

Office of Clinical Pharmacology and Biopharmaceutics/ Pharmacometrics Review

NDA: 20-592-SE5/040, 041

Compound: Olanzapine
Submission Dates: October 30, 2006
Sponsor: Eli Lilly
Reviewer: Andre Jackson

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Executive Summary

A study was done combining data from several centers in adolescents ages 13-17 to determine if the pharmacokinetics were similar or different from that previously observed in adults. The study data from 4 study sites were analyzed by mixed effects modeling to identify any important covariates which impacted Olanzapine pharmacokinetics in adolescents. The study results indicated that weight and gender were the significant covariates which influenced the clearance of Olanzapine in the subject population. Clearance/F in females was found to be 13.6 L/hr whereas that for males was 17.5 L/hr. Exposure in adolescents was higher due to their lower average body weights.

Introduction

Study F1D-MC-HGMF (Study HGMF) was performed to address the request by the United States (US) Food and Drug Administration (FDA) to provide pharmacokinetic information in a population of adolescent patients with schizophrenia or bipolar I disorder. Previous studies in children and adolescents have shown a progressive increase in olanzapine concentrations with corresponding increases in dose. The data also suggested that pediatric patients generally have olanzapine plasma concentrations similar to those for adults for a given weight-adjusted dose (Studies F1D-MC-HGCS, F1D-MCHGGC).

In this report, the pharmacokinetic data from Study HGMF was combined with other existing adolescent pharmacokinetic data (Studies F1D-MC-HGCS, F1D-MCHGCR, F1D-MC-HGGC, and F1D-SB-LOAY) to characterize olanzapine pharmacokinetics in adolescents and to address pharmacokinetic aspects of the FDA Pediatric Written Request for olanzapine.

Summary

The goal of this study was to collect data for Olanzapine in a pediatric population to determine if the levels were similar or different from those observed in adult schizophrenia or bipolar I disorder subjects. Previous studies in adults showed that the CL/F was 13.6 L/hr with smoking and gender being important covariates. In the current analysis the sponsor has used a 1 compartment model similar to that used in adults and analyzed the data obtained following a 4.5 week study in adolescents ages 13-17 following the administration of doses ranging from 2.5 to 20 mg/day. Body weight and gender were identified as important covariates. The label claim from this analysis was that (b) (4)

However this was not accepted by OCP (b) (4)

COMMENTS TO MEDICAL REVIEWER

OCP has revised the following portion of the label based upon the completed Pediatric Written Request:

The firm had a statement saying that (b) (4)

This statement was deleted.

The firm also wanted to include a statement (b) (4)

OCP REVISED LABEL

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents (b) (4)

Objective of the analysis

The primary objective of this study was to characterize olanzapine pharmacokinetics (CL/F and V/F); the inter- and intra-subject variabilities of olanzapine pharmacokinetics; and the potential influence of patient factors such as age, weight, gender, ethnic origin, and smoking status on olanzapine pharmacokinetics in adolescents 13 to 17 years of age that have been diagnosed with schizophrenia or bipolar I disorder.

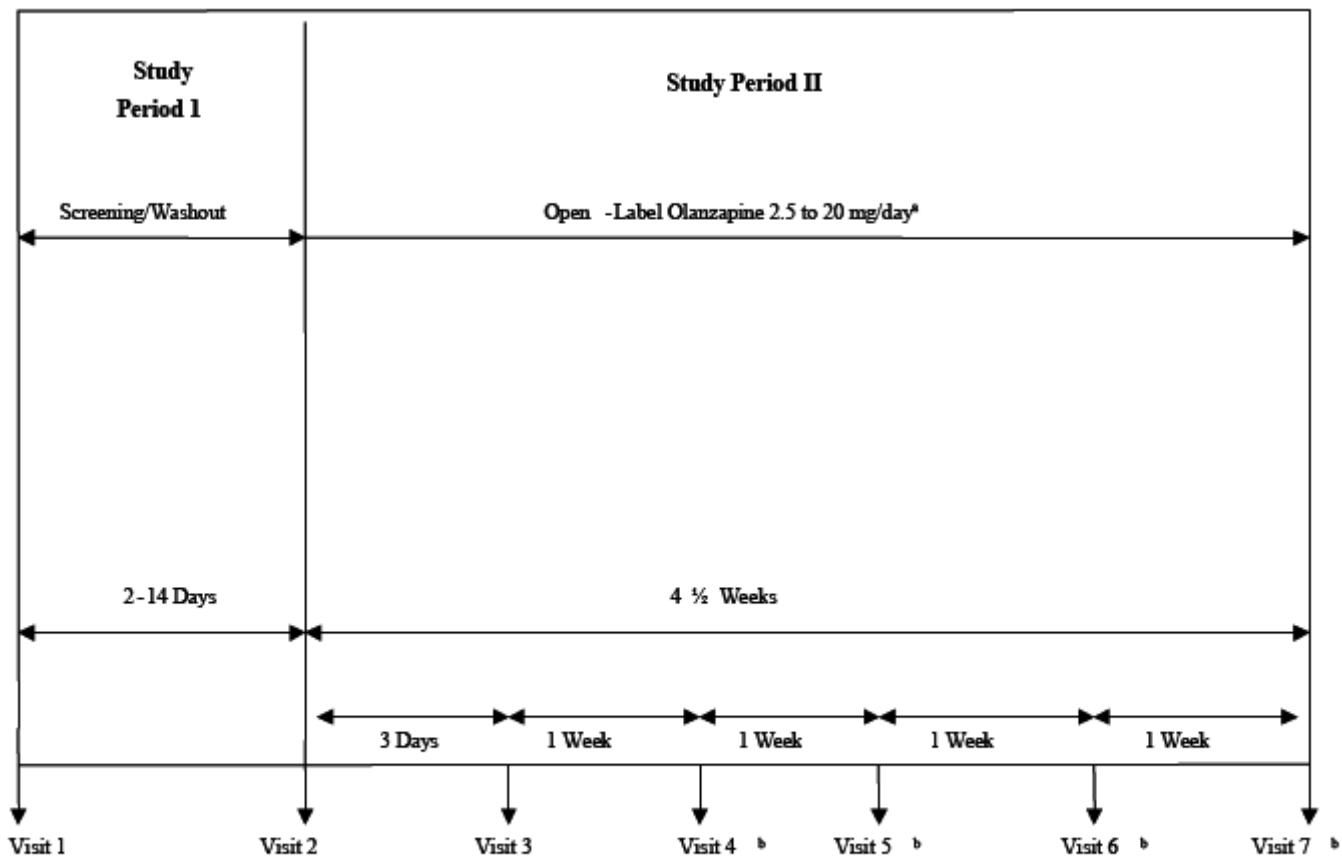
Methods

Design

Study#1:

Study HGMF was a multicenter, openlabel, single arm trial in adolescent patients (13 to 17 years) meeting diagnostic criteria for schizophrenia or bipolar I disorder as defined by the DSM-IV-TR . The study design consisted of two study periods:

Study Period I was a 2- to 14-day Screening and Washout Period, and Study Period II was a 4 and ½ -week Open-Label Treatment Period. In order to protect patient well-being, this study employed as short a washout period as practical and was consistent with washout periods typical of real-world clinical practice. Since the elimination half-life of most orally administered antipsychotics ranges from 20 to 40 hours and the half-life of decanoate depot preparations (for example, fluphenazine) ranges from 7 to 10 days , the washout period was appropriate for this patient population. Patients already taking olanzapine continued on their previous dosage (between 2.5 to 20 mg/day) unless a dose adjustment was deemed necessary by the investigator, while patients new to olanzapine therapy started on an initial dose of 2.5 to 5.0 mg/day, as determined by the investigator.



^aThe starting dose for olanzapine-naïve patients was 2.5 to 5 mg/day. For patients entering the study already on olanzapine treatment, the maximum initial dose was 20 mg/day.

^bPK sampling at Visits 4, 5, 6, and 7.

Table 1. Summary of Olanzapine Studies Included in the Adolescent Population Pharmacokinetic Evaluation

Study	Patient Population	Dose (mg) ^a	Sample Collection ^b	Patients and Observations
HGMF	<ul style="list-style-type: none"> • 80-100 adolescents • 13-17 years old • Diagnosed with schizophrenia or bipolar I disorder 	<ul style="list-style-type: none"> • 2.5 - 20 	<ul style="list-style-type: none"> • 4 blood samples per patient 	<ul style="list-style-type: none"> • To be determined after database lock
LOAY	<ul style="list-style-type: none"> • 88 adolescents and young adults • 12-20 years old • Diagnosed with schizophrenia, shizoaffective or schizophreniform disorders 	<ul style="list-style-type: none"> • 5 - 20 	<ul style="list-style-type: none"> • 1 to 8 blood samples per patient 	<ul style="list-style-type: none"> • 80 adolescents • 293 observations
HGCR/S	<ul style="list-style-type: none"> • 9 children and adolescents • 10-18 years old • Diagnosed with schizophrenia 	<ul style="list-style-type: none"> • 2.5 - 20 	<ul style="list-style-type: none"> • 9 to 15 blood samples per patient 	<ul style="list-style-type: none"> • 6 adolescents • 84 observations
HGGC	<ul style="list-style-type: none"> • 23 children and adolescents • 5-14 years old • Diagnosed with bipolar disorder 	<ul style="list-style-type: none"> • 2.5 - 20 	<ul style="list-style-type: none"> • 1 to 4 blood samples per patient 	<ul style="list-style-type: none"> • 5 adolescents • 15 observations

^a Olanzapine was administered as a once-daily (QD) oral dose

^b All samples were collected at steady-state. Steady-state is defined as a patient being on a fixed olanzapine dose for at least 5 consecutive days.

Analytical

Assay Validation - Zyprexa

Parameter	Zyprexa
Method	Olanzapine was assayed by liquid chromatography with electrochemical detection (LCEC), using extracts based on its acid-base behavior.
Extract Stability	6 days
Number of Freeze-thaw	2 Cycles QC's 80, 40, and 0.64 ng/ml Diff=0.1%, -0.4% and --2.8%

Benchtop Stability at RT	4 hrs
Long term at -20° C -60C -80C	378 days 1017 days 8.5 months
Extraction Recovery	79% @ 80 ng/ml 72% @ 40 ng/ml 80% @ 0.64 ng/ml Internal standard 69%

All samples stored at -80C

1.F1D-MC-HGGC

Date of first sample analysis: 13 April 1999

Date of last sample analysis: 20 April 1999

Date for 1st sample draw 2/27/98

Total storage time= 425 days

Table 2 **Back Calculated Calibration Standard Concentration Data for HPLC Assay for Olanzapine in Human Plasma**

Summary Statistics:		Concentration (ng/mL)									
Nominal	100	50.0	25.0	10.0	5.00	2.50	1.00	0.500	0.250		
Average	99.7	50.8	24.8	9.87	4.81	2.44	1.02	0.521	0.252		
% Error	-0.3	1.7	-0.9	-1.3	-3.8	-2.5	2.1	4.2	0.8		
N	2	2	2	2	2	2	2	2	2	2	2

Individual Results:

Batch											
S03I	97.9	51.3	25.5	10.2	5.09	2.49	1.08	0.493	0.218		
S04I	102	50.4	24.1	9.54	4.52	2.38	0.961	0.549	0.286		

Table 3 Control Results from the HPLC Assay for Olanzapine in Human Plasma

Summary Statistics:

		Concentration (ng/mL)			
Nominal	80.0	40.0	0.640	80.0	(DFAC of 6.67)
Average	84.9	42.9	0.703	82.4	
Std. Dev.	1.80	1.17	0.0343		
Precision (%)	2.1	2.7	4.9		
% Error	6.2	7.3	9.9		
N	4	4	4	2	

Individual Results:

2.F1D-MC-HGCS

Date of First Sample Analysis: 18/11/96 (d/m/y)

Date of Last Sample Analysis: 23/04/97 (d/m/y)

Date for 1st sample draw 10/25/95

Total storage time= 545 days

Table 2 Back-Calculated Calibration Standard Concentrations

		nominal olanzapine concentration (ng/mL)							
batch	100	50.0	25.0	10.0	5.00	2.50	1.00	0.500	0.250
O00F	98.7	49.8	26.6	9.97	4.95	2.52	0.984	0.544	0.222
O01F	99.8	50.2	24.4	9.64	6.13	2.39	1.00	0.436	note 1
O02F	101	51.8	23.8	8.24	4.83	2.65	0.995	0.533	0.272
O03F	99.3	50.3	25.5	9.92	4.96	2.52	1.01	note 2	0.244
O04F	100	50.2	24.8	9.82	4.99	2.33	1.02	0.489	0.273
n	5	5	5	5	5	5	5	4	4
mean	99.9	50.5	25.0	9.52	5.17	2.48	1.00	0.500	0.253
std dev	0.943	0.793	1.08	0.724	0.538	0.126	0.0140	0.0491	0.0245
%rsd	0.9%	1.6%	4.3%	7.6%	10.4%	5.1%	1.4%	9.8%	9.7%
% error	-0.1%	0.9%	0.0%	-4.8%	3.4%	-0.7%	0.3%	0.1%	1.1%

Table 4 Assay Accuracy Data - QC Samples

batch	nominal Olanzapine concentration (ng/mL)					
	80.0	80.0	40.0	40.0	0.640	0.640
O00F	86.1	84.7	42.1	41.3	0.698	0.709
O01F	85.5	85.1	41.4	42.5	0.779	0.738
O02F	80.7	82.3	36.8	37.9	note 1	0.616
O03F	82.0	81.3	39.7	40.5	0.502	0.524
O04f	79.5	79.4	38.2	38.9	0.580	0.599
n	10		10		9	
mean	82.7		39.9		0.638	
std dev	2.53		1.92		0.0971	
% rsd	3.1%		4.8%		15.2%	
% error	3.3%		-0.2%		-0.3%	

3.F1D-MC-HGMF

Date for 1st sample draw 6/1/05

Total storage time=

Analytical Performance: Back-Calculated Concentrations (ng/mL) of LY170053 Calibration Standard in (Human) (Plasma - hep)
in (Protocol 0062-05167)

Assay Date	Analytical Run Number	STD 0.250 ng/mL	STD 0.500 ng/mL	STD 1.00 ng/mL	STD 2.50 ng/mL	STD 5.00 ng/mL	STD 10.0 ng/mL	STD 25.0 ng/mL	STD 50.0 ng/mL	STD 100 ng/mL
11-Jan-2006	1	0.26	0.539	1	2.37	5.02	10.2	23.6	51.4	98.2
		0.244	0.507	0.997	2.44	5.02	9.74	24.6	51.2	101
12-Jan-2006	2	0.251	0.523	1.11	2.43	5.15	9.65	24	50.1	101
		0.269	*0.363	0.954	2.27	4.86	10	24.6	49.9	101
26-Jan-2006	4	0.256	0.477	0.874	2.24	4.77	9.72	22.9	48.3	97.4
		0.285	0.571	1.05	2.44	5.27	10.2	25.2	52.1	104
07-Mar-2006	5	0.262	0.557	1.02	2.41	4.96	9.55	23.3	49.7	102
		*0.347	0.528	*1.21	2.36	4.92	10.1	23.3	51	101
15-Mar-2006	6	0.244	0.488	0.98	2.4	5.05	9.82	24.3	50.8	100
		*0.165	0.473	1.01	2.76	4.95	10.7	25.4	51.1	97.7
22-Mar-2006	7	0.268	0.518	1.02	2.4	4.97	9.75	23.4	50.3	100
		0.213	0.535	0.995	2.47	5.52	9.99	24.2	51.1	101
27-Mar-2006	8	0.254	0.543	1.01	2.35	4.93	9.6	25.1	49.1	95.9
		0.22	0.545	1.07	2.38	5.17	9.23	25.2	55.1	101
Mean		0.252	0.523	1.01	2.41	5.04	9.88	24.2	50.8	100
S.D.		0.0202	0.0301	0.0565	0.119	0.189	0.36	0.829	1.59	2.11
%CV		8	5.8	5.6	4.9	3.8	3.6	3.4	3.1	2.1
%Bias		0.8	4.6	1	-3.6	0.8	-1.2	-3.2	1.6	0
n		12	13	13	14	14	14	14	14	14

Reason Deactivated

* F Calibration standard deactivated due to unacceptable % deviation

Analytical Performance of LY170053 Quality Control Samples in Human Plasma - hep (Protocol 0062-05167)

Run Date	Curve Number	QC 0.640 0.640 ng/mL	QC 40.0 40.0 ng/mL	QC 80.0 80.0 ng/mL	QC 180 180 ng/mL
11-Jan-2006	1	0.652	38.2	77.6	188
		0.663	39.6	76	183
12-Jan-2006	2	0.678	37.9	79.2	
		0.483	38.5	78.1	
26-Jan-2006	4	0.598	36.6	75.9	176
		0.693	41.4	79.9	195
07-Mar-2006	5	0.748	38.4	75.9	189
		0.707	37.3	75.5	276
15-Mar-2006	6	0.618	37.6	77.2	178
		0.566	39.2	77.2	166
22-Mar-2006	7	0.691	40.3	78.1	173
		0.672	43.8	76.2	176
27-Mar-2006	8	0.678	38.5	73.7	169
		0.664	42.1	70.2	176
Mean		0.651	39.2	76.5	187
S.D.		0.0665	2.02	2.41	29.2
%CV		10.2	5.2	3.2	15.6
%Theoretical		101.7	98	95.6	103.9
%Bias		1.7	-2	-4.4	3.9
n		14	14	14	12
Overall %CV					

Data:*Studies:*Pharmacokinetics

No dosing or sampling times were recorded during study LOAY. Each of the ten LOAY study sites provided a window of approximate sampling and dosing times. The firm did an analysis including and excluding the LOAY study however the FDA analysis only verified the analysis without the LOAY data set.

The times from dose for the concentrations were unknown because both actual time of last dose and the actual time of the blood sample were not collected in Study LOAY. Smoking status and ethnic origin information were not documented in Study LOAY.

Smoking status in Study HGMF was determined from the results of the cotinine test. Any concentrations reported as below quantification limit (BQL) were treated as missing values for the analyses.

Pharmacodynamics

N/A.

Data Checking

The data was checked by: perusing entered data to see if it was correct for units and definitions were consistent with entries. Data entry was consistent with the control stream. Scatter plots of the raw data were investigated to determine if the data contained a lot of outliers.

Models*Pharmacokinetics*Structural Model

Base Model Development

Pharmacokinetics of oral olanzapine in an adult population has been previously

characterized by a one compartment model (original NDA submission NDA (b) (4) 21 September 1995). Therefore, a one compartment pharmacokinetic model with parameters such as absorption rate constant (Ka), oral clearance (CL/F), and oral volume of distribution (V/F) was initially tested to evaluate the adolescent pharmacokinetic data. The available data in adolescent patients did not allow reliable estimation of Ka, therefore, Ka was fixed to the adult population value. The base model was able to determine the inter-patient variability in CL/F and V/F with covariance using the omega block.

Three inter-patient variability models (Equation 1) were tested: η on CL/F, η on V/F and η on CL/F and V/F with covariance (omega block).

$$P = \Theta_1 \cdot \exp(\eta) \quad \text{Equation 1}$$

where P is the individual parameter estimate (CL/F or V/F), Θ_1 represents the typical or population value of the parameter and η is a random variable with a mean of zero and variance of ω^2 .

The difference between model predicted olanzapine plasma concentration and the observed olanzapine concentration was modeled using the residual error model. The two residual error models evaluated were proportional (Equation 2) and combined additive and proportional.

Parameter sensitivity analyses were performed on various base models and a final base model was selected for identification of potential significant covariates.

Final Model Development

All potentially significant covariates identified were added in combination to the base model to establish a full model. Each covariate was removed (one covariate at a time) from the full model. When the removal of a covariate from the full model resulted in a significant increase of the minimal objective function (≥ 10.828 , $p < .001$), that covariate was retained in the final model. In case of physiologically related, therefore highly correlated factors, such as age and weight, the covariate that best explained the data was selected for inclusion in the final model.

Covariate Models

Patient factors such as body weight, age, gender, ethnic origin, smoking status, and dose were tested for their influence on CL/F and V/F. Equations 3 to 5 were applied to test continuous covariates (body weight, age) and equation 6 to test categorical covariates (gender, ethnic origin, smoking status, and dose).

$$P = \Theta 1 \cdot [1 + \Theta 2 \cdot (\text{COV} - \text{MED})] \quad \text{Equation 3}$$

$$P = \Theta 1 \cdot \text{EXP}[\Theta 2 \cdot (\text{COV} - \text{MED})] \quad \text{Equation 4}$$

$$P = \Theta 1 \cdot (\text{COV} / \text{MED})^{\Theta 2} \quad \text{Equation 5}$$

$$P = \Theta 1 \cdot (1 + \Theta 2 \cdot \text{IND}) \quad \text{Equation 6}$$

where P is the individual parameter estimate, $\Theta 1$ represents the typical value of a parameter, $\Theta 2$ represents the effect of a covariate, COV is the value of a covariate, and MED is the median value of a covariate. IND is an indicator variable with a value of either 0 or 1 assigned for values of a categorical covariate (for example, smoker=0 and nonsmoker=1).

Each covariate was individually added to the base model and tested. When the objective function of the base model with a covariate was reduced by 6.635 ($p < 0.01$), the covariate was considered to be potentially significant.

Random Variance Models

Two residual error models evaluated were proportional (Equation 7) and combined additive and proportional.

$$C_{ij} = \text{IPRED} \cdot (1 + \text{ERR}) \quad \text{Equation 7}$$

where C_{ij} is the predicted j th olanzapine concentration in the i th patient, IPRED is the model predicted olanzapine concentration in the individual and ERR is a random variable with a mean of zero and variance of σ^2 .

Pharmacodynamics

N/A

Model Selection

Final Model Evaluation

Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model. Posterior predictive check was conducted to examine if the final model reliably predicts the data that was used to develop it.

Parameter Sensitivity Analysis

This analysis examined the parameter space, confirms the absence of local minima, and identifies the 95% confidence interval (CI) of the parameter using a process developed at Eli Lilly and Company (Allerheilgen et al. 1994, O'Brien et al. 1998). The analysis was

performed by fixing the parameter of interest to $\pm 5, 10, 15, 20, 30, 40\%$ of the population estimate and estimating all other parameters. The effect of modifying the parameter value on the overall fit of the data was examined. If needed, the parameter of interest was fixed to additional values up to $\pm 100\%$. The relationship between change in objective function and the parameter value was described using polynomial regression to obtain a 95% CI of the parameter. Assuming a chi-square distribution, the parameter values which produce a change in objective function of 3.841 represent the 95% confidence limits.

Leverage Analysis

The leverage analysis was performed to evaluate the contribution of subsets of patients on the final model. Ten datasets were created with 10% of the patients randomly omitted such that each patient was omitted only once. The final model was run with each dataset containing only 90% of the patients. The parameter estimates from all 10 runs were compared with the 95% confidence limits determined from the parameter sensitivity analysis.

Posterior Predictive Check

The final model parameter estimates, variance covariance matrix, and inter-patient variability estimates were used to perform simulations that predicted olanzapine concentrations at various olanzapine doses. The distributions of the predicted olanzapine concentrations were compared to the observed concentrations for each study.

Comparison of Adolescent and Adult Olanzapine Pharmacokinetics

Individual estimates of the pharmacokinetic parameters in adolescent patients were obtained from the final model post-hoc estimates. The pharmacokinetic model for oral olanzapine in adult patients from Study F1D-MC-HGAJ (original NDA 20-592, 21 September 1995) was developed in NONMEM, Version 4 using first order (FO) method of estimation. In an effort to be consistent with the software version and method of estimation used for adolescent pharmacokinetic modeling, the individual pharmacokinetic parameters in the adult patients were obtained by rerunning the final pharmacokinetic model for adult patients in NONMEM, Version V and using FOCE with interaction method.

Initial Model Selection

The basis of rejecting and/or accepting a particular model (e.g.: additive versus proportional, with or without weight, sex, etc.) should be described. The estimation method and the alpha level of the chi-square test should be included. Further, the type of model selection should also be presented (forward, backward, stepwise, etc.).

Final Model Selection

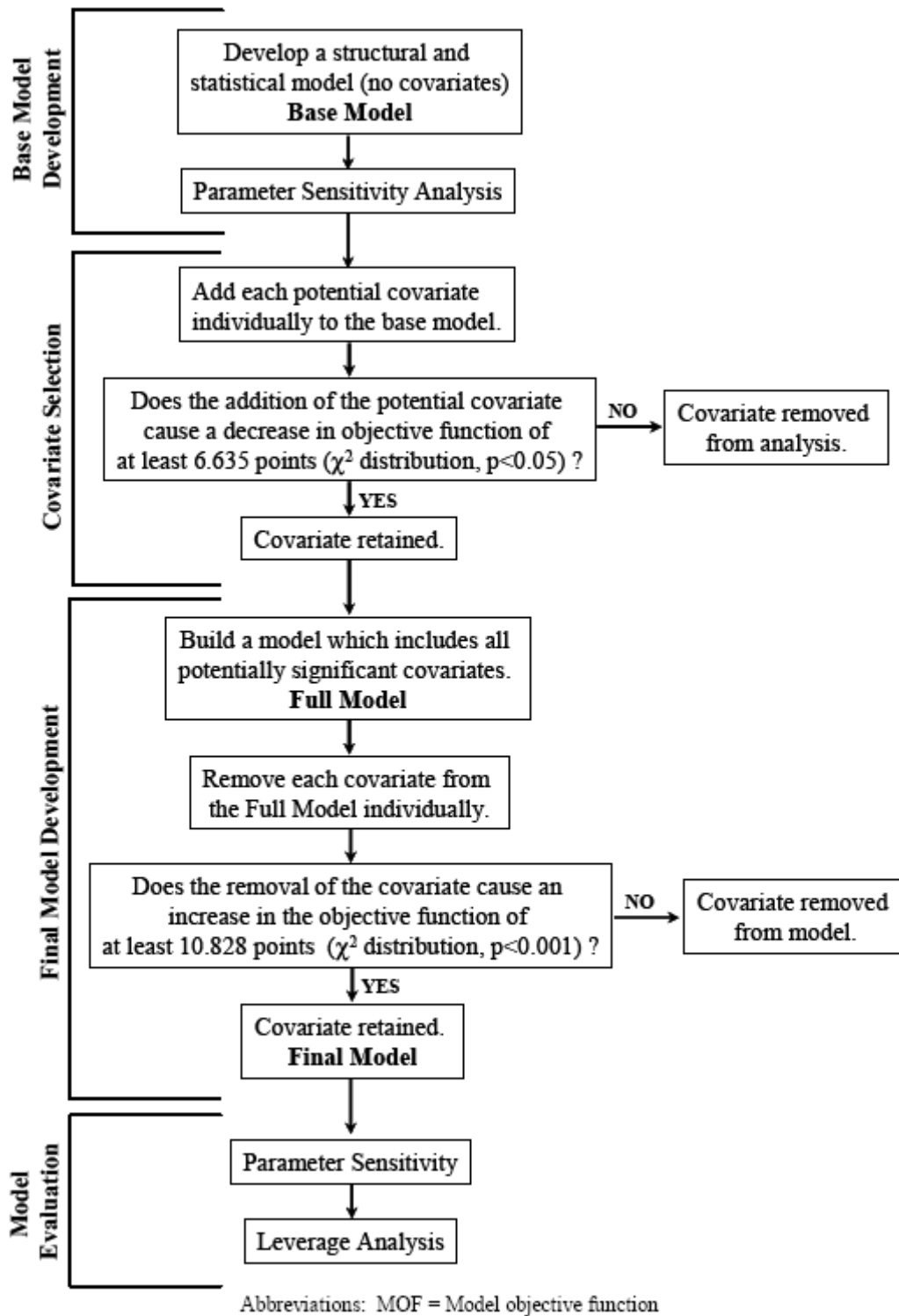


Figure HGMF.5.2. General process for pharmacokinetic model development

Software

The software used for the data formatting, modeling, simulation, graphing, and statistical tests should be included (e.g.; EXCEL, SAS, , S-PLUS, NONMEM version V,,).

Results and Discussion

Design Adequacy

Table HGMF.7.1. Baseline Demographics for Patients Included in the Pharmacokinetic Modeling (Studies HGCS, HGCR, HGGC, HGMF)

Demographic	HGCR	HGCS	HGGC	HGMF	Total
n	9	75	15	363	462
N	1	5	5	105	116
Age (years)					
Mean±SD	16	16.0±1.41	14.3±0.593	16.1±1.37	16.0±1.38
(Min, Max)		(14,17)	(13.3,14.7)	(13.43,17.99)	(13.3,17.99)
Body weight (kg)					
Mean±SD	78.9	65.6±15.8	65.3±10.4	72.9±20.9 ^a	72.3±20.3 ^b
(Min, Max)		(48.2,85.8)	(56.7,77.1)	(41.1,147.7) ^a	(41.1,147.7) ^b
Gender (N)					
Male	1	2	0	64	67
Female	0	3	5	41	49
Smoking status (N)					
Smoker	NA	NA	NA	20	20
Non-smoker	NA	NA	NA	73	73
Origin (N)					
Caucasian	NA	NA	4	90	94
African American	NA	NA	0	8	8
Hispanics	NA	NA	1	7	8

Abbreviations: n = number of observations; N = number of patients; Max = maximum; Min = minimum; SD = standard deviation; NA = not available.

^a n = 103

^b n = 114

The number of subjects appears adequate although it may have been better for them to have more subjects at age 13-14 to replace those in study LOAY.

Data Integrity

The data base contained subjects below 13 and above 17 who were excluded.

Model and Model Selection:

Base Model

Model description

Parameter estimation results

Table HGMF.7.3. Pharmacokinetic Parameters for the Base Population Model (Studies HGCS, HGCR, HGGC, HGMF)

	Units	Estimate	%SEE
Pharmacokinetic Model			
Absorption rate constant, K_a	hr ⁻¹	0.543 (Fixed)	-
Oral clearance, CL/F	L/hr	16.3	4.61
Oral Volume of Distribution, V/F	L	879	17.1
Interpatient Variability			
CL/F	%	45.9	15.9
V/F	%	68.8	42.3
Covariance between CL/F and V/F	-	0.258	22.5
Residual Error			
Proportional	%	27.0	13.7

Abbreviations: SEE = standard error of the estimate.

Goodness of fit

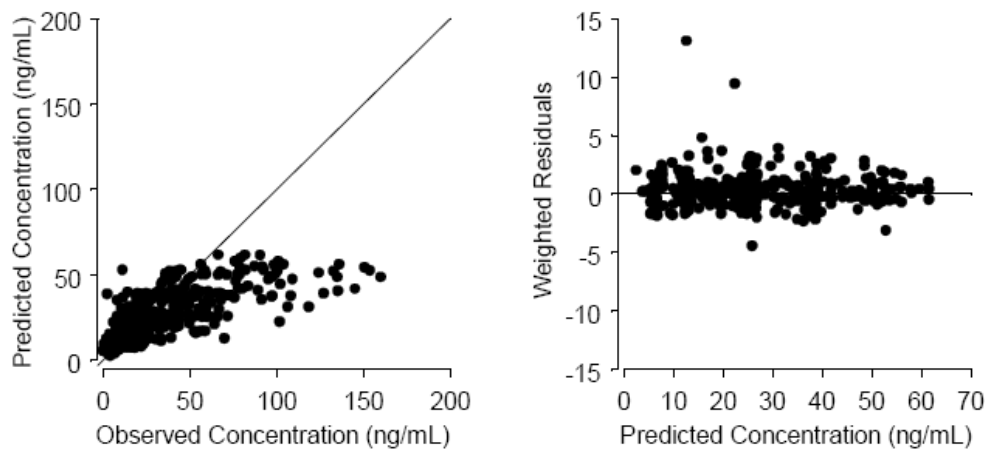


Figure HGMF.7.4. Goodness-of-fit plots for the base pharmacokinetic model. Data from Studies HGCS, HGCR, HGGC and HGMF.

Model Selection

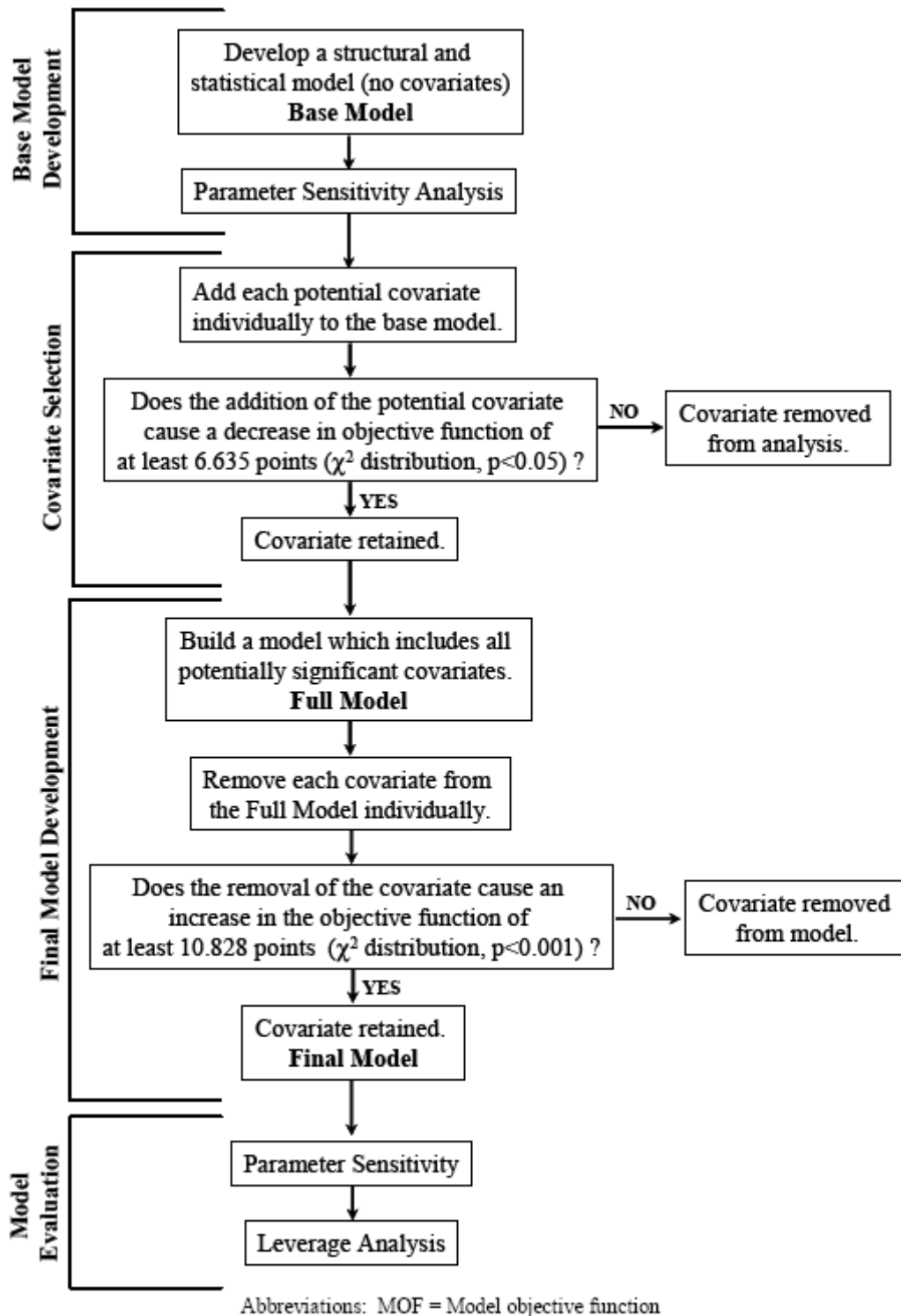


Figure HGMF.5.2. General process for pharmacokinetic model development

Final Model

Model description

Final Model Development

All potentially significant covariates identified were added in combination to the base model to establish a full model. Each covariate was removed (one covariate at a time) from the full model. When the removal of a covariate from the full model resulted in a significant increase of the minimal objective function (≥ 10.828 , $p < .001$), that covariate was retained in the final model. In case of physiologically related, therefore highly correlated factors, such as age and weight, the covariate that best explained the data was selected for inclusion in the final model.

Final Model Evaluation

Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model. Posterior predictive check was conducted to examine if the final model reliably predicts the data that was used to develop it.

Parameter Sensitivity Analysis

This analysis examines the parameter space, confirms the absence of local minima, and identifies the 95% confidence interval (CI) of the parameter using a process developed at Eli Lilly and Company (Allerheilgen et al. 1994, O'Brien et al. 1998). The analysis was performed by fixing the parameter of interest to ± 5 , 10, 15, 20, 30, 40% of the population estimate and estimating all other parameters. The effect of modifying the parameter value on the overall fit of the data was examined. If needed, the parameter of interest was fixed to additional values up to $\pm 100\%$. The relationship between change in objective function and the parameter value was described using polynomial regression to obtain a 95% CI of the parameter. Assuming a chi-square distribution, the parameter values which produce a change in objective function of 3.841 represent the 95% confidence limits.

Leverage Analysis

The leverage analysis was performed to evaluate the contribution of subsets of patients on the final model (Mandema et al. 1992). Ten datasets were created with 10% of the patients randomly omitted such that each patient was omitted only once. The final model was run with each dataset containing only 90% of the patients. The parameter estimates from all 10 runs were compared with the 95% confidence limits determined from the parameter sensitivity analysis.

Posterior Predictive Check

The final model parameter estimates, variance covariance matrix, and inter-patient variability estimates were used to perform simulations that predicted olanzapine concentrations at various olanzapine doses. The distributions of the predicted olanzapine

concentrations were compared to the observed concentrations for each study.

Final Pharmacokinetic Model

Two covariates, gender and body weight had a statistically significant influence on olanzapine pharmacokinetics and were retained in the final model. The effects of gender and body weight were on CL/F. Other patient specific factors such as age, race and smoking status did not have a significant influence on olanzapine pharmacokinetics although the CL/F difference in adolescents due to smoking may have been confounded due to weight..

The following mean concentrations were observed in adolescents.

Olanzapine Concentration (ng/mL)				
Dose (mg)	N	n	Mean ± SD	(Minimum, Maximum)
2.5	20	47	5.11±2.33	(0.290, 9.65)
3.0	1	3	14.5±1.82	(13.11, 16.57)
5.0	47	104	13.8±7.52	(0.890, 70.17)
7.5	28	46	20.6±9.75	(4.41, 52.46)
10.0	47	101	30.9±17.9	(3.18, 101.98)
12.5	10	17	50.3±21.4	(23.86, 118.78)
15.0	26	65	36.6±18.7	(2.56, 97.17)
17.5	7	9	78.2±40.7	(37.14, 145.37)
20.0	16	70	76.5±32.8	(11.36, 160.26)

Abbreviations: N = number of patients, n = number of observations, SD = standard deviation.

Based upon the mean concentrations it appears that dose has no impact on the kinetics of Olanzapine in adolescents. The lack of a dose effect on pharmacokinetics was also observed in adults.

Parameter estimation results Final Model

Table HGMF.7.4. Pharmacokinetic Parameters for the Final Population Model

	Units	Estimate	%SEE	95 % CI
Pharmacokinetic model				
Absorption rate constant, K_a	hr ⁻¹	0.543 (Fixed)	-	-
Oral Clearance (CL/F) ^a	L/hr	13.6	6.16	(12.2 – 15.3)
Effect of gender on CL/F (Θ_3) ^b	-	0.288	31.1	(0.127 – 0.477)
Effect of weight on CL/F (Θ_4) ^{c,d}	1/kg	0.00585	34.4	(0.00248 – 0.00907)
Oral Volume of Distribution (V/F)	L	899	16.2	(687 – 1150)
Interpatient variability				
CL/F	%	40.5	19.7	-
V/F	%	65.4	47.2	-
Covariance between CL/F and V/F	-	0.232	31.8	-
Residual Error				
Proportional	%	27.1	14.2	-

Abbreviations: CI = confidence interval; SEE = standard error of the estimate.

^a CL_{female} = 13.6 L/hr.

^b CL_{male} = CL_{female} · (1 + Θ_3) = 17.5 L/hr.

^c CL_{female} at weight(n) = 13.6 L/hr · e^[Θ_4 (n-70.1)]; where 70.1 is the median.

^d CL_{male} at weight(n) = 17.5 L/hr · e^[Θ_4 (n-70.1)]; where 70.1 is the median.

Goodness of fit

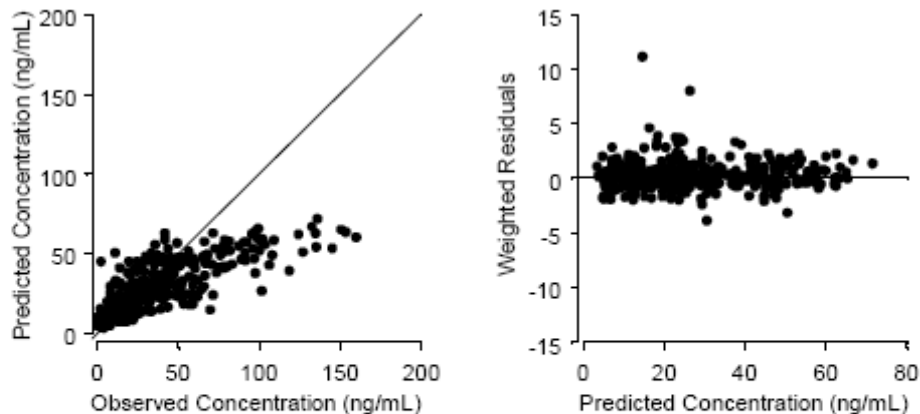
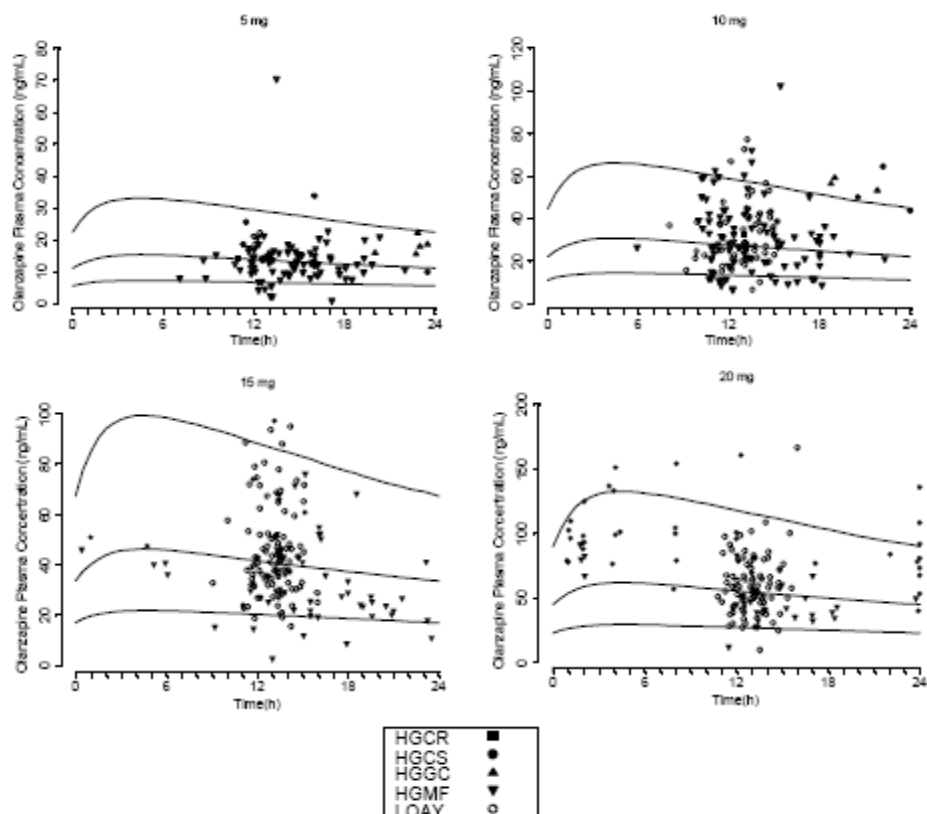


Figure HGMF.7.5. Goodness of fit plots for final model. Data from Studies HGCS, HGCR, HGGC, and HGMF.

Model Qualification

Posterior predictive check allowed for the comparison of the model predicted olanzapine concentrations with the observed olanzapine concentrations for each study. Most of the observed concentrations are within the model predicted concentration range (5th to 95th percentile) (Figure HGMF.7.7).



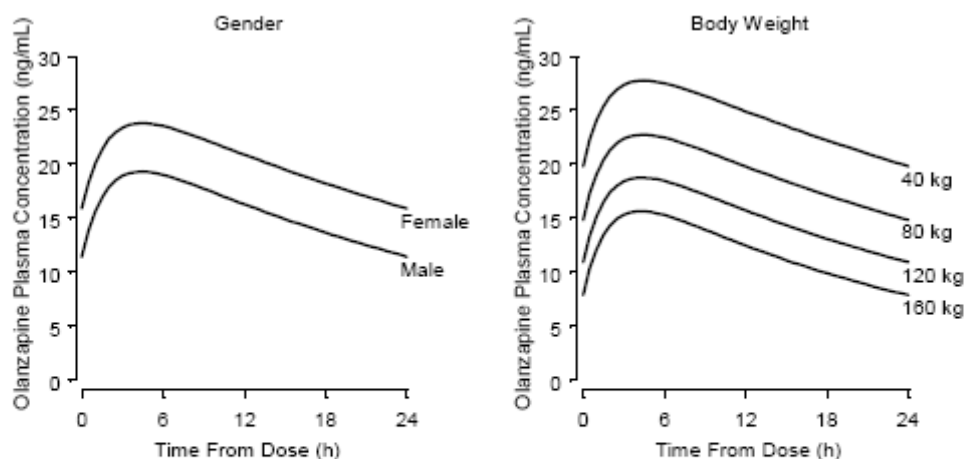
Note: Solid lines represent the 5th, 50th, and 95th percentile of the predicted olanzapine concentration-time profiles obtained simulating 1000 patients. Symbols represent observed olanzapine concentration.

Figure HGME.7.7. Comparison of model predicted olanzapine concentration and observed olanzapine concentration by dose.

Overall Conclusions

Effects of Gender

Gender had a significant influence on CL/F. Inclusion of gender as a covariate reduced inter-patient variability from 45.9% to 40.5%. The CL/F of olanzapine in male patients is approximately 29% higher as compared with the female patients. Thus, on average, female patients receiving the same olanzapine dose as male patients are predicted to have approximately 29% higher steady state olanzapine concentrations. The predicted effect of gender on olanzapine concentrations for typical population is shown in [Figure HGME.7.6](#).



Note: Gender: Predictions shown at the median body weight.
 Body weight: Predictions show the effect of body weight on a female patient.

Figure HGMF.7.6. Final population pharmacokinetic model. Predicted effect of covariates on plasma olanzapine concentrations at 10-mg olanzapine dose.

Variability in Olanzapine Pharmacokinetics

Variability in the final population pharmacokinetic model reflects the combination of inter-patient variability in pharmacokinetic parameters and intra-patient variability characterized by residual error. The interpatient variability in CL/F and V/F is 41% and 65%, respectively and the residual error is 27% (Table HGMF.7.4). The model predicted olanzapine concentrations at various doses of olanzapine are summarized in (Table HGMF.7.5). The maximal olanzapine concentration at steady state ($C_{max,ss}$) ranged from 7.81 ng/mL to 146 ng/mL (5th percentile after 5 mg to 95th percentile after 20 mg) in the dose range of 5 to 20 mg. The mean time of $C_{max,ss}$ was 6.6 hours. The minimal olanzapine concentration at steady state ($C_{min,ss}$) ranged from 5.51 ng/mL to 86.2 ng/mL (5th percentile after 5 mg to 95th percentile after 20 mg).

Table HGMF.7.5. Summary of Predicted Steady-state Olanzapine Concentrations Following Simulated Once-Daily Dosing

	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	$t_{max,ss}$ (h)
5-mg			
Geometric Mean	16.6	10.8	6.55
Geometric CV%	49.7	43.1	7.38
5 th Percentile	7.81	5.51	5.79
50 th Percentile	16.7	10.8	6.56
95 th Percentile	36.4	21.5	7.37
10-mg			
Geometric Mean	33.3	21.7	6.55
Geometric CV%	49.7	43.1	7.38
5 th Percentile	15.6	11.0	5.79
50 th Percentile	33.5	21.6	6.56
95 th Percentile	72.8	43.1	7.37
15-mg			
Geometric Mean	49.9	32.5	6.55
Geometric CV%	49.7	43.1	7.38
5 th Percentile	23.4	16.5	5.79
50 th Percentile	50.2	32.4	6.56
95 th Percentile	109	64.6	7.37
20-mg			
Geometric Mean	66.6	43.3	6.55
Geometric CV%	49.7	43.1	7.38
5 th Percentile	31.2	22.0	5.79
50 th Percentile	66.9	43.2	6.56
95 th Percentile	146	86.2	7.37

Abbreviations: CV = coefficient of variation

Comparison of Adolescent and Adult Olanzapine Pharmacokinetics

(Study HGAJ, 912 patients) which was a study comparing Olanzapine and Haloperidol in the treatment of Schizophrenia.

The results from study HGAJ is presented in the following Table: HGMF7.6

Table HGMF 7.6 Population pharmacokinetic parameters and 90% CI from adult study HGAJ

NONMEM Parameter Estimates		
Parameter	Parameter Value	95% Confidence Interval ^d
CL ₁ ^a (L/hr)	13.50	12.61 - 14.39
CL ₂ _Male_Smoker ^b (L/hr)	28.40	27.28 - 29.52
CL ₂ _Female_Smoker ^b (L/hr)	23.06	22.15 - 23.97
CL ₂ _Male_Nonsmoker ^b (L/hr)	18.01	16.86 - 19.15
CL ₂ _Female_Nonsmoker ^b (L/hr)	12.01	11.35 - 12.68
V_Male_Smoker (L)	1360.0	1196.13 - 1523.87
V_Female_Smoker (L)	961.52	792.24 - 1130.80
V_Male_Nonsmoker (L)	918.00	801.92 - 1034.08
V_Female_Nonsmoker (L)	788.80	688.67 - 888.93
pc	0.731	0.679 - 0.783

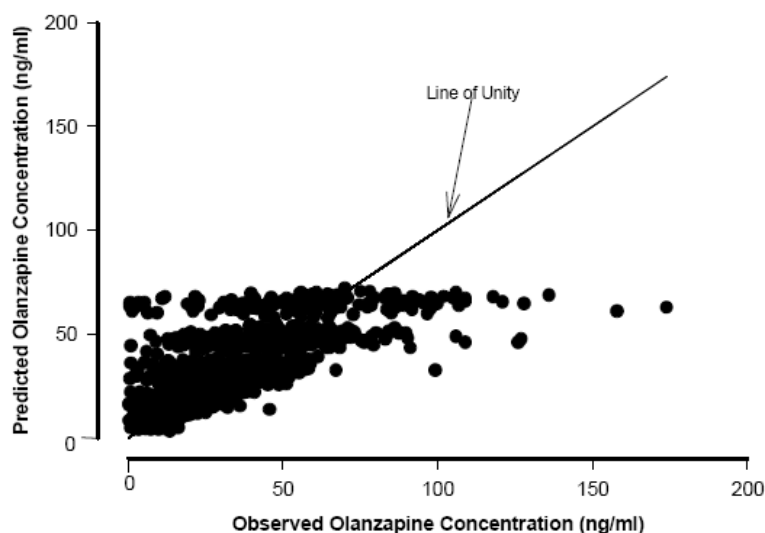
a= Low clearance population

b = High clearance population

c = Fraction of patients in high clearance population

d = Determined from objective function mapping

Predicted vs Observed Olanzapine Concentrations Including The Extreme Outliers In The Final Model (Study HGAJ)



The firm compared the distributions of CL/F and V/F statistically using the Kolmogorov-Smirnov test, a nonparametric method. The test showed that were significantly different in adolescent and adult population ($p < .001$). The common area under the two distributions (adolescent and adult) of [Figure HGMF.7.8](#) represents the proportion of patients having comparable values. Approximately 77% of the adolescent and adult patients had comparable CL/F estimates and approximately 69% of the patients had comparable V/F. The typical values (for example, geometric mean) of CL/F and V/F in adolescent patients are 21% and 17% lower than in adults. It should be noted that in adults, gender and smoking had a significant effect on CL/F and V/F while in

adolescents, gender and body weight had a significant effect. Thus, the effect of body weight on CL/F in adolescent patients and the high proportion of nonsmokers in adolescent patients (78% in adolescents versus 40% in adults) may explain the differences in oral olanzapine pharmacokinetics observed in these populations.

The observed steady state olanzapine concentrations in adolescent patients were also compared with those observed in adults (Study HG AJ). As noted above, the median steady state olanzapine concentrations in adolescent patients were slightly higher than those in adults at each dose ([Figure HGMF.7.9](#)). However, there is considerable overlap in the olanzapine concentration distribution in adolescents and adults. At 20 mg dose, olanzapine concentrations in a few adolescent patients exceeded the maximum concentration observed at 20 mg in adults. Steady state olanzapine concentrations in adolescent patients up to doses of 15 mg were encompassed within the range of olanzapine concentration (10th percentile after 5 mg and 90th percentile after 20 mg) reported in adults.

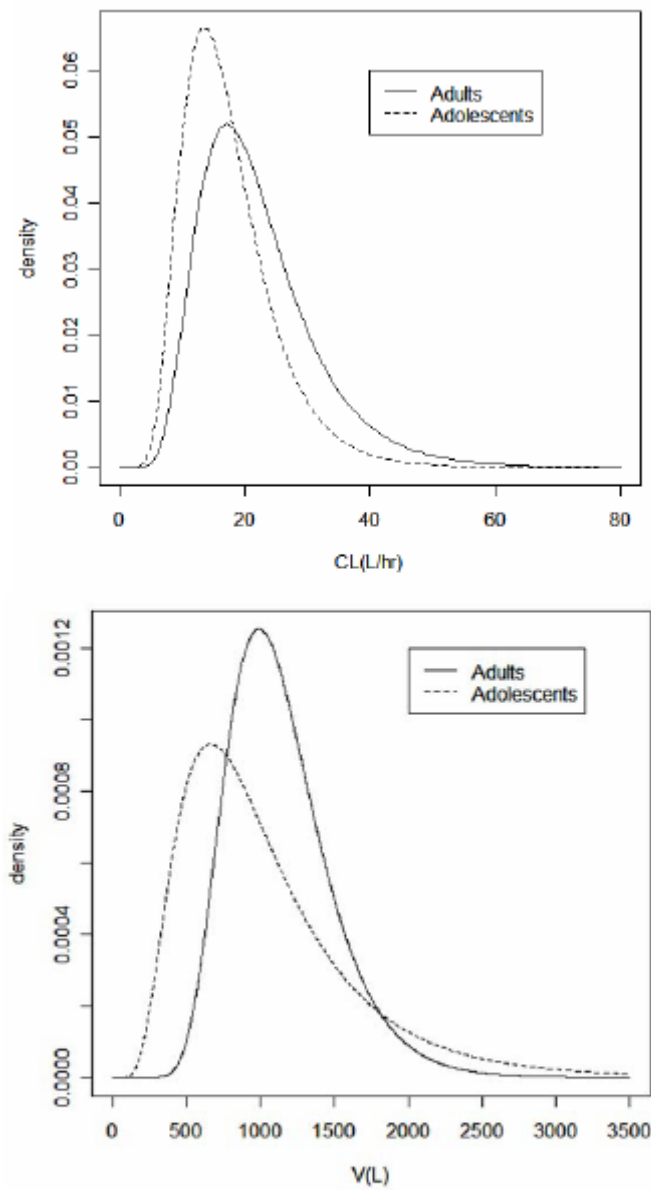
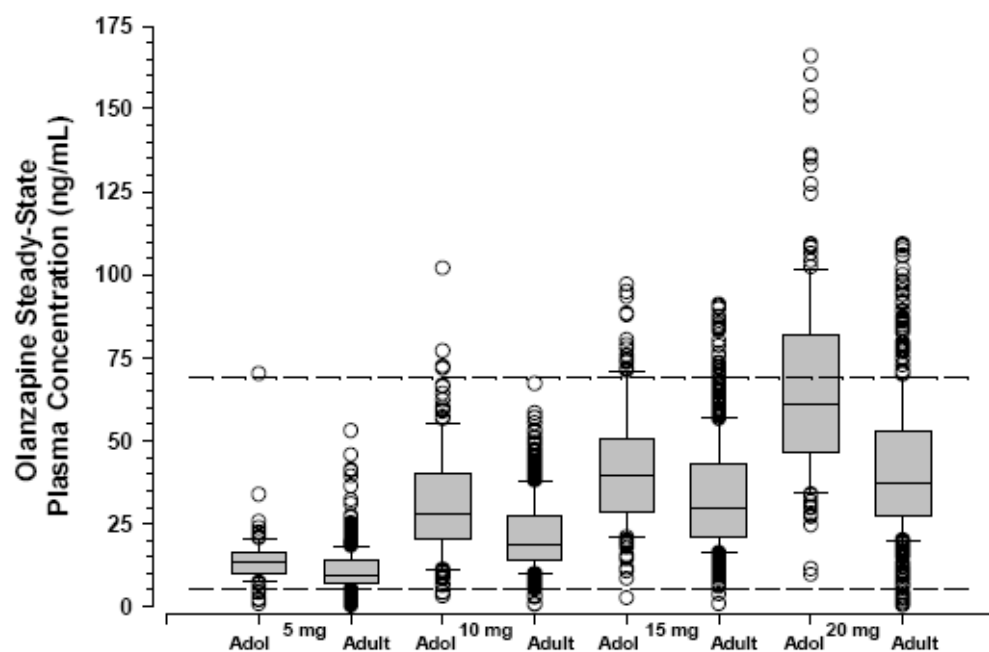


Figure HGMF.7.8. Distribution of individual olanzapine pharmacokinetic parameters (oral clearance and oral volume of distribution) in adult and adolescent patients.



Abbreviations: Adol = Adolescent

Note:

The middle line in each box plot represents the median; the top and bottom margins represent the 75th and 25th percentiles; the whiskers extend to the 90th and 10th percentiles; data points beyond the whiskers represent data in the tails of the distribution.

The dashed lines represent the 10th percentile of olanzapine concentration following 5-mg olanzapine daily and the 90th percentile of olanzapine concentration following oral 20-mg olanzapine daily in adults.

Figure HGMF.7.9.

Steady-state olanzapine plasma concentrations in adolescent and adult patients following oral olanzapine administration.

FDA RESULTS

BASE MODEL

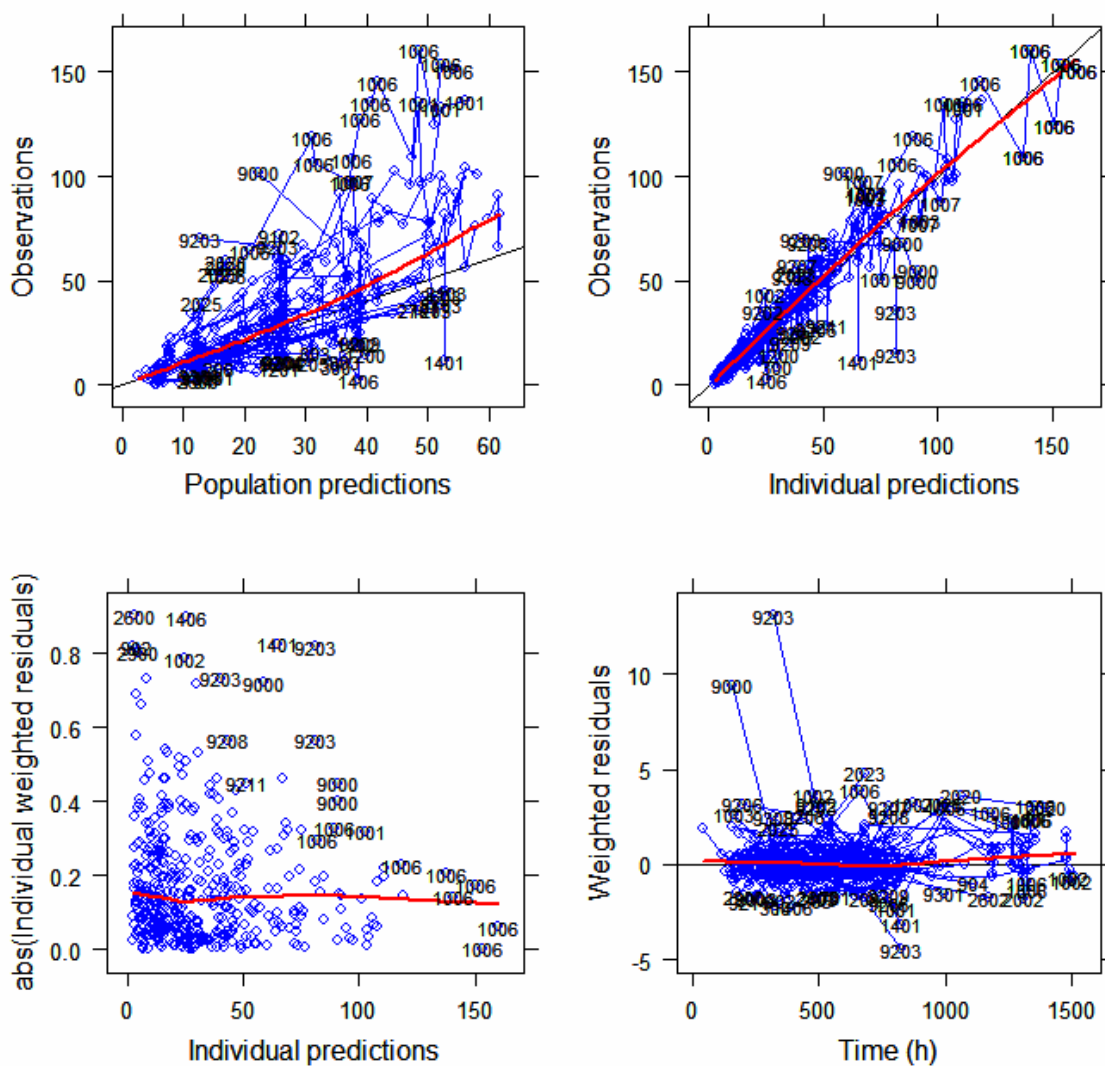


Table Summary of FDA Pharmacokinetic Parameters for the Base Population Model (Studies HGCS, HGCR, HGGC, HGMF)

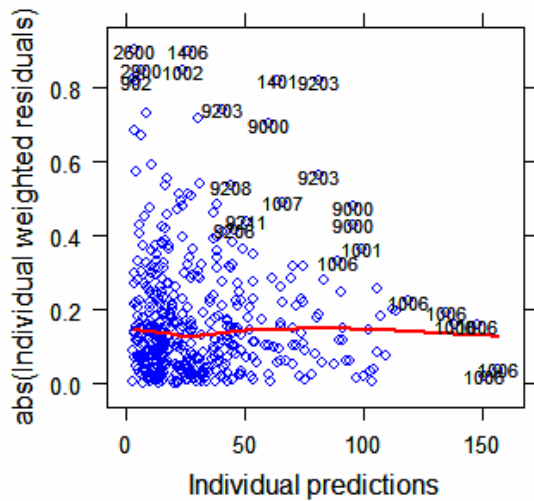
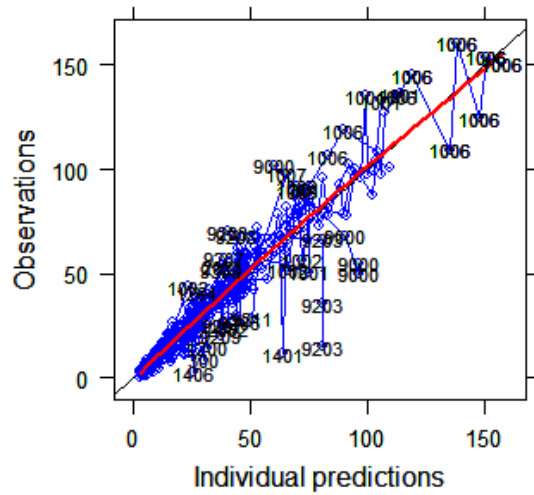
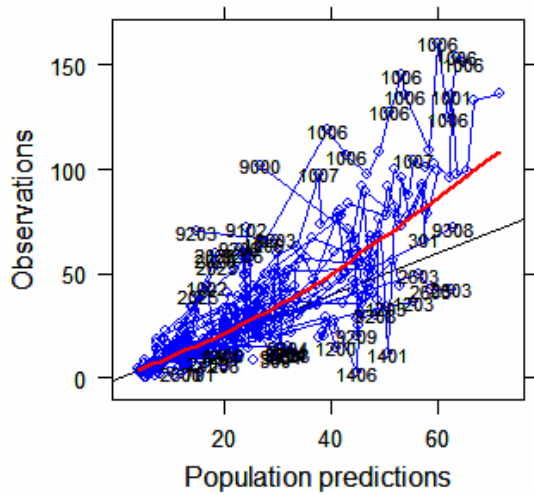
Units Estimate	%SEE	
Pharmacokinetic Model		
Absorption rate constant, Ka hr-1	0.543 (Fixed)	-
Oral clearance, CL/F L/hr	16.3	4.61
Oral Volume of Distribution, V/F L	879	17.1
Interpatient Variability		
CL/F %	43.7	15.9
V/F %	62.2	42.3
Covariance between CL/F and V/F -	0.258	22.5
Residual Error		
Proportional %	27.0	13.7

Abbreviations: SEE = standard error of the estimate.

FDA Values all agree with sponsor for the Base model

Table Summary of FDA Pharmacokinetic Parameters for the Final Population Model (Studies HGCS, HGCR, HGGC, HGMF)

Units Estimate		%SEE
Pharmacokinetic Model		
Absorption rate constant, Ka hr ⁻¹	0.543 (Fixed)	-
Oral clearance, CL/F L/hr	13.66	456
Effect of Gender on CL/F	0.288	1191
Effect of Weight on CL/F	0.00585	80.7
Oral Volume of Distribution, L	899	993
Interpatient Variability		
CL/F %	38	401
V/F %	60	1291
Covariance between CL/F and V/F -	0.27	
Residual Error		
Proportional %	27	599
Abbreviations: SEE = standard error of the estimate.		



FDA's PROPOSED LABEL CHANGES

794 12.3 Pharmacokinetics

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents (b) (4)

Comments:

1 (b) (4)

2. Based upon visual comparison of the observed vs fitted graphs for studies HGAI in adults and the current study, the graphical results indicate higher olanzapine levels in adolescents than in adults.

SIGNATURES

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Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 20592, HFD-860 (Mehta, Baweja, Jackson)
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References

Allerheiligen S, Cerimele B, Milosevich S, Johnson R, Nelson R, Tarassoff P. 1994. A population pharmacokinetic analysis of gemcitabine following variable length infusions. *Pharmaceutical Res* 11(10):S-377. Abstract 8178.

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Mandema JW, Verotta D, Sheiner LB. 1992. Building population pharmacokineticpharmacodynamic models. I. Models for covariate effects. *J Pharmacokinet Biopharm* 20(5):511-528.

Appendix I

Results from prior Adult Data

Parameter		Initial Estimate	Estimate	StdErr	%SEE
-----		-----	-----	-----	-----
THETA #1	ka	(0.543 FIXED)	0.543	Fixed	-
THETA #2	CL1_M_SMOK	(0,30)	27.9	0.988	3.54
THETA #3	CL1_F_SMOK	(0,0.8)	0.762	0.0319	4.19
THETA #4	CL1_M_NONSMOK	(0,0.6)	0.571	0.0268	4.69
THETA #5	CL1_F_NONSMOK	(0,0.4)	0.445	0.0234	5.26
THETA #6	CL2_POP2	(0,13)	19.1	1.57	8.22
THETA #7	V_M_SMOK	(0,1400)	1370	111	8.10
THETA #8	V_F_SMOK	(0,0.7)	0.662	0.154	23.3
THETA #9	V_M_NONSMOK	(0,0.6)	0.739	0.104	14.1
THETA #10	V_F_NONSMOK	(0,0.6)	0.574	0.0632	11.0
THETA #11	Frac_POP	(0,0.5,1)	0.831	0.0586	7.05
OMEGA #1	-	0.05	0.0706	0.00923	13.1
OMEGA #2	-	0.05	0.267	0.0951	35.6
OMEGA #3	-	0.05	0.271	0.0617	22.8
SIGMA #1	-	0.25	0.0502	0.00361	7.19

I. BASE MODEL CONTROL STREAM

(b) (4)

(b) (4)



II. FINAL MODEL CONTROL STREAM

(b) (4)



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Andre Jackson
3/27/2007 08:35:38 AM
BIOPHARMACEUTICS

Raman Baweja
3/27/2007 12:16:22 PM
BIOPHARMACEUTICS