

Agency Background Package

Psychopharmacologic Drugs Advisory Committee Meeting

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FEBRUARY 6, 2008

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought (NDA) 22-173 ZYPREXA ADHERA (olanzapine pamoate depot) long acting intramuscular (IM) injection to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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

DATE: January 7, 2008

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

SUBJECT: February 6, 2008 Meeting of the Psychopharmacologic Drugs Advisory
Committee (PDAC)

TO: Members, PDAC

This one-day PDAC meeting will focus on NDA 22-173 for a Zyprexa Olanzapine Long Acting Injection, a depot formulation of olanzapine intended for administration every 2-4 weeks. This is a pamoate formulation of olanzapine and has been referred to as OP Depot by the sponsor.

The efficacy of OP Depot has been established in studies HGJZ and HGKA.

-Study HGJZ was an 8-week study involving acutely ill patients with schizophrenia. This was a double-blind trial in which patients were randomized in a 1:1:1:1 ratio to 3 fixed doses of OP Depot (300 mg q 2 weeks; 405 mg q 4 weeks; 210 mg q 2 weeks) or placebo. No oral antipsychotic supplementation was permitted. The primary endpoint was change from baseline to endpoint in PANSS total score, and all 3 active drug groups were statistically significantly superior to placebo.

-Study HGKA was a 24-week maintenance study in stable schizophrenic patients who were initially switched from whatever antipsychotic drug they were stable on to oral olanzapine monotherapy. After a minimum of 4 weeks of continued stability on oral olanzapine, patients were randomized in a 2:1:1:1:2 ratio to OP Depot (405 mg q 4 weeks; 300 mg q 2 weeks; 150 mg q 2 weeks; 45 mg q 4 weeks) or oral olanzapine (10, 15, or 20 mg/day). One objective was to show noninferiority of OP Depot to oral olanzapine monotherapy and a second was to show superiority of the 3 higher dose OP Depot arms to the 45 mg q 2-week arm on time to worsening of positive symptoms. FDA has focused on the superiority hypothesis. All 3 of the higher dose OP Depot arms were statistically significantly superior to the 45 mg q 2-week arm.

FDA agrees that the sponsor has shown that OP Depot is effective in both the acute and maintenance treatment of schizophrenia. We also agree that the usual profile of adverse events with OP Depot is comparable to that seen with oral olanzapine. Our concern about this product has focused on an adverse event that appears to be unique for this formulation of olanzapine, i.e., what the sponsor has referred to as “inadvertent intravascular (IAIV) injection events.” These are instances of sometimes profound sedation occurring shortly after an injection (generally 1 to 3 hours). These are believed to have resulted from rapid release of olanzapine into the systemic circulation, and this view is supported by the limited pk data available suggesting that patients

having these events had unusually high plasma concentrations of olanzapine. These events have occurred in 24 out of 1915 patients exposed to OP Depot (i.e., roughly 1.2% of patients).

The Division's presentation for this meeting will be by the clinical reviewer for this NDA, Jing Zhang, M.D., PhD. Her focus will be on the safety findings for this program, primarily on these instances of profound sedation. The Division's background package includes Dr. Zhang's review of the sponsor's NDA and also a statistical review of the efficacy data by George Kordzakhia, PhD.

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

After you have heard all the findings and arguments, we will ask you, first of all, to discuss and comment on several questions pertinent to the safety of OP Depot. Then we will ask you to vote on two questions.

The questions for discussion and comment are as follows:

1. What are the public health consequences of a depot antipsychotic that leads unpredictably to profound sedation in 1% or more of patients exposed to this product?
2. If OP Depot were to be approved and marketed, what risk management procedures would be necessary, including labeling advice, to ensure the safe use of this product? For example, would the labeling changes include a second line status and a black box warning?

The questions for a vote by the committee are as follows:

1. Has OP Depot been shown to be effective for the treatment of schizophrenia?
2. Has OP Depot been shown to be acceptably safe for the treatment of schizophrenia?

cc:

HFD-130/TLaughren/MMathis/GZornberg/JZhang/KKiedrow

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/s/

Thomas Laughren
1/8/2008 08:38:32 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA 22-173
Submission Number 000
Submission Code N

Letter Date April 27, 2007
Stamp Date April 30, 2007
PDUFA Goal Date February 29, 2008

Reviewer Name Jing Zhang, MD, PhD
Review Completion Date January 4, 2008

Established Name Olanzapine Pamoate Depot
(Proposed) Trade Name Pending
Therapeutic Class Atypical Antipsychotic
Applicant Eli Lilly

Priority Designation S

Formulation Intramuscular Injection
Dosing Regimen 210 mg/3 ml, 300 mg/3 ml, and
405 mg/3 ml
Indication Schizophrenia
Intended Population Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The information from this clinical review will be presented to the Psychopharmacologic Drug Advisory Committee (PDAC) on 6 February 2008 because of a serious safety concern regarding the excessive sedation events that occurred in 25 cases of 24 patients during olanzapine depot clinical trials. A total 1915 patients were administered olanzapine depot in these trials. At this time point, no regulatory action is recommended.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

A risk management activity plan is to be determined following the PDAC meeting. An addendum to this NDA review will be filed after the meeting.

1.2.2 Required Phase 4 Commitments

Phase 4 commitment requirement will be determined.

1.2.3 Other Phase 4 Requests

Other Phase 4 requests are to be determined.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The efficacy and safety of olanzapine pamoate depot (OP Depot) in the treatment of schizophrenia were evaluated by Lilly in a total of 8 studies (see Table 1):

- Controlled studies: One double-blind, placebo-controlled, fixed-dose study (HGJZ) and one double-blind, oral olanzapine-controlled, fixed-dose study (HGKA) were conducted to evaluate the efficacy and safety of OP Depot.
- Open-label studies: Six open-label studies were conducted at varying phases of clinical development for OP Depot.

Table 1 Overview of Studies in the Clinical Plan of Development for OP Depot

Study ID/ Study Status	Study Length	# Enroll/ Rand	Dose	Study Design and Objective
HGJZ/ Concluded	8 weeks	404 Rand	OP Depot: 210 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks Placebo	Double-blind, placebo-controlled, fixed-dose PK, efficacy superiority, and safety study in patients with schizophrenia.
HGKA/ Concluded	24 weeks	1065 Rand	OP Depot: 45 mg/4 weeks (reference dose), 405 mg/4 weeks, 150 mg/2 weeks, 300 mg/2 weeks Oral OLZ: 10, 15, 20 mg/day	Double-blind, olanzapine-controlled, fixed-dose study of noninferiority of maintenance of efficacy, superiority of 3 therapeutic OP Depot doses compared to reference dose, safety, and PK in patients with schizophrenia.
HGKB/ Ongoing	Up to 4 years	931 Enroll (725 ongoing as of Jan 2007)	OP Depot: Flexible doses ranging from 45 mg to 405 mg given at 2-, 3-, or 4-week intervals	Long-term, open-label safety, effectiveness, and PK (subset) study in patients with schizophrenia or schizoaffective disorder who previously completed an OP Depot clinical trial (HGJZ, HGKA, or LOBS).
LOBE/ Concluded	Up to 24 weeks	282 Enroll	OP Depot: single dose 50 to 450 mg OP Depot: multi-dose 100 to 405 mg/2 to 4 wks	Open-label, single- and multiple-dose study of safety and PK in symptom-stabilized patients with schizophrenia.
LOBO/ Concluded	8 weeks	9 Enroll	OP Depot: 4 injections of 300 mg/2 wks Oral OLZ: 5 to 20 mg (prior to enrollment)	Open-label study of safety, PK, and OP Depot metabolites in patients with schizophrenia or schizoaffective disorder.
LOBS/ Concluded	Approx 7 weeks	134 Rand	OP Depot: single-dose 405 mg Oral OLZ: 5, 10, 15, 20 mg daily OLZ RAIM: single-dose 5 mg	Oral lead-in phase followed by a fixed-sequence, parallel-design, open-label study of safety, PSD, and PQBP of OP Depot compared with oral OLZ or RAIM in stable patients with schizophrenia or schizoaffective disorder.
HGJW/ Concluded	24 weeks	14 Enroll	OP Depot: 300 mg/4 weeks	Open-label, one-arm, PET study of receptor occupancy, safety, and efficacy in patients with schizophrenia.
HGLQ/ Ongoing	Up to 2 years	524 Rand	OP Depot: 150 to 405 mg/4 weeks Oral OLZ: 5 to 20 mg/day	Randomized, open-label study of safety, effectiveness, and health outcomes in treatment with OP Depot or oral OLZ in patients with schizophrenia at risk for relapse.

In this submission, Lilly submitted completed Clinical Study Reports (CSR) from two controlled studies (HGJZ and HGKA) and the CSR & a report of pharmacokinetic analysis from an ongoing uncontrolled clinical study (HGKB). Integrated safety data obtained from all 8 OP Depot clinical trials were included in the Clinical Overview section.

The efficacy of OP Depot in the treatment of schizophrenia is demonstrated by efficacy data obtained from an 8-week, randomized, double-blind, placebo-controlled study (HGJZ) and a 24-week, double-blind, randomized, maintenance study (HGKA).

The safety evaluation of OP Depot in this review is primarily based on safety data obtained from two controlled studies (HGJZ and HGKA). The Overall Integrated Safety Database was used to detect pattern changes of common adverse events (AEs), unexpected or serious adverse events (SAEs), or deaths and AEs occurring with long-term exposure.

1.3.2 Efficacy

In the short-term (8 weeks) acute efficacy and safety study (HGJZ), the three OP depot treatment groups showed superior improvement over placebo in reducing the PANSS Total Score from baseline to end point starting at week 1 and continuing through the end of the study.

In the long-term (24 weeks) maintenance study (HGKA), the 3 higher dose OP Depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups showed positive maintenance of effect over 24 weeks for stabilized patients with schizophrenia.

1.3.3 Safety

The safety evaluation of OP Depot demonstrated that the safety profile is similar to that of oral olanzapine for most parameters that were measured, with the exception of injection-related adverse events and the excessive sedation events that Lilly named as inadvertent intravascular (IAIV) injection events.

As of 30 November 2007, a total of 25 of these excessive sedation events have been reported in 24 patients. Since the causality of the events has not been established, we prefer to use the descriptive term—excessive sedation to connote the events. From this point forward in my review, the term of excessive sedation will be used to replace the term of IAIV injection events.

The excessive sedation events raised a serious safety concern because of the severity of sedation, combined with unpredictability and a relatively high incidence—0.07% of injection and 1.3% of patients (details can be found in section 7.1.12, Special Safety Studies).

1.3.4 Dosing Regimen and Administration

Both the short-term (HGJZ) and long-term (HGKA) controlled studies were fixed dose studies. In Study HGJZ, the dose regimen was OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 210 mg/2

weeks and placebo. In Study HGKA, the dose regimen was OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 150 mg/2 weeks, 45 mg/4 weeks and oral olanzapine (flexible doses 10 to 20 mg/d). All OP Depot injections were administered by gluteal intramuscular injection.

1.3.5 Drug-Drug Interactions

The existing olanzapine label addresses safety outcomes related to potential drug-drug interactions. There have been no new data generated on this topic from this submission.

1.3.6 Special Populations

The existing olanzapine label addresses safety outcomes related to pediatric population, geriatric population, nursing mothers and pregnant women. There have been no new data generated on these topics with respect to the OP Depot in this submission that have not already been addressed in current olanzapine labeling.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Oral olanzapine, an atypical antipsychotic, is a potent serotonin 5-HT_{2A/2C}, dopamine D₁₋₄ antagonist with affinity for muscarinic receptors. Its mechanism of action is unknown; however, it has been proposed that olanzapine's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT₂) antagonism. Oral olanzapine (Zyprexa) was initially approved by FDA in 1996. Table 2 lists other formulations of olanzapine and their respective approval dates.

Table 2 FDA Approval Dates for Olanzapine Formulations

Approval Month and Year	Formulation Name	Indication
September 1996	Zyprexa (Oral olanzapine tablets)	Schizophrenia, acute manic or mixed episodes of bipolar I disorder
April 2000	Zyprexa Zydis (Oral olanzapine dispersible tablets)	Schizophrenia, acute manic or mixed episodes of bipolar I disorder
March 2004	Zyprexa IntraMuscular (Rapid-acting intramuscular [RAIM] injection formulation)	Agitation associated with schizophrenia and bipolar I mania

2.2 Currently Available Treatment for Indications

Numerous typical and atypical antipsychotics have been approved by FDA for the treatment of schizophrenia in the USA. Compared with the oral preparations, only a few long-acting antipsychotic injections are available in the USA: two typical antipsychotics—haloperidol decanoate and fluphenazine decanoate, and one atypical antipsychotic—Risperidal Consta.

2.3 Availability of Proposed Active Ingredient in the United States

Olanzapine is an approved drug in the United States.

2.4 Important Issues With Pharmacologically Related Products

The safety concerns regarding olanzapine related metabolic syndrome and increased risk of diabetes are under review by our safety team. At this point, no final conclusions regarding these issues have been reached.

2.5 Presubmission Regulatory Activity

26 August 1999	Lilly met with FDA to discuss the required preclinical, pharmacokinetic, and clinical program to support the registration of OP Depot.
14 September 1999	Lilly met with FDA to discuss the manufacturing plans to support the registration and commercial production of OP Depot.
08 November 2000	Lilly met with FDA to discuss the manufacturing plans to support the registration and commercial production of OP Depot.
31 July 2001	Lilly met with FDA to discuss completed preclinical studies and planned clinical studies for the OP Depot.
26 June 2002	FDA issued a written response to Lilly's briefing document dated 11 June 2002 regarding CM&C/Biopharmaceutics issues.
22 July 2003	Lilly met with FDA regarding CMC/Biopharmaceutics issues.
27 April 2004	Lilly met with FDA to discuss their in-vitro dissolution method development plan.
09 September 2005	Lilly met with FDA to discuss CMC/Biopharmaceutics issues.
17 July 2006	Lilly met with FDA (Pre-NDA Meeting) to obtain guidance from FDA on the overall content and format for the anticipated NDA for OP Depot.
27 April 2007	Lilly submitted the NDA for OP Depot.

2.6 Other Relevant Background Information

Olanzapine has not been withdrawn from the market worldwide for any reason.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

David Claffey, PhD. and Prafull Shiromani, PhD. are the CMC reviewers for this submission. Please refer to their reviews for detailed CMC review information.

3.2 Animal Pharmacology/Toxicology

There were no animal pharmacology/toxicology data provided in this submission and these studies were not deemed necessary.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The efficacy data to support this submission are from two controlled, parallel studies—HGJZ, an 8-week, double-blind, randomized, placebo-controlled study and HGKA, a 24-week, double-blind, randomized, olanzapine-controlled maintenance study of OP Depot in the treatment of schizophrenia.

The safety data to support this submission are primarily from the two controlled studies—HGJZ and HGKA. In addition, the integrated safety data from 8 OP Depot clinical trials (mainly from Study HGKB) were also reviewed.

4.2 Tables of Clinical Studies

Table 3 Table of Clinical Studies

Study ID/ Study Status	Study Length	# Enroll/ Rand	Dose	Study Design and Objective
HGJZ/ Concluded	8 weeks	404 Rand	OP Depot: 210 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks Placebo	Double-blind, placebo-controlled, fixed-dose PK, efficacy superiority, and safety study in patients with schizophrenia.
HGKA/ Concluded	24 weeks	1065 Rand	OP Depot: 45 mg/4 weeks (reference dose), 405 mg/4 weeks, 150 mg/2 weeks, 300 mg/2	Double-blind, olanzapine-controlled, fixed-dose study of noninferiority of maintenance of efficacy, superiority of 3 therapeutic OP Depot doses compared to reference dose, safety, and

Study ID/ Study Status	Study Length	# Enroll/ Rand	Dose	Study Design and Objective
			weeks Oral OLZ: 10, 15, 20 mg/day	PK in patients with schizophrenia.
HGKB/ Ongoing	Up to 4 years	931 Enroll (725 ongoing as of Jan 2007	OP Depot: Flexible doses ranging from 45 mg to 405 mg given at 2- , 3-, or 4-week intervals	Long-term, open-label safety, effectiveness, and PK (subset) study in patients with schizophrenia or schizoaffective disorder who previously completed an OP Depot clinical trial (HGJZ, HGKA, or LOBS).

4.3 Review Strategy

A list of the items examined during the course of the review is provided in Table 4. The efficacy results from Study HGJZ and HGKA were reviewed separately. The safety data from the controlled studies (HGJZ and HGKA) were reviewed individually and the integrated safety data from 8 OP Depot trials were combined for analyses.

Table 4 Items Utilized in the Review

Submission Date	Items Reviewed
30 April 2007	Clinical Study Report: HGJZ and HGKA Clinical Summary Clinical Overview Special Topic Report: IAIV Injection Events, Cardiovascular Effects, Metabolic Parameters and Weight Gain, Hepatic Measures Case Report Forms and Narratives
28 August 2007	4 Month Safety Update

4.4 Data Quality and Integrity

Inspectors from the Division of Scientific Investigation (DSI) have inspected 3 clinical sites. Since all studies are multi-center studies and no results from any site drove the efficacy results, the sites for inspection were chosen based on larger enrollment in the site. Dr. Robert E. Litman, Dr. Adam F. Lowy and Dr. Matthew Brams were chosen for inspection. Table 5 summarizes the inspection results.

Table 5 DSI Inspection Results

Name of CI and site #	City, State	Protocol #	Insp. Date	EIR Received Date	Interim Classification	Final Classification
Robert E.Litman, M.D. site 031	Rockville, MD	F1D-MC-HGJZ	9/19/2007-9/27/2007	11/6/2007	N/A	VAI
Adam F.Lowy, M.D. site 032	Washington, DC	F1D-MC-HGJZ	11/26/07-11/30/07	pending	NAI	pending
Matthew Brams, M.D. site 016	Houston, TX	F1D-MC-HGJZ	7/31/2007-8/2/2007	8/17/07	N/A	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

There were no data integrity issues found at any of the sites. Observations for Dr. Lowy's site are based on communications from the field investigator. DSI reports that an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the Establishment Inspection Report (EIR).

4.5 Compliance with Good Clinical Practices

All studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

4.6 Financial Disclosures

Dr. Hans Moller received [redacted] Euros in payment of lecture fees and consulting fees. Two patients were randomized [redacted] site (407), which contributed 0.19% of total patients in Study HGKA. The financial payments the investigator received were unlikely to influence the outcome of the study as the percentage of patients enrolled is negligible compared to the entire study population for the analyses.

Dr. Gerald Maguire received [redacted] in payment of lecture fees and consulting fees. At his site (033), 9 patients were random [redacted] h contributed 2.22% of total patients in Study HGJZ. The financial payments the investigator received were unlikely to influence the outcome of the study for similar reason.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Andre Jackson, PhD. is the clinical pharmacology reviewer for this submission. Please refer to his review for pertinent information.

5.2 Pharmacodynamics

Andre Jackson, PhD. is the clinical pharmacology reviewer for this submission. Please refer to his review for pertinent information.

5.3 Exposure-Response Relationships

Andre Jackson, PhD. is the clinical pharmacology reviewer for this submission. Please refer to his review for pertinent information.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Lilly is submitting this NDA to gain approval for OP Depot for the indication of the treatment of schizophrenia.

Two studies were conducted to evaluate the efficacy and safety of OP Depot in the treatment of schizophrenia. These include one short-term (8 weeks), double-blind, randomized, placebo-controlled study (Study F1D-MC-HGJZ, HGJZ) and a long-term (24 weeks), double-blind, randomized, olanzapine-controlled study (Study F1D-MC-HGKA, HGKA). The efficacy data from both studies are reviewed in detail in the efficacy review section of this review. The efficacy review was performed in consultation with the statistical reviewer, George Kordzakhia, PhD.

George Kordzakhia, PhD concluded in his review that no statistical issues are identified in both studies.

6.2 Efficacy Review on Study F1D-MC-HGJZ

6.2.1 Methods

The clinical study report for the 8-week, placebo-controlled study, HGJZ, is the major data source used for this efficacy review.

6.2.2 General Discussion of Endpoints

The primary endpoint of Study HGJZ was the mean change from baseline to endpoint in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score. The PANSS is one of most commonly used instruments for measuring symptom reduction of schizophrenia patients in antipsychotic therapy trials. The PANSS is a 30-item rating instrument evaluating the presence/absence and severity of positive, negative and general psychopathology of

schizophrenia. The validation and use of the PANSS as a tool for assessing the efficacy of treatments for schizophrenia and other psychotic disorders is well documented.

6.2.3 Study Design

6.2.3.1 Investigators/Sites

Study HGJZ was conducted by 42 principle investigators at 42 study centers in three countries—the United States, Croatia, and Russia from 22 June 2004 to 26 April 2005.

A full list of clinical study sites and investigators for Study HGJZ is included in Appendices 10.1 List of Principle Investigators and Study Sites (see Table 27).

6.2.3.2 Objectives

Primary Objectives

The primary objective of Study HGJZ was to assess the acute efficacy (8-week) of OP Depot at doses of 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks in the treatment of schizophrenia.

Secondary Objectives

None of following secondary objectives was pre-specified as a key secondary objective.

- To assess the efficacy of OP depot treatment compared with placebo as measured by the Clinical Global Impression-Improvement of Illness (CGI-I) Scale.
- The earliest time point at which the percentage of patients with CGI-I score of ≤ 3 .
- The mean change from baseline to endpoint in Clinical Global Impression-Severity of Illness (CGI-S) Scale.
- The mean change from baseline to endpoint in PANSS Positive, PANSS Negative, and PANSS General Psychopathology subscales.
- The mean change from baseline to endpoint in quality of life measured by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the Heinrichs-Carpenter Quality of Life Scale (QLS).
- The safety and tolerability of OP Depot treatments compared with placebo.
- PK of OP Depot following multiple doses at each of dosing regimens.

6.2.3.3 Subjects

Inclusion Criteria:

- Male or female patients, aged 18 to 75, who met the criteria for schizophrenia as defined by DSM-IV.
- PANSS-derived Brief Psychiatric Rating Scale (BPRS) score of ≥ 48 at Visit 1.

Exclusion Criteria:

- Patients who were considered to be treatment-resistant to olanzapine.

- Patients who had received treatment in the 30 days prior to Visit 1 with a drug that had not yet received regulatory approval or who had participated in a trial of another investigational drug.
- Patients who experienced clinically significant AEs while being treated with olanzapine.
- Patients who presents risks of suicide or homicide.
- Patients who had a serious, unstable medical conditions.

6.2.3.4 Overall Study Design

Study HGJZ was an 8-week, inpatient/outpatient, multiple center, randomized, double-blind, and parallel study to assess efficacy and safety of OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks compared with placebo/2 weeks in the treatment of patients with schizophrenia.

After a 2-7 day washout period, eligible patients were randomized into one of the following 4 groups at a 1:1:1:1 ratio: OP depot 300 mg/2 weeks, OP depot 405 mg/4 weeks, OP depot 210 mg/2 weeks, or placebo/2 weeks. During the first 2 weeks following randomization, patients remained inpatient and were assessed daily. During the rest of study period, patients were followed on weekly basis as outpatients.

6.2.3.5 Dose and Administration

After a washout period, patients entered an 8-week double-blind treatment period, during which they were assigned to one of four treatment injections (OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 210 mg/2 weeks or placebo/2 weeks) every two weeks. Patients who were randomized to 405 mg/4 weeks OP depot received a placebo injection at every other injection visit. All study medications were administered by gluteal intramuscular injection.

6.2.3.6 Statistical Analysis Plan

An intent-to-treat (ITT) principle was applied in the efficacy, safety, and health outcomes analyses. Efficacy analyses included all randomized patients (N=404) with baseline and postbaseline observations. Efficacy data were analyzed using the last-observation-carried-forward (LOCF) method. Continuous data were analyzed using ANOVA models. For analysis of proportions, Fisher's exact test was used. The primary comparisons of interest were the pairwise contrast of each OP depot treatment group versus placebo. The pairwise comparisons based on the hierarchical order of the fixed sequence procedure were specified *a priori*, so no further adjustment to the significance levels were necessary. All hypotheses were tested at a two sided α level of 0.05. In order to assess longitudinal effects, a likelihood-based repeated measures analysis was conducted on the post-baseline PANSS Total score and associated subscales.

6.2.4 Efficacy Findings

6.2.4.1 Disposition of Patients

A total of 466 patients were enrolled in the study and 62 patients failed screening. A total of 404 eligible patients were randomized in a 1:1:1:1 ratio to receive double-blind OP depot 300 mg/2 weeks, (n=100), OP depot 405 mg/4 weeks (n=100), OP depot 210 mg/2 weeks (n=106), or placebo (n=98). A total of 267 (66%) patients completed the study.

Table 6 summarizes overall patient disposition and reasons for discontinuation. The most common reasons for discontinuing the study were lack of efficacy (n=59) and patient decision (n=45). There was a higher discontinuation rate due to lack of efficacy in the placebo group. There were no statistically significant differences across treatment groups for overall reasons for discontinuation.

Table 6 Patient Disposition and Reasons for Discontinuation in Study HGJZ

Total Patients Enrolled: 466				
Total Patients Randomized: 404				
	OP Depot 300 mg/2 wks N (%)	OP Depot 405 mg/4 wks N (%)	OP Depot 210 mg/2 wks N (%)	Placebo N (%)
Randomized	100 (100.0)	100 (100.0)	106 (100.0)	98 (100.0)
Completed	67 (67.0)	72 (72.0)	72 (67.9)	56 (57.1)
p-values vs. placebo	0.268	0.114	0.213	
Discontinued	33 (33.0)	28 (28.0)	34 (32.1)	42 (42.9)
AEs	6 (6.0)	4 (4.0)	3 (2.8)	5 (5.1)
Lost to follow up	0 (0.0)	0 (0.0)	2 (1.9)	1 (1.0)
Protocol violation	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.0)
Subject decision	9 (9.0)	12 (12.0)	15 (14.2)	9 (9.2)
Physician decision	5 (5.0)	1 (1.0)	1 (0.9)	2 (2.0)
Sponsor decision	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Lack of efficacy	13 (13.0)	10 (10.0)	12 (11.3)	24 (24.5)

6.2.4.2 Demographic Characteristics

Table 7 summarizes baseline demographic characteristics in Study HGJZ for all randomized patients. The patients randomized were predominantly male (n=285, 70.5%) and Caucasian (n=226, 55.9%). This distribution is consistent with the distribution in the schizophrenic population. The average age of enrolled patients was 40 years, with a range of 18 to 74 years. There were no statistically significant differences across treatment groups with respect to these demographic characteristics.

Table 7 Baseline Demographic Characteristics in Study HGJZ

	300Q2W N=100	405Q4W N=100	210Q2W N=106	PLA N=98	Total N=404	p-Values			
						Overall	300Q2W Vs. PLA	405Q4W Vs. PLA	210Q2W Vs. PLA
<i>Gender</i>									
Female	28 (28.0)	27 (27.0)	27 (25.5)	37 (37.8)	119 (29.5)	0.217	0.144	0.106	0.059
Male	72 (72.0)	73 (73.0)	79 (74.5)	61 (62.2)	285 (70.5)				
<i>Origin</i>									
Caucasian	58 (58.0)	54 (54.0)	61 (57.5)	53 (54.1)	226 (55.9)	0.705	0.373	0.945	0.277
African	38 (38.0)	36 (36.0)	35 (33.0)	37 (37.8)	146 (36.1)				

	300Q2W N=100	405Q4W N=100	210Q2W N=106	PLA N=98	Total N=404	p-Values			
						Overall	300Q2W Vs. PLA	405Q4W Vs. PLA	210Q2W Vs. PLA
Hispanic	4 (4.0)	6 (6.0)	9 (8.5)	3 (3.1)	22 (5.4)				
Others	0 (0.0)	4 (4.0)	1 (0.9)	5 (5.1)	10 (2.5)				
<i>Age (yrs)</i> Mean	41.46	39.54	39.76	42.64	40.82	0.129	0.255	0.030	0.056
<i>BMI</i> Mean	(n=99) 28.9	29.42	(n=105) 28.72	28.26	(n=402) 28.82	0.627	0.671	0.196	0.585
<i>Weight (kg)</i> Mean	(n=99) 85.45	87.29	86.95	82.23	(n=403) 85.52	0.190	0.334	0.053	0.072

6.2.4.3 Disease Characteristics

There were no significant differences in disease characteristics (number of previous episodes or exacerbation in the last 2 years, age of onset, length of current episodes) across treatment groups. Two or more previous episodes or exacerbations of schizophrenia in the last 24 months were reported by 71% of the patients.

The three most frequently used previous antipsychotic therapies were risperidone (n=159, 39.4%), olanzapine (n=153, 37.9%), and haloperidol (n=104, 25.7%). There were no statistically significant differences in previous drug therapies across treatment groups.

Table 8 summarizes baseline severity of illness for all randomized patients. The treatment groups were comparable at baseline with respect to severity of illness. Baseline mean PANSS Total Score across all treatment groups was 101, and the mean score of the extracted BPRS Total (transformed from a 1-to-7 scale to a 0-to-6 scale) was 41. There were no statistically significant differences across treatment groups in baseline severity of illness scores.

Table 8 Baseline Severity of Illness Score in Study HGJZ

	300Q2W N=99 (Mean)	405Q4W N=100 (Mean)	210Q2W N=106 (Mean)	PLA N=98 (Mean)	Total N=403 (Mean)	p-Values			
						Overall	300Q2W Vs. PLA	405Q4W Vs. PLA	210Q2W Vs. PLA
PANSS Total	102.70	101.33	99.55	100.60	101.02	0.471	0.174	0.600	0.993
PANSS Positive Total	25.86	25.74	25.21	25.38	25.54	0.764	0.364	0.389	0.739
PANSS Negative Total	25.97	25.35	24.72	25.09	25.27	0.223	0.091	0.664	0.836
Extracted BPRS Total	41.53	41.07	40.45	40.40	40.86	0.715	0.268	0.389	0.549

6.2.4.4 Concomitant Medications

Lorazepam was the most frequently used concomitant medication, with 232 (57.4%) of the patients reporting its use. There were no statistically significant differences comparing OP depot arms with the placebo arm in regards to concomitant medication use or benzodiazepine use during the study.

6.2.4.5 Efficacy Results

Primary Variable

The primary objective of the study was to demonstrate superiority of the OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks compared to placebo in change from baseline to endpoint in the PANSS Total score in the treatment of patients with schizophrenia.

The mean changes from baseline to end point in PANSS Total Score for the OP depot treatment arms versus the placebo arm are presented in Table 9. Patients in the 300 mg/2 weeks, 405 mg/2 weeks, and 210 mg/2 weeks showed statistically significant improvements over placebo in the PANSS Total Score at endpoint (Week 8). The PANSS Total Scores at Week 8 were -26.32, -22.98 and -22.49 in the 300 mg/2 weeks, 405 mg/2 weeks, and 210 mg/2 weeks arms respectively, and -8.51 in the placebo arm using the LOCF analyses. The difference from placebo in mean change from baseline at Week 8 was -17.81 ($p < .001$) for the 300 mg/2 weeks arm and -14.47 ($p < .001$) for the 405 mg/4 weeks arm and -13.98 ($p < .001$) for the 210 mg/2 weeks arm.

The results of the OC analysis were consistent with the findings from the LOCF analyses. The difference between treatment arms and placebo arms in mean change from baseline to endpoint was -21.00 ($p < .001$) for the 300 mg/2 weeks arm, -12.97 ($p < .001$) for the 405 mg/2 weeks arm and -11.37 ($p < .001$) for the 210 mg/2 weeks arm (see Table 29 in 10.2 Appendix to Efficacy Review).

Table 9 Mean Change from Baseline to Endpoint in PANSS Total Score in Study HGJZ (LOCF) – Primary Efficacy Analysis

	300Q2W N=100	405Q4W N=100	210Q2W N=106	PLA N=98	P – value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline (Mean)	102.58	101.33	99.55	100.60			
Mean Change (Mean)	-26.32	-22.98	-22.49	-8.51	<.001	<.001	<.001

Table 10 summarizes the visit-wise mean change from baseline to endpoint in PANSS total score (LOCF). Patients in OP depot 300 mg/2 weeks and 405 mg/4 weeks, showed significant improvement over placebo treatment after half-week. All three OP depot treatment groups were statistically superior to placebo in mean change of PANSS Total score from Week 1 through the completion of the study.

Table 10 Visit-wise Mean Change from Baseline to Endpoint in PANSS Total Score in Study HGJZ (LOCF)

Visit	300Q2W N=100 (Mean)	405Q4W N=100 (Mean)	210Q2W N=106 (Mean)	PLA N=98 (Mean)	p-value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline	102.58	101.33	99.55	100.60			
Week 0.43	-8.64	-8.22	-7.58	-5.24	.011	.025	.056

Visit	300Q2W N=100 (Mean)	405Q4W N=100 (Mean)	210Q2W N=106 (Mean)	PLA N=98 (Mean)	p-value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Week 1	-14.8	-13.38	-13.68	-9.37	.001	.016	.005
Week 2	-19.61	-16.80	-16.51	-10.97	<.001	.004	.003
Week 3	-22.22	-18.84	-19.33	-10.69	<.001	<.001	<.001
Week 4	-22.68	-20.03	-20.63	-8.83	<.001	<.001	<.001
Week 5	-23.37	-21.77	-21.82	-8.74	<.001	<.001	<.001
Week 6	-24.80	-22.49	-22.76	-8.67	<.001	<.001	<.001
Week 7	-25.79	-22.98	-23.38	-8.64	<.001	<.001	<.001
Week 8	-26.32	-22.57	-22.49	-8.51	<.001	<.001	<.001

Mean change from baseline to endpoint in OP depot 300 mg/2 weeks (p=.005) arm was statistically superior to placebo at Visit 5 (day 3). Overall, all three OP depot treatment groups were statistically significantly superior to placebo at week 1 and through the remainder of the study.

Secondary Variables

No secondary variables in Study HGJZ were pre-specified as key secondary variables.

CGI-I Scores at Endpoint

Table 11 summarizes CGI-I scores at LOCF endpoint. All three OP depot treatment groups demonstrated statistically significant improvement on the CGI-I score compared with placebo at Visit 5 (day 3) and throughout the rest of Study (p<.001).

Table 11 CGI-I Score at Endpoint in Study HGJZ (LOCF)

	300Q2W N=99	405Q4W N=99	210Q2W N=105	PLA N=98	P – value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Day 1 (SE)	3.96 (0.05)	3.96 (0.04)	3.91 (0.04)	3.98 (0.05)			
Day 56 (SE)	2.92 (0.15)	2.96 (0.13)	3.01 (0.13)	4.05 (0.15)	<.001	<.001	<.001

Mean Change from Baseline to Endpoint in CGI-S

Table 12 summarizes mean change from baseline to endpoint in CGI-S Scores. All OP depot treatment groups demonstrated statistically significant improvement in CGI-S scores compared with placebo at Visit 9 (Day 7) and all subsequent visits of the study.

Table 12 Mean Change from Baseline to Endpoint in CGI-S in Study HGJZ (LOCF)

	300Q2W N=99	405Q4W N=99	210Q2W N=105	PLA N=98	P – value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline (SE)	4.83 (0.07)	4.86 (0.08)	4.74 (0.07)	4.71 (0.07)			
Mean Change (SE)	-0.97 (0.12)	-0.92 (0.11)	-0.91 (0.10)	-0.28 (0.11)	<.001	<.001	<.001

Mean Change from Baseline to Endpoint in PANSS Subscale Scores

PANSS Positive Score

All three OP depot treatment groups (300 mg/2 weeks, p=.004; 405 mg/4 weeks, p=.001; 210 mg/2 weeks, p=.032) were statistically superior to placebo in mean change of the PANSS Positive score by Visit 5 (Day 3), and maintained significance through the remainder of the study. There were no statistically significant differences among the OP depot treatment groups. Table 13 summarizes the mean change from baseline to endpoint in PANSS Positive Score.

Table 13 Mean Change from Baseline to Endpoint in PANSS Positive Score in Study HGJZ (LOCF)

	300Q2W N=99	405Q4W N=99	210Q2W N=105	PLA N=98	P – value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline (SE)	25.82 (0.49)	25.74 (0.50)	25.21 (0.49)	25.38 (0.54)			
Mean Change (SE)	-7.42 (0.79)	-7.18 (0.69)	-6.32 (0.66)	-1.99 (0.77)	<.001	<.001	<.001

PANSS Negative Score

All OP depot treatment groups demonstrated statistically significant improvement over placebo by Visit 17 (Week 3). Additionally, OP depot 300 mg/2 weeks showed statistically superior improvement over OP depot 405 mg/4 weeks at Visit 21 (Week 7), and over 405 mg/4 weeks and 210 mg/2 weeks at Visit 22 (Week 8). Table 14 summarizes the mean change from baseline to endpoint in PANSS Positive Score.

Table 14 Mean Change from Baseline to Endpoint in PANSS Negative Score in Study HGJZ (LOCF)

	300Q2W N=98	405Q4W N=100	210Q2W N=106	PLA N=98	P – value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline (SE)	26.02 (0.54)	25.35 (0.51)	24.72 (0.51)	25.09 (0.56)			
Mean Change (SE)	-6.28 (0.62)	-4.55 (0.54)	-4.79 (0.54)	-2.10 (0.59)	<.001	<.001	<.001

6.2.4.6 Subgroup Analyses

Subgroup analyses were performed to evaluate change from baseline to endpoint on the PANSS Total Score within subgroups based on age (<40 and ≥ 40), gender, race and region (US and Non-US). There was no subgroup for which there was a statistically significant therapy-by-subgroup interaction.

6.2.5 Clinical Microbiology

Clinical microbiology was not considered necessary for this product.

6.2.6 Efficacy Conclusions

The three OP depot treatment groups demonstrated superior improvement over placebo in reducing PANSS Total Score starting at week 1 and continuing through the end of the study.

6.3 Efficacy Review on Study F1D-MC-HGKA

6.3.1 Methods

The clinical study report for the 24-week Study HGKA is the major data source for this efficacy study review.

6.3.2 General Discussion of Endpoints

The primary endpoints of Study HGKA were:

- A comparison of pooled 2-Week OP Depot (300 mg/2 weeks and 150 mg/2 weeks) and oral olanzapine group with respect to rates of exacerbation of symptoms
- The pair-wise comparisons of time to exacerbation of symptoms for each of the higher OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) versus the low OP Depot dose (45 mg/4 weeks)

Both exacerbation rates and time to exacerbation of symptoms are commonly used endpoints in long-term relapse prevention trials. In this study, the stabilization phase was relatively short, 4-8 weeks. However, since patients had been clinically stable before enrollment, the actual stabilization period was much longer than 4-8 weeks. The efficacy data from this trial can be used to support this submission.

6.3.3 Study Design

6.3.3.1 Investigators/Sites

Study HGKA was conducted by 113 principle investigators at 112 study sites in 26 countries from 6 July 2004 to 13 September 2006.

A full list of clinical study sites and investigators for Study HGKA is included in Appendices 10.1 List of Principle Investigators and Study Sites (see Table 28).

6.3.3.2 Objectives

Primary Objectives

- Non-inferior efficacy of pooled 2-week OP Depot (300 mg/2 weeks and 150 mg/2 weeks) versus oral olanzapine (10, 15 or 20 mg/d, flexible dosing) as measured by exacerbation rates after 24 weeks of maintenance treatment.

- Superior efficacy of 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks OP Depot versus 45 mg/4 weeks OP Depot as measured by time to exacerbation of symptoms of schizophrenia after 24 weeks of maintenance treatment.

6.3.3.3 Subjects

Inclusion Criteria

- Male or female out-patients meeting DSM-IV criteria for schizophrenia, ages 18 to 75 years.
- Clinically stable on antipsychotics for at least 4 weeks preceding Visit 1 and BPRS Positive items score ≤ 4 .
- If enrolled on parenteral antipsychotics, received their last injection at least 2 weeks (or 1-injection interval, whichever was longer) prior to visit 2.

Exclusion Criteria

- History of treatment-resistance to olanzapine
- Received treatment with an investigational drug or unapproved drug within 30 days prior to enrollment
- Had an allergic reaction to olanzapine or had experienced clinically significant adverse events while treated with olanzapine
- Had a significant suicidal or homicidal risk
- Were pregnant or breast feeding
- Had uncorrected narrow-angle glaucoma, hypo- or hyperthyroidism, history of agranulocytosis
- Had serious or unstable medical conditions
- Had substance dependency within the past 30 days
- Received treatment with remoxipride within 6 months, with clozapine within 4 weeks;
- Had previously participated in an OP depot study
- Required concomitant treatment with a medication with CNS activity other than those allowed in the protocol

6.3.3.4 Overall Study Design

Study HGKA was a randomized, double-blind, parallel group, 24-week maintenance-of-effect study comparing the efficacy and safety of OP Depot (150 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks) with oral olanzapine (10, 15, and 20 mg/day) and low dose OP Depot (45 mg/4 weeks) in clinically stabilized outpatients with schizophrenia. The study consisted of 4 study periods: a 2- to 9-day Lead-In/Screening Phase; a 4- to 8-week Conversion/Stabilization Phase; a 24-week Double-Blind Maintenance Phase; and an up to 24-week Open-Label Restabilization Phase for patients who were discontinued from double-blind therapy due to exacerbation of symptoms associated with schizophrenia. A separate datalock was conducted for the Open-Label Restabilization Phase data, and results from that study period were not included in this submission.

Patients who met the inclusion criteria were discontinued from their current antipsychotic medication (unless it was olanzapine) and converted to oral olanzapine monotherapy (at 10, 15 or 20 mg/d). To enter the double-blind phase of the study, patients had to be stabilized with oral olanzapine for at least 4 weeks. 1060 patients were randomized in a 2:1:1:1:2 ratio, into 1 of 5 treatment groups: 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, 45 mg/4 weeks OP Depot, or oral olanzapine, respectively.

An unbalanced randomization scheme (2:1:1:1:2 ratio) was chosen to ensure that when pooled, an approximately equal number of patients at specific doses would be available for the following comparisons:

- a) Primary efficacy comparison of Pooled 2-Week OP Depot (300 mg/2 weeks pooled with 150 mg/2 weeks) versus oral olanzapine
- b) Comparison of Pooled 2-Week OP Depot (300 mg/2 weeks pooled with 150 mg/2 weeks) versus 405 mg/4 weeks OP Depot
- c) To ensure that fewer patients received the very low dose of OP Depot (45 mg/4 weeks)

6.3.3.5 Dose and Administration

The doses of OP Depot administered in this study (IM buttock injection) were 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, and 45 mg/4 weeks. Doses of oral olanzapine were 10, 15, and 20 mg/day. The dosing schedule is presented in Table 15. No change in dose was permitted during the study.

Table 15 Dosage and Medication Schedule for Study HGKA

Treatment Group	Oral Olanzapine ^a	Oral Placebo ^a	Placebo Injection	OP Depot Injection
Oral olanzapine	Daily	Daily ^b	Every 2 weeks	N/A
OP Depot				
405 mg/4 weeks	N/A	Daily	Every 4 weeks ^c	Every 4 weeks ^c
300 mg/2 weeks	N/A	Daily	N/A	Every 2 weeks
150 mg/2 weeks	N/A	Daily	N/A	Every 2 weeks
45 mg/4 weeks	N/A	Daily	Every 4 weeks ^c	Every 4 weeks ^c

6.3.3.6 Statistical Analysis Plan

All analyses were conducted on an intent-to-treat (ITT) basis. Efficacy analyses included all randomized patients (N=1065) with baseline and postbaseline observations. Noninferiority

analyses were based on Kaplan-Meier estimated 24-week cumulative exacerbation rates. Exacerbation was defined as a BPRS Positive item score >4 (1-7 scale) either with an increase of ≥ 2 points since randomization or with a BPRS Positive subscale increase of ≥ 4 points since randomization, or as hospitalization due to worsening of positive symptoms. Noninferiority was assessed using the upper limit of a two-sided 95% confidence limit for the difference between estimated exacerbation rates, with noninferiority declared if the absolute value of the upper limit was $<.20$. For time-to-relapse analyses, Kaplan-Meier curves were compared using a log-rank test. Baseline to endpoint analyses used last-observation-carried-forward (LOCF) methodology unless otherwise specified. Analysis of variance (ANOVA) models were used to evaluate continuous data and generally included terms for treatment and investigator or geographic region. The analysis of covariance (ANCOVA) on the LOCF mean change from baseline to endpoint in PANSS Total score included baseline PANSS Total score as a continuous covariate as well as terms for treatment and investigator. Type III sums of squares were used to test for significant effects for all ANOVA/ANCOVA models. For analysis of proportions, the Fisher's exact test was used unless otherwise specified. All hypotheses were tested at a two-sided α level of 0.05.

6.3.4 Efficacy Findings

6.3.4.1 Disposition of Patients

Of the 1205 patients entering the Conversion/Stabilization Phase, 1065 eligible patients were randomized during the Double-Blind Maintenance Phase. A total 753 of the 1065 eligible patients (70.7%) completed Study HGKA. Table 16 presents a summary of patient disposition following randomization into the Double-Blind Maintenance Phase.

Table 16 Summary of Patient Disposition in Study HGKA

	OP Depot 405 mg/4 wks N (%)	OP Depot 300 mg/2 wks N (%)	OP Depot 150 mg/2 wks N (%)	OP Depot 45 mg/4 wks N (%)	Oral Olanzapine 10, 20 or 30 mg N (%)
Randomized	318 (100.0)	141 (100.0)	140 (100.0)	144 (100.0)	322 (100)
Completed	222 (69.8)	107 (75.9)	90 (64.3)	76 (52.8)	258 (80.1)
Discontinued	96	34	50	68	64
AEs	10 (3.1)	4 (2.8)	7 (5.0)	6 (4.2)	8 (2.5)
Clinical relapse	39 (12.3)	7 (5.0)	22 (15.7)	42 (29.2)	23 (7.1)
Lack of efficacy	2 (0.6)	2 (1.4)	4 (2.9)	2 (1.4)	4 (1.2)
Lost to follow up	5 (1.6)	2 (1.4)	3 (2.1)	2 (1.4)	2 (0.6)
Physician decision	8 (2.5)	3 (2.1)	2 (1.4)	3 (2.1)	4 (1.2)
Protocol violation	5 (1.6)	4 (2.8)	3 (2.1)	1 (0.7)	3 (0.9)
Sponsor decision	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)
Subject decision	27 (8.5)	12 (8.5)	9 (6.4)	10 (6.9)	20 (6.2)
Entering open-label phase	39	7	22	42	23

Other than those patients who entered the Open-Label Restabilization Phase due to exacerbation, no treatment group showed >8.5% discontinuation for any reason. The most common reason for discontinuing the study during this period was patient decision (n=78). There was a statistically

significant difference ($p < .001$) across treatment groups for all-cause discontinuation. Statistically significant between-group comparisons were as follows:

- A statistically significantly greater percentage of patients treated with oral olanzapine completed the Double-Blind Maintenance Phase compared with patients in all other treatment groups except 300 mg/2 weeks OP Depot (300 mg/2 weeks OP Depot [$p = .324$]; 405 mg/4 weeks OP Depot [$p = .003$]; 150 mg/2 weeks OP Depot [$p < .001$]; and 45 mg/4 weeks OP Depot [$p < .001$]).
- A statistically significantly greater percentage of patients in all treatment groups, other than 150 mg/2 weeks OP Depot, completed the Double-Blind Maintenance Phase compared with 45 mg/4 weeks OP Depot (300 mg/2 weeks OP Depot [$p < .001$]; 405 mg/4 weeks OP Depot [$p < .001$]; 150 mg/2 weeks OP Depot [$p = .055$]; and oral olanzapine [$p < .001$]).
- A statistically significantly greater percentage of patients treated with 300 mg/2 weeks OP Depot completed the Double-Blind Maintenance Phase compared with patients treated with 150 mg/2 weeks OP Depot ($p = .038$).

There was also a statistically significant difference between treatment groups for discontinuation due to clinical relapse ($p < .001$). No other reasons for discontinuation were statistically different across treatment groups.

6.3.4.2 Demographic Characteristics

Table 17 summarizes baseline physical characteristics (gender, ethnic origin, age, BMI, and weight) for all randomized patients. The patient population was predominantly male (65.4%) and Caucasian (71.8%), which is consistent with the distribution of schizophrenia population. Patients' age ranged from 18 to 71 years with a mean age of 39 years at baseline. There were no statistically significant differences across treatment groups with respect to baseline physical characteristics.

Table 17 Baseline Demographic Characteristics of Study HGKA

	OPD405Q4W N=318	OPD300Q2W N=141	OPD150Q2W N=140	OPD45Q4W N=144	Oral OLZ N=322	Total N=1065
<i>Gender</i>						
Female	106 (33.3)	46 (32.6)	56 (40.0)	48 (33.3)	113 (35.1)	369 (34.6)
Male	212 (66.7)	95 (67.4)	84 (60.0)	96 (66.7)	209 (64.9)	696 (65.4)
<i>Origin</i>						
Caucasian	230 (72.3)	99 (70.2)	96 (68.6)	106 (73.6)	234 (72.7)	765 (71.8)
African	12 (3.8)	7 (5.0)	8 (5.7)	5 (3.5)	13 (4.0)	45 (4.2)
Hispanic	51 (16.0)	25 (17.7)	26 (18.6)	21 (14.6)	53 (16.5)	176 (16.5)
Others	25 (7.9)	10 (7.1)	10 (7.1)	12 (8.4)	22 (6.9)	79 (7.4)
<i>Age (yrs)</i>						
Mean	39.00	39.54	37.71	39.47	38.98	38.96

	OPD405Q4W N=318	OPD300Q2W N=141	OPD150Q2W N=140	OPD45Q4W N=144	Oral OLZ N=322	Total N=1065
<i>BMI</i> Mean	(n=317) 26.96	26.5	27.20	27.13	(n=321) 26.76	(n=1063) 26.89
<i>Weight (kg)</i> Mean	77.89	75.30	78.40	78.44	76.95	77.41

6.3.4.3 Disease Characteristics

With respect to historical illness characteristics, approximately 37% of patients reported 2 or more previous episodes or exacerbations of schizophrenia in the last 24 months; approximately 32% of patients reported 1 such episode in the last 24 months, and approximately 31% of patients reported no such episodes in the last 24 months. No statistically significant differences were observed across treatment groups. No statistically significant differences were observed in historical illness characteristics between the Pooled 2-Week OP Depot and the oral olanzapine treatment groups.

Table 18 presents baseline severity of illness scores. The mean PANSS Total score for all randomized patients was 55.87. Statistically significant differences across treatment groups were observed for the PANSS Total ($p=.048$), PANSS Negative Total ($p=.027$), and Extracted Brief Psychiatric Rating Scale (BPRS) Negative ($p=.014$). On each of these measures, the 45 mg/4 weeks OP Depot group had the highest mean scores, while the 150 mg/2 weeks group had the lowest mean scores. Baseline Clinical Global Impression-Severity of Illness (CGI-S) scores were also statistically significantly different across treatment groups ($p=.016$), again with the 45 mg/4 weeks group having the highest mean score, but with the 300 mg/2 weeks group having the lowest mean score. Although statistically significant, these baseline differences between groups were small—within a range of 3.42 points on the PANSS Total, 1.06 points on the PANSS Negative, 0.62 on the BPRS Negative, and 0.19 on the CGI-S. The small differences are not likely to be clinically significant.

No statistically significant differences were observed between the Pooled 2-Week OP Depot and the oral olanzapine treatment groups with respect to baseline severity of illness Scores.

Table 18 Baseline Severity of Illness Scores in Study HGKA

	OPD405Q4W N=99 (Mean)	OPD300Q2W N=100 (Mean)	OPD150Q2W N=106 (Mean)	OPD45Q2W N=98 (Mean)	Oral OLZ N = 322 (Mean)	Total N=403 (Mean)
PANSS Total	55.06	56.81	54.33	57.75	56.08	55.87
PANSS Positive Total	11.12	11.07	11.15	11.63	11.23	11.22
PANSS Negative Total	15.94	16.66	15.82	16.88	16.67	16.37
Extracted BPRS Total	12.10	12.84	11.54	13.42	12.45	12.41
Extracted BPRS Negative	3.44	3.72	3.20	3.82	3.77	3.60
Extracted BPRS Positive	3.21	3.12	3.17	3.65	3.32	3.29

6.3.4.4 Concomitant Medications

A total of 54.1% of patients took at least one concomitant medication during this study. The concomitant medications used by at least 5% of patients during the double-blind phase were lorazepam (11.6%), clonazepam (9.9%), diazepam (7.3%), biperiden (5.6%), and paracetamol (4.9%). There were no statistically significant differences across all treatment groups in concomitant medication use (either overall or for individual drugs listed above) during double-blind treatment phase.

6.3.4.5 Efficacy Results

Superiority Analysis

The superiority analysis assessed the pairwise comparisons of time to exacerbation of symptoms for each of the higher OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) versus the low OP Depot dose (45 mg/4 weeks). In order to control the Type I error, these pairwise tests were conducted sequentially as follows: (1) 300 mg/2 weeks versus 45 mg/4 weeks, (2) 405 mg/4 weeks versus 45 mg/4 weeks, and (3) 150 mg/2 weeks versus 45 mg/4 weeks. Thus, the 405 mg/4 weeks versus 45 mg/4 weeks test would be declared significant only if both this comparison and the first comparison (300 mg/2weeks versus 45 mg/4 weeks) were statistically significant. The 150 mg/2 weeks versus 45 mg/4 weeks comparison would be declared statistically significant only if all 3 comparisons were statistically significant.

Each of the higher OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) was statistically superior to the 45 mg/4 weeks dose with respect to time to exacerbation of symptoms (p-values: <.001, <.001, and =.006, respectively; Figure 1).

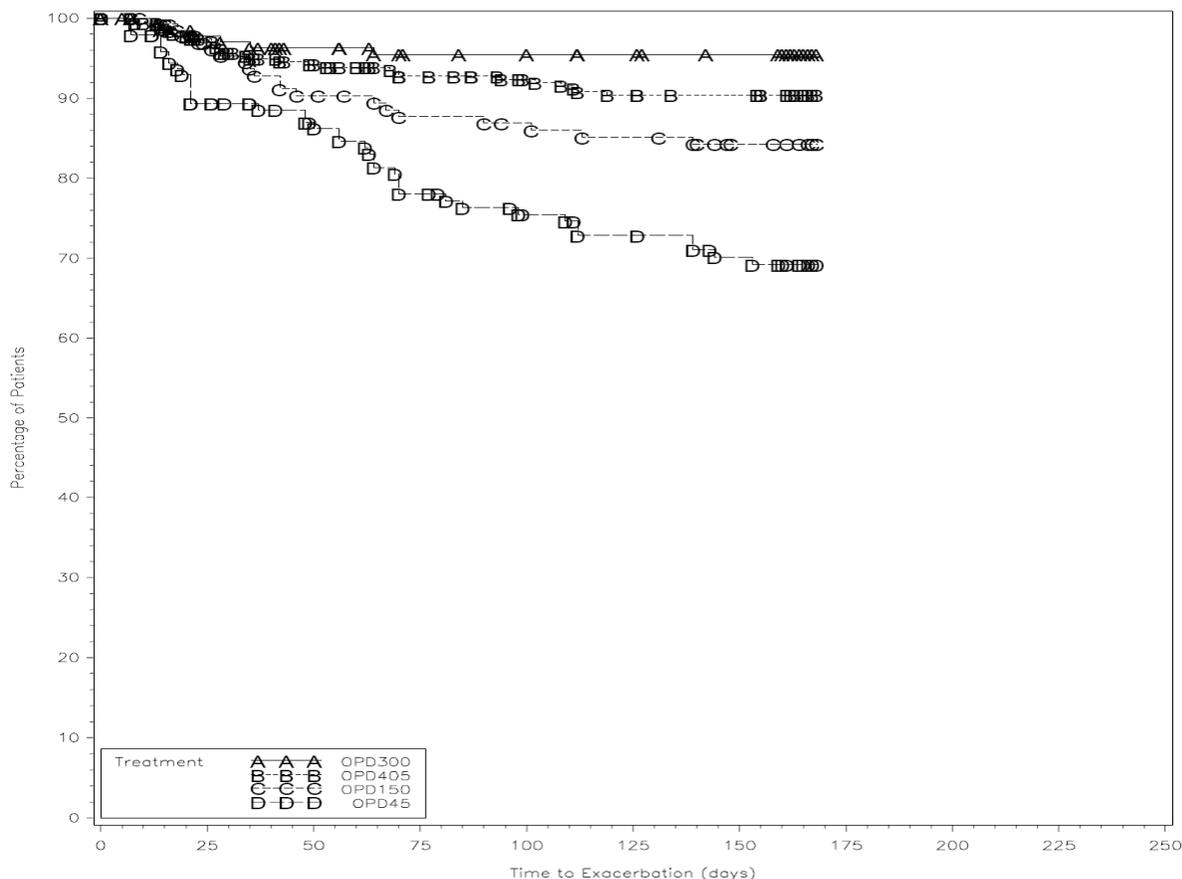


Figure 1 Time to Exacerbation for the Double-Blind Maintenance Phase in Study HGKA

Non-inferiority Analysis

The primary non-inferiority analysis in Study HGKA was a comparison of the Pooled 2-Week OP Depot and the oral olanzapine treatment groups with respect to exacerbation rates. Non-inferiority between these 2 treatment groups was assessed by comparing the Kaplan-Meier estimated exacerbation rates at 24 weeks after randomization.

Ninety percent of the Pooled 2-week OP Depot patients remained free of exacerbation during the 24-week double-blind maintenance period compared to 93% of oral olanzapine patients, for a difference of 3% (Table 19). Per a *priori* criteria specified, the Pooled 2-Week OP Depot treatment group would be declared noninferior to the oral olanzapine treatment group if the 95% confidence interval (CI) excluded a difference of 0.20 (20%). Using this criterion, the Pooled 2-Week OP Depot treatment group was non-inferior to the oral olanzapine treatment group with respect to exacerbation rates at 24 weeks after randomization. Comparison of the 95% CIs indicated that the Pooled 2-week OP Depot survival rate was in the range of 86% to 94%, while the oral olanzapine survival rate was in the range of 90% to 96%, with the likely difference between these rates ranging from -2% to +8%. This finding was also confirmed across regions (US, East Europe, West Europe, and Other).

Table 19 Exacerbation Rates for Pooled 2-Week OP Depot vs. Oral Olanzapine at 24 weeks in Study HGKA (Kaplan-Meier Estimates)

Therapy	Survival Rate	Standard Error	95% CI
OLZ	0.93	0.015	(0.90, 0.96)
OPD2WK	0.90	0.019	(0.86, 0.94)
OLZ – OPD2WK	0.03	0.024	(-0.02, 0.08)

Analysis of time to exacerbation also revealed no statistically significant differences between the Pooled 2-Week OP Depot treatment group and the oral olanzapine treatment group (log-rank test p-value=.167).

6.3.5 Clinical Microbiology

Clinical microbiology was not considered necessary for this product.

6.3.6 Efficacy Conclusions

In Study HGKA, the 3 higher dose OP Depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups demonstrated positive maintenance of effect over 24 weeks for stabilized patients with schizophrenia.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

General safety parameters and special safety topic analyses are summarized using the following 3 databases:

- **Placebo-Controlled Database:** This database includes safety data from patients randomized to OP Depot or placebo for up to 8 weeks in the double-blind, placebo-controlled study (HGJZ) in 404 patients with schizophrenia. Data for the 3 OP Depot treatment groups were pooled for all analyses.
- **Olanzapine-Controlled Database:** This database includes safety data from patients randomized to OP Depot or oral olanzapine for up to 24 weeks in the double-blind maintenance of effect study (HGKA) in 921 patients with schizophrenia. Data for 3 OP Depot treatment groups were pooled for all analyses. This database provides direct comparisons to oral olanzapine.

- OP Depot Integrated Database:** This database includes safety data from all patients (N=1918) treated with OP Depot in the 2 double-blind comparator studies described above and in 6 open-label studies. These studies were conducted in patients with schizophrenia or schizoaffective disorder.

Table 20 presents the databases and analyses discussed throughout this safety review. The updated safety information from the 4 Months Safety Update submitted on 8 August 2007 (data cut-off date of 31 January 2007) was also integrated into this review. The safety data from Placebo-Controlled Database are reviewed in detail in this safety review. The data from the Olanzapine-Controlled Database were used to compare the safety profile of OP Depot with that of oral olanzapine. Overall Integrated Database were used to detecting deaths, rare, unexpected or serious AEs, or any pattern changes of common adverse events.

Table 20 Databases Reviewed for the Integrated Review of Safety

Databases/Description of Databases	Studies	Treatment Groups	Analyses
Placebo-Controlled Database/contains safety data from 404 patients randomized to OP Depot (306) or placebo (98)	HGJZ	Pooled OP Depot treatment groups (210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) Placebo	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and special topic ^a for injection-site-related AEs.
Olanzapine-Controlled Database/contains safety data from 921 patients randomized to OP Depot (599) or oral olanzapine (322)	HGKA	Pooled OP Depot treatment groups ^b (150 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) excluding 45 mg/4 weeks Oral Olanzapine (10, 15, and 20 mg)	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and the following special topics: (IAIV) injection events, cardiovascular events, metabolic parameters and weight gain, and hepatic measures.
Overall Integrated Database/contains safety data from patients who received treatment with OP Depot in any clinical trial conducted in patients with schizophrenia or schizoaffective disorder	HGJW LOBE LOBO LOBS HGJZ HGKA HGKB	Pooled OP Depot treatment groups ^c	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and the following special topics: IAIV injection events, cardiovascular events, metabolic parameters and weight gain, hepatic measures, and injection-site-related AEs.

7.1.1 Deaths

Three deaths (3/1918, 0.2%) have been reported in patients assigned to OP Depot as of the data cut-off date on 31 January 2007. One death was reported in the original submission (HGKA-

HGKB-442-8542). The other 2 deaths occurred after the data cut-off date for the integrated database that was presented in the NDA and were reported in the 4 Month Safety Update. Each death is briefly summarized below:

- Patient HGKA-HGKB-442-8542, a 33-year-old Caucasian female with a history of chr [redacted] received her first dose of 210 mg/2 weeks OP Depot in Study HGKB on [redacted]. Nine days later she was found dead, and the autopsy revealed that the cause of death was acute heart failure with associated toxic/alcoholic heart damage (cardiomyopathy).
- Patient HGKA-HGKB-182-7321, a 30-year-old male of African descen [redacted] ed 300 mg/2 weeks OP Depot in Study HGKB on [redacted]. On [redacted], he experienced the SAE of severe leptospirosis and died 5 days later.
- Patient HGJZ-HGKB-804-8852, a 52-year-old Caucasian male with a 23-year history of essential hypertension, received his first dose of 210 mg/2 weeks OP Depot in Stud [redacted]. The patient was reported to have died of hypertension on [redacted] [redacted], 26 days after the last dose of study drug, while away on a fishing trip. Over the course of the study, the patient had been diagnosed with heart failure, ischemic heart disease, and aortic aneurysm; according to the investigator, these diagnoses were not related to the primary reason for death. According to relatives of the patient, the sudden death was described as very quick and without symptoms. The cause of death provided by the investigator was reported to be essential hypertension, probably hypertension stroke, but autopsy results were not available to confirm this.

7.1.2 Other Serious Adverse Events

A total of 19 (4.7%) patients reported serious AEs in the placebo-controlled database: 14 patients (4.6%) from an OP depot treatment group and 5 patients (5.1%) from the placebo treatment group. There were no statistically significant differences across all four treatment groups in patients reporting SAEs. Psychotic disorder (n=4) was the only SAE reported by more than 1 OP Depot-treated patient. Of the 14 patients on OP depot, 8 patients reported SAEs that were likely to be related to the underlying diagnosis of schizophrenia. A summary of all reported SAEs is presented in Table 21.

Table 21 Serious Adverse Events in the Placebo-Controlled Database

Event Term	300Q2W (N=100) n (%)	405Q4W (N=100) n (%)	210Q2W (N=106) n (%)	PLA (N=98) n (%)	TOTAL (N=404) n (%)
Patients with ≥ 1 SAE	5 (5.0)	3 (3.0)	6 (5.7)	5 (5.1)	19 (4.7)
Psychotic disorder	0 (0.0)	2 (2.0)	2 (1.9)	0 (0.0)	4 (1.0)
Schizophrenia	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.0)	2 (0.5)
Agitation	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.2)
Anxiety	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Blood glucose increased	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Cholecystitis	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Depressed level of consciousness	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Pneumonia	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory acidosis	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Schizophrenia, paranoid type	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Social problem	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)

No statistically significant between-group differences in the incidence of SAEs were observed in the Placebo-Controlled Database and the Olanzapine-Controlled Database. In the Overall Integrated Database, a total of 159 patients (8.9%) reported one or more SAEs. The most commonly reported events (in 5 or more patients) were consistent with symptoms of the underlying disease (psychotic disorder, schizophrenia, agitation, suicidal ideation, anxiety, auditory hallucination, paranoia, paranoid schizophrenia, and suicide attempt).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Eighteen patients (4.5%) discontinued due to an AE in the placebo-controlled database: 13 patients (4.5%) from an OP depot treatment group and 5 patients (5.1%) from the placebo treatment group. Overall, there were no statistically significant differences across all four treatment groups in patients reporting discontinuing due to AEs.

Discontinuations due to adverse events (AEs) were $\leq 5.1\%$ in all databases. In the controlled databases, no statistically significant between-group differences were observed in the overall incidence of discontinuations due to AEs. In addition, no statistically significant differences were observed between treatment groups in the incidence of any specific AE as a reason for study discontinuation.

7.1.3.2 Adverse events associated with dropouts

Table 22 presents incidence of patient discontinuation due to an AE in the placebo-controlled database. There were 18 patients who discontinued due to an AE, of which the most frequently reported AEs were psychotic disorder (n=4), hepatic enzyme abnormalities (n=3; enzyme increased [n=2] and ALT increased [n=1]), and sedation (n=2).

Table 22 Incidence of Discontinuation Due to Adverse Event in the Placebo-Controlled Database

Event Term	300Q2W (N=100) n (%)	405Q4W (N=100) n (%)	210Q2W (N=106) n (%)	PLA (N=98) n (%)	TOTAL (N=404) n (%)
Patients discontinued	6 (6.0)	4 (4.0)	3 (2.8)	5 (5.1)	18 (4.5)
Psychotic disorder	0 (0.0)	2 (2.0)	1 (0.9)	1 (1.0)	4 (1.0)
Hepatic enzyme increased	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Sedation	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	2 (0.5)
Agitation	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Alanine aminotransferase increased	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.2)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Blood glucose increased	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Cholecystitis	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Depressed level of consciousness	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Respiratory acidosis	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Schizophrenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)

In the Overall Integrated Database, AEs most commonly reported as reasons for discontinuation (reported in 5 or more patients) were consistent with the underlying disease (psychotic disorder and schizophrenia) or with events historically reported in patients treated with oral olanzapine (sedation, somnolence, and weight gain).

7.1.3.3 Other significant adverse events

As of 4 September 2007, 25 cases of the excessive sedation with signs and symptoms consistent with those observed in an olanzapine overdose and temporally related to the injection of OP Depot had been reported in 24 patients. No excessive sedation events were reported in the Placebo-Controlled Database. Two cases (HGKA-532-4011, HGKA-571-4437) were reported in the Olanzapine-Controlled Database. Twenty two of 25 events occurred in Study HGKB, and 1 event was reported in Study LOBE. More discussion regarding the excessive sedation events can be found in section 7.1.12 Special Safety Studies.

7.1.4 Other Search Strategies

No other search strategies were considered to be warranted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

During every study, AEs were collected at every visit, regardless of relationship to study drug. These events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA) terms by blinded Lilly clinical personnel.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were appropriately categorized and coded with preferred terms.

7.1.5.3 Incidence of common adverse events

Across all OP depot treatment groups in the Placebo-Controlled Database, the most frequently reported AEs included headache (n=44, 14.4%), insomnia (n=33, 10.8%), and sedation (n=25, 8.2%). The following treatment-emergent adverse events (TEAEs) occurred in at least 2% of OP depot-treated patients and at a rate of at least twice the placebo rate: sedation, nausea, dry mouth, increased appetite, musculoskeletal stiffness, toothache, arthralgia, abdominal pain (upper), injection site pain, and muscle spasms.

Overall, sedation was the only TEAE reported statistically significantly more often by patients treated with OP Depot than by patients treated with placebo. In the Olanzapine-Controlled Database, no clinically meaningful differences between patients treated with OP Depot and patients treated with oral olanzapine were observed with respect to TEAEs. In the Integrated Database, except for injection-site pain (expected with an injectable product) and headache, all other AEs are consistent with events observed historically in patients treated with oral olanzapine or with symptoms of the disease state under treatment.

7.1.5.4 Common adverse event tables

Table 23 summarizes common adverse events in the Placebo-Controlled Database.

Table 23 TEAEs of 2% or More among OP Depot -Treated Patients in the Placebo-Controlled Database

Body System/Adverse Reaction	(Percentage of Patients Reporting Adverse Reaction)			
	Placebo (N=98)	Olanzapine Pamoate 405 mg/4 wks (N=100)	Olanzapine Pamoate 210 mg/2 wks (N=106)	Olanzapine Pamoate 300 mg/2 wks (N=100)
Ear and Labyrinth Disorders				
Ear pain	2	1	1	4
Gastrointestinal Disorders				
Abdominal pain	1	2	0	1
Abdominal pain upper	1	1	3	3
Diarrhea	4	2	7	5
Dry mouth	1	2	6	4
Flatulence	0	2	2	1
Nausea	2	5	5	4
Toothache	0	3	4	3
Vomiting	2	6	1	2

General Disorders and Administration Site Conditions				
Fatigue	2	4	2	3
Injection site pain	0	2	3	2
Pain	0	0	2	3
Pyrexia	0	2	0	0
Infections and Infestations				
Nasopharyngitis	2	3	6	1
Tooth abscess	0	2	0	0
Tooth infection	0	2	0	0
Upper respiratory tract infection	2	3	1	4
Viral infection	0	0	0	2
Injury, Poisoning and Procedural Complications				
Procedural pain	0	2	0	0
Investigations				
Alanine aminotransferase increased	1	3	0	1
Aspartate aminotransferase increased	1	2	0	1
Electrocardiogram QT-corrected interval prolonged	1	0	0	2
Gamma-glutamyltransferase increased	0	2	1	0
Hepatic enzyme increased	0	0	0	2
Weight increased	5	5	6	7
Metabolism and Nutrition Disorders				
Increased appetite	0	4	1	6
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	0	3	3	3
Back pain	4	4	3	5
Muscle spasms	0	3	1	2
Musculoskeletal stiffness	1	1	4	4
Nervous System Disorders				
Dizziness	2	4	4	1
Dysarthria	0	0	1	2
Headache	8	11	15	17
Sedation	2	8	7	10
Somnolence	5	6	1	3
Tension headache	0	2	0	1
Tremor	1	3	0	1
Psychiatric Disorders				
Abnormal dreams	0	0	0	2
Hallucination, auditory	2	3	1	0
Restlessness	2	2	3	1
Sleep disorder	1	0	0	2
Thinking abnormal	1	3	0	0
Reproductive System and Breast Disorders				
Vaginal discharge	0	0	4	4

Respiratory, Thoracic and Mediastinal Disorders				
Cough	5	3	5	9
Nasal congestion	1	1	1	3
Pharyngolaryngeal pain	2	2	3	3
Sinus congestion	2	1	0	4
Sneezing	0	0	0	2
Skin and subcutaneous tissue disorders				
Acne	0	2	0	2
Vascular Disorders				
Hypertension	0	3	2	0

7.1.5.5 Identifying common and drug-related adverse events

Common and drug-related adverse events were identified by 1) the rate of AEs for OP Depot-treated patients was at least 2%, and 2) the rate of AEs was at least twice that of placebo.

7.1.5.5 Additional analyses and explorations

Subgroup Analyses

Subgroup analyses by age, geographic region, and ethnic origin in the Placebo-Controlled Database showed no statistically significant differences of clinical relevance.

Differences in gender were found in paranoia: no more than one female reported paranoia in each of the treatment groups, but no differences were observed between the four treatment groups. However, male patients in OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks treatment groups (1.4%, 1.4%, and 1.3%, respectively) reported significantly less paranoia compared with male patients in the placebo treatment group (11.5%).

Extrapyramidal Symptoms (EPS)

In the Placebo-Controlled Database, patients treated with OP Depot had mean decreases on all EPS rating scales—Simpson-Angus Scale (SAS) total score, Barnes Akathisia Scale (BAS) global scores, and the Abnormal Involuntary Movement Scale (AIMS) total scores, but only the 405 mg/4 weeks treatment group showed a statistically significant reduction compared with the placebo group ($p=.023$). Patients in the 405 mg/4 weeks and 210 mg/2 weeks treatment groups had statistically significantly reduced mean BAS global scores from baseline compared with placebo ($p=.037$ and $p=.023$, respectively). Patients in the 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks treatment groups had statistically significantly reduced mean AIMS total scores from baseline compared to placebo ($p=.018$, $p<.001$, and $p=.037$, respectively). The categorical analyses of the SAS, BAS, and AIMS found no statistical differences across all treatment groups.

In the Olanzapine-Controlled Database, there were no statistically significant differences between OP Depot and oral olanzapine in mean change on any of SAS, BAS and AIMS measures. Mean scores decreased from baseline, though these changes were very small (less than half a point) for either treatment group on any of the 3 scales.

7.1.6 Less Common Adverse Events

The excessive sedation events were identified as a serious safety concern in these studies. More discussion can be found in section 7.1.12 Special Safety Studies.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

During these studies, blood samples were collected at regular intervals per protocol for standard laboratory tests, including chemistry, hematology, and urinalysis panels. Urine drug screens, thyroid function tests, and urine pregnancy tests (if applicable) were completed at baseline. In addition, hepatic safety was assessed and monitored throughout the studies.

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

Study HGJZ is the only placebo-controlled study submitted to his NDA. Therefore, only the laboratory data from Study HGJZ were reviewed in detail in this review and the laboratory data from other OP Depot trials (the Olanzapine-Controlled Database and the Overall Integrated Database) were used to detect rare, unexpected, serious and clinically significant laboratory abnormalities.

7.1.7.3 Standard analyses and explorations of laboratory data

In all 3 databases, there were no patterns in laboratory analyses suggesting clinically relevant differences between OP Depot and the known safety profile of oral olanzapine. Differences among OP Depot treatment groups with respect to prolactin (mean change) and fasting triglycerides (normal to high) were observed.

7.1.7.3.1 Analyses focused on measures of central tendency

Chemistry Laboratory Parameters

Compared to patients on placebo in the Placebo-Controlled Database, patients on 300 mg/2 weeks OP depot demonstrated statistically significant increases in AST, ALT, and CPK; and statistically significant decreases in calcium, potassium, albumin, and direct bilirubin. Patients on 405 mg/4 weeks OP depot demonstrated statistically significant increases in alkaline phosphatase, cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides; and statistically significant decreases in urea nitrogen, potassium, and prolactin, compared with

patients on placebo. Patients on 210 mg/2 weeks OP depot demonstrated statistically significant increases in cholesterol and triglycerides, and statistically significant decreases in calcium, albumin, and prolactin, compared with patients on placebo.

Though the difference in serum prolactin between groups was not statistically significant, OP Depot-treated patients showed a significant within-group decrease of -5.80 µg/L and placebo-treated patients showed a non-significant within-group decrease of -4.11 µg/L in serum prolactin. Many patients in this database received previous antipsychotic medications (39.4% with risperidone and 25.7% with haloperidol) prior to randomization to OP Depot or placebo, which may have affected their serum prolactin levels during the studies.

Hematology Laboratory Parameters

Compared with patients on placebo in the Placebo-Controlled Database, patients on 300 mg/2 weeks OP depot demonstrated statistically significant increases in monocytes and basophils, and statistically significant decreases in mean cell hemoglobin concentration. Compared with patients on placebo, patients on 405 mg/4 weeks OP depot demonstrated statistically significant increases in platelets, while patients on 210 mg/2 weeks OP depot demonstrated statistically significant increases in lymphocytes, eosinophils, and platelets.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Treatment-emergent significant changes in glucose and lipid levels were found in the Placebo-Controlled Database. Compared to placebo-treated patients, more patients on 300 mg/2 weeks OP depot demonstrated shifts from normal baseline LDL cholesterol levels to borderline high post-baseline levels ($p=.038$) and from normal baseline triglyceride levels to high post-baseline levels ($p=.016$). Compared to placebo-treated patients, more patients on 405 mg/4 weeks OP depot demonstrated shifts from normal baseline total cholesterol levels to borderline high post-baseline levels ($p=.005$). Compared to placebo-treated patients, more patients on 210 mg/2 weeks OP depot demonstrated shifts from normal baseline triglyceride levels to high post-baseline levels ($p=.029$).

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were 3 OP Depot-treated patients discontinued from Study HGJZ due to “hepatic enzyme increased”—1 case of ALT increased (405 mg/4 week group) and 2 cases of hepatic enzyme increased (300 mg/2 week group). None of these cases were reported as SAEs and no cases met the criteria of Hy’s Law ($ALT \geq 3$ times upper limit of normal [ULN] and $TBILI \geq 1.5$ times ULN). Transient, asymptomatic elevations of the hepatic transaminases ALT (alanine transaminase) and AST (aspartate transaminase) have been commonly reported in clinical studies of oral olanzapine, especially during early treatment. Asymptomatic elevations of hepatic transaminases and alkaline phosphatase are included in the Warnings and Precautions section of current olanzapine labeling.

One patient in OP Depot 210 mg/2 week group discontinued Study HGJZ due to “moderate blood glucose increased”.

7.1.7.4 Additional analyses and explorations

Hepatic-Related Adverse Events

Special analyses of hepatic-related adverse events were conducted by the sponsor.

In the Placebo-Controlled Database, changes $\geq 3 \times$ ULN in ALT (SGPT) values were observed in 2.7% (8/291) of patients treated with OP Depot compared with 3.2% (3/94) of patients treated with placebo. None of these patients experienced jaundice.

In the Olanzapine-Controlled Database, no statistically significant differences were observed between Olanzapine Pamoate (OP) Depot and oral olanzapine in the incidence of patients with one or more hepatic-related AEs overall ($p=.577$) or for any specific event. The incidence of hepatic-related AEs was 1.3% in the OP Depot treatment group, 1.9% in the oral olanzapine treatment group, and 1.5% overall. In the Overall Integrated Database, the incidence of hepatic-related AEs was 1.6% (29 of 1779 randomized patients). The most commonly reported elevated liver function test was increased alanine aminotransferase, which occurred in 13 patients (0.7%).

7.1.7.5 Special assessments

No special assessments were warranted in this study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

During these studies, blood pressure (systolic and diastolic), pulse rate, weight, and temperature were collected at regular intervals per protocol.

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

The vital sign data from Study HGJZ (the placebo-controlled database) were examined in detail in this review and the vital sign data from other OP Depot trials (the Olanzapine-Controlled Database and the Overall Integrated Database) were examined to detect rare, unexpected, serious and clinically significant vital sign abnormalities.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Patients treated with OP Depot 300 mg/2 weeks exhibited a mean increase in standing systolic blood pressure (+3.735 mm HG, $p=.018$), supine pulse (+3.316 bpm, $p=.030$) and weight (+3.861 kg, $p<.001$). Patients treated with OP Depot 405 mg/4 weeks demonstrated a mean increase in supine systolic blood pressure (+3.870 mm HG, $p=.003$), standing systolic blood pressure (+3.360 mm HG, $p=.024$), supine pulse (+3.010 bpm, $p=.020$), and weight (+2.763 kg, $p<.001$). Patients treated with OP Depot 210 mg/2 weeks exhibited a mean increase in weight (+3.819 kg, $p<.001$). In addition to being statistically significant within each treatment group, the mean increases in weight were statistically significant compared to placebo for each of the OP Depot treatment groups.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no statistically or clinically significant differences in vital sign measurements among any of the treatment groups. However, differences in weight gain and weight loss were statistically significant between the OP-depot treatment groups compared with the placebo group. Each of the OP-depot treatment groups had a statistically significant greater percentage of patients gaining at least 7% of their baseline weight (35.4%, $p<.001$; 27.0%, $p=.012$; and 23.6%, $p=.046$ for 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks, respectively) compared to the placebo group (12.4%). Similarly, the placebo group had a statistically significantly higher percentage of patients losing at least 7% of their baseline weight (12.4%) compared to the OP depot groups (2.0%, $p=.005$; 1.0%, $p=.001$; and 2.8%, $p=.014$ for 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks, respectively).

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no patients discontinued from Study HGJZ due to abnormal vital signs or weight gain.

7.1.8.4 Additional analyses and explorations

Metabolic Parameters and Weight Gain

The purpose of these analyses is to assess changes in weight and metabolic parameters in patients treated with OP Depot and to compare these changes to those seen in patients treated with oral olanzapine.

The analyses of mean changes from baseline to endpoint for weight, fasting glucose & lipids, clinically significant weight gain (at least 7% from baseline) and on incidence rates of treatment-emergent weight gain-related AEs in the Olanzapine-Controlled Database and in the Overall Integrated Database were conducted.

The findings from these analyses show that patients treated with OP Depot doses of 150 mg/2 weeks, 405 mg/4 weeks, and 300 mg/2 weeks (in the Olanzapine-Controlled Database) did not experience a statistically significant higher incidence of weight gain or a statistically significant higher incidence of undesirable changes in lipids parameters when compared to patients treated

with oral olanzapine. In addition, the types of weight gain-, diabetes- and dyslipidemia-related adverse events (AEs) in the patients treated with OP Depot were similar to those seen in the patients treated with oral olanzapine.

Statistically significant dose responses were found for the incidence of potentially clinically significant (PCS) weight gain and elevated triglycerides (from normal to high) in the Olanzapine-Controlled Database. The highest incidence of PCS weight gain and elevated triglycerides (from normal to high) were observed in patients treated with 300 mg/2 weeks OP Depot compared to other OP Depot treatment groups.

7.1.9 Electrocardiograms (ECGs)

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

During these studies, twelve-lead ECGs were collected at regular intervals per protocol. Each ECG was reviewed by a qualified physician to determine whether any findings were clinically significant. If a clinically significant increase from baseline in the QTc interval is observed during the trial, the patient was assessed by the investigator for symptoms (such as palpitations, near syncope, syncope).

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

The ECG data from Study HGJZ (the placebo-controlled database) were examined in detail in this review and the ECG data from other OP Depot trials (the Olanzapine-Controlled Database and the Overall Integrated Database) were examined to detect rare, unexpected, serious and clinically significant ECG abnormalities.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Statistically significant changes from baseline were observed in all OP depot treatment arms in the Placebo-Controlled Database. Patients in the 300 mg/2 weeks treatment group had statistically significant increases in heart rate (5.00 bpm, $p=.003$), QTc Bazett's (7.673 msec, $p<.001$), and QTc Fredericias (3.353 msec, $p=.039$). Patients in the 405 mg/4 weeks treatment group had statistically significant increases in QTc Bazett's (5.13 msec, $p=.019$). Patients in the 210 mg/2 weeks treatment group had statistically significant increases in heart rate (4.095 bpm, $p=.002$), QTc Bazett's (7.952 msec, $p<.001$), and QTc Fredericias (4.316 msec, $p=.008$). Even these QT elongations are statistically significant, the changes are small and the clinical significance is unclear. Olanzapine associated mild tachycardia has been addressed in current olanzapine labeling.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no statistically or clinically significant differences between OP depot and placebo in potentially clinically significant ECG observations in the Placebo-Controlled Database.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Although there were no statistically significant differences in clinically significant outliers across treatment groups in the Placebo-Controlled Database, there were 8 patients with potentially clinically significant QTc observations. One patient randomized to OP depot 300 mg/2 weeks had a reported QTc Bazett's interval ≥ 500 msec. Six patients randomized to OP depot treatment groups showed a QTc Bazett's interval increase ≥ 60 msec. One patient in the placebo treatment group had a QTc Fredericias interval increase ≥ 60 msec.

None of those patients were reported as SAEs and none of them discontinued from the study due to the AE. There was one patient in placebo group discontinued because of atrial fibrillation.

7.1.9.4 Additional analyses and explorations

Cardiovascular Safety

Lilly conducted separate analyses of cardiovascular events for the Olanzapine-Controlled Database and the Overall Integrated Database. In addition, an analysis was conducted comparing treatment-emergent cardiovascular-related AEs and syncope-related AEs between patients treated with OP Depot and patients treated with oral olanzapine.

The analyses of cardiovascular measures did not reveal any new safety findings during treatment with OP Depot that had not been previously reported during treatment with oral olanzapine. The key safety findings are discussed below.

- No statistically significant differences were observed between patients treated with OP Depot and patients treated with oral olanzapine in the incidence of treatment-emergent cardiovascular-related AEs or syncope-related events.
- No statistically significant treatment differences in mean changes at endpoint in vital signs, ECG heart rate, or QT-corrected Fridericia formula (QTcF) were observed between any OP Depot doses in the fixed-dose study HGKA.
- No evidence was found to indicate that patients treated concomitantly with benzodiazepines experienced clinically significant changes in cardiovascular or hemodynamic function as a result of a drug interaction; however, caution is necessary in patients who receive treatment with OP Depot and other drugs having effects that can induce hypotension, bradycardia, and respiratory or central nervous system (CNS) depression.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not required.

7.1.12 Special Safety Studies

The Excessive Sedation Events

1. Summary of the Excessive Sedation Events

Summary of Related Clinical Data

As of 30 November 2007, a total of 25 of these events had been reported in 24 patients. A total of 36,856 injections had been given to 1915 patients in OP Depot clinical trials. Therefore, the incidence of these excessive sedation events is 0.07% of injections and 1.3% of patients.

Adverse event reports have demonstrated a temporal association between the excessive sedation events and symptoms consistent with some of the AEs reported in patients experiencing oral olanzapine overdose, including profound sedation, seizure, dizziness, confusion, disorientation, slurred speech, altered gait, and weakness. However, orthostatic hypotension, arrhythmias, cardiac arrest were not observed in these cases.

The majority of initial signs and symptoms of the excessive sedation events have occurred within 1 hour of injection (21/25; 84%, median time of onset is 20 min.). However, the time onset of the excessive sedation events has ranged from immediately post injection to up to 3 hours after the injection.

Most events occurred after the patient had received several months of injections (mean number of injections was 18.5) and ranged in occurrence from 1 event at the first injection to 1 event at the 40th injection. The mean number of days (from starting treatment with OP Depot) to an event was 278 days. Only one patient experienced two events.

Patients have fully recovered from the excessive sedation events within 3 to 72 hours and without permanent sequelae. The majority of patients (17/24; 68%) who experienced an event continued to receive OP Depot.

Table 30 (10.3 Appendix to Safety Review) summarizes all 25 cases that had been identified as of 30 November 2007. Among these cases, 20 were hospitalized for monitoring or treatment during excessive sedation events. The profound sedation ranged from “drowsiness”, “deep sleep”, “unarousable for hours”, to “altered consciousness” (1 case), “loss of consciousness” (2 cases) and “coma” (2 cases: one was in coma for 13 hours and another one had bilateral miosis, no photomotric reflex and left side Babinski). Two patients were intubated, which the sponsor described as preventive measures (one for tonic clonic convulsions and one for severe agitation).

Delirious symptoms were reported in 2 cases and tonic clonic convulsions were observed in two cases. One patient experienced increased blood pressure (190/110 mmHg, 60 min post injection).

The Possible Cause of the Excessive Sedation Events

The mechanism underlying these events is not clear. However, all the available information from investigations suggested that an excessive amount of olanzapine enters the systemic circulation faster than intended for this IM controlled-release depot form. The olanzapine concentrations in the 7 cases where plasma concentrations were measured further support this etiology. Lilly characterized that these events as most likely related to accidental intravascular injection of a portion of the OP Depot dose, but the exact mechanism producing the excessive sedation events has not been determined.

To address accidental intravascular injection problems which may have been responsible for the excessive sedation events, Lilly retrained their study personnel to reinforce proper IM injection technique and extended the post-injection observation period to 3 hours in their ongoing OP Depot clinical trials in July 2007. However, the incidence of the excessive sedation events didn't change and ten additional cases were reported after then.

Characteristic of Patients Experiencing the Excessive Sedation Events

Table 24 summaries the characteristics of patients experiencing the excessive sedation events.

Table 24 Summary of Excessive Sedation Patients Characteristics

Variable	OP Depot Patients (N = 1918)	IAIV Patients (N = 24)

Gender		
Male	1306 (68.1)	18 (75.0)
Origin		
Caucasian	1260 (65.7)	20 (83.3)
African	291 (15.2)	2 (8.3)
Hispanic	247 (12.9)	2 (8.3)
Age in years		
Mean	39.41	43.13
Median	39.59	
Maximum	74.12	63.49
Minimum	18.10	23.84
Standard Dev.	11.02	11.21

Logistic Regression for Identification of Factors in the Excessive Sedation Events

Lilly analyzed excessive sedation event data for factors that might be associated with a greater risk of an event. An analysis of data for the 25 excessive sedation events was performed. The

logistic regression model identified higher dose ($p=0.037$), greater age ($p=0.055$), and lower BMI ($p=0.052$) as potential risk factors for an excessive sedation event. But, the events have also occurred in patients without these specific risk factors. A statistically significantly increased potential risk of an excessive sedation event was found at higher dose. It is important to note that the higher doses of OP Depot also correspond to an increased volume of IM injection because all doses of the drug product are prepared from a fixed suspension of 150 mg/mL.

2. Investigations to Determine the Cause of the Excessive Sedation Events

Solubility of Olanzapine Pamoate Monohydrate

The low aqueous solubility of the practically insoluble crystalline salt, olanzapine pamoate monohydrate, in muscle tissues is the means by which the release of olanzapine is sustained over a period of weeks when OP Depot is injected intramuscularly. It is reasonable to believe that olanzapine pamoate may be more soluble in certain biological fluids or under certain physiological conditions. Therefore, as a preliminary investigation, in vitro experiments that evaluated the solubility of olanzapine pamoate in plasma or blood were performed by the sponsor. The in vitro solubility experiment demonstrated that the amount of Olanzapine Pamoate Monohydrate dissolved in human blood was much higher (35 – 68% within roughly half an hour) than anticipated for the practically insoluble olanzapine pamoate crystalline salt. The equilibrium solubility experiment demonstrated that the solubility of olanzapine pamoate monohydrate in plasma is about 167 times (plasma 0.5 mg/mL, aqueous buffer 0.003 mg/mL) higher than that in an aqueous medium which is assumed to putatively reflect the solubility of olanzapine pamoate in extracellular fluid of muscle tissue.

PK Investigations

Olanzapine plasma concentrations were measured in 7 of the 25 the excessive sedation events. In each of these events, a much higher olanzapine plasma concentration was observed than would have been expected. Olanzapine plasma concentrations obtained during the excessive sedation events were presented in Table 31 (10.3 Appendix to Safety Review).

Figure 2 from the sponsor's submission illustrates the olanzapine plasma concentration profile after 6 different OP Depot injections in one patient who experienced an excessive sedation event after the second injection. Higher than expected olanzapine plasma concentrations occurred after the second 300 mg OP Depot injection as marked in the graph by an arrow at the point at which the excessive sedation event was experienced. This patient also received five other injections (one 300 mg dose before and four 200 mg doses after the excessive sedation event) all of which exhibited a typical plasma concentration profile associated with the OP Depot regimen.

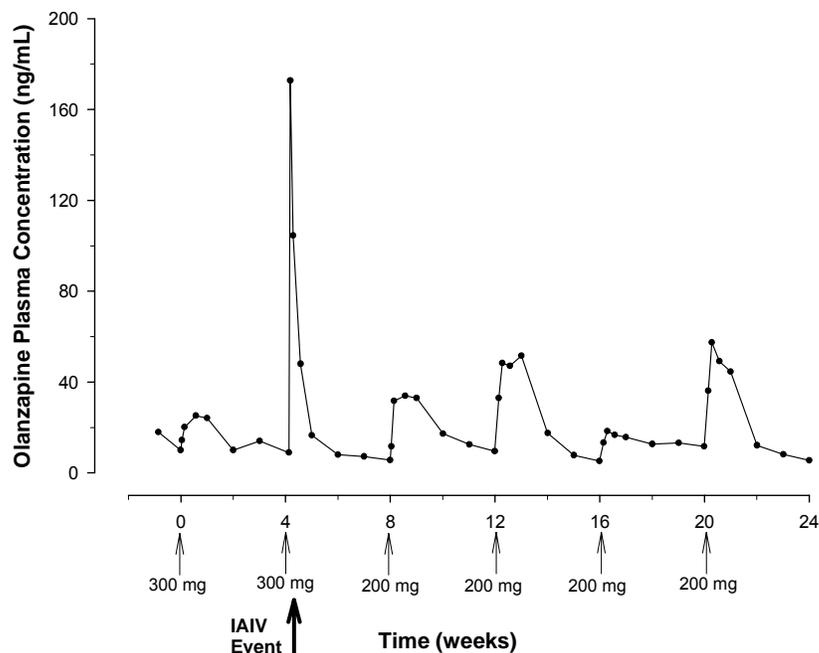


Figure 2 Olanzapine Plasma Concentration vs Time Profile During an Excessive Sedation Event

Olanzapine concentrations for 4 out of the 7 events demonstrated a very similar finding, where the olanzapine concentrations during the excessive sedation event were unexpectedly elevated compared to those drawn after injections where no excessive sedation event had occurred. In the remaining 2 of the 7 events, patients did not have any other blood samples drawn for pharmacokinetic analysis.

Figure 3 from the sponsor's submission illustrates the plasma concentration profiles obtained during the excessive sedation events from all 7 excessive sedation events on a common scale (Lilly refers the excessive sedation events as IAIV events). More detailed PK review can be found in Dr. Andre Jackson's (clinical pharmacology) review.

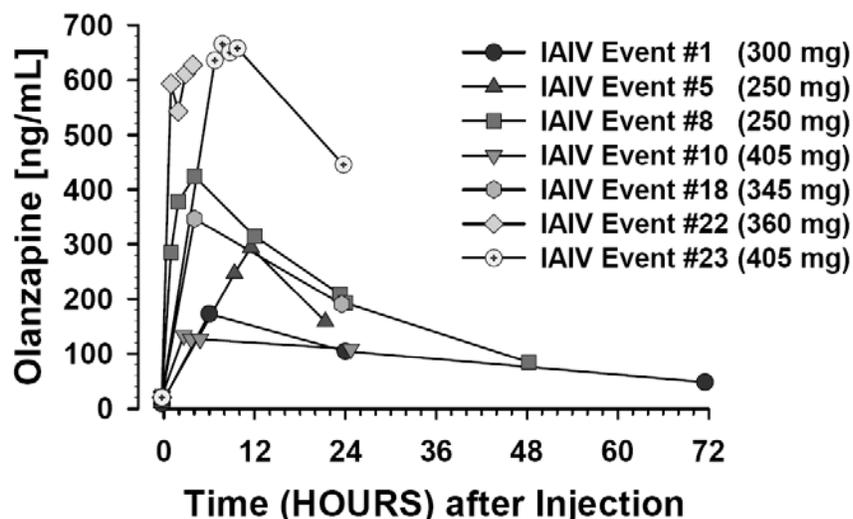


Figure 3 Olanzapine Plasma Concentrations Observed During an Excessive Sedation Event-Data for All Seven Cases

Chemistry, Manufacturing, & Control Investigations

The physicochemical properties of olanzapine salt (crystal form), such as the particle size or surface area, can affect the rate of release. The drug product particle size distribution (PSD) defines the surface area available for dissolution. Significant amounts of small particles giving rise to a very large surface area could potentially result in too rapid an initial dissolution and drug release.

Review of manufacturing data for the clinical trial lots used for these events demonstrated that all lots met the established standards for CM&C during their manufacturing. CM&C approval and stability data were comparable to data from other clinical trial lots in which sedation was not observed. Clinical trial lot CM&C data used to approve the release of the lots for clinical use indicate that there have been no lots with significant amounts of small particles. Furthermore, it has been shown that the PSD does not change upon storage. Homogeneity of the drug product PSD from vial-to-vial has been demonstrated.

Analysis of the residual suspension remaining in the drug product vials after administration of OP Depot was performed for 11 vials. Ten vehicle vials were also tested to confirm the identity of the vehicle. Results of testing demonstrated that the residual suspension exhibited the expected physicochemical properties (potency, related substances, pH, particle size, morphology).

3. Overall Summary and Conclusions

The key findings regarding excessive sedation events can be briefly summarized as follows:

- As of 30 November 2007, a total of 25 excessive sedation events have been identified in 24 patients during OP Depot clinical trials.
- Signs and symptoms reported with excessive sedation events are consistent with AEs reported in patients experiencing oral olanzapine overdose.
- 20 of the 24 patients were hospitalized for monitoring or treatment. Alteration of consciousness was reported in 5 cases which included two cases of coma. Two patients were intubated.
- Higher dose (also corresponding to an increased injection volume), greater age, and low BMI have been identified as potential risk factors of an excessive injection event, based on logistic regression analysis; but the events have also occurred in patients without these specific risk factors.
- The time to onset for 21 of the 25 events was within 1 hour of the injection and within 3 hours of the injection for the 4 remaining events.
- Olanzapine plasma concentrations were higher than expected in the 7 excessive sedation events where samples were collected.
- Preliminary equilibrium solubility experiment demonstrated that the solubility of olanzapine pamoate monohydrate in plasma is about 167 times higher than that in an aqueous medium.
- The incidence of the excessive sedation events didn't change after Lilly retrained their study personnel and reinforced IM injection technique in July 2006. Ten additional cases were reported after then.
- All patients who experienced an excessive sedation event were fully recovered from the event, and the majority (17/24) continued in the study.

The excessive sedation events raised a serious safety concern because of severity of sedation, unpredictable characteristics, delayed onset (a few hours after injection) in some cases, and relatively high risk of occurrence (0.07% of injections and 1.3% of patients).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The current existing clinical trial information does not demonstrate specific risks related to discontinuation or abuse of OP Depot.

7.1.14 Human Reproduction and Pregnancy Data

Women who were pregnant or breast feeding and women of childbearing potential who were not using a medically accepted means of contraception were excluded from enrolling in all clinical studies presented in this application. However, four incidences of pregnancy were identified in OP Depot clinical trials.

Three patients (LOBE-101-1152, HGJZ-HGKB-23-5727, and HGKA-HGKB-570-8634) had elective abortions during OP Depot clinical trials. In these cases, the decision was made by the investigator, in consultation with a Lilly CRP, to continue the patient in the study because the abortions had been confirmed.

In the 4th event, the patient (HGKA-HGKB-224-7595) received an OP Depot injection (300 mg/2 weeks, after total of 189 days on OP Depot) on the same visit in which the positive pregnancy test was obtained. The patient was discontinued from the study because of noncompliance with protocol procedures. Upon follow-up, the investigator reported the pregnancy outcome was a normal birth.

7.1.15 Assessment of Effect on Growth

No pediatric patients were enrolled in these studies. Therefore, the effect of OP Depot on growth was not studied.

7.1.16 Overdose Experience

Because OP Depot is administered intramuscularly by health care professionals, no OP Depot-related intentional overdose cases were reported.

7.1.17 Postmarketing Experience

Because OP Depot has not been approved for marketing, no postmarketing data specific to OP Depot are available as this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

7.2.1.1 Study type and design/patient enumeration

Table 25 summarizes the studies included in OP Depot integrated safety review.

Table 25 Description of Studies Included in the Integrated Safety Database

Databases/Description of Databases	Studies	Treatment Groups	Analyses
Placebo-Controlled Database/contains safety data from 404 patients randomized to OP Depot (306) or placebo (98)	HGJZ	Pooled OP Depot treatment groups (210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) Placebo	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and special topic ^a for injection-site-related AEs.
Olanzapine-Controlled Database/contains safety data from 921 patients randomized to OP Depot (599) or oral olanzapine (322)	HGKA	Pooled OP Depot treatment groups ^b (150 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) excluding 45 mg/4 weeks Oral Olanzapine (10, 15, and 20 mg)	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and the following special topics: (IAIV) injection events, cardiovascular events, metabolic parameters and weight gain, and hepatic measures.
Overall Integrated Database/contains safety data from patients who received treatment with OP Depot in any clinical trial conducted in patients with schizophrenia or schizoaffective disorder	HGJW LOBE LOBO LOBS HGJZ HGKA HGKB	Pooled OP Depot treatment groups ^c	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and the following special topics: IAIV injection events, cardiovascular events, metabolic parameters and weight gain, hepatic measures, and injection-site-related AEs.

7.2.1.2 Demographics

Although a few statistically significant differences were seen (age and gender) in the Placebo-Controlled Database, actual mean differences between groups were small. Patients in both treatment groups of the Olanzapine-Controlled Database were comparable with respect to baseline demographics and physical characteristics at baseline. At baseline, patients in the Overall Integrated Database had a mean age of 39.2 years; 66.0% were Caucasian, and 68.1% were male.

As a whole, baseline Positive and Negative Syndrome Scale (PANSS) scores indicated that patients in the Placebo-Controlled Database were clinically more acutely ill (mean baseline PANSS Total Score = 101), while patients in the Olanzapine-Controlled Database were clinically stable (mean baseline PANSS Total Score = 55).

Discontinuations due to adverse events (AEs) were ≤ 5.1% in all databases.

7.2.1.3 Extent of exposure (dose/duration)

Table 26 summarizes exposure information for all patients who had received at least one injection of OP Depot. Cumulative exposure represents a maximum length of 951 days (approximately 2.6 years).

Table 26 Summary of Patient Exposure to All OP Depot doses (Overall Integrated Database)

N=1915 ^a					
	Min	Med	Mean	Max	Total
Number of injections ^b	1	8	14.21	68	27,210
Days of OP Depot exposure	14	168	278.64	951	533,599
Total patient years of exposure:			1460.91		

Abbreviations: Max = maximum; Med = median; Min = minimum; N = Number of patients with OP Depot exposure; OP = olanzapine pamoate.

- a A total of 1918 patients have been assigned to OP Depot, however, 2 patients discontinued study participation before the first injection and 1 patient received the first injection after datalock in an ongoing study (HGLQ). Thus, only 1915 patients have received at least one injection of OP Depot.
- b All depot dose levels are included in the calculations of the number of injections and days of exposure.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were conducted to evaluate the safety of OD Depot for this submission.

7.2.2.2 Postmarketing experience

Because OP Depot has not been approved for marketing, no postmarketing data specific to OP Depot are available as this time.

7.2.2.3 Literature

A worldwide literature search was conducted on 8 February 2007 using the following databases: Biosis Previews (1989 to 2007 Week 9), Embase (1988 to 2007 Week 5), Ovid Medline (1950 to 2007 Week 5), and Ovid Medline In-Process & Other Non-Indexed Citations (7 February 2007). No citations were identified related to olanzapine pamoate depot, olanzapine and pamoic acid, or olanzapine pamoate. This literature search did not reveal any important new safety information.

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate to evaluate the efficacy and safety of OP Depot.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No animal study was conducted in this submission. In vitro solubility tests were conducted to explore the causality of the excessive sedation events. Details of these solubility tests can be found in section 7.1.12 Special Safety Studies.

7.2.5 Adequacy of Routine Clinical Testing

Generally speaking, routine clinical testing in this submission was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

A detailed review of metabolism, clearance and interaction workup can be found in Dr. Andre Jackson's review.

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

Overall evaluation for potential adverse events for OP Depot was adequate.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of data were acceptable.

7.2.9 Additional Submissions, Including Safety Update

A four month safety update was submitted by Lilly on 8 August 2007 (data cut-off date on 31 January 2007). The updated safety information has been incorporated into the integrated safety review.

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

Other than excessive sedation events and injection site-related AEs, the profile of drug-related adverse events in OP Depot is consistent with that of oral olanzapine. No important limitations of data were found.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Both the Placebo-Controlled Database and the Olanzapine-Controlled Database are comprised of only one study in each database. The Overall Integrated Database included 8 OP Depot clinical trials.

7.4.1.2 Combining data

The Overall Integrated Database combined 8 OP Depot clinical trials.

7.4.2 Explorations for Predictive Factors

No further explorations for predictive factors were conducted in these studies.

7.4.3 Causality Determination

Adverse events were considered as generally treatment-related only if the AE rate occurred in at least 2% of OP Depot treated patients and at a rate of at least twice that of placebo.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Both the short-term (HGJZ) and long-term (HGKA) controlled studies were fixed dose studies. In Study HGJZ, the dose regimen was OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 210 mg/2 weeks and placebo. In Study HGKA, the dose regimen was OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 150 mg/2 weeks, 45 mg/4 weeks and oral olanzapine (flexible doses 10 to 20 mg/d). All OP Depot was administered by gluteal intramuscular injection.

8.2 Drug-Drug Interactions

The existing olanzapine labeling addresses safety outcomes related to potential drug-drug interactions. There have been no new data generated on this topic from this submission.

8.3 Special Populations

The existing olanzapine labeling addresses safety outcomes as they relate to the pediatric population, geriatric population, nursing mothers and pregnant women. There have been no new data generated on these topics that have not already been addressed in the labeling.

8.4 Pediatrics

Lilly requested a full waiver of OP Depot pediatric studies for indication in the treatment of schizophrenia. This waiver requested covers ages from birth to 17 years old. Lilly's main justification for the request is that OP Depot is unlikely to be used in a substantial number of pediatric patients, for several reasons, including that it does not represent a meaningful therapeutic benefit over existing therapies for the pediatric population.

Briefly, schizophrenia is less common overall in children and adolescents than in adults; compliance issues that make depot formulations attractive are less common in pediatric populations than in adult populations; and generally accepted clinical practice guidelines for treatment of schizophrenia in children and adolescents recommend only limited use of depot antipsychotics.

I find Lilly's arguments persuasive. In addition, olanzapine is associated with significant adverse events including metabolic syndrome, weight gain and increased risk of diabetes, which will pose additional risk to children if pediatric trials are conducted. The excessive sedation events occurred in adult OP Depot trials could be life threatening to children. Therefore, I recommend a full waiver of pediatric studies if the agency decides to grant OD Depot an approval status.

8.5 Advisory Committee Meeting

This NDA will be presented to the Psychopharmacologic Drug Advisory Committee (PDAC) on 6 February 2008 because of a significant safety issue—the excessive sedation events (see 7.1.12 Special Safety Studies). A addendum to this review with final recommendation will be filed after the PDAC meeting.

8.6 Literature Review

A worldwide literature search was conducted on 8 February 2007 using the following databases: Biosis Previews (1989 to 2007 Week 9), Embase (1988 to 2007 Week 5), Ovid Medline (1950 to 2007 Week 5), and Ovid Medline In-Process & Other Non-Indexed Citations (7 February 2007).

The following search was performed:
[**{olanzapine}**] and [**{pamoate}**] and [**{depot}**]

Additional search using above databases with similar timeline was conducted to search following key words: [**{olanzapine}**] and [**{pamoic acid}**], [**{olanzapine}**] and [**{pamoate}**].

No citations were identified regarding olanzapine pamoate depot, olanzapine and pamoic acid, or olanzapine pamoate. This literature search did not reveal any important new safety information.

8.7 Postmarketing Risk Management Plan

This application will be presented to the PDAC on Feb. 6, 2008. A risk management plan may be recommended after the meeting.

8.8 Other Relevant Materials

The plasma concentration data in patients who experienced the excessive sedation events were provided by Lilly upon the requests of clinical pharmacology reviewer.

9 OVERALL ASSESSMENT

9.1 Conclusions

In the short-term acute efficacy and safety study (HGJZ), the three OP depot treatment groups showed superiority to placebo in reducing PANSS Total Score from baseline to endpoint starting at week 1 and continuing through the end of the study.

In the long-term maintenance study (Study HGKA), the 3 higher dose OP Depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups demonstrated positive maintenance effect over 24 weeks for stabilized patients with schizophrenia.

The safety evaluation of OP Depot demonstrated that the safety profile is similar to that of oral olanzapine for most parameters that were measured, with the exception of injection-related adverse events and excessive sedation events.

Excessive sedation events are a serious safety concern because of the severity of excessive sedation, the unpredictable characteristics, and relatively high incidence—0.07% of injections and 1.3% of patients.

9.2 Recommendation on Regulatory Action

Since this NDA will be presented to Psychopharmacologic Drug Advisory Committee on February 6, 2008, decisions on final regulatory action will be defined until after the committee recommendations are considered.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The development of a risk management plan will depend on the outcome and conclusions of the PDAC to take place on Feb. 6, 2008.

9.3.2 Required Phase 4 Commitments

To be determined based on regulatory action to be decided after the PDAC meeting.

9.3.3 Other Phase 4 Requests

To be determined.

9.4 Labeling Review

Since this NDA will be presented to advisory committee on February 6, 2008 and no regulatory action is recommended, labeling review is not deemed necessary at this time.

9.5 Comments to Applicant

None at this time.

10 APPENDICES

10.1 List of Principle Investigators and Study Sites

Table 27 List of Principle Investigators in Study HGJZ

Investigator 010 Scott Tyler Aaronson, MD Director of Clinical Research Programs Sheppard Pratt Health System 6501 N. Charles Street Baltimore, MD 21285-6815	Investigator 012 Steven J. Glass, MD Psychiatric Medical Director 130 White Horse Pike Clementon, NJ 08021	Investigator 013 Mohammed A. Bari, MD VP/Director, Clinical Research Synergy Clinical Research Center 1908 Sweetwater Road National City, CA 91950
Investigator 014 Louise M. Beckett, MD Chief Executive Officer and Medical Director IPS Research Company 1111 North Lee, Suite 400 Oklahoma City, OK 73103	Investigator 015 Terrance J. Bellnier Chairman GPI, Inc. 36 Forest Meadow Tr. Rochester, NY 14624	Investigator 016 Matthew Brams, MD Principal Investigator Bayou City Research Corp. 550 Westcott, Suite 310 Houston, Texas 77007
Investigator 017 Ronald Brenner, MD President and CEO Neurobehavioral Research, Inc 371 Central Ave Lawrence, NY 11559	Investigator 018 Menahem Krakowski, MD Research Psychiatrist Nathan Kline Psychiatric Research Institute 140 Old Orangeburg Road Orangeburg, NY 10962	Investigator 020 Carlos M. Figueroa, MD Principal Investigator Advanced Psychiatric Group 4619 N Rosemead Blvd. Rosemead, CA 91770
Investigator 022 Steven E. Holroyd, MD Staff Psychiatrist West Hills Hospital 1240 East Ninth Street Reno, Nevada 89512	Investigator 023 Robert L. Horne, MD Medical Director Montevista Hospital 2915 W. Charleston Blvd. Las Vegas, NV 89102	Investigator 024 Richard L. Jaffe, MD Research Psychiatrist Belmont Center for Comprehensive Treatment 4200 Monument Road Philadelphia, PA 19131
Investigator 025 Andrew J. Cutler, MD Medical Director, President, and Investigator CORE Research, Inc 2020 26 th Avenue East Bradenton, FL 34208	Investigator 026 James A. Knutson, MD Private Practice Physician 512 6 th Street South, Suite 101 Kirkland, WA 98033	Investigator 027 John Lauriello, MD Executive Medical Director The University of New Mexico Department of Psychiatry 943 Stanford Dr. Northeast Albuquerque, New Mexico 87131-5326

<p>Investigator 028 Zinaida Lebedeva, MD Principal Investigator 13207 Ravenna Road, Suite 400 Chardon, OH 44024</p>	<p>Investigator 029 Mark Lerman, MD Director of Clinical Research Program and Principal Investigator Alexian Brother's Behavioral Health Hospital 1721 Moon Lake Blvd, Suite 109 Hoffman Estates, IL 60194</p>	<p>Investigator 030 Michael T. Levy, MD Chairman, Department of Behavioral Sciences Behavioral Medical Research of Staten Island, PC 1361 Hylon Blvd Staten Island, NY 10305</p>
<p>Investigator 031 Robert Enoch Litman, MD Medical Director CBH Health, LLC 9605 Medical Center Drive Main Office: Suit 250 Rockville, MD 20850</p>	<p>Investigator 032 Adam F. Lowy, MD Investigator Psychiatric Institute of Washington 4228 Wisconsin Avenue, NW Washington, DC 20016</p>	<p>Investigator 033 Gerald A. Maguire, MD Attending Physician UC Irvine Medical Center Department of Psychiatry 101 City Drive South, Route 88 Orange, California 92868</p>
<p>Investigator 034 Denis Mee-Lee, M.D. Principal Investigator Hawaii Clinical Research Center 1750 Kalakaua Avenue, Suite 2602 Honolulu, Hawaii 96826</p> <p>Investigator 039 John G. Sonnenberg, PhD Executive Director Uptown Research Institute, LLC 4755 N. Kenmore Avenue Chicago, IL 60640</p>	<p>Investigator 035 Ricky S. Mofsen, MD Medical Director Clinical Research Inc 2639 Miami Street St. Louis, MO 63118</p> <p>Investigator 042 Roger William Sommi, Jr, PharmD Director Western Missouri Mental Health Center 2411 Holmes M3-C19 Kansas City, MO 64108</p>	<p>Investigator 038 Michael G. Plopper, MD Medical Director Sharp Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, California 92123</p> <p>Investigator 043 Marshall R. Thomas, MD Associate Professor, Medical Director, Vice President and Medical Director 4455 East 12th Avenue Box A-011-99 Denver, CO 80220</p>
<p>Investigator 044 Cherian Verghese, MD Principal Investigator Keystone Clinical Studies, LLC 1401 Dekalb Street, Suite 201 Norristown, PA 19401</p>	<p>Investigator 045 Kashinath G. Yadalam, MD Medical Director, Institute for Neuropsychiatry Institute for Neuropsychiatry 1770 3rd Avenue, Suite 340, Lake Charles, LA 70601</p>	<p>Investigator 046 Adrian Leibovici, MD Attending Psychiatrist Strong Memorial Hospital 300 Crittenden Boulevard Rochester, NY 14642</p>
<p>Investigator 047 Saroj Brar, MD Windsor Hospital 115 East Summit Street Chargin Falls, OH 44022</p>	<p>Investigator 048 Himasiri De Silva, MD FAPA Medical Director Clinical Office 801 North Tustin, Suite 600 Santa Ana, CA 92705</p>	<p>Investigator 049 Jean-Pierre Hans Peter Lindenmayer, MD Clinical Director Psychopharmacology Research Program Manhattan Psychiatric Center, Meyer 10A – Wards Island New York, NY 10035</p>

<p>Investigator 050 Kenneth Lovko, MD Principal Investigator CBH Health at Maryview Behavioral Medicine Center 3636 High Street Portsmouth, VA 23703</p>	<p>Investigator 501 Dr. Vera Folnegovic-Smalc Psihijatrijska Bolnica Vrapce Bolnicka Cesta 32 Zagreb HR-10090, Croatia</p>	<p>Investigator 502 Dr. Darko Perusic Psihijatrijska Bolnica Vrapce Bolnicka Cesta 32 Zagreb HR-10090, Croatia</p>
<p>Investigator 503 Dr. Vlado Jukic Psihijatrijska Bolnica Vrapce Bolnicka Cesta 32 Zagreb HR-10090, Croatia</p>	<p>Investigator 800 Prof. Sergey N Mosolov Moscow Research Institute of Psychiatry of the Ministry of Health of the Russian Federation , Federal Scientific Centre for Therapy of Mental Disorders Poteshnaya 3, Moscow, Russia, 107076</p>	<p>Investigator 801 Prof. Vladislav Shamrey Department of Psychiatry Military Medical Academy ul. Botkinskay, 17 Saint Petersburg, Russia , 194044</p>
<p>Investigator 802 Prof. Nikolaj G Neznanov St.-Petersburg State Medical University Obvodniv Kanal, 13 St. Petersburg, 193167, Russia</p>	<p>Investigator 803 Prof. Yuri Popov St. Petersburg Bekhterev Psychoneurological Research Institute Per Matveeva, 3 Saint Petersburg, 190121, Russia</p>	<p>Investigator 804 A/Prof Mikhail Ivanov St. Petersburg Bekhterev Psychoneurological Research Institute ul. Bekhtereva, 3 Saint Petersburg, 192019, Russia</p>

Table 28 List of Investigators and Key Individuals in Study HGKA

<p>Investigator 016 Dr. Matthew Brams Bayou City Research Corporation Suite 310 550 Westcott Houston, TX 77007 United States</p>	<p>Investigator 026 Dr. James Knutson Eastside Therapeutic Resources 830 6th Street South Kirkland, WA 98033 United States</p>	<p>Investigator 130 Dr. Miguel A. Ramirez Instituto Psicoterapeutico De Puerto Rico Hostos Avenue 405 San Juan PR 00918 Puerto Rico</p>
<p>Investigator 131 Dr. Juan J. Fumero Hospital San Juan Capestrano State Road #877 KM1.6 Camino Las Lomas Rio Piedras 00926 Puerto Rico</p>	<p>Investigator 132 Dr. Pedro Fernandez Hospital Perea #15 Dr. Basora Street Mayaguez PR 00680 Puerto Rico</p>	<p>Investigator 133 Dr. Osvaldo Caro Unidad De Medicina Conductual First Hospital Panamericano Hospital Damas 8th Floor 2213 Ponce By Pass Ponce PR 00731-7779 Puerto Rico</p>
<p>Investigator 134 Dr. Luis A. Franco Ponce Medical School CAIMED (Lot #4) Calle Monterrey #280 Street A Ponce 00732 Puerto Rico</p>	<p>Investigator 140 Dr. Francisco Paez Instituto Jalisciense De Salud Mental Col Zoquipan, CP45170 Planta Alta Av. Zoquipan #1000 Colonia Zoquipan Guadalajara Jalisco 45170 Mexico</p>	<p>Investigator 141 Dr. M. E. Herrera-Estrella Hospital Psiquiatrico Fray Bernardino Alvarez Col. Thalpan 3er piso BUENAVENTURA Y NINO JESUS S/N TLALPAN Mexico City 14000 Mexico</p>
<p>Investigator 142 Dr. Ricardo Chapa Centro Avanzado De Salud Animica (C.A.S.A.) Col Centro CP 64000 Dra Quiroga PADRE MIER 1015 PONIENTE ESQ. MIGUEL NIETO COL CENTRO Monterrey Nuevo Leon 64000 Mexico</p>	<p>Investigator 143 Dr. Juan Rosales Clinical Psiquiatrica San Refael INSURGENTES SUR NO 4177 TLALPAN Mexico City 14420 Mexico</p>	<p>Investigator 144 Dr. Eric Landa Hospital San Juan De Dios Av. De los Laureles #55 Col El Capullo Zapopan Guadalajara 14150 Mexico</p>

<p>Investigator 160 Dr. Ricardo M. Corral Centro De Neuropsiquiatria Marcelo T. De Alvear 2430 Buenos Aires C1122AAN Argentina</p>	<p>Investigator 161 Dr. Rodolfo D. Fahrer Hospital De Clinicas Av Cordoba 2351 Ciudad De Buenos Aires 1120 Argentina</p>	<p>Investigator 162 Dr. Perdro Gargoloff Clinica San Juan Calle 115 No.231 La Plata Buenos Aires 1900 Argentina</p>
<p>Investigator 163 Dr. Juio J. Herrera Centro De Psiquiatria Biologica Pedro Molina 249 Mendoza M5500GAC Argentina</p>	<p>Investigator 164 Dr. Carlos Nunez Clinica San Jorge Eva Peron 1536 Lanus Este Buenos Aires B18241BR Argentina</p>	<p>Investigator 165 Dr. Miguel Marquez Hospital Frances La Roiija 951 Ciudad De Buenos Aires 1221 Argentina</p>
<p>Investigator 180 Dr. Sandra I. Ruschel Hospital Mario Kroeff A/C Dra. Sandra Ruschel- Psiquiatria Rue Mage 326 – Penha Circular Rio De Janeiro RJ 21020-130 Brazil</p>	<p>Investigator 181 Dr. Joao O. Campos Clinica Psiquiatrica Pax A/C Dr. Joao Campos BR 153 Km 9,0 Aparecida De Goiania GO 74922-810 Brazil</p>	<p>Investigator 182 Dr. Irismar R. Oliveira Sanatorio Sao Paulo Ladeira Do Aquidaban, 91 Salvador BA 40301500 Brazil</p>
<p>Investigator 200 Prof. Antonio P. Palha Casa de Saude Do Bom Jesus Rua Antonio Alves Palha Braga 4710-200 Portugal</p>	<p>Investigator 201 A/Prof Marques Teixeira Centro Hospitalar Conde De Ferreira Rua de Costa Cabral, 1211 Porto 4200-272 Portugal</p>	<p>Investigator 202 Dr. Joaquim M. Cabecas Hospital Sobral Cid Apartado 1 Ceiro-Coimbra 3031801 Portugal</p>
<p>Investigator 203 Prof. M. Luisa Figueira Hospital De Santa Maria Servico de Psiquiatria, Piso 3 AVENIDA PROF EGAS MONIZ Lisboa 1649-035 Portugal</p>	<p>Investigator 204 Prof. Elsa Lara Hospital Ingles De Lisboa R. Saraiva De Carvalho N49 Lisboa 1250 Portugal</p>	<p>Investigator 205 Dr. Ana Grilo Hospital Julio De Matos Residencia Psiquiatrica 1, Pavilhao 16 Avenida Do Brasil 53 Lisboa 1749002 Portugal</p>

10.2 Appendix to Efficacy Review

Table 29 Visitwise Mean Change from Baseline to Endpoint in PANSS Total Score in Study HGJZ (OC)

Visit	300Q2W N=100 (LS Mean)	405Q4W N=100 (LS Mean)	210Q2W N=106 (LS Mean)	PLA N=98 (LS Mean)	p-value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline	102.58	101.33	99.55	100.60			
Week 0.43	-9.14	-8.45	-7.70	-5.24	.005	.017	.046
Week 1	-15.84	-14.57	-14.10	-9.72	<.001	.009	.010
Week 2	-21.33	-18.86	-16.87	-12.67	<.001	.007	.013
Week 3	-25.34	-21.18	-19.79	-12.95	<.001	<.001	<.001
Week 4	-26.54	-23.19	-21.72	-12.89	<.001	<.001	<.001
Week 5	-29.55	-25.84	-24.06	-14.44	<.001	<.001	<.001
Week 6	-33.94	-26.71	-26.69	-15.23	<.001	<.001	<.001
Week 7	-35.56	-29.33	-28.50	-16.65	<.001	<.001	<.001
Week 8	-36.82	-28.79	-27.19	-15.82	<.001	<.001	<.001

10.3 Appendix to Integrated Safety Review

Table 30 Summary of Excessive Sedation Events Occurring Through 4 September 2007

Patient ID (Reg Subj ID)	Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
LOBE-100- 1039 (LOBE-100- 1039)	Case 1	31-year- old male	Inj #2 17 Apr 2001	300 mg/4 weeks 45 min	No	45 min after inj, pt experienced AEs of severe sedation, moderate akathisia (described as tension in legs), and mild dizziness. Pt also described feeling weakness. Pt given biperiden. 6 hours after inj, pt still sleepy but felt better. Recovered approx 48 hr; Continued in study
HGKA-532- 4011 (HGKA- 532-4011)	Case 2	32-year- old male	Inj #1 21 Dec 2004	405 mg/4 weeks 10 min	Yes	10 min after inj, experienced dizziness and bad general state. Speech progressively altered and somnolence appeared. After 1.5 hr, stopped responding to verbal stimuli. After 2 hr, profound sedation, bilateral miosis with no photomotor reflex, automatic movements, babinski on left side, no response to pain or verbal stimuli. Hospitalized. Tests neg. Treated with fluids, mannitol, lucetam (piracetamum), and infesol and cerebrolysin. Able to speak a little but with difficulty next morning. Recovered approx 60 hr; Discontinued study
HGKA-571- 4437 (HGKA- 571-4437)	Case 3	63-year- old male	Inj #2 27 Dec 2004	405 mg/4 weeks 15–20 min	Yes	15–20 min post inj, appeared pale, yellowish, not standing steady, and a little confused. 30 min post inj, felt bad, disoriented, with seizures in hands and legs. Walked into a wall; suffered superficial injuries. Experienced spasms which began in shoulders and hands. Appeared to want to sleep but remained awake, responded to questions, drank some. Sent to hospital. Tests neg. Treated with midazolam, ranitidine, diazepam, haloperidol, and promethazine. Hospital diagnosed as tonic clonic convulsions with partial consciousness. Ventilated as preventive measure. Extubated shortly thereafter. Recovered approx 60 hr; Discontinued study
HGKB-088- 6257	Case 4	30-year- old male	Inj #4 21 Mar 2005	405 mg/4 weeks Approx 60 min	Yes	Patient appears to have presented himself at hospital. Approx. 1 hr post inj, pt experienced sedation. Became drowsy and irritable, disoriented

(LOBS-HGKB-88-6257)						times 3. Also felt stiff and weak in legs. Stated that he passed out for a while, was very confused. Was slightly febrile (100.6 F). Recovered approx 24 hr; Continued in study
HGKB-035-5910-A (LOBS-HGKB-35-5910)	Case 5	49-year-old male	Inj #22 24 Oct 2005	250 mg/2 weeks Within 60 min	Yes	Historical conditions of mixed substance abuse, diabetes, hypertension, rheumatoid arthritis. Pt returned to site about 1 hr post inj and appeared in drunken state. Speech was slurred, gait unsteady. Sent to hospital for evaluation. All tests neg. Difficulty ambulating, incontinent of urine while at hospital. Admitted to drinking ¾ pint whiskey the evening before the inj. Recovered approx 48 hr; Continued in study
HGKB-182-7318 (HGKA-HGKB-182-7318)	Case 6	51-year-old male	Inj #24 28 Dec 2005	300 mg/2 weeks Within 50 min	Yes	Pt stayed 10 min post inj without complaint, then left site. 50 min post inj, found in coma at bus stop. Sent to hospital. Tests neg. In coma 13 hours post inj. Pt later described not feeling well before he lost consciousness. Patient noted by investigator to abuse alcohol. Recovered approx 24 hr; Continued in study
HGKB-412-8428 (HGKA-HGKB-412-8428)	Case 7	31-year-old female	Inj #11 26 Jan 2006	300 mg/3 weeks 30 min	Yes	30 min post inj, experienced drowsiness and washy speech. Admitted to psych hospital. Also experienced slight confusion (nonserious). Recovered approx 24 hr; Continued in study
HGKB-035-5910-B (LOBS-HGKB-35-5910)	Case 8	49-year-old male	Inj #35 24 Apr 2006	250 mg/2 weeks 15 min	Yes	15 min post inj, began to have slurred speech and unsteady gait. Progressed to point where couldn't speak clearly or ambulate without assistance. Taken to hospital for evaluation. Tests neg. Recovered approx 72 hr; Discontinued study
HGKB-141-6928 (HGKB-141-6928)	Case 9	34-year-old male	Inj #29 17 May 2006	300 mg/4 weeks 5 min	Yes	Pt. diabetic. 5 min post inj, became increasingly sedated, like just woke up from anesthesia. In and out of consciousness. Site assumed low glucose and gave pt Coke to drink. Pt confused, disoriented, ataxic (as if drunk). 30 min post inj, glucose was 275 mg/dL. Site laid pt down in ward where he was in and out of sleeping state. When would try to get up, was restless and had slurred speech. Given fluids and insulin. Glucose cont'd to increase to 360. Temp 37 C. Given haloperidol. Released but readmitted next day due to cont'd problems with alertness and glucose. Sleepy & disoriented, delirious, with slight rigidity in

						extremities. High glucose with slight hypokalemia. Tests indicated hepatic steatosis. Recovered approx 72 hrs; Continued in study
HGKB-235-7685 (LOBS-HGKB-235-7685)	Case 10	43-year-old male	Inj #20 13 Jun 2006	405 mg/4 weeks 30 min	Yes	Pt returned to work soon after injection. A few minutes later (30 min post inj), felt bad and so drank a juice. Coworkers contacted site due to pt's irritability. Pt returned to the site about 60 min post inj in a sedated state. Sent to hospital for observation. Recovered approx 24 hr; Continued in study
HGKB-521-8460 (LOBS-HGKB-521-8460)	Case 11	43-year-old female	Inj #27 14 Jun 2006	100 mg/2 weeks 10 min	Yes	10 min post inj, experienced weakness, dizziness, slurred speech, & profound sedation (described as slightly decreased level of consciousness). Recovered approx 48 hr; Continued in study
HGKB-481-8734 (HGKA-HGKB-481-8734)	Case 12	57-year-old male	Inj #2 13 Jun 2006	210 mg/2 week Unspecified. Within 3 hr	No	3 hr post inj, felt weak. Pt was at home. Wife contacted site, reported that pt experiencing profound sedation, weakness, slurred speech. Not unconscious. Event ended after 3 hours. Recovered approx 3 hr; Continued in study
HGKB-252-7885 (HGKA-HGKB-252-7885)	Case 13	23-year-old male	Inj #12 27 June 2006	270 mg/4 weeks Immediately post injection	Yes	Immediately post inj, pt complained of feeling weak, dizzy, with headache. Stated that he'd been working outside all day in warm weather without eating or drinking. Stayed at site 45 min but then left per investigator instructions to get something to eat. Pt got sandwich on street and as starting to eat felt unwell. Began staggering; attempted to go into bar but was turned away as appeared drunk. Sat on road and shopkeeper called emergency medical services. 3 hours post inj, admitted to hospital confused and dizzy. Tests neg. Recovered approx 24 hr; Continued in study
HGKB-245-7791 (HGKA-HGKB-245-7791)	Case 14	56-year-old female	Inj #25 04 Jul 2006	210 mg/4 weeks Unspecified. Within 75 min	Yes	Elevated WBC at lab draw prior to inj. Complained of hunger, thirst due to fasting. Refused to stay at site. Left 20–25 min post inj. Experienced malaise in the street 1 hr 15 min post inj and admitted to hospital with loss of consciousness. There experienced alternating agitation and somnolence, with dysarthria and sweating. Mild tachycardia (114 bpm) and QTc=421 msec. Blood culture positive for gram +. Due to persistence of agitation, given sedatives and intubated and ventilated to

						perform tests. Temp was 38.1 C. Oliguria noted overnight. Given furosemide. Urine test next day showed bacterial infection. Pt extubated and released.
						Recovered approx 48 hr; Continued in study
HGKB-491-9513 (HGKA-HGKB-491-9513)	Case 15	40-year-old male	Inj #7 11 Jul 2006	300 mg/3 weeks 15 min	Not reported	15 min post inj, became confused and weak. 1 hr 15 min post inj, condition worsened; pt was stunned, had deep sedation, with loss of consciousness. Recovered after 3 hours. (Seen by anesthetist, so assume pt was hospitalized.)
						Recovered approx 3 hr; Discontinued from study
HGKB-242-7758 (HGKA-HGKB-242-7758)	Case 16	36-year-old male	Inj #17 06 Dec 2006	405 mg/4 weeks 90 min	Yes	1 hour 30 min post inj, pt experienced somnolence (during 3-hr observation period). 2.5 to 3 hr post inj, experienced major fatigue, inconsistent speech, mumbling, and automatism (picking invisible things on floor/pseudo-delirium). Hospitalized overnight for observation. Pt later admitted to drinking 1 liter of beer prior to the injection.
						Recovered approx 24 hr; Continued in study
HGKB-143-6958 (HGKA-HGKB-143-6958)	Case 17	59-year-old female	Inj #27 19 Jan 2007	300 mg/2 weeks 2 hours and 45 min	Yes	2 hr 45 min post inj, pt experienced significant somnolence. Pt took 4 mg unprescribed clonazepam 8 hr prior to injection (but did not appear drowsy when arrived at site). 20 min after start of somnolence, experienced difficulty with speech; had motor restlessness, worrying about things she needed to do. Remained alert and oriented. 6 hr 15 min post inj, presented with profound sedation; unarousable for 8 hours. Responsive to pain. Awoke next morning.
						Recovered approx 12 hr; Continued in study
HGKB-406-8350 (HGKA-HGKB-406-8350)	Case 18	26-year-old male	Inj #17 16 Mar 2007 ^a	345 mg/4 weeks 30 min	Yes	30 min post inj, pt experienced dizziness, gummy legs, and insecurity while standing. Symptoms slowly increased, progressing to deep sedation, reported to be like deep sleep but pt could always be aroused by speaking to him loudly. Hospitalized for monitoring and hydration.
						Recovered approx 24 hr; Continued in study
HGKB-476-8620 (LOBS-HGKB-476-8620)	Case 19	38-year-old female	Inj #16 12 Jan 2007	390 mg/4 weeks 5 min	No	5 min post inj, experienced somnolence that worsened gradually, but pt was oriented and able to communicate although had dysarthria. PI did not call it an SAE but CRA had him designate it as serious. At end of 3-hr observation, pt was sent home with a friend in an improved but still slightly somnolent state.
						Recovered approx 72 hr; Discontinued from study

HGKB-200-7420 (HGKA-HGKB-200-7420)	Case 20	48-year-old female	Inj #15 4 Oct 2006	405 mg/4 weeks 20 min	No	20 min post inj, experienced dizziness. 45 min post inj, was severely sedated but always conscious, was disoriented to place and time, with dysarthria and confusion. All nonserious AEs. Site was attached to psych unit where patient lived for social reasons so pt was able to be observed by staff there until recovered. Recovered approx 16 hr; Continued in study
HGKB-202-7446 (HGKA-HGKB-202-7446)	Case 21	52-year-old male	Inj #35 23 May 2007 ^a	210 mg/2 weeks 15 min	Yes	15 min post inj, became confused, somnolent, with blurred vision, dizziness. All events considered nonserious. 2.5 hr post inj, sent to hospital for monitoring. Remained conscious throughout. Vital sign data do not indicate any decrease in BP or HR. Recovered approx 11 hr 30 min; Continued in study
HGKB-476-8622 (LOBS-HGKB-476-8622)	Case 22	52-year-old male	Inj #20 06 Jun 2007 ^a	360 mg/4 weeks 10 min	Yes	10 min post inj, became somnolent, confused, and cramps developed. Pt slept for 30 min. Arousable but couldn't answer questions correctly. Disoriented with altered consciousness but not unconscious. Experienced retention of urine. Sent to hospital after 3 hr observation. Pt did not urinate despite attempts so was catheterized. Cramps of moderate severity localized in arms & legs. Recovered approx 24 hr; Discontinued from study
HGKB-222-7568 (HGKA-HGKB-222-7568)	Case 23	47-year-old male	Inj #17 19 Jun 2007 ^a	405 mg/4 weeks 15 min	Yes	Pt complained of dizziness prior to injection, probably due to fasting. Symptoms reportedly worsened. Pt ate 15–30 min post inj and while eating began to feel nervous and experienced abnormal movements like tonic convulsion in his arms. Sporadic at first and then increasing. 2 hr post inj, began to present somnolence and dysarthria but nervous and with abnormal movements so unable to fall asleep. Pt given 1 mg lorazepam (his usual daily dose). No loss of consciousness at any time. Sent to hospital at 4 hr post inj due to continued symptoms. Recovered approx 24 hr; Discontinued study
HGKB-571-8643 (HGKA-HGKB-571-8643)	Case 24	55-year-old male	Inj # 40 15 Jul 2007 ^a	330 mg/4 weeks 30 min	Yes	Pt had BP 140/90 prior to inj and felt good but had not eaten anything that day or the day prior. 30 min post inj, BP increased to 180/90, HR 96. 45 min post inj, pt complained of headache and stomach ache; BP 160/100. 60 min post inj, pt was confused, ataxic, restless; BP 190/110, HR 100, and glucose 125. Site attempted to treat with captopril but no change. Also treated with enalapril maleate and paracetamol. Pt sent to emergency room and admitted for confusion. BP remained elevated.

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						Diagnosed with urinary tract infection; treated with cefuroxime axetil. Pt also treated with large amount of benzodiazepines and slept thereafter. Recovered approx 48 hr; Continued in study
HGKB-160-7119 (HGKA-HGKB-160-7119)	Case 25	36-year-old male	Inj #36 13 Aug 2007 ^a	405 mg/4 weeks 15 min	Yes	Pt started experiencing dizziness, dysarthria, and gait disturbance 15 min post inj with progressive deepening of sedation over the next 10 min. Patient was sent to the emergency room 6 hours 40 min post inj where pt remained sedated, disoriented, and confused. Vitals were normal and stable. Patient was discharged fully recovered 3 days later. Recovered approx 48 hr; Continued in study

Table 31 Olanzapine Plasma Concentrations Obtained During an Excessive Sedation Event

Study	Date (YYYYMMDD)	Time (Days on Study)	Dose	Time of Sample From Last Dose (hours)	Olanzapine Concentration (ng/mL)
Patient LOBE- 100-1039	IAIV Event #1 20010417		300 mg OP Depot		
LOBE	20010417	29.25		6 hours	172.75
LOBE	20010418	30.00		24 hours	104.48
LOBE	20010420	31.98		72 hours	47.96
Patient HGKB- 035-5910	IAIV Event #5 20051024		250 mg OP Depot		
HGKB	20051024	294.27		9.4 hours	246.78
HGKB	20051024	294.36		11.5 hours	293.84
HGKB	20051025	294.77		21.4 hours	158.45
Patient HGKB- 035-5910	IAIV Event #8 20060424		250 mg OP Depot		
HGKB	20060424	475.93		1 hours	284.80
HGKB	20060424	475.97		2 hours	377.79
HGKB	20060424	476.06		4 hours	423.80
HGKB	20060424	476.39		12 hours	314.43
HGKB	20060425	476.86		23.2 hours	208.64
HGKB	20060425	476.89		24 hours	192.82
HGKB	20060426	477.90		48.2 hours	84.27
Patient HGKB- 235-7685	IAIV Event #10 20060613		405 mg OP Depot		
HGKB	20060613	480.03		2.7 hours	133.47
HGKB	20060613	480.07		3.7 hours	127.07
HGKB	20060613	480.12		4.7 hours	126.73
HGKB	20060614	480.95		24.6 hours	108.77
Patient HGKB- 406-8350	IAIV Event #18 20070316		345 mg OP Depot		
HGKB	20070316	282.17		4 hours	346.56
HGKB	20070317	282.98		23.5 hours	190.38

Study	Date (YYYYMMDD)	Time (Days on Study)	Dose	Time of Sample From Last Dose (hours)	Olanzapine Concentration (ng/mL)
Patient	IAIV Event		360 mg OP Depot		
HGKB-	#22				
476-8622	20070606				
HGKB	20070606	455.00		1 hour	593.03
HGKB	20070606	455.04		2 hours	542.19
HGKB	20070606	455.08		3 hours	611.13
HGKB	20070606	455.12		4 hours	627.18
Patient	IAIV Event		405 mg OP Depot		
HGKB-	#23				
222-7568	20070619				
HGKB	20070619	424.18		6.75 hours	635.54
HGKB	20070619	424.22		7.75 hours	664.96
HGKB	20070619	424.26		8.75 hours	650.04
HGKB	20070619	424.30		9.75 hours	657.32
HGKB	20070620	424.89		23.75 hours	445.08

Abbreviations: IAIV = inadvertent intravascular; OP = olanzapine pamoate.

REFERENCES

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/s/

Jing Zhang
1/7/2008 04:40:30 PM
MEDICAL OFFICER

Gwen Zornberg
1/7/2008 06:32:09 PM
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I concur with Dr. Zhang, the exception to the
olanzapine safety profile are the OP depot overdose-type
ADRs that are unpredictable with respect to person,
place, and time (1.25% of patients) despite RN
training. Efficacy is satisfactory, no dose-response.



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-173 / N000
Drug Name: Olanzapine Depot
Indication(s): Schizophrenia
Applicant: Eli Lilly and Company
Date(s): Initial submission date: April 30, 2007
Review Priority: Standard
Biometrics Division: Division of Biometrics I
Statistical Reviewer: George Kordzakhia, Ph.D.
Concurring Reviewers: Peiling Yang, Ph.D; Kooros Mahjoob, Ph.D.
Medical Division: Division of Psychiatry Products
Clinical Team: Jing Zhang, M.D., Reviewer
Gwen Zornberg, M.D., Team Leader
Project Manager: Mr. Keith Kiedrow
Keywords: clinical studies, NDA review

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Study HGJZ

In the primary analysis of the PANSS Total score, patients on olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were observed to show statistically significant improvement over patients in the placebo treatment group.

Study HGKA

The 3 higher dose olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups showed positive maintenance effect compared with the low dose (45mg/4 weeks) for stabilized patients with schizophrenia.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted results of two pivotal studies F1D-MC-HGJZ and F1D-MC-HGKA in support of efficacy of olanzapine pamoate depot.

In Study F1D-MC-HGJZ, a multicenter, randomized, double-blind, placebo-controlled study, olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) was compared with placebo in the treatment of patients with schizophrenia over an 8-week study period. A total of 466 patients entered Study Period I, 404 patients were enrolled, and 267 patients completed the study. The most common reasons for discontinuing the study were lack of efficacy and patient decision.

Study F1D-MC-HGKA was a large, randomized, double-blind study examining the maintenance of effect of olanzapine pamoate depot (OP Depot) compared to oral olanzapine and a low OP Depot dose group in the treatment of schizophrenia for up to 24 weeks. The study had two primary objectives: (1) to demonstrate that the OP Depot doses of 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks were all superior to a low 45 mg/4 weeks dose in terms of time to exacerbation of symptoms of schizophrenia, and (2) to demonstrate that the 2-week dosing interval of OP Depot was non-inferior to daily oral olanzapine in terms of exacerbation rates at 24 weeks. Since Division of Psychiatry does not accept non-inferiority efficacy claims for labeling purposes in this indication, this reviewer will evaluate only the superiority objective.

Outpatients, age 18–70 and diagnosed with schizophrenia, were tapered off their previous antipsychotic medications and converted to open-label oral olanzapine within 4 weeks. Patients had to demonstrate clinical stability for 4 weeks on 10, 15, or 20 mg/day or oral olanzapine to be eligible for randomization to the double-blind maintenance period. A total of 1065 patients were randomized to one of 5 treatment groups in a 2:1:1:1:2 ratio: 405 mg/4 weeks OP Depot 300 mg/2 weeks OP Depot, 150 mg/2 weeks OP Depot, 45 mg/4 weeks OP Depot, or oral olanzapine. Patients randomized to oral olanzapine remained on the dose at which they had been stabilized previously.

1.3 STATISTICAL ISSUES AND FINDINGS

Study HGJZ

All three olanzapine pamoate depot treatment groups (OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were statistically superior to placebo in mean change from baseline to the endpoint visit in PANSS Total score. The nominal p-values of pairwise comparisons with placebo obtained from ANOVA model with treatment and investigator effects were all < 0.001 .

Study HGKA

Each of the higher olanzapine pamoate depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) was statistically superior to the 45 mg/4-weeks dose with respect to time to exacerbation of symptoms (nominal p-values from the log-rank test : $<.001$, $<.001$, and $=.006$, respectively).

In general, no statistical issues are identified in both studies.

2 INTRODUCTION

2.1 OVERVIEW

The sponsor submitted results of two pivotal studies in support of efficacy of olanzapine pamoate depot. Study F1D-MC-HGJZ had an 8 week double-blind active treatment period. Study F1D-MC-HGJZ was a maintenance study with double-blind maintenance phase up to 24 weeks.

2.2 DATA SOURCES

Data used for review are from the electronic submission received on April 30, 2007. The network path is <\\Cdsub1\NONECTD\N22173> in the EDR.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY F1D-MC-HGJZ (ACUTE PHASE)

3.1.1.1 Objective

The primary objective of Study HGJZ was to demonstrate superiority of olanzapine pamoate depot (OP depot) 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks dosages compared with placebo/2 weeks in change from baseline to endpoint in the Positive and Negative Syndrome Scale (PANSS) Total score in the treatment of patients with schizophrenia.

3.1.1.2 Study Design

Study HGJZ was a randomized, double-blind, parallel study that evaluated OP depot (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) versus placebo in the treatment of patients with schizophrenia. The study consisted of two study periods.

Study Period I was the washout period (see Table 1), with a duration of 2 to 7 days. Patients were inpatients and were expected to meet all the inclusion/ exclusion criteria and complete all examinations prior to entering Visit 2 (Period II). After the washout period, patients were randomized to one of four treatment injections every 2 weeks and entered an 8-week double-blind treatment period. Patients who were randomized to 405 mg/4weeks OP depot received a placebo injection at every other injection visit. During the first 2 weeks following randomization, patients were expected to be inpatients and were assessed daily. During the remainder of Study Period II (after Visit 16), visits occurred weekly.

Table 1. HGJZ Study Design

Study Period I	Study Period II	
Washout	Double-Blind Treatment	Continued Double-Blind Treatment
2-7 days	2 weeks Inpatient	6 weeks Inpatient/Outpatient
Visit 1	Visits 2-16	Visits 17-22

Source: Corresponds to Figure HGJZ.9.1, HGJZ Study Report

3.1.1.3 Patient Disposition, Demographic and Baseline Characteristics

The study was conducted at 42 study centers in three countries (United States, Croatia, and Russia). A total of 466 patients entered Study Period I, where 62 patients failed screening. The two primary reasons for screening failure were patient decision (n=29) and entry criteria not met (n=29). Table 2 presents a summary of patient disposition in HGJZ Study Period II. A total of 404 eligible patients were randomized in a 1:1:1:1 ratio to receive double-blind OP depot 300 mg/2 weeks, (n=100), OP depot 405 mg/4 weeks (n=100), OP depot 210 mg/2 weeks (n=106), or placebo (n=98) during Study Period II. A total of 267 (66%) patients completed the study.

Table 2. HGJZ Study Period II Patient Disposition

Patients	Double-Blind Treatment			
	OPD 300mg/ 2 weeks	OPD 405 mg/ 4 weeks	OPD 210 mg/ 2 weeks	Placebo
Randomized	100	100	106	98
Discontinued	33	28	34	42
Adverse Event	6	4	3	5
Lack of Efficacy	13	10	12	24
Patient Decision	9	12	15	9
Physician Decision	5	1	1	2
Sponsor Decision	0	1	0	0
Protocol Violation	0	0	1	1
Lost to Follow-up	0	0	2	1
Completed	67	72	72	56

Source: HGJZ Study Report, Figure HGJZ.10.1 (pg 67)

Table 3 summarizes baseline physical characteristics (gender, ethnic origin, age, BMI, and weight) and PANSS Total score at baseline for all randomized patients. Patients randomized were predominantly male (n=285, 70.5%) and Caucasian (n=226, 55.9%). The average age of enrolled patients was 40 years, with a range of 18 to 74 years. There were no statistically significant differences across all treatment groups with respect to these physical characteristics and baseline score.

Table 3. HGJZ Baseline Characteristics All Randomized Patients

Variable	OPD300/2weeks N=100	OPD405/4weeks N=100	OPD210/2weeks N=106	Placebo N=98	Total N=404
Gender					
Female	28 (28%)	27 (27%)	27 (25.5%)	37 (37.8%)	119 (29.5%)
Male	72 (72%)	73 (73%)	79 (74.5%)	61 (62.2%)	285 (70.5%)
Origin					
Caucasian	58 (58%)	54	61	53	226
African	38 (38%)	36	35	37	146
Hispanic	4 (4%)	6	9	3	22
Native American	0	1	0	1	2
East Asian	0	2	1	3	6
West Asian	0	1	0	1	2
Age (years)					
Mean(sd)	41.5 (11.1)	39.5 (11.4)	39.8 (10.8)	42.6 (11.2)	40.8 (11.16)
Median	42.35	39.8	41.92	44.23	41.88
Maximum	74.12	65.5	69.04	74.04	74.12
Minimum	18.82	19.7	18.71	18.20	18.20
Weight (kg)					
Mean (SD)	85.5 (20.8)	87.3 (22.1)	87.0 (21.5)	82.2 (19.1)	85.5 (20.9)
Median	82.70	83.70	86.95	79.20	82.70
Maximum	149.00	161.00	152.70	151.40	161.00
Minimum	50.00	42.20	51.60	51.10	42.20
PANSS Total Score at Baseline (ITT population)					
Number of patients	98	100	106	98	402
Mean (SD)	102.58 (15.58)	101.33 (14.41)	99.55 (15.77)	100.60 (16.67)	100.99 (15.61)
Min, Max	73.00, 144.00	74.00, 147.00	71.00, 163.00	73.00, 155.00	71.00, 163.00

Source: HGJZ Study Report, Table HGJZ.11.1 (pg 89)

3.1.1.4 Statistical Methodologies

The primary and secondary analyses were performed on an intent-to-treat (ITT) basis. For each efficacy variable, the analysis included all randomized patients with baseline and postbaseline observations. The primary efficacy variable was the PANSS Total score, and LOCF change from baseline to the endpoint visit in PANSS Total score was the primary efficacy measure. The primary comparisons of interest were the pairwise contrast of each OP depot treatment group versus placebo (300 mg/2 weeks versus placebo, 405 mg/4 weeks versus placebo, and 210 mg/2 weeks versus placebo). An ANOVA LOCF model was used to evaluate the efficacy of the doses and included the terms of treatment and investigator study site.

The sequential pairwise contrasts of each treatment group versus placebo were used in the following sequence: 1) 300 mg/2 weeks versus placebo; 2) 405 mg/4 weeks versus placebo; and 3) 210 mg/2 weeks versus placebo. The 405 mg/4 weeks versus placebo contrast was declared statistically significant only if both this comparison and the first comparison (300 mg/2 weeks versus placebo) were statistically significant. Similarly, the 210 mg/2 weeks versus placebo contrast was declared statistically significant only if all three comparisons were statistically significant. Because of a priori specification of the sequence, no further adjustments to the significance levels were necessary, and each contrast was compared at the significance level of 0.05.

3.1.1.5 Results of Efficacy Analysis

Primary Analysis

Efficacy analysis based on ANOVA model was performed for the 8-week double blind phase of the study. All randomized patients with baseline and at least one postbaseline observations (n=98, OP depot 300 mg/2 weeks; n=100, OP depot 405 mg/4 weeks; n=106, OP depot 210 mg/2 weeks; and n=98, placebo) were included in the primary efficacy analysis. Patients in OP depot treatment groups, 300 mg/2 weeks, 405 mg/4 weeks and 210mg/2 weeks showed statistically significant improvement over patients in the placebo treatment group after one-week of double-blind treatment. All three OP depot treatment groups were statistically superior to placebo in mean change from baseline to the endpoint visit in PANSS Total score.

Table 4. PANSS Total Score LS Mean Change from Baseline to Endpoint, HGJZ Study Period II (ITT Population)

		Placebo	OPD 300mg/ 2w	OPD 405 mg/4w	OPD 210 mg/2w
No patients	N=402	98	98	100	106
Change from Baseline	Mean (SD)	-8.51 (23.03)	-26.32 (24.93)	-22.57 (22.15)	-22.49 (21.84)
Placebo-adjusted difference	LS mean (SE)	NA	-18.23 (2.82)	-14.43 (2.80)	-14.87 (2.76)
	95% CI	NA	(-23.78, -12.68)	(-19.93, -8.93)	(-20.29,-9.44)
	P-Value	NA	<0.0001	<0.0001	<0.0001

Source: Reviewer's results

Note: The reported p-values and 95% CI's are nominal and are not adjusted for multiplicity.

Table 5. PANSS Total Score LS Mean Change from Baseline by Visit, HGJZ Study Period II (ITT Population)

Visit (week)	Placebo	OPD 300 mg/2w	OPD 405mg/4w	OPD 210mg/2w
	Mean (SE)	Mean (SE); p-value vs. placebo	Mean (SE); p-value vs. placebo	Mean (SE); p-value vs. placebo
5 (week 0.43)	-4.61 (1.18)	-8.44 (1.16); 0.011	-7.94 (1.15); 0.025	-7.42 (1.10); 0.056
9 (week 1)	-8.03 (1.45)	-14.05 (1.44); 0.001	-12.48 (1.43); 0.016	-13.11 (1.37); 0.005
16 (week 2)	-8.70 (1.73)	-17.71 (1.72); <0.001	-15.10 (1.70); 0.003	-15.17 (1.63); 0.002
17 (week 3)	-7.62 (1.90)	-20.00 (1.89); <0.001	-16.39 (1.87); <0.001	-17.39 (1.79); <0.001
18 (week 4)	-5.97 (2.04)	-20.20 (2.01); <0.001	-17.57 (2.00); <0.001	-18.77 (1.92); <0.001
19 (week 5)	-6.48 (2.09)	-21.31 (2.06); <0.001	-19.64 (2.05); <0.001	-20.33 (1.96); <0.001
20 (week 6)	-6.37 (2.13)	-22.91 (2.11); <0.001	-20.45 (2.09); <0.001	-21.46 (2.01); <0.001
21 (week 7)	-6.35 (2.16)	-23.96 (2.14); <0.001	-21.02 (2.17); <0.001	-21.99 (2.03); <0.001
22 (week 8)	-5.87 (2.22)	-24.11 (2.19); <0.001	-20.30 (2.17); <0.001	-20.74 (2.09); <0.001

Source: Reviewer's results

Note: The reported p-values are nominal p-values and are not adjusted for multiplicity.

Sensitivity Analysis

This reviewer conducted sensitivity analysis on the primary endpoint. Change from baseline in PANSS Total score was analyzed by mixed effect repeated measures model. The model included treatment, investigator, visit, and interaction of treatment by visit as fixed effects, and baseline as a covariate. The unstructured variance-covariance matrix was used. In the analysis data set PANSS.xpt submitted by the sponsor, the patient with subject ID 5032 (investigator ID 47) has two identical PANSS Total score records for visit 17. The duplicate observation was excluded from the analysis. The findings support the primary analysis results.

Table 6. PANSS Total Score Change from Baseline Visitwise LS means, Mixed Effects Repeated Measures model (ITT Population).

Visit (week)	Study Treatment	Number of patients	LS Mean (SE)	p-value when compared with Placebo
5 (0.43)	Placebo	97	-4.59 (1.15)	
5 (0.43)	OPD 300 mg/ 2w	94	-8.55 (1.15)	0.008
5 (0.43)	OPD 405 mg/4w	98	-8.03 (1.13)	0.020
5 (0.43)	OPD 210 mg/2w	105	-7.63 (1.09)	0.036
9 (1)	Placebo	95	-8.78 (1.36)	
9 (1)	OPD 300 mg/2w	92	-15.26 (1.37)	<0.001
9 (1)	OPD 405 mg/4w	93	-13.99 (1.36)	0.004
9 (1)	OPD 210 mg/2w	100	-13.74 (1.30)	0.005
16 (2)	Placebo	86	-11.29 (1.73)	
16 (2)	OPD 300 mg/2w	90	-20.63 (1.72)	<0.001
16 (2)	OPD 405 mg/4w	88	-17.88 (1.72)	0.005
16 (2)	OPD 210 mg/2w	94	-17.10 (1.65)	0.012
17 (3)	Placebo	82	-11.05 (1.95)	
17 (3)	OPD 300 mg/2w	85	-23.72 (1.93)	<0.001
17 (3)	OPD 405 mg/4w	88	-20.22 (1.92)	<0.001
17 (3)	OPD 210 mg/2w	90	-20.28 (1.85)	<0.001
18 (4)	Placebo	74	-8.75 (2.17)	
18 (4)	OPD 300 mg/2w	81	-24.29 (2.12)	<0.001
18 (4)	OPD 405 mg/4w	81	-21.86 (2.12)	<0.001
18 (4)	OPD 210 mg/2w	83	-21.93 (2.06)	<0.001
19 (5)	Placebo	68	-9.19 (2.25)	
19 (5)	OPD 300 mg/2w	76	-25.69 (2.18)	<0.001
19 (5)	OPD 405 mg/4w	77	-24.27 (2.18)	<0.001
19 (5)	OPD 210 mg/2w	79	-23.83 (2.11)	<0.001
20 (6)	Placebo	62	-9.44 (2.31)	
20 (6)	OPD 300 mg/2w	69	-28.09 (2.25)	<0.001
20 (6)	OPD 405 mg/4w	77	-25.30 (2.22)	<0.001
20 (6)	OPD 210 mg/2w	75	-25.33 (2.17)	<0.001
21 (7)	Placebo	60	-9.60 (2.38)	
21 (7)	OPD 300 mg/2w	68	-29.58 (2.30)	<0.001
21 (7)	OPD 405 mg/4w	73	-26.28 (2.27)	<0.001
21 (7)	OPD 210 mg/2w	72	-26.46 (2.22)	<0.001
22 (8)	Placebo	56	-9.32 (2.52)	
22 (8)	OPD 300 mg/2w	67	-30.75 (2.41)	<0.001
22 (8)	OPD 405 mg/4w	71	-25.71 (2.38)	<0.001
22 (8)	OPD 210 mg/2w	72	-25.06 (2.33)	<0.001

Source: Reviewer's results

Note: The reported p-values are nominal p-values and are not adjusted for multiplicity.

3.1.1.6 Reviewer's Comments.

All three OP depot treatment groups (OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were statistically superior to placebo in mean change from baseline to the endpoint visit in PANSS Total score. The nominal p-values of pairwise comparisons with placebo obtained from ANOVA model with treatment and investigator effects were all < 0.001.

3.1.2 STUDY HGKA (LONG-TERM)

3.1.2.1 Objective

The primary objectives were to determine comparative efficacy in patients with schizophrenia as follows:

1. 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks OP Depot versus 45 mg/4 weeks OP Depot.
2. Pooled 2-Week Olanzapine Pamoate (OP) Depot (300 mg/2 weeks pooled with 150 mg/2 weeks) versus oral olanzapine (10, 15, and 20 mg)

For the OP Depot dose comparison, the primary objective was to demonstrate superior efficacy of 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks as compared to 45 mg/4 weeks in terms of time to exacerbation of symptoms of schizophrenia. For the OP Depot versus oral olanzapine comparison, the primary objective was to demonstrate noninferior efficacy of Pooled 2-Week OP Depot (300 mg/2 weeks pooled with 150 mg/2 weeks) as compared with 10, 15, and 20 mg oral olanzapine in terms of exacerbation rates after 24 weeks of maintenance treatment. Since Division of Psychiatry Products does not accept non-inferiority efficacy claims for labeling purposes in this indication, this reviewer will evaluate only the superiority objective.

3.1.2.2 Study Design

This was a multicenter, randomized, double-blind, parallel study that compared the safety and efficacy of Olanzapine Pamoate (OP) Depot with oral olanzapine, as well as with 45 mg/4 weeks OP Depot, in patients meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revised) (DSM-IV [DSM-IV-TR]) criteria for schizophrenia. Patients eligible to enroll in the study were clinically stable on antipsychotic medication. The study was conducted by 113 investigators at 112 study centers in 26 countries. A total of 1065 patients 18-71 years of age were randomized in a 2:1:1:1:2 ratio, into 1 of 5 treatment groups: 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, 45 mg/4 weeks OP Depot, or oral olanzapine, respectively.

Study Period I was a 2- to 9-day lead-in screening period. Patients receiving oral antipsychotic medication (other than clozapine) continued treatment, whereas patients receiving treatment with an injectable antipsychotic received the last injection at least 2 weeks (or 1-injection interval, whichever was longer) prior to Visit 2. Patients taking risperidone long-acting injections received their last injection at least 4 weeks prior to Visit 2.

Study Period II was a conversion and stabilization period during which patients were discontinued from their current antipsychotic medication (unless it was olanzapine) and converted to oral olanzapine monotherapy (at 10, 15, or 20 mg/day). All patients began the conversion to oral olanzapine monotherapy after enrollment (Visit 2). To enter Study Period III, patients had to demonstrate stability for 4 weeks (5 consecutive visits) during Study Period II by meeting the following stabilization criteria:

- No dose change of oral olanzapine monotherapy (fixed at 10, 15, or 20 mg/day)

- CGI-I score equal to 1, 2, 3, or 4 (when compared with Visit 1 CGI-S score)
- BPRS Positive score ≤ 4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

The length of time a patient remained in Study Period II was dependent on the patient's time of conversion from their existing antipsychotic therapy and how quickly stabilization criteria were met. The maximum length of Study Period II was 8 weeks and included Visit 2 up to Visit 10. In cases where stabilization criteria were met before the 8-week maximum length of Study Period II, the patient skipped to Visit 10 (in Study Period III).

Study Period III was a 24-week maintenance period consisting of double-blind treatment with either oral olanzapine or OP Depot. Patients were assessed weekly from Visit 10 to Visit 22, and then every other week from Visit 22 to Visit 28. Inspections of the injection area (left and right buttocks) were performed at Visit 10, and abnormalities were noted as preexisting conditions. Patients were randomized to 1 of 5 treatment groups in a 2:1:1:1:2 ratio (405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, 45 mg/4 weeks OP Depot, or oral olanzapine, respectively). To maintain the blind, patients who were randomized to the 4-week OP Depot treatment groups also received injections of placebo every 4 weeks (alternating every 2 weeks with the OP Depot injection) and placebo oral study drug daily. Patients randomized to the 2-week OP Depot treatment groups received OP Depot injections every 2 weeks and placebo oral study drug daily. Patients randomized to the oral olanzapine arm received injections of placebo every 2 weeks. Patients randomized to oral olanzapine received the same olanzapine dose that they were stabilized on during Study Period II. Patients remained on a fixed dose of injectable and oral study drug throughout Study Period III. During Study Period III (Visit 11 to Visit 28), CGI-I scores were obtained by comparing them with the Visit 10 CGI-S score.

Study Period IV was an up-to 24-week open-label restabilization period for patients who were discontinued from double-blind therapy (Study Period III) due to exacerbation of symptoms associated with schizophrenia. The purpose of the restabilization period was to ensure that patients who suffered an exacerbation were restabilized before ending study participation.

3.1.2.3 Patient Disposition, Demographic and Baseline Characteristic

The study was conducted by 113 investigators at 112 study centers in 26 countries. Of the 1315 patients screened, 1205 patients entered the Conversion/ Stabilization Phase. The two most common reasons for screening failure prior to the Conversion/ Stabilization Phase (Study Period II) were entry criteria not met (n=50) and patient decision (n=34). The most common reason for patient discontinuation during the Conversion/Stabilization Phase (Study Period II) was patient decision (n=53). Table 7 presents a summary of patient disposition following randomization into the Double-Blind Maintenance Phase (Study Period III) of Study HGKA. Of the 1205 patients entering the Conversion/Stabilization Phase, 1065 eligible patients were randomized in a 2:1:1:1:2 ratio to receive double-blind OP Depot (405 mg/4 weeks [n=318], 300 mg/2 weeks [n=141], 150 mg/2 weeks [n=140], 45 mg/4 weeks [n=144]) or oral olanzapine (n=322), respectively, during the Double-Blind Maintenance Phase (Study Period III). A total 753 of the 1065 eligible patients (70.7%) completed Study HGKA.

Table 7. HGKA Patient Disposition from Randomization (Study Period III)

	Double-Blind Maintenance Phase				
	Total Number of Randomized patients N=1065				
Patients	OP Depot 405 mg/ 4 weeks	OP Depot 300 mg/ 2 weeks	OP Depot 150 mg/ 2 weeks	OP Depot 45 mg/ 4 weeks	Oral Olanzapine 10, 15, or 20 mg/ day
Randomized, N=	318	141	140	144	322
Discontinued, N=	96	34	50	68	64
Lost to Follow up	5	2	3	2	2
Adverse Event	10	4	7	6	8
Lack of Efficacy	2	2	4	2	4
Protocol Violation	5	4	3	1	3
Physical Decision	8	3	2	3	4
Patient Decision	27	12	9	10	20
Sponsor Decision	0	0	0	2	0
Patients Entering Open-Label Re- stabilization phase	39	7	22	42	23
Completers, N=	222	107	90	76	258

Source: Figure HGKA.10.2, HGKA Study Report (pg. 98)

Table 8 summarizes baseline physical characteristics (gender, ethnic origin, age, BMI, and weight) for all randomized patients. The patient population was predominantly male (65.4%) and Caucasian (71.8%), and included patients aged 18 to 71 years with a mean age of 39 years at baseline. There were no statistically significant differences across treatment groups with respect to baseline physical characteristics. The observed Extracted Brief Psychiatric Rating Scale (BPRS) Total and Positive Subscale mean scores at baseline for the 45mg/4 weeks OP Depot group appeared to be higher compared with other treatment groups. This difference was considered not clinically meaningful by the sponsor.

Table 8. HGKA Baseline Physical Characteristics for all Randomized Patients (Study Period III)

Variable	OPD150/2w (N=140)	OPD300/2w (N=141)	OPD405/4w (N=318)	OPD45/2w (N=144)	OLZ (N=322)	Total (N=1065)
Gender						
Female	56 (40%)	46 (32.6%)	106 (33.3%)	48 (33.3%)	113 (35.1%)	369 (34.6%)
Male	84 (60%)	95 (67.4%)	212 (66.7%)	96 (66.7%)	209 (64.9%)	696 (65.4%)
Origin						
Caucasian	96	99	230	106	234	765
African	8	7	12	5	13	45
Hispanic	26	25	51	21	53	176
Native American	0	0	0	1	0	1
East Asian	8	9	20	8	15	60
West Asian	2	1	5	3	7	18
Age (years)						
Mean (SD)	37.7 (10.5)	39.5 (11.2)	39.0 (11.3)	39.5 (11.6)	39.0 (11.6)	39.0 (11.3)
Median	36.75	39.24	37.99	39.07	38.94	38.39
Maximum	64.63	68.85	70.77	66.19	69.61	70.77
Minimum	18.29	20.61	18.12	18.10	18.92	18.10
Weight (kg)						
Mean (SD)	78.4 (16.5)	75.3 (15.6)	77.9 (15.7)	78.4 (17.3)	77.0 (16.0)	77.4 (16.1)
Median	76.00	73.50	76.75	79.45	75.60	76.00
Maximum	126.80	144.20	124.80	143.00	123.00	144.20
Minimum	47.60	36.90	39.00	43.00	43.50	36.90
Extracted BPRS Total Score						
Mean (SD)	11.54 (7.85)	12.99 (9.10)	12.14 (7.80)	13.42 (8.13)	12.46 (8.19)	12.44 (8.15)
Median	10.00	11.00	11.00	13.00	11.50	12.00
Min, Max	0.00, 33.00	0.00, 33.00	0.00, 39.00	0.00, 33.00	0.00, 40.00	0.00, 40.00
Extracted BPRS Positive Score						
Mean (SD)	3.18 (2.39)	3.17 (2.76)	3.22 (2.57)	3.65 (2.69)	3.33 (2.60)	3.30 (2.60)
Median	3.00	2.50	3.00	3.50	3.00	3.00
Min, Max	0.00, 11.00	0.00, 10.00	0.00, 12.00	0.00, 11.00	0.00, 12.00	0.00, 12.00

Source: Table HGKA.11.5, HGKA Study Report (pg. 143); Summary of the Extracted BPRS Total and Extracted BPRS Positive scores at Baseline are the Reviewer's Results.

3.1.2.4 Statistical Methodologies and Endpoints

Primary and secondary analyses were performed on an intent-to-treat (ITT) basis. An ITT analysis is an analysis of data by the treatment groups to which patients were assigned by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. To be included in an efficacy analysis, patients had to have both a baseline and a post-baseline observation.

Time to exacerbation of symptoms of schizophrenia was the primary efficacy endpoint. In general, exacerbation is a worsening in particular items of the BPRS or hospitalization for positive psychotic symptom psychopathology. For this study, exacerbation of symptoms of schizophrenia was defined as follows:

- An increase on any of the BPRS Positive items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score >4 and an absolute increase of ≥ 2 on that specific item since randomization at Visit 10, or
- An increase of any of the BPRS Positive items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score >4 and an absolute increase of ≥ 4 on the BPRS Positive subscale (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization at Visit 10, or
- Hospitalization due to worsening of positive psychotic symptoms.

The primary superiority comparison of interest involved comparing time to exacerbation of the higher dose OP Depot arms (405 mg/4 weeks, 300 mg/2 weeks, and 150 mg/2 weeks) individually versus the time to exacerbation of the low-dose OP Depot arm (45 mg/4 weeks). The log-rank test was used to assess the pairwise comparisons of time to exacerbation of symptoms.

To control the overall Type I error, pairwise tests were conducted sequentially in the following OP Depot dose order: 1) 300 mg/2 weeks versus 45 mg/4 weeks; 2) 405 mg/4 weeks versus 45 mg/4 weeks; and 3) 150 mg/2 weeks versus 45 mg/4 weeks. Thus, the 405 mg/4 weeks versus 45 mg/4 weeks OP Depot comparison were declared statistically significant only if both this comparison and the first comparison (300 mg/2 weeks versus 45 mg/4 weeks) were statistically significant. The 150 mg/2 weeks versus 45 mg/4 weeks OP Depot were declared statistically significant only if all 3 comparisons were statistically significant.

3.1.2.5 Results of Efficacy Analysis

All 1065 randomized patients were included in the primary efficacy analyses. As a primary analysis, the log-rank test was used to assess the pairwise comparisons of time to exacerbation of symptoms. Each of the higher OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) was statistically superior to the 45 mg/4-weeks dose with respect to time to exacerbation of symptoms (nominal p-values: <.001, <.001, and =.006, respectively).

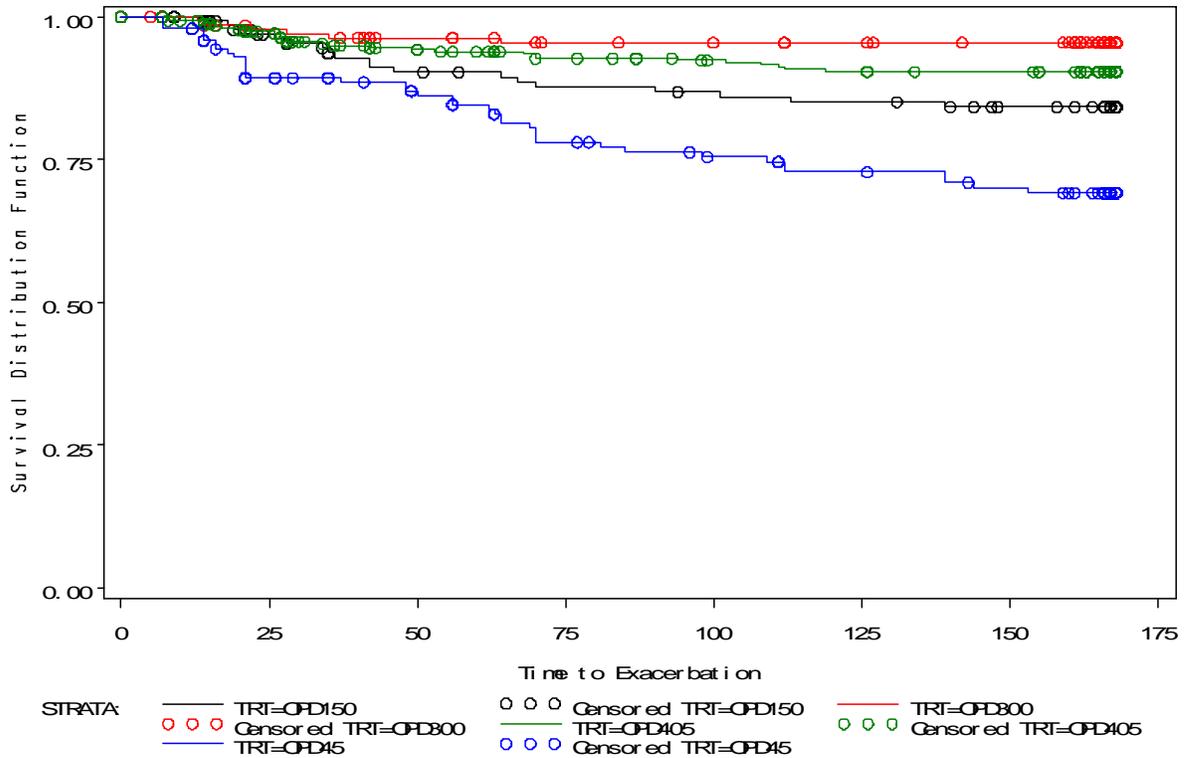
Table 9. Log-rank Test of Time to Exacerbation. OPD150, OPD300, OPD405 vs OPD45.

P-values from Log-Rank Test		
OPD300 vs OPD45	OPD405 vs OPD45	OPD150 vs OPD45
<0.001	<0.001	0.006

Source: Figure HGKA.11.2. , HGKA Study Report (pg .200)

Note: The reported p-values are nominal p-values and are not adjusted for multiplicity.

Figure 1. Kaplan-Meier curves of Time to Exacerbation for the double-blind maintenance phase (curves from top to bottom: OPD300mg/2weeks, OPD405mg/4weeks, OPD150mg/2weeks, OPD45mg/4weeks).



[Source: Reviewer’s results]

Table 10. HGKA Summary of the Patients who had Exacerbation and Censored Patients

	OPD300mg/2w	OPD405mg/4w	OPD150mg/2w	OPD45mg/4w
Total number of patients	141 (100%)	318 (100%)	140 (100%)	144 (100%)
Patients who had exacerbation	6 (4.3%)	27 (8.5%)	19 (13.6%)	39 (27.1%)
Patients who were censored	135 (95.7%)	291 (91.5%)	121 (86.4%)	105 (72.9%)

Source: Reviewer’s Results

To explore the treatment effect, this reviewer used a Cox proportional hazard model with treatment effect to estimate the hazard ratio (OPD 300 vs OPD45, OPD405 vs OPD45 and OPD150 vs OPD45) and corresponding 95% confidence intervals. The Cox-proportional hazard analysis supported the results of the primary analysis.

Table 11. Exploratory Analysis: Cox-proportional Hazard Analysis of Time to Exacerbation

	OPD300 vs OPD45	OPD405 vs OPD45	OPD150 vs OPD45
Hazard Ratio (HR)	0.137	0.286	0.474
95% CI for HR	(0.058, 0.323)	(0.175, 0.468)	(0.274, 0.821)

Source: Reviewer’s results

Note: The reported 95% CI’s are nominal CI’s and are not adjusted for multiplicity.

Recall that exacerbation of symptoms of schizophrenia was defined mainly in terms of Extracted Brief Psychiatric Rating Scale (BPRS) Positive Subscale score. Since the 45mg /4 weeks OP Depot group had the highest observed mean score on Extracted BPRS Positive subscale at baseline, this reviewer explored the impact of the baseline BPRS Positive subscale score on the primary analysis results by considering Cox proportional hazard model with treatment effect and BPRS Positive baseline score as a covariate. The baseline score appeared to be a significant predictor of time to exacerbation (parameter estimate 0.105, p-value 0.007). The results generally still support the superiority of higher doses to the low dose of 45mg/4weeks.

Table 12. Exploratory analysis: Cox-proportional Hazard Analysis of Time to Exacerbation with BPRS Positive Subscale Baseline Score as a Covariate

	OPD300 vs OPD45	OPD405 vs OPD45	OPD150 vs OPD45
Hazard Ratio (HR)	0.143	0.296	0.496
95% CI for HR	(0.060, 0.337)	(0.181, 0.484)	(0.286, 0.859)

Source: Reviewer’s Results

Note: The reported 95% CI’s are nominal CI’s and are not adjusted for multiplicity.

3.1.2.6 Reviewer’s Comments

Superiority of the three higher OP Depot dose groups (300mg/2 weeks, 405mg/4 weeks, and 150 mg/2 weeks) was demonstrated in comparison to a low OP Depot dose group (45 mg/4 weeks) with respect to time to exacerbation. Each of the higher OP Depot doses was statistically superior to the 45 mg/4-weeks dose (nominal p-values from the log-rank test: <.001, <.001, and =.006, respectively).

3.2 EVALUATION OF SAFETY

Not evaluated by this reviewer. Please refer to clinical review of this application for a detailed safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

4.1.1 STUDY HGJZ

This reviewer conducted exploratory subgroup analysis on the primary efficacy variable, PANSS Total score, using ANOVA models, including the terms for treatment and investigator study site. The subgroups of interest included age (dichotomized by age greater than or equal to 40 versus others), gender and origin (dichotomized by Caucasian versus others). For all OP depot treatment arms (300 mg/2 weeks, 405 mg/4 weeks and 210 mg/2 weeks), the treatment effect appeared to be numerically in favor of olanzapine (when compared with placebo) among all subgroups.

Table 13. Subgroup Analysis by Age: PANSS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	OPD 300 mg/2w	OPD 405 mg/4w	OPD 210 mg/2w
Younger than 40 years					
No patients	179	37	43	51	48
Change from Baseline	Mean (SD)	-7.65 (19.29)	-23.63 (22.00)	-21.78 (21.27)	-23.56 (20.89)
Placebo-adjusted difference	LS mean	NA	-14.96 (4.43)	-12.92 (4.19)	-15.68 (4.45)
	95% CI	NA	(-23.73, -6.19)	(-21.19, -4.64)	(-24.47, -6.89)
40 years or older					
No patients	223	61	55	49	58
Change from Baseline	Mean (SD)	-9.03 (25.17)	-28.42 (27.01)	-23.39 (23.22)	-21.60 (22.73)
Placebo adjusted difference	LS mean	NA	-21.30 (4.13)	-14.96 (4.25)	-14.30 (4.11)
	95% CI	NA	(-29.45, -13.15)	(-22.40, -6.20)	(-23.34, -6.58)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 14. Subgroup Analysis by Gender: PANSS Total Score Mean Change from Baseline to Endpoint (ITT Population)

		Placebo	OPD 300mg/2w	OPD 405 mg /4w	OPD 210 mg/2w
Males					
No patients	283	61	70	73	79
Change from Baseline	Mean (SD)	-7.44 (22.18)	-28.47 (25.24)	-21.62 (21.04)	-21.54 (19.07)
Placebo-adjusted difference	LS mean	NA	-20.27 (3.27)	-13.06 (3.21)	-14.96 (3.19)
	95% CI	NA	(-26.72, -13.83)	(-19.39,-6.74)	(-21.24, -8.68)
Females					
No patients	119	37	28	27	27
Change from Baseline	Mean (SD)	-10.27(24.57)	-20.93 (23.72)	-25.15 (25.14)	-25.26 (28.71)
Placebo adjusted difference	LS mean	NA	-12.02 (6.88)	-15.38 (6.81)	-12.11 (7.12)
	95% CI	NA	(-25.69, 1.65)	(-28.91, -1.85)	(-26.26, 2.05)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 15. Subgroup Analysis by Origin: PANSS Total Score Mean Change from Baseline to Endpoint (ITT Population)

		Placebo	OPD 300 mg/2w	OPD 405 mg/4w	OPD 210 mg/2w
Caucasian					
No patients	225	53	57	54	61
Change fr. Baseline	Mean (SD)	-4.30 (23.25)	-25.37 (24.43)	-24.07 (22.47)	-22.80 (23.59)
Placebo-adjusted difference	LS mean	NA	-22.56 (4.02)	-20.78 (4.07)	-20.05 (3.98)
	95% CI	NA	(-30.49, -14.63)	(-28.80, 12.75)	(-27.90, -12.20)
Other					
No patients	177	45	41	46	45
Change fr. Baseline	Mean (SD)	-13.47(21.99)	-27.63 (25.86)	-20.80 (21.87)	-22.07 (19.46)
Placebo adjusted difference	LS mean	NA	-11.81 (4.23)	-6.57 (4.04)	-9.26 (4.14)
	95% CI	NA	(-20.17, -3.44)	(-14.56, 1.43)	(-17.44, -1.09)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.1.2 STUDY HGKA

The reviewer conducted the exploratory Cox-proportional hazard analysis of time to exacerbation for age, gender and origin subgroups. Among all the subgroups, the treatment effect appeared to be numerically in favor of high dose OP depot treatment arms (300 mg/2 weeks, 405 mg/4 weeks and 150 mg/2 weeks) when compared with OPD 45 mg/ 2 weeks.

Table 16. Subgroup Analysis by Age: Cox-proportional Hazard Analysis of Time to Exacerbation.

	OPD 300 vs OPD 45	OPD 405 vs OPD 45	OPD 150 vs OPD 45
Younger than 40year			
Hazard Ratio (HR)	0.159	0.321	0.556
95% CI for HR	(0.047, 0.539)	(0.159, 0.645)	(0.268, 1.154)
Older than 40 years			
Hazard Ratio (HR)	0.119	0.261	0.412
95% CI for HR	(0.035, 0.398)	(0.131, 0.521)	(0.175, 0.970)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 17. Subgroup Analysis by Gender: Cox-proportional Hazard Analysis of Time to Exacerbation.

	OPD 300 vs OPD 45	OPD 405 vs OPD 45	OPD 150 vs OPD 45
Male			
Hazard Ratio (HR)	0.158	0.219	0.514
95% CI for HR	(0.061,0.412)	(0.116, 0.411)	(0.265, 0.995)
Female			
Hazard Ratio (HR)	0.081	0.461	0.426
95% CI for HR	(0.010, 0.621)	(0.207, 1.027)	(0.160, 1.137)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 18. Subgroup Analysis by Origin: Cox-proportional Hazard Analysis of Time to Exacerbation.

	OPD 300 vs OPD 45	OPD 405 vs OPD 45	OPD 150 vs OPD 45
Caucasian			
Hazard Ratio (HR)	0.144	0.243	0.426
95% CI for HR	(0.056, 0.368)	(0.138, 0.428)	(0.224, 0.810)
Other			
Hazard Ratio (HR)	0.129	0.529	0.777
95% CI for HR	(0.015, 1.070)	(0.184, 1.527)	(0.250, 2.412)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

This reviewer conducted exploratory subgroup analysis of efficacy by region for both studies.

4.2.1 STUDY HGJZ

For all OP depot treatment arms (300 mg/2 weeks, 405 mg/4 weeks and 210 mg/2 weeks), the treatment effect appeared to be numerically in favor of olanzapine (when compared with placebo) within both subgroups.

Table 19. Subgroup Analysis by Region: PANSS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	OPD 300 mg/2w	OPD 405 mg/4w	OPD 210 mg/2w
US					
No patients	313	76	77	78	82
Change from Baseline	Mean (SD)	-9.62 (23.69)	-27.00 (26.65)	-21.85 (22.61)	-21.93 (20.74)
Placebo-adjusted difference	LS mean	NA	-17.95 (3.10)	-12.67 (3.07)	-13.43 (3.04)
	95% CI	NA	(-24.06, -11.85)	(-18.72, -6.62)	(-19.42, -7.44)
Eastern Europe (Russia and Croatia)					
No patients	89	22	21	22	24
Change from Baseline	Mean (SD)	-4.68 (20.61)	-23.81 (17.53)	-25.14 (20.70)	-24.42 (25.62)
Placebo adjusted difference	LS mean	NA	-19.10 (6.63)	-20.56 (6.56)	-19.76 (6.42)
	95% CI	NA	(-32.30, -5.90)	(-33.61, -7.51)	(-32.53, -6.99)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2.2 STUDY HGKA

Based on the exploratory Cox-proportional hazard analysis of time to exacerbation by region, the treatment effect appeared to be numerically in favor of high dose OP depot treatment arms (300 mg/2 weeks, 405 mg/4 weeks and 150 mg/2 weeks) when compared with OPD 45 mg/ 2 weeks.

Table 20. Summary of the Patients who had Exacerbation by Region.

	OPD 300mg / 2 weeks	OPD 405mg/ 4 weeks	OPD 150mg/ 2 weeks	OPD 45mg/ 4 weeks
Eastern Europe				
Total number of Patients	24	62	28	27
Patients who had exacerbation	2	2	5	10
Western Europe				
Total number of Patients	47	101	41	44
Patients who had exacerbation	2	11	5	13
South and North America				
Total number of Patients	39	80	36	40
Patients who had exacerbation	1	4	2	6
Other				
Total number of Patients	31	75	35	33
Patients who had exacerbation	1	10	7	10

Source: Reviewer's Results

Table 21. Subgroup Analysis by Region: Cox-proportional Hazard Analysis of Time to Exacerbation.

	OPD300 vs OPD45	OPD405 vs OPD45	OPD150 vs OPD45
Eastern Europe			
Hazard Ratio (HR)	0.192	0.079	0.446
95% CI for HR	(0.042, 0.877)	(0.017, 0.359)	(0.152, 1.305)
Western Europe			
Hazard Ratio (HR)	0.127	0.332	0.398
95% CI for HR	(0.029, 0.563)	(0.149, 0.742)	(0.142, 1.118)
South and North America			
Hazard Ratio (HR)	0.155	0.308	0.345
95% CI for HR	(0.019, 1.286)	(0.087, 1.093)	(0.070, 1.709)
Other			
Hazard Ratio (HR)	0.083	0.388	0.609
95% CI for HR	(0.011, 0.650)	(0.162, 0.934)	(0.232, 1.601)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Study HGJZ

All three olanzapine pamoate depot treatment groups (OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were statistically superior to placebo in mean change from baseline to the endpoint visit in PANSS Total score. The nominal p-values of pairwise comparisons with placebo obtained from ANOVA model with treatment and investigator effects were all < 0.001.

Study HGKA

Each of the higher olanzapine pamoate depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) was statistically superior to the 45 mg/4-weeks dose with respect to time to exacerbation of symptoms (p-values from the log-rank test : <.001, <.001, and =.006, respectively).

In general, no statistical issues are identified in both studies.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Study HGJZ

In the primary analysis of the PANSS Total score, patients on olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were observed to show statistically significant improvement over patients in the placebo treatment group.

Study HGKA

The 3 higher dose olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups showed positive maintenance effect compared with the low dose (45mg/4 weeks) for stabilized patients with schizophrenia.

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