					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 – (b) (6)	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 – (b) (6)	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 – (b) (6)	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 – (b) (6)	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 – (b) (6)	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
4/12/2007 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.

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).

			Baseline		Change to Endpoint				
Efficacy Variable	Therapy	N	Mean	Std	Mean	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

				Baseline		Change to Endpoint					**P-value
Efficacy Variable	Country	Therapy	N	Mean	Std	Mean	Std	LSMean Change	LSMean Diff.	*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	47.06	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	12.54	13.40	0.175
	Median	13.00	13.00	
	St. Dev.	3.18	2.79	
	Minimum	5.0	5.0	
	Maximum	17.0	17.0	
No. of Prev. Schizophrenia episodes	Mean	2.53	2.25	0.672
	Median	2.00	2.00	
	St. Dev.	4.18	1.80	
	Minimum	0.00	0.00	
	Maximum	30.00	6.00	
Total hospitalization for the past year (months)	Mean	2.43	2.21	0.957
	Median	2.00	1.50	
	St. Dev.	2.43	1.96	
	Minimum	0.20	0.10	
	Maximum	11.00	6.50	
Length of current episode (days)	Mean	274.3	233.5	0.675
	Median	109.0	92.0	
	St. Dev.	483.0	435.2	
	Minimum	0.00**	4.00	
	Maximum	2742	2139	
Days since last hospitalization	Mean	335.4	250.9	0.678
	Median	88.0	37.0	
	St. Dev.	618.4	494.0	
	Minimum	1.00	1.00	
	Maximum	2889	2045	
Psychiatric hospitalization within the past year	Yes	38 (52.78%)	22 (62.86%)	0.407
	No	34 (47.22%)	13 (37.14%)	
CGI-S	Mean	4.83	4.94	0.471
	Median	5.00	5.00	
	St. Dev.	0.69	0.80	
	Minimum	4.00	4.00	
	Maximum	6.00	7.00	
BPRS-C Thinking Disturbance	Mean	10.49	10.29	0.730
	Median	10.00	10.00	
	St. Dev.	3.16	3.12	
	Minimum	4.00	6.00	
	Maximum	18.00	17.00	
BPRS-C Total Score	Mean	50.26	50.09	0.894
	Median	49.50	49.00	
	St. Dev.	9.98	8.59	
	Minimum	36.00	35.00	
	Maximum	79.00	68.00	
PANSS Positive Score	Mean	22.75	22.66	0.885
	Median	22.50	22.00	
	St. Dev.	5.22	4.17	
	Minimum	11.00	17.00	
	Maximum	36.00	32.00	
PANSS Total Score	Mean	95.25	95.54	0.902
	Median	96.50	94.00	
	St. Dev.	14.06	14.11	
	Minimum	66.00	68.00	

	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

				Baseline		Change to Endpoint				
Efficacy Variable	Visit	Therapy	N	Mean	Std	Mean	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	.145
		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	-6.01	.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	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	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 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 10.6). 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 TEES	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 $\geq$ 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 $\geq$ 7% increase in body weight ($p = 0.002$). Only 2 patients in the study, both randomized to placebo, had a $\geq$ 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 $\geq$ 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 $\leq$ 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	2.95	-0.36			

Table 2.7.4.70 in Summary-clin-safety

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 (b) (4) 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 (b) (4). 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%	

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%	

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 $\geq$ 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

The proposed labeling language for Dosage and Administration is "[redacted] (b) (4) (b) (4) (b) (4) ".

[redacted] (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: (b) (4)

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)

. It is unknown whether these protocols have been submitted to the Division.

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, (b) (4) 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:
DOSAGE AND ADMINISTRATION – In the clinical trials, it was recommended to dose olanzapine in the evening due to the potential somnolence associated with the drug. In HGIU + HGIN, somnolence occurred in 25% of patients and sedation occurred in 19% of patients. Current proposed labeling (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 ≥ 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 ≥ 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

(b) (4)

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

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, (b) (4) 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 (b) (6). 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[i]	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[i]	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	135.50	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	3.12	
	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 (8.91)	< 0.001 (0.002)
ALT (U/L)	Olanzapine	84	20.8	25.8	29.6		
	Placebo	87	20.4	-3.1	1.0	28.5 (23.0)	< 0.001 (< 0.001)
CPK (U/L)	Olanzapine	84	125	18.1	16.8		
	Placebo	87	164	-23.6	-21.9	38.7 (16.1)	0.037 (0.38)
Glucose, fasting (mg/dL)*	Olanzapine	58	88.8	3.2	4.3		
	Placebo	64	89.7	-2.9	-2.0	6.3 (5.6)	0.001 (< 0.001)
Cholesterol (mg/dL)*	Olanzapine	84	164.1	17.4	13.5		
	Placebo	87	160.2	-1.1	-4.6	18.5 (14.3)	< 0.001 (< 0.001)
Triglycerides (mg/dL)*	Olanzapine	84	97.3	51.3	46.9		
	Placebo	87	110.6	-4.4	-7.1	54.0 (33.6)	< 0.001 (<0.001)
LDL (mg/dL)*	Olanzapine	84	96.1	6.6	3.1		
	Placebo	87	91.5	-0.39	-3.5	6.6 (6.6)	0.038 (0.016)
Prolactin (ng/ml)	Olanzapine	79	13.3	12.6	12.0		
	Placebo	80	14.9	-0.2	-0.9	12.91 (11.7)	< 0.001 (< 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