CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-173

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review
PHARMACOMETRIC REVIEW

PRODUCT (Generic Name):	Olanzapine Pamoate
PRODUCT (Brand Name):	ZYPREXA
DOSAGE FORM:	Long-acting Injection
DOSAGE STRENGTHS:	150 mg/2 wks, 300 mg/4 wks, 210 mg/2 wks, 405 mg/4 wks, 300 mg/2 wks
NDA:	22173
NDA TYPE:	New NDA
SUBMISSION DATE:	March 11, 2009
SPONSOR:	Eli Lilly
REVIEWER	Andre Jackson

REVIEW OF A NEW LONG ACTING INJECTION OF OLANZAPINE PAMOATE SIMULATION AND CHANGES IN DOSING RECOMMENDATIONS

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PURPOSE OF REVIEW

The purpose of this review is to address the following key question.

Can we support the firm's proposed use of a loading dose for the depot administration of Zyprexa?

The firm's recommendation is to institute a loading dose over an 8 week period that would be specifically based upon the prior oral maintenance dose. After the 8 week loading dose, maintenance doses would be the same as recommended in the original NDA. The concern is that the loading dose was obtained from dosing based upon the average efficacy results of before and after 8 weeks of maintenance dosing with simulated plasma levels as supportive evidence. Firm's proposed dosing recommendations:

Target Oral ZYPREXA Dose	Dosing of ZYPREXA RELPREVV During the First 8 Weeks	Maintenance Dose After 8 Weeks of ZYPREXA RELPREVV Treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

The expected exposures during the loading dose period are dose and administration time dependent.

The label is supported by the data that all of the proposed OP (Olanzapine Pamoate) loading doses (300 mg/2weeks, 405 mg/4 weeks, and 210 mg/2 weeks) showed positive maintenance of effect over 24 weeks for stabilized patients with schizophrenia in study HGKA when they were administered as the maintenance doses. Figures 1 and 2 show the plasma concentrations for the 10 mg oral and 15 mg oral dose transition to OP injections at the different loading doses.

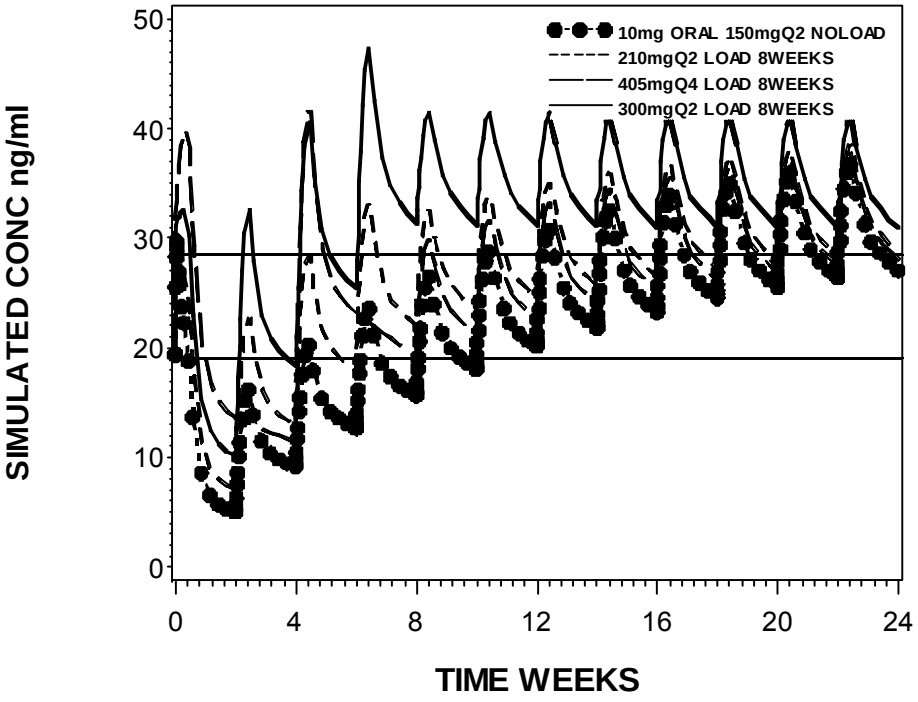


Figure 1. Simulated median olanzapine concentrations for switching from 10 mg oral dose to 150mg Q2(every two weeks) maintenance depot injection without and with loading doses of 210mgQ2, 405mgQ4 and 300mgQ2. The horizontal upper and lower lines represent the median steady state Cmax and Cmin values, respectively for the 10 mg oral dose.

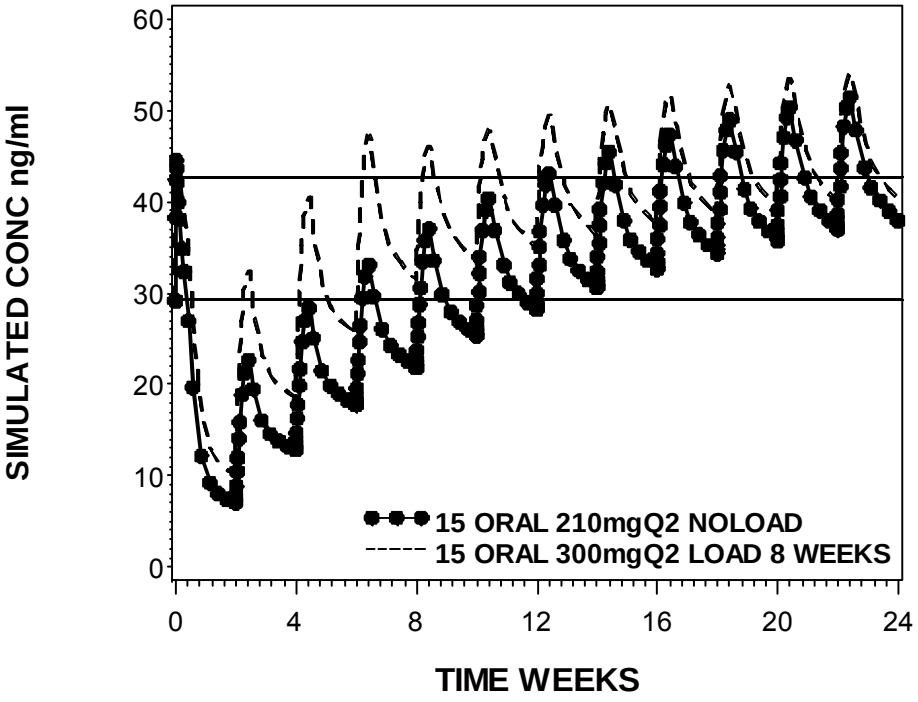


Figure 2. Simulated median olanzapine concentrations for switching from 15 mg oral dose to 210mg Q2 (every two weeks) maintenance depot injection without and with a 300 mg Q2 loading dose. The horizontal upper and lower lines represent the median steady state Cmax and Cmin values, respectively for the 15 mg oral dose.

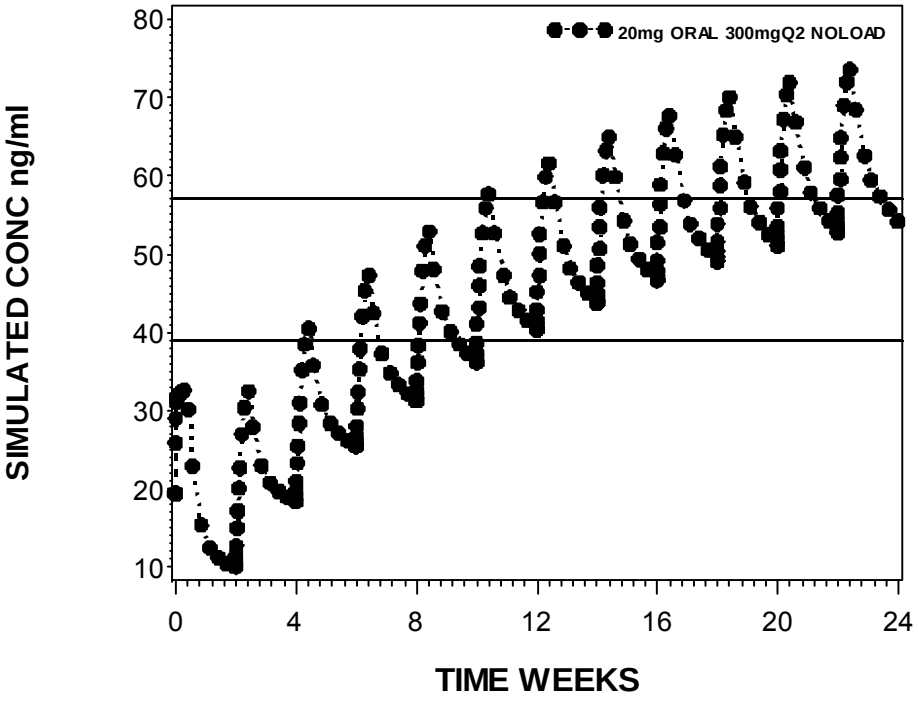


Figure 3. Simulated median olanzapine concentrations for switching from 20 mg oral dose to 300mg Q2(every two weeks) maintenance depot injection without a loading dose. The horizontal upper and lower lines represent the steady state median Cmax and Cmin values, respectively for the 20 mg oral dose.

Graphs for the other proposed loading dose-maintenance dose combinations in individual subjects are presented on pages 33-40 of this review.

COMMENTS

1. Figure 1 and Figure 2 for the 10 mg oral to 150 mg Q2 maintenance dosing with 8 week loading doses of 210mgQ2, 405mgQ4 or 300mgQ2 shows that dose 1 for the 300mgQ2 dose has less initial exposure than the 405mgQ4. The 300mg Q2 loading dose also moves the exposure within the median Cmax and median Cmin for the 10 mg oral dose range by the second dose with a higher exposure than obtained with the 405mg Q4 loading dose.
2. The firm's loading dose recommendations were based on the overall efficacy not based on a period of 8 weeks.

COMMENTS TO THE SPONSOR

The complete response letter dated 12/15/08 from FDA contained a comment from the Office of Clinical Pharmacology requesting that Lilly adopt the following dissolution method and specifications:

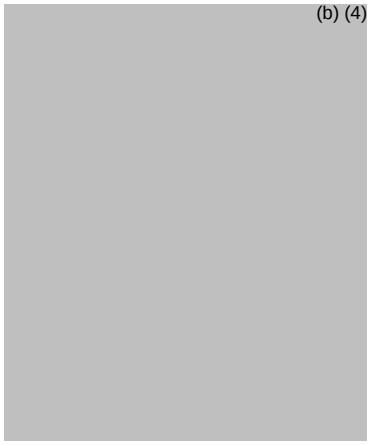
We request you adopt the following dissolution method and specifications-

1% Sodium Lauryl Sulfate in USP buffer pH 6.8 medium using USP Apparatus 4 (or Ph.Eur.2.9.3 Flow-Through Apparatus) at 3 ml/min flow rate.

210 mg:
%released at 30 min
% released at 2 hrs
% released at 8 hrs

300 mg:
%released at 30 min
% released at 2 hrs
% released at 8 hrs

405 mg:
%released at 30 min
% released at 2 hrs
% released at 8 hrs



The firm has replied in a letter to FDA dated March 11, 2009 in which they have **agreed** to adopt the OCP proposed dissolution method and specifications for Olanzapine Pamoate injection.

RECOMMENDATIONS

Even though OCP does not agree that the proposed loading dose strategy can maintain the efficacy during the loading period for all oral dose levels, higher loading doses cannot be recommended for the 15mg and 20 mg oral dose levels due to potential safety concerns. Therefore, OCP believes that the proposed loading dose regimen should have better efficacy compared to a regimen without a loading dose. However, based upon the efficacy analysis during the loading period (first 8 weeks) and pharmacokinetic simulations, OCP would recommend that the 300 mgQ2 dose be used as the loading dose for all levels of oral doses. Post injection delirium/sedation syndrome data also show a lower incidence (0.07%) for the 300 mg/2 week regimen compared to the 405 mg/4 weeks regimen (0.13%).

LABEL STATEMENTS

The FDA is proposing the following language for labeling.

Target Oral ZYPREXA Dose	Dosing of ZYPREXA RELPREVV During the First 8 Weeks	Maintenance Dose After 8 Weeks of ZYPREXA RELPREVV Treatment
10 mg/day	300mg/2 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300mg/2 weeks	300mg/2 weeks

REGULATORY BACKGROUND:

The firm submitted an original application on April 27, 2007 for long acting olanzapine. The proposed dosage strengths and regimens were: 150 mg/2 wks; 300 mg/4 wks; 210 mg /2wks; 405 mg/4 wks. The firm has completed simulations presented in a report located at: \\Cdsnas\pharmacometrics\Zyprexa_NDA22173_AJ\Sponsor Data and Reports\Dosingsimul_ As a result of these simulations the firm is proposing to use a loading dose.

The firm's original recommendation for starting doses were:

(b) (4)

The total dosing recommendations were:

Table 1: Recommended Dosing For Patients Taking Oral ZYPREXA Switching to ZYPREXA Relprev

Target Oral ZYPREXA Dose	Approximate Corresponding Dose of ZYPREXA RELPREVV*
10 mg/day	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks

Subsequent to this submission the firm has re-evaluated Study F1D-MC-HGKA (HGKA) data on the relative risks of exacerbation in each OP Depot group versus the oral olanzapine group and versus a low-dose OP Depot group.

The principal evidence to support the loading dose strategy derives from controlled switching data in Study HGKA in which patients were required to demonstrate clinical stability on a given oral olanzapine dose and were then randomized to a fixed OP Depot dose or to remain on their fixed oral dose.

Table 2: Firm's Recommended Dosing For Patients Taking Oral ZYPREXA Switching to OP depot ZYPREXA

Target Oral ZYPREXA Dose	Dosing of ZYPREXA RELPREVV During the First 8 Weeks	Maintenance Dose After 8 Weeks of ZYPREXA RELPREVV Treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

The steady state maintenance dose recommendations have not changed. The proposed doses have been previously studied. The maintenance dose column heading was also changed to 8 weeks to correspond to the loading dose period.

Based upon the simulated data the initial exposure would be considerably higher for the first 8 weeks.

RESULTS OF SPONSOR'S ANALYSIS

The firm's original population pharmacokinetic report was not reviewed since it did not present any insight into the major problem with the NDA i.e., excessive sedation which is now called PDSS (Post-injection Delirium/Sedation Syndrome) by the firm.

Since the firm has presented graphical information based upon simulations to show plasma levels during the switch from oral to depot injections, the population pharmacokinetic model was reviewed as part of this submission.

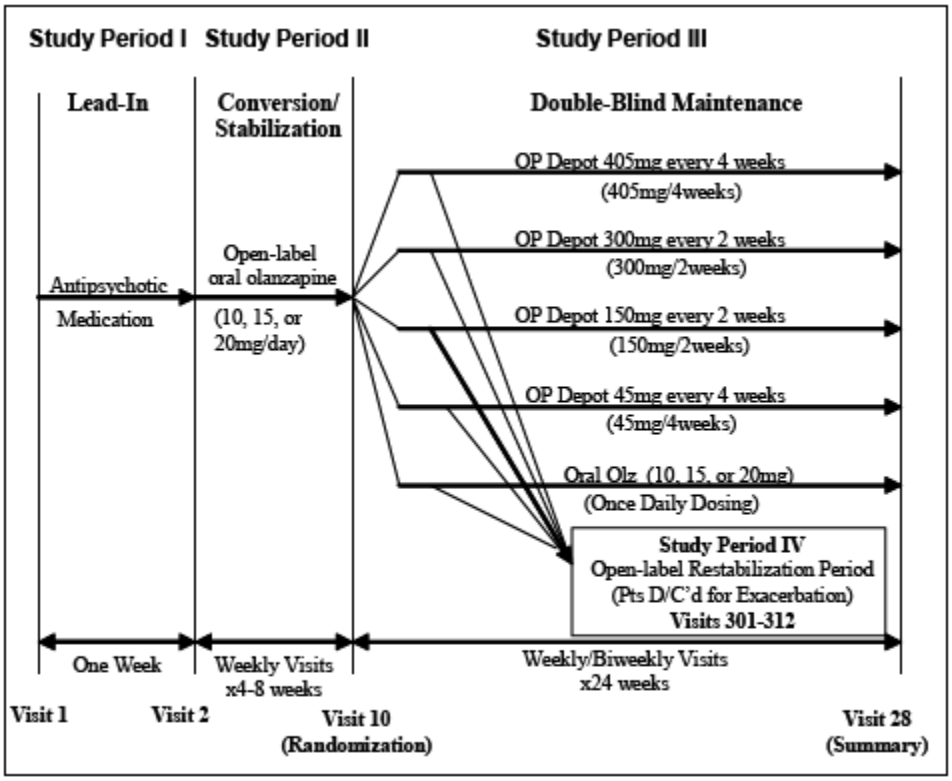
SAMPLE AND DATA COLLECTION

Study HGJZ

A single blood sample was collected from each patient prior to the OP Depot injection at Visits 2, 17, 18, 19, 20, and 22. In addition, a single blood sample was collected at either Visit 4, 5, or 6 to coincide with the electrocardiogram (ECG) measurement. A total of 1345 quantifiable olanzapine plasma concentrations were obtained from 287 patients with the administration of 800 OP Depot injections. Patient demographics included 80 females and 207 males with median body mass index (BMI) of 28.2 kg/m2 and median age of 40.6 years.

Study HGKA

Prior to Visit 10, all patients were stabilized on a fixed oral olanzapine dosage regimen (10, 15, or 20 mg/day) for at least 4 weeks. Therefore, the sample collected on Visit 10 was reflective of steady-state oral olanzapine pharmacokinetics.



Abbreviations: D/C'd = discontinued; Olz = olanzapine; OP = olanzapine pamoate; Pts = patients.

Figure 4**.** Study HGKA study design

Visit[a]	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Weeks	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24
Q2 Dose	D		D		D		D		D		D		D	D	D	D	D	D	D
Q4 Dose	D				D				D				D		D		D		D
PK Sample	S	S	S		S							S	S				S	S	S
Q2 TFDS (day)	<1 (oral dose)	7[b]	14[b,c]	7	14[c]	7	14	7	14	7	14	7	14[c]	14	14	14	14[c,d]	14[c,d]	14[c,d]
Q4 TFDS (day)	<1 (oral dose)	7[b]	14[b]	21	28[b,c]	7	14	21	28	7	14	21	28[c]	14	28	14	28[c,d]	14[d]	28[c,d]

Abbreviations: D = OP Depot dose; IM = intramuscular; OP = olanzapine pamoate; PK = pharmacokinetic; Q2 = once every 2 weeks; Q4 = once every 4 weeks; S = Pharmacokinetic sample (collected prior to OP Depot injection); TFDS = time interval between Pharmacokinetic sample and IM dose.

[a] Visits 10 through 21 occur at weekly intervals (±2 day window). Visits 22 through 28 occur at bi-weekly intervals (±4 day window). Therefore, pharmacokinetic samples may be collected during most of the dosing interval for both Q2 and Q4 week intervals. However, it is unlikely that many samples will be collected on the first few days after dosing.

[b] Single dose samples.

[c] Trough samples.

[d] Potential steady-state samples.

Table 3. Pharmacokinetic Sampling Scheme for Study HGKA

Blood samples were collected from the first 341 patients randomly assigned to treatment groups. Out of the total 340 patients in the Non-linear Mixed Effect Modeling (NONMEM) dataset, 236 patients were in 4 OP Depot groups and 104 patients were in the oral olanzapine group. Patient demographics included 126 females and 214 males with median BMI of 23.8 kg/m2 and median age of 48.6 years. A single blood sample was collected from each patient prior to the OP Depot injection at Visits 10, 11, 12, 14, 21, 22, 26, 27, and 28. A total of 2391 quantifiable olanzapine plasma samples were collected and 1516 OP Depot injections were administered in this study.

Study HGKB

Blood samples to provide the pharmacokinetic data were scheduled on quarterly, 6-month or summary visits. If oral supplementation occurred within the last 5 days prior to blood sampling, the date, time, and amount of the last 5 oral olanzapine doses were recorded. Observations from 273 patients enrolled in the study were used in the NONMEM dataset.

Patient demographics included 84 females and 189 males with median BMI of 27.4 kg/m2 and median age of 38.6 years.

Study LOBS

Patients were enrolled in the study at Visit 1. At Visit 2 (Study Period I), patients had taken oral olanzapine 5 to 20 mg once daily for 14 days and, thereby, achieved steady-state olanzapine concentrations. Blood samples were collected at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours after the 14th oral dose. At Visit 3 (Study Period II), patients received a single intramuscular (IM) injection of OP Depot 405 mg olanzapine. Blood samples were collected at 0 (predose), 2, 6, 12, 18, 24, 36, 48, 72, 120, 144, 168, 192, 216 hours, and then at 11, 13, 16, 19, 22, and 25 days after the OP Depot injection. At Visit 19 (Study Period III), patients received a single injection of rapid-acting intramuscular (RAIM) olanzapine 5 mg. Blood samples were collected at 0 (predose), 0.083, 0.167, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, and 120 hours after the RAIM olanzapine injection. RAIM olanzapine (LOBS Study Period III) were excluded from population analysis.

Out of the 4101 concentrations recorded, 1544 concentrations were recorded after the oral dosing while 2557 concentrations were recorded after injections of OP Depot. Each patient was given a single 405 mg OP Depot injection, thus in total 129 OP Depot injections were administered. Patient demographics included 39 females and 90 males with median BMI of 26.7 kg/m2 and median age of 38.8 years.

Bioanalytical Methods

Sample analysis was reviewed in the 2007 submission since these studies were used to assess the excessive sedation.

Base Model Development

All valid concentration values, including concentrations following both oral and OP Depot dosing, were included in the base model development. The concentration-time data was fit to provide estimates of the population pharmacokinetic parameters and error terms. Interpatient variability (η) was modeled using an exponential error structure and residual variability (σ) was modeled using a proportional or combined additive and proportional error structure. Pharmacokinetic parameters were estimated using the first order conditional estimation method with interaction (FOCEi).

Separate OP Depot and oral dose inputs were included in the base model. A one compartment model was parameterized in terms of the absorption rate constant for OP Depot (ka depot) and the absorption rate constant for oral (ka oral). Different complex absorption schemes were investigated to model the OP Depot plasma concentration. The apparent clearance of olanzapine (CL/F) was estimated by a single CL estimate regardless of the route of administration.

Selection of the most appropriate base model was based upon:

- Convergence of the estimation and covariance routines
- Estimation of ≥3 significant digits for each fixed and random effect
- Reasonable parameter and error estimates based upon the known pharmacokinetics of olanzapine
- Good precision of the parameter and error estimates (%SE<40)
- Comparison of pairs of nested models by a decrease in the minimum objective function (MOF; -2*log likelihood of the data; -2LL) of at least 3.841 points ($p<.05$)
- Agreement between predicted and observed plasma concentrations, as assessed by visual inspection

Final Model Development

A full model was created by adding all covariates, determined clinically and statistically significant individually, together in combination on the base model. The significance of potential covariates was confirmed by removing each covariate individually from the full model. The criterion for retention of a covariate in the final model was an increase of ≥10.828 points in MOF ($p<.001$) when the covariate was omitted from the full model. Upon removal of the least influential covariate from the full model, the process was repeated. Again, each individual covariate was removed from the reduced full model and the effect on the objective function was evaluated. This process was repeated until a model was obtained in which no individual covariates could be removed without a consequent significant (10.828 point) increase in objective function. This model served as the final model.

RESULTS

Base Pharmacokinetic Model

This model incorporates oral and OP Depot dosing. The model incorporates a process for first order oral absorption and a parallel process that models simultaneous zeroth and first order OP Depot absorption. The pharmacokinetic parameters estimated in the model are: Frac (fraction of total OP Depot dose going through the first order OP Depot absorption process), K13 (first order OP Depot absorption rate constant), K23 (first order oral absorption rate constant), D3 (duration of the zero order rate process during which OP Depot is absorbed directly into the central compartment), V3/F (apparent volume of distribution), CL/F (apparent clearance), and F2 (oral bioavailability). Oral bioavailability (F2) is the relative oral bioavailability compared to the OP Depot bioavailability (which is assumed to be 100%).

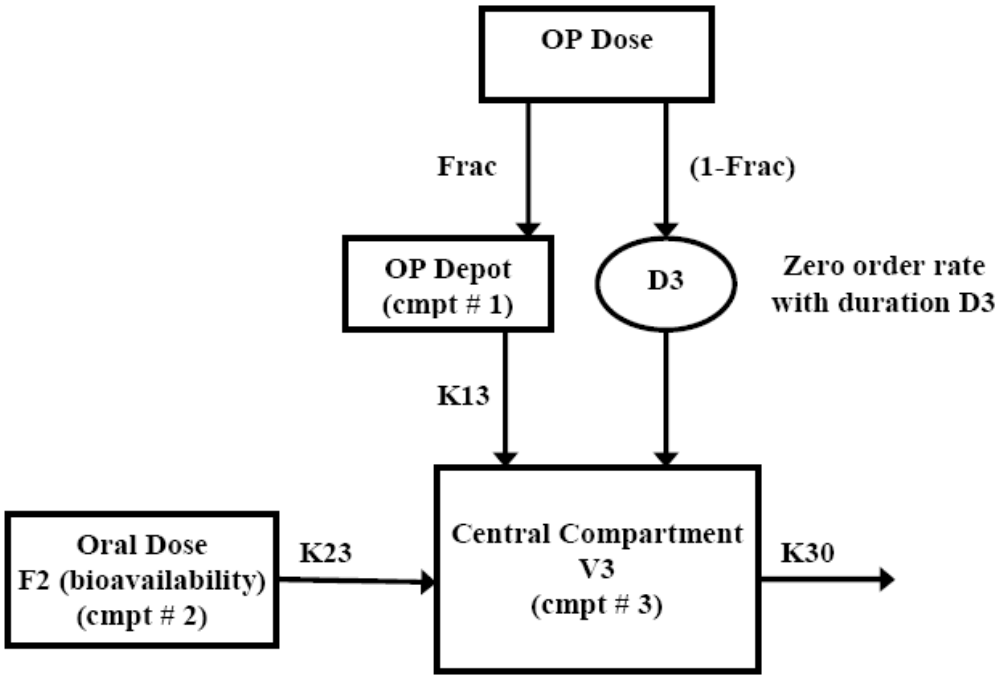


Figure 5. Schematic of first order oral absorption and combined zeroth/first order OP Depot absorption model.

Covariate Selection

A number of statistically significant covariates were identified by a decrease in the minimum value of objective function (MOF) (≥6.635, 1 degree of freedom, $p<.005$) when examined individually. These covariates included effect of smoking status on the apparent clearance, apparent volume, oral bioavailability, duration of OP Depot absorption, oral absorption rate, and OP Depot absorption rate. Gender effect on the oral absorption rate and OP Depot absorption rate were also identified to be significant covariates as well as the effect of body mass index (BMI) on apparent clearance and oral bioavailability.

FINAL PHARMACOKINETIC MODEL

Three covariates with significant influence on olanzapine disposition were retained in the final model. The final model incorporated the effects of smoking status on apparent clearance and apparent volume, and gender on OP Depot absorption rate. Parameter estimates from the final population pharmacokinetic model shown in Table 4 account for the effects of these covariates.

Parameter Description	Population Estimate (%SEE)	Interpatient Variability (%SEE)	Inter-Occasion Variability (%SEE)
Fraction of OP Depot Absorbed via 1st Order Rate			
Frac	0.939 (0.433)	NE	NE
OP Depot 1st Order Rate of Absorption			
K13 (hr^{-1})[a]	0.000529 (4.20)	NE	NE
Effect of gender on K13 (Θ3)[b]	0.331 (23.1)	NE	NE
Oral Olanzapine Rate of Absorption			
K23 (hr^{-1})	0.758 (8.51)	NE	NE
Olanzapine Clearance			
CL/F (L/hr)[c]	12.8 (3.37)	39.5 (12.4)	25.4 (17.0)
Effect of smoking status on CL/F (Θ6)[d]	0.468 (13.5)	NE	NE
Olanzapine Volume of Distribution			
V/F (L)[e]	634 (7.90)	NE	NE
Effect of smoking status on V/F (Θ8)[f]	0.537 (27.0)	NE	NE
Duration of Zero Order OP Depot Absorption			
D3 (hr)	65.9 (1.35)	NE	NE
Oral Bioavailability			
F2	0.748 (3.18)	41.6 (16.9)	NE
Residual Error (proportional)		28.8% (7.48)	
Residual Error (additive)		1.65 ng/ml (22.4)	

Abbreviations: NE = not estimated; OP = olanzapine pamoate; SEE = standard error of the estimate.

[a] $K13_{female} = 0.000529\ hr^{-1}$

[b] $K13_{male} = K13_{female}\ (1+ \Theta 3) = 0.000704\ hr^{-1}$

[c] $CL_{non\text{-}smoker} = 12.8\ L/hr$

[d] $CL_{smoker} = CL_{non\text{-}smoker}\ (1+ \Theta 6) = 18.8\ L/h$

[e] $V_{non\text{-}smoker} = 634\ L$

[f] $V_{smoker} = V_{non\text{-}smoker}\ (1+\Theta 8) = 974.5\ L$

Table 4. Pharmacokinetic and Covariate Parameters in Final Population Model

Goodness-of-fit for this final population model is represented graphically in Figure 6 by the agreement between IPRED and observed concentrations, as well as by IWRES values.

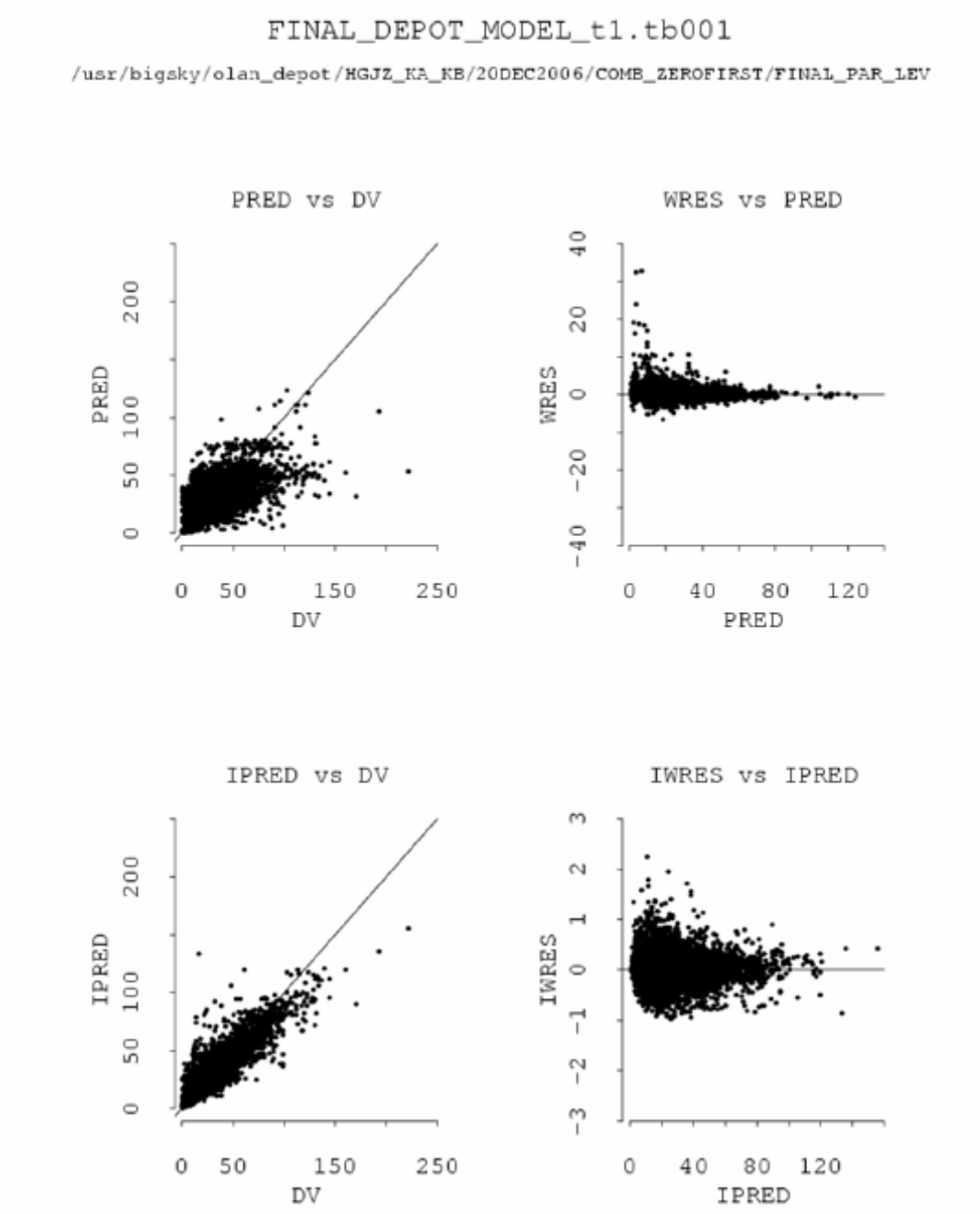


Figure 6. Goodness-of-fit plots for the final model.

COVARIATES

Effect of Smoking Status

Smoking status had a significant influence on olanzapine pharmacokinetics. This effect was parameterized as differences in olanzapine apparent clearance and apparent volume. Smokers were estimated to have 46.8% higher apparent clearance than non-smokers and 53.7% higher apparent volume than non-smokers. Thus, on average, non-smokers receiving the same OP Depot dose as smokers are predicted to have higher systemic exposure. The predicted effect of smoking status on olanzapine concentrations is

illustrated in Figure 7 for typical female patients (a smoker or a nonsmoker) receiving 405 mg OP Depot every 4 weeks. Male patients were estimated to have 33.1% higher depot absorption rate constant than females.

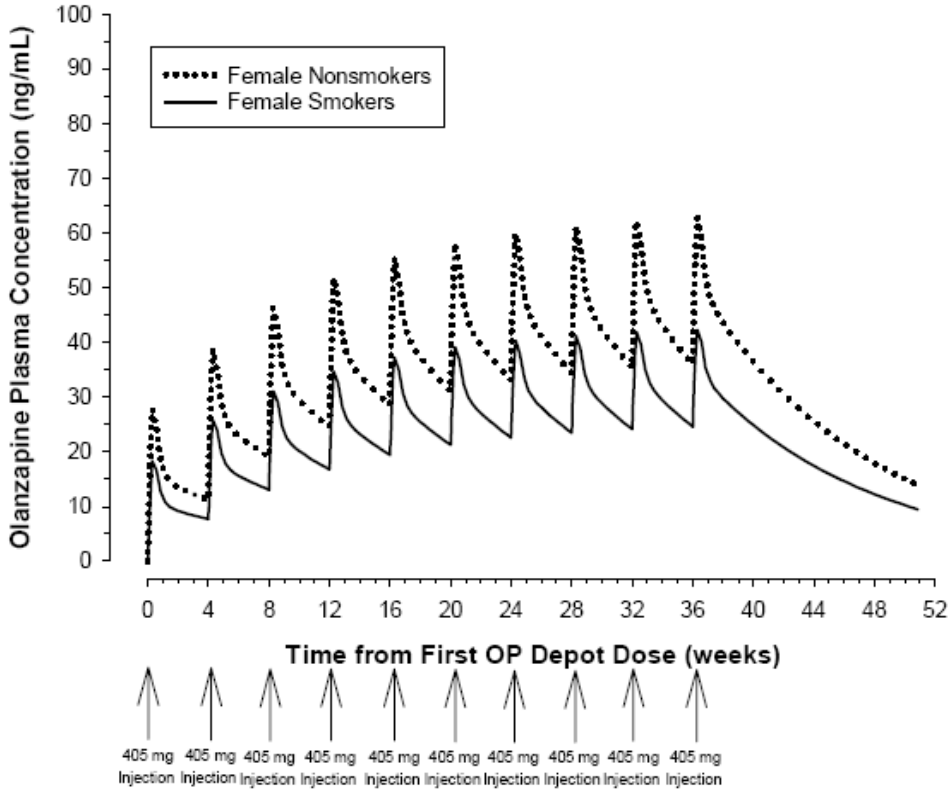


Figure 7. Final population pharmacokinetic model: Predicted effect of smoking status on plasma olanzapine concentrations for a typical female patient receiving 405 mg OP Depot every 4 weeks.

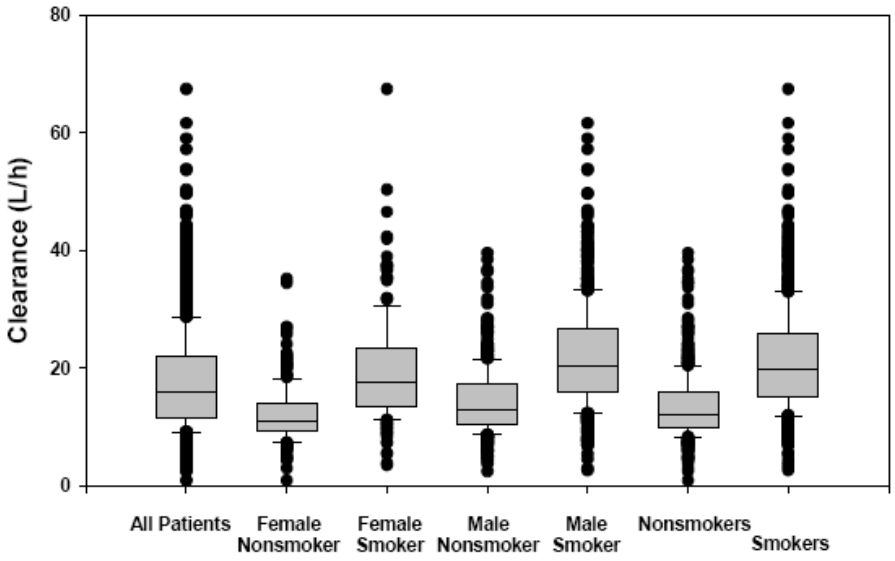


Figure 8. Final population pharmacokinetic model: Post-hoc apparent clearance values depicting differences based on gender and smoking status.

VISUAL PREDICTIVE CHECK

The final model was used in performing simulations utilizing datasets created with 200 patients and relevant covariate fields for the typical dosing schemes in the clinical studies. Simulation datasets were created such that the same percentage of males/females and smokers/non-smokers were present as the actual clinical study. Simulations were performed for the specific dosing regimens used in the clinical studies and the resulting predicted olanzapine concentration profiles were overlaid with the actual observed olanzapine data from the NONMEM dataset.

Figure 9 presents the model simulated median olanzapine plasma concentrations with the 5th and 95th percentile (90% confidence interval) overlaid with the actual olanzapine plasma concentration data obtained in Study LOBS. These graphical evaluations show that less than 10% of the actual observed data fall outside the 90% confidence interval band from the model predicted data. Thus, these visual predictive checks confirm that the developed population pharmacokinetic model describes the data well.

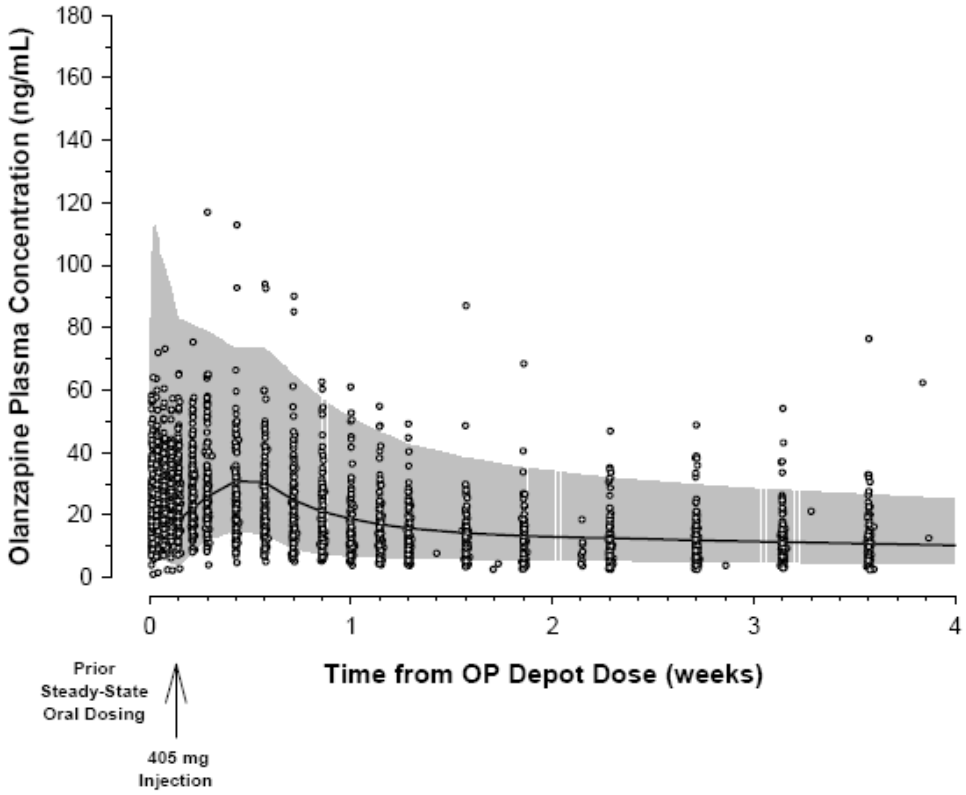


Figure 9. Overlay of LOBS actual data and model simulated data.
Line depicts the median of the simulated values and the shaded region represents the 90% confidence region.

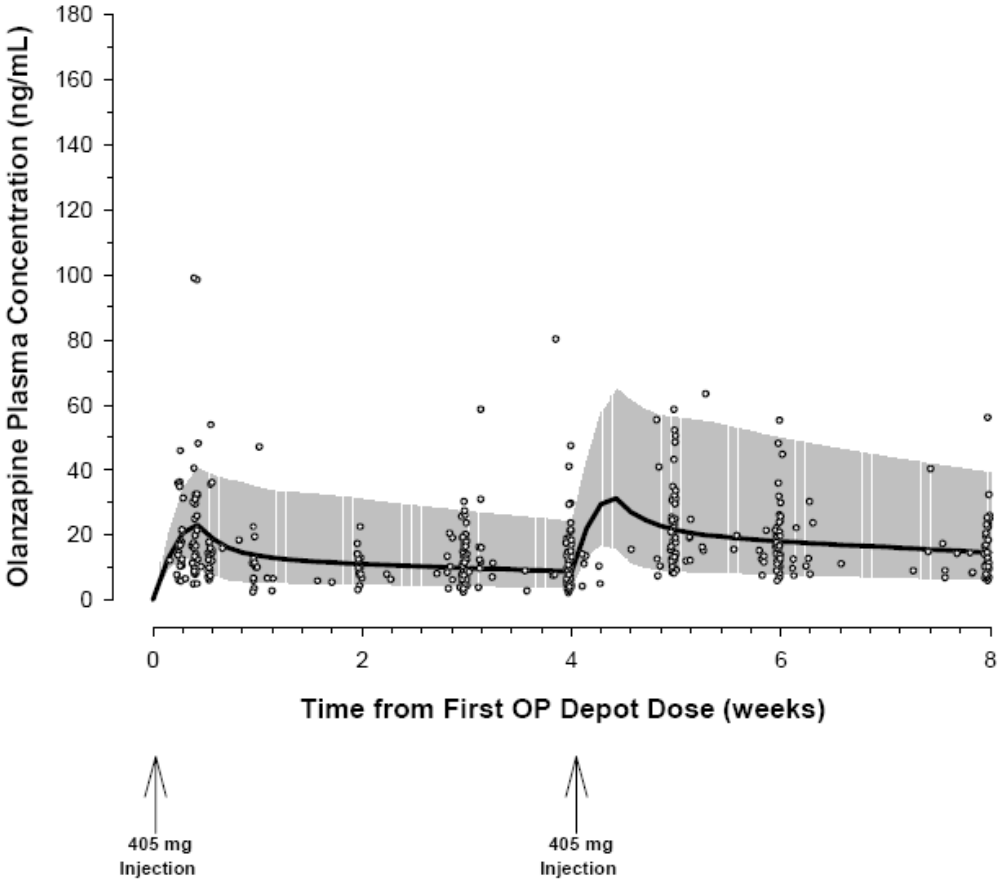


Figure 10. Overlay of HGJZ actual data for 405 mg/ 4 weeks dosing regimen and model simulated data: Line depicts the median of the simulated values and the shaded region represents the 90% confidence region.

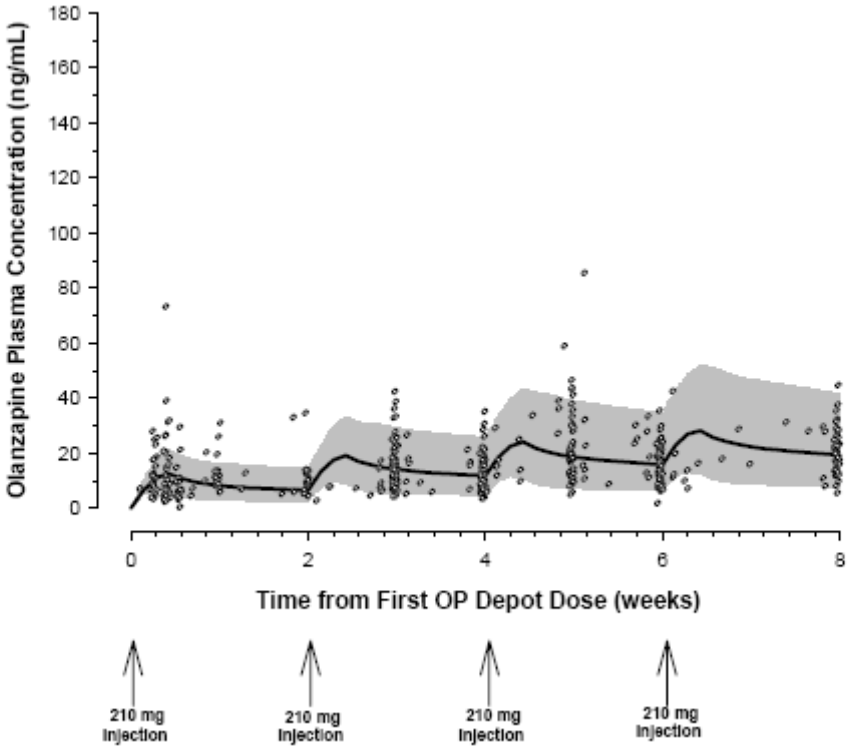


Figure 11. Overlay of HGJZ actual data for 210mg/2weeks dosing regimen and model simulated data: Line depicts the median of the simulated values and the shaded region represents the 90% confidence region.

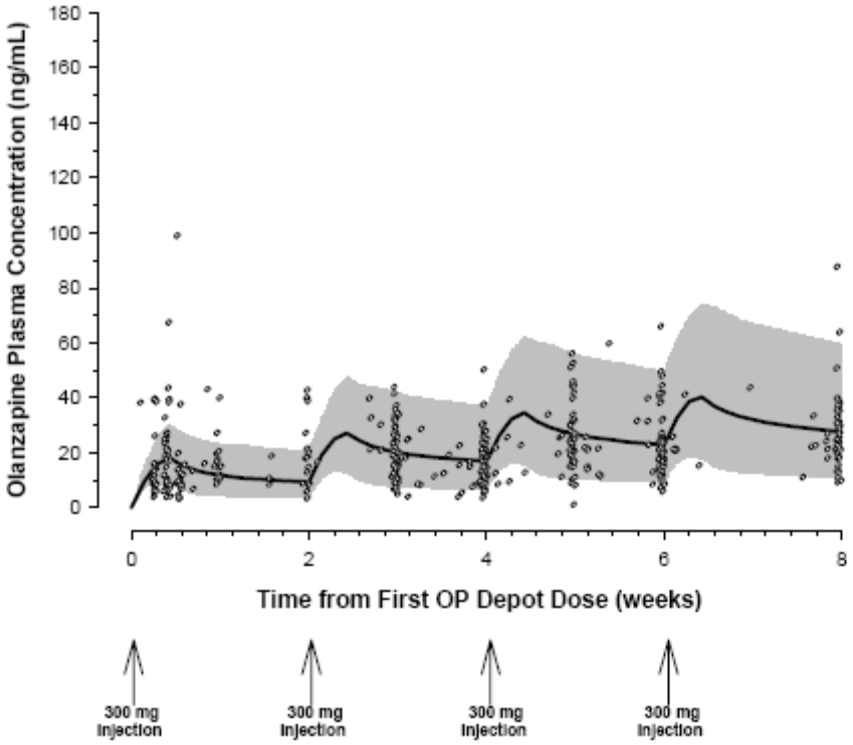


Figure 12. Overlay of HGJZ actual data for 300mg/2weeks dosing regimen and model simulated data: Line depicts the median of the simulated values and the shaded region represents the 90% confidence region.

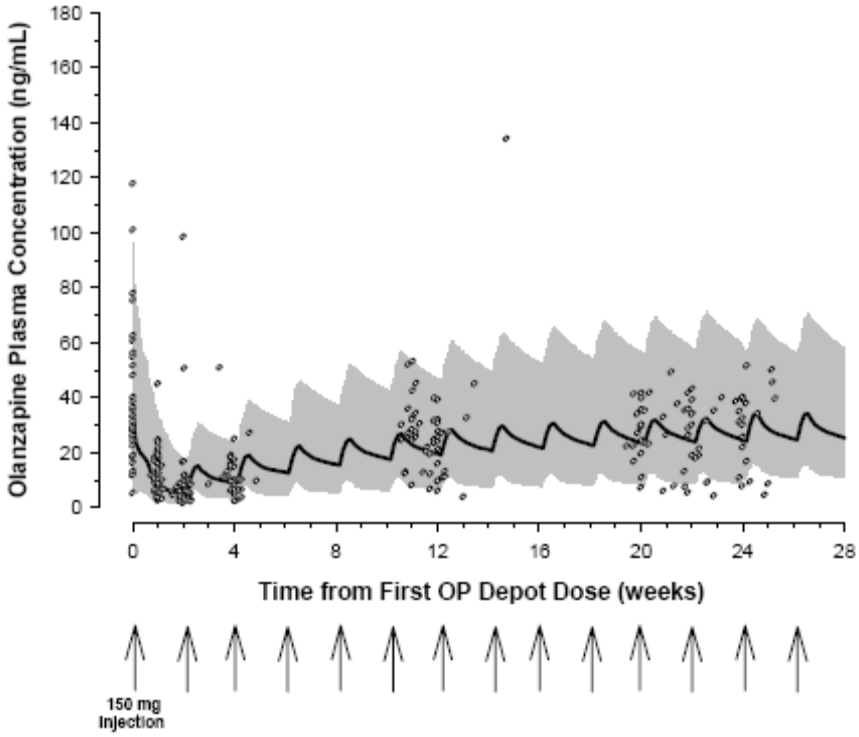


Figure 13. Overlay of HGKA actual data for 150mg/2weeks dosing regimen and model simulated data: Line depicts the median of the simulated values and the shaded region represents the 90% confidence region.

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OP DEPOT COMPARISON WITH ORAL OLANZAPINE

Since there are many dosage and transition regimens only the 15 mg oral dose to the 405 mg Q4 regimen data will be presented for all simulations. Similar results are seen with the other proposed doses.

Raw data collected in the Olanzapine OP studies and presented in a prior review is presented in Figure 14.

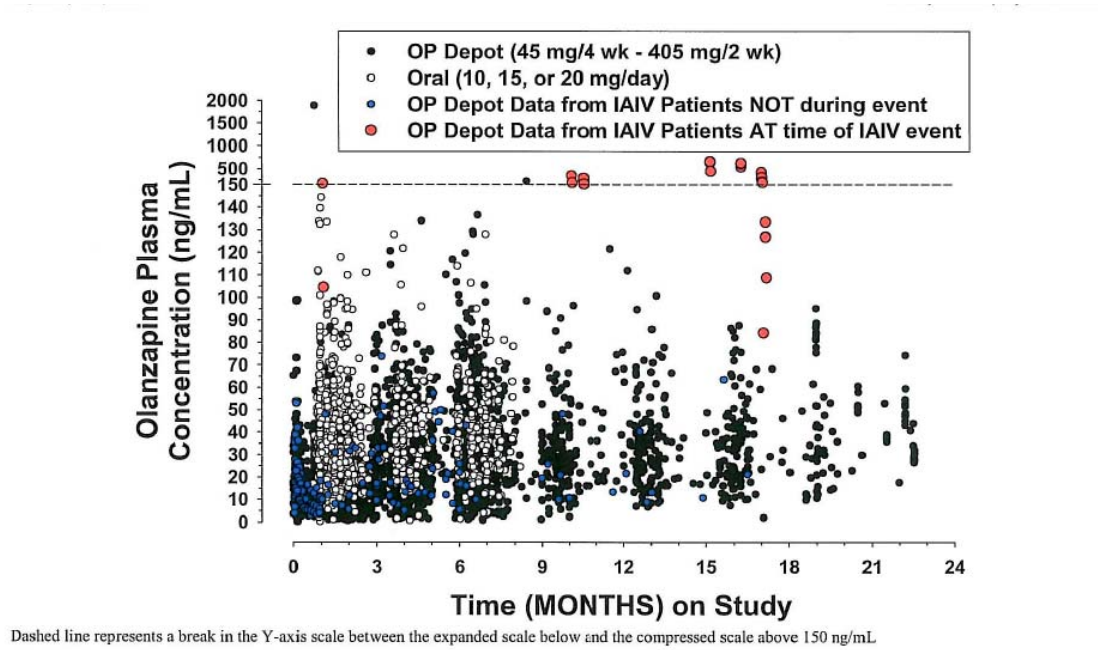


Figure 14. Olanzapine concentrations for patients experiencing an excessive exposure event superimposed upon plasma concentrations in Study HGKA after oral doses of 10, 15, or 20 mg QD and the olanzapine plasma concentrations in Study HGJZ, HGKA, and HGKB after OP Depot doses of 45 mg every 4 weeks to 405 mg every 2 weeks.

The final model was also used to simulate the olanzapine plasma concentration profiles for continuous OP Depot dosing for a period of 1 year. Simulations were performed for the OP Depot dose regimens of 150 mg/ 2 weeks, 210 mg/ 2 weeks, 300 mg/ 2 weeks, and 405 mg/ 4 weeks. An OP Depot regimen of 150 mg/ 2 weeks produces a range of olanzapine concentrations that are comparable to an oral olanzapine dose of 10 mg/day. Correspondingly, an OP Depot regimen of either 210 mg/ 2 weeks or 405 mg/ 4 weeks is comparable to 15 mg/day oral olanzapine, and a 300 mg/ 2 weeks OP Depot regimen is comparable to 20 mg/day.

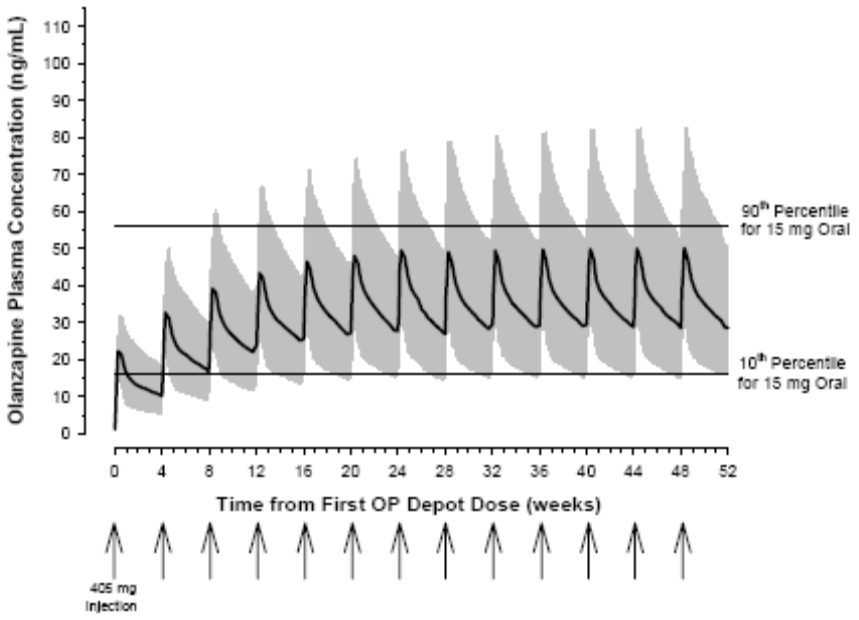


Figure 15. Comparison of OP Depot concentrations with comparable oral olanzapine: 405 mg/ 4 weeks OP Depot and 15 mg oral olanzapine. The shaded area represents the 90th percentile of Cpss values for oral olanzapine at the 15 mg oral dose.

STEADY STATE ATTAINMENT AND WASHOUT PERIOD

Simulations were performed to assess: (1) the transition from oral olanzapine to OP Depot dosing, (2) the time required to attain steady state concentrations and (3) the time required for the washout of olanzapine from the systemic circulation after the last OP Depot dose.

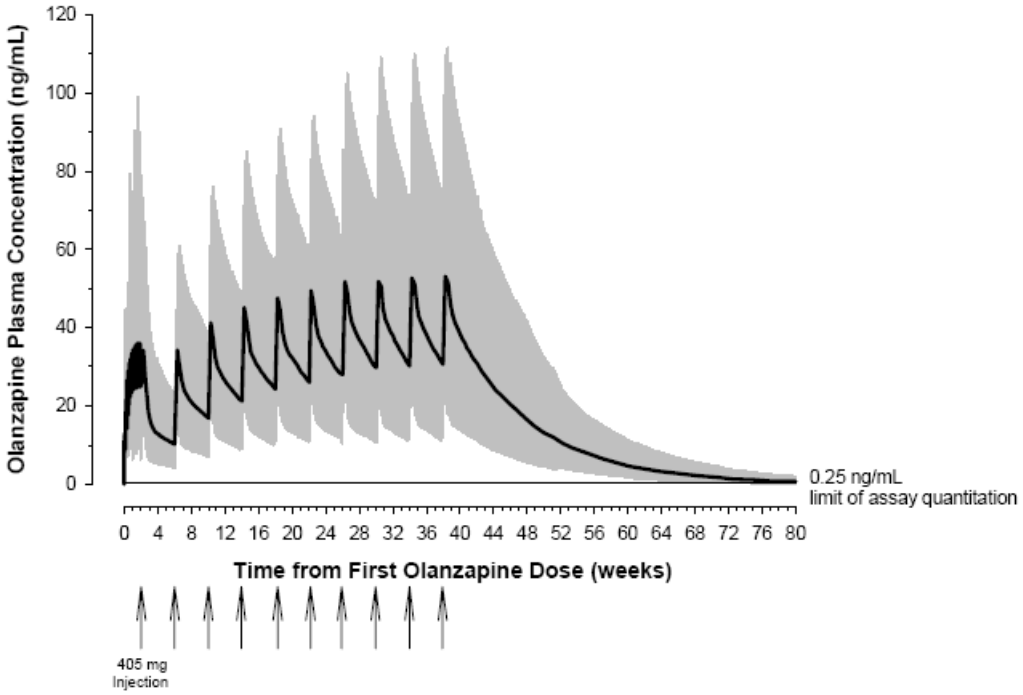


Figure 16. 15 mg oral olanzapine (daily for 14 days) followed by 405 mg OP Depot (every 4 weeks): Attainment of steady state and washout period. Shaded areas are the 90% confidence intervals for the simulations.

The visual examination of these simulations suggests that steady-state median olanzapine plasma concentrations comparable to those for oral dosing are achieved within a period of 3 to 6 months of OP Depot dosing irrespective of OP Depot dose or dosing interval. Exposure to olanzapine concentrations may extend for a prolonged period of months after the last OP Depot injection due to the continuing slow release of OP Depot.

SIMULATIONS FOR LABEL DOSING

The doses studied by the firm are in the Table 5 from the Medical Officers' review. All of these doses have effectiveness data to support the regimen.

Table 5. Doses studied and shown to be effective.

Study ID/ Study Status	Study Length	# Enroll/ Rand	Dose	Study Design and Objective
HGJZ/ Concluded	8 weeks	404 Rand	**OP Depot**: 210 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks **Placebo**	Double-blind, placebo-controlled, fixed-dose PK, efficacy superiority, and safety study in patients with schizophrenia.
HGKA/ Concluded	24 weeks	1065 Rand	**OP Depot**: 45 mg/4 weeks (reference dose), 405 mg/4 weeks, 150 mg/2 weeks, 300 mg/2	Double-blind, olanzapine-controlled, fixed-dose study of noninferiority of maintenance of efficacy, superiority of 3 therapeutic OP Depot doses compared to reference dose, safety, and
			weeks **Oral OLZ**: 10, 15, 20 mg/day	PK in patients with schizophrenia.
HGKB/ Ongoing	Up to 4 years	931 Enroll (725 ongoing as of Jan 2007	**OP Depot**: Flexible doses ranging from 45 mg to 405 mg given at 2-, 3-, or 4-week intervals	Long-term, open-label safety, effectiveness, and PK (subset) study in patients with schizophrenia or schizoaffective disorder who previously completed an OP Depot clinical trial (HGJZ, HGKA, or LOBS).

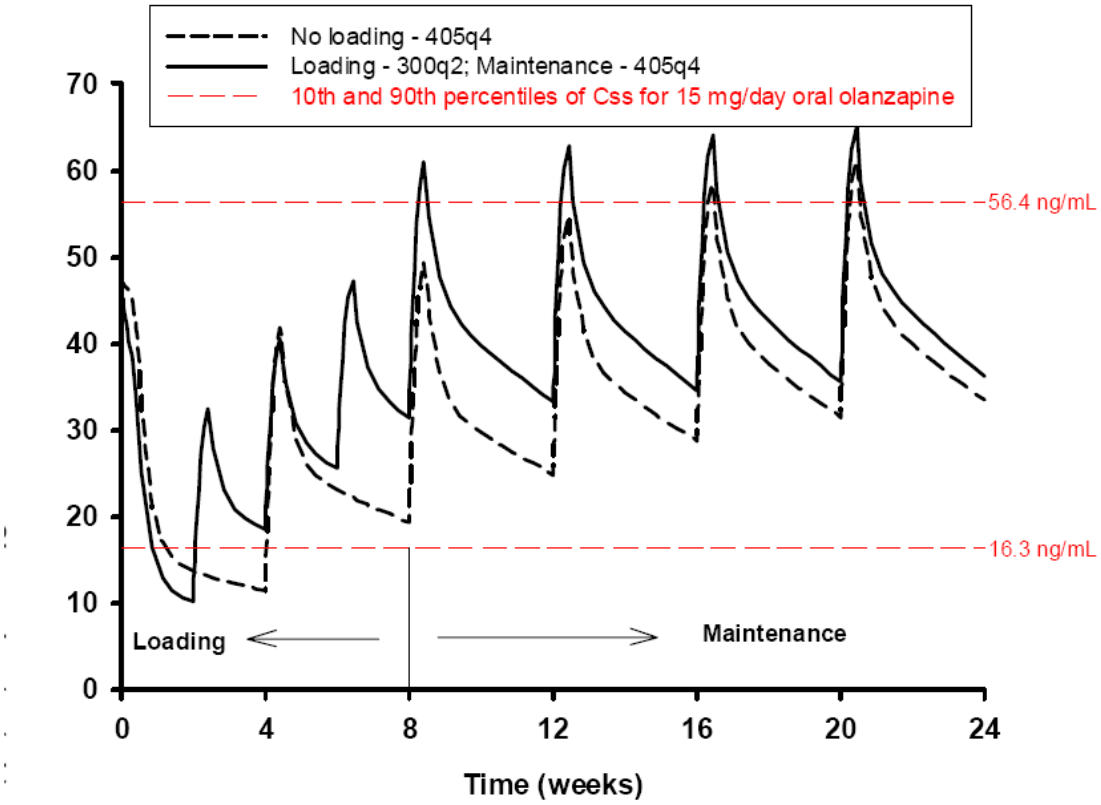
The firm has done several simulation studies to support the proposed loading doses of:

Target Oral ZYPREXA Dose	Dosing of ZYPREXA RELPREVV During the First 8 Weeks	Maintenance Dose After 8 Weeks of ZYPREXA RELPREVV Treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

The major impact of the loading regimen was to shorten the length of time to reach the region of the steady-state values or return to the previously established steady state levels. The sponsor has claimed that the loading dose will decrease relapse in patients although no data was submitted to support this claim.

The switch from oral olanzapine to OP Depot initially produces olanzapine plasma concentrations that are below those simulated during the steady state oral dosing period (Figure 15). Lower olanzapine concentrations occur during the first few OP Depot injection intervals.

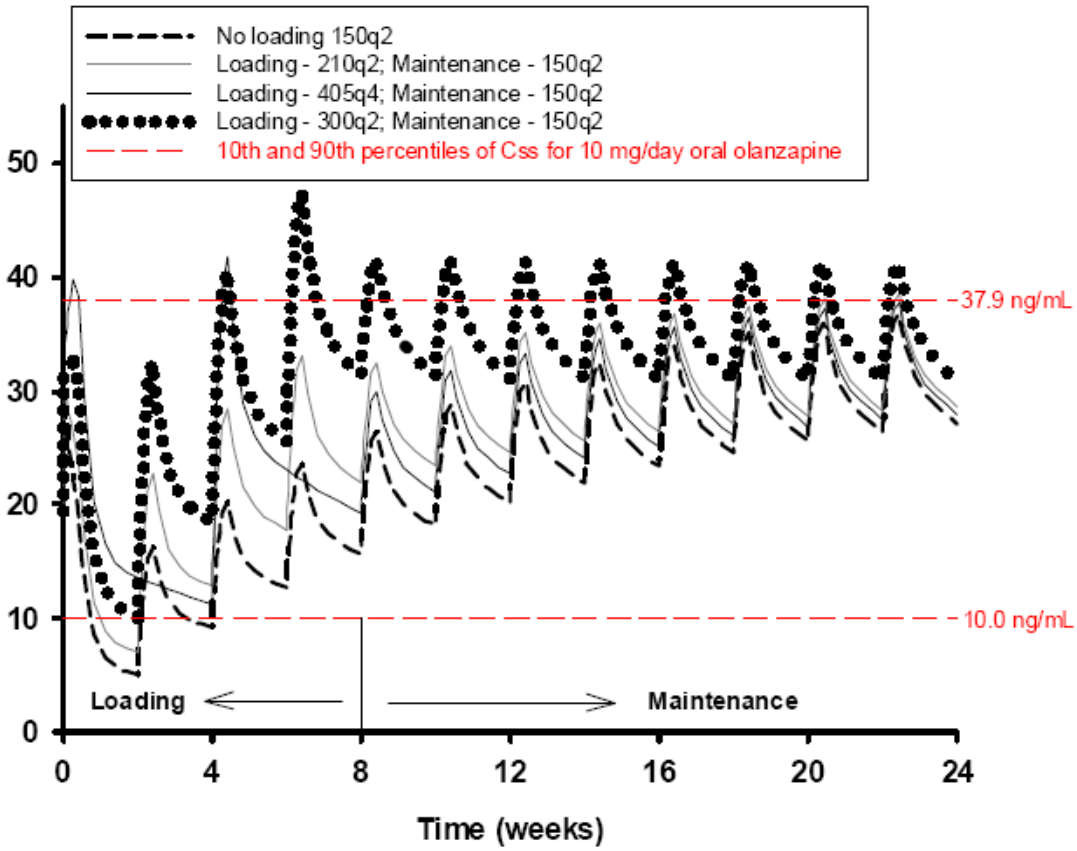
A graphical representation comparing loading and non-loading dose drug administration for the 405 Q4 regimen is presented in Figure 17.



Abbreviation: OP = Olanzapine Pamoate.

Figure 17. Simulated median olanzapine plasma concentration profiles during the loading and maintenance dose periods for regimens recommended to provide approximately 15 mg olanzapine per day with the final maintenance dose of 405 mg/4 weeks OP Depot.

A graphical representation comparing loading doses of 210 Q2, 405Q4 and 300Q2 followed by 150 mg Q2 maintenance dose are presented in Figure 18.



Abbreviation: OP = Olanzapine Pamoate.

Figure 18. Simulated median olanzapine plasma concentration profiles with or without loading doses for a patient stabilized on 10 mg olanzapine per day transitioning to the final maintenance dose of 150 mg/2 weeks OP Depot. Horizontal lines are the 90th and 10th percentiles for Cpss.

FIRM'S RESPONSES TO FDA INQUIRIES

HAZARD RATIO ANALYSIS TO DETERMINE THE APPROPRIATE SWITCHING DOSE

10 MG

Table 6. Relative Risk of Exacerbation versus Oral Olanzapine at 6 Months for Patients Previously Stabilized on 10 mg/day Oral Olanzapine (Study HGKA)

		Vs. OLZ		
Oral Dose	Therapy	HR	95% CI	p-Value
10mg	OPD45	2.78	(1.13 , 6.84)	.027
	OPD150	2.08	(0.77 , 5.59)	.147
	OPD405	1.03	(0.40 , 2.67)	.954
	OPD300	0.25	(0.03 , 2.01)	.194

Abbreviations: CI = confidence interval; HR = hazard ratio; OLZ = oral olanzapine; OPD = Olanzapine Pamoate Depot.

In order to switch patients to a dose with an HR closest to a value of 1.0, the starting dose of OP Depot for patients previously on 10 mg/day oral olanzapine should be 405 mg/4 weeks (or 210 mg/2 weeks, which is a comparable dose to 405 mg/4 weeks).

15 MG

Table 7. Relative Risk of Exacerbation versus Oral Olanzapine at 6 Months for Patients Previously Stabilized on 15 mg/day Oral Olanzapine (Study HGKA)

		Vs. OLZ		
Oral Dose	Therapy	HR	95% CI	p-Value
15mg	OPD45	5.59	(1.68 , 18.59)	.005
	OPD150	1.96	(0.44 , 8.74)	.380
	OPD405	1.44	(0.36 , 5.76)	.606
	OPD300	0.68	(0.08 , 6.08)	.727

Abbreviations: CI = confidence interval; HR = hazard ratio; OLZ = oral olanzapine; OPD = Olanzapine Pamoate Depot.

Based upon these considerations, the optimal recommended starting dose of OP Depot for patients previously on 15 mg/day oral olanzapine would be between 405 mg/4 weeks and 300 mg/2 weeks.

20 MG
Table 8. Relative Risk of Exacerbation versus Oral Olanzapine at 6 Months for Patients Previously Stabilized on 20 mg/day Oral Olanzapine (Study HGKA)

		Vs. OLZ		
Oral Dose	Therapy	HR	95% CI	p-Value
20mg	OPD45	8.00	(3.53 , 18.14)	<.001
	OPD150	2.73	(1.05 , 7.11)	.039
	OPD405	1.70	(0.72 , 4.01)	.227
	OPD300	1.13	(0.34 , 3.75)	.843

Abbreviations: CI = confidence interval; HR = hazard ratio; OLZ = oral olanzapine; OPD = Olanzapine Pamoate Depot.

As 300 mg/2 weeks OP Depot is the highest dose available, and because the HR for this dose is approximately 1, a loading dose is neither possible nor required.
However, a closer examination of clinical data, time for relapse in stable patients who switched to OP Depot in Study HGKA suggests that the best recommendation is to switch using a loading-dose strategy. Therefore, for patients on the equivalent of 10 mg or 15 mg of oral olanzapine per day, a higher dose of OP Depot for an initial period of 8 weeks is recommended in the labeling. This strategy minimizes the risk of relapse and provides higher olanzapine exposure during the transition.

EXCESSIVE EXPOSURE [POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS)]-POSSIBLE RELATION TO NEW LOADING DOSES

A major concern with the increased levels following a loading dose were higher initial levels and the possibility of excessive exposure. The firm was asked several questions and their responses are listed below:

FDA Comment 3 (16 April 2009)
One of the major recommendations from my review of the original data was to avoid the 405 mg/4 wk dose. However, this is one of your loading doses. You need to provide a strong rationale for this choice of loading dose given the higher incidence of the excessive sedation at this dose.

Lilly Response
The data from the OP Depot clinical trials indicate that the 405 mg/4 week dose is safe and effective as a starting and/or maintenance dose. There is no evidence that risk of post-injection delirium/sedation syndrome (PDSS) is greater with 405 mg/4 weeks compared with other doses included in OP Depot clinical trials. Avoidance of the 405 mg/4 week OP Depot loading dose is unwarranted based on clinical and pharmacokinetic (PK) evidence. The 4-week loading dose offers an alternative dosing option that provides additional flexibility and convenience for patients who struggle with adherence and who might otherwise not comply with a 2-week dosing regimen.

Analysis of PDSS events during the first 8 weeks of treatment (the recommended loading dose period) did not show a statistically significant difference in incidence rates between doses. However, due to the small number of events that occurred during the first 8 weeks of OP Depot treatment (n=4), these analyses should be interpreted with caution. Nevertheless, any increase in risk would be minimal and would be heavily outweighed by the reduced risk of relapse of symptoms of schizophrenia that can be achieved by using a loading dose as reflected by the hazard ratio analyses that accompanied the initial dosing table amendment. The 405 mg/4 week dose, compared with the 210 mg/2 week dose, reduces burden on the patient by decreasing the frequency of injections and the corresponding 3-hour observation period required after each injection. This difference in injection frequency may make the difference in whether many patients would be willing to consider starting a depot medication. This type of consideration is particularly important when treating those patients with schizophrenia who are most in need of a depot medication, as compliance can be a major hurdle to successful treatment.

This response provides an analysis of the risk of PDSS events for patients with schizophrenia receiving OP Depot, followed by a summary of the PK data, and concluding statements around risk/benefit for this loading dose.

EXAMINATION OF POTENTIAL RISK FACTORS FOR POST-INJECTION DELIRIUM/SEDATION SYNDROME

INTERACTION BETWEEN DOSE AND TIMING IN TREATMENT

Table 9 displays incidence of PDSS events occurring at any time versus the first 8 weeks of OP Depot treatment through 30 April 2008. The incidence rate during the first 8 weeks of treatment (4 events out of 5334 injections; 0.07%) was the same as the incidence rate at any time during treatment (29 events out of 41,193 injections; 0.07%). Analysis by dose indicated that 2 of these early events occurred with the 405 mg dose, 1 occurred with the 300 mg dose, and 1 with 210 mg dose. Because of the small number of PDSS events and higher number of injections of the 405 mg dose given during the first 8 weeks of OP Depot treatment, there were no statistically significant differences between doses in terms of PDSS incidence during this potential loading period. Given that only 4 events occurred during the first 8 weeks, it is difficult to draw conclusions. The majority of events occurred later in treatment, with the 20th injection being the median time in treatment for occurrence of PDSS.

Table 9. Post-injection Delirium/Sedation Syndrome Events in Patients Receiving OP Depot Injections

Dose (mg)	Total No. Doses Given	PDSS Events (%)[a]	Total Doses Given First 8 Weeks	PDSS Events First 8 Weeks (%)[b]
150	2615	1 (0.04)	589	0
195	175	1 (0.57)	3	0
210	7128	3 (0.04)	1083	1 (0.09)
250	65	2 (3.08)	2	0
270	521	1 (0.19)	8	0
300	14,732	8 (0.05)	1406	1 (0.07)
330	383	1 (0.26)	4	0
345	570	1 (0.18)	24	0
360	177	1 (0.56)	4	0
390	206	1 (0.49)	8	0
405	10,202	9 (0.09)	1585	2 (0.13)
Other[c]	4419	0	618	0
Total	41,193	29 (0.07)	5334	4 (0.07)

Abbreviations: No. = number; p = p-value; OP = Olanzapine Pamoate; PDSS = Post-injection delirium/sedation syndrome.

[a] In the analysis of all PDSS events, there were no statistically significant differences in incidence rate of PDSS in the following OP Depot doses (mg) based on Fisher's Exact test: 150 vs. 210: p=1.000; 150 vs. 300: p=1.000; 150 vs. 405: p=.698; 210 vs. 300: p=1.000; 210 vs. 405: p=.380; 300 vs. 405: p=.332.

[b] In the analysis of PDSS events during the first 8 weeks, there were no statistically significant differences in incidence rate of PDSS in the following OP Depot doses (mg) based on Fisher's Exact test: 150 vs. 210: p=1.000; 150 vs. 300: p=1.000; 150 vs. 405: p=1.000; 210 vs. 300: p=1.000; 210 vs. 405: p=1.000; 300 vs. 405: p=1.000.

[c] Other OP Depot doses, in which no PDSS events occurred, include the following (mg): 45, 50, 60, 75, 90, 100, 105, 120, 135, 160, 165, 180, 190, 200, 204, 205, 225, 240, 255, 260, 275, 280, 285, 301, 305, 310, 315, 375, 400, and 450.

Source: fqdosn01a; fqdosn01c.

Also refuting the likelihood of an increase in risk of PDSS with early use of the 405 mg/4-week dose are data from Study F1D-MC-HGLQ (HGLQ). Study HGLQ is an ongoing, 2-year, flexibly dosed, open-label treatment effectiveness trial comparing oral olanzapine with OP Depot administered every 4 weeks. All patients randomized to OP Depot (n=264) initiated treatment at a dose of 405 mg/4 weeks, and the majority of patients (74%) have remained on that dose regimen throughout the trial as of the 30 April 2008 data lock, at which time all patients had had the opportunity to complete at least 8 months of the study treatment. The study was initiated in April 2006 and will finish in September 2009. As of 30 April 2008, there had been 3059 injections of OP Depot given, including 2459 (80.4%) injections at the 405 mg/4 week dose. Importantly, to date, a total of over 4300 injections have now been administered in Study HGLQ with no PDSS event occurring in this trial.

Therefore, based on the findings of no statistically greater risk of PDSS during the first 8 weeks of treatment and no statistically greater risk with the 405 mg dose during the first 8 weeks of treatment, as well as the lack of any PDSS events in a large 2-year trial which relied solely on the 405 mg/4 week dose as the starting dose as well as the predominant maintenance dose, we do not believe it would be clinically appropriate to limit the use of

this dose.

TIMING IN TREATMENT AS AN INDEPENDENT PDSS RISK FACTOR

Analysis of the 29 PDSS events that have occurred in OP Depot clinical trials as of 30 April 2008 indicate that a PDSS event can occur at any injection, regardless of previous exposure to olanzapine or OP Depot. Because of the striking similarity in the rate of post-injection reactions for OP Depot (0.07% of injections) compared with that of the only other well documented intramuscular medication with a reportable rate of postinjection reaction (penicillin procaine G, 0.08%), Lilly believes that this is the background rate for accidental entry into the blood stream. Therefore, there is an element of randomness which makes these events impossible to predict. The finding that the PDSS per injection rate is no different early in treatment than it is at any time in treatment also lends support to this hypothesis.

DOSE AS AN INDEPENDENT PDSS RISK FACTOR

In order to explore whether there are any risk factors that might predict the occurrence of PDSS events, Lilly has conducted logistic regression analyses at various time points in its study of this event. The first such analysis was conducted on the locked database in which 25 cases of PDSS had been captured (data lock date 30 September 2007). That analysis identified 3 potential but relatively weak risk factors at the significance level of 0.10: body mass index (BMI) (p=.0404), age (p=.0619), and dose (p=.0920). A subsequent analysis on the most recently locked database (data lock date 30 April 2008), which captured 29 cases, identified only 2 statistically significant risk factors at the significance level of 0.10: BMI (p=.0330) and age (p=.0347) (Table 4.2). The risk factor of dose (p=.1264) no longer met the criterion for statistical significance at the alpha level of 0.10, thus highlighting the lack of robustness of the original finding. As with the findings of the original regression analysis, it should be noted that these risk factors are very poor predictors of events. For example, a patient with all of these risk factors might not necessarily experience a PDSS event, while a patient with none of these risk factors still might. Therefore, dose, in particular, should not be modified in an attempt to avoid a PDSS event, but rather should be chosen based on clinical need.

Table 4.2. Analysis of Maximum Likelihood Estimates from Logistic Regression Model with 3 Explanatory Variables

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr >ChiSq
Intercept	1	-7.5566	1.3959	29.3033	<0.0001
BMI	1	-0.0803	0.0377	4.5445	0.0330
Dose	1	0.0035	0.0023	2.3359	0.1264
Age	1	0.0338	0.0160	4.4611	0.0347

Abbreviations: BMI = body mass index; ChiSq = chi square; DF = degrees of freedom; Pr = probability.
Note: Wald test statistic calculated from the data to be compared with the chi-square distribution with 1 degree of freedom.
Source: SMIIVV15.

OLANZAPINE CONCENTRATION AS AN INDEPENDENT PDSS RISK FACTOR

Just as dose per se is not predictive of PDSS events, neither are pre-existing olanzapine concentrations. Patients for whom prior olanzapine concentration data were available and who also experienced a PDSS event did not have a history of high concentrations prior to the event. Also, patients who did not experience a PDSS event but who had concentrations beyond the 90th percentile of steady-state concentration oral exposures did not exhibit adverse events suggestive of a PDSS event or of a subsyndromal event. Moreover, no threshold can be identified for prior olanzapine concentrations that would predict the occurrence of a PDSS event. In other words, although all PDSS events are generally associated with elevated olanzapine concentrations, the presence of elevated olanzapine concentrations is not a predictor of PDSS events. Therefore, elevated olanzapine concentrations can occur under normal circumstances and should be regarded differently from elevated concentrations which occur as a result of olanzapine pamoate inadvertently entering the blood stream following injection.

Predicted Olanzapine Concentrations During Dose Loading
As olanzapine concentrations do not exhibit a well-defined relationship to efficacy or safety, the primary assessment of appropriateness of the proposed dose loading regimens was based on the clinical hazard ratio (HR) assessment. Nonetheless, as a complementary visual aid, PK simulations were conducted to evaluate maintenance doses in the presence or absence of loading doses.

FDA Comment 6 (23 April 2009)

Since the excessive sedation does not occur with oral dosing, therefore you would not be able to assess the likelihood of excessive sedation during the loading dose period? Is that correct?

Lilly Response

We have not specifically analyzed risk of PDSS in relation to our dose loading recommendations because PDSS is understood to be a relatively random event (or accident) that can occur at any injection, at any dose, and regardless of previous dose of oral olanzapine or previous dose of OP Depot. Therefore, a patient who was on 10 mg per day oral olanzapine and who gets a first injection of 405 mg OP Depot would be no more at risk at that injection than they would be at their 100th injection of 405 mg OP Depot. Thus, it is our belief that the use of a loading dose does not increase the likelihood that it can result in a PDSS event. We do believe the loading dose will minimize the risk of a costly and devastating relapse of symptoms of schizophrenia, which has serious long-term consequences for the patient.

REVIEWER'S COMMENTS

The reviewer does not agree with the firm's rationale for choosing the loading dose based on the clinical hazard ratio (HR) assessment since the outcome in each arm is dependent on the cumulative effect of the treatments during the first 8 weeks and after the first 8 weeks.

REVIEWER'S ANALYSIS

INTRODUCTION

FIRM'S MODELLING

The control streams and data were run under NMFE6, Wings and also on the Linux Cluster but it would not run. The data was edited to delete all commented data lines and it still would not run. The issue was discussed with Yaning Wang and he was also unsuccessful. Therefore the firm supplied the results from their data fitting to OCP on a CD and all data confirmation was based upon the CD contents.

The firm only had variability on two parameters clearance and oral Bioavailability whose standard error values were reasonable. This modeling approach is reasonable given the long duration for absorption, i.e., 4 weeks.

MODEL QUALIFICATION

The qualification fits were acceptable although the plots for study HGKB where most of the excessive exposure occurred with very high observed levels up to 600 ng/ml (see Figure 6) were not part of the model.

TRANSITION AND COMPARISON OF ORAL TO OP DEPOT INJECTION

It is noted that OP dosing extends above the average 90th percentile of oral olanzapine dosing. This was surprising since there should be less absorption variables for a depot versus oral administration. The firm provided an explanation that this may be due to the inherent variability in the OP Depot concentration profile, without further explanation. They also pointed out that olanzapine absorbed from an intramuscular dose of OP Depot does not undergo first-pass metabolism suggesting that the relatively higher olanzapine exposure after an OP Depot dose may reflect slightly higher bioavailability than a comparable oral olanzapine dose. The absence of a first-pass would seem to support less variability in absorption not more.

LOADING DOSE AND EXPOSURE

Study HGKA was cited by the firm as supporting the need for a loading dose to prevent relapse.

Table 10. Dosage and Medication Schedule for Study HGKA

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

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

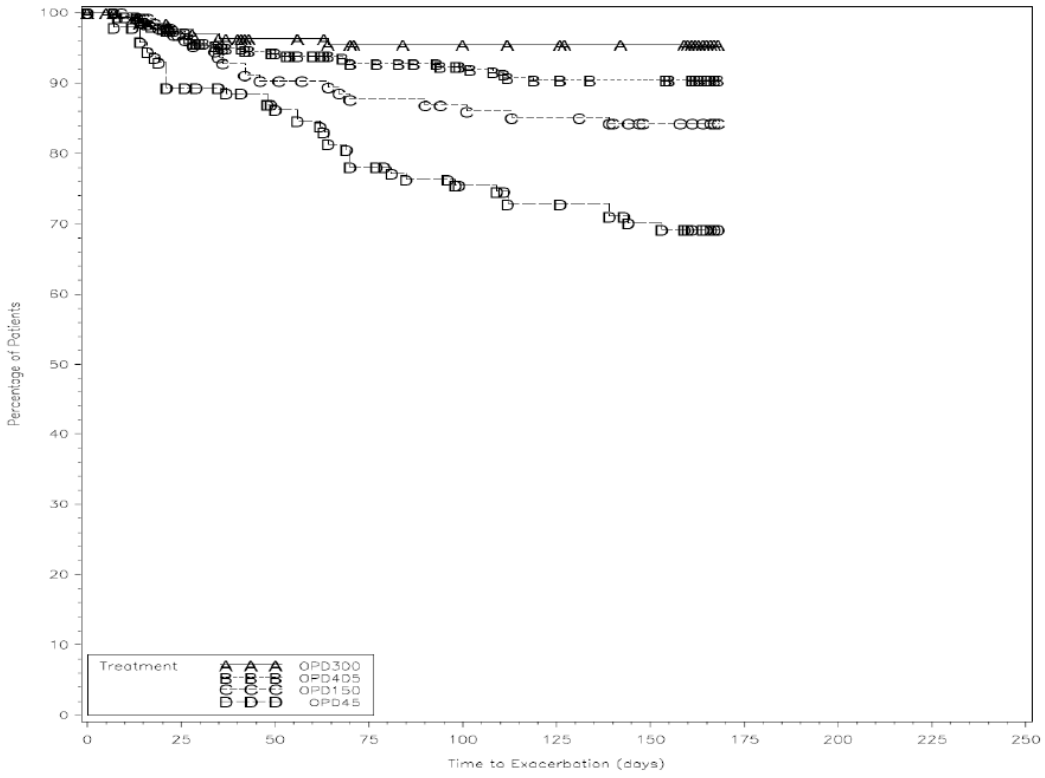


Figure 19. Time to Exacerbation for the double-blind maintenance phase (higher doses of OP depot versus low-dose OP depot; log-rank test).

Table 11. Summary of Patient Disposition in Study HGKA

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

These results clearly show a benefit of less relapse and time to relapse with the higher doses i.e., 300 mgQ2

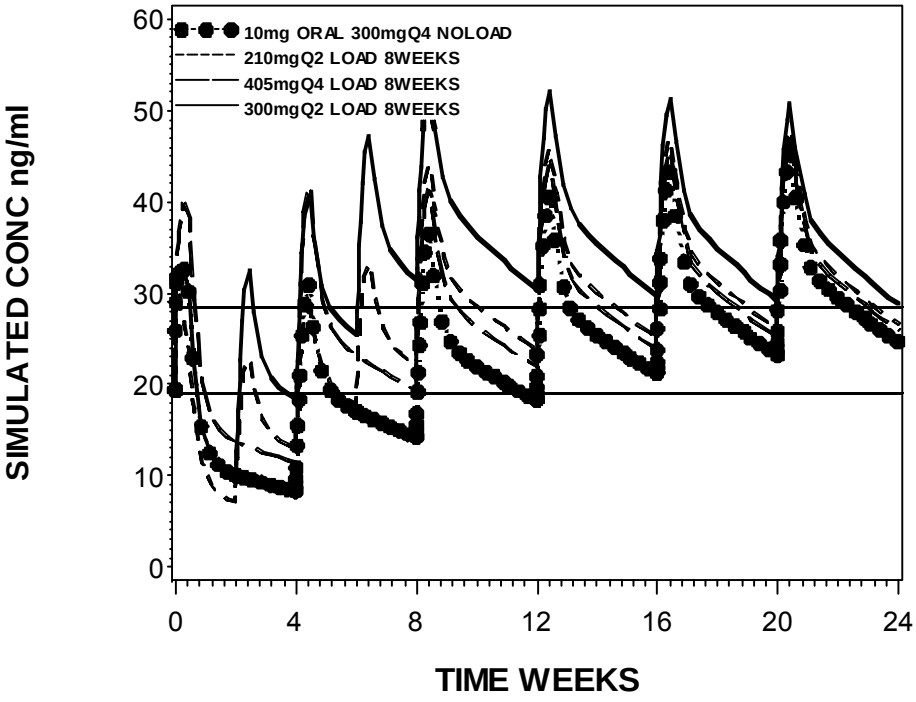


Figure 20. Simulated median olanzapine concentrations for switching from 10 mg oral dose to 300mgQ4(every four weeks) maintenance depot injection without and with loading doses of 210mgQ2, 405mgQ4 and 300mgQ2. The horizontal upper and lower lines represent the median steady-state Cmax and Cmin values, respectively for the 10 mg oral dose. Prepared from SAS program located at:

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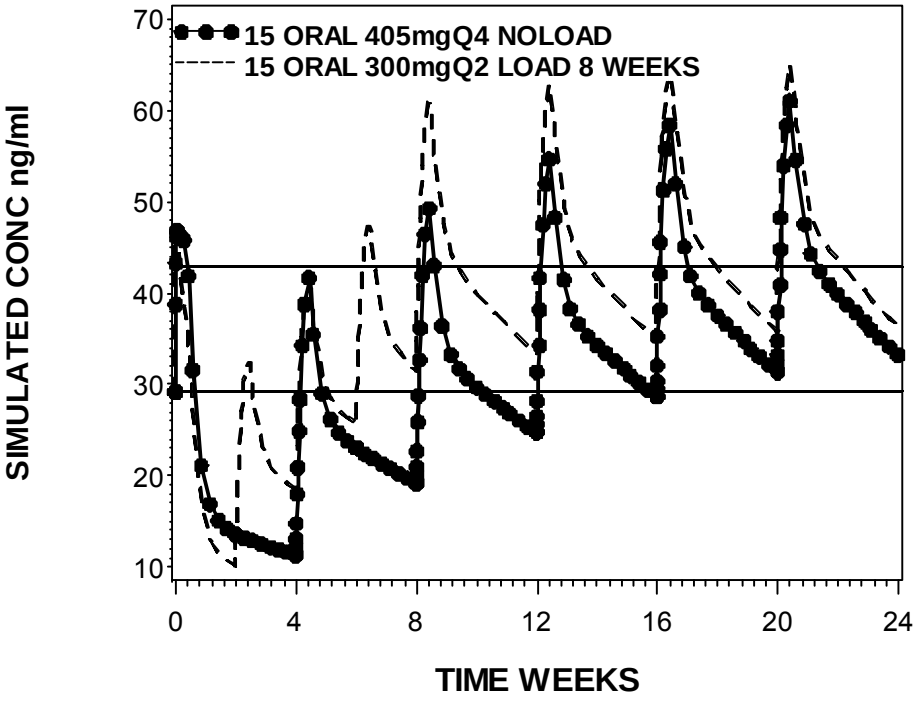

Figure 21. Simulated median olanzapine plasma concentration profiles during the loading and maintenance dose periods for regimens recommended to provide approximately 15 mg olanzapine per day with the final maintenance dose of 405mgQ4 without and with a loading dose of 300mgQ2 over 8 weeks. The horizontal lines are the median Cmax and Cmin values respectively. Prepared from SAS program located at:

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LOADING DOSE POST-INJECTION DELIRIUM/SEDATION SYNDROME-EXCESSIVE EXPOSURE

The statistical analysis from Table 12 does state that dose is not a significant factor in determining PDSS. However, a 50% increase in the incidence for the same number of injections raises concern (i.e., 300 mg 1406 doses vs. 405 mg 1585 doses) 0.07% vs 0.13% from the prior studies.

Table 12. Post-injection Delirium/Sedation Syndrome Events in Patients Receiving OP Depot Injections. Table located at: \\Cdsnas\pharmacometrics\Zyprexa_NDA22173_AJ\Sponsor Data and Reports\20090507 NDA22173 ClinPharm Responses (2).pdf

Dose (mg)	Total No. Doses Given	PDSS Events (%)[a]	Total Doses Given First 8 Weeks	PDSS Events First 8 Weeks (%)[b]
150	2615	1 (0.04)	589	0
195	175	1 (0.57)	3	0
210	7128	3 (0.04)	1083	1 (0.09)
250	65	2 (3.08)	2	0
270	521	1 (0.19)	8	0
300	14,732	8 (0.05)	1406	1 (0.07)
330	383	1 (0.26)	4	0
345	570	1 (0.18)	24	0
360	177	1 (0.56)	4	0
390	206	1 (0.49)	8	0
405	10,202	9 (0.09)	1585	2 (0.13)
Other[c]	4419	0	618	0
Total	41,193	29 (0.07)	5334	4 (0.07)

Abbreviations: No. = number; p = p-value; OP = Olanzapine Pamoate; PDSS = Post-injection delirium/sedation syndrome.

[a] In the analysis of all PDSS events, there were no statistically significant differences in incidence rate of PDSS in the following OP Depot doses (mg) based on Fisher's Exact test: 150 vs. 210: p=1.000; 150 vs. 300: p=1.000; 150 vs. 405: p=.698; 210 vs. 300: p=1.000; 210 vs. 405: p=.380; 300 vs. 405: p=.332.

[b] In the analysis of PDSS events during the first 8 weeks, there were no statistically significant differences in incidence rate of PDSS in the following OP Depot doses (mg) based on Fisher's Exact test: 150 vs. 210: p=1.000; 150 vs. 300: p=1.000; 150 vs. 405: p=1.000; 210 vs. 300: p=1.000; 210 vs. 405: p=1.000; 300 vs. 405: p=1.000.

[c] Other OP Depot doses, in which no PDSS events occurred, include the following (mg): 45, 50, 60, 75, 90, 100, 105, 120, 135, 160, 165, 180, 190, 200, 204, 205, 225, 240, 255, 260, 275, 280, 285, 301, 305, 310, 315, 375, 400, and 450.

Source: fqdosn01a; fqdosn01c.

EXACERBATION OF SYMPTOMS-RELATIONSHIP TO EXPOSURE

The reviewer analyzed the efficacy data during the first 8 weeks to evaluate whether the loading dose is appropriate for each corresponding oral dose. In study HGKA the firm recorded this information and put it in the file SUBJINFO.xpt located at:

\\Cdsnas\pharmacometrics\Zyprexa_NDA22173_AJ\ER Analyses\Final Model\SurvivalModel\.

Event after 8 weeks was treated as censored at week 8 in the Cox regression analysis. Within each oral dose, only 150mgQ2, 405mgQ4 and 300mgQ2 were compared to the oral dose based on Cox regression model since 45mgQ2 was obviously inferior to the established oral dose. The results are listed in Table 13.

Kaplan-Meier plots are shown in Figure 17-19. Based on hazard ratio estimates, 300mgQ2 should be the best loading dose for 10 mg oral dose because it not only provides a better efficacy but also could potentially have lower PDSS rate (Table 12) during the loading period. However, 300mgQ2 does not seem to be able to maintain the efficacy of 15 mg and 20 mg oral doses during the loading period. Even though higher loading doses may maintain or achieve better efficacy, no higher doses can be recommended because 300mgQ2 was the highest tested regimen.

Based on the proposed maintenance doses, the steady state exposures will be higher than all the previously established exposures under oral doses. As a result, the overall efficacy observed in study HGKA for the maintenance doses of (150mgQ2 for 10 mg, 405mgQ4 for 15 mg and 300mgQ2 for 20 mg) is an average of relative sub-optimal efficacy before 8 weeks and improved efficacy after 8 weeks as indicated by the hazard ratio estimates in Tables 13 and 14.

Table 13. Results from Cox regression analysis for the first 8 weeks relative to OLZ

Oral Dose	Therapy	HR	95% CI	p-Value
10mg	OPD150	2.644	0.661, 10.575	0.169
	OPD405	1.093	0.273, 4.371	0.900
	OPD300	0.581	0.065, 5.195	0.627
15mg	OPD150	2.589	0.162, 41.418	0.501
	OPD405	2.792	0.253, 30.796	0.402
	OPD300	2.627	0.164, 42.00	0.495
20mg	OPD150	3.487	1.106, 10.996	0.033
	OPD405	2.132	0.751, 6.053	0.155
	OPD300	1.343	0.321, 5.620	0.686

Table 14. Results from Cox regression analysis after 8 weeks relative to OLZ

Oral Dose	Therapy	HR	95% CI	p-Value
10mg	OPD150	1.689	0.404,7.066	0.4731
	OPD405	0.963	0.259,3.585	0.9548
	OPD300	0	0, NA*	0.9951
15mg	OPD150	1.78	0.297,10.652	0.5277
	OPD405	0.995	0.166,5.954	0.9952
	OPD300	0	0, NA*	0.9965
20mg	OPD150	1.836	0.307,10.991	0.5056
	OPD405	0.912	0.184,4.52	0.9106
	OPD300	0.758	0.079,7.289	0.8105

*NA: not available

Figure 22. Kaplan-Meier plots for the time to exacerbation for the 10 mg oral dose switched respectively to depot injection doses of 150mgQ2, 405mgQ4, 300mgQ2 and 45mgQ4.

10mg

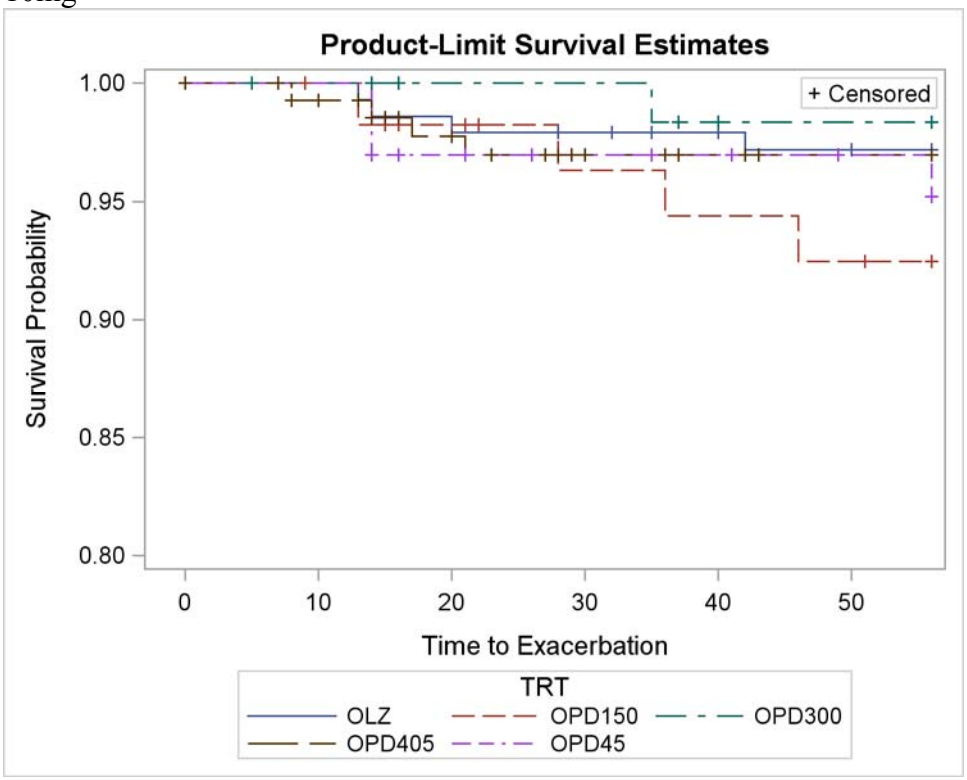


Figure 23. Kaplan-Meier plots for the time to exacerbation for the 15 mg oral doses switched respectively to depot injection doses of 150mgQ2, 405mgQ4, 300mgQ2 and 45mgQ4.

15mg

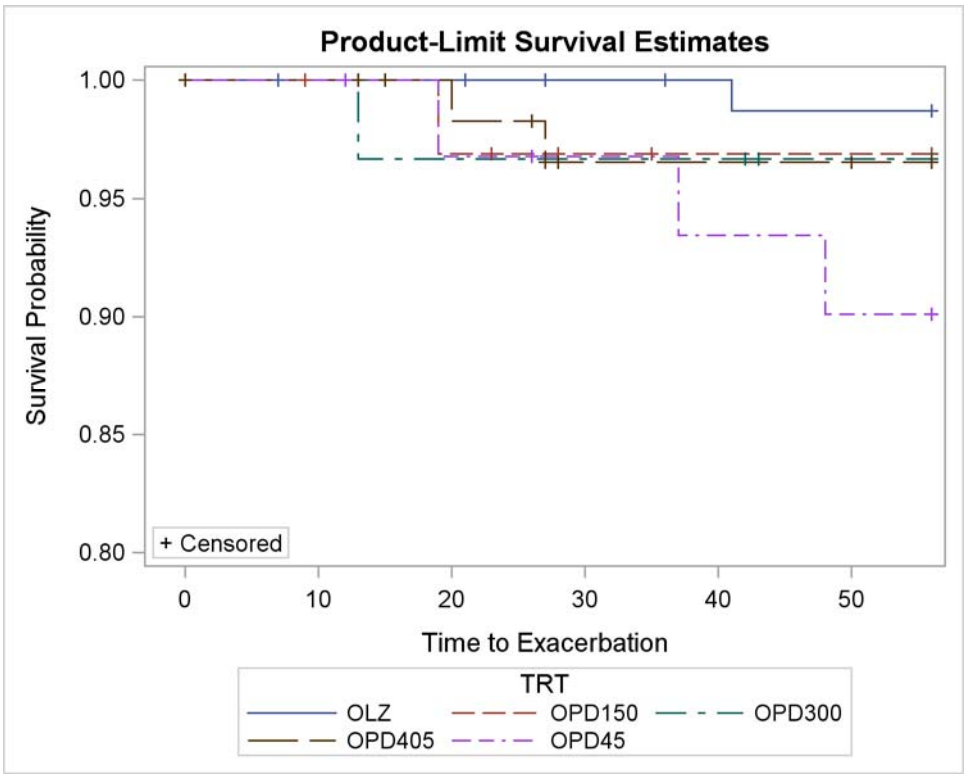
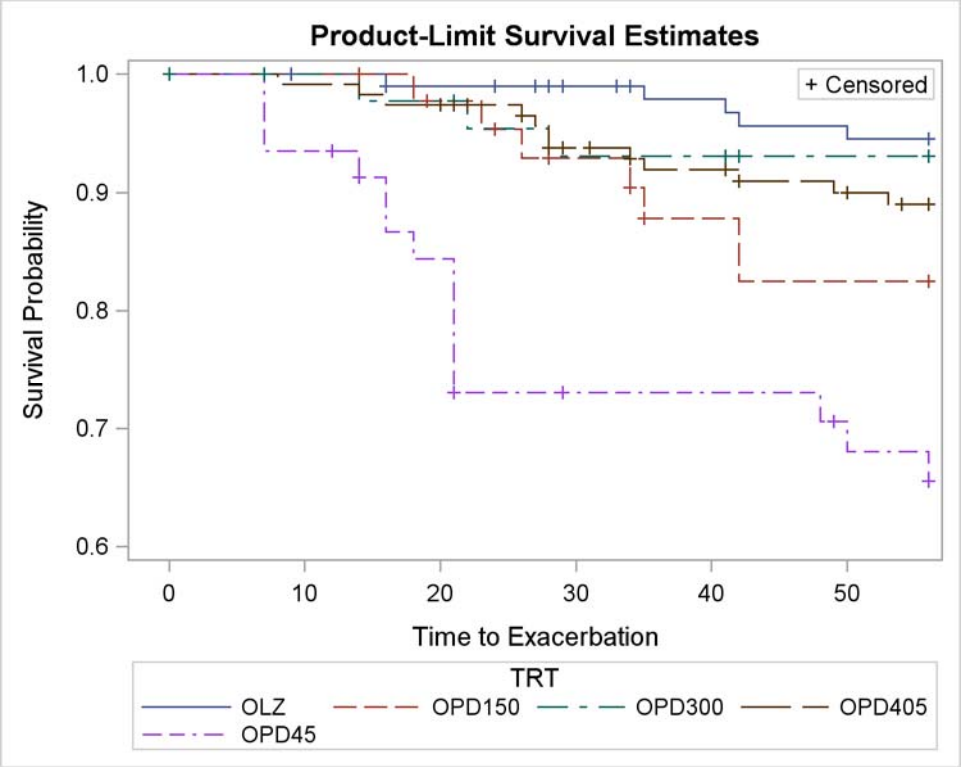


Figure 24. Kaplan-Meier plots for the time to exacerbation for the 20 mg oral doses switched respectively to depot injection doses of 150mgQ2, 405mgQ4, 300mgQ2 and 45mgQ4.

20mg



SIGNATURES

Andre Jackson_____
Reviewer, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology

RD/FTinitialized by Yaning Wang Ph.D._____

Team Leader Pharmacometrics

cc: NDA 22-173, HFD-860(Mehta, Baweja, Jackson,Wang)
C:\Data\REVIEWS\NDA\ZYPREXA_NDA22173LILLY\LABELSIM\LABELSIM_REV4JYW.doc

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22173	ORIG 1		ZYPREXA/ADHERA
NDA 22173	ORIG 1		ZYPREXA/ADHERA

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/s/

ANDRE J JACKSON
08/17/2009

YANING WANG
08/17/2009

RAMAN K BAWEJA
08/17/2009

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Olanzapine Pamoate
PRODUCT (Brand Name):	ZYPREXA
DOSAGE FORM:	Long-acting Injection
DOSAGE STRENGTHS:	150 mg/2 wks, 300 mg/4 wks, 210 mg/2 wks, 405 mg/4 wks, 300 mg/2 wks
NDA:	22173
NDA TYPE:	New NDA
SUBMISSION DATE:	June 13, 2008
SPONSOR:	Eli Lilly
REVIEWER	Andre Jackson

REVIEW OF A COMPLETE RESPONSE FOR THE NEW LONG ACTING INJECTION OF OLANZAPINE PAMOATE

Background:

The submission submitted to OCP for the IM depot formulation for Zyprexa contained the following dissolution data.

DISSOLUTION

ABSTRACT: The rate of release of olanzapine from olanzapine pamoate drug product (426906) is determined by performing the dissolution testing with a 1.0% Sodium Lauryl Sulfate in USP buffer pH 6.8 medium using USP Apparatus 4 (or Ph.Eur. 2.9.3 Flow-Through Apparatus) at 3 mL/min flow rate. The amount of olanzapine present in solution is then determined by using a reversed-phase HPLC system with UV detection. Working standard solutions are stable for 7 days at ambient conditions. Samples are stable for 5 days at ambient conditions. Replicate and average results are treated according to USP testing criteria for extended release dosage forms.

Proposed dissolution specifications for the different doses:

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APPENDIX

Meeting Minutes

Meeting Date: 4/27/04
Location: WOCII - Rm 4028
IND: 60,701
Drug: Olanzapine IM pamoate depot formulation
Sponsor: Lilly
Type of Meeting: CMC/Biopharm Telecon
Meeting Chair/Recorder: Steven D. Hardeman, R.Ph.
Participants:
FDA:
Tom Oliver, Ph.D., CMC Team Leader, DNDP
Vaneeta Tandon, Ph.D., Biopharm Reviewer, HFD-860
Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, DNDP
Lilly:
John Roth, Ph.D., Senior Regulatory Research Scientist, U.S. Regulatory Affairs and team

Meeting Objective: Discussion of in-vitro dissolution method development plan.

Discussion Points:

1. Does the FDA agree with the revised dissolution method development plan for the extended duration method?

Response: The revised dissolution method appears acceptable for the extended duration method showing (J) 9 released by 8-10 days for doses (210 and 300 mg) that will be used every 2-weeks. However, we would like to know how this method could apply to a higher dose (405 mg) that is intended to be released for up to 4-weeks. You should address this concern or provide a rationale as to why the proposed dissolution method would be appropriate for doses that are intended to be every 4 weeks. A dissolution method should correlate with intended in-vivo release and be able to discriminate between the various attributes of drug substance such as crystal form, particle size, surface area etc.

pages

2. Does the FDA agree with the plan to develop an accelerated dissolution method that correlates to the extended duration dissolution method for Quality Control batch release andstability testing?

Response: Yes, the approach seems acceptable.

3. Does the FDA agree that a rank order correlation of the accelerated method to the extended duration method is a sufficient criterion for an acceptable accelerated method?

Response: The approach seems acceptable, contingent upon the results of the study that would show a good correlation.

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this page is the manifestation of the electronic signature.

/s/

Steve Hardeman
4/28/04 07:01:45 AM
signed for Tom Oliver and Vaneeta Tandon

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

/s/

Andre Jackson
11/7/2008 11:14:27 AM
BIOPHARMACEUTICS

Raman Baweja
11/7/2008 11:46:29 AM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Olanzapine Pamoate
PRODUCT (Brand Name):	ZYPREXA
DOSAGE FORM:	Long-acting Injection
DOSAGE STRENGTHS:	150 mg/2 wks, 300 mg/4 wks, 210 mg/2 wks, 405 mg/4 wks, 300 mg/2 wks
NDA:	22173
NDA TYPE:	New NDA
SUBMISSION DATE:	April 27, 2007
SPONSOR:	Eli Lilly
REVIEWER	Andre Jackson

REVIEW OF A NEW LONG ACTING INJECTION OF OLANZAPINE PAMOATE

EXECUTIVE SUMMARY

The firm is seeking approval of an intramuscular depot injection for the following Olanzapine dosing regimens (i.e., 150 mg/2 weeks, 210 mg/2 weeks, 300 mg/2 weeks, 300 mg/4 weeks and 405 mg/4 weeks). Oral Olanzapine is currently approved for the same indication. The IM depot is expected to eliminate daily oral doses and improve convenience/adherence. The PK of the IM depot formulation is well characterized. IM formulation is 86-97% as bioavailable (i.e., based upon AUCinf) as the comparable oral dose.

There is one key question for this submission:

1. Are the symptoms of sedation, dizziness, confusion and coma (perceived to be a consequence of inadvertent intravenous injection (IAIV)) Olanzapine exposure related? Is there a prognostic factor to identify patients at higher risk of this AE? A major adverse event was seen in 24 subjects (approximately 1.2% of treated subjects) related to very high olanzapine plasma levels(>150 ng/ml). resulting from the Olanzapine OP

depot injection. Dose and mean steady-state plasma levels are presented in the following Table.

Oral Dose	OP Depot Dose		
20 mg QD	150mg/2wk 300mg/4wk	210mg/2wk 405mg/4wk	300mg/2wk
49.1 ng/ml	26.5 ng/ml	30.7 ng/ml	49.9 ng/ml

The 405 mg/4 weeks has the highest probability to have these high concentrations. The event was reported within 30 min to 3 hrs post injection. The high drug levels were believed to arise from an IAIV (inadvertent intravenous injection). Symptoms of these injections included sedation, dizziness, confusion and coma. All of the effects were reversible in 24 to 48 hrs. Since drug levels were not collected for all subjects experiencing an event, analysis of available data did not reveal a pattern and the events appeared to be random. The firm conducted additional studies in subjects to define if a small initial release of olanzapine occurred after each injection of OP Depot. However the results indicated no major spike in the observed plasma levels.

Two approaches to manage this risk are:

1. Avoid 405 mg/4 weeks to minimize the probability of high concentrations, and thus potential IAIV related events.
2. Have patients remain in doctor's office for 3 hours after the injection.

COMMENTS TO THE MEDICAL OFFICER

A.The firm should reorganize the Drug/Drug interaction section into:

1)Effect of other drugs on olanzapine
2)Effect of olanzapine on other drugs

B. Section 12.3 Pharmacokinetics

Line 635 -The olanzapine plasma concentration fluctuation between the peak and trough is comparable to the peak and trough fluctuations associated with once daily oral dosing.

change to read

The olanzapine plasma concentration fluctuation between the peak and trough for once-weekly dosing is comparable to the peak and trough fluctuations associated with once daily oral dosing.

B. Dissolution Comments:

The comments section at the end of the review contain comments that should be forwarded to the sponsor related to dissolution.

COMMENTS TO THE SPONSOR:

1. The product on which the dissolution testing is being conducted is not clear. Is it the reconstituted suspension, and if so, what is the stable shelf life of this product as per a stability indicating assay.

2. The concentration of 1% sodium lauryl sulfate (SLS) in the pH 6.8 buffer seems to be very high, essentially implying that all of the drug is 'solubilized' rapidly. Has the sponsor tried experimentation with lower concentrations of SLS, and if so, please provide these results.

3.The sponsor should explain why they request different release specifications for different doses.

4.No dissolution data was provided for the ambient conditions of 25 C/60 % RH. The sponsor should provide this data for relevant clinical, bio-, and finished product stability lots.

5.The sponsor should provide the content uniformity and assay results for relevant batches of this product.

QUESTION BASED REVIEW

1) WAS THERE A DOSE EFFECT OBSERVED FOR THE DEPOT INJECTIONS IN THE EFFICACY STUDIES?

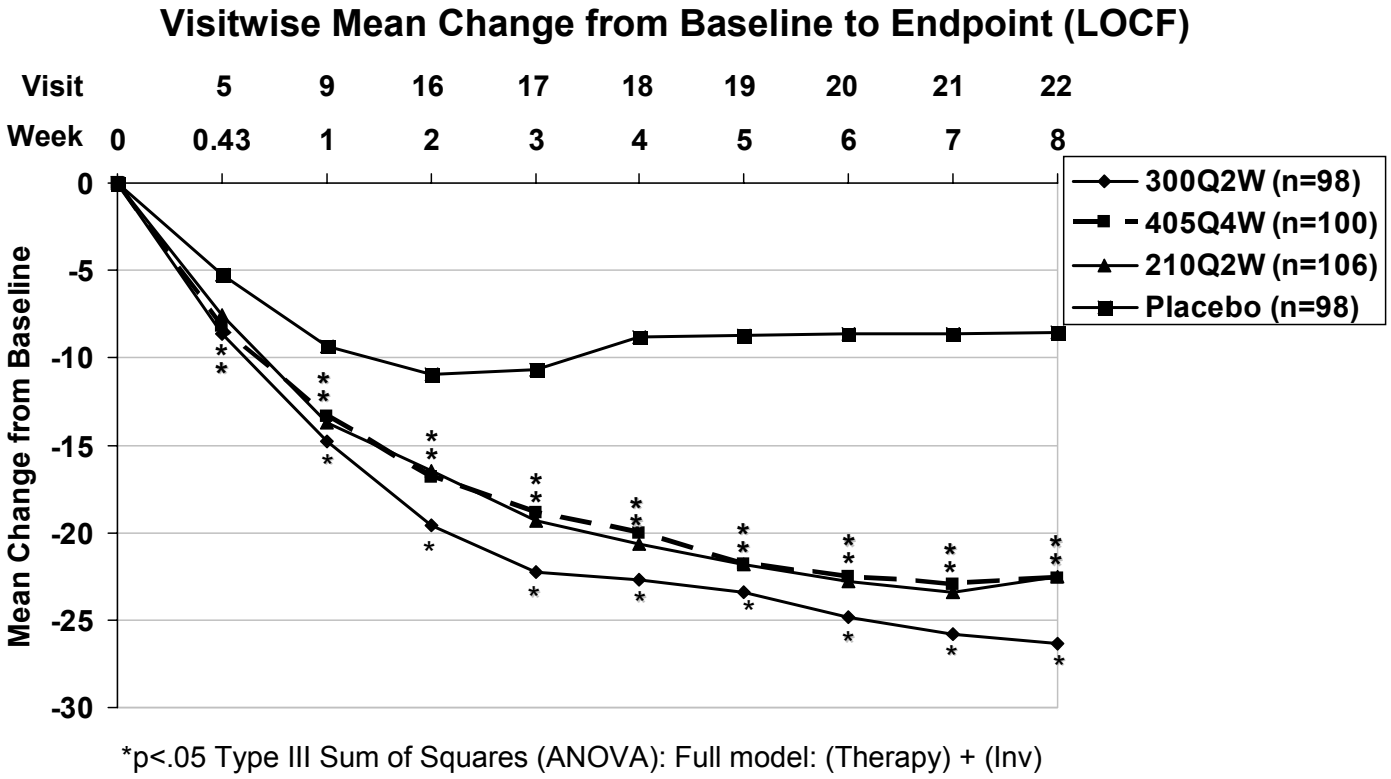


Figure 1. Visit-wise mean change from baseline to LOCF endpoint in PANSS Total score, Study Period II, Study HGJZ.

The data show a statistically significant improvement between each OP Depot dose and placebo at weeks 1 through 8. However, there is not a clear dose response between the total doses at week8 (i.e., 4x300mg/2wks =1200 mg; 2x405mg/4wks=810 mg ; 4x210mg/2wks=840 mg although there is a downwards trend with increase in exposure.

A second study HGKA using a Non inferiority design compared fixed doses of 150 mg/2 wks, 405 mg/4 wks and 300 mg/2 wks vs. a 45 mg/4 wk depot injection during the study maintenance phase and showed the superiority of the doses over the 45 mg/4 wks regimen.

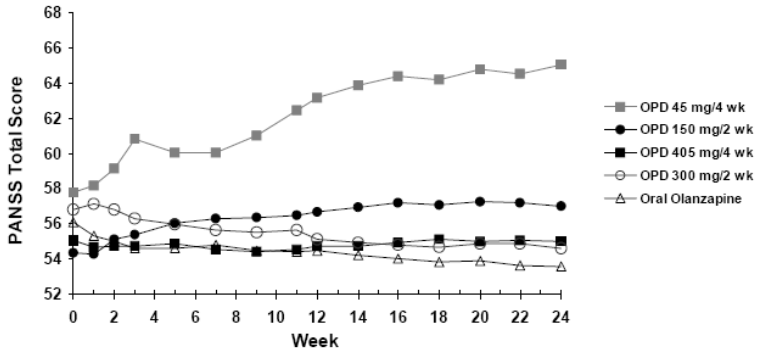
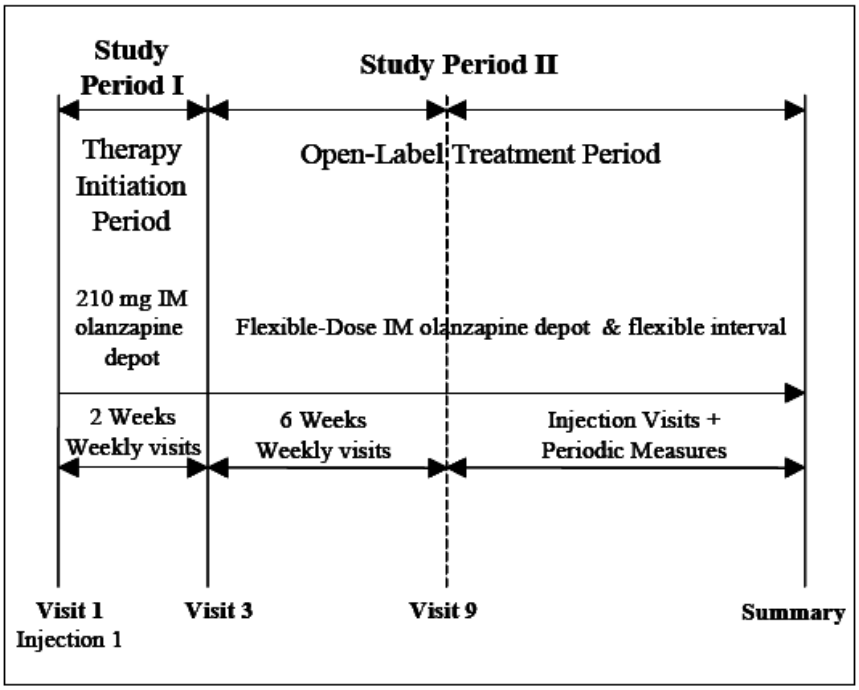


Figure 2. PANSS Total Scores; Visit-wise Change From Baseline to Endpoint (LOCF); All Pairwise Comparisons; Double-Blind Maintenance Phase

2) IS THERE EMPIRICAL EVIDENCE TO SUPPORT THE PROPOSED 300 MG/4 WK REGIMEN?

The 300 mg/4 wk regimen was investigated in study HGKB which had flexible dosing.



Note: In Protocol HGKB, OP Depot was called IM olanzapine depot.

Figure 1. Illustration of study design for Protocol F1D-MC-HGKB.

Cmin plasma levels obtained from a companion study LOBE based upon 4 wk dosing for different doses including effective doses 150 mg and 210 mg/2weeks.

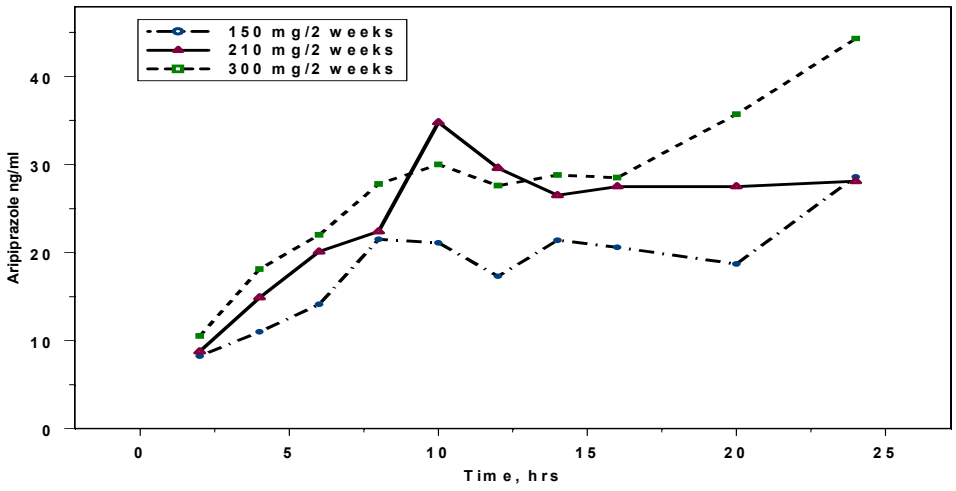


Figure 2. Mean olanzapine plasma concentrations for the Multiple-Dose Group at doses ranging from 150-300 mg/ 2 weeks from study LOBE which was designed to assess the safety and tolerance of IM olanzapine depot after single and multiple doses in subjects with stabilized schizophrenia.

3) DOES THE DATA COLLECTED DURING REPORTED INADVERTENT INTRAVENOUS INJECTIONS (IAIV) EVENTS PROVIDE ANY EXPLANATION AS TO WHY THEY OCCURRED AND ARE THEY PREDICTABLE?

There were 24 reported IAIV events as of July 2007 with 2 occurring in the same subject. All injections were into the gluteal muscle.

All subjects that experienced an IAIV did not have plasma samples collected. The following Table 2 summarizes the subjects and their plasma levels.

Table 2. Summary of the calendar date, days on study, dose, time of sample from last dose and Olanzapine concentrations for those subjects that had plasma levels collected near the occurrence of their IAIV.

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

(continued)

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

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

Patient HGKB 235-7685 was documented to have IAIV event #10 which occurred prior to 2.7 hrs. Blood samples were collected hourly from 2.7 to 4.7 hrs and a final sample at 24.7 hrs. The subjects highest recorded level was 133 ng/ml at 2.7 hours. Some subjects in other studies (e.g., HGKB 015-56001 had a peak level of 100 ng/ml at 1.5 hrs but did not exhibit an IAIV. Based upon these findings the IAIV events appear to be random and not very predictable, however there may be an unknown covariate associated with IAIV that has yet to be identified, (e.g., rate of input) in addition to injection technique.

3) IS THERE AN EXPOSURE RESPONSE RELATIONSHIP FOR THE IAIV EVENTS AND IS IT PREDICTIVE OF IAIV EVENT OCCURRENCE?

Rate of Exposure

If a comparison is made between the most rapidly available dosage form RAIM-(study LOBS) a solution of olanzapine (base) and the OP Depot, which is a crystalline salt formulation—olanzapine pamoate monohydrate—composed of olanzapine and pamoic acid used in study HGKB using the following relationship, rates of change of plasma parameters can be calculated using the following relationships.

$$\Delta C = \frac{C_{max} - C(0)}{C(0)} \times 100 \qquad \text{Eq. 1}$$

$$\Delta AUC = \frac{AUC_{0\text{-}t} - C(0) \times T_{last}}{AUC_{0\text{-}t}} \times 100 \qquad \text{Eq. 2}$$

Where C(0) is the baseline olanzapine concentration, C(0), Cmax is the highest observed concentration and AUC0-t is the area under the curve to time t.

A comparison of rate of change over a 3 hr period (i.e., the longest time interval for IAIV onset) indicated for subjects receiving the RAIM injection vs. subjects in the HGKB extension study.

Table 1. Pharmacokinetic Assessment of the Change in Olanzapine Plasma Concentration Within the 3 Hours After an Injection of OP Depot.

Parameter	C(0) (ng/mL)	T_{last} (hr)	$AUC_{0\text{-}3}$ (ng×hr/mL)	ΔAUC (%)	C_{max} (ng/mL)	ΔC (ng/mL)	ΔC (%)
Study HGKB (Pharmacokinetic Addendum 0-3 hours)†							
Average	45.9	3.0	139	1.7	58.4	12.4	31.8
Minimum	25.0	3.0	72.5	-23.6	26.3	0.0	0.0
Maximum	95.1	3.0	231.	25.8	98.2	62.0	171.
CV (%)	44.7	0.0	33.4	813.	44.6	166.	176.
n	9	9	9	9	9	9	9
Study LOBS (Period III 0-3 hours) †							
Average	11.4	3.0	55.2	40.2	27.7	16.2	180.
Minimum	1.8	2.8	15.2	-2.9	6.4	2.7	29.0
Maximum	62.0	3.2	239.	74.1	112.	50.5	1140.
CV (%)	68.3	1.2	52.6	36.6	55.9	66.0	83.3
n	126	126	126	126	126	126	126

Abbreviations: CV = coefficient of variation; n = number.

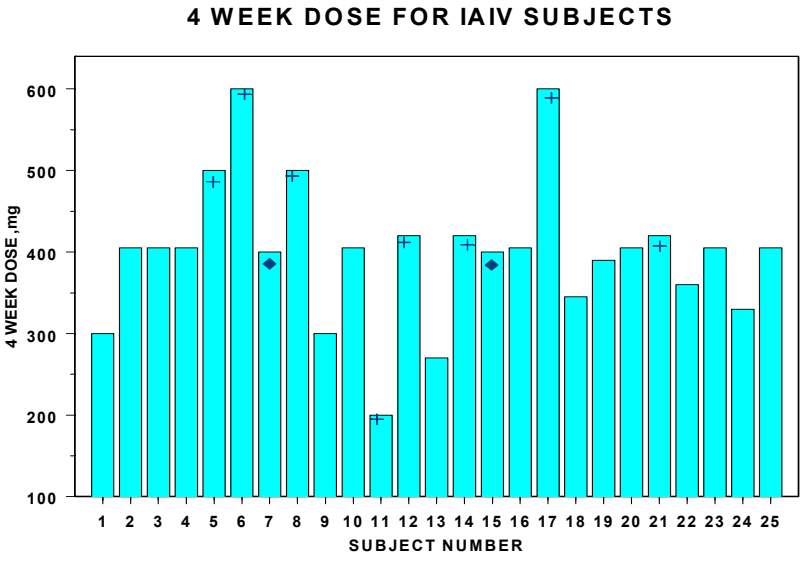


Figure 1. 4 week doses for the all subjects that exhibited an IAIV event with different dosing regimens. Crosses are subjects with 2 week regimens: 5-(250mg); subjects 6 and 17(300 mg); subject 8 (250 mg); subjects 12, 14 and 21 (210 mg); subject 11 (100 mg). Diamonds are subjects 7 and 15 with 300 mg/3 weeks regimen. All remaining subjects received 405 mg/4 weeks.

Table 2. Prior feed in study doses for subjects that had an IAIV with post IAIV plasma samples collected.

Event	Prior Dose mg	Days on Prior Dose	Study Day IAIV	Dose IAIV mg
1	300 OP	Day1-29	29.25	300 OP
5*	250 OP/2 wks 405 OP/4 wks 250 OP/2 wks	Day 14-237.92 Day 251.92-279.87 Day 279.87-294	294 294.27	 250 OP
8*	250 OP/2 wks	Day 294-475	475.93	250 OP
10	405 OP/4 wks	Day 13-479.92	480	405 OP
18	345 OP/4 wks+ 10 mg oral supplement	Day 103-282	282.17	345 OP/4 wks+ 10 mg oral supplement
22	390 OP/4 wks 375 OP/4 wks 360 OP/4 wks	Day 146-173 Day 173-342 Day 342-455	 455	 360 OP
23	210 OP/2 wks 315/4 wks 405/4 wks	Day 189-244 Day 244-273 Day 273-424	424.28	405 OP

All were receiving nearly 400 mg/doses every 4 weeks.

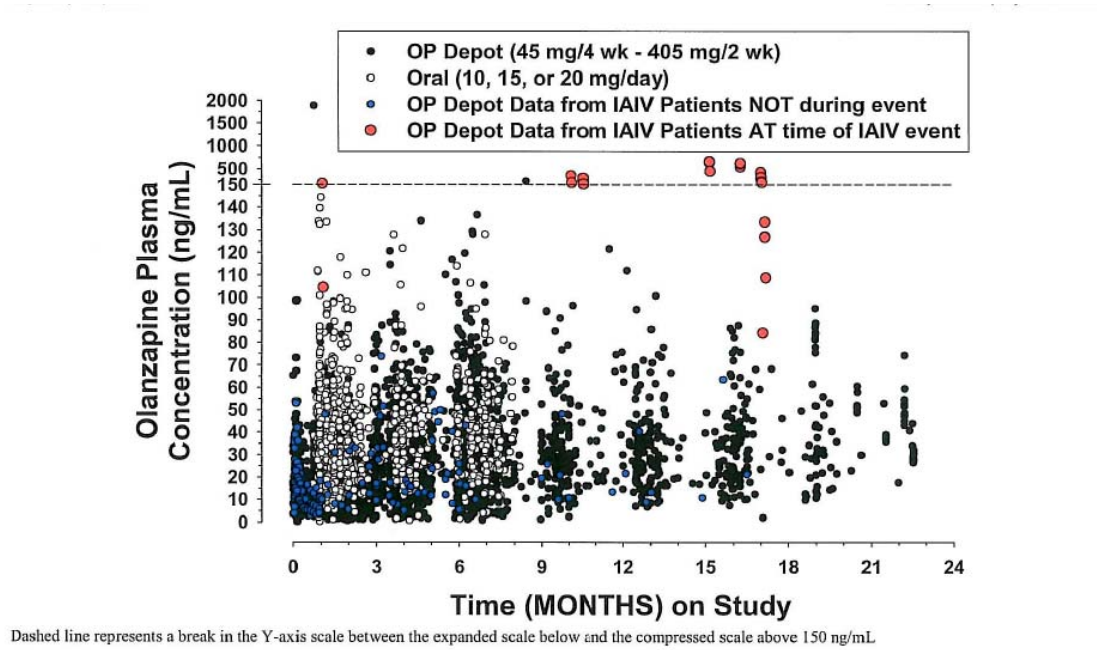


Figure 2. Olanzapine concentrations for patients experiencing an excessive exposure event superimposed upon plasma concentrations in Study HGKA after oral doses of 10,15,or 20 mg QD and the olanzapine plasma concentrations in Study HGJZ, HGKA, and HGKB after OP Depot doses of 45 mg every 4 weeks to 405 mg every 2 weeks.

4) DOES THE IAIV EVENT ALWAYS COINCIDE WITH THE PLASMA CMAX?

Table 1. Observed Cmax and determination if it is true profile Cmax.

Event #	Peak Level, ng/ml	Cmax	Hrs Post injection	Time of IAIV hrs
1	172	ND	6	0.75
5	293	Yes	9.4	1
8	423	Yes	4	0.25
10	133	ND	2.7	0.5
18	346.56	ND	4	0.5
22	627	ND	4	0.16
23	657.32	Yes	9.75	0.25

ND-Cmax Concentration was 1st sample taken or in the case of event # 22 the last. Most subjects with an IAIV had peak exposures in the range of 133-657 ng/ml.

These results indicate that the IAIV does not always occur at Cmax (e.g., events 5, 8 and 23) since the IAIV event clearly preceded Cmax.

5) ARE THE PHARMACOKINETICS OF THE DEPOT INJECTION OF OLANZAPINE PAMOATE (OP) SIMILAR TO THE ORAL FORMULATION?

A study done in eighteen healthy male subjects between 18 and 55 years who received an initial 10 mg oral dose of olanzapine in a standard tablet form on one occasion and a single dose of IM olanzapine depot (10 mg, 15 mg, 20 mg, 30 mg, and 40 mg) on another occasion.
The pharmacokinetic results were:

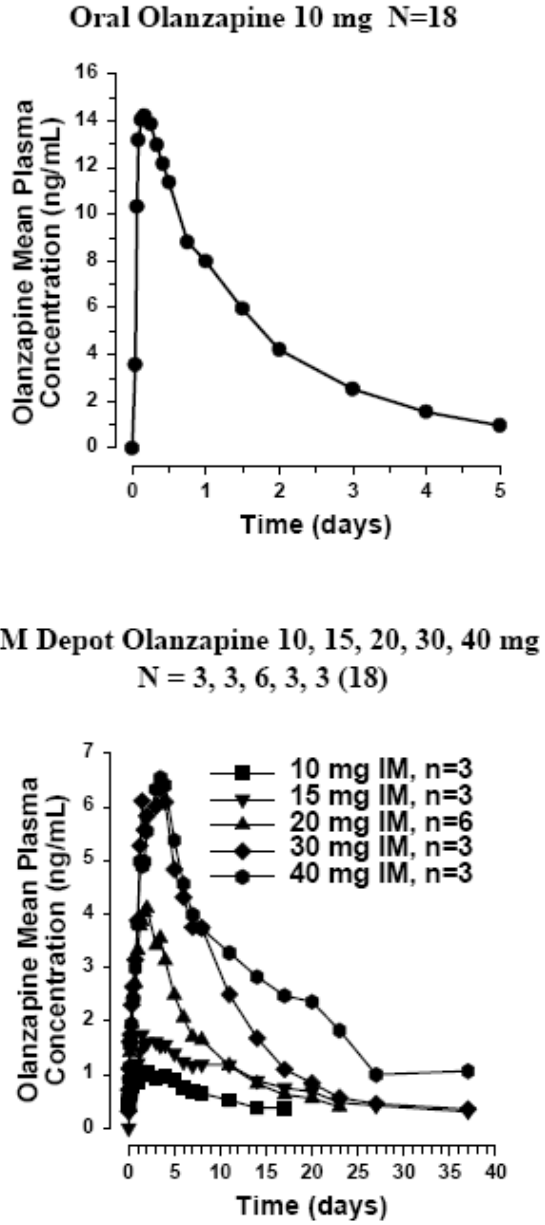


Figure 1 . Mean plasma concentrations of olanzapine for 10 mg oral and 10, 15, 20, 30, and 40 mg IM depot olanzapine doses.

Table 1 . Overall Pharmacokinetic Characteristics of Olanzapine after Oral and IM Depot Administration

Parameter	Units	Oral 10 mg	Depot 10 mg	Depot 15 mg	Depot 20 mg	Depot 30 mg	Depot 40 mg	Depot (Overall)
N		18	3	3	6	3	3	18
C_{max}	(ng/mL)	16.7	1.13	1.85	4.35	6.99	6.77	NA
T_{max}	(hr)	4.8	28.0	56.0	52.0	68.0	132	64.7
$AUC_{0-\infty}$	(ng•hr/mL)	602	375	831	990	1710	2642	NA
C_{max}/Dose	(ng/mL)/(mg/kg)	126	9.60	9.00	16.7	16.1	11.1	13.2
$AUC_{0-\infty}$/Dose	(ng•hr/mL)/(mg/kg)	4549	3230	4081	3885	3927	4839	3974
$t_{1/2}$	(hr)	31.6	242	330	262	241	290	271
Cl_p/F	(L/hr)	17.6	26.7	18.2	21.0	17.6	15.2	20.0
V_{z}/F	(L/kg)	10.3	106	118	96.7	90.4	83.0	98.4
MRT	(hr)	44.4	348	493	343	276	471	379

The 10 mg depot injection had a much lower Cmax and AUCinf compared to the 10 mg oral dose. The depot injections for olanzapine exhibited linear kinetics for both Cmax and AUCinf. The estimated average fluctuation index value (i.e., calculated as the difference between the Cmax and the measured concentration at the time (Tau) of each subsequent dose) for once-daily oral olanzapine is 36%. The estimated average fluctuation index values for the IM depot olanzapine (pamoate monohydrate) are: for once-weekly dosing 28%; for every-two-weeks dosing 81%; and for once-monthly dosing 205%.

The following table compares dose normalized Cmax and AUC values for oral vs. depot injections. Oral administration appears to be approximately 13% more bioavailable than the IM depot. This discrepancy may be related to the time to collect plasma for the IM doses i.e., 28 days and issues related to assay sensitivity.

Table 2. Comparison of oral vs. op injections

PK Parameter	Units	Oral 10 mg	Depot (Overall)
N		18	18
C_{max}	(ng/mL)	16.7	NA
T_{max}	(hr)	4.8	64.7
$AUC_{0-\infty}$	(ng•hr/mL)	602	NA
C_{max}/Dose	(ng/mL)/(mg/kg)	126	13.2
$AUC_{0-\infty}$/Dose	(ng•hr/mL)/(mg/kg)	4549	3974
$t_{1/2}$	(hr)	31.6	271
Cl_p/F	(L/hr)	17.6	20.0
$V_{\lambda z}/F$	(L/kg)	10.3	98.4
MRT	(hr)	44.4	379

NA = Not applicable (different doses administered, see Table LOAZ.11.2)

6) WHAT WAS THE EXPOSURE TO PAMOIC ACID FROM THE FORMULATION?

A study done in Six healthy male subjects, between the ages of 25 and 37 years compared oral OP olanzapine to a marketed compound, hydroxyzine pamoate (Vistaril®) showed that pamoic peaks early (Tmax=3hr) and is rapidly eliminated.

7) HOW DOES PARTICLE SIZE DISTRIBUTION IMPACT THE RELATIVE BA OF THE DEPOT INJECTION COMPARED TO THE ORAL FORMULATION.

A study was designed to investigate several depot lots of Olanzapine prepared by the [redacted](b) (4)" process resulting in fine, nominal and coarse particles compared to particles prepared by a new [redacted](b) (4)" process. The study also assessed the relative BA of depot olanzapine vs. RAIM (rapid-acting intramuscular olanzapine-consisting of olanzapine and the inactive ingredients lactose monohydrate and tartaric acid).

Figure 1. Study design

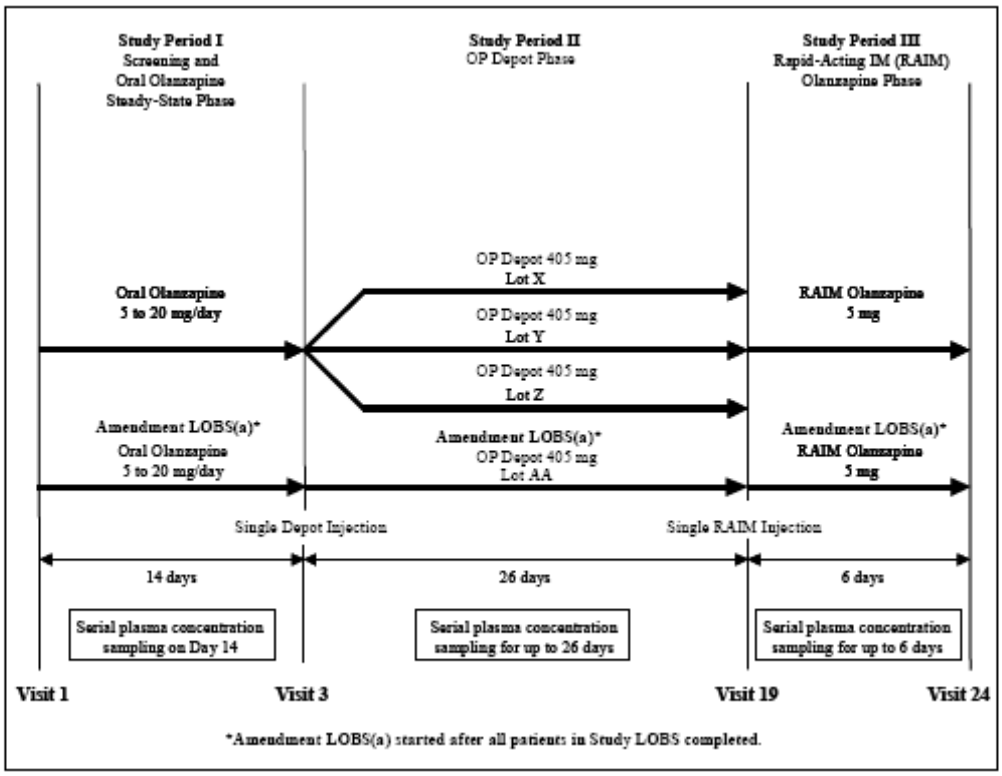
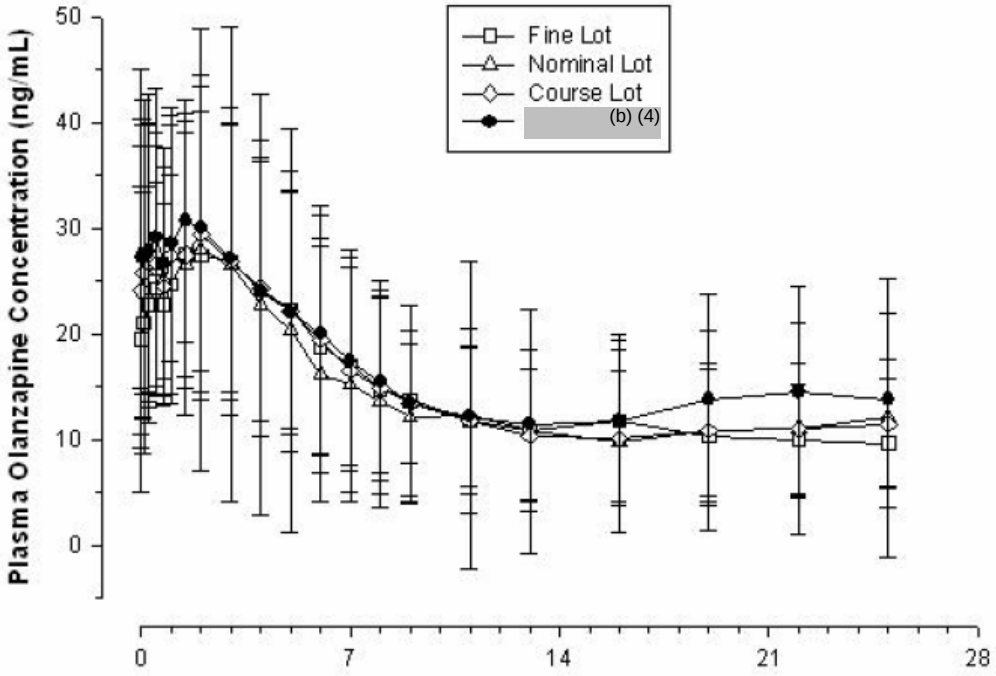


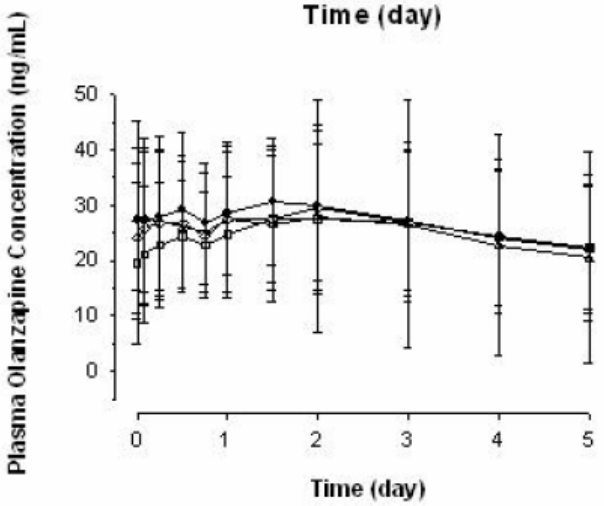
Table 1. Comparison of Relative Bioavailability Following Oral Olanzapine (at Steady State) or OP Depot Injection, Based Upon Dose-Normalized AUC(0-∞) for OP Depot

Lot	Treatment	Least-Squares Geometric Mean for Dose-Normalized AUC(0-inf)(ng*hr/mL/mg)	Ratio of OP Depot versus oral (90% Confidence Interval)	Ratio of OP depot versus RAIM
Fine	OP Depot	35.71	0.89 (0.68, 1.15)	0.96
	Oral	40.24		
Nominal	OP Depot	46.43	0.91 (0.65, 1.28)	1.04
	Oral	50.86		
Coarse	OP Depot	48.04	0.97 (0.80, 1.19)	0.894
	Oral	49.29		

(b) (4)	OP Depot	42.29	0.86 (0.72, 1.02)	1.00
	Oral	49.44		

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; OP Depot = Olanzapine Pamoate Depot.





Single 405-mg OP Depot Injection at time zero
Lot AA ((b) (4) N=30) compared to
Lot X (Fine N=33), Lot Y (Nominal N=33), and Lot Z (Coarse N=33)
Top Graph - Full 28-day OP Depot Observation Interval
Bottom Graph - First 5 Days OP Depot Observation Interval (same data)
Lines and Bars Represent Mean ± Standard Deviation

Figure 2. Mean +_ sd olanzapine plasma concentration-time profiles following a single 405 mg OP depot injection of the (b) (4) versus fine, nominal, and coarse lots.

Absorption and relative Bioavailability were related to particle size with the fine and coarse particles showing a slightly lower availability. The (b) (4) (b) (4) processes gave comparable plasma levels and do not provide a mechanism for IAIV.

What was unexpected from this study was although the study was done in centers in 11 countries involving 418 subjects there were no reported IAIV events with the fixed regimen.

8) DOES THE OP DEPOT INJECTION SHOW ANY CHARACTERISTIC OR TENDENCY FOR INITIAL BURST RELEASE

Study F1D-MC-HGKB (HGKB) pharmacokinetic addendum enrolled 10 patients who were willing to participate in a 1 day intensive blood sampling. Each of these patients had been enrolled and was an ongoing participant in the open-label treatment period of Study HGKB. Each subject had received an OP Depot dose of 300 mg every 2 weeks for at least 1.5 years. The administered dose in the addendum study was OP 210 mg. Typical plasma levels curves indicate that there is no tendency for a burst release. Blood samples were obtained at 5, 15, 30, and 45 minutes and at 1, 2, 4, 6, and 8 hours after the injection.

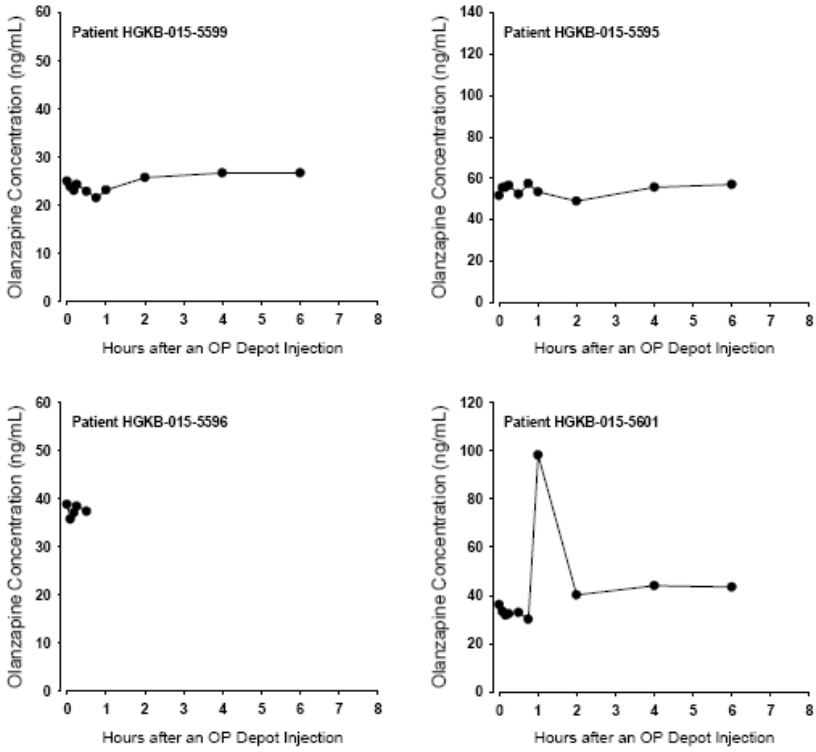


Figure 1. Olanzapine plasma concentrations immediately before and after an injection of OP Depot for patients HGKB-015-5599, HGKB-015-5595, HGKB-015-5596, and HGKB-015-5601.

These results indicate that on average there is no tendency for a burst release for the OP injections.

9) WHAT IS THE HALF-LIFE FOR THE OP DEPOT INJECTION?

The average value for the "half-life" after IM depot administration was 232 hours or 9.7 days. This indicates that the 50 percent of the absorption process is complete within 9.7 days and that it is more than 80% complete within ~29 days (3 times the half-life).

FDA LABEL

(b) (4)

3 pages of clin/pharm has been withheld in full immediately following this page as B4 CCI/TS

DISSOLUTION

ABSTRACT: The rate of release of olanzapine from olanzapine pamoate drug product (426906) is determined by performing the dissolution testing with a 1.0% Sodium Lauryl Sulfate in USP buffer pH 6.8 medium using USP Apparatus 4 (or Ph.Eur. 2.9.3 Flow-Through Apparatus) at 3 mL/min flow rate. The amount of olanzapine present in solution is then determined by using a reversed-phase HPLC system with UV detection. Working standard solutions are stable for 7 days at ambient conditions. Samples are stable for 5 days at ambient conditions. Replicate and average results are treated according to USP testing criteria for extended release dosage forms.

Proposed dissolution specifications for the different doses:

Table 3.2.P.5-12 Dissolution Data: Calculation of Target Value at 30 Minutes

Dose mg	n	Avg	Std Dev	% RSD	Min	Max	Target				
							%	Low %	High %	% <Low	% >High
210	264	19.64	1.07	5.45	16	23	19	14	24	0.0%	0.0%
300	132	13.95	0.77	5.52	13	15	14	9	19	0.0%	0.0%
405	264	10.62	0.64	6.03	9	12	10	5	15	0.0%	0.0%

Table 3.2.P.5-13 Dissolution Data: Calculation of Target Value at 2 Hours

Dose mg	n	Avg	Std Dev	% RSD	Min	Max	Target				
							%	Low %	High %	% <Low	% >High
210	264	60.91	4.26	6.99	47	70	60	45	75	0.0%	0.0%
300	132	47.96	2.52	5.25	38	54	48	38	58	0.0%	0.0%
405	264	38.70	2.33	6.02	33	46	38	28	48	0.0%	0.0%

Table 3.2.P.5-14 Dissolution Data: Calculation of Target Value at 8 Hours

Dose mg	n	Avg	Std Dev	% RSD	Min	Max	Stated Amount	% Less Than Stated Amount
210	264	97.18	4.43	4.56	79	116	80	0.38%
300	132	97.70	4.59	4.70	85	122	80	0.00%
405	264	92.96	3.73	4.01	82	104	80	0.00%

Comments:

1. The product on which the dissolution testing is being conducted is not clear. Is it the reconstituted suspension, and if so, what is the stable shelf life of this product as per a stability indicating assay.

2. The concentration of 1% sodium lauryl sulfate (SLS) in the pH 6.8 buffer seems to be very high, essentially implying that all of the drug is 'solubilized' rapidly. Has the sponsor tried experimentation with lower concentrations of SLS, and if so, please provide these results.

3.The sponsor should explain why they request different release specifications for different doses.

4.No dissolution data was provided for the ambient conditions of 25 C/60 % RH. The sponsor should provide this data for relevant clinical, bio-, and finished product stability lots.

5.The sponsor should provide the content uniformity and assay results for relevant batches of this product.

SIGNATURES

Andre Jackson_____
Reviewer, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology

RD/FTinitialized by Yaning Wang,/Jogarao Gobburu
Ph.D._____
Team Leader Pharmacometrics

cc: NDA 22-173, HFD-860(Mehta, Baweja, Jackson,Wang)
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DETAILED STUDY REPORTS

Olanzapine Assay Validation -

Parameter	
Method	LCEC-Liquid chromatography with electrochemical detection
Number of Freeze-thaw	2 Cycles
Benchtop Stability at RT	48 hrs
Long term at –60° C	33 mos
Extraction Recovery	80% @ 0.64 ng/ml 73% @ 40 ng/ml 80% @ 80 ng/ml %

STUDY 1.

F1D-EW-LOAZ- A Pilot Study to Examine the Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of a New Intramuscular Formulation of Depot Olanzapine (Pamoate Salt) Compared to Oral Olanzapine in Healthy Male Subjects

Primary Objective
The primary objective of this study was to determine the safety and tolerance of IM olanzapine depot (pamoate salt).

Secondary Objectives
The secondary objectives were:

- To evaluate the absorption characteristics and relative bioavailability of IM olanzapine pamoate monohydrate depot compared to oral olanzapine in healthy male subjects.
- To evaluate the pharmacokinetic profile of IM olanzapine depot in healthy male subjects.

- To assess the safety and tolerance of the IM olanzapine depot and the oral olanzapine.

Overall Study Design and Plan: Description
Eighteen healthy male subjects were divided into 6 groups of 3 subjects each. All of the subjects were non-smokers and aged between 18 and 55 years.

All subjects received an initial 10 mg oral dose of olanzapine in a standard tablet form on one occasion and a single dose of IM olanzapine depot on another occasion. Eighteen subjects received the oral formulation during Treatment Period 1 and the depot formulation during Treatment Period 2. There was a washout period of no less than 7 days between oral and depot dose.

The single oral dose (10 mg) of olanzapine was administered as two 5 mg tablets with 150 mL water at approximately 09:00 hours.
Subjects swallowed the tablets in an standing position and were not allowed to lie supine for the next 2 hours (except for study procedures or if clinically indicated). The 10 mg IM olanzapine depot was injected into the upper outer quadrant of the buttock whilst the subject was supine, at approximately 0900 hours. The intramuscular injections were administered using a 23 G needle.

A period of at least 7 days separated the oral dose from the IM injection.

Subject Demographics:

Subject Number	Subject Initials	Age (yrs)	Height (cm)	Weight[a] (kg)	Origin
1	(b) (6)	35	181	88.5	Caucasian
2		37	173	72.4	Caucasian
3		43	183	96.0	Caucasian
4		36	187	80.3	Caucasian
5		26	175	65.2	Caucasian
6		20	173	60.1	Caucasian
7		30	175	67.1	Caucasian
8		33	172	68.2	Caucasian
9		30	180	82.9	Caucasian
10		35	181	93.1	Caucasian
11		48	178	78.1	Caucasian
12		33	192	104.0	Caucasian
13		46	168	68.7	Caucasian
14		45	181	71.3	Caucasian
15		20	178	60.3	Caucasian
16		29	182	91.0	Caucasian
17		21	176	76.5	Caucasian
18		37	170	55.5	Mixed [b]
Mean		**34**	**178**	**76.6**	
SD		**8.6**	**6.0**	**13.69**	
Median		**34**	**178**	**74.5**	
Min		**20**	**168**	**55.5**	
Max		**48**	**192**	**104.0**	
N		**18**	**18**	**18**	

Treatments Administered

Olanzapine 10 mg (2 x 5 mg tablets) given as a single oral dose was compared with IM olanzapine depot given as a single injection (10, 20, 30, or 40 mg).

Blood samples for the measurement of olanzapine were taken at the following times:

Oral formulation

Prior to administration of olanzapine, and 30 minutes, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96 and 120 hours following administration of olanzapine (18 samples).

Depot Dose

Prior to administration of olanzapine, and 1, 2, 4, 6, 8, 12, 18, 24, 30, 36, 42, 48, 72, 84, 96, 120, 144 and 168 hours and on Days 9, 12, 15, 18, 21, 24, 28, and Day 38 following administration of olanzapine (27 samples).

Pharmacokinetic Analyses

The data were analyzed for each dose of oral and IM olanzapine depot. Data representing the mean plasma concentrations were calculated. Mean, standard deviation, minimum, maximum, and coefficient of variation for specific pharmacokinetic parameters were calculated by averaging the individual subject's pharmacokinetic parameter data for the oral data. Descriptive statistics were calculated for all doses.
Pharmacokinetic parameters were calculated using standard noncompartmental pharmacokinetic methods.

The data from these single doses of oral and IM depot olanzapine were used to project multiple-dose, steady-state conditions based upon an assumption of pharmacokinetic linearity and dose proportionality. It is also necessary to assume that there are no time dependencies or nonlinear processes that occur when multiple doses are administered. It is useful to calculate the fluctuation index that would reflect such multiple-dose conditions. That is, the fluctuation index is an expression of how much the maximum and minimum plasma concentrations differ in proportion to the average steady-state concentration. The fluctuation index is expressed as a percentage. The value of 36%, for example, reflects that the difference between the minimum and maximum concentration is as large as 36% of the average steady-state concentration.

Standard pharmacokinetic parameters were calculated.
The fluctuation index, F_{min}^{max} maxmin , was estimated for oral and depot formulations based upon the observed concentrations in this single-dose trial.
The F_{min}^{max} is calculated as the difference between the Cmax and the measured concentration at the time (Tau) of each subsequent dose (for example, orally once-daily at 24 hours, or intramuscularly as the depot formulation once-weekly at 168 hours, once-every-other-week at 336 hours, or once-monthly at 648 hours) divided by the average steady-state concentration, AUC0-∞/Tau. These calculations and predictions of multiple dose fluctuation of steady-state concentrations presume linear pharmacokinetic principles of superposition.

Alertness Scale
In this trial, differentiation between the alert state, and sedation, tranquilization, or hypnosis were made by using a scale. This scale was completed prior to administration and 1, 3, 6, 12, and 24 hours after each dose of olanzapine, and daily until discharge from the unit. It was scored as follows:
Five Point Scale
1. Fully alert and active (includes normal activity)
2. Alertness and activity reduced, eyes open and 'following' movement etc.
3. Alertness and activity greatly reduced, eyes closed but open if *e.g.* name called
4. Sleeping, rousable if e.g. name called, not confused if roused, awakens spontaneously to urinate etc., does not return to sleep immediately following rousing

5. Deeply asleep, not rousable if name called, rousable with difficulty on physical stimulation, confused ('drunk') if roused, returns to sleep immediately after rousing unless strongly stimulated

Injection pain score (Depot only)
A simple pain score was completed at the time of the injection and at 1, 3 and 6 hours following depot dose if the subject was awake. It consisted of a four point scale; no pain, mild pain, moderate pain, and severe pain.

Inspection of Injection Site (Depot only)
The injection site was assessed at 3, 24, 48, and 168 hours after injection, and upon subsequent visits to the unit. The injection site was marked by indelible ink and was remarked in order that the site could be rechecked on each outpatient visit, including the post-study follow-up.

Changes in the Conduct of the Study or Planned Analyses
Amendment (a) approved by Lilly on 22 March 2000

A review of the 20 mg dose safety profile and plasma concentrations of olanzapine, indicated a possible lack of dose proportionality between the 10 and 20 mg depot doses. Consequently, the protocol was amended to specify that the third group of volunteers would receive a dose of 15 mg IM olanzapine depot, thereby providing additional data on the aspects of dose proportionality below 20 mg.

Amendment (b) approved by Lilly on 17 May 2000

Doses up to and including 20 mg were well-tolerated. Following a review of the safety profile and plasma concentrations of olanzapine from the 30 mg depot dose , the protocol was amended to specify a change to the dosing regimen, increasing the dose above the proposed 30 mg, as stated in the original protocol approved on 10 January 2000, to 40 mg.

Dose Investigation
A decision to postpone the study was made between (b) (4) and Eli Lilly, following a discrepancy in the olanzapine plasma concentrations of the two groups receiving the 20 mg depot injection (i.e., Groups B and D).

The initial 20 mg plasma concentration profile was higher than expected (Group B). The repeat 20 mg dose produced a plasma concentration profile that was more consistent with an expected profile (Group D). The difference may have been attributed to reconstitution or a dose delivery inconsistency .
Gravimetric and chemical analysis of the used CT material was carried out by a Lilly analytical lab and (b) (4) in an attempt to provide a rationale for the high initial 20 mg plasma concentration results.

Lilly Methodology
Each vehicle vial was weighed, emptied, rinsed with water, rinsed with methanol, dried, and re-weighed. The weight differences are tabulated below. Each suspension vial was re-suspended, however, proved difficult, taking repeated mixing to achieve visual indication of complete re-suspension. A 1.0 mL dose was removed and assayed. The vial, syringe, and needles were rinsed repeatedly with solvent and the collected volumes assayed (washout).

Lilly Findings
The full evaluation of the pharmacokinetics for oral and IM depot olanzapine revealed that the concentrations for IM depot exhibited at-least 4-fold intersubject variability like that established for orally administered olanzapine. Thus, it is likely that the difference between groups might reflect the small number of subjects per group and the large intersubject variability in pharmacokinetic characteristics.

(b) (4) **Findings**

Despite detailed investigation at the time, no explanation for the anomalous plasma values seen in Group B were found. All documentation, including pharmacy and dose inventory documentation were reviewed and vial weights indicated that the correct formulation and dosing procedures were followed. However, once all the concentration results were examined and compared with oral PK profiles, the results seemed consistent.

Within Study Plasma Analysis Results

Study began: January 31, 2000
Analysis completed: August 24, 2000
Total StorageTime: 8 mos

Parameter	Olanzapine
Method	LCEC-Liquid chromatography with electrochemical detection
Sensitivity/LOQ	0.25 ng/mL
Linearity (Standard curve samples)	1-250 ng/mL
Quality Control (QC) Samples	0.64 ng/ml 40 ng/ml 80 ng/ml
Precision of Standards (%CV)	3.1% @ 0.5 ng/ml 4.3% @ 250 ng/ml
Precision of QC Samples (%CV)	6.4% @ 0.64 ng/ml 3.7% @ 40 ng/ml

	5.2% @ 80 ng/ml
Accuracy of Standards (%)	98% @ 0.5 ng/ml 94% @ 250 ng/ml
Accuracy of QC Samples (%)	102% @ 0.64 ng/ml 103.4% @ 40 ng/ml 100.4% @ 80 ng/ml

RESULTS

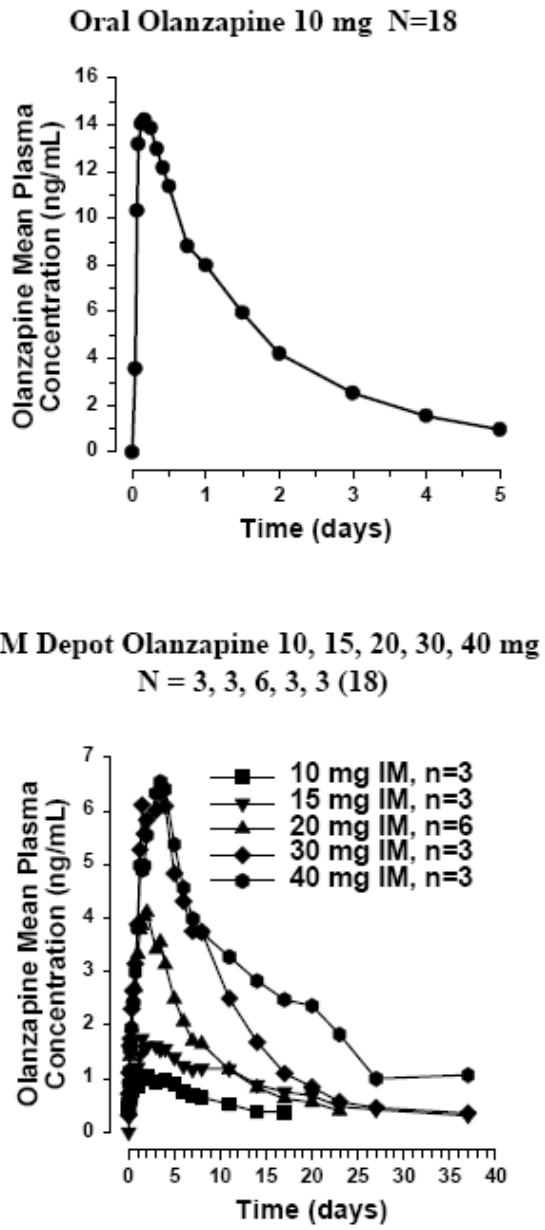


Figure 1 . Mean plasma concentrations of olanzapine for 10 mg oral and 10, 15, 20, 30, and 40 mg IM depot olanzapine doses.

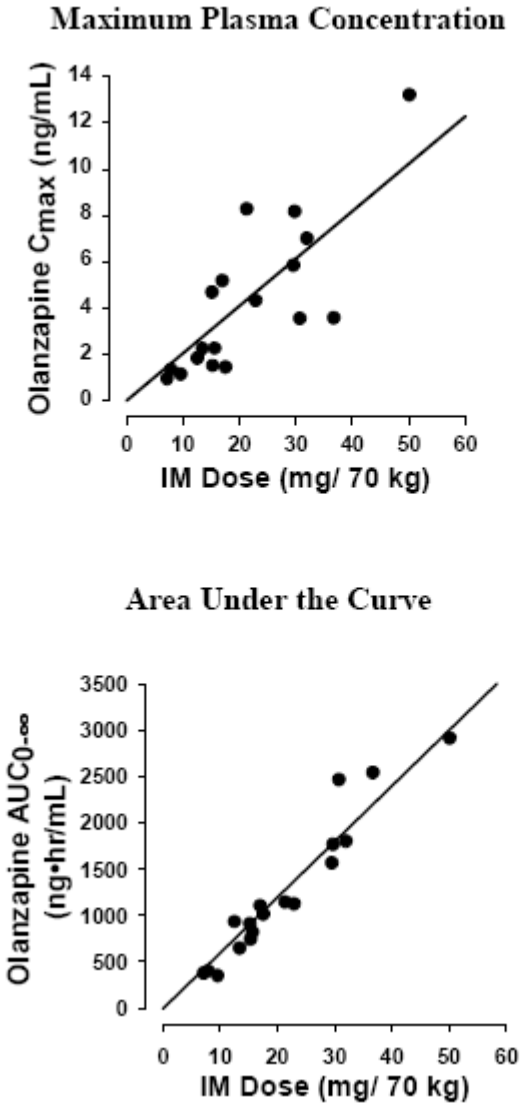


Figure 2. Dose proportional increase in C_{max} and AUC after 10, 15, 20, 30, and 40 mg IM depot olanzapine doses.

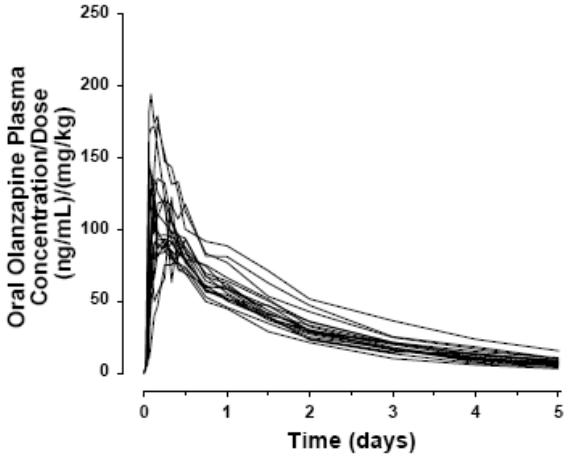
Table 1 . Overall Pharmacokinetic Characteristics of Olanzapine after Oral and IM Depot Administration

PK Parameter	Units	Oral 10 mg	Depot (Overall)
N		18	18
C_{max}	(ng/mL)	16.7	NA
T_{max}	(hr)	4.8	64.7
$AUC_{0-\infty}$	(ng•hr/mL)	602	NA
C_{max}/Dose	(ng/mL)/(mg/kg)	126	13.2
$AUC_{0-\infty}$/Dose	(ng•hr/mL)/(mg/kg)	4549	3974
$t_{1/2}$	(hr)	31.6	271
Cl_p/F	(L/hr)	17.6	20.0
$V_{\lambda z}/F$	(L/kg)	10.3	98.4
MRT	(hr)	44.4	379

Table 2 . Dose Specific Pharmacokinetic Characteristics of Olanzapine after IM Depot Administration

PK Parameter	Units	Depot 10 mg	Depot 15 mg	Depot 20 mg	Depot 30 mg	Depot 40 mg
N		3	3	6	3	3
C_{max}	(ng/mL)	1.13	1.85	4.35	6.99	6.77
T_{max}	(hr)	28.0	56.0	52.0	68.0	132
$AUC_{0-\infty}$	(ng•hr/mL)	375	831	990	1710	2642
C_{max}/Dose	(ng/mL)/(mg/kg)	9.60	9.00	16.7	16.1	11.1
$AUC_{0-\infty}$/Dose	(ng•hr/mL)/(mg/kg)	3230	4081	3885	3927	4839
$t_{1/2}$	(hr)	242	330	262	241	290
Cl_p/F	(L/hr)	26.7	18.2	21.0	17.6	15.2
$V_{\lambda z}/F$	(L/kg)	106	118	96.7	90.4	83.0
MRT	(hr)	348	493	343	276	471

Oral Olanzapine N=18



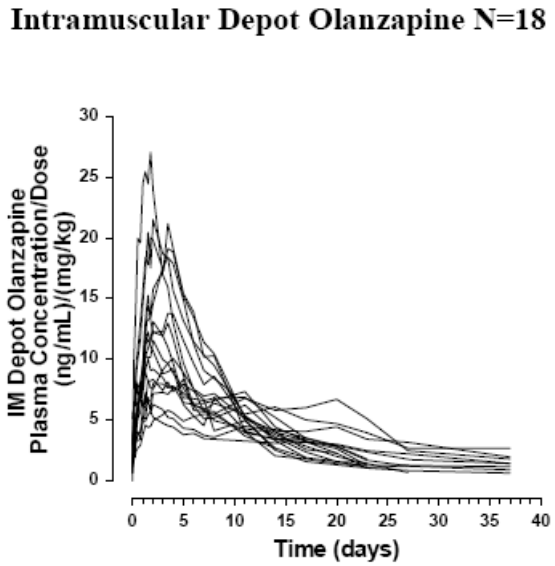


Figure 3. Comparison of dose-normalised plasma concentration profiles for oral and IM olanzapine in 18 healthy subjects.

The coefficient of variation for oral olanzapine across a variety of pharmacokinetic parameters is about 25 to 30% whereas the coefficient of variation for IM depot olanzapine is about 45 to 50%.

The fluctuation index is an expression of how much the maximum and minimum plasma concentrations differ in proportion to the average steady-state concentration. The fluctuation index is expressed as a percentage.

Table 3. Olanzapine Fluctuation Index for Oral and IM doses

Subject	Oral Dose (mg)	F_{min}^{max} Oral Daily (%)	IM Dose (mg)	F_{min}^{max} IM Depot once weekly (%)	F_{min}^{max} IM Depot every 2 weeks (%)	F_{min}^{max} IM Depot once monthly (%)
1	10	21.0	10	34.0	78.8	215
2	10	41.4	10	9.64	72.3	208
3	10	49.7	10	15.2	50.9	160
4	10	43.1	20	40.5	142	302
5	10	42.3	20	95.6	218	468
6	10	30.0	20	39.4	89.3	225
7	10	37.8	15	16.9	51.9	156
8	10	23.6	15	15.4	26.2	97.7
9	10	15.6	15	10.1	38.5	86.1
10	10	35.8	20	44.9	146	333
11	10	12.4	20	9.29	21.6	55.7
12	10	40.6	20	27.9	75.6	223
13	10	40.3	30	31.2	126	299
14	10	48.8	30	26.6	102	227
15	10	67.8	30	37.0	85.6	232
16	10	33.6	40	6.68	11.7	62.0
17	10	39.0	40	4.56	6.74	57.9
18	10	16.2	40	38.5	121	282
Mean		35.5		28.0	81.3	205
S.D.		14.0		21.5	55.0	110
Minimum		12.4		4.56	6.74	55.7
Maximum		67.8		95.6	218	468
C.V. %		39.3		76.8	67.6	53.8
N		18		18	18	18

The estimated average fluctuation index value for once-daily oral olanzapine is 36%. The estimated average fluctuation index values for the IM depot olanzapine (pamoate monohydrate) are: for once-weekly dosing 28%; for every-two-weeks dosing 81%; and for once-monthly dosing 205%.

The firm also mentioned that following the 20 mg IM olanzapine depot, a scoring of asleep but rousable (4) was recorded by all 6 subjects 24 hours following dosing. This had returned to baseline 24 hours later (at 48 hour time point) with the exception of one subject (#4) with a recording of alertness and activity greatly reduced (3). This had returned to baseline by the 72 hour time point. Of the six subjects, three reported a single recording of alertness and activity greatly reduced (3) or sleeping but rousable (4) 120 hours following dose.

Conclusions:

1. Measurable plasma concentrations of olanzapine were detected for up to 5 days after the administration of a single 10 mg oral dose and for up to 35 days after the administration of a single 10 to 40 mg IM depot dose. Thus concentrations of olanzapine in the body can be sustained by administration of the olanzapine pamoate monohydrate intramuscular formulation.

2. Estimates of the rate constant for absorption after IM depot injection were approximated from the terminal phase of the plasma concentration time curve. This characterization was appropriate since the IM depot slows down the rate of absorption to the point that it becomes the rate controlling process during this phase (so-called flip-flop model). Thus, the estimated half-life is really an estimate of the absorption half-time. The average value for the "half-life" after IM depot administration was 232 hours or 9.7 days. This indicates that the 50 percent of the absorption process is complete within 9.7 days and that it is more than 80% complete within ~29 days (3 times the half-time).

Comment:

1. It was unusual that all of the subjects with sedation occurred at the 20 mg dose which would seem to indicate that the sedation may not be dose related or that there may be some other unidentified covariates associated with the 20 mg dose.
2. The apparent differences in the normalized AUC values may have resulted from sample collection times and assay sensitivity and may not be clinically important.

STUDY 2.

LOBQ-Clinical Study Main Report: A Pilot Study to Evaluate Exposure to Pamoic Acid Following Dosing with Hydroxyzine Pamoate (Vistaril®) in Healthy Male Subjects

Introduction

The traditional use of pamoate salts assumed that there was no systemic exposure to the pamoic acid. However, in the thirty plus years since the introduction of some of these salts, assay methodology has improved to such an extent that this may not be factual. In addition, pamoate salts are being increasingly utilized as a formulation for development of depot preparations. As an aid to the development of olanzapine pamoate, it is important to assess pamoic acid exposure with currently marketed compounds, including Vistaril® (hydroxyzine pamoate). Hydroxyzine is an antihistaminic with anxiolytic properties which as the pamoate salt is insoluble in water and in alcohol.

Primary Objective

To determine pamoic acid exposure following dosing with Vistaril® (hydroxyzine pamoate)

Study design

This was an open-label study examining the systemic exposure to pamoic acid following administration of a marketed compound, hydroxyzine pamoate (Vistaril®). Six healthy male subjects, between the ages of 25 and 37 years, were studied in a single group. This was a single-centre, open-label, non-randomized, multiple oral dose study in one cohort of subjects.

Study Drug Administration

During the study, the dose of hydroxyzine pamoate was 100 mg for all subjects on all dosing occasions. On Day 1, four 25 mg hydroxyzine pamoate capsules (100 mg) were administered with 200 mL of water at 0830 hours with a 3 minute interval between subjects. On Days 2 to 4, four 25 mg hydroxyzine pamoate capsules (100 mg) were administered with 200 mL of water at 6 hourly intervals from the morning of Day 2 until the final dose on the morning of Day 4, a total of 9 doses.

Subject Demographics

Subject Number	Age (yr)	Height (cm)	Weight (kg)	Body mass index (kg/m^2)	Origin
1	35	177	68.3	21.8	Caucasian
2	32	179	91.7	28.6	Caucasian
3	25	182	89.7	27.1	Caucasian
4	28	167	58.9	21.1	Caucasian
5	27	175	70.2	22.9	Caucasian
6	37	168	73.8	26.1	Caucasian
Mean	**31**	**175**	**75.4**	**24.6**	
SD	**4.8**	**6.02**	**12.83**	**3.08**	
Median	**30**	**176**	**72.0**	**24.5**	
Min	**25**	**167**	**58.9**	**21.1**	
Max	**37**	**182**	**91.7**	**28.6**	

Biological Samples

Blood samples for the measurement of pamoic acid were taken at the following times: Prior to administration of hydroxyzine pamoate, and 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours following administration of hydroxyzine pamoate (11 samples) on Days 1 and 4

Pharmacokinetic Analyses

Plasma pamoic acid concentrations obtained following oral administration of hydroxyzine pamoate on Days 1 and 4 were subjected to standard noncompartmental analyses using WinNonLin 3.0.

Within Study Plasma Analysis Results

Study began: October 12, 2001
Analysis completed: 1 November 2001
Total Storage Time: 25 days

Parameter	Pamoic Acid

Method	HPLC-Liquid chromatography with fluorescence detection
Sensitivity/LOQ	2 ng/mL
Linearity (Standard curve samples)	2-200 ng/mL
Quality Control (QC) Samples	2 ng/ml 100 ng/ml 200 ng/ml
Precision of Standards (%CV)	6% @ 2.0 ng/ml 2.1% @ 200 ng/ml
Precision of QC Samples (%CV)	7.8% @ 2 ng/ml 7.8% @ 100 ng/ml 11.4% @ 200 ng/ml
Accuracy of Standards (%)	99% @ 2 ng/ml 98% @ 200 ng/ml
Accuracy of QC Samples (%)	99.4% @ 2 ng/ml 101% @ 100 ng/ml 98% @ 200 ng/ml

Sets of human quality control samples were spiked to contain 100 ng/mL olanzapine to test for possible interference. There was no interference.

RESULTS

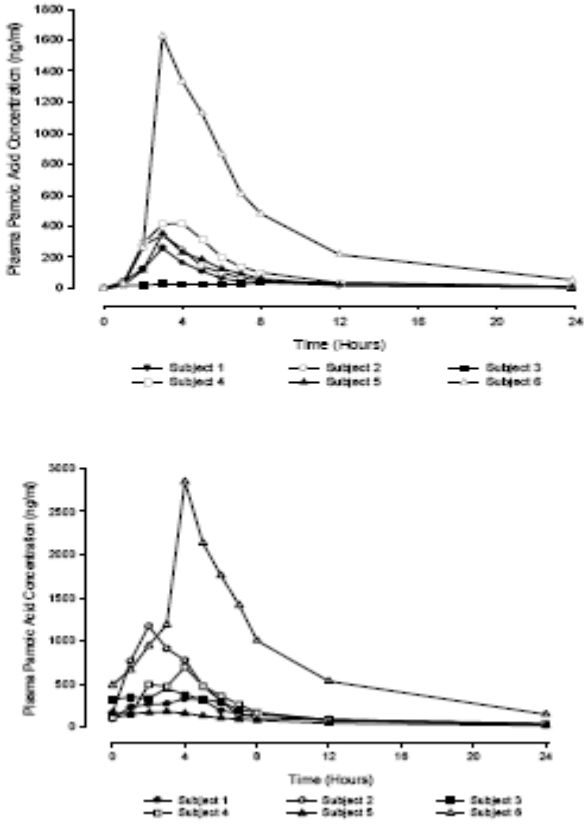


Figure 1. Plasma Pamoic Acid Concentration Profiles Following Administration of Hydroxyzine Pamoate, Orally on Day 1 (Upper Panel) and Day 4 (Lower Panel) (Note Difference in Scale).

Table 1. Primary Pharmacokinetic Parameters on Days 1 and 4 for Individual Subjects

	CL/F or CL_{SS}/F (L/h)		V_2/F (L)	
Subject #	Day 1	Day 4	Day 1	Day 4
1	93.2	67.6	784	911
2	67.1	24.1	576	190
3	166	49.3	1560	465
4	44.0	41.6	326	488
5	67.7	115	574	1200
6	11.3	11.7	84.0	99.1

Table 2. Selected Mean (Range: Min – Max) Pamoic Acid Pharmacokinetic Parameters Following Single and Multiple Doses of Hydroxyzine Pamoate Given Orally (N = 5)

Parameter	Day 1 Mean[d] (Range)	Day 4 Mean[d] (Range)
T_{max}[a] (h)	3 (3-8)	3 (2-4)
C_{max} (ng/mL)	281 (37.80-415.36)	562 (174.28-1167.49)
AUC_{0-6h} (ng*h/mL)	885 (122.5-1541)	2262 (900-4291)
C_{avg} (ng/mL)	147 (20.4-257)	377 (150-715)
$t_{1/2}$[b] (h)	5.84 (5.13-6.49)	7.22 (5.45-9.34)
Accumulation Ratio[c]	-	3.75 (0.494-11.9)

[a] Median value
[b] Geometric mean value
[c] Cmax (Day 4) / Cmax (Day 1)
[d] Excludes values for Subject 6 (see main text)

Conclusions:

Oral dosing of hydroxyzine pamoate, produced measurable systemic concentrations of pamoic acid. Pamoic acid was rapidly absorbed and once in the system, was rapidly eliminated. The rapid absorption and elimination produced systemic exposures within 6 hours that were almost 60% of that observed at 24 hours. The plasma concentrations of Subject 6 were distinctly higher than the rest of the group. Subject 6 had estimates of apparent clearance and volume of distribution that were much lower than the rest of the group. Intra subject variability in estimates of the apparent clearance and volume of distribution on Days 1 and 4 suggest intraday variability in absorption (and thus bioavailability) of pamoic acid. A slight accumulation of pamoic acid was observed on multiple dosing. However, its rapid elimination suggests that once therapy is terminated, pamoic acid will not linger in the system.
Oral administration of the pamoate salt of hydroxyzine produced measurable systemic concentrations of pamoic acid, both after single and multiple doses. Pamoic acid was rapidly absorbed and eliminated from the systemic circulation.

STUDY 3.

LOBS-Clinical Pharmacology Study Report: Pharmacokinetic Characterization of Intramuscular Olanzapine Depot as a Function of Particle Size Distribution

Rationale for Study

Olanzapine Pamoate (OP) Depot is a sustained-release intramuscular dosage form of olanzapine that is intended to be injected every 2 to 4 weeks depending on dose. Thus, a critical performance characteristic of the OP Depot drug product is its slow rate of in vivo dissolution at the site of injection. The slow in vivo dissolution is intended to avoid a burst release and to provide a prolonged period of sustained release. The sustained release allows the OP Depot intramuscular injection to be administered as infrequently as every 4 weeks and yet retain suitable systemic concentrations of olanzapine throughout the prolonged dosage interval.

The slow dissolution rate of the product can be directly impacted by the particle size distribution (PSD) of the OP material.

A critical change in the manufacturing process for OP Depot drug product was addressed in an amendment to the study protocol, known as Amendment LOBS(a). This additional investigation was initiated when a change in the manufacturing process had been mandated by an improvement that achieved more reproducible conditions for drug substance manufacture. Amendment LOBS(a) was implemented after the live (clinical) phase of Study LOBS was complete, thus, Amendment LOBS(a) is a second part of the overall study.

Therefore, the rationale for Amendment LOBS(a) was to collect PQBP data for Lot AA of OP Depot, which was made using the (b) (4) process. As all of the chemical and physical attributes and properties of the drug substance, including the PSD and crystal morphology, were unchanged by the new (b) (4) process, it was anticipated that the change to a (b) (4) process would not have any impact on the PQBP characteristics of OP Depot. The collection of PQBP data from a human clinical trial in Amendment LOBS(a) was done to confirm the acceptable in vivo sustained-release performance of a lot of OP Depot made using the (b) (4) process as compared with oral olanzapine.

Objectives for Study LOBS

The primary objective was:

- to assess the acceptability of sustained-release product performance bioavailability characteristics for 3 OP Depot lots that have discernibly different PSDs, each contained within the range of product particle size specifications, based upon the assessment of bioavailability parameters for OP Depot relative to bioavailability parameters for oral olanzapine in patients with stabilized schizophrenia or schizoaffective disorder

The secondary objectives were:

- to assess the in vivo release profile and sustained-release product performance bioavailability characteristics for 3 OP Depot lots that have discernibly different PSDs, based upon the assessment of bioavailability parameters for OP Depot relative to bioavailability parameters for RAIM

olanzapine (a marketed Zyprexa® product-olanzapine IntraMuscular- that is a parenteral formulation of olanzapine intended for intramuscular administration. The product is reconstituted with sterile water for injection and forms a solution that is rapidly absorbed upon intramuscular injection)

- to evaluate the safety and tolerability of 3 OP Depot lots that have discernibly different PSDs in patients with stabilized schizophrenia or schizoaffective disorder

Objectives for Amendment LOBS(a)

The primary objective was:

- to assess the acceptability of sustained-release product performance bioavailability characteristics for 3 OP Depot lots manufactured using a (b) (4) process (Study LOBS) that had discernibly different PSDs, each contained within the range of product particle size specifications, and 1 OP Depot lot manufactured using a (b) (4) (Amendment LOBS[a]), based upon the assessment of bioavailability parameters for OP Depot relative to bioavailability parameters for oral olanzapine in patients with stabilized schizophrenia or schizoaffective disorder

The secondary objectives were:

- to assess the in vivo release profile and sustained-release product performance bioavailability characteristics for 3 OP Depot lots manufactured using a (b) (4) process (Study LOBS) that had discernibly different PSDs, and 1 OP Depot lot manufactured using a (b) (4) process (Amendment LOBS[a]), based upon the assessment of bioavailability parameters for OP Depot relative to bioavailability parameters for RAIM olanzapine
- to evaluate the safety and tolerability of 3 OP Depot lots manufactured using a (b) (4) process (Study LOBS) that have discernibly different PSDs, and 1 OP Depot lot manufactured using a (b) (4) process (Amendment LOBS[a]) in patients with stabilized schizophrenia or schizoaffective disorder

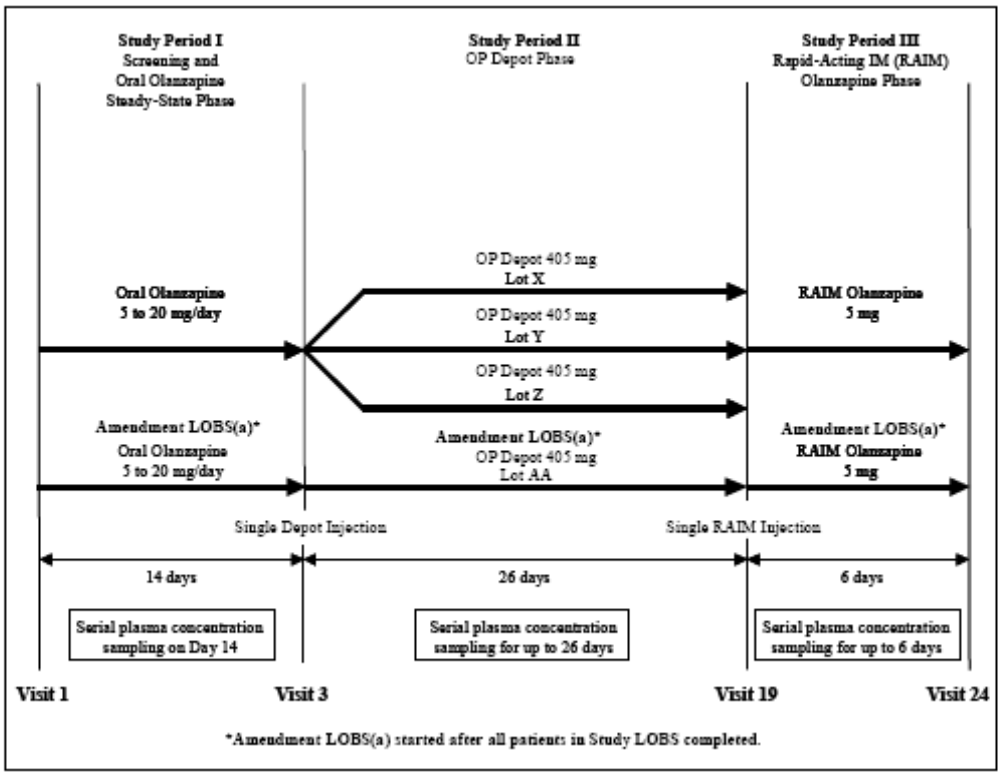
Table1. Baseline Physical Characteristics

Demographic Variables	Lot X (N=33)	Lot Y (N=38)	Lot Z (N=33)	Lot AA (N=30)	Total (N=134)
Gender: No. (%)					
No. Patients	33	38	33	30	134
Male	22(66.7%)	27(71.1%)	24(72.7%)	22(73.3%)	95(70.9%)
Female	11(33.3%)	11(28.9%)	9(27.3%)	8(26.7%)	39(29.1%)
Origin: No. (%)					
No. Patients	33	38	33	30	134
Caucasian	22(66.7%)	23(60.5%)	22(66.7%)	19(63.3%)	86(64.2%)
African	7(21.2%)	10(26.3%)	8(24.2%)	3(10.0%)	28(20.9%)
Hispanic	3(9.1%)	3(7.9%)	3(9.1%)	6(20.0%)	15(11.2%)
Native American	0(0.0%)	1(2.6%)	0(0.0%)	0(0.0%)	1(0.7%)
East Asian	0(0.0%)	1(2.6%)	0(0.0%)	0(0.0%)	1(0.7%)
West Asian	1(3.0%)	0(0.0%)	0(0.0%)	2(6.7%)	3(2.2%)
Age in years					
No. Patients	33	38	33	30	134
Mean	39.20	38.73	40.97	35.44	38.66
Median	41.62	36.13	40.94	33.33	38.88
Standard Dev.	10.44	11.30	10.41	12.63	11.24
Minimum	20.20	20.50	18.93	18.77	18.77
Maximum	60.69	67.15	61.14	64.39	67.15

Baseline Habits	Lot X (N=33)	Lot Y (N=38)	Lot Z (N=33)	Lot AA (N=30)	Total (N=134)
Alcohol: No. (%)					
No. Patients	33	38	33	30	134
Yes	3(9.1%)	5(13.2%)	3(9.1%)	4(13.3%)	15(11.2%)
No	30(90.9%)	33(86.8%)	30(90.9%)	26(86.7%)	119(88.8%)
Tobacco: No. (%)					
No. Patients	33	38	33	30	134
Yes	25(75.8%)	24(63.2%)	25(75.8%)	15(50.0%)	89(66.4%)
No	8(24.2%)	14(36.8%)	8(24.2%)	15(50.0%)	45(33.6%)

Study Period II

STUDY DESIGN



Because Amendment LOBS(a) focused on an additional set of primary and secondary objectives as described above, it is important to note that all patients in Study LOBS had completed the study prior to the start of the Amendment LOBS(a). The original study design for LOBS and the study design for the amendment are identical, except that in Amendment LOBS(a) the participants were not randomized to receive different lots.
Although patients in Study LOBS were not excluded from participating in Amendment LOBS(a) per the protocol, none of the patients from Study LOBS actually participated in Amendment LOBS(a).

Study Periods

Study LOBS and Amendment LOBS(a) both consisted of 3 study periods: patients received oral olanzapine during Study Period I, OP Depot during Study Period II, and RAIM olanzapine(a marketed Zyprexa® product (olanzapine IntraMuscular) that is a parenteral formulation of olanzapine intended for intramuscular administration. The product is reconstituted with sterile water for injection and forms a solution that is rapidly absorbed upon intramuscular injection) during Study Period III. The oral and RAIM olanzapine arms were used as reference treatments. The oral olanzapine arm was used as the primary reference.

The 3 study periods were connected in a continuous serial-time study design, wherein the end of a study period was also the beginning of the next study period. For example, blood samples obtained at the end of Study Period I, at 24

hours after the last oral dose of olanzapine, were also relevant as the time-zero samples for the beginning of Study Period II and the pre-dose concentration data for OP Depot. In summary, there were no time lapses or washout periods between the consecutive study periods.

Study Period I
At Visit 2, serial collections of blood samples over a period of 24 hours were obtained, and the measured plasma concentrations of olanzapine were used to characterize the steady-state pharmacokinetics of oral olanzapine for each individual patient.

Study Period II
Prior to the injection, the following were collected: a blood sample for the measurement of plasma olanzapine concentration, vital signs and weight, laboratory values, safety and psychiatric rating scales, electrocardiograms (ECGs), and adverse events (AEs). Study Period II began immediately after administration of the OP Depot injection. Serial blood samples for measurement of plasma olanzapine concentrations were taken over a period of 26 days post dose.

Study Period III
Study Period III began immediately after the administration of a RAIM olanzapine injection. Patients were given a single dose of RAIM olanzapine 5 mg. Prior to the injection, the following were collected: a blood sample for the measurement of plasma olanzapine concentration, vital signs and weight, laboratory values, safety and psychiatric rating scales, ECGs, and AEs. A 5-day period of obtaining serial blood samples ensued for the measurement of plasma olanzapine concentration.

Study Drug Formulation and Administration
The following treatments were administered:
- Oral olanzapine (5 to 20 mg/day) was supplied in open-label bottles of 2.5-mg tablets and open-label bottles of 10-mg tablets. The 2.5-mg dose was provided in bottles containing 60 tablets and the 10-mg dose was provided in bottles containing 36 tablets. Oral olanzapine was administered once daily for 14 days.
  - The 2.5-mg oral olanzapine tablets were supplied from Lot Number CT510231.
  - The 10-mg oral olanzapine tablets were supplied from Lot Number CT504201.

Six sections of the olanzapine pamoate monohydrate API lot were (b) (4), resulting in 6 drug substance lots with different PSDs. Three lots (ML132, ML130, ML127) were

specifically manufactured to have a PSD that fell within the lower, middle, and upper range of the overall PSD specification for the manufacturing process. The 3 lots were correspondingly identified in the protocol as Lot X (CT513299, fine), Lot Y (CT513459, nominal), and Lot Z (CT513534, coarse).

For Amendment LOBS(a), OP Depot drug product Lot AA was administered. For Lot AA (CT521002), the olanzapine pamoate monohydrate was manufactured using a single (b) (4) process batch and (b) (4) (ML137). The PSD specifications for both the (b) (4) process materials were the same, and these lots met all the same control and process specifications.

Physical Characteristics of OP Depot Lots in Study LOBS

Plasma Sampling Times

At Visit 2 (Study Period I), patients had taken oral olanzapine 5 to 20 mg once daily for 14 days and, thereby, achieved steady-state olanzapine concentrations. Blood samples were collected at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours after the 14th oral dose.

At Visit 3 (Study Period II), patients received a single intramuscular injection of OP Depot 405 mg olanzapine. Blood samples were collected at 0 (predose), 2, 6, 12, 18, 24, 36, 48, 72, 120, 144, 168, 192, 216 hours, and then at 11, 13, 16, 19, 22, and 25 days after the OP Depot injection.

At Visit 19 (Study Period III), patients received a single injection of RAIM olanzapine 5 mg. Blood samples were collected at 0 (predose), 0.083, 0.167, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, and 120 hours after the RAIM olanzapine injection.

Assessment of Product Quality Bioavailability Performance Attributes

The primary pharmacokinetic assessments used to evaluate the sustained-release PQBP
characteristics of each OP Depot lot included the following:

[1] **Plasma concentration-time profiles**:

[2] **Distribution of C_{av}**:

[3] **Relative bioavailability parameters**: The PQBP was also evaluated relative to oral ($F_{depot:oral}$) and RAIM olanzapine ($F_{depot:RAIM}$) dosing.

Adjustment of Observed OP Depot Concentrations

Following administration of the OP Depot injection at Visit 3, the observed olanzapine plasma concentrations reflected olanzapine concentrations resulting from the OP Depot injection as well as those carried over from Study Period I, the prior oral dosing. Each individual's oral terminal rate constant ($\lambda z,oral$) value was used to adjust for the carry-over from the prior oral dosing, yielding the

single-dose OP Depot “adjusted” olanzapine plasma concentration data as described in Equation 1.

Equation 1:

$$Cadj,t_{n,depot} = Cobs,t_{n,depot} - (Ct_{last,oral})\ e\ [-\lambda_{z,oral} \times (t_{n,depot}-t_{last,oral})]$$

where

$Cadj,t_{n,depot}$ is the adjusted olanzapine concentration following the OP Depot injection at time $t_{n,depot}$

$t_{n,depot}$ is the depot sampling time

$Cobs,t_{n,depot}$ is the observed olanzapine concentration following the OP Depot injection at time $t_{n,depot}$

$Ct_{last,oral}$ is the last measurable olanzapine concentration following the oral dose at time $t_{last,oral}$

$t_{last,oral}$ is the time of the last measurable olanzapine concentration following oral dose.

Adjustment of Observed RAIM Olanzapine Concentrations

The observed olanzapine concentration-time data following a single RAIM olanzapine injection reflected olanzapine concentrations resulting from the RAIM olanzapine injection as well as carry-over of olanzapine from the preceding OP Depot injection.
However, establishing a meaningful estimate of $\lambda_{z,depot}$ was confounded by the variable release patterns for OP Depot. As a result, the last observed OP Depot concentration ($C_{last,depot}$) was used to adjust the olanzapine plasma concentrations following RAIM olanzapine administration as described in Equation 2.

Equation 2: $$Cadj,t_{n,RAIM} = Cobs,t_{n,RAIM} - (C_{last,depot})$$

The observed slow release of the OP Depot formulation allowed the assertion that the contribution from OP Depot carry-over into Study Period III was essentially a constant reflected by the $C_{last,depot}$ value.

OP Depot Pharmacokinetic Calculations
The relative bioavailability of single-dose OP Depot injection to steady-state oral olanzapine was calculated as a measure to evaluate the PQBP (Fdepot:oral) according to
Equation .

$$F_{depot:oral} = (AUC(0\text{-}\infty)_{,depot}/AUC_{\tau,ss,oral}) \times (Dose_{oral}/Dose_{depot})$$

The relative bioavailability of single-dose OP Depot injection to a single-dose of RAIM olanzapine was calculated as a measure to evaluate the PQBP (Fdepot:RAIM) according to Equation 6.

$$F_{depot:RAIM} = (AUC(0\text{-}\infty)_{,depot}/AUC(0\text{-}\infty)_{,RAIM})\times(Dose_{RAIM}/Dose_{depot})$$

Deviations from the Description of the Planned Pharmacokinetic Analyses in the Protocol

OP Depot Concentration Adjustments:
Based upon the variability in the OP Depot absorption patterns, the impact of carryover into Study Period III was difficult to estimate. The carry-over had a greater impact on the individual patient RAIM olanzapine profiles than anticipated. Therefore, values for the terminal elimination rate constant calculated after oral olanzapine in Period I of the study were used to adjust the OP Depot concentrations observed in Period II.

Extrapolation of OP Depot to Steady-State Conditions: In general, concentration-time profile data after the OP Depot dose were collected for less than a single absorption half-life. In a number of cases, the olanzapine plasma concentrations appear to be rising at the end of the OP Depot observation interval of 25 days. Therefore, the percent extrapolation (%Extrap), calculated as the difference between AUC(0-∞) and AUC(0-t_{last}) divided by the AUC(0-∞), reflects a large percentage of the AUC (>60%). Therefore, a robust calculation of the OP Depot AUC(0-∞) was not achieved, and the poor estimation had an impact on the ability to accurately predict steady-state average concentrations of olanzapine resulting from OP Depot. Thus, comparative performance evaluations for OP Depot depended more upon the observed single-dose concentration data.

OP Depot Profile Assessment:
The observed patterns of sustained release were not reflective of the expected monophasic or first-order absorption process. Rather, the patterns appear to represent a complex array of absorption profiles. Therefore, robust noncompartmental estimation of the rate of absorption of olanzapine derived from the terminal log-linear portion of the OP Depot plasma concentration data was difficult.
The assumptions made when designing Study LOBS were not upheld by the actual observed concentration patterns. For example, it was assumed that following the OP Depot injection, olanzapine systemic plasma concentration-time profile would reach a peak value and then have a segment that declined in a log-linear or monoexponential manner reflecting a very slow first-order (flip-flop) absorption. Indeed, this type of firstorder decline was observed in Study LOBS for a number of the profiles (19%). However, other, more complex, patterns that deviate from an expectation of a monophasic pattern were frequently observed (81%).

Plasma Analysis Results

Study began: September 23, 2004
Analysis completed: April 5, 2006
Total Storage Time: 1 yr and 7 months

Parameter	
Method	HPLC-Liquid chromatography with
Sensitivity/LOQ	0.25 ng/mL
Linearity (Standard curve samples)	0.25-200 ng/mL
Quality Control (QC) Samples	ng/ml 100 ng/ml 150 ng/ml
Precision of Standards (%CV)	6.3% @ 2.0 ng/ml 3.0% @ 200 ng/ml
Precision of QC Samples (%CV)	7.3% @ 10 ng/ml 4.7% @ 100 ng/ml 4.6% @ 150 ng/ml
Accuracy of Standards (%)	99% @ 0.5 ng/ml 99% @ 250 ng/ml
Accuracy of QC Samples (%)	% @ 0.64 ng/ml % @ 40 ng/ml % @ 80 ng/ml

Table 1. Particle Size Distribution for OP Depot Lot X, Lot Y, and Lot Z

PSD Parameters	CT513299 Fine Lot X (µm)	CT513459 Nominal Lot Y (µm)	CT513534 Coarse Lot Z (µm)	Drug Substance PSD Limits (µm)
(b) (4)				(b) (4)
				(b) (4)

Figure 1. Cumulative particle size distributions for OP Depot Lot x, Lot Y, and Lot Z.

STUDY 3A .

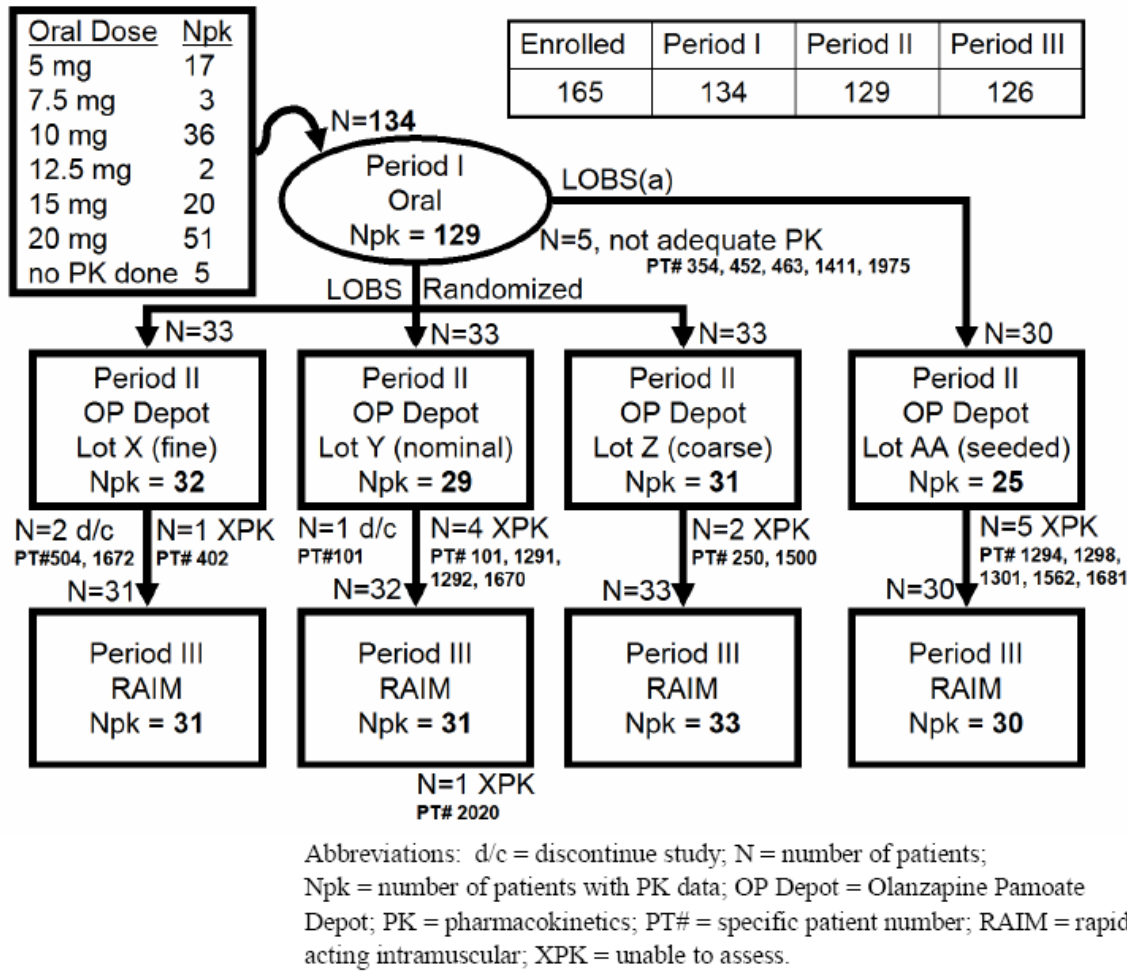
LOBS(a) Physical Characteristics of OP Depot Lot in Amendment

Table 1. Particle Size Distribution for OP Depot Lot AA Compared with Lot X, Lot Y, and Lot Z

PSD Parameters	CT513299 Fine Lot X (µm)	CT513459 Nominal Lot Y (µm)	CT513534 Coarse Lot Z (µm)	CT521002 Seeded Lot AA (µm)	Drug Substance PSD Limits (µm)
(b) (4)					(b) (4)
					(b) (4)

There were 134 patients with plasma concentration data from both oral and OP Depot treatments. Of these, 5 patients (Patients 354, 452, 463, 1411, and 1975) were excluded from the pharmacokinetic analysis of either oral or OP Depot, as their concentration-time profile after depot dosing was considered inadequately informative (less than 2 weeks of measurable concentrations).

Of the 129 patients with complete OP Depot profiles, there were 12 patients (Patients 101, 250, 402, 1291, 1292, 1294, 1298, 1301, 1500, 1562, 1670, and 1681) for whom a terminal rate constant for OP Depot could not be calculated; therefore, these patients were not included in the pharmacokinetic analysis for OP Depot. Of the 129 patients, 3 did not receive the rapid-acting intramuscular (RAIM) olanzapine dose (Patients 101, 504, and 1672), leaving 126 patients who did receive a RAIM olanzapine dose. Of these 126 patients, there was 1 patient (Patient 2020) for whom a terminal rate constant for RAIM olanzapine could not be calculated; therefore, the data for this patient were not included in the pharmacokinetic analysis for RAIM olanzapine.



Abbreviations: d/c = discontinue study; N = number of patients; Npk = number of patients with PK data; OP Depot = Olanzapine Pamoate Depot; PK = pharmacokinetics; PT# = specific patient number; RAIM = rapid acting intramuscular; XPK = unable to assess.

Figure 1. Number of patients with pharmacokinetic data at various stages of the study.

Plasma Concentration Profiles

As the study design included 3 consecutive periods of treatment, the carry-over of concentrations from the oral treatment (Study Period I) into the OP Depot treatment (Study Period II), and from the OP Depot treatment (Study Period II) into the RAIM olanzapine treatment (Study Period III) was addressed by concentration adjustment for the carry-over. Unless otherwise specified, all references to an olanzapine concentration in the text, a table, a figure, or a description refer to the actual (observed) measurement of olanzapine concentration in the plasma sample. In contrast, plasma concentration data values reported after an adjustment for the carry-over are reported with the clear designation of "adjusted" olanzapine plasma concentration. Nonetheless, it is also important to note that specific pharmacokinetic parameters based upon adjusted olanzapine plasma concentration data are not labeled as "adjusted."

Like the profiles following oral or RAIM olanzapine, the concentrationtime patterns after OP Depot administration share common distinctive features in most, if not all, of the patients, such as the lack of a sudden burst release and sustainability, but also are different among individual patients, and possibly after each injection. The

differences in the OP Depot concentration patterns involve (1) the shape (or pattern) of the concentration curve reflecting the slow absorption of olanzapine, (2) the peak or flatness of the concentration curve, and (3) the rough or smoothness of the concentration curve.

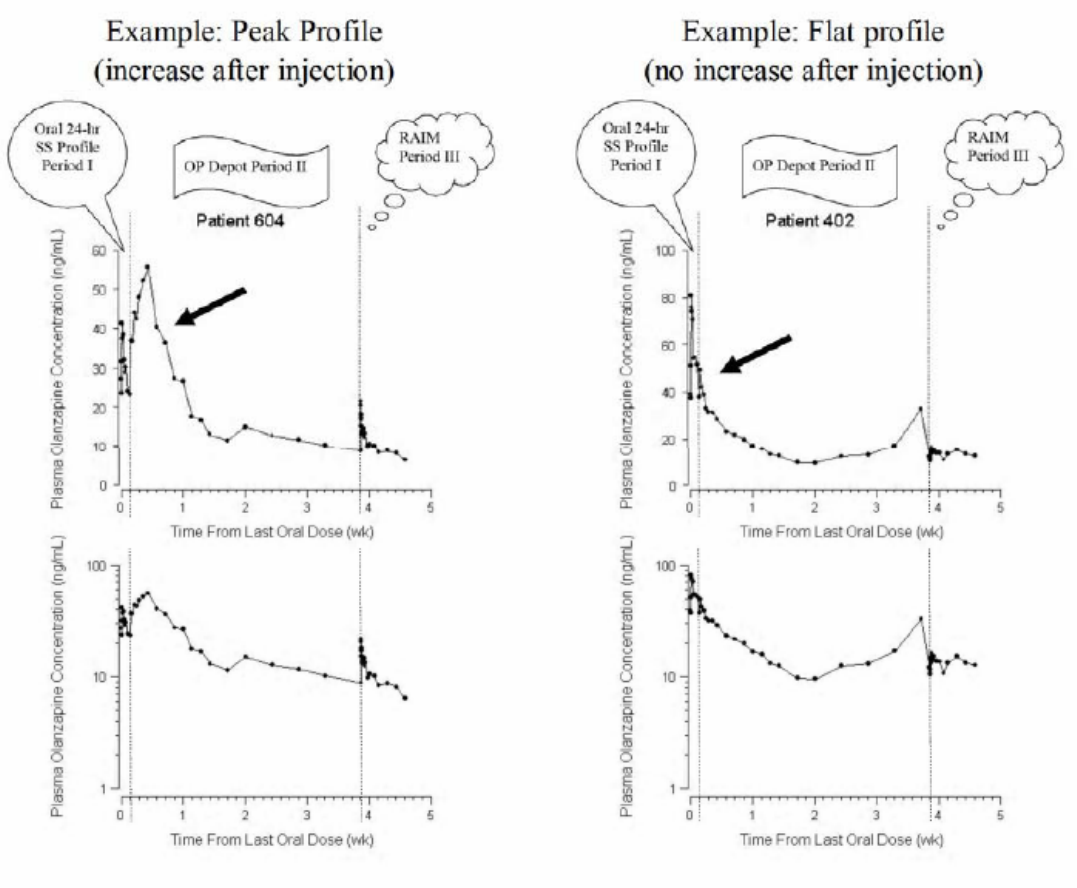
To assess whether any of the specific lots of OP Depot or patient demographics are associated with a specific concentration-time pattern, a visual profile assessment was performed. Seven professional staff members of Eli Lilly and Company independently rated each of 129 individual patient profiles in 3 specific categories. The categories were (1) Monophasic or Biphasic concentration or absorption patterns, (2) Initial Peak or No Initial Peak (flat) concentration patterns, and (3) Rough or Smooth concentration patterns.

Table 2. Percentage of OP Depot Concentration profiles exhibiting specific subjective profiles as assessed by a visual inspection for all lots overall, for lot X, lot Y, lot Z, and lot AA, for males and females, and for smokers and nonsmokers.

OP Depot Concentration Profile Pattern Assessment	Percentage of Profiles Exhibiting a Pattern Reflecting		
	Category 1 Monophasic/Biphasic	Category 2 Peak/Flat	Category 3 Rough/Smooth
Overall Profiles N=129	19/81	54/46	43/57
Lot X (fine) Profiles N=33	33/67	61/39	48/52
Lot Y (nominal) Profiles N=33	15/85	42/58	39/61
Lot Z (coarse) Profiles N=33	18/82	67/33	33/67
Lot AA (b) (4) Profiles N=30	7/93	47/53	53/47
Male Patients Profiles N=90	14/86	57/43	43/57
Female Patients Profiles N=39	28/72	49/51	44/56
Smoker Profiles N=85	16/84	54/46	36/64
Nonsmoker Profiles N=44	23/77	55/45	57/43

Abbreviations: N = number of patients.

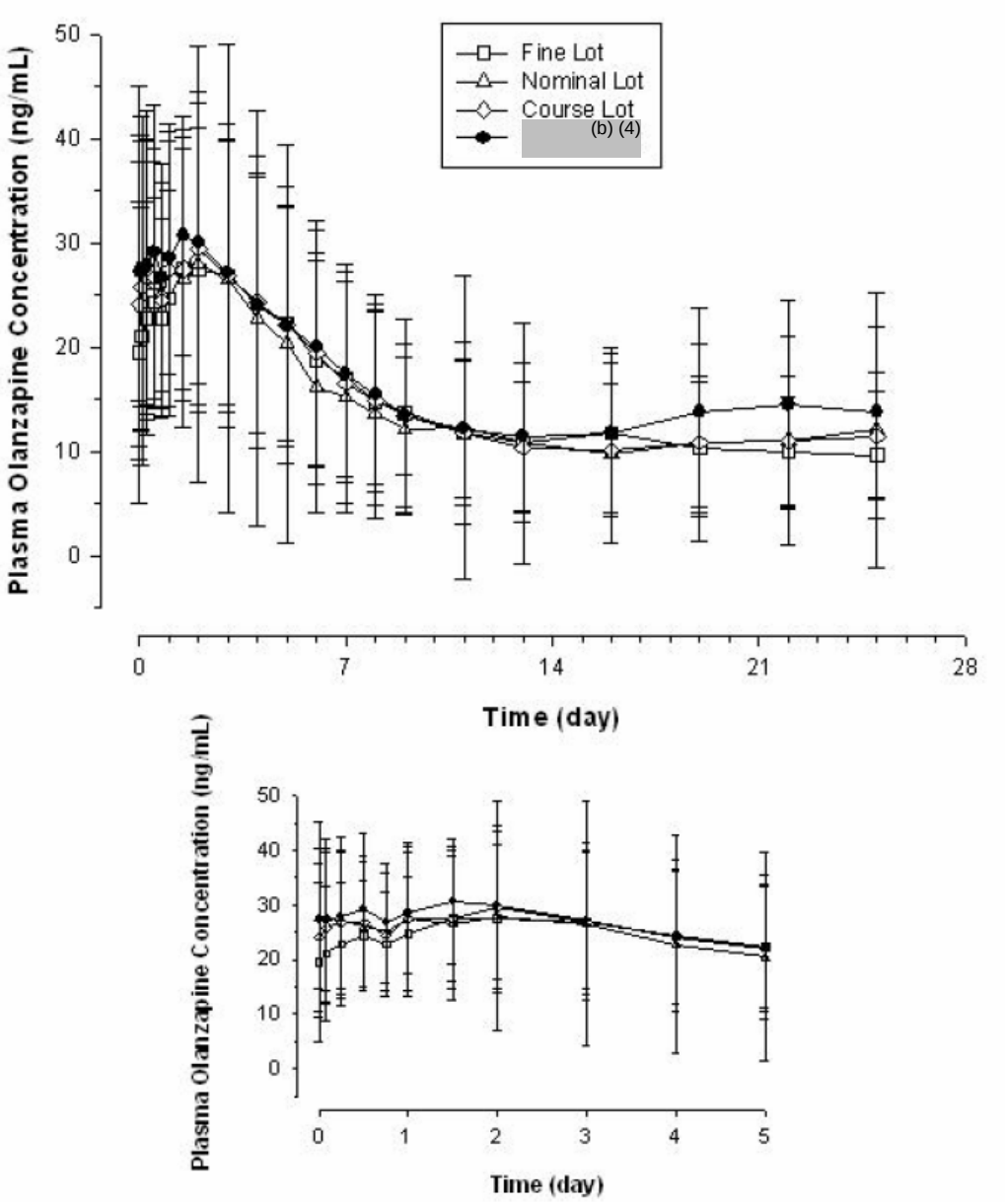
As illustrated in Figure LOBS.7.3, some individuals (54%) exhibited a peak immediately after the OP Depot injection, whereas, for other individuals (46%) the concentrations of olanzapine are flat or decline after the injection, and there is no apparent peak in the profile.



Abbreviations: OP Depot = Olanzapine Pamoate Depot; RAIM = rapid-acting intramuscular; SS = steady state; wk = week.

Figure LOBS.7.3. Examples of olanzapine plasma concentration-time profiles after OP Depot administration illustrating a peak after injection versus a flat or no peak profile.

The slow absorption of olanzapine when given as OP Depot injection was reflected in the long terminal half-life observed (approximately 30 days,, suggesting that the sustained concentrations following each injection might be present for as long as 3 to 6 months. Thus, the pharmacokinetics of OP Depot demonstrated classical flip-flop pharmacokinetics, where the terminal rate of decline reflects the slow absorption process rather than the elimination process. The slow in vivo dissolution at the site of injection and subsequent absorption process is responsible for sustained-release product characteristics.



Single 405-mg OP Depot Injection at time zero
Lot AA (b) (4) N=30) compared to
Lot X (Fine N=33), Lot Y (Nominal N=33), and Lot Z (Coarse N=33)
Top Graph - Full 28-day OP Depot Observation Interval
Bottom Graph - First 5 Days OP Depot Observation Interval (same data)
Lines and Bars Represent Mean ± Standard Deviation

Figure LOBS.7.8. **Mean (±SD) olanzapine plasma concentration-time profiles following a single 405-mg OP Depot injection of the (b) (4) versus the fine, nominal, and coarse lots.**

Weekly Comparison of Sustained OP Depot Concentrations

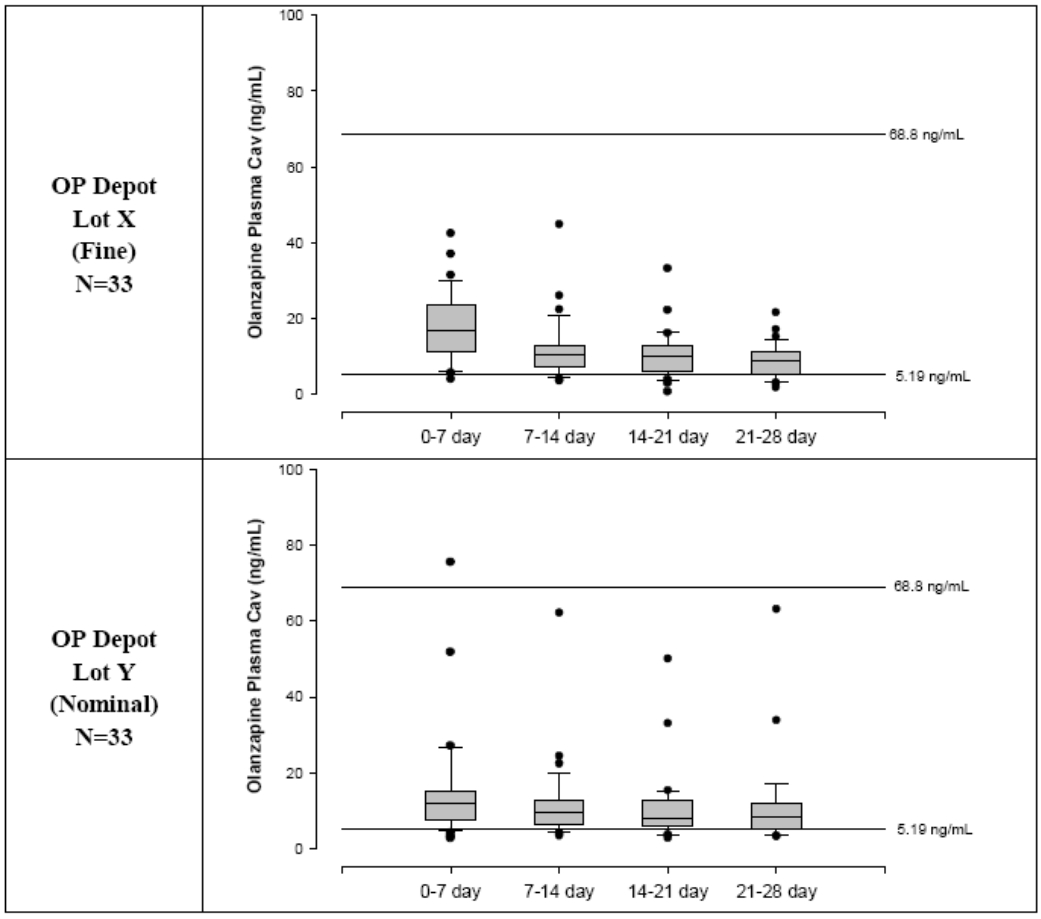


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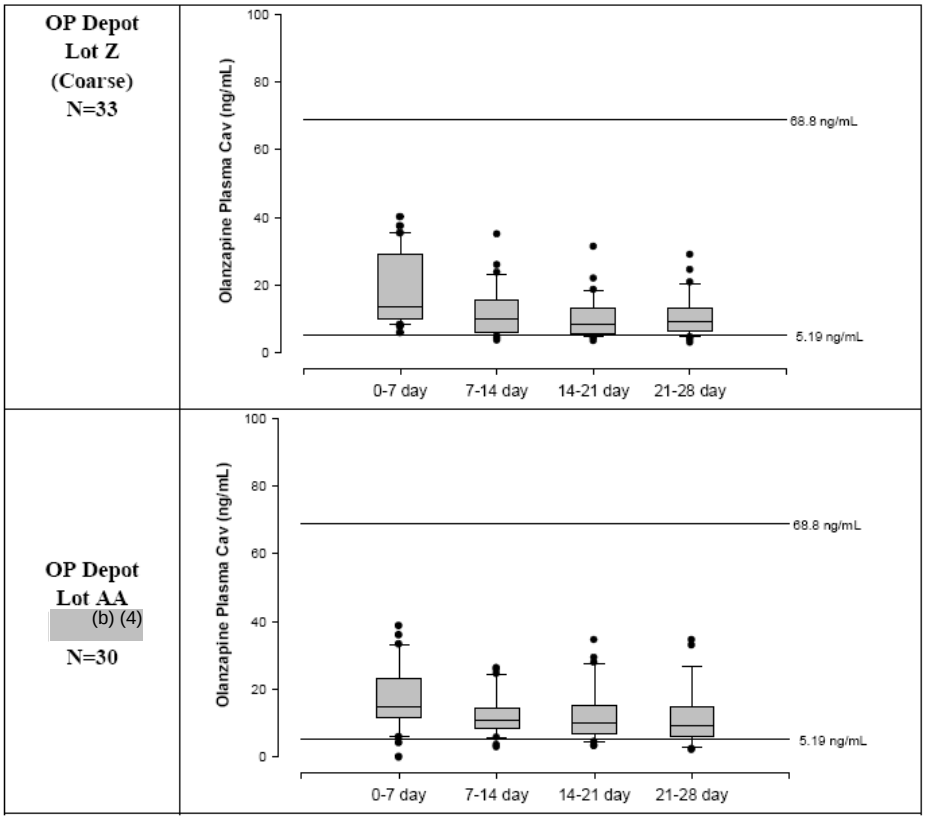
Figure LOBS.7.10. Distribution of average olanzapine plasma concentrations at weekly intervals following a single 405-mg OP Depot injection of the fine, nominal, coarse, and (b) (4) lots.



$_{av}$ = average drug concentration during the dosing interval for a single dose; N = total number of patients; OP Depot = Olanzapine Pamoate Depot.

The middle line in each box plot represents the median; the top and bottom margins of the box represent the 75th and 25th percentiles; the whiskers extend to the 90th and 10th percentiles; data points outside the whiskers represent data at the tail end of the distribution.
Some bars represent data that have less than the number of patients indicated on the left.

Figure LOBS.7.10. Distribution of average olanzapine plasma concentrations at weekly intervals following a single 405-mg OP Depot injection of the fine, nominal, coarse, and (b) (4) lots. (Concluded)

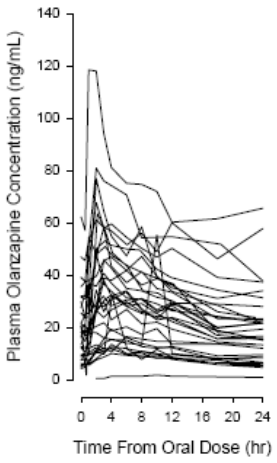
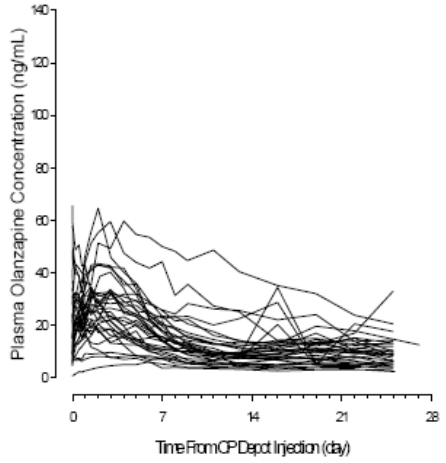
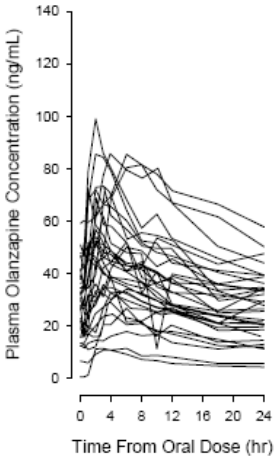
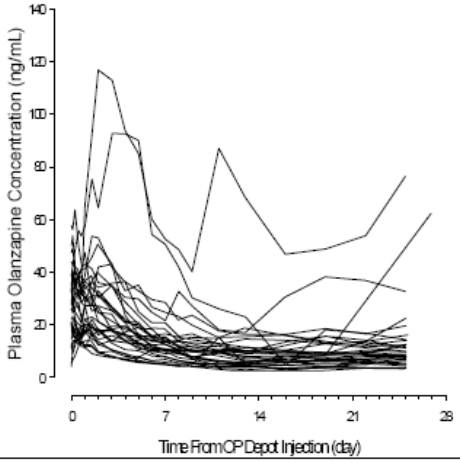
	Oral 24-hr SS Profile Period I	OP Depot Period II
Oral N=33 versus OP Depot Fine Lot X N=33		
Oral N=33 versus OP Depot Nominal Lot Y N=33		

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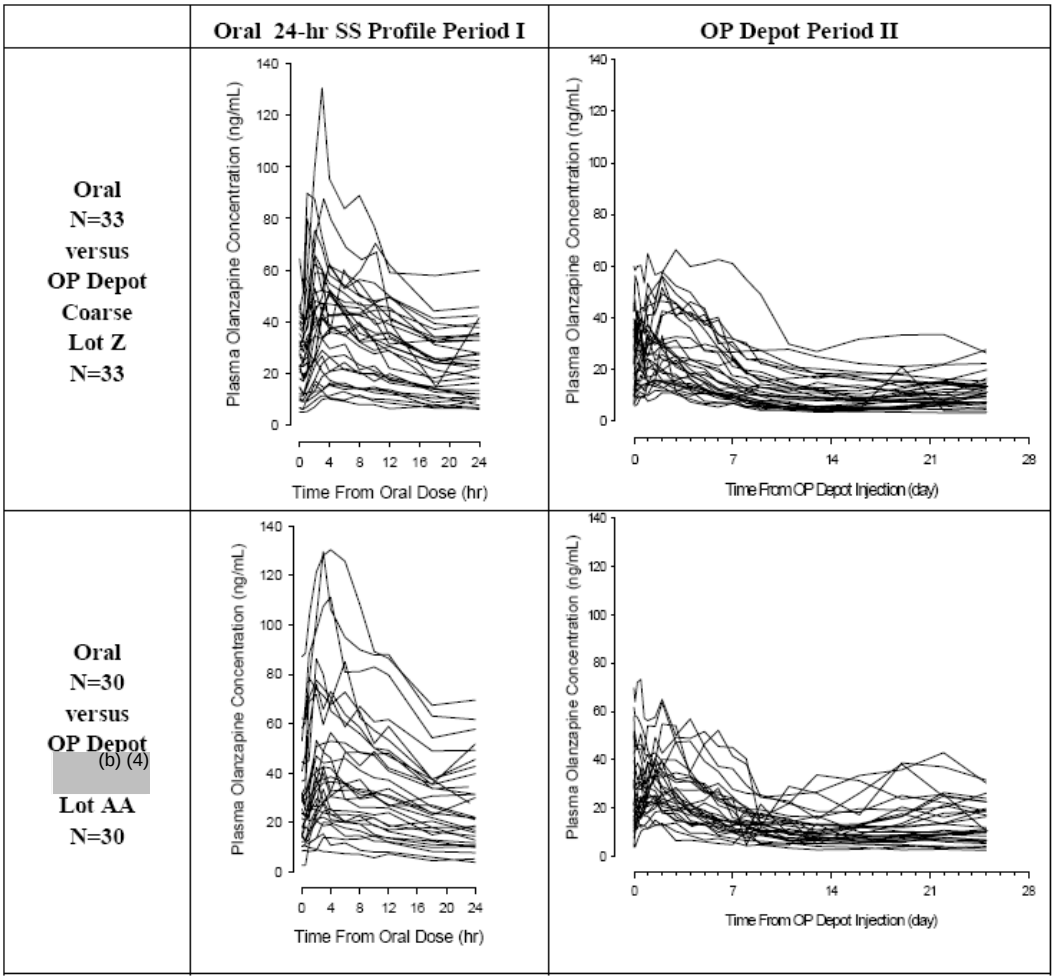
Figure LOBS.7.12. Composite individual olanzapine plasma concentration-time profiles for oral versus OP Depot fine, nominal, course, and (b) (4) lots.



Abbreviations: N = total number of patients; OP Depot = Olanzapine Pamoate Depot; Oral 24-hr SS = oral 24-hour interval at steady state.

Figure LOBS.7.12. Composite individual olanzapine plasma concentration-time profiles for oral versus OP Depot fine, nominal, course, and (b) (4) lots. (Concluded)

Relative Bioavailability Evaluations for OP Depot and Oral Olanzapine

Dose-normalized C_{max} and AUC ($AUC_{0\text{-}tau,ss,oral}$, $AUC_{(0\text{-}t_{last})depot}$, and $AUC_{(0\text{-}\infty)depot}$) were compared between OP Depot and oral olanzapine to evaluate the relative bioavailability for each OP Depot treatment group. C_{max} for each of the OP Depot lots was about half of that for oral olanzapine at steady state (Table LOBS.7.7).

Table LOBS.7.9. Comparison of Relative Bioavailability Following Oral Olanzapine (at Steady State) or OP Depot Injection, Based Upon Dose-Normalized AUC(0-∞) for OP Depot

Lot	Treatment	Least-Squares Geometric Mean for Dose-Normalized AUC(0-∞) (ng*hr/mL/mg)	Ratio of OP Depot versus oral (90% Confidence Interval)
Fine	OP Depot	35.71	
	Oral	40.24	0.89 (0.68, 1.15)
Nominal	OP Depot	46.43	
	Oral	50.86	0.91 (0.65, 1.28)
Coarse	OP Depot	48.04	
	Oral	49.29	0.97 (0.80, 1.19)
(b) (4)	OP Depot	42.29	
	Oral	49.44	0.86 (0.72, 1.02)

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; OP Depot = Olanzapine Pamoate Depot.

Table LOBS.7.10. Geometric Mean (Geometric CV) Olanzapine Noncompartmental Pharmacokinetic Parameters for Steady-State Oral Olanzapine and Single-Dose OP Depot Injection

Treatment	N	C_{max} (ng/mL)	t_{max}[a] (hr)	AUC(0-t_{last})[b] (ng*hr/mL)	C_{av}[c] (ng/mL)	AUC(0-∞) (ng*hr/mL)	C_{av}[d] (ng/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)	$F_{depot:oral}$	$F_{depot:RAIM}$
Oral	12 9	39.1 (76.0)	3.00 (0.50 – 10.08)	617 (76.8)	25.7 (76.8)	-- --	-- --	27.7 (52.4)	20.7 (59.1)	828 (63.7)	-- --	-- --
Fine Lot (X)	32	22.2 (61.6)	72.00 (24.00 – 384.00)	6660 (57.2)	11.1 (56.8)	14500 (70.0)	21.5 (70.0)	634 (83.7)	28.0 (70.0)	25600 (74.1)	0.887 (106)	0.961 (163)
Nominal Lot (Y)	29	18.7 (75.0)	72.00 24.00 – 600.00	6130 (65.7)	10.2 (65.4)	18800 (177)	28.0 (177)	951 (136)	21.5 (177)	29500 (66.8)	0.912 (148)	1.04 (299)
Coarse Lot (Z)	31	23.6 (52.3)	72.08 (35.50 – 600.00)	6980 (53.8)	11.7 (54.1)	19500 (82.0)	29.0 (82.0)	893 (71.4)	20.8 (82.0)	26800 (56.7)	0.975 (73.5)	0.894 (146)
(b) (4) Lot (AA)	25	25.1 (54.0)	72.00 (36.00 – 384.00)	7470 (52.4)	12.5 (51.1)	17100 (74.3)	25.5 (74.3)	648 (89.5)	23.6 (74.3)	22100 (79.5)	0.855 (55.2)	1.00 (104)

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{av} = average drug concentration during the dosing interval for a single dose; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; C_{max} = maximum observed drug concentration; $F_{depot:oral}$ = the ratio of the dose-normalized AUC following depot administration to that following oral administration; $F_{depot:RAIM}$ = the ratio of the dose-normalized AUC following depot administration to that following rapid-acting intramuscular administration; $t_{1/2}$ = half-life associated with elimination rate constant; t_{max} = time of the maximum observed plasma concentration;
Vz/F = apparent volume of distribution during the terminal phase after extra-vascular administration.

[a] Median (range).

[b] AUCτ is reported for oral olanzapine; t_{last} is approximately 25 days for OP Depot and τ is 24 hours for oral olanzapine.

[c] C_{av} calculated from AUC(0-t_{last}).

[d] C_{av} calculated from AUC(0-∞).

Conclusions

The 3 OP Depot lots (Lots X, Y, and Z) with different PSD showed similar and acceptable sustained-release drug delivery, as evidenced by the plasma olanzapine concentration-time profiles.

Each of the 3 lots of OP Depot were made using olanzapine pamoate monohydrate that was manufactured to be within the range of PSD specification limits and met the pre-specified criteria for product quality

bioavailability performance. Therefore, future lots manufactured that meet these PSD and other in vitro specifications will assure appropriate sustained-release drug delivery performance of the OP Depot drug product.

All 3 OP Depot lots met the pre-specified criteria for PQBP characteristics; therefore, all 3 OP Depot lots are clinically acceptable.

The OP Depot lot manufactured using the (b) (4) showed similar and acceptable sustained-release drug delivery, as evidenced by the plasma olanzapine concentration-time profiles.

The OP Depot lot manufactured using material from the (b) (4) (b) (4) met the pre-specified criteria for PQBP. Therefore, OP Depot lots made from drug substance using the (b) (4) (b) (4) will provide suitable sustained-release performance characteristics, as observed with OP Depot lots made using materials from the (b) (4)

Given the pharmacokinetic performance similarity of the 4 OP Depot lots, these data combined with either the in vitro dissolution data or PSD data do not support the development of an IVIVC for OP Depot lots within the PSD range investigated in this study.

Comment:

It was surprising that no subjects in this study exhibited the severe sedation or sleepiness as seen in the Clinical study although the study was done in centers in 11 countries involving 418 subjects.

STUDY 4.

F1D-EW-LOBE(d)-Study to Assess the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of an Intramuscular Formulation of Depot Olanzapine (Pamoate Salt) in Stable Schizophrenic Subjects

Primary Objective
To assess the safety and tolerance of IM olanzapine depot after single and multiple doses in subjects with stabilized schizophrenia.

Study design

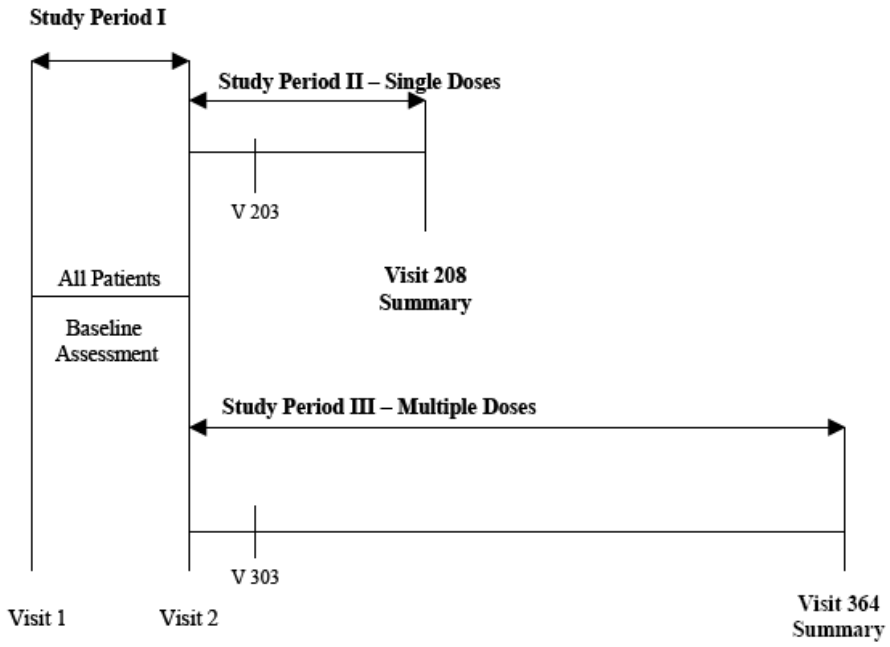


Figure 1. Illustration of study design for Protocol F1D-EW-LOBE.

Table 1. Subject Characteristics Single-Dose Group

Variable	DPO1z-P (N=34)
Sex: No. (%)	
No. Patients	34
Male	27 (79.4)
Female	7 (20.6)
Origin: No. (%)	
No. Patients	34
Caucasian	19 (55.9)
African Descent	10 (29.4)
Hispanic	4 (11.8)
Other Origin	1 (2.9)
Age:yrs.	
No. Patients	34
Mean	38.50
Median	39.45
Standard Dev.	9.09
Minimum	20.17
Maximum	55.21

Table 2. Subject Characteristics Multiple-Dose Group 2-Week Injection Interval

Variable	DPOlz100 (N=6)	DPOlz150 (N=20)	DPOlz160 (N=7)	DPOlz200 (N=41)	DPOlz300 (N=36)
Sex: No. (%)					
No. Patients	6	20	7	41	36
Male	3 (50.0)	15 (75.0)	6 (85.7)	29 (70.7)	26 (72.2)
Female	3 (50.0)	5 (25.0)	1 (14.3)	12 (29.3)	10 (27.8)
Origin: No. (%)					
No. Patients	6	20	7	41	36
Caucasian	2 (33.3)	10 (50.0)	4 (57.1)	24 (58.5)	28 (77.8)
African Descent	4 (66.7)	9 (45.0)	2 (28.6)	16 (39.0)	5 (13.9)
Hispanic	0	1 (5.0)	1 (14.3)	1 (2.4)	3 (8.3)
Age:yrs.					
No. Patients	6	20	7	41	36
Mean	34.49	41.19	31.01	37.86	38.57
Median	32.52	40.61	30.43	38.81	38.57
Standard Dev.	13.35	10.16	8.71	9.65	8.44
Minimum	20.99	24.73	21.28	18.94	22.62
Maximum	52.24	64.36	45.08	51.89	55.96

Table 3. Subject Characteristics LOBE(d) Subject Group 4-Week Injection Interval

Variable	DPOlz210 (N=5)
Sex: No. (%)	
No. Patients	5
Male	5 (100)
Origin: No. (%)	
No. Patients	5
Caucasian	3 (60.0)
African Descent	2 (40.0)
Age:yrs.	
No. Patients	5
Mean	38.66
Median	42.18
Standard Dev.	8.12
Minimum	25.70
Maximum	45.36

Study Period II: Single Dose

The study included a Single-Dose Phase (1 injection [Study Period II]) and, subsequently, a Multiple-Dose Phase (lasting approximately 3 and/or 6 months [Study Period III]). Subjects were not permitted to participate in both Study Periods II and III.
Stabilized subjects with schizophrenia who were being treated with oral olanzapine and had demonstrated the drug is both efficacious and tolerable were recruited into the study. The planned starting dose of IM olanzapine depot was expected to be 60 mg. The maximum dose was not to exceed 450 mg. The doses used ranged from 50 to 450 mg. At Visit 2, the first day of Study Period II, subjects had their oral olanzapine discontinued. Subjects did not receive an oral dose of olanzapine on the day they received their injection (Day 1). In order to establish a baseline plasma concentration of olanzapine, a predose blood sample was taken on Day 1 prior to administration of IM olanzapine depot.

Study Period III: Multiple Dose

Study Period III was between 3 and 6 months in length. The dosing intervals were 14, 21, or 28 days.

At Visit 2, the first day of Study Period III, subjects had their oral olanzapine discontinued. Subjects did not receive an oral dose of olanzapine on the day they received the first injection (Day 1). In order to establish a baseline plasma level of olanzapine, a predose blood sample was taken on Day 1 prior to administration of IM olanzapine depot. Also, throughout Study Period III, blood samples were drawn and used to determine the plasma concentration of olanzapine after the administration of IM olanzapine depot. Pamoic acid was analyzed in a pooled subset of these plasma samples to explore its systemic exposure; however, this did not require a collection of additional blood samples or increase the volume of blood samples.

Each subject was required to have a Visit 1 and 2, and subjects would then enter either Study Period II or III. The visits during Study Period II were prefixed with the number 2 (for example, V203, 204 = Visit 3, 4 of Study Period II). The visits during Study Period III were prefixed with the number three (for example, V303, 304 = Visit 3, 4 of Study Period III).

Study Drug Administration

IM olanzapine depot was to be administered within 30 minutes of preparation. Prior to the injection, the injection site was examined to ensure there were no previous existing abnormalities. The injection was intended to be administered to the upper outer quadrant of the buttocks. The deltoid muscle was used as an alternative injection site. During the injection, the muscle was to be relaxed.

Biological Samples

Blood samples were taken at scheduled time points throughout the study and were used to determine the plasma concentrations of olanzapine. The date and time samples were taken were recorded on the laboratory requisition forms.

PK Analyses

Serial blood samples collected after single- and multiple-dose regimens of IM olanzapine depot were used to calculate the PK characteristics of olanzapine using standard noncompartmental methods (WinNonlin Professional Version 3.1). Subjects enrolled in the LOBE(d) segment of the study were administered IM olanzapine depot from a clinical trial lot different from that administered to other subjects; therefore, PK data from these subjects were summarized separately.

A single blood sample was collected on the first and last days of the Oral Olanzapine Lead-In Phase (Study Period I), during which subjects remained on a fixed oral dose for approximately 1 to 3 weeks. The blood sample collected at the end of the Lead-In Phase was used to assess baseline plasma olanzapine concentrations during steady-state oral dosing. Single-dose subjects were sampled for up to 4 weeks after a single injection (Study Period II). Mutiple-dose subjects were sampled for up to 6 months of multiple dosing (Study Period III). Serial blood samples collected throughout the study were used to determine plasma olanzapine concentrations. After the IM olanzapine depot dose, samples were collected daily for the first 4 days (0, 24, 48, 72, and 96 hours postinjection) and then were collected weekly (1, 2, 3, and 4 weeks postinjection) until the end of the dosing interval. The initial subjects enrolled in LOBE had a blood sample collected at 6 hours, rather than 72 hours, after each injection.

Individual plasma olanzapine concentration-versus-time data were plotted for each subject for the duration of the study. Plasma concentration profiles were summarized across subjects based upon their common dose and injection interval. Only concentrations with actual sampling times deviating less than 10% from the scheduled sampling time, and not deemed outliers or influenced by oral usage, were included in summary calculations. If less than half of the subjects contributed a concentration meeting these criteria, the summary statistics were not calculated for that time point. Average plasma concentration-versus-time plots were used to assess accumulation to steady state, intersubject variability, and dose proportionality in plasma olanzapine concentrations during multiple IM olanzapine depot dosing.

There were several study amendments related to sample size, number of injections and sampling period. The amendment which may impact the study was:
Amendment (d), approved 17 September 2002, allowed the number of subjects entering the study to increase from 300 subjects to 400 subjects. Study duration was reduced from 6 months to 3 months. Finally, the study was amended in order to evaluate a new lot of IM olanzapine depot. Nineteen of the 25 subjects enrolled in this part of the study also participated in previous amendments of the study.

However the firm reported that the data from this amendment were analyzed separately.

Study Subjects
Three hundred fourteen unique subjects entered, and 281 enrolled. Of these 281 enrolled subjects, 202 unique subjects completed the study according to the protocol. Data from all subjects enrolled are included in the pharmacokinetic (PK) and statistical analyses. Data from all subjects who entered the study are included in subject listings. For the purpose of this report, the subjects enrolled in this study will be reported on in three groups:

A = Single-Dose Group: those subjects enrolled in Phase II of the study. Thirty-four subjects enrolled in the study, and 30 subjects completed according to the protocol. Two subjects discontinued due to adverse events (AEs).

B = Multiple-Dose Group: those subjects enrolled in Phase III of the study who participated in the study up to the implementation of protocol amendment (d). Two hundred twenty-three subjects enrolled in the study, and 153 subjects completed according to the protocol. Seven subjects discontinued due to AEs.

C = LOBE(d) Subject Group: those subjects enrolled in Phase III of the study who participated in protocol amendment (d). Twenty-five subjects enrolled in the study, and 23 subjects completed according to the protocol. One subject discontinued due to an AE. Eighteen of the 25 subjects who participated in the LOBE(d) amendment also participated in earlier amendments of this study. Thus, the data from the LOBE(d) Group were analyzed separately

Plasma Analysis Results

Study began: August 2000
Analysis completed: May 2003
Total Storage Time: 2 yrs and 9 months

Parameter	
Method	HPLC-Liquid chromatography with electrochemical detection
Sensitivity/LOQ	0.25 ng/mL
Linearity (Standard curve samples)	0.25-100 ng/mL
Quality Control (QC) Samples	0.64 ng/ml 40 ng/ml 80 ng/ml
Precision of Standards (%CV)	8.9% @ 0.25 ng/ml 1.4% @ 100 ng/ml
Precision of QC Samples (%CV)	6.2% @ 0.64 ng/ml 3.8% @ 40 ng/ml 4.7% @ 80 ng/ml
Accuracy of Standards (%)	98% @ 0.25 ng/ml 99% @ 100 ng/ml
Accuracy of QC Samples (%)	101% @ 0.64 ng/ml 97.5% @ 40 ng/ml 99.6% @ 80 ng/ml

RESULTS

Single Dosing

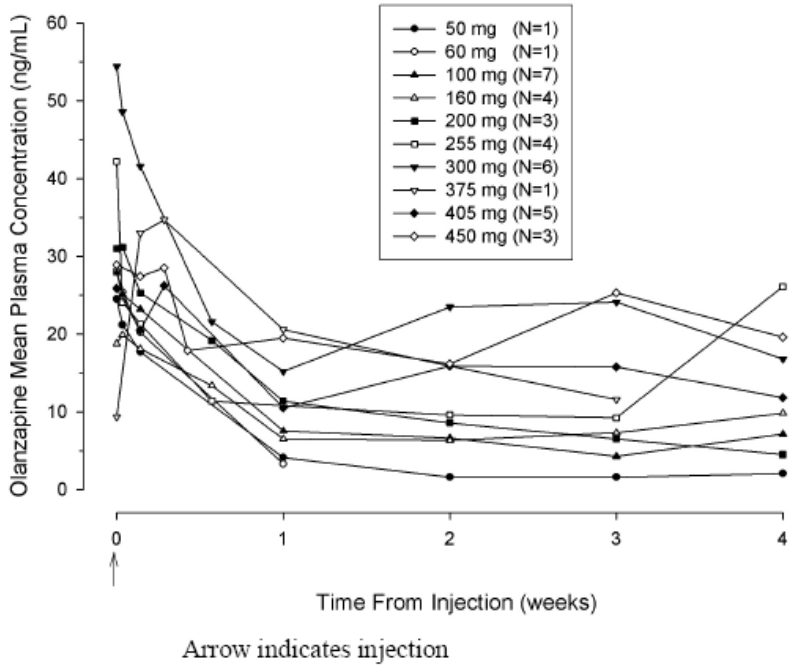


Figure 2. Mean plasma olanzapine concentrations following a single dose of IM olanzapine depot over the dosage range of 50 to 450 mg.

Pharmacokinetics After Multiple-Dose Administration

Pharmacokinetic results will be summarized by dosing interval.

Preliminary exploratory evaluations were also conducted to assess the utility of the deltoid as an alternative injection site. In addition, a loading-dose strategy was explored; that is, dosing every 2 weeks for the first 3 injections, followed by dosing every 4 weeks for the remaining 4 injections. Both strategies were conducted in a limited number of subjects; therefore, definitive conclusions cannot be made.
Subjects in LOBE(d) received either 300 mg/2 weeks, 300 mg/4 weeks, or 405 mg/4 weeks for a period of 3 months.

Two-Week Dosing Interval

Figure 3 provides a comparison of mean plasma olanzapine concentrations following IM olanzapine depot doses ranging from 100 to 300 mg/2 weeks. The concentrations show a gradual monoexponential decline at all doses and remain measurable until the end of the 2-week injection interval, which is true even after the first dose. In general, mean concentrations appear to be proportional to the dose administered. The plasma olanzapine concentration patterns suggest that there is accumulation over the first few injection intervals. Concentrations achieve steady state in 2 to 3 months.

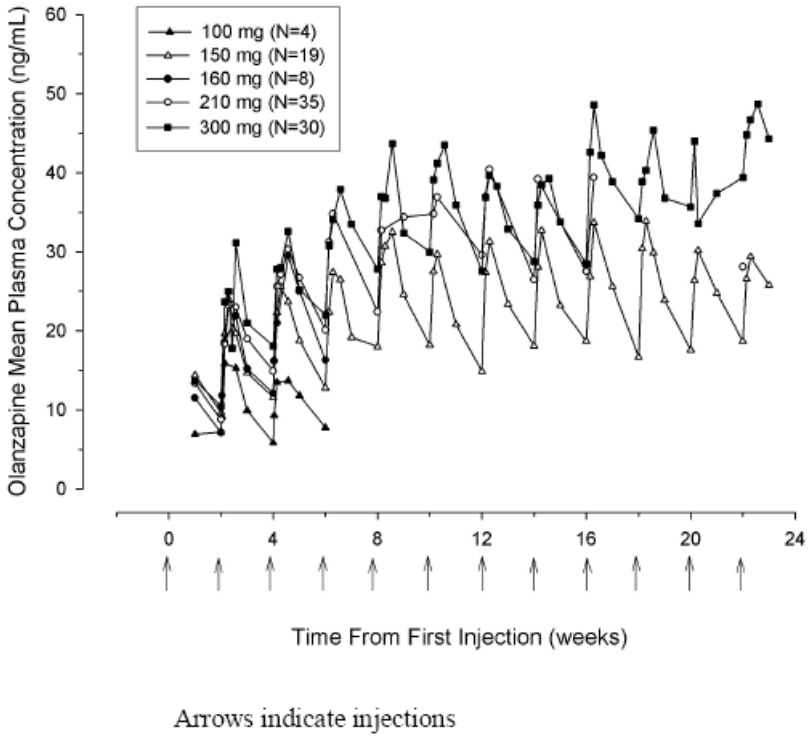


Figure 3. Mean plasma olanzapine concentrations following IM olanzapine depot doses ranging from 100 to 300 mg/2 weeks. The mean plasma olanzapine profile for 150 mg shows attainment of steady state within 8 to 12 weeks, after a small degree of accumulation. Concentrations achieve steady state in 2 to 3 months.

Table 4. Geometric Mean (%CV) Steady-State PK Parameters Multiple-Dose Group 2-Week Injection Interval

Dose (mg)	N_{PK}[a]	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$[b] (hr)	$AUC_{\tau,ss}$ (ng•hr/mL)	$t_{1/2}$[c] (hr)	CL_{ss}/F (L/hr)	V_{ss}/F (L)	$C_{av,ss}$ (ng/mL)	PTF (%)
100[d]	3	13.5	96.0	3530	322	28.4	13700	10.5	73.8
		(56.2)	(95.68 - 167.83)	(46.7)	(28.7)	(46.7)	(82.9)	(46.7)	(34.5)
150	12	29.7	48.1	7540	422	19.9	12800	22.4	54.1
		(29.0)	(19.28 - 334.23)	(26.2)	(75.8)	(26.2)	(86.8)	(26.2)	(48.5)
160[e]	7	26.1	95.9	6870	352	23.3	13200	20.4	82.9
		(63.6)	(48 - 312)	(51)	(189)	(51.0)	(383)	(51.0)	(53.9)
210	17	39.3	48.7	10400	561	19.2	16300	31.0	50.7
		(37.7)	(0 - 190.92)	(46.2)	(90.4)	(46.2)	(73.5)	(46.2)	(53.5)
300	19	46.1	82.8	12400	751	24.1	28300	37.0	39.5
		(41.7)	(19.87 - 335.72)	(46.5)	(192)	(46.5)	(168)	(46.5)	(42.6)

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration-versus-time curve during one dosing interval at steady state; $C_{av,ss}$ = predicted average olanzpapine concentration at steady state; CL_{ss}/F = apparent plasma clearance at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; N_{PK} = number of subjects used to calculate mean $AUC_{\tau,ss}$, $CL_{ss/F}$, and $C_{av,ss}$, and may differ slightly for other parameters; PTF = peak-to-trough fluctuation; $t_{1/2}$ = apparent terminal elimination half-life; $T_{max,ss}$ = observed sampling time of $C_{max,ss}$; V_{ss}/F = apparent volume of distribution at steady state.

[a] N_{PK} = number of subjects used to calculate mean $AUC_{\tau,ss}$, CL_{ss}/F, and $C_{av,ss}$, and may differ slightly for other parameters.

[b] Median and range reported.

[c] Prolonged half-life reflects depot absorption.

[d] Parameters estimated for 3rd injection.

[e] Parameters estimated for 2nd or 3rd injection.

Both volume and half-life are approximately 10-fold larger than that observed following oral olanzapine dosing (mean volume=1150 L; mean half-life=33 hours after oral dosing). The increased half-life may be explained by "flip-flop" (absorption rate-limited) kinetics, whereby the slow in vivo dissolution of the poorly soluble pamoate salt prolongs absorption of olanzapine into the systemic circulation.

Mean clearance of olanzapine remains constant across the IM olanzapine depot dosage range and is consistent with clearance estimates following oral olanzapine. This emphasizes the fact that the basic intrinsic PK properties of olanzapine, such as clearance, are unaffected by route of administration. The intersubject variability in clearance following 2-week IM olanzapine depot dosing is slightly larger than the variability associated with oral olanzapine (% CV typically ranges from 35% to 40%).

Effect of Smoking

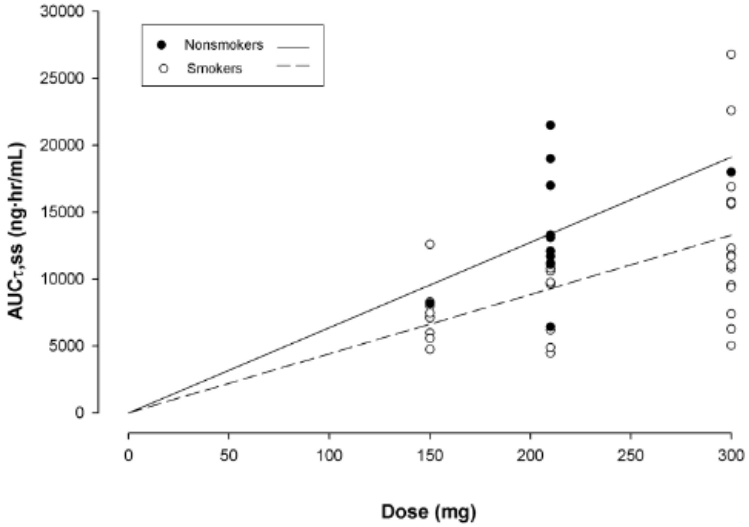


Figure 4. Relationship between $AUC_{\tau,ss}$ and dose for smokers and nonsmokers in the Multiple-Dose Group receiving IM olanzapine depot every 2 weeks.

Smokers appear to have a higher clearance than nonsmokers.

Comparison to IM levels to Oral levels Study HGAJ(5-20 mg/day)

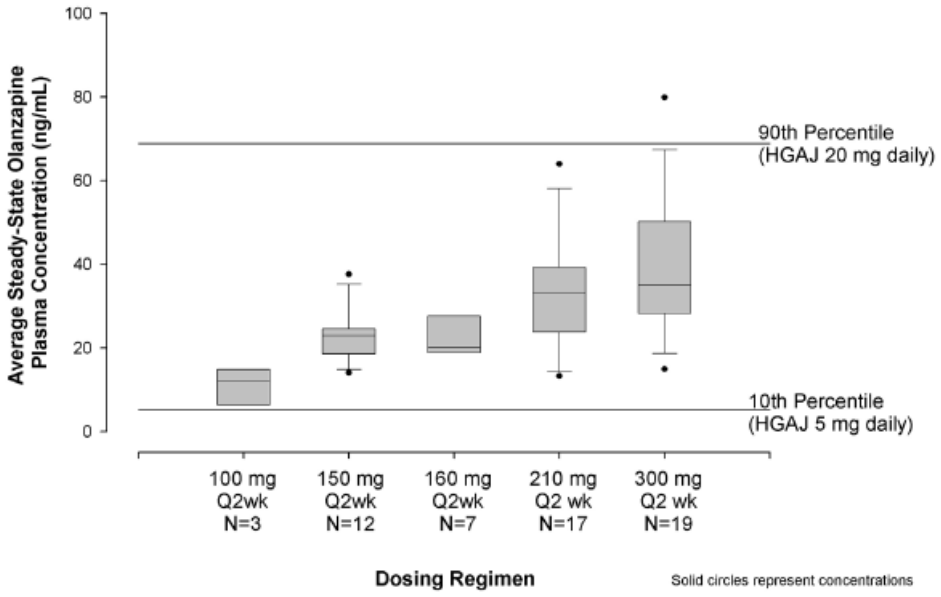


Figure 5. The distribution of time-averaged steady-state olanzapine plasma concentrations for each 2-week regimen.

Comments:

Given the small sample size for each dose group and the confounding effects of lead-in oral olanzapine, especially during the first several days after the injection, limited PK

analyses of single-dose data was conducted.

Three-Week Dosing Interval

Very few PK data values were available for the 3-week interval. Many of the subjects on this regimen received extensive oral supplementation. In addition, several subjects in this group were escalated to a higher IM olanzapine depot dose or withdrew from the study.

Four-Week Dosing Interval

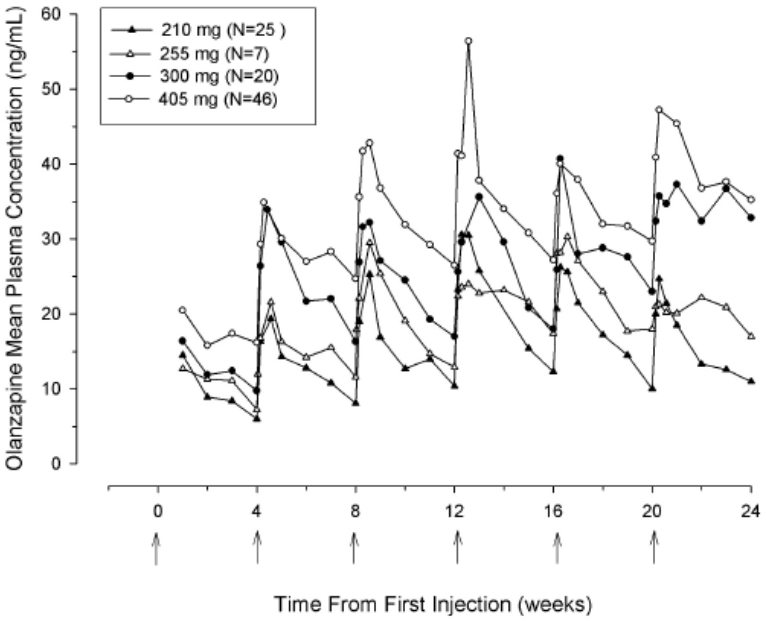


Figure .6. Mean olanzapine plasma concentrations for the Multiple-Dose Group at doses ranging from 210 to 405 mg/4 weeks. The extent of accumulation appears less for the monthly dosing regimen than for the 2-week dosing regimen, consistent with general PK principles.

Table 5. Geometric Mean (%CV) Steady-State PK Parameters Multiple-Dose Group 4-Week Injection Interval

Dose (mg)	N_{PK}[a]	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$[b] (hr)	$AUC_{\tau,ss}$ (ng•hr/mL)	$t_{1/2}$[c] (hr)	CL_{ss}/F (L/hr)	V_{ss}/F (L)	$C_{av,ss}$ (ng/mL)	PTF (%)
210	21	22.8 (57.2)	48 (0 – 503)	9150 (44.7)	553 (87.5)	21.9 (44.7)	18300 (128)	13.6 (44.7)	99.6 (56.5)
255	6	25.4 (44.8)	336 (0 - 503)	12400 (51.5)	718 (102)	20.6 (51.5)	20800 (101)	18.4 (51.5)	50.8 (55.0)
300	14	39.6 (45.2)	167 (44 – 507)	18900 (44.0)	590 (93.3)	15.9 (44.0)	16700 (113)	28.1 (44.0)	79.6 (45.0)
405	29	47.6 (52.5)	96.0 (24 - 669)	23600 (50.0)	995 (110)	17.1 (50.0)	24600 (120)	35.2 (50.0)	65.1 (48.4)

Abbreviations: $AUC\tau,ss$ = area under the concentration-versus-time curve during one dosing interval at steady state; $C_{av,ss}$ = predicted average olanzpapine concentration at steady state; CL_{ss}/F = apparent plasma clearance at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; N_{PK} = number of subjects used to calculate mean $AUC_{\tau,ss}$, CL_{ss}/F, and $C_{av,ss}$, and may differ slightly for other parameters; PTF = peak-to-trough fluctuation; $t_{1/2}$ = apparent terminal elimination half-life; $T_{max,ss}$ = observed sampling time of $C_{max,ss}$; V_{ss}/F = apparent volume of distribution at steady state.

[a]N_{PK} = number of subjects used to calculate mean $AUC_{\tau,ss}$, CL_{ss}/F, and $C_{av,ss}$, and may differ slightly for other parameters.

[b]Median and range reported.

[c]Prolonged half-life reflects depot absorption.

Figure 7 illustrates the within-subject relationship between olanzapine concentrations after IM olanzapine depot and oral olanzapine dosing. The figure illustrates data from a small subset of 10 subjects who were given 10 mg daily during the Oral Lead-In Phase of the study and were subsequently randomized to IM olanzpapine depot 405 mg/4 weeks. The figure illustrates that, in general, subjects with higher olanzapine concentrations during oral dosing tend to have correspondingly higher concentrations following 405-mg/4 weeks IM olanzapine depot dosing, in keeping with the fact that the clearance of olanzapine appears to be unaltered after oral and IM olanzapine depot dosing.

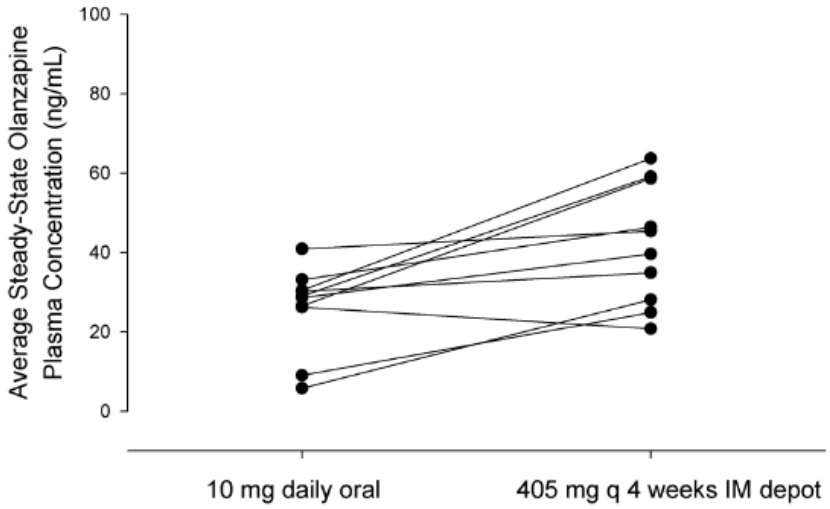
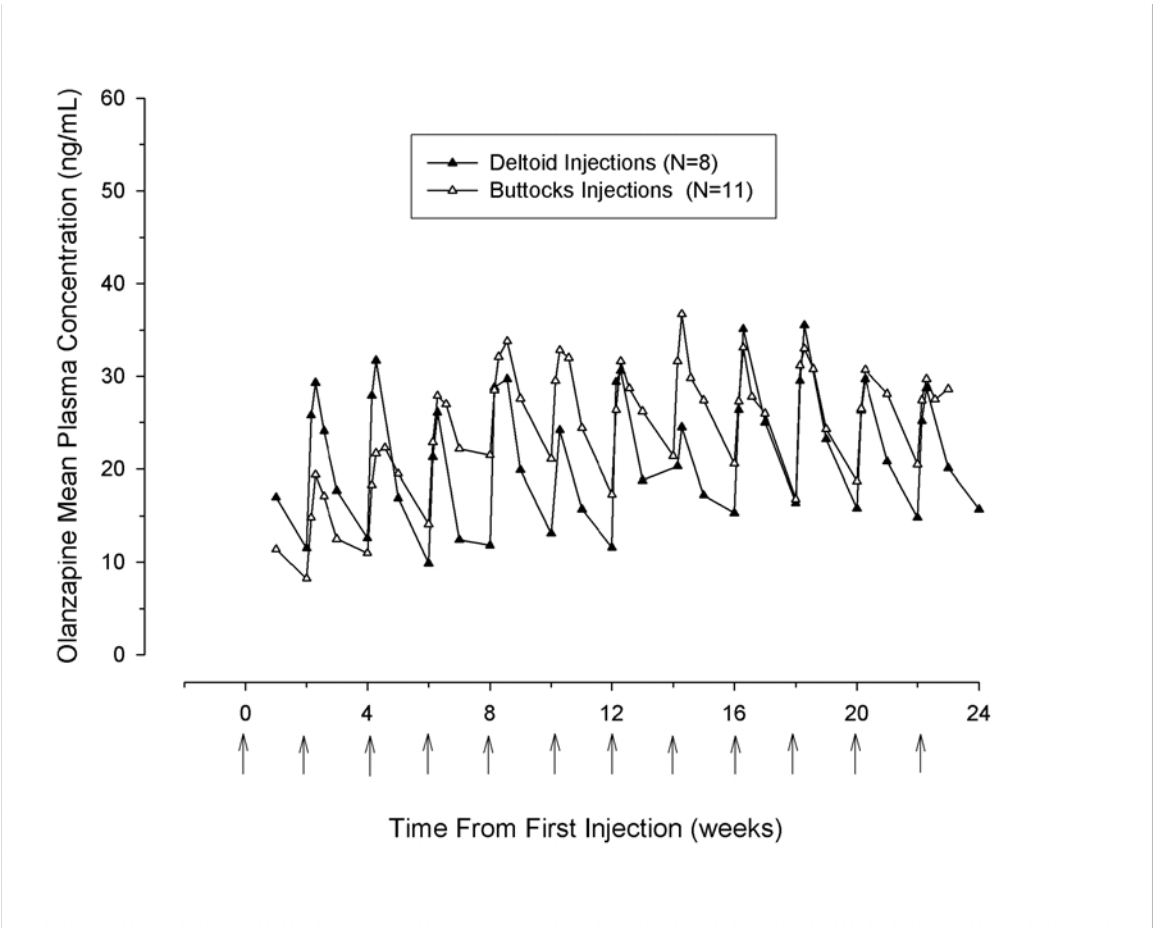


Figure7. Illustrates the within-subject relationship between olanzapine concentrations after IM olanzapine depot and oral olanzapine dosing.

Figure 8. Comparison of deltoid vs. buttocks injections-both dosed at 150mg/2 weeks



PK Comparison to Oral Olanzapine

Historical oral data from Study HGAJ is used as a reference PK database of steady-state plasma olanzapine concentrations observed after daily doses of 5 to 20 mg. This database is composed of approximately 2800 steady-state plasma olanzapine concentrations from more than 900 subjects. Figure 9 illustrates the range of concentrations obtained after oral dosing in Study HGAJ.

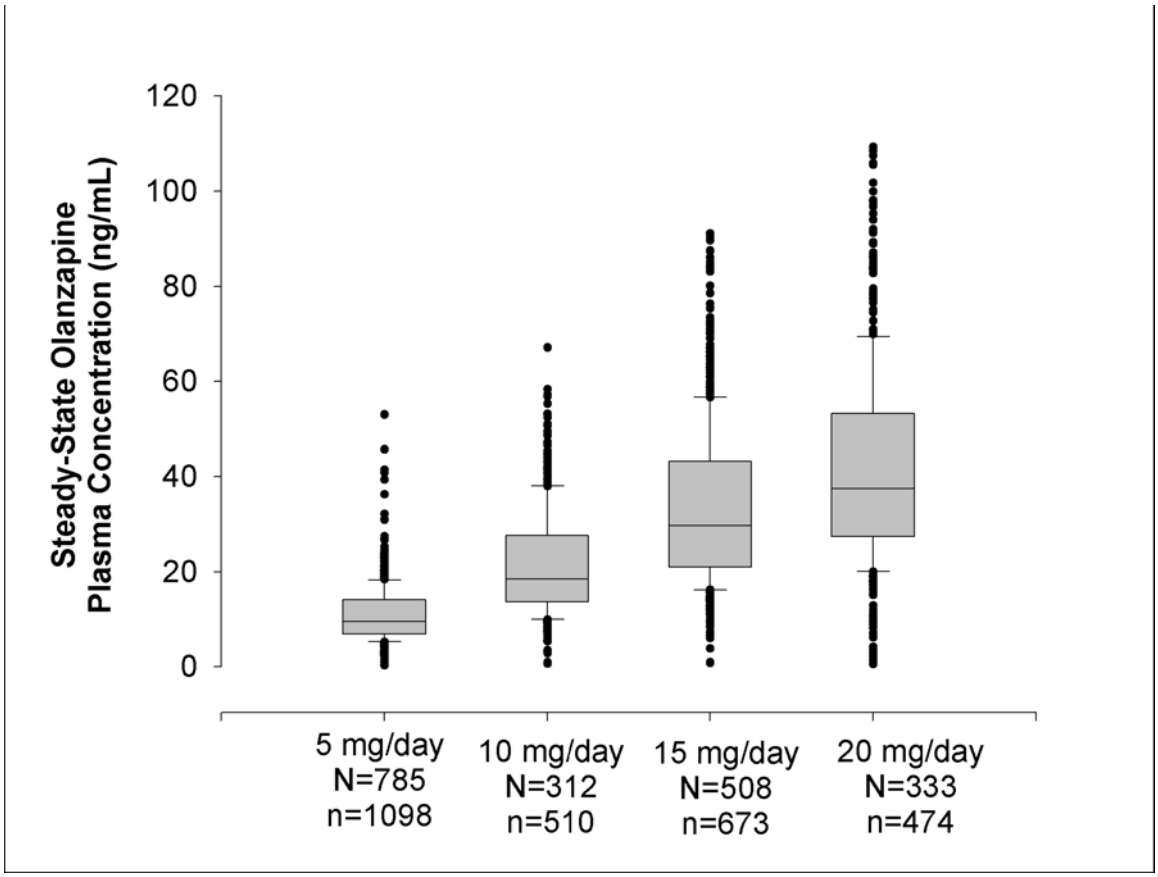


Figure 9. Distribution of steady-state olanzapine plasma concentrations after oral dosing in Study HGAJ.

Comments:

1.The lack of response for the 3 week regimen needs more explanation from the firm.
2. It appears that the deltoid injections seemed to give higher initial values.
3.The loading dose study resulted in higher initial levels but reach steady-state values that remain higher than subjects not on loading dose.
4. The firm did report 1 IAIV event in this study LOBE-100-1039.

STUDY 5.

FID-EW-LOBO-A Study to Investigate the Metabolites of Olanzapine Following Administration of Oral Olanzapine and the Pamoate Formulation of Intramuscular Olanzapine Depot in Stable Patients With Schizophrenia or Schizoaffective Disorder

Primary Objective

To further investigate the pharmacokinetic (PK) profile and gather information on the metabolic profile of intramuscular (IM) olanzapine depot following multiple administrations in comparison with those following oral administration in patients with stabilized schizophrenia or schizoaffective disorder.

Study Design Including Choice of Control

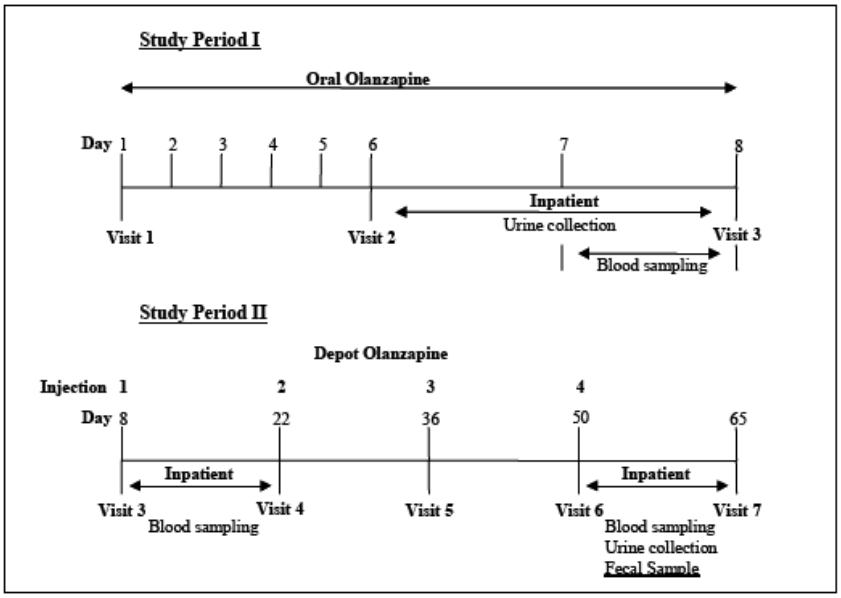


Figure LOBO.9.1. Illustration of study design for Study F1D-EW-LOBO.

Patient Demographic Characteristics

Patient Number[a]	Gender	Age (yr)	Origin	Height	Weight	Smoking[b]	Alcohol[c]
002[d]	M	54	African Descent	160cm	71 kg	Y	N
003[d]	M	51	Caucasian	180cm	92 kg	Y	N
004[d]	M	31	African Descent	158cm	48 kg	Y	N
008	M	40	African Descent	175cm	64 kg	Y	N
031	M	25	African Descent	185cm	112 kg	Y	N
032	M	31	African Descent	170cm	57 kg	Y	N
033	M	24	African Descent	180cm	113 kg	Y	N
034	M	30	African Descent	163cm	61 kg	Y	N
035	F	40	African Descent	163cm	71 kg	Y	N

Abbreviations: N = no; Y= yes; yr = year.

[a] Patient Number = study specific identifier.

[b] Denotes if patient was currently smoking (Y=Yes; N = No).

[c] Denotes if patient currently consumes alcohol (Y=Yes; N = No).

[d] Denotes patients who participated in metabolic profiling

Patients were to have been receiving oral olanzapine up to 20 mg/day for the 4 weeks prior to study entry and were to continue their current oral olanzapine dosage through the last day of the baseline assessment.

The first 3 patients who completed the study were evaluated for the primary objective of metabolic profiling. Subsequent patients were evaluated for PK profiling of IM olanzapine depot only. For patients participating in the PK profiling, only PK sampling was done and no urine or blood samples were collected for metabolite identification.

For those patients participating in the protocol for metabolic profiling, the following applied:

at Visit 2, patients were required to be hospitalized for the last

48 hours of Study Period I. Following the final two oral doses (Day 6 and Day 7), urine was collected at intervals up to 24 hours after each dose. Additionally, following the last oral dose (Day 7), plasma samples from whole blood collections were used to assess the metabolites following oral administration.

a blood sample was taken immediately before dosing with IM olanzapine depot at Visit 3. This blood sample was used to establish baseline plasma concentrations of olanzapine resulting from oral dosing with olanzapine. Patients did not receive oral olanzapine at Visit 3, the day of the first injection (Day 8). In order to establish a baseline plasma concentration of olanzapine, a blood sample was taken prior to the first injection.

Intramuscular olanzapine depot 300 mg was given every 14 days in Study Period II, and patients were discontinued from metabolic profiling if this dose was found to be clinically unsuitable.

During Study Period II, patients were to receive a dose of IM olanzapine depot 300 mg every 14 days until 4 injections were administered.

Intramuscular olanzapine depot was to be administered within 30 minutes of preparation. Prior to the injection, the injection site was to be examined to ensure that no abnormalities were present. The IM olanzapine depot dose was to be administered to the upper, outer quadrant of the buttock, preferably in the prone position. During the injection, the muscle was to be relaxed.

Biological Samples

Venous blood samples were used to determine the plasma concentrations of olanzapine, N-desmethyl olanzapine, glucuronide of olanzapine, and/or pamoic acid.

Study Period I

Blood samples were collected on Day 7 before the oral dose, and at 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours after the dose. Additional blood samples were taken to assess olanzapine-related metabolites in plasma, namely those taken at 3, 8, and 24 hours.

Study Period II

Blood samples were collected during each of the inpatient periods following Injection 1 and Injection 4. The samples were collected prior to the injection and at 2, 6, 12, 18, 24, 36, and 48 hours after the injection. Beginning on the third day following Injection 1 and Injection 4, a blood sample was drawn daily on Day 11 through Day 22 and Day 53 through Day 64. In addition, for metabolite profiling, blood samples were taken at times following the fourth injection (2, 4, 7, and 14 days).

Urine and Fecal Samples (for patients having metabolic profile)

During Study Period I, urine was collected over intervals of 0 to 6, 6 to 12, and 12 to 24 hours following the second to last oral dose (Day 6) and over an interval of 0 to 24 hours following the last oral dose (Day 7).

During Study Period II, urine was collected on the 2nd, 4th, 7th, and 14th day following Injection 4. This was collected over a 12-hour period on each occasion. One fecal sample was collected following Injection 4. This sample was to represent the first bowel movement following Injection 4.

Pharmacokinetic (PK) Analyses

Serial blood samples collected after multiple-dose oral and single (first dose) and multiple (fourth dose) doses of IM olanzapine depot were used to calculate the PK characteristics of olanzapine, 4'-N-desmethyl olanzapine, glucuronide of olanzapine, and pamoic acid (following IM olanzapine depot only) using standard noncompartmental methods (WinNonlin Professional Version 3.1). An evaluation of the PK characteristics for olanzapine following the depot injection by depot lot and overall was performed.

The portions of measured plasma olanzapine, 4'-N-desmethyl olanzapine, and glucuronide of olanzapine concentrations attributable to any oral olanzapine doses, given during Study Period I, were addressed in the PK analysis. A method of residuals was used to estimate the contribution of the depot alone. The terminal rate constant from the oral dose was used to calculate the residual amount from prior oral olanzapine at each timepoint following the first IM olanzapine depot injection. The estimated residual concentration was subtracted from the measured concentration at each timepoint to determine the corrected concentration for each depot sample point. The corrected concentrations were used in the noncompartmental analysis and in individual and mean plots of the concentration data following the first IM olanzapine depot injection in Study Period II.

The time-averaged steady-state concentration was determined as $AUC0\text{-}tau_{,ss}$ divided by the depot-dosing interval (tau). The peak-to-trough fluctuation (PTF) was determined as the ratio $(C_{max,ss}\text{-}C_{min,ss})/C_{av,ss}$. The time-averaged steady-state concentration was determined as $AUC0\text{-}tau_{,ss}$ divided by the depot-dosing interval (tau). The peak-to-trough fluctuation (PTF) was determined as the ratio $(C_{max,ss}\text{-}C_{min,ss})/C_{av,ss}$. The metabolic ratio for 4'-N-desmethyl olanzapine and glucuronide of olanzapine was determined as the ratio of $(AUC\tau_{,metabolite}/ AUC\tau_{,parent})$.

The $C_{max,ss}$, $C_{av,ss}$, and $AUC0\text{-}tau_{,ss}$ estimates from the oral phase were dose-normalized to a 10-mg dose to aid in the comparison of parameters across patients according to the following equation: (10 mg/olanzapine dose [mg])*parameter

Plasma Analysis Results

Study began: June 2002
Analysis completed: July 2003
Total Storage Time: 13 months

Parameter	Olanzapine	Ndesmethyl Olanzapine	*Acid Hydrolyzed Olanzapine
Method	HPLC-Liquid chromatography with electrochemical	HPLC-Liquid chromatography with	HPLC-Liquid chromatography with

	detection	electrochemical detection	electrochemical detection
Sensitivity/LOQ	0.25 ng/mL	0.25 ng/mL	0.25 ng/mL
Linearity (Standard curve samples)	0.25-50 ng/mL	0.25-50 ng/mL	0.25-50 ng/mL
Quality Control (QC) Samples	1 ng/ml 15 ng/ml 40 ng/ml	1 ng/ml 15 ng/ml 40 ng/ml	1 ng/ml 15 ng/ml 40 ng/ml
Precision of Standards (%CV)	7.6% @ 0.25 ng/ml 1.6% @ 50 ng/ml	10% @ 0.25 ng/ml 7.4% @ 50 ng/ml	7.3% @ 0.25 ng/ml 2% @ 50 ng/ml
Precision of QC Samples (%CV)	4.1% @ 1 ng/ml 2.3% @ 15 ng/ml 3.4% @ 40 ng/ml	10% @ 1 ng/ml 10% @ 15 ng/ml 7.6% @ 40 ng/ml	6% @ 1 ng/ml 5% @ 15 ng/ml 5% @ 40 ng/ml
Accuracy of Standards (%)	103% @ 0.25 ng/ml 101% @ 50 ng/ml	99% @ 0.25 ng/ml 99% @ 50 ng/ml	101% @ 0.25 ng/ml 99% @ 50 ng/ml
Accuracy of QC Samples (%)	97% @ 1 ng/ml 99% @ 15 ng/ml 99.6% @ 40 ng/ml	102% @ 1 ng/ml 99% @ 15 ng/ml 104% @ 40 ng/ml	100% @ 1 ng/ml 98% @ 15 ng/ml 100% @ 40 ng/ml

* The glucuronide values were obtained by determining the acid hydrolyzed value (representing the sum of the free olanzapine and glucuronide conjugate) and subtracting from this the concentration of free olanzapine for that sample.

RESULTS

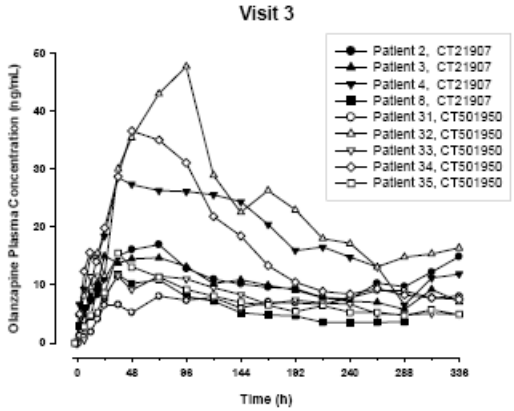


Figure LOBO.11.1. Individual olanzapine plasma concentrations at Visit 3 after the first 300-mg dose of IM olanzapine depot.

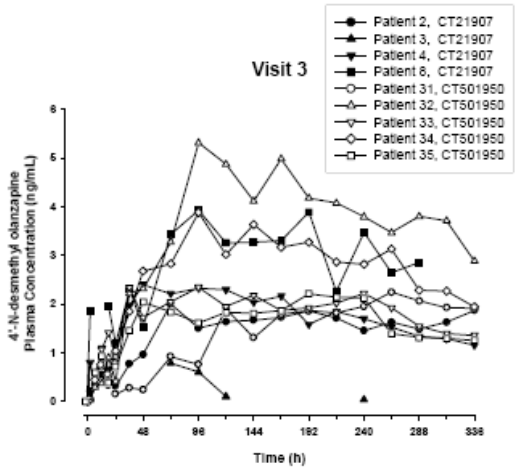


Figure LOBO.11.2. Individual 4'-N-desmethyl olanzapine plasma concentrations on Visit 3 after the first 300-mg dose of IM olanzapine depot.

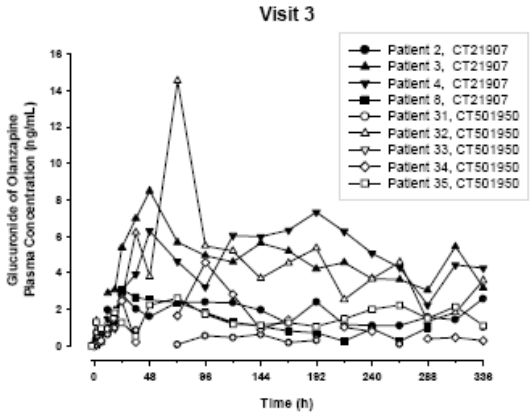


Figure LOBO.11.3. Individual glucuronide of olanzapine plasma concentrations on Visit 3 after the first 300-mg dose of IM olanzapine depot.

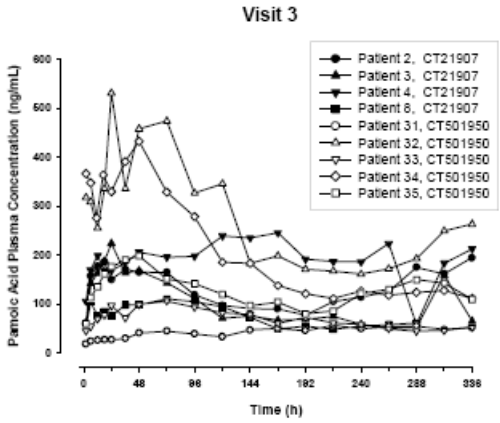


Figure LOBO.11.4. Individual pamoic acid plasma concentrations on Visit 3 after the first 300-mg dose of IM olanzapine depot.

Table LOBO.11.1. Comparison of Geometric Mean (Geometric CV) Olanzapine Pharmacokinetic Parameters After the First 300-mg Dose of IM Olanzapine Depot

CT Lot	N_{PK}	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/hr)	V_z/F (L)
Overall	9	18.4 (61.4)	36.0 (24 – 264)	7200 (65.7)	313 (70.7)	41.7 (65.7)	18800 (63.2)
CT21907	4	17.1 (38.6)	36.0 (24 – 71.88)	7720 (102)	353 (120)	38.9 (102)	19800 (71.8)
CT501950	5	19.5 (83.2)	48.0 (36 – 264)	6810 (43.9)	284 (35.5)	44.0 (43.9)	18100 (65.4)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-versus-time curve from zero to infinity; CL/F = apparent plasma clearance; C_{max} = maximum plasma concentration; CT = clinical trial; h = hour; N_{PK} = minimum observed drug concentration during a dosing interval at steady state; t_{max} = time to maximum concentration; $t_{1/2}$ = apparent terminal elimination half-life; V_z/F = apparent volume of distribution during the terminal phase.

[a] Median and range reported.

Table LOBO.11.2. Comparison of Geometric Mean (Geometric CV) 4'-N-Desmethyl Olanzapine Pharmacokinetic Parameters After the First 300-mg Dose of IM Olanzapine Depot

CT Lot	N_{PK}	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)
Overall	8	2.86 (37.1)	96.0 (48 – 264)	1850 (85.5)	378 (127)
CT21907	3	2.66 (36.0)	71.9 (48 – 96)	2650 (155)	636 (283)
CT501950	5	2.99 (41.4)	96.0 (96 – 264)	1490 (45.8)	277 (54.2)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-versus-time curve from zero to infinity; CT = clinical trial; C_{max} = maximum plasma concentration; h = hour; N_{PK} = minimum observed drug concentration during a dosing interval at steady state; t_{max} = time to maximum concentration; $t_{½}$ = apparent terminal elimination half-life.

Table LOBO.11.3. Comparison of Geometric Mean (Geometric CV) Glucuronide of Olanzapine Pharmacokinetic Parameters After the First 300-mg Dose of IM Olanzapine Depot

CT Lot	N_{PK}	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)
Overall	8	4.20 (99.0)	72.0 (24 – 336)	997 (109)	190 (92.7)
CT21907	4	4.81 (62.5)	36.0 (24 – 192)	1460 (111)	213 (83.6)
CT501950	4	3.67 (154)	84.0 (72 – 336)	682 (94.6)	170 (119)

Abbreviations: $AUC_{0-\infty}$ = area under the time-versus-time curve from zero to infinity; CT = clinical trial; C_{max} = maximum plasma concentration; h = hour; N_{PK} = minimum observed drug concentration during a dosing interval at steady state; t_{max} = time to maximum concentration; $t_{½}$ = apparent terminal elimination half-life.

[a] Median and range reported.

Table LOBO.11.4. Comparison of Geometric Mean (Geometric CV) Pamoic Acid Pharmacokinetic Parameters After the First 300-mg Dose of IM Olanzapine Depot

CT Lot	N_{PK}	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)
Overall	9	189 (80)	72.0 (24 – 335.97)	114000 (127)	500 (145)
CT21907	4	185 (37.1)	120 (24 - 335.97)	116000 (217)	510 (223)
CT501950	5	193 (120)	48.0 (24 - 216)	112000 (92.8)	493 (123)

Abbreviations: $AUC_{0-\infty}$ = area under the time-versus-time curve from zero to infinity; CT = clinical trial; C_{max} = maximum plasma concentration; h = hour; N_{PK} = minimum observed drug concentration during a dosing interval at steady state; t_{max} = time to maximum concentration; $t_{½}$ = apparent terminal elimination half-life.

[a] Median and range reported.

Comparison of Oral and IM Olanzapine Depot at Steady-State

Concentration data for steady-state oral olanzapine and after the fourth injection of IM olanzapine depot allow a direct comparison within and between patients of the PK characteristics arising from oral versus intramuscular depot administration.

Table LOBO.11.12. Comparison of Geometric Mean (Geometric CV) Metabolic Ratios at Each Study Visit

Treatment	Visit	4'-N-Desmethyl Metabolic Ratio	N_{PK}	Glucuronide of Olanzapine Metabolic Ratio	N_{PK}
Oral Olanzapine[a]	2	0.185 (36.4)	8	0.215 (69.9)	7
Depot Olanzapine Injection 4	6	0.160 (22.4)	7	0.0762 (90.6)	7

Abbreviations: N_{PK} = minimum observed drug concentration during a dosing interval at steady state.
[a] Patient 32 excluded.

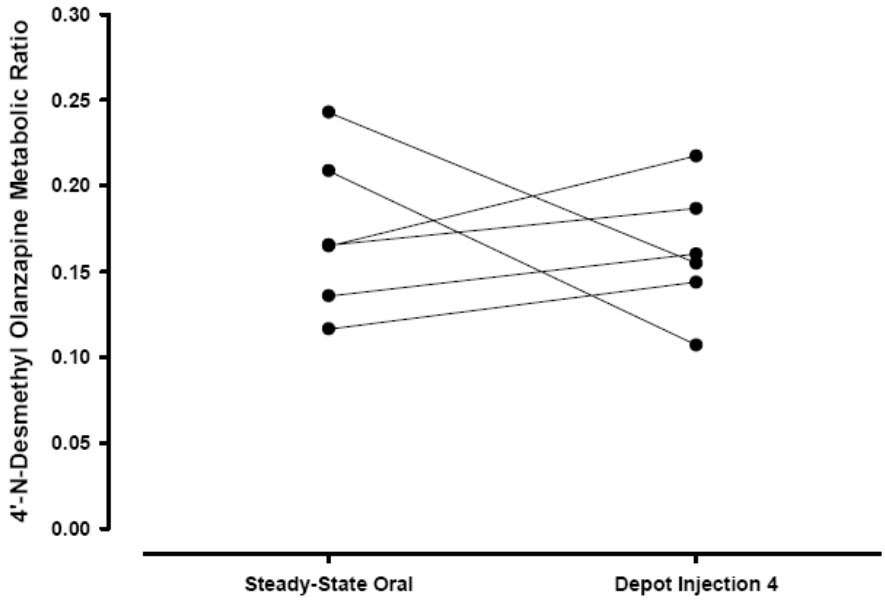


Figure LOBO.11.14. Individual 4'-N-desmethyl olanzapine metabolic ratios following multiple dosing with oral olanzapine and after the fourth injection of IM olanzapine depot.

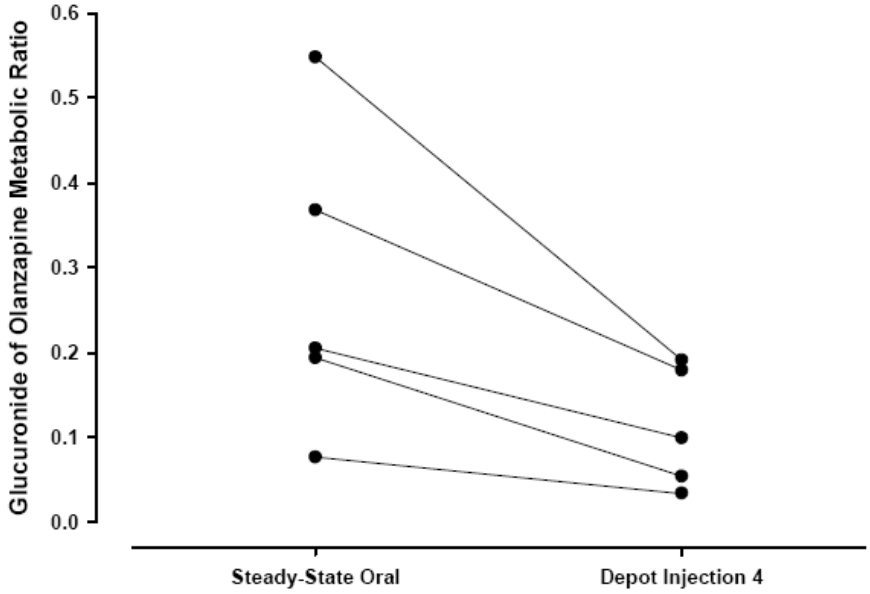


Figure LOBO.11.15. Individual glucuronide of olanzapine metabolic ratios following multiple dosing with oral olanzapine and after the fourth injection of IM olanzapine depot.

Figure LOBO.11.14 demonstrates that the individual 4'-N-desmethyl olanzapine metabolic ratios have a comparable range across oral and depot dosing. The mean glucuronide of olanzapine metabolic ratio after the fourth injection of IM olanzapine depot was approximately 2/3 less than that following multiple dosing of oral olanzapine. The ratios for the glucuronide tended to be lower following depot injection.

Comments:

1. There seemed to be comparable metabolic ratios for the 4'-N-desmethyl olanzapine following oral and intramuscular (im)administration.
2. The metabolic ratios were 2/3 lower for the im glucuronide compared to oral administration meaning that less of this metabolite was formed.

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APPENDIX I

SYNOPSIS AND SUMMARY OF OBSERVED IAIV (INADVERTENT IV INJECTION) EVENTS

Background

During OP Depot clinical trials, 16 events were identified in association with the injection and involved unanticipated degrees of sedation and delirium. The signs and symptoms associated with these events were consistent with some of those reported with oral olanzapine overdose. The most likely hypothesis to explain these events has been described as accidental intravascular injection of a portion of the OP Depot dose.

Results

As of December 10, 2007, there have been seven (7) IAIV injection events in six (6) patients for which blood samples were obtained that provide olanzapine plasma concentrations during the event. These specific cases are denoted as IAIV injection event number 1, 5, 8, 10, 18, 22, and 23. Events number 5 and 8 are two separate IAIV events that occurred in the same patient. There have been a total of 25 cases, Table 1A but plasma was collected in only the 7 cases listed. Table 2A lists the olanzapine plasma concentrations that have been obtained during all 7 of these events.

Table 1A. List of subjects which experienced an IAIV incident. All injections were gluteal.

LY170053
Regulatory Response

Event #	Case ID	Event Date	NONMEM ID	Dose Record TMDY	Approx Dose Record TMDY	Last NONMEM Record TMDY
1	LOBE-100-1039	17-Apr-01	[NONE]	none	none	none
2	HGKA-532-4011	21-Dec-04	[274011]	none	27.46	27.46
3	HGKA-571-4437	27-Dec-04	[274437]	none	54.5	61.5
4	HGKB-088-6257	21-Mar-05	[19509]	90.02	90.02	463.04
5	HGKB-035-5910	24-Oct-05	[19356]	341.03	341.03	525.04
6	HGKB-182-7318	28-Dec-05	[271331]	none	369.42	194.42
7	HGKB-412-8428	26-Jan-06	[27283]	none	404.45	195.45
8	HGKB-035-5910	24-Apr-06	[19356]	none	523	525.04
9	HGKB-141-6928	17-May-06	[27731]	none	591.49	207.49
10	HGKB-235-7685	13-Jun-06	[191413]	none	531	531.16
11	HGKB-521-8460	14-Jun-06	[191772]	none	541	469.07
12	HGKB-481-8734	13-Jun-06	[NONE]	none	none	none
13	HGKB-252-7885	27-Jun-06	[NONE]	none	none	none
14	HGKB-245-7791	04-Jul-06	[NONE]	none	none	none
15	HGKB-491-9513	11-Jul-06	[NONE]	none	none	none
16	HGKB-242-7758	06-Dec-06	[NONE]	none	none	none
17	HGKB-143-6958	19-Jan-07	[NONE]	none	none	none
18	HGKB-406-8350	16-Mar-07	[NONE]	none	none	none
19	HGKB-476-8620	12-Jan-07	[191684]	none	373	40
20	HGKB-200-7420	04-Oct-06	[NONE]	none	none	none
21	HGKB-202-7446	23-May-07	[271546]	none	879	199.6
22	HGKB-476-8622	06-Jun-07	[191687]	none	505	40
23	HGKB-222-7568	19-Jun-07	[NONE]	none	none	none
24	HGKB-571-8643	15-Jul-07	[NONE]	none	none	none

Table 2A. Subjects with Olanzapine Plasma Concentrations Obtained During an IAIV Injection Event

Injection Event

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

(continued)

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

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

Injection Technique

The firm provided training on injection site location (upper quadrant of gluteal muscle) and technique (aspiration), but didn't specify alternating sides with each injection, though this is common practice. Injection procedures were not defined in the protocols. Each site was to follow its local SOP.

In Study LOBE many of these subjects received all OP Depot injections into their deltoid muscles typically alternating between right and left arm. A few of the subjects received an OP Depot injection into either the deltoid or the buttocks for different injections.

A review of the olanzapine plasma concentration data for these subjects shows that the olanzapine systemic plasma concentration profile resulting from either an injection into the deltoid or into the buttocks (gluteus) muscles produces a similar profile of olanzapine plasma concentrations postinjection. Based upon a larger muscle mass, common medical practice, and the amassed clinical trial experience with OP Depot injections, the injection of OP Depot into the gluteus muscle is regarded as the preferred IM injection site.

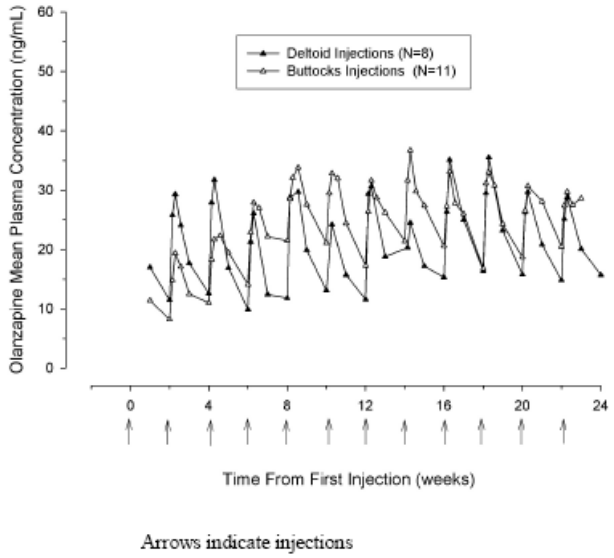


Figure . Mean plasma concentrations following 150-mg/2 weeks injections in subjects receiving deltoid injections versus subjects receiving buttocks injections.

Results from this subject was similar to other subjects that received injections via more than one site. There seemed to be no difference in levels resulting from buttocks vs. deltoid injections.

Feeder Studies

Most of the subjects that experienced an IAIV had participated in a feeder study prior to enrollment in study HGKB. A graphical representation of the time course and levels from both studies is presented in Figure .

Table gives the days on study and the dosing regimen.

Subj # IAIV #	Study	Dosage Form-Dose	Day	Study Day of IAIV
LOBE-100-1039 Event #1	LOBE	Oral 10 mg	Chronic	
		300 mg OP 200 mg OP@day 56	29 168	[Day-29.25- IAIV] No IAIV
HGKB-035-5910 Event #5 Event #8	LOBS	Oral 20 mg	Chronic	No IAIV
		405 mg OP	26.88	No IAIV
		5 mg RAIM	26-31	No IAIV
	HGKB	250 mg OP	32-293	[Day-294 (#5)]
		250 mg OP	293-475.89	[475.83 (#8)]

HGKB-235-7685 Event #10	LOBS	Oral 20 mg	Chronic	No IAIV
		405 mg OP	25.94	No IAIV
		5 mg RAIM	26.97	No IAIV
	HGKB	210 mg OP	31	No IAIV
		405 mg OP	44-479	[Day-479- IAIV]
HGKB-406-8350 Event #18	HGKA	405 mg OP	0-145	No IAIV
		210 mg OP+S*	173-282	[Day-282-IAIV]
HGKB-476-8622 Event #22	LOBS	Oral 20 mg	Chronic	No IAIV
		405 mg OP	1	No IAIV
		5 mg RAIM	27-32	No IAIV
	HGKB	360 mg OP	36-455	[Day-455-IAIV]
HGKB-222-7568 Event #23	HGKA	Oral 20 mg	202	
	HGKB	210 mg OP	0-28	
		315 mg OP	28-189	
		210 mg OP	189-244	
		315 mg OP	244-273	
		405 mg OP	273-424	[Day424-IAIV]
HGKB-406-8350 Event #18	HGKA	405 mg OP	0-259	
	HGKB			
		345 mg OP+20 oral	222-254	
		345 mg OP+10 mg Oral	254-282	
		345 mg OP	282	[Day 282-IAIV]

APPENDIX II-HGKB ADDENDUM STUDY

Pharmacokinetic Analysis of Study:Protocol Addendum F1D-MC-HGKB(3) An Open-Label Study of Intramuscular Olanzapine Depot in Patients with Schizophrenia or Schizoaffective Disorder

Brief Overview of Study

This report is about a specific pharmacokinetic addendum to Study HGKB, specifically Protocol Addendum F1D-MC-HGKB(3). Whereas Study HGKB is a much bigger and

longer study in total, the HGKB pharmacokinetic addendum includes just a small subset of patients and was conducted over approximately an 8 hour period for each individual patient and was completed in a period of just a few weeks for all the participants.

Study HGKB is an open-label study conducted in adult patients with schizophrenia or schizoaffective disorder to assess the long-term safety of OP Depot. Patients from previous OP Depot studies were transitioned into this study. Therapy initiation consisted of 2 weeks of open-label therapy (single dose OP Depot 210 mg). Thereafter, patients received a flexible dose of OP Depot (45 to 405 mg) on a flexible 2- to 4-week interval. The HGKB study is planned to continue for as long as approximately 3 years following the first visit of each patient and is currently scheduled to end when the OP Depot product is launched.

There were 10 patients who participated in the HGKB pharmacokinetic addendum. All patients had previously participated in the open-label treatment period of HGKB and had received an OP Depot dose of 300 mg every 2 weeks for at least 1.5 years. Patients who had also received oral olanzapine supplementation were discontinued from oral olanzapine use prior to the start of HGKB addendum. In the HGKB study addendum, each patient provided an intensive series of olanzapine plasma concentrations collected immediately before and for up to 8 hrs after the OP Depot injection.

Objectives

To characterize the initial release of Olanzapine Pamoate (OP) Depot by examination of the olanzapine plasma concentration versus time profile immediately following an OP Depot injection.

To determine whether or not there is an initial burst release of olanzapine into the systemic circulation following an OP Depot injection.

To contrast the plasma concentration profile after an injection of OP Depot to the profile of plasma concentrations after a RAIM dose from Study LOBS.

Patients

Each patient had participated for at least 1.5 years in Study HGKB. Table 8.1 lists the number of OP Depot injections, concurrently administered oral dose of olanzapine, and length of treatment in Study HGKB for each of the pharmacokinetic addendum patients.

Table . Study HGKB Pharmacokinetic Addendum Patient Participants

Case	HGKB Patient ID	Study HGKB Participation (years)	Prior OP Depot Doses (number)	Prior Oral Doses (number)
1	HGKB-015-5599	1.7	38	497
2	HGKB-015-5595	2.0	47	575
3	HGKB-015-5596	2.0	45	598
4	HGKB-015-5601	1.5	35	453
5	HGKB-023-5718	1.9	45	0
6	HGKB-023-5719	1.7	42	0
7	HGKB-023-5720	1.9	42	470
8	HGKB-023-5723	1.6	39	0
9	HGKB-023-5717	1.9	46	0
10	HGKB-023-5715	2.0	48	0

Doses and Formulation

All patients included in the addendum analysis had received at least 34 injections of 300 mg OP Depot every 2 weeks (subsequent to the initial 210 mg OP Depot injection administered to all patients at the start of Study HGKB) at the time of the addendum period of the study. Five of the patients had received supplementation with oral olanzapine prior to the HGKB addendum and all but one of these patients discontinued oral olanzapine at least 5 days prior to the addendum sampling. None of the participants in the addendum had experienced an inadvertent intravascular (IAIV) injection event.

All patients received a 300 mg injection of OP Depot during the pharmacokinetic addendum period of the study approximately 2 weeks after the previous OP Depot injection administered in Study HGKB.

Biological Sampling

After the OP Depot injection, blood samples were obtained at 5, 15, 30, and 45 minutes and at 1, 2, 4, 6, and 8 hours after the injection.

Dataset for Pharmacokinetic Analysis

Because of the limited and specific focus of the data, the olanzapine plasma concentration data obtained from the Study HGKB pharmacokinetic addendum were not included in the production of the NONMEM dataset for Study HGKB. Furthermore, the HGKB pharmacokinetic addendum data are not included in the Final OP Depot Population Pharmacokinetic Report, or the Interim HGKB Clinical Study Report.
The olanzapine plasma concentration data specifically generated for the HGKB pharmacokinetic addendum were analyzed graphically and descriptively only in this report.

There are also observations of sparse olanzapine plasma concentrations for each of the 10 patients who were addendum participants. These data are a part of the NONMEM dataset for Study HGKB used in the population pharmacokinetic analysis. A listing of

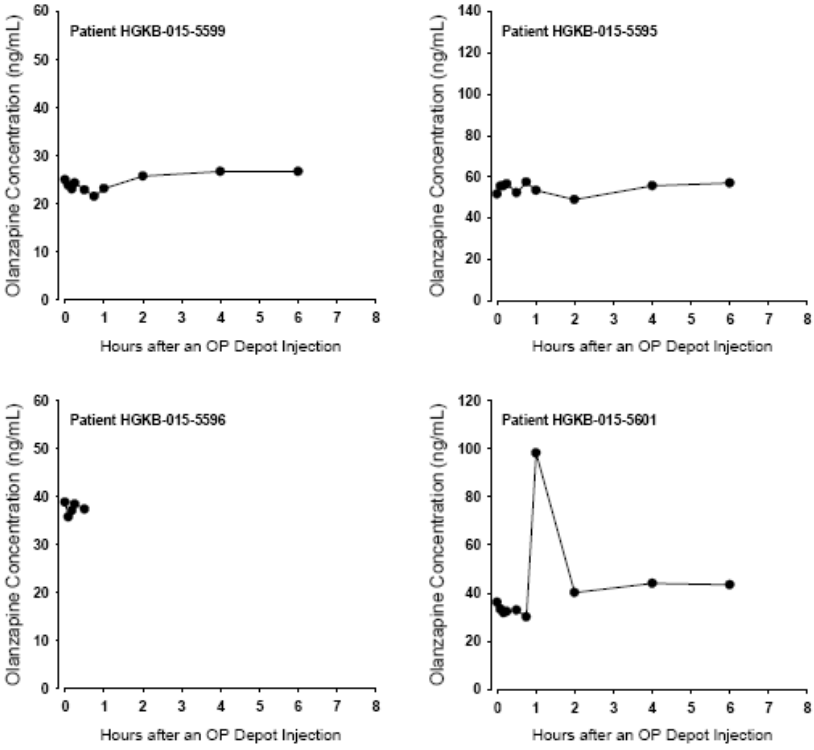
these other data are provided in the Appendix (Table HGKB(3).APP.1). These data were not included in the analysis of the HGBK Pharmacokinetic Addendum, but are provided in the appendix as a reference.

Pharmacokinetic Analysis Methods

The observed plasma concentrations were analyzed graphically to characterize the olanzapine concentration versus time profile immediately after the injection and to detect any potential initial burst release of olanzapine as demonstrated by an apparent spike in plasma olanzapine concentrations.
In addition, noncompartmental analysis methods were utilized to calculate selected pharmacokinetic parameters, such as maximum plasma concentration, change from baseline to maximum concentration, and the area under the plasma concentration versus time curve up to the last sampling point.

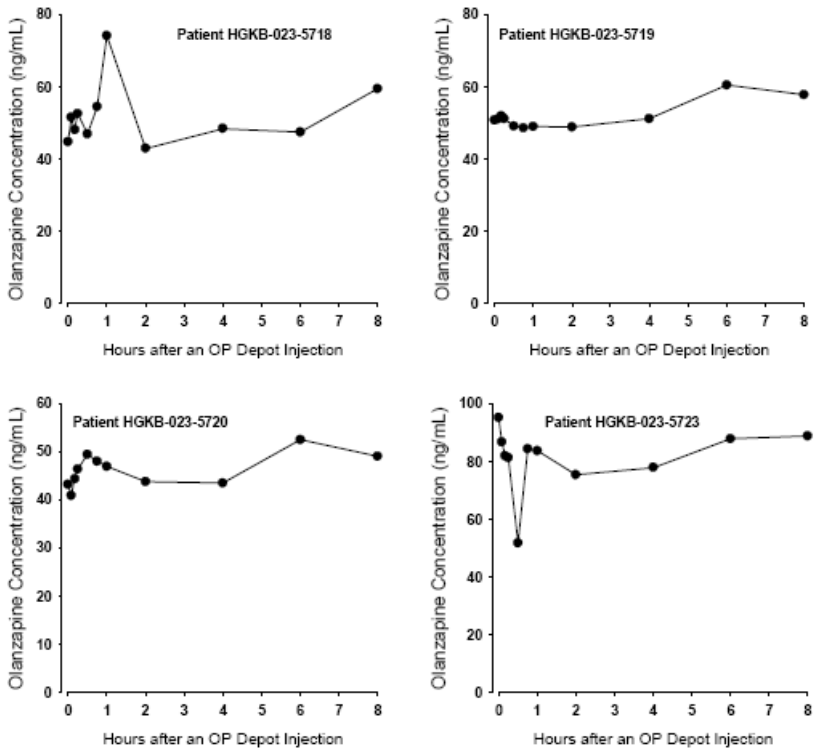
The results following the OP Depot injection were compared to data from Study LOBS obtained over the same sampling period after a single 5 mg injection of immediate release (rapid acting) Zyprexa→ IntraMuscular Olanzapine for Injection (RAIM). In Study LOBS, serial blood samples were obtained immediately before (0 hour) and for 8 hours after the RAIM injection at 5, 15, 30, and 45 minutes and at 1, 2, 4, 6, and 8 hours.

RESULTS



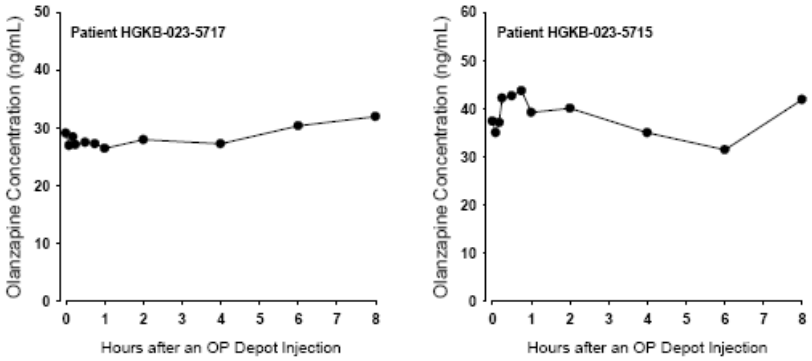
NB: each patient's data shown are on a different y-axis scale because a common scale would obscure some of the plots.

Figure 9.1. **Olanzapine plasma concentrations immediately before and after an injection of OP Depot for patients HGKB-015-5599, HGKB-015-5595, HGKB-015-5596, and HGKB-015-5601.**



NB: each patient's data are shown on a different y-axis scale because a common scale would obscure some of the plots.

Figure 9.2. **Olanzapine plasma concentrations immediately before and after an intramuscular injection of OP Depot for patients HGKB-023-5718, HGKB-023-5719, HGKB-023-5720, and HGKB-023-5723.**



NB: each patient's data are shown on a different y-axis scale because a common scale would obscure some of the plots.

Figure 9.3. **Olanzapine plasma concentrations immediately before and after an intramuscular injection of OP Depot for patients HGKB-023-5717 and HGKB-023-5716.**

COMMENTS:

1. The most notable result is that even for those subjects that showed peak levels post-injection, the levels were much lower than those observed for the subjects with an IAIV.

For example:

Study	Date (YYYYMMDD)	Time (Days on Study)	Dose	Time of Sample From Last Dose (hours)	Olanzapine Concentration (ng/mL)
Patient LOBE-100-1039	**IAIV Event #1** 20010417		300 mg OP Depot		
LOBE	20010417	29.25		6 hours	172.75
LOBE	20010418	30.00		24 hours	104.48
LOBE	20010420	31.98		72 hours	47.96
Patient HGKB-235-7685	**IAIV Event #10** 20060613		405 mg OP Depot		
HGKB	20060613	480.03		2.7 hours	133.47
HGKB	20060613	480.07		3.7 hours	127.07
HGKB	20060613	480.12		4.7 hours	126.73
HGKB	20060614	480.95		24.6 hours	108.77

Subjects for events #1 and #10 showed comparable plasma levels comparable for subjects HGKB 015-5601; 023-5718; and 023-5723 in the current extension study. However the extension study subjects did not have an IAIV. This would lead one to conclude that there must be some other covariates involved such as injection technique or subject factor the causes and IAIV to occur.

2. Compared to the IntraMuscular Olanzapine for Injection (RAIM), an approved product (free base olanzapine solution) exhibits extremely rapid absorption(Study LOBS). However, the levels achieved with the 5 mg dose of the RAIM formulation are much lower than those seen in study HGKB(see graph below).

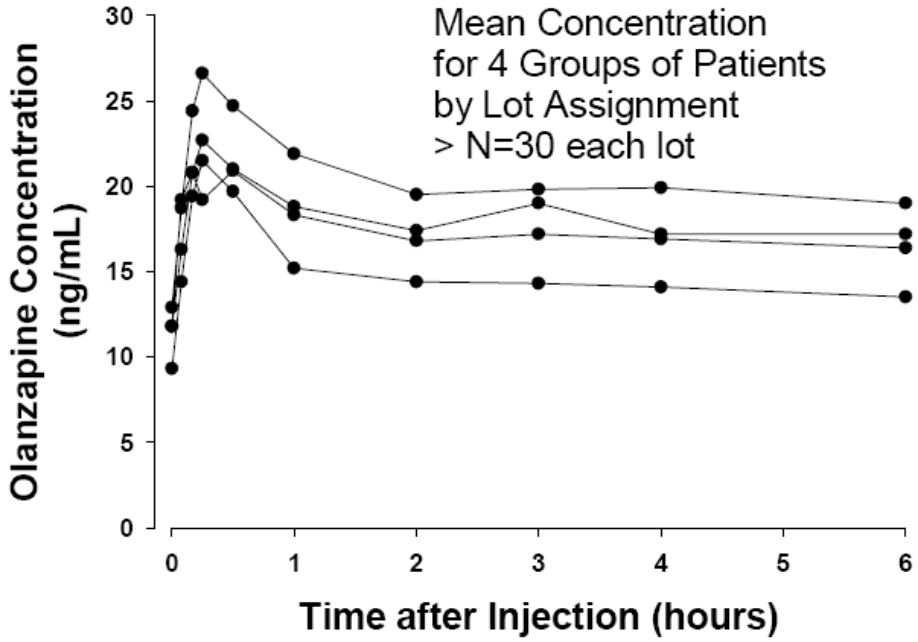


Figure 9.5. **Mean olanzapine plasma concentration profiles immediately before and after an intramuscular injection of olanzapine (free base solution) in N=126 patients, 26 days after a 405 mg OP Depot injection(Study LOBS).**

This result shows the importance of not only rate but overall exposure in the IAIV events.

3. In comparison to the post-injection increase in olanzapine concentration observed in Study LOBS after a single dose of 5 mg RAIM, an OP depot injection does not produce a substantial increase the 0 to 8 hour postinjection olanzapine concentration profile. Therefore the post-injection
OP Depot profiles typically do not reflect an initial burst release.

APPENDIX III –GRAPHS FOR IAIV EVENTS

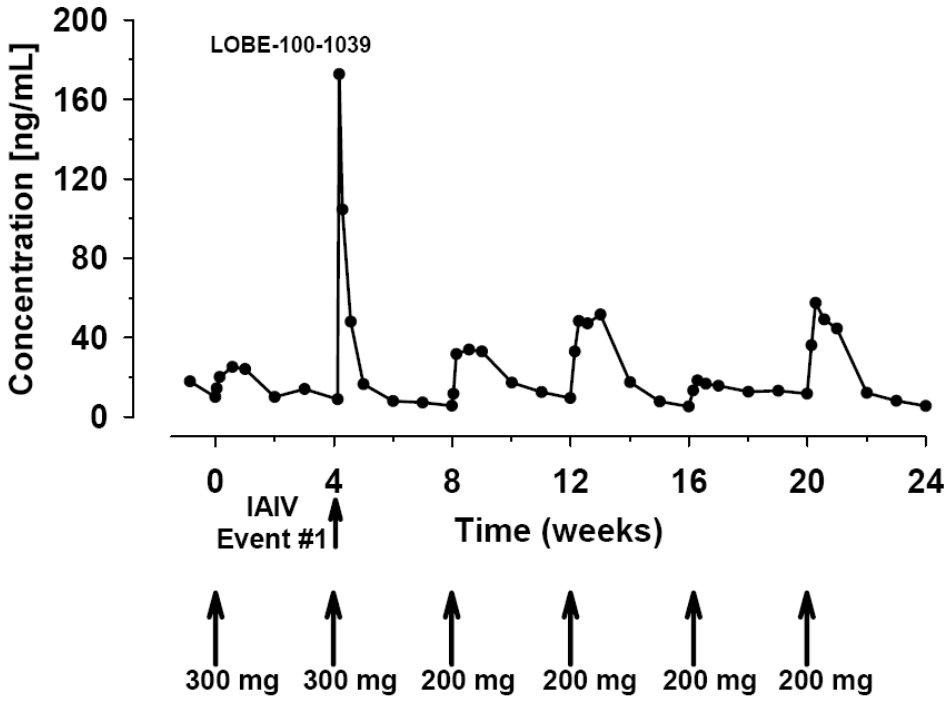


Figure 1. Olanzapine plasma concentrations for Patient LOBE-100-1039 showing the concentration profile after 6 OP Depot doses in which an IAIV injection event occurred after the 2nd OP Depot dose.

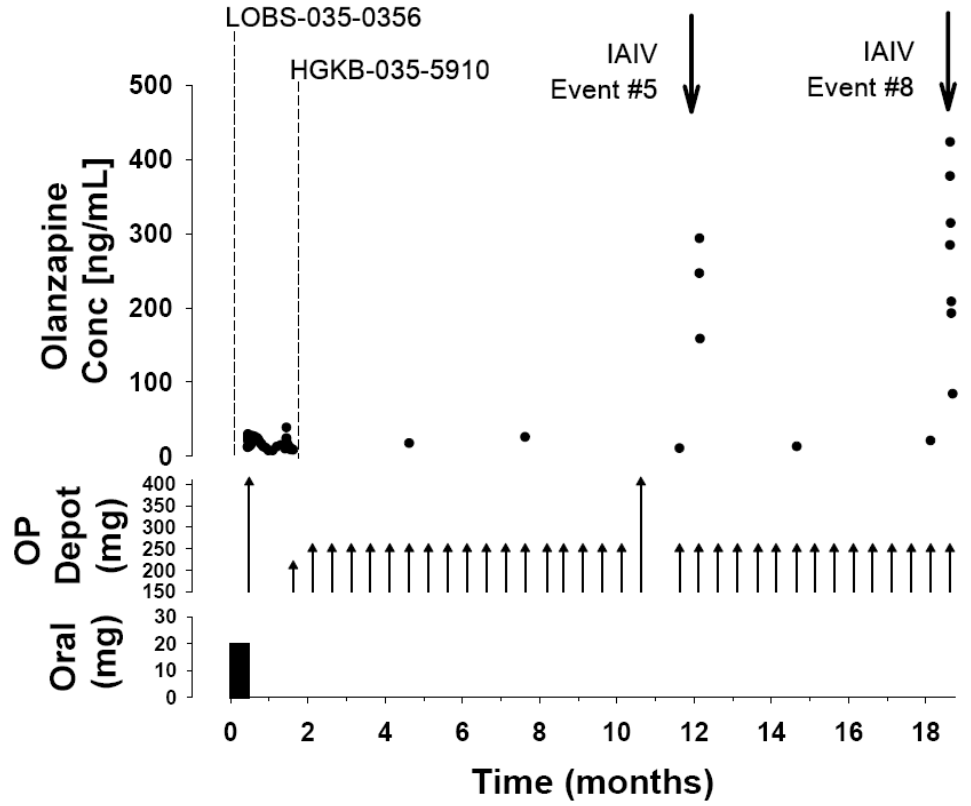


Figure 13. **Olanzapine plasma concentrations in patient HGKB-035-5910 who had two IAIV Events (#5 and #8) compared to other plasma concentrations measured in this patient at other times during Study HGKB and the prior Study LOBS.**

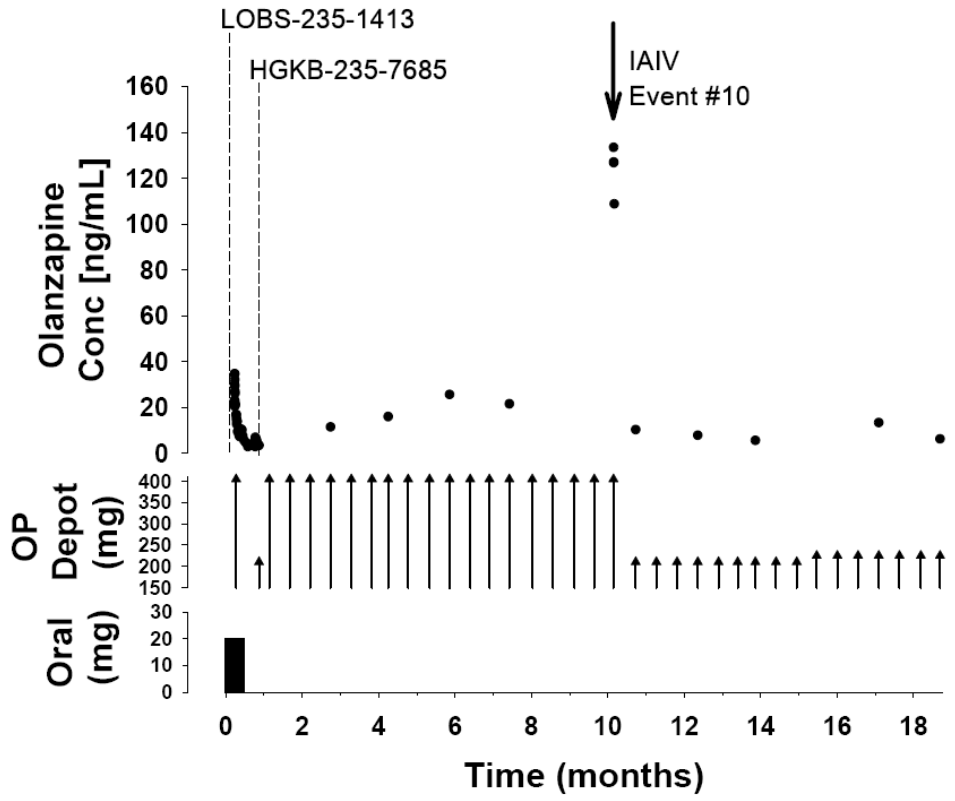


Figure 14. **Olanzapine plasma concentrations in patient HGKB-235-7685 who had IAIV Event (#10) compared to other plasma concentrations measured in this patient at other times during Study HGKB and the prior Study LOBS.**

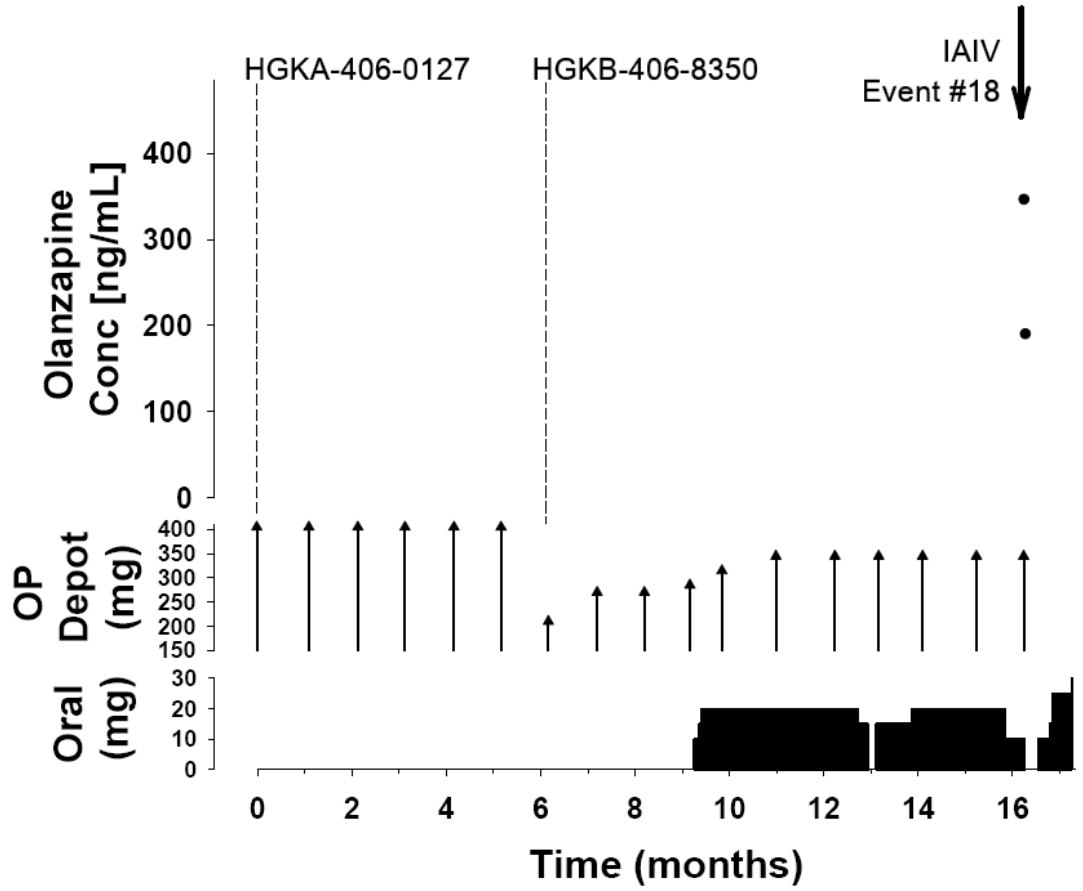
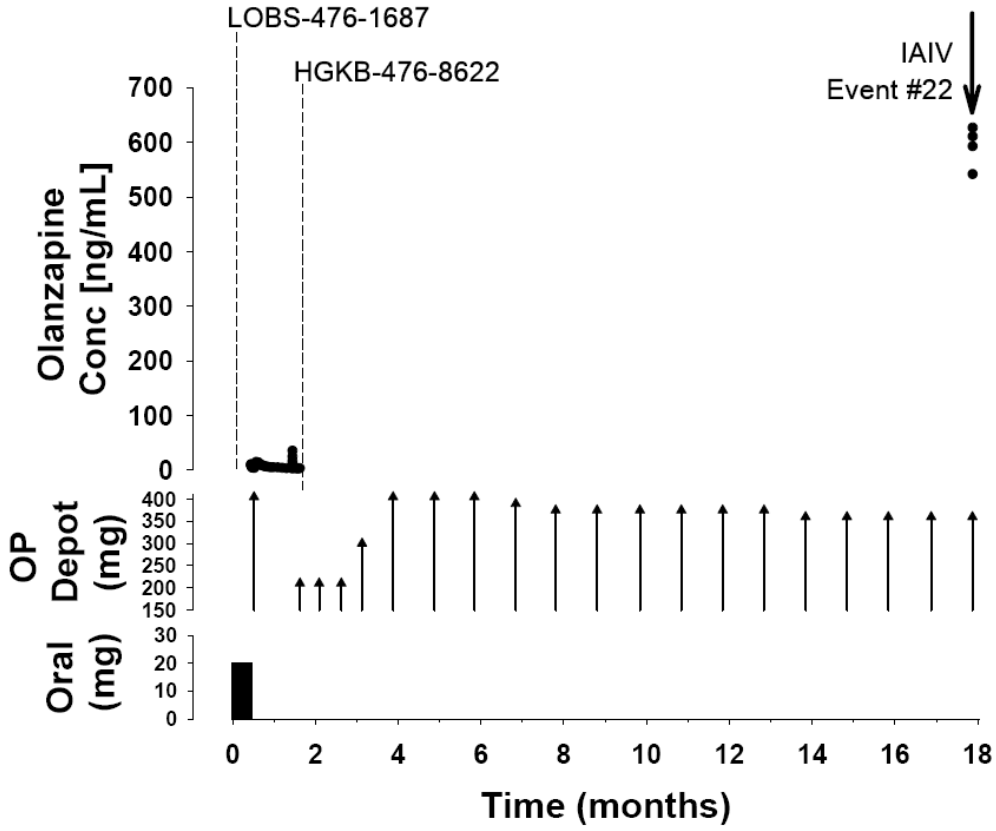


Figure 15. **Olanzapine plasma concentrations in patient HGKB-406-8350 who had IAIV Event (#18) for which there were no other plasma concentrations measured in this patient at other times during Study HGKB and the prior Study HGKA.**


LOBS-476-1687
HGKB-476-8622
IAIV
Event #22
Olanzapine
Conc [ng/mL]
700
600
500
400
300
200
100
0
OP
Depot
(mg)
400
350
300
250
200
150
Oral
(mg)
30
20
10
0
0
2
4
6
8
10
12
14
16
18
Time (months)

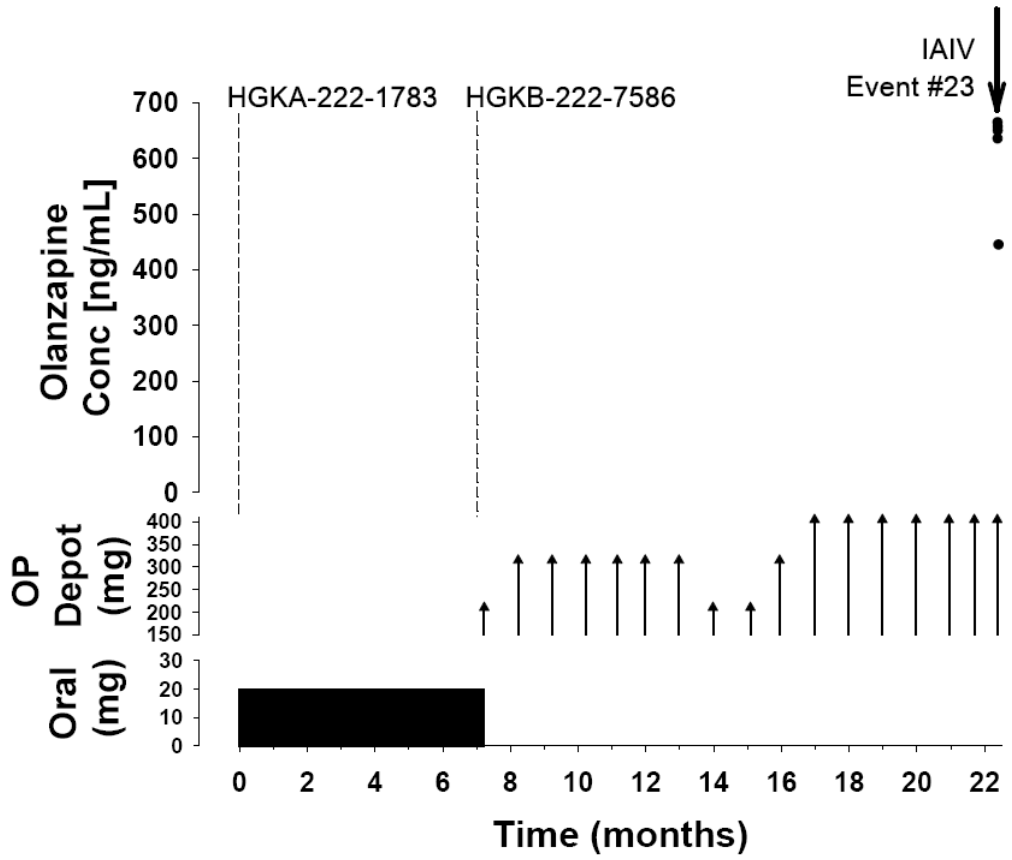


Figure 17. **Olanzapine plasma concentrations in patient HGKB-222-7568 who had IAIV event #23 for which there were no other plasma concentrations measured in this patient at other times during Study HGKB and the prior Study HGKA.**

APPENDIX IV-LOCATION OF IAIV EVENTS

Table 1. Subjects that experienced an IAIV event through 30 November 2007. Subjects were mainly from study HGKB with case 1 from LOBE while cases 2 and 3 were from study HGKA.

Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Study Location
Case 1	31-year-old male	Inj #2 Apr 2001	300 mg/4 weeks 45 min	Croatia
Case 2	32-year-old male	Inj #1 Dec 2004	405 mg/4 weeks 10 min	Romania
Case 3	63-year-old male	Inj #2 Dec 2004	405 mg/4 weeks 15–20 min	Israel*
Case 4	30-year-old male	Inj #4 Mar 2005	405 mg/4 weeks Approx 60 min	US
Case 5	49-year-old male	Inj #22 Oct 2005	250 mg/2 weeks Within 60 min	US**
Case 6	51-year-old male	Inj #24 Dec 2005	300 mg/2 weeks Within 50 min	Brazil
Case 7	31-year-old female	Inj #11 Jan 2006	300 mg/3 weeks 30 min	Germany
Case 8	49-year-old male	Inj #35 Apr 2006	250 mg/2 weeks 15 min	US**
Case 9	34-year-old male	Inj #29 May 2006	300 mg/4 weeks 5 min	Mexico
Case 10	43-year - ld male	Inj #20 Jun 2006	405 mg/4 weeks 30 min	Spain
Case 11	43-year-old female	Inj #27 Jun 2006	100 mg/2 weeks 10 min	Crotia
Case 12	57-year-old male	Inj #2 Jun 2006	210 mg/2 week Unspecified. Within 3 hr	Poland
Case 13	23-year-old male	Inj #12 June 2006	270 mg/4 weeks Immediately post injection	France
Case 14	56-year-old female	Inj #25 Jul 2006	210 mg/4 weeks Unspecified. Within 75 min	France
Case 15	40-year-old male	Inj #7 Jul 2006	300 mg/3 weeks	Italy

			15 min	
Case 16	36-year-old male	Inj #17 Dec 2006	405 mg/4 weeks 90 min	France
Case 17	59-year-old female	Inj #27 Jan 2007	300 mg/2 weeks 2 hours and 45 min	Mexico
Case 18	26-year-old male	Inj #17 Mar 2007	345 mg/4 weeks 30 min	Germany
Case 19	38-year-old female	Inj #16 Jan 2007	390 mg/4 weeks 5 min	Slovakia***
Case 20	48-year-old female	Inj #15 Oct 2006	405 mg/4 weeks 20 min	Portugal
Case 21	52-year-old male	Inj #35 May 2007	210 mg/2 weeks 15 min	Portugal
Case 22	52-year-old male	Inj #20 Jun 2007	360 mg/4 weeks 10 min	Slovakia***
Case 23	47-year-old male	Inj #17 Jun 2007	405 mg/4 weeks 15 min	Spain
Case 24	55-year-old male	Inj # 40 Jul 2007	330 mg/4 weeks 30 min	Israel*
Case 25	36-year-old male	Inj #36 Aug 2007	405 mg/4 weeks 15 min	Argentina

* 2 events at this site-different subjects
** 2 events at this site-same subject
***2 events at this site-different subjects

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/s/

Andre Jackson
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Raman Baweja
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