CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020592Orig1s040s041

<u>MEDICAL REVIEW(S)</u>

DATE: July 18, 2008

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

TO: NDA 20-592/SE5-040 (bipolar I disorder, acute mania)
NDA 20-592/SE5-041 (schizophrenia)
(This overview should be filed with the 02-05-2008 submission in response to the
Agency's Approvable Letter dated 04-30-2007)

SUBJECT: Recommendation of an approvable action for use of Zyprexa (olanzapine) in the
treatment of 1) Bipolar I disorder, Mania, and 2) schizophrenia in Adolescents.

1.   BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic agent, approved in the U.S. for treatment of
schizophrenia and bipolar disorder, mania or mixed episodes, as monotherapy (both acute and
maintenance) or combination therapy in adults.   It is available as oral 2.5, 5, 10, 15, or 20 mg
strength tablets; 5, 10, 15, or 20 mg oral disintegrating tablets (Zydis).   The target dose for adults
with schizophrenia is 10 mg/day. Zyprexa intramuscular injection (10 mg) is indicated for agitation
associated with schizophrenia and Bipolar I Mania.

Currently, two atypical antipsychotic drugs, Risperdal and Abilify, are approved for treatment of
schizophrenia and bipolar disorder in the pediatric population.

In response to the Agency's written request (original 11/30/2001; amended 4/9/02, 7/3/02, 5/7/04,
6/29/05), the sponsor conducted clinical trials for two indications: schizophrenia (F1D-MC-HGIN)
and bipolar disorder (F1D-MC-HGIU) in adolescents, and submitted the study results to the above
referenced supplemental NDA on 10/30/2006.

The Agency issued an approvable letter (AE letter) on 4/30/07 asking the sponsor to provide
additional safety data analysis regarding risks of weight gain, hyperglycemia and hyperlipidemia in
patients taking Zyprexa. In the AE letter, we noted our intent to ensure that the Zyprexa label is
enhanced with the updated information to characterize these risks. We also requested the sponsor to
address the geographic discrepancy in the efficacy results between the US and Russia in adolescent
schizophrenia trial, and other information pertaining to high prolactin levels in adolescents. In
addition, we asked to provide the MedWatch reports for 4 fatalities.

The sponsor submitted their complete response to the AE letter on 02/05/2008. This submission
was reviewed by Cara Alfaro, Pharm.D. Clinical Analyst, DPP (review dated 07/14/2008). Evelyn

Mentari, M.D., Safety Medical Officer (review dated 07/15/2008) reviewed the additional analyses provided by the sponsor regarding the metabolic data. Sally Yasuda, Pharm.D., Safety Team Leader, provided a secondary review of the metabolic data and the sponsor's proposed Risk Minimization Plan (memo dated 07/17/2008).

2.0   CHEMISTRY

No new CMC information required for review in this submission. Dr. Nallaperun Chidambarm, Chemistry Team Leader from the ONDQA, stated that there were no CMC comments regarding the PLR conversion of the Zyprexa labeling included in this submission.

3.0   PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues required for review in this submission. Dr. Barry Rosloff, Supervisory Pharmacologist, provided his PLR labeling comments for the pharm/tox sections.

4.0   CLINICAL PHARMACOLOGY

Dr. Andre Jackson has provided labeling comments to reflect the adolescent PK findings (F1D-MC-HGMF) and also, for the clinical pharmacology sections in the PLR labeling.

5.0   CLINICAL DATA

5.1   Efficacy Data

As noted by Dr. Alfaro in her prior review, the sites in Russia appeared to drive the entire efficacy signal for the adolescent schizophrenia clinical trial (HGIN), primarily due to the very low placebo response in the sites in Russia.

The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$).

Study HGIN	Placebo	Olanzapine
USA	N=19	N=38
Mean Change From Baseline of BPRS-C Total (SD)	-15.0 (18.3)	-21.2 (16.3)
Russia	N=16	N=34
Mean Change From Baseline of BPRS-C Total (SD)	-2.6 (17.4)	-17.4 (14.5)

In our 04/30/2007 approvable letter, we had asked the sponsor for additional analyses (e.g. baseline illness characteristics) to evaluate potential differences between subjects enrolled in the US and Russian sites. In the sponsor's 02/05/2008 response to the AE letter, the sponsor provided details for further exploratory analyses including:

1. Between-country comparisons, comparison of baseline characteristics, and inclusion of significant baseline characteristics into the ANCOVA model
2. Analyses by country for disposition, effect size, response rate, modal dose, concomitant medication use, and weight gain

3. Visit-wise LOCF and OC mean change for BPRS-C total score by country
4. Analysis of treatment-by-country interaction and within-country effect for secondary efficacy measures
5. Evaluation of data from placebo-treated patients with therapeutic improvements similar to the olanzapine treatment magnitude

As Dr. Alfaro commented in her review dated 07/14/2008, no significant differences that might account for the low placebo response rate at the Russian sites was identified during review of these additional analyses.

In the 02/05/2008 response, the sponsor reiterated that discontinuation due to lack of efficacy was significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US (15.8% in olazapine; 42.1% in placebo; p = 0.049) and Russia (11.8% in olazapine; 62.5% in placebo; p < 0.001). The effect sizes were 0.63 for all patients, 0.32 for the US and 0.96 for the Russian patients. The mean modal doses were 13.2 mg for the U.S. and 11.8 mg for Russia. The sponsor also reiterated that the treatment-by-country interaction was not significant (p = 0.146).

Dr. Alfaro mentioned in her review that she also looked at the data from two recently approved drugs in adolescent population in the treatment of schizophrenia [i.e., for the aripiprazole (NDA 21-436/SE5-017) and risperidone (NDA 20-272/SE5-046) adolescent schizophrenia programs]. By comparing Russian data from these programs, Dr. Alfaro's concerns are seemed satisfactorily addressed.

5.2 Safety Data

Metabolic Effects

As stated in Dr. Mentari's safety review, the sponsor's additional analysis results and their labeling proposals for the Weight Gain, Hyperglycemia and Hyperlipidemia sections seemed adequately addressed our concerns on the issue.

There was statistically significant treatment emergent increase in lipid profile, glucose and weight in both olanzapine treated adults and adolescents as compared to placebo. It should be noted that the magnitude of mean changes from baseline was greater in adolescents treated with olanzapine than changes for the adults in total cholesterol, LDL and triglycerides. In addition, adolescents were likely to gain more weight and have greater increases in prolactin and hepatic transaminase levels.

Dr. Mentari recommended some further modification in the labeling for weight gain (adding description of data on treatment emergent glycosuria) and hyperglycemia sections to more clearly communicate the information in both adult and adolescent subsections. She also recommended fasting blood glucose testing and lipid profile at the beginning of and periodically during olanzapine treatment be added as part of the laboratory tests.

Additionally, Dr. Mentari noted that a proposal for a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide to be requested from the sponsor. The same was reflected by Dr. Yasuda in her secondary safety review memo. I agree with their recommendations, and we should ask the sponsor to do so.

Response to Other Additional Data: Hyperprolactinemia, Hepatic Analytes, AIMS analysis and Case Narratives

In Dr. Alfaro's review dated 07/14/08, she provided her item-by-item evaluation of the sponsor's response to the clinical safety questions imposed in the 04/30/2007 approvable letter. She reviewed results from additional requested analysis on prolactin, hepatic analytes and AIMS scores.

The sponsor provided additional analyses on the subset of patients with baseline prolactin within the normal range and also, a subgroup analysis for gender and age. The sponsor was asked to include the frequency of hyperprolactinemia in adolescents in the hyperprolactinemia section and the information was now included in the proposed labeling. In clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168). Dr. Alfaro recommends that these adverse events (gynecomastia and galactorrhea) should also be noted in the Adverse Events section of labeling. I have no objection to add these events. A greater percentage of adolescent subjects had treatment emergent increases in AST, ALT and alkaline phosphatase compared to adult subjects. The hepatic results are reflected in the sponsor's proposed labeling. Dr. Alfaro recommends no further labeling changes based on results of AIMS analysis provided in this submission.

She also reviewed case narratives of 8 cases of gynecomastia, 2 cases with elevated prolactin, and one CPK elevation case. Most of these cases were from the open-label studies. Based on the limited information provided, Dr. Alfaro's review of the 4 additional requested fatalities narratives from the MedWatch reports revealed that these subjects were on multiple concomitant medications. Based on her review of these requested case narratives, no further labeling changes was recommended.

Safety Update

In this submission, the sponsor provided an analysis of their database (Lilly Safety System) for spontaneously reported adverse events occurring from the time of product launch to May 31, 2007. Based on Dr. Alfaro's review this safety update, no new safety signals emerged that would require additional changes to product labeling.

Risk Minimization Plan (RMP)

The sponsor's proposed RMP includes routine pharmacovigilance of spontaneous case reports with target AEs, a long term open-label safety study (study F1D-MC-HCMX) and a pharmacoepidemiology study with retrospective cohort analysis of a large US health claims database to estimate the incidence and prevalence of diabetes mellitus and dyslipidemia among adolescent patients with schizophrenia or bipoloar disorder compared with the general adolescent population. The sponsor also states that the RMP would include the labeling and the product website which would provide advice on weight management and nutrition, and the Lilly Wellness Program which is a program of heath care professionals and patients education. The sponsor has not submitted the full protocol for study HCMX yet. Dr. Yasuda noted in her safety memo that we should ask the sponsor to submit a full protocol for review. The outcome of the Lilly Wellness Program in terms of random blood glucose or dyslipidemia has not been provided.

Given the metabolic safety profile observed with olanzapine, Drs. Alfaro, Mentari and Yasuda unanimously recommended the need to highlight to a larger extent of these metabolic risks in development of a Medication Guide for this product, and should ask the sponsor to do so. I am agreeing with them.

The OSE was consulted on this proposed risk management plan. The OSE would provide their input on the appropriateness of the RMP after the sponsor submits a complete response to the action letter.

5.3   Conclusion Regarding Overall Efficacy and Safety Data

I concur with Dr. Alfaro that the sponsor has adequately responded to our concern regarding the discrepancy in the efficacy data primarily driven by the differential placebo response between the United States and Russian sites in the schizophrenia study HGIN.

As mentioned before, significant safety signals that emerged in these adolescent clinical trial databases were a greater magnitude of weight gain, hypertriglyceridemia, hypercholesterolemia, hyperprolactinemia and transaminase elevations. These findings should be adequately described in the labeling. We will be asking the sponsor to develop a Medication Guide as well.

The greater metabolic risks observed in the adolescent population should be considered in our overall risk benefit evaluation. I concur with Dr. Alfaro's recommendation of olanzapine as a second-line treatment in adolescent schizophrenia and bipolar disorder given the greater metabolic risks and the morbidity associated with potential chronic use of this product in the patient population once approved.

As a second-line treatment of olanzapine for the acute treatment in adolescent schizophrenia and bipolar disorder, I have no further objection to giving as a similar statement as in recently approved other atypical psychotics that maintenance treatment effect may be extrapolated from adult data in the clinical studies section of the labeling.

6.0   WORLD LITERATURE

The sponsor provided a comprehensive literature review pertaining to the safety of olanzapine for the time period August 25, 2006 through May 31, 2007. The sponsor reported that adverse events and changes in laboratory parameters described in the citations are consistent with the types of adverse events reported for adult patients receiving olanzapine.

7.0   FOREIGN REGULATORY ACTION

According to the information provided by the sponsor in this submission, as of August 21, 2007, olanzapine has not been approved for pediatric use in any country.

8.0   PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take these supplemental NDA to the PDAC.

9.0   DSI INSPECTIONS

No additional DSI inspection requested. Refer to the DSI Clinical Inspection Summary from the first review cycle.

10.0   LABELING AND ACTION LETTER

Although there are some improvements in the labeling language by the sponsor, we have made further modifications so that all pertinent safety findings are clearly reflected in the labeling. Our modified version of draft labeling in the PLR format should be attached in our action letter.

11.0   CONCLUSION AND RECOMMENDATION

In my opinion, the sponsor has adequately addressed the issues noted in our 04/30/2007 approvable letter. I have no doubt about effectiveness of olanzapine in the treatment of schizophrenia and bipolar disorder in both adults and adolescents. However, a greater safety risk observed in adolescents treated with olanzapine in terms of significant weight gain and metabolic effects should be accounted in our risk-benefit determination. I concur with Dr. Alfaro that we should make olanzapine as a second-line treatment in the adolescent population. I also concur with Drs. Alfaro, Mentari and Yasuda that we should ask the sponsor to provide a proposal for a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide. Therefore, I recommend the Division issue a second approvable letter for this set of NDA supplements.

Cc: HFD-130/Laughren/Mathis/Alfaro/Grewal
File: NK/NDA20592/Memo_SE5_040041_peds_ResptoAEltr_07182008.doc

CLINICAL REVIEW

Application Type	NDA
	(Complete Response to Approvable Action)
Submission Number	020592
Submission Code	SE5 040/041
Letter Date	2/5/2008
Stamp Date	2/5/2008
PDUFA Goal Date	8/5/2008
Reviewer Name	Cara Alfaro, Pharm.D.
Review Completion Date	7/14/2008
Established Name	Olanzapine
Trade Name	Zyprexa
Therapeutic Class	Antipsychotic
Applicant	Eli Lilly & Co
Priority Designation	S
Formulation	Oral tablets
Dosing Regimen	2.5 – 5 mg starting, maximum dose 20 mg/day
Indications	Treatment of Bipolar I Disorder (040) and Schizophrenia (041)
Intended Population	Adolescents

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and SE5-041 "treatment of schizophrenia in adolescents". It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents including weight gain, hyperglycemia, hyperlipidemia, increases in hepatic analytes, and hyperprolactinemia. Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

1.2   Recommendation on Postmarketing Actions

1.2.1   Risk Management Activity

The Sponsor submitted a "risk management plan" document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

1.2.2   Required Phase 4 Commitments

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents). This study is being considered as a Phase 4 commitment. As of this time, the protocol for this study has not been submitted.
No additional Phase 4 commitments are recommended.

2   INTRODUCTION AND BACKGROUND

On 10/30/06, Eli Lilly and Company submitted NDA 20-592 SE5-040 and SE5-041 to support the indications "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and "treatment of schizophrenia in adolescents" respectively. An approvable action was taken 4/30/2007 and the Sponsor was asked to submit additional safety analyses as well as further exploration of the disparity in efficacy results between the US and Russian sites (largely driven by a very low placebo response in the Russian sites) in the pivotal adolescent schizophrenia trial (HGIN). The Sponsor was also asked to submit updated information on risks of weight gain, hyperglycemia and hyperlipidemia that would be reflected not only in Zyprexa labeling, but also in Symbyax labeling.

The Sponsor submitted a response on 8/30/2007, this response was considered incomplete (letter date 9/13/2007) since the submission did not include all requested data regarding the risks of weight gain, hyperglycemia and hyperlipidemia. The Sponsor submitted a response on 2/5/2008 and it was considered a complete response. For the purposes of this review, this reviewer is addressing the portions of the complete response pertaining to SE5-040 and SE5-041, specifically the questions posed to the Sponsor for issues relating to the pivotal trials for the bipolar and schizophrenia adolescent trials. Another clinical reviewer (Evelyn Mentari, M.D.) will be reviewing the requested safety information relating to risks of weight gain, hyperglycemia and hyperlipidemia for both adult and adolescent populations.

2.1 Brief Overview of Pivotal Trials HGIU and HGIN
Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar I disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Study HGIN was the pivotal trial for establishing efficacy and safety for the indication "treatment of schizophrenia in adolescent patients". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 6-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 72), or placebo (n = 35).

2.2 Summary Table of Clinical Trials in Original Submission

This summary table is included in this review as some of the Sponsor's responses included additional data from some of the supportive trials.

Study	Description	Length	Age Range (years)	Number of Patients
HGIN	MC, DB, PC study in adolescent patients with schizophrenia. Flexible dose olanzapine (2.5 – 20 mg) U.S. and Russia sites	6 weeks DB 26 weeks OL extension	13 to 17	107 (n = 72 olanzapine, n = 35 placebo)
HGIU	MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder. Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico	3 weeks DB 26 weeks OL extension	13 – 17	161 (n = 107 olanzapine, n = 54 placebo)
LOAY	OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders Flexible dose olanzapine (5 – 20 mg) German sites	24 weeks	12 – 21	96 (n = 89, 13-17 years)
HGMF	OL study in adolescent patients with schizophrenia or bipolar I disorder Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico, Russia	4.5 weeks	13 – 17	107 (n = 37 schizophrenia, n = 70 bipolar)
HGCS	OL study in adolescent patients with schizophrenia Dosing: 2.5 to 20 mg/day Single site	8 weeks	10 – 18	8
HGCR	DB study in adolescent patients with schizophrenia, haloperidol as active comparator Dosing: 2.5 qod – 20 mg/day Single site	8 weeks	12 – 16	2
HGGC	OL study in children and adolescents with bipolar disorder Dosing: 2.5 to 20 mg/day Single site (U.S.)	8 weeks	5 – 14	23

3. REQUESTS FOR INFORMATION

This section includes the requests for information that were outlined in the 4/30/2007 approvable letter, the Sponsor's response and reviewer's comments.

Table 3.1, below, is from the original NDA submission and defines the different databases used to address various safety signals. Some of the requests for information asked for reanalysis in the Overall Olanzapine Exposure Database.

Table 3.1. Sponsor's Table – Databases for Summary of Clinical Safety

Table 2.7.4.1. Databases for Summary of Clinical Safety

Database	Indication	Studies Used	Number of Patients
Acute Placebo-Controlled Databases	Schizophrenia	HGIN	N=107 (Olz=72, Pla=35)
	Bipolar	HGIU	N=161 (Olz=107, Pla=54)
	Combined	HGIN, HGIU	N=268 (Olz=179, Pla=89)
Overall Olanzapine Exposure Databases	Schizophrenia	HGIN, LOAY, HGMFa	N=227
	Bipolar	HGIU, HGMFa	N=227
	Combined	HGIN, HGIU, LOAY, HGMF	N=454

a   Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

3.1 Prolactin

Division Request #1

For the acute phases of HGIU and HGIN, many patients have elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses for the change from baseline to endpoint on the subset of patients with baseline prolactin within the normal range. Please also provide a separate analysis for gender and age.

Data Submitted in the Original Submission

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU[1]: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

In the original analysis of the HGIN + HGIU acute studies, the following change from baseline to endpoint in prolactin concentrations were provided (Table 3.1.1). However, this analysis included subjects with abnormal (usually elevated due to prior therapies) prolactin concentrations making a change from baseline difficult to interpret.

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[1] Covance did not have pediatric reference ranges for prolactin. The Sponsor obtained these reference ranges from the Tietz Textbook of Clinical Chemistry (Burtis CA and Ashwood ER 1999).

Table 3.1.1. Prolactin: Change from Baseline To Endpoint, All Subjects (HGIN + HGIU)

			Baseline		Change to Endpoint				
		N	Mean	Std	**Mean**	Std	LS Mean Change	LS Mean Difference	P-value
Prolactin (mcg/L)	Olanzapine	163	14.06	9.92	**11.44**	14.52	10.51		
	Placebo	80	14.95	11.86	**-0.16**	10.69	-1.15	11.66	< 0.001

The Sponsor also included a prolactin analysis by gender since it is well established that females have a more pronounced elevation in prolactin concentration with antipsychotic therapy.

Table 3.1.2. Prolactin Analysis by Gender

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                                                  Change to
                                      Baseline    Endpoint
                                      ----------- -----------  LSMean   LSMean
Laboratory
Evaluations        Gender   Therapy    N  Mean  Std   Mean  Std   Change   Difference    *P-value    **P-value
-----------------------------------------------------------------------------------------------------------

PROLACTIN          Female   Olz       63  15.87 10.06  15.63 16.86  14.26    14.25         <.001         .236
                            Placebo   37  15.25  7.59   1.35  9.20   0.00

                   Male     Olz      100  12.92  9.71   8.80 12.20   8.70    10.12         <.001
                            Placebo   43  14.70 14.67  -1.46 11.78  -1.42
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In the original analysis, the Sponsor did not provide a prolactin analysis by age.

Sponsor's Response
Seventy percent of olanzapine-treated subjects (114/163) and 71% of placebo-treated subjects (57/80) had normal baseline prolactin concentrations. Table 3.1.3 provides the reanalysis by the Sponsor including only those subjects with normal baseline prolactin levels.

Table 3.1.3. Prolactin: Change from Baseline To Endpoint, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

			Baseline		Change to Endpoint				
		N	Mean	Std	**Mean**	Std	LS Mean Change	LS Mean Difference	P-value
Prolactin (mcg/L)	Olanzapine	114	11.72	6.63	**12.98**	11.93	12.24		
	Placebo	57	12.07	6.34	**2.32**	7.30	1.48	10.76	< 0.001

From Sponsor table APP.1.1 in Regulatory Response document

Table 3.1.4. Prolactin Analysis by Gender and Age, Subjects with Normal Baseline Prolactin
(HGIN + HGIU)

Laboratory Evaluations	Subgroup	Group	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value	**P-value
PROLACTIN	Gender	Female	Olz	47	14.65	8.68	15.14	15.25	12.66	11.96	<.001	.574
			Placebo	29	15.14	7.21	3.19	8.98	0.70			
		Male	Olz	67	9.67	3.53	11.47	8.72	11.57	10.01	<.001	
			Placebo	28	8.90	2.99	1.41	5.01	1.56			
	Age	<15	Olz	46	12.02	6.37	14.70	13.60	11.15	14.86	<.001	.080
			Placebo	18	10.97	2.98	-0.22	3.72	-3.71			
		>=15	Olz	68	11.52	6.84	11.82	10.61	11.76	8.53	<.001	
			Placebo	39	12.58	7.38	3.49	8.24	3.23			

Reviewer Comments
In the reanalysis including only those subjects with normal baseline prolactin (Table 3.1.3), the
change from baseline to endpoint in olanzapine-treated subjects is slightly greater (12.98 mcg/L)
compared to the original analysis (11.44 mcg/L). However, change from baseline to endpoint in
placebo-treated subjects was also greater (2.32 mcg/L) compared to the original analysis (-0.16
mcg/L) such that the LS mean difference is lower in this analysis (10.76) compared to the
original analysis (11.66). Both analyses found these differences between treatment groups to be
statistically significant (p < 0.001).

For the gender analysis, the results from this reanalysis including only those subjects with
normal baseline prolactin concentrations was similar to the original analysis; however, the
change from baseline to endpoint in olanzapine-treated males was higher in this analysis (11.47
mcg/L) compared to the original analysis (8.80 mcg/L). The LS mean differences in this
analysis were less than the original analysis primarily due to an increase in change from baseline
to endpoint in placebo-treated subjects. The overall results are essentially the same – no
differential gender effects were noted; olanzapine increases prolactin concentrations to the same
degree in both male and female adolescents.

The Sponsor had not provided an age subgroup analysis in the original submission. This analysis
(including only those subjects with normal baseline prolactin concentrations) found a statistically
significant (p = 0.08) increase in prolactin concentrations in olanzapine-treated subjects < 15
years old compared to subjects ≥ 15 years old. Mean change from baseline to endpoint for
olanzapine-treated subjects < 15 years old was 14.7 mcg/L compared to 11.82 mcg/L in subjects
≥ 15 years old. It does appear, however, that the statistical differences may have been driven by
differences in the placebo-treated subjects: change in prolactin for subjects < 15 years old was -
0.22 mcg/L compared to 3.49 mcg/L for subjects ≥ 15 years old.

Division Request #2
Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall
combined database. Please provide a similar table for only those patients who completed 19-32

weeks in the study (n = 83 bipolar, n = 93 schizophrenia) – e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

Data Submitted in the Original Submission
In the original submission, the Sponsor had included prolactin concentrations for all subjects in the Overall Olanzapine Exposure Combined Database (see Table 3.1.5). However, it was difficult to evaluate patterns over time in subjects completing the trials since these data also included subjects who dropped out over the course of these trials. Therefore, the Sponsor was asked to provide these data only for subjects completing these trials in order to evaluate a potential pattern in prolactin concentration for subjects with exposures up to 6 -8 months.

Table 3.1.5 Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Olanzapine Exposure Combined Database

Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points
Overall Olanzapine Exposure Combined Database

Database	Olz Exposure	N	Summary Mean	Std	Median	Max
Bipolar	Baseline	217	15.35	12.58	11.28	110.30
	1-6 weeks	174	26.60	16.18	23.10	129.66
	7-18 weeks	122	19.24	11.89	16.71	59.49
	19-32 weeks	83	18.03	10.42	14.36	49.53
Schizophrenia	Baseline	214	18.84	19.97	11.87	131.57
	1-6 weeks	190	31.82	20.75	26.48	110.84
	7-18 weeks	88	22.75	16.24	18.62	112.00
	19-32 weeks	93	19.01	15.60	14.81	109.97
Overall	Baseline	431	17.08	16.74	11.60	131.57
	1-6 weeks	364	29.33	18.86	25.00	129.66
	7-18 weeks	210	20.71	13.95	17.13	112.00
	19-32 weeks	176	18.55	13.38	14.70	109.97

Sponsor's Response

Table 3.1.6. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database for Subjects Completing 19-32 weeks of Olanzapine Exposure

		Summary				
Database	Olz Exposure	N	Mean	Std	Median	Max
Bipolar	Baseline	83	12.91	8.04	10.36	37.41
	1-6 weeks	49	27.21	11.65	25.86	60.72
	7-18 weeks	83	18.88	10.78	17.11	59.49
	19-32 weeks	83	18.03	10.42	14.36	49.53
Schizophrenia	Baseline	93	18.03	17.37	11.98	100.00
	1-6 weeks	74	31.22	21.54	24.34	104.00
	7-18 weeks	55	20.03	11.60	16.83	54.11
	19-32 weeks	93	19.01	15.60	14.81	109.97
Overall	Baseline	176	15.62	13.98	11.17	100.00
	1-6 weeks	123	29.62	18.30	24.68	104.00
	7-18 weeks	138	19.34	11.09	16.87	59.49
	19-32 weeks	176	18.55	13.38	14.70	109.97

Reviewer Comments
For this reanalysis (as in the original analysis), sample sizes vary by timepoint likely due to differences in the various protocols. Similar to the original analysis, the increase in mean prolactin values appears to occur early (1-6 weeks) and decreases at subsequent timepoints; though still elevated compared to baseline concentrations. This analysis was requested so that data could be evaluated over time in the same group of subjects – however, obviously, if subjects dropped out of the study due to prolactin elevations (or other reasons but also had elevated prolactin concentrations), this analysis would not include those subjects and may underestimate the effect. However, the prior analysis did include all subjects and results between the analyses were very similar.

Proposed Language in Product Labeling re: Prolactin
The Sponsor was asked to include the frequency of hyperprolactinemia in adolescents in this section and also included this data for the adult populations.

Section 5 – WARNINGS AND PRECAUTIONS; 5.16 Hyperprolactinemia
"In clinical studies, plasma prolactin concentrations were elevated in 34% of adults treated with olanzapine. These elevations were mild and transient (end-point mean not above upper limits of normal and not statistically significantly different from placebo). Associated clinical manifestations (e.g. gynecomastia, galactorrhea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.
In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), elevated prolactin concentrations occurred in 47.4% of olanzapine-treated patients compared to 6.8% of patients in the placebo group."

This frequency data is also reflected in Section 6 ADVERSE REACTIONS, 6.2 Vital Signs and Laboratory Studies.

The frequency data do not indicate the magnitude of the elevations in prolactin, the adult data included in currently approved labeling also do not indicate the magnitude of prolactin elevation (only the frequency of occurrence). Unlike adverse events of weight gain or ALT increases, there is not a well recognized potentially clinically significant change in which to further categorize these increases. Therefore, it is reasonable to include only the frequencies of prolactin increases and then to note elsewhere in labeling adverse events that may be related to hyperprolactinemia.

Since the Sponsor has now included data about the frequency of potentially prolactin-related adverse events for adults, this data should also be included for adolescents – however, these effects are not rare in the latter population (refer to Sections 3.2 [Additional Narrative Summaries] and 4 [Safety Update] of review).

I would propose to add the following data which is from the original submission (Table 2.7.4.31 in summary-clin-safety document):

In clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168).

These adverse events (gynecomastia and galactorrhea) should also be noted in the section of labeling: 6 ADVERSE REACTIONS, 6.1 Clinical Trials Experience, Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine. These events would be considered frequent (based on the 1/100 definition).

3.2 Additional Narrative Summaries

Division Request #3

Please provide narrative summaries for the following: 8 cases of gynecomastia, 2 cases with high prolactin concentrations (HGIN 005-503, HGIN 900-9009) and the case with a CPK of 7289 U/L.

The Sponsor supplied the requested narratives. This reviewer compiled a table (Table 3.2.1) summarizing some of the relevant information for the cases of gynecomastia (7 cases, one subject experienced the adverse event twice).

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

Prolactin reference ranges for adolescents in study LOAY:
Males $\geq$ 12 but $\leq$ 13 years = 2.8 – 24 ng/ml; $\geq$ 14 but $\leq$ 16 years = 2.8 – 16.1 ng/ml; > 16 but $\leq$ 19 years = 2.1 – 17.7 ng/ml
Females $\geq$ 12 but $\leq$ 13 years = 2.5 – 16.9 ng/ml; $\geq$ 14 but $\leq$ 16 years = 4.2 – 29 ng/ml; > 16 but $\leq$ 19 years = 2.8 – 29.2 ng/ml

Table 3.2.1. Summary Table for Gynecomastia Cases

Patient ID	Demographics	Baseline Prolactin (mcg/L)	Prolactin During Study (mcg/L) *indicates prolactin at time of AE report	Clinical Description	Resolved?
HGIN-910-9103*	15 YOM	6.12	21.3 (~5 weeks)* 19.1 (3 months) 12.2 (7 months)	Left side gynecomastia (mild)	Ongoing at study completion
LOAY-400-4008	17 YOM	10.50	23.0 (~2 weeks)* 16.8 (1 month) 16.8 (2 months) 7.4 (6 months)	Gynecomastia (mild)	Ongoing at study completion
LOAY-400-4009	14 YOM	3.90	30 (2 weeks) 28 (3 weeks) 32 (5 weeks) NA* 41 (2 months)	Gynecomastia (moderate)	Noted at baseline visit. Severity changed to severe at 2 months. Ongoing at time of discontinuation.
LOAY-406-4063	17 YOM	5.50	25 (2 weeks) 36 (1 month) 34 (5 weeks) 30 (6 weeks)*	Gynecomastia (mild)	NA
LOAY-407-4074	17 YOM	9.50	23 (2 weeks) 24 (1 month) 20 (5 weeks) 12.80 (6 months)*	Gynecomastia (mild)	AE noted at last study visit
LOAY-407-4077	16 YOM	17.7	31 (2 weeks) 37 (1 month) 37 (6 weeks) 14.7 (7 months)*	Gynecomastia (mild)	AE noted at last study visit
LOAY-407-4201	16 YOM	17.3	27 (2 weeks) 24 (1 month)* 20 (6 weeks)* 28 (2 months)	Gynecomastia (mild)	Ongoing at study discontinuation.

* Sponsor indicates that 2 cases of gynecomastia occurred in this patient – the narrative indicates that the subject had these symptoms "periodically" since ~2 years prior to study participation. It is noteworthy that this subject had a prolactin concentration of 95.35 mcg/ml at Visit 1 (presumably screening visit).

Reviewer Comments
Seven subjects participating in the clinical trials for bipolar disorder and schizophrenia had an adverse event "gynecomastia". Interestingly, six of these subjects participated in the 24-week open label LOAY study conducted exclusively in Germany (these cases occurred at 3 different sites and 3 different investigators). These cases were associated with some elevations in prolactin concentration and most were considered by the investigators to be of mild severity. Though the narratives did not include vital sign data, this reviewer wanted to evaluate the weight gain in these subjects since fat deposition in the breast area, "pseudogynecomastia", might be mistaken as gynecomastia. Not surprisingly, these subjects gained a significant amount of weight over the course of these studies – from 9.1 to 24.6 kg over ~24 weeks (Table 3.2.2).

Table 3.2.2. Weight Changes in Subjects with the Adverse Event Gynecomastia

	Baseline		End of Study		Change from Baseline to Endpoint	
	Weight	BMI	Weight	BMI	Weight	BMI
HGIN-910-9103	58 kg	20.1	82 kg	28.4	24 kg	8.3
LOAY-400-4008	83.5 kg	24.7	108.1 kg	31.9	24.6 kg	7.2
LOAY-400-4009	66.6 kg	23.6	78.8 kg	27.9	12.2 kg	4.3
LOAY-406-4063	62.7 kg	20	71.8 kg	22.9	9.1 kg	2.9
LOAY-407-4074	65.9 kg	20.3	82.6 kg	25.5	16.7 kg	5.2
LOAY-407-4077	63.3 kg	19.8	82 kg	25.6	18.7 kg	5.8
LOAY-407-4201	65.5 kg	22.7	81.7 kg	28.3	16.2 kg	5.6

According to Harrison's medical textbook, gynecomastia is not uncommon in teenage boys with 65% of 14 year-old boys having gynecomastia that usually goes away on its own in 2 or 3 years (hormonally-related). However, the temporal association with olanzapine therapy may implicate the antipsychotic in this adverse event. These cases are not, however, associated with remarkably elevated prolactin concentrations (upper range of normal in males in this age range = 16 to 18 ng/ml for reference ranged used in LOAY) such that it is not clear that these were in fact cases of gynecomastia and may be cases of pseudogynecomastia secondary to significant weight gain. However, since the investigators used the term "gynecomastia" as an adverse event term for these cases, this reviewer will assume this to be correct (since it does not appear to have been queried by the Sponsor) and will recommend some labeling changes to reflect this information (see Section 3.1 [Prolactin] of review). It is not clear to this reviewer why the majority of these cases were from one clinical trial (LOAY).

Elevated Prolactin Cases
HGIN-005-0503 14 YOF. Baseline prolactin 17.2 mcg/L, increased to 90.68 mcg/L at ~6 weeks (no other labs available between these two values). Subsequent prolactin concentrations were 40.2 mcg/L at ~4.5 months and 45.5 mcg/L at ~7.5 months. The subject was receiving olanzapine 20 mg/day when the 90.68 and 45.5 mcg/L concentrations were obtained. No adverse events reported that were associated with elevated prolactin.

HGIN-900-9009 17 YOF. Baseline prolactin 17.5, elevation to 109.97 mcg/L noted at study completion (~8 months); prolactin concentration prior to this was 17.0 mcg/L at ~4 months. Subject was receiving olanzapine 10 mg/day when elevated concentration obtained. No adverse events associated with elevated prolactin were noted.

CPK Elevation Case
HGIN-004-0401 14 YOM. No baseline CPK available. Elevated CPK of 7289 U/L (reference range = 0 – 363 U/L noted one week after randomization – this was the highest CPK value obtained. CPKs were monitored weekly/monthly thereafter and ranged from 445 – 1766 U/L with no clear trend; last CPK noted as 781 U/L at ~8 months. CK-MB concentrations were obtained at some timepoints and most were elevated (5.2 – 10 ng/ml; reference range 0 – 4.9 ng/ml). Urine myoglobin obtained once (at ~2 months when CPK = 531 U/L) and was < 0.006.

Of note, the subject was receiving haloperidol decanoate prior to the study and, if narrative is correct, received his last dose approximately 9 days prior to randomization. No comments regarding extent of exercise or other potential contributing causes.

Reviewer Comments
This reviewer has recommended some labeling language to reflect the gynecomastia cases (see section 3.1 [Prolactin] of review).
The elevated prolactin cases appear to be related to olanzapine therapy and both occurred in female subjects who tend to have a more robust prolactin response to antipsychotics. These were the most significant elevations noted during the original review and appear to represent outliers. Per the Sponsor, there were no adverse events associated with the elevated prolactin, though it is not clear how this was determined (spontaneous reports vs. specific queries for prolactin-related adverse events).
The elevated CPK case was impressive and the highest value (7289 U/L0 was noted one week after randomization – it is possible that this could have been secondary to a haloperidol decanoate injection which appears to have been received 9 days prior to randomization (protocol violation). The CPK was consistently elevated over the course of the 8 month trial, though concentrations were quite variable.
No further labeling changes based on these additional cases (elevated prolactin and CPK) is recommended.

3.3 Hepatic Analytes
Division Request #4
The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes. Although it is stated in the submission that the hepatic laboratory analyte comparisons were not provided due to differences in reference ranges for adults and adolescents, these comparisons were provided for the prolactin data despite differences in reference ranges for these populations.

Sponsor's Response
The Sponsor provided the following data for mean change from baseline to endpoint in hepatic analytes using normalized units for comparing the adolescent and adult populations. Statistically significant, though small, changes were noted for alkaline phosphatase (adolescents > adults) and total bilirubin (decreases noted in both populations).

Table 3.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint in Hepatic Analytes
(Normalized Units). Comparison of Adult Versus Adolescent Patients (Overall Exposure
Database)

Laboratory Evaluations	Unit	Population	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
AST/SGOT	%URL	Adolescent	446	59.35	51.72	9.00	54.59	7.29	-0.81	.767
		Adult	7074	63.19	36.97	7.99	59.21	8.10		
ALT/SGPT	%URL	Adolescent	446	57.30	74.23	21.39	82.65	18.09	3.49	.520
		Adult	7084	66.00	57.78	14.39	115.43	14.60		
ALKALINE PHOSPHATASE	%URL	Adolescent	446	65.27	30.13	4.38	18.19	4.33	1.96	.019
		Adult	7132	65.59	20.42	2.37	17.36	2.37		
GGT (GGPT/SGGT/YGGT)	%URL	Adolescent	446	43.60	31.34	8.19	32.44	5.88	1.33	.582
		Adult	7051	54.40	52.99	4.40	51.93	4.54		
BILIRUBIN, TOTAL	umol/L	Adolescent	446	8.56	5.96	-1.12	4.60	-1.19	-0.94	<.001
		Adult	7182	8.71	5.22	-0.26	6.05	-0.25		

The Sponsor also provided an analysis for treatment-emergent abnormally high hepatic analyte
values (> 1X ULN) at anytime for adolescent and adult populations – the Sponsor did not include
these data for ALT $\geq$ 3x ULN. In general, a greater percentage of adolescent subjects had
increases in AST, ALT and alkaline phosphatase compared to adult subjects.

Table 3.3.2. Sponsor's Table. Treatment-Emergent Abnormally High Hepatic Analyte Values
(> 1X ULN) at Anytime, Adult versus Adolescents (Overall Exposure Database)

Laboratory Analyte	Direction	Population	N	n	(%)	*P-Value
AST/SGOT	High	Adolescent	418	127	30.4%	<.001
		Adult	6338	1459	23.0%	
ALT/SGPT	High	Adolescent	396	169	42.7%	<.001
		Adult	5891	1791	30.4%	
ALKALINE PHOSPHATASE	High	Adolescent	387	52	13.4%	<.001
		Adult	6655	469	7.0%	
GGT (GGPT/SGGT/YGGT)	High	Adolescent	432	34	7.9%	.136
		Adult	6292	642	10.2%	
BILIRUBIN, TOTAL	High	Adolescent	423	9	2.1%	.054
		Adult	7080	75	1.1%	

Reviewer Comments
The mean change from baseline to endpoint in hepatic analytes for adult versus adolescents
(including the open-label trials) did not indicate significant differences between these
populations. In contrast, the percentage of subjects experiencing an abnormally high hepatic
analyte concentration was generally higher for adolescents compared to adults; especially for
AST, ALT and alkaline phosphatase.

Proposed Language in Product Labeling re: Hepatic Analytes

The proposed labeling includes data from the placebo-controlled trials and indicates the increased incidence of elevations in ALT ($\geq$ 3x ULN) in adolescents compared to adults. This reviewer has no additional recommendations for further labeling based on these additional analyses.

In Section 5 Warnings and Precautions (5.12 Transaminase Elevations)
"In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from < 3 times the upper limit of normal at baseline to > 3 times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine".

In Section 6.2 Vital Signs and Laboratory Studies
"In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (> 3x ULN in patients with ALT at baseline < 3 X ULN) (12.1% vs. 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%)…"

3.4 Fatalities
Division Request #5
Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had "DRAFT" at the top of the page and the date of the report was 7/27/06. Have all of these reports been previously filed with the Agency?

Sponsor's Response
The Sponsor indicated that because these MedWatch forms were generated for the purposes of a submission dossier, they all showed the date that they were generated (7/27/06) and were marked "draft". The Sponsor also stated that all of the MedWatch forms for fatalities had been previously filed to NDA 20-592 (submission dates 12/16/97 to 5/19/06).

Reviewer Comments
No further information is requested.

Division Request #6

For MedWatch fatality case US_010158510, the narrative states "this is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in _____ (b) (6). The reported stated he has also notified the FDA…". The only MedWatch report included in this submission

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is for US_010158510. Please provide the MedWatch reports for the additional 4 deaths indicated in this narrative.

Sponsor's Response
The Sponsor stated that all these cases had been previously filed to NDA 20-592. The Sponsor included brief narrative summaries for these cases. This reviewer compiled a table summarizing data from these cases (Table 3.4.1). As with most MedWatch cases, these patients were taking numerous concomitant medications.

Table 3.4.1. Summary of Additional Requested Fatality Narratives

	Demographics	Olanzapine dose/duration	Diagnosis	Date of Death	Cause of Death
US_010158520	52 YOWF	20 mg ~1 year	MDD with psychotic features	(b) (6)	Unknown, found dead in home. No autopsy
US_010158524	29 YOWF	30 mg ~9 months	MDD with psychotic features	(b) (6)	Diabetic ketoacisosis
US_010158498	19 YOWM	5 mg ~7 weeks	Intermittent explosive disorder, antisocial PD	(b) (6)	Unknown
US_010158510	17 YOWM	2.5 mg not provided	Dysthymic disorder, schizophreniform disorder	(b) (6)	Accidental overdose vs. suicide
US_010158537	34 YOWF	30 mg ~9 months	Psychotic disorder	(b) (6)	Unknown, found dead in home. No autopsy. Coroner comments indicate possible narcotic overdose.

Reviewer Comments
It is difficult to interpret the relatedness of these fatalities to olanzapine therapy especially in light of the usual confounds inherent in MedWatch spontaneous reports. It is of interest that these cases were clustered in one geographic area with the majority occurring in 2000, but this could reflect reporting bias to some extent. It is troubling that there is very little data available for 3 of these cases – the narratives indicate that the Sponsor did attempt to obtain further information but was unable to do so.

3.5 AIMS Analysis
Division Request #7
Please provide an analysis of AIMS individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

This item was requested to evaluate potential emergent tardive dyskinesia for subjects who completed the long-term extension phases of the acute studies – since duration of antipsychotic use is a risk factor for development of this adverse event.

Sponsor's Response

Table 3.5.1. Sponsor's Table. Mean Change from Baseline to Endpoint in AIMS Scores. All Patients who Completed the Study – Overall Exposure Database.

EPS Variables	Database	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	*P-value
AIMS Non-Global Total(1-7)	Bipolar	129	0.06	0.35	-0.04	0.29	.132
	Schizophrenia	85	0.29	0.88	-0.22	0.88	.021
	Overall	214	0.15	0.63	-0.11	0.60	.007
AIMS Total(1-10)	Bipolar	129	0.10	0.50	-0.05	0.54	.332
	Schizophrenia	85	0.59	1.77	-0.51	1.76	.010
	Overall	214	0.29	1.20	-0.23	1.21	.006
AIMS Item 1 - Muscles of Facial Expression	Bipolar	129	0.00	0.00	0.01	0.09	.319
	Schizophrenia	85	0.11	0.44	-0.07	0.51	.203
	Overall	214	0.04	0.28	-0.02	0.33	.298
AIMS Item 2 - Lips and Perioral Area	Bipolar	129	0.00	0.00	0.00	0.00	
	Schizophrenia	85	0.04	0.19	-0.04	0.19	.083
	Overall	214	0.01	0.12	-0.01	0.12	.083
AIMS Item 3 - Jaw	Bipolar	129	0.01	0.09	-0.01	0.09	.319
	Schizophrenia	85	0.00	0.00	0.00	0.00	
	Overall	214	0.00	0.07	-0.00	0.07	.318
AIMS Item 4 - Tongue	Bipolar	129	0.02	0.12	-0.02	0.12	.158
	Schizophrenia	85	0.04	0.33	-0.04	0.33	.320
	Overall	214	0.02	0.23	-0.02	0.23	.132
AIMS Item 5 - Upper Extremity	Bipolar	129	0.01	0.09	0.00	0.12	1.00

EPS Variables	Database	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	*P-value
AIMS Item 5 - Upper Extremity	Schizophrenia	85	0.06	0.28	-0.05	0.30	.159
	Overall	214	0.03	0.19	-0.02	0.22	.207
AIMS Item 6 - Lower Extremity	Bipolar	129	0.02	0.12	-0.01	0.09	.319
	Schizophrenia	85	0.05	0.34	-0.04	0.36	.369
	Overall	214	0.03	0.24	-0.02	0.24	.249
AIMS Item 7 - Neck, Shoulders, Hips	Bipolar	129	0.02	0.12	-0.02	0.12	.158
	Schizophrenia	85	0.01	0.11	0.00	0.15	1.00
	Overall	214	0.01	0.12	-0.01	0.14	.318
AIMS Item 8 - Global Severity	Bipolar	129	0.00	0.00	0.01	0.09	.319
	Schizophrenia	85	0.13	0.48	-0.12	0.47	.024
	Overall	214	0.05	0.31	-0.04	0.31	.049
AIMS Item 9 - Global Incapacitation	Bipolar	129	0.00	0.00	0.00	0.00	
	Schizophrenia	85	0.05	0.21	-0.05	0.21	.045
	Overall	214	0.02	0.14	-0.02	0.14	.045
AIMS Item 10 - Patient's Awareness	Bipolar	129	0.04	0.19	-0.02	0.28	.529
	Schizophrenia	85	0.12	0.45	-0.12	0.45	.018
	Overall	214	0.07	0.32	-0.06	0.36	.023

Reviewer Comments
For the AIMS non-global (items 1-7), AIMS total (items 1-10) and most individual AIMS items, there was a decrease in score rating at endpoint compared to baseline for the bipolar, schizophrenia and overall (bipolar + schizophrenia) treatment groups. Based on this mean change analysis, there is no signal for increased risk of tardive dyskinesia in this dataset.

3.6 Disparity in Efficacy Results US vs. Russian Sites in HGIN

Division Request #8

One concern we have for study HGIN is a finding that the positive results for this trial appeared to come predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data from the Russian sites appeared to be driving the overall result. For the US patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -21 and -15 respectively (p = 0.258). For the Russian patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -17 and -3, respectively (p = 0.003). So, the treatment effect in olanzapine patients was roughly the same in both regions, however, the placebo response was much larger in the US sites compared to the Russian sites. Please address this geographic discrepancy in the efficacy results.

Sponsor's Response

The Sponsor provided details for further exploratory analyses including:
1. Between-country comparisons, comparison of baseline characteristics, and inclusion of significant baseline characteristics into the ANCOVA model
2. Analyses by country for disposition, effect size, response rate, modal dose, concomitant medication use, and weight gain
3. Visit-wise LOCF and observed case (OC) mean change for BPRS-C total score by country
4. Analysis of treatment-by-country interaction and within-country effect for secondary efficacy measures
5. Evaluation of data from placebo-treated patients with therapeutic improvements similar to the olanzapine treatment magnitude

The Sponsor also reiterated in this response that the treatment-by-country interaction was not significant (p = 0.146):
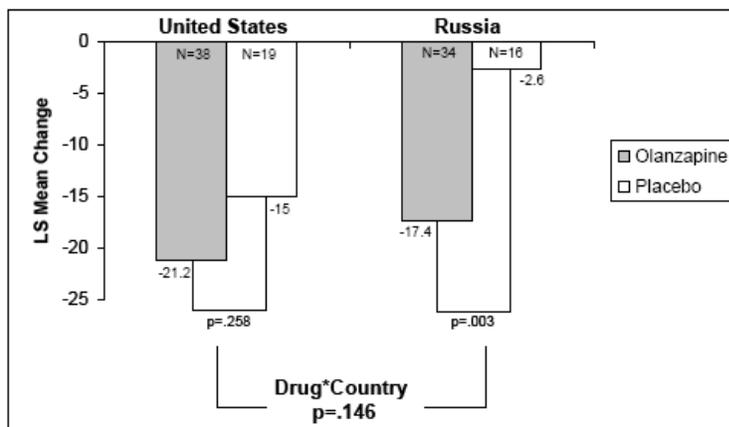
Abbreviation: LS = least-squares.
Source: CLOBPRA1, CLOBPRA4.

Figure APP.4.1. Brief Psychiatric Rating Scale for Children Total score mean change by country.

The Sponsor reiterated that discontinuation due to lack of efficacy was significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US (p = 0.049) and Russia (p < 0.001). "This result is supportive of the efficacy demonstrated with olanzapine treatment compared with placebo treatment in both countries."
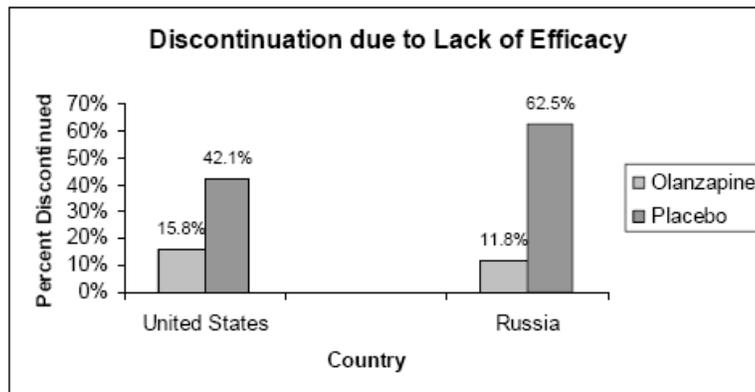
Source: INACMGA1.

Figure APP.4.2. Percentage of patients discontinuing due to lack of efficacy in the United States and Russia.

- The effect sizes were .63 for all patients, .32 for the US patients, and .96 for Russian patients.

- Protocol-defined response rate was not statistically different between the two treatment groups in either the United States (39.5% for olanzapine; 31.6% for placebo; p=.772) or in Russia (35.3% for olanzapine; 18.8% for placebo; p=.328).

- Use of concomitant benzodiazepine medication was not statistically significantly different in the United States (26.3% for olanzapine; 42.1% for placebo; p=.244) or in Russia (32.4% for olanzapine; 62.5 % for placebo; p=.066).

- The mean modal doses were calculated for patients in both countries. The mean modal doses were 13.2 mg for the United States and 11.8 for Russia.

Overall conclusion by Sponsor:

Despite numerous statistical and clinical evaluations, an explanation for the difference in placebo response between the United States and Russia remains unclear. It is possible that factors such as population heterogeneity or cultural availability of adjunct therapy may have influenced the placebo response, but this cannot be proven with the available data. Lilly believes that the lack of a clear explanation for the difference in placebo response in the two countries should be considered in light of the fact that a similar magnitude of efficacy response was observed for the olanzapine treatment group in both countries, and that the treatment-by-country interaction was not significant. Furthermore, the overall results of the trial are positive, and are consistent with the abundance of positive efficacy data for the use of olanzapine for the treatment of schizophrenia in adults.

Reviewer Comments
During the review of the original submission, this reviewer had asked the Sponsor for additional analyses (e.g. baseline illness characteristics) to evaluate potential differences between subjects enrolled in the US and Russian sites. No significant differences that might account for the low placebo response rate at the Russian sites was identified during review of these additional analyses.

Discontinuations Due to Lack of Efficacy
The Sponsor commented that the discontinuations due to lack of efficacy were significantly greater among placebo-treated patients compared with olanzapine-treated patients in both the US ($p = 0.049$) and Russia ($p < 0.001$) and that this result is supportive of the efficacy demonstrated with olanzapine treatment compared with placebo treatment in both countries. While this statement is true, the p-value for the US sites is marginally significant and could change depending on how you might categorize "lost to follow up" (1.4% in olanzapine group vs. 0% in placebo) and "patient decision" (5.6% in olanzapine group vs. 2.9% in placebo group). It bears mentioning that lack of efficacy, though different between the olanzapine and placebo groups, is the main reason for study discontinuation in both groups.

This reviewer also referred to the recent NDA submissions for the aripiprazole (NDA 21436 SE5-021) and risperidone (NDA 20272 SE5-046) adolescent schizophrenia programs (both recently granted approval actions). Though there are obvious limitations in comparing study HGIN to the pivotal trials for these other antipsychotics, there are certainly noteworthy differences with respect to several issues including discontinuations due to lack of efficacy:

Table 3.6.1. Subject Disposition: Adolescent Schizophrenia Pivotal Trials for Olanzapine, Aripiprazole, and Risperidone

	Sample Size	Discontinuation Rates	DC due to Lack of Efficacy	DC due to AE	Withdrew Consent/Patient Decision	Lost to Follow-up
Olanzapine	72	32%	13.9%	6.9%	5.6%	1.4%
Placebo	35	57%	51.4%	0	2.9%	0
Aripiprazole 10 mg	99	16%	5%	7%	4%	0
Aripiprazole 30 mg	97	18%	1%	3.9%	11.8%	0
Placebo	98	10%	1%	2%	5%	1%
Risperidone 1-3 mg	54	18%	5%	5%	5%	NA
Risperidone 4-6 mg	50	14%	2%	8%	2%	NA
Placebo	54	33%	24%	4%	4%	NA

Comparing across these trials, the overall discontinuation rates for the olanzapine study (HGIN) are much higher compared to the aripiprazole and risperidone pivotal trials. This disparity is also reflected in the discontinuations due to lack of efficacy across these trials including what appear to be significant differences between the olanzapine-treated subjects compared to aripiprazole or risperidone-treated subjects. However, the discontinuations due to lack of efficacy in the aripiprazole 30 mg group may be more similar to the olanzapine group depending on the definition of "withdrew consent".

Evaluating the Low Placebo Response in Russian Sites Compared to US Sites.

Table HGIN.14.21.   BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

```
                                                   Change to                              **P-value
                                        Baseline   Endpoint                               -----------
                                        --------   --------       LSMean    LSMean         (Therapy by
Efficacy Variable  Country  Therapy    N  Mean  Std   Mean   Std  Change    Diff.  *P-value Country )
-------------------------------------------------------------------------------------------------------

BPRS-C Total Score America  Olanzapine  38 53.18 10.10 -21.21 16.30 -20.89   -5.26   .258      .146
                            Placebo     19 51.42  8.64 -15.00 18.28 -15.64

                    Russia  Olanzapine  34 47.00  8.88 -17.41 14.55 -17.44  -14.95   .003
                            Placebo     16 48.50  8.52  -2.56 17.38  -2.49
```

Source: Original NDA submission

This reviewer again referred to the recent NDA submissions for the aripiprazole and risperidone adolescent schizophrenia programs to compare placebo response between the Russian sites in HGIN compared to the aripiprazole and risperidone pivotal schizophrenia trials. For these latter pivotal trials, the primary efficacy variable was the PANSS total score.

Approximately 32 % (93/294) of subjects in the aripiprazole pivotal trial were from US sites and 22% (64/294) from Russian sites (the remaining from Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Serbia, South Africa, south Korea and Ukraine). In the statistical analysis for this NDA, a separate subgroup analysis for the Russian sites was not performed by

the statistician. However, upon request from this reviewer, the statistician (Yeh Fong, Ph.D.) did provide an analysis of change from baseline for the Russian sites (Table 3.6.2). Contrary to the olanzapine pivotal trial (HGIN), the placebo response in the Russian sites was similar to the US sites (-17.8 vs. -23.7).

Table 3.6.2. Region Subgroup Analysis: Adolescent Schizophrenia Pivotal Trials for **Aripiprazole**

Table 7 Sponsor's Region Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
US			
Arip-10 mg (N=31)	Baseline	97.2 (16.5)	-31.4 (22.5)
	Last Visit (Week 6)	65.8 (21.8)	
Arip-30 mg (N=31)	Baseline	101.3 (15.1)	-30.7 (21.4)
	Last Visit (Week 6)	70.5 (24.1)	
Placebo (N=31)	Baseline	98.6 (17.0)	-23.7 (20.9)
	Last Visit (Week 6)	74.9 (26.8)	

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
Russia			
Arip-10 mg (N=21)	Baseline	91.14 (15.56)	-19.57 (21.70)
	Last Visit (Week 6)	71.57 (21.43)	
Arip-30 mg (N=25)	Baseline	88.28 (12.31)	-19.76 (16.77)
	Last Visit (Week 6)	68.52 (17.59)	
Placebo (N = 18)	Baseline	95.72 (13.46)	-17.83 (14.33)
	Last Visit (Week 6)	77.89 (11.67)	

Approximately 21 % (33/160) of subjects in the risperidone pivotal trial were from US sites and 23% (37/160) from Russian sites (the remaining from India and Ukraine). In the risperidone pivotal trial, the placebo response in the Russian sites is consistent with the olanzapine HGIN pivotal trial (Table 3.6.3). Interestingly, the risperidone change from baseline is also much lower in the Russian sites compared to the US sites.

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Table 3.6.3. Region Subgroup Analysis: Adolescent Schizophrenia Pivotal Trials for
Risperidone

Treatment	Change from Baseline to Endpoint LS Mean Change	P-value
Russia		
Risperidone 1-3 mg (N=12)	-9.29	0.23
Risperidone 4-6 mg (N=13)	-11.6	0.09
Placebo (N = 12)	-0.44	

Treatment	Change from Baseline to Endpoint LS Mean Change	P-value
United States		
Risperidone 1-3 mg (N= 12)	-29.2	0.030
Risperidone 4-6 mg (N= 11)	-27.7	0.046
Placebo (N = 10)	-11.1	

Overall, though the placebo response is quite low in the Russian sites in the olanzapine pivotal trial HGIN, a similarly low placebo response in Russian sites has been noted in similar studies in similar populations (risperidone) though not all (aripiprazole). This reviewer did not look at individual investigators or individual sites within Russia for any further comparisons.

Evaluating the Change from Baseline to Endpoint in Olanzapine Groups (US vs. Russia)
The Sponsor states that although the olanzapine vs. placebo comparisons were statistically significant for the Russian sites and not the US sites (primarily due to the low placebo response rate in the Russian sites), the change from baseline to endpoint in the olanzapine groups are similar between the these geographic sites. This reviewer agrees that the overall decrease from baseline to endpoint between the olanzapine groups in the US and Russian sites is similar. Again the overall statistically significant finding is largely driven by the low placebo response in the Russian sites and not due to disparities between the olanzapine groups. It is also entirely likely that, when the US sites are evaluated separately, there is insufficient power to detect a statistical difference. In efforts to further evaluate efficacy signals, this reviewer also looked at the adolescent schizophrenia pivotal trials for aripiprazole and risperidone. It should be noted that the primary efficacy variable in the pivotal trials for aripiprazole and risperidone was the PANSS total score. MMRM analyses were not available for the aripiprazole and risperidone pivotal trials.

In general, when comparing the change from baseline to endpoint in the olanzapine group in the US sites (-21.2), it is of a similar magnitude to changes from baseline in other antipsychotic clinical trials in similar populations (most of these clinical trials enrolled ~20% of subjects from

US sites). Since study HGIN used the BPRS as the primary endpoint whereas the aripiprazole and risperidone pivotal trials used the PANSS, a decrease of this magnitude in HGIN (-21.2) may be more significant given the higher baseline scores in the latter trials due to the differences in the BPRS and PANSS instruments.

It is noteworthy that, largely due to differences in subject discontinuation rates (see Table 3.6.1), the OC analyses for the aripiprazole and risperidone pivotal trials were statistically significant whereas the OC analysis for the olanzapine HGIN trial was not (Table 3.6.4). Due to the 2:1 randomization scheme in HGIN, only 35 subjects received placebo and 57% of subjects in the placebo group discontinued the study leaving 15 subjects for the OC analysis.

Table HGIN.14.21. BPRS-C Total Score
Mean Change from Baseline to Endpoint (LOCF) by Country
Double-Blind Period

Efficacy Variable	Country	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy by Country)
BPRS-C Total Score	America	Olanzapine	38	53.18	10.10	-21.21	16.30	-20.89	-5.26	.258	.146
		Placebo	19	51.42	8.64	-15.00	18.28	-15.64			
	Russia	Olanzapine	34	47.00	8.88	-17.41	14.55	-17.44	-14.95	.003	
		Placebo	16	48.50	8.52	-2.56	17.38	-2.49			

Table 3.6.4. LOCF and OC Analyses: Adolescent Schizophrenia Pivotal Trials for Olanzapine (US + Russian sites), Aripiprazole, and Risperidone

	Primary Endpoint	Baseline	Change from Baseline to Endpoint or LS Mean Change					
			LOCF analysis			OC analysis		
			Change	P-value	Sample Size	Change	P-value	Sample Size
Olanzapine	BPRS	50.3	-19.3	p = 0.003	72	-24.5	p = 0.947	50
Placebo		50.1	-9.1		35	-23.7		15
Aripiprazole 10 mg	PANSS	93.7	-26.7	p = 0.04	99	-30.6	p = 0.001	84
Aripiprazole 30 mg		94.9	-28.6	p = 0.006	97	-31.9	p = 0.0002	84
Placebo		95.0	-21.2		98	-22.3		90
Risperidone 1-3 mg	PANSS	95.4	-21.3	p < 0.001	54	-24.6	p < 0.001	44
Risperidone 4-6 mg		93	-21.2	p < 0.001	50	-24.5	p < 0.001	43
Placebo		93.2	-8.9		54	-13.6		35

Discrepancies in MMRM analyses depending on model chosen
The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C total score by LOCF analysis with OC and MMRM as supportive analyses. The LOCF analysis was statistically significant favoring olanzapine (LS mean difference = -10.12; p = 0.003) as was the MMRM analysis (LS mean difference = -8.90; p = 0.015). The OC analysis was not statistically significant (LS mean difference = -0.26; p = 0.947).

In his original review, the statistician had indicated that the MMRM analysis was not statistically significant based on his analysis (not the Sponsor's). In an addendum to his review, he indicated that he had used a different model for the MMRM analysis (default variance-covariance structure model) than the Sponsor had used (unstructured model); however, he indicated that the unstructured model was the most appropriate to use based on the fit of the data.
However, it should be noted that, based on the MMRM model, the p-values are very different:

Variance-covariance Structure	Placebo	Olanzapine	AIC
Variance Components			
LS Mean change from baseline (SE)	-24.1 (3.13)	-24.5 (1.73)	
Difference between LS Means and C.I.	-0.43 (-6.6,7.5)		
P-value	0.90		4691
Unstructured			
LS Mean change from baseline (SE)	-12.6 (2.99)	-21.5 (1.97)	
Difference between LS Means and C.I.	-8.9 (-16.0, -1.9)		
P-value	0.015		4055.2
Compound Symmetry			
LS Mean change from baseline (SE)	-17.8 (2.61)	-22.9 (1.60)	
Difference between LS Means and C.I.	-5.1 (-11.1, 0.9)		
P-value	0.10		4353.0
Toeplitz			
LS Mean change from baseline (SE)	-14.3 (2.68)	-21.9 (1.65)	
Difference between LS Means and C.I.	-7.67 (-13.8, -1.5)		
P-value	0.015		4129.0
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-21.7 (2.70)	-24.4 (1.53)	
Difference between LS Means and C.I.	-2.68 (-8.8, 3.4)		
P-value	0.39		4356.0
First Order Auto-regression			
LS Mean change from baseline (SE)	-15.4 (2.71)	-22.3 (1.64)	
Difference between LS Means and C.I.	-7.0 (-13.8, -0.8)		
P-value	0.029		4129.0

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Statistician's review – addendum to review

Evaluating the different MMRM models for the data for study HGIU (bipolar study) yields very consistent results with p-values ranging from < 0.0001 to 0.0004 (see Appendix). It appears that the MMRM analyses are very unstable for the schizophrenia data (HGIN) and are quite dependent on the specific MMRM model used in contrast to the very stable results for the bipolar data (HGIU). It should also be noted that the drop-out rates in the two studies were different with more subjects remaining in study HGIU – how this impacts the various MMRM models is beyond the expertise of this clinical reviewer. The OC analysis for study HGIU was statistically significant.

Since the Sponsor prespecified the LOCF as the primary analysis and the statistician agrees that the unstructured MMRM model is the most appropriate, it would appear that the Sponsor's data support efficacy of olanzapine versus placebo in study HGIN.

DSI inspections for Russian sites

Fifty subjects were enrolled in Russian sites – 10 subjects in each of 5 sites in Moscow. Upon query, the Sponsor indicated that the maximum number of subjects any one site could enroll was 10. 20 US sites enrolled 57 subjects (only one US site enrolled 10 subjects).

Because of the discrepancy in efficacy findings between the US and Russian sites, the Division requested that The Division of Scientific Investigations (DSI) inspect 2 Russian sites. The Moscow Research Institute of Psychiatry, Moscow, Russia; Valery Kransov, M.D. (principle investigator) was inspected between February 26 – March 2, 2007. The Moscow Medical University, Moscow, Russia; Leonid Bardenstein, M.D. (principle investigator) was inspected between February 19 – 22, 2007.

An audit of all subjects' records at these two sites was conducted and revealed few protocol violations. The overall conclusions of the DSI medical officer was that the study appeared to have been conducted adequately and the data generated by these sites may be used.

3.7 Other Issues

In this complete response document, the Sponsor included data comparing weight gain between the US and Russian sites:

- Comparison of weight gain in the 2 countries is illustrated in Figure APP.4.3. The significant differences between countries in weight do not explain the placebo effect difference seen within countries, but do suggest potential cultural differences in the two countries that may impact weight gain.
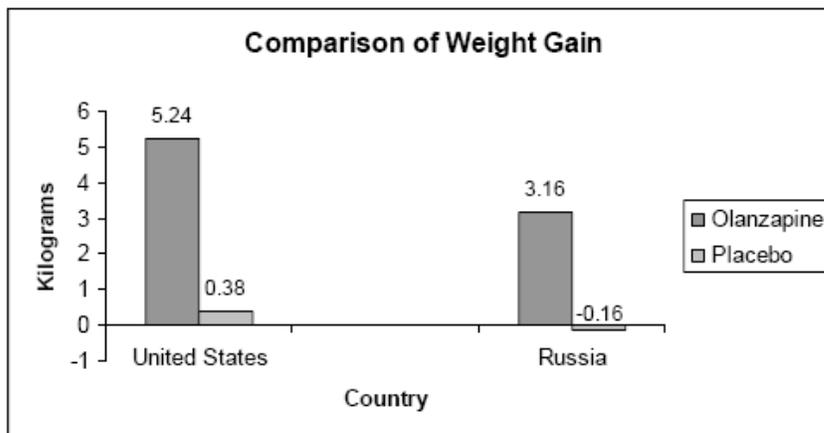
Source: INACMGA6.

Figure APP.4.3.   Comparison of weight gain in the United States and Russia.

For the HGIN study (US + Russian sites), the increase in weight was 4.26 kg in the olanzapine group and 0.13 kg in the placebo group. The Sponsor did not include additional weight analyses between these geographic sites such as % of subjects having $\geq$ 7% weight gain. However, these

data do indicate a difference in the magnitude of weight gain in the US and Russian populations. The currently proposed labeling with regard to weight gain does not differentiate between these populations and the Sponsor was not asked to perform separate analyses for differences in geographic sites for the adult data either. However, the important issue of weight gain is being evaluated by another clinical reviewer and significant changes to proposed labeling are being made to further highlight this issue for both the adult and adolescent populations - though these data may underestimate the weight gain in the US population.

4.   SAFETY UPDATE

The Sponsor provided an analysis of their database (Lilly Safety System) for spontaneously reported adverse events occurring from the time of product launch to May 31, 2007. The purpose of the review was to identify differences in the safety information between adolescent and adult patients treated with olanzapine.

As in the original submission, a proportional reporting ratio (PRR) and Chi-square value were calculated to compare the frequency of adverse event reports between the adolescent and adult populations. The Sponsor indicated the following general guidelines that may indicate an adverse event signal: at least 3 reports, a PRR > 2 and a Chi-square > 4.

The following table includes adverse events that indicate an increased frequency in the adolescent compared to the adult populations, again, based on spontaneous reports. It is noteworthy that galactorrhea occurs more frequently in the adolescent population and is further evidence that this adverse event should be included in product labeling (as recommended in section 3.1 of review).

The Sponsor commented that when evaluated the cases of aggression, some reported a history of the event, some reported use of concomitant medications, some of the events were considered to be disease-related, and some cases lacked sufficient information for an evaluation.

Table 6.   Adverse Events Reported with a PRR ≥2 in Olanzapine-Treated Patients Aged 13-17 Years Compared with Events Reported in Patients Aged 18-64 Years, with a Proportion of the Event of Interest ≥1.0% of All Events Reported in Patients Aged 13-17 Years, and with a Chi-Square Value ≥4

MedDRA Preferred Term (# of events in patients 13-17 years)	Proportion of Event in Patients 13-17 years (%) (N=3,754 events)	Proportion of Event in Patients 18-64 years (%) (N=85,420 events)	PRR[a]	Chi-Square Value
Somnolence (118)	3.14	1.40	2.24	73.69
Aggression (47)	1.25	0.29	4.38	102.90
Galactorrhoea (43)	1.15	0.31	3.72	73.51
Sedation (40)	1. 07	0.41	2.62	35.80

[a]   Ratio of event proportion in patients aged 13-17 years to event proportion in patients aged 18-64 years.

Based on this safety update, no new safety signals emerged that would require additional changes to product labeling.

5. LITERATURE UPDATE

A worldwide literature search was conducted for the time period August 25, 2006 through May 31, 2007 using Ovid Embase and Ovid Medline. Per the Sponsor, all resulting articles were reviewed by a Lilly clinical research physician. The Sponsor indicated that the adverse events and changes in laboratory parameters described in the citations are consistent with the types of adverse events reported for adult patients receiving olanzapine.

6. FOREIGN REGULATORY UPDATE

As of August 21, 2007, olanzapine has not been approved for pediatric use in any country.

7. STUDIES TO BE CONDUCTED IN ADOLESCENTS

In the Risk Management Plan document, the Sponsor indicated that they would be conducting a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects.

The Sponsor provided a very brief synopsis of this safety study. The primary objective of this study is to evaluate the long-term safety of oral olanzapine in these adolescent populations. The study will enroll _____ (b) (4) patients recruited at sites in the US and possibly other countries. Measurements to be included in the protocol are assessment of body weight, reported adverse events, vital signs, ECG parameters, and clinical laboratory tests including hepatic enzymes, insulin, fasting glucose, fasting lipids (total cholesterol, LDL and HDL cholesterol, triglycerides), and prolactin. The secondary objectives are to evaluate efficacy of olanzapine in these adolescent populations as well as the effect of an intervention program on weight gain.

The protocol for this study has not yet been submitted to the Division for review.

8. OVERALL ASSESSMENT

8.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents" and SE5-041 "treatment of schizophrenia in adolescents". It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and

reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents including weight gain, hyperglycemia, hyperlipidemia, increases in hepatic analytes, and hyperprolactinemia. Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

8.2 Recommendation on Postmarketing Actions

8.2.1 Risk Management Activity

The Sponsor submitted a "risk management plan" document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

8.2.2 Required Phase 4 Commitments

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents). This study is being considered as a Phase 4 commitment. As of this time, the protocols for this study has not been submitted.
No additional Phase 4 commitments are recommended.

9   APPENDICES

9.1 MMRM Analyses for HGIU (Bipolar Study)

**Table 1 MMRM Analysis Results Using Different Variance-Covariance Structure
in Study HGIU (Without Country in Model)**

Variance-covariance Structure	Placebo	Olanzapine	AIC
Sample Size	54	105	
Variance Components (Default)			
LS Mean change from baseline (SE)	-11.3 (1.33)	-16.9 (0.86)	
Difference between LS Means and C.I.	-5.6 (-8.7,-2.5)		
P-value	0.0004		4171.5
Unstructured			
LS Mean change from baseline (SE)	-9.4 (1.37)	-16.4 (0.92)	
Difference between LS Means and C.I.	-6.9 (-10.2, -3.7)		
P-value	<0.0001		3994.6
Compound Symmetry			
LS Mean change from baseline (SE)	-10.3 (1.26)	-16.8 (0.84)	
Difference between LS Means and C.I.	-6.4 (-9.4, -3.5)		
P-value	<0.0001		4038.2
Toeplitz			
LS Mean change from baseline (SE)	-9.6 (1.26)	-16.4 (0.84)	
Difference between LS Means and C.I.	-6.8 (-9.8, -3.8)		
P-value	<0.0001		4005.7
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-9.9 (1.25)	-16.6 (0.82)	
Difference between LS Means and C.I.	-6.7 (-9.6, -3.7)		
P-value	<0.0001		4043.2
First Order Auto-regression			
LS Mean change from baseline (SE)	-9.6 (1.26)	-16.4 (0.84)	
Difference between LS Means and C.I.	-6.8 (-9.8, -3.9)		
P-value	<0.0001		4003.4

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment,
visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Statistician, upon request

```
 /s/
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Cara Alfaro
7/14/2008 12:33:38 PM
PHARMACIST



Ni Aye Khin
7/18/2008 09:57:26 AM
MEDICAL OFFICER
I concur with Dr. Alfaro's recommendations; see memo to
file for additional comments.
```

Review and Evaluation of Clinical Data - **Addendum**

Application Type: NDA 20-592
Submission Number: S-041 SE5
Established Name: Olanzapine (Zyprexa)
Therapeutic Class: Antipsychotic
Indication: Treatment of schizophrenia in adolescent patients
Letter Date: 10/30/06
Stamp Date: 10/31/06
Priority Designation: P
PDUFA Goal Date: 4/30/07
Reviewer: Cara Alfaro, Pharm.D.
Date: 5/19/07

Background
This is an addendum to the Clinical Review of NDA 20-592 S-041 SE5 that was completed (signed off) on 4/18/07. Prior to the action date of this NDA, a conference call was held to discuss issues related to this NDA. During this discussion, it was mentioned that the MMRM analysis conducted by the statistical reviewer was not statistically significant ($p = 0.72$) while the MMRM analysis conducted by the Sponsor was statistically significant ($p = 0.015$). The statistical reviewer was not able to explain the discrepancy and was going to recheck his analysis.

This addendum describes the results of the statistician's reanalysis as well as an additional analysis requested by this reviewer. It is noteworthy that this new information did not alter the final recommendation of this reviewer for a not approvable action (though the Division did take a different action).

MMRM Analysis
The primary analysis for this submission was the LOCF analysis for the BPRS-C total score mean change from baseline at endpoint. The Sponsor included OC and MMRM as secondary analyses for this primary endpoint.

The results from the Sponsor's analyses are in the table below:

		N	Baseline		Change to Endpoint				
			Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
LOCF	Olanzapine	72	50.3	10.0	-19.4	15.5	-19.3		
	Placebo	35	50.1	8.6	-9.3	18.7	-9.1	-10.1	0.003
OC	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.4		
	Placebo	15	49.0	8.5	-23.7	14.6	-24.1	-0.26	0.947
MMRM	Olanzapine	50	50.6	10.6	-24.5	13.5	-21.3		
	Placebo	15	49.0	8.5	-23.7	14.6	-12.4	-8.90	0.015

The results from the MMRM analysis conducted by the statistician (Fanhui Kong) are as follows*:

| | | N | Baseline | | Change to Endpoint | | | | |
			Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
MMRM	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.7		
	Placebo	15	49.0	8.5	-23.7	14.6	-23.5	-1.25	0.72

*In the addendum to Dr. Kong's review, a recalculation of this MMRM analysis provided a p-value of 0.90

In the addendum to Dr. Kong's review, he stated that the reason for the discrepancy between MMRM analyses was due to the different models/assumptions used for these calculations. In his investigation of the different models, Dr. Kong did indicate that the best fit for the data was the unstructured variance-covariance model which the Sponsor used and that yielded significant results. However, it is also noteworthy that the results of the various MMRM analyses are quite variable and not consistent yielding p-values from 0.015 to 0.90 and LS mean differences ranging from -0.43 to -8.9 (table from Dr. Kong's addendum):

Table 2.1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIN

Variance-covariance Structure	Placebo	Olanzapine	AIC
Variance Components			
LS Mean change from baseline (SE)	-24.1 (3.13)	-24.5 (1.73)	
Difference between LS Means and C.I.	-0.43 (-6.6,7.5)		
P-value	0.90		4691
Unstructured			
LS Mean change from baseline (SE)	-12.6 (2.99)	-21.5 (1.97)	
Difference between LS Means and C.I.	-8.9 (-16.0, -1.9)		
P-value	0.015		4055.2
Compound Symmetry			
LS Mean change from baseline (SE)	-17.8 (2.61)	-22.9 (1.60)	
Difference between LS Means and C.I.	-5.1 (-11.1, 0.9)		
P-value	0.10		4353.0
Toeplitz			
LS Mean change from baseline (SE)	-14.3 (2.68)	-21.9 (1.65)	
Difference between LS Means and C.I.	-7.67 (-13.8, -1.5)		
P-value	0.015		4129.0
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-21.7 (2.70)	-24.4 (1.53)	
Difference between LS Means and C.I.	-2.68 (-8.8, 3.4)		
P-value	0.39		4356.0
First Order Auto-regression			
LS Mean change from baseline (SE)	-15.4 (2.71)	-22.3 (1.64)	
Difference between LS Means and C.I.	-7.0 (-13.8, -0.8)		
P-value	0.029		4129.0

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

One of the reasons that this reviewer recommended a not approvable action was the disparity between results from the U.S. and Russia sites. The Sponsor included the LOCF analysis for evaluation of the primary endpoint between the two geographic regions, but did not include companion OC or MMRM analyses. This reviewer asked Dr. Kong to perform an MMRM analysis between the U.S. and Russia sites (table from Dr. Kong's addendum):

Table 2.2 Treatment Effect by Country by MMRM Analysis

Country	Placebo	Olanzapine
Russia		
N (Number of patients)	16	34
LS Mean change from baseline (SE)	-5.3 (4.46)	-19.0 (2.73)
Difference between LS Means and C.I.	-13.7 (-23.9,3.3)	
P-value	0.012	
US		
N (Number of patients)	19	35
LS Mean change from baseline (SE)	-18.7 (4.13)	-23.5 (2.89)
Difference between LS Means and C.I.	-4.8 (-14.7, -5.1)	
P-value	0.35	

While exploratory in nature, this analysis is consistent with the LOCF analysis – robust findings in the Russia sites and not the U.S. sites.

Due to the inconsistent findings in the various MMRM analyses performed by Dr. Kong for study HGIN, this reviewer asked him to perform similar MMRM analyses for the HGIU study (SE5-040, bipolar disorder in adolescent patients) since the LOCF, OC and MMRM analyses performed by the Sponsor were consistent and statistically significant. Dr. Kong provided the summary table below (this table is not included in Dr. Kong's addendum). It is noteworthy that the different MMRM analyses for HGIU were consistent and robustly positive – in contrast to the inconsistent findings for these same analyses for study HGIN.

**Table 1 MMRM Analysis Results Using Different Variance-Covariance Structure
in Study HGIU (Without Country in Model)**

Variance-covariance Structure	Placebo	Olanzapine	AIC
Sample Size	54	105	
Variance Components (Default)			
LS Mean change from baseline (SE)	-11.3 (1.33) │ -16.9 (0.86)		
Difference between LS Means and C.I.	-5.6 (-8.7,-2.5)		
P-value	0.0004		4171.5
Unstructured			
LS Mean change from baseline (SE)	-9.4 (1.37) │ -16.4 (0.92)		
Difference between LS Means and C.I.	-6.9 (-10.2, -3.7)		
P-value	<0.0001		3994.6
Compound Symmetry			
LS Mean change from baseline (SE)	-10.3 (1.26) │ -16.8 (0.84)		
Difference between LS Means and C.I.	-6.4 (-9.4, -3.5)		
P-value	<0.0001		4038.2
Toeplitz			
LS Mean change from baseline (SE)	-9.6 (1.26) │ -16.4 (0.84)		
Difference between LS Means and C.I.	-6.8 (-9.8, -3.8)		
P-value	<0.0001		4005.7
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-9.9 (1.25) │ -16.6 (0.82)		
Difference between LS Means and C.I.	-6.7 (-9.6, -3.7)		
P-value	<0.0001		4043.2
First Order Auto-regression			
LS Mean change from baseline (SE)	-9.6 (1.26) │ -16.4 (0.84)		
Difference between LS Means and C.I.	-6.8 (-9.8, -3.9)		
P-value	<0.0001		4003.4

Note: Test for no difference between treatments at the endpoint from MMRM model with
treatment, visit and the interaction of treatment and visit as factors and baseline efficacy
measure as covariate.

Conclusions
This reviewer continues to be troubled by the disparity in the results of the statistical analyses between the U.S. and Russia sites. While the overall LOCF and MMRM were positive, these results are largely driven by the Russia sites. It is noteworthy that of the various MMRM analyses that were performed by the statistician, results range from a p-value of 0.015 to 0.90 and LS mean differences ranging from -0.43 to -8.9. However, when the statistician performed this same set of MMRM analyses on the data from HGIU (a study in which the LOCF, OC and MMRM analyses were significant), the results were consistent and robust.

It is unclear why there is such a disparity in the efficacy results between the U.S. and Russia sites. While the Sponsor did include the LOCF analysis evaluating the efficacy endpoint between the U.S. and Russia sites, there is no further discussion on the disparate findings. The Sponsor has been asked to address this issue in the action letter.

Cara Alfaro, Pharm.D.
Clinical Reviewer
May 19, 2007

Cc: Khin/Bates/Laughren/Alfaro

 /s/

Cara Alfaro
5/19/2007 04:02:20 PM
PHARMACIST

Ni Aye Khin
5/21/2007 07:37:22 PM
MEDICAL OFFICER

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

DATE: April 29, 2007

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

SUBJECT: Recommendation for approvable actions for Zyprexa Pediatric Supplements for bipolar disorder (acute mania) and schizophrenia

TO: File NDA 20-592 (S-040 [bipolar] and S-041 [schizophrenia])
[Note: This overview should be filed with the 10-30-06 original submission of these supplements.]

1.0   BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic (5HT2 and D2 receptor antagonist) that is approved for both schizophrenia and bipolar disorder in adults, including maintenance claims for both. We issued a written request (WR) for both indications, and these supplements are a response to that WR. The 10-30-06 response includes the results from acute studies in mania (HGIU) and schizophrenia (HGIN), and also pediatric PK data from study HGMF.

2.0   CHEMISTRY

The only CMC issue requiring review was environmental assessment. The sponsor sought and was granted a categorical exclusion.

3.0   PHARMACOLOGY

There were no pharm/tox issues requiring review for these supplements.

4.0   BIOPHARMACEUTICS

The sponsor utilized pk data from a formal pk study (HGMF) and also from 3 other studies (HGCS, HGCR, and HGGC) to characterize olanzapine pk in adolescents. Based on these data,

they concluded that overall olanzapine pk was similar in adolescents and adults, and that the one observed difference was greater exposure (by 27%) due to lower weights. Dr. Jackson from OCP agreed, except that he felt that the increased exposure by 27% was an underestimate. He estimated that exposure was increased by about 30-63%. This difference has resulted in a slight modification to the labeling regarding exposure.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on 2 short-term, multicenter, double-blind, placebo-controlled, flexible-dose (2.5 to 20 mg/day), randomized, efficacy and safety studies in adolescents (ages 13-17). One of these studies was in patients with acute mania in bipolar I disorder (HGIU) and the other in schizophrenia (HGIN).

5.1.1 Study HGIU (Acute Mania in Bipolar I Disorder)

This was a 3-week study in bipolar I disorder patients with acute manic or mixed episodes. It was mostly conducted in the US (23 sites) but had 2 sites in Puerto Rico as well. N=161 patients were randomized, and the randomization was 2:1 for olanzapine vs placebo. The mean modal olanzapine dose was 10.7 mg, and the mean daily dose was 8.9 mg. The overall dropouts for this trial favored olanzapine (20% for olanzapine vs 35% for placebo). Of these, the dropouts were mostly for lack of efficacy (11% for olanzapine vs 30% for placebo). The primary endpoint was change from baseline to endpoint on an Adolescent Structured YMRS (total score) and the primary analysis was ANCOVA (LOCF). The results on this analysis were highly favorable to olanzapine ($p < 0.0001$), as were the results for the MMRM (p=0.0004) and the OC (p=0.0013). Drs. Alfaro, Kong, and Khin all considered this a positive study, and I agree.

5.1.2 Study HGIN (Acute Schizophrenia)

This was a 6-week study in adolescent patients with schizophrenia. It was conducted partly in the US (20 sites, comprising 53% of the total sample) and partly in Russia (5 sites, comprising 47% of the total sample). N=107 patients were randomized, and the randomization was 2:1 for olanzapine vs placebo. The mean modal olanzapine dose was 12.5 mg, and the mean daily dose was 11.1 mg. The overall dropouts for this trial again favored olanzapine (32% for olanzapine vs 57% for placebo). Of these, the efficacy dropouts were most striking, with a 51% loss due to lack of efficacy for placebo compared to only 14% for olanzapine. This finding by itself is almost enough, in my view, to convince one of the benefits of olanzapine in this condition. The primary endpoint was change from baseline to endpoint on a children's version of the BPRS (BPRS-C) total score, and the primary analysis was ANCOVA (LOCF). The overall results on this analysis were highly favorable to olanzapine (p = 0.003). However, there were 2 aspects to the data that the review team found troubling, resulting in conclusions by Drs. Alfaro, Kong, and Khin that this should be considered a negative study. Their concerns were as follows:

Highly Non-Significant Results on the MMRM and OC Analyses

Dr. Kong conducted an MMRM analysis as a sensitivity analysis, which yielded a p-value of 0.72. An OC analysis was also highly non-significant result (p=0.95).

> Comment: In my tertiary evaluation, I found this discrepancy between LOCF and MMRM quite unusual, in my experience, and asked for further exploration. As it turned out, Dr. Kong's MMRM analysis was quite discrepant with the sponsor's MMRM analysis (p=0.015). Upon further evaluation, Dr. Kong discovered that the program he had used to conduct the analysis included, as a default, a variance-covariance structure that required independence between the repeated observations for any subject. This is an unusual requirement, and not the variance-covariance structure that we generally recommend. In fact, we almost always recommend an unstructured variance-covariance structure, i.e., the same one used by the sponsor, and a goodness-of-fit exploration for different variance-covariance structures revealed the best fit for this structure. Thus the biometrics group has now recommended that we accept the sponsor's highly significant MMRM result (see addendum to original biometrics review).
>
> Regarding the OC analysis, this remains a discrepancy with the LOCF and the revised MMRM analyses. However, I am not as troubled by this outcome on the OC analysis. As noted, the dropouts on placebo were very substantial, and I'm inclined to view the patients completing a study such as this to 6 weeks on placebo as quite different than the remaining patients. I think the diagnosis of schizophrenia in this younger population is challenging, and likely results in the inclusion of some patients who improve spontaneously, and thus, are doing as well as drug-treated patients at 6 weeks simply because they represent a very different group of patients. This, I think the OC results for this trial can be largely discounted.

Treatment by Geographic Region Interaction

A second problem for the review team was a finding that the positive results were coming predominantly from the Russian sites. For this study, the total sample was roughly split between these 2 regions. Although olanzapine was favored over placebo numerically in both regions, the data from the Russian sites appeared to be driving the overall result:
> -For the US patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -21 and -15, respectively (p=0.258).
> -For the Russian patients, the mean changes from baseline on the BPRS-C for olanzapine and placebo were -17 and -3, respectively (p=0.003).
> -So the treatment effect in olanzapine patients was roughly the same in both regions, however, the placebo response was much larger in the US sites compared to the Russian sites.

Comment: In addition to the difference in outcome by region, Dr. Alfaro expressed concern that the Russian sites were far more successful in recruiting patients than the US sites. Implicit in such a concern is a suggestion of a problem in study conduct. It is important to note that we did have DSI inspect the Russian sites, and they found no evidence for fraud. It is also important to point out that there are alternative explanations for more successful recruitment at the Russian sites and also a more successful outcome. The sites may have been drawing patients from larger catchment areas than US sites, many of which were single investigators. There also may have been less competition for patients than is the case in the US. There are numerous studies ongoing in the US, and routine treatment is likely also more readily available in the US than in Russia. These same factors may also explain the different results. If difficulty in recruitment in the US sites led to enrollment of a more heterogeneous group of subjects, this could have led to a higher placebo response rate. It is possible that the Russian patients were the more representative schizophrenic patients who typically have very little response to placebo. There is also the expressed concern about relying primarily on non-US data for an approval action. Although I agree this is generally a concern, I think it is more a concern for an initial claim than it is in this case, where we already have a very strong prior belief that olanzapine is an effective treatment for schizophrenia, based on an abundance of positive data in adults. In summary, while I agree this geographic discrepancy is a concern, I do not think it is, by itself, a sufficient justification for a nonapproval action, when the trial is positive overall on the primary analysis and on the MMRM. Nevertheless, we will ask the sponsor to further address our concern about this discrepancy.

5.1.3 Summary of Efficacy

There is unanimous agreement within the review team on the positive outcome for study HGIU. For study HGIN, I disagree with the review team on the recommendation for a nonapproval action. One of the concerns, namely Dr. Kong's original finding on the MMRM, has now been addressed, and we are in agreement that an appropriate MMRM analysis yields a highly significant outcome. On the issue of geographic differences in outcome, I disagree that this is of sufficient concern to justify a nonapproval action. Nevertheless, we will ask the sponsor to further address this concern.

5.2 Safety Data

Safety data for these supplements were derived from the 2 pivotal controlled trials (HGIU and HGIN), and also from studies LOAY and HGMF. The combined total for these studies was n=454 patients, and this included 89 placebo patients from the 2 controlled trials. Thus, there were 365 olanzapine-exposed patients in this safety database. This included 136 patients who were treated with olanzapine for at least 23 weeks.

There were no deaths among the olanzapine-exposed patients. There were 44 serious adverse events, the majority of which represented a worsening of psychiatric symptoms. Overall, the profile of common and drug-related adverse events included events already well-recognized for olanzapine, i.e, increased appetite and weight gain, somnolence, sedation, fatigue, dizziness, and dry mouth. Other findings included the following:

  -<u>Weight Gain</u>: For the 2 short-term trials (HGIU and HGIN), olanzapine patients gained almost 4 kg more than placebo patients ($p<0.001$). Almost 44% of olanzapine patients gained > 7% of their body weight compared to only 7% of placebo patients ($p<0.001$).

  -<u>Transaminase Increases</u>: For the 2 short-term trials (HGIU and HGIN), 12% of olanzapine patients compared to only 2% of placebo patients had ALT increases to > 3xULN ($p=0.009$). None of these patients had bilirubin abnormalities, and transaminase elevation is a well-known finding for olanzapine.

  -<u>Hyperprolactinemia</u>: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in prolactin of 11.44 mcg/L compared to a decrease of -0.16 mcg/L for placebo ($p<0.001$).

  -<u>Hyperlipidemia</u>: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in triglycerides of 29.2 mg/dL compared to a decrease of -4.4 mg/dL for placebo ($p<0.001$). For total cholesterol, olanzapine patients had a mean increase from baseline of 13.1 mg/dL compared to a decrease of -1.2 mg/dL for placebo ($p<0.001$).

  -<u>Hyperglycemia</u>: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in fasting glucose of 2.7 mg/dL compared to a decrease of -2.9 mg/dL for placebo ($p<0.001$).

  -<u>Heart Rate Increase</u>: For the 2 short-term trials (HGIU and HGIN), olanzapine patients had a mean increase from baseline in heart rate of 6.3 bpm compared to a decrease of 5.1 bpm for placebo. These changes were thought to be related to orthostatic changes seen with olanzapine, especially early in treatment.

<u>Summary of Safety Experience with Olanzapine in Adolescents</u>: Overall, the adverse event profile and other safety parameters for olanzapine in the adolescent population is similar to that seen in adult patients treated with this drug, however, with some differences in magnitude. These differences will need to be reflected in labeling. In addition, we have recently asked the sponsor to provide more complete information generally with regard to effects on weight, glucose regulation, and lipid levels so that labeling for olanzapine can be enhanced with regard to these risks.

5.3   Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would add important new information to the existing database regarding the safety of olanzapine in the treatment of schizophrenia or bipolar disorder in adolescents.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, olanzapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in adolescents.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 US sites and at 2 Russian sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included an extensively modified version of labeling with the approvable letter.

10.2 Foreign Labeling

Olanzapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in adolescents.

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for additional data.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that olanzapine is effective and acceptably safe in the treatment of adolescents with schizophrenia and acute mania/mixed episodes in bipolar disorder. However, before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling.

cc:
Orig NDA 20-592/S-040 and 041
HFD-130/TLaughren/MMathis/NKhin/CAlfaro/KKiedrow/DBates/SHardeman

DOC: Zyprexa_Peds_Laughren_AE_Memo.doc

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

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 /s/
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Thomas Laughren
4/29/2007 10:55:29 AM
MEDICAL OFFICER
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DATE: April 18, 2007

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

TO: NDA 20-592/SE5-040 (bipolar I disorder, acute mania)
NDA 20-592/SE5-041 (schizophrenia)
(This overview should be filed with the 10-30-2006 submission)

SUBJECT: Zyprexa (olanzapine)
Recommendation of 1) an approvable action - treatment of bipolar I disorder, acute mania in adolescents; and 2) a non-approvable action - treatment of schizophrenia in adolescents.

1.   BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic agent, approved in the U.S. for treatment of schizophrenia and bipolar disorder, mania or mixed episodes, as monotherapy (both acute and maintenance) or combination therapy in adults.   It is available as oral 2.5, 5, 10, 15, or 20 mg strength tablets; 5, 10, 15, or 20 mg oral disintegrating tablets (Zydis).   The usual oral dose range is 10-20 mg/day. Zyprexa intramuscular injection is indicated for agitation associated with schizophrenia and Bipolar I Mania. The recommended dose in these patients is 10 mg injection. Currently, none of the available atypical antipsychotic drugs are approved for treatment of schizophrenia or bipolar disorder in adolescents.

The Agency has issued a written request on 11/30/2001 under 505A(c) [patent or exclusivity protection] that the sponsor to conduct clinical trials for two indications: schizophrenia and bipolar disorder in adolescents. It was further amended on 4/9/02 (timeframe to submit study reports by 11/30/2006), 7/3/02 [informing notification requirement to the FDA when pediatric studies be initiated or not agree to conduct the requested studies according to the BPCA provision new section 505(d)(4)(A)], 5/7/04 (to include ethnic and racial minorities in accordance to the BPCA) and 6/29/05 (conduct as acute inpatient or outpatient trial).

The sponsor submitted the above referenced supplemental NDAs for schizophrenia and bipolar claim in adolescents on 10/30/2006. The application included the efficacy and safety result from protocols F1D-MC-HGIN and F1D-MC-HGIU for schizophrenia and bipolar indications, respectively. In addition, the sponsor also included PK results from study F1D-MC-HGMF.

The data submitted was reviewed by Cara Alfaro, Pharm.D., Clinical Reviewer, DPP (review dated 4/6/2007), Andre Jackson, Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology (review dated 3/27/07) and Fanhui Kong, Ph.D., Statistics Reviewer, Office of Biostatistics (review dated

4/6/2007).   An environmental assessment review (dated 1/17/2007) was performed by Janice Brown, Ph.D., Office of New Drug Quality Assessment.

2.0   CHEMISTRY

No new CMC information required for review in this submission except environmental assessment issues. A categorical exclusion was requested and granted.

3.0   PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues required for review in this submission.

4.0   CLINICAL PHARMACOLOGY

Based on results from study F1D-MC-HGMF (Study HGMF) and other existing adolescent pharmacokinetic data from studies F1D-MC-HGCS, F1DMCHGCR, F1D-MC-HGGC, and F1D-SB-LOAY, the sponsor submitted a study report in which olanzapine pharmacokinetics in adolescents was characterized. I would refer to Dr. Jackson's review for detail.

In brief, the sponsor reported that olanzapine pharmacokinetics was similar in adolescents and adults. The sponsor also claimed in their proposed labeling that   (b) (4)

However, Dr. Jackson noted that due to the poor quality of the prediction of the true steady-state values with the model, only the observed range of steady-state values was used. As Dr. Jackson pointed out in his review that in clinical studies, most adolescents had a lower average body weight compared to adults, resulting in an average range of olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients. Dr. Jackson provided labeling comments to reflect these findings.

5.0   CLINICAL DATA

5.1   Efficacy Data

5.1.1   Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the result of two short-term double-blind, placebo-controlled, randomized, efficacy and safety studies of olanzapine: one in the treatment of the adolescents (ages 13 to 17) with schizophrenia (Study HGIN); and the other study in the treatment of the adolescents with Bipolar I Disorder, Acute Mania or Mixed Episodes (Study HGIU).

The sponsor indicated that the result of each study supported for the treatment claim. Both Drs. Alfaro and Kong in their reviews indicated that only study HGIU support the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not seem to provide data to support the effectiveness claim of olanzapine in the treatment of schizophrenia in adolescents.

I would briefly describe the study design and then discuss the primary efficacy analysis results in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

5.1.2.1 Study F1D-MC-HGIN (Schizophrenia)

This study was a multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescent with schizophrenia, with a 6-week acute period. The primary objective of this study was to assess the efficacy and safety of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents with schizophrenia. After the screening and washout period (2-14 days), subjects were randomized to receive treatment with either olanzapine or placebo for up to 6 weeks of double-blind treatment.

The study was conducted in 20 U.S. centers which enrolled 53% of the study population; and in 5 Russian centers which enrolled 47% of the study population. One hundred and fifteen subjects entered the study. Of these, 107 (72 to olanzapine and 35 to placebo) were randomized and 64 subjects (49 to olanzapine and 15 to placebo) completed the acute phase of the study. Lack of efficacy was the most common reason for early termination in both groups: 18 (51%) patients for the placebo group; and 10 (14%) in the olanzapine group. 7.9% of study patients discontinued due to an adverse event.

Seventy two percent (N=77) of the patients were Caucasian; 22% were Africa-Americans; and 3% Hispanics. Seventy percent (N=75) were male and 30% (N=32) were female. 66% (N=71) were between 12 and 16 years and 33.6% (N=36) were 17 yrs of age; mean age of 16.1 yrs. There was no difference in demographic and baseline disease characteristics between the olanzapine and placebo groups.

The primary efficacy endpoint was the change from baseline to endpoint (up to 6 weeks double-blind treatment) in the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with covariate baseline scores, treatment and country factors. The protocol allowed interim analysis that the interim analysis result consistent with the final analysis results at α=.0294 level. According to the sponsor, there was no interim analysis conducted. Dr. Kong confirmed the primary efficacy results on LOCF dataset. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on BPRS Total Scores for Study HGIN in ITT population (LOCF):

	Mean Baseline BPRS (SD)	LS Mean Change from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=72	50.3	-19.3 (1.91)	-10.1 (-16.7, -3.5); p=0.003
Placebo N=35	50.1	-9.1 (2.73)	

Efficacy Results on BPRS Total Scores for Study HGIN (MMRM):

	Mean Baseline BPRS (SD)	LS MeanChange from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=72	50.3	-24.7 (1.70)	-1.25 (-8.11, 5.61); p=0.72
Placebo N=35	50.1	-23.5 (3.06)	

Efficacy Results on BPRS Total Scores for Study HGIN (OC):

	Mean Baseline BPRS (SD)	LS MeanChange from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=50	50.3	-24.4 (1.82)	-0.25 (-7.9, 7.4); p=0.95
Placebo N=15	50.1	-24.1 (3.35)	

According to Dr. Kong's assessments, there does not seem to have an advantage of olazapine over placebo. Both the OC and MMRM showed highly non-significant results. Although the LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. Given the high percentages of patient dropout as indicated in Drs. Kong and Alfaro's reviews, there seemed an impact on reliability of efficacy result in this study. Dr. Kong noted in his review that olanzapine reduced the BPRS-C total score in both the dropout group and the non-dropouts groups, while placebo reduced the score only in the non-dropouts group, not in the dropouts group. Although this phenomenon was observed in both US and Russia, the primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia (p = 0.003) but not the sites in the United States (p = 0.258). As Dr. Alfaro pointed out in her review, the sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia (see also section 5.1.3. Treatment Effect by Country).

Comment:

Both Drs. Alfaro and Kong did not consider this study as a positive study for olanzapine in treatment of schizophrenia in adolescents, and I agree with them.

5.1.2.2 Study F1D-MC-HGIU (Bipolar I Disorder)

This study was a multicenter, randomized, double-blind, placebo-controlled, flexible dose study of olanzapine (2.5 to 20mg/day) in adolescents with Bipolar I Disorder, acute mania or mixed episodes. After the screening and washout period (2-14 days), subjects were randomized to receive treatment with either olanzapine or placebo for 3 weeks of double blind treatment.

The study was conducted in 23 centers in the Unites States and 2 centers in Puerto Rico. Two hundred and three subjects entered the study. Of these, 161 (107 to olanzapine and 54 to placebo) were randomized and 120 subjects (85 in olanzapine and 35 in placebo) completed the acute phase of the study. The most common reason for the early withdrawal in both treatment groups was the lack of efficacy which had a total of 28 subjects (17.4%): 16 patients in the placebo group and 12. The difference between the two treatment groups is statistically significant (p=0.007). 14.5% of study patients discontinued due to an adverse event.

Seventy percent (N=112) of the patients were Caucasian, 16% (N=26) Hispanics and 9% (N=15) were Africa-Americans. More than half were male (N=85). 81% were between 12 and 16 years of age and 9.3% (N=15) were 17 yrs of age; mean age of 15.1 yrs. There was no difference in demographic characteristics between the olanzapine and placebo groups at baseline. The treatment groups, however, differed at baseline on measures of disease characteristics. Patients in the placebo group had greater numbers of previous manic, depressive, and mixed episodes. Patients in the olanzapine treatment group had much higher baseline scores on the CGI Severity for Depression;

more numbers reported in terms of history of psychiatric hospitalizations and paternal history of psychosis.

The primary efficacy endpoint was change from baseline to endpoint in the Adolescent Structured Young-Mania Rating Scale (YMRS) total score. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with covariate baseline scores, treatment and country factors. Dr. Kong confirmed the primary efficacy results on LOCF dataset. He also applied MMRM as a sensitivity analysis.

Efficacy Results on YMRS Total Scores for Study HGIU in ITT population (LOCF):

	Mean Baseline BPRS (SD)	LS Mean Change from Baseline (SD)	Difference between LS Means and C.I.; P-values (vs. placebo)
Olanzapine N=105	33.1	-17.8 (0.87)	-7.7 (-10.7, -4.6); p<0.0001
Placebo N=54	32	-10 (1.53)	

Both MMRM and OC showed similar results, p=0.0004 and p=0.0013, respectively.

Comment:

Both Drs. Alfaro and Kong consider this study as a positive study for efficacy of olanzapine in treatment of bipolar I disorder, acute mania, in adolescents. I agree with them.

5.1.3   Comments on Other Important Efficacy Issues

Dose Response Relationship
Since both studies conducted were flexible dose (2.5 to 20 mg olanzapine) trials by design, there is no adequate data to address dose response for efficacy. The mean daily dose of olanzapine was 8.9 mg and in bipolar study and in schizophrenia study was 11.1 mg.

Treatment Effect by Country
The primary endpoint of schizophrenia study HGIN, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia (p = 0.003) but not the sites in the United States (p = 0.258). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Study HGIN	Placebo	Olanzapine
USA	N=19	N=38
Mean Change From Baseline of BPRS-C Total (SD)	-15.0 (18.3)	-21.2 (16.3)
Russia	N=16	N=34
Mean Change From Baseline of BPRS-C Total (SD)	-2.6 (17.4)	-17.4 (14.5)

There were about 89% patients in US and only 11% patients in Puerto Rico in bipolar study HGIU.

Predictors of Efficacy in Subgroup Populations
Exploratory analyses in order to detect subgroup interactions on the basis of gender (M,F), age (<15 yrs, ≥15 yrs) and race (Caucasian, non-Caucasian).   As stated in Dr. Kong's review, there were no

statistically significant effects in any of these subgroups in both studies although the effect was numerically larger in males compared to females; and in ≥15 yr age group than <15 yrs.

Duration of Treatment
The studies conducted were for short-term use of Olanzapine in the treatment of adolescent schizophrenia and bipolar disorder. There is no data pertinent to the long-term efficacy in this submission. Since these disorders are chronic illnesses, it would be good to have data from a longer term study. However, Olanzapine is approved for maintenance treatment in adults with schizophrenia or bipolar disorder. We could infer the efficacy data from adult maintenance trials to adolescent population. According to the 05-30-2002 meeting minute, we agreed to grant a waiver for bipolar maintenance studies in adolescents.

5.1.4 Conclusions Regarding Efficacy Data

I concur with both Drs. Kong and Alfaro's recommendation and conclusion that the data from study HGIN did not seem to support the schizophrenia claim; and that results from study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with acute mania in Bipolar I Disorder.

5.2 Safety Data

5.2.1 Safety Database

Dr. Alfaro's safety review was based on an integrated database covering Acute Database from both pivotal double-blind studies (HGIN - 6weeks; and HGIU – 3 weeks) ; and the Overall Combined Database from the 26 week open label extension phase of HGIN and HGIU, other open label studies (HGMF and LOAY). A total of 268 patients (179 olanzapine; 89 placebo) were enrolled in the Acute Placebo-Controlled Database and 454 patients were included in the Overall Combined Database. Total exposure of olanzapine in adolescents was 48,946 patient-days.

As requested in the Written Request letter, there were sufficient numbers of adolescents enrolled in the 26 week open label phase that followed the double blind trials. Eighty-two subjects from the bipolar study HGIU received olanzapine during this open-label phase for > 23 weeks (n = 30, 23-26 weeks; n = 52, > 26 weeks). Fifty-four subjects from the schizophrenia study HGIN received olanzapine during this open-label phase for > 23 weeks (n = 19, 23-26 weeks; n = 35, > 26 weeks).

There were no deaths reported in the olanzapine treatment group in the double-blind studies. A total of 7 SAE reported; 6 patients in the olanzapine treatment arm in the Acute Database for weight increased, migraine, arm fracture, worsening of bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the overall combined database. The majority of these SAEs, 19/35 patients, were listed as worsening of existing psychiatric disorder (schizophrenia, bipolar disorder).

The sponsor also reported data from the postmarketing safety database including 2359 case reports in patients 13 to 17 years of age. There were 27 deaths in the adolescent age group based on the post marketing spontaneous MedWatch reports and the published literature. Based on the limited information provided in these reports, 15 of the cases occurred in the US. Seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus,

diabetic coma or diabetic ketoacidosis. Based on the proportion of events (%) in patients 13-17 yrs potential safety signals reported by the sponsor included weight increased, overdose, fatigue, ALT increase, diabetes mellitus and increased appetite.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). In the double-blind studies, the most common AEs were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (24%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies HGIN and HGIU.

In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to < 5% of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

5.2.2.2 Weight Gain

The following table summarizes the significant mean weight changes by mean change in weight to endpoint, mean change in BMI to endpoint and % of patients with ≥ 7% increase in body weight based on the results obtained from the two double-blind studies. Similar results were obtained for OC.

	Olanzapine	Placebo	LS Mean Diff	P-value
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
BMI Mean Change to Endpoint (LOCF)	1.22	0.05	1.17	< 0.001
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001

A significant mean weight changes from baseline by mean change in weight to endpoint (7.35 Kg), mean change in BMI to endpoint (2.31) and % of patients with ≥ 7% increase in body weight (65%) based on the results from the overall combined database including the open label studies.

For each double-blind study, mean change in weight (kg) was evaluated between the subgroups gender and age. No statistical significant differences were noted between these subgroups. The change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for olanzapine group in study HGIN.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months.

5.2.2.3 Abnormal Laboratory Tests

Liver function tests

The percentage of adolescent patients with ALT baseline $\leq$ 3x ULN who had ALT > 3x ULN at any time during the acute double blind studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).   The percentage was higher compared to the finding in adults (i.e., 2% in olanzapine group). Six patients discontinued HGIN and HGIU due to increases in liver transaminases (ALT).   Four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and two in the placebo group. Six subjects in olanzapine group discontinued due to elevated liver enzymes. There were no subjects who had ALT $\geq$ 3x ULN and TBili $\geq$ 1.5 x ULN.

Comment: The sponsor proposed these LFT abnormalities in adolescents as part of the transaminase elevations subsection under the Warnings/Precautions section of the labeling. I consider this as a reasonable proposal. In the adolescent section, I concur with Dr. Alfaro's recommendation to include the number of patients who discontinued due to elevations in LFTs in the labeling.

Lipid profile (Hypertriglyceridemia, Hypercholesterolemia)

The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, p < 0.001). There were 11 marked outliers noted for elevated triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) (p = 0.039).

The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, p < 0.001). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) (p = 0.023).

Comment: The sponsor proposed labeling changes in this submission, the finding on cholesterol and triglyceride was placed in the Adverse Reactions, laboratory changes subsections.   I believe the finding on lipids should be placed more prominently in the labeling. Given other significant findings on weight, liver enzymes and glucose are part of the Warning/Precautions in the labeling, we should consider placing this topic in the same section.

Hyperglycemia

The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, p < 0.001). Regarding the percentage of patients with shifts from normal (< 100 mg/dL) to high fasting glucose, it was not significantly different between olanzapine (0/122) and placebo (1/51).   Similarly, the percentage of patients with changes in fasting glucose from impaired glucose tolerance ($\geq$ 100 mg/dL and < 126 mg/dL) to high ($\geq$ 126 mg/dL) fasting glucose was not statistically different between olanzapine (2/13) and placebo (0/13).

In the Acute Database, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes). There was no change from baseline to endpoint in this parameter.

Comment: In this adolescent population, olanzapine did not appear to be associated with significant hyperglycemia. This finding could be attributable to initial development of insulin resistance in younger age group before actual increase in glucose level is observed. The finding on HbA1c was not unexpected either since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months.

Current Zyprexa labeling contains standard warning language on hyperglycemia and diabetes for atypical antipsychotics. The sponsor did not propose any changes to this warning section. Given the finding that the adolescent population experienced significant weight gain, it is important that sufficient information on these risks needs to be described in the labeling. Recently, the Division has asked the sponsor to provide more data on the glucose and lipid findings with Zyprexa in our March 28, 2007 approvable letter for Symbyax in treatment resistant depression and in our January 12, 2007 letter regarding the New York Times story. The sponsor has not adequately addressed to our concerns on these issues yet. We should reference these two letters in our action letter.

Hyperprolactinemia

Based on the acute database from the two double-blind studies, the mean change from baseline to endpoint in prolactin was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days. In study HGIN, 17% (11/64) of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The mean prolactin concentration at the end of study was 55.8 ± 15.8 ng/ml. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study.

It was noted that many patients had elevated prolactin at baseline. For those patients with normal baseline, it was found that 47.4% of patients in the olanzapine group had a treatment-emergent high prolactin concentration at anytime compared to 6.8% of patients in the placebo group (p < 0.001). No significant treatment by gender interaction on prolactin level was found.

Gynecomastia occurred in 1 (0.9%) patient in the olanzapine group and no patients in the placebo group and amenorrhea occurred in no patients in the olanzapine group and 1 (2.4%) patient in the placebo group. As Dr. Alfaro stated in her review, the Overall Combined Database was evaluated since adverse events such as gynecomastia are not expected to occur with acute use but rather more long term use of antipsychotics. In the Overall Combined Database, gynecomastia occurred in 7 (4.3%) of patients (all from schizophrenia trials), galactorrhea occurred in 2 (3.1%) patients with schizophrenia and 1 (1%) patient with bipolar disorder and amenorrhea occurred in 1 (1.5%) patient with schizophrenia and 1 (1%) patient with bipolar disorder. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Comment: The proposed labeling contains the paragraph on hyperprolactinemia from the approved labeling in the Warning/Precaution section. The sponsor did not propose any labeling changes with adolescent data in the Warning section and the Pediatric Use section. We should ask the sponsor that more specific information be included in the Pediatric Use section.

I concur with Dr. Alfaro's recommendation that the sponsor should provide additional analyses on the subset of patients with baseline prolactin within the normal range and also, a subgroup analysis for gender and age. While I note Dr. Alfaro's request to obtain narratives on 8 cases of gynecomastia (1 case in the acute trials and 7 cases in the open trials) and two cases of high prolactin concentrations from study HGIN (1 in acute trial and 1 during the open label). It will be difficult to interpret such data if they came from the open-label phase, but we may be able to note any potential signal. It would be worthwhile to look at the individual narratives in this population, although it will be difficult to distinguish this AE from normal breast development in adolescent female. Given the fact that Dr. Alfaro was unable to identify gender in any of these cases, I have no objection to her request for more information from the sponsor.

Elevated CPK

In Dr. Alfaro's comments to the sponsor section, she recommends that we ask for narrative summaries for cases with CPK >500 U/L in our action letter. From her review, I am not able to identify which one of these CPK elevations were noted during the double-blind treatment. Upon follow up with Dr. Alfaro on this issue, we agree that we could just limit our request to one patient with a CK of 7289 U/L in the acute trial.

5.2.2.4 Vital signs and ECG changes

There was a mean increase in heart rate of 6.3 bpm in adolescents treated with olanzapine compared to a decrease of 5.1 bpm in the placebo group. The sponsor attributed this increase in heart rate to olanzapine's potential for inducing orthostasis. There were no significant changes in ECG parameters including QTc.

5.2.2.5 Extrapyrimidal Symptoms

For both HGIN and HGIU, change from baseline to endpoint in the EPS rating scales was similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups. I note Dr. Alfaro's request to the sponsor for case narratives regarding one case of opisthotonus and one case of oculogyration. Since these AEs occurred during the open-label phase, I do not think it is necessary to review these 2 case narratives. It may be difficult to ascertain causality in the open label trials. I also note as part of Dr. Alfaro's request for additional information on how was "treatment-emergent" parkinsonism, akathisia and dyskinesia defined by the respective rating scales, and an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database. It is doubtful that further assessment would give any significant result.

5.2.2.6 Suicidality

No completed suicides occurred in the clinical trials. In the acute double-blind studies, 2 events occurred in the olanzapine group (suicidal ideation/behavior – intent unknown and suicidal ideation) and 1 event occurred in the placebo group. These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in

bipolar disorder patients. I agree with Dr. Alfaro that suicidal behaviors or ideation is not uncommon in these patients and it is difficult to interpret any causality to olanzapine therapy in the absence of a placebo comparator. One of the exclusion criteria for HGIU was "patients who have been judged clinically to be at serious suicidal risk". However, Dr. Alfaro noted that three patients (012-1203, 012-1212, and 024-2402) who were rated the maximum score of "7" at baseline (has made a suicide attempt within the last month or is actively suicidal) of the CDRS-R individual item "suicidal ideation." She recommended that we ask the sponsor in the approvable letter to provide more information regarding inclusion of these patients in this study. Given the study results from the acute double-blind phase of the study, I do not think we need to convey this question to the sponsor.

5.2.2.7 Risk Management Plan

The sponsor's proposed risk management plan includes routine pharmacovigilance of spontaneous case reports with target AEs, a long term safety study and a pharmacoepidemiology study with retrospective cohort analysis of a large US health claims database to estimate the incidence and prevalence of diabetes mellitus and dyslipidemia among adolescent patients with schizophrenia or bipoloar disorder compared with the general adolescent population. The OSE was consulted on this proposed risk management plan. The OSE has stated that they would provide their input on the appropriateness of the RMP after the sponsor submits a complete response to the action letter.

5.2.3 Conclusion Regarding Safety Data

This submission revealed safety findings of Olanzapine in adolescent population in which most AEs consistent with the previously observed AE profile of olanzapine as described in current labeling. The sponsor has included all the percentages in the treatment emergent AE of $\geq$5% and $\geq$2% table as the commonly observed AEs in controlled adolescent clinical trials under the adverse events section of the labeling. I think this portion of their labeling proposal seems acceptable.

Significant safety signals that emerged in these adolescent clinical trial databases were weight gain, hypertriglyceridemia, hypercholesterolemia, hyperprolactinemia and transaminase elevations. Although there are some changes proposed in the labeling by the sponsor, we need to work on the labeling language so that all pertinent safety findings are adequately reflected in the labeling. We have already asked the sponsor for an extensive search for data to address the concerns regarding weight, glucose and lipid profiles in our 1/12/2007 letter and our 3/28/2007 approvable letter for symbyax (olanzapine/fluoxetine combination) in treatment of treatment resistant depression. In our action letter for this set of olanzapine pediatric supplements, we should reiterate related safety concerns and ask the sponsor to make relevant safety changes in the labeling.

6.0 WORLD LITERATURE

The sponsor has provided a literature update pertaining to the safety of Olanzapine. As Dr. Alfaro noted, the sponsor reported that none of the articles would change safety conclusion for olanzapine.

7.0 FOREIGN REGULATORY ACTION

I am not aware of any foreign regulatory action of this drug for adolescent claim.

8.0   PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take these supplemental NDAs to the PDAC.

9.0   DSI INSPECTIONS

DSI data audit inspections were requested for two domestic sites and two Russian sites. DSI did not indicate any major inspectional issues that would impact data integrity on efficacy and safety.

We also informed DSI of GCP non-compliance reported by the sponsor in one clinical trial site 021 for study HGIN (CI: Dr. A. Robb). DSI will decide if further investigation of this clinical investigator site is needed. The sponsor has excluded data from at this site (N=3) in their analysis and reported no impact on efficacy results.

10.0   LABELING AND ACTION LETTER

Since we are recommending a non-approval action on schizophrenia indication, we should delete the labeling language in reference to this efficacy claim. We have made modifications to the proposed labeling and should provide our labeling comments to the sponsor with respect to safety language in labeling, and related safety issues in our action letter. Our modified version of draft labeling in the new PLR format is attached in our action letter for bipolar indication.

11.0   CONCLUSION AND RECOMMENDATION

I concur with both Drs. Alfaro and Kong that the sponsor has not provided sufficient evidence to convince that olanzapine is effective for treatment of schizophrenia in adolescents. Therefore, I recommend the Division issue a non-approvable letter for this NDA supplement (SE5-041).

Regarding the NDA supplement (SE5-040), results from study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Although there are some changes in the labeling proposed by the sponsor in the submission, we will need more information in order to adequately address the safety findings regarding changes in weight, glucose and lipid profiles. We may need further modification in the labeling to reflect all significant findings. Therefore, I recommend that the Division issue an approvable action letter with our labeling comments.

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File: NK/NDA20592/Memo_SE5_040041_peds_042007.doc

CLINICAL EXECUTIVE SUMMARY

Application Type	NDA 20-592
Submission Number	S-040
Submission Code	SE5
Letter Date	10/30/06
Stamp Date	10/31/06
PDUFA Goal Date	04/30/07
Reviewer Name	Cara Alfaro, Pharm.D.
Established Name	Olanzapine
Trade Name	Zyprexa
Therapeutic Class	Antipsychotic
Applicant	Eli Lilly
Priority Designation	P
Formulation	Oral tablets
Dosing Regimen	2.5 – 5 mg starting, maximum dose 20 mg/day
Indication	Treatment of Bipolar I Disorder
Intended Population	Adolescents (13 – 17 years)

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included in the clinical review. If acceptable, these requests could be included in the action letter.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

1.2.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be adequately addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

1.3.2   Efficacy

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score. The overall study results were statistically significant for olanzapine versus placebo in the primary LOCF analysis as well as the supporting OC and MMRM analyses (see Table). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

		N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LS Mean Change	LS Mean Difference	P-value
LOCF	Olanzapine	105	33.1	6.5	-15.9	10.0	-17.6		
	Placebo	54	32.0	6.2	-7.7	9.4	-10.0	-7.7	< 0.001
OC	Olanzapine	88	33.2	6.5	-17.2	9.7	-19.1		
	Placebo	37	32.4	6.2	-11.1	9.0	-13.4	-5.7	0.001
MMRM	Olanzapine	88	33.2	6.5	-17.2	9.7	-15.8		
	Placebo	37	32.4	6.2	-11.1	9.0	-8.8	-6.9	< 0.001

Subgroup analyses included gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds (p = 0.094), patients with psychotic features (p = 0.111) and rapid cyclers (p = 0.271) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found (see Table). The Sponsor conducted

three additional posthoc analyses, two of these did not indicate a treatment-by-age interaction.

| | | N | Baseline | | Change to Endpoint | | | | |
			Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
< 15 years	Olanzapine	49	32.8	7.0	-14.6	10.2	-16.6		
	Placebo	20	32.4	5.7	-9.4	11.0	-12.1	-4.5	0.094
≥ 15 years	Olanzapine	56	33.3	6.2	-17.0	9.9	-18.9		
	Placebo	34	31.8	6.6	-6.7	8.4	-9.0	-9.9	< 0.001

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

1.3.3 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 (HGIN is the pivotal trial for schizophrenia) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events (≥ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%), sedation (19% vs. 6%), headache (17% vs. 12%), fatigue (10% vs. 5%), dizziness (7% vs. 2%), dry mouth (6% vs. 0%) and pain in extremity (5% vs. 1%). 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 $\geq 7\%$ 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
$\geq 7\%$ 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)
$\geq 7\%$ 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 $\leq$ 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 $\geq$ 3x ULN and TBili $\geq$ 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 and HGIN.

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group (p < 0.001).

Hypertriglyceridemia
The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, p < 0.001). In reviewing the individual lab data, 11 marked outliers were noted for triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) (p = 0.039).

Hypercholesterolemia
The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, p < 0.001). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) (p = 0.023).

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, $p < 0.001$). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation ($n = 13$) and SIB – intent unknown ($n = 6$). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation are not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

Although there are significant risks outlined in this review, there is also significant morbidity and mortality associated with untreated bipolar I disorder.

1.3.4 Dosing Regimen and Administration

Proposed labeling
"Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg. Efficacy in adolescents with

bipolar disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg per day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials."

This dosing regimen is essentially the same as that in the protocol with two differences. In the protocol, the investigator had to increase the dose to 10 mg by the end of week 1 (based on tolerability) and could thereafter increase or decrease dose as necessary. Per protocol, it was suggested that olanzapine should be dosed in the evening due to the adverse event somnolence.

1.3.5   Drug-Drug Interactions

No formal drug-drug interaction studies were done as part of this clinical development program and none are needed.

1.3.6   Special Populations

These studies were conducted in accordance with a pediatric Written Request and the Agency has granted the Sponsor's request for pediatric exclusivity.

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 /s/
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Ni Aye Khin
4/12/2007 04:48:56 PM
This is the revised version.
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CLINICAL EXECUTIVE SUMMARY

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.
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 (13 – 17 years)

1   EXECUTIVE SUMMARY

1.1   Recommendation on Regulatory Action

I recommend that the Division take a not approvable 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 in the clinical review. If acceptable, these requests could be included in the action letter.

1.2   Recommendation on Postmarketing Actions

Since a not approvable action 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. The overall study results were statistically significant for olanzapine versus placebo in the primary LOCF analysis but not the supporting OC and MMRM (recalculated by statistician reviewer) analyses (see Table).

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
LOCF	Olanzapine	72	50.3	10.0	-19.4	15.5	-19.3		
	Placebo	35	50.1	8.6	-9.3	18.7	-9.1	-10.1	0.003
OC	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.4		
	Placebo	15	49.0	8.5	-23.7	14.6	-24.1	-0.26	0.947
MMRM	Olanzapine	50	50.6	10.6	-24.5	13.5	-24.7		
	Placebo	15	49.0	8.5	-23.7	14.6	-23.5	-1.25	0.72

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.

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
U.S.	Olanzapine	38	53.2	10.1	-21.1	16.3	-20.9		
	Placebo	19	51.4	8.6	-15.0	18.3	-15.6	-5.3	0.258
Russia	Olanzapine	34	47.0	8.9	-17.4	14.5	-17.4		
	Placebo	16	48.5	8.5	-2.6	17.4	-2.5	-14.9	0.003

Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a not approvable 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 ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%), sedation (19% vs. 6%), headache (17% vs. 12%), fatigue (10% vs. 5%), dizziness (7% vs. 2%), dry mouth (6% vs. 0%) and pain in extremity (5% vs. 1%). 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 $\geq$ 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
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Weight (kg) Mean Change to Endpoint	10.8	-	-	< 0.001 (compared to baseline)

(OC)				
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.

1.3.4 Dosing Regimen and Administration

This section not completed since a not approvable action was recommended.

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were done as part of this clinical development program and none are needed.

1.3.6 Special Populations

These studies were conducted in accordance with a pediatric Written Request and the Agency has granted the Sponsor's request for pediatric exclusivity.

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Ni Aye Khin
4/12/2007 11:33:33 AM
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CLINICAL REVIEW

Application Type	NDA 20-592
Submission Number	S-040
Submission Code	SE5

Letter Date	10/30/06
Stamp Date	10/31/06
PDUFA Goal Date	04/30/07

Reviewer Name	Cara Alfaro, Pharm.D.
Review Completion Date	04/06/07

Established Name	Olanzapine
Trade Name	Zyprexa
Therapeutic Class	Antipsychotic
Applicant	Eli Lilly

Priority Designation	P

Formulation	Oral tablets
Dosing Regimen	2.5 – 5 mg starting, maximum dose 20 mg/day
Indication	Treatment of Bipolar I Disorder
Intended Population	Adolescents

Table of Contents

1 EXECUTIVE SUMMARY

Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

Recommendation on Postmarketing Actions

1.1.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

1.1.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be adequately addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

Summary of Clinical Findings

1.1.3 Brief Overview of Clinical Program

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication "treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar I disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Additional open-label studies were also submitted by the Sponsor primarily in support of safety. The primary supportive studies were LOAY (n = 89 adolescents) and HGMF (n = 107), the latter study was the primary pharmacokinetic study in this population.

1.1.4 Efficacy

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -7.66, $p < 0.001$).

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                                              Change to
                                 Baseline      Endpoint
                                ------------  -------------  LSMean    LSMean
Efficacy Variable    Therapy    N   Mean  Std   Mean   Std   Change    Difference   *P-value
-----------------------------------------------------------------------------------------------

YMRSTOT:Total(1-11)  Olanzapine 105 33.08 6.55 -15.90 10.03 -17.65    -7.66        <.001
                     Placebo     54 32.04 6.23  -7.72  9.42  -9.99
```

The supportive OC analysis was similar to the LOCF analysis (LS Mean Diff = -5.74, p = 0.001). The supportive MMRM analysis was similar to the LOCF analysis (LS Mean Diff = -6.95, p < 0.001). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

Subgroup analyses included gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds (p = 0.094), patients with psychotic features (p = 0.111) and rapid cyclers (p = 0.271) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found.

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

1.1.5 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIN is the pivotal trial for schizophrenia) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

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The most common adverse events ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with $\geq$ 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
HGIN + HGIU Acute Database				
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Weight (kg) Mean Change to Endpoint (OC)	3.6 (n = 154)	0.08 (n = 67)	3.57	< 0.001
BMI	1.22	0.05	1.17	< 0.001

Mean Change to Endpoint (LOCF)				
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001
Overall Combined Database				
Weight (kg) Mean Change to Endpoint (LOCF)	7.35	-	-	< 0.001 (compared to baseline)
Weight (kg) Mean Change to Endpoint (OC)	10.8	-	-	< 0.001 (compared to baseline)
BMI Mean Change to Endpoint (LOCF)	2.31	-	-	< 0.001 (compared to baseline)
≥ 7% increase in body weight (%)	65%	-	-	-

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff = 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to perform further analyses in the subgroup of patients with baseline prolactin within normal limits.

In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction, though there was a numerically greater mean change to endpoint in females (15.6 mcg/L) compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIN + HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group (p < 0.001).

Hypertriglyceridemia
The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, p < 0.001). In reviewing the individual lab data, 11 marked outliers were noted for triglycerides at any time (> 250 mg/dL). The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher percentage of patients in the olanzapine group had a shift from normal to high triglycerides (12.4%) compared to placebo (1.9%) (p = 0.039).

Hypercholesterolemia
The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, p < 0.001). A higher percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol (15.7%) compared to placebo (3.6%) (p = 0.023).

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, p < 0.001). The percentage of patients with shifts from normal to high fasting glucose and impaired glucose tolerance to high fasting glucose were not different between olanzapine and placebo (very few patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these

types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms

For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality

Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in patients with bipolar disorder. Suicidal behaviors or ideation is not uncommon in these disorders and, in the absence of a placebo comparator, it is difficult to interpret causality to olanzapine therapy.

Although there are significant risks outlined in this review, there is also significant morbidity and mortality associated with untreated bipolar I disorder.

1.1.6 Dosing Regimen and Administration

Proposed labeling

"Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg. Efficacy in adolescents with bipolar disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg per day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials."

This dosing regimen is essentially the same as that in the protocol with two differences. In the protocol, the investigator had to increase the dose to 10 mg by the end of week 1 (based on tolerability) and could thereafter increase or decrease dose as necessary. Per protocol, it was suggested that olanzapine should be dosed in the evening due to the adverse event somnolence.

2   INTRODUCTION AND BACKGROUND

Product Information

Olanzapine (Zyprexa) is an atypical antipsychotic. Olanzapine oral tablets were approved on 9/30/1996 for the treatment of schizophrenia in adults. Olanzapine is also available as Zyprexa Zydis, orally disintegrating tablets and Zyprexa IntraMuscular for injection.
Olanzapine oral tablets are currently approved for the following indications: treatment of schizophrenia, treatment of acute mixed or manic episodes associated with bipolar I disorder, maintenance monotherapy for bipolar I disorder, and combination therapy (with lithium or valproate) for the short-term treatment of acute mixed or manic episodes associated with bipolar I disorder.

Olanzapine is not currently indicated for use in child/adolescent populations.

Currently Available Treatment for Indications

Other currently available atypical antipsychotics include clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify), quetiapine (Seroquel), ziprasidone (Geodon). Many of these atypical antipsychotics are approved for the indication treatment of acute mixed or manic episodes associated with bipolar I disorder, but none are approved for use in children/adolescents.

Risperidone (Risperdal) was recently approved for the indication "treatment of irritability associated with autistic disorder in children and adolescents" (5 to 16 years of age).

Lithium (various salts) and divalproex sodium are indicated in the treatment of manic episodes of bipolar I disorder in adults.

Important Issues With Pharmacologically Related Products

Although the atypical antipsychotics have less extrapyramidal side effects compared to typical antipsychotics, the adverse event profile is notable for weight gain, hyperglycemia, and diabetes mellitus in adults. Little data is available with regard to the adverse event profile in other populations including children and adolescents.

Presubmission Regulatory Activity

This summary was taken from the note to reviewer document contained in the Sponsor's submission.

On June 11, 1999, Eli Lilly and Company (Lilly) submitted a Proposed Pediatric Study Request to FDA related to the conduct of pediatric studies of Zyprexa.

In response to Lilly's proposed pediatric study request, the FDA issued to Lilly a Written Request for Pediatric Studies dated November 30, 2001 (reissued under the Best Pharmaceuticals for Children Act (BPCA) on July 3, 2002) and amended on April 9, 2002, May 7, 2004, and June 29, 2005. FDA's Written Request (WR) as amended, included a request for clinical data on the use of Zyprexa to treat adolescents with schizophrenia and adolescents with acute bipolar mania in order to make Zyprexa eligible for the pediatric exclusivity extension under Section 505A of the Federal Food, Drug, and Cosmetic Act. More details regarding FDA's WR, and Lilly's response, are provided in Item 20 of this submission.

FDA granted an indication for olanzapine for the treatment of bipolar mania in adults (NDA 20-592/S006) on March 17, 2000. As part of the approval, the FDA requested a study in pediatric patients with bipolar mania as a post-marketing commitment. Study F1D-MC-HGIU is included in this submission to fulfill this post-marketing commitment.

On January 15, 2004, the FDA met with Lilly to discuss the PK package proposed by Lilly to fulfill FDA's Written Request for Pediatric Studies. At this meeting, Lilly provided an overview of the available PK data. FDA requested additional justification of

the utility of the data from Study LOAY in order to make a final decision on whether or not the data is acceptable to sufficiently meet the PK aspects of the Written Request.

On March 22, 2004 Lilly submitted to IND 28,705 additional information regarding study LOAY and requested a meeting to further discuss fulfillment of the PK aspects of the WR. In response to questions from FDA sent to Lilly on July 7, 2004, Lilly submitted additional information to IND 28,705 on July 13, 2004.

Lilly met with FDA on July 21, 2004 to again discuss the PK information needed to fulfill the WR. At that meeting, FDA agreed with Lilly's proposal to provide PK data in adolescents from Studies HGCS, HGCR, HGGC, and LOAY to address the PK requirements outlined in the Written Request.

In discussions with FDA, it was noted that information about the exact sampling time relative to the dose were not collected as part of the protocol in Study LOAY; however, extensive simulations showed that lack of data regarding timing of samples in Study LOAY should not adversely affect the ability to perform a meaningful population analysis. Nonetheless, to assure the robustness of the PK data, Lilly collected additional population PK data in adolescent patients with schizophrenia or bipolar disorder by conducting Study HGMF. Inclusion of data from Study HGMF in this submission was discussed at a pre-NDA meeting on March 17, 2006. At that meeting, FDA requested that Lilly conduct the population PK analysis both with and without the data from Study LOAY. Both analyses were conducted by Lilly and are included with this submission. The population PK analysis also includes a comparison of pediatric olanzapine PK data with the adult olanzapine PK data from Study HGAJ.

The format and content of the submission were also discussed and agreed to at the March 17, 2006 pre-sNDA meeting. The FDA indicated that, based on the pre-sNDA package and discussions, the proposed submission content appeared to be adequate to respond to FDA's Written Request and that Study HGIU appeared to be adequate to fulfill the post-marketing commitment which was part of the bipolar mania in adults approval.

In the 11/30/01 written request, the Division stated "We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug". The Division also recommended that a relapse prevention trial should follow the acute treatment trial. The Sponsor did not follow either recommendation and neither was required in order to fulfill the pediatric written request.

Other Relevant Background Information

The Pediatric Exclusivity Board met on January 10, 2007 to determine whether the Sponsor had fulfilled the requirements in the written request. It was determined that the requirements had been met and exclusivity was granted.

3   SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Statistics

The statistician (Fanhui Kong) reviewed the efficacy data from the pivotal trial, HGIU. In general, the data submitted by the Sponsor provide evidence for efficacy per his review (see Statistical review).

4   DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Tables of Clinical Studies

The Sponsor included study reports for 9 pediatric studies in this submission. HGIN is the pivotal study for adolescent schizophrenia and HGIU is the pivotal study for adolescent bipolar I disorder. HGMF is the primary study for determining pharmacokinetic parameters in the adolescent population. The other studies are supportive and provide safety and pharmacokinetic data.

Table 4.1.1 Summary of Clinical Studies

Study	Description	Length	Age Range (years)	Number of Patients
HGIN	MC, DB, PC study in adolescent patients with schizophrenia. Flexible dose olanzapine (2.5 – 20 mg) U.S. and Russia sites	6 weeks DB 26 weeks OL extension	13 to 17	107 (n = 72 olanzapine, n = 35 placebo)
HGIU	MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder. Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico	3 weeks DB 26 weeks OL extension	13 – 17	161 (n = 107 olanzapine, n = 54 placebo)
LOAY	OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders Flexible dose olanzapine (5 – 20 mg) German sites	24 weeks	12 – 21	96 (n = 89, 13-17 years)
HGMF	OL study in adolescent patients with schizophrenia or bipolar I disorder Flexible dose olanzapine (2.5 – 20 mg) U.S., Puerto Rico, Russia	4.5 weeks	13 – 17	107 (n = 37 schizophrenia, n = 70 bipolar)

HGCS	OL study in adolescent patients with schizophrenia Dosing: 2.5 to 20 mg/day Single site	8 weeks	10 – 18	8
HGCR	DB study in adolescent patients with schizophrenia, haloperidol as active comparator Dosing: 2.5 qod – 20 mg/day Single site	8 weeks	12 – 16	2
HGGC	OL study in children and adolescents with bipolar disorder Dosing: 2.5 to 20 mg/day Single site (U.S.)	8 weeks	5 – 14	23

Modified from Sponsor Table 2.5.1.1 clinical-overview.
MC = multicenter, DB = double-blind, PC = placebo-controlled, OL = open-label

Data Quality and Integrity

The Division of Scientific Investigations was asked to inspect a number of sites for studies HGIN and HGIU – some sites enrolled patients for both studies. DSI was asked to audit one site in Georgia (n = 7 HGIU, n = 5 HGIN) and one site in Ohio (n = 15 HGIU, n = 6 HGIN). The final DSI report was not available at the time this review was completed, but preliminary comments from the investigator did not indicate any major issues thought to effect efficacy.

Compliance with Good Clinical Practices

Per protocols, the studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Of note, one clinical trial site was omitted from the primary efficacy analyses due to significant GCP issues. This site enrolled patients in both HGIU (site 028) and HGIN (site 021). Details regarding the GCP issues are in Section 6.1.3 (Efficacy Findings) of this review.

Financial Disclosures

Financial disclosure information was provided for the study   (b) (6). Two investigators received ~$40,000 in honoraria or other grant monies (sites   (b) (6)), a small number of patients were randomized from these sites ((b) (6)).

5   CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of oral olanzapine were evaluated primarily in study HGMF (see Table 4.1.1 in Section 4.1 Tables of Clinical Studies) via population pharmacokinetic analyses. These data have been extensively reviewed by the biopharmaceutical reviewer (see Biopharm review).

6   INTEGRATED REVIEW OF EFFICACY

One pivotal trial, F1D-MC-HGIU, was submitted to support the efficacy of olanzapine in the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents.

Indication

The Sponsor proposes the following indication "indicated for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents".

6.1.1   General Discussion of Endpoints

The primary efficacy endpoint for the clinical trial was the change from baseline to endpoint on the YMRS-adolescent structured rating scale total score. The YMRS is a standard rating scale used to evaluate efficacy in adult bipolar populations and is appropriate for evaluating efficacy in this clinical trial.
The Sponsor also included the Clinical Global Impression-Severity rating scale to rate severity of mania, depression and overall severity of bipolar disorder. The Children's Rating Scale for Depression was also included to assess depressive symptoms. Due to the presence of mania and depression in bipolar illness, inclusion of these endpoints was appropriate.

6.1.2   Study Design

Protocol F1D-MC-HGIU is the pivotal study submitted to support the indication "for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents". The other studies submitted as supportive studies in this population are open-label trials and are supportive primarily from a safety and not efficacy perspective. Therefore, only study HGIU is reviewed here.

Protocol HGIN
"Olanzapine versus placebo in the treatment of mania in adolescents with bipolar I disorder"
First patient enrolled 11/18/02, last patient completed 5/9/05.

Investigators and sites
This study enrolled patients at 23 sites in the United States and 2 sites in Puerto Rico. Investigator and site information (including numbers of patients randomized and completing the trial) are included in Appendix 10.1.

Study Objectives
Primary objective: To assess the efficacy of a flexible dose of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of mania in bipolar I disorder (manic or mixed episode associated with bipolar I disorder, with or without psychotic features) in adolescents (ages 13 – 17) as measured by the difference between treatment groups in mean change from baseline to endpoint in the Adolescent Structured Young-Mania Rating Scale (YMRS) total score.

Secondary objectives:
To assess secondary efficacy measures 1) YMRS individual items; 2) Clinical Global Impression Scale – Bipolar Version Severity of Illness (Severity of Mania, Severity of Depression, Severity Overall); 3) Children's Depression Rating Scale-Revised; 4) Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (investigator administered and scored) and 5) Overt Aggression Scale.

To assess the safety of olanzapine compared with placebo for up to 3 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

To assess the health-related quality of life associated with olanzapine compared with placebo for up to 3 weeks of double-blind treatment and for up to an additional 26 weeks of open-label olanzapine treatment.

Compare the frequency of response during the double-blind treatment period (up to 3 weeks), as defined by a $\geq 50\%$ reduction in YMRS total score from baseline to endpoint and a CGI-BP Severity of Mania score of ≤ 3 at endpoint for olanzapine vs. placebo treatment.

Study Population
The study population consisted of generally healthy adolescents, ages 13 to 17 inclusive, with a DSM-IV-TR diagnosis of bipolar I disorder and currently displaying an acute manic or mixed episode (with or without psychotic features). The diagnosis was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime (K-SADS-PL). The inclusion and exclusion criteria are listed in Appendix 10.2. Patients must have obtained an YMRS total score ≥ 20 at Visit 1 and 2. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations. Exclusion criteria included patients who have been judged clinically to be at serious suicidal risk; patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment; patients currently meeting DSM-IV-TR criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Design

This was a multicenter, randomized, double-blind, parallel, placebo-controlled trial consisting of three periods: screening/washout, 3-week double-blind trial, 26-week open-label olanzapine treatment. The screening/washout period was 2-14 days. Patients were then randomized to olanzapine flexible dose (2.5 to 20 mg/day) or placebo treatment (2:1 randomization) for the 3-week acute double-blind trial. Olanzapine was initiated at 2.5 or 5 mg/day and the dose could be increased by 2.5 or 5 mg/day dose increments at the investigator's discretion. If no tolerability or safety issues were apparent, the dose had to be titrated to at least 10 mg/day by Visit 4 (end of week 1). The investigator could continue to increase the dose by 2.5 or 5 mg/day to the maximum tolerable dose not to exceed 20 mg/day. The investigator could decrease the dose at any time and in any number of dose decrements if patients experienced an adverse event. The minimum allowable olanzapine dose was 2.5 mg/day. During this 3-week acute trial, 3 study visits occurred during the first week and then weekly thereafter.

Patients who did not respond after at least 10 days during the 3-week double-blind trial could participate in the optional 26-week open-label extension study and receive open-label olanzapine therapy (2.5 to 20 mg/day). Response was defined as having a $\geq 20\%$ decrease in the YMRS total score compared to baseline and a CGI-BP Severity of Mania score ≤ 3. Study visits occurred weekly x 2 visits, biweekly x 4 visits and then monthly until the end of the 26-week study.

Assessments (The Schedule of Events is in Appendix 10.3)
Rating scales – efficacy:
Primary efficacy endpoint: Adolescent Structured Young-Mania Rating Scale (YMRS)
Secondary efficacy endpoints: Clinical Global Impression – Severity of Mania, Severity of Depression, Severity Overall; Children's Depression Rating Scale-Revised; Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version; Overt Aggression Scale (OAS); Child Health Questionnaire (CHQ)

Safety assessments:
Vital signs (blood pressure, pulse, weight, height, temperature) – including orthostatic assessments, ECG, Labs (hematology, clinical chemistry, urinalysis, lipid panel, hepatitis screen and panel, serum pregnancy test, prolactin, thyroid stimulating hormone, HgbA1c, urine drug screen.
Fasting glucose at baseline, end of 3-week study and end of 26-week open-label study.
HbA1c was only obtained for patients with diabetes.

Rating scales: Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Abnormal Involuntary Movement Scale (AIMS)
Spontaneous reporting of adverse events.

6.1.3 Efficacy Findings

One hundred sixty one patients were randomized, 107 to the olanzapine group and 54 to the placebo group. In the olanzapine group, 22 patients discontinued with lack of efficacy as the primary reason for discontinuation for 54.5% of drop-outs. In the placebo group, 19 patients discontinued with lack of efficacy as the primary reason for discontinuation for 84.2% of drop-outs. Drop-outs due to adverse events were the primary reason for discontinuation for 3 patients in the olanzapine group and 1 patient in the placebo group.

Table 6.1.3.1 Patient Disposition

	Olanzapine N = 107	Placebo N = 54	P-value
Completers	85 (79.4%)	35 (64.8%)	0.056
Drop Outs	22 (20.6%)	19 (35.2%)	
Adverse Event	3 (2.8%)	1 (1.9%)	1.00
Lack of Efficacy	12 (11.2%)	16 (29.6%)	0.007
Lost to Follow-up	0	0	-
Patient Decision	4 (3.7%)	1 (1.9%)	0.665
Criteria Not Met/Compliance	0	1 (1.9%)	0.335
Sponsor Decision	0	0	-
Physician Decision	1 (0.9%)	0	1.00
Other	2 (1.9%)	0	0.551

Modified from Sponsor table HGIU.10.1 in study report

Demographics and Baseline Disease Severity
There were no statistically significant differences between the olanzapine and placebo groups with regard to baseline demographics.
Statistically significant differences indicating a potential imbalance in severity of illness were found for several categories – most indicated that more ill patients were randomized into the olanzapine treatment group (although the YMRS baseline scores, the primary efficacy measure, were not statistically different between the groups). Statistical differences were found for the mean number of previous mania episodes (olanzapine = 2.07, placebo = 4.43), mean number of previous depressive episodes (olanzapine = 1.6, placebo = 3.98), mean number of previous mixed episodes (olanzapine = 1.19, placebo = 3.85), psychiatric hospitalization within the past year (olanzapine = 32.1%, placebo = 16.7%). Scores on most rating scales at baseline did not differ between the two treatment groups with the exception of the CGI-Severity Depression (olanzapine = 3.1, placebo = 2.6).
The groups did not differ with regard to the number of patients with psychotic features (olanzapine = 21%, placebo = 13%) or current episode, manic (olanzapine = 41%, placebo = 54%). The groups did differ with regard to the number of rapid cyclers (olanzapine = 23%, placebo = 9%).

Table 6.1.3.2 Baseline Demographics and Severity of Disease

		Olanzapine N = 107	Placebo N = 54	P-value
Gender	Male	61 (57.0%)	24 (44.4%)	0.137
	Female	46 (43%)	30 (55.6%)	
Age (years)	Mean	15.14	15.38	0.250
	Median	15.12	15.41	
	St. Dev	1.28	1.20	
	Minimum	13.02	13.07	
	Maximum	17.89	17.68	
Origin	African descent	13 (12.1%)	2 (3.7%)	0.247
	Caucasian	71 (66.4%)	41 (75.9%)	
	East/Southeast Asian	0	1 (1.8%)	
	Hispanic	18 (16.8%)	8 (14.8%)	
	Other	5 (4.7%)	2 (3.7%)	
Country	America	95 (88.8%)	48 (88.9%)	1.00
	Puerto Rico	12 (11.2%)	6 (11.1%)	
Age of onset of illness (years)	Mean	10.93	11.46	0.331
	Median	12.00	12.00	
	St. Dev.	3.32	3.13	
	Minimum	1.00*	4.00	
	Maximum	17.00	17.00	
No. of Prev. Mania episodes	Mean	2.07	4.43	0.048
	Median	1.00	1.00	
	St. Dev.	4.97	8.95	
	Minimum	0.00	0.00	
	Maximum	35.00	42.00	
No. of Prev. Depressive episodes	Mean	1.60	3.98	0.014
	Median	1.00	1.50	
	St. Dev.	2.84	8.26	
	Minimum	0.00	0.00	
	Maximum	20.00	50.00	
No. of Prev. mixed episodes	Mean	1.19	3.85	0.027
	Median	0.00	0.00	
	St. Dev.	3.65	9.40	
	Minimum	0.00	0.00	
	Maximum	25.00	42.00	
Total hospitalization for the past year (months)	Mean	0.85	1.43	0.327
	Median	0.50	0.50	
	St. Dev.	1.23	2.53	
	Minimum	0.13	0.10	
	Maximum	6.00	8.00	
Length of current episode (days)	Mean	309.8	237.2	0.521
	Median	45.50	50.50	
	St. Dev.	749.1	542.20	
	Minimum	2.00	4.00	
	Maximum	4441	2902	
Days since last hospitalization	Mean	145.4	361.0	0.072
	Median	8.00	33.00	
	St. Dev.	310.3	540.9	
	Minimum	0.00	0.00	
	Maximum	1688	1651	
Psychiatric	Yes	34 (32.08%)	9 (16.67%)	0.040

hospitalization within the past year	No	72 (67.92%)	45 (83.33%)	
Current episode has concurrent psychotic features	Yes No	22 (20.75%) 84 (79.25%)	7 (12.96%) 47 (87.04%)	0.281
Current episode, manic	Yes No	44 (41.1%) 63 (58.9%)	29 (53.7%) 25 (46.3%)	0.136
Rapid Cyclers	Yes No Unknown	25 (23.4%) 71 (66.4%) 11 (10.3%)	5 (9.3%) 43 (79.6%) 6 (11.1%)	0.031
CDRS Raw Total Score	Mean Median St. Dev. Minimum Maximum	40.2 39 15.3 17 82	36.2 33.5 15.5 17 101	0.096
CGI-Severity of depression	Mean Median St. Dev. Minimum Maximum	3.14 4.00 1.57 1.00 6.00	2.65 2.00 1.60 1.00 6.00	0.043
CGI-Severity of mania	Mean Median St. Dev. Minimum Maximum	4.79 5.00 0.70 4.00 6.00	4.81 5.00 0.75 3.00 6.00	0.852
CGI-Severity overall	Mean Median St. Dev. Minimum Maximum	4.79 5.00 0.71 4.00 6.00	4.83 5.00 0.75 3.00 6.00	0.727
YMRS Total score	Mean Median St. Dev. Minimum Maximum	33.05 33.00 6.53 20.00 48.00	32.04 32.00 6.23 21.00 43.00	0.347

Modified from Sponsor table HGIU.11.1, HGIU.11.2, HGIU.11.3, HGIU.11.4, HGIU.11.6 in study report
*An age of onset of 1 year old is highly suspect.

No statistically significant differences were noted between groups in baseline OAS verbal aggression total, OAS physical aggression toward self total, OAS physical aggression toward objects, OAS total, ADHD total, ADHD inattention subtotal. Baseline ADHD hyperactivity-impulsivity subtotal bordered on significance (olanzapine 13.68 vs. placebo 11.67; $p = 0.051$).

A diagnosis of comorbid ADHD was present in more patients in the olanzapine group compared to the placebo group (42% vs. 24%, $p = 0.024$). Though not common, a diagnosis of comorbid conduct disorder was present in more patients in the olanzapine group compared to the placebo group (n = 14, n = 1, $p = 0.021$).

Efficacy Analyses

Site Issues
In the efficacy analysis, the sponsor included analyses with and without site 028. Per the sponsor, site 028 had significant GCP issues and patients from this site were dropped from the primary analyses (efficacy analyses were similar with and without this site). The study report did not specify what the GCP issues were with this site. The sponsor was asked to provide details and indicated the following:

Lilly discontinued site 021 (Dr. Robb) from study HGIN, and also discontinued Dr Robb's site (site 028) from study HGIU. Lilly informed FDA of the discontinuation of Dr Robb's site from these studies in a submission to IND 28,705; serial number 953, dated May 21, 2004. In a letter dated May 2, 2004 sent to Dr Robb, Lilly listed the following GCP issues that occurred at this site related to studies HGIN and HGIU:

- Not following the randomization procedures outlined in the protocol

- Not submitting protocol amendment A, approved by Lilly on October 17, 2002, to the Institutional Review Board (IRB) for approval before use

- Not submitting revised informed consent documents to IRB

- Not communicating to patients about safety issues in risk profile of study drug. The risk profile was updated by Lilly on December 4, 2003 and faxed to the site on January 6, 2004 and a reminder fax was sent on January 28, 2004.

- Significant problems with drug accountability

- Not being able to reconstruct the regulatory document in the Clinical Trial Record Binder

- Violation of inter-active voice response system (IVRS) security personal identification number process.

Concomitant Medications
Interestingly, 39.3% (42/107) of patients in the olanzapine group and 46.3% (25/54) of patients in the placebo group had no previous medications for bipolar I disorder. It is not known whether these patients participated in nonpharmacological treatment of their disorder.

The most commonly used concomitant medications (> 5% of patients) included benzodiazepines (see next paragraph) and mixed amphetamine salts in 7.5% (8/107) of patients in the olanzapine group and 5.6% (3/54) patients in the placebo group.

There were no statistically significant differences in the frequency of concomitant benzodiazepine use between the olanzapine and placebo groups. Concomitant lorazepam use occurred in 9.3% (10/107) patients in the olanzapine group and 7.4% (4/54) patients in the placebo group. Concomitant temazepam use occurred in 3.7% (4/107) patients in the olanzapine

group and 1.9% (1/54) patients in the placebo group. A few patients in both groups had concomitant clonazepam, alprazolam and diazepam use. There was a statistically significant difference in the mean number of days of benzodiazepine use between the treatment groups: 2.8 $\pm$ 3.5 days in the olanzapine group and 10 ± 7.0 days in the placebo group (p = 0.019). The mean dose of benzodiazepines (using equivalent doses) did not differ between the treatment groups: 1.4 ± 0.5 mg in the olanzapine group and 2.0 ± 1.7 mg in the placebo group.

There were no statistically significant differences in the frequency of concomitant anticholinergic medication use between the olanzapine and placebo groups. However, only 5 patients in the study had concomitant use of anticholinergic medications and all 5 were in the olanzapine group: benztropine mesylate (n = 3), amantadine (n = 1), and diphenhydramine (n = 1). The mean number of days on anticholinergic medication was 3 ± 2.6 days. The mean dose of anticholinergic medication was 1.4 ± 0.5 mg.

Primary Endpoint
Primary Analysis - LOCF
The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg.

The primary efficacy analysis is in Table 6.1.3.3 below. The analysis including site 028 was similar, least square mean difference was 7.88 favoring the olanzapine group (p < 0.001).

Table 6.1.3.3 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint – *LOCF*. (Excluding site 028)

Efficacy Variable	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Difference	*P-value
YMRSTOT:Total(1-11)	Olanzapine	105	33.08	6.55	-15.90	10.03	-17.65	-7.66	<.001
	Placebo	54	32.04	6.23	-7.72	9.42	-9.99		

Supportive Analyses – OC and MMRM
The findings for the OC analysis (Table 6.1.3.4) and MMRM analysis (Table 6.1.3.5) were similar to the LOCF analysis.

Table 6.1.3.4 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Visit– *OC*.

Efficacy Variable	Visit	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Difference	*P-value
YMRSTOT:Total(1-11)	3	Olanzapine	105	33.08	6.55	-7.98	7.26	-6.37	-2.24	.048
		Placebo	54	32.04	6.23	-5.37	6.83	-4.13		
	4	Olanzapine	104	33.11	6.57	-12.62	9.01	-11.46	-3.97	.002
		Placebo	53	32.17	6.21	-8.06	7.38	-7.49		
	5	Olanzapine	103	33.03	6.56	-15.46	9.47	-16.16	-7.40	<.001
		Placebo	53	32.17	6.21	-7.49	10.56	-8.77		
	6	Olanzapine	88	33.23	6.48	-17.17	9.71	-19.14	-5.74	.001
		Placebo	37	32.41	6.19	-11.11	9.05	-13.40		

Sponsor's Table HGIU.14.21

Table 6.1.3.5 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Visit– *MMRM*

Efficacy Variable	Visit (Week)	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean StdErr	LSMean Difference	Diff StdErr	*P-value
YMRSTOT:Total(1-11)	Combined	Olanzapine						-12.41	0.85	-5.19	1.08	<.001
		Placebo						-7.23	1.05			
	3 (0.5)	Olanzapine	105	33.08	6.55	-7.98	7.26	-7.27	0.88	-2.14	1.14	.062
		Placebo	54	32.04	6.23	-5.37	6.83	-5.13	1.09			
	4 (1)	Olanzapine	104	33.11	6.57	-12.62	9.01	-11.84	0.94	-4.08	1.28	.002
		Placebo	53	32.17	6.21	-8.06	7.38	-7.76	1.19			
	5 (2)	Olanzapine	103	33.03	6.56	-15.46	9.47	-14.77	1.06	-7.58	1.53	<.001
		Placebo	53	32.17	6.21	-7.49	10.56	-7.19	1.37			
	6 (3)	Olanzapine	88	33.23	6.48	-17.17	9.71	-15.78	1.10	-6.95	1.68	<.001
		Placebo	37	32.41	6.19	-11.11	9.05	-8.83	1.50			

Sponsor's Table HGIU.14.27

U.S. vs. Puerto Rico Sites
The Sponsor did perform an analysis comparing the efficacy between U.S. and Puerto Rico sites. There were, however, very few subjects from the latter sites.

Table 6.1.3.6 Sponsor's Table. YMRS Total Score Mean Change from Baseline to Endpoint by Country– U.S. vs. Puerto Rico sites.

Efficacy Variable	Country	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy*Country)
YMRSTOT:Total(1-11)	America	Olanzapine	93	32.80	6.65	-15.28	9.99	-15.09	-7.87	<.001	.668
		Placebo	48	31.71	6.38	-6.85	8.63	-7.22			
	Puerto Rico	Olanzapine	12	35.25	5.45	-20.75	9.38	-20.71	-5.97	.297	
		Placebo	6	34.67	4.37	-14.67	13.23	-14.74			

Secondary Analyses
Efficacy results from select secondary analyses were reviewed.

YMRS Individual Item Analyses
Mean change from baseline to endpoint (LOCF) for the individual items of the YMRS were analyzed. Statistically significant differences favoring olanzapine were evident for all YMRS items except sexual interest and insight (see Appendix 10.4).

CGI-BP (Severity)
Mean change from baseline to endpoint (LOCF) for CGI-BP Severity of Mania, Depression and Overall were analyzed. Statistically significant differences favoring olanzapine were found for CGI-BP Severity – Mania and CGI-BP Severity-Overall, but not for CGI-BP Severity-Depression (see Table 6.1.3.7). Patients enrolled in this clinical trial were exhibiting acute manic or mixed bipolar symptoms. In the olanzapine group, 42% (44/105) exhibited manic symptoms and 58% (61/105) exhibited mixed symptoms at baseline. In the placebo group, 54% (29/54) exhibited manic symptoms and 46% (25/54) exhibited mixed symptoms at baseline. The CGI-BP Depression mean scores at baseline indicated mildly ill severity while the CGI-BP Mania and Overall mean scores at baseline indicated moderate-markedly ill severity.

Table 6.1.3.7 Sponsor's Table. CGI-BP Severity for Mania, Depression and Overall

Table HGIU.11.23. CGI-BP Severity (Mania, Depression, Overall) Mean Change from Baseline to Endpoint (LOCF) Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
CGI Severity Depression	Olanzapine	105	3.12	1.59	-0.86	1.21	-0.89	-0.10	.533
	Placebo	54	2.65	1.60	-0.54	1.04	-0.80		
CGI Severity Mania	Olanzapine	105	4.81	0.69	-1.70	1.29	-1.73	-0.67	<.001
	Placebo	54	4.81	0.75	-1.04	1.12	-1.05		
CGI Severity Overall	Olanzapine	105	4.81	0.71	-1.60	1.30	-1.63	-0.64	<.001
	Placebo	54	4.83	0.75	-0.98	1.17	-0.99		

Children's Depression Rating Scale - Revised
No statistically significant differences were found between olanzapine and placebo for mean change from baseline to endpoint for CDRS-R Total Score (The CDRS-R contains 17 anchored items, most are rated from 1 to 7 for severity; maximum score = 113). Some statistical differences were found for individual items – one favored olanzapine (sleep disturbance) and three items favored placebo (appetite disturbance, excessive fatigue, and depressed facial affect) [See Appendix 10.5]. Most of these statistical differences on individual items could have been related more to the side effect profile of olanzapine. Of note, the baseline mean score for suicidal ideation[1] was 1.77 in the olanzapine group and 1.42 in the placebo group, mean change

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1 CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to

to endpoint was -0.47 and -0.23 respectively (p = NS) [one of the exclusion criterion was "patients who have been judged clinically to be at serious suicidal risk"]. A further analysis and discussion of the suicidal ideation item is in Section 7.1.5 (Less Common Adverse Events).

Table 6.1.3.8 Sponsor's Table. CDRS-R Total Score

Table HGIU.11.24.   CDRS-R Total Score
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Difference	*P-value
CDRS Raw Total Score	Olanzapine	100	40.43	15.60	-7.18	12.09	-8.37	1.14	.508
	Placebo	53	35.77	15.35	-5.85	13.27	-9.50		

Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHDRS) and Overt Aggression Scale (OAS)
Statistically significant differences favoring olanzapine were found for the mean change from baseline to endpoint in the ADHDRS hyperactivity-impulsivity subtotal (-4.96 vs. -1.62, p = 0.008) and the ADHDRS total score (-9.47 vs. -3.97, p = 0.048) [See Appendix 10.6]. It should be noted that at baseline, there were more patients with comorbid ADHD in the olanzapine group compared to the placebo group (42% vs. 24%, p = 0.024). The Sponsor did not provide changes in the ADHDRS separately for patients with and without comorbid ADHD.
Statistically significant differences favoring olanzapine were found for the mean change from baseline to endpoint for all subscales (except physical aggression towards self) and total score for the OAS. Comorbid conduct disorder was present in a small number of patients (olanzapine n = 14, placebo n = 1). See Appendix 10.6.

Subgroup Analyses
The Sponsor evaluated the following subgroups: gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features, rapid vs. nonrapid cycling.
Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds (p = 0.094), patients with psychotic features (p = 0.111) and rapid cyclers (p = 0.271). The mean change to endpoint was similar in both the patients with and without psychotic features; failure to show efficacy in patients with psychotic features may have been due to the small sample size (n = 20 olanzapine, n = 7 placebo). The mean change to endpoint was also similar in both rapid and nonrapid cyclers – again, the small sample size in the rapid cycler

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himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does ont understand the concept of suicide), usually when angry; 4 = intermediate rating, not anchored; 5 = has recurrent thoughts of suicide; 6 = intermediate rating, not anchored; 7 = has made a suicide attempt within the last month or is actively suicidal

subgroup may have contributed to the negative findings. A significant treatment-by-age interaction was found.

Table 6.1.3.9 Sponsor's Table. YMRS Total Score - Subgroup Analyses

Efficacy Variable	Subgroup	Strata	N Therapy	n	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy* Subgroup)
YMRSTOT:Total(1-11)	Gender	Female	75 Olanzapine	45	32.69	6.41	-14.73	10.06	-20.07	-5.98	.005	.213
			Placebo	30	33.17	6.38	-9.27	9.33	-14.10			
		Male	84 Olanzapine	60	33.37	6.69	-16.78	10.01	-17.47	-9.87	<.001	
			Placebo	24	30.63	5.85	-5.79	9.35	-7.60			
	Age	< 15	69 Olanzapine	49	32.78	6.96	-14.63	10.17	-16.61	-4.49	.094	.089
			Placebo	20	32.40	5.70	-9.45	10.96	-12.12			
		>=15	90 Olanzapine	56	33.34	6.21	-17.02	9.87	-18.90	-9.86	<.001	
			Placebo	34	31.82	6.59	-6.71	8.39	-9.03			

Efficacy Variable	Subgroup	Strata	N Therapy	n	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy* Subgroup)
YMRSTOT:Total(1-11)	Origin	Caucasian	111 Olanzapine	70	32.84	6.90	-14.17	9.58	-13.90	-6.95	<.001	.570
			Placebo	41	31.05	6.40	-6.49	8.85	-6.95			
		Non-Caucasian	48 Olanzapine	35	33.54	5.85	-19.37	10.16	-20.00	-9.19	.005	
			Placebo	13	35.15	4.58	-11.62	10.44	-10.82			
	Mania Type	Manic	73 Olanzapine	44	34.50	5.63	-16.43	10.67	-17.44	-5.59	.019	.160
			Placebo	29	33.10	5.20	-10.07	9.15	-11.85			
		Mixed	86 Olanzapine	61	32.05	7.00	-15.52	9.62	-19.66	-9.70	<.001	
			Placebo	25	30.80	7.15	-5.00	9.16	-9.96			
	Psychotic features	N	132 Olanzapine	85	32.53	6.49	-15.94	9.82	-18.07	-7.92	<.001	.739
			Placebo	47	31.72	6.09	-7.62	9.58	-10.15			
		Y	27 Olanzapine	20	35.40	6.45	-15.75	11.17	-7.71	-7.24	.111	
			Placebo	7	34.14	7.24	-8.43	8.89	-0.46			

Subgroup	Strata	N Therapy	n	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy* Subgroup)
Rapid Cycling	N	114 Olanzapine	71	32.97	6.48	-15.63	9.17	-18.75	-7.64	<.001	.885
		Placebo	43	32.51	6.56	-7.72	9.55	-11.11			
	Y	29 Olanzapine	24	33.50	7.07	-16.79	12.70	-13.67	-6.35	.271	
		Placebo	5	30.60	4.22	-7.40	10.57	-7.32			

The Sponsor further evaluated the age subgroup in post hoc analyses since the findings suggested a differential effect. Three additional analyses were performed: age as a continuous variable, age subgroups defined as < 16 and ≥ 16 years of age and age subgroups defined by age at last birthday. The treatment-by-age interaction was not significant in the first two analyses, but the last analysis did not show a similar treatment effect (i.e. change to endpoint) for the 14 year olds compared to the 13, 15, 16 and 17 year olds. In this last analysis, neither the 14 year old subgroup nor the 17 year old subgroup showed a statistically significant treatment effect, the

smaller sample size in the 17 year old group could have contributed to those findings. See Appendix 10.7 for these additional analyses.

The Sponsor also evaluated the subgroups with or without past or current ADHD or ODD diagnoses. Statistically significant differences favoring olanzapine occurred within each subgroup with no differences between patients with and without a past or current ADHD diagnosis or between patients with and without a past or current ODD diagnosis (data not shown).

6.1.4 Efficacy Conclusions

The mean modal daily dose of olanzapine was 10.7 mg and the mean daily dose was 8.9 mg. Seventy-nine percent of patients in the olanzapine group and 65% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIU was change from baseline in the Adolescent-Structured YMRS Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -7.66, $p < 0.001$).

The supportive OC analysis was similar to the LOCF analysis (LS Mean Diff = -5.74, $p = 0.001$). The supportive MMRM analysis was similar to the LOCF analysis (LS Mean Diff = -6.95, $p < 0.001$). The LOCF analysis for the secondary endpoint CGI-Severity Mania and CGI-Severity Overall were statistically significant favoring olanzapine.

Subgroup analyses included gender, age ($< 15, \geq 15$), Caucasian vs. nonCaucasian, manic vs. mixed, psychotic vs. without psychotic features and rapid vs. nonrapid cycling. Statistically significant differences favoring olanzapine were found for all subgroups except < 15 year olds ($p = 0.094$), patients with psychotic features ($p = 0.111$) and rapid cyclers ($p = 0.271$) – the latter two groups had few patients in those subgroups. A significant treatment-by-age interaction was found.

Since HGIU was a flexible-dose study, it is not possible to evaluate the dose-response with regard to efficacy. Proposed labeling states the range that was included in the clinical trial, but no data is available to determine whether higher doses confer greater efficacy and it is likely that higher doses confer greater risk from an adverse event perspective.

7 INTEGRATED REVIEW OF SAFETY

The Sponsor used the following databases for assessment of safety (see Table 4.1.1 in Section 4.1 – Tables of Clinical Studies for more information on individual studies). For studies HGCS (n = 8), HGCR (n = 2), and HGGC (n = 23), the Sponsor included only information regarding deaths, serious adverse events and discontinuations due to adverse events.

Sponsor's Table. Databases for Summary of Clinical Safety

Table 2.7.4.1. Databases for Summary of Clinical Safety

Database	Indication	Studies Used	Number of Patients
Acute Placebo-Controlled Databases	Schizophrenia	HGIN	N=107 (Olz=72, Pla=35)
	Bipolar	HGIU	N=161 (Olz=107, Pla=54)
	Combined	HGIN, HGIU	N=268 (Olz=179, Pla=89)
Overall Olanzapine Exposure Databases	Schizophrenia	HGIN, LOAY, HGMFa	N=227
	Bipolar	HGIU, HGMFa	N=227
	Combined	HGIN, HGIU, LOAY, HGMF	N=454

a   Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

The Sponsor also included information on serious adverse events and discontinuations due to adverse events for the 37 adolescent patients who participated in the olanzapine <u>adult</u> studies:

Study HGBG and HGCL were clinical trials for adult patients aged 18 or older – two adolescent patients were enrolled in those trials (17.9 and 17.8 years of age).
Study HGDH – acute and long-term efficacy of olanzapine in first-episode psychotic patients aged 16 – 40 years (n = 7 adolescents).
Study HGGF – delaying or preventing psychosis onset in persons aged 12 to 45 years prodromal to psychosis (n = 24 adolescents).
Study HGKL – clinical trial in patients aged 15 to 65 years with borderline personality disorder (n = 4 adolescents).

"Acute Placebo Controlled Database" hereafter called HGIN + HGIU Acute Database
A total of 268 patients were included in the HGIN + HGIU Acute Database**.** Eight (4.5%) patients discontinued due to adverse events in the olanzapine treatment group.

Patient Disposition (HGIN + HGIU)

	Olanzapine N = 179	Placebo N = 89	P-value
Completers	134 (74.9%)	50 (56.2%)	0.003
Drop Outs	45 (25%)	39 (44%)	
Adverse Event	8 (4.5%)	1 (1.1%)	0.279
Lack of Efficacy	22 (12.3%)	34 (38.2%)	< 0.001
Lost to Follow-up	1 (0.6%)	0	1.00
Patient Decision	8 (4.5%)	2 (2.2%)	0.504
Criteria Not Met/Compliance	2 (1.1%)	2 (2.2%)	0.602
Sponsor Decision	1 (0.6%)	0	1.00
Physician Decision	1 (0.6%)	0	1.00
Other	2 (1.1%)	0	1.00

Modified from Sponsor table 2.7.4.20 in summary-clin-safety document

Patient demographics (HGIN + HGIU): The majority of patients were male (60%), Caucasian (70%) with a mean age of ~ 15.6 years (see Appendix 10.8). For study HGIN, the majority of patients were 16 and 17 years of age at baseline (61%); for study HGIU, the majority of patients were 14 and 15 (55%). This is expected and consistent with the psychiatric diagnoses in these two trials. A table of age distribution at baseline is in Appendix 10.8.

"Overall Olanzapine Exposure Combined Database" hereafter called Overall Combined Database
A total of 454 patients were included in the Overall Combined Database. The patient disposition by diagnoses (bipolar vs. schizophrenia) is given in Table 6.1.4.2. Twice as many patients with bipolar disorder discontinued due to an adverse event compared to patients with schizophrenia (14.5% vs. 7.9%). More than twice as many patients with schizophrenia discontinued due to lack of efficacy compared to patients with bipolar disorder (16.3% vs. 5.7%).

Sponsor's Table. Patient Disposition (Overall Combined Database)

Table 2.7.4.23.   Patient Disposition
All Patients with Olanzapine Exposure
Overall Olanzapine Exposure Combined Database

	Bipolar		Schizophrenia		Overall	
Patient Disposition	N	%	N	%	N	%
Reporting Interval Completed	130	57.3%	119	52.4%	249	54.8%
Adverse Event	33	14.5%	18	7.9%	51	11.2%
Lack of Efficacy	13	5.7%	37	16.3%	50	11.0%
Lost To Follow-Up	9	4.0%	4	1.8%	13	2.9%
Patient Decision	24	10.6%	10	4.4%	34	7.5%
Criteria Not Met/Compliance/Protocol Violation	2	0.9%	28	12.3%	30	6.6%
Sponsor Decision	3	1.3%	5	2.2%	8	1.8%
Physician Decision	10	4.4%	4	1.8%	14	3.1%
Other	3	1.3%	2	0.9%	5	1.1%
Total	227	100.0%	227	100.0%	454	100.0%

The patient demographics in the Overall Combined Database were fairly consistent with the demographics of the HGIU + HGIN Acute Database with the exception of country – 89 additional patients with schizophrenia from study LOAY (German sites) were included in the Overall Combined Database. Patient demographics for the Overall Combined Database are included in Appendix 10.8.

Methods and Findings

7.1.1 Deaths

No deaths occurred in the HGIU + HGIN Acute Database, Overall Combined Database, studies HGCS, HGCR, HGGC or in adolescent patients from the adult studies.

7.1.2 Other Serious Adverse Events

The following tables for serious adverse events were compiled from narratives provided by the Sponsor.

A total of 7 serious adverse events occurred in 6 patients in the olanzapine treatment arm in the HGIU + HGIN Acute Database (see Table 7.1.2.1).
One serious adverse event (schizophrenia) occurred in 1 patient in the placebo arm of study HGIN (no SAEs in the placebo group in study HGIU).

Table 7.1.2.1. Serious Adverse Events: HGIN + HGIU Acute Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGIN 025-2504	15 YOWF	Olanzapine DB phase	Migraine	Migraine	Severe Worsened from baseline; failed to restart study med and discontinued from study
HGIN 930-9301	15 YOWM	Olanzapine DB phase	Closed fracture of right forearm	Forearm fracture	Severe Fracture from fall, treated in hospital
HGIN 026-2603	14 YOWF	Olanzapine DB phase	Weight gain	Weight increased	Mild/moderate Onset of AE in DB phase, patient discontinued OL phase due to weight gain of 18.3 kg over 4 months
HGIU 012-1211	14 YOWF	Olanzapine DB phase	Exacerbation of bipolar symptoms	Bipolar disorder	Severe Discontinued during OL phase
HGIU 035-3501	14 YOWF	Olanzapine DB phase	Relapse of bipolar disorder	Bipolar disorder	Moderate Hospitalized, Discontinued due to weight gain
HGIU 031-3103	14 YOWM	Olanzapine DB phase	Decreased WBC count and decreased neutrophils	WBC count decreased, neutrophil count decreased	Moderate WBC 4.04 to 2.52; ANC 1.63 to 0.83; Discontinued in OL phase due to persistently low counts

A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database (see Table 7.1.2.2). The majority of these SAEs, 19/35 patients, were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

Table 7.1.2.2 Serious Adverse Events: Overall Combined Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGIN 007-0704	15 YOBM	Olanzapine OL phase	Exacerbation of schizophrenia	Schizophrenia	Severe Hospitalization, discontinuation from study
HGIN 013-1302	17 YOM	Olanzapine OL phase	Wosening of schizophrenia symptoms	Schizophrenia	Moderate
HGIN 019-1901	15 YOWF	Olanzapine OL phase	Depressive with psychotic features, weight gain	Major depression, weight increased	Severe Hospitalization, discontinuation from study
HGIN 021-2101	14 YOBM	Olanzapine OL phase	Worsening of schizophrenia	Schizophrenia	Severe
HGIN 026-2603	14 YOWF	Olanzapine OL phase	Exacerbation of schizophrenia, suicidal ideation, weight gain	Schizophrenia, weight increased	Severe (schiz) Moderate (weight) Hospitalization, weight gain of 18.3 kg over 4 months
HGIN 030-3001	17 YOWM	Olanzapine OL phase, 1st visit	Exacerbation of psychosis	Psychotic disorder	Severe Hospitalized
HGIN 910-9101	16 YOWF	Olanzapine OL phase	Worsening of Schizophrenia	Schizophrenia	Moderate Hospitalized
HGIN 930-9301	15 YOWM	Olanzapine OL phase	Closed fracture of right forearm	Forearm fracture	Severe Fracture from fall, treated in hospital
HGIN 930-9307	15 YOWF	Olanzapine OL phase	Attempted suicide	Suicide attempt	Severe Attempted overdose with Phenobarbital, hospitalized, discontinued from study
HGIU 001-0103	13 YOWM	Olanzapine OL phase	Increased agitation	Agitation	Severe Hospitalized, completed study
HGIU 001-0107	13 YOWM	Olanzapine OL phase	Agitation, aggression	Agitation, aggression	Severe Hospitalized, completed study
HGIU 001-0108	14 YOWF	Olanzapine OL phase	Alcohol intoxication, suicidal ideation	Alcohol poisoning, suicidal ideation	Severe (alcohol) Moderate (SI) Discontinued from study
HGIU 012-1202	15 YOWF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, completed study
HGIU 012-1211	14 YOWF	Olanzapine OL phase	Exacerbation of bipolar	Bipolar disorder	Severe Discontinued study

			symptoms		
HGIU 012-1212	14 YOBF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, discontinued "patient decision"
HGIU 020-2016	14 YOWF	Olanzapine OL phase	Attempted suicide	Suicide attempt	Mild Overdose of Benadryl and ibuprofen, recovered without treatment; completed study
HGIU 026-2604	16 YOHM**	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, completed study
HGIU 026-2605	14 YOM	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized and discontinued study
HGIU 026-2608	13 YOWF	Olanzapine OL phase	Exacerbation of bipolar disorder	Bipolar disorder	Severe Hospitalized, discontinued study
HGIU 027-2705	15 YOBM	Olanzapine OL period	Worsening of bipolar disorder, self-inflicted superficial lacerations	Bipolar disorder, Intentional self-injury	Severe (BP) Moderate (SIB) Hospitalized, discontinued study (cut arms with fingernails)
HGIU 027-2707	14 YOBF	Olanzapine OL phase	Worsening of bipolar disorder	Bipolar disorder	Severe Hospitalized, completed study
HGIU 028-2804	15 YOWF	Olanzapine OL phase	Recurrence of bipolar symptoms	Bipolar disorder	Severe Hospitalized, discontinued study "sponsor's decision" – GCP issues at site
HGIU 028-2805	14 YOWF	Olanzapine OL phase	Suicidal ideation	Suicidal ideation	Severe Hospitalized, discontinued – GCP issues at site
HGIU 028-2806	15 YOBF	Olanzapine OL phase	Bipolar mania	Bipolar disorder	Severe Hospitalized, discontinued study
HGIU 031-3103	14 YOWM	Olanzapine OL phase	Decreased WBC count and decreased neutrophils	WBC count decreased, neutrophil count decreased	See Table 7.1.2.1.
HGIU 033-3304	15 YOWF	Olanzapine OL phase	Intensifying aggressiveness and irritability	Aggression, irritability	Severe Hospitalized, discontinued study
HGIU 035-3519	14 YOWM	Olanzapine OL phase	Violent behavior	Aggression	Severe Hospitalized, discontinued study
HGIU 730-7302	13 YOHM	Olanzapine OL phase	Oppositional defiant behavior	Oppositional defiant disorder	Severe Hospitalized, discontinued due to noncompliance
HGMF 003-0303	17 YOWF	Olanzapine OL	Acute appendicitis	Appendicitis	Severe Hospitalized, completed study
HGMF	16 YOWF	Olanzapine	Exacerbation of	Bipolar disorder	Severe

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
003-0304		OL	bipolar illness with positive suicidal ideation		Hospitalized, discontinued study
LOAY 407-4078	17 YOWM	Olanzapine OL	Recurrence of acute psychotic symptoms	Psychotic disorder	Severe Hospitalized
LOAY 407-4207	14 YOWM	Olanzapine OL	Borrelia infection	Borrelia infection	Mild Discontinued study
LOAY 413-4145	16 YOWM	Olanzapine OL	Worsening of underlying disease schizophrenia	Schizophrenia	Severe Hospitalized Discontinued study

Table 7.1.2.3 Serious Adverse Events: HGCR, HGCS, HGGC

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
HGCR 001-2001	12 YOWM	Olanzapine OL	Headache lumbar puncture	Headache	Moderate Completed study
HGCS 001-1001	14 YOHF	Olanzapine OL	Mallory Weiss tear, vomiting blood	Esophageal hemorrhage, hematemesis	Severe Completed study
HGGC 001-2023	14 YOWF	Olanzapine	Suicidality	Depression	Hospitalized and discontinued from study

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who experienced serious adverse events (Table 7.1.2.4).

Table 7.1.2.4 Serious Adverse Events: Adolescent Patients from Adult Studies (n = 37)

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGDH 007-1607	17 YOWM	Olanzapine	Overdose	Overdose	Ingested 175 mg olanzapine, completed the study
HGGF 001-0102	15 YOWM	Olanzapine	Worsening depression with suicidal ideation	Depression, affective disorder, suicidal ideation	Gained significant amount of weight- 14 kg in 17 weeks; patient discontinued
HGGF 001-113	16 YOWF	Olanzapine	Dysphoria, Superficial self-mutilation	Dysphoria, self mutilation	Cuts on upper arm made with piece of glass, discontinued from study
HGGF 004-405	17 YOWF	Olanzapine	Auditory perceptual abnormalities, depersonalization, depressed mood, suicidal ideation, worsening psychosis	Auditory hallucination, depersonalization, depressed mood, illusion, suicidal ideation, psychotic disorder	
HGGF 004-406	17 YOWF	Olanzapine	Depressed mood, suicidal ideation	Depressed mood, suicidal ideation	Discontinued study

Narratives were provided by Sponsor upon request

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Adverse events associated with dropouts

Table 7.1.3.1.1 Discontinuations Due to Adverse Events: HGIN + HGIU Acute Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGIN 007-703	13 YOBF	Olanzapine DB phase	Clinically significant increased ALT	ALT increased	ALT up to 231 (AST up to 142) Returned to WNL after discontinuation from study
HGIN 010-1001	17 YOWM	Olanzapine DB phase	Elevated liver function	Liver function test abnormal	ALT = up to 597 AST = up to 410 GGT = up to 129 Noted at randomization visit (was taking olanzapine prior to study) Discontinued study
HGIN 021-2103	17 YOBM	Olanzapine DB phase	Elevated transaminases	Transaminases increased	AST up to 136 ALT up to 396 Returned to WNL after discontinuation from study
HGIN 910-9110	17 YOWM	Olanzapine DB phase	AST increased	AST increased	AST up to 190 (ALT up to 321) Returned to WNL after discontinuation from study
HGIN 920-9202	17 YOWM	Olanzapine DB phase	Rise ALT	ALT increased	ALT up to 393 (AST up to 179 GGT up to 82) ALT and GGT returned to WNL after discontinuation from study (AST N/A)
HGIU 035-3503	16 YOBF	Olanzapine DB phase	Heart rate increased	Elevated pulse	Holter noted sinus tachycardia Discontinued from study, pulse WNL at 4th follow-up visit
HGIU 012-1203	15 YOWF	Olanzapine DB phase	Hepatic enzyme increased	Elevated liver enzymes	AST up to 148 ALT up to 325 GGT up to 53 Returned to near WNL after discontinuation from study (ALT 48)
HGIU 035-3501	14 YOWF	Olanzapine DB phase	Weight increased	Weight gain	Weight increase of 4.5 kg in ~ 15 days

Table 7.1.3.1.2 Discontinuations Due to Adverse Events: Overall Combined Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGIN 003-0302	17 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.7 kg in 3 months
HGIN 019-1901	15 YOWF	Olanzapine OL	Weight increased	Weight gain	Gained 6.62 kg during DB phase, Gained 15.88 kg over 5.7 months
HGIN 020-2002	15 YOBM	Olanzapine OL	Sedation	Sedation	
HGIN 025-2502	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.2 kg over 183 days
HGIN 027-2701	17 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12 kg over 92 days
HGIN 027-2702	13 YOWF	Olanzapine OL	Weight increased	Weight gain	Gained 17.5 kg over 148 days
HGIN 030-3007	13 YOWF	Olanzapine OL	Increased appetite	Increased appetite	Gained 21.8 kg over 94 days
HGIN 900-9003	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.8 kg over 169 days
HGIN 930-9307	15 YOWF	Olanzapine OL	Suicide attempt	Suicide attempt	See Table 7.1.2.2
HGIN 940-9403	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 13.4 kg over 152 days
HGIU 001-108	14 YOWF	Olanzapine OL	Alcohol intoxication	Alcohol poisoning	See Table 7.1.2.2.
HGIU 007-708	15 YOWM	Olanzapine OL	Drowsiness	Somnolence	
HGIU 009-902	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 14.2 kg over 78 days
HGIU 013-1303	17 YOWF	Olanzapine OL	Syncope	Syncope	100/60 mm Hg, 88 bpm supine, 98/62 mmHg, 100 bpm standing
HGIU 013-1308	14 YOHF	Olanzapine OL	Weight gain	Weight increased	Gained 9.1 kg over 103 days
HGIU 013-1310	16 YOWF	Olanzapine OL	Increased appetite	Increased appetite	Gained 9.5 kg over ~ 56 days (at time of weight patient had been off drug for 11 days)
HGIU 013-1311	13 YOHM	Olanzapine OL	Worsened aggressive behavior	Aggression	
HGIU 019-1901	16 YOBF	Olanzapine OL	Pregnancy	Pregnancy	
HGIU 019-1907	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 17.7 kg over 170 days
HGIU 020-2007	14 YOWF	Olanzapine OL	Elevated liver function test	Liver function test abnormal	AST up to 204, ALT up to 330 Resolved after discontinuation from study
HGIU 020-2008	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 9.3 kg over 58 days

HGIU 020-2019	16 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 9.5 kg over 81 days
HGIU 024-2404	13 YOWF	Olanzapine OL	Fear of more weight gain	Fear of weight gain	Gained 5.9 kg over 34 days
HGIU 026-2608	13 YOWF	Olanzapine OL	Exacerbation of bipolar disorder	Bipolar disorder	
HGIU 027-2701	15 YOWF	Olanzapine OL	Sedation	Sedation	
HGIU 027-2704	15 YOBM	Olanzapine OL	Weight gain	Weight increased	Gained 18.6 kg over 119 days
HGIU 027-2705	15 YOBM	Olanzapine OL	Worsening of bipolar disorder	Bipolar disorder	
HGIU 028-2806	15 YOBF	Olanzapine OL	Bipolar mania	Bipolar disorder	
HGIU 031-3103	14 YOWM	Olanzapine OL	Decreased WBC	WBC count decreased	See Table 7.1.2.1.
HGIU 033-3304	15 YOWF	Olanzapine OL	Intensifying aggressiveness	Aggression	See Table 7.1.2.2
HGIU 035-3510	15 YOWM	Olanzapine OL	Weight gain	Weight increased	Gained 5.4 kg over 89 days
HGIU 035-3517	13 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 5 kg over ~6 weeks
HGIU 720-7217	15 YOHM	Olanzapine OL	Hepatic enzymes increases	Hepatic enzyme increased	AST up to 103, ALT up to 125 (also had significant weight gain, 21 kg over ~ 5 months)
HGIU 720-7219	14 YOHF	Olanzapine OL	Pregnancy	Pregnancy	
HGMF 002-0211	17 YOWF	Olanzapine OL	Somnolence	Somnolence	
HGMF 003-0304	16 YOWF	Olanzapine OL	Exacerbation of bipolar illness with positive suicidal ideation	Bipolar disorder	See Table 7.1.2.2.
HGMF 008-0806	15 YOWM	Olanzapine OL	Increased depression	Depression	
HGMF 014-1400	17 YOBF	Olanzapine OL	Elevated CK level lab	Blood creatine phosphokinase	CK up to 690 U/L
HGMF 025-2501	15 YOWM	Olanzapine OL	Drowsiness	Somnolence	
HGMF 028-2801	18 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 8.9 kg over 27 days
LOAY 405-4057	13 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 10.1 kg over 42 days
LOAY 407-4207	14 YOWM	Olanzapine OL	Suspicion of neuroborreliosis	Neuroborreliosis	See Table 7.1.2.2.
LOAY 407-4218	15 YOWF	Olanzapine OL	Galactorrhea	Galactorrhea	Prolactin up to 35 mcg/L (ULN = 29)

There were no discontinuations due to adverse events for studies HGCS, HGCR and HGGC.

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who discontinued due to adverse events (Table 7.1.3.1.3).

Table 7.1.3.1.3 Discontinuations Due to Adverse Events: Adolescent Patients from Adult Studies

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGGF 001-127	13 YOWM	Olanzapine	Weight gain	Weight increased	Gained 23 kg in ~5 months (BMI from 32 to 39)
HGKL 014-1416	15 YOWM	Olanzapine	Weight gain	Weight increased	Gained 12.5 kg over 3 months; triglycerides also increased from 260 to 508 mg/dL

7.1.4   Common Adverse Events

7.1.4.1   Eliciting adverse events data in the development program

Adverse events were obtained by spontaneous reports, patient observation and investigator query at every study visit. Rating scales were included for evaluation of extrapyramidal symptoms (SAS), akathisia (BAS) and dyskinesias (AIMS). Vital signs, ECGs and laboratory tests were obtained at intervals throughout the study.

7.1.4.2   Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the MedDRA version 8.0 coding dictionary. A sample of patient narratives was reviewed and the coding of verbatim terms to preferred terms was appropriate.

7.1.4.3   Common adverse event tables

Adverse events occurring in $\geq 2\%$ of patients in the HGIU + HGIN Acute Database is in Table 7.1.4.3.1. The majority of adverse events in this table occurred more than twice as frequently in the olanzapine group compared to the placebo group, that adverse events that were statistically more frequent in the olanzapine group were weight increased (30% vs. 6%), somnolence (25% vs. 3%), increased appetite (24% vs. 6%) and sedation (24% vs. 6%).

Table 7.1.4.3.1 Sponsor's Table. Adverse Events Occurring in ≥ 2% of Patients: HGIN +
HGIU Acute Database

	Therapy						
	Olanzapine			Placebo			
Event Classification	N	n	%	N	n	%	*P-value
Patients with >=1 TESS	179	158	88.3%	89	54	60.7%	<.001
Weight increased	179	53	29.6%	89	5	5.6%	<.001
Somnolence	179	44	24.6%	89	3	3.4%	<.001
Increased appetite	179	43	24.0%	89	5	5.6%	<.001
Sedation	179	34	19.0%	89	5	5.6%	.003
Headache	179	30	16.8%	89	11	12.4%	.374
Fatigue	179	17	9.5%	89	4	4.5%	.227
Dizziness	179	13	7.3%	89	2	2.2%	.155
Dry mouth	179	11	6.1%	89	0	0.0%	.018
Dysmenorrhoea	67	4	6.0%	41	4	9.8%	.475
Pain in extremity	179	9	5.0%	89	1	1.1%	.173
Vomiting	179	9	5.0%	89	6	6.7%	.580
Constipation	179	8	4.5%	89	0	0.0%	.055
Nausea	179	8	4.5%	89	8	9.0%	.172
Nasopharyngitis	179	7	3.9%	89	2	2.2%	.722
Abdominal pain upper	179	6	3.4%	89	5	5.6%	.514
Diarrhoea	179	6	3.4%	89	0	0.0%	.183
Irritability	179	6	3.4%	89	4	4.5%	.735
Pharyngolaryngeal pain	179	6	3.4%	89	3	3.4%	1.00
Restlessness	179	6	3.4%	89	2	2.2%	1.00
Alanine aminotransferase increased	179	5	2.8%	89	0	0.0%	.174
Dyspepsia	179	5	2.8%	89	1	1.1%	.667
Epistaxis	179	5	2.8%	89	0	0.0%	.174
Hepatic enzyme increased	179	5	2.8%	89	0	0.0%	.174
Insomnia	179	5	2.8%	89	10	11.2%	.009
Sinusitis	179	5	2.8%	89	0	0.0%	.174

Sponsor's Table 2.7.4.27 from summary-clin-safety document

The common adverse events for the two trials are listed separately in Table 7.1.4.3.2 since the
trials differed in duration (6 vs. 3 weeks) and study population. For study HGIN, the adverse
events that were statistically different between olanzapine and placebo included weight increased
(p = 0.014) and somnolence (p = 0.0006). For study HGIU, the adverse events that were
statistically different between olanzapine and placebo included weight increased (p < 0.001),
increased appetite (p < 0.001), somnolence (p < 0.001) and sedation (p = 0.011). The adverse
events and frequencies occurring in the olanzapine group between the two clinical trials were
fairly similar though more patients in HGIU exhibited somnolence (25% vs. 17%), increased
appetite (29% vs. 17%), sedation (22% vs. 15%), dry mouth (8% vs. 4%) and fatigue (14% vs.
3%)

Table 7.1.4.3.2 Adverse Events Occurring in > 2% of Patients with Olanzapine > 2x Placebo: HGIU and HGIN Clinical Trials

	Percentage of Patients Reporting Event			
	6 Week Trial % Schizophrenia Patients		3 Week Trial % Bipolar Patients	
Adverse Event	Olanzapine (N = 72)	Placebo (N = 35)	Olanzapine (N = 107)	Placebo (N = 54)
Weight increased	31%*	9%	29%*	4%
Somnolence	17%*	3%	25%*	4%
Headache	17%	6%	17%	17%
Increased appetite	17%	9%	29%*	4%
Sedation	15%	6%	22%*	6%
Dizziness	8%	3%	7%	2%
Pain in extremity	6%	3%	5%	0
Abdominal pain	4%	0	5%	7%
ALT increase	4%	0	-	-
AST increase	4%	1%	1%	0
Constipation	4%	0	5%	0
Dry mouth	4%	0	8%	0
Fatigue	3%	3%	14%	6%
Diarrhea	1%	0	5%	0
Dyspepsia	-	-	5%	0
Hepatic enzyme increased	1%	0	4%	0
Sinusitis	1%	0	4%	0

From Tables HGIN.12.4, HGIN.14.27 and HGIU.12.4 clinical study reports
   *p < 0.05

7.1.4.4   Common adverse events – further analysis

Weight Gain
Weight gain was a significant adverse event occurring in these clinical trials and is further analyzed and discussed in this section along with the weight data.

HGIU + HGIN Acute Database
In the HGIU + HGIN Acute Database, patients in the olanzapine treatment group had significantly greater weight gain and increase in BMI compared to the placebo group (see Table 7.1.4.4.1).

Table 7.1.4.4.1 Weight and BMI Data (LOCF): HGIN + HGIU Database

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	177	66.03	17.93	3.90	2.72	3.68		
	Placebo	88	67.63	17.24	0.24	2.16	0.01	3.66	< 0.001
BMI	Olanzapine	177	23.91	6.01	1.22	1.01	1.11		
	Placebo	88	23.98	5.67	0.05	0.91	-0.07	1.17	< 0.001

From Table 2.7.4.43 in summary-clin-safety document

The visit wise weight change for observed cases was similar to the LOCF analysis. The mean change at visit 6 was + 3.63 kg for olanzapine (n = 154) and + 0.08 kg for placebo (n = 67) (LS Mean Diff = 3.57, p < 0.001).

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Seventy-seven (43.5%) patients in the olanzapine group and 6 (6.8%) of patients in the placebo group had a ≥ 7% increase in body weight (p < 0.001). Only 2 patients, both randomized to placebo, had a ≥ 7% decrease in body weight.

Since studies HGIN and HGIU were different with respect to types of patients and duration of the double-blind period (HGIN 6 weeks, HGIU 3 weeks), the weight and BMI data were also evaluated separately:

Table 7.1.4.4.2. Weight and BMI Data: Study HGIU

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	105	65.33	20.55	3.66	2.18	3.51		
	Placebo	54	66.83	17.55	0.30	1.67	0.16	3.36	< 0.001
BMI	Olanzapine	105	24.21	6.82	1.18	0.85	1.15		
	Placebo	54	24.05	5.44	0.02	0.62	0.00	1.15	< 0.001

From Table HGIU.12.44 in study report

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Forty-four (41.9%) patients in the olanzapine group and 1 (1.9%) patient in the placebo group had a ≥ 7% increase in body weight (p < 0.001). No patients in the study had a ≥ 7% decrease in body weight.

Table 7.1.4.4.3. Weight and BMI Data: Study HGIN

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	72	67.04	13.31	4.26	3.33	4.22		
	Placebo	34	68.91	16.93	0.13	2.80	0.08	4.13	< 0.001
BMI	Olanzapine	72	23.45	4.59	1.39	1.21	1.37		
	Placebo	34	24.02	6.12	-0.05	1.03	-0.07	1.44	< 0.001

From Table HGIN.12.42 in study report

The results for the OC analysis for change in weight and BMI were similar to the LOCF analysis. At end of study, patients in the olanzapine group (n = 50) gained 4.95 kg from baseline and patients in the placebo group (n = 15) gained 0.61 kg [LS mean diff = 4.65, p < 0.001]. BMI increased by 1.56 in the olanzapine group and decreased by 0.04 in the placebo group [LS mean diff = 1.62, p < 0.001].

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Thirty-three (45%) patients in the olanzapine group and 5 (14.7%) of patients in the placebo group had a ≥ 7% increase in body weight (p = 0.002). Only 2 patients in the study, both randomized to placebo, had a ≥ 7% decrease in body weight.

Only 1 of the 8 discontinuations due to adverse events was due to weight gain in the HGIU + HGIN Acute Database (4.5 kg increase over ~15 days).
Unfortunately, insufficient data were collected during the follow-up visits to adequately address weight loss after patients completed the clinical trial (if they switched to a different antipsychotic). Though many of the investigators noted that the adverse event of "weight gain" had resolved at some of the follow-up visits, no actual weights were obtained for the majority of patients (or at least not recorded in the CRFs).

Overall Combined Database
Though no placebo comparison is available in this database, weight change over longer duration of time could be evaluated in general terms. Similar to the acute data, weight did appear to increase over time. This patient population (adolescents) are expected to increase in height and weight during this developmental period, however, the increases in weight are well above what would be considered expected (see Section 7.1.9 – Assessment of Effect on Growth).

Table 7.1.4.4.4. Weight and BMI Data (LOCF): Overall Combined Database

			Baseline		Change to Endpoint		
		N	Mean	Std	Mean	Std	P-value
Weight (kg)	Bipolar	224	68.58	21.21	7.63	6.62	< 0.001
	Schizophrenia	226	65.71	13.30	7.07	6.53	< 0.001
	Overall	450	67.13	17.72	7.35	6.58	< 0.001
BMI	Bipolar	216	24.92	7.34	2.37	2.39	< 0.001
	Schizophrenia	223	22.40	4.17	2.24	2.25	< 0.001
	Overall	439	23.64	6.07	2.31	2.31	< 0.001

From Table 2.7.4.45 in summary-clin-safety document

Sixty-five percent of patients in the Overall Combined Database gained ≥ 7% body weight.

The Sponsor provided a summary of weight change by visit for observed cases for the Overall Combined Database (see Appendix 10.9). For the 131 patients who completed visits > 25 and ≤ 32 weeks, the mean increase in weight was 10.8 kg (p < 0.001 compared to baseline).

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months. The patient who gained 21.8 kg did so over a period of 3 months.

For those patients in the Overall Combined Database who participated in HGIU or HGIN, the weight gain for the acute phase of these trials was also evaluated to determine whether they

gained a greater amount of weight early in the trial. These data were readily available for only 10 patients (some of the patients had been randomized to placebo and are not included here). The mean weight gain at the end of the double-blind phase of the study (or early termination) was 4.8 ± 2.6 kg, similar to the overall mean weight gain of 3.9 ± 2.7 kg in the acute database (see Table 7.1.4.4.1).

Weight – Subgroup Analyses
Because of the different duration of dosing in the HGIN and HGIU acute phases, these data were reviewed separately for each study.
The Sponsor evaluated weight changes for the subgroups gender and age (< 15, ≥ 15 years) for the adverse event "weight increased". Approximately 30% of females and males had this adverse event in the olanzapine group in both HGIU and HGIN acute studies while this adverse event was ~4% for the placebo group (with the exception of females in HGIN). No significant differences were noted between the gender subgroups (see Appendix 10.9). For the age subgroups, 28-40% had the adverse event "weight increased" in the olanzapine group compared to 0 – 14% in the placebo group. No significant differences were noted between the age subgroups (see Appendix 10.9).

Mean change in weight (kg) was also evaluated between the subgroups gender and age. These data were not included in the study report for HGIU, the Sponsor has been asked to submit these data (per the study report, only those data where results were significant were included). Data from HGIN are included in Appendix 10.9. Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine.

The Sponsor also did not include mean change in weight for the age subgroup for the HGIN + HGIU Acute Database (per the study reports, only those data where results were significant were included). The Sponsor has been asked to provide these data. In the HGIN + HGIU Acute Database, significant treatment-by-gender differences were noted (see Table 7.1.4.4.5). However, these findings are likely due to the differences in the placebo group since the weight gain (mean change to endpoint) in the olanzapine group was similar between females and males.

Table 7.1.4.4.5 Sponsor's Table. Mean Change in Weight (kg) – Gender Subgroup Analysis: HGIU + HGIN Acute Database

By Subgroup: Gender

Vital Signs	Subgroup	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean	LSMean Diff.	*P-value	**P-value
Weight in Kg	Female	106	Olz	66	61.79	16.68	3.66	2.65	3.63	3.05	<.001	.083
			Placebo	40	62.83	13.65	0.55	2.27	0.59			
	Male	159	Olz	111	68.54	18.25	4.05	2.76	3.79	4.16	<.001	
			Placebo	48	71.64	18.97	-0.03	2.05	-0.36			

Table 2.7.4.70 in Summary-clin-safety

The Sponsor was asked to evaluate the relationship of weight gain to baseline BMI. The Sponsor evaluated 4 BMI subgroups: < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30. There was a similar magnitude of weight gain by patients in each of these categories (Table 7.1.4.4.6). The percentage of patients who had a $\geq 7\%$ weight gain was greatest in the < 18 BMI group and least in the ≥ 30 BMI group (Table 7.1.4.4.7).

Table 7.1.4.4.6 Sponsor's Table. Mean Change in Weight by Baseline BMI: HGIN + HGIU Acute Database

Table 1.   Mean Change in Weight (kg) from Baseline to Endpoint (LOCF) by Baseline BMI
                  Acute Placebo-Controlled Combined Database

BMI (Baseline)	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
BMI<18	Olz	15	45.68	5.62	4.21	2.29	4.39	3.51	.005
	Placebo	10	48.19	6.54	0.70	2.89	0.88		
18<=BMI<25	Olz	107	58.84	9.37	3.52	2.53	3.24	3.12	<.001
	Placebo	49	61.18	8.41	0.50	2.16	0.12		
25<=BMI<30	Olz	30	76.31	10.29	4.44	3.61	4.25	3.93	<.001
	Placebo	19	77.50	9.32	-0.09	1.41	0.32		
BMI>=30	Olz	25	96.66	15.02	4.71	2.33	3.93	5.59	<.001
	Placebo	10	99.93	16.42	-0.90	2.37	-1.66		

Table 7.1.4.4.7 Sponsor's Table. PCS Weight Changes by Baseline BMI: HGIN + HGIU Acute Database

Table 2.   Potentially Clinically Significant Weight Changes (7% Weight Gain)
                  By Baseline BMI
                  Acute Placebo-Controlled Combined Database

Vital Signs	BMI (Baseline)	Direction	Therapy	N	n	%	*P-value
Weight in kg	BMI<18	Gain	Olz	15	12	80.0%	.005
			Placebo	10	2	20.0%	
	18<=BMI<25	Gain	Olz	107	49	45.8%	<.001
			Placebo	49	4	8.2%	
	25<=BMI<30	Gain	Olz	30	12	40.0%	.001
			Placebo	19	0	0.0%	
	BMI>=30	Gain	Olz	25	4	16.0%	.303
			Placebo	10	0	0.0%	

The Sponsor was also asked to provide data regarding the numbers of patients at baseline and endpoint who were obese (BMI > 30) and whether there were differences between the treatment groups. At baseline, 14% (25/177) of patients in the olanzapine group and 11.4% (10/88) patients in the placebo group had BMI > 30. At endpoint, 18.6% of patients in the olanzapine group and 11.4% of patients in the placebo group had BMI > 30 ($p = 0.158$, NS).

The Sponsor was also asked to provide an analysis of laboratory parameters for patients who gained > 3.9 kg (mean weight gain). The major differences between olanzapine and placebo in this subgroup are noted in Table in Appendix 10.9. The LS mean change appears to be fairly similar between this subgroup and the entire study population except for a larger increase in CPK (LS mean diff 39 vs. 16 U/L) and triglycerides (LS mean diff 54 vs. 34 mg/dL) in the subgroup with > 3.9 kg weight gain. Of course, the entire population includes this subgroup – the Sponsor was not asked to provide laboratory data for patients with < 3.9 kg weight gain.

7.1.5 Less Common Adverse Events

Hyperprolactinemia
The summary of the prolactin laboratory data is included in Sections 7.1.6 (Laboratory Findings) and 7.1.6.3 (Special Assessments). The adverse event tables were reviewed for any terms that might be related to hyperprolactinemia. In the HGIU + HGIN Acute Database, gynecomastia occurred in 1 (0.9%) patient in the olanzapine group and no patients in the placebo group and amenorrhea occurred in no patients in the olanzapine group and 1 (2.4%) patient in the placebo group.

The Overall Combined Database was evaluated since adverse events such as gynecomastia are not expected to occur with acute use but rather more long term use of antipsychotics. In the Overall Combined Database, gynecomastia occurred in 7 (4.3%) of patients (all from schizophrenia trials), galactorrhea occurred in 2 (3.1%) patients with schizophrenia and 1 (1%) patient with bipolar disorder and amenorrhea occurred in 1 (1.5%) patient with schizophrenia and 1 (1%) patient with bipolar disorder. The Sponsor has been asked to provide narrative summaries for all cases of gynecomastia – it is unknown whether this adverse event occurred in both male and female patients. If cases of gynecomastia occurred exclusively in female patients, it would be important to differentiate this adverse event from usual adolescent female physical development. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Extrapyramidal Symptoms
Due to the difference in frequency of EPS occurring in patients with schizophrenia and bipolar disorder taking antipsychotics, these data are summarized separately for each diagnostic group from the individual study reports (HGIN and HGIU).

Data for EPS is from a number of sources including rating scales (primarily the BAS and SAS), use of anticholinergic medications (though benzodiazepines may be used to treat EPS, they are more commonly used for managing psychiatric symptoms) and adverse events.

HGIN
Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.1. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown). In both the olanzapine and placebo groups, the mean change to endpoint was a decrease in rating scale score. This is not necessarily surprising depending on which

antipsychotics patients may have been taking during screening and the length of the washout period prior to obtaining the baseline rating.

Table 7.1.5.1. Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIN

EPS Variables	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Difference	*P-value
AIMS Non-Global Total(1-7)	Olanzapine	72	0.38	0.94	-0.18	0.84	-0.18	0.02	.897
	Placebo	35	0.54	1.50	-0.20	0.72	-0.21		
BRNS 4:Global Assessment of Akathisia	Olanzapine	72	0.31	0.66	-0.15	0.69	-0.15	0.05	.747
	Placebo	35	0.31	0.63	-0.20	0.76	-0.20		
Simpson-Angus Total(1-10)	Olanzapine	72	0.81	1.87	-0.22	1.51	-0.24	0.33	.260
	Placebo	35	0.97	2.41	-0.54	1.34	-0.57		

The Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined. The Sponsor has been asked to provide an analysis for the individual items of these scales.

Only 5 patients in study HGIN (acute phase) had concomitant anticholinergic medication use: 4.2% (3/72) in the olanzapine group and 5.7% (2/35) in the placebo group (p = 0.661).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.2. Adverse Events Potentially Related to EPS: HGIN

	Olanzapine N = 72	Placebo N = 35
Akathisia	2 (2.8%)	2 (5.7%)
Drooling	2 (2.8%)	0
Restlessness	2 (2.8%)	0
Dyskinesia	1 (1.4%)	0
Muscle twitching	1 (1.4%)	0
Musculoskeletal stiffness	1 (1.4%)	0
Cogwheel rigidity	0	1 (2.9%)
Tremor	0	1 (2.9%)

From Sponsor Table HGINB.14.27 in study report

Open-Label Phase HGIN
Noteworthy EPS-related adverse events occurring in the open-label phase of HGIN included oculogyration (n = 1, 0.4%) and opisthotonus (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for these events.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIN. The mean change to endpoint on the AIMS was -0.12 ± 0.94. The incidence of "treatment emergent" dyskinesia was 2.6% - again, it is

unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

HGIU

Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.3. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown) – though the mean baseline scores were numerically higher in the olanzapine group.

Table 7.1.5.3 Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIU

EPS Variables	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
AIMS Non-Global Total(1-7)	Olanzapine	105	0.16	0.90	-0.10	0.71	-0.12	-0.10	.289
	Placebo	54	0.04	0.19	0.00	0.19	-0.02		
BRNS 4:Global Assessment of Akathisia	Olanzapine	105	0.20	0.49	-0.04	0.44	-0.06	-0.09	.264
	Placebo	54	0.09	0.35	0.06	0.60	0.03		
Simpson-Angus Total(1-10)	Olanzapine	105	0.24	0.89	0.02	0.93	0.02	0.04	.769
	Placebo	54	0.07	0.33	-0.02	0.14	-0.02		

As with study HGIN, the Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined.

Only 5 patients in study HGIU (acute phase) had concomitant anticholinergic medication use, all in the olanzapine group: 4.7% (5/107) in the olanzapine group and 0% (0/54) in the placebo group (p = 0.169).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.3. Adverse Events Potentially Related to EPS: HGIU

	Olanzapine N = 107	Placebo N = 54
Restlessness	4 (3.7%)	2 (3.7%)
Musculoskeletal stiffness	3 (2.8%)	0
Tremor	2 (1.9%)	0
Akathisia	1 (0.9%)	0
Drooling	1 (0.9%)	0
Dysarthria	1 (0.9%)	0
Dyskinesia	1 (0.9%)	0
Muscle tightness	1 (0.9%)	0
Muscle twitching	1 (0.9%)	0
Salivary hypersecretion	1 (0.9%)	0

From Sponsor's table HGIU.14.30 in study report

Open-Label Phase HGIU
Noteworthy EPS-related adverse events occurring in the open-label phase of HGIU included oculogyration (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for this event.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIU. The mean change to endpoint on the AIMS was -0.03 ± 0.30. The incidence of "treatment emergent" dyskinesia was 0.7% - again, it is unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

Suicidality

The Sponsor included an analysis of suicide-related events, specifically the incidence of possible suicidal behavior or ideation, in the HGIN + HGIU Acute Database. These data were summarized for the Overall Combined Database. The following suicide-related categories were included: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, self-injurious behavior (intent unknown), not enough information (fatal), not enough information (non-fatal).

The analysis for events included categorizing suicidal behaviors as follows: suicidal behavior or ideation (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation), suicidal behavior (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior), suicidal ideation (includes suicidal ideation) and possible suicidal behavior or ideation (includes all categories). The searches included the subsequent visit (if available) after stopping treatment.

To identify cases, all preferred AE term, verbatim AE terms and comments of clinical trial data were searched for the following: accident, attempt, burn, cut, drown, gas, gun, hang, hung, immolat, injur, jump, monoxide, mutilat, overdos, self-damag, self-harm, self-inflict, self-damage, self harm, shoot, slash, suic, poison, asphyxiation, suffocation, firearm. All blinded patient listings were independently reviewed by two members of the Sponsor's medical staff "trained to evaluate suicide-related events". If a discrepancy arose, the case was discussed between them and, if necessary, a third reviewer was consulted to achieve consensus.

HGIN + HGIU Acute Database
Three possible suicidal behaviors or ideation events were identified, all three occurred in study HGIU. Two events occurred in patients treated with olanzapine (self-injurious behavior [intent unknown] in a 14.2 YOWF, suicidal ideation in a 14.6 YOWF) and one occurred in a patient receiving placebo (self-injurious behavior [intent unknown] in a 13.9 YOWM). The Sponsor's brief description of the event (from the case narratives) are provided in Appendix 10.10. No statistical differences were noted between treatment groups. The risk ratio was calculated as 1.01 (95% CI [0.09, 10.88], p = 1.000). Additional analyses (Mantel-Haenszel risk diff) also did not show statistical differences between the olanzapine and placebo groups (data not shown).

Overall Combined Database

Twenty-four cases of possible suicidal behaviors or ideation were identified – two of these events occurred in olanzapine-treated patients during the acute phase of study HGIU. The events were as follows: completed suicide (n = 0), suicide attempt (n = 2), preparatory acts toward imminent suicidal behavior (n = 2), suicidal ideation (n = 13), self-injurious behavior (intent unknown) (n = 6), not enough information (fatal) (n = 0), not enough information (non-fatal) (n = 1). The number of days to the event ranged from 4 to 214 (mean/SD = 73.5 ± 57.4 days, median = 57 days). The cases occurred in the following trials: HGIN (4), HGIU (13), HGMF (2), LOAY (5).

It is more difficult to ascertain whether a medication is associated with this adverse event in this database due to lack of a comparison group as well as the presence of a psychiatric disorder that can be associated with suicidal behaviors (esp. bipolar disorder). Of the 24 cases of suicide-related behaviors, 15 (62%) occurred in bipolar patients.

This reviewer also evaluated the individual item "suicidal ideation" in the Children's Depression Rating Scale-Revised. Though rating scales may not capture this specific adverse event, these data were reviewed to see if any trends in worsening occurred on the suicide-related item. For the CDRS[2], most patients scored a "1" at baseline. For patients who scored > 1, most showed improvement (decrease in score). Two patients in the placebo group had worsening on this item; one patient had an increase from a 1 to a 3 and another from a 2 to a 3 severity rating. Two patients in the olanzapine group had worsening on this item; one patient had an increase from a 2 to a 3 and another from a 2 to a 4 severity rating. Of note, 3 patients had a severity rating of 7 at baseline (all were randomized to olanzapine). The Sponsor will be asked to provide details regarding inclusion of these patients in the clinical trial.

Hostility and Aggression Adverse Events

Similar to the strategy used to identify possible suicide-related behaviors, the Sponsor identified patient cases for hostility and aggression. The following categories were used for these cases: aggressive behavior with physical harm directed toward another person, aggressive behavior with physical harm directed toward animals, aggressive behavior with physical harm directed toward objects, aggressive behavior with nonspecific information, aggressive behavior with indirect or no potential for direct physical harm, hostility without aggression, anger without hostility or aggressive behavior, violent ideation with no anger, hostility or aggressive behavior, and does not meet case definition.

In the HGIN + HGIU Acute Database, 7 cases were identified (1 case in HGIN, 6 cases in HGIU). Four cases occurred in patients in the olanzapine treatment groups. The olanzapine

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2 CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does ont understand the concept of suicide), usually when angry; 4 = intermediate rating, not anchored; 5 = has recurrent thoughts of suicide; 6 = intermediate rating, not anchored; 7 = has made a suicide attempt within the last month or is actively suicidal

cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, hostility without aggression and anger without hostility or aggressive behavior. The placebo cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, and hostility without aggression. Given the patient population, it is surprising that not more cases of hostility or aggression were identified. However, overtly hostile patients or patients with a strong history of hostility or aggression would be less likely to be enrolled in a clinical trial. No statistical differences were noted between treatment groups (data not shown).

In the Overall Combined Database, 23 cases of possible hostility or aggression-related events were identified: HGIN (5), HGIU (13), HGMF (1), LOAY (4). It is not unexpected for hostility or aggressive behaviors to be exhibited by patients with inadequately controlled symptoms of schizophrenia or bipolar disorder.

7.1.6 Laboratory Findings

The data from the HGIN + HGIU Acute Database was the primary source of data reviewed. When individual patient labs were being reviewed, it was noticed that many labs were missing from the study reports – most commonly the last (third) page of labs for many patients. Though all of the lab data appeared to be present in the JMP datasets, it was sometimes more difficult to look for trends or other signals using the dataset than the individual lab profile.

7.1.6.1 Overview of laboratory testing in the development program

During the acute 3 week trial labs were obtained as follows:
Clinical chemistry, electrolytes – baseline and weekly during trial
Lipids - baseline and weekly during trial; fasting glucose/lipids were obtained at baseline and end of study
Hematology - baseline and weekly during trial
Urinalysis – baseline and end of study
TSH – screening only
Prolactin – baseline and end of study
HbA1c – screening and end of study for patients with known diabetes
Hepatitis screen, urine drug screen, pregnancy test – screening only

7.1.6.2 Standard analyses and explorations of laboratory data

7.1.6.2.1 Analyses focused on measures of central tendency

The mean change from baseline to endpoint for the laboratory evaluations for HGIN + HGIU Acute Database is included in Appendix 10.11. Statistically significant decreases in lab parameters in the olanzapine group compared to placebo included hematocrit, hemoglobin, erythrocyte count, basophils, mean cell volume, albumin, total bilirubin and direct bilirubin – though these mean changes were small. Statistically significant increases in lab parameters in

the olanzapine group compared to placebo included ALT, AST, GGT, fasting glucose, cholesterol, LDL cholesterol, triglycerides, uric acid, prolactin, eosinophils and urea nitrogen.

The mean change from baseline to endpoint for selected laboratory parameters is in Table 7.1.6.2.1.1 below. For ALT and AST, the standard deviation at *baseline* in these laboratory parameters for the olanzapine group was very large (SD > mean) compared to the SD at baseline in the placebo group. For change to endpoint, the SD is still quite large in the olanzapine group compared to the placebo group indicating considerable variability and some significant increases in these parameters. The fasting glucose, triglyceride and cholesterol data were converted from SI units to the more conventional mg/dL units in this table.

It should be noted that there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. Elevated baseline prolactin was more common in study HGIN, as would be expected. A cursory review of the JMP dataset found that approximately 17% of patients in HGIN had a baseline prolactin > 30 ng/ml (maximum baseline prolactin = 65 ng/ml). The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range. Of note, the Sponsor did acknowledge this limitation and provided some additional analyses (see Section 7.1.6.3 – Special Assessments).

Table 7.1.6.2.1.1. Select Laboratory Analytes of Interest: HGIN + HGIU Acute Database

			Baseline		Change to Endpoint				
		N	Mean	Std	**Mean**	Std	LS Mean Change	LS Mean Difference	P-value
Alkaline Phosp (U/L)	Olanzapine	175	152.3	82.3	**-1.3**	25.6	-2.7		
	Placebo	87	138.7	86.9	**-4.0**	16.6	-5.3	2.6	0.396
ALT (U/L)	Olanzapine	175	24.1	45.9	**19.95**	54.84	28.11		
	Placebo	87	20.4	13.0	**-3.08**	11.69	5.13	22.98	< 0.001
AST (U/L)	Olanzapine	175	24.5	29.9	**6.43**	26.41	9.89		
	Placebo	87	23.6	8.5	**-2.47**	7.51	0.98	8.91	0.002
GGT (U/L)	Olanzapine	175	19.0	12.3	**7.47**	20.02	7.73		
	Placebo	87	17.7	8.5	**-0.43**	5.96	-0.16	7.89	< 0.001
Glucose, fasting (mg/dL)*	Olanzapine	135	88.1	9.91	**2.70**	10.4	2.70		
	Placebo	64	89.7	10.27	**-2.88**	10.1	-3.06	5.59	< 0.001
Cholesterol (mg/dL)*	Olanzapine	175	161.0	32.0	**13.1**	22.78	12.74		
	Placebo	87	160.2	32.8	**-1.16**	24.32	-1.54	14.29	< 0.001
Triglycerides (mg/dL)*	Olanzapine	175	104.4	58.4	**29.2**	80.53	26.55		
	Placebo	87	110.6	64.6	**-4.42**	54.87	-6.19	33.63	< 0.001
Prolactin (mcg/L)	Olanzapine	163	14.06	9.92	**11.44**	14.52	10.51		
	Placebo	80	14.95	11.86	**-0.16**	10.69	-1.15	11.66	< 0.001

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113

Since urinalysis for ketones, glucose and protein is noted as 1+, 2+ etc., no mean change from baseline was provided for these parameters. It was noted, however, that there were no patients with PCS changes in these parameters (defined as increase ≥ 2) in either the olanzapine or placebo groups. Only 1 patient exhibited a PCS change in urinalysis – protein in the Overall Combined Database.

In the HGIN + HGIU Acute Database, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes). There was no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

7.1.6.2.2 Analyses focused on outliers or shifts from normal to abnormal

Percentage of patients with statistically significant treatment-emergent abnormal high laboratory values at any time (HGIN + HGIU Acute Database).
AST –27.6% of olanzapine and 3.8% of placebo-treated patients ($p < 0.001$)
ALT - 38.6% of olanzapine and 2.5% of placebo-treated patients ($p < 0.001$)
GGT – 10.1% of olanzapine and 1.2% of placebo-treated patients ($p = 0.008$)
Total bilirubin –0% of olanzapine and 7.1% of placebo-treated patients ($p = 0.001$)
Albumin –6.3% of olanzapine and 23.2% of placebo-treated patients ($p = 0.002$)
Fasting glucose – 3.7% of olanzapine and 3.2% of placebo-treated patients ($p = NS$)
Cholesterol –19.7% of olanzapine and 3.9% of placebo-treated patients ($p = 0.001$)
Triglycerides –54.7% of olanzapine and 19.6% of placebo-treated patients ($p < 0.001$)
HDL –9.7% of olanzapine and 1.2% of placebo-treated patients ($p = 0.014$) [shift to low were NS between groups]
Further analyses for shifts in fasting glucose, cholesterol, and triglycerides is included in Section 7.1.6.3 – Special Assessments.

7.1.6.2.3 Marked outliers and dropouts for laboratory abnormalities

In the HGIN + HGIU Acute Database, six patients discontinued due to elevations in ALT and/or AST. See Table 7.1.3.1.1 in Section 7.1.3.1 (Adverse events associated with dropouts).

The Sponsor did not provide a summary of marked outliers in the laboratory analysis. The individual patient labs and/or JMP datasets were reviewed from HGIN and HGIU study reports to identify marked outliers. It should be noted that the marked outliers in Table 7.1.6.2.3.1. may include lab values that were less than the potentially clinically significant (PCS) abnormalities defined by the Sponsor. For example, the cholesterol PCS was defined as > 15.516 mmol/L (> 599 mg/dL), whereas the values noted as marked outliers were usually lower than this PCS value. Of note, there was no defined PCS for triglycerides.

Table 7.1.6.2.3.1 includes the marked outlier (in bold font), other related analytes at the same timepoint, end of acute study value for the marked outlier (resolution?) and a column for comments which included any additional values for the marked outlier in the open-label phase. Individual patient profiles were not readily available so it is not known if resolutions in marked outlier values were related to decreases in olanzapine dose.

Table 7.1.6.2.3.1. Marked Outliers for Laboratory Values – HGIN and HGIU

			Marked Outlier Related Analytes at Same Timepoint *(Italics = values > ULN)*			
Patient	Lab Analyte	Reference Range*	Baseline	Highest	End of Study	Comments
HGIU 005-501	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	102.6 125.9 68.7	**1237** (v.4) *220.8* NA	*389.4* *205.8* 90.0	TG = *160* at v.307 EOS
HGIU 012-1203	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	18 19 0.41 18	**325** (v.5) **148** 0.29 *53*	*230* (150 repeat) *92* (51 repeat) 0.29 (0.18 repeat) *48* (52 repeat)	ALT = *48*, AST = 24 at v. 501 (follow-up)
HGIU 012-1207	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	45 49 0.53 30	**147** (v.4) *60* 0.41 **163**	**147** 60 0.41 **163**	None
HGIU 013-1303	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	110.6 178.8 123.9	**261.9** (v.5) 179.5 *95.7*	**261.9** 179.5 95.7	TG = 111 at v.306
HGIU 019-1901	Creatine Phosphokinase	0 – 169 U/L	83	**256** (v.5)	*256*	CK = 168 at v. 301 (repeat 72)
HGIU 020-2007	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	67.2 149.8 98.8	**536.3** (v.4) 165.6 NA	*365.5* *231.7* 120.8	*TG = 103 at v. 307*
HGIU 020-2011	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	22 19 0.41 11	**124** (v.6) *87* 0.29 27	**124** *87* 0.29 27	ALT = 11 at v. 309
HGIU 026-2607	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	59.3 201.5 125.9	**324.8** (v.4) 171.8 62.9	179.6 164.9 84.9	TG = 72 at v. 310
HGIU 027-2704	Creatine Phosphokinase	0 – 363 U/L	326	**619** (v.6)	**619**	CK = 261 at v. 307
HGIU 031-3103	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	16 19 1 13	**135** (v.4) 35 0.82 **153**	*75* *62* 0.53 *87*	ALT = 33/25 at v. 302
HGIU 035-3503	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	62.8 164.9 120.8	**317.7** (v.4) 167.6 74.9	100 203.9 *141.7*	None
HGIU 035-3518	Creatine Phosphokinase	0 – 187 U/L	55	**257** (v.6)	**257**	CK = 56 at v. 310
HGIU	ALT	6 – 43 U/L	43	**208** (v.6)	**208**	ALT = *99* at

036-3607	AST TBili GGT	10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	27 0.71 36	*91* 0.29 *65*	*91* 0.29 *65*	v. 307
HGIU 720-7202	Creatine Phosphokinase	0 – 363 U/L	71	**650** (v.5)	**650**	CK = 70 at v. 310
HGIU 720-7203	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	11 15 0.41 21	**128** (v.6) *58* 0.29 *98*	**128** *58* 0.29 *98*	ALT = 15 at v. 310
HGIU 720-7210	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	108.8 172.6 109.6	**382.3** (v.4) 195.7 88.0	*171.7* 199.6 127.8	TG = *148* at v. 310
HGIU 720-7214	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	38 31 0.71 20	**448** (v.6) **164** 0.41 46	**448** **164** 0.41 46	ALT = *69* at v. 302
HGIU 720-7217	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	20 32 0.88 21	**125** (v.6) *103* 0.53 35	**125** *103* 0.53 35	ALT = *58* at v. 308
HGIU 720-7221	Glucose, fasting	70 – 115 mg/dL	86.5	**145.9 (v.4)**	72	Glucose = 77 at v. 306
HGIU 730-7302	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	22 29 0.29 13	**123** (v.5) *77* 0.18 27	41 28 0.18 22	ALT = 16 at v. 310
HGIN 003-302	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	19 17 0.29 10	**132** (v.9) 38 0.29 18	**132** 38 0.29 18	ALT = 27 at v. 305
HGIN 004-401	ALT AST TBili GGT	6 – 43 U/L 10 - 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	18 19 0.18 19	*39* **157** (v.4) 0.18 18	19 25 0.41 17	AST = 22 at v. 309
	Creatine Phosphokinase	0 – 363 U/L	289	**7289** (v.4)	*610*	CPK = *781* at v. 309 (was *1766* at v. 306)
HGIN 006-602	ALT AST TBili GGT	6 – 43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	22 27 0.88 44	**240** (v.8) **141** 0.29 **206**	*134* *60* 0.53 *216*	ALT = 32 AST = *49* GGT = 38 at v. 308
	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	136.3 171.8 96.9	**532.7** (v.7) *210.8* NA	*207.1* 185.7 102.7	TG = 93 at v. 308
HGIN 007-703	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	29 33 0.41 11	**231** (v.6) **142** 0.41 *34*	*199* *101* 0.29 *34*	ALT = *66*, AST = 33 at v. 501 (follow-up)
HGIN 007-705	Creatine Phosphokinase	0 – 408 U/L	115	**855** (v.8)	189	CK = 141 at v. 305
HGIN 016-1601	ALT AST	6 – 43 U/L 10 – 40 U/L	23 26	**159** (v.6) *67*	36 32	ALT = 43 at v. 309

	TBili	0.18 – 1.23 mg/dL	*1.41*	1.23	1.11	
	GGT	0 – 51 U/L	22	*64*	36	
HGIN 017-1703	ALT	6 – 43 U/L	*60*	**210** (v.5)	*79*	ALT = 15 at v. 309
	AST	10 – 40 U/L	40	*96*	*50*	
	TBili	0.18 – 1.23 mg/dL	0.18	0.18	0.29	
	GGT	0 – 33 U/L	23	29	18	
HGIN 020-2004	ALT	6 – 34 U/L	21	**163** (v.5)	18	ALT = 9 at v. 309
	AST	10 – 40 U/L	21	*87*	22	
	TBili	0.18 – 1.23 mg/dL	0.29	0.29	0.18	
	GGT	0 – 33 U/L	29	*81*	*43*	
HGIN 021-2102	ALT	6 – 34 U/L	8	**105** (v.9)	**105**	ALT = 13 at v. 307
	AST	10 – 40 U/L	19	*90*	*90*	
	TBili	0.18 – 1.23 mg/dL	0.29	0.41	0.41	
	GGT	0 – 33 U/L	12	23	23	
	Triglycerides	38.9 – 123.9 mg/dL	84.9	111.5	109.7	TG = *293*
	Cholesterol	124.7 – 211.6 mg/dL	201.5	**289.6** (v.6)	*237.4*	Chol = *240*
	LDL	59.1 – 136.7 mg/dL	102.7	*165.6*	132.8	at v. 307
HGIN 021-2103	ALT	6 – 43 U/L	16	**396** (v.7)	**396**	ALT = *154*,
	AST	10 – 40 U/L	20	**136**	**136**	AST = 36 at
	TBili	0.18 – 1.23 mg/dL	0.41	0.41	0.41	v. 502
	GGT	0 – 51 U/L	18	*63*	*63*	(follow-up)
HGIN 030-3002	ALT	6 – 43 U/L	11	**175** (v.7)	*61*	ALT = 39 at v. 309
	AST	10 – 40 U/L	19	*69*	*60*	
	TBili	0.18 – 1.23 mg/dL	0.71	0.29	0.29	
	GGT	0 – 51 U/L	23	*72*	48	
HGIN 033-3301	Triglycerides	31.8 – 124.8 mg/dL	87.6	**426.5** (v.9)	**426.5**	None
	Cholesterol	129.7 – 203.9 mg/dL	*214.7*	*214.7*	*214.7*	
	LDL	64.1 – 132.8 mg/dL	*139.8*	*149.8*	*149.8*	
HGIN 900-9003	Triglycerides	37.2 – 147.8 mg/dL	85.8	**270.8** (v.8)	195.6	TG = 143 at v. 307
	Cholesterol	113.9 – 197.7 mg/dL	118.1	167.2	147.1	
	LDL	61.8 – 129.7 mg/dL	82.6	84.5	79.5	
HGIN 900-9006	Triglycerides	37.2 – 147.8 mg/dL	*231*	**363.7** (v.7)	170.8	AST = 23 at v.309
	Cholesterol	113.9 – 197.7 mg/dL	194.5	*241.3*	228.2	
	LDL	61.8 – 129.7 mg/dL	107.3	130.9	*147.9*	
HGIN 900-9010	ALT	6 – 43 U/L	20	*68*	35	AST = 31/29 at v. 309
	AST	10-40 U/L	26	**161** (v.8)	31	
	TBili	0.18 – 1.23 mg/dL	0.41	0.47	0.65	
	GGT	0 – 51 U/L	20	20	15	
HGIN 910-9101	ALT	6 – 34 U/L	*65*	*51*	16	GGT = *46* at v. 309
	AST	10 – 40 U/L	27	38	24	
	TBili	0.18 – 1.23 mg/dL	0.47	0.23	0.18	
	GGT	0 – 33 U/L	*36*	**95** (v.5)	26	
HGIN 910-9103	ALT	6 – 43 U/L	29	**141** (v.6)	36	ALT = 23 at v. 309
	AST	10-40 U/L	30	*84*	38	
	TBili	0.18 – 1.23 mg/dL	0.35	0.76	0.53	
	GGT	0 – 51 U/L	22	29	20	
HGIN 910-9105	Glucose, Fasting	70 – 115 mg/dL	108	**127.9** (v.9)	*127.9*	Glucose, fasting = 92 at v. 309
HGIN 910-9107	Triglycerides	37.2 – 147.8 mg/dL	132.7	**285.8** (v.4)	*178.8*	TG = 107 at v. 309
	Cholesterol	113.9 – 197.7 mg/dL	190	*213.5*	197.7	
	LDL	61.8 – 129.7 mg/dL	128.2	118.9	127.0	
HGIN	ALT	6-43 U/L	40	**117** (v.5)	28	ALT = 28 at

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910-9108	AST	10-40 U/L	20	*52*	23	v. 309
	TBili	0.18 – 1.23 mg/dL	0.35	0.35	0.35	
	GGT	0 – 51 U/L	32	34	23	
HGIN 910-9110	ALT	6-43 U/L	25	**321** (v.5)	*128*	ALT = 17, AST = 19 at v. 501 (follow-up)
	AST	10-40 U/L	25	**190**	*53*	
	TBili	0.18 – 1.23 mg/dL	0.47	0.59	0.41	
	GGT	0 – 51 U/L	19	37	29	
HGIN 920-9202	ALT	6-43 U/L	15	**393** (v.6)	**393** (231 repeat)	ALT = 20 at v. 501 (follow-up), AST NA
	AST	10-40 U/L	19	**177**	**177** (59 repeat)	
	TBili	0.18 – 1.23 mg/dL	1	1	1 (0.71 repeat)	
	GGT	0 – 51 U/L	27	*78*	*78* (82 repeat)	
HGIN 920-9207	Triglycerides	31.8 – 124.8 mg/dL	123.9	**336.3** (v.6)	**336.3**	None
	Cholesterol	129.7 – 203.9 mg/dL	*205.0*	*233.2*	*233.2*	
	LDL	64.1 – 132.8 mg/dL	*135.1*	126.2	126.2	

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259, bilirubin = 17.1 (micromol/L to mg/dL)

Very few patients exhibited an increase in fasting glucose that might be considered a marked outlier in the HGIN + HGIU Acute Database. In reviewing the JMP dataset, 3 patients were noted with markedly elevated fasting glucose in the open-label phase of HGIN and HGIU:

Patient HGIN-900-9011 was randomized to placebo in the DB phase and had a baseline fasting glucose of 110 mg/dL. At visit 301, fasting glucose was 169 mg/dL on 7.5 mg olanzapine which normalized with continued dosing at 10 mg to 97 mg/dL at end of the study.
Patient HGIN 910-9108 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 95 mg/dL. At visit 7 of the acute phase, fasting glucose was 101 mg/dL, at visit 303 fasting glucose was 149 mg/dL on 20 mg olanzapine which normalized with continued dosing to 94 mg/dL at visit 309.

Patient HGIU 026-2602 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 104 mg/dL. At visit 6 of the acute phase, fasting glucose was 112 mg/dL, at visit 310 fasting glucose was 205 mg/dL on 12.5 mg olanzapine and at visit 501 (follow-up) fasting glucose was 113 mg/dL.

The Sponsor did not include prolactin in the list of analytes for definitions of potentially clinically significant changes. For purposes of this review, the laboratory data in the JMP database was reviewed and a PCS value of $\geq$ 40 ng/ml was arbitrarily chosen. Prolactin levels were obtained at screening, baseline, end of study in the double-blind acute phase of HGIN and HGIU and visit 305 (HGIN) and 307 (HGIU) (~8-10 weeks into OL) and end of OL phase. The reference ranges used for prolactin were males 2.8 – 22 ng/ml and females 3.2 – 20 ng/ml. – per protocol amendment.
However, in the summary-clin-safe-app, the following Covance adolescent reference ranges were noted:

Gender	Age	Low (ug/L)	High (ug/L)
Male	12<=Age<14	2.84	24.0
	14<=Age<19	2.76	16.1
Female	12<=Age<14	2.52	16.9
	14<=Age<19	4.20	39.0

In the double-blind phase of HGIU, 13% (13/99) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 99/107 patients]. Only 3 of the 13 patients were male. The mean prolactin concentration at the end of study for this subgroup was 50.4 ± 8.3 ng/ml.

In the double-blind phase of HGIN, 17% (11/64) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 64/72 patients]. Only 4 of the 11 patients were male. The mean prolactin concentration at the end of study for this subgroup was 55.8 ± 15.8 ng/ml. One patient receiving placebo in the acute HGIN study had an increase from 18.2 ng/ml at baseline to 42.4 ng/ml at end of study. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

With the exception of one patient, it is not known whether these patients exhibited any clinical symptoms associated with hyperprolactinemia (narratives not available for these cases). Galactorrhea was not reported as an adverse event in the acute phases of HGIU or HGIN and one patient in the olanzapine group had the adverse event "gynecomastia" (see Section 7.1.4.3 Special Assessments). Patient HGIU 028-2804, who had an increase in prolactin concentration to 129.7 ng/ml, exhibited bilateral galactorrhea. Of note, one female patient in the LOAY study (data not included here) discontinued due to the adverse event galactorrhea – the narrative stated that her prolactin increased to 35 ng/ml. Therefore, clinical symptoms may have been associated with these prolactin elevations. It is possible that patients, especially adolescents, might be reluctant to report the types of adverse events associated with hyperprolactinemia.
Some patients who continued into the open-label phase had a decrease in their prolactin concentrations, others did not. Due to time constraints, this reviewer was unable to evaluate each case to determine whether decrease/resolution of hyperprolactinemia was related to a reduction in olanzapine dose.

Table 7.1.6.2.3.2. Prolactin Outliers: HGIN + HGIU Acute Database

Patient	Age/Gender	Prolactin (ng/ml)		
		Baseline	End of Double-Blind Phase	End of Open-Label Phase
HGIU 010-1005	14 YOM	23.4	60.7	17.6
HGIU 012-1216	16 YOM	18.9	51.1	51.6
HGIU 019-1901	16 YOF	9.2	43.8	35.0
HGIU 019-1905	14 YOF	18.8	44.5	32.6
HGIU 020-2007	14 YOF	16.5	57.6	14.5
HGIU 020-2011	13 YOF	8.1	57.5	10.9
HGIU 020-2020	16 YOF	12.7	44.4	40.3
HGIU 021-2103	17 YOF	20.6	45.1	13.5
HGIU 024-2403	15 YOF	31.1	49.8	31.5
HGIU 024-2405	13 YOM	15.2	40.3	24.3
HGIU 026-2602	13 YOF	20.2	50.3	49.5
HGIU 028-2803	15 YOF	31.6	68.1	11.7
HGIU 035-3517	13 YOF	13.8	42.3	17.4
HGIN 005-503	14 YOF	17.2	90.7	45.5
HGIN 013-1303	16 YOF	17.3	48.3	NA
HGIN 020-2003	17 YOF	26.3	79.9	NA
HGIN 021-2102	16 YOF	30.8	59.9	16.7
HGIN 026-2602	15 YOF	36	41.5	9.6
HGIN 026-2603	14 YOF	33	44.9	59.4
HGIN 030-3010	13 YOF	17.4	55	NA
HGIN 034-3401	16 YOM	22.7	43.8	30.4
HGIN 900-9006	17 YOM	28	55.5	40.1
HGIN 910-9107	16 YOM	45.8	48.2	43.2
HGIN 940-9408	15 YOM	12	45.8	21.7

NA = not applicable, patient was not enrolled in open-label phase

Table 7.1.6.2.3.3. Prolactin Outliers: HGIN + HGIU Open Label Phase

Patient	Age/Gender	Treatment in DB Phase	Baseline	Visit #307(HGIU) #305 (HGIN)	End of Open-Label Phase Visit #310 (HGIU) Visit #309 (HGIN)
HGIU 007-704	15 YOM	Placebo	32.5	36.1	**47.3**
HGIU 019-1904	15 YOF	Placebo	5.5	28.5	**43.7**
HGIU 019-1907	15 YOF	Olanzapine	10.1	**40.6**	38.5 (v. 308)
HGIU 020-2003	13 YOF	Olanzapine	18.4	**41.8**	23.6
HGIU 021-2102	17 YOF	Olanzapine	25	**57.7**	10.6
HGIU 026-2608	13 YOF	Olanzapine	20.5	-	**57** (v. 304)
HGIU 028-2804	15 YOF	Placebo	11.8	**129.7** (v.302)	**49.8** (v. 307)
HGIU 035-3519	14 YOM	Olanzapine	28.3	-	**41.7** (v. 302)
HGIU 036-3606	16 YOF	Placebo	20.7	**59.5**	**44.0**
HGIN 900-9009	17 YOF	Olanzapine	17.5	17	**110**
HGIN 020-2005	14 YOM	Olanzapine	41.1	-	**64.7** (v. 305)

7.1.6.3   Special assessments

Hyperprolactinemia
A discussion of the adverse events potentially related to hyperprolactinemia are in Section 7.1.5
(Less Common Adverse Events). The mean change from baseline to endpoint in prolactin
concentration is in Section 7.1.6.2.1 and marked outliers are in Section 7.1.6.2.3.
As was mentioned in Section 7.1.6.2.1, there are limitations in evaluating the mean change from
baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU
could be as short as 2 days, some baseline prolactin concentrations were increased likely due to
the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin
concentration is difficult if the analysis includes patients with an elevated baseline. The Sponsor
will be asked to perform an analysis for the subset of patients with a baseline prolactin within the
normal range (including treatment by gender and treatment by age analyses).

Elevations in prolactin due to antipsychotics occur more frequently in females compared to
males. The Sponsor did include an analysis of these laboratory data by gender for the individual
HGIU and HGIN studies. For each separate study, no significant treatment by gender interaction
was found. However, there was a numerically greater mean change to endpoint in prolactin in
females (16.2) compared to males (5.4) in study HGIN. Also, for the patients with an end of

study prolactin > 40 ng/ml, the majority of these patients were female (see Section 7.1.6.2.3.).
For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction
(see Appendix 10.12), though there was a numerically greater mean change to endpoint in
females (15.6) compared to males (8.8).

Table 7.1.6.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by
Gender: Study HGIU

Laboratory Analyte	Gender	N	Therapy	n	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean	LSMean Diff.	*P-value	**P-value
PROLACTIN	Female	70	Olanzapine	43	15.23	10.01	15.38	13.73	15.96	12.75	<.001	.590
			Placebo	27	14.99	8.00	2.67	8.60	3.21			
	Male	79	Olanzapine	56	11.36	5.46	11.50	9.50	11.91	10.83	<.001	
			Placebo	23	10.00	6.40	0.66	3.06	1.08			

Table HGIU.12.13 in study report

Table 7.1.6.3.2. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by
Gender: Study HGIN

Laboratory Analyte	Gender	N	Therapy	n	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean	LSMean Diff.	*P-value	**P-value
PROLACTIN	Female	30	Olanzapine	20	17.24	10.31	16.17	22.59	14.25	17.99	.025	.258
			Placebo	10	15.95	6.67	-2.20	10.26	-3.73			
	Male	64	Olanzapine	44	14.89	13.11	5.37	14.35	5.43	9.27	.028	
			Placebo	20	20.10	19.26	-3.91	16.86	-3.84			

This reviewer could not find an analysis of prolactin concentrations by the subgroup "age". The
Sponsor will be asked to provide these data.

The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the
acute trials (only patients with normal baseline included in this analysis). For the HGIU + HGIN
Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at
anytime compared to 6.8% of patients in the placebo group (p < 0.001). No significant
treatment-by-gender interactions were noted in this analysis, though a higher percentage of males
(41/68, 60.3%) had a high prolactin concentration at any time compared to females (14/48, 29%).

The Sponsor did evaluate prolactin concentrations over time for the Overall Combined Database.
In general, there is a decrease in mean prolactin concentration over the course of the 32 weeks
which approaches baseline concentrations. There are still outliers in this analysis at the 19-32
week timepoint. The Sponsor will be asked to provide a similar summary for only those patients
completing the 19-32 weeks.

Table 7.1.6.3.3. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints:
Overall Combined Database

Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points
Overall Olanzapine Exposure Combined Database

Database	Olz Exposure	N	Mean	Std	Median	Max
Bipolar	Baseline	217	15.35	12.58	11.28	110.30
	1-6 weeks	174	26.60	16.18	23.10	129.66
	7-18 weeks	122	19.24	11.89	16.71	59.49
	19-32 weeks	83	18.03	10.42	14.36	49.53
Schizophrenia	Baseline	214	18.84	19.97	11.87	131.57
	1-6 weeks	190	31.82	20.75	26.48	110.84
	7-18 weeks	88	22.75	16.24	18.62	112.00
	19-32 weeks	93	19.01	15.60	14.81	109.97
Overall	Baseline	431	17.08	16.74	11.60	131.57
	1-6 weeks	364	29.33	18.86	25.00	129.66
	7-18 weeks	210	20.71	13.95	17.13	112.00
	19-32 weeks	176	18.55	13.38	14.70	109.97

Metabolic Parameters

The Sponsor performed more detailed analyses on several adverse event profiles including
"metabolic parameters".

The analyses included LOCF mean change from baseline to endpoint in fasting glucose and
lipids; incidence of significant changes in fasting glucose and lipids, nonfasting glucose and
lipids, weight gain-related adverse events, diabetes-related adverse events and dyslipidemia
related adverse events; mean weight over time; correlations between mean changes in weight,
glucose and lipids.

HGIN + HGIU Acute Database

LOCF mean change from baseline to endpoint:
There were statistically significant greater mean increases in fasting glucose levels (+ 2.7 mg/dL
olanzapine vs. -2.9 mg/dL placebo, p < 0.001), total cholesterol (+ 12.7 mg/dL vs. +1.5 mg/dL, p
= 0.002), and triglycerides (+27.4 mg/dL vs. -1.8 mg/dL, p = 0.007).

Significant changes in fasting glucose and lipids <u>at any time</u>:
There was a greater incidence of significant changes in patients treated with olanzapine than in
patients treated with placebo for normal to borderline total cholesterol (15.7% vs. 3.6%, p =
0.023) and for normal to high fasting triglycerides (12.4% vs. 1.9%, p = 0.039).
The change from normal to borderline LDL cholesterol was approaching statistical significance
(13.7% vs. 3.8%, p = 0.064).

The changes in fasting glucose were not statistically different:

60

Normal (< 100 mg/dL) to high ($\geq$ 126 mg/dL) = 0% (0/122) olanzapine, 2% (1/51) placebo
Impaired glucose tolerance ($\geq$ 100 mg/dL and < 126 mg/dL) to high ($\geq$ 126 mg/dL): 15.4% (2/13) olanzapine, 0% (0/13) placebo
Normal/impaired glucose tolerance (< 126 mg/dL) to high ($\geq$ 126 mg/dL): 1.5% (2/135) olanzapine, 1.6% (1/64) placebo.

The lack of a statistically significant difference in the change from impaired glucose tolerance to high fasting glucose levels (15.4% olanzapine vs. 0% placebo) is likely due to the low number of subjects enrolled with baseline impaired glucose tolerance (n = 13 each group).

Significant changes in fasting glucose and lipids at endpoint:
The only parameter that was statistically significant was normal to borderline cholesterol (14% olanzapine, 3.6% placebo, p = 0.039). The change from normal to high triglycerides was approaching statistical significance (10.6% olanzapine, 1.9% placebo, p = 0.064).

For the fasting glucose data, only 1 subject in the olanzapine treatment arm had a change from impaired glucose tolerance to high and 1 subject in the olanzapine treatment arm had a change from normal/impaired glucose tolerance to high.

In the Overall Combined Dataset, few patients had baseline impaired glucose (n = 47). Of those subjects, 6 (12.8%) had a shift from impaired glucose tolerance to high fasting glucose.
As mentioned in Section 7.1.6.2.1, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes) in the HGIN + HGIU Acute Database. There was no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

The Sponsor provided correlation coefficients of change at endpoint between weight, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (it is unclear what correlation coefficient was used):
For the Overall Combined Dataset, there were statistically significant correlations between weight and total cholesterol (corr = 0.166, p = 0.005) and between weight and triglycerides (corr = 0.210, p < 0.001).
The Sponsor was asked to provide these correlations for the HGIN + HGIU Acute Database. In this database, there were statistically significant correlations between weight and total cholesterol (corr = 0.211, p = 0.003), between weight and triglycerides (corr = 0.223, p = 0.002) and between weight and fasting glucose (corr = 0.165, p = 0.021). Though these correlations are statistically significant, they are not particularly robust.

Hepatic-related Parameters

The Sponsor performed more detailed analyses on several adverse event profiles including "hepatic-related parameters".

For this analysis, a potentially clinically significant increase is defined as a change from a value less than or equal to the PCS high limit at all baseline visits to a value greater than the PCS high limit at endpoint or for two consecutive measures during therapy.

HGIN + HGIU Database
Mean change to endpoint in hepatic laboratory analytes in provided in Section 7.1.6 (Laboratory Findings).

The Sponsor analyzed treatment emergent high values at anytime (Table 7.1.6.3.4) and at endpoint (Table 7.1.6.3.5) for alkaline phosphatase, ALT, AST, GGT and total bilirubin. A higher percentage of patients in the olanzapine group had elevations in ALT, AST and GGT for both analyses.

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at <u>Anytime</u>: HGIN + HGIU Acute Database

Table APP.2.7.4.7.2.2. Hepatic Laboratory Analytes
Treatment-Emergent Abnormally High Values Anytime
(>1 X ULN)
All Randomized Patients with Normal Baseline Values
Acute Placebo-Controlled Combined Database

Hepatic Analytes	Olanzapine			Placebo			p-value*
	N	n	%	N	n	%	
ALKPH	159	11	6.9%	77	2	2.6%	.231
ALT	153	59	38.6%	79	2	2.5%	<.001
AST	163	45	27.6%	79	3	3.8%	<.001
GGT	169	17	10.1%	83	1	1.2%	.008
T. Bili	170	0	0.0%	85	6	7.1%	.001

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at <u>Endpoint</u>:
HGIN + HGIU Acute Database

Table APP.2.7.4.7.2.24. **Hepatic Laboratory Analytes**
Treatment-Emergent Abnormally High Values at Endpoint (>1 X ULN)
All Randomized Patients with Normal Baseline Values
Acute Placebo-Controlled Combined Database

Hepatic Analytes	Olanzapine			Placebo			p-value*
	N	n	%	N	n	%	
ALKPH	159	6	3.8%	77	1	1.3%	.432
ALT	153	32	20.9%	79	1	1.3%	<.001
AST	163	19	11.7%	79	1	1.3%	.005
GGT	169	14	8.3%	83	0	0.0%	.006
T. Bili	170	0	0.0%	85	5	5.9%	.004

Abnormal ALT values at anytime
> 3X ULN: olanzapine 11.1% (17/153) vs. placebo 1.3% (1/79) p = 0.008
> 5X ULN : olanzapine 3.9% (6/153) vs. placebo 0% p = 0.098
> 10X ULN : olanzapine 0.7% (1/153) vs. placebo 0% p = 1.00

> 3X ULN ALT anytime for patients with ALT baseline $\leq$ 3X ULN:olanzapine 12.1% (21/174)
vs. 2.3% placebo (2/87) p = 0.009. [This analysis is the one that is included in proposed labeling
for ALT elevations]

Only four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and
two in the placebo group.

The Sponsor also used Hy's rule (ALT $\geq$ 3 times and TBili $\geq$ 1.5 times ULN) to identify any
patients with potential severe hepatic injury. There were no patients who met Hy's rule criteria
at any time in the clinical trials or at endpoint.

7.1.7   Vital Signs

7.1.7.1   Overview of vital signs testing in the development program

Blood pressure and heart rate were taken at every visit during the acute study – supine for 5
minutes and after standing for 2 minutes
Weight and temperature were taken at every visit
Height was taken at screening, at multiple study visits and end of study.

7.1.7.2   Standard analyses and explorations of vital signs data

7.1.7.2.1 Analyses focused on measures of central tendencies

Mean change from baseline to endpoint (LOCF) for vital signs is included in Appendix 10.13. Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events). Statistically significant differences in mean change from baseline to endpoint between the olanzapine and placebo groups were noted for:

Supine SBP: olanzapine + 2.94 mmHg, placebo - 0.71 mm Hg (p = 0.009)
Standing DBP: olanzapine + 1.42 mmHg, placebo -1.28 mmHg (p = 0.033)
Supine pulse: olanzapine + 7.07 bpm, placebo - 0.60 bpm (p < 0.001)
Standing pulse: olanzapine +6.97 bpm, placebo - 0.89 bpm (p < 0.001)
Orthostatic SBP and pulse were not significantly different between olanzapine and placebo.
Weight: olanzapine +3.90 kg, placebo +0.24 kg (p < 0.001)
BMI: olanzapine + 1.22, placebo + 0.05 (p < 0.001)

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially clinically significant definitions for vital signs are in Appendix 10.14.
There were no statistically significant differences between olanzapine and placebo for percentages of patients with potentially clinically significant changes (high or low) with the exception of weight. Of note, 5.7% of olanzapine and 4.5% of placebo-treated patients exhibited orthostatic hypotension (p = NS).
The percentage of patients who gained ≥ 7% body weight was higher in the olanzapine group (43.5%) compared to the placebo group (6.8%) (p < 0.001). Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events).

7.1.7.2.3 Marked outliers and dropouts for vital sign abnormalities

Individual vital signs were reviewed from the JMP datasets. In general, few patients had markedly abnormal vital signs. Isolated systolic BP 150 – 155 mmHg was noted in both olanzapine and placebo groups, no diastolic BPs > 110 mmHg were noted and pulse rates > 130 bpm were noted in few patients but more olanzapine-treated patients than placebo-treated patients (highest pulse was 148 bpm in placebo patient).
Patient HGIU-035-3503 (16 YOBF) receiving olanzapine discontinued study HGIU due to an elevated pulse (standing pulse 140 bpm from baseline 96 bpm).

7.1.8   Electrocardiograms (ECGs)

7.1.8.1   Overview of ECG testing in the development program

The reviewer focused mainly on the two placebo-controlled acute trials, HGIN and HGIU, for evaluation of ECG data. Though the Sponsor states that differences from baseline were analyzed, it should be noted that ECGs were not obtained at baseline (visit 2), but were obtained during the screening period (visit 1):

"Twelve-lead ECGs were collected on each patient at baseline to determine the eligibility of the patient for entry into the study, and at the Final Visits of Study Period II and Study Period III to monitor the general safety of the patient during the course of the study".
Therefore, patients could be on other medications since this was the washout period prior to randomization.
Mean "baseline" ECG parameters appear fairly similar between the olanzapine and placebo groups such that any differences between the groups with regard to concomitant medications taken during screening might have been "equalized" by randomization.

7.1.8.2 Standard analyses and explorations of ECG data

7.1.8.2.1 Analyses focused on measures of central tendency

Statistically significant differences were found between olanzapine and placebo on all ECG parameters except QTcF (see Table 7.1.1.2.1.1). The most notable was the increase in heart rate in the olanzapine group (+6.3 bpm) compared to the placebo (-5.1 bpm) group ($p < 0.001$). Because of this effect on heart rate, the QTcB interval was also significantly longer in the olanzapine group compared to the placebo group.

Table 7.1.8.2.1.1. Sponsor's Table. ECG Intervals and Heart Rate: HGIN + HGIU Acute Database

ECG Intervals/ Heart Rate	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	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 ≥ 60 msec. No patients had QTcB or QTcF ≥ 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

Measure	Value	N	Baseline Mean	Std	Endpoint Mean	Std	Change Mean	Std	P-value *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

Measure	Gender	Value	N	Baseline Mean	Std	Endpoint Mean	Std	Change Mean	Std	P-value *P-value
Weight	Female	Actual	167	64.41	18.15	70.94	19.34	6.53	6.08	<.001
		Expected	167	64.41	18.15	65.05	18.29	0.64	0.73	<.001
		Z-Score	167	0.64	1.12	1.05	0.97	0.40	0.45	<.001
		Percentile	167	67.26	28.90	77.62	23.18	10.36	14.04	
	Male	Actual	283	68.74	17.30	76.58	18.64	7.83	6.81	<.001
		Expected	283	68.74	17.30	70.01	17.43	1.27	1.08	<.001
		Z-Score	283	0.47	1.13	0.94	1.05	0.47	0.44	<.001
		Percentile	283	61.35	29.74	73.98	25.20	12.64	14.23	
Height	Female	Actual	163	162.07	7.82	162.78	7.63	0.71	1.45	<.001
		Expected	163	162.07	7.82	162.35	7.75	0.27	0.37	<.001
		Z-Score	163	0.04	1.15	0.10	1.13	0.07	0.20	<.001
		Percentile	163	51.74	30.32	53.86	29.83	2.12	6.40	
	Male	Actual	277	171.88	8.86	173.09	8.26	1.21	2.48	<.001
		Expected	277	171.88	8.86	172.78	8.42	0.90	1.05	<.001
		Z-Score	277	0.00	0.95	0.04	0.92	0.04	0.26	.012
		Percentile	277	49.94	28.44	51.09	28.11	1.15	6.68	
BMI	Female	Actual	162	24.46	6.76	26.78	7.12	2.32	2.30	<.001
		Expected	162	24.46	6.76	24.66	6.83	0.20	0.17	<.001
		Z-Score	162	0.66	1.07	1.08	0.88	0.42	0.48	<.001
		Percentile	162	67.73	28.52	79.04	21.25	11.31	15.25	
	Male	Actual	277	23.16	5.58	25.46	5.57	2.30	2.33	<.001
		Expected	277	23.16	5.58	23.35	5.42	0.19	0.36	<.001

The Sponsor noted a number of limitations in the evaluation of these data. Tanner Stage information was not collected during these studies, so the pubertal effects on individual standard deviation scores for height, weight or BMI are not known. The observational period of these studies (up to 8 months) did not allow for "meaningful evaluation" of the potential effect of

olanzapine on height. Additionally, the CDC reference database is based on the US population and may not be representative of patients from Germany or Russia – both countries had significant numbers of patients in this combined database.

Adequacy of Patient Exposure and Safety Assessments

7.2.1 Extent of exposure (dose/duration)

Acute, placebo-controlled trials: Total exposure for olanzapine in adolescent patients was 4776 patient-days. The mean daily dose was 9.75 mg/day, the modal daily dose was 11.46 mg/day.

Overall olanzapine exposure combined database: Total exposure for olanzapine in adolescent patients was 48,946 patient-days. The mean daily dose was 10.56 mg/day, the modal daily dose was 11.36 mg/day.

The highest olanzapine dose allowed in trials HGIN and HGIU was 20 mg/day. The Sponsor provided exposure data regarding the numbers of patients taking olanzapine 20 mg at any time, who had a modal dose of 20 mg and who had a final dose of 20 mg.

Table 2.7.4.14. Anytime, Modal Dose, and Final Dose of 20 mg
All Randomized Patients
Acute Placebo-Controlled Combined Database

	HGIN (N= 72) n(%)	HGIU (N= 106) n(%)	Combined (N= 178) n(%)
20 mg Dose (Anytime)	21(29.17%)	13(12.26%)	34(19.10%)
20 mg Modal Dose	12(16.67%)	10(9.43%)	22(12.36%)
20 mg Final Dose	18(25.00%)	11(10.38%)	29(16.29%)

Table 2.7.4.19.   Anytime, Modal Dose, and Final Dose of 20 mg
All Patients with Olanzapine Exposure
Overall Olanzapine Exposure Combined Database

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-------------------------------------------------------------------
Summary of Patients Who Took >= 20 mg OLZ at Any Time

           Schizophrenia           Bipolar              Combined
         ---------------------  ---------------------  ---------------------
Dose      N      n     %         N      n     %         N      n     %
         ---------------------  ---------------------  ---------------------

  20     227    81    35.7%     226    52    23.0%     453    133   29.4%

  25     227     0     0.0%     226     2     0.9%     453      2    0.4%

-----------------------------------------------------------------------
Summary of Patients Who Had Modal Dose at 20 mg OLZ

             Schizophrenia           Bipolar              Combined
           ---------------------  ---------------------  ---------------------
Modal Dose   N      n     %         N      n     %         N      n     %
           ---------------------  ---------------------  ---------------------

    20      227    46    20.3%     226    26    11.5%     453    72    15.9%

-----------------------------------------------------------------------
Summary of Patients Who Had Final Dose at 20 mg OLZ

             Schizophrenia           Bipolar              Combined
           ---------------------  ---------------------  ---------------------
Final Dose   N      n     %         N      n     %         N      n     %
           ---------------------  ---------------------  ---------------------

    20      227    46    20.3%     226    30    13.3%     453    76    16.8%
```

7.2.3 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.3.1 Postmarketing experience

The Lilly Safety System was searched for spontaneously reported adverse events involving patients younger than 18 years of age treated with olanzapine for the time period of product launch through May 31, 2006. The search identified 5,633 spontaneously reported adverse events (in 2,359 case reports) for patients $\leq$ 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 $\geq$ 1% of all events in patients aged 13 – 17 years (see Table 7.2.3.1.1).

Table 7.2.3.1.1 Sponsor's Table. Potential Safety Signals in Postmarketing Database for
Patients 13 to 17 Years of Age – Proportion, PRR and Chi-Square Criteria Met

MedDRA Preferred Term (# of events in patients 13-17 years)	Proportion of Event in Patients 13-17 years (%) (N=3,288 events)	Proportion of Event in Patients 18-64 years (%) (N=68,450 events)	PRRa	Chi-Square Value
Somnolence (108)	3.28	1.60	2.06	53.39
Aggression (41)	1.25	0.33	3.76	70.36
Galactorrhoea (39)	1.19	0.32	3.67	64.51
Sedation (38)	1.16	0.46	2.50	30.41

From Sponsor table 2.7.4.79 in summary-clin-safety document

The Sponsor also included an additional table for adverse events reported with a proportion of
the event of interest > 1% of all events in patients aged 13 to 17 years not meeting additional
criteria (PRR and Chi-square) (see Table 7.2.3.1.2).

Table 7.2.3.1.2. Sponsor's Table. . Potential Safety Signals in Postmarketing Database for
Patients 13 to 17 Years of Age – Proportion Criteria Met

MedDRA Preferred Term (# of events in patients 13-17 years)	Proportion of Event in Patients 13-17 years (%) (N=3,288 events)	Proportion of Event in Patients 18-64 years (%) (N=68,450 events)	PRRa	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) (6). 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

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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) (6). The reporter stated he has also notified the FDA."

in the submission. The Sponsor will be asked to provide these reports as well as to submit any new reports that may have occurred since this search was last completed.

The MedWatch reports were incomplete and many details regarding the deaths (autopsy reports, pertinent laboratory values, clinical description of death) were not available. In some cases, it appears that the Sponsor attempted to obtain more information, it is not known to what extent these attempts were made. Fifteen of the cases occurred in the United States, a number of these cases were reported by an attorney via the legal department – it is not known if litigation is ongoing in these cases.
Of note, seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus, diabetic coma or diabetic ketoacidosis. A brief summary of these cases is in Appendix 10.15.

Safety Conclusions

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar disorder) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks). The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with > 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
HGIN + HGIU Acute Database				
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Weight (kg) Mean Change to Endpoint (OC)	3.6 (n = 154)	0.08 (n = 67)	3.57	< 0.001
BMI Mean Change to Endpoint (LOCF)	1.22	0.05	1.17	< 0.001
≥ 7% increase in body weight (%)	43.5%	6.8%	-	< 0.001
Overall Combined Database				
Weight (kg) Mean Change to Endpoint (LOCF)	7.35	-	-	< 0.001 (compared to baseline)
Weight (kg) Mean Change to Endpoint (OC)	10.8	-	-	< 0.001 (compared to baseline)
BMI Mean Change to Endpoint (LOCF)	2.31	-	-	< 0.001 (compared to baseline)
≥ 7% increase in body weight (%)	65%	-	-	-

In the Acute Database, weight gain (mean change from baseline to endpoint) was similar for the groups with baseline BMI < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30.

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months.

Weight changes were evaluated for the subgroups gender and age (< 15, ≥ 15 years). At the time this review was finalized, mean change in weight for the age subgroup analysis was only available for study HGIN (not HGIU or the Acute Database). Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine. A treatment-by-gender interaction was noted in the Acute Database, but was likely due to differences in the placebo groups since mean change in weight was similar in the olanzapine groups for males and females.

Liver Function Abnormalities
Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).
No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia
The mean change from baseline to endpoint in prolactin in the HGIN + HGIU Acute Database
was 11.44 mcg/L for the olanzapine group and -0.16 mcg/L for the placebo group (LS Mean Diff
= 11.66, p < 0.001). The washout period prior to baseline could be as short as 2 days and it was
noted that many patients had elevated prolactin at baseline. The Sponsor will be asked to
perform further analyses in the subgroup of patients with baseline prolactin within normal limits.
In study HGIN, 17% of patients in the olanzapine group had prolactin concentrations > 40 mcg/L
at end of study. In study HGIU, 13% of patients in the olanzapine group had prolactin
concentrations > 40 mcg/L at end of study. The majority of these patients were female. Three
patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin
elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and
HGIN (n = 1).

For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction,
though there was a numerically greater mean change to endpoint in females (15.6 mcg/L)
compared to males (8.8 mcg/L). The Sponsor will be asked to provide a subgroup analysis by
age. The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during
the acute trials (only patients with normal baseline included in this analysis). For the HGIN +
HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin
concentration at anytime compared to 6.8% of patients in the placebo group (p < 0.001).

Hypertriglyceridemia
The mean change from baseline to endpoint for triglycerides was 29.2 mg/dL for the olanzapine
group and -4.4 mg/dL for the placebo group (LS Mean Diff = 33.6, p < 0.001). In reviewing the
individual lab data, 11 marked outliers were noted for triglycerides at any time (> 250 mg/dL).
The most significant was an increase from 103 mg/dL at baseline to 1237 mg/dL. A higher
percentage of patients in the olanzapine group had a shift from normal to high triglycerides
(12.4%) compared to placebo (1.9%) (p = 0.039).

Hypercholesterolemia
The mean change from baseline to endpoint for cholesterol was 13.1 mg/dL for the olanzapine
group and -1.2 mg/dL for the placebo group (LS Mean Diff = 14.3, p < 0.001). A higher
percentage of patients in the olanzapine group had a shift from normal to borderline cholesterol
(15.7%) compared to placebo (3.6%) (p = 0.023).

Hyperglycemia
Olanzapine did not appear to be associated with significant hyperglycemia in this patient
population. The mean change from baseline to endpoint for fasting glucose was 2.7 mg/dL for
the olanzapine group and -2.9 mg/dL for the placebo group (LS Mean Diff = 5.59, p < 0.001).
The percentage of patients with shifts from normal to high fasting glucose and impaired glucose
tolerance to high fasting glucose were not different between olanzapine and placebo (very few
patients with impaired glucose tolerance were enrolled in the trials).

In the Overall Combined Database, 23 patients with diabetes were included (presumed since HbA1c data were available for these patients). There was no change at endpoint in this laboratory parameter though the actual duration of study participation is not known for these patients.

The Sponsor included MedWatch reports for fatalities occurring in their postmarketing database for patients 13 to 17 years of age. Though there are limitations with regard to evaluating these types of reports, it is noteworthy that there were several deaths attributed to diabetic coma, diabetic ketoacidosis and diabetes mellitus.

Extrapyramidal Symptoms
For both HGIN and HGIU, anticholinergic drug use was low in both olanzapine and placebo groups. Change from baseline to endpoint in the EPS rating scales were also similar between the olanzapine and placebo groups. Frequencies of adverse events potentially related to EPS were also low in both groups.

Suicidality
Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in bipolar disorder patients. Suicidal behaviors or ideation is not uncommon in these patients and, in the absence of a placebo comparator, it is difficult to interpret any causality to olanzapine therapy.

General Methodology

7.4.1 Explorations for dose dependency for adverse findings

All of the clinical trials, both placebo-controlled and open-label, included a flexible dosing paradigm for olanzapine. Therefore, it is not possible to evaluate the dose-dependency of adverse events.

7.4.2 Explorations for drug-demographic interactions

The drug – demographic interactions summarized here are the adverse events occurring in HGIN + HGIU Acute Database. Subgroup analyses, particularly for gender and age, for efficacy and some safety data (prolactin, weight gain, etc.) are summarized in those relevant sections of the review. Most of the patients enrolled in the pivotal clinical trials were Caucasian, therefore any analyses by race/ethnicity are of limited usefulness.

Treatment-by-gender interactions were significant for the following adverse events: myalgia, nasal congestion, sinus congestion and tremor (see Table 7.4.2.1); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.2.1. Sponsor's Table. Adverse Events – Treatment-by-Gender Interactions: HGIN + HGIU Acute Database

By Subgroup: Gender

		Therapy							
		Olanzapine			Placebo				**Homogeneity
Event Classification	Gender	N	n	%	N	n	%	*P-value	of Odds Ratio
Myalgia	Female	67	0	0.0%	41	1	2.4%	.380	.070
	Male	112	3	2.7%	48	0	0.0%	.555	
Nasal congestion	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	
Sinus congestion	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	
Tremor	Female	67	2	3.0%	41	0	0.0%	.525	.055
	Male	112	0	0.0%	48	1	2.1%	.300	

Treatment-by-age (< 15, ≥ 15 years) interactions were significant for ear pain and migraine (see Table 7.4.2.2); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.2.2. Sponsor's Table. Adverse Events – Treatment-by-Age Interactions: HGIN + HGIU Acute Database

By Subgroup: Age

		Therapy							
		Olanzapine			Placebo				**Homogeneity
Event Classification	Age	N	n	%	N	n	%	*P-value	of Odds Ratio
Ear pain	< 15	64	1	1.6%	27	0	0.0%	1.00	.100
	>=15	115	0	0.0%	62	2	3.2%	.121	
Migraine	< 15	64	0	0.0%	27	1	3.7%	.297	.062
	>=15	115	2	1.7%	62	0	0.0%	.542	

Comparing adolescent and adult data

The common adverse event tables for adults in current product labeling and the common adverse events occurring in HGIN and HGIU were compared. In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to $< 5\%$ of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

Table 7.5.1. Common Adverse Events ($\geq$ 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 ($\geq$ 5% incidence) – Adult versus Adolescents: 3 Week Acute Trials in *Bipolar Disorder*

	Adults	
	Olanzapine N = 125	Placebo N = 129
Somnolence	35%	13%
Dry mouth	22%	7%
Dizziness	18%	6%
Asthenia	15%	6%
Constipation	11%	5%
Dyspepsia	11%	5%
Increased appetite	6%	3%
Tremor	6%	3%

	Adolescents	
	Olanzapine N = 107	Placebo N = 54
Weight increased	29%	4%
Increased appetite	29%	4%
Somnolence	25%	4%
Sedation	22%	6%
Headache	17%	17%
Fatigue	14%	6%
Dry mouth	8%	0%
Pain in extremity	5%	0%

The Sponsor included an analysis of select adverse events occurring in the adult clinical trials databases and adolescent clinical trials databases. These analyses summarized all data including the open-label trials. The Sponsor was asked if a similar analysis could be done for the placebo-controlled studies only and they responded that none of the placebo-controlled studies included fasting glucose and lipid data so these analyses were not available.

Metabolic parameters (fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides):
Mean change from baseline to endpoint – the only statistically significant differences between populations was in fasting glucose and triglycerides. Mean change to endpoint for fasting glucose was 1.8 ± 13 mg/dL for adolescents and 4.9 ± 32.8 mg/dL for adults (p = 0.002), triglycerides was 23.0 ± 76 mg/dL for adolescents and 20.3 ± 124 mg/dL for adults (p = 0.007).

Treatment-emergent significant changes at any time: statistically significant differences were noted for most of the parameters with a higher percentage of adults having significant changes at any time (see Table 7.5.3).

Table 7.5.3. Treatment-Emergent Significant Changes at Any Time – Adults vs. Adolescents

```
Laboratory
Analytes              Categories                                                  Population  N   n    %    *P-value
------------------------------------------------------------------------------------------------------------------------
Fasting Glucose       Normal to High (< 100 mg/dL to >=126 mg/dL)                Adolescent 251  3   1.2%   .033
                                                                                 Adult      251 12   4.8%

                      Impaired Glucose Tolerance to High(>=100 & <126 mg/dL to >=126 mg/dL)  Adolescent  47  6  12.8%  .066
                                                                                 Adult      121 32  26.4%

                      Normal/Impaired Glucose Tolerance to High(<126 mg/dL to >=126 mg/dL)   Adolescent 298  9   3.0%  <.001
                                                                                 Adult      372 44  11.8%

Total Cholesterol     Normal to Borderline(<200 mg/dL to >=200 mg/dL and <240 mg/dL)  Adolescent 262 54  20.6%  <.001
                                                                                 Adult      216 82  38.0%

                      Normal to High(<200 mg/dL to >=240 mg/dL)                  Adolescent 262  3   1.1%   .001
                                                                                 Adult      216 15   6.9%

LDL Cholesterol       Normal to Borderline(<130 mg/dL to >=130 mg/dL and <160 mg/dL)  Adolescent 270 48  17.8%  <.001
                                                                                 Adult      241 75  31.1%

                      Normal to High(<130 mg/dL to >=160 mg/dL)                  Adolescent 270  4   1.5%   .014
                                                                                 Adult      241 14   5.8%

HDL Cholesterol       Normal to Low(>=50 mg/dL to <40 mg/dL)                     Adolescent 107 10   9.3%   .052
                                                                                 Adult      155 28  18.1%
```

```
Laboratory
Analytes              Categories                                                  Population  N   n    %    *P-value
------------------------------------------------------------------------------------------------------------------------
Fasting Triglycerides Normal to Borderline(<150 mg/dL to >=150 mg/dL and <200 mg/dL)  Adolescent 247 51  20.6%  <.001
                                                                                 Adult      253 91  36.0%

                      Normal to High(<150 mg/dL to >=200 mg/dL)                  Adolescent 247 43  17.4%   .030
                                                                                 Adult      253 65  25.7%

                      Normal to Extremely High(<150 mg/dL to >=500 mg/dL)        Adolescent 247  1   0.4%  1.00
                                                                                 Adult      253  1   0.4%
```

From Sponsor table APP.2.7.4.7.1.24 in summary-clin-safe-app document

Weight Gain

Mean change from baseline to endpoint – There was a statistically significant greater mean increase in body weight for adolescents compared to adults (see Table 7.5.4).

Table 7.5.4. Sponsor's Table. Mean Change from Baseline to Endpoint - Adolescents vs. Adults. Overall Combined Databases

		Baseline		Change to Endpoint		LSMean	LSMean	
Population	N	Mean	Std	Mean	Std	Change	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

Dosing Regimen and Administration

The proposed labeling language for Dosage and Administration is "Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg. Efficacy in adolescents with bipolar disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg per day). When dosage adjustments are

necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials."

This dosing regimen is the same used in study HGIU – though the investigators were instructed to target 10 mg within the first week if tolerated (e.g. not based on efficacy) ["if no tolerability or safety issues are apparent, the dose **must** be titrated to at least 10 mg/day by visit 4"]. In the trial, dosing in the evening was recommended due to the possibility of somnolence. The Sponsor has not made a recommendation regarding the timing of dosing in proposed labeling.

Advisory Committee Meeting

No advisory committee meeting was held for this submission.

Literature Review

The Sponsor submitted a literature review though there was no attempt to summarize key findings. The Sponsor stated that none of the reviewed articles presented safety data contradictory to the conclusions presented in the NDA. Due to time constraints for this priority application, a separate literature review was not conducted by this reviewer.

Postmarketing Risk Management Plan

The Sponsor submitted a Risk Management document outlining their proposed actions for risk minimization. The identified risks in this document included weight gain, sedation, hepatic changes, hyperprolactinemia, glucose dysregulation, dyslipidemia. For all of these safety issues, the Sponsor has proposed the following actions for pharmacovigilance: clinical trial surveillance, routine pharmacovigilance, targeted surveillance, long-term safety study and   (b) (4). For glucose dysregulation and dyslipidemia, an additional action was to perform a retrospective cohort claims database study.

Routine pharmacovigilance was defined as periodic reporting per PSUR or as appropriate. Targeted surveillance was similar but targeted weight gain, hepatic changes, glucose dysregulation and dyslipidemia. The Sponsor has proposed a long-term safety study to evaluate the safety of olanzapine in adolescent patients with schizophrenia or bipolar disorder and to estimate the incidence and prevalence of identified and potential risks associated with olanzapine treatment. The study is still in the planning phase.

(b) (4)

The actions proposed for risk minimization include product labeling and prescriber education – no details were provided regarding the latter proposal.

9 OVERALL ASSESSMENT

Recommendation on Regulatory Action

I recommend that the Division take an approvable action on NDA 20-592 SE5-040 that was filed to support the indication "treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents".

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

Recommendation on Postmarketing Actions

9.1.1 Risk Management Activity

The Sponsor included a document discussing risk management in the submission. The actions proposed for risk minimization included product labeling and prescriber education though details for the latter were not included. These actions are the minimum steps that could be taken to manage risk associated with olanzapine therapy in this patient population. Distribution of a medication education guide could reinforce risk information to patients and their families.

9.1.2 Required Phase 4 Commitments

Pivotal trial HGIU (as well as HGIN – schizophrenia; SE5-041) included a flexible-dose paradigm for olanzapine. As such, a dose-response relationship for efficacy and safety cannot be determined since the important parameters of dose and time on drug can only be addressed in a fixed dose trial. To minimize risk, it would be important to use the minimum effective dose to the extent that risk may be dose-related – however, in a flexible-dose design one cannot determine the dose-response for efficacy. I recommend that the Sponsor perform a fixed dose study in adolescent patients with bipolar disorder to better characterize the relationship of dose to efficacy and adverse events so that risk may be reduced.

Since bipolar disorder is a chronic illness, patients will likely require medication for a prolonged period. Some of the adverse events occurring in this adolescent patient population are significant (see Summary of Clinical Findings). It is important not only to identify these risks but to study the effect of interventions on these adverse events. The long-term cardiovascular risk of significant weight gain, hypertriglyceridemia and hypercholesterolemia is significant and efforts

to minimize these adverse events is important. I recommend that the Sponsor perform a clinical study to evaluate interventions (e.g. dietary modification, exercise) on these adverse events.

Labeling Review

Changes to proposed labeling are being made directly to the annotated labeling submitted by the Sponsor, this was the first PLR labeling so there were many changes from prior approved labeling. The project manager, Dr. Doris Bates, reviewed the PLR labeling against the prior approved labeling and noted any differences – especially differences that were not highlighted by the Sponsor.
In the proposed labeling, all of the "frequent" adverse events in the "Other Adverse Events Observed" section were removed and some of the adverse events in other categories (infrequent, rare) were also removed. The Sponsor has been asked to address this and had not responded at the time this review was finalized.

This section will briefly discuss some of the labeling that may require revision:
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 does not specify whether dosing should occur in the morning or evening. Since the Sponsor recommended dosing in the evening in the clinical trials, this should also be reflected in labeling.

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
All of the adverse events in the category   (b) (4)
                            The Sponsor has been asked to address this. Similar issues occur in this same section for IM olanzapine.

Clinical Trials in Adolescent Patients
ECG Changes – correct spelling of Frederica to Fredericia

Postmarketing Experience
When was the last time the Sponsor updated this section? There have been some postmarketing reports of death due to diabetic ketoacidosis occurring in adolescents – should this data be included in this section?

Comments to Applicant

Requests for information

The Sponsor has responded to the following requests and the reviewer has reviewed the responses

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.

2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.

3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the CRF, it does not appear that there is an area where the recorder could state the source of the ratings. Are both ratings, patient and parent/legal guardian, available for subjects in this study? If so, please provide these ratings and indicate the primary source for the ratings.

4. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF analysis (similar to table HGIN 14.20 for OC analysis) - with and without site 021.

5. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF and OC analysis for the US and Russia sites separately.

6. Provide patient baseline demographics and analysis for US vs. Russia sites (similar to HGIN.11.1 but comparing US vs. Russia).

7. It is noted that 50 patients were randomized at the 5 sites in Russia - 10 patients per site. Is it coincidental that 10 subjects were randomized at each of these sites? Were caps specified to the investigators such that each site could randomize no more than 10 patients?

8. Please provide patient baseline severity of illness and statistical analysis for US vs. Russia sites (similar to HGIN.11.2 but comparing US vs. Russia). Include the following variables: age of onset of illness, # of previous schizophrenia episodes, total hospitalization, length of current

episode, days since last hospitalization, psychiatric hospitalization, CGI-S, BPRS-C subscales, BPRS-C total score, PANSS subscales, and PANSS total score

9. Do study reports for HGIN and HGIU include information regarding the adverse events associated with patient drop-outs? Please indicate where this information may be found.

10. In table HGIN.11.2, it is noted that the minimum value for age for Age of Illness Onset was 5 years old for each treatment group. Please provide the study numbers for all patients with an age of illness onset < 10 years old and CRFs for these patients.

11. In table HGIN.11.2, it is noted that the minimum value for the Length of Current Episode is "0" - please clarify.

12. For Psychiatric Hospitalization in table HGIN.11.2, please clarify whether this is past or current hospitalization.

13. Please provide # of prior psychiatric hospitalizations for both treatment groups with statistical analysis for this variable.

14. In the brief summary for study HGCS, it is noted that 2 patients experienced the adverse event "intentional injury". Please provide brief summaries for these two events.

15. For study HGGC, were there any serious adverse events? The synopsis states that no patients experienced serious adverse events associated with cardiac abnormalities or weight gain - but there is no mention of other SAEs that may have occurred in this trial.

16. For the adult studies HGDH and HGGF that included adolescent patients, please submit narratives for the serious adverse events (per Table 2.7.4.4 in the summary-clin-safety document).

17. For the adult studies HGGF and HGKL, please submit narratives for the discontinuations due to adverse event cases.

18. For patient HGIU-028-2804, the narrative indicates that she experienced bilateral galactorrhea while hospitalized for a recurrence of bipolar symptoms. Please provide the prolactin concentrations that were obtained by the hospital (pending at time patient was discharged).

19. Patient HGMF-003-0304 had the SAE "exacerbation of bipolar illness with positive suicidal ideation". However, it appears that this was coded to the preferred term "bipolar disorder". Why weren't both verbatim terms coded to preferred terms - i.e. bipolar disorder and suicidal ideation?

20. For the discontinuations due to the adverse event "weight gain" in the acute and combined databases, please provide weight data for the post-study follow-up visits. Some of the narratives

have this information, but the majority indicate that the adverse event had resolved without providing weight data.

21. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.

22. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?

23. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

The following questions were submitted to the Sponsor via email on 3/19/07. The Sponsor attempted to send an email response on 3/26/07 but encountered technical difficulties. The Sponsor faxed the response on 3/27/07 and was asked to also fax the response to this reviewer (working in another location). The Sponsor did not fax the response to this reviewer. This reviewer received the response on 4/2/07 (working in office) and had insufficient time to review the responses to meet the internal NDA deadline. Of note, request #30 was not addressed in this response and the Sponsor indicated that the response will be provided at a later date.

24. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15, >= 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.

25. Please provide a subgroup analysis for age (< 15 and >=15) and gender for the variable "PCS weight change (> 7%)" for the Acute Placebo Controlled Combined Database.

26. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.

27. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.

28. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.

29. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?

30. In proposed labeling, some adverse events have been removed from the sections "other adverse events observed during the clinical trial evaluation of oral olanzapine" and "other adverse events observed during the clinical trial evaluation of intramuscular olanzapine for injection". In the former section, it appears that all of the frequently occurring AEs ("frequent") have been removed. In both sections, many adverse events that were included in the infrequent and rare categories have been removed. Please provide a justification for removal of these adverse events from proposed product labeling.

<u>Requests for additional information from the Sponsor – may be included in action letter:</u>

31. Please provide narrative summaries for the following: 8 cases of gynecomastia, 1 case of opisthotonus, 1 case of "oculogyration", and two cases with high prolactin concentrations (HGIN 900-9009, HGIN 005-503) and the cases with CPK > 500 U/L.

32. Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had "DRAFT" at the top of the page and the date of the report was 7/27/06 - have all of these reports been previously filed with the Agency?

33. For MedWatch fatality case US_010158510, the narrative states "This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in   (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

Site #	Principal Investigator	Site & Address	# Pts Randomized	# Pts Completing DB; OL
1	Gupta, Sanjay	Global Research and Consulting 515 Main Street Olean, NY 14760 USA	9	6;7
5	Bastani, Bijan	Northcoast Clinical Trials 3733 Park East Drive, Suite 100 Beachwood, OH 44122 USA	3	1;1
7	Brams, Matthew	Bayou City Research Corp 550 Westcott, #310 Houston, TX 77007 USA	11	6;5
9	Childress, Ann	Nevada Behavioral Health, Inc. 2055 W. Charlestone Blvd, Ste B Las Vegas, NV 89102 USA	2	2;0
10	Cueva, Jeanette	Bioscience Research, Llc 222 W. 14th Street New York, NY 10011 USA	5	4;3
12	DelBello, Melissa	Univ of Cincinnati Med Center 231 Albert B. Sabin Way Dept. of Psychiatry Cincinnati, OH 45267 USA	15	6;6
13	Dempsey, G. Michael	Albuquerque Neurosciences 715 Dr. Martin Luther King Jr. Ave NE ; Suite 203 Albuquerque, NM 87102 USA	8	5;3
14	Duesenberg, David	Mercy Health Research 12680 Olive Blvd, Suite 200 St. Louis, MO 63141 USA	5	5;4
16	Gracious, Barbara	Strong Memorial Hospital 300 Crittenden Blvd Dept. of Psychiatry, Box PSYCH Rochester, NY 14642 USA	6	3;1

17	Gutierrez, Rosben	Psycare, Inc. 2120 Thibodo Court, #230 Vista, CA 92083 USA	1	0;0
19	Kaczenski, Gregory	Summit Research Group, Llc 1014 Autumn Rd, Suite 3 Little Rock, AR 72211 USA	7	4;4
20	Khan, Arifulla	NW Clinical Research Center 1900 116th Ave, NE Bellevue, WA 98004 USA	16	14;9
21	Krishnasastry, Chandra	Tennessee Christian Med Center 320 Hospital Drive Madison, TN 37115 USA	4	4;2
23	Mintz, Mark	Bancroft Neurohealth 201 King's Highway South Cherry Hill, NJ 08034 USA	2	2 ;2
24	Pathak, Anjali	AP Psychiatric & Counseling Service, Inc. 5251 Emerson St Jacksonville, FL 32207 USA	5	5;3
26	Plopper, Michael	Sharp Mesa Vist Hospital 7850 Vista Hill Avenue San Diego, CA 92123 USA	7	6;3
27	Riesenberg, Robert	Atlanta Center of Med Research 811 Juniper Street Atlanta, GA 30308 USA	7	7;3
28	Robb, Adelaide	Children's National Med Center 111 Michigan Ave, NW Washington, DC 20010 USA	4	3; 0 [1]
31	Soni, Poonam	Univ of Utah School of Medicine Mood Disorder Clinic, Rm 5R218 Dept. of Psychiatry 30 N. 1900 East Salt Lake City, UT 84132 USA	4	3;2

33	Wozniak, Janet	Massachusetts General Hospital 185 Alewife Brook Parkway, Suite 200 Cambridge, MA 02138 USA	3	3;1
34	Bhatia, Prakash	Synergy Clinical Research 5577 University Avenue San Diego, CA 92105 USA	1	1;0
35	Yadalam, Kashinath	Institute for Neuropsychiatry 2829 4th Avenue Lake Charles, LA 70601 USA	10	7;3
36	Terry, William	Mountain West Clinical Trials 1166 N. Cole Road, Suite D Boise, ID 89704 USA	8	7;5
720	Varela, Alberto	Instituto Psicoterapeutico de Puerto Rico Hostos Avenue 405 San Juan, 00918 Puerto Rico	17	15;10
730	Velez, Jesus	RCMI-Clinic Research Center University District Hospital 1st Floor Clinical Research Center Rio Piedras, 00936 Puerto Rico	1	1;0

[1] Site was closed by sponsor due to protocol violations. Patients were discontinued.

10.2 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Are male or female patients, 13 to 17 years of age, but must not yet have reached their 18th birthday prior to Visit 1, when informed consent is obtained.
2. Patient must have a diagnosis of bipolar I disorder and currently display an acute manic or mixed episode (with or without psychotic features) according to DSM-IV-TR and confirmed by the K-SADS-PL. Patients must meet diagnostic criteria at Visits 1 and 2.
3. Female patients of childbearing potential (not surgically sterilized) must test negative for pregnancy at the time of enrollment based on a serum pregnancy test. Furthermore, female patients must agree to abstain from sexual activity or to use a medically acceptable method of birth control during their participation in the study.
4. Each patient and the patient's parent/authorized legal representative must understand the nature of the study. The patient's parent/authorized legal representative must sign an informed consent document and the patient must sign an informed consent document/assent document as required by local regulations.

5. Each patient and the patient's parent/authorized legal representative must have a level of understanding sufficient to perform all tests and examinations required by the protocol.
6. Patients must have a YMRS total score $\geq$ 20 at both Visits 1 and 2.
7. Patients must be capable of swallowing study medication whole (without crushing, dissolving, etc.).

Exclusion criteria
1. Are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
2. Are employed by Lilly (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
3. Patients who have participated in a clinical trial of oral olanzapine or have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.
4. Female patients who are either pregnant or nursing.
5. Patients, who, in the opinion of the investigator, are unsuitable in any other way to participate in this study including being unable to comply with the requirements of the study for any reason.
6. Patients with acute or unstable medical conditions, including (but not limited to) inadequately controlled diabetes, hepatic insufficiency (specifically any degree of jaundice), uncorrected hypothyroidism or hyperthyroidism, acute systemic infection, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic diseases (specifically current agranulocytosis with an absolute neutrophil count < 500 mm^3).
7. Patients with acute or unstable medical conditions, such that intensive care unit hospitalization for the disease is anticipated within 6 months.
8. DSM-IV-TR substance (except nicotine and caffeine) dependence within the past 30 days.
9. Patients who have undergone treatment with remoxipride within 6 months (180 days) prior to Visit 2.
10. Any concomitant medication with primarily central nervous system activity, including alternative medications, other than specified as permitted in Table HGIU.2 and HGIU.3 at Visit 2.
11. Patients who have been judged clinically to be at serious suicidal risk.
12. Patients who have experienced one or more seizures without a clear and resolved etiology.
13. Patients with a documented history of allergic reaction to olanzapine.
14. Treatment with an injectable neuroleptic $\leq$ 14 days before Visit 2.
15. Prolactin level at Visit 1 $\geq$ 200 ng/ml.
16. Patients who have previously not responded to an adequate dose and/or duration of olanzapine treatment.

17. Laboratory results, including serum chemistries, hematology, and urinalysis, must show no clinically significant abnormalities. In addition, there must be no clinical information that, in the judgment of a physician, should preclude a patient's participation at study entry.
18. Use of any concomitant medication(s) at Visit 2 as specified in Section 5.7 or expected to need treatment with any medication during the study other than what is allowed.
19. Patients who have a history of mental retardation, current comorbid autism, or current comorbid pervasive developmental disorder.
20. Patients who have used monoamine oxidase inhibitors (MAOIs) within 14 days prior to Visit 2 or are expected to need treatment at any time during this study.
21. Patients having psychosis or bipolar symptoms related to an underlying medical condition.
22. Current diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder as defined in the DSM-IV-TR.

10.3 Sponsor's Table. Schedule of Events – HGIU

Table HGIU.9.4.   Study Schedule, Protocol F1D-MC-HGIU

Description of Data	V1	V2	V3	V4	V5	V6	Sum. Visit SP II[i]	V301	V302	V303	V304	V305	V306	V307	V308	V309	V310	Sum. Visit SP III[i]	Follow-Up (V501)
Weeks until next visit	2-14 days	3 days	4 days	1	1	1		1	1	2	2	2	2	4	4	4			
Screening and Inclusion Measures																			
Informed Consent	X																		
K-SADS-PL	X																		
Study drug compliance			X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Study drug dispensed		X	X	X	X	X		X	X	X	X	X	X	X	X	X			
Safety Measures																			
Demographics	X																		
Weight and temperature	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Height	X		X		X	X		X		X	X	X	X	X	X	X	X		
Blood pressure[a] and heart rate	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Psychiatric examination	X																		
Physical examination	X																		
Electrocardiography[b]	X					X												X	
Preexisting conditions and adverse events	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
AIMS, Barnes Akathisia, Simpson-Angus	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Historical illnesses / Previous medications Family history	X																		

Description of the Data	V1	V2	V3	V4	V5	V6	Sum. Visit SP IIi	V301	V302	V303	V304	V305	V306	V307	V308	V309	V310	Sum. Visit SP IIIi	Follow-Up (V501)
Weeks until next visit	2-14 days	3 days	4 days	1	1	1		1	1	2	2	2	2	4	4	4			
Safety Measures, Cont.																			
Habits (tobacco, alcohol, drugs)	X																		
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
Visit comments	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
Patient summary including comments							X											X	
Adverse event follow-up, if necessary																			X
Laboratory Tests[c]																			
Clinical chemistry[d] / Electrolytes / Lipids[e]	X	X		X	X	X	X		X		X		X	X	X	X	X	X	
Hematology	X	X		X	X	X	X		X		X		X	X	X	X	X	X	
Urinalysis	X						X											X	
Hepatitis screen, urine drug screen[f], serum pregnancy test[f], and TSH	X																		
Prolactin[g]	X	X					X							X				X	
HgbA1c [h]	X						X							X				X	
Behavioral Intervention (optional)							X	X	X	X	X	X	X	X	X	X	X		

Description of the Data	V1	V2	V3	V4	V5	V6	Sum. Visit SP IIi	V301	V302	V303	V304	V305	V306	V307	V308	V309	V310	Sum. Visit SP IIIi	Follow-Up (V501)
Weeks until next visit	2-14 days	3 days	4 days	1	1	1		1	1	2	2	2	2	4	4	4			
Efficacy Measures																			
YMRS	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
CGI-BP Severity of Illness	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
OAS		X					X											X	
ADHDRS-IV-PI		X					X											X	
CDRS-R		X					X			X			X					X	
Health Outcome Measures																			
CHQ		X					X											X	
General																			
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
Visit comments	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X
Patient summary including comments							X											X	
Adverse event follow-up, if necessary																			X

10.4 YMRS Individual Item Analyses

Table 10.4.1. Sponsor's Table. YMRS Individual Item Analyses

Table HGIU.11.22.   YMRS Individual Items
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Difference	*P-value
YMRS1: Elevated Mood	Olanzapine	105	2.79	0.99	-1.50	1.19	-1.40	-0.71	<.001
	Placebo	54	2.74	0.78	-0.76	1.26	-0.69		
YMRS2: Increased Motor Activity-Energy	Olanzapine	105	2.95	0.90	-1.32	1.44	-1.21	-0.70	<.001
	Placebo	54	2.80	0.76	-0.52	1.13	-0.51		
YMRS3: Sexual Interest	Olanzapine	105	1.14	1.08	-0.63	0.95	-0.72	-0.14	.249
	Placebo	54	1.33	1.13	-0.59	0.94	-0.58		
YMRS4: Sleep	Olanzapine	105	2.42	1.08	-1.79	1.43	-1.98	-0.71	<.001
	Placebo	54	2.30	1.19	-0.98	1.30	-1.26		
YMRS5: Irritability	Olanzapine	105	5.48	1.32	-1.90	2.10	-2.32	-0.92	.004
	Placebo	54	5.28	1.37	-0.91	1.72	-1.40		
YMRS6: Speech(Rate and Amount)	Olanzapine	105	5.14	1.53	-2.93	2.01	-2.96	-1.59	<.001
	Placebo	54	4.69	1.66	-1.07	2.21	-1.37		
YMRS7: Language Thought Disorder	Olanzapine	105	2.24	0.58	-0.92	0.90	-1.18	-0.47	<.001
	Placebo	54	2.11	0.66	-0.37	0.90	-0.71		
YMRS8: Content	Olanzapine	105	3.41	2.29	-1.86	2.39	-2.08	-0.73	.019
	Placebo	54	3.11	2.13	-0.94	2.12	-1.35		

Efficacy Variable	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Difference	*P-value
YMRS9: Disruptive-Aggressive Behavior	Olanzapine	105	4.84	1.37	-1.84	2.12	-2.10	-0.93	.006
	Placebo	54	4.74	1.58	-0.87	1.94	-1.18		
YMRS10: Appearance	Olanzapine	105	1.18	1.05	-0.52	0.94	-0.61	-0.47	<.001
	Placebo	54	1.24	1.10	-0.09	1.17	-0.14		
YMRS11: Insight	Olanzapine	105	1.49	1.39	-0.69	1.15	-0.96	-0.19	.268
	Placebo	54	1.70	1.37	-0.61	1.45	-0.77		

10.5 Children's Depression Rating Scale - Individual Items
Table 10.5.1. Sponsor's Table. CDRS-R Individual Items

Table HGIU.11.25.   CDRS-R Individual Items
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
CDRS1: Impaired School Work	Olanzapine	100	3.64	1.83	-0.79	1.56	-1.06	-0.17	.482
	Placebo	53	3.23	1.94	-0.36	2.06	-0.89		
CDRS2: Difficulty Having Fun	Olanzapine	100	2.74	1.73	-0.33	1.54	-0.56	0.35	.103
	Placebo	53	2.49	1.85	-0.53	1.65	-0.91		
CDRS3: Social Withdrawal	Olanzapine	100	2.41	1.46	-0.37	1.34	-0.43	0.31	.098
	Placebo	53	1.98	1.65	-0.45	1.32	-0.74		
CDRS4: Sleep Disturbance	Olanzapine	100	3.36	1.67	-1.56	1.87	-1.59	-0.64	.009
	Placebo	53	2.87	1.65	-0.55	1.75	-0.96		
CDRS5: Appetite Disturbance	Olanzapine	100	1.92	1.29	0.51	1.54	0.33	1.00	<.001
	Placebo	53	1.87	1.23	-0.45	1.32	-0.66		
CDRS6: Excessive Fatigue	Olanzapine	100	2.66	2.06	-0.58	2.03	-0.75	0.56	.014
	Placebo	53	2.45	1.88	-0.98	1.78	-1.31		
CDRS7: Physical Complaints	Olanzapine	100	1.90	1.47	-0.35	1.42	-0.48	-0.02	.925
	Placebo	53	1.75	1.25	-0.23	1.38	-0.47		
CDRS8: Irritability	Olanzapine	100	4.60	1.44	-1.29	1.87	-1.29	-0.38	.124
	Placebo	53	4.45	1.53	-0.79	1.79	-0.90		

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
CDRS9: Excessive Guilt	Olanzapine	100	1.68	1.13	-0.31	0.83	-0.26	0.07	.515
	Placebo	53	1.45	0.87	-0.28	0.74	-0.33		
CDRS10: Low Self-Esteem	Olanzapine	100	2.76	1.75	-0.37	1.64	-0.49	-0.05	.824
	Placebo	53	2.23	1.35	-0.11	1.28	-0.44		
CDRS11: Depressed Feelings	Olanzapine	100	2.57	1.46	-0.45	1.33	-0.56	-0.02	.912
	Placebo	53	2.02	1.35	-0.13	1.37	-0.54		
CDRS12: Morbid Ideation	Olanzapine	100	1.81	1.35	-0.33	1.10	-0.37	-0.10	.530
	Placebo	53	1.62	1.21	-0.13	1.21	-0.27		
CDRS13: Suicidal Ideation	Olanzapine	100	1.77	1.32	-0.47	1.21	-0.44	0.03	.769
	Placebo	53	1.42	0.95	-0.23	0.91	-0.47		
CDRS14: Excessive Weeping	Olanzapine	100	1.87	1.32	-0.30	1.39	-0.39	0.04	.840
	Placebo	53	1.75	1.33	-0.26	1.60	-0.43		
CDRS15: Depressed Facial Affect	Olanzapine	100	1.90	1.17	-0.03	1.18	-0.18	0.32	.042
	Placebo	53	1.62	1.16	-0.15	1.18	-0.50		
CDRS16: Listless Speech	Olanzapine	100	1.35	0.59	-0.02	0.70	-0.09	0.13	.155
	Placebo	53	1.28	0.69	-0.09	0.77	-0.22		

Efficacy Variable	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
CDRS17: Hypoactivity	Olanzapine	100	1.49	0.95	-0.14	0.89	-0.15	0.10	.334
	Placebo	53	1.28	0.86	-0.11	0.78	-0.26		

10.6 ADHDRS and OAS Analyses

Table 10.6.1 Sponsor's Table. Mean Change from Baseline to Endpoint: ADHDRS Total Score

Table HGIU.11.26.   ADHDRS-IV-PI Total Score
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value
ADHDRS - hyperactivity-impulsivity subtotal	Olanzapine	100	13.84	6.81	-4.96	6.19	-5.29	-2.42	.008
	Placebo	50	11.56	5.39	-1.62	4.33	-2.87		
ADHDRS - Inattention subtotal	Olanzapine	99	15.21	8.02	-3.15	6.11	-4.43	-0.81	.388
	Placebo	51	13.67	7.49	-1.73	5.77	-3.62		
ADHDRS-IV inv. scored total	Olanzapine	99	73.46	16.45	-9.47	13.64	-11.36	-3.96	.048
	Placebo	50	69.72	13.86	-3.97	10.64	-7.40		

Table 10.6.2 Sponsor's Table. Mean Change from Baseline to Endpoint: Overt Aggression Scale

Table HGIU.11.27.   OAS Total and Subtotal Scores
Mean Change from Baseline to Endpoint (LOCF)
Double-Blind Period

Efficacy Variable	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Difference	*P-value
Verbal Aggression Total	Olanzapine	100	2.74	1.31	-1.17	1.65	-1.43	-0.68	.004
	Placebo	52	2.73	1.21	-0.48	1.34	-0.75		
Physical Aggression Toward Self Total	Olanzapine	100	0.84	1.12	-0.58	1.03	-0.54	-0.18	.071
	Placebo	52	0.58	0.85	-0.19	0.91	-0.36		
Physical Aggression Towards Others Total	Olanzapine	100	1.18	1.20	-0.72	1.39	-0.65	-0.42	.010
	Placebo	52	1.00	1.12	-0.15	1.26	-0.23		
Physical Aggression Toward Objects	Olanzapine	100	1.58	1.14	-0.86	1.14	-0.99	-0.36	.026
	Placebo	52	1.42	1.02	-0.40	1.19	-0.63		
Total of OAS01-OAS16	Olanzapine	100	6.34	3.67	-3.33	3.92	-3.60	-1.70	<.001
	Placebo	52	5.73	2.94	-1.23	3.08	-1.90		

10.7 YMRS Total Score – Additional Age Subgroup Analyses

Table 10.7.1 Sponsor's Table.

Table HGIU.11.19.   YMRS Total Score Age Subgroup Analysis
Mean Change from Baseline to Endpoint (LOCF)
Age as a Continuous Variable

N	Therapy	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value Age*Therapy
105	Olanzapine	33.08	6.55	-15.90	10.03	-17.65	-7.66	<.001	.626
54	Placebo	32.04	6.23	-7.72	9.42	-9.99			

Table 10.7.2 Sponsor's Table

Table HGIU.11.20.   YMRS Total Score Age Subgroup Analysis
Mean Change from Baseline to Endpoint (LOCF)
Alternative Age Subgroup Categorization

Strata	N	Therapy	n	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value Therapy*Age
<16	118	Olanzapine	79	32.91	6.72	-15.80	10.23	-17.73	-7.13	<.001	.577
		Placebo	39	32.85	6.27	-8.31	9.64	-10.61			
>=16	41	Olanzapine	26	33.58	6.09	-16.23	9.59	-17.26	-8.37	.010	
		Placebo	15	29.93	5.79	-6.20	8.95	-8.88			

Table 10.7.3 Sponsor's Table.

Table HGIU.11.21.   YMRS Total Score Age Subgroup Analysis
Mean Change from Baseline to Endpoint (LOCF)
Age Subgroups Based on Age at Last Birthday

				Baseline		Change to Endpoint		LSMean	LSMean		**P-value
Strata	N	Therapy	n	Mean	Std	Mean	Std	Change	Diff.	*P-value	Therapy*Age
13	31	Olanzapine	22	32.73	6.90	-16.50	8.94	-18.95	-10.49	.007	.068
		Placebo	9	31.89	7.52	-4.22	10.23	-8.46			
14	38	Olanzapine	27	32.81	7.15	-13.11	11.00	-13.58	0.64	.865	
		Placebo	11	32.82	4.00	-13.73	9.98	-14.22			
15	49	Olanzapine	30	33.13	6.41	-17.70	10.22	-19.73	-10.52	<.001	
		Placebo	19	33.32	6.94	-7.11	8.14	-9.21			
16	27	Olanzapine	17	34.00	6.06	-16.65	6.44	-20.18	-9.86	.008	
		Placebo	10	29.50	5.17	-6.60	9.05	-10.32			
17	14	Olanzapine	9	32.78	6.44	-15.44	14.27	-15.61	-8.35	.213	
		Placebo	5	30.80	7.46	-5.40	9.76	-7.27			

10.8 Patient Baseline Demographics – HGIN + HGIU Acute Database and Overall Combined
Database
Table 10.8.1 Sponsor's Table

Table 2.7.4.21.   Patient Demographics at Baseline
All Randomized Patients
Acute Placebo-Controlled Combined Database

Demographic Variables	Statistics/ Category	Olanzapine (N=179) n (%)	Placebo (N=89) n (%)	*P-value
Gender	Male	112(62.57)	48(53.93)	.188
	Female	67(37.43)	41(46.07)	
Age	No. of Patients	179	89	
	Mean	15.54	15.74	.200
	Median	15.54	15.62	
	Std. Dev.	1.36	1.42	
	Minimum	13.02	13.06	
	Maximum	17.99	18.00	
Origin	African Descent	30(16.76)	9(10.11)	.359
	Caucasian	123(68.72)	66(74.16)	
	East/Southeast Asian	0(0.0)	1(1.12)	
	Hispanic	20(11.17)	9(10.11)	
	Other	6(3.35)	4(4.49)	
Country	United States	133(74.30)	67(75.28)	1.00
	Puerto Rico	12(6.70)	6(6.74)	
	Russia	34(18.99)	16(17.98)	

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Table 10.8.2 Sponsor's Table. Age Distribution at Baseline (HGIN + HGIU)

Table 2.7.4.22.   Age Distribution at Baseline
                        All Randomized Patients
                        Acute Placebo-Controlled Combined Database

Age Group	HGIN n	HGIN %	HGIU n	HGIU %	Combined n	Combined %
13	9	8.4%	31	19.3%	40	14.9%
14	13	12.1%	38	23.6%	51	19.0%
15	20	18.7%	50	31.1%	70	26.1%
16	29	27.1%	27	16.8%	56	20.9%
17	36	33.6%	15	9.3%	51	19.0%
Total	107	100.0%	161	100.0%	268	100.0%

Table 10.8.3 Sponsor's Table. Patient Demographics at Baseline – Overall Olanzapine
Combined Database

Table 2.7.4.24.   Patient Demographics at Baseline
                        All Patients with Olanzapine Exposure
                        Overall Olanzapine Exposure Combined Database

Demographic Variables	Statistics/ Category	Bipolar (N=227) n (%)	Schizophrenia (N=227) n (%)	Overall (N=454) n (%)
Gender	Male	124(54.63)	162(71.37)	286(63.00)
	Female	103(45.37)	65(28.63)	168(37.00)
Age	No. of Patients	227	227	454
	Mean	15.44	16.38	15.91
	Median	15.43	16.67	16.02
	Std. Dev.	1.33	1.27	1.38
	Minimum	13.02	13.03	13.02
	Maximum	18.00	18.00	18.00
Origin	African Descent	22(9.69)	28(12.33)	50(11.01)
	Caucasian	166(73.13)	189(83.26)	355(78.19)
	East/Southeast Asian	1(0.44)	0(0.0)	1(0.22)
	Hispanic	31(13.66)	6(2.64)	37(8.15)
	Other	7(3.08)	4(1.76)	11(2.42)
Country	United States	205(90.31)	58(25.55)	263(57.93)
	Puerto Rico	21(9.25)	1(0.44)	22(4.85)
	Russia	1(0.44)	79(34.80)	80(17.62)
	Germany	0(0.0)	89(39.21)	89(19.60)

10.9 Weight Gain – Additional Analyses

Table 10.9.1. Weight Change by Visit (OC): Overall Combined Database

		Visit Week	N	Change to Maximum		
				Mean	Std	P-value
Weight (kg)	Bipolar	≤ 1	224	1.27	1.55	< 0.001
	Schizophrenia		224	1.75	1.51	< 0.001
	Overall		448	1.51	1.55	< 0.001
	Bipolar	> 1 ≤ 2	221	2.29	2.04	< 0.001
	Schizophrenia		219	2.73	1.96	< 0.001
	Overall		440	2.51	2.01	< 0.001
	Bipolar	> 2 ≤ 3	183	3.07	2.62	< 0.001
	Schizophrenia		148	3.46	2.24	< 0.001
	Overall		331	3.25	2.46	< 0.001
	Bipolar	> 3 ≤ 4	199	3.74	2.84	< 0.001
	Schizophrenia		201	4.02	2.51	< 0.001
	Overall		400	3.88	2.68	< 0.001
	Bipolar	> 4 ≤ 5	167	4.05	3.31	< 0.001
	Schizophrenia		147	4.66	2.42	< 0.001
	Overall		314	4.34	2.94	< 0.001
	Bipolar	> 5 ≤ 9	157	6.03	3.80	< 0.001
	Schizophrenia		130	7.12	3.80	< 0.001
	Overall		287	6.52	3.83	< 0.001
	Bipolar	> 9 ≤ 13	121	7.59	4.95	< 0.001
	Schizophrenia		117	8.17	4.84	< 0.001
	Overall		238	7.87	4.89	< 0.001
	Bipolar	> 13 ≤ 17	114	8.84	5.87	< 0.001
	Schizophrenia		103	9.01	6.03	< 0.001
	Overall		217	8.92	5.93	< 0.001
	Bipolar	> 17 ≤ 21	102	9.69	6.43	< 0.001
	Schizophrenia		88	10.2	6.75	< 0.001
	Overall		190	9.93	6.56	< 0.001
	Bipolar	> 21 ≤ 25	93	10.19	6.98	< 0.001
	Schizophrenia		81	10.84	6.92	< 0.001
	Overall		174	10.49	6.94	< 0.001
	Bipolar	> 25 ≤ 32	53	9.60	7.12	< 0.001
	Schizophrenia		78	11.68	7.62	< 0.001
	Overall		131	10.84	7.46	< 0.001

From Sponsor table APP.2.7.4.7.1.18 in summary-clin-safe-app document

Table 10.9.2. Adverse Event "Weight Increased" Gender Analysis: HGIU and HGIN Acute Phases

			Olanzapine			Placebo			p-value	Homogeneity of Odds Ratio
		Gender	N	n	%	N	n	%		
Weight Increased	HGIU	Female	46	16	35%	30	1	3%	0.001	
		Male	61	15	25%	24	1	4%	0.033	0.628
	HGIN	Female	21	6	29%	11	2	18%	0.681	
		Male	51	16	31%	24	1	4%	0.008	0.186
Weight Increased	HGIU	< 15 yrs	49	14	29%	20	0	0	0.007	
		≥ 15 yrs	58	17	29%	34	2	6%	0.008	0.280
	HGIN	< 15 yrs	15	6	40%	7	1	14%	0.350	
		≥ 15 yrs	57	16	28%	28	2	7%	0.045	0.868

From Sponsor Tables HGIN.14.28 and HGIU.14.31

Table 10.9.3. Mean Change in Weight (kg) – Subgroup Analyses: HGIN

				Baseline		Change to Endpoint					
	Subgroup	Therapy	n	Mean	St.Dev	Mean	St. Dev	LS Mean	LSMean Diff	P-value	P-value
HGIN											
Weight (kg)	Female	Olanzapine	21	64.0	16.6	3.8	3.7	3.4			
		Placebo	10	61.0	12.5	0.8	3.5	0.7	2.73	0.063	
	Male	Olanzapine	51	68.3	11.6	4.5	3.2	4.6			
		Placebo	24	72.2	17.6	-0.2	2.5	-0.2	4.76	< 0.001	0.140
	< 15 yrs	Olanzapine	15	64.7	14.0	6.3	4.2	5.2			
		Placebo	7	62.5	9.6	1.1	4.1	-0.2	5.37	0.009	
	≥ 15 yrs	Olanzapine	57	67.7	13.2	3.7	2.9	3.8			
		Placebo	27	70.6	18.1	-0.1	2.4	-0.1	3.84	< 0.001	0.370

From Sponsor Tables HGIN.14.47

Table 10.9.4. Mean Change from Baseline to Endpoint in Laboratory Values – Patients Who Gained > 3.9 kg vs. Placebo
The LS Mean Change and p-value for the entire population is in parenthesis for comparison purposes

	Therapy	n	Baseline Mean	Change to Endpoint 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

10.10 Patients with Possible Suicidal Behavior or Ideation Events
HGIU + HGIN Acute Database

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                                                                          Days
       Patient ID                                                          to
 (Study-Inv-Patient)   Brief Description of Event            Code   Therapy  Event   Fatal?
-----------------------------------------------------------------------------------------------

   HGIU-001-0103        THE PATIENT HAS REPORTEDLY BEEN HAVING    5   Placebo    23     No
                        DIFFICULTIES WITH DYSPHORIC MOOD.  IN MID TO
                        LATE APRIL, 2003, HE TRIED TO TIE A BELT
                        AROUND HIS NECK RESULTING IN A RASH.
   HGIU-012-1206        INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT   5   Olz    22     No
                        MARKS ON FOREARM
   HGIU-012-1211        SUICIDAL IDEATION / SUICIDAL IDEATION     4   Olz    14     No
```

Overall Combined Database

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIN-019-1901	SUICIDAL IDEATION / SUICIDAL IDEATION	4	167	No
HGIN-026-2603	SUICIDAL IDEATION / SUICIDAL IDEATION	4	135	No
HGIN-030-3001	SUBJECT IS EXPERIENCING SYMPTOMS OF DELUSIONS, AUDITORY AND VISUAL HALLUCINATIONS, AND SUICIDAL IDEATIONS SUBJECT WILL BE HOSPITALIZED FOR STABILIZATION ON TRADITIONAL MEDICATION	4	51	No
HGIN-930-9307	SUICIDE ATTEMPT / SUICIDE ATTEMPT	2	59	No
HGIU-001-0108	ALCOHOL POISONING / ETOH INTOXICATION. LSS: ON (b) (6) NEARLY SIX MONTHS AFTER STARTING STUDY DRUG, THE PATIENT WAS ADMITTED TO THE HOSPITAL WITH ALCOHOL ("ETOH") POISONING. THE PATIENT WAS RECEIVING 15MG OLANZAPINE AT THE TIME OF THE EVENT. THIS WAS THE FIRST PSYCHIATRIC HOSPITALIZATION FOR THIS 14-YEAR OLD WHO WAS BROUGHT TO THE EMERGENCY ROOM (ER) BY POLICE AFTER THE PATIENT BECAME INTOXICATED, VOICED SUICIDAL IDEATION, AND PASSED OUT AT SCHOOL. APPROXIMATELY (b) (6) (A WEEK AND A HALF A GO), THE PATIENT TRIED TO JUMP OUT OF HER MOTHER'S MOVING VEHICLE AT 55 MILES PER HOUR, BUT THE MOTHER PREVENTED HER FROM FALLING OUT.	3	157	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIU-012-1206	INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM	5	22	No
HGIU-012-1211	SUICIDAL IDEATION / SUICIDAL IDEATION	4	14	No
HGIU-012-1212	THE PATIENT HAD BEEN DRAWING PICTURES OF HOW THE PATIENT COULD DIE . . . THE PATIENT COULD NOT ASSURE THE INVESTIGATOR THAT SHE WOULDN'T HARM HERSELF.	4	34	No
HGIU-013-1301	SUICIDAL IDEATION / OCCASIONAL SUICIDAL THOUGHTS	4	71	No
HGIU-013-1310	INTENTIONAL SELF-INJURY / SELF INJURY	5	64	No
HGIU-020-2016	SUICIDE ATTEMPT / ATTEMPTED SUICIDE	2	214	No
HGIU-026-2604	SELF INJURIOUS BEHAVIOUR / SELF-INJURIOUS BEHAVIOR. LSS: THE PATIENT REPORTED THAT HIS DEPRESSION WORSENED APPROXIMATELY ONE WEEK PRIOR (~05-NOV-2003). ADDITIONALLY HE BEGAN FEELING SUICIDAL (WITHOUT PLAN) APPROXIMATELY THREE DAYS PRIOR (~09-NOV-2003). THE PATIENT'S MOTHER CALLED THE SITE TO REPORT THAT THE PATIENT HAD CUT HIMSELF THE PRIOR EVENING AND DIDN'T FEEL SAFE. THE PATIENT WAS BROUGHT TO THE HOSPITAL FOR SAFETY AND STABILIZATION.	4	59	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIU-026-2605	THE PATIENT WAS BEHAVING INAPPROPRIATELY AND WAS ON THE ROOF OF HIS HOME REFUSING TO COME DOWN	9	53	No
HGIU-026-2606	SUICIDAL IDEATION / SUICIDAL IDEATION	4	35	No
HGIU-027-2705	INTENTIONAL SELF-INJURY / SELF-INFLICTED SUPERFICIAL LACERATIONS	5	76	No
HGIU-028-2805	SUICIDAL IDEATION / SUICIDAL IDEATION. LSS: THE PATIENT'S MOTHER CALLED THE INVESTIGATOR'S SITE ON 14-MAY-2004 TO STATE THAT HER DAUGHTER HAD BECOME SUICIDAL WITH A PLAN TO OVERDOSE ON LORAZEPAM (ATIVAN) DURING THE LAST WEEK OF MAY 2004, BUT ENDED UP TELLING HER PARENTS THE EVENING OF 09-MAY-2004.	3	108	No
HGIU-730-7302	SUICIDAL IDEATION / PASSIVE SUICIDAL IDEATION	4	177	No
HGMF-003-0304	EXACERBATION OF BIPOLAR ILLNESS WITH POSITIVE SUICIDAL IDEATION	4	29	No
HGMF-008-0805	INTENTIONAL SELF-INJURY, CUTTING LEFT ARM	5	93	No
LOAY-400-4001	PATIENT IS IN A DEPRESSIVE MOOD AROUND 10-11.05.99 AND EXPRESSES SUICIDALTHOUGHTS, SIGNIFICANTLY SLOWED MOVEMENT.	4	44	No
LOAY-401-4012	SELF-INJURIOUS BEHAVIOR, SELF-INJURY	5	16	No
LOAY-407-4077	SELF INJURIOUS BEHAVIOR, SELF-INFLICTING TENDENCIES	5	55	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
LOAY-407-4078	SUICIDAL IDEATION, ACUTE SUICIDAL TENDENCIES	4	4	No
LOAY-413-4150	SUICIDAL IDEATION, SUICIDAL TENDENCY	4	27	No

10.11 Laboratory Evaluations – Mean Change from Baseline to Endpoint

Table 10.11.1 Sponsor's Table. Mean Change from Baseline to Endpoint: HGIN + HGIU Acute Database

Table 2.7.4.33. Laboratory Evaluations
Mean Change from Baseline to Endpoint
Acute Placebo-Controlled Combined Database

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
HEMATOCRIT	1	Olz	174	0.43	0.03	-0.01	0.03	-0.01	-0.01	<.001
		Placebo	87	0.43	0.04	-0.00	0.03	-0.00		
HEMOGLOBIN	mml/L-F	Olz	174	8.93	0.78	-0.30	0.47	-0.30	-0.22	<.001
		Placebo	87	8.93	0.83	-0.08	0.41	-0.07		
ERYTHROCYTE COUNT	TI/L	Olz	174	5.00	0.39	-0.15	0.27	-0.15	-0.11	.002
		Placebo	87	4.99	0.49	-0.04	0.26	-0.04		
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mml/L-F	Olz	174	20.87	0.92	-0.00	0.76	0.02	0.16	.100
		Placebo	87	21.00	0.79	-0.17	0.73	-0.14		
LEUKOCYTE COUNT	GI/L	Olz	174	7.27	1.92	-0.19	1.86	-0.10	-0.32	.201
		Placebo	87	7.18	1.91	0.14	1.99	0.21		
NEUTROPHILS, SEGMENTED	GI/L	Olz	174	4.22	1.59	-0.13	1.67	-0.06	-0.29	.203
		Placebo	87	4.29	1.48	0.17	1.79	0.23		
LYMPHOCYTES	GI/L	Olz	174	2.38	0.66	-0.09	0.49	-0.06	-0.07	.297
		Placebo	87	2.24	0.60	-0.02	0.51	0.01		
MONOCYTES	GI/L	Olz	174	0.43	0.14	0.02	0.17	0.01	0.01	.544
		Placebo	87	0.41	0.16	0.01	0.17	0.00		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
EOSINOPHILS	GI/L	Olz	174	0.20	0.21	0.01	0.16	0.01	0.04	.042
		Placebo	87	0.19	0.14	-0.02	0.10	-0.03		
BASOPHILS	GI/L	Olz	174	0.05	0.03	-0.01	0.03	-0.01	-0.01	.008
		Placebo	87	0.05	0.03	0.00	0.03	0.00		
MEAN CELL VOLUME (MCV)	fL	Olz	174	85.96	4.66	-0.25	2.53	-0.02	-0.97	.005
		Placebo	87	85.76	4.59	0.72	2.78	0.95		
PLATELET COUNT	GI/L	Olz	173	291.08	68.65	1.26	46.42	2.44	6.09	.339
		Placebo	87	286.54	63.84	-4.68	52.18	-3.66		
LYMPHOCYTES, ATYPICAL	GI/L	Olz	1	0.06		0.03		0.03		
UA-SPECIFIC GRAVITY	NO UNIT	Olz	156	1.02	0.01	-0.00	0.01	-0.00	-0.00	.292
		Placebo	72	1.02	0.01	-0.00	0.01	-0.00		
AST/SGOT	U/L	Olz	175	24.53	29.87	6.43	26.41	9.89	8.91	.002
		Placebo	87	23.63	8.46	-2.47	7.51	0.98		
ALT/SGPT	U/L	Olz	175	24.13	45.95	19.95	54.84	28.11	22.98	<.001
		Placebo	87	20.39	13.05	-3.08	11.69	5.13		
CREATINE PHOSPHOKINASE	U/L	Olz	175	141.28	138.78	-7.31	131.11	2.81	16.06	.376
		Placebo	87	164.36	160.04	-23.62	152.22	-13.25		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
ALKALINE PHOSPHATASE	U/L	Olz	175	152.33	82.35	-1.35	25.61	-2.74	2.57	.396
		Placebo	87	138.67	86.92	-3.97	16.63	-5.31		
GGT (GGPT/SGGT/YGGT)	U/L	Olz	175	18.99	12.31	7.47	20.02	7.73	7.89	<.001
		Placebo	87	17.68	8.49	-0.43	5.96	-0.16		
THYROID STIMULATING HORMONE	mU/L	Olz	6	2.73	2.32	0.11	1.02	-0.12		
UREA NITROGEN	mmol/L	Olz	175	4.40	1.18	0.22	1.18	0.14	0.39	.010
		Placebo	87	4.37	1.06	-0.17	1.06	-0.25		
CREATININE	umol/L	Olz	175	93.29	14.47	-2.90	9.85	-2.07	-1.80	.147
		Placebo	87	95.83	12.43	-1.08	8.56	-0.27		
CALCIUM	mmol/L	Olz	175	2.48	0.08	-0.03	0.09	-0.03	-0.02	.215
		Placebo	87	2.50	0.12	-0.01	0.10	-0.02		
SODIUM	mmol/L	Olz	175	141.70	2.27	-0.05	2.83	-0.12	0.49	.190
		Placebo	87	141.78	2.44	-0.53	2.94	-0.61		
POTASSIUM	mmol/L	Olz	175	4.32	0.33	-0.04	0.36	-0.07	0.04	.462
		Placebo	87	4.41	0.42	-0.07	0.41	-0.10		
ALBUMIN	g/L	Olz	175	45.07	3.75	-2.01	3.20	-2.13	-1.70	<.001
		Placebo	87	45.39	3.03	-0.31	2.90	-0.43		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
GLUCOSE, FASTING	mmol/L	Olz	135	4.89	0.55	0.15	0.58	0.15	0.31	<.001
		Placebo	64	4.98	0.57	-0.16	0.56	-0.17		
GLUCOSE, NON-FASTING	mmol/L	Olz	141	5.04	0.83	0.17	1.13	0.12	0.15	.374
		Placebo	73	5.01	0.79	0.03	1.23	-0.03		
URIC ACID	umol/L	Olz	175	331.18	74.27	25.21	51.54	30.87	26.95	<.001
		Placebo	87	329.40	84.01	-1.86	53.02	3.92		
CHOLESTEROL	mmol/L	Olz	175	4.17	0.83	0.34	0.59	0.33	0.37	<.001
		Placebo	87	4.15	0.85	-0.03	0.63	-0.04		
TRIGLYCERIDES	mmol/L	Olz	175	1.18	0.66	0.33	0.91	0.30	0.38	<.001
		Placebo	87	1.25	0.73	-0.05	0.62	-0.07		
LDL CHOLESTEROL	mmol/L	Olz	175	2.42	0.74	0.16	0.52	0.14	0.17	.016
		Placebo	87	2.37	0.76	-0.01	0.53	-0.02		
BILIRUBIN, TOTAL	umol/L	Olz	175	7.84	5.27	-1.73	3.82	-2.21	-2.52	<.001
		Placebo	87	8.56	5.33	0.78	5.96	0.31		
BILIRUBIN, DIRECT	umol/L	Olz	175	1.84	1.07	-0.33	1.07	-0.36	-0.38	.005
		Placebo	87	2.01	1.08	0.05	0.93	0.02		
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Olz	175	1.22	0.31	0.03	0.23	0.02	0.03	.331

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Placebo	87	1.21	0.25	-0.00	0.25	-0.01		
PROLACTIN	ug/L	Olz	163	14.06	9.92	11.44	14.52	10.51	11.66	<.001
		Placebo	80	14.95	11.86	-0.16	10.69	-1.15		
HEMOGLOBIN A1C	1	Olz	6	0.05	0.00	-0.00	0.00	-0.00	0.00	.741
		Placebo	3	0.05	0.01	-0.00	0.00	-0.00		

10.12 Prolactin Analysis by Gender

Table 10.12.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: HGIU + HGIN Acute Database.

Laboratory Evaluations	Gender	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value	**P-value
PROLACTIN	Female	Olz	63	15.87	10.06	15.63	16.86	14.26	14.25	<.001	.236
		Placebo	37	15.25	7.59	1.35	9.20	0.00			
	Male	Olz	100	12.92	9.71	8.80	12.20	8.70	10.12	<.001	
		Placebo	43	14.70	14.67	-1.46	11.78	-1.42			

10.13 Vital Signs – Mean Change from Baseline to Endpoint

Table 10.13.1 Vital Signs, Weight, Height and BMI - Mean Change from Baseline to Endpoint (LOCF). HGIN + HGIU Acute Database

Vital Signs	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Systolic Blood Pressure - Supine	Olz	177	111.52	10.95	2.94	10.57	1.73	3.66	.009
	Placebo	89	112.79	13.18	-0.71	10.90	-1.93		
Systolic Blood Pressure - Standing	Olz	177	113.33	12.25	3.14	12.06	2.16	1.94	.225
	Placebo	89	112.18	13.25	1.22	12.51	0.23		
Systolic Blood Pressure - Orthostatic	Olz	177	-1.81	9.63	-0.20	11.68	-0.43	1.72	.262
	Placebo	89	0.61	8.33	-1.93	11.83	-2.15		
Diastolic Blood Pressure - Supine	Olz	177	67.71	9.27	1.24	9.74	1.56	2.17	.095
	Placebo	89	68.19	8.53	-0.92	10.27	-0.61		
Diastolic Blood Pressure - Standing	Olz	177	72.86	10.12	1.42	10.25	-0.24	2.73	.033
	Placebo	89	73.56	9.48	-1.28	9.14	-2.97		
Pulse - Supine	Olz	177	73.88	11.40	7.07	13.99	7.55	7.71	<.001
	Placebo	89	74.15	12.81	-0.60	12.04	-0.16		
Pulse - Standing	Olz	177	83.77	12.73	6.97	14.83	6.55	7.90	<.001
	Placebo	89	85.55	12.98	-0.89	14.69	-1.35		
Pulse - Orthostatic	Olz	177	9.89	11.23	-0.11	13.37	-1.01	0.19	.914
	Placebo	89	11.40	11.15	-0.29	13.09	-1.19		

Vital Signs	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Temperature in Centigrade	Olz	177	36.57	0.44	-0.03	0.49	-0.03	-0.03	.695
	Placebo	88	36.58	0.42	-0.00	0.49	-0.00		
Weight in Kg	Olz	177	66.03	17.93	3.90	2.72	3.68	3.66	<.001
	Placebo	88	67.63	17.24	0.24	2.16	0.01		
Height in cm	Olz	177	165.84	10.13	0.48	1.22	0.46	0.18	.235
	Placebo	88	167.59	9.67	0.31	1.01	0.28		
Body Mass Index	Olz	177	23.91	6.01	1.22	1.01	1.11	1.17	<.001
	Placebo	88	23.98	5.67	0.05	0.91	-0.07		

10.14 Potentially Clinically Significant Definitions for Safety Analyses

Table 2.7.4.6. **Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs and Weight**

Parameter	Low	High
Orthostatic hypotension (mm Hg)	≥20 mm Hg decrease in systolic BP (supine to standing) and ≥10 bpm increase in pulse (supine to standing)	--
Supine systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Standing systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Supine diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Standing diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Supine pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Standing pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Temperature (°F)[a]	--	≥101°F and increase ≥2
Weight (kg)	decrease ≥7%	increase ≥7%

10.15 Postmarketing Reports - Fatalities
Table 10.15.1. Postmarketing Reports – Fatalities

Patient Identifier	Date of Death	Dose/Duration	Event	Concom Rx	Comments
BR200605002130 16 YOM	(b) (6)	7.5 mg 10/05 – 4/06	Sudden death, cardiac arrest, prescribed overdose, suicide attempt, depression, psychosis	Alprazolam	Brazil Autopsy done, result will be available by June 2006 (per summary)
BE200602002031 17 YOF	(b) (6)	Unknown ~6 years	Bilateral pneumonia, gastric hemorrhagia, fever, coma	Not reported	Belgium (no autopsy)
US_0510123183 14 YO	(b) (6)	Unknown	Toxic exposure, completed suicide	Fluoxetine Risperidone	Literature
JP_051007889 17 YOM	(b) (6)	5 mg, 8/2005 – 10/05	Completed suicide, suicidal ideation, apathy	Lorazepam	Japan "Police told psychiatrist about patient's death, no details provided" [prior suicide attempt per hx]
CA_050708496 17 YOM	(b) (6)	15 mg 11/03 – 6/05	Completed suicide	Lorazepam Flupentixol decanoate	Canada 5 days after discontinuing olanzapine, committed suicide (method unknown) Not known whether

					autopsy performed.
US_0506118439 17 YOF	Unknown (b) (6) estimated	Unknown, 7/1999 - 2004	Death, weight increased, diabetes mellitus, hyperglycemia, multiple drug overdose, triglycerides increased, cholesterol abnormal, musculoskeletal chest pain		Reported by attorney via legal department
EWC050644285 17 YOF	(b) (6)	5 mg 3/5/05 – 3/6/05	Endotoxic shock, kidney infection, sepsis, acute abdomen, disseminated intravascular blood coagulation, myeloid hyperplasia of spleen, pancreatitis, gastric ulcer perforation, peritoneal infection		Russian Federation
US_0506118189 15 YOM	Unknown (b) (6) estimated	~ May 2003 - unknown	Death		Reported by an attorney via the legal department Cause of death not provided
CA_050207717 16 YOM	(b) (6)	Unknown	Completed suicide	Isotretinoin mepha	Canada No details provided
US_0412108962 16 YOM	Unknown (b) (6) estimated	1-2002 – unknown	Death, diabetes mellitus		Reported by an attorney via the legal department Cause of death not provided, not known if autopsy performed
JP_041105122 17 YOF	(b) (6)	50 mg 11/10/2004 – 11/10/2004	Intentional overdose, completed suicide	Paroxetine, sulpiride, amoxapine, fluvoxamine, flunitrazepam	Japan "Coroner refused to provide any information"
USA040979162 US_0402100550 15 YOM	(b) (6)	10/29/2003?	Death, coma Accidental overdose, drug toxicity, intentional drug misuse	Metronidazole, topiramate, clonazepam	Reported by an attorney via the legal department Case reported in a newspaper "Patient was sold olanzapine by another individual, not prescribed"

					Olanzapine Cp = 490 ng/ml postmortem
US_0412109585 15 YOF	(b) (6)	11/2000 - unk	Diabetic ketoacidosis, diabetic coma, diabetes mellitus, pain, anxiety, drug ineffective	Methylphenidate, sertraline	Reported to company by an attorney No details provided about the event, unknown if an autopsy was performed
EWC031237179 16 YOM	(b) (6)	5 mg, 11/24/2003 – 11/25/2003	Death, pulmonary infarction		Greece Pulmonary infarction per autopsy
USA030742307 13 YOF	(b) (6)	5 mg Unknown	Diabetic ketoacidosis, loss of consciousness, dizziness		Diabetic ketoacidosis per autopsy. No labs provided.
USA030741953 17 YOM	(b) (6)	8/2002 – 11/2002	Convulsion, heart rate increased	Mixed amphetamine salts, trazodone	Cause of death listed as idiopathic seizure disorder, toxicology screen negative
GBS030413039 17 YOM	(b) (6)	12.5 mg 10/2002 – unk	Completed suicide, sedation, eczema	Risperidone, biperiden	United Kingdom Death by drowning, autopsy did not reveal other significant findings
US_020180581 15 YOM	(b) (6)	20 mg Unknown	Acute asthma		Patient had been in blinded study 3/01 – 9/01 prior [F1D-US-X090]; did not receive olanzapine; taking marketed olanzapine at time of event.
US_010973481 17 YOM	Unknown (received by Sponsor (b) (6)	30 mg Unknown	Prescribed overdose, drug toxicity		No details provided, unknown if autopsy performed
EWC010928155 15 YOM	(b) (6)	10 mg 8/1/2001 – 8/28/2001	Death	Dextro-amphetamine	Switzerland Asperger's syndrome Patient drowned while swimming in lake; autopsy unremarkable
CA_010603921 17 YOF	Unknown (received by Sponsor (b) (6)	Unknown	Death	Citalopram, valproate semisodium	Canada Patient "died suddenly", autopsy was completed but not available.

					"Several attempts at follow-up unsuccessful".
CA_010603802 16 YOM	Unknown (received by Sponsor (b) (6)	10 mg 90 days	Diabetic coma	Valproate sodium Topiramate	Canada No personal history of diabetes. Weight at time of event unknown, labs not provided. "Numerous attempts to obtain follow-up unsuccessful".
US_010566315 16 YOM	(b) (6)	5 mg 730 days	Drug interaction, death, hepatic steatosis	Mixed amphet-Amine salts	Patient found dead. Hepatic steatosis per autopsy, no cause of death provided. Autopsy never provided.
US_010158510 17 YOM	(b) (6)	2.5 mg Unknown	Accidental overdose	Citalopram, trazodone	Patient found dead by family member. Cause of death presumed overdose. Olanzapine Cp = 158 ng/ml.
US_000542556 15 YOM	(b) (6)	Unknown 1998 x 120 days	Necrotizing pancreatitis, diabetes mellitus, increased cholesterol	Carbamazepine, paroxetine	Follow-up in the literature
US_000236591 17 YOM	(b) (6)	22.5 mg Unknown	Overdose, death	Fluoxetine, valproate semisodium, nortriptyline, buspirone, haloperidol, thioridazine	Patient died while being restrained by staff in group home.
US97121702A 14 YOM	(b) (6)	12.5 mg 150 days	Asphyxia, agitation	Haloperidol, sertraline	Became agitated on school bus and was restrained and died. Per coroner, cause of death by mechanical asphyxia due to the restraining position.

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 /s/
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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.
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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		LSMean	LSMean	
Efficacy Variable	Therapy	N	Mean	Std	Mean	Std	Change	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		LSMean	LSMean		**P-value (Therapy by
Efficacy Variable	Country	Therapy	N	Mean	Std	Mean	Std	Change	Diff.	*P-value	Country)
BPRS-C Total Score	America	Olanzapine	38	53.18	10.10	-21.21	16.30	-20.89	-5.26	.258	.146
		Placebo	19	51.42	8.64	-15.00	18.28	-15.64			
	Russia	Olanzapine	34	47.00	8.88	-17.41	14.55	-17.44	-14.95	.003	
		Placebo	16	48.50	8.52	-2.56	17.38	-2.49			

Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a non approval action.

1.3.3 Safety

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar disorder) and the Overall Combined Database that included studies HGIN, HGIU, LOAY and HGMF. The HGIN + HGIU Acute Database included a placebo group as a comparator. Due to the similarities between schizophrenia and bipolar disorder populations, safety was evaluated in this combined database but also separately by reviewing the individual study reports if differences in certain safety signals were thought to occur between either the populations or the different duration of dosing in these acute studies (HGIN – 6 weeks, HGIU – 3 weeks).   The Overall Combined Database did not have a placebo comparator (mostly open-label data) but did provide safety data for a longer duration of dosing (up to 8 months).

No deaths occurred in the clinical trials. Serious adverse events occurring in the HGIN + HGIU Acute Database included migraine, forearm fracture, weight increased, bipolar disorder and WBC count decreased. A total of 44 serious adverse events occurred in 35 patients in the Overall Combined Database. The majority of these SAEs were coded to the primary disorder (schizophrenia, psychotic disorder, bipolar disorder) indicating a worsening of psychiatric symptoms.

The most common adverse events ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with $\geq$ 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
$\geq$ 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 ≤ 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

Efficacy Variable	Visit	Therapy	N	Baseline Mean	Std	Change to Endpoint 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	Std	Change to Endpoint Mean	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	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy by Country)
BPRS-C Total Score	America	Olanzapine	38	53.18	10.10	-21.21	16.30	-20.89	-5.26	.258	.146
		Placebo	19	51.42	8.64	-15.00	18.28	-15.64			
	Russia	Olanzapine	34	47.00	8.88	-17.41	14.55	-17.44	-14.95	.003	
		Placebo	16	48.50	8.52	-2.56	17.38	-2.49			

Because of these differences in efficacy, this reviewer asked the Sponsor to analyze the baseline psychiatric illness variables of patients between the U.S. and Russia sites. This analysis is in Appendix 10.4. In general, patients from the U.S. sites had fewer days since last hospitalization (149 vs. 477 days, p = 0.012) [other differences between the countries may account for this difference], higher baseline BPRS-C scores (52.6 vs. 47.5, p = 0.005) and higher baseline scores on several BPRS-C subscales including behavioral problems, depression, thinking disturbance

(11.04 vs. 9.72, p = 0.030), and psychomotor excitation. The PANSS total scores were not different between the sites though there were some inconsistent differences on the subscales. Although not statistically significant, the PANSS total scores were numerically higher in the Russia sites (97.6 vs. 93.3, p = 0.116). Therefore, it does not appear that there is a consistent signal indicating that the patients enrolled in the Russia sites are more severely ill compared to the patients enrolled in the U.S. sites.

Secondary Analyses
BPRS-C Individual Items and Composite Scores
When evaluating the BPRS-C individual items, statistical differences favoring olanzapine were found only for uncooperativeness (p = 0.003), hostility (p < 0.001), manipulativeness (p = 0.035), hyperactivity (p = 0.004) and sleep difficulties (p < 0.001) (see Appendix 10.5). Although there were statistical differences favoring olanzapine for the Thinking Disturbance composite (p = 0.050), the effect is only significant for peculiar fantasies (p = 0.014) but not delusions (p = 0.151) or hallucinations (p = 0.249) – despite the similar severity ratings at baseline for all three symptoms. Interestingly, the "peculiar fantasies" item is one that has been noted to have poor interrater reliability in psychometric testing.[1]

Subgroup Analyses
The Sponsor evaluated the following subgroups: gender, age (< 15, ≥ 15), Caucasian vs. nonCaucasian.
Statistically significant differences favoring olanzapine were found for all subgroups except females (p = 0.203), < 15 years of age (p = 0.302) and nonCaucasians – the greater change to endpoint in the placebo group in these subgroups may have contributed to these findings. However, the treatment-by-subgroup analyses were not significant.

Table 6.1.3.6. Sponsor's Table. BPRS-C Total Score - Subgroup Analyses

Efficacy Variable	Subgroup	Strata	N	Therapy	n	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Diff.	*P-value	**P-value (Therapy*Subgroup)
BPRS-C Total Score	Gender	Female	32	Olanzapine	21	51.90	11.92	-18.67	12.77	-17.66	-8.08	.203	.682
				Placebo	11	53.36	7.58	-10.45	21.88	-9.58			
		Male	75	Olanzapine	51	49.59	9.10	-19.73	16.61	-20.03	-10.99	.009	
				Placebo	24	48.58	8.75	-8.79	17.55	-9.03			
	Age	< 15	22	Olanzapine	15	50.73	9.27	-17.27	17.80	-10.20	-8.01	.302	.561
				Placebo	7	54.71	8.88	-12.57	20.40	-2.19			
		>=15	85	Olanzapine	57	50.14	10.23	-19.98	14.97	-19.95	-11.07	.004	
				Placebo	28	48.93	8.27	-8.50	18.56	-8.88			

1 Lachar D, Randle SL, Harper RA et al. The Brief Psychiatric Rating Scale for Children (BPRS-C): validity and reliability of an anchored version. J Am Acad Child Adolesc Psychiatry 2001;40:333-340.

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_____
                                              Change to
                                   Baseline    Endpoint                          **P-value
                                   ----------- ------------  LSMean LSMean       -----------------
Efficacy Variable  Subgroup Strata    N Therapy   n Mean   Std   Mean   Std  Change Diff. *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
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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, HGMFa	N=227
	Bipolar	HGIU, HGMFa	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

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Severity Outcome
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

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
					Returned to WNL after discontinuation from study
HGIN 910-9110	17 YOWM	Olanzapine DB phase	AST increased	AST increased	AST up to 190 (ALT up to 321) Returned to WNL after discontinuation from study
HGIN 920-9202	17 YOWM	Olanzapine DB phase	Rise ALT	ALT increased	ALT up to 393 (AST up to 179 GGT up to 82) ALT and GGT returned to WNL after discontinuation from study (AST N/A)
HGIU 035-3503	16 YOBF	Olanzapine DB phase	Heart rate increased	Elevated pulse	Holter noted sinus tachycardia Discontinued from study, pulse WNL at 4th follow-up visit
HGIU 012-1203	15 YOWF	Olanzapine DB phase	Hepatic enzyme increased	Elevated liver enzymes	AST up to 148 ALT up to 325 GGT up to 53 Returned to near WNL after discontinuation from study (ALT 48)
HGIU 035-3501	14 YOWF	Olanzapine DB phase	Weight increased	Weight gain	Weight increase of 4.5 kg in ~ 15 days

Table 7.1.3.1.2 Discontinuations Due to Adverse Events: Overall Combined Database

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGIN 003-0302	17 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.7 kg in 3 months
HGIN 019-1901	15 YOWF	Olanzapine OL	Weight increased	Weight gain	Gained 6.62 kg during DB phase, Gained 15.88 kg over 5.7 months
HGIN 020-2002	15 YOBM	Olanzapine OL	Sedation	Sedation	
HGIN 025-2502	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.2 kg over 183 days
HGIN 027-2701	17 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12 kg over 92 days
HGIN 027-2702	13 YOWF	Olanzapine OL	Weight increased	Weight gain	Gained 17.5 kg over 148 days
HGIN 030-3007	13 YOWF	Olanzapine OL	Increased appetite	Increased appetite	Gained 21.8 kg over 94 days
HGIN 900-9003	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 12.8 kg over 169 days
HGIN 930-9307	15 YOWF	Olanzapine OL	Suicide attempt	Suicide attempt	See Table 7.1.2.2.
HGIN 940-9403	16 YOWM	Olanzapine OL	Weight increased	Weight gain	Gained 13.4 kg over 152 days
HGIU	14 YOWF	Olanzapine	Alcohol	Alcohol	See Table 7.1.2.2.

001-108		OL	intoxication	poisoning	
HGIU 007-708	15 YOWM	Olanzapine OL	Drowsiness	Somnolence	
HGIU 009-902	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 14.2 kg over 78 days
HGIU 013-1303	17 YOWF	Olanzapine OL	Syncope	Syncope	100/60 mm Hg, 88 bpm supine, 98/62 mmHg, 100 bpm standing
HGIU 013-1308	14 YOHF	Olanzapine OL	Weight gain	Weight increased	Gained 9.1 kg over 103 days
HGIU 013-1310	16 YOWF	Olanzapine OL	Increased appetite	Increased appetite	Gained 9.5 kg over ~ 56 days (at time of weight patient had been off drug for 11 days)
HGIU 013-1311	13 YOHM	Olanzapine OL	Worsened aggressive behavior	Aggression	
HGIU 019-1901	16 YOBF	Olanzapine OL	Pregnancy	Pregnancy	
HGIU 019-1907	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 17.7 kg over 170 days
HGIU 020-2007	14 YOWF	Olanzapine OL	Elevated liver function test	Liver function test abnormal	AST up to 204, ALT up to 330 Resolved after discontinuation from study
HGIU 020-2008	15 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 9.3 kg over 58 days
HGIU 020-2019	16 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 9.5 kg over 81 days
HGIU 024-2404	13 YOWF	Olanzapine OL	Fear of more weight gain	Fear of weight gain	Gained 5.9 kg over 34 days
HGIU 026-2608	13 YOWF	Olanzapine OL	Exacerbation of bipolar disorder	Bipolar disorder	
HGIU 027-2701	15 YOWF	Olanzapine OL	Sedation	Sedation	
HGIU 027-2704	15 YOBM	Olanzapine OL	Weight gain	Weight increased	Gained 18.6 kg over 119 days
HGIU 027-2705	15 YOBM	Olanzapine OL	Worsening of bipolar disorder	Bipolar disorder	
HGIU 028-2806	15 YOBF	Olanzapine OL	Bipolar mania	Bipolar disorder	
HGIU 031-3103	14 YOWM	Olanzapine OL	Decreased WBC	WBC count decreased	See Table 7.1.2.1
HGIU 033-3304	15 YOWF	Olanzapine OL	Intensifying aggressiveness	Aggression	See Table 7.1.2.2.
HGIU 035-3510	15 YOWM	Olanzapine OL	Weight gain	Weight increased	Gained 5.4 kg over 89 days
HGIU 035-3517	13 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 5 kg over ~6 weeks
HGIU 720-7217	15 YOHM	Olanzapine OL	Hepatic enzymes increases	Hepatic enzyme increased	AST up to 103, ALT up to 125 (also had significant weight gain, 21 kg over ~ 5 months)

HGIU 720-7219	14 YOHF	Olanzapine OL	Pregnancy	Pregnancy	
HGMF 002-0211	17 YOWF	Olanzapine OL	Somnolence	Somnolence	
HGMF 003-0304	16 YOWF	Olanzapine OL	Exacerbation of bipolar illness with positive suicidal ideation	Bipolar disorder	See Table 7.1.2.2.
HGMF 008-0806	15 YOWM	Olanzapine OL	Increased depression	Depression	
HGMF 014-1400	17 YOBF	Olanzapine OL	Elevated CK level lab	Blood creatine phosphokinase	CK up to 690 U/L
HGMF 025-2501	15 YOWM	Olanzapine OL	Drowsiness	Somnolence	
HGMF 028-2801	18 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 8.9 kg over 27 days
LOAY 405-4057	13 YOWF	Olanzapine OL	Weight gain	Weight increased	Gained 10.1 kg over 42 days
LOAY 407-4207	14 YOWM	Olanzapine OL	Suspicion of neuroborreliosis	Neuroborreliosis	See Table 7.1.2.2.
LOAY 407-4218	15 YOWF	Olanzapine OL	Galactorrhea	Galactorrhea	Prolactin up to 35 mcg/L (ULN = 29)

There were no discontinuations due to adverse events for studies HGCS, HGCR and HGGC.

The Sponsor was asked to provide narratives for the adolescent patients in the adult studies who discontinued due to adverse events (Table 7.1.3.1.3).

Table 7.1.3.1.3 Discontinuations Due to Adverse Events: Adolescent Patients from Adult Studies

Study Patient #	Demographics	Treatment	Verbatim Term	Preferred Term	Comments
HGGF 001-127	13 YOWM	Olanzapine	Weight gain	Weight increased	Gained 23 kg in ~5 months (BMI from 32 to 39)
HGKL 014-1416	15 YOWM	Olanzapine	Weight gain	Weight increased	Gained 12.5 kg over 3 months; triglycerides also increased from 260 to 508 mg/dL

7.1.4   Common Adverse Events

7.1.4.1   Eliciting adverse events data in the development program

Adverse events were obtained by spontaneous reports, patient observation and investigator query at every study visit. Rating scales were included for evaluation of extrapyramidal symptoms (SAS), akathisia (BAS) and dyskinesias (AIMS). Vital signs, ECGs and laboratory tests were obtained at intervals throughout the study.

7.1.4.2   Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the MedDRA version 8.0 coding dictionary. A sample of
patient narratives was reviewed and the coding of verbatim terms to preferred terms was
appropriate.

7.1.4.3   Common adverse event tables

Adverse events occurring in ≥ 2% of patients in the HGIU + HGIN Acute Database is in Table
7.1.4.3.1. The majority of adverse events in this table occurred more than twice as frequently in
the olanzapine group compared to the placebo group, that adverse events that were statistically
more frequent in the olanzapine group were weight increased (30% vs. 6%), somnolence (25%
vs. 3%), increased appetite (24% vs. 6%) and sedation (24% vs. 6%).

Table 7.1.4.3.1 Sponsor's Table. Adverse Events Occurring in ≥ 2% of Patients: HGIU +
HGIN Acute Database

		Therapy					
	Olanzapine			Placebo			
Event Classification	N	n	%	N	n	%	*P-value
Patients with >=1 TESS	179	158	88.3%	89	54	60.7%	<.001
Weight increased	179	53	29.6%	89	5	5.6%	<.001
Somnolence	179	44	24.6%	89	3	3.4%	<.001
Increased appetite	179	43	24.0%	89	5	5.6%	<.001
Sedation	179	34	19.0%	89	5	5.6%	.003
Headache	179	30	16.8%	89	11	12.4%	.374
Fatigue	179	17	9.5%	89	4	4.5%	.227
Dizziness	179	13	7.3%	89	2	2.2%	.155
Dry mouth	179	11	6.1%	89	0	0.0%	.018
Dysmenorrhoea	67	4	6.0%	41	4	9.8%	.475
Pain in extremity	179	9	5.0%	89	1	1.1%	.173
Vomiting	179	9	5.0%	89	6	6.7%	.580
Constipation	179	8	4.5%	89	0	0.0%	.055
Nausea	179	8	4.5%	89	8	9.0%	.172
Nasopharyngitis	179	7	3.9%	89	2	2.2%	.722
Abdominal pain upper	179	6	3.4%	89	5	5.6%	.514
Diarrhoea	179	6	3.4%	89	0	0.0%	.183
Irritability	179	6	3.4%	89	4	4.5%	.735
Pharyngolaryngeal pain	179	6	3.4%	89	3	3.4%	1.00
Restlessness	179	6	3.4%	89	2	2.2%	1.00
Alanine aminotransferase increased	179	5	2.8%	89	0	0.0%	.174
Dyspepsia	179	5	2.8%	89	1	1.1%	.667
Epistaxis	179	5	2.8%	89	0	0.0%	.174
Hepatic enzyme increased	179	5	2.8%	89	0	0.0%	.174
Insomnia	179	5	2.8%	89	10	11.2%	.009
Sinusitis	179	5	2.8%	89	0	0.0%	.174

Sponsor's Table 2.7.4.27 from summary-clin-safety document

The common adverse events for the two trials are listed separately in Table 7.1.4.3.2 since the
trials differed in duration (6 vs. 3 weeks) and study population. For study HGIN, the adverse
events that were statistically different between olanzapine and placebo included weight increased
(p = 0.014) and somnolence (p = 0.0006). For study HGIU, the adverse events that were
statistically different between olanzapine and placebo included weight increased (p < 0.001),
increased appetite (p < 0.001), somnolence (p < 0.001) and sedation (p = 0.011). The adverse
events and frequencies occurring in the olanzapine group between the two clinical trials were
fairly similar though more patients in HGIU exhibited somnolence (25% vs. 17%), increased

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appetite (29% vs. 17%), sedation (22% vs. 15%), dry mouth (8% vs. 4%) and fatigue (14% vs. 3%)

Table 7.1.4.3.2 Adverse Events Occurring in > 2% of Patients with Olanzapine > 2x Placebo: HGIU and HGIN Clinical Trials

	Percentage of Patients Reporting Event			
	6 Week Trial % Schizophrenia Patients		3 Week Trial % Bipolar Patients	
Adverse Event	Olanzapine (N = 72)	Placebo (N = 35)	Olanzapine (N = 107)	Placebo (N = 54)
Weight increased	31%*	9%	29%*	4%
Somnolence	17%*	3%	25%*	4%
Headache	17%	6%	17%	17%
Increased appetite	17%	9%	29%*	4%
Sedation	15%	6%	22%*	6%
Dizziness	8%	3%	7%	2%
Pain in extremity	6%	3%	5%	0
Abdominal pain	4%	0	5%	7%
ALT increase	4%	0	-	-
AST increase	4%	1%	1%	0
Constipation	4%	0	5%	0
Dry mouth	4%	0	8%	0
Fatigue	3%	3%	14%	6%
Diarrhea	1%	0	5%	0
Dyspepsia	-	-	5%	0
Hepatic enzyme increased	1%	0	4%	0
Sinusitis	1%	0	4%	0

From Tables HGIN.12.4, HGIN.14.27 and HGIU.12.4 clinical study reports
  *p < 0.05

7.1.4.4 Common adverse events – further analysis

Weight Gain
Weight gain was a significant adverse event occurring in these clinical trials and is further analyzed and discussed in this section along with the weight data.

HGIU + HGIN Acute Database
In the HGIU + HGIN Acute Database, patients in the olanzapine treatment group had significantly greater weight gain and increase in BMI compared to the placebo group (see Table 7.1.4.4.1).

Table 7.1.4.4.1 Weight and BMI Data (LOCF): HGIN + HGIU Database

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	177	66.03	17.93	3.90	2.72	3.68		
	Placebo	88	67.63	17.24	0.24	2.16	0.01	3.66	< 0.001
BMI	Olanzapine	177	23.91	6.01	1.22	1.01	1.11		

Placebo	88	23.98	5.67	0.05	0.91	-0.07	1.17	< 0.001

From Table 2.7.4.43 in summary-clin-safety document

The visit wise weight change for observed cases was similar to the LOCF analysis. The mean change at visit 6 was + 3.63 kg for olanzapine (n = 154) and + 0.08 kg for placebo (n = 67) (LS Mean Diff = 3.57, p < 0.001).

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Seventy-seven (43.5%) patients in the olanzapine group and 6 (6.8%) of patients in the placebo group had a ≥ 7% increase in body weight (p < 0.001). Only 2 patients, both randomized to placebo, had a ≥ 7% decrease in body weight.

Since studies HGIN and HGIU were different with respect to types of patients and duration of the double-blind period (HGIN 6 weeks, HGIU 3 weeks), the weight and BMI data were also evaluated separately:

Table 7.1.4.4.2. Weight and BMI Data: Study HGIU

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	105	65.33	20.55	3.66	2.18	3.51		
	Placebo	54	66.83	17.55	0.30	1.67	0.16	3.36	< 0.001
BMI	Olanzapine	105	24.21	6.82	1.18	0.85	1.15		
	Placebo	54	24.05	5.44	0.02	0.62	0.00	1.15	< 0.001

From Table HGIU.12.44 in study report

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Forty-four (41.9%) patients in the olanzapine group and 1 (1.9%) patient in the placebo group had a ≥ 7% increase in body weight (p < 0.001). No patients in the study had a ≥ 7% decrease in body weight.

Table 7.1.4.4.3. Weight and BMI Data: Study HGIN

			Baseline		Change to Endpoint				
		N	Mean	Std	Mean	Std	LS Mean Change	LS Mean Difference	P-value
Weight (kg)	Olanzapine	72	67.04	13.31	4.26	3.33	4.22		
	Placebo	34	68.91	16.93	0.13	2.80	0.08	4.13	< 0.001
BMI	Olanzapine	72	23.45	4.59	1.39	1.21	1.37		
	Placebo	34	24.02	6.12	-0.05	1.03	-0.07	1.44	< 0.001

From Table HGIN.12.42 in study report

The results for the OC analysis for change in weight and BMI were similar to the LOCF analysis. At end of study, patients in the olanzapine group (n = 50) gained 4.95 kg from baseline and patients in the placebo group (n = 15) gained 0.61 kg [LS mean diff = 4.65, p < 0.001]. BMI

increased by 1.56 in the olanzapine group and decreased by 0.04 in the placebo group [LS mean diff = 1.62, p < 0.001].

A ≥ 7% increase in body weight from baseline was considered a potentially clinically significant change. Thirty-three (45%) patients in the olanzapine group and 5 (14.7%) of patients in the placebo group had a ≥ 7% increase in body weight (p = 0.002). Only 2 patients in the study, both randomized to placebo, had a ≥ 7% decrease in body weight.

Only 1 of the 8 discontinuations due to adverse events was due to weight gain in the HGIU + HGIN Acute Database (4.5 kg increase over ~15 days).
Unfortunately, insufficient data were collected during the follow-up visits to adequately address weight loss after patients completed the clinical trial (if they switched to a different antipsychotic). Though many of the investigators noted that the adverse event of "weight gain" had resolved at some of the follow-up visits, no actual weights were obtained for the majority of patients (or at least not recorded in the CRFs).

Overall Combined Database
Though no placebo comparison is available in this database, weight change over longer duration of time could be evaluated in general terms. Similar to the acute data, weight did appear to increase over time. This patient population (adolescents) are expected to increase in height and weight during this developmental period, however, the increases in weight are well above what would be considered expected (see Section 7.1.9 - Assessment of Effect on Growth).

Table 7.1.4.4.4. Weight and BMI Data (LOCF): Overall Combined Database

			Baseline		Change to Endpoint		
		N	Mean	Std	Mean	Std	P-value
Weight (kg)	Bipolar	224	68.58	21.21	7.63	6.62	< 0.001
	Schizophrenia	226	65.71	13.30	7.07	6.53	< 0.001
	Overall	450	67.13	17.72	7.35	6.58	< 0.001
BMI	Bipolar	216	24.92	7.34	2.37	2.39	< 0.001
	Schizophrenia	223	22.40	4.17	2.24	2.25	< 0.001
	Overall	439	23.64	6.07	2.31	2.31	< 0.001

From Table 2.7.4.45 in summary-clin-safety document

Sixty-five percent of patients in the Overall Combined Database gained ≥ 7% body weight.

The Sponsor provided a summary of weight change by visit for observed cases for the Overall Combined Database (see Appendix 10.7). For the 131 patients who completed visits > 25 and ≤ 32 weeks, the mean increase in weight was 10.8 kg (p < 0.001 compared to baseline).

Of the 43 discontinuations due to adverse events in the Overall Combined Database, 20 patients (46%) discontinued due to weight gain/increased appetite. The mean weight gain in the patients who discontinued was 12.1 ± 4.6 kg (range: 5 kg to 21.8 kg); median = 12.1 kg. The mean duration of olanzapine exposure in these patients was 3.3 ± 1.7 months; median = 3 months. The patient who gained 21.8 kg did so over a period of 3 months.

For those patients in the Overall Combined Database who participated in HGIU or HGIN, the weight gain for the acute phase of these trials was also evaluated to determine whether they gained a greater amount of weight early in the trial. These data were readily available for only 10 patients (some of the patients had been randomized to placebo and are not included here). The mean weight gain at the end of the double-blind phase of the study (or early termination) was 4.8 ± 2.6 kg, similar to the overall mean weight gain of 3.9 ± 2.7 kg in the acute database (see Table 7.1.4.4.1).

Weight – Subgroup Analyses
Because of the different duration of dosing in the HGIN and HGIU acute phases, these data were reviewed separately for each study.
The Sponsor evaluated weight changes for the subgroups gender and age (< 15, > 15 years) for the adverse event "weight increased". Approximately 30% of females and males had this adverse event in the olanzapine group in both HGIU and HGIN acute studies while this adverse event was ~4% for the placebo group (with the exception of females in HGIN). No significant differences were noted between the gender subgroups (see Appendix 10.7). For the age subgroups, 28-40% had the adverse event "weight increased" in the olanzapine group compared to 0 – 14% in the placebo group. No significant differences were noted between the age subgroups (see Appendix 10.7).

Mean change in weight (kg) was also evaluated between the subgroups gender and age. These data were not included in the study report for HGIU, the Sponsor has been asked to submit these data (per the study report, only those data where results were significant were included). Data from HGIN are included in Appendix 10.7. Though no significant treatment by age interaction was noted, the change to endpoint in weight was numerically higher in the < 15 year old subgroup (6.3 kg) compared to the ≥ 15 year old subgroup (3.7 kg) for patients treated with olanzapine.
The Sponsor also did not include mean change in weight for the age subgroup for the HGIN + HGIU Acute Database (per the study reports, only those data where results were significant were included). The Sponsor has been asked to provide these data. In the HGIN + HGIU Acute Database, significant treatment-by-gender differences were noted (see Table 7.1.4.4.5). However, these findings are likely due to the differences in the placebo group since the weight gain (mean change to endpoint) in the olanzapine group was similar between females and males.

Table 7.1.4.4.5 Sponsor's Table. Mean Change in Weight (kg) – Gender Subgroup Analysis: HGIU + HGIN Acute Database

By Subgroup: Gender

Vital Signs	Subgroup	N	Therapy	n	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean	LSMean Diff.	*P-value	**P-value
Weight in Kg	Female	106	olz	66	61.79	16.68	3.66	2.65	3.63	3.05	<.001	.083
			Placebo	40	62.83	13.65	0.55	2.27	0.59			
	Male	159	olz	111	68.54	18.25	4.05	2.76	3.79	4.16	<.001	
			Placebo	48	71.64	18.97	-0.03	2.05	-0.36			

Table 2.7.4.70 in Summary-clin-safety

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The Sponsor was asked to evaluate the relationship of weight gain to baseline BMI. The Sponsor evaluated 4 BMI subgroups: < 18, ≥ 18 and < 25, ≥ 25 and < 30, ≥ 30. There was a similar magnitude of weight gain by patients in each of these categories (Table 7.1.4.4.6). The percentage of patients who had a ≥ 7% weight gain was greatest in the < 18 BMI group and least in the ≥ 30 BMI group (Table 7.1.4.4.7).

Table 7.1.4.4.6 Sponsor's Table. Mean Change in Weight by Baseline BMI: HGIN + HGIU Acute Database

Table 1.   Mean Change in Weight (kg) from Baseline to Endpoint (LOCF) by Baseline BMI
             Acute Placebo-Controlled Combined Database

BMI (Baseline)	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
BMI<18	Olz	15	45.68	5.62	4.21	2.29	4.39	3.51	.005
	Placebo	10	48.19	6.54	0.70	2.89	0.88		
18<=BMI<25	Olz	107	58.84	9.37	3.52	2.53	3.24	3.12	<.001
	Placebo	49	61.18	8.41	0.50	2.16	0.12		
25<=BMI<30	Olz	30	76.31	10.29	4.44	3.61	4.25	3.93	<.001
	Placebo	19	77.50	9.32	-0.09	1.41	0.32		
BMI>=30	Olz	25	96.66	15.02	4.71	2.33	3.93	5.59	<.001
	Placebo	10	99.93	16.42	-0.90	2.37	-1.66		

Table 7.1.4.4.7 Sponsor's Table. PCS Weight Changes by Baseline BMI: HGIN + HGIU Acute Database

Table 2.   Potentially Clinically Significant Weight Changes (7% Weight Gain)
             By Baseline BMI
             Acute Placebo-Controlled Combined Database

Vital Signs	BMI (Baseline)	Direction	Therapy	N	n	%	*P-value
Weight in kg	BMI<18	Gain	Olz	15	12	80.0%	.005
			Placebo	10	2	20.0%	
	18<=BMI<25	Gain	Olz	107	49	45.8%	<.001
			Placebo	49	4	8.2%	
	25<=BMI<30	Gain	Olz	30	12	40.0%	.001
			Placebo	19	0	0.0%	
	BMI>=30	Gain	Olz	25	4	16.0%	.303
			Placebo	10	0	0.0%	

The Sponsor was also asked to provide data regarding the numbers of patients at baseline and endpoint who were obese (BMI > 30) and whether there were differences between the treatment groups. At baseline, 14% (25/177) of patients in the olanzapine group and 11.4% (10/88) patients in the placebo group had BMI > 30. At endpoint, 18.6% of patients in the olanzapine group and 11.4% of patients in the placebo group had BMI > 30 (p = 0.158, NS).

The Sponsor was also asked to provide an analysis of laboratory parameters for patients who gained > 3.9 kg (mean weight gain). The major differences between olanzapine and placebo in this subgroup are noted in Table in Appendix 10.7. The LS mean change appears to be fairly similar between this subgroup and the entire study population except for a larger increase in CPK (LS mean diff 39 vs. 16 U/L) and triglycerides (LS mean diff 54 vs. 34 mg/dL) in the subgroup with > 3.9 kg weight gain. Of course, the entire population includes this subgroup – the Sponsor was not asked to provide laboratory data for patients with ≤ 3.9 kg weight gain.

7.1.5   Less Common Adverse Events

Hyperprolactinemia
The summary of the prolactin laboratory data is included in Sections 7.1.6 (Laboratory Findings) and 7.1.6.3 (Special Assessments). The adverse event tables were reviewed for any terms that might be related to hyperprolactinemia. In the HGIU + HGIN Acute Database, gynecomastia occurred in 1 (0.9%) patient in the olanzapine group and no patients in the placebo group and amenorrhea occurred in no patients in the olanzapine group and 1 (2.4%) patient in the placebo group.

The Overall Combined Database was evaluated since adverse events such as gynecomastia are not expected to occur with acute use but rather more long term use of antipsychotics. In the Overall Combined Database, gynecomastia occurred in 7 (4.3%) of patients (all from schizophrenia trials), galactorrhea occurred in 2 (3.1%) patients with schizophrenia and 1 (1%) patient with bipolar disorder and amenorrhea occurred in 1 (1.5%) patient with schizophrenia and 1 (1%) patient with bipolar disorder. The Sponsor has been asked to provide narrative summaries for all cases of gynecomastia – it is unknown whether this adverse event occurred in both male and female patients. If cases of gynecomastia occurred exclusively in female patients, it would be important to differentiate this adverse event from usual adolescent female physical development. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Extrapyramidal Symptoms
Due to the difference in frequency of EPS occurring in patients with schizophrenia and bipolar disorder taking antipsychotics, these data are summarized separately for each diagnostic group from the individual study reports (HGIN and HGIU).

Data for EPS is from a number of sources including rating scales (primarily the BAS and SAS), use of anticholinergic medications (though benzodiazepines may be used to treat EPS, they are more commonly used for managing psychiatric symptoms) and adverse events.

HGIN
Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.1. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown). In both the olanzapine and placebo groups, the mean change to endpoint was a decrease in rating scale score. This is not necessarily surprising depending on which

antipsychotics patients may have been taking during screening and the length of the washout period prior to obtaining the baseline rating.

Table 7.1.5.1. Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIN

EPS Variables	Therapy	N	Baseline Mean	Std	Change to Endpoint Mean	Std	LSMean Change	LSMean Difference	*P-value
AIMS Non-Global Total(1-7)	Olanzapine	72	0.38	0.94	-0.18	0.84	-0.18	0.02	.897
	Placebo	35	0.54	1.50	-0.20	0.72	-0.21		
BRNS 4:Global Assessment of Akathisia	Olanzapine	72	0.31	0.66	-0.15	0.69	-0.15	0.05	.747
	Placebo	35	0.31	0.63	-0.20	0.76	-0.20		
Simpson-Angus Total(1-10)	Olanzapine	72	0.81	1.87	-0.22	1.51	-0.24	0.33	.260
	Placebo	35	0.97	2.41	-0.54	1.34	-0.57		

The Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined. The Sponsor has been asked to provide an analysis for the individual items of these scales.

Only 5 patients in study HGIN (acute phase) had concomitant anticholinergic medication use: 4.2% (3/72) in the olanzapine group and 5.7% (2/35) in the placebo group (p = 0.661).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.2. Adverse Events Potentially Related to EPS: HGIN

	Olanzapine N = 72	Placebo N = 35
Akathisia	2 (2.8%)	2 (5.7%)
Drooling	2 (2.8%)	0
Restlessness	2 (2.8%)	0
Dyskinesia	1 (1.4%)	0
Muscle twitching	1 (1.4%)	0
Musculoskeletal stiffness	1 (1.4%)	0
Cogwheel rigidity	0	1 (2.9%)
Tremor	0	1 (2.9%)

From Sponsor Table HGINB.14.27 in study report

Open-Label Phase HGIN
Noteworthy EPS-related adverse events occurring in the open-label phase of HGIN included oculogyration (n = 1, 0.4%) and opisthotonus (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for these events.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores were evaluated from the open-label phase of HGIN. The mean change to endpoint on the AIMS was -0.12 ± 0.94. The incidence of "treatment emergent" dyskinesia was 2.6% - again, it is

unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to perform a similar analysis (as well as analyses for individual items) for completers since time on therapy is a risk factor for tardive dyskinesia.

HGIU

Mean change from baseline for the BAS, SAS and AIMS are in Table 7.1.5.3. There were no statistically significant differences between the olanzapine and placebo groups at baseline (data not shown) – though the mean baseline scores were numerically higher in the olanzapine group.

Table 7.1.5.3 Sponsor's Table. AIMS, BAS and SAS Rating Scale Scores: HGIU

EPS Variables	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
AIMS Non-Global Total(1-7)	Olanzapine	105	0.16	0.90	-0.10	0.71	-0.12	-0.10	.289
	Placebo	54	0.04	0.19	0.00	0.19	-0.02		
BRNS 4:Global Assessment of Akathisia	Olanzapine	105	0.20	0.49	-0.04	0.44	-0.06	-0.09	.264
	Placebo	54	0.09	0.35	0.06	0.60	0.03		
Simpson-Angus Total(1-10)	Olanzapine	105	0.24	0.89	0.02	0.93	0.02	0.04	.769
	Placebo	54	0.07	0.33	-0.02	0.14	-0.02		

As with study HGIN, the Sponsor provided a categorical analysis of the proportion of patients exhibiting treatment-emergent parkinsonism, akathisia or dyskinetic symptoms using these rating scales. Although no statistical differences were noted between the olanzapine and placebo groups, it is unclear how this treatment-emergent EPS was defined.

Only 5 patients in study HGIU (acute phase) had concomitant anticholinergic medication use, all in the olanzapine group: 4.7% (5/107) in the olanzapine group and 0% (0/54) in the placebo group (p = 0.169).

The adverse event tables were reviewed for any terms that might be related to an extrapyramidal symptom adverse event. There were no statistically significant differences between the olanzapine and placebo groups for any of these adverse events.

Table 7.1.5.3. Adverse Events Potentially Related to EPS: HGIU

	Olanzapine N = 107	Placebo N = 54
Restlessness	4 (3.7%)	2 (3.7%)
Musculoskeletal stiffness	3 (2.8%)	0
Tremor	2 (1.9%)	0
Akathisia	1 (0.9%)	0
Drooling	1 (0.9%)	0
Dysarthria	1 (0.9%)	0
Dyskinesia	1 (0.9%)	0
Muscle tightness	1 (0.9%)	0
Muscle twitching	1 (0.9%)	0
Salivary hypersecretion	1 (0.9%)	0

From Sponsor's table HGIU.14.30 in study report

Open-Label Phase HGIU
Noteworthy EPS-related adverse events occurring in the open-label phase of HGIU included
oculogyration (n = 1, 0.4%). The Sponsor has been asked to provide narrative summaries for
this event.

Since tardive dyskinesia is a risk with longer duration of antipsychotic use, the AIMS scores
were evaluated from the open-label phase of HGIU. The mean change to endpoint on the AIMS
was -0.03 ± 0.30. The incidence of "treatment emergent" dyskinesia was 0.7% - again, it is
unclear how this was defined. Because this analysis was LOCF, the Sponsor will be asked to
perform a similar analysis (as well as analyses for individual items) for completers since time on
therapy is a risk factor for tardive dyskinesia.

Suicidality

The Sponsor included an analysis of suicide-related events, specifically the incidence of possible
suicidal behavior or ideation, in the HGIN + HGIU Acute Database. These data were
summarized for the Overall Combined Database. The following suicide-related categories were
included: completed suicide, suicide attempt, preparatory acts toward imminent suicidal
behavior, suicidal ideation, self-injurious behavior (intent unknown), not enough information
(fatal), not enough information (non-fatal).

The analysis for events included categorizing suicidal behaviors as follows: suicidal behavior or
ideation (includes completed suicide, suicide attempt, preparatory acts toward imminent suicidal
behavior, suicidal ideation), suicidal behavior (includes completed suicide, suicide attempt,
preparatory acts toward imminent suicidal behavior), suicidal ideation (includes suicidal
ideation) and possible suicidal behavior or ideation (includes all categories). The searches
included the subsequent visit (if available) after stopping treatment.

To identify cases, all preferred AE term, verbatim AE terms and comments of clinical trial data
were searched for the following: accident, attempt, burn, cut, drown, gas, gun, hang, hung,
immolat, injur, jump, monoxide, mutilat, overdos, self-damag, self-harm, self-inflict, self-
damage, self harm, shoot, slash, suic, poison, asphyxiation, suffocation, firearm. All blinded
patient listings were independently reviewed by two members of the Sponsor's medical staff
"trained to evaluate suicide-related events". If a discrepancy arose, the case was discussed
between them and, if necessary, a third reviewer was consulted to achieve consensus.

HGIN + HGIU Acute Database
Three possible suicidal behaviors or ideation events were identified, all three occurred in study
HGIU. Two events occurred in patients treated with olanzapine (self-injurious behavior [intent
unknown] in a 14.2 YOWF, suicidal ideation in a 14.6 YOWF) and one occurred in a patient
receiving placebo (self-injurious behavior [intent unknown] in a 13.9 YOWM). The Sponsor's
brief description of the event (from the case narratives) are provided in Appendix 10.8. No
statistical differences were noted between treatment groups. The risk ratio was calculated as
1.01 (95% CI [0.09, 10.88], p = 1.000). Additional analyses (Mantel-Haenszel risk diff) also did
not show statistical differences between the olanzapine and placebo groups (data not shown).

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Overall Combined Database

Twenty-four cases of possible suicidal behaviors or ideation were identified – two of these events occurred in olanzapine-treated patients during the acute phase of study HGIU. The events were as follows: completed suicide (n = 0), suicide attempt (n = 2), preparatory acts toward imminent suicidal behavior (n = 2), suicidal ideation (n = 13), self-injurious behavior (intent unknown) (n = 6), not enough information (fatal) (n = 0), not enough information (non-fatal) (n = 1). The number of days to the event ranged from 4 to 214 (mean/SD = 73.5 ± 57.4 days, median = 57 days). The cases occurred in the following trials: HGIN (4), HGIU (13), HGMF (2), LOAY (5).

It is more difficult to ascertain whether a medication is associated with this adverse event in this database due to lack of a comparison group as well as the presence of a psychiatric disorder that can be associated with suicidal behaviors (esp. bipolar disorder). Of the 24 cases of suicide-related behaviors, 15 (62%) occurred in bipolar patients.

This reviewer also evaluated the individual item "suicidal ideation" in the Children's Depression Rating Scale-Revised. Though rating scales may not capture this specific adverse event, these data were reviewed to see if any trends in worsening occurred on the suicide-related item. For the CDRS[2], most patients scored a "1" at baseline. For patients who scored > 1, most showed improvement (decrease in score). Two patients in the placebo group had worsening on this item; one patient had an increase from a 1 to a 3 and another from a 2 to a 3 severity rating. Two patients in the olanzapine group had worsening on this item; one patient had an increase from a 2 to a 3 and another from a 2 to a 4 severity rating. Of note, 3 patients had a severity rating of 7 at baseline (all were randomized to olanzapine). The Sponsor will be asked to provide details regarding inclusion of these patients in the clinical trial.

Hostility and Aggression Adverse Events

Similar to the strategy used to identify possible suicide-related behaviors, the Sponsor identified patient cases for hostility and aggression. The following categories were used for these cases: aggressive behavior with physical harm directed toward another person, aggressive behavior with physical harm directed toward animals, aggressive behavior with physical harm directed toward objects, aggressive behavior with nonspecific information, aggressive behavior with indirect or no potential for direct physical harm, hostility without aggression, anger without hostility or aggressive behavior, violent ideation with no anger, hostility or aggressive behavior, and does not meet case definition.

In the HGIN + HGIU Acute Database, 7 cases were identified (1 case in HGIN, 6 cases in HGIU). Four cases occurred in patients in the olanzapine treatment groups. The olanzapine

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2 CDRS-R Suicidal ideation item scoring: 1 = understands the word "suicide" but does not apply the term to himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does ont understand the concept of suicide), usually when angry; 4 = intermediate rating, not anchored; 5 = has recurrent thoughts of suicide; 6 = intermediate rating, not anchored; 7 = has made a suicide attempt within the last month or is actively suicidal

cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, hostility without aggression and anger without hostility or aggressive behavior. The placebo cases included aggressive behavior with physical harm directed toward another person, aggressive behavior with nonspecific information, and hostility without aggression. Given the patient population, it is surprising that not more cases of hostility or aggression were identified. However, overtly hostile patients or patients with a strong history of hostility or aggression would be less likely to be enrolled in a clinical trial. No statistical differences were noted between treatment groups (data not shown).

In the Overall Combined Database, 23 cases of possible hostility or aggression-related events were identified: HGIN (5), HGIU (13), HGMF (1), LOAY (4). It is not unexpected for hostility or aggressive behaviors to be exhibited by patients with inadequately controlled symptoms of schizophrenia or bipolar disorder.

7.1.6   Laboratory Findings

The data from the HGIN + HGIU Acute Database was the primary source of data reviewed. When individual patient labs were being reviewed, it was noticed that many labs were missing from the study reports – most commonly the last (third) page of labs for many patients. Though all of the lab data appeared to be present in the JMP datasets, it was sometimes more difficult to look for trends or other signals using the dataset than the individual lab profile.

7.1.6.1   Overview of laboratory testing in the development program

During the acute 3 week trial labs were obtained as follows:
Clinical chemistry, electrolytes – baseline and weekly during trial
Lipids - baseline and weekly during trial; fasting glucose/lipids were obtained at baseline and end of study
Hematology - baseline and weekly during trial
Urinalysis – baseline and end of study
TSH – screening only
Prolactin – baseline and end of study
HbA1c – screening and end of study for patients with known diabetes
Hepatitis screen, urine drug screen, pregnancy test – screening only

7.1.6.2   Standard analyses and explorations of laboratory data

7.1.6.2.1   Analyses focused on measures of central tendency

The mean change from baseline to endpoint for the laboratory evaluations for HGIN + HGIU Acute Database is included in Appendix 10.9. Statistically significant decreases in lab parameters in the olanzapine group compared to placebo included hematocrit, hemoglobin, erythrocyte count, basophils, mean cell volume, albumin, total bilirubin and direct bilirubin – though these mean changes were small. Statistically significant increases in lab parameters in

the olanzapine group compared to placebo included ALT, AST, GGT, fasting glucose, cholesterol, LDL cholesterol, triglycerides, uric acid, prolactin, eosinophils and urea nitrogen.

The mean change from baseline to endpoint for selected laboratory parameters is in Table 7.1.6.2.1.1 below. For ALT and AST, the standard deviation at *baseline* in these laboratory parameters for the olanzapine group was very large (SD > mean) compared to the SD at baseline in the placebo group. For change to endpoint, the SD is still quite large in the olanzapine group compared to the placebo group indicating considerable variability and some significant increases in these parameters. The fasting glucose, triglyceride and cholesterol data were converted from SI units to the more conventional mg/dL units in this table.

It should be noted that there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. Elevated baseline prolactin was more common in study HGIN, as would be expected. A cursory review of the JMP dataset found that approximately 17% of patients in HGIN had a baseline prolactin > 30 ng/ml (maximum baseline prolactin = 65 ng/ml). The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range. Of note, the Sponsor did acknowledge this limitation and provided some additional analyses (see Section 7.1.2.3 – Special assessments).

Table 7.1.6.2.1.1. Select Laboratory Analytes of Interest: HGIN + HGIU Acute Database

			Baseline		Change to Endpoint				
		N	Mean	Std	**Mean**	Std	LS Mean Change	LS Mean Difference	P-value
Alkaline Phosp (U/L)	Olanzapine	175	152.3	82.3	**-1.3**	25.6	-2.7		
	Placebo	87	138.7	86.9	**-4.0**	16.6	-5.3	2.6	0.396
ALT (U/L)	Olanzapine	175	24.1	45.9	**19.95**	54.84	28.11		
	Placebo	87	20.4	13.0	**-3.08**	11.69	5.13	22.98	< 0.001
AST (U/L)	Olanzapine	175	24.5	29.9	**6.43**	26.41	9.89		
	Placebo	87	23.6	8.5	**-2.47**	7.51	0.98	8.91	0.002
GGT (U/L)	Olanzapine	175	19.0	12.3	**7.47**	20.02	7.73		
	Placebo	87	17.7	8.5	**-0.43**	5.96	-0.16	7.89	< 0.001
Glucose, fasting (mg/dL)*	Olanzapine	135	88.1	9.91	**2.70**	10.4	2.70		
	Placebo	64	89.7	10.27	**-2.88**	10.1	-3.06	5.59	< 0.001
Cholesterol (mg/dL)*	Olanzapine	175	161.0	32.0	**13.1**	22.78	12.74		
	Placebo	87	160.2	32.8	**-1.16**	24.32	-1.54	14.29	< 0.001
Triglycerides (mg/dL)*	Olanzapine	175	104.4	58.4	**29.2**	80.53	26.55		
	Placebo	87	110.6	64.6	**-4.42**	54.87	-6.19	33.63	< 0.001
Prolactin (mcg/L)	Olanzapine	163	14.06	9.92	**11.44**	14.52	10.51		
	Placebo	80	14.95	11.86	**-0.16**	10.69	-1.15	11.66	< 0.001

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113

Since urinalysis for ketones, glucose and protein is noted as 1+, 2+ etc., no mean change from baseline was provided for these parameters. It was noted, however, that there were no patients with PCS changes in these parameters (defined as increase ≥ 2) in either the olanzapine or placebo groups. Only 1 patient exhibited a PCS change in urinalysis – protein in the Overall Combined Database.

In the HGIN + HGIU Acute Database, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes). There was no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

7.1.6.2.2 *Analyses focused on outliers or shifts from normal to abnormal*

Percentage of patients with statistically significant treatment-emergent abnormal <u>high</u> laboratory values at any time (HGIN + HGIU Acute Database).
AST –27.6% of olanzapine and 3.8% of placebo-treated patients (p < 0.001)
ALT - 38.6% of olanzapine and 2.5% of placebo-treated patients (p < 0.001)
GGT – 10.1% of olanzapine and 1.2% of placebo-treated patients (p = 0.008)
Total bilirubin –0% of olanzapine and 7.1% of placebo-treated patients (p = 0.001)
Albumin –6.3% of olanzapine and 23.2% of placebo-treated patients (p = 0.002)
Fasting glucose – 3.7% of olanzapine and 3.2% of placebo-treated patients (p = NS)
Cholesterol –19.7% of olanzapine and 3.9% of placebo-treated patients (p = 0.001)
Triglycerides –54.7% of olanzapine and 19.6% of placebo-treated patients (p < 0.001)
HDL –9.7% of olanzapine and 1.2% of placebo-treated patients (p = 0.014) [shift to low were NS between groups]
Further analyses for shifts in fasting glucose, cholesterol, and triglycerides is included in Section 7.1.2.3 – Special Assessments.

7.1.6.2.3 *Marked outliers and dropouts for laboratory abnormalities*

In the HGIN + HGIU Acute Database, six patients discontinued due to elevations in ALT and/or AST. See Table 7.1.3.1.1 in Section 7.1.3.1 (Adverse events associated with dropouts).

The Sponsor did not provide a summary of marked outliers in the laboratory analysis. The individual patient labs and/or JMP datasets were reviewed from HGIN and HGIU study reports to identify marked outliers. It should be noted that the marked outliers in Table 7.1.6.2.3.1. may include lab values that were less than the potentially clinically significant (PCS) abnormalities defined by the Sponsor. For example, the cholesterol PCS was defined as > 15.516 mmol/L (> 599 mg/dL), whereas the values noted as marked outliers were usually lower than this PCS value. Of note, there was no defined PCS for triglycerides.

Table 7.1.6.2.3.1 includes the marked outlier (in bold font), other related analytes at the same timepoint, end of acute study value for the marked outlier (resolution?) and a column for comments which included any additional values for the marked outlier in the open-label phase.

Individual patient profiles were not readily available so it is not known if resolutions in marked outlier values were related to decreases in olanzapine dose.

Table 7.1.6.2.3.1. Marked Outliers for Laboratory Values – HGIN and HGIU

Patient	Lab Analyte	Reference Range*	Baseline	Highest	End of Study	Comments
				Marked Outlier Related Analytes at Same Timepoint *(Italics = values > ULN)*		
HGIU 005-501	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	102.6 125.9 68.7	**1237** (v.4) *220.8* NA	*389.4* *205.8* 90.0	TG = *160* at v.307 EOS
HGIU 012-1203	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	18 19 0.41 18	**325** (v.5) **148** 0.29 *53*	*230* (150 repeat) *92* (51 repeat) 0.29 (0.18 repeat) *48* (52 repeat)	ALT = *48*, AST = 24 at v. 501 (follow-up)
HGIU 012-1207	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	45 49 0.53 30	**147** (v.4) *60* 0.41 **163**	**147** 60 0.41 **163**	None
HGIU 013-1303	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	110.6 178.8 123.9	**261.9** (v.5) 179.5 *95.7*	**261.9** 179.5 95.7	TG = 111 at v.306
HGIU 019-1901	Creatine Phosphokinase	0 – 169 U/L	83	**256** (v.5)	*256*	CK = 168 at v. 301 (repeat 72)
HGIU 020-2007	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	67.2 149.8 98.8	**536.3** (v.4) 165.6 NA	*365.5* *231.7* 120.8	*TG = 103* at *v. 307*
HGIU 020-2011	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	22 19 0.41 11	**124** (v.6) *87* 0.29 27	**124** *87* 0.29 27	ALT = 11 at v. 309
HGIU 026-2607	Triglycerides Cholesterol LDL	31.8 – 124.8 mg/dL 129.7 – 203.9 mg/dL 64.1 – 132.8 mg/dL	59.3 201.5 125.9	**324.8** (v.4) 171.8 62.9	179.6 164.9 84.9	TG = 72 at v. 310
HGIU 027-2704	Creatine Phosphokinase	0 – 363 U/L	326	**619** (v.6)	**619**	CK = 261 at v. 307
HGIU 031-3103	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	16 19 1 13	**135** (v.4) 35 0.82 **153**	*75* *62* 0.53 *87*	ALT = 33/25 at v. 302
HGIU 035-3503	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	62.8 164.9 120.8	**317.7** (v.4) 167.6 74.9	100 203.9 *141.7*	None
HGIU 035-3518	Creatine Phosphokinase	0 – 187 U/L	55	**257** (v.6)	**257**	CK = 56 at v. 310
HGIU 036-3607	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	43 27 0.71 36	**208** (v.6) *91* 0.29 *65*	**208** *91* 0.29 *65*	ALT = *99* at v. 307
HGIU	Creatine					CK = 70 at v.

720-7202	Phosphokinase	0 – 363 U/L	71	**650** (v.5)	**650**	310
HGIU 720-7203	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	11 15 0.41 21	**128** (v.6) *58* 0.29 *98*	**128** *58* 0.29 *98*	ALT = 15 at v. 310
HGIU 720-7210	Triglycerides Cholesterol LDL	38.9 – 123.9 mg/dL 124.7 – 211.6 mg/dL 59.1 – 136.7 mg/dL	108.8 172.6 109.6	**382.3** (v.4) 195.7 88.0	*171.7* 199.6 127.8	TG = *148* at v. 310
HGIU 720-7214	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	38 31 0.71 20	**448** (v.6) **164** 0.41 46	**448** **164** 0.41 46	ALT = *69* at v. 302
HGIU 720-7217	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	20 32 0.88 21	**125** (v.6) *103* 0.53 35	**125** *103* 0.53 35	ALT = *58* at v. 308
HGIU 720-7221	Glucose, fasting	70 – 115 mg/dL	86.5	**145.9 (v.4)**	72	Glucose = 77 at v. 306
HGIU 730-7302	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	22 29 0.29 13	**123** (v.5) *77* 0.18 27	41 28 0.18 22	ALT = 16 at v. 310
HGIN 003-302	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	19 17 0.29 10	**132** (v.9) 38 0.29 18	**132** 38 0.29 18	ALT = 27 at v. 305
HGIN 004-401	ALT AST TBili GGT	6 – 43 U/L 10 - 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	18 19 0.18 19	*39* **157** (v.4) 0.18 18	19 25 0.41 17	AST = 22 at v. 309
	Creatine Phosphokinase	0 – 363 U/L	289	**7289** (v.4)	*610*	CPK = *781* at v. 309 (was *1766* at v. 306)
HGIN 006-602	ALT AST TBili GGT	6 – 43 U/L 10-40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	22 27 0.88 44	**240** (v.8) **141** 0.29 **206**	*134* *60* 0.53 *216*	ALT = 32 AST = *49* GGT = 38 at v. 308
	Triglycerides Cholesterol LDL	37.2 – 147.8 mg/dL 113.9 – 197.7 mg/dL 61.8 – 129.7 mg/dL	136.3 171.8 96.9	**532.7** (v.7) *210.8* NA	*207.1* 185.7 102.7	TG = 93 at v. 308
HGIN 007-703	ALT AST TBili GGT	6 – 34 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 33 U/L	29 33 0.41 11	**231** (v.6) **142** 0.41 *34*	*199* *101* 0.29 *34*	ALT = *66*, AST = 33 at v. 501 (follow-up)
HGIN 007-705	Creatine Phosphokinase	0 – 408 U/L	115	**855** (v.8)	189	CK = 141 at v. 305
HGIN 016-1601	ALT AST TBili GGT	6 – 43 U/L 10 – 40 U/L 0.18 – 1.23 mg/dL 0 – 51 U/L	23 26 *1.41* 22	**159** (v.6) 67 1.23 *64*	36 32 1.11 36	ALT = 43 at v. 309
HGIN 017-1703	ALT AST	6 – 43 U/L 10 – 40 U/L	*60* 40	**210** (v.5) *96*	*79* *50*	ALT = 15 at v. 309

	TBili	0.18 – 1.23 mg/dL	0.18	0.18	0.29	
	GGT	0 – 33 U/L	23	29	18	
HGIN 020-2004	ALT	6 – 34 U/L	21	**163** (v.5)	18	ALT = 9 at v. 309
	AST	10 – 40 U/L	21	*87*	22	
	TBili	0.18 – 1.23 mg/dL	0.29	0.29	0.18	
	GGT	0 – 33 U/L	29	*81*	*43*	
HGIN 021-2102	ALT	6 – 34 U/L	8	**105** (v.9)	**105**	ALT = 13 at v. 307
	AST	10 – 40 U/L	19	*90*	*90*	
	TBili	0.18 – 1.23 mg/dL	0.29	0.41	0.41	
	GGT	0 – 33 U/L	12	23	23	
	Triglycerides	38.9 – 123.9 mg/dL	84.9	111.5	109.7	TG = *293*
	Cholesterol	124.7 – 211.6 mg/dL	201.5	**289.6** (v.6)	*237.4*	Chol = *240*
	LDL	59.1 – 136.7 mg/dL	102.7	*165.6*	132.8	at v. 307
HGIN 021-2103	ALT	6 – 43 U/L	16	**396** (v.7)	**396**	ALT = *154*,
	AST	10 – 40 U/L	20	**136**	**136**	AST = 36 at
	TBili	0.18 – 1.23 mg/dL	0.41	0.41	0.41	v. 502
	GGT	0 – 51 U/L	18	*63*	*63*	(follow-up)
HGIN 030-3002	ALT	6 – 43 U/L	11	**175** (v.7)	*61*	ALT = 39 at v. 309
	AST	10 – 40 U/L	19	*69*	*60*	
	TBili	0.18 – 1.23 mg/dL	0.71	0.29	0.29	
	GGT	0 – 51 U/L	23	*72*	48	
HGIN 033-3301	Triglycerides	31.8 – 124.8 mg/dL	87.6	**426.5** (v.9)	**426.5**	None
	Cholesterol	129.7 – 203.9 mg/dL	*214.7*	*214.7*	*214.7*	
	LDL	64.1 – 132.8 mg/dL	*139.8*	*149.8*	*149.8*	
HGIN 900-9003	Triglycerides	37.2 – 147.8 mg/dL	85.8	**270.8** (v.8)	*195.6*	TG = 143 at v. 307
	Cholesterol	113.9 – 197.7 mg/dL	118.1	167.2	147.1	
	LDL	61.8 – 129.7 mg/dL	82.6	84.5	79.5	
HGIN 900-9006	Triglycerides	37.2 – 147.8 mg/dL	*231*	**363.7** (v.7)	*170.8*	AST = 23 at v.309
	Cholesterol	113.9 – 197.7 mg/dL	194.5	*241.3*	228.2	
	LDL	61.8 – 129.7 mg/dL	107.3	130.9	*147.9*	
HGIN 900-9010	ALT	6 – 43 U/L	20	*68*	35	AST = 31/29 at v. 309
	AST	10-40 U/L	26	**161** (v.8)	31	
	TBili	0.18 – 1.23 mg/dL	0.41	0.47	0.65	
	GGT	0 – 51 U/L	20	20	15	
HGIN 910-9101	ALT	6 – 34 U/L	*65*	*51*	16	GGT = *46* at v. 309
	AST	10 – 40 U/L	27	38	24	
	TBili	0.18 – 1.23 mg/dL	0.47	0.23	0.18	
	GGT	0 – 33 U/L	*36*	**95** (v.5)	26	
HGIN 910-9103	ALT	6 – 43 U/L	29	**141** (v.6)	36	ALT = 23 at v. 309
	AST	10-40 U/L	30	*84*	38	
	TBili	0.18 – 1.23 mg/dL	0.35	0.76	0.53	
	GGT	0 – 51 U/L	22	29	20	
HGIN 910-9105	Glucose, Fasting	70 – 115 mg/dL	108	**127.9** (v.9)	*127.9*	Glucose, fasting = 92 at v. 309
HGIN 910-9107	Triglycerides	37.2 – 147.8 mg/dL	132.7	**285.8** (v.4)	*178.8*	TG = 107 at v. 309
	Cholesterol	113.9 – 197.7 mg/dL	190	*213.5*	197.7	
	LDL	61.8 – 129.7 mg/dL	128.2	118.9	127.0	
HGIN 910-9108	ALT	6-43 U/L	40	**117** (v.5)	28	ALT = 28 at v. 309
	AST	10-40 U/L	20	*52*	23	
	TBili	0.18 – 1.23 mg/dL	0.35	0.35	0.35	
	GGT	0 – 51 U/L	32	34	23	
HGIN	ALT	6-43 U/L	25	**321** (v.5)	*128*	ALT = 17,

52

910-9110	AST	10-40 U/L	25	**190**	*53*	AST = 19 at
	TBili	0.18 – 1.23 mg/dL	0.47	0.59	0.41	v. 501
	GGT	0 – 51 U/L	19	37	29	(follow-up)
HGIN 920-9202	ALT	6-43 U/L	15	**393** (v.6)	**393**(231 repeat)	ALT = 20 at
	AST	10-40 U/L	19	**177**	**177** (59 repeat)	v. 501
	TBili	0.18 – 1.23 mg/dL	1	1	1 (0.71 repeat)	(follow-up),
	GGT	0 – 51 U/L	27	*78*	*78* (82 repeat)	AST NA
HGIN 920-9207	Triglycerides	31.8 – 124.8 mg/dL	123.9	**336.3** (v.6)	**336.3**	None
	Cholesterol	129.7 – 203.9 mg/dL	*205.0*	*233.2*	*233.2*	
	LDL	64.1 – 132.8 mg/dL	*135.1*	126.2	126.2	

*Converted from SI units: conversion factor for glucose = 0.0555, cholesterol = 0.0259, triglycerides = 0.0113, LDL = 0.0259, bilirubin = 17.1 (micromol/L to mg/dL)

Very few patients exhibited an increase in fasting glucose that might be considered a marked outlier in the HGIN + HGIU Acute Database. In reviewing the JMP dataset, 3 patients were noted with markedly elevated fasting glucose in the open-label phase of HGIN and HGIU:

Patient HGIN-900-9011 was randomized to placebo in the DB phase and had a baseline fasting glucose of 110 mg/dL. At visit 301, fasting glucose was <u>169 mg/dL</u> on 7.5 mg olanzapine which normalized with continued dosing at 10 mg to 97 mg/dL at end of the study.

Patient HGIN 910-9108 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 95 mg/dL. At visit 7 of the acute phase, fasting glucose was 101 mg/dL, at visit 303 fasting glucose was <u>149 mg/dL</u> on 20 mg olanzapine which normalized with continued dosing to 94 mg/dL at visit 309.

Patient HGIU 026-2602 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 104 mg/dL. At visit 6 of the acute phase, fasting glucose was 112 mg/dL, at visit 310 fasting glucose was <u>205 mg/dL</u> on 12.5 mg olanzapine and at visit 501 (follow-up) fasting glucose was 113 mg/dL.

The Sponsor did not include prolactin in the list of analytes for definitions of potentially clinically significant changes. For purposes of this review, the laboratory data in the JMP database was reviewed and a PCS value of $\geq$ 40 ng/ml was arbitrarily chosen. Prolactin levels were obtained at screening, baseline, end of study in the double-blind acute phase of HGIN and HGIU and visit 305 (HGIN) and 307 (HGIU) (~8-10 weeks into OL) and end of OL phase. The reference ranges used for prolactin were males 2.8 – 22 ng/ml and females 3.2 – 20 ng/ml. – per protocol amendment.
However, in the summary-clin-safe-app, the following Covance adolescent reference ranges were noted:

Gender	Age	Low (ug/L)	High (ug/L)
Male	12<=Age<14	2.84	24.0
	14<=Age<19	2.76	16.1
Female	12<=Age<14	2.52	16.9
	14<=Age<19	4.20	39.0

In the double-blind phase of HGIU, 13% (13/99) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 99/107 patients]. Only 3 of the 13 patients were male. The mean prolactin concentration at the end of study for this subgroup was 50.4 ± 8.3 ng/ml.

In the double-blind phase of HGIN, 17% (11/64) olanzapine patients had prolactin elevations > 40 ng/ml at end of study [baseline and end of study prolactin levels available for 64/72 patients]. Only 4 of the 11 patients were male. The mean prolactin concentration at the end of study for this subgroup was 55.8 ± 15.8 ng/ml. One patient receiving placebo in the acute HGIN study had an increase from 18.2 ng/ml at baseline to 42.4 ng/ml at end of study. Three patients had prolactin elevations > 90 ng/ml during treatment with olanzapine. These prolactin elevations occurred in two of the patients during the open-label phases of HGIU (n = 1) and HGIN (n = 1).

With the exception of one patient, it is not known whether these patients exhibited any clinical symptoms associated with hyperprolactinemia (narratives not available for these cases). Galactorrhea was not reported as an adverse event in the acute phases of HGIU or HGIN and one patient in the olanzapine group had the adverse event "gynecomastia" (see Section 7.1.4.3 Special Assessments). Patient HGIU 028-2804, who had an increase in prolactin concentration to 129.7 ng/ml, exhibited bilateral galactorrhea. Of note, one female patient in the LOAY study (data not included here) discontinued due to the adverse event galactorrhea – the narrative stated that her prolactin increased to 35 ng/ml. Therefore, clinical symptoms may have been associated with these prolactin elevations. It is possible that patients, especially adolescents, might be reluctant to report the types of adverse events associated with hyperprolactinemia.
Some patients who continued into the open-label phase had a decrease in their prolactin concentrations, others did not. Due to time constraints, this reviewer was unable to evaluate each case to determine whether decrease/resolution of hyperprolactinemia was related to a reduction in olanzapine dose.

Table 7.1.6.2.3.2. Prolactin Outliers: HGIN + HGIU Acute Database

Patient	Age/Gender	Prolactin (ng/ml)		
		Baseline	End of Double-Blind Phase	End of Open-Label Phase
HGIU 010-1005	14 YOM	23.4	60.7	17.6
HGIU 012-1216	16 YOM	18.9	51.1	51.6
HGIU 019-1901	16 YOF	9.2	43.8	35.0
HGIU 019-1905	14 YOF	18.8	44.5	32.6
HGIU 020-2007	14 YOF	16.5	57.6	14.5
HGIU 020-2011	13 YOF	8.1	57.5	10.9
HGIU 020-2020	16 YOF	12.7	44.4	40.3
HGIU 021-2103	17 YOF	20.6	45.1	13.5

HGIU 024-2403	15 YOF	31.1	49.8	31.5
HGIU 024-2405	13 YOM	15.2	40.3	24.3
HGIU 026-2602	13 YOF	20.2	50.3	49.5
HGIU 028-2803	15 YOF	31.6	68.1	11.7
HGIU 035-3517	13 YOF	13.8	42.3	17.4
HGIN 005-503	14 YOF	17.2	90.7	45.5
HGIN 013-1303	16 YOF	17.3	48.3	NA
HGIN 020-2003	17 YOF	26.3	79.9	NA
HGIN 021-2102	16 YOF	30.8	59.9	16.7
HGIN 026-2602	15 YOF	36	41.5	9.6
HGIN 026-2603	14 YOF	33	44.9	59.4
HGIN 030-3010	13 YOF	17.4	55	NA
HGIN 034-3401	16 YOM	22.7	43.8	30.4
HGIN 900-9006	17 YOM	28	55.5	40.1
HGIN 910-9107	16 YOM	45.8	48.2	43.2
HGIN 940-9408	15 YOM	12	45.8	21.7

Table 7.1.6.2.3.3. Prolactin Outliers: HGIN + HGIU Open Label Phase

Patient	Age/Gender	Treatment in DB Phase	Baseline	Visit #307(HGIU) #305 (HGIN)	End of Open-Label Phase Visit #310 (HGIU) Visit #309 (HGIN)
HGIU 007-704	15 YOM	Placebo	32.5	36.1	**47.3**
HGIU 019-1904	15 YOF	Placebo	5.5	28.5	**43.7**
HGIU 019-1907	15 YOF	Olanzapine	10.1	**40.6**	38.5 (v. 308)
HGIU 020-2003	13 YOF	Olanzapine	18.4	**41.8**	23.6
HGIU 021-2102	17 YOF	Olanzapine	25	**57.7**	10.6
HGIU 026-2608	13 YOF	Olanzapine	20.5	-	**57** (v. 304)
HGIU 028-2804	15 YOF	Placebo	11.8	**129.7** (v.302)	**49.8** (v. 307)

HGIU 035-3519	14 YOM	Olanzapine	28.3	-	**41.7** (v. 302)
HGIU 036-3606	16 YOF	Placebo	20.7	**59.5**	**44.0**
HGIN 900-9009	17 YOF	Olanzapine	17.5	17	**110**
HGIN 020-2005	14 YOM	Olanzapine	41.1	-	**64.7** (v. 305)

7.1.6.3   Special assessments

Hyperprolactinemia
A discussion of the adverse events potentially related to hyperprolactinemia are in Section 7.1.5 (Less Common Adverse Events). The mean change from baseline to endpoint in prolactin concentration is in Section 7.1.6.2.1 and marked outliers are in Section 7.1.6.2.3.
As was mentioned in Section 7.1.6.2.1, there are limitations in evaluating the mean change from baseline to endpoint for the prolactin data. Since the washout period in studies HGIN and HGIU could be as short as 2 days, some baseline prolactin concentrations were increased likely due to the effect of the prior antipsychotic. Interpretation of the effect of olanzapine on prolactin concentration is difficult if the analysis includes patients with an elevated baseline. The Sponsor will be asked to perform an analysis for the subset of patients with a baseline prolactin within the normal range (including treatment by gender and treatment by age analyses).

Elevations in prolactin due to antipsychotics occur more frequently in females compared to males. The Sponsor did include an analysis of these laboratory data by gender for the individual HGIU and HGIN studies. For each separate study, no significant treatment by gender interaction was found. However, there was a numerically greater mean change to endpoint in prolactin in females (16.2) compared to males (5.4) in study HGIN. Also, for the patients with an end of study prolactin > 40 ng/ml, the majority of these patients were female (see Section 7.1.6.2.3.).
For the HGIN + HGIU Acute Database, there was no significant treatment-by-gender interaction (see Appendix 10.10), though there was a numerically greater mean change to endpoint in females (15.6) compared to males (8.8).

Table 7.1.6.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: Study HGIU

```
                                            Change to
                              Baseline      Endpoint
Laboratory                  ------------  -----------------            LSMean
Analyte    Gender  N  Therapy      n  Mean   Std    Mean    Std   LSMean  Diff.  *P-value **P-value
-----------------------------------------------------------------------------------------------

PROLACTIN  Female  70 Olanzapine  43 15.23  10.01  15.38  13.73  15.96  12.75   <.001    .590
                      Placebo     27 14.99   8.00   2.67   8.60   3.21

           Male    79 Olanzapine  56 11.36   5.46  11.50   9.50  11.91  10.83   <.001
                      Placebo     23 10.00   6.40   0.66   3.06   1.08
```

Table HGIU.12.13 in study report

Table 7.1.6.3.2. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: Study HGIN

```
                                                  Change to
                                      Baseline     Endpoint
                                     ------------  --------------------         LSMean
Laboratory
Analyte    Gender  N   Therapy      n   Mean   Std    Mean     Std    LSMean   Diff.   *P-value **P-value
-----------------------------------------------------------------------------------------------------------

PROLACTIN  Female  30  Olanzapine   20  17.24  10.31   16.17   22.59   14.25   17.99    .025     .258
                       Placebo      10  15.95   6.67   -2.20   10.26   -3.73

           Male    64  Olanzapine   44  14.89  13.11    5.37   14.35    5.43    9.27    .028
                       Placebo      20  20.10  19.26   -3.91   16.86   -3.84
```

This reviewer could not find an analysis of prolactin concentrations by the subgroup "age". The Sponsor will be asked to provide these data.

The Sponsor evaluated treatment-emergent high prolactin concentrations at any time during the acute trials (only patients with normal baseline included in this analysis). For the HGIU + HGIN Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group (p < 0.001). No significant treatment-by-gender interactions were noted in this analysis, though a higher percentage of males (41/68, 60.3%) had a high prolactin concentration at any time compared to females (14/48, 29%).

The Sponsor did evaluate prolactin concentrations over time for the Overall Combined Database. In general, there is a decrease in mean prolactin concentration over the course of the 32 weeks which approaches baseline concentrations. There are still outliers in this analysis at the 19-32 week timepoint. The Sponsor will be asked to provide a similar summary for only those patients completing the 19-32 weeks.

Table 7.1.6.3.3. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database

Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points
Overall Olanzapine Exposure Combined Database

		Summary				
Database	Olz Exposure	N	Mean	Std	Median	Max
Bipolar	Baseline	217	15.35	12.58	11.28	110.30
	1-6 weeks	174	26.60	16.18	23.10	129.66
	7-18 weeks	122	19.24	11.89	16.71	59.49
	19-32 weeks	83	18.03	10.42	14.36	49.53
Schizophrenia	Baseline	214	18.84	19.97	11.87	131.57
	1-6 weeks	190	31.82	20.75	26.48	110.84
	7-18 weeks	88	22.75	16.24	18.62	112.00
	19-32 weeks	93	19.01	15.60	14.81	109.97
Overall	Baseline	431	17.08	16.74	11.60	131.57
	1-6 weeks	364	29.33	18.86	25.00	129.66
	7-18 weeks	210	20.71	13.95	17.13	112.00
	19-32 weeks	176	18.55	13.38	14.70	109.97

Metabolic Parameters

The Sponsor performed more detailed analyses on several adverse event profiles including "metabolic parameters".

The analyses included LOCF mean change from baseline to endpoint in fasting glucose and lipids; incidence of significant changes in fasting glucose and lipids, nonfasting glucose and lipids, weight gain-related adverse events, diabetes-related adverse events and dyslipidemia related adverse events; mean weight over time; correlations between mean changes in weight, glucose and lipids.

HGIN + HGIU Acute Database

LOCF mean change from baseline to endpoint:
There were statistically significant greater mean increases in fasting glucose levels (+ 2.7 mg/dL olanzapine vs. -2.9 mg/dL placebo, p < 0.001), total cholesterol (+ 12.7 mg/dL vs. +1.5 mg/dL, p = 0.002), and triglycerides (+27.4 mg/dL vs. -1.8 mg/dL, p = 0.007).

Significant changes in fasting glucose and lipids <u>at any time</u>:
There was a greater incidence of significant changes in patients treated with olanzapine than in patients treated with placebo for normal to borderline total cholesterol (15.7% vs. 3.6%, p = 0.023) and for normal to high fasting triglycerides (12.4% vs. 1.9%, p = 0.039).
The change from normal to borderline LDL cholesterol was approaching statistical significance (13.7% vs. 3.8%, p = 0.064).

The changes in fasting glucose were not statistically different:
Normal (< 100 mg/dL) to high ($\geq$ 126 mg/dL) = 0% (0/122) olanzapine, 2% (1/51) placebo
Impaired glucose tolerance ($\geq$ 100 mg/dL and < 126 mg/dL) to high ($\geq$ 126 mg/dL): 15.4% (2/13) olanzapine, 0% (0/13) placebo
Normal/impaired glucose tolerance (< 126 mg/dL) to high ($\geq$ 126 mg/dL): 1.5% (2/135) olanzapine, 1.6% (1/64) placebo.
The lack of a statistically significant difference in the change from impaired glucose tolerance to high fasting glucose levels (15.4% olanzapine vs. 0% placebo) is likely due to the low number of subjects enrolled with baseline impaired glucose tolerance (n = 13 each group).

Significant changes in fasting glucose and lipids <u>at endpoint</u>:
The only parameter that was statistically significant was normal to borderline cholesterol (14% olanzapine, 3.6% placebo, p = 0.039). The change from normal to high triglycerides was approaching statistical significance (10.6% olanzapine, 1.9% placebo, p = 0.064).

For the fasting glucose data, only 1 subject in the olanzapine treatment arm had a change from impaired glucose tolerance to high and 1 subject in the olanzapine treatment arm had a change from normal/impaired glucose tolerance to high.

In the Overall Combined Dataset, few patients had baseline impaired glucose (n = 47). Of those subjects, 6 (12.8%) had a shift from impaired glucose tolerance to high fasting glucose.
As mentioned in Section 7.1.6.2.1, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes) in the HGIN + HGIU Acute Database. There was

no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

The Sponsor provided correlation coefficients of change at endpoint between weight, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (it is unclear what correlation coefficient was used):
For the Overall Combined Dataset, there were statistically significant correlations between weight and total cholesterol (corr = 0.166, p = 0.005) and between weight and triglycerides (corr = 0.210, p < 0.001).
The Sponsor was asked to provide these correlations for the HGIN + HGIU Acute Database. In this database, there were statistically significant correlations between weight and total cholesterol (corr = 0.211, p = 0.003), between weight and triglycerides (corr = 0.223, p = 0.002) and between weight and fasting glucose (corr = 0.165, p = 0.021). Though these correlations are statistically significant, they are not particularly robust.

Hepatic-related Parameters
The Sponsor performed more detailed analyses on several adverse event profiles including "hepatic-related parameters".

For this analysis, a potentially clinically significant increase is defined as a change from a value less than or equal to the PCS high limit at all baseline visits to a value greater than the PCS high limit at endpoint or for two consecutive measures during therapy.

HGIN + HGIU Database
Mean change to endpoint in hepatic laboratory analytes in provided in Section 7.1.6 (Laboratory Findings).
The Sponsor analyzed treatment emergent high values at anytime (Table 7.1.6.3.4) and at endpoint (Table 7.1.6.3.5) for alkaline phosphatase, ALT, AST, GGT and total bilirubin. A higher percentage of patients in the olanzapine group had elevations in ALT, AST and GGT for both analyses.

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at <u>Anytime</u>: HGIN + HGIU Acute Database

Table APP.2.7.4.7.2.2. Hepatic Laboratory Analytes
Treatment-Emergent Abnormally High Values Anytime
(>1 X ULN)
All Randomized Patients with Normal Baseline Values
Acute Placebo-Controlled Combined Database

Hepatic Analytes	Olanzapine			Placebo			p-value*
	N	n	%	N	n	%	
ALKPH	159	11	6.9%	77	2	2.6%	.231
ALT	153	59	38.6%	79	2	2.5%	<.001
AST	163	45	27.6%	79	3	3.8%	<.001
GGT	169	17	10.1%	83	1	1.2%	.008
T. Bili	170	0	0.0%	85	6	7.1%	.001

Table 7.1.6.3.4. Sponsor's Table. Hepatic Laboratory Analytes – High Values at <u>Endpoint</u>: HGIN + HGIU Acute Database

Table APP.2.7.4.7.2.24. Hepatic Laboratory Analytes
Treatment-Emergent Abnormally High Values at Endpoint (>1 X ULN)
All Randomized Patients with Normal Baseline Values
Acute Placebo-Controlled Combined Database

Hepatic Analytes	Olanzapine			Placebo			p-value*
	N	n	%	N	n	%	
ALKPH	159	6	3.8%	77	1	1.3%	.432
ALT	153	32	20.9%	79	1	1.3%	<.001
AST	163	19	11.7%	79	1	1.3%	.005
GGT	169	14	8.3%	83	0	0.0%	.006
T. Bili	170	0	0.0%	85	5	5.9%	.004

Abnormal ALT values at anytime
> 3X ULN: olanzapine 11.1% (17/153) vs. placebo 1.3% (1/79) p = 0.008
> 5X ULN : olanzapine 3.9% (6/153) vs. placebo 0% p = 0.098
> 10X ULN : olanzapine 0.7% (1/153) vs. placebo 0% p = 1.00

> 3X ULN ALT anytime for patients with ALT baseline ≤ 3X ULN:olanzapine 12.1% (21/174) vs. 2.3% placebo (2/87) p = 0.009. [This analysis is the one that is included in proposed labeling for ALT elevations]

Only four patients had an increase in TBili to > 1.5 times ULN – two in the olanzapine group and two in the placebo group.

The Sponsor also used Hy's rule (ALT $\geq$ 3 times and TBili $\geq$ 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 $\geq$ 7% body weight was higher in the olanzapine group (43.5%) compared to the placebo group (6.8%) (p < 0.001). Data for weight change is discussed further in Section 7.1.4.4 (Common Adverse Events).

7.1.7.2.3 Marked outliers and dropouts for vital sign abnormalities

Individual vital signs were reviewed from the JMP datasets. In general, few patients had markedly abnormal vital signs. Isolated systolic BP 150 – 155 mmHg was noted in both olanzapine and placebo groups, no diastolic BPs > 110 mmHg were noted and pulse rates > 130 bpm were noted in few patients but more olanzapine-treated patients than placebo-treated patients (highest pulse was 148 bpm in placebo patient).

Patient HGIU-035-3503 (16 YOBF) receiving olanzapine discontinued study HGIU due to an elevated pulse (standing pulse 140 bpm from baseline 96 bpm).

7.1.8   Electrocardiograms (ECGs)

7.1.8.1   Overview of ECG testing in the development program

The reviewer focused mainly on the two placebo-controlled acute trials, HGIN and HGIU, for evaluation of ECG data. Though the Sponsor states that differences from baseline were analyzed, it should be noted that ECGs were not obtained at baseline (visit 2), but were obtained during the screening period (visit 1):

 "Twelve-lead ECGs were collected on each patient at baseline to determine the eligibility of the patient for entry into the study, and at the Final Visits of Study Period II and Study Period III to monitor the general safety of the patient during the course of the study".

Therefore, patients could be on other medications since this was the washout period prior to randomization.

Mean "baseline" ECG parameters appear fairly similar between the olanzapine and placebo groups such that any differences between the groups with regard to concomitant medications taken during screening might have been "equalized" by randomization.

7.1.8.2   Standard analyses and explorations of ECG data

7.1.8.2.1   *Analyses focused on measures of central tendency*

Statistically significant differences were found between olanzapine and placebo on all ECG parameters except QTcF (see Table 7.1.8.2.1.1). 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	Std	Change to Endpoint Mean	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

Measure	Value	N	Baseline Mean	Baseline Std	Endpoint Mean	Endpoint Std	Change Mean	Change Std	P-value *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

Measure	Gender	Value	N	Baseline Mean	Baseline Std	Endpoint Mean	Endpoint Std	Change Mean	Change Std	P-value *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 $\leq$ 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 $\geq$ 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) (6) 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

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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) (6). 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 ($\geq$ 5%, olanzapine > placebo) occurring in the HGIN + HGIU Acute Database were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

Significant safety signals that emerged in these databases were weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia.

Weight Gain
The following table summarizes the mean weight changes by mean change in weight to endpoint (LOCF and OC), mean change in BMI to endpoint and % of patients with > 7% increase in body weight.

	Olanzapine	Placebo	LS Mean Diff	P-value
HGIN + HGIU Acute Database				
Weight (kg) Mean Change to Endpoint (LOCF)	3.90 (n = 177)	0.24 (n = 88)	3.66	< 0.001
Weight (kg) Mean Change to Endpoint (OC)	3.6 (n = 154)	0.08 (n = 67)	3.57	< 0.001
BMI Mean Change to Endpoint (LOCF)	1.22	0.05	1.17	< 0.001
$\geq$ 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 ($< 15, \geq 15$ 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 $\geq$ 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 $\leq$ 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 $\geq$ 3x ULN and TBili $\geq$ 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				**Homogeneity
Event Classification	Gender	N	n	%	N	n	%	*P-value	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
                                           --------------------  --------------------          **Homogeneity
Event Classification          Age            N     n     %        N     n     %      *P-value   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 ($\geq 5\%$ 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 ($\geq 5\%$ 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%		Sedation	22%	6%
Constipation	11%	5%		Headache	17%	17%
Dyspepsia	11%	5%		Fatigue	14%	6%
Increased appetite	6%	3%		Dry mouth	8%	0%
Tremor	6%	3%		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

```
_____
                              Change to
                 Baseline     Endpoint
               --------------  --------------  LSMean   LSMean
Population    N   Mean   Std    Mean   Std    Change   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 a 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

```
_____
                                                    Change to
                                        Baseline    Endpoint
                                        ----------  ----------  LSMean   LSMean
Laboratory                                                      Change   Difference
Evaluations        Unit   Population   N  Mean  Std  Mean  Std                    *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 "Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg. Efficacy in adolescents with bipolar disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg per day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials."

This dosing regimen is the same used in study HGIU – though the investigators were instructed to target 10 mg within the first week if tolerated (e.g. not based on efficacy) ["if no tolerability or safety issues are apparent, the dose **must** be titrated to at least 10 mg/day by visit 4"]. In the trial, dosing in the evening was recommended due to the possibility of somnolence. The Sponsor has not made a recommendation regarding the timing of dosing in proposed labeling.

8.2   Advisory Committee Meeting

No advisory committee meeting was held for this submission.

8.3   Literature Review

The Sponsor submitted a literature review though there was no attempt to summarize key findings. The Sponsor stated that none of the reviewed articles presented safety data contradictory to the conclusions presented in the NDA. Due to time constraints for this priority application, a separate literature review was not conducted by this reviewer.

8.4   Postmarketing Risk Management Plan

The Sponsor submitted a Risk Management document outlining their proposed actions for risk minimization. The identified risks in this document included weight gain, sedation, hepatic changes, hyperprolactinemia, glucose dysregulation, dyslipidemia. For all of these safety issues, the Sponsor has proposed the following actions for pharmacovigilance: clinical trial surveillance, routine pharmacovigilance, targeted surveillance, long-term safety study and _____ (b) (4) For glucose dysregulation and dyslipidemia, an additional action was to perform a retrospective cohort claims database study.

Routine pharmacovigilance was defined as periodic reporting per PSUR or as appropriate. Targeted surveillance was similar but targeted weight gain, hepatic changes, glucose dysregulation and dyslipidemia. The Sponsor has proposed a long-term safety study to evaluate the safety of olanzapine in adolescent patients with schizophrenia or bipolar disorder and to estimate the incidence and prevalence of identified and potential risks associated with olanzapine treatment. The study is still in the planning phase.

(b) (4)

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.

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I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

A number of additional requests for safety information and analysis regarding this submission are included at the end of this review. If acceptable, these requests could be included in the action letter.

9.2   Recommendation on Postmarketing Actions

Since non approval is recommended, there are no recommendations for postmarketing actions.

9.3   Labeling Review

Changes to proposed labeling are being made directly to the annotated labeling submitted by the Sponsor, this was the first PLR labeling so there were many changes from prior approved labeling. The project manager, Dr. Doris Bates, reviewed the PLR labeling against the prior approved labeling and noted any differences – especially differences that were not highlighted by the Sponsor.
In the proposed labeling, all of the "frequent" adverse events in the "Other Adverse Events Observed" section were removed and some of the adverse events in other categories (infrequent, rare) were also removed. The Sponsor has been asked to address this and had not responded at the time this review was finalized.

This section will briefly discuss some of the labeling that may require revision:
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 does not specify whether dosing should occur in the morning or evening. Since the Sponsor recommended dosing in the evening in the clinical trials, this should also be reflected in labeling.
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
All of the adverse events in the category "frequent" have been removed in the proposed labeling. Other adverse events in the categories infrequent and rare have also been removed. The Sponsor has been asked to address this. Similar issues occur in this same section for IM olanzapine.

Clinical Trials in Adolescent Patients
ECG Changes – correct spelling of Frederica to Fredericia

Postmarketing Experience
When was the last time the Sponsor updated this section? There have been some postmarketing reports of death due to diabetic ketoacidosis occurring in adolescents – should this data be included in this section?

9.4   Comments to Applicant

Requests for information

The Sponsor has responded to the following requests and the reviewer has reviewed the responses

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.

2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.

3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the CRF, it does not appear that there is an area where the recorder could state the source of the ratings. Are both ratings, patient and parent/legal guardian, available for subjects in this study? If so, please provide these ratings and indicate the primary source for the ratings.

4. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF analysis (similar to table HGIN 14.20 for OC analysis) - with and without site 021.

5. Provide statistical analysis for olanzapine vs. placebo for weekly visits for LOCF and OC analysis for the US and Russia sites separately.

6. Provide patient baseline demographics and analysis for US vs. Russia sites (similar to HGIN.11.1 but comparing US vs. Russia).

7. It is noted that 50 patients were randomized at the 5 sites in Russia - 10 patients per site. Is it coincidental that 10 subjects were randomized at each of these sites? Were caps specified to the investigators such that each site could randomize no more than 10 patients?

8. Please provide patient baseline severity of illness and statistical analysis for US vs. Russia sites (similar to HGIN.11.2 but comparing US vs. Russia). Include the following variables: age of onset of illness, # of previous schizophrenia episodes, total hospitalization, length of current episode, days since last hospitalization, psychiatric hospitalization, CGI-S, BPRS-C subscales, BPRS-C total score, PANSS subscales, and PANSS total score

9. Do study reports for HGIN and HGIU include information regarding the adverse events associated with patient drop-outs? Please indicate where this information may be found.

10. In table HGIN.11.2, it is noted that the minimum value for age for Age of Illness Onset was 5 years old for each treatment group. Please provide the study numbers for all patients with an age of illness onset < 10 years old and CRFs for these patients.

11. In table HGIN.11.2, it is noted that the minimum value for the Length of Current Episode is "0" - please clarify.

12. For Psychiatric Hospitalization in table HGIN.11.2, please clarify whether this is past or current hospitalization.

13. Please provide # of prior psychiatric hospitalizations for both treatment groups with statistical analysis for this variable.

14. In the brief summary for study HGCS, it is noted that 2 patients experienced the adverse event "intentional injury". Please provide brief summaries for these two events.

15. For study HGGC, were there any serious adverse events? The synopsis states that no patients experienced serious adverse events associated with cardiac abnormalities or weight gain - but there is no mention of other SAEs that may have occurred in this trial.

16. For the adult studies HGDH and HGGF that included adolescent patients, please submit narratives for the serious adverse events (per Table 2.7.4.4 in the summary-clin-safety document).

17. For the adult studies HGGF and HGKL, please submit narratives for the discontinuations due to adverse event cases.

18. For patient HGIU-028-2804, the narrative indicates that she experienced bilateral galactorrhea while hospitalized for a recurrence of bipolar symptoms. Please provide the prolactin concentrations that were obtained by the hospital (pending at time patient was discharged).

19. Patient HGMF-003-0304 had the SAE "exacerbation of bipolar illness with positive suicidal ideation". However, it appears that this was coded to the preferred term "bipolar disorder". Why weren't both verbatim terms coded to preferred terms - i.e. bipolar disorder and suicidal ideation?

20. For the discontinuations due to the adverse event "weight gain" in the acute and combined databases, please provide weight data for the post-study follow-up visits. Some of the narratives have this information, but the majority indicate that the adverse event had resolved without providing weight data.

21. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.

22. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?

23. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

The following questions were submitted to the Sponsor via email on 3/19/07. The Sponsor attempted to send an email response on 3/26/07 but encountered technical difficulties. The Sponsor faxed the response on 3/27/07 and was asked to also fax the response to this reviewer (working in another location). The Sponsor did not fax the response to this reviewer. This reviewer received the response on 4/2/07 (working in office) and had insufficient time to review the responses to meet the internal NDA deadline. Of note, request #30 was not addressed in this response and the Sponsor indicated that the response will be provided at a later date.

24. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15, >= 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.

25. Please provide a subgroup analysis for age (< 15 and >=15) and gender for the variable "PCS weight change (> 7%)" for the Acute Placebo Controlled Combined Database.

26. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.

27. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.

28. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.

29. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?

30. In proposed labeling, some adverse events have been removed from the sections "other adverse events observed during the clinical trial evaluation of oral olanzapine" and "other adverse events observed during the clinical trial evaluation of intramuscular olanzapine for injection". In the former section, it appears that all of the frequently occurring AEs ("frequent") have been removed. In both sections, many adverse events that were included in the infrequent and rare categories have been removed. Please provide a justification for removal of these adverse events from proposed product labeling.

Requests for additional information from the Sponsor – may be included in action letter:

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																					
HbgA1c[f]	X									X						X					X	
Prolactin[g]	X	X								X						X					X	
EFFICACY ASSESSMENTS/Measurements																						
Anchored BPRS-C[j]	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
CGI Severity		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
CGI-Improvement			X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
PANSS		X			X					X											X	
OAS		X			X					X											X	
Child Health Questionnaire (CHQ)[k]		X								X											X	
Brief Assessment of Cognition for Schizophrenia (BACS)[k]		X								X											X	

10.4 Severity of Illness: Russia vs. U.S. Sites

Table 1. Illness Characteristics at Baseline by Country
All Randomized Patients
F1D-MC-HGIN, Acute Phase

		Country		
		Russia	U.S.	
		(N=50)	(N=57)	
Illness Characteristics	Statistics			*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

		Country		
		Russia	U.S.	
		(N=50)	(N=57)	
Illness Characteristics	Statistics			*P-value
Length of current episode in days	No. of Patients	50	56	
	Mean	262.44	259.43	.974
	Median	125.50	80.00	
	Std. Dev.	396.21	524.28	
	Minimum	7.00	0.00	
	Maximum	2139.00	2742.00	
Days since the last hospitalization	No. of Patients	37	40	
	Mean	476.95	149.58	.012
	Median	163.00	7.00	
	Std. Dev.	632.51	477.26	
	Minimum	31.00	1.00	
	Maximum	2718.00	2889.00	

Illness Characteristics	Category	Russia (N=50) n (%)	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	Russia (N=50)	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	Russia (N=50)	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	

| | | Country | | |
| | | Russia | U.S. | |
Illness Characteristics	Statistics	(N=50)	(N=57)	*P-values
BPRS-C Thinking Disturbance(Sum 7-9)	No. of Patients	50	57	
	Mean	9.72	11.04	.030
	Median	10.00	11.00	
	Std. Dev.	3.29	2.88	
	Minimum	4.00	5.00	
	Maximum	18.00	18.00	
BPRS-C Psychomotor Excitation Subtotal(Sum 10-12)	No. of Patients	50	57	
	Mean	6.08	7.32	.038
	Median	5.00	7.00	
	Std. Dev.	2.84	3.19	
	Minimum	2.00	2.00	
	Maximum	13.00	14.00	
BPRS-C Withdrawal Subtotal(Sum 13-15)	No. of Patients	50	57	
	Mean	9.54	7.98	.021
	Median	10.00	8.00	
	Std. Dev.	2.76	3.93	
	Minimum	4.00	1.00	
	Maximum	18.00	15.00	

| | | Country | | |
| | | Russia | U.S. | |
Illness Characteristics	Statistics	(N=50)	(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	

```
                                                        Country
                                                ------------------------
                                                Russia        U.S.
                                                ----------    ----------
                                                (N=50)        (N=57)      *P-values
Illness Characteristics          Statistics
----------------------------------------------------------------------------------

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

Efficacy Variable	Therapy	N	Baseline Mean	Std	Change to Endpoint 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

Age Group	HGIN n	HGIN %	HGIU n	HGIU %	Combined n	Combined %
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

| | | Visit Week | N | Change to Maximum | | |
				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

	Subgroup	Therapy	n	Baseline		Change to Endpoint		LS Mean	LSMean Diff	P-value	P-value
				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

	Therapy	n	Baseline Mean	Change to Endpoint 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

```
                                                                    Days
        Patient ID                                                   to
 (Study-Inv-Patient)   Brief Description of Event        Code  Therapy  Event  Fatal?
-----------------------------------------------------------------------------------

   HGIU-001-0103       THE PATIENT HAS REPORTEDLY BEEN HAVING    5   Placebo   23     No
                       DIFFICULTIES WITH DYSPHORIC MOOD.  IN MID TO
                       LATE APRIL, 2003, HE TRIED TO TIE A BELT
                       AROUND HIS NECK RESULTING IN A RASH.
   HGIU-012-1206       INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT  5   Olz   22     No
                       MARKS ON FOREARM
   HGIU-012-1211       SUICIDAL IDEATION / SUICIDAL IDEATION     4   Olz   14     No
```

Overall Combined Database

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIN-019-1901	SUICIDAL IDEATION / SUICIDAL IDEATION	4	167	No
HGIN-026-2603	SUICIDAL IDEATION / SUICIDAL IDEATION	4	135	No
HGIN-030-3001	SUBJECT IS EXPERIENCING SYMPTOMS OF DELUSIONS, AUDITORY AND VISUAL HALLUCINATIONS, AND SUICIDAL IDEATIONS SUBJECT WILL BE HOSPITALIZED FOR STABILIZATION ON TRADITIONAL MEDICATION	4	51	No
HGIN-930-9307	SUICIDE ATTEMPT / SUICIDE ATTEMPT	2	59	No
HGIU-001-0108	ALCOHOL POISONING / ETOH INTOXICATION. LSS: ON (b) (6) NEARLY SIX MONTHS AFTER STARTING STUDY DRUG, THE PATIENT WAS ADMITTED TO THE HOSPITAL WITH ALCOHOL ("ETOH") POISONING. THE PATIENT WAS RECEIVING 15MG OLANZAPINE AT THE TIME OF THE EVENT. THIS WAS THE FIRST PSYCHIATRIC HOSPITALIZATION FOR THIS 14-YEAR OLD WHO WAS BROUGHT TO THE EMERGENCY ROOM (ER) BY POLICE AFTER THE PATIENT BECAME INTOXICATED, VOICED SUICIDAL IDEATION, AND PASSED OUT AT SCHOOL. APPROXIMATELY (b) (6) (A WEEK AND A HALF A GO), THE PATIENT TRIED TO JUMP OUT OF HER MOTHER'S MOVING VEHICLE AT 55 MILES PER HOUR, BUT THE MOTHER PREVENTED HER FROM FALLING OUT.	3	157	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIU-012-1206	INTENTIONAL SELF-INJURY / SELF-INFLICTED CUT MARKS ON FOREARM	5	22	No
HGIU-012-1211	SUICIDAL IDEATION / SUICIDAL IDEATION	4	14	No
HGIU-012-1212	THE PATIENT HAD BEEN DRAWING PICTURES OF HOW THE PATIENT COULD DIE . . . THE PATIENT COULD NOT ASSURE THE INVESTIGATOR THAT SHE WOULDN'T HARM HERSELF.	4	34	No
HGIU-013-1301	SUICIDAL IDEATION / OCCASIONAL SUICIDAL THOUGHTS	4	71	No
HGIU-013-1310	INTENTIONAL SELF-INJURY / SELF INJURY	5	64	No
HGIU-020-2016	SUICIDE ATTEMPT / ATTEMPTED SUICIDE	2	214	No
HGIU-026-2604	SELF INJURIOUS BEHAVIOUR / SELF-INJURIOUS BEHAVIOR. LSS: THE PATIENT REPORTED THAT HIS DEPRESSION WORSENED APPROXIMATELY ONE WEEK PRIOR (~05-NOV-2003). ADDITIONALLY HE BEGAN FEELING SUICIDAL (WITHOUT PLAN) APPROXIMATELY THREE DAYS PRIOR (~09-NOV-2003). THE PATIENT'S MOTHER CALLED THE SITE TO REPORT THAT THE PATIENT HAD CUT HIMSELF THE PRIOR EVENING AND DIDN'T FEEL SAFE. THE PATIENT WAS BROUGHT TO THE HOSPITAL FOR SAFETY AND STABILIZATION.	4	59	No

```
                                                                    Days
   Patient ID                                                        to
(Study-Inv-Patient)   Brief Description of Event            Code    Event   Fatal?
-----------------------------------------------------------------------------------

  HGIU-026-2605       THE PATIENT WAS BEHAVING INAPPROPRIATELY AND    9      53      No
                      WAS ON THE ROOF OF HIS HOME REFUSING TO COME
                      DOWN
  HGIU-026-2606       SUICIDAL IDEATION / SUICIDAL IDEATION           4      35      No
  HGIU-027-2705       INTENTIONAL SELF-INJURY / SELF-INFLICTED        5      76      No
                      SUPERFICIAL LACERATIONS
  HGIU-028-2805       SUICIDAL IDEATION / SUICIDAL IDEATION. LSS:     3     108      No
                      THE PATIENT'S MOTHER CALLED THE
                      INVESTIGATOR'S SITE ON 14-MAY-2004 TO STATE
                      THAT HER DAUGHTER HAD BECOME SUICIDAL WITH A
                      PLAN TO OVERDOSE ON LORAZEPAM (ATIVAN)
                      DURING THE LAST WEEK OF MAY 2004, BUT ENDED
                      UP TELLING HER PARENTS THE EVENING OF
                      09-MAY-2004.
  HGIU-730-7302       SUICIDAL IDEATION / PASSIVE SUICIDAL IDEATION   4     177      No
  HGMF-003-0304       EXACERBATION OF BIPOLAR ILLNESS WITH            4      29      No
                      POSITIVE SUICIDAL IDEATION
  HGMF-008-0805       INTENTIONAL SELF-INJURY, CUTTING LEFT ARM       5      93      No
  LOAY-400-4001       PATIENT IS IN A DEPRESSIVE MOOD AROUND          4      44      No
                      10-11.05.99 AND EXPRESSES SUICIDALTHOUGHTS,
                      SIGNIFICANTLY SLOWED MOVEMENT.
  LOAY-401-4012       SELF-INJURIOUS BEHAVIOR, SELF-INJURY            5      16      No
  LOAY-407-4077       SELF INJURIOUS BEHAVIOR, SELF-INFLICTING        5      55      No
                      TENDENCIES
```

```
                                                                    Days
   Patient ID                                                        to
(Study-Inv-Patient)   Brief Description of Event            Code    Event   Fatal?
-----------------------------------------------------------------------------------

  LOAY-407-4078       SUICIDAL IDEATION, ACUTE SUICIDAL TENDENCIES    4       4      No
  LOAY-413-4150       SUICIDAL IDEATION, SUICIDAL TENDENCY            4      27      No
```

10.9 Laboratory Evaluations – Mean Change from Baseline to Endpoint
Table 10.9.1 Sponsor's Table. Mean Change from Baseline to Endpoint: HGIN + HGIU Acute
Database

Table 2.7.4.33.   Laboratory Evaluations
                    Mean Change from Baseline to Endpoint
                    Acute Placebo-Controlled Combined Database

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
HEMATOCRIT	1	Olz	174	0.43	0.03	-0.01	0.03	-0.01	-0.01	<.001
		Placebo	87	0.43	0.04	-0.00	0.03	-0.00		
HEMOGLOBIN	mml/L-F	Olz	174	8.93	0.78	-0.30	0.47	-0.30	-0.22	<.001
		Placebo	87	8.93	0.83	-0.08	0.41	-0.07		
ERYTHROCYTE COUNT	TI/L	Olz	174	5.00	0.39	-0.15	0.27	-0.15	-0.11	.002
		Placebo	87	4.99	0.49	-0.04	0.26	-0.04		
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mml/L-F	Olz	174	20.87	0.92	-0.00	0.76	0.02	0.16	.100
		Placebo	87	21.00	0.79	-0.17	0.73	-0.14		
LEUKOCYTE COUNT	GI/L	Olz	174	7.27	1.92	-0.19	1.86	-0.10	-0.32	.201
		Placebo	87	7.18	1.91	0.14	1.99	0.21		
NEUTROPHILS, SEGMENTED	GI/L	Olz	174	4.22	1.59	-0.13	1.67	-0.06	-0.29	.203
		Placebo	87	4.29	1.48	0.17	1.79	0.23		
LYMPHOCYTES	GI/L	Olz	174	2.38	0.66	-0.09	0.49	-0.06	-0.07	.297
		Placebo	87	2.24	0.60	-0.02	0.51	0.01		
MONOCYTES	GI/L	Olz	174	0.43	0.14	0.02	0.17	0.01	0.01	.544
		Placebo	87	0.41	0.16	0.01	0.17	0.00		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
EOSINOPHILS	GI/L	Olz	174	0.20	0.21	0.01	0.16	0.01	0.04	.042
		Placebo	87	0.19	0.14	-0.02	0.10	-0.03		
BASOPHILS	GI/L	Olz	174	0.05	0.03	-0.01	0.03	-0.01	-0.01	.008
		Placebo	87	0.05	0.03	0.00	0.03	0.00		
MEAN CELL VOLUME (MCV)	fL	Olz	174	85.96	4.66	-0.25	2.53	-0.02	-0.97	.005
		Placebo	87	85.76	4.59	0.72	2.78	0.95		
PLATELET COUNT	GI/L	Olz	173	291.08	68.65	1.26	46.42	2.44	6.09	.339
		Placebo	87	286.54	63.84	-4.68	52.18	-3.66		
LYMPHOCYTES, ATYPICAL	GI/L	Olz	1	0.06		0.03		0.03		
UA-SPECIFIC GRAVITY	NO UNIT	Olz	156	1.02	0.01	-0.00	0.01	-0.00	-0.00	.292
		Placebo	72	1.02	0.01	-0.00	0.01	-0.00		
AST/SGOT	U/L	Olz	175	24.53	29.87	6.43	26.41	9.89	8.91	.002
		Placebo	87	23.63	8.46	-2.47	7.51	0.98		
ALT/SGPT	U/L	Olz	175	24.13	45.95	19.95	54.84	28.11	22.98	<.001
		Placebo	87	20.39	13.05	-3.08	11.69	5.13		
CREATINE PHOSPHOKINASE	U/L	Olz	175	141.28	138.78	-7.31	131.11	2.81	16.06	.376
		Placebo	87	164.36	160.04	-23.62	152.22	-13.25		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
ALKALINE PHOSPHATASE	U/L	Olz	175	152.33	82.35	-1.35	25.61	-2.74	2.57	.396
		Placebo	87	138.67	86.92	-3.97	16.63	-5.31		
GGT (GGPT/SGGT/YGGT)	U/L	Olz	175	18.99	12.31	7.47	20.02	7.73	7.89	<.001
		Placebo	87	17.68	8.49	-0.43	5.96	-0.16		
THYROID STIMULATING HORMONE	mU/L	Olz	6	2.73	2.32	0.11	1.02	-0.12		
UREA NITROGEN	mmol/L	Olz	175	4.40	1.18	0.22	1.18	0.14	0.39	.010
		Placebo	87	4.37	1.06	-0.17	1.06	-0.25		
CREATININE	umol/L	Olz	175	93.29	14.47	-2.90	9.85	-2.07	-1.80	.147
		Placebo	87	95.83	12.43	-1.08	8.56	-0.27		
CALCIUM	mmol/L	Olz	175	2.48	0.08	-0.03	0.09	-0.03	-0.02	.215
		Placebo	87	2.50	0.12	-0.01	0.10	-0.02		
SODIUM	mmol/L	Olz	175	141.70	2.27	-0.05	2.83	-0.12	0.49	.190
		Placebo	87	141.78	2.44	-0.53	2.94	-0.61		
POTASSIUM	mmol/L	Olz	175	4.32	0.33	-0.04	0.36	-0.07	0.04	.462
		Placebo	87	4.41	0.42	-0.07	0.41	-0.10		
ALBUMIN	g/L	Olz	175	45.07	3.75	-2.01	3.20	-2.13	-1.70	<.001
		Placebo	87	45.39	3.03	-0.31	2.90	-0.43		

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
GLUCOSE, FASTING	mmol/L	Olz	135	4.89	0.55	0.15	0.58	0.15	0.31	<.001
		Placebo	64	4.98	0.57	-0.16	0.56	-0.17		
GLUCOSE, NON-FASTING	mmol/L	Olz	141	5.04	0.83	0.17	1.13	0.12	0.15	.374
		Placebo	73	5.01	0.79	0.03	1.23	-0.03		
URIC ACID	umol/L	Olz	175	331.18	74.27	25.21	51.54	30.87	26.95	<.001
		Placebo	87	329.40	84.01	-1.86	53.02	3.92		
CHOLESTEROL	mmol/L	Olz	175	4.17	0.83	0.34	0.59	0.33	0.37	<.001
		Placebo	87	4.15	0.85	-0.03	0.63	-0.04		
TRIGLYCERIDES	mmol/L	Olz	175	1.18	0.66	0.33	0.91	0.30	0.38	<.001
		Placebo	87	1.25	0.73	-0.05	0.62	-0.07		
LDL CHOLESTEROL	mmol/L	Olz	175	2.42	0.74	0.16	0.52	0.14	0.17	.016
		Placebo	87	2.37	0.76	-0.01	0.53	-0.02		
BILIRUBIN, TOTAL	umol/L	Olz	175	7.84	5.27	-1.73	3.82	-2.21	-2.52	<.001
		Placebo	87	8.56	5.33	0.78	5.96	0.31		
BILIRUBIN, DIRECT	umol/L	Olz	175	1.84	1.07	-0.33	1.07	-0.36	-0.38	.005
		Placebo	87	2.01	1.08	0.05	0.93	0.02		
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Olz	175	1.22	0.31	0.03	0.23	0.02	0.03	.331

Laboratory Evaluations	Unit	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Placebo	87	1.21	0.25	-0.00	0.25	-0.01		
PROLACTIN	ug/L	Olz	163	14.06	9.92	11.44	14.52	10.51	11.66	<.001
		Placebo	80	14.95	11.86	-0.16	10.69	-1.15		
HEMOGLOBIN A1C	1	Olz	6	0.05	0.00	-0.00	0.00	-0.00	0.00	.741
		Placebo	3	0.05	0.01	-0.00	0.00	-0.00		

10.10 Prolactin Analysis by Gender

Table 10.10.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: HGIU + HGIN Acute Database.

Laboratory Evaluations	Gender	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value	**P-value
PROLACTIN	Female	Olz	63	15.87	10.06	15.63	16.86	14.26	14.25	<.001	.236
		Placebo	37	15.25	7.59	1.35	9.20	0.00			
	Male	Olz	100	12.92	9.71	8.80	12.20	8.70	10.12	<.001	
		Placebo	43	14.70	14.67	-1.46	11.78	-1.42			

10.11 Vital Signs – Mean Change from Baseline to Endpoint

Table 10.11.1 Vital Signs, Weight, Height and BMI - Mean Change from Baseline to Endpoint (LOCF). HGIN + HGIU Acute Database

Vital Signs	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Systolic Blood Pressure - Supine	Olz	177	111.52	10.95	2.94	10.57	1.73	3.66	.009
	Placebo	89	112.79	13.18	-0.71	10.90	-1.93		
Systolic Blood Pressure - Standing	Olz	177	113.33	12.25	3.14	12.06	2.16	1.94	.225
	Placebo	89	112.18	13.25	1.22	12.51	0.23		
Systolic Blood Pressure - Orthostatic	Olz	177	-1.81	9.63	-0.20	11.68	-0.43	1.72	.262
	Placebo	89	0.61	8.33	-1.93	11.83	-2.15		
Diastolic Blood Pressure - Supine	Olz	177	67.71	9.27	1.24	9.74	1.56	2.17	.095
	Placebo	89	68.19	8.53	-0.92	10.27	-0.61		
Diastolic Blood Pressure - Standing	Olz	177	72.86	10.12	1.42	10.25	-0.24	2.73	.033
	Placebo	89	73.56	9.48	-1.28	9.14	-2.97		
Pulse - Supine	Olz	177	73.88	11.40	7.07	13.99	7.55	7.71	<.001
	Placebo	89	74.15	12.81	-0.60	12.04	-0.16		
Pulse - Standing	Olz	177	83.77	12.73	6.97	14.83	6.55	7.90	<.001
	Placebo	89	85.55	12.98	-0.89	14.69	-1.35		
Pulse - Orthostatic	Olz	177	9.89	11.23	-0.11	13.37	-1.01	0.19	.914
	Placebo	89	11.40	11.15	-0.29	13.09	-1.19		

Vital Signs	Therapy	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	LSMean Change	LSMean Difference	*P-value
Temperature in Centigrade	Olz	177	36.57	0.44	-0.03	0.49	-0.03	-0.03	.695
	Placebo	88	36.58	0.42	-0.00	0.49	-0.00		
Weight in Kg	Olz	177	66.03	17.93	3.90	2.72	3.68	3.66	<.001
	Placebo	88	67.63	17.24	0.24	2.16	0.01		
Height in cm	Olz	177	165.84	10.13	0.48	1.22	0.46	0.18	.235
	Placebo	88	167.59	9.67	0.31	1.01	0.28		
Body Mass Index	Olz	177	23.91	6.01	1.22	1.01	1.11	1.17	<.001
	Placebo	88	23.98	5.67	0.05	0.91	-0.07		

10.12 Potentially Clinically Significant Definitions for Safety Analyses

Table 2.7.4.6.   Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs and Weight

Parameter	Low	High
Orthostatic hypotension (mm Hg)	≥20 mm Hg decrease in systolic BP (supine to standing) and ≥10 bpm increase in pulse (supine to standing)	--
Supine systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Standing systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Supine diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Standing diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Supine pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Standing pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Temperature (°F)[a]	--	≥101°F and increase ≥2
Weight (kg)	decrease ≥7%	increase ≥7%

10.13 Postmarketing Reports - Fatalities
Table 10.13.1. Postmarketing Reports – Fatalities

Patient Identifier	Date of Death	Dose/Duration	Event	Concom Rx	Comments
BR200605002130 16 YOM	(b) (6)	7.5 mg 10/05 – 4/06	Sudden death, cardiac arrest, prescribed overdose, suicide attempt, depression, psychosis	Alprazolam	Brazil Autopsy done, result will be available by June 2006 (per summary)
BE200602002031 17 YOF	(b) (6)	Unknown ~6 years	Bilateral pneumonia, gastric hemorrhagia, fever, coma	Not reported	Belgium (no autopsy)
US_0510123183 14 YO	(b) (6)	Unknown	Toxic exposure, completed suicide	Fluoxetine Risperidone	Literature
JP_051007889 17 YOM	(b) (6)	5 mg, 8/2005 – 10/05	Completed suicide, suicidal ideation, apathy	Lorazepam	Japan "Police told psychiatrist about patient's death, no details provided" [prior suicide attempt per hx]
CA_050708496 17 YOM	(b) (6)	15 mg 11/03 – 6/05	Completed suicide	Lorazepam Flupentixol decanoate	Canada 5 days after discontinuing olanzapine, committed suicide (method unknown) Not known whether autopsy performed.
US_0506118439 17 YOF	Unknown (b) (6) estimated	Unknown, 7/1999 - 2004	Death, weight increased, diabetes mellitus, hyperglycemia, multiple drug overdose, triglycerides increased, cholesterol abnormal, musculoskeletal chest pain		Reported by attorney via legal department
EWC050644285 17 YOF	(b) (6)	5 mg 3/5/05 – 3/6/05	Endotoxic shock, kidney infection, sepsis, acute abdomen, disseminated intravascular blood coagulation, myeloid hyperplasia of spleen, pancreatitis, gastric		Russian Federation

			ulcer perforation, peritoneal infection		
US_0506118189 15 YOM	Unknown (b) (6) estimated	~ May 2003 - unknown	Death		Reported by an attorney via the legal department Cause of death not provided
CA_050207717 16 YOM	(b) (6)	Unknown	Completed suicide	Isotretinoin mepha	Canada No details provided
US_0412108962 16 YOM	Unknown (b) (6) estimated	1-2002 – unknown	Death, diabetes mellitus		Reported by an attorney via the legal department Cause of death not provided, not known if autopsy performed
JP_041105122 17 YOF	(b) (6)	50 mg 11/10/2004 – 11/10/2004	Intentional overdose, completed suicide	Paroxetine, sulpiride, amoxapine, fluvoxamine, flunitrazepam	Japan "Coroner refused to provide any information"
USA040979162 US_0402100550 15 YOM	(b) (6)	10/29/2003?	Death, coma Accidental overdose, drug toxicity, intentional drug misuse	Metronidazole, topiramate, clonazepam	Reported by an attorney via the legal department Case reported in a newspaper "Patient was sold olanzapine by another individual, not prescribed" Olanzapine Cp = 490 ng/ml postmortem
US_0412109585 15 YOF	(b) (6)	11/2000 - unk	Diabetic ketoacidosis, diabetic coma, diabetes mellitus, pain, anxiety, drug ineffective	Methylphenidate, sertraline	Reported to company by an attorney No details provided about the event, unknown if an autopsy was performed
EWC031237179 16 YOM	(b) (6)	5 mg, 11/24/2003 – 11/25/2003	Death, pulmonary infarction		Greece Pulmonary infarction per autopsy
USA030742307 13 YOF	(b) (6)	5 mg Unknown	Diabetic ketoacidosis, loss of consciousness, dizziness		Diabetic ketoacidosis per autopsy. No labs provided.
USA030741953 17 YOM	(b) (6)	8/2002 – 11/2002	Convulsion, heart rate increased	Mixed amphetamine salts, trazodone	Cause of death listed as idiopathic seizure disorder, toxicology screen

					negative
GBS030413039 17 YOM	(b) (6)	12.5 mg 10/2002 – unk	Completed suicide, sedation, eczema	Risperidone, biperiden	United Kingdom Death by drowning, autopsy did not reveal other significant findings
US_020180581 15 YOM	(b) (6)	20 mg Unknown	Acute asthma		Patient had been in blinded study 3/01 – 9/01 prior [F1D-US-X090]; did not receive olanzapine; taking marketed olanzapine at time of event.
US_010973481 17 YOM	Unknown (received by Sponsor (b) (6)	30 mg Unknown	Prescribed overdose, drug toxicity		No details provided, unknown if autopsy performed
EWC010928155 15 YOM	(b) (6)	10 mg 8/1/2001 – 8/28/2001	Death	Dextro-amphetamine	Switzerland Asperger's syndrome Patient drowned while swimming in lake; autopsy unremarkable
CA_010603921 17 YOF	Unknown (received by Sponsor (b) (6))	Unknown	Death	Citalopram, valproate semisodium	Canada Patient "died suddenly", autopsy was completed but not available. "Several attempts at follow-up unsuccessful".
CA_010603802 16 YOM	Unknown (received by Sponsor (b) (6))	10 mg 90 days	Diabetic coma	Valproate sodium Topiramate	Canada No personal history of diabetes. Weight at time of event unknown, labs not provided. "Numerous attempts to obtain follow-up unsuccessful".
US_010566315 16 YOM	(b) (6)	5 mg 730 days	Drug interaction, death, hepatic steatosis	Mixed amphet-Amine salts	Patient found dead. Hepatic steatosis per autopsy, no cause of death provided. Autopsy never provided.
US_010158510 17 YOM	(b) (6)	2.5 mg Unknown	Accidental overdose	Citalopram, trazodone	Patient found dead by family member. Cause of death presumed

					overdose. Olanzapine Cp = 158 ng/ml.
US_000542556 15 YOM	(b) (6)	Unknown 1998 x 120 days	Necrotizing pancreatitis, diabetes mellitus, increased cholesterol	Carbamazepine, paroxetine	Follow-up in the literature
US_000236591 17 YOM	(b) (6)	22.5 mg Unknown	Overdose, death	Fluoxetine, valproate semisodium, nortriptyline, buspirone, haloperidol, thioridazine	Patient died while being restrained by staff in group home.
US97121702A 14 YOM	(b) (6)	12.5 mg 150 days	Asphyxia, agitation	Haloperidol, sertraline	Became agitated on school bus and was restrained and died. Per coroner, cause of death by mechanical asphyxia due to the restraining position.

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 /s/
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Cara Alfaro
4/6/2007 10:42:11 AM
PHARMACIST



Ni Aye Khin
4/18/2007 11:20:56 AM
MEDICAL OFFICER
I agree with Dr. Alfaro's recommendation that this application
be considered for non-approval; see memo to file
for additional comments.
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