

DRAFT
REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #: 21-253
Sponsor: Eli Lilly and Company
Due Date: April 15, 2001

Drug Name:

Generic Name: Short-Acting Intramuscular
Olanzapine
Trade Name: Zyprexa IM

Drug Categorization:

Pharmacological Class: Dopamine/Serotonin Receptor
Antagonist
Proposed Indication: Rapid control of agitation
Dosage Forms: 10mg Vials
Route: Intramuscular

Review Information

Clinical Reviewer: Gregory M. Dubitsky, M.D.
Completion Date: December 20, 2000 (draft)

NDA 21-253
ZYPREXA IM
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1.0 Materials Utilized in the NDA Review

1.1 Materials from NDA/IND

This NDA review utilized the following materials:

NDA VOLUMES	SUBMISSION DATE	MATERIAL
1.1	6/15/00	Table of contents Financial disclosure data Draft labeling
1.2	"	Foreign marketing information Application summary
1.33-1.35	"	LOAC Study Report
1.36-1.37	"	LOAW Study Report
1.38-1.40	"	LOAV Study Report
1.41-1.44	"	LOAR Study Report
1.45-1.48	"	LOAT Study Report
1.49-1.54	"	HGHB Study Report
1.55-1.59	"	HGHV Study Report
1.60-1.64	"	HGHW Study Report
1.65-1.72	"	HGHX Study Report
1.83	"	Integrated Summary of Efficacy
1.84-1.86	"	Integrated Summary of Safety
2.1	9/1/00	Errors in original submission
3.1	10/11/00	HGIO Study Report
3.2-3.3	"	HGJA Study Report

Additionally, Case Report Tabulations (as SAS transport (.XPT) files) and Case Report Forms were provided in electronic format with the original submission and were accessed via the CDER Electronic Document Room (EDR) at Y:\CDSESUB1\N21253\N_000\2000-06-15.

Since much individual patient data were derived from Narrative Summaries, summaries were audited to check the accuracy and completeness of safety information compared to the information in the corresponding Case Report Forms (see section 8.3). This audit entailed a review of Case Report Forms for the following four patients:

Study HGHB, Patients 0272 and 3051
Study HGHX, Patient 3602
Study LOAV, Subject 2843

1.2 Related Reviews and Consultations

This NDA will be presented to the Psychopharmacological Drugs Advisory Committee (PDAC) in February 2001.

A statistical review of the key efficacy studies was performed by Ohidul Siddiqui, Ph.D., of the Division of Biometrics I.

Formal consultation was requested from the Division of Cardioresenal Drug Products (HFD-110) for an assessment of sinus pauses documented on telemetry in clinical pharmacology studies (see sections 8.1.2, 8.1.3.2, and 8.4.3).

2.0 Background

2.1 Indication

This NDA is intended to obtain approval of intramuscular olanzapine (Zyprexa IM) for the treatment of acute agitation.

At present, acutely agitated patients in the clinical setting who require parenteral medication generally receive a benzodiazepine or a older, typical antipsychotic. Benzodiazepines have some potential disadvantages, such as sedation, ataxia, and abuse liability. Among the typical antipsychotics, the low potency agents, such as chlorpromazine, tend to produce excessive sedation and orthostatic hypotension; the higher potency agents, such as haloperidol, are associated with acute dystonic reactions and other extrapyramidal symptoms.

Although olanzapine and other atypical antipsychotics also possess some disadvantages, such as postural hypotension, they are thought by many to have less propensity to cause extrapyramidal effects and are not felt to have abuse potential. Since there are no other atypical antipsychotics available in the U.S. for parenteral administration, intramuscular olanzapine may be a useful addition to the armamentarium for treating acute agitation.

Agitation has not generally been viewed as a specific diagnostic entity but instead as a non-specific behavior that commonly occurs across a number of disorders. The Agency is willing to recognize such non-specific signs and symptoms (e.g., pain and fever) as an indication for drug treatment under certain circumstances, the following of which are considered ideal: 1) if they can be universally defined, 2) if they can be assessed using a commonly accepted method, 3) if they have a well understood pathophysiologic basis, 4) if they are equally responsive to treatment regardless of context, and 5) if the claim is supported across several disease models.¹

While our understanding of the pathophysiologic basis for agitation (condition 3 above) is admittedly incomplete, the sponsor does presume that agitation can be universally defined and can be assessed by generally accepted methods. Furthermore, in this application, they purport to demonstrate that agitation is equally and rapidly responsive to treatment with intramuscular olanzapine across three diagnostic groups (patients with schizophrenic illness, bipolar disorder, and dementia). Hence, Lilly contends that agitation is a legitimate indication for treatment with intramuscular olanzapine.

2.2 Important Information from Related IND's and NDA's

Olanzapine is structurally related to the approved atypical antipsychotic clozapine and shares many features of the safety profile of that drug, such as orthostatic hypotension, weight gain, and constipation. However, at oral doses to 20 mg/day, olanzapine is not known to be associated with agranulocytosis, a major toxic effect of clozapine.

2.3 Administrative History²

IND [] for intramuscular olanzapine was received by the Agency on [] The review team met on [] and it was decided to allow the sponsor to proceed.

¹ From "Regulatory Issues in the Development of Drug Treatments for Various Psychiatric and Behavioral Disturbances Associated with Dementia," presented by Thomas Laughren, M.D., at a meeting of the Psychopharmacological Drugs Advisory Committee, Gaithersburg, MD, March 9, 2000.

² Most of the information in this section was derived from the sponsor's submission (volume 1.1, Tab 0.C) since many items (e.g., meeting minutes) were missing from the Division file.

The sponsor met with the Division on May 14, 1998, to discuss several options for developing intramuscular olanzapine, including a potential plan for the treatment of acute agitation. The sponsor was informed that pursuing an agitation indication would require clinical trials in a variety of patient populations, analogous to development programs for the indication of pain relief.

A teleconference was held on November 12, 1998, between Lilly and the Agency regarding a plan to study IM olanzapine for agitation in three patient populations (schizophrenia, bipolar mania, and dementia). We indicated general agreement with this plan.

On January 15, 1999, the sponsor submitted a written summary of their proposed development program for the use of intramuscular olanzapine in the treatment of acute agitation. This plan was reviewed by Paul Andreason, M.D., and was deemed to be adequate; however, a biometrics consultation was requested to evaluate the impact of an interim analysis in study HGHB.

A pre-NDA meeting was held with the sponsor on January 6, 2000. We acknowledged that the program conducted to support an agitation indication was consistent with our previous recommendations and stated that input from the Psychopharmacological Drugs Advisory Committee would be sought regarding the new agitation indication. Since all clinical studies to that point had been conducted with the "vial alone" product, we indicated that a clinical study utilizing the short-acting intramuscular (SAIM) kit (using a syringe pre-filled with aqueous sodium chloride diluent) would be necessary to gain approval for the SAIM product. It would also be necessary to conduct a trial to study the pharmacokinetics of dosing under the conditions of maximum dose and frequency of administration to be recommended in labeling. Finally, we agreed that submission of pediatric data could be deferred until after approval of IM olanzapine for adult use.

On March 6 and April 13, 2000, the sponsor submitted protocol summaries for two clinical pharmacology studies (HGJA and HGIO) intended to address concerns raised at the pre-NDA meeting, i.e., pharmacokinetic data under maximal dosing conditions and data from use of the SAIM kit, respectively. Lilly also requested permission to submit

the reports from these studies within 4 months of the initial NDA submission. We responded by E-Mail that the study designs were acceptable as was their plan to submit the reports within 4 months of the initial submission.

This NDA was submitted on June 15, 2000. A Refuse-to-File meeting was convened on [] and the submission was judged to be fileable.

2.4 Financial Disclosure Information

There are four trials in this NDA submission that are considered "covered clinical studies" in accordance with 21 CFR 54.2(e): HGHB, HGHV, HGHW, and HGHX.

Among the clinical investigators in these trials, two were identified by the sponsor as having participated in financial arrangements with the sponsor that require disclosure:

1) Gerald Maguire, M.D., was the principal investigator for site 017 in study HGHW and site 015 in study HGHX. As speakers fees, Dr. Maguire received [] in 1999 and [] in 2000. He contributed 3% of the randomized patients in HGHW and 3% of the randomized patients in study HGHX.

2) Sumer Verma, M.D., was the principal investigator for site 033 in study HGHX. As speakers fees, Dr. Verma received [] in 1999 and [] in 2000. She contributed 1% of the randomized patients in study HGHX.

Given the double-blind design of these studies and the relatively small numbers of patients contributed by these investigators, it is very unlikely that these financial interests have an appreciable impact on the reliability of these studies.

A number of sub-investigators in these trials were identified by Lilly as not having provided financial disclosure information: 9 sub-investigators in study HGHB, 5 in HGHV, 24 in HGHW, and 34 in HGHX. The sponsor indicated that, despite due diligence, the required information could not be obtained because of lack of response to repeated requests or departure of the individual from the research site with no available forwarding address.

2.5 Directions for Use

The directions for the administration of Zyprexa IM for the rapid control of agitation, as described in the sponsor's proposed labeling, are as follows:

Vials containing 10mg of olanzapine should be reconstituted with either 2.1 ml of sterile water to yield a ~5mg/ml solution or with the contents of {
} to yield a 10 mg/ml solution.

Reconstituted Zyprexa IM should be used within one hour. Zyprexa IM is intended for intramuscular use only and is to be injected slowly, deeply into the muscle mass.

The optimal dose for agitated patients with schizophrenia or bipolar mania is 10mg. Depending on response, subsequent doses up to 10mg may be given. The safety of total daily doses above 30mg or of 10mg injections given more frequently than 2 hours after the first dose and 4 hours after the second dose have not been evaluated.

In agitated patients with dementia, the optimal dose is 2.5mg. Depending on response, subsequent doses up to 5mg may be given. The safety of total daily doses over 12.5mg or of injections given more frequently than 2 hours after the first dose have not been evaluated.

A dose of 5mg should be considered for geriatric patients or when other clinical factors warrant. A 2.5mg dose should be considered for patients with dementia or for those who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacologically sensitive to olanzapine.

2.6 Foreign Marketing

The short-acting intramuscular (SAIM) formulation of olanzapine is not marketed in any country. The first marketing application was submitted during {
}

3.0 Drug Substance and Product Information

3.1 Chemistry

For the two methods of reconstituting Zyprexa IM (using a pre-filled Hyporet syringe and using sterile water), the resulting solutions will have different concentrations of olanzapine according to the directions in proposed labeling (10 mg/ml and 5 mg/ml, respectively). This could be confusing for healthcare practitioners working in settings that employ both methods and may increase the risk of a medical error. The rationale for this difference is not known.

3.2 Microbiology

The sponsor submitted detailed information on facilities, operations, validation methods, and microbiological monitoring practices. Olanzapine for injection is made by Eli Lilly and Company using an () process. Olanzapine diluent is manufactured by () () using an () process followed by ()

There are no known outstanding microbiology issues.

4.0 Animal Pharmacology

Non-clinical pharmacology information is cross-referenced to NDA 20-592 for oral olanzapine. At the time of this review, the pharmacology/toxicology review had not yet been completed. The information below has been extracted from the Nonclinical Pharmacology, ADME, and Toxicology Summary in the NDA (volume 1.2, Tab 3.E).

A one-month study in beagle dogs administered IM olanzapine doses of 0, 0.5, 1.25, or 2.5 mg/kg/day in 1.5ml of solution revealed no compound-related systemic changes. The maximum solution concentration was about 8.4 mg/ml.³ Injection site lesions were variable both between dogs and between sites on the same dog and were generally mild.

³ This information was obtained from the Pharmacology/Toxicology reviewer, Lois Freed, Ph.D.

In an in vitro study using rat skeletal myoblast cell cultures, olanzapine concentrations ≥ 4.2 mg/ml were slightly to moderately irritating.

An in vivo study in rabbits demonstrated that olanzapine formulations of 1.7, 4.2, and 8.4 mg/ml were slightly irritating to skeletal muscle, with the high dose being associated with slightly more reaction.

ADME studies were conducted in beagle dogs and cynomolgus monkeys. After intramuscular injection, olanzapine was rapidly absorbed in both species. The absolute bioavailability in dogs was about 100%. Intramuscular administration produced greater peak plasma levels and AUC's, shorter times to Cmax, and similar half-lives compared to oral administration.

The only identified preclinical issue at this time is whether the animal dermal irritation studies are adequate to gauge potential problems in humans injected with a 10 mg/ml solution (using the Hyporet method of reconstitution), since this concentration exceeds the maximum solution concentration used in the preclinical studies. Almost all human experience to date utilized sterile water reconstitution, which produces the less concentrated 5 mg/ml solution. Study HGIO used 10 mg/ml solutions in 18 healthy males to evaluate the pharmacokinetics of two different intramuscular formulations of olanzapine (see section 8.1.8.2). No problems with injection site reactions were reported in this study but apparently injection sites were not specifically monitored. Also, only 5mg doses were administered; whether 10mg doses given as 10 mg/ml would be associated with poorer dermal tolerance is not known.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Design and Patient Enumeration

As of October 11, 2000, the Lilly development program for intramuscular olanzapine consisted of 11 completed human studies involving a total of 848 patients/healthy volunteers who received at least one dose of IM olanzapine:

- 4 studies in healthy volunteers (F1D-EW-LOAC, F1D-EW-LOAW, F1D-LC-LOAV, and F1D-BD-HGIO).
- 2 open-label studies in patients with acute non-organic psychosis (F1D-EW-LOAR and F1D-EW-LOAT).
- 1 open-label tolerance and pharmacokinetic study in patients with chronic schizophrenia (F1D-MC-HGJA)
- 4 randomized, double-blind, placebo-controlled studies in schizophrenia/schizophreniform disorder/schizoaffective disorder (F1D-MC-HGHB and F1D-MC-HGHV), bipolar I disorder (F1D-MC-HGHW), and dementia (Alzheimer's, vascular, or mixed type) (F1D-MC-HGHX).

For sake of brevity, these studies will hereafter be referred to by the last four letters of the protocol number.

Table 5.1.1.1 in Appendix 5.0 summarizes the 11 completed studies. Table 5.1.1.2 in Appendix 5.0 provides an enumeration of these subjects by treatment group.

The safety review will focus on two subsets of the pool of the four placebo-controlled studies in patients:

- the pool of studies HGHB, HGHV, and HGHW; this is referred to as the placebo-controlled IM safety database.
- study HGHX, referred to as the geriatric study.

5.1.2 Demographic Characteristics

Demographic characteristics for the placebo-controlled IM safety database and for the geriatric study (HGHX) are displayed in Appendix 5.0, Tables 5.1.2.1 and 5.1.2.2, respectively. For both datasets, treatment groups were comparable with respect to age, race, and gender.

5.1.3 Extent of Exposure

Appendix 5.0, Table 5.1.3, summarizes patient exposure to IM olanzapine based on total dose during the 24 hour IM period for the placebo-controlled IM safety database and for the geriatric study.

Over half of the IM olanzapine patients in the placebo-controlled IM safety database received a total dose of 10.0mg of IM olanzapine over 24 hours (223/415 or 54%). The mean dose in this dataset was 10.8mg.

In the geriatric study, most patients randomized to the 2.5mg IM olanzapine group (42/71 or 59%) and to the 5.0mg IM olanzapine group (42/66 or 64%) received only one injection over 24 hours. Mean doses in these two dose groups were 3.8mg and 7.2mg, respectively.

5.2 Secondary Sources of Clinical Data

5.2.1 Post-Marketing Experience

The short-acting intramuscular formulation of olanzapine had not been marketed in any country as of the time of this NDA submission (June 15, 2000). A marketing application was submitted in

5.2.2 Literature Review

The sponsor conducted no search of the published literature for articles directly relevant to intramuscular olanzapine.

A literature search conducted by the undersigned on October 5, 2000, revealed no published articles with data relevant to intramuscular olanzapine.⁴

6.0 Human Pharmacokinetics

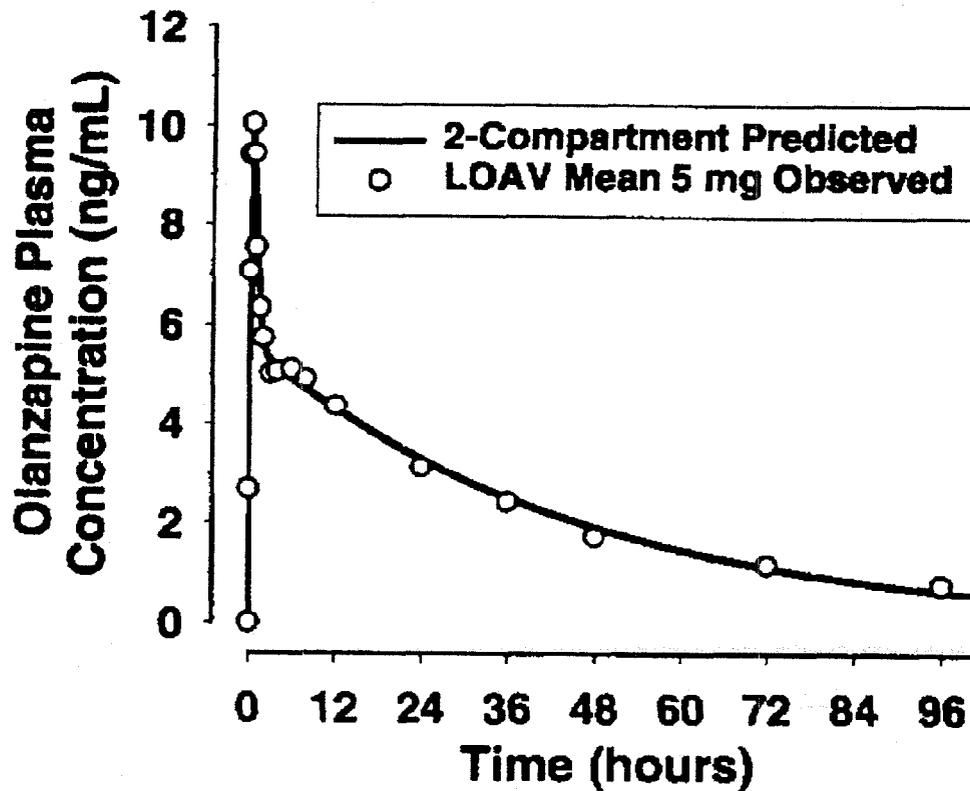
The pharmacokinetics of olanzapine after intramuscular administration in man is described by a two-compartment model. After intramuscular injection, there is a rapid rise in plasma olanzapine concentration to a peak value within minutes secondary to rapid absorption. This is followed by a sharp drop in plasma concentration for another brief period, representing rapid redistribution from a central to a peripheral compartment. Finally, there is a monoexponential terminal elimination phase after the first 2 hours, with sustained concentrations for at least 96 hours post-injection. Please see Figure 6.0 below.

Pharmacokinetic attributes of olanzapine administered intramuscularly can be summarized as follows:

⁴ This search utilized the search string "intramuscular olanzapine" in the PubMed database.

- IM administration of olanzapine produces a 2.5-fold higher C_{max} than the same oral dose.
- T_{max} after IM administration is 15-45 minutes versus 5-8 hours after oral administration.
- with both intramuscular and oral administration, C_{max} and AUC are directly proportional to dose.
- administration of the same dose by the intramuscular route and orally produces an equivalent AUC and similar half-life, plasma clearance, and volume of distribution.
- metabolic profiles after intramuscular and oral administration are quantitatively similar and qualitatively identical.
- intramuscular doses given daily produced a 2-fold accumulation in plasma concentration between day 1 and day 3, consistent with oral dosing.

FIGURE 6.0:
Time-Concentration Relationship
After Olanzapine 5mg IM In Healthy Volunteers



7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The sponsor has conducted four multicenter, placebo-controlled trials to evaluate the efficacy of intramuscular olanzapine in the rapid control of agitation. These studies were performed in three different diagnostic groups:

- two trials (HGHB and HGHV) were done in patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder.
- one trial (HGHW) was in patients with bipolar I disorder in an acute manic or mixed state.
- one trial (HGHX) was in patients with dementia of the Alzheimer's, vascular, or mixed type.

In addition to the above four trials, the sponsor also conducted two open-label studies in South Africa in patients with acute, non-organic psychosis (LOAR and LOAT) and a third open-label study in patients with chronic stable schizophrenia (HGJA). In studies LOAR and LOAT, assessment of efficacy was a secondary objective. In study HGJA, efficacy was neither a primary nor secondary objective. By design, these trials are not capable of demonstrating the efficacy of IM olanzapine in the treatment of agitation and they will not be reviewed in detail here.

The Excited Component of the Positive and Negative Symptom Scale (PANSS), consisting of the poor impulse control, tension, hostility, uncooperativeness, and excitement items of the PANSS, was selected as the primary efficacy variable for the key IM olanzapine studies.⁵ This variable was selected for the following reasons: 1) it has high face validity in measuring agitation, 2) it has been validated by the sponsor (see next paragraph), 3) it based on clinician observation as opposed to a verbal report from the patient, making it useful in diverse patient populations, and 4) it can be generalized to the populations studied.

⁵ This component was derived by factor analysis from the PANSS by its creators. Each item was analyzed on a scale from 0 to 6 by subtracting 1 from each score, yielding a range for total scores of 0 to 30.

The PANSS Excited Component met all criteria for internal consistency, construct and discriminant validity, responsiveness, and reliability that were established in the sponsor's validation plan using a large sample of agitated and non-agitated patients in a premarketing study of oral olanzapine (HGAJ, N=1995, including 742 agitated patients). Internal consistency was assessed by Cronbach's alpha ($.7 < \alpha < .9$). Evaluation of construct validity entailed investigation of the correlation at baseline of the Excited Component with the CGI-severity score ($r > .3$, $p < .05$). Discriminant validity was evaluated by demonstrating greater changes from baseline in the Excited Component for patients with CGI-severity scores >3 vs. ≤ 3 in the total population and for patients with a CGI score >4 vs. ≤ 4 in the agitated subset. Responsiveness was assayed by showing that the Excited Component change over time was greater for patients showing improvement on the CGI vs. those showing no improvement. Measurement of reliability demonstrated an intraclass correlation coefficient $>.70$.

Other scales for assessing agitation have been designed for specific patient groups and were assessed in these trials. The Corrigan Agitated Behavior Scale is used in patients with mania, psychoactive substance abuse, schizophrenia, schizophreniform disorder, and psychosis not otherwise specified. This is a 14 item scale, each item being a specific behavior that is rated 1 to 4. Also, the Cohen-Mansfield Agitation Inventory is a 30 item checklist of behaviors reflecting agitation and aggression (e.g., hitting, biting, screaming) that has been validated in patients with dementia.

Additionally, to help insure that improvement in agitation was not merely secondary to oversedation, the sponsor developed a scale to differentiate between agitated, calm, and sleep states, the Agitation-Calmness Evaluation Scale (ACES). This single item scale is rated as 1 (marked agitation) to 9 (unarousable).

Results with respect to these additional, secondary scales will also be reviewed below.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Study HGHB

Investigators/Locations

The 51 principal investigators and study sites are identified in Appendix 7.0, Table 7.2.1.1.

Objectives

The primary objectives of this study were :

- 1) to compare the efficacy of IM olanzapine to IM placebo as measured by the change from baseline to 2 hours post-injection on the PANSS Excited Component.
- 2) to determine if IM olanzapine is "non-inferior" to IM haloperidol as measured by the change from baseline to 2 hours post-injection on the PANSS Excited Component.

Patient Sample

Study inclusion criteria included the following:

- male or female at least 18 years old.
- inpatient status during the study.
- DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder.
- illness must not have been secondary to substance abuse, in the opinion of the investigator.
- considered clinically agitated and appropriate candidates for treatment with IM medication.
- prior to the first IM injection, a PANSS Excited Component total score ≥ 14 with at least one item score ≥ 4 on a 1-7 scale.

Important exclusion criteria were:

- previous participation in a Lilly olanzapine trial.
- serious suicide risk.
- serious, unstable medical illness.
- benzodiazepine treatment within 4 hours of the first IM administration of study drug.

- treatment with an injectable depot neuroleptic or injectable zuclopenthixol acetate within one injection interval prior to study drug administration.
- treatment with psychostimulants or reserpine within one week of study drug.
- treatment with clozapine within 6 weeks of study drug.
- requiring concomitant ECT.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

For at least 2 hours prior to randomization, antipsychotic medication was stopped and patients were screened. Also, patients were not to receive any benzodiazepine treatment during the four hours prior to the first injection of study drug.

Eligible patients were then randomized in a 2:2:1 ratio to olanzapine, haloperidol, or placebo, respectively, and received an intramuscular injection of the assigned medication (i.e., 10mg of olanzapine, 7.5mg of haloperidol, or placebo), which marked the beginning of the 24 hour "injectable treatment phase" of the study. During this phase, the following dosing rules applied:

- minimum number of injections was one.
- maximum number of injections was three.
- if a second injection was clinically indicated, it would be given at least 2 hours after the first injection and subsequent to the 2 hour post-first injection assessments.
- if a third injection was clinically indicated, it would be given at least 4 hours after the second injection.
- all injections would be given within 20 hours of the first injection.
- the maximum cumulative dose of IM olanzapine was 30mg and of IM haloperidol was 22.5mg within 20 hours.

The decision whether to administer a second or third injection of study drug was made by the investigator based on clinical judgement.

The study drug for the injectable treatment phase was supplied in unblinded form. Blinding of the patient and personnel involved in clinical assessments was preserved by

utilizing an unblinded third party to prepare and administer the injections.

Vials for IM injections and all ancillary supplies (e.g., needles and syringes) were provided in randomized patient kits. Olanzapine powder for injection was reconstituted using sterile water provided by the study site. All injections prepared on-site must have been used within 30 minutes of preparation.

The concomitant use of benzodiazepines was discouraged but were allowed during the IM treatment phase according to the following rules:

- patients who received only one injection of study drug could not be given a benzodiazepine.
- patients who received two injections of study drug may have received a benzodiazepine once, at least one hour after the second injection.
- patients who received a third injection may have been given a benzodiazepine dose at least one hour after the third injection.
- if no benzodiazepine was administered after the second injection, either one or two benzodiazepine doses may have been given after the third injection.
- permitted benzodiazepines and maximum total doses during the injectable treatment phase were as follows:

Lorazepam (IM or oral)	4mg
Diazepam (IM, IV, or oral)	20mg
Oxazepam (oral)	30mg
Chlorazepate (IM or oral)	50mg

Anticholinergic medication (specifically benztropine, biperiden, or procyclidine) was allowed to control extrapyramidal symptoms. However, their use as prophylaxis was not permitted.

An oral treatment phase followed the injectable treatment phase. This part of the study will be discussed in section 7.3.5.

Analysis

The primary analysis was performed on an intent-to-treat basis, i.e., by the groups randomly assigned even if the

assigned medication was not taken, the correct treatment was not received, or the protocol was not followed. LOCF analyses included only patients with both a baseline and a post-baseline assessment.

The primary efficacy variable was the change from baseline to 2 hours post first IM dose on the PANSS Excited Component, which was assessed pre-dose and at 15, 30, 45, 60, 90 and 120 minutes after the first injection. A baseline measure was the score obtained immediately prior to the first IM injection.

Analysis was performed using an ANOVA model with terms for treatment, country, and treatment-by-country interaction. If the interaction was not significant ($p > 0.10$), then it was removed from the model. Comparisons of IM olanzapine with IM placebo were tested at a two-sided significance level of 0.05.

Investigator sites were pooled within country for analysis. If there were less than 10 patients in a country, those data were pooled with data from other countries enrolling a small number of patients.

For total scores derived from individual scale items, the total score was treated as missing if any of the individual items were missing.

A re-estimation of sample size was conducted under the auspices of a data monitoring board from the first 109 patients that completed the 24 hour injectable treatment phase. This was not considered a formal interim analysis. Based on data from both active therapy groups ($n=89$), it was calculated that the originally planned sample size was adequate.

Baseline Demographics

Demographic characteristics of patients entered into the injectable period are displayed in Appendix 7.0, Table 7.2.1.2. Treatment groups were comparable with respect to age, gender composition, and race.

Baseline Severity of Illness

Baseline mean scores on the PANSS Excited Component were comparable across treatment groups (13.35, 13.17, and 13.37

for the IM olanzapine, haloperidol, and placebo groups, respectively).

Patient Disposition

A total of 325 patients entered the screening period. Ten patients were excluded due to entry criteria not being met and 4 due to patient decision. The remaining 311 eligible patients were randomized and, of these, 285 patients completed the injectable phase of the study. Patient disposition is displayed in Table 7.2.1.3 below. The proportion of completers was lowest in the placebo group (87%); most of the dropouts in this group (5/7) were for lack of efficacy.

Protocol Violations

Over 350 protocol violations were noted in this trial. Table 7.2.1.4 below enumerates the types of violations that could confound the efficacy results of the study.

The impact of these violations on the efficacy results cannot be accurately gauged but, given the generally small number of violations, it is unlikely that the results were significantly biased.

TABLE 7.2.1.3: STUDY HGHB INJECTABLE PHASE PATIENT DISPOSITION			
Reason	IM Olanz	IM Hal	IM Placebo
Randomized	131	126	54
Dropouts (by reason)			
Adverse Event	2	3	0
Lack of Efficacy	2	0	5
Patient Decision	5	4	2
Criteria/Compliance	0	2	0
Physician Decision	0	1	0
Completed Phase	122	116	47

TABLE 7.2.1.4 STUDY HGHB INJECTABLE PHASE ENUMERATION OF POTENTIALLY SIGNIFICANT PROTOCOL VIOLATIONS			
Violation Category	IM Olanz	IM Hal	IM Plac
Use of excluded medication ≤2 hours before first injection	2 ⁶	4	0
Use of excluded medication during the entire study	3 ⁷	0	0
Prohibited use of benzodiazepines after the first injection	2	2	1
Inadequate study drug dose for first injection	5	6	0
Excessive study drug dose for first injection	1	1	0
Same person administered drug and performed ratings	3	1	2

Efficacy Results

The efficacy results for the first 2 hour period of the injectable treatment phase on the PANSS Excited Component, the primary efficacy variable, are presented in Appendix 7.0, Table 7.2.1.5.

IM Olanzapine was superior to placebo to a highly significant degree ($p < 0.001$) on the PANSS Excited Component at 30, 60, 90, and 120 minutes post-injection for the observed cases dataset and at 120 minutes using an LOCF analysis.

The Corrigan Agitated Behavior Scale and the Agitation-Calmness Evaluation Scale were examined as supportive secondary efficacy variables. Data for these variables are displayed in Appendix 7.0, Tables 7.2.1.6 and 7.2.1.7, respectively. Results were the same as for the primary variable.

Data for the Agitation-Calmness Evaluation Scale suggest that improvement with IM olanzapine occurred without

⁶ Patient 102-1063 received a dose of clomipramine, sodium valproate, thioridazine, and maprotiline. Patient 013-0611 received temazepam.

⁷ Patient 202-2081 received propranolol, patient 851-8556 received cyproterone (an antiandrogenic steroid), and patient 006-0254 received nifedipine intermittently.

excessive sedation on average. The mean change on this 9 point rating scale was +1.79 (range -1.0 to +6.0): from a baseline mean of 2.59 (indicating mild-moderate agitation) to 4.37 (normal-mild calmness) at 120 minutes post-injection (LOCF).

There was no evidence to suggest a treatment-by-country interaction ($p=0.843$ in the LOCF analysis of the PANSS Excited Component at 120 minutes).

Efficacy assessments conducted during the IM treatment phase but subsequent to the 2 hour period following the first injection are potentially confounded by 1) a variable number of doses of study medication, 2) variable timing of the optional injections, and 3) benzodiazepine use. These efficacy data cannot be reliably interpreted and are not germane to the primary study objectives. These data will be summarized in section 7.3.4.

Data from the oral treatment phase of this study will be presented in section 7.3.5.

Conclusions

Study HGHB provides strong evidence for the efficacy of IM olanzapine 10mg versus placebo in the acute treatment of agitation in patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder.

7.2.2 Study HGHV

Investigators/Locations

The 14 investigators and study sites are listed in Appendix 7.0, Table 7.2.2.1.

Objectives

The primary study objective was to evaluate the efficacy of IM olanzapine 2.5, 5, 7.5, and 10mg relative to IM placebo for agitation as measured by changes from baseline to 2 hours post-injection on the PANSS Excited Component.

Patient Sample

Study inclusion criteria included the following:

- male or female at least 18 years old.
- inpatient status.
- DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder.
- illness must not have been secondary to substance abuse, in the opinion of the investigator.
- considered clinically agitated and appropriate candidates for treatment with IM medication.
- prior to the first IM injection, a PANSS Excited Component total score ≥ 14 with at least one item score ≥ 4 on a 1-7 scale.

Important exclusion criteria were:

- previous participation in a Lilly intramuscular olanzapine trial.
- serious suicide risk.
- serious, unstable medical illness.
- benzodiazepine treatment within 4 hours of the first IM administration of study drug.
- treatment with an injectable depot neuroleptic or injectable zuclopenthixol acetate within one injection interval prior to study drug administration.
- treatment with psychostimulants or reserpine within one week of study drug.
- treatment with clozapine within 6 weeks of study drug.
- requiring concomitant ECT.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

For at least 2 hours prior to randomization, antipsychotic medication was stopped and patients were screened. Also, patients were not to receive any benzodiazepine treatment during the four hours prior to the first injection of study drug.

Eligible patients were then randomized to one of four fixed doses of IM olanzapine (2.5, 5, 7.5, or 10mg), IM haloperidol 7.5mg, or IM placebo. The following rules for dosing applied:

- minimum number of injections was one.

- maximum number of injections was three.
- if a second injection was clinically indicated, it would be given at least 2 hours after the first injection and subsequent to the 2 hour post-first injection assessments.
- if a third injection was clinically indicated, it would be given at least 4 hours after the second injection.
- all injections would be given within 20 hours of the first injection.
- the maximum cumulative dose within 20 hours for IM olanzapine was 7.5, 15, 22.5, and 30mg for each of the above dose groups, respectively; the maximum dose of IM haloperidol was 22.5mg within this period.
- if a concomitant benzodiazepine was administered, at least one hour was to elapse between this administration and further injection of study drug.

The decision whether to administer a second or third injection of study drug was made by the investigator based on clinical judgement.

The study drug was supplied in unblinded form. Blinding of the patient and personnel involved in clinical assessments was preserved by utilizing an unblinded third party to prepare and administer the injections.

Vials for IM injections and all ancillary supplies (e.g., needles and syringes) were provided in randomized patient kits. Olanzapine powder for injection was reconstituted using sterile water provided by the study site. All injections prepared on-site must have been used within 30 minutes of preparation.

The concomitant use of benzodiazepines was discouraged but were allowed during the IM treatment phase according to the following rules:

- patients who received only one injection of study drug could not be given a benzodiazepine.
- patients who received two injections of study drug may have received a benzodiazepine once, at least one hour after the second injection.
- patients who received a third injection may have been given a benzodiazepine dose at least one hour after the third injection.

- if no benzodiazepine was administered after the second injection, either one or two benzodiazepine doses may have been given after the third injection.
- permitted benzodiazepines and maximum total doses during the injectable treatment phase were as follows:

Lorazepam (IM or oral)	4mg
Diazepam (IM, IV, or oral)	20mg
Oxazepam (oral)	30mg
Chlorazepate (IM or oral)	50mg

Anticholinergic medication (specifically benztropine, biperiden, or procyclidine) was allowed to control extrapyramidal symptoms. However, their use as prophylaxis was not permitted.

Analysis

The primary analysis was performed on an intent-to-treat basis, i.e., by the groups randomly assigned even if the assigned medication was not taken, the correct treatment was not received, or the protocol was not followed. LOCF analyses included only patients with both a baseline and a post-baseline assessment.

The primary efficacy variable was the change from baseline to 2 hours post first IM dose on the PANSS Excited Component, which was assessed pre-dose and at 30, 60, 90 and 120 minutes after the first injection. A baseline measure was the score obtained immediately prior to the first IM injection.

Analysis was performed using an ANOVA model with terms for treatment, country, and treatment-by-country interaction. If the interaction was not significant ($p > 0.10$), then it was removed from the model.

Investigator sites were pooled within country for analysis. If there were less than 12 patients in a country, those data were pooled with data from other countries enrolling a small number of patients.

For total scores derived from individual scale items, the total score was treated as missing if any of the individual items were missing.

Baseline Demographics

Demographic characteristics of patients entered into the injectable period are displayed in Appendix 7.0, Table 7.2.2.2. Treatment groups were comparable with respect to age, gender composition, and race.

Baseline Severity of Illness

Baseline mean scores on the PANSS Excited Component were comparable across treatment groups: 13.25, 14.71, 13.85, 14.30, 14.28, 13.78 for the IM olanzapine 2.5, 5, 7.5, and 10mg groups; the haloperidol group, and the placebo group, respectively.

Patient Disposition

A total of 282 patients were screened. Twelve patients were not randomized, 2 due to physician decision, 9 due to not meeting entry criteria, and 1 due to patient decision.

The remaining 270 patients were randomized and, of these, 268 patients completed the study. There were only 2 dropouts, both from the IM olanzapine 5mg group: one due to lack of efficacy and one due to physician decision. Both dropped out after the 2 hour post-first injection period.

Protocol Violations

Over 100 protocol violations were noted in this trial. Table 7.2.2.3 below enumerates the types of violations that would seem to possess the most potential to confound the efficacy results of the study.

Violation Category	IM Olanz				IM Hal	IM Plac
	2.5	5	7.5	10		
Prohibited use of benzodiazepines	2	1	0	4	0	2
Use of excluded medication	0	1	0	2	2	1
Study drug not administered per protocol	1	1	1	1	1	3

The impact of these violations on the efficacy results cannot be accurately gauged but, given the relatively small number of violations, it is unlikely that the results were significantly biased.

Efficacy Results

The efficacy results at 2 hours after the first injection of study drug on the PANSS Excited Component, the primary efficacy variable, are presented in Appendix 7.0, Table 7.2.2.4.

The sponsor did not specify a method of adjusting for multiplicity when comparing each dose of olanzapine to placebo in pairwise fashion. For purposes of interpreting these efficacy data, this reviewer used the conservative Bonferroni procedure, which yields an alpha level of 0.0125 (0.0500÷4) for declaring statistical significance.

IM Olanzapine 5, 7.5, and 10mg were superior to placebo to a highly significant degree ($p < 0.001$) on the PANSS Excited Component at 60, 90, and 120 minutes post-injection for the observed cases dataset and at 120 minutes using an LOCF analysis. The 2.5mg dose was superior to placebo at 120 minutes post-injection in both OC and LOCF analyses.

The Agitation-Calmness Evaluation Scale was examined as a supportive secondary efficacy variable. Data for this variable are displayed in Appendix 7.0, Tables 7.2.2.5. Results were the same as for the primary variable except that the low dose (2.5mg) was not superior to placebo.

Additionally, the results of the LOCF analysis of the mean change from baseline to 2 hours post-first injection for the Corrigan Agitated Behavior Scale are shown in Table 7.2.2.6 below. (Results for the observed cases analysis are expected to be similar since there were no dropouts in the 2 hour period after the first injection.) All active drug groups were superior to placebo on this variable at 120 minutes post-first injection, with the 5, 7.5, and 10mg doses of olanzapine highly superior.

TABLE 7.2.2.6
STUDY HGHV
MEAN CHANGE FROM BASELINE IN THE
CORRIGAN AGITATED BEHAVIOR SCALE AFTER FIRST INJECTION
LOCF ANALYSIS

	Baseline		120 minutes	p-value vs. placebo
	N	Mean	Mean Δ	
Olz 2.5	48	29.27	-5.81	0.012
Olz 5	45	31.38	-8.96	<0.001
Olz 7.5	46	31.24	-10.50	<0.001
Olz 10	46	30.76	-10.39	<0.001
Hal 7.5	39	30.13	-7.69	<0.001
Plac	45	29.98	-3.00	---

Data for the Agitation-Calmness Evaluation Scale suggest that improvement with IM olanzapine occurred without excessive sedation on average. The mean changes on this 9 point rating scale were in the range +1 to +3, from baseline means of just over 2 (indicating mild-moderate agitation) to generally over 4 (normal-mild calmness) at 120 minutes post-injection (LOCF).

There was no evidence to suggest a treatment-by-country interaction (p=0.135 in the LOCF analysis of the PANSS Excited Component at 120 minutes).

Efficacy assessments conducted subsequent to the 2 hour period following the first injection are potentially confounded by 1) a variable number of doses of study medication, 2) variable timing of the optional injections, and 3) benzodiazepine use. These efficacy data cannot be reliably interpreted and are not germane to the primary study objectives. These data will be summarized in section 7.3.4.

Conclusions

Data from study HGHV demonstrate the efficacy of IM olanzapine in doses of 5, 7.5, and 10mg in the acute treatment of agitation in patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder. Data for the 2.5mg dose are weaker and less consistent but positive on the primary efficacy variable as well as the Corrigan Agitated Behavior Scale in the LOCF analysis.

7.2.3 Study HGHW

Investigators/Locations

This trial was conducted by 29 principal investigators, who are listed in Appendix 7.0, Table 7.2.3.1.

Objectives

The primary study objective was to evaluate the efficacy of IM olanzapine versus IM placebo in treating agitation as measured by the change from baseline to 2 hours post-first injection on the PANSS Excited Component.

Patient Sample

Study inclusion criteria included the following:

- male or female at least 18 years old.
- inpatient status.
- considered clinically agitated and appropriate candidates for treatment with IM medication.
- DSM-IV diagnosis of bipolar I disorder with an acute manic or mixed episode. Diagnosis was confirmed via SCID at some point during the double-blind treatment period.
- illness must not have been secondary to substance abuse, in the opinion of the investigator.
- prior to the first IM injection, a PANSS Excited Component total score ≥ 14 with at least one item score ≥ 4 on a 1-7 scale.

Important exclusion criteria were:

- previous participation in a Lilly short-acting intramuscular olanzapine trial.
- serious suicide risk.
- serious, unstable medical illness.
- DSM-IV substance dependence (except nicotine or caffeine) within 30 days.
- treatment with clozapine within the prior 6 weeks.
- benzodiazepine treatment (oral or IM) within 4 hours of the first IM administration of study drug.
- treatment with carbamazepine with 24 hours.
- treatment with short-acting IM injection or oral neuroleptics within 4 hours.

- treatment with psychostimulants or reserpine within one week of study drug.
- any other medication with primarily CNS activity within 48 hours.⁸

Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

For a period of at least 2 hours prior to randomization, patients were screened for study eligibility. Eligible patients were then randomized to one of three treatment groups in a 2:1:1 ratio: IM olanzapine, IM lorazepam, or IM placebo. The double-blind treatment period was 24 hours in duration, during which the following rules for dosing applied:

- maximum number of IM injections was three.
- minimum number of IM injections was one.
- if a second injection was clinically indicated, it would be given at least 2 hours after the first injection and subsequent to the 2 hour post-first injection assessments.
- if a third injection was clinically indicated, it would be given at least 1 hour after the second injection.
- the maximum cumulative dose within 20 hours was 25mg for IM olanzapine and 5mg for IM lorazepam.

The decision whether to administer a second or third injection of study drug was made by the investigator based on clinical judgement.

The dosage for each injection is displayed in Table 7.2.3.2 below.

⁸ Except for currently prescribed anti-manic medication and anticholinergics (benztropine, biperiden, procyclidine) for control of EPS.

TABLE 7.2.3.2 STUDY HGHW INTRAMUSCULAR DOSING			
Treatment	Injection #1	Injection #2	Injection #3
Olanzapine	10mg	10mg	5mg
Lorazepam	2mg	2mg	1mg
Placebo	0mg	0mg	Olanzapine 10mg

The study drug was supplied in unblinded form (open-label vials). Blinding of the patient and personnel involved in clinical assessments was preserved by utilizing an unblinded third party to prepare and administer the injections. Olanzapine powder for injection was reconstituted using sterile water provided by the study site. All injections prepared on-site must have been used within 30 minutes of preparation.

The use of concurrent anti-manic medication (lithium or valproate) and other non-pharmacologic interventions (hospitalization, quiet room, psychotherapy) were permitted.

Anticholinergic medication (specifically benztropine, biperiden, or procyclidine) was allowed to control extrapyramidal symptoms. However, their use as prophylaxis was not permitted.

The concomitant use of benzodiazepines was not allowed in this trial.

Analysis

The primary analysis was performed on an intent-to-treat basis, i.e., by the groups randomly assigned even if the assigned medication was not taken or the protocol was not followed. LOCF analyses included only patients with both a baseline and a post-baseline assessment.

The primary efficacy variable was the change from baseline to 2 hours post-first IM dose on the PANSS Excited Component, which was assessed pre-dose and at 30, 60, 90 and 120 minutes after the first injection. A baseline measure was the score obtained immediately prior to the first IM injection.

Analysis was performed using an ANOVA model with terms for treatment, country, and treatment-by-country interaction. If the interaction was not significant ($p > 0.10$), then it was removed from the model.

Comparisons of IM olanzapine with IM placebo were tested at a two-sided significance level of 0.05.

Investigator sites were pooled for statistical analysis if there were fewer than one patient per treatment group in any treatment group.

For total scores derived from individual scale items, the total score was treated as missing if any of the individual items were missing.

Baseline Demographics

Demographic characteristics of patients entered into the injectable period are displayed in Appendix 7.0, Table 7.2.3.3. Treatment groups were comparable with respect to age, gender composition, and race except for a slight preponderance of females in the lorazepam group.

Baseline Severity of Illness

Baseline mean scores on the PANSS Excited Component were comparable across treatment groups: 12.96, 12.39, and 12.72 for the olanzapine, lorazepam, and placebo groups, respectively.

Patient Disposition

A total of 228 patients were screened. Seventeen patients were excluded by protocol entry criteria, nine were excluded because of personal conflict or other patient decision, and one was excluded by the sponsor due to a computer error.

The remaining 201 patients were randomized. A total of 21 placebo group patients were crossed over to olanzapine for their third injection and there were 7 dropouts. Patient disposition is summarized in Table 7.2.3.4 below.

TABLE 7.2.3.4: STUDY HGHW PATIENT DISPOSITION			
Reason	Olanz	Lor	Placebo
Randomized	99	51	51
Dropouts (by reason)			
Lack of Efficacy	0	2	0
Patient Decision	1	0	2
Criteria/Compliance	0	1	1
Crossover (Plac→Olanz)	0	0	21
Completed Study	98	48	27

Protocol Violations

Over 260 protocol violations occurred in this study. Except as discussed below, the types of violations were not likely to bias the efficacy findings, in my opinion.

A total of 9 patients who completed the study received medication in violation of the study entry criteria: 3 were in the olanzapine group, 2 in the lorazepam group, and 3 in the placebo group. While it is difficult to estimate the influence of this use on the efficacy results, it is likely to be minimal given the small number of violators.

One placebo patient (009-0902) received IM olanzapine as injection #1 by mistake. This error is unlikely to bias the results in favor of olanzapine.

Violations in the use of concomitant anti-manic medication occurred in 9 patients: 4 olanzapine patients, 3 lorazepam patients, and 2 placebo patients. The timing of these violations is not known (i.e., ≤ 2 hours of first injection versus > 2 hours after first injection). The effect of these violations on the efficacy results is unknown but, given the relatively small number of violations, it seems unlikely that the results were significantly biased.

Concomitant Medications

The percentages of patients who used various anti-manic agents concomitantly are provided in Table 7.2.3.5 below.

The only statistically significant difference between treatment groups was noted for the use of lithium carbonate (p=0.019): 2 olanzapine and 5 placebo patients used this agent concomitantly. This use is unlikely to bias the efficacy results in favor of olanzapine.

	Olanz N=99	Lor N=51	Plac N=51
Gabapentin ⁹	0.0%	3.9%	0.0%
Lithium	10.1%	9.8%	19.6%
Lithium Carbonate	2.0%	0.0%	9.8%
Lithium Citrate	1.0%	0.0%	0.0%
Valproate Semisodium	30.3%	19.6%	23.5%
Valproate Sodium	2.0%	0.0%	0.0%
Valproic Acid	0.0%	3.9%	2.0%

Efficacy Results

The efficacy results at 2 hours after the first injection of study drug on the PANSS Excited Component, the primary efficacy variable, are presented in Appendix 7.0, Table 7.2.3.6.

IM Olanzapine was superior to placebo to a highly significant degree ($p \leq 0.003$) on the PANSS Excited Component at 30, 60, 90, and 120 minutes post-injection for the observed cases dataset and at 120 minutes using an LOCF analysis.

The Corrigan Agitated Behavior Scale and the Agitation-Calmness Evaluation Scale were examined as supportive secondary efficacy variables. Data for these variables are displayed in Appendix 7.0, Tables 7.2.3.7 and 7.2.3.8, respectively. Results were the same as for the primary variable.

Data for the Agitation-Calmness Evaluation Scale suggest that improvement with IM olanzapine occurred without excessive sedation on average. The mean change on this 9 point rating scale was +2.90 (range 0.0 to +6.0): from a baseline mean of 2.24 (indicating mild-moderate agitation).

⁹ Gabapentin is not approved by the Agency as an anti-manic agent. However, it is listed since some feel that it has anti-manic properties.

to 5.14 (mild-moderate calmness) at 120 minutes post-injection (LOCF).

There was no evidence to suggest a treatment-by-country interaction (p=0.362 in the LOCF analysis of the PANSS Excited Component at 120 minutes).

Efficacy assessments conducted subsequent to the 2 hour period following the first injection are potentially confounded by 1) a variable number of doses of study medication, 2) variable timing of optional dosing, and 3) possible olanzapine administration to placebo patients as a third injection. These efficacy data cannot be reliably interpreted and are not germane to the primary study objectives. These data will be summarized in section 7.3.4.

Conclusions

Study HGHW provides strong evidence for the efficacy of IM olanzapine 10mg versus placebo in the acute treatment of agitation in patients with bipolar I disorder.

7.2.4 Study HGHX

Investigators/Locations

This study was conducted by 38 principal investigators. Investigators and site locations are listed in Appendix 7.0, Table 7.2.4.1.

Objectives

The primary study objective was to determine if the efficacy of IM olanzapine 5mg is greater than that for IM placebo in treating agitation as measured by changes in the PANSS Excited Component from baseline to 2 hours post-first injection.

Patient Sample

Study inclusion criteria included the following:

- male or female at least 55 years old.
- inpatient status.
- considered clinically agitated and appropriate candidates for treatment with IM medication.

- DSM-IV or NINCDS-ADRDA diagnosis of possible or probable Alzheimer's disease, vascular dementia, or mixed dementia (Alzheimer's and vascular). The diagnosis may have been confirmed after study completion as long as the patient was thought to meet these criteria at the outset.
- a PANSS Excited Component total score ≥ 14 with at least one item score ≥ 4 on a 1-7 scale.
- illness must not have been secondary to substance abuse, in the opinion of the investigator.

Important exclusion criteria were:

- patient with any serious neurological condition that could contribute to psychosis or dementia other than Alzheimer's disease or vascular dementia.
- previous participation in a Lilly intramuscular olanzapine trial.
- serious suicide risk.
- serious, unstable medical illness such that death was anticipated within 1 year or intensive care unit hospitalization was anticipated within 6 months.
- treatment with benzodiazepines, antipsychotics, or prophylactic anticholinergics within 4 hours of the first IM administration of study drug.
- treatment with an irreversible MAOI within 2 weeks.
- treatment with psychostimulants or reserpine within one week.
- treatment with clozapine within the prior 6 weeks.
- patients who required concomitant ECT.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

Following a screening period of at least 2 hours duration, eligible patients were equally randomized to one of four treatment groups: IM olanzapine 5mg, IM olanzapine 2.5mg, IM lorazepam 1mg, or IM placebo. The double-blind treatment period was 24 hours in duration, during which the following rules for dosing applied:

- maximum number of IM injections was three.
- minimum number of IM injections was one.

- if a second injection was clinically indicated, it would be given at least 2 hours after the first injection and subsequent to the 2 hour post-first injection assessments.
- if a third injection was clinically indicated, it would be given at least 1 hour after the second injection.
- the maximum cumulative dose within 20 hours was 12.5mg for IM olanzapine and 2.5mg for IM lorazepam.

The decision whether to administer a second or third injection of study drug was made by the investigator based on clinical judgement.

The dosage for each injection is displayed in Table 7.2.4.2 below.

TABLE 7.2.4.2 STUDY HGHX INTRAMUSCULAR DOSING			
Treatment	Injection #1	Injection #2	Injection #3
Olanzapine	2.5mg	2.5mg	1.25mg
Olanzapine	5mg	5mg	2.5mg
Lorazepam	1mg	1mg	0.5mg
Placebo	Placebo	Placebo	5mg olanzapine

The study drug was supplied in unblinded form (open-label vials). Blinding of the patient and personnel involved in clinical assessments was preserved by utilizing an unblinded third party to prepare and administer the injections. Olanzapine powder for injection was reconstituted using sterile water provided by the study site. All injections prepared on-site must have been used within 30 minutes of preparation.

Concomitant medication with primarily CNS activity was not allowed during the 24 hour study period. Patient receiving chronic benzodiazepine or antipsychotic therapy could be enrolled into the trial but this treatment could not be given 4 hours prior to study drug injection or during the 24 hour study period. Patients who needed this treatment during the study period were to be discontinued.

Anticholinergic medication was allowed to treat acute dystonia in the 4 hours preceding first injection and during the 24 hour study period. However, their use as prophylaxis was not permitted.

Analysis

The primary analysis was performed on an intent-to-treat basis, i.e., by the groups randomly assigned even if the assigned medication was not taken or the protocol was not followed. LOCF analyses included only patients with both a baseline and a post-baseline assessment.

The primary efficacy variable was the change from baseline to 2 hours post-first IM dose on the PANSS Excited Component, which was assessed pre-dose and at 30, 60, 90 and 120 minutes after the first injection. A baseline measure was the score obtained immediately prior to the first IM injection.

Analysis was performed using an ANOVA model with terms for treatment, investigator, and treatment-by-investigator interaction. If the interaction was not significant ($p > 0.10$), then it was removed from the model.

Comparisons of IM olanzapine with IM placebo were tested at a two-sided significance level of 0.05.

Investigator sites were pooled for statistical analysis if there were fewer than one patient per treatment group in any treatment group.

For total scores derived from individual scale items, the total score was treated as missing if any of the individual items were missing.

Baseline Demographics

Demographic characteristics of patients entered into the double-blind treatment period are displayed in Appendix 7.0, Table 7.2.4.3. Treatment groups were comparable with respect to age, gender composition, and race.

Baseline Severity of Illness

Baseline mean scores on the PANSS Excited Component were comparable across treatment groups: 14.58, 14.86, 14.22, and 15.36 for the olanzapine 2.5mg, olanzapine 5mg, lorazepam, and placebo groups, respectively.

Patient Disposition

A total of 331 patients were screened. Of these, 59 patients were not randomized: 42 were excluded by protocol entry criteria, 5 due to personal conflict or other patient decision, 9 by the physician's decision, 2 due to adverse events, and one because of the sponsor's decision.

The remaining 272 patients were randomized. A total of 31 placebo group patients were crossed over to olanzapine for their third injection and there were 20 dropouts. Patient disposition is summarized in Table 7.2.4.4 below.

Reason	Olanz 2.5mg	Olanz 5mg	Lor	Plac
Randomized	71	66	68	67
Dropouts (by reason)				
Lack of Efficacy	4	2	5	1
Patient Decision	0	0	0	1
Criteria/Compliance	0	2	0	1
Physician Decision	0	1	2	1
Crossover (Plac→Olanz)	0	0	0	31
Completed Study	67	61	61	32

Protocol Violations

Three patients were discontinued from the study due to use of excluded medications. This usage was subsequent to the 2 hour post-first injection period.

A total of 270 other protocol violations occurred that did not result in dropout. The most common protocol violation was omission of study procedures, which was related to difficulty obtaining the cooperation of patients in completing assessments. This seemed to occur evenly across all treatment groups.

Two violations were due to use of excluded medication during the 2 hour post-first dose treatment period. Both occurred in patients in the lorazepam treatment group.

In 25 patients, the study drug was not administered according to the protocol. Most of these violations involved use of an incorrect injection site (e.g., deltoid muscle instead of buttock) or administration of study drug more than 30 minutes after preparation, usually about 35 minutes after injection. But two patients (050-5007 and 050-5008) did received injections 80 and 90 minutes after preparation, respectively. The first patient was in the lorazepam group and the second in the olanzapine group.

One lorazepam patient received a dose of Haldol within 4 hours of the first injection.

On the whole, it is felt that these violations are unlikely to have significantly biased the findings in favor of olanzapine.

Efficacy Results

The efficacy results at 2 hours after the first injection of study drug on the PANSS Excited Component, the primary efficacy variable, are presented in Appendix 7.0, Table 7.2.4.5.

Although this study did incorporate two olanzapine treatment arms, the protocol-specified primary study objective was to compare the 5mg dose group to placebo. Thus, the efficacy conclusion hinges on the comparison of this dose group with placebo and no adjustment for multiplicity is indicated.

IM olanzapine 5mg was superior to IM placebo to a statistically significant ($p \leq 0.05$) on the PANSS Excited Component at 30, 60, 90, and 120 minutes post-injection for the observed cases dataset and at 120 minutes using an LOCF analysis, with a high degree of significance ($p = 0.004$) at 120 minutes for both datasets.

The Cohen-Mansfield Agitation Inventory and the Agitation-Calmness Evaluation Scale were examined as supportive secondary efficacy variables. Data for these variables are displayed in Appendix 7.0, Tables 7.2.4.6 and 7.2.4.7, respectively. Results on these scales revealed superiority for the IM olanzapine 5mg dose over IM placebo at 120 minutes post-first injection for both observed cases and LOCF datasets. Results at earlier timepoints did not indicate statistical superiority.

Data for the Agitation-Calmness Evaluation Scale suggest that improvement with IM olanzapine 5mg occurred without excessive sedation on average. The mean change on this 9 point rating scale was +1.88 (range -1.0 to +5.0): from a baseline mean of 2.17 (indicating mild-moderate agitation) to 4.05 ("normal") at 120 minutes post-injection (LOCF).

With respect to the 2.5mg dose group, superiority over placebo was evident at 120 minutes post-first injection on the PANSS Excited Component and the Agitation-Calmness Evaluation Scale (OC and LOCF), assuming an alpha level for statistical significance of 0.050. Statistical superiority was not seen on the Cohen-Mansfield Agitation Inventory, although there was a trend toward superiority at 120 minutes.

There was no evidence to suggest a treatment-by-country interaction (p=0.563 in the LOCF analysis of the PANSS Excited Component at 120 minutes).

Efficacy assessments conducted subsequent to the 2 hour period following the first injection are potentially confounded by 1) a variable number of doses of study medication, 2) variable timing of optional doses, and 3) possible olanzapine administration to placebo patients as a third injection. These efficacy data cannot be reliably interpreted and are not germane to the primary study objectives. These data will be summarized in section 7.3.4.

Conclusions

Study HGHX provides evidence for the efficacy of IM olanzapine 2.5 and 5mg in the acute treatment of agitation in patients with Alzheimer's and/or vascular dementia. Data supporting the efficacy of the 2.5mg IM dose were relatively weak.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

The sponsor conducted subgroup analyses within each of the four key efficacy studies to detect significant treatment-by-subgroup interactions (p<0.10) for the following demographic variables: gender, age (<40 vs. ≥40 years for

HGHB, HGHV, and HGHW and ≤ 75 vs. > 75 for study HGHX), and origin (Caucasian vs. other racial groups). These analyses examined the changes in the PANSS Excited Component for all four studies as well as the Corrigan Agitated Behavior Scale (for HGHB, HGHV, and HGHW) and the Cohen-Mansfield Agitation Inventory (for HGHX). This review focused on possible interactions at the 2 hour post-first injection timepoint.

Only two such interactions were reported. In both HGHV and HGHW, there were significant treatment-by-origin interactions.

In HGHV, there were greater improvements on the PANSS Excited Component in the IM haloperidol- and IM placebo-treated patients of non-Caucasian origin compared to Caucasian patients ($p=0.013$).¹⁰

In HGHW, there were greater improvements on both the PANSS Excited Component and the Corrigan Agitated Behavior Scale in olanzapine-treated patients of Caucasian origin compared to non-Caucasian patients (p -values of 0.074 and 0.034, respectively).¹¹

There were no significant differences between demographic subgroups that were consistent across the four key efficacy studies.

7.3.2 Size of Treatment Effect

The mean differences between drug and placebo on the primary efficacy variable (PANSS Excited Component) at 2 hours post-first injection for each of the four key efficacy studies are displayed in Table 7.3.2 below.¹²

¹⁰ Data are displayed in volume 1.55, page 149.

¹¹ Data are displayed in volume 1.60, pages 140-143.

¹² The drug-placebo difference equals the mean change from baseline for drug minus the mean change from baseline for placebo in the LOCF database; thus, negative differences indicate superiority of drug over placebo.

TABLE 7.3.2		
MEAN DRUG-PLACEBO DIFFERENCES ON THE PANSS EXCITED COMPONENT AT TWO HOURS POST-FIRST INJECTION		
Study	Olanzapine Dose	Mean Difference
HGHB	10mg	-4.27
HGHV	2.5mg	-2.59
	5mg	-5.18
	7.5mg	-5.74
	10mg	-6.44
HGHW	10mg	-4.76
HGHX	2.5mg	-2.59
	5mg	-3.40

It is difficult to evaluate the size of the drug-placebo differences for these studies since there exists no historical data for comparison.

Also, a given change on the Excited Component of the PANSS might represent a large change in one of the five items comprising this score, a much smaller change in each of the five items, or something in between these two extremes. This renders an assessment of the clinical relevance of a change in this measure uncertain.

Finally, the clinical importance of a change in any of the individual items may depend on the baseline rating for that item. For example, a change of -1 on the hostility item may reflect a severely hostile patient becoming moderately severely hostile or, on the other hand, a mildly hostile patient becoming minimally hostile.

The only other approach which is reasonable, albeit not ideal, is to compare these differences with those observed in the comparator treatment arms. Although both IM haloperidol and IM lorazepam have been found to be useful in treating agitation in clinical settings, it is interesting that the drug-placebo differences with haloperidol seen in studies HGHB and HGHV are somewhat larger (-4.09 and -4.62, respectively) than those seen for lorazepam in studies HGHW and HGHX (-1.91 and -3.22, respectively). However, these observations may be confounded by diagnosis or other factors. Nonetheless, if the comparator data are used as a standard for clinically important effect sizes, then the above differences for olanzapine at doses of 5mg and higher can be considered

clinically relevant and for the 2.5mg dose possibly relevant.

7.3.3 Choice of Dose

Study HGHV examined the relationship between dose and therapeutic response in patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder. A series of step-down linear contrasts was used to determine the minimum effective dose based on the PANSS Excited Component during the two hour post-first injection period while protecting the overall experiment-wise error rate at $\alpha=0.05$. From among the four doses examined (2.5, 5, 7.5, and 10mg), the minimum effective dose was shown to be 2.5mg and a statistically significant monotonic dose response relationship was seen across the dose range of 2.5 to 10mg ($p<0.001$).

Data were not available to perform a similar analysis in the studies in bipolar disorder patients (HGHW) and in patients with dementia (HGHX). The above data do support use of the 10mg IM dose in agitation associated with bipolar disorder and both the 2.5 and 5mg IM doses in patients with dementia.

7.3.4 Duration of Treatment

Most (59% to 76%) of the olanzapine-treated patients in each of the dose groups of the four key efficacy studies required only one injection of olanzapine during the entire injectable treatment phase, except for patients in the 2.5mg dose group of study HGHV, where 52% needed more than one dose. All olanzapine dose groups in these studies, except for the 2.5mg dose in study HGHV, were statistically superior to placebo at 24 hours post-first injection based on an LOCF analysis of change in the PANSS Excited Component at the end of the injectable treatment phase. The 2.5mg dose group in HGHV showed a trend toward superiority.¹³

However, conclusions about the multiple dose efficacy of IM olanzapine based on these data must be drawn with a measure of caution because these studies were not adequately designed to rigorously assess the efficacy of repeated doses of intramuscular olanzapine in the treatment of acute

¹³ These data are summarized in volume 1.83, pages 133-136.

agitation. In addition to the fact that most olanzapine patients received only one IM dose and that those who received more than one injection were probably poorly responsive to the initial dose, there are multiple confounding factors: 1) a variable number of doses of study medication, 2) variable timing of optional doses, 3) use of concomitant benzodiazepines after the first injection in two studies (HGHB and HGHV), and 4) the switching of some placebo patients to olanzapine for the third injection in two studies (HGHW and HGHX).¹⁴

On a more intuitive level, if the efficacy of a single IM dose for acute agitation is established, then it may be reasonable to infer the efficacy of subsequent IM doses for this condition.

7.3.5 Transition from Intramuscular to Oral Dosing

Study HGHB was comprised of a 24 hour IM treatment period followed by a period of oral treatment for 4 additional days.

IM treatment consisted of 1 to 3 injections of olanzapine 10mg, haloperidol 7.5mg, or placebo.

Immediately after the assessments at 24 hours post-first injection, the oral treatment phase commenced. Patients who had been randomized to IM olanzapine or IM placebo were switched to oral olanzapine, 5-20 mg/day. Patients who had been randomized to IM haloperidol were switched to oral haloperidol, 5-20 mg/day. Oral doses were administered in the morning and were selected by the investigator as being clinically appropriate, within the above ranges.

Benzodiazepines were discouraged but permitted only in oral form during the oral treatment period according to the following maximum doses:

¹⁴ The proportion of olanzapine patients who received a benzodiazepine during the injectable treatment phases of studies HGHB and HGHV ranged from 4% to 16%. Usage among placebo patients was greater: 39% (HGHB) and 36% (HGHV). Benzodiazepine use in studies HGHW and HGHX, where concomitant benzodiazepine use was prohibited, was less, e.g., 5% or less among olanzapine patients. In studies HGHW and HGHX, 41% and 46%, respectively, of the placebo patients were switched to olanzapine for their third injection of study drug.

Lorazepam	8 mg/day
Diazepam	40 mg/day
Oxazepam	60 mg/day
Chlorazepate	100 mg/day

Roughly 90% of the patients randomized to each IM treatment group continued into the oral treatment period: 122 IM olanzapine, 47 IM placebo, and 116 IM haloperidol patients entered the oral treatment phase. About 91% of the patients in each of these groups completed the oral treatment period.

The modal daily dose for all patients receiving oral olanzapine was 10 mg/day and for those receiving oral haloperidol also 10 mg/day.

Among the IM olanzapine and IM haloperidol patients who entered the oral treatment phase, 43% and 53%, respectively, used a benzodiazepine during oral treatment.

An LOCF analysis of the change from baseline, which was the beginning of the oral treatment phase for purposes of this analysis, to the end of the oral treatment period for the PANSS Excited Component revealed no significant difference between the IM olanzapine patients who received oral olanzapine and the IM haloperidol patients who received oral haloperidol. Data are summarized in Table 7.3.5 below. An examination of the mean changes for these patients by each day of the study revealed no major difference at any timepoint.¹⁵

Treatment Group	Baseline		Mean Δ	p-value Olanz vs. Hal
	N	Mean		
Olanzapine	119	6.31	-0.60	0.307
Haloperidol	115	6.44	-1.26	

Interpretation of this analysis is complicated by the lack of a placebo control group and by the concomitant use of benzodiazepines. However, it does suggest there was a continued effect of oral therapy on agitation over the 4

¹⁵ These data are plotted in volume 1.83 on page 141.

day period following intramuscular treatment with both olanzapine and haloperidol.

7.3.6 Pediatric Use

The sponsor has requested a deferral for submitting pediatric data for IM olanzapine until after approval of the adult indication. A post-marketing pediatric study to address the requirements of the Pediatric Rule (21 CFR 314.55) is planned.

7.4 Conclusions Regarding Efficacy

Table 7.4 in Appendix 7.0 summarizes the efficacy results for the four key efficacy studies at the primary endpoint, i.e., 2 hours after the first injection of study medication. These data demonstrate the superiority of single doses of intramuscular olanzapine over the range of 2.5 to 10mg versus intramuscular placebo in the treatment of acute agitation across the three classes of diagnostic patient groups studied.

8.0 Integrated Review of Safety

The intramuscular olanzapine safety database is comprised of 11 human studies with a cutoff date of April 1, 2000, for 9 of these trials. For the remaining 2 studies (HGJA and HGIO), which were completed later than the other trials, the cutoff date is considered to be June 2000.

The evaluation of safety consisted of two general approaches:

- 1) an examination of the pool of all 11 studies, referred to as the overall IM safety database (848 IM olanzapine-treated patients), for more serious adverse events, specifically deaths (section 8.1.1), other serious adverse events (section 8.1.2), and dropouts related to unexpected, clinically important adverse events (section 8.1.3).
- 2) an examination of less serious safety findings within two pools of the placebo-controlled Phase 2/3 trials: a pool of those studies that enrolled younger patients (HGHB, HGHV, and HGHW), referred to as the placebo-controlled IM safety database, and the single study (HGHX) that enrolled older patients with dementia, referred to as the geriatric study. This examination entailed an evaluation of common

adverse events (section 8.1.4), laboratory test data (section 8.1.5), vital signs (section 8.1.6), and ECG data (section 8.1.7). Finally, the results of three studies conducted to evaluate special issues relevant to IM olanzapine will be summarized (section 8.1.8).

8.1 Safety Findings

8.1.1 Deaths

There were no deaths during or within five days of participation in any study. However, three patients did expire several days after study completion:

- Patient 016-1606 received IM lorazepam in study HGHW and was found dead 11 days after the study. The cause of death was determined to be an accidental intoxication with morphine, cocaine, and alcohol.
- Patient 007-0701, a 90 year old male, had received IM olanzapine 5mg in study HGHX and was found dead 9 days after completing the trial.
- Patient 036-3637, a 77 year old male, received two IM injections of placebo and a final IM injection of olanzapine 5mg in study HGHX. The patient was found without respiration 8 days after the study and Advanced Cardiac Life Support was administered, with no success. No autopsy was conducted.

None of these deaths are felt to be reasonably attributable to IM olanzapine.

8.1.2 Other Serious Adverse Events

In the overall IM safety database, there were five subjects who experienced adverse events classified as serious.¹⁶ Narrative summaries for these cases were reviewed and each is summarized below:

#1 Subject 2843 in study LOAV was a 37 year old healthy male volunteer smoker who experienced loss of consciousness, extremity shaking (for 10 seconds), and apnea one hour after receiving an intramuscular injection

¹⁶ An event was considered serious if it resulted in death, caused or prolonged inpatient hospitalization, was life-threatening, produced severe or permanent disability, was a cancer or congenital anomaly, or was significant for some other reason.

of olanzapine 5mg and after standing to urinate. Plasma level data indicate that this subject had a Cmax at about 30 minutes post-dose; Cmax was about two-fold higher than the mean for other subjects in this study (one other subject had a slightly higher Cmax). Pre-treatment vital signs were BP=120/51, heartrate=82 bpm, and respiratory rate(RR)=16/min. Following this event, supine blood pressure was 104/68, pulse was 33 bpm, and RR was 4-7/min. There were no obvious vasovagal signs. Most of the bradycardia was sinus bradycardia with a question of a few junctional escape beats. However, the sponsor also indicated that this subject probably experienced a sinus pause.¹⁷ He was assessed as being apneic and was given one breath mouth-to-mouth. He responded after a second breath was attempted and was briefly agitated on recovery. Thereafter, he was alert and oriented. Heartrate was about 50 bpm at that point but subsequently fell to 37 bpm with RR=13/min and BP=107/65. Atropine 0.2mg IV was administered but his pulse had spontaneously increased. There was a drop in oxygen saturation during the event, the lowest recording being 94%; however, he was off oximetry for a short period surrounding the time of the event. This subject had received olanzapine 2.5mg IM and lorazepam 2mg IM 14 days and 7 days, respectively, prior to this occurrence without remarkable incident. His medical history was unremarkable and there were no concomitant medications. He was discontinued from the trial after this event.

The etiology of case #1 is difficult to know with certainty but the clinical picture strongly suggests that this event most likely represents a syncopal seizure.¹⁸ This healthy volunteer may have been unusually susceptible to olanzapine-induced orthostatic hypotension, which may have played a causative role in this event along with increased cholinergic tone and vasodilatation associated with micturition. But, the sponsor also raises the possibility that this patient experienced a sinus pause, which was noted in other healthy volunteers (see below).

#2 Subject 32 in study LOAC was a 26 year old non-smoking male with no significant medical history except for

¹⁷ See comment in volume 1.84, page 230. The evidence for this statement was not provided.

¹⁸ This opinion is based in large part on an informal consultation with a neurologist within the Division, Armando Oliva, M.D.

seasonal allergies.¹⁹ Prior to dosing, this subject manifested an orthostatic decrease in systolic blood pressure. He received an oral dose of olanzapine 10mg and, about 2 hours later, complained of nausea. Supine blood pressure and pulse were 128/61 and 60 bpm (116/66 and 59 bpm pre-dose). At 3 hours post-dose, supine vital signs were 84/34 and 50 bpm (no standing measurements were taken). The foot of his bed was elevated. At 4 hours, 35 minutes post-dose, the subject collapsed returning from the toilet and was helped back to bed. At 5 hours post-dose, supine vital signs were 113/59 and 50 bpm. Telemetry revealed that this subject had experienced a 5 second sinus pause on 2 occasions. The first was 2 hours post-dose and the second occurred about 4.5 hours after dosing and 4 minutes prior to his collapse. Two unifocal PVC's were noted preceding the latter sinus pause. A cardiology consult that the subject was "vagotonic" and inclined to sinus bradycardia. Pharmacokinetic data indicated that the olanzapine plasma concentrations for this subject were not remarkably different from the means of other subjects in this trial. Tmax was about 4 hours.

The occurrence of 2 sinus pauses in this reasonably healthy subject, one of which occurred as plasma levels were beginning to rapidly rise and the second shortly after Tmax and associated with collapse, suggest that these events were related to olanzapine.

This case was considered by the Division review team at the time the original IND application was evaluated (see the () clinical review of IND()

#3 Patient 0272 in study HGHB was a 27 year old Hispanic male with schizophrenia who received one injection of olanzapine 10mg. Twenty minutes later, he experienced markedly increased levels of anxiety and nervousness as well as a number of somatic complaints such as difficulty breathing, hyperventilation, palpitations, and sweating. He was discontinued from the study 3.5 hours after the injection and treated with Seroquel and lorazepam, with complete resolution 4-5 hours later. Based on the temporal association with the study drug injection, the investigator

¹⁹ It should be noted that the experience of this subject is not listed as "serious" in the ISS (vol. 1.84, page 223) but it is designated as a serious adverse event in the study report (vol. 1.33, page 205) and did lead to discontinuation from the study (vol. 1.33, page 405). Hence, it will be discussed in this section.

concluded that the severe anxiety was caused by an allergic reaction to the drug. However, no steroids, epinephrine, or antihistamines were required to treat this event and no other symptoms consistent with an allergic reaction (e.g., rash) were reported. Medical history was remarkable only for back pain and there were no concomitant medications at the time of the event.

The clinical presentation and course of events in Case #3 are more consistent with worsening anxiety and agitation than an allergic reaction to olanzapine.

#4 Patient 2610 in study HGHV was a 48 year old female who experienced a decrease in supine blood pressure from 110/70 (pulse=72 bpm) pre-dose to 90/60 (pulse=62 bpm) 60 minutes after an intramuscular injection of olanzapine 10mg. At 90 and 120 minutes post-injection, her blood pressure remained 90/60 (pulse increased to 80 bpm at both points). By 240 minutes post-injection, her blood pressure had returned to pre-dose values and remained essentially unchanged thereafter. This patient also had an abnormal ECG, anemia, and a high TSH before treatment. Additionally, 24 hours post-injection, she experienced acute urinary retention. A catheter was placed and the event resolved within 24 hours. An endocrinology evaluation revealed a diagnosis of myxedema, which was suggested to be the probable cause of her ECG changes, anemia, and urinary retention.

The patient in case #4 did experience a slight decrease in supine blood pressure, which could be related to olanzapine. This is not considered a serious event. However, it seems that the other events, which were attributable to a pre-existing thyroid disorder, were classified as serious because their evaluation prolonged hospitalization.

#5 Patient 0909 in study HGHW was a 53 year old male with bipolar disorder who had received two IM doses of placebo followed by an injection of olanzapine 10mg. Approximately 4 hours after the latter, he experienced tachycardia (standing pulse=100 bpm) and an increase in hypertension (standing BP=210/110) (pre-IM olanzapine pulse=60 bpm and BP=192/90). Due to increased agitation, he was administered rescue medication (IM lorazepam, IM haloperidol, and IM diphenhydramine) over the next several hours. Vital signs 9 hours after IM olanzapine and after four doses of rescue medication revealed a pulse of 138 bpm

and BP=192/114. At that point, the patient was cool and clammy and was transferred to the emergency room, where IV diltiazem was given and an ECG revealed poor R wave progression but no evidence suggesting a myocardial infarction. Within 4 hours, blood pressure had stabilized and tachycardia had resolved. Hypertension had been documented at several timepoints prior to olanzapine injection and tachycardia was attributed by the investigator to increased agitation. The patient had a history of hypertension and postural hypotension and concomitant medications consisted of enalapril and glyceryl trinitrate, both of which were continued during the study.

The patient in case #5 had substantially elevated blood pressure readings prior to olanzapine treatment which were not much worse after treatment. His tachycardia, especially 9 hours after olanzapine injection, seems more likely related to his agitated state than to olanzapine.

In summary, cases #1 and #2 may represent an unexpected hazard (sinus pause) attributable to olanzapine. The other three cases are not felt to suggest an unexpected safety risk associated with IM olanzapine.

8.1.3 Dropouts

8.1.3.1 Overall Pattern of Dropouts

Table 8.1.3.1 below depicts the percentages of patients dropping out from the placebo-controlled IM safety database by reason for dropout. This table excludes 21 patients from the HGHW IM placebo group who received IM olanzapine as a third injection: among these, 2 patients discontinued due to an adverse event.

Reason for Dropout	IM Olanzapine (N=415)	IM placebo (N=129)
Adverse Event	2 (0.5%)	0
Lack of Efficacy	3 (0.7%)	5 (3.9%)
Patient Decision	6 (1.4%)	4 (3.1%)
Criteria not met/Compliance	0	1 (0.8%)
Physician Decision	1 (0.2%)	0

In the geriatric study HGHX, there was only one dropout due to an adverse event. This occurred in a placebo patient who received olanzapine as the third injection. The most common reason for premature discontinuation in this study was due to lack of efficacy.

8.1.3.2 Dropouts Due to Adverse Events

Among the 11 studies in the overall IM safety database, there were 9 subjects who received IM olanzapine and 1 subject who received oral olanzapine who dropped out due to an adverse event. These patients are listed in Table 8.1.3.2 below.

Four of these patients (0272, 0909, 2843, and 32) were discussed section 8.1.2 as having serious adverse events. The narrative summary for each of these 9 dropouts was reviewed. There are an additional two cases that could represent an unexpected hazard associated with olanzapine; these are described below.

TABLE 8.1.3.2 OVERALL IM SAFETY DATATBASE LISTING OF DROPOUTS DUE TO ADVERSE EVENTS		
Study	Subject #	Event Leading to Dropout
HGHB	0272	Anxiety
HGHB	3051	Rash
HGHW	0909	Agitation
HGHW	1801	Hostility
HGHX	3602	Tachycardia
LOAV	2843	Apnea/Syncope/? Sinus pause
LOAC	32	Sinus pause
LOAW	002	Sinus pause
LOAW	015	Sinus pause

Case #1 Subject 002 in study LOAW was a 55 year old healthy male non-smoker who received olanzapine 5mg IM and, about one hour later, experienced loss of consciousness (LOC) after standing for 1-2 minutes. Supine vital signs were BP=103/70 with a pulse of 39 bpm (pre-dose supine BP=105/73 and pulse=53). He was placed in bed with feet elevated and gradually recovered. However, he lost consciousness a second time about 6 hours post-dose, again after standing for 1-2 minutes. Vital signs 5 minutes prior to this event

revealed a 47 and 30 mmHg orthostatic decrease in systolic and diastolic pressures with a 4 bpm orthostatic decrease in pulse. The subject was laid down and his vital signs spontaneously normalized. Telemetry was remarkable for 2 episodes of vagal sinus arrest (longest duration was 5-6 seconds) associated with sinus bradycardia.²⁰ His olanzapine plasma level was slightly higher than the mean for most other subjects (i.e., excluding subjects 2 and 15) at Tmax, about the time of the first LOC; however, 8 other subjects had higher Cmax's. His level at the time of the second LOC was much lower.

Case #2 Subject 015 in study LOAW was a 47 year old male smoker (5 cigarettes/day) who was healthy except for an upper respiratory tract infection. He received an intramuscular dose of olanzapine 5mg. About 50 minutes later, he complained of nausea and 60 minutes post-dose experienced dizziness and had to lie down with his bed elevated. Supine blood pressure and pulse were 106/61 and 55 bpm (101/68 and 80 bpm pre-dose). Four hours after his first IM dose, he received a second intramuscular dose of olanzapine 5mg. An hour after that dose, he again experienced dizziness and had to lie down. Supine blood pressure and pulse were 95/60 and 92 bpm (108/73 and 86 bpm pre-dose). He remained lying for at least 4 hours. Telemetry data revealed that he had experienced a vagal sinus pause approximately 3.5 hours after his second injection. This was associated with hypotension and bradycardia: supine BP and pulse were 71/41 and 45 bpm 2 minutes after the sinus pause; no standing vital signs were taken. Due to the sinus pause and dizziness, the patient was withdrawn from the study. Olanzapine plasma levels indicate that this subject experienced Cmax levels roughly 30% higher than the mean for most other subjects (i.e., excluding subjects 2 and 15) after both injections.

Overall, there were 3 normal volunteers who manifested at least one sinus pause on telemetry, and an additional subject with a suspected sinus pause, associated with the administration of olanzapine, usually by the intramuscular route but in one case orally. These pauses were associated with bradycardia and variably with collapse and loss of consciousness.

²⁰ The association with bradycardia and syncope is documented in the Post-Study Discharge note in the CRF.

8.1.4 Adverse Event Incidence

8.1.4.1 Categorization of Adverse Events

Adverse events were recorded as COSTART terms. The accuracy of the translation of actual adverse event terminology to COSTART terms was assessed by examining line listings of adverse events in the reports for studies HGHB, HGHV, HGHW, and HGHX.

This examination revealed two instances in which the event coding was not felt to be reasonably accurate:

- For patient 35-3502 in study HGHW, the actual term "hypothyroid" was coded to "hyperthyroidism."
- For patient 13-1309 in study HGHX, the actual term "premature atrial contraction" was coded to "ventricular arrhythmia."

It is unlikely that these errors will substantially affect conclusions drawn from the submitted data about the safety of IM olanzapine.

8.1.4.2 Appropriateness of Data Pooling

Assessment of adverse event incidence is based on data from two groups of studies from the pool of Phase 2/3, double-blind, placebo-controlled trials:

- the placebo-controlled IM safety database: studies HGHB, HGHV, and HGHW, which enrolled patients in the age range 18-79 years (mean age 38) with schizophrenia, schizophreniform disorder, schizoaffective disorder, or bipolar I disorder.
- the geriatric study: study HGHX, which enrolled patients 54-97 years old (mean age 78) with dementia.

Based on the difference in patient age ranges in these two groups and, to a lesser extent, the difference in diagnoses, this pooling of studies is reasonable.

8.1.4.3 Common, Drug-Related Adverse Events

The incidence of treatment-emergent adverse events in the placebo-controlled IM safety database during the 24 hour injectable treatment phase is displayed in Table 8.1.4.3 in Appendix 8.0 for those events reported by at least 1.0% of

the patients in the IM olanzapine treatment group. Please note that data subsequent to the third injection for 21 placebo patients in study HGHW who received olanzapine as the third injection are excluded.

None of these events meet the customary criteria for common, drug-related adverse events (i.e., reported by at least 5% of the drug-treated patients at a rate at least twice that among the placebo-treated patients).²¹

A similar analysis in the geriatric study also revealed no common, drug-related adverse events utilizing the above criteria.

8.1.4.4 Dose-Relatedness

Study HGHV employed four fixed doses of IM olanzapine (2.5, 5, 7.5, and 10mg) with approximately 45 patients per dose. Visual inspection of the proportions of patients reporting treatment-emergent adverse events across these dose groups revealed no obvious dose relationship for any events.

8.1.4.5 Demographic Effects on Adverse Events

Treatment-emergent adverse event occurrence was examined by various demographic subgroups for the placebo-controlled IM safety database: age (<40 vs. ≥40), gender (male vs. female), and racial origin (Caucasian vs. other). Odds ratios (IM olanzapine:IM placebo) were computed and compared across subgroups using the Breslow-Day test for homogeneity of odds ratios.²²

Although the odds ratios for several events were significantly different statistically (Breslow-Day p-value ≤0.10), none of these differences were deemed by this reviewer to be clinically significant.

8.1.4.6 Additional Analysis of Adverse Events

Additional analyses of adverse events which are of special interest with the acute use of an intramuscular antipsychotic were examined.

²¹ Based on percentages rounded to the nearest 0.1%.

²² Data are displayed in volume 1.85, page 117ff.

Injection Site Reactions

In two studies (LOAC and LOAR), subjects were systematically monitored for injection site reactions.

Three subjects in LOAC (N=30) reported "severe pain" after IM injection, one after receiving IM olanzapine 0.2mg and two after IM placebo. Overall, inspection of the injection sites revealed occasional minor bruising.

Study LOAR (N=26) revealed no adverse events related to the injection site.

In studies HGHB, HGHV, HGHW, and HGHX, there were reports of injection site pain (burning and stinging sensations) in 3/604 IM olanzapine patients, 2/119 IM lorazepam patients, 0/166 haloperidol patients, and 0/217 IM placebo patients.

In sum, there was no evidence of significant injection site reactions associated with IM olanzapine.

Dystonic Reactions/Extrapyramidal Symptoms

The sponsor surveyed the placebo-controlled IM safety database and the geriatric study for adverse events potentially representing dystonia (events terms dystonia, oculogyric crisis, opisthotonus, and torticollis). No such adverse events were reported among IM olanzapine- or IM placebo-treated patients in these trials.

The sponsor also searched the two fixed-dose studies HGHV and HGHX for other treatment-emergent extrapyramidal events by event category: Parkinsonian events, akathisia events, dyskinetic events, and residual events (e.g., myoclonus, twitching). Very few patients experienced these events and there was no evidence to suggest a dose-relationship for any of these event categories.

Sedation/Tranquilization

Among patients in the placebo-controlled IM safety database, 4.3% (18/414) of IM olanzapine and 0.7% (1/149) of IM placebo patients had a maximum ACES (Agitation-Calmness Evaluation Scale) score of 8 (deep sleep); this difference was statistically significant (p=0.033). No patient in either group had a maximum ACES score of 9 (unarousable). The proportion of IM olanzapine patients reporting treatment-emergent somnolence was not significantly greater than that in the IM placebo group (5.5% vs. 3.3%).

In the geriatric study, 7.3% (10/137) of IM olanzapine and 4.5% (3/67) of IM placebo patients had a maximum ACES score of 8 (p=0.552).²³ None had a maximum score of 9. The fraction of IM olanzapine patients reporting somnolence was almost identical to that in the IM placebo group (about 3%).

No patient in either study pool had treatment-emergent CNS depression, stupor, or coma.

Thus, it does not appear that IM olanzapine is associated with excessive sedation.

Seizures

During pre-marketing studies with oral olanzapine, seizures occurred in 0.9% of olanzapine-treated patients. No patient in the placebo-controlled IM safety database or geriatric study was reported as having experienced a seizure.

8.1.5 Laboratory Data

8.1.5.1 Laboratory Assessments

Laboratory studies (clinical chemistry, CBC with differential WBC count, and urinalysis) were conducted at screening and 24 hours after the first IM injection in studies HGHV, HGHW, and HGHX.²⁴

Patients from study HGHB were excluded from the following analyses since laboratory tests were not performed during the 24 hour injectable treatment period in that study. Thus, the placebo-controlled IM safety database refers to the pool of studies HGHV and HGHW in this section.

8.1.5.2 Potentially Clinically Significant Lab Changes

The sponsor examined the proportions of patients meeting criteria for potentially clinically significant changes in laboratory analytes during the 24 hour injectable treatment phase. These criteria are displayed in Appendix 8.0, Table

²³ The 2.5 and 5mg dose groups were pooled for these analyses.

²⁴ Clinical chemistry parameters included electrolytes, SGOT, SGPT, GGT, total bilirubin, alkaline phosphatase, BUN, creatinine, uric acid, calcium, nonfasting glucose, creatine phosphokinase, phosphorus, total protein, albumin, and cholesterol.

8.1.5.2. The analysis excluded patients who met the criteria at baseline for any particular analyte. In the placebo-controlled IM safety database and in the geriatric study, there were no significant differences ($\alpha=0.100$) in pairwise comparisons of the IM olanzapine and IM placebo treatment groups with respect to the fraction of patients who met these criteria.²⁵

There were 4 patients in the pool of studies HGHV and HGHW who met criteria for potentially clinically significant increases in SGPT.²⁶ All had considerable SGPT elevations pre-treatment with no substantial increase after receiving IM olanzapine.

Also in this pool, there was one IM olanzapine patient who met criteria for a potentially clinically significant low neutrophil count (<15% of the WBC count): Patient 3607 was a 32 year old male in study HGHW received olanzapine 10mg IM. Baseline WBC count was 8.98 GI/L with 29% neutrophils; At study endpoint, WBC count was 8.01 GI/L with 14% neutrophils (ANC=1.12 GI/L). There were no pre-existing conditions, concomitant medications, or adverse events reported. Further information was not reported. No other patient in this study pool or in the geriatric study met criteria for a potentially clinically significant low WBC or neutrophil count.

8.1.5.3 Mean Change from Baseline in Lab Values

Laboratory analyte mean changes from baseline to LOCF endpoint during the 24 hour injectable treatment phase were compared between IM olanzapine and IM placebo treatment groups in the placebo-controlled IM safety database and in the geriatric study.²⁷ Although the changes for some analytes were different to a statistically significant degree ($\alpha=0.100$), the magnitude of these changes was small and none were deemed to be clinically important.

8.1.5.4 Dropouts Due to Lab Abnormalities

No IM olanzapine-treated patient in the placebo-controlled IM safety database nor in the geriatric study reportedly

²⁵ These data are displayed in volume 1.84, pages 88-93 and 147-155, respectively.

²⁶ HGHV: patients 1315 and 9075; HGHW: patients 1605 and 2512.

²⁷ Data are displayed in volume 1.84, pages 83-85, and in volume 1.85, pages 318-352, respectively.

dropped out because of a laboratory abnormality (see section 8.1.3.2).

8.1.6 Vital Sign Data

8.1.6.1 Vital Sign Assessments

Heartrate and blood pressure assessments were conducted at screening, pre-dose, and at 30 min, 60 min, 90 min, 120 min, 4 hrs, and 6 hrs after the first, second, and third injections and at 12 hrs and 24 hrs after the first injection in the placebo-controlled IM safety database studies and the geriatric study.

8.1.6.2 Potentially Clinically Significant VS Changes

Table 8.1.6.2.1 in Appendix 8.0 displays the criteria for identifying a vital sign measure as potentially clinically significant during the 24 hour injectable treatment phase. In both the placebo-controlled IM safety database and the geriatric study, the proportions of patients meeting these criteria at any time during the 24 IM treatment period were compared between the IM olanzapine and IM placebo treatment groups for each vital sign variable.

Statistically significant differences ($\alpha=0.100$) between IM olanzapine and IM placebo in the placebo-controlled IM safety database are displayed in Table 8.1.6.2.2 below. No such differences were noted in the geriatric study.

Vital Sign Variable	TX	N total	Abnormal		p-value Olz vs. Pl
			n	%	
Low Standing Diastolic BP	Olz	406	20	4.9%	0.021
	Plac	146	1	0.7%	
Low Standing Systolic BP	Olz	396	43	10.9%	0.017
	Plac	144	6	4.2%	
Low Supine Diastolic BP	Olz	413	26	6.3%	0.003
	Plac	149	1	0.7%	

The low standing blood pressures are consistent with the well-known orthostatic hypotensive effect of olanzapine,

which is probably due to the α -1 adrenergic blockade. This mechanism is likely to also play a role in the low supine diastolic blood pressure finding. While a larger fraction of IM olanzapine patients experienced potentially significant orthostatic hypotension compared to IM placebo patients (8.7% vs. 4.9%), this difference was not statistically significant ($p=0.200$).

Normally, hypotension results in a reflexive increase in heartrate and vascular tone to maintain adequate perfusion. To assess the extent to which this reflex may be impaired, the sponsor searched the nine studies contained in the original NDA submission for instances of bradycardia with hypotension or bradycardia without a reflexive increase in pulse on standing.²⁸ The criteria used for identifying such cases are listed in Appendix 8.0, Table 8.1.6.2.3.

This search revealed ten olanzapine-treated patients, who are listed in Appendix 8.0, Table 8.1.6.2.4. The vast majority of these subjects experienced low supine blood pressure in conjunction with low heartrate compared to pre-dose readings. Many did not have corresponding standing vital sign data due to symptoms in the supine position or inability to remain standing, but the occurrence of poorly compensated orthostatic hypotension would be a reasonable assumption. Most of these individuals experienced symptoms, usually dizziness or syncope. Six of these were subjects in clinical pharmacology studies (LOAC, LOAV, and LOAW), three were patients with non-organic psychosis in an open-label clinical trial (LOAT) who received a 12.5mg dose of IM olanzapine, and one was a patient with schizophrenic illness in study HGHV. Two had received oral olanzapine (10mg). The sponsor reported one IM placebo-treated patient meeting these criteria, Patient 3634 in study HGHX who experienced a low supine systolic blood pressure with a low supine pulse.

Given the distribution of these subjects, it appears that psychiatric patients receiving a relatively high dose of IM olanzapine (12.5mg in study LOAT) as well as healthy volunteers are more susceptible to impairment in compensatory mechanisms for drops in blood pressure compared to patients with psychiatric conditions receiving a maximum IM dose of 10mg.

²⁸ This encompassed all studies listed in Appendix 5.0, Table 5.1.1.1, except for studies HGIO and HGJA, which were forwarded after the original submission.

8.1.6.3 Mean Change from Baseline in VS

There was only one statistically significant difference ($\alpha=0.100$) between IM olanzapine and IM placebo in terms of mean change from baseline to LOCF endpoint for vital sign measures during the 24 hour injectable treatment phase in the placebo-controlled IM safety database and in the geriatric study.²⁹ IM olanzapine patients in study HGHX had a mean decrease in supine diastolic blood pressure of 1.44 mmHg compared to a mean increase of 1.87 mmHg among the IM placebo patients ($p=0.091$). This difference is unlikely to be clinically important.

8.1.6.4 Dropouts Due to VS Abnormalities

Only one patient dropped out due to a vital sign abnormality (see section 8.1.3.2): Patient 036-3602 was an 86 year old female in study HGHX who dropped out about 4 hours after receiving IM olanzapine 5mg due to tachycardia (last supine and standing pulse 100 bpm; pre-dose pulse was 90 bpm). This event resolved by the following day.

8.1.7 Electrocardiographic Data

8.1.7.1 ECG Assessments

In the placebo-controlled Phase 2/3 studies, 12-lead ECG's were performed at screening and at 2 and 24 hours after the first injection. Also, in study HGHB, an ECG tracing was obtained on the last day of oral dosing.

8.1.7.2 Potentially Clinically Significant ECG Changes

Criteria used by the sponsor to identify potentially clinically significant ECG measures during the 24 hour injectable treatment phase are displayed in Appendix 8.0, Table 8.1.7.2. With one exception, the proportion of patients meeting any of these criteria at any time during the 24 hour IM treatment period was not significantly different ($\alpha=0.100$) between IM olanzapine and IM placebo patients in either the placebo-controlled IM safety database or the geriatric study.³⁰ The exception occurred

²⁹ Data are presented in volume 1.84, page 94, and volume 1.86, pages 61-72, respectively.

³⁰ Data are displayed in volume 1.84, page 100 and pages 173-174, respectively.

in the placebo-controlled IM safety database, where 2.8% of IM placebo and 0.7% of IM olanzapine patients met criteria for a prolonged PR interval; this is not a clinical concern since the placebo incidence was higher than that for olanzapine.

In the placebo-controlled IM safety database, no IM olanzapine (N=411) nor IM placebo (N=149) patient with a baseline QTc<500 msec had a post-baseline QTc ≥500 msec.

In the geriatric study, a few patients with baseline QTc values <500 msec had post-baseline values ≥500 msec:

<u>Treatment Group</u>	<u>Ntotal</u>	<u>n≥500</u>	<u>%≥500</u>
IM Olz 2.5	69	3	4.3%
IM Olz 5	62	1	1.6%
IM Placebo	62	0	0.0%
IM Lorazepam	63	3	4.8%

None of the intergroup differences were statistically significant. It is notable that a few of the IM lorazepam patients met these criteria in this study, since benzodiazepines are not generally thought to prolong the QTc interval.

8.1.7.3 Mean Change from Baseline in ECG Values

The mean changes from baseline to LOCF endpoint during the 24 hour injectable treatment phase were compared between the IM olanzapine and IM placebo treatment groups for ECG parameters in the placebo-controlled IM safety database and the geriatric study.³¹ Statistically significant differences were found only in the geriatric study: relative to placebo, there was a small shortening of the mean PR interval in the IM olanzapine 5mg group and shortening of the mean QT and QTc intervals in the olanzapine 2.5mg group. A lengthening of these intervals among drug-treated patients relative to placebo would be a potential concern but a shortening is of questionable clinical significance.

Further analyses of changes in QTc were conducted by the sponsor. Changes in ECG parameters from baseline to 24

³¹ Data are displayed in volume 1.84, page 99 and pages 166-171, respectively.

hours after the first injection are difficult to interpret because of the variable number and timing of doses administered after the first injection and the fact that plasma drug levels are only one-third to one-half of Cmax at 24 hours. Thus, the analyses presented here are from 2 hours post-first injection.

In the placebo-controlled IM safety database, QTc change from baseline to 2 hours post-first injection (LOCF) reflected a greater mean decrease in the IM olanzapine group relative to placebo (-3.04 (N=408) vs. -0.70 msec (N=148)). The percentage of patients with various degrees of QTc prolongation at 2 hours is displayed in Table 8.1.7.3.1 below. At each level of prolongation, the percentage of IM placebo patients was slightly greater than for IM olanzapine.

QTc Prolongation	TX	N-total	n- prolonged	% prolonged
≥30 msec	IM Olz	408	17	4.2%
	IM Plac	148	10	6.8%
≥60 msec	IM Olz	408	2	0.5%
	IM Plac	148	1	0.7%
≥75 msec	IM Olz	408	0	0.0%
	IM Plac	148	1	0.7%

In the geriatric study, there was a small mean increase in the change from baseline to two hours post-first injection (LOCF) for the 5mg IM olanzapine group:

<u>Treatment Group</u>	<u>Mean Change</u>	<u>N</u>
IM Olz 2.5mg	-3.98 msec	69
IM Olz 5mg	+8.97 msec	61
IM Placebo	+2.45 msec	62

This difference was not statistically significant, although the difference between the IM olanzapine groups was significant (p=0.009). The mean change in the IM lorazepam group (N=64) was -1.19 msec.

Presumably, the QT interval for these analyses was corrected using Bazett's Formula. Since it is felt by many that Bazett's adjustment produces an over-correction for drugs that elevate the heartrate, one could argue that the above change in the 5mg group (about a 9 msec increase) is an overestimate and that a more appropriate method of correction (e.g., Fredricia's Formula) would reveal a much smaller effect. However, the small mean increases in heartrate observed in this study (+1.23 bpm for IM olanzapine 5mg and +0.36 for IM placebo) suggests that the difference between the two methods would be small.

The percentage of patients experiencing various degrees of QTc prolongation at 2 hours post-first injection in the geriatric study is shown in Table 8.1.7.3.2 below.

TABLE 8.1.7.3.2 GERIATRIC STUDY NUMBER (%) OF PATIENTS WITH QTc PROLONGATION AT TWO HOURS POST-FIRST DOSE				
QTc Prolongation	TX	N-total	N-prolonged	% Prolonged
≥30 msec	IM Olz 2.5	69	8	11.6%
	IM Olz 5	61	10	16.4%
	IM Plac	62	6	9.7%
	IM Lor	64	6	9.4%
≥60 msec	IM Olz 2.5	69	1	1.4%
	IM Olz 5	61	3	4.9%
	IM Plac	62	2	3.2%
	IM Lor	64	1	1.6%
≥75 msec	IM Olz 2.5	69	1	1.4%
	IM Olz 5	61	3	4.9%
	IM Plac	62	1	1.6%
	IM Lor	64	1	1.6%

Although none of the intergroup differences at any degree of QTc prolongation are statistically significant, it is notable that the percentage of patients with a prolongation of at least 75 msec was about three-fold higher in the 5mg IM olanzapine group compared to IM placebo and low dose IM olanzapine. Data from the IM lorazepam group tended to shadow the IM placebo and low dose IM olanzapine data.

As a further exploration of potential QTc prolongation, data from the fixed dose study HGHV was examined. The mean QTc change from baseline to two hours post-first injection (LOCF) in this study is as follows:

<u>Treatment Group</u>	<u>Mean Change</u>	<u>N</u>
IM Olz 2.5	-2.87 msec	47
IM Olz 5	-3.27 msec	45
IM Olz 7.5	-2.33 msec	46
IM Olz 10	+0.33 msec	46
IM Placebo	+3.03 msec	44

These data do not suggest dose-related prolongation of QTc associated with IM olanzapine albeit in a younger, probably healthier patient sample vis-à-vis the geriatric study.

8.1.7.4 Dropouts Due to ECG Abnormalities

No patient in the placebo-controlled IM safety database or in the geriatric study dropped out due to an ECG abnormality.

However, as discussed in sections 8.1.2 and 8.1.3.2 above, there were three healthy volunteers who manifested at least one sinus pause on telemetry, and an additional volunteer with a suspected sinus pause, associated with the administration of olanzapine in clinical pharmacology studies.

8.1.8 Special Studies

8.1.8.1 Study HGJA

Study HGJA was an open-label trial conducted to evaluate the pharmacokinetics (N=20) and tolerability (N=37) of IM olanzapine 10mg given as three doses four hours apart. There was a step-wise pattern of increasing concentrations, with mean Cmax and AUC(0-4) slightly higher with each dose:

	<u>Dose 1</u>	<u>Dose 2</u>	<u>Dose 3</u>
Cmax(ng/ml)	27.1	29.5	41.5
AUC(0-4)(ng-hr/ml)	45.2	79.5	115

Since the mean concentrations at 2 and 4 hours post injection were very similar following each dose, the

sponsor asserts that dosing every 2 hours should produce similar cumulative concentrations as dose administration every 4 hours as in this study.

In this study, 37 patients (ages 19-62) with chronic schizophrenia received 3 injections of olanzapine 10mg within 24 hours, the majority receiving injections at approximately 4 hour intervals. There were no serious adverse events or adverse experiences that led to dropout. Somnolence, postural hypotension, and dizziness were common adverse events, each occurring in more than 5% of the patients. Also, about one-third of all patients in this study (32.6%) experienced significant orthostatic hypotension at some point during the study (≥ 30 mmHg decrease in systolic blood pressure from supine to standing). One patient (#2014) had a QTc ≥ 500 msec (512 msec); this was discovered 24 hours after receiving a single dose and was considerably higher than the QTc found at 2 hours post-dose (479 msec). Thus, this finding is unlikely to be drug-related.

8.1.8.2 Study HGIO

Study HGIO compared the bioavailability of single 5mg doses of 1) injectable olanzapine reconstituted with water, 2) injectable olanzapine reconstituted with 0.33% sodium chloride, and 3) oral olanzapine. This study was conducted because Lilly plans to market a short-acting intramuscular (SAIM) kit () with aqueous sodium chloride diluent. The results of this trial compare the two intramuscular formulations of olanzapine with the reference oral formulation.

Results of this study indicated that the saline and water formulations were bioequivalent with respect to AUC but that the Cmax for the saline formulation was 24% higher than the water formulation, with the upper 90% confidence interval for the ratio being 150%. There was no significant difference between the medians for Tmax.

8.1.8.3 Study LOAV

Study LOAV was conducted to evaluate the potential pharmacokinetic and pharmacodynamic interaction of IM olanzapine and IM lorazepam. Basically, this was a three-way crossover study in 15 healthy males and females who

received, in randomized order, IM olanzapine 5mg, IM lorazepam 2mg, or IM olanzapine 5mg followed one hour later by IM lorazepam 2mg. There was a 6-17 day washout between treatment periods.

The pharmacokinetics of olanzapine, unconjugated lorazepam, and total lorazepam were not affected by co-administration of these drugs.

Pharmacodynamic effects (performance on the Digit Symbol Substitution Test and onset and duration of somnolence) tended to be additive with combined use. With the exception of one subject (#2843) who experienced syncope and apnea after IM olanzapine 5mg alone, there were no serious adverse events in this study. Subject 2843 was discussed in section 8.1.2 above.

There is one caveat in interpreting the results of this study. IM lorazepam reaches C_{max} in less than one hour and its concentration falls rapidly thereafter. C_{max} for IM lorazepam occurs 1-1.5 hours after dosing. Thus, the administration of IM lorazepam one hour after IM olanzapine means that when lorazepam levels are at C_{max}, the olanzapine levels will be approximately ¼ of C_{max}. In a June 25, 1998, letter, we recommended to the sponsor that the interval between the administration of the two drugs be shortened to better detect any interaction between the drugs. This recommendation was not implemented. The above results may underestimate the potential for an interaction.

8.2 Adequacy of Patient Exposure and Safety Assessments

There are a number of factors pertaining to the short-term administration of IM olanzapine that potentially impact on its safety: 1) the size of the individual injected dose, 2) the number of injections administered, and 3) the timing of those injections. Ideally, an assessment of the adequacy of patient exposure would simultaneously consider all of these factors. However, such an approach is not fruitful in this case because of the dosing strategy used in the four key studies: the number of IM doses given and the timing of those doses were dependent on the clinical status of the patient. If patients tend to respond after a single dose, as apparently was the case here, then safety experience from an adequate number of patients exposed to more extreme dosing (multiple doses injected at rapid

frequency), which is more likely to reveal safety problems, is not available.

Among the 415 IM olanzapine-treated patients in the placebo-controlled IM safety database, the total olanzapine dose during the 24 hour injectable period was greater than 20mg for only 14 patients; five of these patients received the maximum dose, 30mg. Only 18 patients received three injections.³²

Considering the 137 patients in the geriatric study HGHX, 13 patients received a total olanzapine dose of 10mg during the 24 hour injectable period; another 11 patients received 12.5mg. Twenty-nine patients received three injections.³³

The relatively safe passage of patients in study HGJA, where 37 patients received three doses of 10mg, generally separated by 4 hour periods, provides some evidence supporting the safety of multiple dosing with IM olanzapine. Pharmacokinetic data from that study also suggests that dosing at 2 hour intervals could be expected to produce plasma levels of olanzapine comparable to those seen at 4 hour intervals.

Few patients in the other open-label studies, LOAR and LOAT, received dosing with IM olanzapine similar to that in study HGJA.

Safety experience with oral olanzapine is only partially reassuring, since IM administration tends to produce, on average, a 2.5-fold higher Cmax than the same dose of oral drug. This would tend to support the safety of the single 10mg dose, since oral olanzapine is labeled for use in daily doses to 20mg, but repeated doses given frequently may produce plasma levels considerably higher than those experienced with oral drug at maximum dose.

Overall, the patient exposure does appear to be sufficient to support the safety of single doses of IM olanzapine. Experience with multiple dosing is also adequate, although marginally so given the small number of patients who received more than one injection of olanzapine.

³² These figures exclude the 21 placebo patients in HGHW who crossed over to olanzapine for their final dose.

³³ These figures do not reflect the 31 placebo patients who received olanzapine as their third dose.

In terms of safety assessments, there are two issues worth mentioning. First, in light of the sinus pauses documented in healthy volunteers in the Phase 1 studies, it would have been reasonable and helpful for the sponsor to conduct cardiac telemetry in some portion of the patients studied in the placebo-controlled Phase 2/3 trials. The lack of this information leaves unanswered the question of whether sinus pauses also occur in patients with psychiatric illness.

Second, the first post-baseline 12-lead ECG in the Phase 2/3 studies was obtained 2 hours after the first injection. After injection of olanzapine, T_{max} is 15-45 minutes, with a rapid decline in plasma concentration thereafter see Figure 6.0 in section 6.0). Hence, at 2 hours post injection, plasma levels are likely to be well below C_{max} (~50% of C_{max}) and changes from baseline in ECG parameters (such as QTc) may be considerably underestimated.

Otherwise, the safety assessments seem reasonable.

8.3 Assessment of Data Quality and Completeness

Data contained in this NDA submission appear to be reasonably reliable and complete.

Twenty percent (4/20) of the Case Report Forms (CRF's) that were electronically submitted in the original NDA submission were audited by comparing adverse event data in those CRF's with the corresponding data contained in the Narrative Summaries. These four patients are identified in section 1.1. Each Narrative Summary was deemed to completely and accurately reflect the adverse event data in the CRF.

8.4 Summary of Potentially Important Safety Issues

8.4.1 Orthostatic Hypotension

Oral olanzapine is known to be associated with orthostatic hypotension, probably due to α -1 adrenergic blockade. In the placebo-controlled IM safety database, 3.0% (12/404) of the IM olanzapine and 1.4% (2/144) of the IM placebo patients had a decrease in systolic blood pressure ≥ 30 mmHg from supine to standing (p=0.375).

In the geriatric study, the proportions of patients having this magnitude of change from supine to sitting were:

IM Olz 2.5mg	2.4% (1/41)
IM Olz 5mg	0.0% (0/41)
IM Placebo	2.4% (1/41)

Syncope is often a manifestation of significant orthostatic hypotension. In the placebo-controlled IM safety database, 0.2% (1/415) of the IM olanzapine and 0.0% (0/150) of the IM placebo patients experienced syncope. No patient in the geriatric study reported syncope.

Further analysis of these data suggest that supine hypotension in conjunction with bradycardia or orthostatic hypotension with poor heartrate response may be associated with IM olanzapine. However, this seems to be much more prevalent in healthy volunteers and psychiatric patients receiving IM doses of olanzapine above 10mg compared to patients with psychiatric disorders receiving lower IM doses.

Overall, these analyses revealed little data suggesting a significant problem with orthostatic hypotension. A number of caveats must be kept in mind, however: 1) in study HGJA, which utilized more aggressive dosing consistent with the maximal dosing proposed for labeling, a relatively high proportion (about 1/3 of the patients) experienced significant orthostatic hypotension; 2) the above criterion is set rather high and the incidence of smaller, yet important, magnitudes of orthostatic change may be appreciably higher, 3) many of these patients may have been bedridden during the study, minimizing the clinical consequences of orthostasis, and 4) measuring change from supine to sitting in the elderly (as opposed to supine to standing) likely minimizes the findings in the geriatric study.

8.4.2 QTc Prolongation

At the outset, it should be mentioned, as discussed in section 8.2, that the ECG data obtained 2 hours post-first injection in the Phase 2/3 studies likely coincided with olanzapine plasma levels well below C_{max} for most patients. Thus, it is quite possible that larger changes from baseline in QTc were missed. Also, while many patients received multiple doses of IM olanzapine that could have

produced plasma levels higher than those seen at 2 hours after first injection, most received only one dose and the likely timing of additional doses was well before the 24 hour timepoint. Hence, the ECG data from 24 hours post-first injection are not reassuring in this regard. Additionally, it does not appear that ECG data collected in other studies of the IM development program were captured at Cmax. This potential flaw should be borne in mind during the following discussion.

Also, as discussed in section 8.1.7.3 above, it is not felt that an alternative method of correcting the QT interval (e.g., Fredricia's Formula) would make much difference given the small mean increase in heartrate observed.

Analysis of change from baseline in QTc and the percentage of patients with a post-baseline QTc ≥ 500 msec revealed no remarkable findings in the placebo-controlled IM safety database, comprised of younger patients with schizophrenic or bipolar illness (see sections 8.1.7.2 and 8.1.7.3).

However, the corresponding data from the geriatric study, which enrolled older patients with dementia, suggested that IM olanzapine 5mg might be associated with some appreciable degree of QTc prolongation. These data are summarized in Table 8.4.2.1 below.

Analysis	Treatment Group			
	Olz 2.5	Olz 5	Plac	Lor
Mean Δ from BL(msec)	-3.98	+8.97	+2.45	-1.19
% w/ $\Delta \geq 75$ msec	1.4%	4.9%	1.6%	1.6%
% w/QTc ≥ 500 msec	4.3%	1.6%	0.0%	4.8%

It is curious, though, that a higher percentage of patients in the lower dose group (2.5mg) experienced a QTc ≥ 500 msec; this might be explained, in part, by higher values at baseline in the lower dose group (means of 430 (2.5mg) and 419 (5mg)). It is also notable that IM lorazepam was

³⁴ Mean change from baseline and percentage with a change ≥ 75 msec were based on data collected 2 hours post-first dose. Percentage with a QTc ≥ 500 msec was based on any reading during the 24 hour post-baseline period.

associated with the emergence of a QTc ≥ 500 msec in 4.8% of the patients in that group.

While it is true that the differences between the IM olanzapine groups and IM placebo were not statistically significant, this begs the question of whether this trial was adequately powered to detect clinically significant differences between treatment groups.

The sponsor contends that QTc analyses based on a priori criteria derived from younger, healthier patients are not appropriate in this trial with older, demented patients. Of particular interest, they conducted a post hoc analysis based on the distribution of change in QTc observed in the placebo-treated patients in this study. Then, the 97.5th percentile for this distribution was determined for each gender (about 75 msec for females and 65 msec for males). Finally, the proportion of patients in each treatment group who exceeded this 97.5th percentile was computed and compared. Results are displayed in Table 8.4.2.2 below.

	Females		Males	
	Proportion	%	Proportion	%
IM Olz 2.5	0/38	0.0%	1/31	3.2%
IM Olz 5	2/40	5.0%	1/21	4.8%
IM Plac	1/37	2.7%	0/25	0.0%
IM Lor	1/39	2.6%	0/25	0.0%

Again, no differences between groups were statistically significant. The highest proportions were in the 5mg dose group for both sexes.

There were no reports of syncope or sudden death during this study, which might suggest the occurrence of a ventricular arrhythmia related to excessive QTc prolongation.

In conclusion, these are insufficient data to infer that IM olanzapine, in geriatric patients with dementia, prolongs the QTc interval to a hazardous degree. However, given the caveat at the beginning of this section, one cannot

conclude with certainty that such prolongation does not occur.

8.4.3 Sinus Pauses

There were three healthy volunteers in two clinical pharmacology studies with documented pauses in sinus rhythm subsequent to olanzapine administration. See sections 8.1.2 and 8.1.3.2 for a description of these cases.³⁵ These were associated with bradycardia and, in one patient each, collapse and loss of consciousness. The longest reported duration of pause was 6 seconds. All resolved without specific intervention.

The two studies in which these three subjects participated were the only trials in the IM development program in which telemetry was performed. Hence, the fact that there are no documented cases of sinus pause in other studies may be due to lack of detection as opposed to an actual absence of such events.

Adverse events that might have accompanied the occurrence of a sinus pause in other trials include syncope, bradycardia, and dizziness. The placebo-controlled IM safety database as well as the geriatric study were examined for the proportion of patients who reported these adverse experiences in the IM olanzapine and IM placebo treatment groups, which were then compared. For none of these events was the proportion of IM olanzapine patients reporting the event significantly greater than that for IM placebo ($\alpha=0.100$).

Only one patient in the placebo-controlled Phase 2/3 studies (604 patients treated with IM olanzapine) experienced syncope: Patient 1503 in study HGHW was a 30 year old male who experienced syncope about 20 minutes after receiving IM olanzapine 10mg. This event may have been due to severe orthostatic hypotension: supine blood pressure shortly after the episode was 97/67 but the first standing blood pressure obtainable after this experience (6 hours later) was 81/55.

Additionally, the mean change from baseline in ECG heartrate and the percentages of patients meeting criteria

³⁵ In an additional case (LOAV Subject 2843), sinus pause was suspected by the sponsor.

for potentially clinically significant decreases in pulse or heartrate were examined. Again, there were no significant differences between IM olanzapine and IM placebo.

There is one postmarketing report of a patient experiencing sinus pause associated with an olanzapine overdose.³⁶ There was spontaneous resumption of normal rhythm.

In conclusion, these examinations did not produce a signal suggesting the occurrence of sinus pauses in the placebo-controlled Phase 2/3 studies. However, it must be borne in mind that the above analyses are not particularly sensitive for this purpose and certainly cannot rule out the possibility of sinus pauses, especially asymptomatic pauses, in these studies.

8.5 Conclusions Regarding Safety

These data reveal no clear evidence of any significant toxicities or previously unrecognized hazards that can be reasonably attributed to IM olanzapine. However, the limitations discussed above should be kept in mind.

9.0 Labeling

The following comments are based on the labeling proposed by the sponsor, as submitted in the original submission to this NDA, as well as the most recently approved labeling for Zyprexa.³⁷

DESCRIPTION

In paragraph 1, sentence 1, the adjective "psychotropic" may be replaced with "antipsychotic" since, in this context, it refers to the whole class of agents used to treat psychosis as opposed to the specific indications for Zyprexa.

CLINICAL PHARMACOLOGY, Clinical Efficacy Data, Agitation

The discussions of the findings of studies HGHV, HGHB, and HGHW (paragraphs 1, 2, and 3, respectively) each end with a statement indicating the earliest timepoint at which IM olanzapine was superior to placebo. These studies were not

³⁶ See the Overdosage/Human Experience section of Zyprexa labeling. No other information about this case was reported.

³⁷ The most recently approved labeling was attached to the approval letter for supplement SE1-011 to NDA 20-592.

designed to assess time to effect onset and these statements should be deleted.

The discussion of the findings from study HGHX (paragraph 4) mention the 2.5mg dose group. Since an assessment of the 2.5mg dose was not a primary objective in this study and no statistical adjustment was made for comparisons involving this dose, reference to this dose group should be removed. The discussion must rely on the 5mg dose findings.

This subsection should end with a sentence indicating that an examination of population subgroups (age, gender, and racial origin) did not reveal any differential responsiveness on these variables.

INDICATIONS AND USAGE, Agitation

This subsection should end with a sentence indicating that the safety and efficacy of Zyprexa IM beyond 24 hours have not been studied.

ADVERSE REACTIONS

The total number of patients exposed to intramuscular olanzapine should be updated from 722 to 765 since study HGJA, which was forwarded after the original NDA, entailed an additional 43 patients exposed.

In the first paragraph, statement #5 should include the diagnostic category "acute non-organic psychosis" since patients from studies LOAR and LOAT, which enrolled such patients, are included in the 722 patient total.

ADVERSE REACTIONS, Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials; Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials, Agitation

The percentage of IM olanzapine-treated patients who dropped out due to an adverse event in the placebo-controlled Phase 2/3 studies was not 0.4% but 0.5% (3/604). The numerator includes one IM placebo patient in HGHX who apparently dropped out after crossing over to IM olanzapine; the denominator includes 21 and 31 IM placebo patients who crossed over to IM olanzapine in studies HGHW and HGHX, respectively.

ADVERSE REACTIONS, Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials; Adverse Events Occurring at an Incidence of 1% or More Among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials

In paragraph 1, it would be more informative to cite the dose range (2.5-10.0 mg/injection) as opposed to the minimum dose (doses \geq 2.5 mg/injection).

Table 2 appears to be based on a cutoff for adverse event incidence of 1.00%. Hence, this table is very slightly different from Table 8.1.4.3 in Appendix 8.0, where a cutoff of 1.0% was used.

For the geriatric study, it would be more informative in paragraph 2 to cite the doses administered (2.5 and 5.0 mg/injection) than the minimum dose (doses \geq 2.5 mg/injection).

Table 3 omits two adverse events: ECG abnormal (2% in the IM olanzapine group and 0% in the IM placebo group) and hallucinations (1% in the IM olanzapine group and 0% in the IM placebo group). The term ECG abnormal should be footnoted to provide the more specific findings represented by this term.

ADVERSE REACTIONS, Additional Findings Observed in Clinical Trials, Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

The table that displays the percentages of patients with extrapyramidal symptoms by ratings scales in the geriatric study should be footnoted to indicate that the Barnes Akathisia Scale was not performed in that study. Otherwise, this table, in the context of the table above it, may be interpreted to mean that no patient had akathisia by the stated criteria in the geriatric trial.

ADVERSE REACTIONS, Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine

In the preface to the listing of other adverse events observed with intramuscular olanzapine, the number of patients treated should be updated to 765.

In the listing itself, the term "ventricular arrhythmia" was omitted by the sponsor from the Cardiovascular System section because it only occurred once and was not felt to have a substantial probability of being acutely life

threatening. I disagree that this event is not likely to be serious; it should be added to this section.

DOSAGE AND ADMINISTRATION, Agitation, Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania

The last phrase in the first paragraph, stating that dosing more frequently than 4 hours after the second dose has not been evaluated, is not quite correct: in study HGHW, the third dose may have been given one hour after the second dose. However, of the 18 patients in studies HGHB, HGHV, and HGHW who received three injections, 10 were from studies HGHB and HGHV, where the third dose was given at least 4 hours after the second dose, and 8 were from HGHW. Thus, for most of these patients, the minimum 4 hour interval was true. Additionally, it is not known how many patients in HGHW actually received a third dose only one hour after the second dose. Hence, I have no strong objection to this statement.

DOSAGE AND ADMINISTRATION, Agitation, Usual Dose for Agitated Patients with Dementia

The sponsor's proposal for dosing patients with dementia is problematic.

The sponsor's reason for declaring the 2.5mg (as opposed to the 5mg) dose in study HGHX as optimal is not clear: the 2.5mg dose was not clearly superior to placebo on the CMAI and the superiority for the 5mg dose over placebo was more robust than for the 2.5mg dose. Additionally, an assessment of the 2.5mg dose in this trial was not a primary study objective. This study was declared as positive based on the data from the 5mg dose group.

Also, the rationale for starting with a 2.5mg dose and increasing to a 5mg dose for subsequent doses is the opposite of the dosing in this trial, where 5mg was given as the first and second doses and the lower 2.5mg dose as the third dose.

Furthermore, the statement that the safety of doses given more frequently than 2 hours after the first dose is confusing. While the second dose was given at least 2 hours after the first dose, the third dose could have been given only one hour after the second.

These issues should be addressed by the sponsor.

DOSAGE AND ADMINISTRATION, Agitation, Intramuscular Dosing in Special Populations

Intuitively, the sponsor's recommendation to use a dose of 5mg in geriatric patients (compared to 10mg in younger patients) seems prudent although they have provided no data-based analysis to support this. Likewise, the recommendation for a dose of 2.5mg in patients with dementia (see above) or who might otherwise be debilitated, be predisposed to hypotensive reactions, or be more pharmacologically sensitive to olanzapine is presented without explanation. The sponsor should provide a rationale for these recommendations.

DOSAGE AND ADMINISTRATION, Agitation, Administration of Zyprexa IM

As discussed in section 3.1, the two methods of reconstituting Zyprexa IM yield solutions of different concentrations, which is likely to increase the risk of a medical error. This potential problem should be addressed by the sponsor.

10.0 Conclusions

This NDA presents evidence supporting the safety and efficacy of Zyprexa IM for the treatment of acute agitation across a variety of indications, consistent with the pain model used to evaluate analgesics.

Before approval, however, feedback from the Psychopharmacological Drugs Advisory Committee (PDAC) will be obtained and considered, particularly with respect to the "agitation" indication.

Additionally, there are some important labeling issues that must be resolved prior to approval, particularly with respect to dosage and administration (see section 9.0).

Also deserving further consideration are some cardiac and cardiovascular findings among healthy volunteers (sinus pauses and hypotension with bradycardia) as well as suboptimal evaluation for QTc prolongation in the Phase 2/3 studies. The available evidence does not clearly indicate a hazard in patients associated with these phenomena and, thus, is not felt to contraindicate approval. However, data accrued during postmarketing experience may indicate otherwise by virtue of use of Zyprexa IM in a larger number of relatively unscreened patients.

In addition to the above clinical issues, the acceptability of the two proposed methods for reconstituting Zyprexa IM, which produce solutions of different concentrations (section 3.1), as well as the adequacy of dermal irritation studies in animals (section 4.0) should be addressed.

11.0 Recommendations

It is recommended that this NDA be deemed approvable, with final approval contingent on: 1) consideration of PDAC recommendations, 2) resolution of the above labeling issues, and 3) a focused post-marketing surveillance plan, conducted by the Agency or the sponsor or both, to closely monitor adverse event reports suggesting safety hazards related to sinus pauses, hypotension with bradycardia, and QTc prolongation (e.g., reports of sudden, unexplained death or syncope) as well as consideration of a telemetry study in patients, and 4) resolution of the non-clinical issues mentioned above (section 10.0).

DRAFT

Gregory M. Dubitsky, M.D.
December 20, 2000

Cc: NDA 21-253
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 /PAndreason
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APPENDIX 5.0

DATA SOURCES

TABLE 5.1.1.1
TABLE OF COMPLETED STUDIES

Clinical Pharmacology Studies (healthy volunteers)

LOAC	Single blind, ascending dose tolerance, safety, and pharmacokinetic study in 31 healthy males (age 18-65) using single doses of IM olanzapine up to 4mg.
LOAW	Open-label, randomized, 2 period crossover study comparing the bioavailability of IM olanzapine (two 5mg injections given 4 hours apart) with PO olanzapine (2x5mg tablets) in 24 healthy males (age 18-65).
LOAV	Open-label, randomized, 3 period crossover study comparing the safety and pharmacokinetics of IM olanzapine 5mg and IM lorazepam 2mg, each given separately and together as single doses, in 15 healthy subjects (4 males, 11 females) (age 21-40) to evaluate PK/PD interactions.
HGIO	Open-label, 3-period, 3-treatment, 6-sequence crossover study comparing the bioavailability of 5mg single doses of two intramuscular formulations of olanzapine and a reference oral formulation in 18 healthy males (age 18-45).

Open-Label Clinical Studies

LOAR	Open-label, ascending dose range, pilot study of the safety, efficacy, and PK of IM olanzapine in 26 male inpatients (age 18-65) with acute non-organic psychosis treated with 2-5 doses of IM olanzapine, up to 10mg each, over 3 days.
LOAT	Open-label study of the safety and efficacy of IM olanzapine in 92 male and female inpatients (age ≥ 18) with acute non-organic psychosis treated with at least two doses of IM olanzapine (2.5, 5, 7.5, or 10mg each) over 3 days.
HGJA	Open-label study in 43 inpatients with chronic schizophrenia to evaluate the tolerance and pharmacokinetics of up to 3 intramuscular doses of olanzapine 10mg within 20 hours during each of two phases of this trial.

TABLE 5.1.1.1
TABLE OF COMPLETED STUDIES

Placebo-Controlled Studies

HGHB	Randomized, double-blind, placebo- and haloperidol-controlled parallel group study in 311 inpatients (age ≥18) with schizophrenia, schizophreniform disorder, or schizoaffective disorder treated with 1-3 IM injections of olanzapine 10mg, haloperidol 7.5mg, or placebo (2:2:1 ratio) over 24 hours followed by oral olanzapine (5-20 mg/d) or haloperidol (5-20 mg/d) for 4 days.
HGHV	Randomized, double-blind, placebo- and haloperidol-controlled parallel group study in 270 inpatients (age ≥18) with schizophrenia, schizophreniform disorder, or schizoaffective disorder treated with 1-3 IM fixed dose injections of olanzapine (2.5, 5, 7.5, or 10mg), haloperidol 7.5mg, or placebo over 24 hours.
HGHW	Randomized, double-blind, placebo- and lorazepam-controlled parallel group study in 201 inpatients (age ≥18) with bipolar I disorder, with an acute manic or mixed episode, treated with 1-3 IM injections of olanzapine (10, 10, and 5mg, respectively), lorazepam (2, 2, and 1mg, respectively), or placebo (0, 0, and IM olanzapine 10mg, respectively) over 24 hours.
HGHX	Randomized, double-blind, placebo- and lorazepam-controlled parallel group study in 272 inpatients (age ≥55) with dementia (Alzheimer's, vascular, or mixed type) treated with 1-3 IM injections of olanzapine (2.5, 2.5, and 1.25mg, respectively), olanzapine (5, 5, and 2.5mg, respectively), lorazepam (1, 1, and 0.5mg, respectively), or placebo (0, 0, and IM olanzapine 5mg, respectively) over 24 hours.

TABLE 5.1.1.2: PATIENT ENUMERATION BY STUDY TYPE				
Study Type	IM Olanzapine	Placebo	Haloperidol	Lorazepam
Clinical Pharmacology Trials	83	18	0	12
Open-Label Trials	161	0	0	0
Placebo-Controlled Trials	604	217	166	119
Total	848	235	166	131

TABLE 5.1.2.1:						
PLACEBO-CONTROLLED IM SAFETY DATABASE						
PATIENT DEMOGRAPHIC CHARACTERISTICS						
	Age (yrs)		Sex (%)		Race (%)	
	Mean	Range	Male	Female	White	Non-white
IM Olanzapine (N=415)	37.69	18-79	61%	39%	69%	31%
IM Placebo (N=150)	38.31	18-70	57%	43%	70%	30%

TABLE 5.1.2.2:						
GERIATRIC STUDY (HGXX)						
PATIENT DEMOGRAPHIC CHARACTERISTICS						
	Age (yrs)		Sex (%)		Race (%)	
	Mean	Range	Male	Female	White	Non-white
IM Olanzapine 2.5	77.36	54-95	44%	56%	92%	8%
IM Olanzapine 5.0	79.21	56-97	35%	65%	92%	8%
IM Placebo	76.98	56-96	40%	60%	94%	6%
IM Lorazepam	76.97	55-95	37%	63%	91%	9%

**TABLE 5.1.3:
PATIENT EXPOSURE TO IM OLANZAPINE**

Placebo-Controlled IM Safety Database		Geriatric Study (HGXX)		
Dose (mg/24 hours)	% Receiving Dose N=415	Dose (mg/24 hours)	% Receiving Dose	
			IM Olanz 2.5mg N=71	IM Olanz 5.0mg N=66
2.5	5.5%	2.5	59.2%	0%
5.0	12.3%	5.0	15.5%	63.6%
7.5	8.7%	6.2	25.4%	0%
10.0	53.7%	10.0	0%	19.7%
15.0	3.1%	12.5	0%	16.7%
20.0	13.3%			
22.5	0.2%			
25.0	1.9%			
30.0	1.2%			

APPENDIX 7.0

EFFICACY

**TABLE 7.2.1.1:
STUDY HGHB
INVESTIGATORS/LOCATIONS**

Principal Investigator (Site #)	Location
Battaglia (001)	Anchorage, Alaska
Kang (003)	Center Township, Pennsylvania
Plopper (004)	San Diego, California
Reinstein (005)	Chicago, Illinois
Riesenberg (006)	Decatur, Georgia
Sack (007)	Cerritos, California
Adityanjee (008)	Cleveland, Ohio
Wang (009)	Milwaukee, Wisconsin
Chappell (011)	Olympia, Washington
Mofsen (012)	St. Louis, Missouri
Small (013)	Indianapolis, Indiana
Lerman (014)	Oak Brook, Illinois
Fabre (015)	Houston, Texas
Levine (016)	Torrance, California
Figueroa (017)	Torrance, California
Dantendorfer/Katschnig (100)	Austria
Geretsegger (101)	Austria
Zapotoczky (102)	Austria
Fleischhacker (103)	Austria
Seifertova (121)	Czech Republic

**TABLE 7.2.1.1:
STUDY HGHB
INVESTIGATORS/LOCATIONS**

Principal Investigator (Site #)	Location
Tuma (131)	Czech Republic
Janka (141)	Hungary
Bartko (142)	Hungary
Bitter (143)	Hungary
Peuskens (200)	Belgium
Renier (202)	Belgium
Seghers (203)	Belgium
Herregodts (204)	Belgium
DeClercq (205)	Belgium
Daumer (301)	France
Kannas (302)	France
Gudej (303)	France
Passamar (304)	France
Bonnafoux (305)	France
Wertenschlag (306)	France
Chinchilla (600)	Spain
Bernardo (601)	Spain
Peralta (602)	Spain
De la Gandara (603)	Spain
San Molina (604)	Spain

**TABLE 7.2.1.1:
STUDY HGHB
INVESTIGATORS/LOCATIONS**

Principal Investigator (Site #)	Location
McCreadie (801)	Scotland
Chouinard (850)	Canada
Labelle (851)	Canada
Siekiersky (853)	Canada
Brook (900)	South Africa
Hart (903)	South Africa
Belmaker (920)	Israel
Grunhaus (921)	Israel
Elizur (922)	Israel
Christodoulou (930)	Greece
Morris (960)	Australia

**TABLE 7.2.1.2:
STUDY HGHB
PATIENT DEMOGRAPHICS
INJECTABLE PERIOD**

Treatment	IM Olanz	IM Hal	IM Placebo
N	131	126	54
AGE (years)			
Mean	38.17	38.54	37.60
Range	18-72	18-70	19-70
GENDER (%)			
Male	64.9	68.3	61.1
Female	35.1	31.7	38.9
RACE (%)			
Caucasian	72.5	77.0	63.0
African	18.3	17.5	24.1
Hispanic	6.1	3.2	9.3
E/SE Asian	0.8	1.6	0.0
Other	2.3	0.8	3.7

TABLE 7.2.1.5
STUDY HGHB
MEAN CHANGE FROM BASELINE IN THE PANSS EXCITED COMPONENT
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
IM Olanz	131	13.35	130	-6.33	130	-8.10	129	-8.50	129	-8.09	131	-8.01
IM Hal	126	13.17	126	-4.27	126	-7.22	125	-7.96	126	-7.83	126	-7.83
IM Plac	54	13.37	54	-2.39	54	-3.50	54	-3.69	54	-3.74	54	-3.74
2-sided p-values for pairwise comparisons												
IM Olanz vs. IM Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
IM Hal vs. IM Plac			0.007		<0.001		<0.001		<0.001		<0.001	
IM Olanz vs. IM Hal			<0.001		0.171		0.422		0.793		0.868	

TABLE 7.2.1.6
STUDY HGHB
MEAN CHANGE FROM BASELINE IN THE CORRIGAN AGITATED BEHAVIOR SCALE
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
IM Olanz	131	27.60	129	-6.53	130	-8.12	128	-8.34	129	-8.01	131	-7.89
IM Hal	126	26.92	126	-5.20	125	-7.37	125	-7.98	126	-7.79	126	-7.79
IM Plac	54	28.52	54	-3.37	54	-4.81	54	-5.06	54	-4.39	54	-4.39
2-sided p-values for pairwise comparisons												
IM Olanz vs. IM Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
IM Hal vs. IM Plac			0.020		0.003		0.001		<0.001		<0.001	
IM Olanz vs. IM Hal			0.036		0.290		0.644		0.849		0.940	

TABLE 7.2.1.7
STUDY HGHB
MEAN CHANGE FROM BASELINE IN THE AGITATION-CALMNESS EVALUATION SCALE
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
IM Olanz	131	2.59	131	+1.34	131	+1.95	131	+1.95	130	+1.81	131	+1.79
IM Hal	126	2.48	126	+0.96	126	+1.67	126	+1.81	126	+1.65	126	+1.65
IM Plac	54	2.43	54	+0.48	54	+0.74	54	+0.87	54	+0.74	54	+0.74
2-sided p-values for pairwise comparisons												
IM Olanz vs. IM Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
IM Hal vs. IM Plac			0.024		<0.001		<0.001		<0.001		<0.001	
IM Olanz vs. IM Hal			0.017		0.114		0.439		0.406		0.448	

**TABLE 7.2.2.1:
STUDY HGHV
INVESTIGATORS/LOCATIONS**

Principal Investigator (Site #)	Location
Folnegovic-Smalc (131)	Croatia
Dodig (132)	Croatia
Mandic (133)	Croatia
Jakovljevic (134)	Croatia
Prelipceanu (260)	Romania
Boisteanu (261)	Romania
Lazarescu (262)	Romania
Caserta (502)	Italy
Rataemane (901)	South Africa
Brook (902)	South Africa
Van Wyk (904)	South Africa
Hart (905)	South Africa
Strauss (906)	South Africa
Emsley (907)	South Africa

**TABLE 7.2.2.2:
STUDY HGHV
PATIENT DEMOGRAPHICS**

Treatment Group	IM Olanzapine				IM Hal 7.5mg	IM Plac
	2.5mg	5mg	7.5mg	10mg		
N	48	45	46	46	40	45
AGE (years)						
Mean	36.24	35.08	35.87	36.73	37.41	36.65
Range	19-70	18-54	20-71	18-71	21-73	19-58
GENDER (%)						
Male	64.6	60.0	56.5	56.5	55.0	51.1
Female	35.4	40.0	43.5	43.5	45.0	48.9
RACE (%)						
Caucasian	60.4	68.9	63.0	69.6	62.5	71.1
African	22.9	24.4	26.1	23.9	30.0	17.8
W Asian	4.2	0.0	0.0	0.0	0.0	4.4
Other	12.5	6.7	10.9	6.5	7.5	6.7

TABLE 7.2.2.4
STUDY HGHV
MEAN CHANGE FROM BASELINE IN THE PANSS EXCITED COMPONENT
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olz 2.5	48	13.25	48	-1.71	48	-3.98	48	-5.15	48	-5.50	48	-5.50
Olz 5	45	14.71	45	-2.93	45	-5.82	45	-7.18	45	-8.09	45	-8.09
Olz 7.5	46	13.85	46	-3.26	46	-6.28	46	-8.35	46	-8.65	46	-8.65
Olz 10	46	14.30	45	-2.87	46	-6.83	46	-9.15	46	-9.35	46	-9.35
Hal 7.5	40	14.28	40	-2.00	40	-5.38	40	-6.40	39	-7.69	40	-7.53
Placebo	45	13.78	45	-1.40	45	-2.22	45	-2.80	45	-2.91	45	-2.91
2-sided p-values for pairwise comparisons												
Olz 2.5 vs. Placebo			0.646		0.050		0.016		0.010		0.010	
Olz 5 vs. Placebo			0.029		<0.001		<0.001		<0.001		<0.001	
Olz 7.5 vs. Placebo			0.007		<0.001		<0.001		<0.001		<0.001	
Olz 10 vs. Placebo			0.046		<0.001		<0.001		<0.001		<0.001	
Hal 7.5 vs. Placebo			0.343		<0.001		<0.001		<0.001		<0.001	

TABLE 7.2.2.5
STUDY HGHV
MEAN CHANGE FROM BASELINE IN THE AGITATION-CALMNESS EVALUATION SCALE
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olz 2.5	48	2.42	48	+0.31	48	+0.85	48	+1.25	48	+1.27	48	+1.27
Olz 5	45	2.18	45	+0.56	45	+1.49	45	+1.91	45	+2.31	45	+2.31
Olz 7.5	46	2.26	46	+0.67	46	+1.48	46	+2.15	46	+2.37	46	+2.37
Olz 10	46	2.26	45	+0.84	46	+1.91	46	+2.59	46	+2.57	46	+2.57
Hal 7.5	40	2.15	40	+0.28	40	+1.20	40	+1.60	39	+1.82	40	+1.78
Placebo	45	2.38	45	+0.24	45	+0.44	45	+0.62	45	+0.69	45	+0.69
2-sided p-values for pairwise comparisons												
Olz 2.5 vs. Placebo			0.715		0.142		0.044		0.064		0.064	
Olz 5 vs. Placebo			0.112		<0.001		<0.001		<0.001		<0.001	
Olz 7.5 vs. Placebo			0.026		<0.001		<0.001		<0.001		<0.001	
Olz 10 vs. Placebo			0.004		<0.001		<0.001		<0.001		<0.001	
Hal 7.5 vs. Placebo			0.787		0.008		0.002		<0.001		0.001	

**TABLE 7.2.3.1:
STUDY HGHW
INVESTIGATORS/LOCATIONS**

Principal Investigator (Site #)	Location
Bari (001)	Chula Vista, CA
Fossey (003)	Tulsa, OK
Janicak and Winans (004)	Chicago, IL
El-Mallakh (005)	Louisville, KY
Kwentus (006)	Madison, TN
Pavlinac (007)	Oceanside, CA
Plopper (008)	San Diego, CA
Ranjan (009)	Medina, OH
Reinstein (010)	River Park, IL
Small (011)	Indianapolis, IN
Charuvastra (012)	San Fernando, CA
Wang (013)	Milwaukee, WI
Achamallah (014)	Vallejo, CA
Brown (015)	Austin, TX
Feifel (016)	San Diego, CA
Maguire (017)	Orange, CA
Mee-Lee (018)	Honolulu, HI
Printz (019)	New York, NY
Vivek (020)	Jamaica, NY

**TABLE 7.2.3.1:
STUDY HGHW
INVESTIGATORS/LOCATIONS**

Principal Investigator (Site #)	Location
Munoz (023)	Birmingham, AL
Rosenthal (025)	San Diego, CA
Oxenkrug (029)	Brighton, MA
Moss (030)	North Chicago, IL
Gupta (031)	Olean, NY
Beckett (035)	Oklahoma City, OK
Fabre (036)	Houston, TX
Prelipceanu (101)	Romania
Boisteanu (102)	Romania
Lazarescu (103)	Romania

**TABLE 7.2.3.3:
STUDY HGHW
PATIENT DEMOGRAPHICS**

Treatment	IM Olanzapine	IM Lorazepam	IM Placebo
N	99	51	51
AGE (years)			
Mean	40.24	38.96	40.54
Range	18-79	19-60	18-67
GENDER (%)			
Male	57.6	41.2	56.9
Female	42.4	58.8	43.1
RACE (%)			
Caucasian	69.7	74.5	76.5
African	17.2	13.7	15.7
E/SE Asian	3.0	0.0	3.9
W Asian	1.0	2.0	2.0
Hispanic	7.1	7.8	2.0
Other	2.0	2.0	0.0

TABLE 7.2.3.6
STUDY HGHW
MEAN CHANGE FROM BASELINE IN THE PANSS EXCITED COMPONENT
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanzapine	98	12.96	98	-5.58	98	-8.32	98	-9.41	98	-9.60	98	-9.60
Lorazepam	51	12.39	51	-3.45	50	-5.22	51	-6.61	51	-6.75	51	-6.75
Placebo	50	12.72	50	-3.24	50	-4.32	49	-4.84	48	-5.04	50	-4.84
2-sided p-values for pairwise comparisons												
Olanz vs. Plac			0.003		<0.001		<0.001		<0.001		<0.001	
Lor vs. Plac			0.862		0.345		0.066		0.088		0.053	
Olanz vs. Lor			0.005		<0.001		<0.001		<0.001		0.001	

TABLE 7.2.3.7
STUDY HGHW
MEAN CHANGE FROM BASELINE IN THE CORRIGAN AGITATED BEHAVIOR SCALE
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanzapine	98	28.79	98	-7.34	98	-9.78	98	-11.02	98	-11.30	98	-11.30
Lorazepam	51	28.14	51	-4.35	50	-6.10	51	-8.00	51	-8.39	51	-8.39
Placebo	50	27.66	50	-3.56	50	-4.66	49	-4.98	48	-5.06	50	-4.78
2-sided p-values for pairwise comparisons												
Olanz vs. Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
Lor vs. Plac			0.535		0.199		0.009		0.007		0.003	
Olanz vs. Lor			0.003		<0.001		0.002		0.006		0.006	

TABLE 7.2.3.8
STUDY HGHW
MEAN CHANGE FROM BASELINE IN THE AGITATION-CALMNESS EVALUATION SCALE
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanzapine	98	2.24	98	+1.68	98	+2.37	98	+2.76	98	+2.90	98	+2.90
Lorazepam	51	2.33	51	+0.75	50	+1.22	51	+1.67	51	+1.88	51	+1.88
Placebo	50	2.26	50	+0.62	50	+0.94	49	+0.80	48	+0.90	50	+0.82
2-sided p-values for pairwise comparisons												
Olanz vs. Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
Lor vs. Plac			0.710		0.406		0.006		0.004		0.002	
Olanz vs. Lor			<0.001		<0.001		<0.001		<0.001		0.001	

**TABLE 7.2.4.1:
STUDY HGHX
INVESTIGATORS/LOCATIONS**

Principal Investigator (Site #)	Location
Achamallah (001)	Vallejo, CA
Bari (002)	San Diego, CA
Ferrell (006)	Concord, NH
Gordon (007)	Providence, RI
Kaplan (008)	Concord, CA
Knesevich (010)	Hampstead, NH
Kumar (011)	Venice, FL
Kwentus (012)	Madison, TN
Lantz (013)	New York, NY
Levy (014)	Staten Island, NY
Maguire (015)	Orange, CA
Mintzer (018)	North Charleston, SC
Mofsen (019)	St. Louis, MO
Parsa (023)	Cleveland, OH
Petrie (024)	Nashville, TN
Plopper (025)	La Mesa, CA
Rayner (027)	Madisonville, KY
Richter (028)	Tulsa, OK
Toups (031)	Lafayette, CA

**TABLE 7.2.4.1:
STUDY HGXX
INVESTIGATORS/LOCATIONS**

Principal Investigator (Site #)	Location
Usman (032)	Pittsburgh, PA
Verma (033)	Belmont, MA
Oxenkrug (034)	Brighton, MA
DaBiri-Beckett (036)	Oklahoma City, OK
Zubillaga (039)	New Port Richey, FL
Chenault (040)	Huntsville, AL
Prelipceanu (041)	Romania
Boisteanu (042)	Romania
Morozova (043)	Russia
Tochilov (044)	Russia
Reid (046)	Little Rock, AR
Sokolski (047)	Anaheim, CA
Figueroa (048)	San Gabriel, CA
Burdick (050)	South Miami, FL
Privitera (051)	Austin, TX
Harris (052)	Phoenix, AZ
Gheorghe (053)	Romania
Sack (054)	Cerritos, CA
Pro (055)	Kansas City, MO

**TABLE 7.2.4.3:
STUDY HGXX
PATIENT DEMOGRAPHICS**

Treatment	Olanz 2.5mg	Olanz 5mg	Lorazepam	Placebo
N	71	66	68	67
AGE (years)				
Mean	77.36	79.21	76.97	76.98
Range	54-95	56-97	55-95	56-96
GENDER (%)				
Male	43.7	34.8	36.8	40.3
Female	56.3	65.2	63.2	59.7
RACE (%)				
Caucasian	91.5	92.4	91.2	94.0
African	5.6	6.1	7.4	4.5
Hispanic	2.8	1.5	0.0	1.5
Other	0.0	0.0	1.5	0.0

TABLE 7.2.4.5
STUDY HGHX
MEAN CHANGE FROM BASELINE IN THE PANSS EXCITED COMPONENT
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanz 2.5mg	71	14.58	71	-4.90	71	-6.72	71	-7.96	71	-7.86	71	-7.86
Olanz 5mg	66	14.86	66	-5.09	66	-7.35	66	-8.41	66	-8.67	66	-8.67
Lorazepam	68	14.22	68	-3.78	68	-7.47	68	-9.12	68	-8.49	68	-8.49
Placebo	67	15.36	66	-3.29	66	-5.12	67	-6.16	67	-5.27	67	-5.27
2-sided p-values for pairwise comparisons												
Olanz 2.5mg vs. Placebo			0.075		0.121		0.104		0.024		0.024	
Olanz 5mg vs. Placebo			0.050		0.031		0.044		0.004		0.004	
Lorazepam vs. Placebo			0.477		0.012		0.004		0.004		0.004	

TABLE 7.2.4.6
STUDY HGHX
MEAN CHANGE FROM BASELINE IN THE COHEN-MANSFIELD AGITATION INVENTORY
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LCCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanz 2.5mg	71	6.44	71	-2.65	71	-3.44	71	-3.86	71	-3.77	71	-3.77
Olanz 5mg	66	6.92	66	-2.74	66	-3.61	66	-4.00	66	-3.97	66	-3.97
Lorazepam	68	6.74	68	-2.19	67	-3.78	66	-4.18	66	-4.14	68	-4.18
Placebo	67	7.81	66	-2.09	67	-2.67	67	-3.21	67	-2.78	67	-2.78
2-sided p-values for pairwise comparisons												
Olanz 2.5mg vs. Placebo			0.280		0.166		0.267		0.091		0.090	
Olanz 5mg vs. Placebo			0.227		0.098		0.185		0.047		0.047	
Lorazepam vs. Placebo			0.758		0.042		0.094		0.025		0.020	

TABLE 7.2.4.7
STUDY HGXX
MEAN CHANGE FROM BASELINE IN THE AGITATION-CALMNESS EVALUATION SCALE
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanz 2.5mg	71	2.27	71	+1.23	71	+1.55	71	+1.87	71	+1.80	71	+1.80
Olanz 5mg	66	2.17	66	+1.05	66	+1.58	66	+1.64	66	+1.88	66	+1.88
Lorazepam	68	2.16	68	+0.91	68	+1.68	68	+2.34	68	+2.19	68	+2.19
Placebo	67	2.13	66	+0.73	67	+1.06	67	+1.28	67	+1.04	67	+1.04
2-sided p-values for pairwise comparisons												
Olanz 2.5mg vs. Placebo			0.036		0.085		0.054		0.013		0.013	
Olanz 5mg vs. Placebo			0.206		0.072		0.257		0.006		0.006	
Lorazepam vs. Placebo			0.359		0.022		<0.001		<0.001		<0.001	

TABLE 7.4 SUMMARY OF EFFICACY RESULTS (significance of olanzapine/placebo comparisons for mean change from baseline to 2 hours post-first injection)							
Study	TX Group	PEC		CABS/CMAI ³⁸		ACES	
		LOCF	OC	LOCF	OC	LOCF	OC
HGHB	Olz 10	**	**	**	**	**	**
HGHV	Olz 2.5	*	*	*	NR ³⁹	ns	ns
	Olz 5	**	**	**	NR	**	**
	Olz 7.5	**	**	**	NR	**	**
	Olz 10	**	**	**	NR	**	**
HGHW	Olz 10	**	**	**	**	**	**
HGHX	Olz 2.5	*	*	tr	tr	*	*
	Olz 5	**	**	*	*	**	**

Abbreviations

Significance Codes

	p-value interval			
	HGHB	HGHV	HGHW	HGHX ⁴⁰
ns	p>0.1	p>0.025	p>0.1	p>0.1
tr	0.05<p≤0.1	0.0125<p≤0.025	0.05<p≤0.1	0.05<p≤0.1
*	0.01<p≤0.05	0.0025<p≤0.0125	0.01<p≤0.05	0.01<p≤0.05
**	p≤0.01	p≤0.0025	p≤0.01	p≤0.01

Datasets: LOCF=Last Observation Carried Forward OC=Observed Cases

Rating Instruments

PEC = PANSS Excited Component

CABS = Corrigan Agitated Behavior Scale

CMAI = Cohen-Mansfield Agitation Inventory

ACES = Agitation-Calmness Evaluation Scale

³⁸ CABS for studies HGHB, HGHV, and HGHW. CMAI for study HGHX.

³⁹ NR = Not reported but expected to be similar to the LOCF analysis.

⁴⁰ p-values for HGHX were not adjusted for multiple comparisons since only the 5mg dose group was declared as primary in the study protocol.

APPENDIX 8.0

SAFETY FINDINGS

TABLE 8.1.4.3
PLACEBO-CONTROLLED IM SAFETY DATABASE
TREATMENT-EMERGENT ADVERSE EVENTS DURING THE
INJECTABLE TREATMENT PHASE

	Percentage of Patients Reporting Adverse Event	
	IM Olanzapine (N=415)	IM Placebo (N=150)
Somnolence	5.5%	3.3%
Dizziness	4.1%	2.0%
Agitation	2.9%	8.7%
Headache	2.2%	2.0%
Hypotension	2.2%	0.0%
Insomnia	1.9%	3.3%
Asthenia	1.7%	0.7%
Anxiety	1.4%	4.0%
Dry Mouth	1.4%	0.7%
Hypertension	1.2%	1.3%
Nervousness	1.2%	1.3%
Postural Hypotension	1.2%	0.0%
Tremor	1.2%	0.0%
Akathisia	1.0%	0.0%

TABLE 8.1.5.2
CRITERIA FOR IDENTIFYING POTENTIALLY CLINICALLY SIGNIFICANT
CHANGES IN LABORATORY VALUES

Analyte	Units	Low Limit	High Limit
AST/SGOT	U/L		150
ALT/SGPT	U/L		165
CPK: Female	U/L		507
Male	U/L		594
Alkaline Phosphatase	U/L		420
GGT: Female	U/L		135
Male	U/L		195
Urea Nitrogen	mmol/L		10.71
Creatinine	μmol/L		176.8
Calcium	mmol/L	1.7465	2.994
Inorganic Phosphorous	mmol/L	0.48435	1.77595
Sodium	mmol/L	129	160
Total Protein	g/L	50	
Albumin	g/L	25	
Glucose (nonfasting)	mmol/L	2.4975	13.875
Uric Acid: Female	μmol/L		505.58
Male	μmol/L		624.54
Total Cholesterol	mmol/L		15.516
Total Bilirubin	μmol/L		34.2
Hematocrit: Female	l	0.32	0.50
Male	l	0.37	0.55
Hemoglobin: Female	mmol/L (Fe)	5.8957	10.2399
Male	mmol/L (Fe)	7.1369	11.4811
Erythrocyte Count	T/L	3	6
Leukocyte Count	G/L	2.8	16.0
Platelet Count	G/L	75	700
Neutrophils, Segmented	% WBC	15	
Eosinophils	% WBC		10
UA-Specific Gravity		1.001	1.035
UA-pH		4.6	8.0
UA-RBC			Increase ≥2 and score ≥3
UA-WBC			Increase ≥2 and score ≥3
UA-Casts, Hyaline			Increase ≥2 and score ≥3
UA-Protein			Increase ≥2 and score ≥3
UA-Ketones			Increase ≥2 and score ≥3
UA-Glucose			Increase ≥2 and score ≥3

Abbreviations: AST/SGOT = aspartate transaminase/serum glutamic oxaloacetic transaminase;
 ALT/SGPT = alanine transaminase/serum glutamic pyruvic transaminase; CPK = creatine
 phosphokinase; GGT = Gamma-glutamyl transferase; UA = urinalysis analyte.

TABLE 8.1.6.2.1 CRITERIA FOR IDENTIFYING POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS ⁴¹		
Variable	Low	High
Supine systolic BP	≤90 & ↓ ≥20	≥180 & ↑ ≥20
Standing systolic BP	≤90 & ↓ ≥20	≥180 & ↑ ≥20
Sitting systolic BP	≤90 & ↓ ≥20	≥180 & ↑ ≥20
Supine diastolic BP	≤50 & ↓ ≥15	≥105 & ↑ ≥15
Standing diastolic BP	≤50 & ↓ ≥15	≥105 & ↑ ≥15
Sitting diastolic BP	≤50 & ↓ ≥15	≥105 & ↑ ≥15
Supine pulse	<50 & ↓ ≥15	>120 & ↑ ≥15
Standing pulse	<50 & ↓ ≥15	>120 & ↑ ≥15
Sitting pulse	<50 & ↓ ≥15	>120 & ↑ ≥15
Orthostatic hypotension	≥30 ↓ in systolic BP ⁴²	---
Sitting orthostatic hypotension	≥30 ↓ in systolic BP ⁴³	---

⁴¹ Blood pressure is measured in mmHg and pulse in beats per minute.

⁴² Supine to standing (placebo-controlled IM safety database).

⁴³ Supine to sitting (geriatric study).

TABLE 8.1.6.2.3
CRITERIA FOR IDENTIFYING PATIENTS WITH COMBINATIONS OF
POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN BLOOD
PRESSURE AND PULSE

Combination of Potentially Clinically Significant Vital Signs	Indication
Supine Pulse Low and Standing Pulse Low	Supine and standing pulse rate <50 and decrease from baseline of ≥ 15 (bpm)
Supine Pulse Low and Orthostatic Systolic Blood Pressure Drop	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and ≥ 30 mmHg decrease in systolic BP (supine to standing)
ECG Heart Rate Low and Standing Pulse Low	ECG heart rate ≤ 40 bpm and standing pulse rate <50 and decrease from baseline of ≥ 15 (bpm)
ECG Heart Rate Low and Orthostatic Systolic Blood Pressure Drop	ECG heart rate ≤ 40 bpm and ≥ 30 mmHg decrease in systolic BP (supine to standing)
Supine Pulse Low and Supine Systolic Blood Pressure Low	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and supine systolic blood pressure ≤ 90 and decrease from baseline of ≥ 20 (mmHg)
Supine Pulse Low and Supine Diastolic Blood Pressure Low	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and supine diastolic blood pressure ≤ 50 and decrease from baseline of ≥ 15 (mmHg)
ECG Heart Rate Low and Supine Systolic Blood Pressure Low	ECG heart rate ≤ 40 bpm and supine systolic blood pressure ≤ 90 and decrease from baseline of ≥ 20 (mmHg)
ECG Heart Rate Low and Supine Diastolic Blood Pressure Low	ECG heart rate ≤ 40 bpm and blood pressure ≤ 50 and decrease from baseline of ≥ 15 (mmHg)

TABLE 8.1.6.2.4
OLANZAPINE-TREATED PATIENTS WITH COMBINATIONS OF
POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN
BLOOD PRESSURE AND PULSE

Study/ Subject#	Age	Sex	Preceding Dose	Event
LOAC/32	26	M	10mg PO	Supine hypotension with bradycardia, collapse
LOAC/33	24	M	10mg PO	Supine hypotension with bradycardia
LOAV/2766	35	F	5mg IM	Supine hypotension with bradycardia, sleepiness
LOAV/2843	37	M	5mg IM	Supine hypotension with bradycardia, syncope
LOAW/2	55	M	5mg IM	Orthostatic hypotension without heartrate increase, syncope
LOAW/15	47	M	5mg IM	Supine hypotension with bradycardia, dizziness
LOAT/162	29	M	12.5mg IM	Supine hypotension with bradycardia, syncope
LOAT/163	25	M	12.5mg IM	Supine hypotension with bradycardia, dizziness
LOAT/164	33	M	12.5mg IM	Supine hypotension with bradycardia, dizziness
HGHV/9090	26	M	7.5mg IM	Supine hypotension with bradycardia, dizziness

TABLE 8.1.7.2
CRITERIA FOR IDENTIFYING POTENTIALLY CLINICALLY SIGNIFICANT
ECG MEASURES

Variable	Low	High
PR	---	200 msec
QRS	---	100 msec
QT	---	450 msec
QTc	---	430 msec
Heartrate	40 bpm	120 bpm