CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-253

STATISTICAL REVIEW(S)

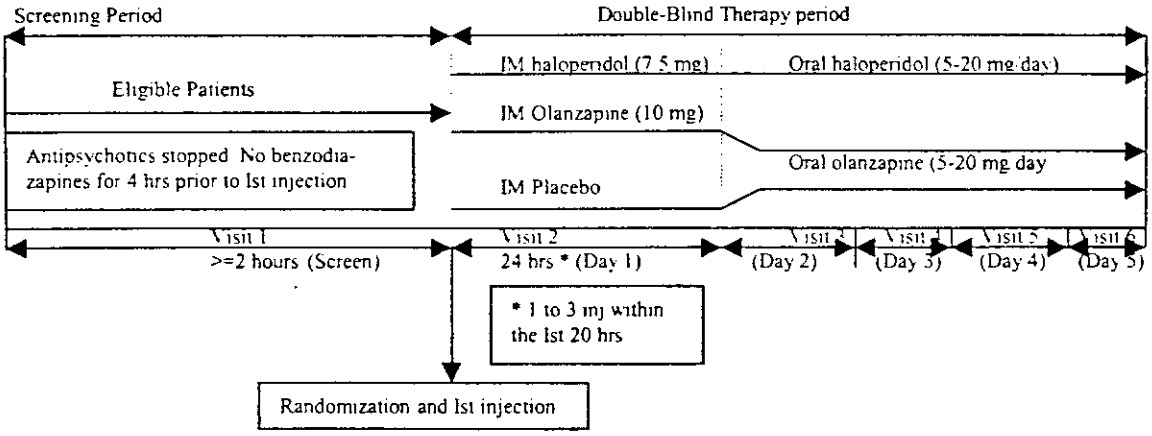

Figure 1. Illustration of Study design of F1D-MC-HGHB

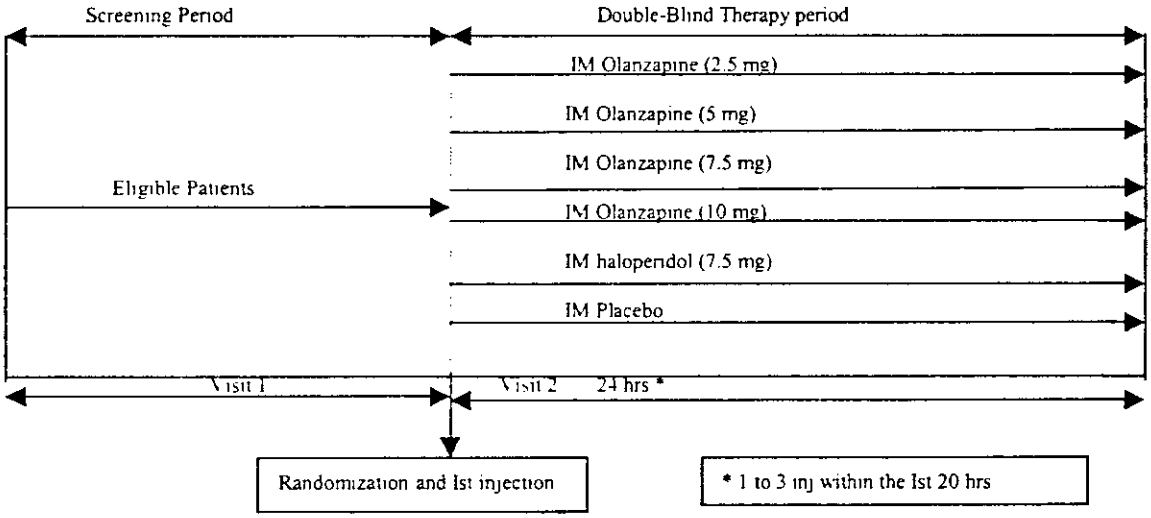

Figure 2. Illustration of Study design of F1D-MC-HGHV.

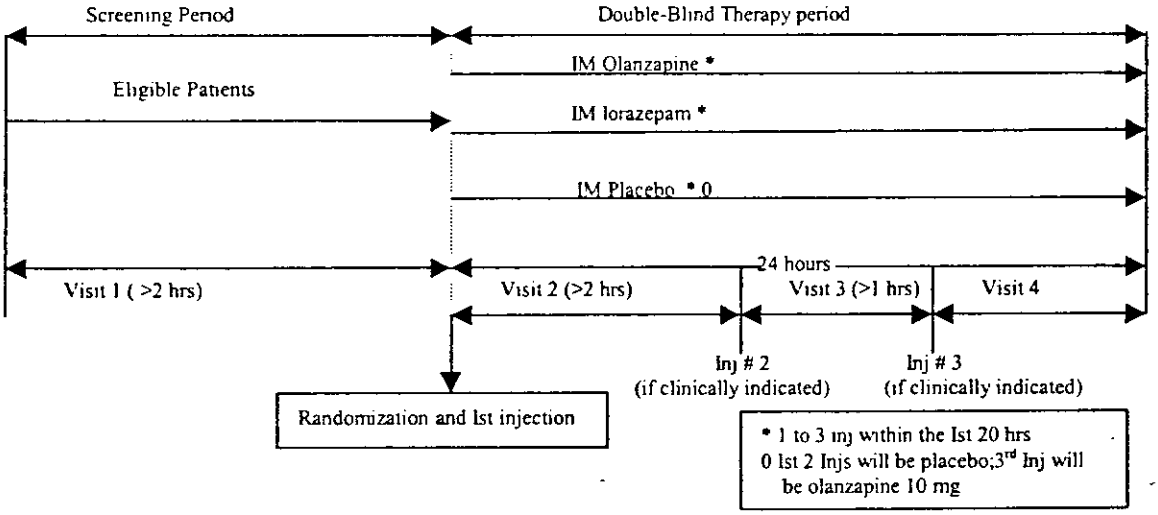

Figure 3. Illustration of Study design of F1D-MC-HGHW.

Reviewer: Ohidul Siddiqui

Statistical Review and Evaluation

NDA#	21-253
Submission Date	June 21, 2000
Due Date	April 16, 2001
Sponsor	Eli Lilly and Company
Name of Drug	Zyprexa — (Olanzapine for Injection)
Indication	For the rapid control of agitation
Documents Reviewed	The findings from the statistical analyses.

MAR 2 3 2001

Introduction

The sponsor submitted results of four randomized, double-blinded, placebo controlled pivotal studies to demonstrate the effectiveness of a new short-acting intramuscular (IM) formulation of olanzapine, ZYPREXA — (olanzapine for injection) for rapid control of agitation in three distinct patient populations (Schizophrenia, bipolar mania, and ——— ` Table 1 and Figures 1-4 list an overview of the designs of the four studies. Table 2 lists the inclusion criteria of patients in each of the four studies. Table 3 lists the primary objectives, and primary efficacy measures of each of the studies. Table 4 lists the demographic characteristics of the randomized patients by treatment group. Next, the findings of each of the four studies submitted by the sponsor will be reviewed.

Table 1: Overview of Designs of the four Primary Placebo Controlled Studies.

Study #	Study Design	Conducted site locations
F1D-MC-HGHB	A multicenter, double-blind randomized comparison of the efficacy and safety of short-acting Intramuscular Olanzapine **(10 mg)**, short-acting Intramuscular Haloperidol (7.5mg) and Intramuscular Placebo in **Patients (N=311) with Schizophrenia**. Non-inferiority of IM olanzapine to IM haloperidol	51 sites in 13 countries (Australia, Austria, Belgium, Canada, Czech Republic, France, Hungary, Greece, Israel, South Africa, Spain, UK, and US)
F1D-MC-HGHV	A double-blind **dose-response** study comparing short-acting Intramuscular Olanzapine (2.5, 5, 7.5, 10 mg), short-acting Intramuscular Haloperidol and Intramuscular Placebo on the **Patients (N=270) with Schizophrenia.**	14 sites in 4 countries (Croatia, Italy, Romania, and South Africa).
F1D-MC-HGHW	A double-blind randomized comparison of the efficacy and safety of short-acting Intramuscular Olanzapine **(10 mg)**, short-acting Intramuscular Lorazepam and Intramuscular Placebo in acutely agitated **Patients (N= 201) diagnosed with mania associated with bipolar disorder.**	30 sites in 2 countries (Romania and the US).
⌐		¬
⌊		⌋

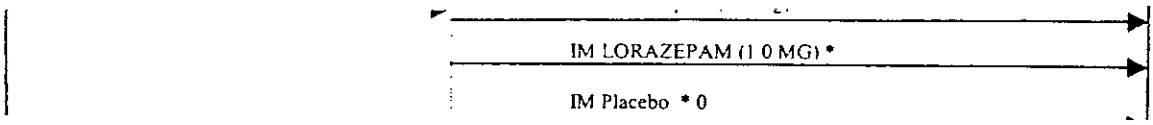

Table 2: Entry Criteria of the patients in each of the four studies.

Study F1D-MC-HGHB	Study F1D-MC-HGHV	Study F1D-MC-HGHW
Male and female inpatients 18 years and older were eligible for participation in the study. Patients had to meet diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder according to DSM-IV section 295xx, 295.40, 295.70. Patients were to have a minimum total score of >=14 on the five items of the PANSS Excited Component (poor impulse control, tension, hostility, uncooperativeness, and excitement), and at least one individual item score of >=4 using the 1 to 7 scoring system, prior first IM injection of study drug.	Same criteria as for the study F1D-MC-HGHB	Male and female inpatients 18 years and older were eligible for participation in the study. Patients had to meet diagnostic criteria for bipolar I disorder, and must have been displaying an acute manic or mixed episode (with or without psychotic features) according to DSM-IV section 296.4x, Bipolar I Disorder, Most Recent Episode Manic or 296.6x, Bipolar I Disorder, Most Recent Episode Mixed. The diagnosis was confirmed through the SCID by study completion. Patients were to have a minimum total score of >=14 on the five items of the PANSS Excited Component (poor impulse control, tension, hostility, uncooperativeness, and excitement), and at least one individual item score of >=4 using the 1 to 7 scoring system, prior first IM injection of study drug.

Table 3: Primary objectives of each of the four studies.

Study No.	Primary Objectives
F1D-MC-HGHB	1. To determine if efficacy of IM olanzapine is greater than IM placebo by comparing changes from baseline to 2 hours post first IM injection of agitation, as measured by the Positive and Negative Syndrome Scale (PANSS) Excited Component 2. To determine if efficacy of IM olanzapine is "non-inferior" to IM haloperidol by comparing changes from baseline to 2 hours post first IM injection of agitation, as measured by the PANSS Excited Component. **This objective was only for registration in Europe.**
F1D-MC-HGHV	1. To determine if efficacy of 2.5, 5, 7.5, or 10 mg of IM olanzapine is greater than IM placebo by comparing changes from baseline to 2 hours post first IM injection of agitation, as measured by the PANSS excited component.
F1D-MC-HGHW	1. To determine the efficacy of IM olanzapine, as compared to IM placebo in improving severity of agitation as measured by reductions from baseline to 2 hours post-first IM injection on the PANSS Excited Component.
[redacted]	

Table 4: Patients Characteristics by treatment groups of each of the four studies.

Study No.	Treatment Group (N)	Mean Age (years) [Range]	Mean Age at Onset	# Male (%)	Race (%)
F1D-MC-HGHB	IM OLZ (10 mg) (N=131)	38.17 [18-73]	23.53 [7-51]	85 (64.9%)	Caucasian : 95 (72.5%) African American: 24 (18.3%) Others: 12 (10%)
	IM Haloparidol 7.5 mg (N=126)	38.54 [18-71]	25.09 [10-58]	86 (68.3%)	Caucasian : 97 (77.0%) African American: 22 (17.5%) Others: 7 (5.5%)
	IM Placebo (N=54)	37.60 [19-71]	24.53 [10-46]	33 (61.1%)	Caucasian : 34 (63.0%) African American: 13 (24.1%) Others: 7 (12.9%)
F1D-MC-HGHV	IM OLZ (2.5mg) (N=48)	36.24 [19-71]	24.96 [15-42]	31 (64.6%)	Caucasian : 29 (60.4%) African American: 11 (22.91%) Others: 8 (16.7%)
	IM OLZ (5.0mg) (N=45)	35.08 [18-55]	23.91 [12-48]	27 (60%)	Caucasian : 31 (68.9%) African American: 11 (24.4%) Others: 3 (6.7%)
	IM OLZ (7.5mg) (N=46)	35.87 [20-72]	25.89 [15-52]	26 (56.5%)	Caucasian : 29 (63.0%) African American: 12 (26.1%) Others: 5 (10.9%)
	IM OLZ (10mg) (N=46)	36.73 [18-72]	25.28 [14-45]	26 (56.5%)	Caucasian : 32 (69.6%) African American: 11 (23.9%) Others: 3 (6.5%)
	IM haloparidol (7.5 mg) (N=40	37.41 [21-73]	25.90 [12-47]	22 (55.0%)	Caucasian : 25 (62.5%) African American: 12 (30.0%) Others: 3 (7.5%)
	IM Placebo (N=45)	36.65 [19-59]	24.89 [15-52]	23 (51.1%)	Caucasian : 32 (71.1%) African American: 8 (17.8%) Others: 5 (11.1%)
F1D-MC-HGHW	IM OLZ (10mg) (N=99)	40.24 [18-80]	24.59 [6-60]	57 (57.6%)	Caucasian : 69 (69.7%) African American: 17 (17.2%) Others: 13 (13.1%)
	IM LZP (2mg) (N=51)	38.96 [19-61]	22.48 [5-44]	21 (41.2%)	Caucasian : 38 (74.5%) African American: 7 (13.7%) Others: 6 (11.8%)

IM Placebo (N=51)	40.51 [18-68]	23.49 [3-59]	29 (56.9%)	Caucasian : 39 (76.5%) African American: 8 (15.7%) Others: 4 (7.9%)

Sponsor's Findings:

Study F1D-MC-HGHB:

This was a multicenter, randomized, double-blind, parallel study of inpatients meeting diagnostic criteria for schizophrenia according to DSM-IV in the clinical judgement of the investigator. Randomization was performed in a 2:2:1 ratio between the olanzapine, haloperidol, and placebo treatment groups. A total of 311 patients who met inclusion criteria (as stated in table 2) were randomized to the three treatment groups. The patients who were randomized to the olanzapine treatment group (n=131) received one to three 10-mg IM injections of olanzapine followed by treatment with oral olanzapine 5 to 20 mg per day. Patients who were randomized to the haloperidol treatment group (n=126) received one to three 7.5 mg IM injections of haloperidol followed by treatment with oral haloperidol 5 to 20 mg per day. Patients who were randomized to the placebo treatment group (n=54) received one to three IM injections of placebo followed by treatment with oral olanzapine 5 to 20 mg per day. After randomization, first injection of either 10 mg IM olanzapine, 7.5 mg IM haloperidol, or IM placebo was administered. A second injection could have been administered >2 hours after the first injection, and following completion of the 2-hours post-dose measures. An optional third injections was permitted >4 hours following the second injection, and following completion of the 4-hour post-injection measurements. Optional second/third injections had to be administered within 20 hours of the first injection. Figure 1 illustrates the study design of the trial. There was no washout period prior to enrollment into the study. During the screening period patients must not have received any antipsychotic treatment (except for benzodiazepines). Additionally, no benzodiazepines were allowed within 4 hours preceding the first injection.

The randomized patients had a mean age of 38.2 years, the majority was Caucasians (72.7%), and 65.6% were male. Table 4 lists the demographic characteristics by treatment groups. The three treatment groups were comparable with respect to their demographic characteristics. There was no evidence of any statistically significant treatment differences at baseline with respect to the primary (PANSS Excited

Component) and secondary (Corrigan Agitated Behavior Scale, PANSS-derived BPRS Total and Positive scores, CGI-S, NOSIE, and ACES) efficacy measures.

Primary efficacy criteria was the comparison of the change from baseline (pre-dose ratings recorded at the beginning of visit 2) to 2 hours post first IM injection of agitation, as measured by the PANSS Excited Component, served as the primary efficacy measure and calculated using a LOCF approach. PANSS Excited Component consisted of 5 items that rated poor impulse control, tension, hostility, uncopperativeness, and excitement.

Secondary efficacy assessments included the ABS, ACES, PANSS derived BPRS Total score, PANSS derived BPRS positive Score, OAS, CGI-S, CGI-I, and NOSIE. Changes from baseline in these scores were evaluated except for CGI-I where the endpoint score was used.

Table 3 lists the primary objectives of the study. To evaluate the first primary objective (if the efficacy of IM olanzapine was greater than IM placebo, based upon the change from baseline to 2 hours post first IM injection utilizing the PANSS Excited Component), an ANOVA model was used to evaluate the PANSS Excited Component (LOCF mean change from baseline to endpoint was assessed). The primary analysis was based on an Intent-to-treat (ITT) sample. ITT sample included the patients who were assigned to treatment groups by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. The ANOVA model initially included the terms for treatment, country, and treatment-by-country interaction as covariates and the LOCF mean change from baseline to endpoint of PANSS score as dependent measure. The treatment-by-country interaction was not statistically significant (p=.843) and was dropped from the model. There was an overall statistically significant difference between treatment groups (p<.001). Least-square means for the change from baseline were –7.74 units for IM olanzapine, –7.63 units for IM haloperidol, and –3.55 units for IM placebo. IM olanzapine showed statistically significantly greater mean improvement in the PANSS Excited Component compared with IM placebo (p<.001), the difference in the least-squares means being –4.19 units. IM haloperidol also showed statistically significantly greater mean improvement in the PANSS score compared with IM placebo (p<.001), the difference in the least square means being –4.08 units. Table 5 lists all of the statistics by treatment groups.

The study HGHB was also designed to provide comparator data for registration in Europe. A second primary objective "non-inferiority" of IM olanzapine to IM haloperidol, was assessed based upon the change from baseline to 2 hours post first IM injection utilizing the PANSS Excited Component. Since the non-inferiority objective was not for registration in US, this reviewer has not reviewed the criteria of non-inferiority and the testing procedure.

As defined a *priori* in the protocol, patients with a reduction of >=40% in the PANSS Excited Component at 2 hours post first IM injection compared to baseline were classified as responders. Ninety-six (73.3%) IM olanzapine-treated patients were responders compared to 87 (69.0%) IM haloperidol-treated patients and 18 (33.3%) IM placebo-treated patients. Using a Fisher's exact test, both the IM olanzapine and IM haloperidol treatment groups demonstrated significantly greater response rates compared with the IM placebo treatment group (p<.001 in both cases), but did not differentiate between IM olanzapine and haloperidol groups.

The survival analysis on time to response yielded an overall statistically significant difference (p<.001) between treatment groups with time to response being much shorter in the IM olanzapine and IM haloperidol treatment groups compared to IM placebo group (p<.001 in both cases). Pairwise comparison between IM olanzapine and IM haloperidol was not statistically significant (p=.092).

Both IM olanzapine and IM haloperidol showed statistically significantly greater mean improvement in the secondary efficacy measures: Corrigan Agitated Behavior Scale, PANSS-derived BPRS total, PANSS-derived BPRS Positive, and ACES compared to IM placebo. Comparisons between IM olanzapine and IM haloperidol yielded no statistically significant differences.

A few measurements were missing during the 2-hour post first IM injection period. So, the findings from the LOCF analyses were almost same as the findings from the observed case analyses.

A likelihood-based repeated measure analyses were conducted on the PANSS Excited Component, Corrigan Agitated Behavior Scale, and ACES during 2-hour post first IM injection period. For PANSS Excited Component, the overall treatment effect was statistically significant (p<.001). There was a statistically significant timepoint effect (p<.001), indicating that the scores for PANSS decreased over time. The treatment-by-timepoint interaction was statistically significant (p=.012), which indicated that the post-baseline treatment differences changed over time. The overall therapy least-square mean for IM olanzapine was 6.67 units, for IM haloperidol was 7.69 units, and for IM placebo was 10.74 units. Pairwise comparisons indicated that both IM olanzapine and IM haloperidol differed significantly from IM placebo (p<.001, in both cases).

At the 24-hour post first IM injection period, there was an overall statistically significant difference between treatment groups (p<.001). Least-squares means of PANSS Excited Component scale for the change from baseline [LOCF population] were –6.31 units for IM olanzapine, -6.50 units for IM haloperidol, and –2.91 units for IM placebo. The Least-square means for IM olanzapine and IM haloperidol groups were statistically significantly different (p<.001) as compared with the mean for placebo group. There was no statistically significant difference between IM olanzapine and IM haloperidol groups (p=.764). In addition, both IM olanzapine and IM haloperidol showed statistically significantly greater mean improvement in the Corrigan Agitated Behavior Scale, PANSS-derived BPRS Total, PANSS-derived BPRS Positive, CGI-S, and CGI-I

compared to IM placebo. No statistically significant differences in these measures were found between IM olanzapine and IM haloperidol groups. For ACES, IM haloperidol showed statistically significantly greater mean improvement compared to both IM olanzapine and IM placebo. IM olanzapine was not statistically significantly different to IM placebo.

The IM olanzapine treatment group consistently showed greater mean improvement at each timepoint (within the 2-hour post first IM injection period) on all efficacy measures compared with the IM placebo treatment group. The IM haloperidol treatment group did not differ statistically significantly to the IM placebo treatment group until the 30-minute timepoint on the PANSS Excited Component. The IM olanzapine treatment group showed greater mean improvement at the early timepoints compared to the IM haloperidol treatment group and was statistically significantly different at 15, 30, and 45 minutes ($p<.001$, $p<.001$, $p<,016$, respectively) on the PANSS Excited Component.

Subgroup analyses were performed on the change from baseline to 2-hour post first IM injection (LOCF) in the PANSS Excited Component and Corrigan Agitated Behavior Scales to examine the consistency of treatment effects over the stratum of various demographic characteristics (gender, racial origin: Caucasian, other, and age: <40 years & >=40 years). Comparisons between treatment groups within subgroups yielded consistent results to those of the overall efficacy analysis.

No formal interim analyses were planned for this study.

Table 5. Mean Change from Baseline to Endpoint (2-hour post First IM Injection period) [LOCF population].

Scale	TRT (N)	Baseline Mean	Endpoint Mean	LS Mean for change from baseline (from ANOVA model)	P-Value Vs. Placebo	P-Value Vs. Haloperidol
PANSS Excited Component	IMOLZ 10mg (131)	13.35	5.34	-7.74	<.001	.868
	IMHAL 7.5mg (126)	13.17	5.34	-7.63	<.001	--
	IM Placebo (54)	13.37	9.63	-3.55	--	--
Corrigan Agitated Behavior Scale	IMOLZ 10mg (131)	27.60	19.71	-8.25	<.001	.940
	IMHAL 7.5mg (126)	26.92	19.13	-8.20	<.001	--
	IM Placebo (54)	28.52	24.13	-4.77	--	--
PANSS-derived BPRS total	IMOLZ 10mg (122)	39.27	25.11	-13.03	<.001	.502
	IMHAL 7.5mg (125)	38.34	25.25	-12.20	<.001	--
	IM Placebo (54)	39.48	32.35	-6.41	--	--
PANSS-derived BPRS Positive	IMOLZ 10mg (122)	10.70	7.75	-2.65	.006	.654
	IMHAL 7.5mg (125)	10.72	8.00	-2.47	.016	--
	IM Placebo (54)	10.80	9.31	-1.24	--	--
Agitation-Calmness Evaluation (ACE) scale	IMOLZ 10mg (131)	2.59	4.37	1.65	<.001	.448
	IMHAL 7.5mg (126)	2.48	4.13	1.51	<.001	--
	IM Placebo (54)	2.43	3.17	.59	--	--

Extent of Exposure (Injectable Period)

The injectable treatment period of the study began at randomization (visit 2) with the first IM injection, and continued for 24 hours. After screening and upon randomization, first injection of either 10 mg olanzapine, 7.5 mg IM haloperidol, or IM placebo was administered. A second injection may have been administered at least 2 hours post IM injection and following completion of the 2-hours post-dose measures. A third IM injection may have been administered at least 4-hours following the second IM injection and following completion of the 4-hour post-dose measures. Table 6 lists the summary of injection frequency. The majority of patients received either one or two injections, 69.8% and 27.3%, respectively. The mean dose of IM olanzapine was 12.7 mg within the 24 hour IM period and the mean dose of IM haloperidol was 9.8 mg with the 24 hour IM period.

Table 6. Summary of Injection Frequency

No. of Injections	Imolz10 (N=131)	IMHal7.5 (N=126)	IM Pla (N=54)	Total (N=311)
1	100 (76.3%)	90 (71.4%)	27 (50.0%)	217 (69.8%)
2	27 (20.6%)	34 (27.0%)	24 (44.4%)	85 (27.3%)
3	4 (3.1%)	2 (1.6%)	3 (5.6%)	9 (2.9%)

Adverse Events:

Agitation was the most frequently occurring treatment-emergent adverse event reported in the injectable period. No other treatment-emergent adverse event had an incidence >=10% in any treatment group. During the injectable period, 3 patients (2 patient from IM haloperidol and 1 patient from IM olanzapine group) experienced serious adverse events. During the injectable period, 5 patients (2 patients from IM olanzapine group and 3 patients from IM haloperidol group) discontinued the study due to an adverse event. No patients died during the injectable period.

Sponsor's Final Conclusion:

IM olanzapine- and IM haloperidol-treated patients showed statistically greater improvement compared to IM placebo-treated patients for the reduction in agitation, as measured by the PANSS Excited Component at 2 hours post first IM injection. IM olanzapine showed statistically significantly greater improvement at all postbaseline timepoints compared to IM placebo, but IM haloperidol did not show a statistically significant improvement to IM placebo until 30 minutes. IM olanzapine showed statistically significant improvement to IM haloperidol at 15, 30, and 45 minutes ($p<.013$), indicating a faster onset of action. The sustained alleviation of acute agitation in IM olanzapine- and IM haloperidol-treated patients versus IM placebo-treated patients was also demonstrated at 24 hours ($p<.001$ in both cases). The study provides evidence that IM olanzapine rapidly and effectively provides a sustained and safe alleviation of acute agitation in patients with schizophrenia.

Reviewer's Analysis and comments:

This reviewer reanalyzed the data set according to the statistical plan specified in the protocol. The findings were consistent with the sponsor's reported findings. These were true for both primary and secondary outcome measures. The sponsor did not include the respective baseline measure as a covariate in the ANOVA models. This reviewer included the baseline measure as a covariate in the ANOVA model. The significance levels for the treatment effects were very close to the levels obtained in the sponsor's analyses and the conclusions were consistent with the sponsor's conclusion.

Study F1D-MC-HGHV:

This was a multicenter, randomized, double-blind, parallel study of inpatients meeting diagnostic criteria for schizophrenia according to DSM-IV in the clinical judgement of the investigator. Patients were randomized to one of six treatment groups: one of four fixed doses of olanzapine, haloperidol, or placebo treatment groups. Patients who were randomized to the olanzapine treatment groups received one to three IM injections of olanzapine 2.5, 5, 7.5, or 10 mg. Patients who were randomized to the haloperidol treatment group received one to three IM injections of 7.5 mg haloperidol. Patients who were randomized to the placebo treatment group received one to three IM injection of placebo. Randomization was performed in an equal proportion among the six treatment groups. A total of 270 patients who met inclusion criteria (as stated in table 2) were randomized to the six treatment groups. After randomization, first injection of either a fixed dose of IM olanzapine (2.5, 5, 7.5, or 10 mg), 7.5 mg IM haloperidol, or IM placebo was administered. If clinically indicated, the administration of up to two additional injections of study drug was permitted. A second injection could have been administered >2 hours after the first injection, and following completion of the 2-hours post-dose measures. An optional third injections was permitted >4 hours following the second injection, and following completion of the 4-hour post-injection measurements. Optional second/third injections had to be administered within 20 hours of the first injection. Figure 2 illustrates the study design of the trial. There was no washout period prior to enrollment into the study. During the screening period patients must not have received any antipsychotic treatment (except for benzodiazepines). Additionally, no benzodiazepines were allowed within 4 hours preceding the first injection.

The randomized patients had a mean age of 36.3 years, the majority was Caucasian (65.9%), and 57.4% were male. Table 4 lists the demographic characteristics by treatment groups. The treatment groups were comparable with respect to their demographic characteristics. There was no evidence of any statistically significant treatment differences at baseline with respect to the primary (PANSS Excited Component) and secondary (Corrigan Agitated Behavior Scale, PANSS-derived BPRS Total and Positive scores, CGI-S, NOSIE, and ACES) efficacy measures.

Primary efficacy criteria was the comparison of the change from baseline (pre-dose ratings recorded at the beginning of visit 2) to 2 hours post first IM injection of

agitation, as measured by the PANSS Excited Component, served as the primary efficacy measure and calculated using a LOCF approach. PANSS Excited Component consisted of 5 items that rated poor impulse control, tension, hostility, uncoperativeness, and excitement.

Secondary efficacy assessments included the ACES, PANSS derived BPRS Total score, PANSS derived BPRS positive Score, CGI-S, and CGI-I. Changes from baseline in these scores were evaluated except for CGI-I where the endpoint score was used.

Table 3 lists the primary objectives of the study. To evaluate the first primary objective (if the efficacy of 2.5, 5, 7.5, or 10 mg of IM olanzapine was greater than IM placebo, based upon the change from baseline to 2 hours post first IM injection utilizing the PANSS Excited Component), an ANOVA model was used to evaluate the PANSS Excited Component (LOCF mean change from baseline to endpoint was assessed). The primary analysis was based on an Intent-to-treat (ITT) sample. ITT sample included the patients who were assigned to treatment groups by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. The ANOVA model initially included the terms for treatment, country, and treatment-by-country interaction as covariates and the LOCF mean change from baseline to endpoint of PANSS score as dependent measure. The treatment-by-country interaction was not statistically significant ($p=0.135$) and was dropped from the model. There was an overall statistically significant difference between treatment groups ($p<.001$). Least-square means for the change from baseline decreased with increasing IM olanzapine dose: -5.20, -7.80, -8.42, and –8.95 units for the IM olanzapine 2.5, 5, 7.5, and 10 mg treatment groups, respectively. Least-squares means were –7.29 units for IM haloperidol, and –2.59 units for IM placebo. All IM olanzapine treatment groups showed statistically significantly greater mean improvement in the PANSS Excited Component compared with IM placebo ($p=.010$ for IM olanzapine 2.5 mg, $p<.001$ for IM olanzapine 5, 7.5, and 10 mg). Individual treatment group comparisons also revealed statistically significant difference between the IM olanzapine 2.5 mg treatment group and each of the other active treatment groups ($p<.05$). Table 7 lists all of the statistics by treatment groups.

All IM olanzapine treatment groups showed statistically significantly greater mean improvement in the secondary measures (Corrigan Agitated Behavior Scale, PANSS derived BPRS Total score, PANSS derived BPRS positive Score) when compared to IM placebo. In addition, all IM olanzapine doses, with the exception of the IM olanzapine 2.5 mg treatment group, showed a statistically significant greater mean improvement in the ACES compared to IM placebo. The differences between the IM haloperidol 7.5 mg treatment and IM placebo were also statistically significant, except for the PANSS derived BPRS Positive Score. Comparisons between IM olanzapine and IM haloperidol yielded no statistically significant differences. Table 7 lists all of the statistics by treatment groups.

A statistically significant ($p<.001$) monotonic dose response relationship was shown to exist across the IM olanzapine dose range (2.5 mg to 10 mg) as determined

from the PANSS Excited Component during the 2-hour post first IM injection period. The minimum effective IM olanzapine dose was shown to be 2.5 mg. For all secondary measures except the PANSS derived BPRS Positive score, statistically significant monotonic dose response relationships exist across the IM olanzapine dose range (2.5 mg to 10 mg).

As defined a *priori* in the protocol, patients with a reduction of >=40% in the PANSS Excited Component at 2 hours post first IM injection compared to baseline were classified as responders. The percentage of responders increased with increasing doses of olanzapine, ranging from 50% responders in the IM olanzapine 2.5 mg treatment group to 80.4% responders in the IM olanzapine 10 mg treatment group. In the IM haloperidol 7.5 mg and IM placebo groups, 60.0% and 20.0%, respectively. Were responders. Using a Fisher's exact test, statistically significantly greater response rates were observed in each IM olanzapine groups and haloperidol group compared with IM placebo. There was no statistically significant difference between IM olanzapine groups and haloperidol group.

Both IM olanzapine and IM haloperidol showed statistically significantly greater mean improvement in the secondary efficacy measures: Corrigan Agitated Behavior Scale, PANSS-derived BPRS total, PANSS-derived BPRS Positive, and ACES compared to IM placebo. Comparisons between IM olanzapine and IM haloperidol yielded no statistically significant differences.

Only two observations on each measurement scale were missing during the 2-hour post first IM injection period. So, the findings from the LOCF analyses were virtually same as the findings from the observed case analyses.

A likelihood-based repeated measure analyses were conducted on the PANSS Excited Component during 2-hour post first IM injection period. For PANSS Excited Component, the overall treatment effect was statistically significant ($p<.001$). There was a statistically significant timepoint effect ($p<.001$), indicating that the scores for PANSS decreased over time. The treatment-by-timepoint interaction was statistically significant ($p<.001$), which indicated that the post-baseline treatment differences changed over time. The overall therapy least-square mean on the PANSS Excited Component for IM olanzapine 2.5, 5.0, 7.5, and 10 mg treatment groups were 9.96, 8.47, 7.54, 7.41 units, respectively, for IM haloperidol 7.5 mg was 8.96 units, and for IM placebo was 11.89 units. Pairwise comparisons of least-squares means yielded similar conclusions to the analyses of LOCF mean change from baseline to 2 hours post first IM injection. The only exceptions were that the comparison between the IM olanzapine 2.5 mg and IM olanzapine 5 mg treatment groups, and the comparison between the IM olanzapine 2.5 mg and IM haloperidol 7.5 mg treatment groups, were not statistically significant in the likelihood based repeated measures analysis ($p=0.200$ and $p=0.052$, respectively). whereas in the LOCF analysis they were statistically significantly different ($p=0.044$ and $p=0.010$, respectively).

The IM olanzapine 5, 7.5, and 10 mg groups and haloperidol 7.5 mg group consistently showed a statistically significant difference at all timepoint (within the 2-

hour post first IM injection period) in the PANSS Excited Component, as compared with the IM placebo treatment group. For IM olanzapine 2.5 mg and haloperidol 7.5 mg the difference compared to IM placebo was not observed until 60 minutes but was maintained until 120 minutes.

At the 24-hour post first IM injection period, there was an overall statistically significant difference in the PANSS Excited Component score among the treatment groups (p=.033). Least-squares means of PANSS Excited Component scale for the change from baseline [LOCF population] were –4.97, -5.59, -5.50, and –5.92 units for IM olanzapine 2.5, 5, 7.5, and 10 mg, respectively, and -4.50 units for IM haloperidol, and –3.13 units for IM placebo. The Least-square means for the IM olanzapine and IM haloperidol groups were statistically significantly different as compared with the mean for placebo group.

Subgroup analyses were performed on the change from baseline to 2-hour post first IM injection (LOCF) in the PANSS Excited Component and Corrigan Agitated Behavior Scales to examine the consistency of treatment effects over the stratum of various demographic characteristics (gender, racial origin: Caucasian, other, and age: <40 years & >=40 years). Comparisons between treatment groups within subgroups yielded consistent results to those of the overall efficacy analysis.

No formal interim analyses were planned for this study.

Table 7. Mean Change from Baseline to Endpoint (2-hour post First IM Injection period) [LOCF population].

Scale	TRT (N)	Baseline Mean	Endpoint Mean	LS Mean for change from baseline (from ANOVA model)	P-Value Vs. Placebo	P-Value Vs. Haloperidol
PANSS Excited Component	IMOLZ 2.5 mg (48)	13.25	7.75	-5.20	.010	.044
	IMOLZ 5 mg (45)	14.71	6.62	-7.80	<.001	.062
	IMOLZ 7.5 mg (46)	13.85	5.20	-8.42	<.001	.0284
	IMOLZ 10 mg (46)	14.30	4.96	-8.95	<.001	.115
	IMHAL 7.5 mg (40)	14.28	6.75	-7.29	<.001	--
	IM Placebo (45)	13.78	10.87	-2.59	--	--
Corrigan Agitated Behavior Scale	IMOLZ 2.5 mg (48)	29.27	23.46	-5.73	.012	.113
	IMOLZ 5 mg (45)	31.38	22.42	-8.86	<.001	.276
	IMOLZ 7.5 mg (46)	31.24	20.74	-10.43	<.001	.016
	IMOLZ 10 mg (46)	30.76	20.37	-10.25	<.001	.023
	IMHAL 7.5 mg (40)	30.13	22.44	-7.58	<.001	--
	IM Placebo (45)	29.98	26.98	-2.91	--	--
PANSS-derived BPRS total	IMOLZ 2.5 mg (48)	35.96	27.73	-7.91	.002	.469
	IMOLZ 5 mg (45)	40.04	29.62	-10.16	<.001	.455
	IMOLZ 7.5 mg (46)	37.78	25.74	-11.80	<.001	.068
	IMOLZ 10 mg (46)	37.74	25.72	-11.65	<.001	.084
	IMHAL 7.5 mg (40)	37.64	28.41	-9.01	<.001	--
	IM Placebo (45)	35.53	31.80	-3.39	--	--
PANSS-derived BPRS Positive	IMOLZ 2.5 mg (48)	11.40	9.90	-1.45	.037	.955
	IMOLZ 5 mg (45)	13.02	11.31	-1.68	.013	.635
	IMOLZ 7.5 mg (46)	12.43	10.30	-2.09	.001	.213
	IMOLZ 10 mg (46)	12.57	10.70	-1.82	.006	.455
	IMHAL 7.5 mg (40)	11.97	10.54	-1.42	.054	--

	IM Placebo (45)	11.27	10.84	-0.37	--	--
Agitation-Calmness Evaluation (ACE) scale	IMOLZ 2.5 mg (48)	2.42	3.69	1.19	.064	.119
	IMOLZ 5 mg (45)	2.18	4.49	2.23	< 001	.113
	IMOLZ 7.5 mg (46)	2.26	4.63	2.30	< 001	.068
	IMOLZ 10 mg (46)	2.26	4.83	2.44	<.001	.025
	IMHAL 7.5 mg (40)	2.15	3.93	1.70	< 001	--
	IM Placebo (45)	2.38	3.07	0.60	--	--

Extent of Exposure (Injectable Period)

The injectable treatment period of the study began at randomization (visit 2) with the first IM injection, and continued for 24 hours. After screening and upon randomization, first injection of either 2.5, 5.0, 7.5, 10 mg olanzapine, 7.5 mg IM haloperidol, or IM placebo was administered. A second injection may have been administered at least 2 hours post IM injection and following completion of the 2-hours post-dose measures. A third IM injection may have been administered at least 4-hours following the second IM injection and following completion of the 4-hour post-dose measures. Table 8 lists the summary of injection frequency. The majority of patients received either one or two injections, 61.1% and 27.8%, respectively. The mean dose of IM olanzapine 2.5, 5.0, 7.5, and 10 mg groups were 4.0, 6.9, 9.8, and 12.6 mg, respectively, within the 24 hour IM period and the mean dose of IM haloperidol was 9.9 mg with the 24 hour IM period.

Table 8. Summary of Injection Frequency

No. of Injections	IMOLZ 2.5 (N=48)	IMOLZ 5.0 (N=45)	IMOLZ 7.5 (N=46)	IMOLZ 10.0 (N=46)	IMHAL 7.5 (N=40)	IMPla (N=45)	Total (N=270)
1	23 (47.9%)	29 (64.4%)	33 (71.7%)	35 (76.1%)	30 (75.0%)	15 (33.3%)	165 (61.1%)
2	22 (45.8%)	15 (33.3%)	12 (26.1%)	10 (21.7%)	7 (17.5%)	9 (20.0%)	75 (27.8%)
3	3 (6.3%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	3 (7.5%)	21 (46.7%)	30 (11.1%)

Adverse Events:

During the injectable period , a total of 36 patients experienced at least one treatment-emergent adverse event; there was no statistically significant difference between treatment groups (p=0.900). The most frequently reported event was hypertension (7 patients, 2.6%), followed by dizziness and tremor (each event experienced by 5 patients, 1.9%). There was no deaths, discontinuations due to adverse events, or serious and unexpected possibly causally related events.

Sponsor's Final Conclusion:

As measured by the PANSS Excited Component at 2 hours post first IM injection, IM olanzapine in the dose range 2.5 to 10 mg per injection and IM haloperidol was statistically superior to placebo in reducing agitation at 2 hours after injection, and a dose response relationship was present across the olanzapine dose range. IM olanzapine in the dose range 5 to 10 mg per injection was statistically superior to placebo 30 minutes after injection while IM olanzapine 2.5 mg did not separate from placebo until 60 minutes after injection.

Reviewer's Analysis and comments:

This reviewer reanalyzed the data set according to the statistical plan specified in the protocol. The findings were consistent with the sponsor's reported findings. These were true for both primary and secondary outcome measures. The sponsor did not include the respective baseline measure as a covariate in the ANOVA models. This reviewer included the baseline measure as a covariate in the ANOVA model. The significance levels for the treatment effects were very close to the levels obtained in the sponsor's analyses and the conclusions were consistent with the sponsor's conclusion .

Study F1D-MC-HGHW:

This was a multicenter, randomized, double-blind, parallel study of inpatients meeting diagnostic criteria for bipolar I disorder and currently displaying an acute manic or mixed episode according to DSM-IV in the clinical judgement of the investigator. Randomization was performed in a 2:1:1 ratio into 3 treatment groups: IM olanzapine, IM lorazepam, or IM placebo. A total of 201 patients who met inclusion criteria (as stated in table 2) were randomized to the three treatment groups. The patients who were randomized to the IM olanzapine (n=99) received 1 to 3 IM injections of olanzapine, based on the clinical judgment of the investigator. The first and second IM injections of olanzapine were 10 mg/injection; the third IM injection was 5 mg. Patients who were randomized to receive IM lorazepam (n=51) received from1 to 3 injections of lorazepam. The first and second IM injections of lorazepam were 2 mg/injection; the third IM injection was 1 mg. Patients randomized to receive placebo (n=51) received from 1 to 3 IM injections. The first and second IM injections were placebo; the third injection was olanzapine 10 mg. After randomization, first injection was administered. A second injection could have been administered >2 hours after the first injection, and following completion of the 2-hours post-dose measures. An optional third injections was permitted >=1 hours following the second injection. Optional second/third injections had to be administered within 20 hours of the first injection. Figure 3 illustrates the study design of the trial. The patient's current medication for mood stabilization (if either lithium or valproate) was permitted to be continued, however, dosage adjustments were not permitted during the study period. There were 46 patients (46.5%) in the IM olanzapine, 20 patients (39.2%) in the IM lorazepam, and 27 patients (52.9%) in the IM placebo were being prescribed at least one mood stabilizer (lithium or valproate) or other medication used as a mood stabilizer at study entry. There was no statistically significant differences between treatment groups (p=0.404).

The randomized patients had a mean age of 40 years, the majority was Caucasian (72.6%) or African descent (15.9%), and 53.2% were male. Table 4 lists the demographic characteristics by treatment groups. The three treatment groups were comparable with respect to their physical characteristics. There was no evidence of any statistically significant treatment differences at baseline with respect to the primary (PANSS Excited Component) and secondary (Corrigan Agitated Behavior Scale, PANSS-derived BPRS Total and Positive scores, CGI-S, Y-MRS, and ACES) efficacy measures.

Primary efficacy criteria was the comparison of the change from baseline (pre-dose ratings recorded at the beginning of visit 2) to 2 hours post first IM injection of agitation, as measured by the PANSS Excited Component, served as the primary efficacy measure and calculated using a LOCF approach. PANSS Excited Component consisted of 5 items that rated poor impulse control, tension, hostility, uncopperativeness, and excitement.

Secondary efficacy assessments included the Corrigan Agitated Behavior Scale, ACES, PANSS derived BPRS Total score, PANSS derived BPRS positive Score, Y-MARS, and CGI-S. Changes from baseline in these scores were evaluated.

Table 3 lists the primary objective of the study. To evaluate the primary objective (if the efficacy of IM olanzapine was greater than the efficacy of IM placebo in improving severity of agitation as measured by reductions from baseline to 2 hours post-first IM injection on the PANSS Excited Component), an ANOVA model was used to evaluate the PANSS Excited Component (LOCF mean change from baseline to endpoint was assessed). The primary analysis was based on an Intent-to-treat (ITT) sample. ITT sample included the patients who were assigned to treatment groups by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. The ANOVA model initially included the terms for treatment, country, and treatment-by-country interaction as covariates and the LOCF mean change from baseline to endpoint of PANSS score as dependent measure. The treatment-by-country interaction was not statistically significant ($p=0.362$) and was dropped from the model. There was an overall statistically significant difference between treatment groups ($p<.001$). Least-square means for the change from baseline were –8.98 units for IM olanzapine, –6.08 units for IM lorazepam, and –4.20 units for IM placebo. IM olanzapine showed statistically significantly greater mean improvement in the PANSS Excited Component compared with IM placebo ($p<.001$), the difference in the least-squares means being –4.78 units. IM olanzapine also showed statistically significantly greater mean improvement in the PANSS Excited Component compared with IM lorazepam ($p=.001$), the difference in the least-squares means being –2.90 units. IM lorazepam showed greater mean improvement in the PANSS score compared with IM placebo ($p<.053$), the difference in the least square means being –1.88 units. Table 9 lists all of the statistics by treatment groups.

As defined a priori in the protocol, patients with a reduction of >=40% in the PANSS Excited Component at 2 hours post first IM injection compared to baseline were classified as responders. Seventy nine (80.6%) IM olanzapine-treated patients were responders compared to 33 (64.7%) IM lorazepam-treated patients and 22 (44.0%) IM placebo-treated patients. Using a Fisher's exact test, both the IM olanzapine and IM lorazepam treatment groups demonstrated significantly greater response rates compared with the IM placebo treatment group ($p<.001$ and $p=.046$, respectively. The IM olanzapine group also showed a significantly greater response rate compared with the IM lorazepam group ($p=.045$).

The survival analysis on time to response yielded an overall statistically significant difference (p<.001) between treatment groups with time to response being much shorter in the IM olanzapine treatment group compared to IM placebo group (p<.001). Pairwise comparison between IM olanzapine and IM lorazepam groups also yielded a statistically significant difference in time to response (p<.001). There were 48 (50.0%) patients who had responded at 30 minutes in the IM olanzapine group compared to 18 (35.5%) patients in the IM lorazepam group, and 14 (28.0%) in the IM placebo group.

Both IM olanzapine- and IM lorazepam-treated patients showed statistically significantly greater mean improvement in the secondary efficacy measures: Corrigan Agitated Behavior Scale (p<.003), and ACES (p<.002) compared to IM placebo-treated patients. IM olanzapine-treated patients showed statistically significantly greater mean improvement in the PANSS-derived BPRS total score (p<.0010 and PANSS-derived BPRS positive subscore (p=.002) compared to IM placebo-treated patients. Comparisons between the IM olanzapine and IM lorazepam treatment groups showed statistically significantly greater improvement in the IM olanzapine treatment group in the PANSS-derived BPRS total score (p=.001), Corrigan Agitated Behavior Scale (p=.006), and ACES (p=.001).

A few measurements were missing during the 2-hour post first IM injection period. So, the findings from the LOCF analyses were almost same as the findings from the observed case analyses.

A likelihood-based repeated measure analyses were conducted on the PANSS Excited Component, Corrigan Agitated Behavior Scale, and ACES during 2-hour post first IM injection period. For PANSS Excited Component, the overall treatment effect was statistically significant (p<.001). There was a statistically significant timepoint effect (p<.001), indicating that the scores for PANSS decreased over time. The treatment-by-timepoint interaction was statistically significant (p=.07), which indicated that the post-baseline treatment differences changed over time. The overall therapy least-square mean for IM olanzapine group was 5.83 units, for IM lorazepam group it was 8.38 units, and for IM placebo group it was 9.66 units. Pairwise comparisons indicated that the IM olanzapine group differed significantly from both IM placebo and IM lorazepam groups (p<.001, in both cases). Similar conclusions were also found from the repeated measure analyses on the Corrigan Agitated Behavior Scale and ACES measures.

At the 24-hour post first IM injection period, the overall treatment difference was not statistically significant (p<.069), however, IM olanzapine-treated patients continued to show statistically significantly (p=.025) greater mean improvement in PANSS Excited Component scale compared with IM placebo-treated patients. There was no statistically significant difference between IM olanzapine and IM lorazepam groups (p=.808), as well as between IM lorazepam and IM placebo groups (p=.080). Both IM olanzapine and IM lorazepam groups showed statistically significantly greater mean improvement in the Corrigan Agitated Behavior Scale (p<.010), and ACES (p<.005) compared to IM placebo. IM olanzapine group showed statistically significantly greater mean

improvement in the PANSS-derived BPRS total score(p=.008) and PANSS-derived BPRS positive subscore (p=.011) compared to IM placebo group. There were no overall statistically significant differences observed among treatment groups in the CGI-S and Y-MRS. Comparisons between the IM olanzapine and IM lorazepam groups yielded no statistically significant differences in the these measures

The IM olanzapine treatment group consistently showed greater mean improvement at each timepoint (within the 2-hour post first IM injection period) on the PANSS Excited Component compared with the IM placebo treatment group. The IM lorazepam treatment group did not differ statistically significantly to the IM placebo treatment group at any time point on the PANSS Excited Component. The IM olanzapine treatment group showed statistically significantly (p<.002) greater mean improvement at each timepoint compared to the IM lorazepam treatment group on the PANSS Excited Component.

Subgroup analyses were performed on the change from baseline to 2-hour post first IM injection (LOCF) in the PANSS Excited Component and Corrigan Agitated Behavior Scales to examine the consistency of treatment effects over the stratum of various demographic characteristics (gender, racial origin: Caucasian, other, and age: <40 years & >=40 years). Comparisons between treatment groups within subgroups yielded consistent results to those of the overall efficacy analysis. Similar findings were also obtained from the subgroup analyses based on the change from baseline to 24-hour post first IM injection.

No formal interim analyses were planned for this study.

Table 9. Mean Change from Baseline to Endpoint (2-hour post First IM Injection period) [LOCF population].

Scale	Treatment group (N)	Baseline Mean	Endpoint Mean	LS Mean for change from baseline (from ANOVA model)	P-Value Vs. Placebo	P-Value Vs. lorazepam
PANSS Excited Component	IMOLZ 10mg (98)	12 96	3.36	-8.98	<.001	0.001
	IMLZP 2.0mg (51)	12 39	5.65	-6 08	0.053	--
	IM Placebo (50)	12.72	7.88	-4.20	--	--
Corrigan Agitated Behavior Scale	IMOLZ 10mg (98)	28 79	17.49	-11.21	< 001	0 006
	IMLZP 2.0mg (51)	28.14	19.75	-8.30	0.003	--
	IM Placebo (50)	27.66	22.88	-4 69	--	--
PANSS-derived BPRS total	IMOLZ 10mg (95)	30.58	13.28	-14.23	<0 001	0.001
	IMLZP 2.0mg (51)	29.24	17.59	-8.34	0.232	--
	IM Placebo (48)	28.75	19.67	-5.94	--	--
PANSS-derived BPRS Positive	IMOLZ 10mg (95)	6 83	3.35	-2 46	0 002	0.056
	IMLZP 2.0mg (51)	6.43	4.02	-1.30	0.280	--
	IM Placebo (48)	6.04	4.44	-0.55	--	--
Agitation-Calmness Evaluation (ACE) scale	IMOLZ 10mg (98)	2.24	5.14	2.84	<.001	0 001
	IMLZP 2.0mg (51)	2.33	4.44	1.82	0.002	
	IM Placebo (50)	2.26	3.08	0.76	--	

Extent of Exposure (Injectable Period)

The injectable treatment period of the study began at randomization (visit 2) with the first IM injection, and continued for 24 hours. After screening and upon randomization, first injection of either 10 mg olanzapine, 2 mg IM lorazepam, or IM placebo was administered. A second injection may have been administered at least 2 hours post IM injection and following completion of the 2-hours post-dose measures. A third IM injection may have been administered at least 1-hours following the second IM injection. Table 10 lists the summary of injection frequency. The majority of patients received either one or two injections, 60.2% and 18.9%, respectively. The mean dose of IM olanzapine was 13.0 mg within the 24 hour IM period and the mean dose of IM lorazepam was 3.3 mg with the 24 hour IM period.
Table 10. Summary of Injection Frequency

No. of Injections	Imolz10 (N=99)	IMLZp 2.0 (N=51)	IM Pla (N=51)	Total (N=201)
1	73 (73.7%)	24 (47.1%)	24 (47.1%)	121 (60.2%)
2	18 (18.2%)	14 (27.5%)	6 (11.8%)	38 (18.9%)
3	8 (8.1%)	13 (25.5%)	31 (41.2%)	42 (20.9%)

Adverse Events:

Somnolence was the most frequently occurring treatment-emergent adverse event reported in the 24-hour post first IM injection period, with an incidence of 13.1% in the IM olanzapine group, 9.8% in the IM lorazepam group, and 5.9% in the placebo group Dizziness had an incidence of 9.1% in the IM olanzapine group, 13.7% in the lorazepam group, and 2.0% in placebo group. No other treatment-emergent adverse event had an incidence >=10% in any treatment group. During the injectable period, two placebo-treated patient who received a third injection of olanzapine 10 mg experienced adverse event, and discontinued from the study. No patients died during the study.

Sponsor's Final Conclusion:

IM olanzapine-treated patients showed statistically greater improvement compared to IM placebo-treated patients for the reduction in agitation at 2 hours post first IM injection. IM olanzapine-treated patients also showed that (i) IM olanzapine reduced agitation more rapidly than IM lorazepam; (ii) a significantly greater proportion of patients responded to IM olanzapine than IM lorazepam and IM placebo. IM olanzapine showed statistically significantly greater improvement at all postbaseline timepoints compared to IM placebo. But IM lorazepam did not show a statistically significant improvement to IM placebo at any time points within 2-hour post first injection. The study provides evidence that IM olanzapine rapidly and effectively provides a sustained and safe alleviation of acute agitation in patients with bipolar I disorder with a current manic or mixed episode.

Reviewer's Analysis and comments:

This reviewer reanalyzed the data set according to the statistical plan specified in the protocol. The findings were consistent with the sponsor's reported findings. These were true for both primary and secondary outcome measures. The sponsor did not include the respective baseline measure as a covariate in the ANOVA models. This reviewer included the baseline measure as a covariate in the ANOVA model. The significance levels for the treatment effects were very close to the levels obtained in the sponsor's analyses and the conclusions were consistent with the sponsor's conclusion.

[redacted]

4 page(s) have been
removed because it
contains
trade secret
and/or
confidential information
that is not disclosable

Reviewer's Overall Conclusion:

In this new drug application, the sponsor submitted four randomized trials' results to support the efficacy of IM olanzapine in the rapid control of agitation. The sponsor designed the trials and analyzed the data sets accordingly as specified in the protocols. Two of the four studies (HGHB, HGHV) were conducted with the intention to demonstrate the efficacy of IM olanzapine in agitated patients with schizophrenia and related psychoses (schizophrenia, schizoaffective disorder and schizophreniform disorder). Third study (HGHW) was conducted in agitated patients with bipolar I disorder mixed or manic episode. [redacted]. The primary analysis in each of the four studies was the mean change from baseline to endpoint in the PANSS Excited Component at 2 hours post first IM injection. The primary analyses showed that IM olanzapine was statistically significantly efficacious as compared to placebo in controlling agitation within 2 hours. In study HGHV (during the 2-hour post first IM injection period), a statistically significant dose response relationship was also shown to exist across all IM olanzapine dose range of 2.5 to 10 mg. The findings from the four studies confirm that IM olanzapine is effective in the rapid control of agitation across different disease states.

Ohidul Siddiqui, Ph.D
Mathematical Statistician

Concur: Dr. Kun Jin

Dr. George Chi

CC:
Arch NDA # 21-253
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Dubitsky
HFD-120/Mr. Hardeman
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Siddiqui
HFD-710/Chron