

CLINICAL REVIEW

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Reviewer Name Cara Alfaro, Pharm.D.
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Established Name Olanzapine
Trade Name Zyprexa
Therapeutic Class Antipsychotic
Applicant Eli Lilly

Priority Designation P

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

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that the Division take a non approval action on NDA 20-592 SE5-041 that was filed to support the indication “treatment of schizophrenia in adolescents”.

Fifty-three percent of randomized patients in pivotal trial HGIN were from sites in the United States and 47% of randomized patients were from sites in Russia. The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Though the LOCF analysis was the primary analysis, it is also concerning that the OC and MMRM analyses (the latter by recalculation by the reviewing statistician in the Division) are substantially different from the LOCF analysis and not statistically significant.

I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

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

1.2 Recommendation on Postmarketing Actions

Since non approval is recommended, there are no recommendations for postmarketing actions.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

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

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

1.3.2 Efficacy

The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg. Seventy-five percent of patients in the olanzapine group and 56% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -10.12, p = 0.003).

| Efficacy Variable | Therapy | N | Baseline | | Change to Endpoint | | LSMean Change | LSMean Diff. | *P-value |
|--------------------|------------|----|----------|------|--------------------|-------|---------------|--------------|----------|
| | | | Mean | Std | Mean | Std | | | |
| BPRS-C Total Score | olanzapine | 72 | 50.26 | 9.98 | -19.42 | 15.51 | -19.26 | -10.12 | .003 |
| | Placebo | 35 | 50.09 | 8.59 | -9.31 | 18.70 | -9.14 | | |

The supportive OC analysis was discordant from the LOCF analysis (LS Mean Diff = -0.26, p = 0.947). The reviewing statistician recalculated the MMRM supportive analysis and found similar results to the OC analysis (LS Mean Diff = -1.25, p = 0.72) though the Sponsor's results for the MMRM analysis were statistically significant.

When evaluating the efficacy signal for the sites in the United States and the sites in Russia, only the latter were statistically significant in favor of olanzapine. The low placebo response in the sites in Russia appears to be driving these results.

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

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

Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a non approval action.

1.3.3 Safety

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

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

The most common adverse events ($\geq 5\%$, 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 |
|--|----------------|---------------|--------------|---------|
| <i>HGIN + HGIU Acute Database</i> | | | | |
| 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 |
| <i>Overall Combined Database</i> | | | | |

| | | | | |
|--|------|---|---|-----------------------------------|
| 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 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 HGAI.

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

| | | | | |
|--|---------|--------|-------|--|
| | Maximum | 122.00 | 123.0 | |
|--|---------|--------|-------|--|

Modified from Sponsor table HGIN.11.1 and HGIN.11.2 in study report

*The Sponsor was asked to provide a list of patients with age of onset < 10 along with CRFs. Seventeen patients had age of onset < 10 years of age, only two patients had age of onset = 5 years of age (both from U.S. sites).

**Only 1 patient had length of current episode = 0. This patient entered the study when he had just started his most recent episode – the month was in the CRF, the actual date was imputed.

Efficacy Analyses

Site Issues

In the efficacy analysis, the sponsor included analyses with and without site 021. Per the sponsor, site 021 had significant GCP issues and patients from this site were dropped from the primary analyses (efficacy analyses were similar with and without this site). The study report did not specify what the GCP issues were with this site. The sponsor was asked to provide details and indicated the following:

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

- Not following the randomization procedures outlined in the protocol
- Not submitting protocol amendment A, approved by Lilly on October 17, 2002, to the Institutional Review Board (IRB) for approval before use
- Not submitting revised informed consent documents to IRB
- Not communicating to patients about safety issues in risk profile of study drug. The risk profile was updated by Lilly on December 4, 2003 and faxed to the site on January 6, 2004 and a reminder fax was sent on January 28, 2004.
- Significant problems with drug accountability
- Not being able to reconstruct the regulatory document in the Clinical Trial Record Binder
- Violation of inter-active voice response system (IVRS) security personal identification number process.

Concomitant Medications

Interestingly, 29.2% (21/72) patients in the olanzapine group and 14.3% (5/35) patients in the placebo group did not have any previous medications for schizophrenia.

There were no statistically significant differences in the frequency of concomitant benzodiazepine use between the olanzapine and placebo groups. Concomitant lorazepam use occurred in 18.1% (13/72) patients in the olanzapine group and 34.3% (12/35) patients in the placebo group (p = 0.088). Concomitant diazepam use occurred in 12.5% (9/72) patients in the

olanzapine group and 8.6% (3/35) patients in the placebo group. A few patients in both groups had concomitant clonazepam, temazepam and phenazepam use. The mean number of days of benzodiazepine use did not differ between the treatment groups: 6.25 days in the olanzapine group and 7.39 days in the placebo group. The mean dose of benzodiazepines (using equivalent doses) did not differ between the treatment groups: 1.64 ± 0.80 mg in the olanzapine group and 1.80 ± 0.64 mg in the placebo group.

There were no statistically significant differences in the frequency of concomitant anticholinergic medication use between the olanzapine and placebo groups. Three patients had concomitant benztropine mesylate use – 2 in the olanzapine group and 1 in the placebo group. One patient in the olanzapine group had concomitant dimenhydrinate use. One patient in the placebo group had concomitant trihexyphenidyl use. There was a statistically significant difference in the number of days of concomitant anticholinergic use: 22.5 ± 0.7 days in the olanzapine group and 6.5 ± 6.4 days in the placebo group. The mean dose of anticholinergic medication did not differ between the treatment groups: 2.6 ± 2.0 mg in the olanzapine group and 2.0 ± 1.4 mg in the placebo group.

Primary Endpoint

Primary Analysis - LOCF

The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg.

The Sponsor was asked to provide statistical analysis for the weekly visits for the primary endpoint (BPRS-C total score). Statistical differences favoring the olanzapine group occurred beginning at visit 5 and were maintained to the end of study (visit 9). The analysis including site 021 was similar, least square mean difference was 10.38 favoring the olanzapine group ($p = 0.003$).

Table 6.1.3.3 Sponsor’s Table. BPRS-C Total Score Mean Change from Baseline to Endpoint by Visit– LOCF. (without site 021)

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

Because of these differences in efficacy, this reviewer asked the Sponsor to analyze the baseline psychiatric illness variables of patients between the U.S. and Russia sites. This analysis is in Appendix 10.4. In general, patients from the U.S. sites had fewer days since last hospitalization (149 vs. 477 days, p = 0.012) [other differences between the countries may account for this difference], higher baseline BPRS-C scores (52.6 vs. 47.5, p = 0.005) and higher baseline scores on several BPRS-C subscales including behavioral problems, depression, thinking disturbance

(11.04 vs. 9.72, $p = 0.030$), and psychomotor excitation. The PANSS total scores were not different between the sites though there were some inconsistent differences on the subscales. Although not statistically significant, the PANSS total scores were numerically higher in the Russia sites (97.6 vs. 93.3, $p = 0.116$). Therefore, it does not appear that there is a consistent signal indicating that the patients enrolled in the Russia sites are more severely ill compared to the patients enrolled in the U.S. sites.

Secondary Analyses

BPRS-C Individual Items and Composite Scores

When evaluating the BPRS-C individual items, statistical differences favoring olanzapine were found only for uncooperativeness ($p = 0.003$), hostility ($p < 0.001$), manipulativeness ($p = 0.035$), hyperactivity ($p = 0.004$) and sleep difficulties ($p < 0.001$) (see Appendix 10.5). Although there were statistical differences favoring olanzapine for the Thinking Disturbance composite ($p = 0.050$), the effect is only significant for peculiar fantasies ($p = 0.014$) but not delusions ($p = 0.151$) or hallucinations ($p = 0.249$) – despite the similar severity ratings at baseline for all three symptoms. Interestingly, the “peculiar fantasies” item is one that has been noted to have poor interrater reliability in psychometric testing.¹

Subgroup Analyses

The Sponsor evaluated the following subgroups: gender, age (< 15 , ≥ 15), Caucasian vs. nonCaucasian.

Statistically significant differences favoring olanzapine were found for all subgroups except females ($p = 0.203$), < 15 years of age ($p = 0.302$) and nonCaucasians – the greater change to endpoint in the placebo group in these subgroups may have contributed to these findings. However, the treatment-by-subgroup analyses were not significant.

Table 6.1.3.6. Sponsor’s Table. BPRS-C Total Score - Subgroup Analyses

| Efficacy Variable | Subgroup | Strata | N | Therapy | Baseline | | Change to Endpoint | | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy*Subgroup) | |
|--------------------|----------|------------|------------|------------|----------|--------|--------------------|--------|---------------|--------------|----------|------------------------------|------|
| | | | | | n | Mean | Std | Mean | | | | | Std |
| BPRS-C Total Score | Gender | Female | 32 | Olanzapine | 21 | 51.90 | 11.92 | -18.67 | 12.77 | -17.66 | -8.08 | .203 | .682 |
| | | | 11 | 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 | | |
| | | 24 | 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 |
| | | | 7 | 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 | | | |
| | 28 | Placebo | 28 | 48.93 | 8.27 | -8.50 | 18.56 | -8.88 | | | | | |

¹ Lachar D, Randle SL, Harper RA et al. The Brief Psychiatric Rating Scale for Children (BPRS-C): validity and reliability of an anchored version. J Am Acad Child Adolesc Psychiatry 2001;40:333-340.

| Efficacy Variable | Subgroup | Strata | N | Therapy | Baseline | | Change to Endpoint | | LSMean Change | LSMean Diff. | *P-value | **P-value (Therapy*Subgroup) | |
|--------------------|---------------|-----------|------------|------------|----------|-------|--------------------|--------|---------------|--------------|----------|------------------------------|------|
| | | | | | n | Mean | Std | Mean | | | | | Std |
| BPRS-C Total Score | Origin | Caucasian | 77 | Olanzapine | 52 | 50.02 | 10.08 | -17.65 | 15.02 | -18.22 | -10.92 | .007 | .802 |
| | | | | Placebo | 25 | 49.08 | 8.33 | -6.72 | 18.42 | -7.30 | | | |
| | Non-Caucasian | 30 | Olanzapine | 20 | 50.90 | 9.92 | -24.00 | 16.21 | -24.55 | -9.85 | .092 | | |
| | | | Placebo | 10 | 52.60 | 9.16 | -15.80 | 18.73 | -14.70 | | | | |

Efficacy issues

1. It is troubling to this reviewer that the efficacy signal appears to be coming entirely from the sites in Russia (p = 0.003), whereas the efficacy data is far from significant in the sites in the U.S. (p = 0.258). The mean change to endpoint in the BPRS-C total score in the olanzapine groups are similar between the sites and the difference in efficacy signal appears to be driven by the very low mean change in the placebo group in the Russia sites.
2. Because of this discrepancy in efficacy findings, DSI was sent to inspect two of the sites in Russia. Although a final report has not been issued, they did not find any major compliance issues.
3. It is interesting that all 5 of the sites in Russia randomized 10 patients each while most of the 20 U.S. sites (80%) randomized between 1 and 3 patients. Only one of the 20 U.S. sites randomized 10 patients (no sites randomized more than 10). It is not surprising that many U.S. sites did not enroll a high number of patients since adolescent schizophrenia is a rare disorder. It is surprising that the sites in Russia were able to randomize that many patients. This reviewer asked the Sponsor if enrollment was capped at 10 for the Russia sites – the Sponsor indicated that the “target number of patients for each site in Russia was 10 patients for a total of 50 patients”.
4. The efficacy results from the clinical trial are not consistent among different analyses. While the LOCF analysis is significant (p = 0.003), the OC analysis is not (p = 0.947). Significant numbers of patients were still in the study at endpoint (50/72, 69% in the olanzapine group and 15/35, 43% in the placebo group). The least squares mean difference was -10.12 in the LOCF analysis, -8.90 in the MMRM analysis and -0.26 in the OC analysis.
5. The statistician reanalyzed the dataset per MMRM and obtained very different results compared to the Sponsor’s MMRM analysis. The statistician calculated a LS Mean Difference of -1.25, p = 0.72 (see Statistician’s review).

6.1.4 Efficacy Conclusions

The mean modal daily dose of olanzapine was 12.5 mg and the mean daily dose was 11.1 mg. Seventy-five percent of patients in the olanzapine group and 56% of patients in the placebo group completed the study.

The primary efficacy endpoint for study HGIN was change from baseline in the BPRS-C Total Score (LOCF analysis). The overall study results were statistically significant for olanzapine versus placebo (LS Mean Diff = -10.12, p = 0.003).

The supportive OC analysis was discordant from the LOCF analysis (LS Mean Diff = -0.26, p = 0.947). The reviewing statistician recalculated the MMRM supportive analysis and found similar results to the OC analysis (LS Mean Diff = -1.25, p = 0.72) though the Sponsor’s results for the MMRM analysis were statistically significant.

When evaluating the efficacy signal for the sites in the United States and the sites in Russia, only the latter were statistically significant in favor of olanzapine. The LS Mean Diff for United States sites -5.26 (p = 0.258) and for Russia -14.95 (p = 0.003). The low placebo response in the sites in Russia appears to be driving these results. Since efficacy could not be demonstrated in patients in sites from the United States, this reviewer recommended a non approval action.

7 INTEGRATED REVIEW OF SAFETY

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

Sponsor’s Table. Databases for Summary of Clinical Safety

Table 2.7.4.1. Databases for Summary of Clinical Safety

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

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

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

Study HGBG and HGCL were clinical trials for adult patients aged 18 or older – two adolescent patients were enrolled in those trials (17.9 and 17.8 years of age).

Study HGDH – acute and long-term efficacy of olanzapine in first-episode psychotic patients aged 16 – 40 years (n = 7 adolescents).

Study HGGF – delaying or preventing psychosis onset in persons aged 12 to 45 years prodromal to psychosis (n = 24 adolescents).

Study HGKL – clinical trial in patients aged 15 to 65 years with borderline personality disorder (n = 4 adolescents).

“Acute Placebo Controlled Database” hereafter called HGIN + HGIU Acute Database

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

Patient Disposition (HGIN + HGIU)

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

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

Patient demographics (HGIN + HGIU): The majority of patients were male (60%), Caucasian (70%) with a mean age of ~ 15.6 years (see Appendix 10.6). For study HGIN, the majority of patients were 16 and 17 years of age at baseline (61%); for study HGIU, the majority of patients were 14 and 15 (55%). This is expected and consistent with the psychiatric diagnoses in these two trials. A table of age distribution at baseline is in Appendix 10.6.

“Overall Olanzapine Exposure Combined Database” hereafter called Overall Combined Database

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

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

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

| Patient Disposition | Bipolar | | Schizophrenia | | Overall | |
|--|------------|---------------|---------------|---------------|------------|---------------|
| | 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 | Worsening 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, 1 st visit | Exacerbation of psychosis | Psychotic disorder | Severe Hospitalized |
| HGIN 910-9101 | 16 YOWF | Olanzapine OL phase | Worsening of Schizophrenia | Schizophrenia | Moderate Hospitalized |
| HGIN 930-9301 | 15 YOWM | Olanzapine OL phase | Closed fracture of right forearm | Forearm fracture | Severe Fracture from fall, treated in hospital |
| HGIN 930-9307 | 15 YOWF | Olanzapine OL phase | Attempted suicide | Suicide attempt | Severe Attempted overdose with Phenobarbital, hospitalized, discontinued from study |
| HGIU 001-0103 | 13 YOWM | Olanzapine OL phase | Increased agitation | Agitation | Severe Hospitalized, completed study |
| HGIU 001-0107 | 13 YOWM | Olanzapine OL phase | Agitation, aggression | Agitation, aggression | Severe Hospitalized, completed study |
| HGIU 001-0108 | 14 YOWF | Olanzapine OL phase | Alcohol intoxication, suicidal ideation | Alcohol poisoning, suicidal ideation | Severe (alcohol) Moderate (SI) Discontinued from study |
| HGIU 012-1202 | 15 YOWF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, completed study |
| HGIU 012-1211 | 14 YOWF | Olanzapine OL phase | Exacerbation of bipolar symptoms | Bipolar disorder | Severe Discontinued study |
| HGIU 012-1212 | 14 YOBF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, discontinued "patient decision" |
| HGIU 020-2016 | 14 YOWF | Olanzapine OL phase | Attempted suicide | Suicide attempt | Mild Overdose of Benadryl and ibuprofen, recovered without treatment; completed study |
| HGIU 026-2604 | 16 YOHM** | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, completed study |
| HGIU 026-2605 | 14 YOM | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized and discontinued study |
| HGIU 026-2608 | 13 YOWF | Olanzapine OL phase | Exacerbation of bipolar disorder | Bipolar disorder | Severe Hospitalized, discontinued study |
| HGIU 027-2705 | 15 YOBM | Olanzapine OL period | Worsening of bipolar disorder, self-inflicted superficial lacerations | Bipolar disorder, Intentional self-injury | Severe (BP) Moderate (SIB) Hospitalized, discontinued study (cut arms with fingernails) |
| HGIU | 14 YOBF | Olanzapine | Worsening of | Bipolar disorder | Severe |

| | | | | | |
|------------------|---------|------------------------|--|--|--|
| 027-2707 | | OL phase | bipolar disorder | | Hospitalized, completed study |
| HGIU 028-2804 | 15 YOWF | Olanzapine OL phase | Recurrence of bipolar symptoms | Bipolar disorder | Severe Hospitalized, discontinued study “sponsor’s decision” – GCP issues at site |
| HGIU 028-2805 | 14 YOWF | Olanzapine OL phase | Suicidal ideation | Suicidal ideation | Severe Hospitalized, discontinued – GCP issues at site |
| HGIU 028-2806 | 15 YOBF | Olanzapine OL phase | Bipolar mania | Bipolar disorder | Severe Hospitalized, discontinued study |
| HGIU 031-3103 | 14 YOWM | Olanzapine OL phase | Decreased WBC count and decreased neutrophils | WBC count decreased, neutrophil count decreased | See Table 7.1.2.1. |
| HGIU 033-3304 | 15 YOWF | Olanzapine OL phase | Intensifying aggressiveness and irritability | Aggression, irritability | Severe Hospitalized, discontinued study |
| HGIU 035-3519 | 14 YOWM | Olanzapine OL phase | Violent behavior | Aggression | Severe Hospitalized, discontinued study |
| HGIU 730-7302 | 13 YOHM | Olanzapine OL phase | Oppositional defiant behavior | Oppositional defiant disorder | Severe Hospitalized, discontinued due to noncompliance |
| HGMF 003-0303 | 17 YOWF | Olanzapine OL | Acute appendicitis | Appendicitis | Severe Hospitalized, completed study |
| HGMF 003-0304 | 16 YOWF | Olanzapine OL | Exacerbation of bipolar illness with positive suicidal ideation | Bipolar disorder | Severe Hospitalized, discontinued study |
| LOAY 407-4078 | 17 YOWM | Olanzapine OL | Recurrence of acute psychotic symptoms | Psychotic disorder | Severe Hospitalized |
| LOAY 407-4207 | 14 YOWM | Olanzapine OL | Borrelia infection | Borrelia infection | Mild Discontinued study |
| LOAY 413-4145 | 16 YOWM | Olanzapine OL | Worsening of underlying disease schizophrenia | Schizophrenia | Severe Hospitalized Discontinued study |

Table 7.1.2.3 Serious Adverse Events: HGCR, HGCS, HGGC

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

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

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

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

Narratives were provided by Sponsor upon request

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Adverse events associated with dropouts

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

| Study Patient # | Demographics | Treatment | Verbatim Term | Preferred Term | Comments |
|-----------------|--------------|---------------------|--------------------------------------|------------------------------|--|
| HGIN 007-703 | 13 YOBF | Olanzapine DB phase | Clinically significant increased ALT | ALT increased | ALT up to 231 (AST up to 142) Returned to WNL after discontinuation from study |
| HGIN 010-1001 | 17 YOWM | Olanzapine DB phase | Elevated liver function | Liver function test abnormal | ALT = up to 597 AST = up to 410 GGT = up to 129 Noted at randomization visit (was taking olanzapine prior to study) Discontinued study |
| HGIN 021-2103 | 17 YOBF | 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 4 th 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 YOBF | 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 YOBF | Olanzapine OL | Weight gain | Weight increased | Gained 18.6 kg over 119 days |
| HGIU 027-2705 | 15 YOBF | 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 HGCC.

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 $\geq 2\%$ of Patients: HGIU + HGIN Acute Database

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

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

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

appetite (29% vs. 17%), sedation (22% vs. 15%), dry mouth (8% vs. 4%) and fatigue (14% vs. 3%)

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

| Adverse Event | Percentage of Patients Reporting Event | | | |
|--------------------------|--|---------------------|------------------------------------|---------------------|
| | 6 Week Trial % Schizophrenia Patients | | 3 Week Trial % Bipolar Patients | |
| | 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

| | | N | Baseline | | Change to Endpoint | | LS Mean Change | LS Mean Difference | P-value |
|-------------|------------|-----|----------|-------|--------------------|------|----------------|--------------------|---------|
| | | | Mean | Std | Mean | Std | | | |
| Weight (kg) | Olanzapine | 177 | 66.03 | 17.93 | 3.90 | 2.72 | 3.68 | 3.66 | < 0.001 |
| | Placebo | 88 | 67.63 | 17.24 | 0.24 | 2.16 | 0.01 | | |
| 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 $\geq 7\%$ 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 $\geq 7\%$ increase in body weight (p < 0.001). Only 2 patients, both randomized to placebo, had a $\geq 7\%$ 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

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

From Table HGIU.12.44 in study report

A $\geq 7\%$ 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 $\geq 7\%$ increase in body weight (p < 0.001). No patients in the study had a $\geq 7\%$ decrease in body weight.

Table 7.1.4.4.3. Weight and BMI Data: Study HGIN

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

From Table HGIN.12.42 in study report

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

increased by 1.56 in the olanzapine group and decreased by 0.04 in the placebo group [LS mean diff = 1.62, $p < 0.001$].

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

Only 1 of the 8 discontinuations due to adverse events was due to weight gain in the HGIU + HGIN Acute Database (4.5 kg increase over ~15 days).

Unfortunately, insufficient data were collected during the follow-up visits to adequately address weight loss after patients completed the clinical trial (if they switched to a different antipsychotic). Though many of the investigators noted that the adverse event of “weight gain” had resolved at some of the follow-up visits, no actual weights were obtained for the majority of patients (or at least not recorded in the CRFs).

Overall Combined Database

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

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

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

From Table 2.7.4.45 in summary-clin-safety document

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

The Sponsor provided a summary of weight change by visit for observed cases for the Overall Combined Database (see Appendix 10.7). For the 131 patients who completed visits > 25 and ≤ 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 | | Change to Endpoint | | LSMean Diff. | *P-value | **P-value | |
| | | | | Mean | Std | Mean | Std | | | | LSMean |
| Weight in Kg | Female | 106 olz | 66 | 61.79 | 16.68 | 3.66 | 2.65 | 3.63 | 3.05 | <.001 | .083 |
| | | Placebo | 40 | 62.83 | 13.65 | 0.55 | 2.27 | 0.59 | | | |
| | Male | 159 olz | 111 | 68.54 | 18.25 | 4.05 | 2.76 | 3.79 | 4.16 | <.001 | |
| | | Placebo | 48 | 71.64 | 18.97 | -0.03 | 2.05 | -0.36 | | | |

Table 2.7.4.70 in Summary-clin-safety

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

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

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

| BMI (Baseline) | Therapy | N | Baseline | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|----------------|---------|-----|----------|-------|--------------------|------|---------------|-------------------|----------|
| | | | Mean | Std | Mean | Std | | | |
| 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 \leq 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|---------------------------------------|------------|----|----------|------|--------------------|------|---------------|-------------------|----------|
| | | | Mean | Std | Mean | Std | | | |
| 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 | | |
| BRMS 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 dyskinesic 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|---------------------------------------|------------|-----|----------|------|--------------------|------|---------------|-------------------|----------|
| | | | Mean | Std | Mean | Std | | | |
| 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 dyskinesic 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, immolates, injure, jump, monoxide, mutilate, overdose, self-damage, self-harm, self-inflict, self-damage, self-harm, shoot, slash, suicide, poison, asphyxiation, suffocation, firearm. All blinded patient listings were independently reviewed by two members of the Sponsor’s medical staff “trained to evaluate suicide-related events”. If a discrepancy arose, the case was discussed between them and, if necessary, a third reviewer was consulted to achieve consensus.

HGIN + HGIU Acute Database

Three possible suicidal behaviors or ideation events were identified, all three occurred in study HGIU. Two events occurred in patients treated with olanzapine (self-injurious behavior [intent unknown] in a 14.2 YOWF, suicidal ideation in a 14.6 YOWF) and one occurred in a patient receiving placebo (self-injurious behavior [intent unknown] in a 13.9 YOWM). The Sponsor’s brief description of the event (from the case narratives) are provided in Appendix 10.8. No statistical differences were noted between treatment groups. The risk ratio was calculated as 1.01 (95% CI [0.09, 10.88], p = 1.000). Additional analyses (Mantel-Haenszel risk diff) also did not show statistical differences between the olanzapine and placebo groups (data not shown).

Overall Combined Database

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

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

This reviewer also evaluated the individual item “suicidal ideation” in the Children’s Depression Rating Scale-Revised. Though rating scales may not capture this specific adverse event, these data were reviewed to see if any trends in worsening occurred on the suicide-related item. For the CDRS², most patients scored a “1” at baseline. For patients who scored > 1, most showed improvement (decrease in score). Two patients in the placebo group had worsening on this item; one patient had an increase from a 1 to a 3 and another from a 2 to a 3 severity rating. Two patients in the olanzapine group had worsening on this item; one patient had an increase from a 2 to a 3 and another from a 2 to a 4 severity rating. Of note, 3 patients had a severity rating of 7 at baseline (all were randomized to olanzapine). The Sponsor will be asked to provide details regarding inclusion of these patients in the clinical trial.

Hostility and Aggression Adverse Events

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

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

2 CDRS-R Suicidal ideation item scoring: 1 = understands the word “suicide” but does not apply the term to himself/herself, 2 = sharp denial of suicidal thoughts, 3 = has thoughts about suicide, or of hurting himself/herself (if he/she does not 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), HGFM (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

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

*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 7.1.2.3 – Special Assessments.

7.1.6.2.3 Marked outliers and dropouts for laboratory abnormalities

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

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

Table 7.1.6.2.3.1 includes the marked outlier (in bold font), other related analytes at the same timepoint, end of acute study value for the marked outlier (resolution?) and a column for comments which included any additional values for the marked outlier in the open-label phase.

Individual patient profiles were not readily available so it is not known if resolutions in marked outlier values were related to decreases in olanzapine dose.

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

| | | | Marked Outlier | | | |
|------------------|-------------------------------------|---|--|---|--|---|
| | | | Related Analytes at Same Timepoint (<i>Italics = values > ULN</i>) | | | |
| 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 | <i>389.4</i> 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 | <i>230</i> (150 repeat) <i>92</i> (51 repeat) 0.29 (0.18 repeat) <i>48</i> (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) <i>60</i> 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) <i>179.5</i> <i>95.7</i> | 261.9 <i>179.5</i> <i>95.7</i> | TG = 111 at v.306 |
| HGIU 019-1901 | Creatine Phosphokinase | 0 – 169 U/L | 83 | 256 (v.5) | <i>256</i> | 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) <i>165.6</i> NA | <i>365.5</i> <i>231.7</i> <i>120.8</i> | 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) <i>87</i> 0.29 <i>27</i> | 124 <i>87</i> 0.29 <i>27</i> | 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) <i>171.8</i> <i>62.9</i> | <i>179.6</i> <i>164.9</i> <i>84.9</i> | 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) <i>35</i> 0.82 153 | <i>75</i> <i>62</i> 0.53 <i>87</i> | 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) <i>167.6</i> <i>74.9</i> | <i>100</i> <i>203.9</i> <i>141.7</i> | 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) <i>91</i> 0.29 <i>65</i> | 208 <i>91</i> 0.29 <i>65</i> | 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) <i>103</i> 0.53 35 | 125 <i>103</i> 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 <i>1.41</i> 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 Chol = 240 at v. 307 |
| | Cholesterol | 124.7 – 211.6 mg/dL | 201.5 | 289.6 (v.6) | 237.4 | |
| | LDL | 59.1 – 136.7 mg/dL | 102.7 | 165.6 | 132.8 | |
| HGIN 021-2103 | ALT | 6 – 43 U/L | 16 | 396 (v.7) | 396 | ALT = 154, AST = 36 at v. 502 (follow-up) |
| | AST | 10 – 40 U/L | 20 | 136 | 136 | |
| | TBili | 0.18 – 1.23 mg/dL | 0.41 | 0.41 | 0.41 | |
| | GGT | 0 – 51 U/L | 18 | 63 | 63 | |
| 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, |

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

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

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

Patient HGIN-900-9011 was randomized to placebo in the DB phase and had a baseline fasting glucose of 110 mg/dL. At visit 301, fasting glucose was 169 mg/dL on 7.5 mg olanzapine which normalized with continued dosing at 10 mg to 97 mg/dL at end of the study.

Patient HGIN 910-9108 was randomized to olanzapine in the DB phase and had a baseline fasting glucose of 95 mg/dL. At visit 7 of the acute phase, fasting glucose was 101 mg/dL, at visit 303 fasting glucose was 149 mg/dL on 20 mg olanzapine which normalized with continued dosing to 94 mg/dL at visit 309.

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

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

However, in the summary-clin-safe-app, the following Covance adolescent reference ranges were noted:

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

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

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

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

Table 7.1.6.2.3.2. Prolactin Outliers: HGIN + HGIU Acute Database

| 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

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

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

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

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

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

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

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

Metabolic Parameters

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

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

HGIN + HGIU Acute Database

LOCF mean change from baseline to endpoint:

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

Significant changes in fasting glucose and lipids at any time:

There was a greater incidence of significant changes in patients treated with olanzapine than in patients treated with placebo for normal to borderline total cholesterol (15.7% vs. 3.6%, $p = 0.023$) and for normal to high fasting triglycerides (12.4% vs. 1.9%, $p = 0.039$).

The change from normal to borderline LDL cholesterol was approaching statistical significance (13.7% vs. 3.8%, $p = 0.064$).

The changes in fasting glucose were not statistically different:

Normal (< 100 mg/dL) to high (≥ 126 mg/dL) = 0% (0/122) olanzapine, 2% (1/51) placebo

Impaired glucose tolerance (≥ 100 mg/dL and < 126 mg/dL) to high (≥ 126 mg/dL): 15.4% (2/13) olanzapine, 0% (0/13) placebo

Normal/impaired glucose tolerance (< 126 mg/dL) to high (≥ 126 mg/dL): 1.5% (2/135) olanzapine, 1.6% (1/64) placebo.

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

Significant changes in fasting glucose and lipids at endpoint:

The only parameter that was statistically significant was normal to borderline cholesterol (14% olanzapine, 3.6% placebo, $p = 0.039$). The change from normal to high triglycerides was approaching statistical significance (10.6% olanzapine, 1.9% placebo, $p = 0.064$).

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

In the Overall Combined Dataset, few patients had baseline impaired glucose ($n = 47$). Of those subjects, 6 (12.8%) had a shift from impaired glucose tolerance to high fasting glucose.

As mentioned in Section 7.1.6.2.1, 9 patients (6-olanzapine, 3-placebo) had baseline HbA1c values (presumed to be patients with diabetes) in the HGIN + HGIU Acute Database. There was

no change from baseline to endpoint in this parameter – not unexpected since this parameter is an indicator of blood glucose concentrations over the previous 3 to 4 months. In the Overall Combined Database, 23 patients had baseline HbA1c and there was no change at endpoint (the duration of study participation is not known for these patients).

The Sponsor provided correlation coefficients of change at endpoint between weight, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (it is unclear what correlation coefficient was used):

For the Overall Combined Dataset, there were statistically significant correlations between weight and total cholesterol (corr = 0.166, p = 0.005) and between weight and triglycerides (corr = 0.210, p < 0.001).

The Sponsor was asked to provide these correlations for the HGIN + HGIU Acute Database. In this database, there were statistically significant correlations between weight and total cholesterol (corr = 0.211, p = 0.003), between weight and triglycerides (corr = 0.223, p = 0.002) and between weight and fasting glucose (corr = 0.165, p = 0.021). Though these correlations are statistically significant, they are not particularly robust.

Hepatic-related Parameters

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

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

HGIN + HGIU Database

Mean change to endpoint in hepatic laboratory analytes is provided in Section 7.1.6 (Laboratory Findings).

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

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

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

| Hepatic Analytes | olanzapine | | | 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. Billi | 170 | 0 | 0.0% | 85 | 6 | 7.1% | .001 |

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

**Table APP.2.7.4.7.2.2.4. 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. Billi | 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 | Baseline | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|---------------------------------------|---------|----------|---------|-----------------------|---------|------------------|----------------------|----------|
| | | N | Mean | Std | Mean | | | |
| Heart Rate/Minute | Olz | 158 | 72.291 | 13.183 | 6.266 | 14.039 | 4.335 | <.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 | .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 | .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 | <.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 | <.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 | .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% | |
| | | | 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 | | Endpoint | | Change | | P-value |
|---------|------------|-----|----------|-------|----------|-------|--------|-------|----------|
| | | | Mean | Std | Mean | Std | Mean | Std | *P-value |
| Weight | Actual | 450 | 67.13 | 17.72 | 74.48 | 19.07 | 7.35 | 6.58 | <.001 |
| | Expected | 450 | 67.13 | 17.72 | 68.17 | 17.90 | 1.03 | 1.01 | <.001 |
| | Z-Score | 450 | 0.53 | 1.13 | 0.98 | 1.02 | 0.45 | 0.44 | <.001 |
| | Percentile | 450 | 63.54 | 29.54 | 75.33 | 24.50 | 11.79 | 14.19 | |
| Height | Actual | 440 | 168.24 | 9.71 | 169.27 | 9.45 | 1.03 | 2.17 | <.001 |
| | Expected | 440 | 168.24 | 9.71 | 168.92 | 9.60 | 0.67 | 0.91 | <.001 |
| | Z-Score | 440 | 0.02 | 1.02 | 0.07 | 1.00 | 0.05 | 0.24 | <.001 |
| | Percentile | 440 | 50.60 | 29.13 | 52.11 | 28.76 | 1.51 | 6.58 | |
| BMI | Actual | 439 | 23.64 | 6.07 | 25.95 | 6.21 | 2.31 | 2.31 | <.001 |
| | Expected | 439 | 23.64 | 6.07 | 23.83 | 6.01 | 0.19 | 0.30 | <.001 |
| | Z-Score | 439 | 0.50 | 1.14 | 0.99 | 0.95 | 0.49 | 0.53 | <.001 |
| | Percentile | 439 | 63.51 | 29.85 | 76.77 | 23.48 | 13.26 | 16.47 | |

Table 7.1.9.2. Sponsor’s Table.

**Table APP.2.7.4.7.3.3. Standardized Growth (Z-Score)
 LOCF Mean Change in Weight, Height, and BMI from Baseline to Endpoint by Gender
 Overall Olanzapine Exposure Combined Database**

| Measure | Gender | Value | N | Baseline | | Endpoint | | Change | | P-value | |
|---------|--------|------------|-----|----------|-------|----------|-------|--------|-------|----------|--|
| | | | | Mean | Std | Mean | Std | Mean | Std | *P-value | |
| Weight | Female | Actual | 167 | 64.41 | 18.15 | 70.94 | 19.34 | 6.53 | 6.08 | <.001 | |
| | | Expected | 167 | 64.41 | 18.15 | 65.05 | 18.29 | 0.64 | 0.73 | <.001 | |
| | | Z-Score | 167 | 0.64 | 1.12 | 1.05 | 0.97 | 0.40 | 0.45 | <.001 | |
| | Male | Percentile | 167 | 67.26 | 28.90 | 77.62 | 23.18 | 10.36 | 14.04 | | |
| | | 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 | |
| | Male | Percentile | 163 | 51.74 | 30.32 | 53.86 | 29.83 | 2.12 | 6.40 | | |
| | | 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 | |
| | Male | Percentile | 162 | 67.73 | 28.52 | 79.04 | 21.25 | 11.31 | 15.25 | | |
| | | 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

| Dose | Schizophrenia | | | Bipolar | | | Combined | | |
|------|---------------|----|-------|---------|----|-------|----------|-----|-------|
| | 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

| Modal Dose | Schizophrenia | | | Bipolar | | | Combined | | |
|------------|---------------|----|-------|---------|----|-------|----------|----|-------|
| | 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

| Final Dose | Schizophrenia | | | Bipolar | | | Combined | | |
|------------|---------------|----|-------|---------|----|-------|----------|----|-------|
| | 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 Tennessee. Further investigation may be deemed necessary. It is not known if the reporter had contacted the FDA regarding these cases as was mentioned in the case narrative. MedWatch reports for these additional cases were not included in the submission. The Sponsor will be asked to provide these reports as well as to submit any new reports that may have occurred since this search was last completed.

The MedWatch reports were incomplete and many details regarding the deaths (autopsy reports, pertinent laboratory values, clinical description of death) were not available. In some cases, it appears that the Sponsor attempted to obtain more information, it is not known to what extent these attempts were made. Fifteen of the cases occurred in the United States, a number of these cases were reported by an attorney via the legal department – it is not known if litigation is ongoing in these cases.

Of note, seven of the cases involved completed suicide or possible suicide and five of the cases related to diabetes mellitus, diabetic coma or diabetic ketoacidosis. A brief summary of these cases is in Appendix 10.13.

7.3 Safety Conclusions

The Sponsor submitted safety data in the study report for pivotal trial HGIN as well as a summary of safety for HGIN + HGIU Acute Database (HGIU is the pivotal trial for bipolar

³ In the narrative summary for US_010158510, the following statements were noted: “This is one of five deaths (Cases: US_01058498, US_010158510, US_010158520, US_010158524, US_010158537) reported by the same reporter. All deaths occurred in Roane County, Tennessee. The reporter stated he has also notified the FDA.”

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

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

The most common adverse events ($\geq 5\%$, 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 |
|--|----------------|---------------|--------------|-----------------------------------|
| <i>HGIN + HGIU Acute Database</i> | | | | |
| 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 |
| <i>Overall Combined Database</i> | | | | |
| Weight (kg) Mean Change to Endpoint (LOCF) | 7.35 | - | - | < 0.001 (compared to baseline) |
| Weight (kg) Mean Change to Endpoint (OC) | 10.8 | - | - | < 0.001 (compared to baseline) |

| | | | | |
|--|------|---|---|-----------------------------------|
| BMI Mean Change to Endpoint (LOCF) | 2.31 | - | - | < 0.001 (compared to baseline) |
| ≥ 7% increase in body weight (%) | 65% | - | - | - |

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

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

Liver Function Abnormalities

Six patients discontinued HGIN and HGIU due to increases in liver transaminases (esp. ALT). The percentage of patients with ALT baseline ≤ 3x ULN who had ALT > 3x ULN at any time during the acute studies was 12% (21/174) in the olanzapine group and 2.3% (2/87) in the placebo group (p = 0.009).

No patients met criteria for Hy's rule (ALT ≥ 3x ULN and TBili ≥ 1.5 x ULN).

Hyperprolactinemia

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

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

HGIU Acute Database, 47.4% of patients in the olanzapine group had a high prolactin concentration at anytime compared to 6.8% of patients in the placebo group ($p < 0.001$).

Hypertriglyceridemia

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

Hypercholesterolemia

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

Hyperglycemia

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

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

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

Extrapyramidal Symptoms

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

Suicidality

Both the HGIN + HGIU Acute Database and Overall Combined Database were searched for terms that could be related to suicidal behavior. No completed suicides occurred in the clinical trials. In the Acute Database, 2 events occurred in the olanzapine group (SIB – intent unknown

and suicidal ideation) and 1 event occurred in the placebo group (SIB – intent unknown). These differences were not statistically significant. In the Overall Combined Database, 24 cases of possible suicidal behaviors or ideation were identified (this includes the 2 cases in the Acute Database). The most common behaviors were suicidal ideation (n = 13) and SIB – intent unknown (n = 6). Fifteen of these 24 cases occurred in bipolar disorder patients. Suicidal behaviors or ideation is not uncommon in these patients and, in the absence of a placebo comparator, it is difficult to interpret any causality to olanzapine therapy.

7.4 General Methodology

7.4.1.1 Explorations for dose dependency for adverse findings

All of the clinical trials, both placebo-controlled and open-label, included a flexible dosing paradigm for olanzapine. Therefore, it is not possible to evaluate the dose-dependency of adverse events.

7.4.1.2 Explorations for drug-demographic interactions

The drug – demographic interactions summarized here are the adverse events occurring in HGIN + HGIU Acute Database. Subgroup analyses, particularly for gender and age, for efficacy and some safety data (prolactin, weight gain, etc.) are summarized in those relevant sections of the review. Most of the patients enrolled in the pivotal clinical trials were Caucasian, therefore any analyses by race/ethnicity are of limited usefulness.

Treatment-by-gender interactions were significant for the following adverse events: myalgia, nasal congestion, sinus congestion and tremor (see Table 7.4.1.2.1); though none of these adverse events were significantly different between olanzapine and placebo.

Table 7.4.1.2.1. Sponsor’s Table. Adverse Events – Treatment-by-Gender Interactions: HGIN + HGIU Acute Database

| Event Classification | Gender | Therapy | | | | | | *P-value | **Homogeneity of Odds Ratio |
|----------------------|--------|------------|---|------|---------|---|------|----------|-----------------------------|
| | | olanzapine | | | Placebo | | | | |
| | | N | n | % | N | n | % | | |
| Myalgia | Female | 67 | 0 | 0.0% | 41 | 1 | 2.4% | .380 | .070 |
| | Male | 112 | 3 | 2.7% | 48 | 0 | 0.0% | | |
| Nasal congestion | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | | |
| Sinus congestion | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | | |
| Tremor | Female | 67 | 2 | 3.0% | 41 | 0 | 0.0% | .525 | .055 |
| | Male | 112 | 0 | 0.0% | 48 | 1 | 2.1% | | |

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

| Event Classification | Age | Therapy | | | | | | *P-value | **Homogeneity of Odds Ratio |
|----------------------|------|------------|---|------|---------|---|------|----------|-----------------------------|
| | | Olanzapine | | | Placebo | | | | |
| | | N | n | % | N | n | % | | |
| Ear pain | < 15 | 64 | 1 | 1.6% | 27 | 0 | 0.0% | 1.00 | .100 |
| | ≥15 | 115 | 0 | 0.0% | 62 | 2 | 3.2% | | |
| Migraine | < 15 | 64 | 0 | 0.0% | 27 | 1 | 3.7% | .297 | .062 |
| | ≥15 | 115 | 2 | 1.7% | 62 | 0 | 0.0% | | |

7.5 Comparing adolescent and adult data

The common adverse event tables for adults in current product labeling and the common adverse events occurring in HGIN and HGIU were compared. In the schizophrenia trials, 31% of adolescent patients experienced weight gain compared to 6% of adult patients. Somnolence and sedation were experienced by 24% and 15% of adolescent patients compared to < 5% of adult patients. Similar patterns occurred in the bipolar disorder trials except that somnolence was very common in the adult population as well as the adolescent population.

Table 7.5.1. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 6 Week Acute Trials in *Schizophrenia*

| | Adults | | Adolescents | |
|----------------------|-----------------------|--------------------|----------------------|-------------------|
| | Olanzapine N = 248 | Placebo N = 118 | Olanzapine N = 72 | Placebo N = 35 |
| Dizziness | 11% | 4% | 31% | 9% |
| Constipation | 9% | 3% | 24% | 3% |
| Personality disorder | 8% | 4% | 17% | 6% |
| Weight gain | 6% | 1% | 17% | 9% |
| Akathisia | 5% | 1% | 15% | 6% |
| Postural hypotension | 5% | 2% | 8% | 3% |
| | | | Pain in extremity | 6% |

Table 7.5.2. Common Adverse Events (≥ 5% incidence) – Adult versus Adolescents: 3 Week Acute Trials in *Bipolar Disorder*

| | Adults | | Adolescents | |
|------------|-----------------------|--------------------|-----------------------|-------------------|
| | Olanzapine N = 125 | Placebo N = 129 | Olanzapine N = 107 | Placebo N = 54 |
| Somnolence | 35% | 13% | 29% | 4% |
| Dry mouth | 22% | 7% | 29% | 4% |
| Dizziness | 18% | 6% | 25% | 4% |

| | | |
|--------------------|-----|----|
| Asthenia | 15% | 6% |
| Constipation | 11% | 5% |
| Dyspepsia | 11% | 5% |
| Increased appetite | 6% | 3% |
| Tremor | 6% | 3% |

| | | |
|-------------------|-----|-----|
| Sedation | 22% | 6% |
| Headache | 17% | 17% |
| Fatigue | 14% | 6% |
| Dry mouth | 8% | 0% |
| Pain in extremity | 5% | 0% |

The Sponsor included an analysis of select adverse events occurring in the adult clinical trials databases and adolescent clinical trials databases. These analyses summarized all data including the open-label trials. The Sponsor was asked if a similar analysis could be done for the placebo-controlled studies only and they responded that none of the placebo-controlled studies included fasting glucose and lipid data so these analyses were not available.

Metabolic parameters (fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides):

Mean change from baseline to endpoint – the only statistically significant differences between populations was in fasting glucose and triglycerides. Mean change to endpoint for fasting glucose was 1.8 ± 13 mg/dL for adolescents and 4.9 ± 32.8 mg/dL for adults ($p = 0.002$), triglycerides was 23.0 ± 76 mg/dL for adolescents and 20.3 ± 124 mg/dL for adults ($p = 0.007$).

Treatment-emergent significant changes at any time: statistically significant differences were noted for most of the parameters with a higher percentage of adults having significant changes at any time (see Table 7.5.3).

Table 7.5.3. Treatment-Emergent Significant Changes at Any Time – Adults vs. Adolescents

| Laboratory Analytes | Categories | Population | N | n | % | *P-value |
|---------------------|--|------------|-----|----|-------|----------|
| Fasting Glucose | Normal to High (< 100 mg/dL to >=126 mg/dL) | Adolescent | 251 | 3 | 1.2% | .033 |
| | | Adult | 251 | 12 | 4.8% | |
| | Impaired Glucose Tolerance to High (>=100 & <126 mg/dL to >=126 mg/dL) | Adolescent | 47 | 6 | 12.8% | .066 |
| | | Adult | 121 | 32 | 26.4% | |
| | Normal/Impaired Glucose Tolerance to High (<126 mg/dL to >=126 mg/dL) | Adolescent | 298 | 9 | 3.0% | <.001 |
| | | Adult | 372 | 44 | 11.8% | |
| Total Cholesterol | Normal to Borderline (<200 mg/dL to >=200 mg/dL and <240 mg/dL) | Adolescent | 262 | 54 | 20.6% | <.001 |
| | | Adult | 216 | 82 | 38.0% | |
| | Normal to High (<200 mg/dL to >=240 mg/dL) | Adolescent | 262 | 3 | 1.1% | .001 |
| | | Adult | 216 | 15 | 6.9% | |
| LDL Cholesterol | Normal to Borderline (<130 mg/dL to >=130 mg/dL and <160 mg/dL) | Adolescent | 270 | 48 | 17.8% | <.001 |
| | | Adult | 241 | 75 | 31.1% | |
| | Normal to High (<130 mg/dL to >=160 mg/dL) | Adolescent | 270 | 4 | 1.5% | .014 |
| | | Adult | 241 | 14 | 5.8% | |
| HDL Cholesterol | Normal to Low (>=50 mg/dL to <40 mg/dL) | Adolescent | 107 | 10 | 9.3% | .052 |
| | | Adult | 155 | 28 | 18.1% | |

| Laboratory Analytes | Categories | Population | N | n | % | *P-value |
|-----------------------|---|------------|-----|-------|-------|----------|
| Fasting Triglycerides | Normal to Borderline (<150 mg/dL to >=150 mg/dL and <200 mg/dL) | Adolescent | 247 | 51 | 20.6% | <.001 |
| | | Adult | 253 | 91 | 36.0% | |
| | Normal to High (<150 mg/dL to >=200 mg/dL) | Adolescent | 247 | 43 | 17.4% | .030 |
| | Adult | 253 | 65 | 25.7% | | |
| | Normal to Extremely High (<150 mg/dL to >=500 mg/dL) | Adolescent | 247 | 1 | 0.4% | 1.00 |
| | | Adult | 253 | 1 | 0.4% | |

Weight Gain

Mean change from baseline to endpoint – There was a statistically significant greater mean increase in body weight for adolescents compared to adults (see Table 7.5.4).

Table 7.5.4. Sponsor’s Table. Mean Change from Baseline to Endpoint - Adolescents vs. Adults. Overall Combined Databases

| Population | N | Baseline | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|------------|------|----------|-------|--------------------|------|---------------|-------------------|----------|
| | | Mean | Std | Mean | Std | | | |
| 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 $\geq 3 \times$ 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 $> 3 \times$ ULN (from baseline $\leq 3 \times$ 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|------------------------|------|------------|------|----------|--------|--------------------|--------|---------------|-------------------|----------|
| | | | | Mean | Std | Mean | Std | | | |
| PROLACTIN | %URL | Adolescent | 431 | 78.73 | 76.47 | 23.01 | 83.69 | 9.70 | 12.62 | .004 |
| | | Adult | 4503 | 99.42 | 126.56 | -4.19 | 125.57 | -2.92 | | |

From Sponsor’s table APP.2.7.4.7.4.31 in summary-clin-app document

Treatment-emergent high prolactin concentrations at any time: a higher percentage of adolescent patients (55.5%) had high prolactin concentrations at any time compared to adult patients (29%) ($p < 0.001$). The Sponsor did not provide an analysis for adolescent vs. adult patients by gender.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

(b) (4)

(b) (4)

8.2 Advisory Committee Meeting

No advisory committee meeting was held for this submission.

8.3 Literature Review

The Sponsor submitted a literature review though there was no attempt to summarize key findings. The Sponsor stated that none of the reviewed articles presented safety data contradictory to the conclusions presented in the NDA. Due to time constraints for this priority application, a separate literature review was not conducted by this reviewer.

8.4 Postmarketing Risk Management Plan

The Sponsor submitted a Risk Management document outlining their proposed actions for risk minimization. The identified risks in this document included weight gain, sedation, hepatic changes, hyperprolactinemia, glucose dysregulation, dyslipidemia. For all of these safety issues, the Sponsor has proposed the following actions for pharmacovigilance: clinical trial surveillance, routine pharmacovigilance, targeted surveillance, long-term safety study and studies in pediatric patients with PDD. For glucose dysregulation and dyslipidemia, an additional action was to perform a retrospective cohort claims database study.

Routine pharmacovigilance was defined as periodic reporting per PSUR or as appropriate. Targeted surveillance was similar but targeted weight gain, hepatic changes, glucose dysregulation and dyslipidemia. The Sponsor has proposed a long-term safety study to evaluate the safety of olanzapine in adolescent patients with schizophrenia or bipolar disorder and to estimate the incidence and prevalence of identified and potential risks associated with olanzapine treatment. The study is still in the planning phase.

(b) (4)



The actions proposed for risk minimization include product labeling and prescriber education – no details were provided regarding the latter proposal.

9 OVERALL ASSESSMENT

9.1 Recommendation on Regulatory Action

I recommend that the Division take a non approval action on NDA 20-592 SE5-041 that was filed to support the indication “treatment of schizophrenia in adolescent patients”.

Fifty-three percent of randomized patients in pivotal trial HGIN were from sites in the United States and 47% of randomized patients were from sites in Russia. The primary endpoint, change from baseline to endpoint in BPRS-C Total Score (LOCF analysis) was statistically significant for the sites in Russia ($p = 0.003$) but not the sites in the United States ($p = 0.258$). The sites in Russia appeared to drive the entire efficacy signal for this clinical trial, primarily due to the very low placebo response in the sites in Russia.

Though the LOCF analysis was the primary analysis, it is also concerning that the OC and MMRM analyses (the latter by recalculation by the reviewing statistician in the Division) are substantially different from the LOCF analysis and not statistically significant.

I recommend that the Sponsor conduct another clinical trial in this population if they wish to pursue this indication. The majority of patients in this clinical trial should be from sites in the United States and efficacy will need to be established in these patients. It is also strongly recommended that this clinical trial be a fixed dose design since dose-response data for efficacy or safety cannot be evaluated in a flexible dose design.

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

9.2 Recommendation on Postmarketing Actions

Since non approval is recommended, there are no recommendations for postmarketing actions.

9.3 Labeling Review

Changes to proposed labeling are being made directly to the annotated labeling submitted by the Sponsor, this was the first PLR labeling so there were many changes from prior approved labeling. The project manager, Dr. Doris Bates, reviewed the PLR labeling against the prior approved labeling and noted any differences – especially differences that were not highlighted by the Sponsor.

In the proposed labeling, all of the “frequent” adverse events in the “Other Adverse Events Observed” section were removed and some of the adverse events in other categories (infrequent, rare) were also removed. The Sponsor has been asked to address this and had not responded at the time this review was finalized.

This section will briefly discuss some of the labeling that may require revision:

[REDACTED] (b) (4)

WARNINGS AND PRECAUTIONS – The team will have to discuss the order of the items under this heading.

Weight Gain: should be placed earlier in this section

Transaminase Elevations: in the adult section, the number of patients with ALT ≥ 3 times ULN data is provided. In the adolescent section, the number of patients with ALT > 3 times ULN data is provided. These should be consistent (should both be $\geq 3 \times$ 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 Roane County, Tennessee. The reporter stated he has also notified the FDA...". The only MedWatch report included in this submission is

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

34. Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed the 19-32 weeks in the study (n = 83 bipolar, n = 93 schizophrenia) - e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

35. One of the exclusion criteria for HGIU was "patients who have been judged clinically to be at serious suicidal risk". However, a review of the CDRS-R individual item "suicidal ideation" noted a number of patients who were rated the maximum score of "7" at baseline (has made a suicide attempt within the last month or is actively suicidal". These patients include 012-1203, 012-1212, and 024-2402. Please provide more information regarding inclusion of these patients in this study.

36. Please provide an analysis of AIMs individual items and total score (change from baseline to endpoint) for the completers in the overall combined database.

37. For HGIU and HGIN, how was "treatment-emergent" parkinsonism, akathisia and dyskinesia defined by the respective rating scales?

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

39. For study HGIN, it is noted that 21/72 patients in the olanzapine group and 5/35 patients in the placebo group did not have any previous medications for schizophrenia (Table HGIN.14.4). How many of these patients were from the sites in Russia? How many were first-break schizophrenic patients?

40. The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes.

41. Please provide an analysis of mean change to endpoint for prolactin by age (< 15, > 15) for HGIN + HGIU Acute Database, HGIN and HGIU.

10 APPENDICES

10.1 Investigators and Sites (HGIN)

| Site # | Principal Investigator | Site & Address | # Pts Randomized | # Pts Completing DB; OL |
|--------|--------------------------------|---|---------------------|-------------------------------|
| 3 | Bastani, Bijan | Northcoast Clinical Trials 3733 Park East Drive, Suite 100 Beachwood, OH 44122 USA | 2 | 2;1 |
| 4 | Kaplan, Stuart Busner, Joan | Penn State University Milton S. Hershey Medical Center 500 University Drive Dept. of Psychiatry, HO73, Rm H1141 Hershey, PA 17033 USA | 1 | 1;1 |
| 5 | Childress, Ann | Nevada Behavioral Health, Inc. 2055 W. Charlestone Blvd, Ste B Las Vegas, NV 89102 USA | 2 | 1;1 |
| 6 | Cueva, Jeanette | Bioscience Research, Llc 222 W. 14 th 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 | Kaczynski, 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 6 th Street, Suite 101 Kirkland, WA 98033 USA | 2 | 2;0 |

Clinical Review
 Cara Alfaro, Pharm.D.
 NDA 20-592 S-040
 Zyprexa (olanzapine)

| | | | | |
|----|---------------------------|--|---|-------------------|
| 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 |

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 Cara Alfaro, Pharm.D.
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 Zyprexa (olanzapine)

| | | | | |
|-----|---------------------------|--|----|-----|
| 27 | Yadalam, Kashinath | Institute for Neuropsychiatry 2829 4 th Avenue Lake Charles, LA 70601 USA | 2 | 1;0 |
| 30 | Punjwani, Sohail | Segal Institute for Clinical Research 1065 NE 125 th 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 mm³).

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 | X |
| Hematology | X | X | | X | X | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | X |
| Urinalysis | X | | | | | | | | | X | | | | | | | | | | | | X |
| Hepatitis screen ^c , urine drug screen ^d , serum pregnancy test ^d , and TSH | X | | | | | | | | | | | | | | | | | | | | | |
| HbgA1 _c ^f | X | | | | | | | | | X | | | | | | X | | | | | | X |
| Prolactin ^g | X | X | | | | | | | | X | | | | | | X | | | | | | X |
| EFFICACY ASSESSMENTS/Measurements | | | | | | | | | | | | | | | | | | | | | | |
| Anchored BPRS-C _i | X | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | X | |
| CGI Severity | | X | 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 | X | |
| PANSS | | X | | | | X | | | | X | | | | | | | | | | | | X |
| OAS | | X | | | | X | | | | X | | | | | | | | | | | | X |
| Child Health Questionnaire (CHQ) ^k | | X | | | | | | | | X | | | | | | | | | | | | X |
| Brief Assessment of Cognition for Schizophrenia (BACS) ^k | | X | | | | | | | | X | | | | | | | | | | | | X |

Table HGIN.9.4. Schedule of Events for F1D-MC-HGIN (continued)

| Description of the Data | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | Final SPII Visit ⁱ | Visit501 | V301 | V302 | V303 | V304 | V305 | V306 | V307 | V308 | V309 | Final SPIII Visit ⁱ | Visit 501 |
|--|----|----|----|----|----|----|----|----|----|-------------------------------|----------|------|------|------|------|------|------|------|------|------|--------------------------------|-----------|
| AIMS, Barnes Akathisia Scale, Simpson-Angus Scale | X | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | |
| LABORATORY TESTS ^b | | | | | | | | | | | | | | | | | | | | | | |
| Clinical chemistry ^c /electrolytes/lipids ^e | X | X | | X | X | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | X |
| Hematology | X | X | | X | X | X | X | X | X | X | | | X | | X | X | X | X | X | X | X | X |
| Urinalysis | X | | | | | | | | | X | | | | | | | | | | | | X |
| Hepatitis screen ^c , urine drug screen ^d , serum pregnancy test ^d , and TSH | X | | | | | | | | | | | | | | | | | | | | | |
| HbgA1 _c ^f | X | | | | | | | | | X | | | | | | X | | | | | | X |
| Prolactin ^g | X | X | | | | | | | | X | | | | | | X | | | | | | X |
| EFFICACY ASSESSMENTS/Measurements | | | | | | | | | | | | | | | | | | | | | | |
| Anchored BPRS-C _i | X | X | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X | X | X | |
| CGI Severity | | X | 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 | X | |
| PANSS | | X | | | | X | | | | X | | | | | | | | | | | | X |
| OAS | | X | | | | X | | | | X | | | | | | | | | | | | X |
| Child Health Questionnaire (CHQ) ^k | | X | | | | | | | | X | | | | | | | | | | | | X |
| Brief Assessment of Cognition for Schizophrenia (BACS) ^k | | X | | | | | | | | X | | | | | | | | | | | | X |

10.4 Severity of Illness: Russia vs. U.S. Sites

**Table 1. Illness Characteristics at Baseline by Country
 All Randomized Patients
 F1D-MC-HGIN, Acute Phase**

| Illness Characteristics | Statistics | Country | | *P-value |
|-------------------------------------|-----------------|------------------|----------------|----------|
| | | Russia (N=50) | U.S. (N=57) | |
| Onset Age | No. of Patients | 50 | 57 | .536 |
| | Mean | 13.02 | 12.65 | |
| | Median | 14.00 | 13.00 | |
| | Std. Dev. | 2.64 | 3.43 | |
| | Minimum | 6.00 | 5.00 | |
| No. of Prev. Schizophrenia episode | No. of Patients | 40 | 45 | .416 |
| | Mean | 2.10 | 2.73 | |
| | Median | 2.00 | 2.00 | |
| | Std. Dev. | 1.45 | 4.71 | |
| | Minimum | 0.00 | 0.00 | |
| Total cum hospitalization in months | No. of Patients | 26 | 34 | .065 |
| | Mean | 2.96 | 1.88 | |
| | Median | 2.00 | 1.00 | |
| | Std. Dev. | 1.92 | 2.40 | |
| | Minimum | 1.00 | 0.10 | |
| | Maximum | 9.50 | 11.00 | |

* Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): Model= Country

| Illness Characteristics | Statistics | Country | | *P-value |
|-------------------------------------|-----------------|------------------|----------------|----------|
| | | Russia (N=50) | U.S. (N=57) | |
| Length of current episode in days | No. of Patients | 50 | 56 | .974 |
| | Mean | 262.44 | 259.43 | |
| | Median | 125.50 | 80.00 | |
| | Std. Dev. | 396.21 | 524.28 | |
| | Minimum | 7.00 | 0.00 | |
| Days since the last hospitalization | No. of Patients | 37 | 40 | .012 |
| | Mean | 476.95 | 149.58 | |
| | Median | 163.00 | 7.00 | |
| | Std. Dev. | 632.51 | 477.26 | |
| | Minimum | 31.00 | 1.00 | |
| | Maximum | 2718.00 | 2889.00 | |

| Illness Characteristics | Category | Country | | *P-value |
|-----------------------------|----------|------------|------------|----------|
| | | Russia | U.S. | |
| | | (N=50) | (N=57) | |
| | | n (%) | n (%) | |
| Psychiatric hospitalization | Yes | 26 (52.00) | 34 (59.65) | .442 |
| | No | 24 (48.00) | 23 (40.35) | |

**Table 2. Severity of Illness at Baseline by Country
 All Randomized Patients
 F1D-MC-HGIN, Acute Phase**

| Illness Characteristics | Statistics | Country | | *P-values |
|------------------------------------|-----------------|---------|--------|-----------|
| | | Russia | U.S. | |
| | | (N=50) | (N=57) | |
| CGI Severity | No. of Patients | 50 | 57 | .904 |
| | Mean | 4.86 | 4.88 | |
| | Median | 5.00 | 5.00 | |
| | Std. Dev. | 0.70 | 0.76 | |
| | Minimum | 4.00 | 4.00 | |
| BPRS-C Behavioral Problem(Sum 1-3) | No. of Patients | 50 | 57 | <.001 |
| | Mean | 5.46 | 7.77 | |
| | Median | 6.00 | 8.00 | |
| | Std. Dev. | 2.54 | 3.70 | |
| | Minimum | 0.00 | 0.00 | |
| BPRS-C Depression(Sum 4-6) | No. of Patients | 50 | 57 | .044 |
| | Mean | 5.30 | 6.47 | |
| | Median | 5.50 | 6.00 | |
| | Std. Dev. | 2.61 | 3.25 | |
| | Minimum | 0.00 | 1.00 | |
| | Maximum | 11.00 | 16.00 | |

* Means are analyzed using a Type III Sum of Squares analysis of variance(ANOVA): Model= Country

| Illness Characteristics | Statistics | Country | | *P-values |
|-------------------------|-----------------|---------|--------|-----------|
| | | Russia | U.S. | |
| | | (N=50) | (N=57) | |
| PANSS Total Score | No. of Patients | 50 | 57 | .116 |
| | Mean | 97.62 | 93.35 | |
| | Median | 96.00 | 95.00 | |
| | Std. Dev. | 13.09 | 14.60 | |
| | Minimum | 74.00 | 66.00 | |
| | Maximum | 122.00 | 123.00 | |

| Illness Characteristics | Statistics | Country | | *P-values |
|--|-----------------|------------------|----------------|-----------|
| | | Russia (N=50) | U.S. (N=57) | |
| BPRS-C Thinking Disturbance(Sum 7-9) | No. of Patients | 50 | 57 | |
| | Mean | 9.72 | 11.04 | .030 |
| | Median | 10.00 | 11.00 | |
| | Std. Dev. | 3.29 | 2.88 | |
| | Minimum | 4.00 | 5.00 | |
| | Maximum | 18.00 | 18.00 | |
| BPRS-C Psychomotor Excitation Subtotal(Sum 10-12) | No. of Patients | 50 | 57 | |
| | Mean | 6.08 | 7.32 | .038 |
| | Median | 5.00 | 7.00 | |
| | Std. Dev. | 2.84 | 3.19 | |
| | Minimum | 2.00 | 2.00 | |
| | Maximum | 13.00 | 14.00 | |
| BPRS-C Withdrawal Subtotal(Sum 13-15) | No. of Patients | 50 | 57 | |
| | Mean | 9.54 | 7.98 | .021 |
| | Median | 10.00 | 8.00 | |
| | Std. Dev. | 2.76 | 3.93 | |
| | Minimum | 4.00 | 1.00 | |
| | Maximum | 18.00 | 15.00 | |

| Illness Characteristics | Statistics | Country | | *P-values |
|---------------------------------------|-----------------|------------------|----------------|-----------|
| | | Russia (N=50) | U.S. (N=57) | |
| BPRS-C Anxiety Subtotal(Sum 16-18) | No. of Patients | 50 | 57 | |
| | Mean | 8.16 | 8.58 | .467 |
| | Median | 9.00 | 9.00 | |
| | Std. Dev. | 2.76 | 3.13 | |
| | Minimum | 2.00 | 1.00 | |
| | Maximum | 15.00 | 14.00 | |
| BPRS-C Organicity Subtotal(Sum 19-21) | No. of Patients | 50 | 57 | |
| | Mean | 3.22 | 3.44 | .708 |
| | Median | 2.50 | 3.00 | |
| | Std. Dev. | 3.29 | 2.74 | |
| | Minimum | 0.00 | 0.00 | |
| | Maximum | 12.00 | 10.00 | |
| BPRS-C Total Score | No. of Patients | 50 | 57 | |
| | Mean | 47.48 | 52.60 | .005 |
| | Median | 46.50 | 52.00 | |
| | Std. Dev. | 8.71 | 9.60 | |
| | Minimum | 36.00 | 35.00 | |
| | Maximum | 68.00 | 79.00 | |

| Illness Characteristics | Statistics | Country | | *P-values |
|-------------------------------------|-----------------|------------------|----------------|-----------|
| | | Russia (N=50) | U.S. (N=57) | |
| 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 | |
| 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 | |
| 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 | Olanzapine | | Placebo | | LSMean Change | LSMean Difference | *P-value |
|-------------------------|------------|----|------------|------|---------|------|---------------|-------------------|----------|
| | | | Mean | Std | Mean | Std | | | |
| 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 |
| | Placebo | 35 | 3.21 | 1.74 | -1.61 | 1.98 | -1.56 | | |

| | | | | | | | | | |
|--------------------------|------------|----|------|------|-------|------|-------|-------|------|
| 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 | | Change to Endpoint | | LSMean Change | LSMean Diff. | *P-value |
|---|------------|----|----------|------|--------------------|------|---------------|--------------|----------|
| | | | Mean | Std | Mean | Std | | | |
| 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) | | Placebo (N=89) | | *P-value |
|-----------------------|-------------------------|-----------------------|---------|-------------------|---------|----------|
| | | n | (%) | n | (%) | |
| Gender | Male | 112 | (62.57) | 48 | (53.93) | .188 |
| | Female | 67 | (37.43) | 41 | (46.07) | |
| Age | No. of Patients | 179 | | 89 | | .200 |
| | Mean | 15.54 | | 15.74 | | |
| | 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 | | HGIU | | Combined | |
|--------------|------------|---------------|------------|---------------|------------|---------------|
| | n | % | n | % | n | % |
| 13 | 9 | 8.4% | 31 | 19.3% | 40 | 14.9% |
| 14 | 13 | 12.1% | 38 | 23.6% | 51 | 19.0% |
| 15 | 20 | 18.7% | 50 | 31.1% | 70 | 26.1% |
| 16 | 29 | 27.1% | 27 | 16.8% | 56 | 20.9% |
| 17 | 36 | 33.6% | 15 | 9.3% | 51 | 19.0% |
| Total | 107 | 100.0% | 161 | 100.0% | 268 | 100.0% |

Table 10.6.3 Sponsor's Table. Patient Demographics at Baseline – Overall Olanzapine Combined Database

**Table 2.7.4.24. Patient Demographics at Baseline
 All Patients with Olanzapine Exposure
 Overall Olanzapine Exposure Combined Database**

| Demographic Variables | Statistics/ Category | Bipolar | Schizophrenia | Overall |
|-----------------------|-------------------------|-------------|---------------|-------------|
| | | (N=227) | (N=227) | (N=454) |
| | | n (%) | n (%) | 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 | | P-value |
|-------------|---------------|------------|-----|-------------------|------|---------|
| | | | | Mean | Std | |
| Weight (kg) | Bipolar | ≤ 1 | 224 | 1.27 | 1.55 | < 0.001 |
| | Schizophrenia | | 224 | 1.75 | 1.51 | < 0.001 |
| | Overall | | 448 | 1.51 | 1.55 | < 0.001 |
| | Bipolar | > 1 ≤ 2 | 221 | 2.29 | 2.04 | < 0.001 |
| | Schizophrenia | | 219 | 2.73 | 1.96 | < 0.001 |
| | Overall | | 440 | 2.51 | 2.01 | < 0.001 |
| | Bipolar | > 2 ≤ 3 | 183 | 3.07 | 2.62 | < 0.001 |
| | Schizophrenia | | 148 | 3.46 | 2.24 | < 0.001 |
| | Overall | | 331 | 3.25 | 2.46 | < 0.001 |
| | Bipolar | > 3 ≤ 4 | 199 | 3.74 | 2.84 | < 0.001 |
| | Schizophrenia | | 201 | 4.02 | 2.51 | < 0.001 |
| | Overall | | 400 | 3.88 | 2.68 | < 0.001 |
| | Bipolar | > 4 ≤ 5 | 167 | 4.05 | 3.31 | < 0.001 |
| | Schizophrenia | | 147 | 4.66 | 2.42 | < 0.001 |
| | Overall | | 314 | 4.34 | 2.94 | < 0.001 |
| | Bipolar | > 5 ≤ 9 | 157 | 6.03 | 3.80 | < 0.001 |
| | Schizophrenia | | 130 | 7.12 | 3.80 | < 0.001 |
| | Overall | | 287 | 6.52 | 3.83 | < 0.001 |
| | Bipolar | > 9 ≤ 13 | 121 | 7.59 | 4.95 | < 0.001 |
| | Schizophrenia | | 117 | 8.17 | 4.84 | < 0.001 |
| | Overall | | 238 | 7.87 | 4.89 | < 0.001 |
| | Bipolar | > 13 ≤ 17 | 114 | 8.84 | 5.87 | < 0.001 |
| | Schizophrenia | | 103 | 9.01 | 6.03 | < 0.001 |
| | Overall | | 217 | 8.92 | 5.93 | < 0.001 |
| | Bipolar | > 17 ≤ 21 | 102 | 9.69 | 6.43 | < 0.001 |
| | Schizophrenia | | 88 | 10.2 | 6.75 | < 0.001 |
| | Overall | | 190 | 9.93 | 6.56 | < 0.001 |
| | Bipolar | > 21 ≤ 25 | 93 | 10.19 | 6.98 | < 0.001 |
| | Schizophrenia | | 81 | 10.84 | 6.92 | < 0.001 |
| | Overall | | 174 | 10.49 | 6.94 | < 0.001 |
| | Bipolar | > 25 ≤ 32 | 53 | 9.60 | 7.12 | < 0.001 |
| | Schizophrenia | | 78 | 11.68 | 7.62 | < 0.001 |
| | Overall | | 131 | 10.84 | 7.46 | < 0.001 |

From Sponsor table APP.2.7.4.7.1.18 in summary-clin-safe-app document

Table 10.7.2. Adverse Event “Weight Increased” Gender Analysis: HGIU and HGIN Acute Phases

| | | Olanzapine | | | Placebo | | | p-value | Homogeneity of Odds Ratio | |
|------------------|------|------------|----|----|---------|----|---|---------|---------------------------|-------|
| | | Gender | N | n | % | N | n | % | | |
| Weight Increased | HGIU | Female | 46 | 16 | 35% | 30 | 1 | 3% | 0.001 | |
| | | Male | 61 | 15 | 25% | 24 | 1 | 4% | 0.033 | 0.628 |
| | HGIN | Female | 21 | 6 | 29% | 11 | 2 | 18% | 0.681 | |
| | | Male | 51 | 16 | 31% | 24 | 1 | 4% | 0.008 | 0.186 |
| Weight Increased | HGIU | < 15 yrs | 49 | 14 | 29% | 20 | 0 | 0 | 0.007 | |
| | | ≥ 15 yrs | 58 | 17 | 29% | 34 | 2 | 6% | 0.008 | 0.280 |
| | HGIN | < 15 yrs | 15 | 6 | 40% | 7 | 1 | 14% | 0.350 | |
| | | ≥ 15 yrs | 57 | 16 | 28% | 28 | 2 | 7% | 0.045 | 0.868 |

From Sponsor Tables HGIN.14.28 and HGIU.14.31

Table 10.7.3. Mean Change in Weight (kg) – Subgroup Analyses: HGIN

| | | | | Baseline | | Change to Endpoint | | | | | |
|-------------|----------|------------|----|----------|--------|--------------------|---------|---------|-------------|---------|---------|
| | Subgroup | Therapy | n | Mean | St.Dev | Mean | St. Dev | LS Mean | LSMean Diff | P-value | P-value |
| HGIN | | | | | | | | | | | |
| Weight (kg) | Female | Olanzapine | 21 | 64.0 | 16.6 | 3.8 | 3.7 | 3.4 | | | |
| | | Placebo | 10 | 61.0 | 12.5 | 0.8 | 3.5 | 0.7 | 2.73 | 0.063 | |
| | Male | Olanzapine | 51 | 68.3 | 11.6 | 4.5 | 3.2 | 4.6 | | | |
| | | Placebo | 24 | 72.2 | 17.6 | -0.2 | 2.5 | -0.2 | 4.76 | < 0.001 | 0.140 |
| | < 15 yrs | Olanzapine | 15 | 64.7 | 14.0 | 6.3 | 4.2 | 5.2 | | | |
| | | Placebo | 7 | 62.5 | 9.6 | 1.1 | 4.1 | -0.2 | 5.37 | 0.009 | |
| | ≥ 15 yrs | Olanzapine | 57 | 67.7 | 13.2 | 3.7 | 2.9 | 3.8 | | | |
| | | Placebo | 27 | 70.6 | 18.1 | -0.1 | 2.4 | -0.1 | 3.84 | < 0.001 | 0.370 |

From Sponsor Tables HGIN.14.47

Table 10.7.4. Mean Change from Baseline to Endpoint in Laboratory Values – Patients Who Gained > 3.9 kg vs. Placebo

The LS Mean Change and p-value for the entire population is in parenthesis for comparison purposes

| | Therapy | n | Baseline | Change to Endpoint | LS Mean Change | LSMean Diff | P-value |
|---------------------------|------------|----|----------|--------------------|----------------|-----------------|----------------------|
| | | | Mean | Mean | | | |
| AST (U/L) | Olanzapine | 84 | 21.9 | 9.5 | 11.3 | 11.7 (8.91) | < 0.001 (0.002) |
| | Placebo | 87 | 23.6 | -2.5 | -0.4 | | |
| ALT (U/L) | Olanzapine | 84 | 20.8 | 25.8 | 29.6 | 28.5 (23.0) | < 0.001 (< 0.001) |
| | Placebo | 87 | 20.4 | -3.1 | 1.0 | | |
| CPK (U/L) | Olanzapine | 84 | 125 | 18.1 | 16.8 | 38.7 (16.1) | 0.037 (0.38) |
| | Placebo | 87 | 164 | -23.6 | -21.9 | | |
| Glucose, fasting (mg/dL)* | Olanzapine | 58 | 88.8 | 3.2 | 4.3 | 6.3 (5.6) | 0.001 (< 0.001) |
| | Placebo | 64 | 89.7 | -2.9 | -2.0 | | |
| Cholesterol (mg/dL)* | Olanzapine | 84 | 164.1 | 17.4 | 13.5 | 18.5 (14.3) | < 0.001 (< 0.001) |
| | Placebo | 87 | 160.2 | -1.1 | -4.6 | | |
| Triglycerides (mg/dL)* | Olanzapine | 84 | 97.3 | 51.3 | 46.9 | 54.0 (33.6) | < 0.001 (<0.001) |
| | Placebo | 87 | 110.6 | -4.4 | -7.1 | | |
| LDL (mg/dL)* | Olanzapine | 84 | 96.1 | 6.6 | 3.1 | 6.6 (6.6) | 0.038 (0.016) |
| | Placebo | 87 | 91.5 | -0.39 | -3.5 | | |
| Prolactin (ng/ml) | Olanzapine | 79 | 13.3 | 12.6 | 12.0 | 12.91 (11.7) | < 0.001 (< 0.001) |
| | Placebo | 80 | 14.9 | -0.2 | -0.9 | | |

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

10.8 Patients with Possible Suicidal Behavior or Ideation Events HGIU + HGIN Acute Database

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Therapy | Days to Event | Fatal? |
|-----------------------------------|--|------|---------|---------------|--------|
| HGIU-001-0103 | THE PATIENT HAS REPORTEDLY BEEN HAVING DIFFICULTIES WITH DYSPHORIC MOOD. IN MID TO LATE APRIL, 2003, HE TRIED TO TIE A BELT AROUND HIS NECK RESULTING IN A RASH. | 5 | Placebo | 23 | No |
| HGIU-012-1206 | INTENTIONAL SELF-INJURY / SELF-IMPLICATED CUT MARKS ON FOREARM | 5 | 01z | 22 | No |
| HGIU-012-1211 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 01z | 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 WORSENER APPROXIMATELY ONE WEEK PRIOR (~05-NOV-2003). ADDITIONALLY HE BEGAN FEELING SUICIDAL (WITHOUT PLAN) APPROXIMATELY THREE DAYS PRIOR (~09-NOV-2003). THE PATIENT'S MOTHER CALLED THE SITE TO REPORT THAT THE PATIENT HAD CUT HIMSELF THE PRIOR EVENING AND DIDN'T FEEL SAFE. THE PATIENT WAS BROUGHT TO THE HOSPITAL FOR SAFETY AND STABILIZATION. | 4 | 59 | No |

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|-----------------------------------|--|------|---------------------|--------|
| HGIU-026-2605 | THE PATIENT WAS BEHAVING INAPPROPRIATELY AND WAS ON THE ROOF OF HIS HOME REFUSING TO COME DOWN | 9 | 53 | No |
| HGIU-026-2606 | SUICIDAL IDEATION / SUICIDAL IDEATION | 4 | 35 | No |
| HGIU-027-2705 | INTENTIONAL SELF-INJURY / SELF-INFLICTED SUPERFICIAL LACERATIONS | 5 | 76 | No |
| HGIU-028-2805 | SUICIDAL IDEATION / SUICIDAL IDEATION. LSS: THE PATIENT'S MOTHER CALLED THE INVESTIGATOR'S SITE ON 14-MAY-2004 TO STATE THAT HER DAUGHTER HAD BECOME SUICIDAL WITH A PLAN TO OVERDOSE ON LORAZEPAM (ATIVAN) DURING THE LAST WEEK OF MAY 2004, BUT ENDED UP TELLING HER PARENTS THE EVENING OF 09-MAY-2004. | 3 | 108 | No |
| HGIU-730-7302 | SUICIDAL IDEATION / PASSIVE SUICIDAL IDEATION | 4 | 177 | No |
| HGMF-003-0304 | EXACERBATION OF BIPOLAR ILLNESS WITH POSITIVE SUICIDAL IDEATION | 4 | 29 | No |
| HGMF-008-0805 | INTENTIONAL SELF-INJURY, CUTTING LEFT ARM | 5 | 93 | No |
| LOAY-400-4001 | PATIENT IS IN A DEPRESSIVE MOOD AROUND 10-11.05.99 AND EXPRESSES SUICIDALTHOUGHTS, SIGNIFICANTLY SLOWED MOVEMENT. | 4 | 44 | No |
| LOAY-401-4012 | SELF-INJURIOUS BEHAVIOR, SELF-INJURY | 5 | 16 | No |
| LOAY-407-4077 | SELF INJURIOUS BEHAVIOR, SELF-INFLICTING TENDENCIES | 5 | 55 | No |

| Patient ID (Study-Inv-Patient) | Brief Description of Event | Code | Days to Event | Fatal? |
|-----------------------------------|--|------|---------------------|--------|
| LOAY-407-4078 | SUICIDAL IDEATION, ACUTE SUICIDAL TENDENCIES | 4 | 4 | No |
| LOAY-413-4150 | SUICIDAL IDEATION, SUICIDAL TENDENCY | 4 | 27 | No |

10.9 Laboratory Evaluations – Mean Change from Baseline to Endpoint

Table 10.9.1 Sponsor's Table. Mean Change from Baseline to Endpoint: HGIN + HGIU Acute Database

Table 2.7.4.33. Laboratory Evaluations
 Mean Change from Baseline to Endpoint
 Acute Placebo-Controlled Combined Database

| Laboratory Evaluations | Unit | Therapy | N | Baseline | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|---|---------|---------|-----|----------|------|--------------------|------|---------------|-------------------|----------|
| | | | | Mean | Std | Mean | Std | | | |
| 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|------------------------|---------|---------|-----|----------|--------|--------------------|--------|---------------|-------------------|----------|
| | | | | Mean | Std | Mean | Std | | | |
| 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|-----------------------------|--------|---------|-----|----------|-------|--------------------|-------|---------------|-------------------|----------|
| | | | | Mean | Std | Mean | Std | | | |
| 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|---------------------------------|--------|---------|-----|----------|-------|--------------------|-------|---------------|-------------------|----------|
| | | | | Mean | Std | Mean | Std | | | |
| | | | | ----- | | ----- | | | | |
| 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 |
| | | Placebo | 87 | 1.21 | 0.25 | -0.00 | 0.25 | -0.01 | | |

| Laboratory Evaluations | Unit | Therapy | N | Baseline | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|---------------------------------|--------|---------|-----|----------|-------|--------------------|-------|---------------|-------------------|----------|
| | | | | Mean | Std | Mean | Std | | | |
| | | | | ----- | | ----- | | | | |
| 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value | **P-value |
|------------------------|--------|---------|-----|----------|-------|--------------------|-------|---------------|-------------------|----------|-----------|
| | | | | Mean | Std | Mean | Std | | | | |
| | | | | ----- | | ----- | | | | | |
| 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|---------------------------------------|---------|-----|----------|-------|--------------------|-------|---------------|-------------------|----------|
| | | | Mean | Std | Mean | Std | | | |
| 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 | | Change to Endpoint | | LSMean Change | LSMean Difference | *P-value |
|---------------------------|---------|-----|----------|-------|--------------------|------|---------------|-------------------|----------|
| | | | Mean | Std | Mean | Std | | | |
| 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, flvoxamine, 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) | 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. |

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

/s/

Cara Alfaro
4/6/2007 10:42:11 AM
PHARMACIST

Ni Aye Khin
4/18/2007 11:20:56 AM
MEDICAL OFFICER

I agree with Dr. Alfaro's recommendation that this application
be considered for non-approval; see memo to file
for additional comments.