
	Placebo	Olanzapine
Study HGIN	(N=35)	(N=72)
N (Analysis population)	35	72
N (BPRS-C Total Score)	35	72
Baseline Mean	50.1	50.3
Median change from baseline	-9.3	-19.4
ANCOVA Analysis (LOCF)		
LS Mean change from baseline (SE) [a]	-9.1 (2.73)	-19.3 (1.91)
Difference between LS Means and C.I.[a]	-10.1 (-16.7, -3.5)	
P-value [a]	0.003	
MMRM Analysis		
LS Mean change from baseline (SE) [b]	-23.5 (3.06)	-24.7 (1.70)
Difference between LS Means and C.I.[b]	-1.25 (-8.11, 5.61)	
P-value [b]	0.72	
OC Analysis		
N (BPRS-C Total Score)	15	50
LS Mean change from baseline (SE) [c]	-24.1 (3.35)	-24.4 (1.82)
Difference between LS Means and C.I.[c]	-0.25 (-7.9, 7.4)	
P-value [b]	0.95	

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Reviewer.

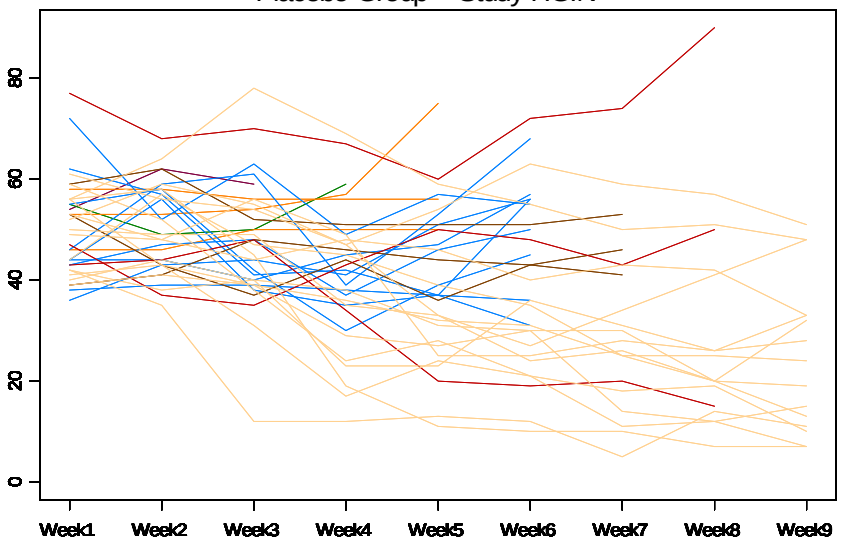
Using the data sets provided by the sponsor, the OC and MMRM analyses yield statistically **very non-significant** efficacy results for the primary outcomes. OC analysis yields **a p-value of 0.95** while MMRM analysis yields **a p-value of 0.72**. These results contradict that of the LOCF analysis on the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. To see why this is the case, this reviewer plotted both the population mean profiles and individual profiles for both treatment groups. These are depicted in Figures 3.1 to 3.3.

Figure 3.1: Population Mean Profiles by Dropout Time
for BPRSC Total Scale by Treatment Group -- Study HGIN



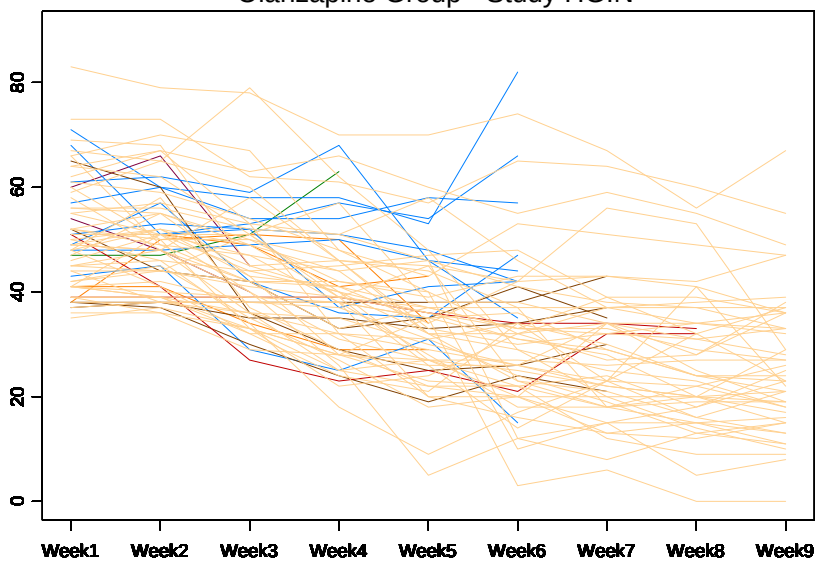
Source: Reviewer

Figure 3.2: Patient Profiles of BPRSC Total Score
Placebo Group -- Study HGIN



Source: Reviewer

Figure 3.3: Patient Profiles of BPRSC Total Score
Olanzapine Group - Study HGIN



Source: Reviewer

These figures clearly indicate that there appears to be no difference between the treatment groups among those who stayed to the end of Period II of the study. The difference appears only among those who dropped out before the end of Period II. Among those patients, olanzapine seems to have improved patient BPRS-C total score over placebo. In fact, Figures 3.2 and 3.3 seem to indicate that olanzapine reduced the BPRS-C total score in both the dropout group and the non-dropouts group while placebo reduced the score only in the non-dropouts group, not in the dropouts group.

This phenomenon was observed in both US and Russia.

STUDY HGIU:

The protocol for this study was approved by the sponsor on 15 July 2002. According to the sponsor, the statistical analysis plan (SAP) addressed the planned statistical analyses prior to unblinding, and was approved prior to the unblinding of the reporting database. The sponsor stated that the SAP was approved on 21 June 2005. The reporting database was validated and subsequently locked for analysis on 24 June 2005. It was not submitted to the Agency for review until 26 March 2006.

Of the 161 randomized patients, 159 were analyzed for the primary efficacy measure. Two of the patients randomized to receive olanzapine did not have a post baseline observation that could be used for the primary efficacy analysis. In addition, the primary analysis, LOCF mean change from baseline to endpoint in the YMRS total score, was conducted without data from patients in Site 021. The efficacy result in Table 3.8 was derived using the data set provided by the sponsor with Site 021 included. Similar results were obtained when Site 021 was excluded.

Table 3.8: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Study HGIU --- ITT Population

	Placebo	Olanzapine
Study HGIU	(N=54)	(N=107)
N (Analysis population)	54	107
N (YMS-R Total Score) ITT	54	105
Baseline Mean	32.0	33.1
Median change from baseline	-6.5	-15.0
ANCOVA Analysis (LOCF)		
LS Mean change from baseline (SE) [a]	-10.0 (1.53)	-17.7 (1.27)
Difference between LS Means and C.I.[a]	-7.7 (-10.7, -4.6)	
P-value [a]	<0.0001	
MMRM Analysis		
LS Mean change from baseline (SE) [b]	-12.6 (1.28)	-17.8 (0.87)
Difference between LS Means and C.I.[b]	-5.6 (-8.7, -2.5)	
P-value [b]	0.0004	
OC Analysis		
N (BPRS-C Total Score)	37	88
LS Mean change from baseline (SE) [c]	-13.4 (1.70)	-19.1 (1.31)
Difference between LS Means and C.I.[c]	-5.7 (-9.2, -2.3)	
P-value [b]	0.0013	

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Reviewer.

Using the data sets provided by the sponsor, the reviewer confirmed the efficacy results in the Clinical Study Report. The efficacy result in the primary analysis was highly statistically significant. The OC and MMRM analyses were conducted by the reviewer and they yielded similar results as that of ANCOVA. These efficacy results are depicted in Table 3.8. These results all support the effectiveness of olanzapine in reducing the YMRS total score in adolescents with schizophrenia compared to placebo.

The treatment-by-country interaction for the primary efficacy measure was explored using the ANCOVA model, including baseline, country, treatment, and treatment-by-country interaction. The corresponding estimated treatment effect was -6.8, which was close to that in Table 3.8. But the p-value for treatment difference became 0.006. The interaction was not statistically significant. There were a total of 143 patients in US and 18 patients in Puerto Rico. In addition to including country as a factor in the efficacy model, statistical comparisons were made between treatment groups on the primary efficacy parameter in US alone and it yielded similar result.

In conclusion, the primary efficacy results using LOCF data set in both Studies HGIN and HGIU support the effectiveness of olanzapine in the treatment of schizophrenia in adolescent patients. However, only the

results in Study HGIU were supported by the results using OC data and MMRM procedure. The efficacy results using OC data set and MMRM strongly contradicted that using LOCF data set in Study HGIN. The OC and MMRM results were both highly nonsignificant. The population mean profiles and individual profiles suggest that the difference of the treatment effect only occurred among the patients who dropped out of the Period II of the study.

3.2 Evaluation of Safety

See medical review for detail.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Using LOCF data, subgroup analyses were performed on the primary efficacy measure, for age (younger than 15 years versus 15 years and older), gender and origin (Caucasian versus non-Caucasian) provided there were at least 10 patients in each treatment group. All subgroup analyses were considered exploratory. The treatment-by-subgroup interaction was tested using an ANCOVA model including the terms for baseline, treatment, country, subgroup, and the treatment-by-subgroup interaction. The treatment-by-subgroup interaction was tested to find out whether treatment differences in the mean primary efficacy measure were similar for each subgroup. In addition, the primary measure was analyzed for each country using the ANCOVA model including terms for baseline and treatment.

In both Studies HGIN and HGIU, neither sex nor the interaction between sex and treatment group was statistically significant at the nominal significance level of 0.05 in the ANCOVA analysis. The treatment effects and their significance levels stayed similar whether sex or the interaction between sex and treatment group was adjusted. However, Table 4.1 shows that the improvement on the primary endpoint was numerically larger for male than for female patients.

In both Studies HGIN and HGIU, neither age group (younger than 15 years versus 15 years and older) nor the interaction between age group and treatment was statistically significant at the nominal significance level of 0.05 in the ANCOVA analysis. The treatment effects and their significance levels were similar whether age group or the interaction between age group and treatment was adjusted. However, Table 4.2 shows that the improvement on the primary endpoint was numerically larger for older patients (15 years and older) than for younger ones.

Table 4.1 Treatment Effect by Sex on the effect size in Studies HGIN and HGIU (LOCF Analysis)

Study	Placebo	Olanzapine
Study HGIN		
Male	N=24	N=51
Mean Change From Baseline of BPRS-C Total (SD)	-8.8 (17.5)	-19.7 (16.6)
Female **Mean Change From Baseline of BPRS-C Total (SD)**	N=11 -10.5 (21.9)	N=21 -18.7 (12.8)
Study HGIU		
Male **Mean Change From Baseline of YMRS Total (SD)**	24 -5.8 (9.35)	60 -16.8 (10.0)
Female **Mean Change From Baseline of YMRS Total (SD)**	30 -9.3 (9.3)	45 -14.7 (10.1)

Source: FDA analysis.

Table 4.2 Treatment Effect by Age Group on the effect size in Studies HGIN and HGIU (LOCF Analysis)

Study	Placebo	Olanzapine
Study HGIN		
Age below 15	N=7	N=15
Mean Change From Baseline of BPRS-C Total (SD)	-12.6 (20.4)	-17.3 (17.8)
Age 15 and Above **Mean Change From Baseline of BPRS-C Total (SD)**	N=28 -8.5 (18.6)	N=57 -20.0 (15.0)
Study HGIU		
Age below 15 **Mean Change From Baseline of YMRS Total (SD)**	20 -9.5 (11.0)	49 -14.6 (10.2)
Age 15 and Above **Mean Change From Baseline of YMRS Total (SD)**	34 -6.7 (8.4)	56 -17.0 (9.9)

Source: FDA analysis.

Table 4.3 Treatment Effect by Country on the effect size in Study HGIN (LOCF Analysis)

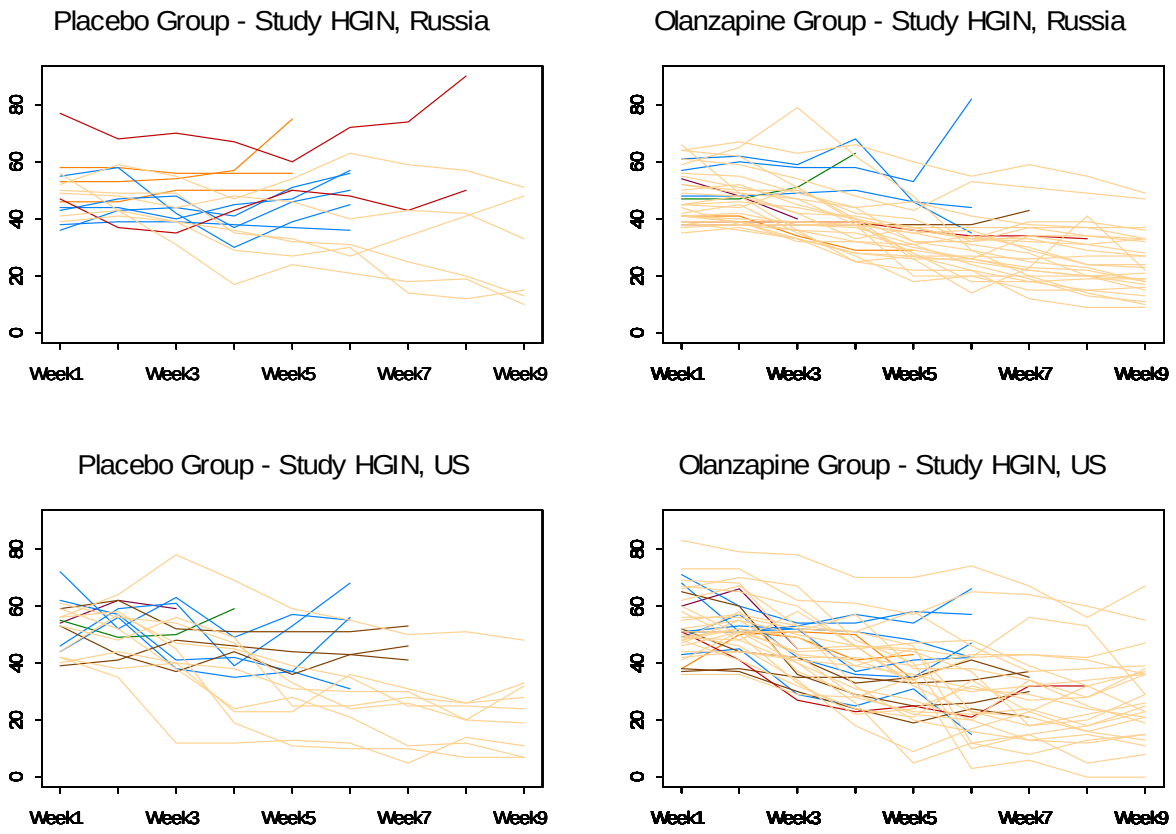
Study	Placebo	Olanzapine
Study HGIN		
USA	N=19	N=38
Mean Change From Baseline of BPRS-C Total (SD)	-15.0 (18.3)	-21.2 (16.3)
Russia **Mean Change From Baseline of BPRS-C Total (SD)**	N=16 -2.6 (17.4)	N=34 -17.4 (14.5)

Source: FDA analysis.

To explore the treatment effect in different countries, we noted that there were about 89% patients in US and only 11% patients in Puerto Rico in Study HGIU, so efficacy analysis was considered in US alone. In Study HGIN, country was not statistically significant at the nominal level of 0.05 but the interaction between country and treatment group yielded a p-value of 0.15 in the ANCOVA analysis. However, Table 4.3 suggests that treatment effect of olanzapine over placebo occurred mainly in Russian rather than in US patients. From Figure 4.1, it appears that the Russian patients in placebo group received very little improvement. Of the 16 patients in the placebo group, 10 dropout patients hardly received any

improvement by the time when they dropped out. The remaining 6 received very limited improvement. Of the 34 patients in the olanzapine group, only 8 dropped out. The improvement in this group appeared to be in line with that of the US patients.

Figure 4.1 Patient Profiles for BPRSC Total Score, by Country



Source: Reviewer.

4.2 Other Special/Subgroup Populations

Not available.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Studies HGIN and HGIU were 6-week (Study HGIU was 3-week), Phase IV, multicenter, randomized, double blind, placebo-controlled, flexible-dose studies with treatment arms of olanzapine and placebo for adolescent outpatients in the United States, Russia and Puerto Rico. The primary objective for Study

HGIN was to assess the efficacy and safety of olanzapine (2.5 to 20 mg/day) in the treatment of adolescents (ages 13 to 17) with schizophrenia. The primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. In Study HGIU, the primary objective was to evaluate the efficacy and safety of olanzapine (2.5 to 20mg/day) in the treatment of adolescents with Mania in Bipolar I Disorder. The primary efficacy for the study was the YMRS total score. In both studies, the primary efficacy analyses were performed on the primary efficacy measure using the ANCOVA procedure with LOCF data.

In Study HGIU, the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder is supported by both the primary efficacy results using LOCF, and the sensitivity analysis results using OC and MMRM. In Study HGIN, however, the efficacy results using OC and MMRM strongly contradict that of the LOCF result. Both the OC and MMRM results are highly nonsignificant. Although LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. This does not seem to be the case in this study. On the other hand, MMRM gives quite reliable result if patient dropout mechanism depends only on the observed data, not on unobserved ones. This seems to be a more reasonable assumption in this study. Indeed, the individual outcome profile plots suggest that most dropouts happened when there were no obvious improvements. On the other hand, both the population mean profile plot and individual profile plot suggest that the difference between treatment groups only occurred in the patients who dropped out before the Endpoint. Together, Study HGIN does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents (ages 13 to 17) with schizophrenia.

5.2 Conclusions and Recommendations

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies between November 2002 and May 2005 in the United States, Russia and Puerto Rico. The primary objective of Study HGIN was to evaluate the efficacy and safety of olanzapine in the treatment of the adolescents (ages 13 to 17) with schizophrenia. The primary objective of Study HGIU was to evaluate the efficacy and safety of olanzapine in the adolescents with Mania in Bipolar I Disorder. The primary efficacy measure for Study HGIN was the change from baseline to Endpoint of the BPRS-C total score and the primary efficacy measure for Study HGIU was the change from baseline to Endpoint of the YMRS total score.

In the two studies, only Study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. Indeed, the difference between treatment groups only occurred in the patients who dropped out of Period II of the study.

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Addendum

NDA/Serial Number:	20-592
Drug Name:	Olanzapine
Indication(s):	Schizophrenia for Adolescents
Applicant:	Eli Lilly and Company
Date(s):	December 29, 2006
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Fanhui Kong, PhD
Concurring Reviewers:	Peiling Yang, H. M. James Hung
Medical Division:	Division of Psychiatry Products
Clinical Team:	Cara Alfaro, Mitchell Mathis, Thomas Laughren
Project Manager:	Doris J. Bates

1. BACKGROUND

Reference is made to Statistical Review of NDA 20592 submitted to DFS on April 6, 2007.

In this NDA submission, the sponsor conducted 2 pivotal short-term olanzapine studies HGIN and HGIU on adolescent patients, one (HGIU) for the treatment of Mania in Bipolar I Disorder and the other (HGIN) is for the treatment of schizophrenia. These studies were reviewed in the Statistical Review. The primary efficacy endpoint for Study HGIN was the change from baseline to Endpoint of BRPS-C total score and the primary statistical analysis was the ANCOVA procedure using LOCF for missing data. The sponsor provided the efficacy analysis results for LOCF, along with that of OC and MMRM.

In the statistical review that I submitted, with the data sets provided by the sponsor, the corresponding analysis results were also given. They are given in Table 1.

Table 1.1: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Studies HGIN --- ITT Population

	Placebo	Olanzapine
Study HGIN	(N=35)	(N=72)
N (Analysis population)	35	72
N (BPRS-C Total Score)	35	72
Baseline Mean	50.1	50.3
Median change from baseline	-9.3	-19.4
ANCOVA Analysis (LOCF)		
LS Mean change from baseline (SE) [a]	-9.1 (2.73)	-19.3 (1.91)
Difference between LS Means and C.I.[a]	-10.1 (-16.7, -3.5)	
P-value [a]	0.003	
MMRM Analysis		
LS Mean change from baseline (SE) [b]	-23.5 (3.06)	-24.7 (1.70)
Difference between LS Means and C.I.[b]	-1.25 (-8.11, 5.61)	
P-value [b]	0.72	
OC Analysis		
N (BPRS-C Total Score)	15	50
LS Mean change from baseline (SE) [c]	-24.1 (3.35)	-24.4 (1.82)
Difference between LS Means and C.I.[c]	-0.25 (-7.9, 7.4)	
P-value [b]	0.95	

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Table 3.7 in Statistical Review

Due to the contradictory results between LOCF, MMRM and OC, I suggested that this study did not support the claim of the effectiveness of Olanzapine on the adolescents with schizophrenia.

2. CORRECTIONS

The MMRM analysis was conducted based on the default variance-covariance structure of Variance Components in SAS software package, which requires the independence between the repeated observations for any subject. In fact, the choice of the variance-covariance structure affects the estimate of treatment effect as well as its significance levels dramatically. Usually, the Unstructured variance-covariance matrix is used for MMRM analysis. In order to see which variance-covariance structure gives a better fit for the data, I applied the MMRM procedure using several different variance-covariance structures and gave the corresponding results along with the AIC values. The AIC values are generally used as a goodness-of-fit criterion of the model. The smaller the AIC value is, the better the model seems to fit the data. These results are depicted in Table 2.1

Table 2.1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIN

Variance-covariance Structure	Placebo	Olanzapine	AIC
Variance Components			
LS Mean change from baseline (SE)	-24.1 (3.13)	-24.5 (1.73)	
Difference between LS Means and C.I.	-0.43 (-6.6,7.5)		
P-value	0.90		4691
Unstructured			
LS Mean change from baseline (SE)	-12.6 (2.99)	-21.5 (1.97)	
Difference between LS Means and C.I.	-8.9 (-16.0, -1.9)		
P-value	0.015		4055.2
Compound Symmetry			
LS Mean change from baseline (SE)	-17.8 (2.61)	-22.9 (1.60)	
Difference between LS Means and C.I.	-5.1 (-11.1, 0.9)		
P-value	0.10		4353.0
Toeplitz			
LS Mean change from baseline (SE)	-14.3 (2.68)	-21.9 (1.65)	
Difference between LS Means and C.I.	-7.67 (-13.8, -1.5)		
P-value	0.015		4129.0
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-21.7 (2.70)	-24.4 (1.53)	
Difference between LS Means and C.I.	-2.68 (-8.8, 3.4)		
P-value	0.39		4356.0
First Order Auto-regression			
LS Mean change from baseline (SE)	-15.4 (2.71)	-22.3 (1.64)	
Difference between LS Means and C.I.	-7.0 (-13.8, -0.8)		
P-value	0.029		4129.0

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Reviewer

In this analysis, country is not used as a factor in the statistical models since it was not prespecified in the protocol. These results indicate that the Unstructured variance-covariance structure in the statistical model seems to give a better fitting. The significance results derived seem to support the claim that Olanzapine improves placebo in treating the adolescents with schizophrenia. Another important observation is that treatment effect estimates and the corresponding p-values are dramatically different for different choices of variance-covariance structure of the repeated observations. This suggests that the efficacy results derived from this model may not be as stable as we expect. Extra care should be exercised in doing such analyses.

Efficacy analysis for each country. The subgroup analysis with respect to country is considered as exploratory. In Table 2.2, the nominal p-values for the treatment effects at Endpoint using MMRM procedure are provided for each country using the Unstructured variance-covariance structure model.

Table 2.2 Treatment Effect by Country by MMRM Analysis

Country	Placebo	Olanzapine
Russia		
N (Number of patients)	16	34
LS Mean change from baseline (SE)	-5.3 (4.46)	-19.0 (2.73)
Difference between LS Means and C.I.	-13.7 (-23.9,3.3)	
P-value	0.012	
US		
N (Number of patients)	19	35
LS Mean change from baseline (SE)	-18.7 (4.13)	-23.5 (2.89)
Difference between LS Means and C.I.	-4.8 (-14.7, -5.1)	
P-value	0.35	

Recourse: Reviewer

Based on the above results, treatment effects seem to be more evident in Russia than in US. Given similar number of subjects in these two countries, the estimated treatment effect in Russia is 13.7 US while that of US is only 4.8. The data suggests that the there was a very small placebo effect in Russia while there was a certain placebo effect in US. Careful investigations might be needed to find why this is the case.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 11, 2008-FINAL
To:	Lisa L. Mathis MD, Associate Director Pediatric and Maternal Health Staff (PMHS) Office of New Drugs (OND), CDER and M. Dianne Murphy, MD, Director Office of Pediatric Therapeutics (OPT), OC
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From:	Ida-Lina Diak, Pharm.D., Safety Evaluator Division of Pharmacovigilance (DPV I) Office of Surveillance and Epidemiology (OSE), CDER
Subject:	1-year Pediatric Exclusivity Postmarketing Adverse Event Review-FINAL
Drug Name(s):	Olanzapine (Zyprexa®)
Pediatric Exclusivity Approval Date:	January 10, 2007
Application Type/Number:	NDA 20592
Applicant/sponsor:	Lilly
OSE RCM #:	2007-1386

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EXECUTIVE SUMMARY

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of olanzapine in pediatric patients. Up to the "data lock" date of February 10, 2008, AERS contained 21,435 reports for olanzapine (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 4.4 % of the total (949/21435).

DPV I was asked to focus on the 1-year period following the approval of pediatric exclusivity, January 10, 2007. We used an AERS data lock date of February 10, 2008, to allow time for reports received up to January 10, 2008, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received 3277 total reports (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review. Pediatric reports represent approximately 2.5% of the total number of cases (81/3277). The projected number of olanzapine prescriptions dispensed from U.S. retail pharmacies in 2007 for the pediatric population (0-17 years) was 4.5 % and the total patient share was 5.5%.[1] In addition, as requested, we provide crude numbers[2] (see appendix) of reports submitted to the AERS database (from marketing approval) of metabolic syndrome, weight gain, hyperglycemia, hyperlipidemia, and hyperprolactinemia in both the adult and pediatric populations.

A review of the pediatric post-marketing cases submitted during the period of pediatric exclusivity, and a review of the 44 pediatric cases with an outcome of death submitted since the beginning of marketing did not reveal any new safety concerns. The review revealed adverse events that are qualitatively similar to those currently found in the product label and described in the adult population. Among the associated adverse events in these pediatric cases, expected (labeled) metabolic effects (hyperglycemia, weight gain, etc) were described in the majority of the pediatric cases.

Based on the potential long-term consequences of weight gain, hyperglycemia and metabolic effects DPV 1 recommends:

- Revise the current olanzapine label to include language regarding the potential risk of the metabolic effects that are also experienced among the pediatric population.
- Continue routine monitoring of the AERS database for adverse events with the use of olanzapine in pediatric patients.

1 BACKGROUND

Olanzapine, an atypical antipsychotic agent (marketed as Zyprexa by Eli Lilly) received FDA approval on September 30, 1996. Pediatric exclusivity was granted on January 10, 2007 based on two short-term, multicenter, double-blind, placebo-controlled, flexible dose, randomized, efficacy and safety studies in adolescents aged 13 to 17 years old. The first study[3] was a 3 week study in patients with acute mania in bipolar I disorder (abbreviated HGIU in the medical officer's

[1] Borders-Hemphill V. Zyprexa (olanzapine) tablets BPCA Drug Use Review. FDA Postmarketing Review. June 26, 2008.
[2] Duplicated reports have not been reconciled and causality has not been assessed for crude number reports.
[3] Study HGIU (Acute Mania in Bipolar I Disorder): 23 sites in the US and 2 sites in Puerto Rico; 161 randomized patients, with 2:1 randomization for olanzapine versus placebo.

review), and the second study[4] was a 6 week study in adolescents with schizophrenia (abbreviated HGIN in same review).[5] There was unanimous agreement among the members of the DPP review team that efficacy was demonstrated in study HGIU, and after further information and discussion agreement that efficacy was also demonstrated in study HGIN.

In reference to safety, the safety data was derived from the two pivotal controlled studies (HGIU and HGIN) and from studies LOAY and HGMF (referenced in the medical officer's review, but not described in detail). There were 454 patients combined from these four studies, including 89 placebo patients from the two controlled trials previously described. Therefore, there were 365 olanzapine treated patients in this safety database, of which 136 of the patients were treated for at least 23 weeks. Overall, the adverse event profile and other safety parameters (with some differences in magnitude) are similar to those seen in adult patients treated with olanzapine. The DPP medical officer recommended highlighting these differences in the product label. Based on this information, DPP determined that the sponsor needed to respond to various requests made by the Agency, and that consensus needed to be reached on labeling prior to taking an approval action. Thus an approvable letter was issued along with DPP's proposal for labeling.

Previous OSE Post-Marketing Reviews:

- September 2, 1997. A review of reports of *hematologic events: aplastic anemia, pancytopenia, bone marrow depression, agranulocytosis, thrombocytopenia, and leukopenia* associated with olanzapine use. The review recommended continued monitoring of the safety of olanzapine.[6]
- February 9, 1999. A two-year postmarketing safety review of olanzapine. The findings of the review included a possible association between olanzapine and bradycardia, first and second-degree heart block, pancreatitis, leukopenia, neutropenia, and priapism.[7]
- December 17, 1999. A review (all ages) of the atypical antipsychotics clozapine, olanzapine, risperidone, and quetiapine and the event of *new-onset diabetes mellitus*. Although not specifically focusing on children, the review mentioned cases of diabetes mellitus with hyperosmolarity associated with olanzapine. Based on the review, recommendation to increase prominence of diabetes mellitus in the labeling for clozapine, risperidone, olanzapine, and quetiapine was made.[8]
- June 25, 2003. A literature review concerning the issue of *diabetes mellitus/hyperglycemia* associated with the atypical antipsychotic drugs. The findings of the review suggested that a risk management program be put in place for these drugs.[9]
- August 15, 2003. A review of *acute liver injury* associated with olanzapine use. No actions were recommended because of the review except for continued close monitoring for well-documented cases of serious hepatic injury associated with olanzapine.[10]
- October 4, 2005. A class review of *galactorrhea* with atypical antipsychotic drugs in pediatric patients. The review supported further analysis of hyperprolactinemia and

[4] Study HGIN (Acute Schizophrenia); 20 sites in US (comprising 53% of sample) and 5 sites in Russia (comprising 47% of sample); 107 patients randomized, with 2:1 randomization for olanzapine versus placebo.
[5] Laughren T. Recommendation for approvable actions for Zyprexa Pediatric Supplements for bipolar disorder (acute mania) and schizophrenia. April 29, 2007.
[6] Friedman B. A review of reports of hematologic events: aplastic anemia, pancytopenia, bone marrow depression, agranulocytosis, thrombocytopenia, and leukopenia with Zyprexa. FDA Postmarketing Safety Review. September 2, 1997.
[7] Bennett K. A two-year postmarketing safety review of olanzapine. FDA Postmarketing Safety Review. February 9, 1999.
[8] Wysowski D. New onset Diabetes Mellitus. FDA Postmarketing Safety Review. December 17, 1999.
[9] Mosholder A. Literature review concerning the issue of diabetes mellitus/hyperglycemia associated with the atypical antipsychotic drugs. FDA Postmarketing Safety Review. June 25, 2003.
[10] Kortepeter C. A review of acute liver injury associated with olanzapine use. FDA Postmarketing Safety Review. August 15, 2003.

galactorrhea with atypical antipsychotics in order to update risperidone labeling to reflect the increased numbers of reports of hyperprolactinemia and galactorrhea associated with risperidone relative to other atypical antipsychotic drugs.[11]

- October 4, 2005. A class review of *pituitary tumors* with atypical antipsychotic drugs. The review recommended further investigation, perhaps including reanalysis of the risperidone NDA, in order to update the risperidone label to include increased hyperprolactinemia compared to other atypical antipsychotic agents.[12]
- May 25, 2006. A review of cases of *myocarditis and cardiomyopathy* associated with the use of olanzapine and quetiapine. The review recommended that both cardiomyopathy and myocarditis be added to the Adverse Events section of both olanzapine and quetiapine labels as well as continued monitoring of cardiac adverse events associated with the two drug products. In particular, pediatric cases and fatal cases with hypertrophic cardiomyopathy associated with these two drug products should undergo heightened monitoring.[13]
- January 25, 2008. A class review of selected antipsychotics and the occurrence of *agranulocytosis*. The review recommended the addition of agranulocytosis to the Precautions section of the olanzapine and risperidone label as well as elevating agranulocytosis to the Precautions section for chlorpromazine and haloperidol.[14]
- April 29, 2008. A class review of post-marketing cases coded with *death in children 16 years old and younger.* In general, for the cases reviewed, the causes of death were all cause death with the most cases reporting cardiac disorders/sudden death. The review recommended continued surveillance of the AERS database for deaths associated with pediatric patients treated with atypical antipsychotics with a particular focus on cardiac and diabetes related cases.[15]

1.1 INTRODUCTION (PRODUCT FORMULATIONS AND INDICATIONS)

Olanzapine is available in three formulations.

- Oral tablet- FDA approved September 30, 1996 and is available in 2.5, 5, 7.5, 10, 15, and 20 mg tablets
- Orally disintegrating tablets- FDA approved April 6, 2000 and is available as 5, 10, 15, and 20 mg tablets
- Intramuscular injection- FDA approved March 29, 2004 and is available in a 10mg vial

Olanzapine is indicated for:

- The treatment of Schizophrenia
- The treatment of Bipolar Disorder as monotherapy or in combination with lithium or valproate
- The treatment of agitation associated with Schizophrenia and Bipolar I Mania

[11] Phelan K. A class review of galactorrhea with atypical antipsychotic drugs in pediatric patients. FDA Postmarketing Safety Review. October 4, 2005.
[12] Phelan K. A class review of pituitary tumors with atypical antipsychotic drugs. FDA Postmarketing Safety Review. October 4, 2005.
[13] LaGrenade L. A review of cases of Myocarditis and Cardiomyopathy associated with the use of olanzapine and quetiapine. FDA Postmarketing Safety Review. May 25, 2006.
[14] Diak I. A mixed class review of antipsychotics and the occurrence of agranulocytosis. FDA Postmarketing Safety Review. January 25, 2008.
[15] Diak I. A class review of postmarketing cases coded with death in children 16 years old and younger. FDA Postmarketing Safety Review. April 29, 2008.

1.2 PEDIATRIC LABELING[16]

The safety and efficacy of olanzapine have not been established in patients under the age of 18 years; however, the current labeling contains clinical trial data regarding adolescents.

WARNINGS:

- Olanzapine monotherapy in adolescents was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo.
- Olanzapine monotherapy in adolescents during long-term continuation therapy found that 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.
- Olanzapine monotherapy in adolescents was associated with no statistically significant difference in fasting HDL cholesterol levels between olanzapine-treated patients and placebo-treated patients.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

This section describes the AERS searches performed as well as the case series selection.

2.2 AERS SELECTION OF CASES

We searched the AERS database on May 1, 2008 for all reports in the database of pediatrics (age 0-16 years) and adults (17 years and greater) associated with olanzapine use from market approval until February 10, 2008 and from the pediatric exclusivity date of January 10, 2007 to February 10, 2008. We conducted separate searches as follows:

1. From Marketing to February 10, 2008 – Adults, 17 years old and older, (Section 3.1, Results, Table 1)
    - All adult cases
    - All adult cases coded serious
    - All adult cases coded 'death'
2. From Marketing to February 10, 2008 – Pediatrics aged 0 to 16 years old, (Section 3.1, Results, Table 1)
    - All pediatric cases
    - All pediatric cases coded serious
    - All pediatric cases coded 'death'
3. Pediatric Exclusivity Period – January 10, 2007 to February 10, 2008 – Adults, (Section 3.2, Results, Table 2)
    - All adult cases
    - All adult cases coded serious
    - All adult cases coded 'death'

[16] Zyprexa Product Label, March 2008, Eli Lilly & Co. USA; http://www.zyprexa.com/index.jsp.

4. Pediatric Exclusivity Period – January 10, 2007 to February 10, 2008 – Pediatrics, (Section 3.2, Results, Table 2)
   - All pediatric cases
   - All pediatric cases coded serious
   - All pediatric cases coded 'death'

The crude counts that resulted from the searches are included in section 3. However, for cases that will receive a hands-on review, the search retrieved 69 serious outcome reports and of these 69 reports, 59 cases met the inclusion criteria for our case series. Of the 10 cases not included in our case series, three cases were duplicates and the remaining seven did not meet our inclusion criteria. The search of all pediatric reports with an outcome of death from marketing approval to February 10, 2008 retrieved 60 reports. Of these 60 reports, 14 were duplicates and two were excluded for miscoding as a pediatric patient, therefore, 44 cases are included in our case series.

3 AERS RESULTS FOR *OLANZAPINE*

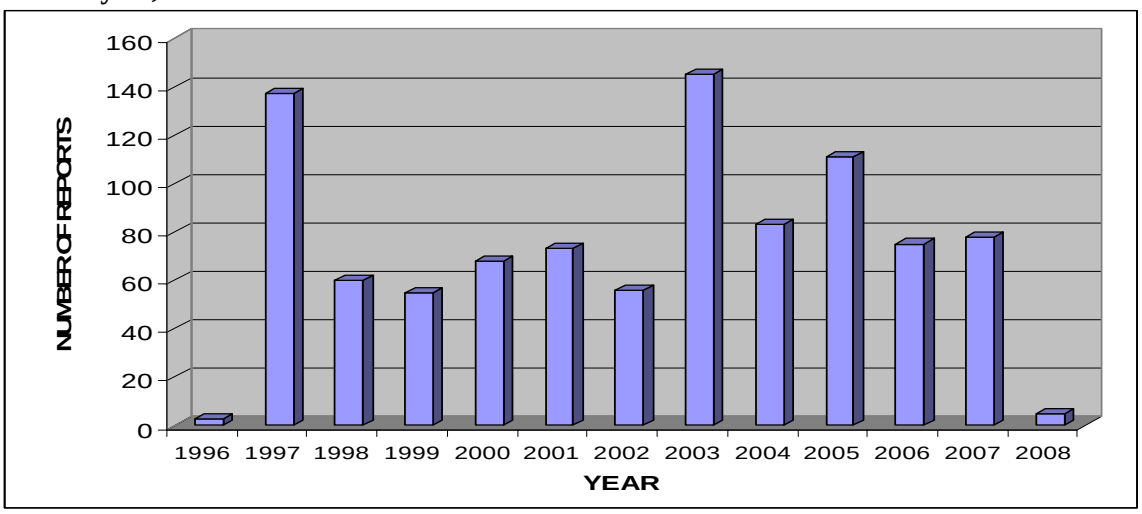
3.1 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM MARKETING APPROVAL TO FEBRUARY 10, 2008 (TABLE 1)

Table 1: Crude counts[1] of AERS Reports for All Sources from Marketing Approval Date (US counts in parentheses)

	All reports (US)	Serious[2] (US)	Death (US)
Adults (≥ 17 yrs.)	16819 (11047)	13594 (8578)	2792 (1577)
Pediatrics (0-16 yrs.)	949 (732)	631 (444)	60 (41)
Age unknown (Null values)	3667	2616	603
Total	21435	16841	3455

[1] May include duplicates
[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, other serious.

Figure 1: Reporting trend for pediatric reports from approval date (September 30, 1996) to February 10, 2008:



3.2 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM PEDIATRIC EXCLUSIVITY (TABLE 2)

Table 2: Crude counts[1] of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (US counts in parentheses)

	All reports (US)	Serious[2] (US)	Death (US)
Adults (≥ 17 yrs.)	2425(1651)	2256 (1544)	258 (127)
Pediatrics (0-16 yrs)	81 (52)	69 (42)	7 (3)
Age unknown (Null Values)	771	707	85
Total	3277	3032	350

[1] May include duplicates
[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, other serious.

3.3 CASE CHARACTERISTICS FROM ONE-YEAR REVIEW (TABLE 3)

Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

Table 3: Characteristics of serious and non-serious pediatric cases reported during the pediatric exclusivity period (January 10, 2007 through February 10, 2008) n=81	
Gender [n=74]	Male: 30 Female: 44
Age [n=78]	0- <1 month (5) 1 month - <2 yrs (10) 2-5 yrs (4) 6-11 yrs (16) 12-16 yrs (43) Mean 11 years, Median 13 years, Range 1 day to 16 years

Table 3: Characteristics of serious and non-serious pediatric cases reported during the pediatric exclusivity period (January 10, 2007 through February 10, 2008) n=81	
Origin [n=79]	US 52, Foreign 27
Event date (n=63)	1999 (2) 2000 (2) 2001 (1) 2002 (7) 2003 (8) 2004 (5) 2005 (12) 2006 (13) 2007 (13)
Daily dose [n=50] Overdose [n=1]	Mean 11 mg, Median 10 mg , Range 2.5 to 25 mg Dose ingested: 250 mg
Duration of therapy [n=24]	Mean 261 days, Median 88 days, Range 1 to 2095 days
Indications [n=37][17]	ADHD (1), Agitation (1), Anger (1), Anorexia (1), Autism (2), Behavior (1), Bipolar Disorder (9), Brief psychotic disorder (1), Delusional disorder (1), Depression (4), Emotional disorder (1), Mania (1), Muscle twitching (1), OCD (3), PTSD (1), Psychotic disorder (3), Schizophrenia (4), and Sleep disorder (1)
Outcomes, non-overlapping [n=68][18]	Death (7*), Life-Threatening (2), Hospitalization (40), Disability (1), Congenital Anomaly (2), and Other Serious (16)

*** 7 Crude death cases representing six unique unduplicated cases**

4 DISCUSSION/SUMMARY OF CASES

Summary of Cases received during the 1-year post-pediatric exclusivity period

4.1 TOTAL REPORTS WITH AN OUTCOME OF DEATH (N = 44)

In light of the fact that six unique pediatric cases coded with death were reported during the pediatric exclusivity period, all pediatric reports with a coded outcome of death from marketing approval until February 10, 2008 were reviewed. The AERS database contained 44 pediatric cases with an outcome of death in association with olanzapine use *since market approval*. Overall, for the 44 cases, 28 are US cases and 16 are foreign cases, including 24 males and 13 females (seven cases did not provide a gender). The patients involved ranged in age from 1 day to 16 years with a median of 13 years (two cases described fetal demise and therefore, their ages were not included).

4.1.1 Drug Exposure during Pregnancy (n = 12)

Twelve cases reported drug exposure to olanzapine in utero with two cases describing fetal demise at 22 weeks and 31-32 weeks. Of the 12 cases, five cases were of US origin and seven were foreign with four cases each of male and female and four cases of unknown gender. Five of the twelve cases provided information regarding time to death and reported the deaths occurring from as early as 30 minutes after birth to as late as 2&1/2 months after birth. Four cases reported concomitant prescription drug therapies with FDA pregnancy categories ranging from A to D[19].

[17] ADHD= Attention-Deficit Hyperactivity Disorder, OCD = Obsessive Compulsive Disorder, PTSD = Post-Traumatic Stress Disorder

[18] Cases are assigned to one outcome according to the following hierarchy: death, hospitalization, life-threatening

[19] **FDA Pregnancy Category A:** Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Of these four cases, two described benzodiazepine use, which do not currently hold an FDA pregnancy category status; however, the label suggests an increased risk of congenital malformations associated with benzodiazepine use. An additional two cases reported illicit drug use by the mother. The time of drug exposure in utero among the 12 cases ranged from 19 days to "throughout the entire pregnancy." Three of the twelve cases reported some mechanism thought to be related to the cause of death. The first case reported that the baby had a mild heart murmur at birth and ultimately died from SIDS. The second case reported the patient died because of "heart and kidney complications", and the final case reported sepsis as the cause of death. In the other nine cases, a cause of death could not be determined. Olanzapine currently holds an FDA pregnancy category C status.

4.1.2 Other Deaths (n = 32)

For the remaining 32 deaths, 23 were of US origin and 9 were foreign with 20 males, 9 females and 3 unknown gender cases. The ages of the patients ranged from 1 to 16 years with a median of 13.5 years. A contributing factor or definite cause of death determined on autopsy could be identified in 24 of the 32 cases.

Suicide (6)

Suicide accounted for six cases with one of those cases describing a patient that purchased the olanzapine, as he did not have a current prescription for the medication. Of note, the ages of the patients that committed suicide ranged from 12 to 16 years with a median of 13.5 years. Olanzapine has labeling describing an association with increased risk of suicidal thinking as well as stating, "the possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder and close supervision of high-risk patients should accompany drug therapy." [11] This caution may lend to the thought that psychiatric illness is a confounding factor in many suicides. Thus, from AERS cases alone, it is not possible to distinguish events linked to the underlying condition from paradoxically heightened suicidality due to drug effect.

Metabolic effects (5)

In five cases, patients experienced metabolic effects described as diabetes mellitus, diabetic coma, diabetic ketoacidosis, and weight gain as contributing factors to their deaths. In two cases, one each described Diabetes Mellitus Type I and II and the remaining three did not specify. The current olanzapine label states, "Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine." [11]

FDA Pregnancy Category B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
FDA Pregnancy Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
FDA Pregnancy Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Cardiac events (4)

An additional four cases described the deaths resulting from cardiac events; including cardiac arrhythmia, myocarditis, "presumably myocardial infarction", and cardiac arrest leading to sudden death. Olanzapine has a boxed warning in the label describing an association with sudden death in the elderly as well as labeling suggesting an association with cardiac arrest and arrhythmias.

Unusual use of olanzapine (5)

Five cases described patients whose cause of death was indirectly related to prescribed olanzapine use; these include three intentional deaths at the hand of their parents, one case described the manner of death as accidental and the remaining case described a drowning. In all three cases, the olanzapine was prescribed for the parents.

The remaining four cases that reported a cause of death each describe a different adverse event relating to the death, and they include acute asthma attack, necrotizing pancreatitis, hepatic steatosis, and endocranial hemorrhage along with multiple blood dyscrasias (thrombocytopenia and sickle cell beta thalassemia). Thrombocytopenia is the only adverse event labeled of these five cases.

Eight cases did not provide enough information to determine a cause of death or olanzapine's contributing role in the outcome.

**A narrative summary for each death case is located in Appendix 1.

4.2 TOTAL NON-FATAL SERIOUS ADVERSE EVENT REPORTS (N = 59)

The AERS database contained 59 cases of non-fatal serious adverse event reports in the pediatric population (0-16 years) from January 10, 2007 to February 10, 2008. This included 37 US, 18 foreign, and 4 unknown origin cases with 34 females, 20 males, and 5 unknown gender cases ranging in age from 1 day to 16 years with a median of 13 years. Various lawyers in connection with legal cases reported twenty-three cases.

4.2.1 Metabolic Effects (n = 27)

Twenty-seven cases ranging in age from 4 to 16 years with a median of 13.5 years reported various metabolic effects associated with olanzapine therapy; including diabetes mellitus, diabetic coma, diabetic ketoacidosis, and weight gain. A possible explanation for this comes from the current olanzapine label, which states, "the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics." [11] We will provide a summary of the 27 cases. Fifteen cases reported a time to onset of adverse event that ranged from 11 days after initiation of olanzapine up to approximately five years after the discontinuation of olanzapine therapy. Eleven cases reported a positive family history of diabetes mellitus with two of those also reporting a family history for hypertension. Five cases reported a past medical history of obesity and three reported a history of diabetes mellitus with one of those cases reporting a history of both obesity and diabetes mellitus. Approximately 50% of the cases were confounded by the use of concomitant medications. Of note, one of the cases of weight gain was the result of a medication error. The patient received Zyprexa® rather than Zyrtec® for 29 days and

experienced a weight gain of 15 pounds.[20] Weight gain appears in the current olanzapine label in the Warnings section and hyperglycemia, diabetic ketoacidosis and coma appear in the Precautions section. See Appendix 4, Table 1 for a summary of the metabolic effects case counts.

4.2.2 Drug exposure during pregnancy (n = 11)

Eleven cases reported in utero exposure of olanzapine. In the nine cases reporting the duration of fetal drug exposure, the time ranged from approximately 60 days to as long as the entire length of the pregnancy (exact durations unspecified). Four cases reported congenital anomalies/birth defects, which included breast malformation, congenital hand malformation, atrial septal defect, and patent ductus arteriosus. Of the remaining seven cases, four cases described neonatal tonicity problems (i.e. hypertonia, hypotonia, dystonia) of which all four infants recovered completely, one case each described neonatal drug withdrawal syndrome, necrotizing enterocolitis and septicemia, and the final case reported the baby as being small for the dates. Nine of the 11 cases reported maternal use of concomitant medications with the FDA pregnancy categories ranging from A to D. Of these nine cases, three described benzodiazepine use, which do not currently hold an FDA pregnancy category status; however, the label suggests an increased risk of congenital malformations associated with benzodiazepine use.

4.2.3 Nervous System (n = 4)

Four cases reported nervous system involvement. Three of the cases described the occurrence of seizures. The first case describes a 4-year old male who experienced a grand mal seizure after one year of concomitant therapy with olanzapine and lamotrigine. Lamotrigine is labeled for an association with grand mal seizures. At the time of reporting, olanzapine therapy was discontinued (the status of lamotrigine was unknown) and the patient no longer experienced seizures. The second case described the occurrence of a seizure 65 days after the initiation of concomitant therapy with olanzapine and sertraline. Both olanzapine and sertraline are labeled for an association with seizures. The third case described a patient that experienced recurrent seizures starting at an unknown time after the initiation of therapy with olanzapine. The case was confounded by the use of the concomitant medications escitalopram and risperidone, which are labeled for an association with seizures. The final case described a 16-year old male that attempted suicide by overdosing on 250mg of olanzapine leading to neuroleptic malignant syndrome. Seizures appear in the current olanzapine label in the Precautions section and neuroleptic malignant syndrome appears in the Warnings section.

4.2.4 Blood Dyscrasias (n = 3)

Three cases reported the occurrence of blood dyscrasias. Two of these cases described leukopenia each in a 14-year old female patient. In the first case, the leukopenia occurred within seven days of olanzapine initiation and the patient recovered two days later without discontinuation of olanzapine therapy. This case was possibly confounded by the use of the concomitant medications valproic acid, clonazepam, lorazepam, and esomeprazole, which are all labeled for an association with leukopenia. In the second case, the patient experienced leukopenia at an unknown time after olanzapine initiation, however treatment with olanzapine continued and at the time of reporting the event of leukopenia was ongoing. The final case described a case of hemolytic anemia in a 16-year old female occurring at an unknown time during concomitant therapy with clozapine and olanzapine. The hemolytic anemia resolved within a few days of

[20] The medication error between Zyprexa and Zyrtec was reviewed by the Division of Medical Errors and Prevention Analysis in 2006. Dallas S. DMETS Post-Marketing Medication Errors Safety Review between Zyrtec, Zyprexa, and Zantac. April 14, 2006.

clozapine discontinuation and olanzapine therapy continued throughout the event. Leukopenia appears in the current olanzapine label under the adverse events section and hemolytic anemia is not labeled.

4.2.5 Miscellaneous/Other (n = 14)

Fourteen cases reported adverse events that did not fall into any of the previously described categories. The 14 cases included three pancreatitis cases and one each of the following: accidental overdose, blepharospasm/dry eye, dystonia/dyskinesia, hyperprolactinemia and gynecomastia, intentional overdose of medications other than olanzapine, lithium toxicity, maculo-papular rash, multiple sclerosis, priapism, sinus disease, and systemic lupus erythematosus. Of the three cases of pancreatitis, one case was confounded by the concomitant use of risperidone and quetiapine, which are labeled for an association with pancreatitis. Overall, for all 14 cases, the role of olanzapine in the occurrence of the adverse event was not highly likely in six cases, but olanzapine's role could not be ruled out completely. Specifically, in the case of intentional overdose, the medications ingested were promethazine and cyproheptadine and the adverse events reported (i.e. hypertonia, mydriasis, myoclonus, dry mouth, etc.) are consistent with overdosage situations for those two agents. In the case of hyperprolactinemia with gynecomastia, the adverse event was more temporally associated with the use of risperidone. In addition, causality could not be assessed in the cases of multiple sclerosis, systemic lupus erythematosus, sinus disease, and lithium toxicity in which olanzapine was discontinued five months prior to the reported adverse events. As far as the labeling status of these adverse events in the current olanzapine label, blepharitis and dry eye, dystonia and dyskinesia, hyperprolactinemia and gynecomastia, maculo-papular rash, and priapism are all labeled.

4.2.6 Neural tube defect (n = 1)

This case was not captured in the AERS database during the pediatric exclusivity period and is not included in the 59 non-fatal serious cases

We were also asked to identify any cases of neural tube defects reported in the AERS database in association with olanzapine therapy. The search retrieved one case of an infant exposed to olanzapine for two months during the first trimester of pregnancy and born with a neural tube defect. It is important to note that incomplete information was provided in this case, including the absence of information regarding the mother's prenatal care and/or nutritional status, therefore making an accurate assessment of the risk to the fetus from olanzapine exposure difficult.

5 CONCLUSION

Among the 44 reviewed post-marketing cases with an outcome of death and the 59 post-marketing cases identified during the period of pediatric exclusivity, the safety profile of the pediatric population is very similar compared to the adults, and the adverse events occurred in much the same manner as well. In 2007, the pediatric population (0-17 years) accounted for approximately 4.5% [1.9% (0-12 years) and 2.6% (13-17 years)] of all olanzapine prescriptions dispensed in US retail pharmacies as well as making up approximately 5.5% [~2.4% (0-12 years) and ~3.3% (13-17 years)] of the total patient share.[21] In addition, the adverse events reported amongst children and adolescents appear to occur in a similar frequency. Across all cases of death and non-fatal serious outcomes, metabolic effects were reported as a majority of the adverse

[21] Borders-Hemphill V. Zyprexa (olanzapine) tablets BPCA Drug Use Review. FDA Postmarketing Review. June 26, 2008.

events. Although metabolic effects such as weight gain, hyperglycemia, and dyslipidemia are well-known effects in the adult population, special attention should be focused on the impact they have among the pediatric population. No new safety signals emerged as part of this review; however, it has made us aware that the pediatric population is not spared from the adverse events caused by olanzapine therapy. The potential risks of olanzapine therapy should be weighed against the potential benefit when choosing to initiate therapy.

6 RECOMMENDATIONS

- Revise the current olanzapine label to include language regarding the potential risk of the metabolic effects that are also experienced among the pediatric population.
- Continue routine monitoring of the AERS database for adverse events with the use of olanzapine in pediatric patients.

APPENDICES

Appendix 1- A narrative summary of all cases with an outcome of 'death' associated with olanzapine use from market approval to February 10, 2008.

Drug exposure during pregnancy (12):

- **ISR# 5123410; Foreign, 2006**. This fetus died at 22 weeks of gestation after exposure to olanzapine 20 mg daily throughout the pregnancy. The mother's concomitant medications included fluoxetine, diazepam, acetaminophen, loratadine, and desloratadine.

- **ISR# 4999149; US, 2006.** This infant died 30 minutes after birth because of Trisomy 13 after exposure to olanzapine 5-10mg daily for 19 days.

- **ISR# 5130133; US, 2006.** This infant died at an unknown time after exposure to olanzapine 5 mg daily throughout the pregnancy. The mother's concomitant medications included citalopram, trazodone, bupropion, and aripiprazole.

- **ISR# 4665076; Foreign, 2005.** This infant was born at 38 weeks of gestation "presented with severe neonatal cardiomegaly, macrosomia and died" after exposure to olanzapine 20mg daily for three months during the pregnancy. The mother developed gestational diabetes at some point in the pregnancy.

- **ISR# 3464646; Foreign, 2000.** This fetus was born still at 32 weeks of gestation after exposure to olanzapine 10-20 mg daily throughout the pregnancy. The mother smoked tobacco as well as cannabis. Autopsy results revealed, "extensive placental infarction and chronic underperfusion."

- **ISR# 4895608; US, 2006.** This infant died after exposure to olanzapine throughout the pregnancy. The mother also used heroin and cocaine during the pregnancy.

- **ISR# 3747959; Foreign, 2001.** This infant died after exposure to olanzapine 5 mg daily throughout the pregnancy. The infant had birth defects that included enlarged kidneys, extra digits, and a cleft palate as well as, Trisomy 18 and a low heart rate.

- **ISR# 4300562; US, 2004.** This fetus died at 31-32 weeks of gestation after exposure to olanzapine 20 mg daily during the 2nd and 3rd trimesters of the pregnancy. The mother's concomitant medications included lorazepam, prenatal vitamin, nicotine resin, and docusate sodium. The autopsy found "apparent hypertelorism, eccentric umbilical cord placement at the periphery of the placenta, and placental insufficiency" with low placental weight and a short umbilical cord.

- **ISR# 3025914; US, 1998.** This infant died within the first two months of life from sudden infant death syndrome (SIDS) after exposure to olanzapine during the 2nd and 3rd trimesters of pregnancy. The autopsy reported, "nothing structurally wrong with the baby."

- **ISR# 5306046; US, 2007.** This infant died after exposure to olanzapine (dose unknown) throughout the pregnancy. The mother's concomitant medications included sertraline and oxazepam. SIDS was the possible cause of death although the autopsy results could not confirm the cause.

- **ISR# 4246991; US, 2003.** This infant died within the first two months of life because of "heart and kidney complications" after exposure to olanzapine 7.5-10mg daily throughout the pregnancy. The patient underwent an autopsy with no results reported.

- **ISR #4765562; US, 2005.** This infant died within the first 2&1/2 months of life because of a sepsis infection. Exposure to olanzapine (dose unknown) occurred throughout the pregnancy

Suicide (6):

- **ISR# 4244394; US, 2003.** This 12-year old patient experienced a "pre-hospital cardiac and /or respiratory arrest and died" after the intentional ingestion of an unknown amount of olanzapine. The report did not state if the patient had a current prescription for the medication.
- **ISR# 4854277; US, 2005.** This 14-year old patient ingested unknown amounts of olanzapine, risperidone, and fluoxetine along with other unspecified substances. The post mortem blood concentrations for all of the drugs were elevated. The report did not state if the patent had a current prescription for the medication.
- **ISR# 4526000; US, 2004.** This 15-year old male died after ingesting an unknown amount olanzapine that he received from someone else. He did not currently have a prescription for this medication. The autopsy results reported an elevated olanzapine level and a cause of death as olanzapine intoxication.
- **ISR# 5388427; Foreign, 2007.** This 13-year old male hanged himself one month after an increase in dose of olanzapine to 20 mg daily, sertraline to 200mg daily, and clonazepam to 4mg daily for the treatment of depression. Sertraline and clonazepam both have labeling describing an association with suicidal ideation. The report stated that the patient had thoughts of suicide that began within two months of initiating therapy with olanzapine.
- **ISR# 5545401; Foreign, 2007.** This 14-year old hanged herself within two months of initiating therapy with olanzapine 2.5 mg daily for the treatment of agitation/anxiety and her level of arousal. Her concomitant medication included venlafaxine, which has labeling describing an association with suicidal ideation. The patient had previously attempted to commit suicide. The autopsy confirmed the cause of death to be the hanging and it revealed skin scarring from her self-inflicted cutting. The report also revealed undetectable levels of olanzapine, fluoxetine, venlafaxine, zolpidem, and amitriptyline in her blood.
- **ISR# 4588081; Foreign, 2005.** This 16-year old male committed suicide within two months of initiating therapy with olanzapine for the treatment of generalized anxiety disorder. His concomitant medication included isotretinoin, which has labeling for an association with suicide.

Metabolic Effect (5):

- **ISR# 4164689; US, 2003.** This 13-year old female experienced diabetic ketoacidosis and died after an unknown duration of therapy with olanzapine 5 mg daily (indication unknown). She also took ziprasidone. Autopsy results confirmed the cause of death.
- **ISR# 4957302; US, 2006.** This 15-year old female experienced diabetes, diabetic ketoacidosis and diabetic coma and died after over one year of therapy with olanzapine (dose unknown) for the treatment of unspecified psychiatric illnesses. Her concomitant medications included ziprasidone, methylphenidate, and sertraline.

- **ISR# 4367813; US, 2004.** This 12-year old child "lapsed into a diabetic coma and died" after an unknown duration of therapy with olanzapine 15 mg daily (indication unknown).
- **ISR# 3814020; Foreign, 2001.** This 16-year old male experienced diabetic coma and died three months after initiating therapy with olanzapine 10mg daily for the treatment of manic depressive illness and mania. His concomitant medications included valproate and topiramate.

- **ISR# 4697426; US, 2005.** This 6-year old male died from an unknown cause after an unspecified duration of therapy with risperidone for the treatment of "bipolarism" and autism. Prior to commencing therapy with risperidone (dose unknown), he received olanzapine 15mg daily and this resulted in excessive weight gain and the diagnosis of hyperglycemia, which ultimately led to its discontinuation. His concomitant medications included amphetamine/dextroamphetamine, valproate, risperidone, dexmethylphenidate, and gabapentin. The initial report from a lawyer stated, "on an unknown date, the patient experienced diabetes mellitus, diabetic coma, ketoacidosis, and pancreatitis."

Cardiac disorders (4):

- **ISR# 5016888; Foreign, 2006.** This 16-year old male died because of cardiac arrest eight days after an increase in his olanzapine dose to 30 mg daily. Olanzapine therapy began 6&1/2 months prior to his death for the treatment of psychosis. The patient also took alprazolam (dose and duration unknown). Autopsy results were pending at the time of the report.

- **ISR# 1966741; US, 1997.** This 7-year old male experienced a cardiac arrhythmia and suddenly died four days after an increase in his olanzapine to 10 mg daily for the treatment of autism. The duration of olanzapine therapy lasted seven days. He also received diphenhydramine 25mg and droperidol 2.5mg the day of his death. Both diphenhydramine and droperidol are labeled for an association with cardiac arrhythmia. The autopsy performed reported "no gross findings."

- **ISR# 3937929; US, 2002.** This 8-year old male died of myocarditis after experiencing ventricular fibrillation and asystole. The patient received therapy with olanzapine (dose and duration unknown) for the treatment of bipolar disorder. His concomitant medication included carbamazepine. The autopsy reported, "extensive areas of the myocardium infiltrated by a mixed lymphohistiocytic infiltrate with scattered polys and other monocytic cells."

- **ISR# 5121343; US, 2006.** This 11-year old male died from "presumably myocardial infarction" 2&1/2 years after initiating therapy with olanzapine 2.5 mg daily for the treatment of insomnia and depression. Concomitant medications included doxepin, prednisone, and fluticasone and many other medications were mentioned, but it was unknown if they were concomitant medications. The patient experienced a thrombus prior to death (unknown date).

Unusual death (5):

- **ISR#4207658; US, 2003.** The medical examiner ruled this 2-year old female's death accidental. The patient initiated therapy with olanzapine 5 mg daily and atomoxetine 20 mg daily for the treatment of hyperactivity and possible bipolar disorder. Within 2&1/2 months of initiating therapy, there was an increase in the atomoxetine dose with no change in the

olanzapine dose. Eight days later, she died. "The medical examiner suggested a possible drug interaction which decreased the metabolism of olanzapine" as the cause of death. The autopsy confirmed no "significant findings."

- **ISR# 3800810; Foreign, 2001.** This 15-year old male died after drowning in a lake. His medications included olanzapine 10mg daily for three to four weeks and dextroamphetamine for years (dose unknown) for the treatment of Asberger syndrome and ADHD. Two weeks prior to the accident, there was an increase in dose of olanzapine from 5mg to 10mg daily and the patient experienced an episode of epistaxis. The autopsy results revealed no pathological abnormality.
- **ISR# 5274611; US, 2007.** This 1-year old male died from an opiate toxicity because of his father "feeding his son morphine and hydromorphone." The urinalysis also found olanzapine in his system. The autopsy reported diagnoses of "respiratory arrest secondary to opiate toxicity, pulmonary congestion and edema, rare petechial hemorrhages of thoracic organs, congestion of the viscera, and fresh, superficial 1.5" contusion of nape of neck."
- **ISR# 4833425; Foreign, 2005.** This 4-year old female died from asphyxiation by her mother. The patient's mother gave her 5mg of olanzapine to sleep at which time she asphyxiated the patient.
- **ISR# 5564489; Foreign, 2007.** This 12-year old female patient's father killed her and cut her into pieces. The patient also had traces of olanzapine found in her lungs, stomach, and kidneys.

Miscellaneous (4):

- **ISR# 3872860; US, 2002.** This 14-year old male experienced an acute asthma attack and died while taking olanzapine 20mg daily (duration and indication unknown). The patient had a medical history of asthma.
- **ISR# 3763759; US, 2001.** This 16-year old "experienced a possible drug interaction, hepatic steatosis, and was found dead" after initiating therapy with olanzapine 5 mg daily 1-2 years prior for ADHD and personality disorder. His concomitant medication included amphetamine/dextroamphetamine. The autopsy confirmed the diagnosis of hepatic steatosis, but not the cause of death.
- **ISR# 3957742; US, 2002.** This 15-year old male died from necrotizing pancreatitis within three months of initiating therapy with olanzapine (dose unknown) for the treatment of bipolar disorder and depression. His death came one month after his diagnosis of diabetes mellitus. His concomitant medications included carbamazepine, paroxetine, and valproate and they all have labeling describing an association with pancreatitis.
- **ISR# 4790560; US, 2005.** This 12- year old female died from an unknown cause within one month of initiating therapy with quetiapine and discontinuing olanzapine therapy (doses unknown). In the months just prior to her death, she had a diagnosis of diabetes mellitus and experienced diabetic ketoacidosis. Over almost two years of therapy with olanzapine, she experienced a weight gain of 29 pounds. Her concomitant medications included clonidine, escitalopram, methylphenidate, and diphenhydramine. On discharge, she was diagnosed with sickle cell beta thalassemia, thrombocytopenia, endocranial hemorrhage, encephalopathy, hypertension, and anemia.

Indeterminate cause (8):

- **ISR# 5466763; US, 2007.** This 3-year old female died from "hepatic issues" at an unspecified time after initiating therapy with olanzapine (dose and indication unknown). This was a hearsay case and details are incomplete and unconfirmed.
- **ISR# 4254663; US, 2003.** This 10-year old male died sometime after initiating therapy with olanzapine (dose and indication unknown). The patient's medical history included a severe cardiac pathology.
- **ISR# 4234811; US, 2003.** This 12-year old female initiated olanzapine 5mg daily and died "within a few days of olanzapine introduction".
- **ISR# 3011672; US, 1997.** This 14-year old male "became agitated on the school bus" and needed restraining and he died. He received therapy with olanzapine 12.5mg daily at the time of his death (duration and indication unknown). His concomitant medication included haloperidol.
- **ISR# 4692944; US, 2005.** This 15-year old male died approximately one month after initiating therapy with olanzapine (dose unknown) for the treatment of bipolar disorder.
- **ISR# 4747126; US, 2005.** This 15-year old male died on an unspecified date after a hospitalization for "severe right side pain" with no diagnosis determined. He currently received therapy with olanzapine 5 mg daily for the treatment of bipolarism, depression, and ADHD for the previous five years along with methylphenidate, mirtazapine, paroxetine and valproate. He had a prior history of pancreatitis.
- **ISR# 4538924; US, 2004.** This 16-year old male experienced diabetes and died after two years of therapy with olanzapine (dose unknown) for the treatment of schizophrenia and bipolar disorder.
- **ISR# 4249552; Foreign, 2003.** This 16-year old male died one day after initiating therapy with olanzapine 5 mg (indication unknown). Three days prior to his death, he received metoclopramide and biperiden resulting in an "extrapyramidal type adverse event" and the psychiatrist made the diagnosis of "catatonic type psychomotor agitation in an apparently detached person". The autopsy revealed a pulmonary infarction, but stated the cause of death was unknown.

APPENDIX 2

Count of Metabolic Syndrome, Weight Increased, Hyperglycemia, and Hyperlipidemia Reports: All Sources Combined- US and Foreign from marketing approval until February 10, 2008

AERS search criteria:

Time period: Marketing approval to February 10, 2008

Coded outcomes: all reports, all serious reports, all death reports

Ages: 17 years and older AND 16 years and younger

MedDRA Preferred Terms: Metabolic Syndrome, Weight Increased, Hyperglycaemia, and Hyperlipidaemia

Table 1 - Crude counts[1] of AERS Reports from all sources from Marketing Approval until 2/10/08

	All reports		Serious[2]		Death	
MedDRA Preferred Term	**> 17 yrs**	**0-16 yrs**	**> 17 yrs**	**0-16 yrs**	**>17 yrs**	**0-16 yrs**
Metabolic Syndrome	49	1	45	1	4	0
Weight Increased	1546	115	1234	67	124	3*
Hyperglycaemia	780	22	718	19	78	1**
Hyperlipidaemia	144	2	132	2	8	0

[1] May include duplicates
[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, other serious.
*Two deaths occurred in 2005 and the remaining death occurred in 2007.
** The one death occurred in 2005

** Table 2 is derived from the 0-16 yrs all reports column in Table 1 above

Table 2 –Pediatric age stratification of crude count AERS reports from all sources from Marketing Approval until 2/10/08 for Metabolic Syndrome, Weight Increased, Hyperglycaemia, & Hyperlipidaemia**

MedDRA Preferred Term	All reports Total	0-6 years	7-11 years	12-16 years
Metabolic Syndrome	1	0	0	1
Weight Increased	115	13	30	72
Hyperglycaemia	22	4	5	13
Hyperlipidaemia	2	0	0	2

APPENDIX 3

Count of Hyperprolactinemia Reports: All Sources Combined- US and Foreign from marketing approval until February 10, 2008

AERS search criteria:

Time period: Marketing approval to February 10, 2008

Coded outcomes: all reports, all serious reports, all death reports

Ages: 17 years and older AND 16 years and younger

MedDRA Preferred Term: Hyperprolactinemia

Table 3 - Crude counts[1] of AERS Reports from all sources from Marketing Approval until 2/10/08

	All reports	Serious[2]	Death
Adults (> 17 yrs)	21	16	1*
Pediatrics (0-16 yrs)	1	1	0
Age unknown (Null values)	1	1	0
Total	23	18	1

[1] May include duplicates

[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, and other serious.

* The one case of death occurred in 2001

APPENDIX 4

Table 1- Summary of the 27 non-fatal serious metabolic effect cases reported from January 10, 2007 to February 10, 2008

DC= Diabetic Coma, DM= Diabetes mellitus, DKA= Diabetic Ketoacidosis, MD= Metabolic Disorder[22], MS= Metabolic Syndrome[23], and WI= Weight Increased

Adverse Event	Number of Cases
Weight Increased	6
Diabetes Mellitus[24]	5
DM + DKA	3
DM + MD	3
DM + DC + DKA + WI	2
DM + WI	2
DM + DC	1
DM + DC + DKA + MD	1
DM + DKA + DC	1
DM + MD + WI	1
Hyperglycemia + Elevated triglycerides	1
MS + WI	1

[22] Metabolic disorder is coded as abnormal glucose metabolism (hypoglycemia, hyperglycemia, polydipsia, polyphagia, polyuria)

[23] The components of metabolic syndrome include abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance ± glucose intolerance, proinflammatory state, prothrombotic state.

[24] Not all cases specified Type I or II.

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/s/

Ida-Lina Diak
9/11/2008 10:21:51 AM
DRUG SAFETY OFFICE REVIEWER

Marilyn Pitts
9/11/2008 10:33:32 AM
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Mark, this is the final after meeting with OPT and PMHS. The appendix case narrative numbers were corrected, as well as an additional table (as requested) is included in the appendix.

Mark Avigan
9/11/2008 05:43:12 PM
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