U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 20-592 |
| **Drug Name:** | Olanzapine |
| **Indication(s):** | Schizophrenia for Adolescents |
| **Applicant:** | Eli Lilly and Company |
| **Date(s):** | December 29, 2006 |
| **Review Priority:** | Priority |
| | |
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**Keywords:** Olanzapine, Adolescent, Schizophrenia, ANCOVA, LOCF, MMRM

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies between November 2002 and May 2005 in the United States, Russia and Puerto Rico. The primary objectives of the studies were to evaluate the efficacy and safety of olanzapine compared with placebo in the treatment of the adolescents (ages 13 to 17) with schizophrenia (Study HGIN) and in the treatment of the adolescents with Mania in Bipolar I Disorder (Study HGIU). The primary efficacy measures were the change from baseline to Endpoint of the BPRS-C total score (Study HGIN) and the change from baseline to Endpoint of the YMRS total score (Study HGIU).

In the two studies, only Study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. Indeed, the difference between treatment groups only occurred in the patients who dropped out of Period II of the study.

## 1.2 Brief Overview of Clinical Studies

Two pivotal studies were submitted for the evaluation of the efficacy of olanzapine (2.5 to 20mg/day) in the treatment of adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU). The studies were conducted between November 2002 and May 2005 (26 November 2002 to 29 April 2005 for Study HGIN and 18 November 2002 to 9 May 2005 for Study HGIU) in the United States, Russia and Puerto Rico.

Study HGIN was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescent with schizophrenia, with a 6-week acute period conducted in the Unites States and Russia. The primary objective of this study was to assess the efficacy of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents (ages 13 to 17) with schizophrenia. The primary efficacy measure was the change from baseline to endpoint (up to 6 weeks double-blind treatment) in the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

Study HGIU was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescents with Mania in Bipolar I Disorder, with an acute double-blind treatment period of 3 weeks in the Unites States and Puerto Rico. The primary objective was to evaluate the efficacy and safety of olanzapine (2.5 to 20mg/day) compared with placebo in adolescents with Mania in Bipolar I Disorder. The primary efficacy measure was the change from baseline to Endpoint of the Adolescent Structured Young-Mania Rating Scale (YMRS) total score.

In Study HGIN, 99 subjects were planned in a 2:1 ratio to have 80% power at the Type I error rate of 0.05 to test a treatment group difference of 7.93, a common standard deviation estimate of 12.15. One hundred and fifteen subjects entered the study. Of these, 107 (72 to olanzapine and 35 to placebo) were randomized and 64 subjects (49 to olanzapine and 15 to placebo) completed the acute phase of the study. Seventy two percent (72%) of the patients were Caucasian and 22% were Africa-Americans. Seventy percent (70%) were male and 30% were female. All the patients were between 13 and 17 years of age (inclusive).

In Study HGIU, 130 to 200 subjects were planned in a 2:1 ratio to have 80% power at the Type I error rate of 0.05 to detect an anticipated treatment group difference of 7.00, a common standard deviation estimate of 12.50. Two hundred and three subjects entered the study. Of these, 161 (107 to olanzapine and 54 to placebo) were randomized and 120 subjects (85 in olanzapine and 35 in placebo) completed the acute phase of the study. Seventy percent (70%) of the patients were Caucasian, 16% Hispanics and 9% were Africa-Americans. More than half were male. All the patients were between 13 and 17 years of age (inclusive).

After the screening and washout period (2 days to 2 weeks for screening and washout), subjects in Study HGIN were treated for 6 weeks, and subjects in Study HGIU were treated for 3 weeks, during a double-blind phase.

### 1.3 Statistical Issues and Findings

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies. In Study HGIN, the primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. In Study HGIU, the primary efficacy measure was the change from baseline to Endpoint of the YMRS total score. The treatment efficacy was analyzed using ANCOVA with LOCF data.

In Study HGIU, the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder is supported by both the primary efficacy results using LOCF, and the results using OC and MMRM. In Study HGIN, however, the efficacy results using OC and MMRM strongly contradict that of the LOCF result. Both the OC and MMRM results are highly nonsignificant. Although LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. This is not the case in this study. On the other hand, MMRM yields quite reliable result if patient dropout mechanism depends only on the observed data, not on unobserved ones. This seems to be a more reasonable assumption. Indeed, the individual outcome profile plots indicate that most dropouts happened when there were no obvious improvements. On the other hand, both the population mean profile plot and individual profile plot suggest that the difference between treatment groups only occurred in the patients who dropped out before the Endpoint. Together, Study HGIN does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents (ages 13 to 17) with schizophrenia.

## 2. INTRODUCTION

### 2.1 Overview

In this submission, two efficacy studies were submitted for the evaluation of the efficacy and safety of olanzapine in doses from 2.5 to 20 mg/day in the treatment of adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU) (Table 2.1). In the pooled pivotal Studies HGIN and HGIU, a total of 268 subjects were randomized. Of those, 179 subjects were in the olanzapine group (2.5 to 20mg/day) and 89 subjects were in the placebo group. The numbers of subjects in these studies are given in Table 2.1.

**Table 2.1: Studies Supporting the Efficacy of Olanzapine**

| Protocol | Study Description | Study Treatment | No. of Subjects[a] |
|---|---|---|---|
| **Study HGIN** | 6-week, randomized, double-blind, placebo-controlled, multicenter, flexible dose study | Placebo | 35 |
| | | Olanzapine (flexible doses) | 72 |
| **Study HGIU** | 3-week, randomized, double-blind, placebo-controlled, multicenter, flexible dose study | Placebo | 54 |
| | | Olanzapine (flexible dose) | 107 |

a: Includes all subjects who were randomized.
Source: FDA analysis.

## 2.2 Data Sources

The Clinical Study Reports and SAS transport data sets for the studies were provided in electronic form in \\CDSESUB1\N20592\S_040\2006-10-30.

# 3. STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy

Efficacy studies were designed to evaluate the efficacy and safety of olanzapine compared with placebo in adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU). In both studies, eligible subjects were randomly assigned to receive olanzapine or placebo in a 2:1 ratio (Table 2.1). The subjects received a screening or washout period of 2 to 14 days before randomization. Following randomization, all subjects went through a 6-week (3-week for Study HGIU) double-blind acute period starting with 2.5 or 5mg/day of olanzapine or placebo given once daily. The dose was increased by 2.5 or 5 mg/day dose increments at the investigator's discretion to the maximum tolerable dose, not to exceed 20 mg/day.

In Study HGIN, the primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. The secondary measures included CGI-I, CGI-S, PANSS total score and Overt Aggressive Scale (OAS), ECGs, AIMS, CHQ and BACS. In Study HGIU, the primary efficacy measure was the change from baseline to Endpoint of the Y-MRS total score. The secondary measures included Y-MRS individual scores, CGI scale Bipolar Version Severity of Illness, CDRS-R, OAS, EPS, AIMS, CHQ and CGI-S.

Eligible subjects were from 13 to 17 years of age. Patient must have a diagnosis of schizophrenia according to DSM-IV-TR and confirmed by the K-SADS-PL in Study HGIN. Patients were diagnosed as bipolar I disorder and currently displayed an acute manic or mixed episode according to DSM-IV-TR in Study HGIU.

### 3.1.1 Baseline Demographic Characteristics

The patient baseline demographic characteristics are summarized in Tables 3.1 to 3.2 for these two studies. In Study HGIN, the majority of patients were male, Caucasian, and from the United States. The mean age of patients in the study was 16.1 years in the olanzapine treatment group and 16.3 years in the placebo group. There were 71% males and 29% females in the olanzapine group, 69% males and 31% females in the placebo group. In Study HGIU, the majority of patients were Caucasian and from the United States, with a mean age of 15.1 years in the olanzapine group and 15.4 years in the placebo group. There were 57% males and 43% females in the olanzapine group, 44% males and 56% females in the placebo group. Patient demographic characteristics were not significantly different between treatment groups at baseline.

**Table 3.1 Demographic Characteristics for Study HGIN at Baseline of Period II**

| | | Therapy | | |
|---|---|---|---|---|
| | | Olanzapine (N=72) | Placebo (N=35) | |
| Demographic Variables | Statistics/ Category | n (%) | n (%) | *P-value |
| Gender | Male | 51(70.83) | 24(68.57) | .825 |
| | Female | 21(29.17) | 11(31.43) | |
| Age | No. of Patients | 72 | 35 | |
| | Mean | 16.14 | 16.30 | .536 |
| | Median | 16.31 | 17.00 | |
| | Std. Dev. | 1.25 | 1.55 | |
| | Minimum | 13.03 | 13.06 | |
| | Maximum | 17.99 | 18.00 | |
| Origin | African Descent | 17(23.61) | 7(20.00) | .656 |
| | Caucasian | 52(72.22) | 25(71.43) | |
| | Hispanic | 2(2.78) | 1(2.86) | |
| | Other | 1(1.39) | 2(5.71) | |
| Country | America | 38(52.78) | 19(54.29) | 1.00 |
| | Russia | 34(47.22) | 16(45.71) | |

* Frequencies are analyzed using the Fisher's Exact Test

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

Source: Table HGIN.11.1 of sponsor's HGIN Study Report.

**Table 3.2 Demographic Characteristics for Study HGIU at Baseline Period II**

| Demographic Variables | Statistics/ Category | Olanzapine (N=107) n (%) | Placebo (N=54) n (%) | *P-value |
|---|---|---|---|---|
| Gender | Male | 61(57.01) | 24(44.44) | .137 |
| | Female | 46(42.99) | 30(55.56) | |
| Age | No. of Patients | 107 | 54 | |
| | Mean | 15.14 | 15.38 | .250 |
| | Median | 15.12 | 15.41 | |
| | Std. Dev. | 1.28 | 1.20 | |
| | Minimum | 13.02 | 13.07 | |
| | Maximum | 17.89 | 17.68 | |
| Origin | African Descent | 13(12.15) | 2(3.70) | .247 |
| | Caucasian | 71(66.36) | 41(75.93) | |
| | East/Southeast Asian | 0(0.0) | 1(1.85) | |
| | Hispanic | 18(16.82) | 8(14.81) | |
| | Other | 5(4.67) | 2(3.70) | |
| Country | America | 95(88.79) | 48(88.89) | 1.00 |
| | Puerto Rico | 12(11.21) | 6(11.11) | |

* Frequencies are analyzed using a Fisher's Exact Test

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

Source: Table HGIU.11.1 of sponsor's HGIN Study Report.

### 3.1.2 Baseline Disease Characteristics

Across the individual studies, the baseline disease characteristics between the treatment and placebo groups were compared.

In Study HGIN, there were no statistically significant differences between the two treatment groups on the age of onset, the number of previous schizophrenia episode, the total cumulative hospitalization in months, the length of current episode in days, the BPRS-C total score and corresponding subtotal scores.

In Study HGIU, The treatment groups differed considerably at baseline on several illness characteristics. Patients in the placebo group had greater numbers of previous manic, depressive, and mixed episodes. Patients in the olanzapine treatment group had much higher baseline scores on the CGI Severity of Depression scale. In addition, the treatment groups differed on several subscales of the CHQ at baseline. Finally, considerably more patients in the olanzapine treatment group reported a paternal history of psychosis and a history of psychiatric hospitalization at baseline. These are depicted in Table 3.3. The different Quality-of-Life scores at baseline in CHQ are given by the sponsor in Table HGIU.11.9 in the Clinical Study Report. A more specific assessment of these differences will be made by the medical officer.

**Table 3.3 Patient Differences in Illness Characteristics and Family History at Baseline in Study HGIU**

| Illness Characteristics | Placebo | Olanzapine | P-value |
|---|---|---|---|
| | (N=54) | (N=106) | |
| **No. Prev. Mania Episode** | 4.43 (8.95)* | 2.07 (4.97) | 0.048 |
| | (N=46) | (N=92) | |
| **No. Prev. Depression Episodes** | 3.98 (8.26) | 1.60 (2.84) | 0.014 |
| | (N=50) | (N=92) | |
| **No. of Prev. Mixed Episodes** | 3.85 (9.40) | 1.19 (3.65) | 0.027 |
| | (N=46) | (N=81) | |
| **CGI Severity Depression** | 2.65 (1.60) | 3.14 (1.57) | 0.043 |
| | N=54 | (N=107) | |
| **Paternal History of Psychosis-Fahter** | 0/51/3† | 8/78/20 | 0.025 |
| | (N=54) | (N=106) | |
| **Paternal History of Hospitalization** | 9/45‡ | 34/72 | 0.040 |
| | (N=54) | (N=106) | |

*Standard Deviation. †Yes/No/Unknown. ‡Yes/No.

Source: Tables HGIU.11.2, HGIU.11.6 in Clinical Study Report.

### 3.1.3 Patient Discontinuation

In Study HGIN, 107 subjects were randomized and 63 (60%) subjects completed the 3-week double-blind phase of the study (Table 3.4), including 49 (32%) subjects from the olanzapine group and 15 (43%) from the placebo group. Lack of efficacy was the most common reason for early termination in both groups. But there was a dramatic difference, which was also statistically significant in nominal sense, between the two treatment groups. In the placebo group, eighteen (51%) patients dropped because of lack of efficacy and the corresponding number for the olanzapine group was 10 (14%).

In Study HGIU, 161 subjects were randomized and 120 (74.5%) completed the 3-week double-blind phase, as shown in Table 3.4. The most common reason for the early withdrawal in both treatment groups was the Lack of Efficacy which had a total of 28 subjects (17.4%). Sixteen (30%) patients dropped out of study because of lack of efficacy in the placebo group and the corresponding number in the olanzapine group was 12 (12%). The difference between the two treatment groups is highly statistically significant in nominal sense (p-value = 0.007).

**Table 3.4 Number (%) of Subjects Who Discontinued Treatment During the Double-Blind Period by Primary Reason for Withdrawal in Studies HGIN and HGIU**

| | Placebo | Olanzapine | Overall |
|---|---|---|---|
| **Study HGIN** | (N=35) | (N=72) | (N=107) |
| **Total withdrawal** | 20 (57.1%) | 23 (31.9%) | 43 (40.2%) |
| **Reason for Withdrawal** | | | |
| Adverse event | 0 | 5 (6.9) | 5 (4.7) |
| Lack of efficacy | 18 (51.4) | 10 (13.9) | 28 (26.2) |
| Patient decision/ Personal conflict | 1 (2.9) | 4 (5.6) | 5 (4.7) |
| Noncompliance | 1 (2.9) | 2 (2.8) | 3 (2.8) |
| Sponsor decision | 0 | 1 (1.4) | 1 (0.9) |
| Lost to follow-up | 0 | 1 (1.4) | 1 (0.9) |
| **Study HGIU** | (N=54) | (N=107) | (N=161) |
| **Total withdrawal** | 19 (35.2%) | 22 (20.1%) | 41 (25.5%) |
| **Reason for Withdrawal** | | | |
| Adverse event | 1 (1.9) | 3 (2.8) | 4 (2.5) |
| Lack of efficacy | 16 (29.6) | 12 (11.2) | 28 (17.4) |
| Patient decision/Personal conflict | 1 (1.9) | 4 (3.7) | 5 (3.1) |
| Non-compliance | 1 (1.9) | 0 | 1 (0.6) |
| Physician decision | 0 | 1 (0.9) | 1 (0.6) |
| Other | 0 | 2 (1.9) | 2 (1.2) |

Source: Tables HGIN.10.1 and HGIU.10.1 – Results in Clinical Study Report.

### 3.1.4 Statistical Issues and Results

According to the protocol, efficacy analyses were performed on an intent-to-treat (ITT) basis. An ITT analysis defines the treatment groups as those to which patients were assigned by random allocation, even if a patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. For each efficacy variable, the analysis included all randomized patients with baseline and post baseline observations. Using LOCF for missing observations, only patients with a baseline and a post baseline measure were to be included in the analysis. All total scores from rating scales and subscales were derived from individual items. If any of the individual items were missing, the total score was treated as missing.

According to the protocol, the null hypothesis for primary analysis was that there was no difference between treatment groups in the mean change from baseline to Endpoint in the BPRS-C total score for Study HGIN (the YMRS total score for Study HGIU). For efficacy analyses, baseline was defined as the

last observation prior to the end of Study Period II of the study (the period for efficacy study) and Endpoint was defined as the last observation within the period. This was analyzed using the ANCOVA model which included baseline score as covariate, treatment and country as factors.

**Interim Analyses:** According to the protocol, an interim analysis might be conducted after approximately half of the required patients finished the double-blind acute therapy phase of the study, regardless of whether they completed the 6-week double-blind therapy or discontinued from the double-blind therapy. This interim analysis was planned with the intent to terminate the double-blind phase if overwhelming efficacy of olanzapine was shown. If enrollment was faster than initially anticipated, the sponsor might elect not to conduct the interim analysis. Statistical evidence of overwhelming efficacy was defined to be a statistically significant difference between the placebo and olanzapine group in the change from baseline to Endpoint of the BPRS-C total score, consistent with the primary efficacy analysis, at the $\alpha$=.0294 level. In the final analysis, the treatment comparison on the BPRS-C total score would also be tested at $\alpha$=.0294 level. This adjustment followed the methodology described in Pocock (1977).

## STUDY HGIN

The protocol for this study was approved by the sponsor on 15 July 2002 and was amended on: 17 October 2002; 03 February 2004; and 08 July 2004. According to the sponsor, the statistical analysis plan (SAP), which supersedes the statistical plans described in the protocol, was approved on 10 June 2005, the same day the reporting database was validated and subsequently locked for analysis. The sponsor made substantial changes on Version C of the protocol. The SAP was not submitted to FDA for review until 21 March 2006, upon the request of the agency. Some changes were made to the planned analyses outlined in the Final SAP after the unblinding of the database. These additional analyses did not alter the interpretation of the primary efficacy analysis of this study (See 9.8.2.2.1 of the Clinical Study Report).

Based on the data set of Study HGIN, the normality test for the primary endpoint gives a p-value of 0.76 using the Shapiro-Wilk test, density plot also shows a symmetric and single mode distribution so the normality assumption is not seriously violated in my opinion. Therefore, no nonparametric method is used on the efficacy test. The analysis results are presented in Table 3.7.

According to the sponsor, the interim analysis was not conducted.

Using the data sets provided by the sponsor, the reviewer confirmed the efficacy results on LOCF data set. The ANCOVA with the primary efficacy measure gave similar significance results as reported in the Clinical Study Report. The homoscedasticity was assessed through the plot of residuals against the predicted values from ANCOVA model on the primary efficacy measure. No heteroscedasticity was found from the plots.

Given the high percentages of patient dropout as indicated in Table 3.4, the reliability and interpretability of the efficacy results becomes an issue. In general, LOCF procedure is reliable only when the mean outcome measure is stable over the whole study period. This is obviously not the case as the mean BPRS-C total score decreased 24.5 points from a baseline mean of 56 for those stayed to the Endpoint of Study Period II. Alternatively, the MMRM method gives reliable efficacy results if the patient dropouts were non-informative, with dropouts only depending on the observed outcome values, not on the unobserved values. This seems to be a reasonable assumption in this study.

**Table 3.7: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Studies HGIN --- ITT Population**

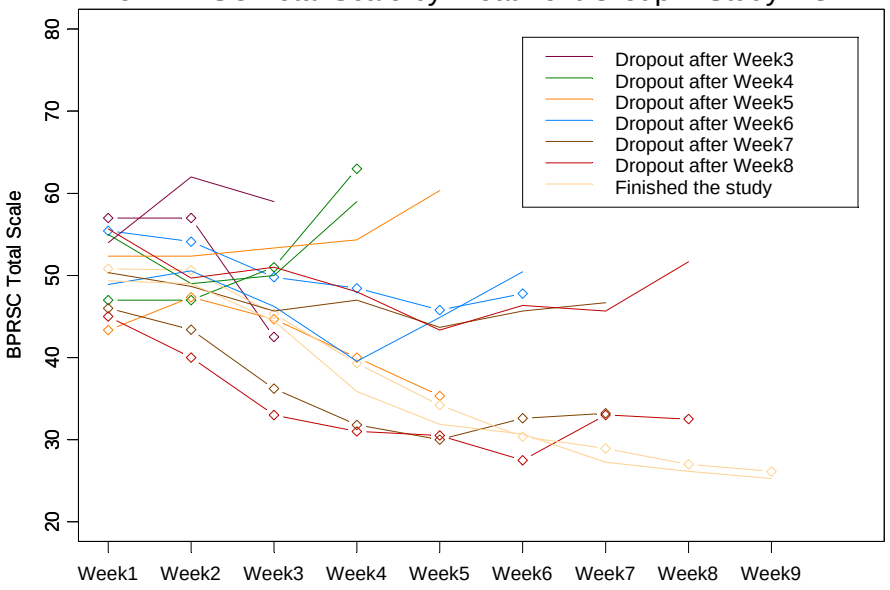
| | Placebo | Olanzapine |
|---|---|---|
| **Study HGIN** | (N=35) | (N=72) |
| **N (Analysis population)** | 35 | 72 |
| **N (BPRS-C Total Score)** | 35 | 72 |
| Baseline Mean | 50.1 | 50.3 |
| Median change from baseline | -9.3 | -19.4 |
| **ANCOVA Analysis (LOCF)** | | |
| LS Mean change from baseline (SE) [a] | -9.1 (2.73) | -19.3 (1.91) |
| Difference between LS Means and C.I.[a] | -10.1 (-16.7, -3.5) | |
| P-value [a] | 0.003 | |
| **MMRM Analysis** | | |
| LS Mean change from baseline (SE) [b] | -23.5 (3.06) | -24.7 (1.70) |
| Difference between LS Means and C.I.[b] | -1.25 (-8.11, 5.61) | |
| P-value [b] | 0.72 | |
| **OC Analysis** | | |
| **N (BPRS-C Total Score)** | 15 | 50 |
| LS Mean change from baseline (SE) [c] | -24.1 (3.35) | -24.4 (1.82) |
| Difference between LS Means and C.I.[c] | -0.25 (-7.9, 7.4) | |
| P-value [b] | 0.95 | |

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Reviewer.

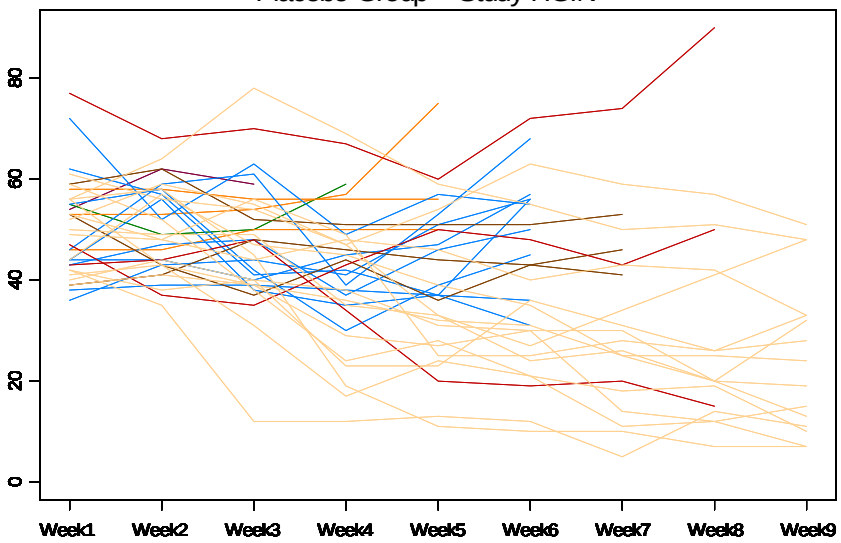
Using the data sets provided by the sponsor, the OC and MMRM analyses yield statistically **very non-significant** efficacy results for the primary outcomes. OC analysis yields **a p-value of 0.95** while MMRM analysis yields **a p-value of 0.72**. These results contradict that of the LOCF analysis on the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. To see why this is the case, this reviewer plotted both the population mean profiles and individual profiles for both treatment groups. These are depicted in Figures 3.1 to 3.3.

Figure 3.1: Population Mean Profiles by Dropout Time
for BPRSC Total Scale by Treatment Group -- Study HGIN



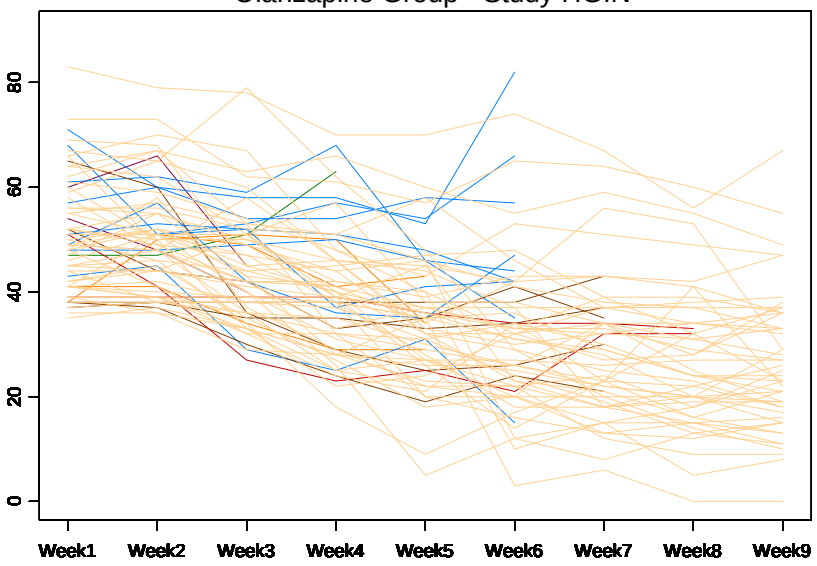

Source: Reviewer

Figure 3.2: Patient Profiles of BPRSC Total Score
Placebo Group -- Study HGIN




Source: Reviewer

Figure 3.3: Patient Profiles of BPRSC Total Score
Olanzapine Group - Study HGIN




Source: Reviewer

These figures clearly indicate that there appears to be no difference between the treatment groups among those who stayed to the end of Period II of the study. The difference appears only among those who dropped out before the end of Period II. Among those patients, olanzapine seems to have improved patient BPRS-C total score over placebo. In fact, Figures 3.2 and 3.3 seem to indicate that olanzapine reduced the BPRS-C total score in both the dropout group and the non-dropouts group while placebo reduced the score only in the non-dropouts group, not in the dropouts group.

This phenomenon was observed in both US and Russia.

## STUDY HGIU:

The protocol for this study was approved by the sponsor on 15 July 2002. According to the sponsor, the statistical analysis plan (SAP) addressed the planned statistical analyses prior to unblinding, and was approved prior to the unblinding of the reporting database. The sponsor stated that the SAP was approved on 21 June 2005. The reporting database was validated and subsequently locked for analysis on 24 June 2005. It was not submitted to the Agency for review until 26 March 2006.

Of the 161 randomized patients, 159 were analyzed for the primary efficacy measure. Two of the patients randomized to receive olanzapine did not have a post baseline observation that could be used for the primary efficacy analysis. In addition, the primary analysis, LOCF mean change from baseline to endpoint in the YMRS total score, was conducted without data from patients in Site 021. The efficacy result in Table 3.8 was derived using the data set provided by the sponsor with Site 021 included. Similar results were obtained when Site 021 was excluded.

**Table 3.8: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Study HGIU --- ITT Population**

| | Placebo | Olanzapine |
|---|---|---|
| **Study HGIU** | (N=54) | (N=107) |
| **N (Analysis population)** | 54 | 107 |
| **N (YMS-R Total Score) ITT** | 54 | 105 |
| Baseline Mean | 32.0 | 33.1 |
| Median change from baseline | -6.5 | -15.0 |
| **ANCOVA Analysis (LOCF)** | | |
| LS Mean change from baseline (SE) [a] | -10.0 (1.53) | -17.7 (1.27) |
| Difference between LS Means and C.I.[a] | -7.7 (-10.7, -4.6) | |
| P-value [a] | <0.0001 | |
| **MMRM Analysis** | | |
| LS Mean change from baseline (SE) [b] | -12.6 (1.28) | -17.8 (0.87) |
| Difference between LS Means and C.I.[b] | -5.6 (-8.7, -2.5) | |
| P-value [b] | 0.0004 | |
| **OC Analysis** | | |
| **N (BPRS-C Total Score)** | 37 | 88 |
| LS Mean change from baseline (SE) [c] | -13.4 (1.70) | -19.1 (1.31) |
| Difference between LS Means and C.I.[c] | -5.7 (-9.2, -2.3) | |
| P-value [b] | 0.0013 | |

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Reviewer.

Using the data sets provided by the sponsor, the reviewer confirmed the efficacy results in the Clinical Study Report. The efficacy result in the primary analysis was highly statistically significant. The OC and MMRM analyses were conducted by the reviewer and they yielded similar results as that of ANCOVA. These efficacy results are depicted in Table 3.8. These results all support the effectiveness of olanzapine in reducing the YMRS total score in adolescents with schizophrenia compared to placebo.

The treatment-by-country interaction for the primary efficacy measure was explored using the ANCOVA model, including baseline, country, treatment, and treatment-by-country interaction. The corresponding estimated treatment effect was -6.8, which was close to that in Table 3.8. But the p-value for treatment difference became 0.006. The interaction was not statistically significant. There were a total of 143 patients in US and 18 patients in Puerto Rico. In addition to including country as a factor in the efficacy model, statistical comparisons were made between treatment groups on the primary efficacy parameter in US alone and it yielded similar result.

In conclusion, the primary efficacy results using LOCF data set in both Studies HGIN and HGIU support the effectiveness of olanzapine in the treatment of schizophrenia in adolescent patients. However, only the

results in Study HGIU were supported by the results using OC data and MMRM procedure. The efficacy results using OC data set and MMRM strongly contradicted that using LOCF data set in Study HGIN. The OC and MMRM results were both highly nonsignificant. The population mean profiles and individual profiles suggest that the difference of the treatment effect only occurred among the patients who dropped out of the Period II of the study.

## 3.2 Evaluation of Safety

See medical review for detail.

# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Race and Age

Using LOCF data, subgroup analyses were performed on the primary efficacy measure, for age (younger than 15 years versus 15 years and older), gender and origin (Caucasian versus non-Caucasian) provided there were at least 10 patients in each treatment group. All subgroup analyses were considered exploratory. The treatment-by-subgroup interaction was tested using an ANCOVA model including the terms for baseline, treatment, country, subgroup, and the treatment-by-subgroup interaction. The treatment-by-subgroup interaction was tested to find out whether treatment differences in the mean primary efficacy measure were similar for each subgroup. In addition, the primary measure was analyzed for each country using the ANCOVA model including terms for baseline and treatment.

In both Studies HGIN and HGIU, neither sex nor the interaction between sex and treatment group was statistically significant at the nominal significance level of 0.05 in the ANCOVA analysis. The treatment effects and their significance levels stayed similar whether sex or the interaction between sex and treatment group was adjusted. However, Table 4.1 shows that the improvement on the primary endpoint was numerically larger for male than for female patients.

In both Studies HGIN and HGIU, neither age group (younger than 15 years versus 15 years and older) nor the interaction between age group and treatment was statistically significant at the nominal significance level of 0.05 in the ANCOVA analysis. The treatment effects and their significance levels were similar whether age group or the interaction between age group and treatment was adjusted. However, Table 4.2 shows that the improvement on the primary endpoint was numerically larger for older patients (15 years and older) than for younger ones.

**Table 4.1 Treatment Effect by Sex on the effect size in Studies HGIN and HGIU**

**(LOCF Analysis)**

| Study | Placebo | Olanzapine |
|---|---|---|
| **Study HGIN** | | |
| **Male** | N=24 | N=51 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -8.8 (17.5) | -19.7 (16.6) |
| **Female** | N=11 | N=21 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -10.5 (21.9) | -18.7 (12.8) |
| **Study HGIU** | | |
| **Male** | 24 | 60 |
| **Mean Change From Baseline of YMRS Total (SD)** | -5.8 (9.35) | -16.8 (10.0) |
| **Female** | 30 | 45 |
| **Mean Change From Baseline of YMRS Total (SD)** | -9.3 (9.3) | -14.7 (10.1) |

Source: FDA analysis.

**Table 4.2 Treatment Effect by Age Group on the effect size in Studies HGIN and HGIU**

**(LOCF Analysis)**

| Study | Placebo | Olanzapine |
|---|---|---|
| **Study HGIN** | | |
| **Age below 15** | N=7 | N=15 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -12.6 (20.4) | -17.3 (17.8) |
| **Age 15 and Above** | N=28 | N=57 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -8.5 (18.6) | -20.0 (15.0) |
| **Study HGIU** | | |
| **Age below 15** | 20 | 49 |
| **Mean Change From Baseline of YMRS Total (SD)** | -9.5 (11.0) | -14.6 (10.2) |
| **Age 15 and Above** | 34 | 56 |
| **Mean Change From Baseline of YMRS Total (SD)** | -6.7 (8.4) | -17.0 (9.9) |

Source: FDA analysis.

**Table 4.3 Treatment Effect by Country on the effect size in Study HGIN**

**(LOCF Analysis)**

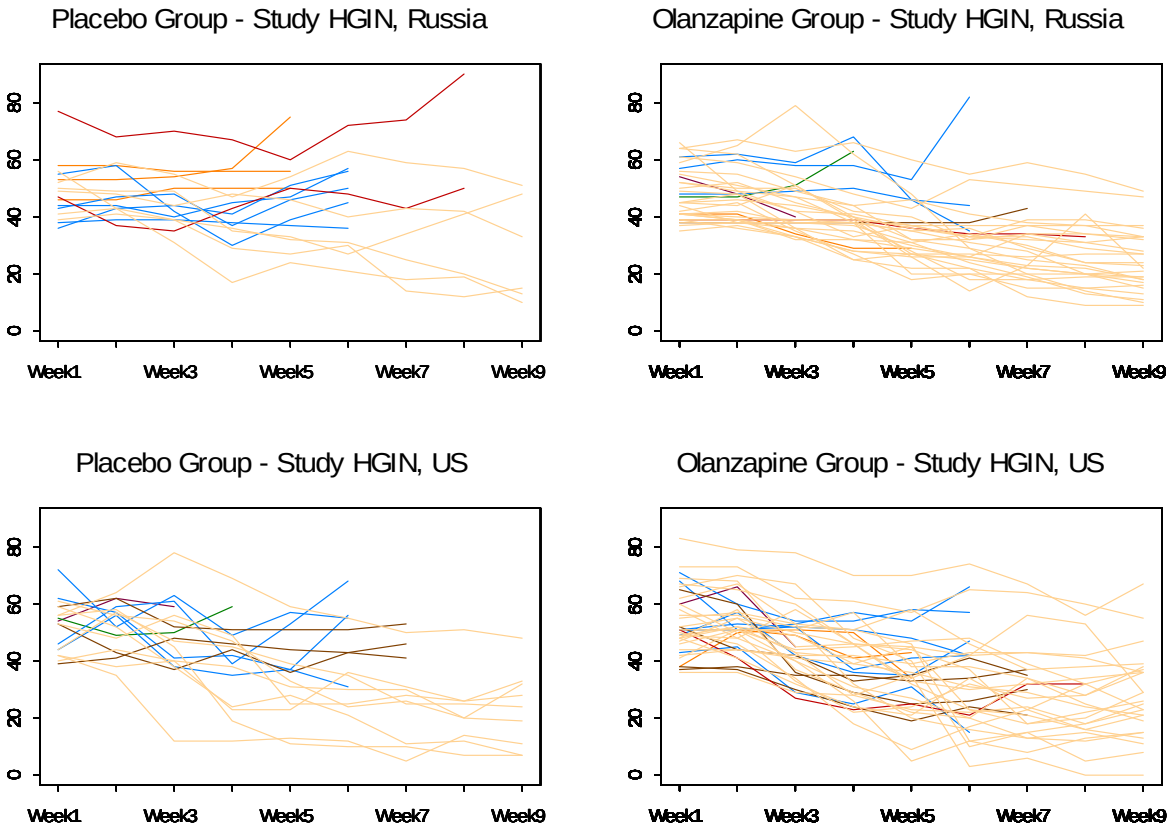
| Study | Placebo | Olanzapine |
|---|---|---|
| **Study HGIN** | | |
| **USA** | N=19 | N=38 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -15.0 (18.3) | -21.2 (16.3) |
| **Russia** | N=16 | N=34 |
| **Mean Change From Baseline of BPRS-C Total (SD)** | -2.6 (17.4) | -17.4 (14.5) |

Source: FDA analysis.

To explore the treatment effect in different countries, we noted that there were about 89% patients in US and only 11% patients in Puerto Rico in Study HGIU, so efficacy analysis was considered in US alone. In Study HGIN, country was not statistically significant at the nominal level of 0.05 but the interaction between country and treatment group yielded a p-value of 0.15 in the ANCOVA analysis. However, Table 4.3 suggests that treatment effect of olanzapine over placebo occurred mainly in Russian rather than in US patients. From Figure 4.1, it appears that the Russian patients in placebo group received very little improvement. Of the 16 patients in the placebo group, 10 dropout patients hardly received any

improvement by the time when they dropped out. The remaining 6 received very limited improvement. Of the 34 patients in the olanzapine group, only 8 dropped out. The improvement in this group appeared to be in line with that of the US patients.

Figure 4.1 Patient Profiles for BPRSC Total Score, by Country




Source: Reviewer.

## 4.2 Other Special/Subgroup Populations

Not available.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

Studies HGIN and HGIU were 6-week (Study HGIU was 3-week), Phase IV, multicenter, randomized, double blind, placebo-controlled, flexible-dose studies with treatment arms of olanzapine and placebo for adolescent outpatients in the United States, Russia and Puerto Rico. The primary objective for Study

HGIN was to assess the efficacy and safety of olanzapine (2.5 to 20 mg/day) in the treatment of adolescents (ages 13 to 17) with schizophrenia. The primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. In Study HGIU, the primary objective was to evaluate the efficacy and safety of olanzapine (2.5 to 20mg/day) in the treatment of adolescents with Mania in Bipolar I Disorder. The primary efficacy for the study was the YMRS total score. In both studies, the primary efficacy analyses were performed on the primary efficacy measure using the ANCOVA procedure with LOCF data.

In Study HGIU, the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder is supported by both the primary efficacy results using LOCF, and the sensitivity analysis results using OC and MMRM. In Study HGIN, however, the efficacy results using OC and MMRM strongly contradict that of the LOCF result. Both the OC and MMRM results are highly nonsignificant. Although LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. This does not seem to be the case in this study. On the other hand, MMRM gives quite reliable result if patient dropout mechanism depends only on the observed data, not on unobserved ones. This seems to be a more reasonable assumption in this study. Indeed, the individual outcome profile plots suggest that most dropouts happened when there were no obvious improvements. On the other hand, both the population mean profile plot and individual profile plot suggest that the difference between treatment groups only occurred in the patients who dropped out before the Endpoint. Together, Study HGIN does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents (ages 13 to 17) with schizophrenia.

## 5.2 Conclusions and Recommendations

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies between November 2002 and May 2005 in the United States, Russia and Puerto Rico. The primary objective of Study HGIN was to evaluate the efficacy and safety of olanzapine in the treatment of the adolescents (ages 13 to 17) with schizophrenia. The primary objective of Study HGIU was to evaluate the efficacy and safety of olanzapine in the adolescents with Mania in Bipolar I Disorder. The primary efficacy measure for Study HGIN was the change from baseline to Endpoint of the BPRS-C total score and the primary efficacy measure for Study HGIU was the change from baseline to Endpoint of the YMRS total score.

In the two studies, only Study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. Indeed, the difference between treatment groups only occurred in the patients who dropped out of Period II of the study.

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