Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Ziprasidone
PRODUCT (Brand Name):	Geodon
DOSAGE FORM:	Capsules
DOSAGE STRENGTHS:	20 mg, 40 mg , 60 mg and 80 mg capsules
NDA:	20825 SE5032
NDA TYPE:	Pediatric Supplement
SUBMISSION DATE:	October 21, 2008
SPONSOR:	Pfizer
REVIEWER PM SECONDARY REVIEWER	Andre Jackson Hao Zhu

REVIEW OF NDA

EXECUTIVE SUMMARY

The firm has submitted new studies in children and adolescents and old studies in children, adolescents, and adults to address a Pediatric Written Request issued for Ziprasidone on February 11, 2003. The indication is for Manic and Mixed Episodes associated with Bipolar Disorder.

The firm has conducted two new studies in children and adolescents :

Study A1281132 which was a pivotal 4-week, double-blind, placebo-controlled safety and efficacy trial that supports the efficacy and safety of Ziprasidone in children and adolescents.

Study A1281123 which was a safety and tolerability study that explored the range of tolerated doses of open-label ziprasidone during 3-weeks of low or high fixed dose administration.

Two other studies in children and adolescents for Tourette's syndrome were previously submitted to the FDA under the IND on January 23rd, 1998.

Adult studies were all submitted and reviewed previously by the FDA.

Exposure for Ziprasidone is related to body weight which is the basis of the dosage recommendations i.e., 80-160 mg/day (40-80 mg BID) for patients weighing ≥45 kg, or 40-80 mg/day (20-40 mg BID) for patients weighing <45 kg.

Ziprasidone did not show a dose response for either weight group with respect to the clinical end point, Young Mania Rating Scale.

Exposure to Ziprasidone in children, adolescents and adults was similar for the high and low dose groups for both weight groups. Therefore no further adjustments in dose are needed.

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BACKGROUND ON FORMULATIONS

The firm submitted a study on September 29, 2005 with studies to evaluate the BE between Ziprasidone Oral Suspension (OS) and the approved Ziprasidone Oral Capsule. Results from that study were:

1. Ziprasidone Oral Suspension is not bioequivalent to the approved ziprasidone oral capsules.

Table 1: Statistical Analyses of PK Parameters of Ziprasidone after Administration of the Oral Suspension Compared to the Oral Capsule Pharmacokinetic Adjusted Geometric Means Parameter Ziprasidone OS Suspension Compared to the Oral Capsule

Pharmacokinetic Parameter	Adjusted Geometric Means			
	Ziprasidone OS Fasted (Test) (N=13)	Ziprasidone Capsue Fasted (Ref.) (N=13)	Point Estimate	90% CI
Cmax (ng/mL)	24.5	29.7	82.68	67.35, 101.50
AUC(∞) (ng*h/mL)	212.0	242.7	87.36	76.92, 99.23
AUC(0-T) (ng*h/mL)	203.1	228.1	89.05	77.56, 102.24

In a single dose study under fasting conditions, the Cmax and AUC(∞) were 17% and 13% lower, respectively, for ziprasidone oral suspension compared to the capsule formulation.

Table 2: Statistical Analyses of Cmax, AUC(∞), and AUC(0-T) for Ziprasidone OS Food Effect

Pharmacokinetic Parameter	Adjusted Geometric Means			
	Ziprasidone OS Fed (Test) (N=13)	Ziprasidone OS Fasted (Ref.) (N=13)	Point Estimate	90% CI
Cmax (ng/mL)	40.0	24.5	163.03	133.18, 199.57
AUC(∞) (ng*h/mL)	417.3	212.0	196.83	173.64, 223.13
AUC(0-T) (ng*h/mL)	408.5	203.1	201.09	175.52, 230.37

Table 3. Summary of all formulation studies conducted by the firm.

Ziprasidone Oral Suspension BA/BE Studies in Adults: PK Results Summary						
Study Number	**Parameter (units)**	**Treatments Compared (Test vs Reference)**	**Test** Geometric Mean	**Reference** Geometric Mean	**Adjusted Geometric Mean Ratio**	**90%CI**
A1281131	AUC_{inf} (ng-h/mL)	OS fasted vs Cap fasted	212.0	242.7	87.36%	76.92%, 99.23%
	AUC_{inf} (ng-h/mL)	OS fed vs OS fasted	417.3	212.0	196.83%	173.64%, 223.13%
	Cmax (ng/mL)	OS fasted vs Cap fasted	24.5	29.7	82.68%	67.35%, 101.50%
	Cmax (ng/mL)	OS fed vs OS fasted	40.0	24.5	163.03%	133.18%, 199.57%
128-056	AUC_{inf} (ng-h/mL)	OS fed vs cap fed	474.8	503.6	94%	90%, 99%
	Cmax (ng/mL)	OS fed vs cap fed	43.6	51.3	85%	77%, 94%
A1281037	$AUC_{11.5h}$ (ng-h/mL)	OS fed vs cap fed	558.8	580.4	96.3%	86.1%, 107.7%
	Cmax (ng/mL)	OS fed vs cap fed	74.9	83.6	89.6%	80.1%, 100.3%
128-034	AUC_{inf} (ng-h/mL)	OS fed vs cap fed	924	982	94.4%	90%, 99%
	Cmax (ng/mL)	OS fed vs cap fed	97	110	86.5%	71%, 106%

A high fat meal increased the Cmax and AUC (∞□) of ziprasidone following administration of the OS by 63% and 97%, respectively. The increase in ziprasidone concentration after a high fat meal with the OS is similar to that observed when ziprasidone capsules are administered with a high fat meal. The studies indicate that for AUC capsule and oral solution are BE but not for Cmax. The OS formulations deliver a 10-17% lower Cmax than the capsule under both fed and fasting conditions.

SPONSOR'S CLAIMS

The sponsor argued that the fact that in study A1281131 the 90% CI around the point estimate for AUC and Cmax are not contained within the regulatory criteria for bioequivalence is not clinically relevant under conditions of actual use of Ziprasidone. Cmax is 10 -17% lower after administration of the OS compared to the capsule formulation.
The sponsor contends that the principal concern about a lower Cmax is the possibility of diminished efficacy. The sponsor states that a review of pharmacodynamic properties of antipsychotic drugs and data obtained from

Ziprasidone PET dopamine-D2 occupancy clinical studies suggest that a reduction in Cmax will not impair efficacy.

CONTENTS CURRENT SUBMISSION

Pharmacokinetic studies submitted were studies in children and adolescents between the ages of 10 and 17 years:

1. Study A1281132 was a pivotal 4-week, double-blind, placebo-controlled safety and efficacy trial that supports the efficacy and safety of flexibly dosed ziprasidone in the treatment of Bipolar I Disorder in pediatric patients. This study has not been previously submitted to the FDA.

2) Study A1281123 was a safety and tolerability study that explored the range of tolerated doses of open-label ziprasidone during 3-weeks of low or high fixed dose administration, and also characterized the long-term safety and tolerability of open-label ziprasidone flexibly dosed for an additional 24 weeks. This study has not been previously submitted to the FDA.

3) Study A1281133 was a safety and tolerability study that assessed the safety and tolerability of open-label ziprasidone during long-term administration to subjects who had enrolled in the short-term double-blind study. No pharmacokinetic samples from this study.

4) Studies 128-044 and 128-122 were exploratory studies conducted in children and adolescents with Tourette's syndrome. This study has been previously submitted to the FDA under the IND on January 23rd, 1998. However, I could not determine if these studies had ever been reviewed.

5) Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone which consisted of previously mentioned studies 128-044 and 128-122 and five studies conducted in adult subjects (A1281037, 128-109, 128-114, 128-115, and 128-303). All of these studies were previously reviewed by FDA.

STUDY DESIGN SYNOPSIS AND SAMPLING TIMES

Protocol No.	1281132	1281123	128-044	128-122
Type of Study	Placebo-controlled safety and efficacy	Safety and tolerability	Pharmacokinetics and safety	Safety, tolerability, pharmacokinetics, and efficacy in children and adolescents with Tourette's syndrome (TS)
Study Design	Titration dosing continued to Week 4, further dosing adjustments if necessary within the range of 80-160 mg/day depending on body weight	Titration of 10 days followed by 3 weeks of open label treatment. periods: 1. (low or high dose, fixed titration) 2. (flexible dosing).		BID with food After 3 days subjects titrated every 3-4 days to 40 mg. Dose increments were 5m to 10mg. Escalation was to be complete by day 22 which varied by subject.
Dosage Regimen	Oral ziprasidone capsules of 20 mg, 40 mg, 60 mg, and 80 mg strength	1.Low dose-10-40 mg BID;10day titration 2. High dose; 20-80 mg BID;10-day titration. Oral suspension was used in period 1 and subjects could switch to capsules in period 2.	Oral suspension In three Groups dosed based on body weight: Group 1 (>60 kg) received 20 mg of ziprasidone; Group 2 (31-60 kg) received 10 mg of ziprasidone; Group 3 (16-30 kg) received 5 mg of ziprasidone.	5 mg or placebo, 10 mg or placebo, or 20 mg or placebo.
Intent to treat	Ziprasidone-143 Placebo-86	63	24	Ziprasidone 16 Placebo-12

No. of Subjects analyzed	Ziprasidone-103 Placebo-66	38	24	Ziprasidone 15 Placebo-9
Study Population	Subjects 10-18 yrs old with a primary diagnosis of Bipolar I disorder -	Adolescents 10-17 y/o with schizophrenia	Males or females aged 7-17.	Adolescents 7-14 M(14) 11-14 F(2) y/o
Duration of Treatment	4-weeks	3 weeks	32 hours	56 days
Dosing with respect to food	Doses given with food.		Dosed with breakfast	Dosed with food

Population Pharmacokinetic Sampling Times	
Protocol No.	
1281132	PK samples were obtained at 2 times after the first dose of study medication. Hours after first dose-0.5-1.5 hr 1.5-3.0hr --- At the week 4 visits prior to an observed morning dose, a (trough) PK sample was drawn. Subjects then took their morning dose of study medication. A second PK sample was taken between 0.75-3.0 hours (45-180 minutes) post-dose. A third sample between 5-7 hours postdose, the time when drug concentrations are typically highest, a third PK sample was drawn.
1281123	At Week 3/end of therapy in Period 1, a trough sample (taken immediately prior to the morning dose) and a peak sample (taken 5-7 hours after the morning dose) were obtained.

	Additional PK samples were obtained at random at Weeks 1, 12 and 27/end of therapy in Period 2, at only 1 time-point per visit.
128-044	Blood samples were taken immediately prior to (time zero), and 1, 2, 4, 6, 8, 12, 16, 24, and 32 hours after study drug administration.
128-122	Samples were collected from each subject at screening and immediately prior to the administration of the morning dose of study drug on days 8 and 57. Serum samples were also collected at a randomly selected sampling interval (2-4 hours, 4-6 hours, or 6-8 hours) following the administration of the morning dose on days 29 and 57.

DETAILS OF STUDY DESIGNS

STUDY 1281132

OBJECTIVES

To develop a population pharmacokinetic model to describe ziprasidone concentration data arising from study A1281132 in children and adolescents with Bipolar I Disorder (manic or mixed)
• To identify and characterize patient factors which influence the variability in ziprasidone pharmacokinetics
• To estimate the magnitude of unexplained variability in ziprasidone pharmacokinetics
• To evaluate the performance of the pharmacokinetic model developed for Ziprasidone

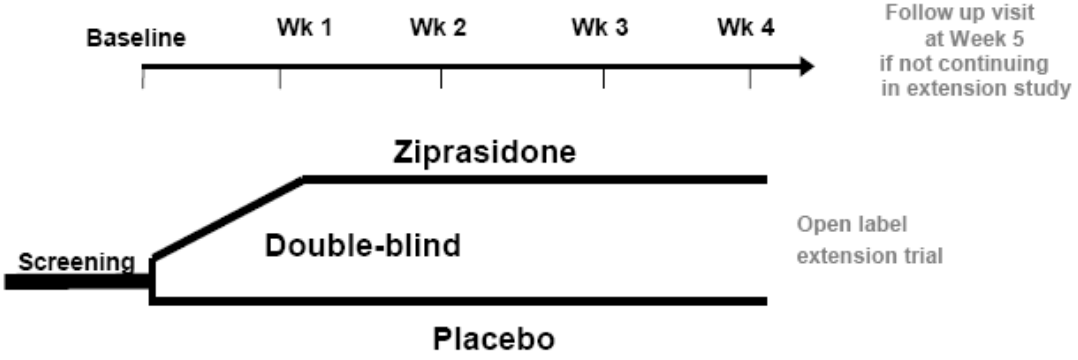
STUDY METHODS

The dose of ziprasidone was titrated over a 2-week period from a starting dose of 20 mg/day (starting with an evening dose) with dose increases of 20 mg/day every 2nd day up to a target dose of 120-160

mg/day for subjects weighing ≥ 45 kg. The target dose was 60-80 mg/day for subjects weighing < 45 kg.

In subjects requiring a more rapid onset of action based on their clinical history and symptoms, the dose was titrated more rapidly, with the same dose increases and from the same starting dose but increased daily in order to achieve the same target dose range. A dose of 160 mg/day was not given before Day 8 of treatment.

Following the titration, double-blind dosing continued to Week 4, during which time further dosing adjustments were made if necessary within the range of 80-160 mg/day for subjects with a body weight ≥ 45 kg, or between 60–80 mg/day for subjects weighing < 45 kg.
The target dose was to be obtained by Day 14. The dose was increased above 120 mg/day only in subjects who tolerated 120 mg/day.



Subjects were instructed to take only 1 capsule (from the 4 in the AM or PM columns) with food for each administration.

Table 1. D-Optimal Pharmacokinetic Sample Windows (hours)

Hours after First Dose (Baseline Visit)	Hours after Dosing (Week 4)
0.5-1.5* 1.5-3.0	-0.1-0**,*** 0.75-3.0*** 5.00-7.00***

'*'- wait at least 15 minutes before subsequent PK sampling.
**Samples collected after ECG is collected but before morning dose is administered at the clinic
'***' - Note that PK samples should be immediately after the associated ECG collection

DEMOGRAPHICS

Table 2. Baseline Demographics for Population Pharmacokinetic Analysis (n=128)

Demographic (units)	Mean (SD)	Median	Range
Age (y)	13.47 (2.21)	13	10-18
Height (cm)	159.0 (11.5)	158.8	132-184.5
Weight (kg)	56.62 (13.97)	57.15	28-86.63
BMI	22.13 (3.88)	21.44	15.11-31.91
BSA (m^2)	1.569 (0.235)	1.6	1.02-2.0
CrCL (mL/min) Total Body Weight	139.2 (32.35)	135.7	40.6-247
CrCL (mL/min) Lean Body Weight	108.9 (23.93)	104.9	35.9-203.2
CrCL (mL/min) Lean Body Weight Imputed*	107.5 (23.82)	104.9	35.9-150
ALT (IU)	18.01 (9.878)	15	5-82
AST (IU)	22.7 (6.149)	22	11-50
Bilirubin (mg/dL)	0.3578 (0.2006)	0.3	0.1-1.5
Albumin (g/dL)	4.693 (0.2873)	4.7	3.8-5.5
Sex	Male = 73; Female = 55		
Race	White = 105; Black = 16; Asian = 1; Other = 6		

Source: cov.summary_final_model.txt; cov.summary.crclimp.txt

ANALYTICAL

ASSAY VALIDATION

Parameter	Ziprasidone
Method	(LC-MS/MS)
Concentration Range	*(b) (4)* ng/mL
Number of Freeze-thaw	3
Long term at –80° C	716

Analytical Study 1281132

Study	1st PK Sample Collected	Last PK Sample Collected	Begin Analysis	End Analysis	Total Storage (Days)
Study 1281132	January 2006	July 2007	Oct 2006	Jan 2008	730

Parameter	Ziprasidone
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	*(b) (4)*
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	

FIRM'S PHARMACOMETRIC METHODS

Calculated Covariate Values

Creatinine clearance (CrCL) was estimated using the Schwartz Equation for subjects less than 13 years of age and by the Cockroft and Gault equation for subjects 13 years old and older. Creatinine clearance was estimated using total body weight in the original dataset. However there were quite a few subjects with very high CrCL values in the original dataset. Creatinine clearance was also calculated using lean body weight with the Cockroft and Gault equation, which reduced the number of excessively high CrCL values in the database. CrCL values greater than 150 mL/min were imputed as 150 mL/min.

$\text{CLCR (mL/min)} = \frac{(\text{Length (cm)} \times \text{k}}{\text{Serum Creatinine}}$ For infants over 1 week old through adolescence (18 years old) k = 0.45 for infants 1 to 52 weeks old k = 0.55 for children 1 to 13 years old k = 0.55 for adolescent females 13 - 18 years old	Schwartz Equation
$\text{CLCR (mL/min)} = \frac{(140 - \text{Age(y)}) \cdot \text{Body Weight}^{*}\text{ (kg)}}{72 \cdot \text{Serum Creatinine (mg/dL)}} \cdot 0.85$ for Females	Cockroft and Gault Equation

*Either lean or total body weight

Structural Model

Ziprasidone was previously described by a 1 compartment model with first order absorption and elimination. The model was parameterized as the absorption rate constant (*Ka*), clearance (*CL/F*), central volume of distribution (*V/F*). Between-subject variability was estimated for *Ka*, CL/F

and *V/F*. CL/F was found to be dependent on age and weight. The rate of absorption was found to be dependant on age.

Unexplained inter-individual variability in structural model parameters were estimated using the following error model:

$$P_j = TVP \cdot e^{\eta_j}$$

In this equation, *Pj* is the individual value for the pharmacokinetic parameter (e.g., CL) in the *jth* individual and ηj is an independent random variable with a mean of zero and variance ω^2.

Variance terms in the OMEGA matrix were retained if they were non zero or not large, the model converged with the $COV step and the associated p values were near 1 and the eta bar values were near 0.

Models that converged successfully with the completion of the $COV step were considered superior regardless of change in the objective function.

Statistical Model for Inter-Occasion Variability

When diagnostic procedures suggested the presence of inter-occasion variability in individual parameter estimates, an additional level of random effects was added to the inter-individual error model below.

$$P_{jk} = TVP \cdot e^{\eta_j + \kappa_{jk}}$$

In this equation, Pjk is the individual value for the pharmacokinetic parameter in the *jth* individual on the *kth* occasion, ηj is an independent random variable with mean zero and variance ωp^2, and κjk is an independent random variable with mean zero and variance πp^2 on the *kth* occasion, and zero otherwise. With this error model, ωP represents the approximate time-averaged inter-individual coefficient of variation for the parameter value P, and πp represents the approximate coefficient of variation in P between occasions for the typical individual.

Covariate Models

The covariates available for evaluation in the pharmacokinetic

analysis were sex, race, total body weight, height, body surface area, age, creatinine clearance, albumin, aspartate transaminase (AST), alanine transaminase (ALT) and total bilirubin.

Continuous covariates, such as body weight, were modeled using the general equation:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} \mathrm{cov}_i{}^{\theta_i}$$

where TVP represents the model predicted pharmacokinetic parameter (CL/F, V/F, or KA) for the "typical" individual with covariate value(s) covi., *Ppop* represents the population central tendency for the pharmacokinetic parameter TVP, covi represents the individual value for the covariate (i.e., body weight) normalized for the population mean or median, and θ *i* represents a scale factor.

Categorical covariates, such as gender, were modeled using the general equation:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} \theta_i{}^{\mathrm{cov}_i}$$

In this equation, θi is a direct proportionality constant. With this type of model, θi is fixed to 1 for the reference subgroup (e.g., males) where the covariate value is set to 0, and estimated for the test subgroup (e.g., females) where the covariate value is set to 1.

An allometric scale function of the form given below was also tested to evaluate the effect of body size.

$$TVP_{Clearance} = P_{pop} * \left(\frac{Wt}{Median} \right)^{0.75}$$

$$TVP_{Volume} = P_{pop} * \left(\frac{Wt}{Median} \right)$$

Discrete binomial covariates (e.g. race when stratified for Caucasian vs. non Caucasian) were explored using the following function:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} \theta_i^{\mathrm{COV}_i}$$

In this equation, TVP represents the model predicted pharmacokinetic parameter (e.g., CL/F, V2/F) for the "typical" individual, *Ppop* represents the population central tendency for the pharmacokinetic parameter *TVP*, *covi* represents the individual value for the covariate (i.e., 0 for Caucasian and 1 for non Caucasian), and θ *i* represents a scale factor. With this type of model, when *covi* is 0, the covariate value does not affect the parameter value. Further, if θi=1, the influence of the covariate is dropped from the model.

Identification and Addition of Covariates

The covariance step ($COV) was implemented with each NONMEM run, and standard errors for parameter estimates as well as correlation between parameters were evaluated. Models that resulted in parameter estimates with high associated standard error (> 35% of the parameter estimate), models with a high degree of correlation between parameters (>90%), and models that included a covariate(s) whose effect on the estimated parameter value was negligible, were carefully evaluated and reparameterized, or rejected.

If necessary (e.g. for the evaluation of non-nested models), the Akaike Information Criterion (AIC) was computed from the NONMEM OFV as

$$AIC = OFV + 2p$$

Where p is the number of estimable parameters in the model.

Pharmacostatistical model

Standard model building approaches were employed for this analysis. For nested models, during each step in the model building process, improvements to the model were assessed primarily using the likelihood ratio test (LRT; reduction in the objective function).
LRT = OFVM1 – OFVM2
In this equation, LRT is the test statistic, OFVM2 represents the value of the objective function obtained from the fit of the full model (e.g., a model with a covariate function), and OFVM1 represents the value of the objective function obtained from the fit of a reduced or reference model (M1). Using the conditional estimation method (e.g. First Order Conditional Estimation method (FOCE)), LRT is approximately distributed as a chi-square ($\chi 2$) random variable with q degrees of freedom, where q is the difference in the number of estimable model parameters between the full and reduced model. A LRT value of >3.841 ($p<0.05$) and 1 degree of freedom would indicate that the full model (M2) was the superior model. With 1 degree of freedom, if the LRT was <3.841, then no difference between the two models was discernable and the simpler (reduced) model was retained.

PHARMACOKINETIC SAMPLE ANALYSIS

The firm log transformed all concentration data for two reasons:

1) the resulting model developed using LTBS (Log Transform Both Sides) will not simulate negative concentrations when developed using an LTBS approach and

2) the use of LTBS generally ensures the distribution of weighted residuals is normal.

Residual Variability

Because the LTBS approach was used, the residual variability was initially described using a constant coefficient of variation (CCV) shown below.

$$Cs_{ij} = \hat{C}s_{ij} + \varepsilon_{ij_1}$$

Alternative error structures, including a composite of an additive error in combination with a CCV error were also evaluated.

$$Ln(C_{ij}) = Ln(\hat{C}_{ij}) + \sqrt{\varepsilon_{ij_1}^{\ 2} + \frac{\varepsilon_{ij_2}^{\ 2}}{\hat{C}_{ij}^{\ 2}}}$$

In these equations, Csij is the *i*th concentration measured in the *j*th subject, Ĉsij is the model predicted Csij, and εij1 is the CCV error term with a mean of zero and variance $\sigma 1^2$, εij2 represents an additive error, also with a mean of zero and variance of $\sigma 2^2$.

Estimation Methods

The first order approximation with conditional estimation (FOCE) method was primarily used in this analysis.

Because preliminary evaluations of the distributions of individual parameter estimates suggested that the distributions were symmetrical and the p-values associated with etabar values suggested that the mean values of eta were 0 (e.g. the null hypothesis could not be rejected), the application of the CENTERING option was not tested on the base or final models. However, when running the YLO/LAPLACIAN model which included BQL samples, the CENTERING option was used. This option forces the mean value of the variance terms to be zero (etabar=0), and should therefore result in parameter estimates that more closely follow the central tendency of the data.

Model Qualification

Parameter Stability

Where feasible, model stability was tested through the evaluation of the condition number. Condition numbers can be calculated only if the $COV step completes successfully. The condition number was used to ascertain stability of parameter estimates. A condition number (computed as the square root of the ratio of the largest eigenvalue to the smallest eigenvalue of the correlation matrix) of less than 20 suggests that the degree of collinearity between the parameter estimates is acceptable. A condition number that is in

excess of 100 indicates that the model may be unstable due to high collinearity.

Visual Predictive Check

A visual predictive check was conducted for this analysis. This study had an individualized dose titration and as a result each subject received different doses. Due to this design, the typical assessment of overlaying the observed data onto the prediction interval following the dose administered in the study could not be completed. Instead 400 simulations were performed for only the samples that were collected in the dataset using the doses that each subject received and the final model parameters. From these simulations the concentrations were corrected for the last dose the subject received and the 2.5th percentile, the median and the 97.5th percentile were calculated. Various plots of the results were generated comparing the simulated data to the observed data.

RESULTS

Table 1. Subject Disposition

	Ziprasidone	Placebo
Number (%) of subjects:		
Screened: N=327		
Assigned to study treatment: N=238		
Treated	149	88
Completed	97 (65.1)	51 (58.0)
Discontinued	52 (34.9)	37 (42.0)
Reason for discontinuation:		
Related to study drug:	14 (9.4)	3 (3.4)
Adverse event	13 (8.7)	3 (3.4)
Laboratory abnormality	1 (0.7)	0 (0)
Not related to study drug:	38 (25.5)	34 (38.6)
Adverse event	5 (3.4)	10 (11.4)
Lost to follow-up	8 (5.4)	1 (1.1)
Other	16 (10.7)	21 (23.9)
Subject no longer willing to participate	9 (6.0)	2 (2.3)
Analyzed for efficacy:		
Intent-to-treat	143 (96.0)	86 (97.7)
Per protocol	103 (69.1)	66 (75.0)
Analyzed for safety:		
Adverse events	149 (100)	88 (100)
Laboratory data	134 (89.9)	84 (95.5)

Sixty-three subjects had a dose reduction or temporary discontinuation due to 1 or more AEs. The majority of these subjects (61 out of 63) were receiving ziprasidone and all but 3 of these subjects had a dose reduction (ie, 3 had temporary discontinuation) due to the AE. Nervous system disorders (primarily sedation and somnolence) were the most frequently reported AEs leading to dose reduction and most of these subjects had the AE during the dose titration phase of the study.

Figure 1. Ziprasidone Concentration Versus Time Following the First Dose of the Study For Both Study Periods (Baseline to Week 4)

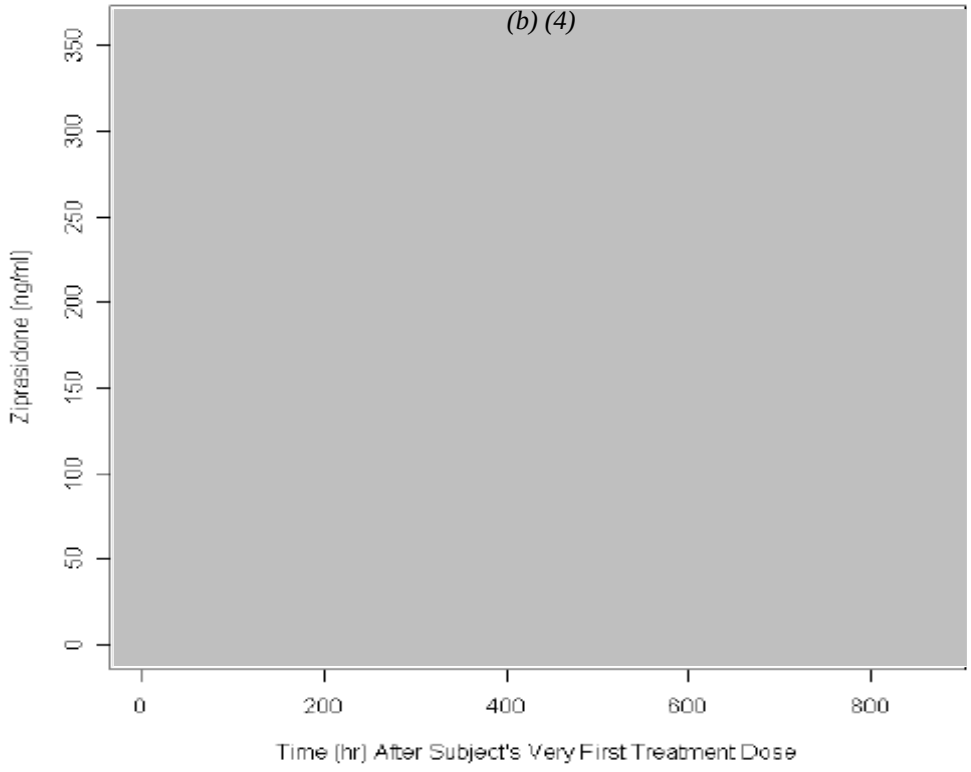
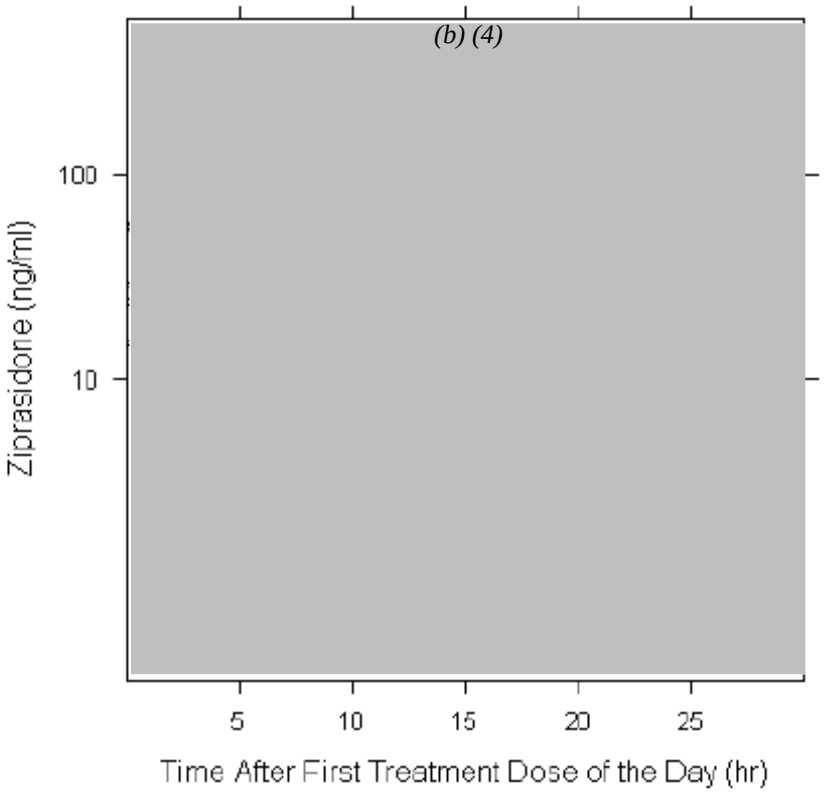


Figure 2. Ziprasidone Concentration Versus Relative Time After Morning Dose Following the First Dose of the Day For Both Study Periods (Pooled 24-hr Profile).



Best Base Structural Model

The best base pharmacokinetic model for ziprasidone was a one compartment linear model with first order input following a lag time and linear elimination (Model 34). The model was parameterized for a lag time prior to absorption (ALAG1), the first order absorption rate

constant (Ka), the apparent clearance (CL/F), and the apparent volume of distribution of the central (V2/F) compartment.
The model included variance terms for CL/F, V2/F, and included a block describing the correlation between CL/F and V2/F. The model fit log transformed data (LTBS) and used a constant coefficient of variation (CCV) plus additive residual error model. The FOCE method with interaction and SLOW options was used.

Figure 3. Schematic Diagram of Base Pharmacokinetic Model

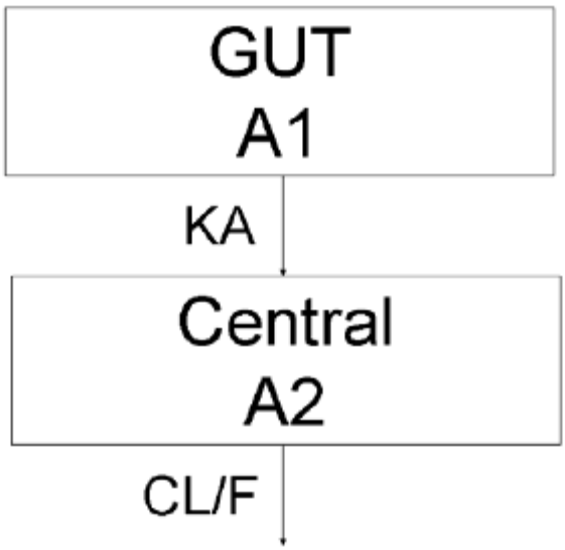


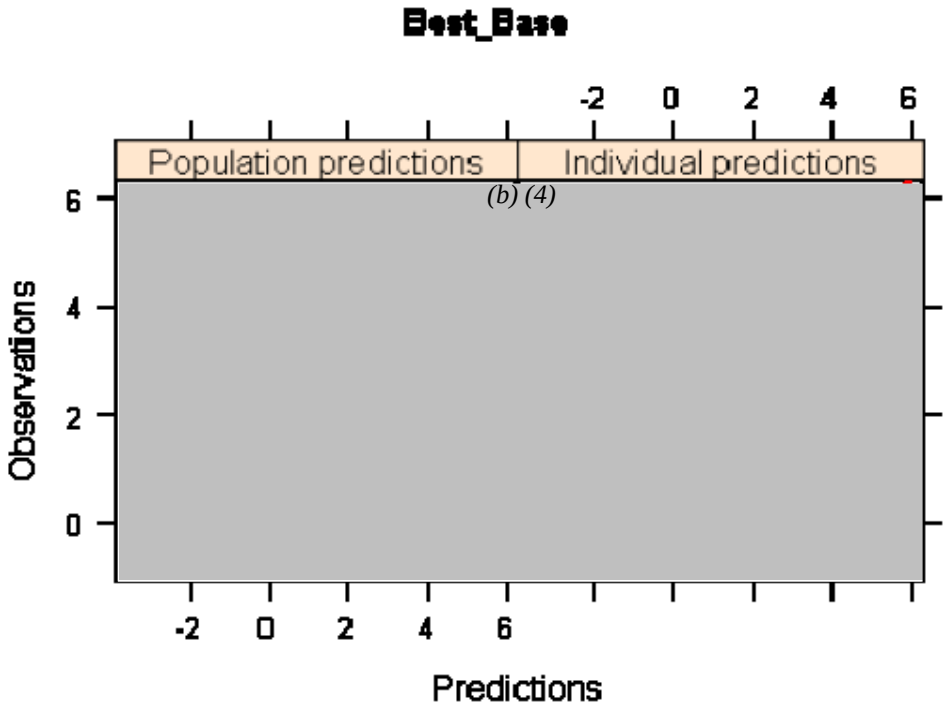
Table 2. Parameter Estimates for Base Pharmacokinetic Model

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL/F (L/h)	Θ_1	50.9 (7.7)	62.7 (17.7)
V2/F (L)	Θ_2	405 (13.9)	74.0 (20.7)
Ka (1/h)	Θ_3	0.301 (12.3)	
ALAG (h)	Θ_4	0.244 (27.4)	
LTBS (CCV + Additive) Residual Error CCV Additive	 Θ_5 Θ_6	 56.9 (13.1) 8.09 (25.5)	

* - SE given as %CV

Source: best_base.SMR

Figure 4. Ln Transformed Observed versus Typical / Individual Predicted Ziprasidone Concentrations – Base Model



The observed versus typical predicted ziprasidone concentration plot (left panel) shows that the data are generally uniformly scattered about the line of unity although there is a overprediction for the lowest concentration values.

COMMENT:

1. The data fitting and analysis was acceptable to OCP.

STUDY 1281123

Study Objectives: Primary Objective: To characterize the safety and tolerability of three dosage regimens of open-label oral ziprasidone treatment for up to 3 weeks in children and adolescent subjects (10-17 years of age) with Bipolar I Disorder (manic or mixed), schizophrenia or schizoaffective disorder.

METHODS

The study consisted of a Screening Period to determine subject eligibility and two open-label periods; Period 1 (low or high dose, fixed titration) and Period 2 (flexible dosing). Period 1 was designed to evaluate the safety and tolerability of different titration regimens of open-label ziprasidone over the initial 3 weeks of treatment.

Dosing:
Period 1 lasted 21 days (through Week 3 Visit or end of therapy in Period 1) and was designed to evaluate the safety and tolerability of different fixed titration schedules of ziprasidone. Open-label, oral suspension ziprasidone was used in this period and the use of concomitant mood stabilizers, antidepressants, or stimulants were prohibited. Subjects could discontinue early from Period 1 and still enter Period 2, safety permitting. Qualified subjects were randomized to either Group 1 or Group 2.
• Group 1 (low dose; 10-day fixed titration): Started at 10 mg BID; titrated up sequentially by 10 mg BID increments to 40 mg BID to achieve the maximum dose by Day 10.
• Group 2 (high dose; 10-day fixed titration): Started at 20 mg BID; titrated up sequentially by 20 mg BID to 80 mg BID to achieve the maximum dose by Day 10.

In Period 1, subjects randomized to Group 1 (low dose; 10-day titration) started at 10 mg BID and titrated up sequentially by 10 mg BID increments to 40 mg BID to achieve the maximum dose by Day 10. Subjects in Group 2 (high dose; 10-day titration) started at 20 mg BID and titrated up sequentially by 20 mg BID to 80 mg BID to achieve the maximum dose by Day 10. **Oral suspension was used in Period 1.** In Period 1, subjects with a body weight ≤45 kg received half the designated doses of

ziprasidone, but were titrated within the same 10-day regimen.

In Period 2, subjects could switch to capsules or remain on oral suspension. Subjects were required to adhere strictly to the dosing schedule of their assigned treatment group and to remain on the maximum dose for the duration of Period 1. Subjects who could not meet these requirements were terminated early from Period 1 and entered Period 2, safety permitting. Drug administration in Period 2 involved a flexible titration of ziprasidone (10 – 80 mg BID) and was based on the individual needs of the subjects, as determined by the investigator.

DEMOGRAPHICS

Table 1. Demographic Characteristics By Treatment Group

	Low Dose		High Dose	
Sex				
Male	12		30	
Female	11		10	
Age (years)				
10-13	11		19	
14-15	5		7	
16-18	7		14	
Mean	13.6		14.0	
SD	2.2		2.3	
Range	10 – 17		10 - 17	
Race				
White	20		33	
Black	2		7	
Other	1		0	
Weight (kg)	**Males**	**Females**	**Males**	**Females**
Mean	57.8	57.5	63.9	56.6
SD	18.2	12.4	21.6	11.2
Range	37.5 – 92.7	34.9 – 76.2	30.9 – 113.2	43.1 – 75.0
Body Mass Index[1]				
Mean	22.0	22.8	23.7	22.1
SD	4.5	2.8	4.8	4.9
Range	15.4 – 28.3	18.3 – 28.0	16.7 – 35.7	17.5 – 30.6
Height (cm)				
Mean	160.6	157.8	161.9	160.2
SD	10.5	10.3	14.0	3.8
Range	139 – 181	138 – 169	135 – 183	153 – 167

Source: Table 13.2.1.1; [1]BMI = weight /(height x 0.01)^2

Analytical Study 1281123

Study	1st PK Sample Collected	Last PK Sample Collected	Begin Analysis	End Analysis	Total Storage (Days)
Study 1281123	December 3, 2003	May 16, 2005	June 2004	June 3 2005	547

Parameter	Ziprasidone
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	*(b) (4)*
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	

Pharmacokinetic Sampling

Serum samples were obtained at the following scheduled visits for the purpose of determining serum concentrations of ziprasidone and the major metabolites, S-methyldihydroziprasidone (M9) and ziprasidone sulfoxide (M10): At Week 3/end of therapy in Period 1, a trough sample

(taken immediately prior to the morning dose) and a peak sample (taken 5-7 hours after the morning dose) were obtained. Additional PK samples were obtained at random at Weeks 1, 12, and 27/end of therapy in Period 2, at only 1 time-point per visit. When possible,

samples were to be obtained from fasted subjects (at least 8 hours fasting prior to sample taken).

Pharmacokinetic Model Evaluation

All evaluable pharmacokinetic concentration-time data from Pfizer study A1281123, which assessed the effect of ziprasidone on pediatric patients with schizophrenia during acute phase episodes, were evaluated using the software program NONMEM (Version V Level 1.1).
A pharmacokinetic model derived previously was applied
to the dataset to obtain individual estimates of pharmacokinetic parameters, as well as individual and typical predicted concentration-time profiles. This was performed using the NONMEM command MAXEVALS=0 (maximum *a posteriori* Bayesian assessment). The typical and individual concentration predictions were graphically compared to the actual observed concentrations. The individual estimates of clearance were compared to those obtained previously in the retrospective pooled assessment.

The model describing the pharmacokinetics of ziprasidone was initially developed in a different retrospective evaluation ("Retrospective Pooled Population Pharmacokinetic and Pharmacodynamic Analysis of Ziprasidone"). Data from 6 studies were pooled (Pfizer studies 044, 122, 109, 114, 115, 303, and 1037) for this analysis.
The pharmacokinetic data were best described by a one compartment model with first order input and elimination. The model was parameterized for apparent clearance (CL/F), apparent volume of distribution (V/F) and the absorption rate constant (Ka). Inter-individual variability was described using an exponential function for CL/F, V/F and Ka. The inter-individual variability parameters were found to be nearly independent, so there were no terms describing the correlation of these parameters. Random residual variability was described using a combined additive and constant coefficient of variation (CCV) model.

RESULTS

A total of 56 subjects moved from Period 1 into Period 2 (flexible dosing) as per the protocol. Of the 56 subjects who entered Period 2, 22 subjects entered from the low dose treatment group and 34 subjects entered from the high dose treatment group. Table 2 below, summarizes the disposition of all subjects

Table 2. Subject Disposition

		Period 1		Period 2	
		Low Dose	High Dose	From Low Dose	From High Dose
All Subjects	63				
Treated		23	40	22	34
Completed		17 (74%)	21 (53%)	16 (73%)	15 (44%)
Discontinued		6 (26%)	19 (48%)	6 (27%)	19 (56%)
Analyzed for Safety					
Adverse events		23 (100%)	40 (100%)	22 (100%)	34 (100%)
Laboratory		22 (96%)	36 (90%)	19 (86%)	33 (97%)
Bipolar Disorder I	46				
Treated		15	31	14	25
Completed		11 (73%)	17 (55%)	8 (57%)	11 (44%)
Discontinued		4 (27%)	14 (45%)	6 (43%)	14 (56%)
Schizophrenia/Schizoaffective	17				
Treated		8	9	8	9
Completed		6 (75%)	4 (44%)	8 (100%)	4 (44%)
Discontinued		2 (25%)	5 (56%)	0	5 (56%)

Group 1 = Low Dose; Group 2 = High Dose

The pharmacokinetics of ziprasidone were found to be influenced by age and weight. Clearance was affected by both age and weight, and absorption was influenced by age. Other covariates were evaluated but were not found to impact the pharmacokinetics of ziprasidone. The final model also included a separate lag time, relative bioavailability and absorption rate constant for the oral suspension data, as well as a relative bioavailability term for the oral suspension data. The equations for the typical values of the parameters in the final model are given below and the parameter estimates and their associated standard deviations are given in Table 3.

$$\frac{CL}{F} = \theta_1 \bullet \left(\frac{WT}{70}\right)^{\theta 4} \bullet \left(\frac{AGE}{50}\right)^{\theta 5} \bullet \exp(\eta_1)$$

$$\frac{V2}{F} = \theta_2 \bullet \exp(\eta_2)$$

$$Ka = \theta_3 \bullet \left(\frac{AGE}{50}\right)^{\theta 6} \bullet \exp(\eta_3)$$

$$Ka_{OralSuspnsion} = \theta_7 \bullet \exp(\eta_4)$$

$$ALAG1 = \theta_8^{Formulatio}$$

$$F1 = \theta_9^{Formulatio}$$

In these equations, "Formulation" was set to 0 for the capsule and 1 for the oral suspension.

Table 3. Ziprasidone Best Pharmacokinetic Model Parameters for Capsule and Oral Suspension

Parameter (Units)		Population Mean
CL/F (L/h)	T_1	49.3
Effect of Weight	T_2	0.46
Effect of Age	T_3	0.0747
V/F (L)	T_4	68.1
Ka Capsule (h-1)	T_5	0.065
Effect of age	T_6	-0.253
Ka Oral Suspension (h-1)	T_7	0.109
ALAG1 Oral Suspension (h)	T_8	1.41
F1 Oral Suspension (%BA)	T_9	0.889
CCV Residual Error (%CV)		
Additive Residual Error (ug/L)		

* - given as %CV NE – not estimated

Figure 1. Empirical Bayesian Estimated Clearance versus Typical Predicted Clearance

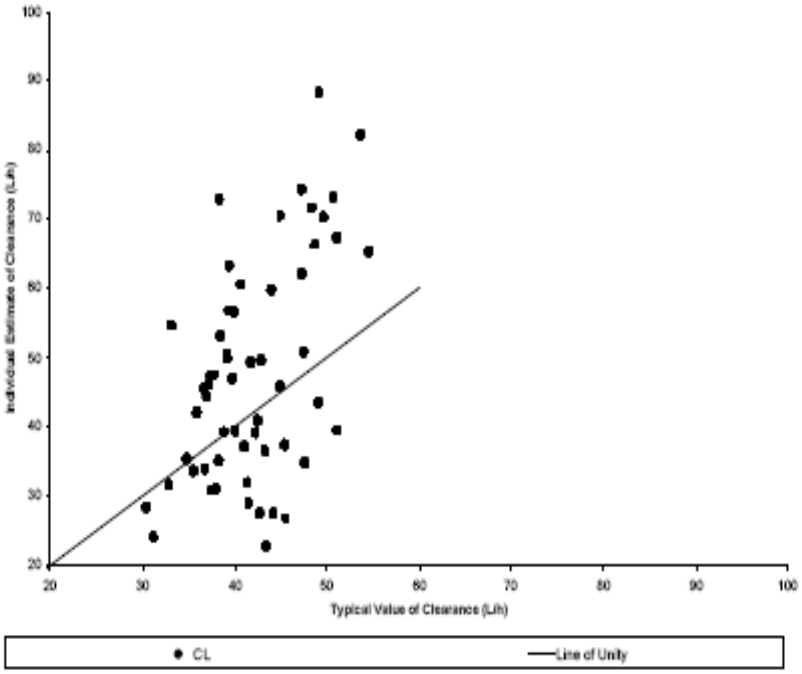
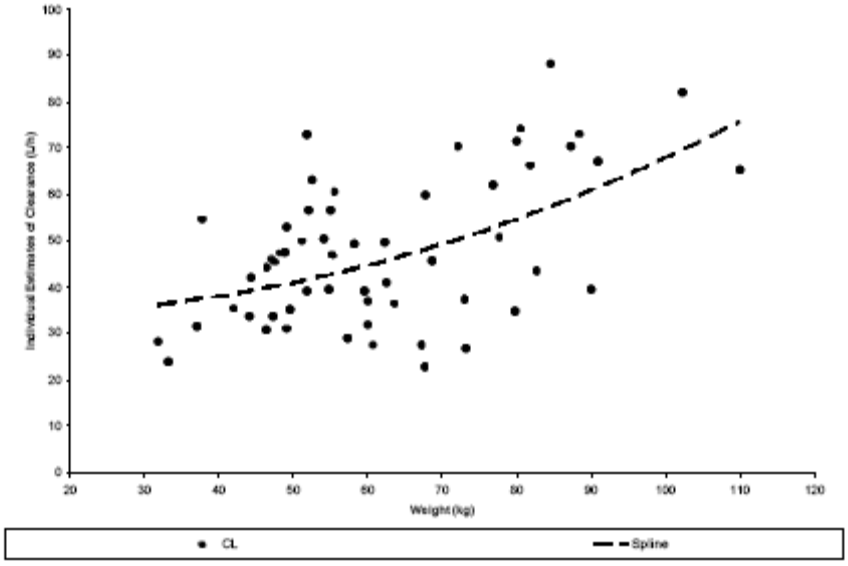


Figure 2. Empirical Bayesian Estimated Clearance versus Weight



Typical Predicted Concentrations based upon post-hoc analysis-Analysis done by OCP

Figure 3. Regression of DV vs predicted value based upon the empirical bayesian estimates for the capsule data.

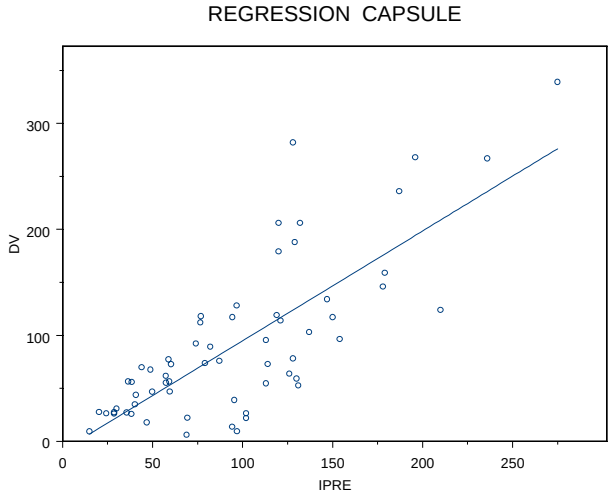


Figure 4. Regression of DV vs predicted value based upon the empirical bayesian estimates for the oral suspension data.

Comments:

1. The post-hoc fits by the firm show a definite trend towards overpredicting the true data Figure 3 and Figure 4 (prepared by FDA) and over-predicting the typical predicted clearance Figure 1.
2. However, the overall quality of the predictions are close enough and should not overly influence other predictions using these parameters.

PROTOCOL 128-044

PHASE I OPEN, SINGLE DOSE, ORAL STUDY TO EVALUATE THE PHARMACOKINETICS OF ZIPRASIDONE IN CHILDREN AND ADOLESCENTS WITH TOURETTE'S SYNDROME

STUDY OBJECTIVES

The purpose of this study was to evaluate the pharmacokinetics and safety of a single oral dose of ziprasidone hydrochloride in children and adolescents who have either TS (Tourette's Syndrome) or CTD (Chronic (Motor or Vocal) Tic Disorder).

Methods

This was an open trial of single oral doses of ziprasidone, given as a suspension formulation following consumption of a standardized breakfast.

Subjects meeting entry criteria were assigned a study identification number that was retained throughout the study. Subjects were assigned to groups of 8 based on body weight. Subject groups 1 (>60 kg body weight), 2 (31-60 kg body weight), and 3 (16-30 kg body weight) were assigned doses of 20 mg, 10 mg, and 5 mg, respectively.

Twenty-four subjects (19 male, 5 female) entered and completed this study. Eight subjects were assigned to one of three groups, based on subject weight.

Table 1. Demographic characteristics

Demographic Characteristics

	Group 1 (20 mg)		Group 2 (10 mg)		Group 3 (5 mg)	
	Males	Females	Males	Females	Males	Females
Number of subjects	7	1	5	3	7	1
Mean Age (years)	14.1	14.0	10.2	12.3	7.7	7.0
Age Range	11-16	14	7-13	11-13	7-9	7
Mean Weight (kg)	62.8	67.6	39.1	42.8	25.7	26.5

Source: Table 2.1.1

Analytical Study 128-044

Study	1st PK Sample Collected	Last PK Sample Collected	Begin Analysis	End Analysis	Total Storage (Days)
Study	June 19, 1996	April 20, 1997	1/17/97	2/19/98	216 days

Parameter	Ziprasidone
Method	LC-MS/MS
Sensitivity/LOQ	1 ng/mL
Linearity (Standard curve samples)	*(b) (4)*
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	

Pharmacokinetic Sampling

Blood samples sufficient to provide 2.5 ml of serum were collected in tubes containing no preservative, anticoagulant, or serum separator from each subject immediately prior to (time zero), and 1, 2, 4, 6, 8, 12, 16, 24, and 32 hours after study drug administration.

Statistical and Analytical Plans

Pharmacokinetic and safety results were summarized using descriptive statistics and graphical presentations. Geometric means and standard deviations were calculated for Cl/F, AUC(0-∞), AUC(0-t), and Cmax. Arithmetic means and standard deviations were calculated for Tmax and Kel. Mean T1/2 was calculated as 0.693/mean Kel.

Serum concentrations were plotted as a function of time. No specific statistical hypotheses were tested.

RESULTS

Table 2. Summary or pharmacokinetic parameters for subjects with Tourette's Syndrome.

Syndrome or CTD

			Mean (%CV) of Pharmacokinetic Variables						
	N	BW (kg)	Dose (mg/kg)	AUC(0-∞)[a] (ng•hr/ml)	Cmax[a] (ng/ml)	Tmax (hr)	Kel (1/hr)	T 1/2[b] (hr)	Cl/F (ml/min/kg)
Group 1 20 mg	8	63.4(6)	0.32(6)	457(25)	51(44)	5.5(57)	0.171(21)	4.1	11.5(21)
Group 2[c] 10 mg	7	40.8(25)	0.26(22)	338(30)	45(45)	5.1(21)	0.210(27)	3.3	12.4(19)
Group 3 5 mg	8	25.8(8)	0.20(9)	247(30)	36(38)	5.0(57)	0.213(45)	3.3	13.1(27)

(Source: Tables 5.2.1 and 5.2.3)

BW = Body weight

[a] geometric mean

[b] $T_{1/2}$ = 0.693/mean K_{el}

[c] Summary statistics exclude Subject 7440011. Exclusion was based on systemic exposure being greater than 8 times the Group 2 mean. Pharmacokinetic data for this 13 year old female subject were as follows: Body weight: 38.3 kg; dose: 0.26 mg/kg; AUC(0-∞): 3748 ng·hr/ml; Cmax: 366 ng/ml; Tmax: 4.0 hr; Kel: 0.240 1/hr; T1/2: 2.9 hr; Cl/F: 1.2 ml/min/kg.

Figure 1. Ziprasidone AUC(0-inf) Values Versus Dose (mg/kg) in Tourette's Subjects Receiving Single Oral Doses of Ziprasidone

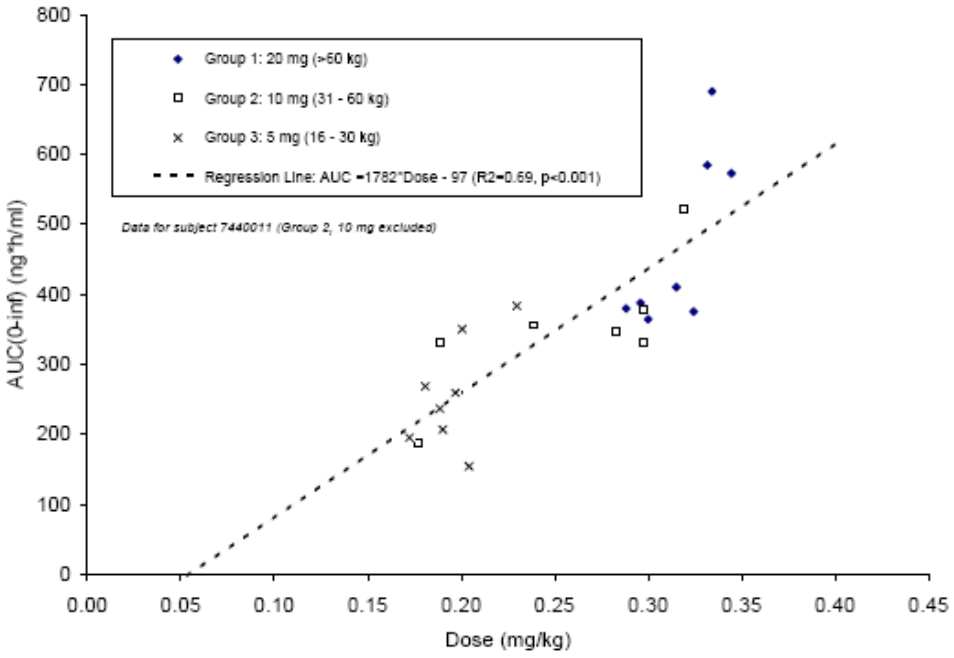
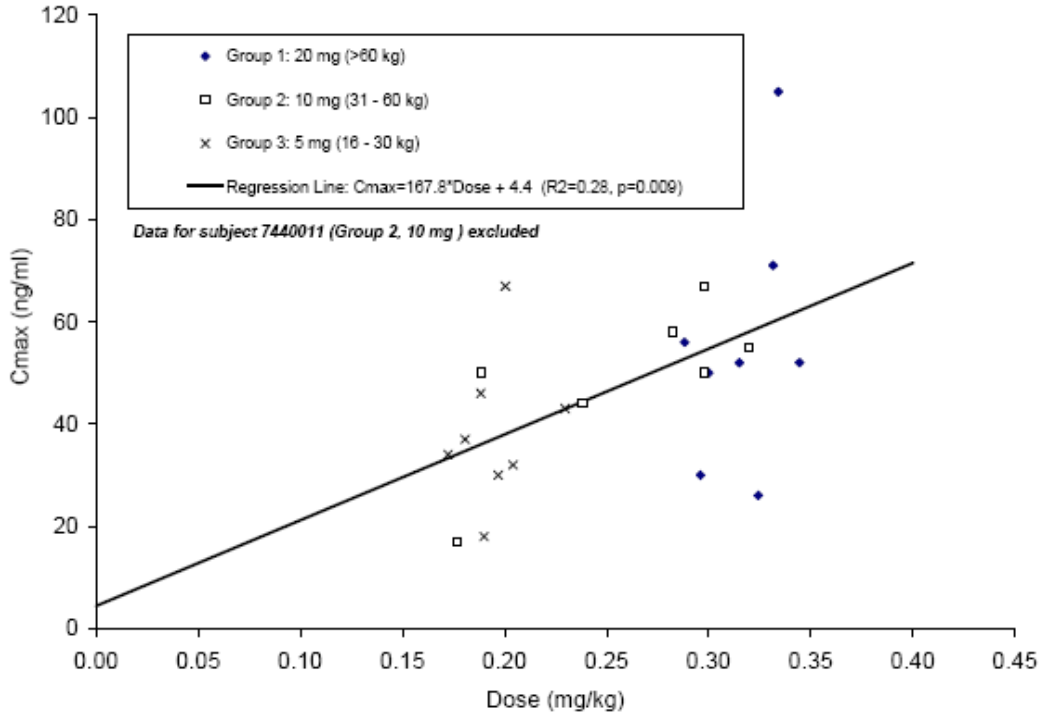


Figure 2. Ziprasidone Cmax Values Versus Dose (mg/kg) in Tourette's Subjects Receiving Single Oral Doses of Ziprasidone



COMMENTS:

Across the range of mean ages (7.6 to 14.1) and mean body weights (25.8 kg to 63.4 kg) included in this study, oral clearance, Tmax, and terminal elimination half life were comparable across study groups. Exposure to ziprasidone increased in a linear fashion for Cmax but not for AUC with increasing weight-adjusted dose. There appears to be some initial saturation for AUC followed by a linear increase with dose.

PROTOCOL 128-122

PHASE II, EIGHT WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY EVALUATING THE TOLERATION, SAFETY, AND EFFICACY OF ORAL ZIPRASIDONE (CP-88,059-1) IN CHILDREN AND ADOLESCENTS WITH TOURETTE'S SYNDROME

STUDY OBJECTIVES

The purpose of this study was to evaluate the safety, efficacy, and pharmacokinetics of 56-day treatment with flexible escalating oral doses of ziprasidone (from 5 mg once daily to a maximum of 20 mg twice daily) in children and adolescents with Tourette's syndrome (TS) or chronic motor or vocal tic disorder (CTD), and to establish the tolerated dose range in these subjects.

MATERIALS AND METHODS

Study Design

Protocol 128-122 was a double-blind, randomized, parallel group, placebo-controlled study of flexible escalating oral doses of ziprasidone in children and adolescents with moderate to severe TS or CTD.

Ziprasidone and placebo were supplied as identical capsules providing either 5 mg or placebo, 10 mg or placebo, or 20 mg or placebo.

Doses of ziprasidone or placebo were administered orally twice daily (BID) with food approximately twelve hours apart (at breakfast and bedtime), except for days 1-3 when subjects received either the starting dose of 5 mg ziprasidone or placebo at bedtime only. Following the initial 3 day period, subjects receiving ziprasidone were titrated every 3-4 days to a maximum dose of 40 mg daily (one 20 mg ziprasidone and one placebo capsule BID). Initial dosage increments were limited to 5 mg, and the maximum dosage increment was 10 mg. Dose escalation was completed by day 22 of the study; however, in any individual subject dosage escalation may have been allowed to proceed more slowly, dosage was reduced, or subjects were maintained at any dose level for any length of time dependent on efficacy, toleration, and the site investigator's clinical judgment.

Demographics

Demographic Characteristics
Ziprasidone Protocol 122

	Ziprasidone			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects	14	2	16	8	4	12
Age (years):						
<18	14	2	16	8	4	12
Mean age (years)	11.1	12.5	11.3	12.0	11.5	11.8
Age range	7-14	11-14	7-14	8-16	10-13	8-16
Race:						
BIRACIAL	0	0	0	1	0	1
BLACK	1	0	1	0	0	0
WHITE	13	2	15	7	4	11
Mean weight (kg)	47.1	51.1		44.0	44.0	
Weight range	27-96	35-68		25-71	35-58	

Analytical Study 128-122

Study	1st PK Sample Collected	Last PK Sample Collected	Begin Analysis	End Analysis	Total Storage (Days)
Study	June 28, 1996	April 25, 1997	June 9, 1997	June 12, 1997	346

Parameter	Ziprasidone
Method	LC-MS/MS
Sensitivity/LOQ	1 ng/mL
Linearity (Standard curve samples)	*(b) (4)*
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	

Pharmacokinetic sampling

Serum samples were collected from each subject at screening and immediately prior to the administration of the morning dose of study drug on days 8 and 57. Serum samples were also collected at a randomly selected sampling interval (2-4 hours, 4-6 hours, or 6-8 hours) following the administration of the morning dose on days 29 and 57.

Pharmacokinetic Analysis

The ziprasidone serum concentration data from this study were compared to a two compartment pharmacokinetic model that was developed using the software NONMEM Version 4 Level 2.1 using an extended least-squares algorithm with data from 89 samples collected from 10 subjects between the ages of 8 and 16 who participated in a previous single dose ziprasidone study. This methodology used mixed-effects models which describe pharmacokinetic observations by including terms for both fixed effects and random effects. Fixed effects (Θ) included dose, time, pharmacokinetic parameters (clearance, volume of distribution, absorption coefficient, absorption lag time), and parameters that measured the influence of covariates (age, weight, gender). Two types of random effects were considered. One was the interindividual variability (η) across the population sampled, which provided a measure of the population variance of a given pharmacokinetic parameter. The residual intrasubject variability (ε) considered effects due to random fluctuations on an individual's pharmacokinetic parameter values and measurement errors such as inaccuracies in time of dosing or sample collection, assay errors, and model specification error.

RESULTS

Figure 1. Observed Serum Ziprasidone Concentrations vs Time post-dose (Clinical Study #128-122)

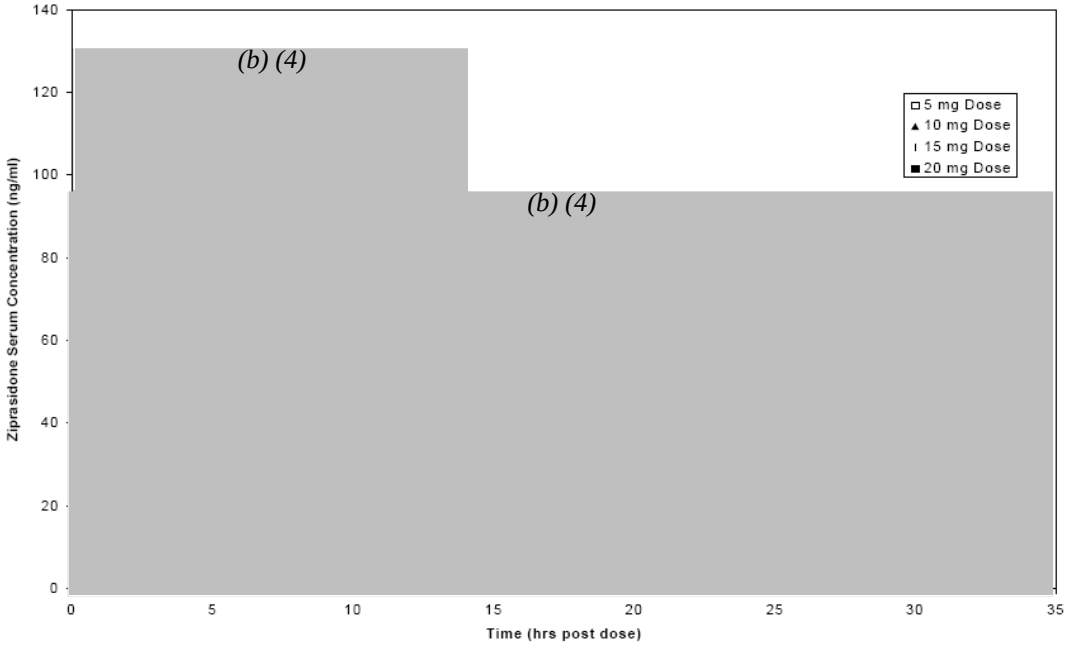


Figure 2. Population Prediction and Observed Ziprasidone Concentration (ng/ml) vs Time Post Dose (hr) Following Twice Daily Doses of 5 mg of Ziprasidone to Subjects Less Than 10 years old. (Clinical Study #128-122)

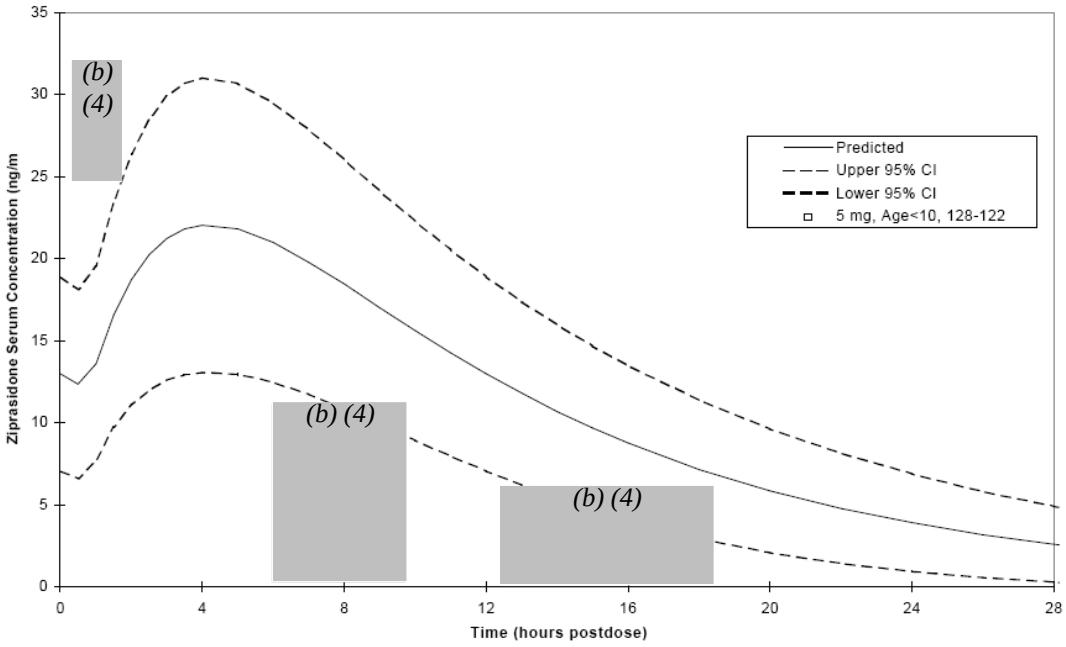


Figure 3. Population Prediction and Observed Ziprasidone Concentration (ng/ml) vs Time Post Dose (hr) Following Twice Daily Doses of 5 mg of Ziprasidone to Subjects Greater Than 10 years old.

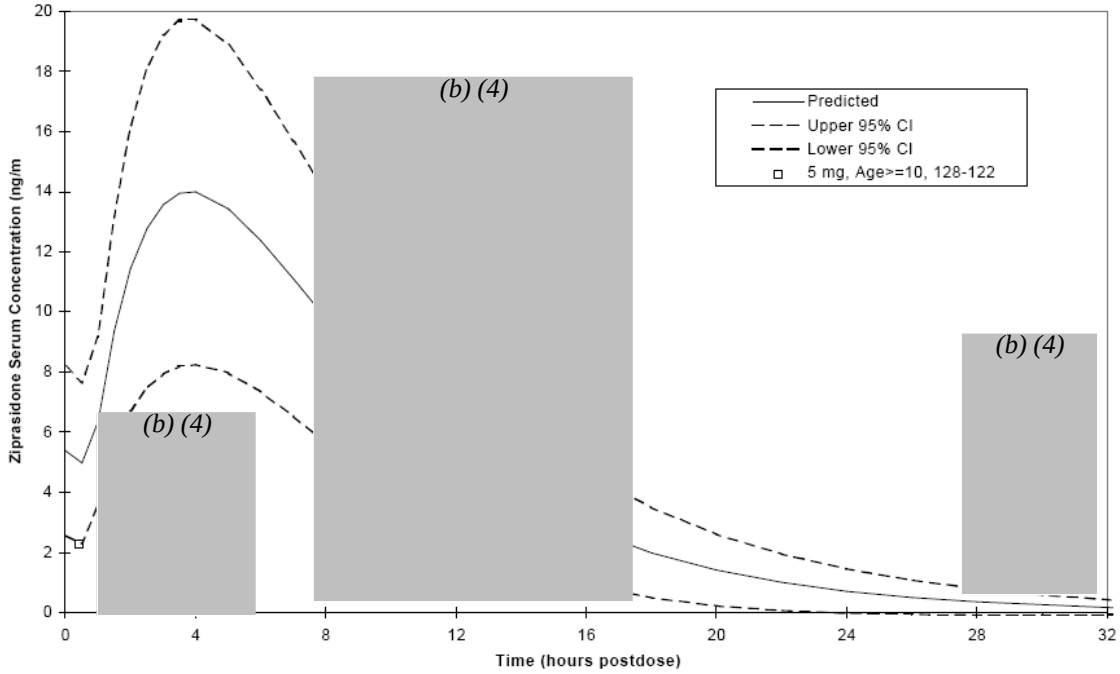


Table 4. Estimated Population Pharmacokinetic Parameters.

Subject #	Gender	Age (yr)	WT (kg)	HT (cm)	CL/F (L/hr)	V2/F (L)	K_a (/hr)	ALAG1[a] (hr)	K^b_e (/hr)	$T^c_{1/2}$ (hr)
7420006	Male	14	60.1	168						
7430011	Male	14	95.9	165						
7430013	Male	11	42.7	140						
7430014	Male	14	53.8	165						
7430036	Male	14	60.0	173						
7440018	Male	7	32.8	132						
7440019	Female	11	34.6	145						
7440020	Male	10	34.4	140						
7440026	Male	8	31.2	130						
7440029	Female	14	67.7	157						
7440030	Male	10	29.2	127						
7440031	Male	14	59.0	180						
7440032	Male	8	26.8	135						
7440033	Male	8	29.4	137						
7440041	Male	11	60.4	145						
7440043	Male	12	43.0	155						
Mean		11	48	150	33.9	185.6	0.41	0.8	0.188	3.9
S.D.		3	18.9	17	7.3	41.2	0.41	0.1	0.044	0.9
Min		7	27	127						
Max		14	96	180						

(b) (4)

(b) (4)

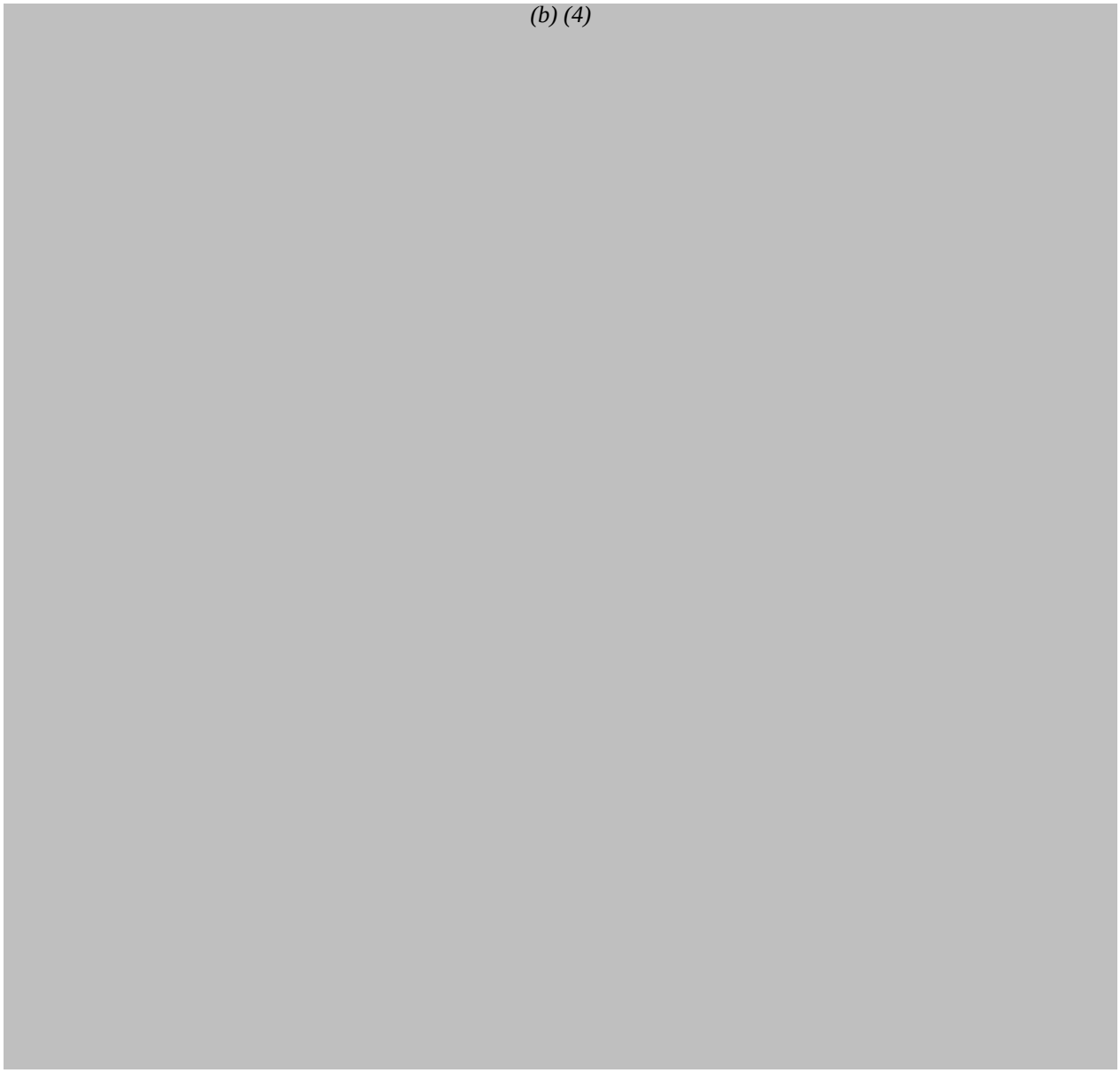
COMMENTS:

The data presented by the firm shows that serum levels of ziprasidone were generally related to dose. However , observed levels for many of the doses were outside of the 95% confidence intervals (i.e., doses at 10 mg and 20 mg not presented) which raises some question about the applicability of the previously developed pharmacokinetic model. Therefore it is difficult to support the firm's claims of clearance appearing to be related to both age and subject weight, with age being the better predictor for this study.

FIRM'S PROPOSED LABEL

(b) (4)

(b) (4)



OCP COMMENTS ON PROPOSED LABEL:

1. Based upon the appended pharmacometric report, OCP agrees with the firm's proposed label.

PHARMACOMETRIC REVIEW

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Ziprasidone
PRODUCT (Brand Name):	Geodon
DOSAGE FORM:	Capsules
DOSAGE STRENGTHS:	20 mg, 40 mg, 60 mg, 80 mg capsules
NDA:	20825 SE5032
NDA TYPE:	Pediatric Supplement
SUBMISSION DATE:	October 21, 2008
SPONSOR:	Pfizer
REVIEWER	Andre Jackson
PM SECONDARY REVIEWER	Hao Zhu

Office of Clinical Pharmacology:
Pharmacometric review

Summary of Findings
Key Review Questions
The purpose of this review is to address the following key question.

Can we support labeling language for dosing and administration with the data and Pharmcokinetic analysis submitted by the sponsor?
The firm's recommendations for maintenance dosing are, *(b) (4)*

(b) (4)

”

The label is supported by the submitted data.

The analysis of calculated Cmin and AUC values for adult studies (A1281037, 128-109, 128-114, 128-115, and 128-303) when compared to pediatric studies 128-044, 128-122, A1281132, and A1281123 shows that the exposures are comparable for high dose (40 and 80 mg) and low dose (20 and 40 mg) groups across the weight groups.

Figures 1 and 2 show respectively the Cmin exposures for the high dose and low dose in all subjects (i.e., children, adolescents and adults).

Figure 1.

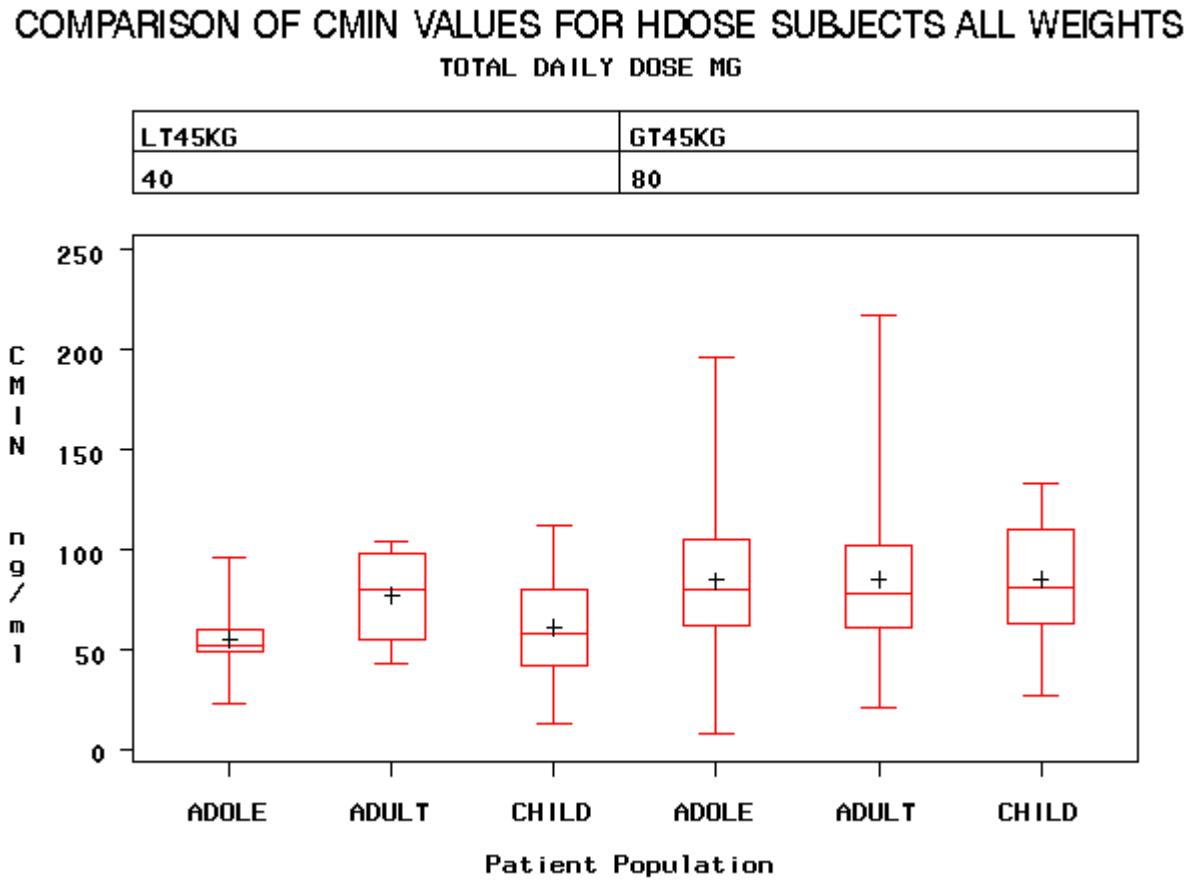
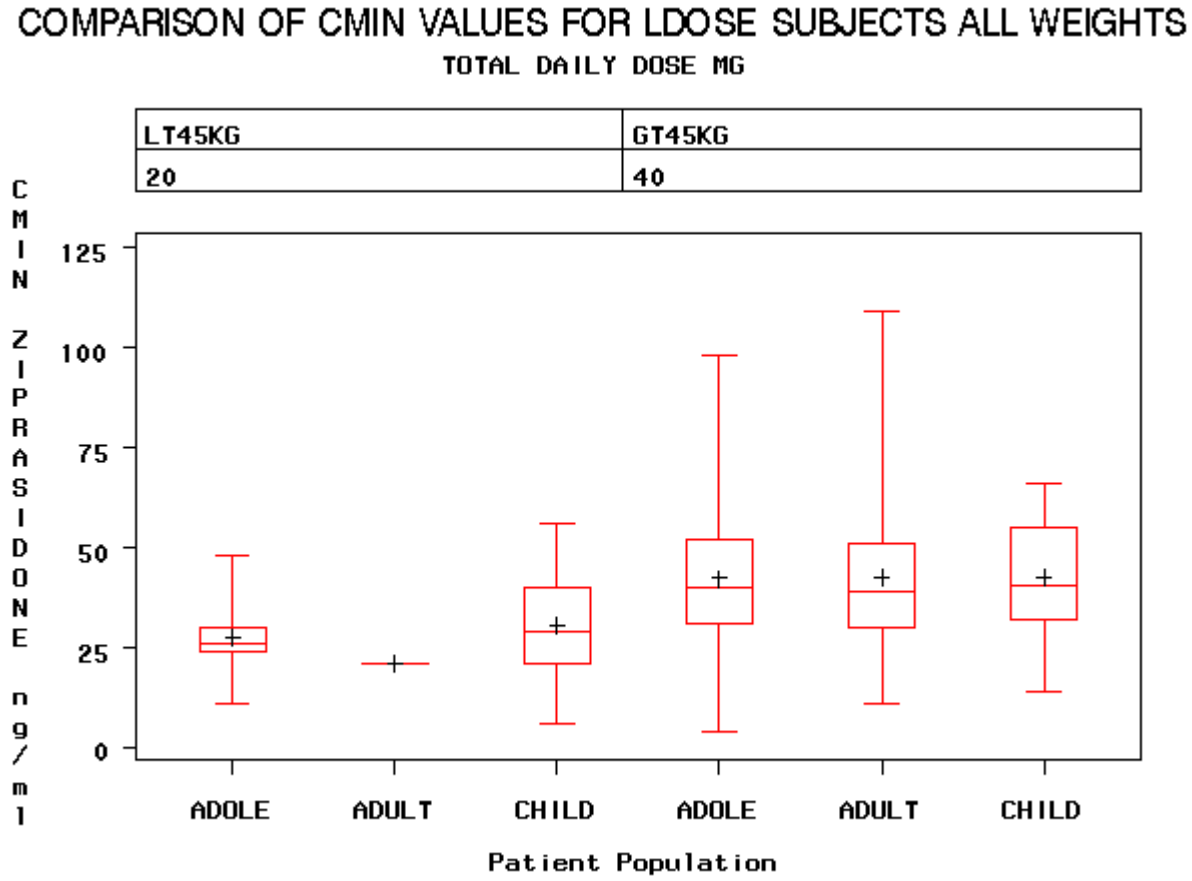


Figure 2.



Graphs for the AUC low and high doses in all subjects are presented on pages 27 and 28 of this review. AUC also shows comparable exposures in children, adolescents and adults for high doses groups and low dose groups.

1.1.2

Does the Ziprasidone Clinical endpoint YMRS (i.e., Young Mania Ratings Score) exhibit a dose response in children and adolescents?

Figures 3 and 4 indicate that there is no dose response for subjects with weights below 45 kg or those with weights greater than or equal to 45 kg.

Figure 3. Effect of dose on the Young Mania Rating Scale for subjects with weights less than 45 kg as a function of day of dose administration in study A1281132.

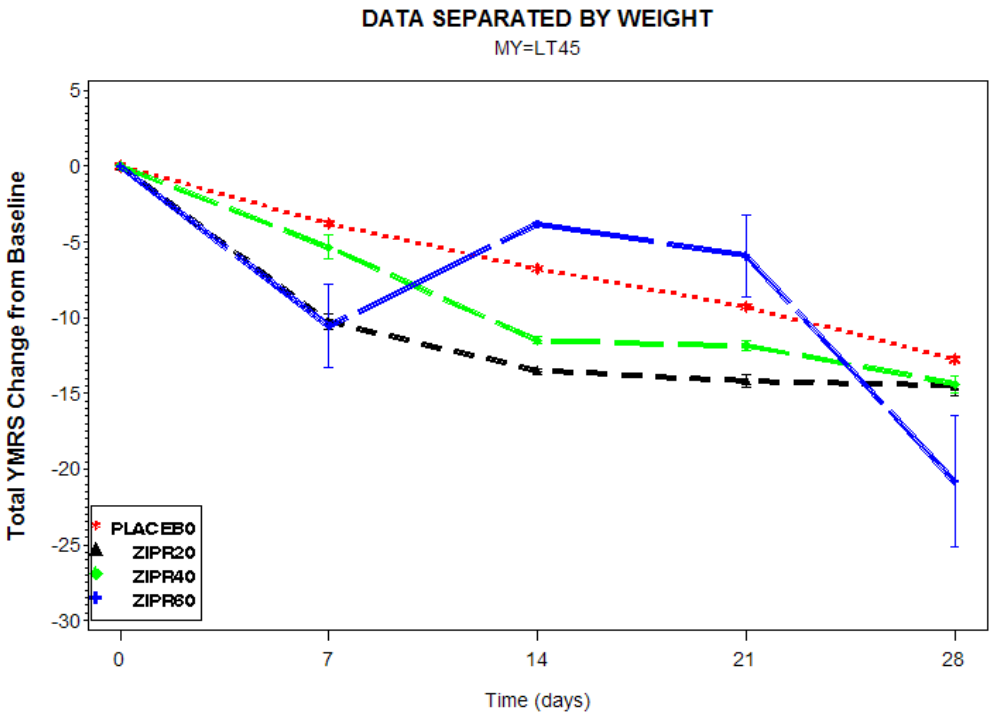


Figure 4. Effect of dose on the Young Mania Rating Scale for subjects with weights greater than or equal to 45 kg as a function of day of dose administration in study A1281132.

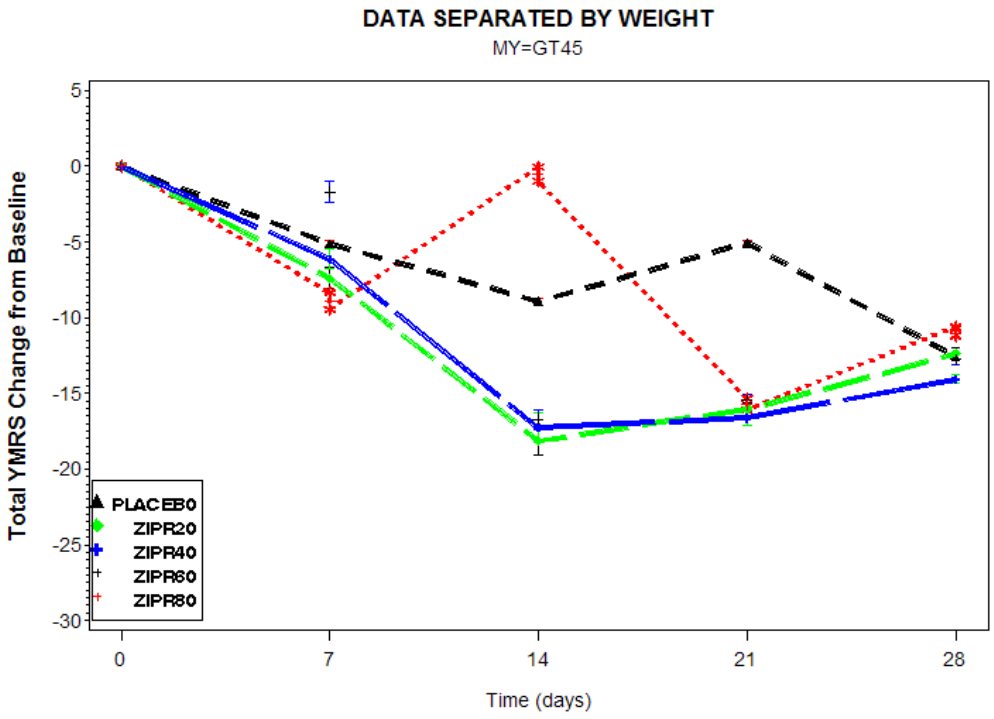
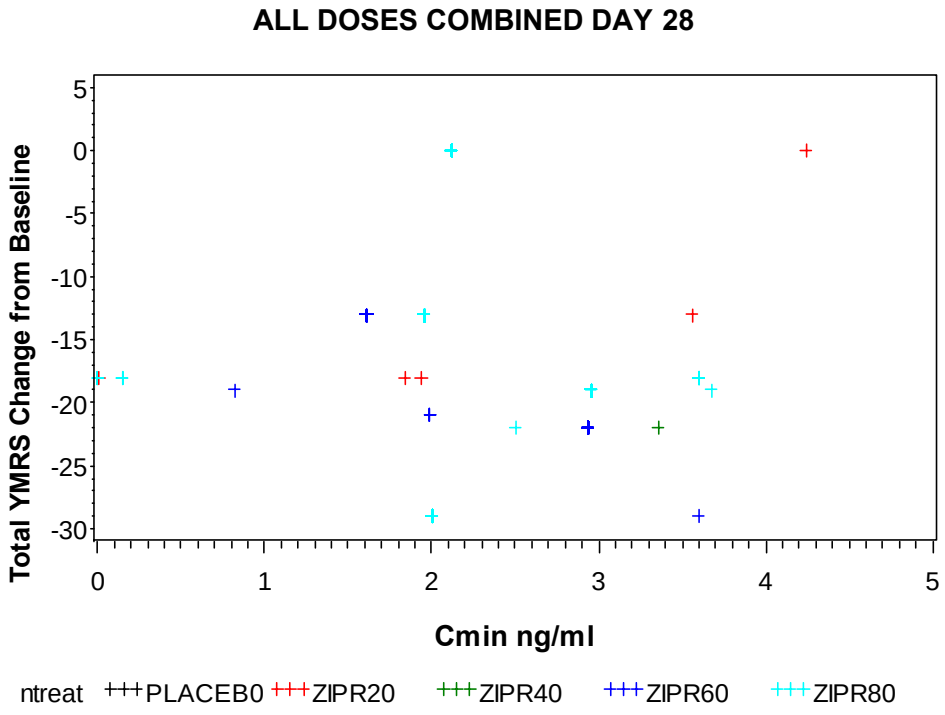


Figure 5. Comparison of observed Cmin values from study A1281132 versus the total YMRS score on final study day 28.



Recommendations

There is an equivalent level of exposure for Ziprasidone in children, adolescents and adults after adjusting dose based on body weight.

Label Statements

The firm's proposed labeling statement is acceptable to OCP:

(b) (4)

(b) (4)

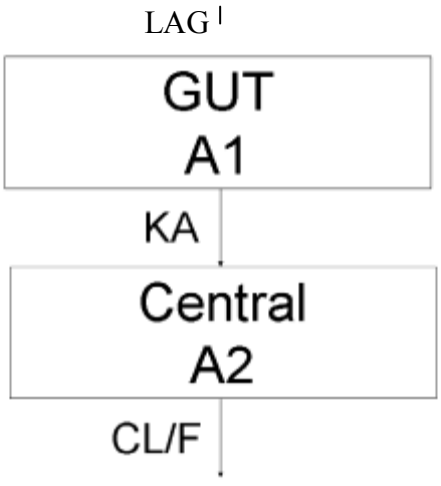
Pertinent regulatory background

The firm has conducted the studies for this NDA using an oral suspension and a capsule formulation for Ziprasidone. Ziprasidone Oral Suspension is **not bioequivalent** to the approved ziprasidone oral capsules.
A previous study by the firm has shown under fasting conditions, the Cmax and AUC(∞) were 17% and 13% lower, respectively, for ziprasidone oral suspension compared to the capsule formulation. This would not have a major impact on the results, since all studies were done under post-prandial conditions. Zaprasidone oral suspension and capsules are BE for AUC under all post-prandial scenarios. On the other hand, two studies have reported a lower CI for Cmax of 71%.

Results of Sponsor's Analysis

3.1 STUDY A1281132

Final Pharmacokinetic Model Study A1281132-Four week Placebo controlled efficacy, safety and pharmacokinetic study with flexible doses-Capsule dosage form.
The best final pharmacokinetic model for ziprasidone was a one compartment model with first order input following a lag time and linear elimination. The model was parameterized for a lag time prior to absorption (ALAG), the first order absorption rate constant (Ka), the apparent clearance (CL/F), the apparent volumes of distribution of the central compartment (V2/F).



Source:Page 42 Report A1281132

The model included the allometric effects of body weight on clearance and volume. The model included variance terms for CL/F and V2/F with an OMEGA block describing the correlation between these parameters. The model fit was on log transformed data (LTBS) and used a constant coefficient of variation (CCV) plus additive residual error model. The FOCE with interaction method and the SLOW option was used. The equations for the parameters describing this model are shown below with parameters for the final model presented in Table 1.

$$\frac{CL}{F} = \theta_1 \bullet \exp(\eta_1) \bullet \left(\frac{WT}{60}\right)^{0.75}$$

$$\frac{V2}{F} = \theta_2 \bullet \exp(\eta_2) \bullet \left(\frac{WT}{60}\right)^{1}$$

$$Ka = \theta_3$$

$$ALAG1 = \theta_4$$

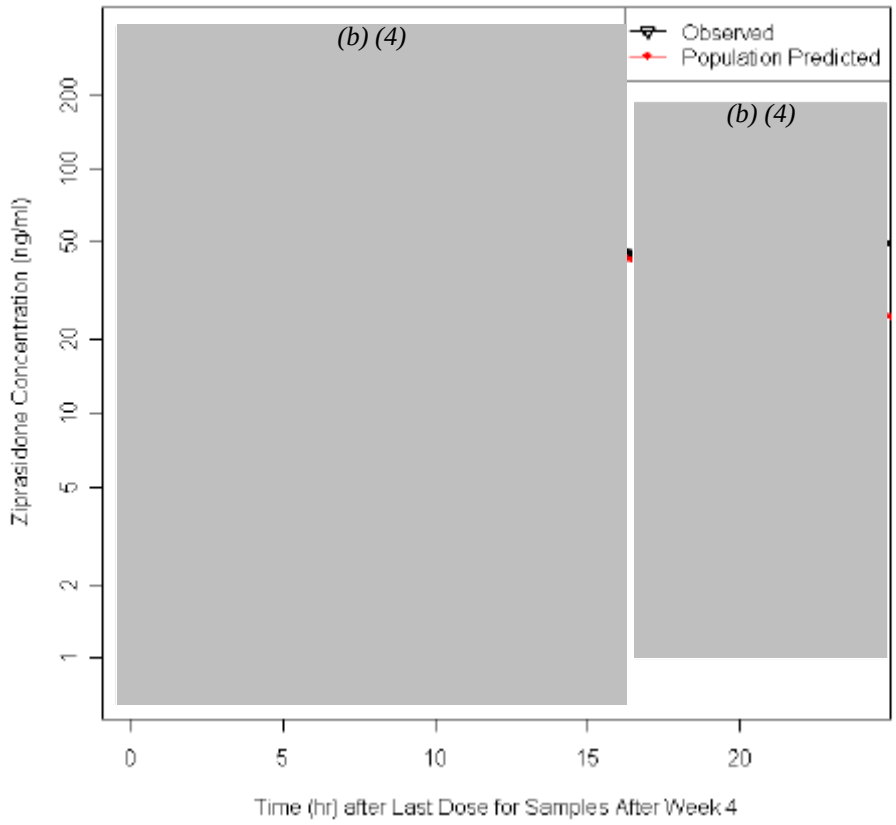
Table 1 Parameter Estimates for Final Pharmacokinetic Model-

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL/F (L/h) Effect of Weight	Θ_1	55.1 (7.4) 0.75 FIX	54.4 (19.8)
V2/F (L) Effect of Weight	Θ_2	439 (14.6) 1 FIX	70.4 (19.8)
Ka (1/h)	Θ_3	0.292 (13.1)	
ALAG (h)	Θ_4	0.259 (24.3)	
LTBS (CCV + Additive) Residual Error CCV Additive	 Θ_5 Θ_6	 56.9 (15.9) 8.34 (27.1)	

* - SE given as %CV

Source:Page 48 Report A1281132

Figure 1. Overlay of the Observed and Final Model Population Predicted Concentrations versus Time After the Last Dose For Period 2 (Greater Than or Equal to 4 Weeks)



Source:Page 52 Report A1281132
Reviewer's Comments:

Model development and model results were acceptable, however it would have been preferred for the sponsor to use the data from study A1281123 which had more extensive samples taken. Study A1281123 used an oral suspension.

3.2 STUDY A1281123
A 27 WEEK SAFETY STUDY TO EXPLORE TOLERATED DOSES-ORAL SUSPENSION

The study was a 27-Week Open-Label Trial to Characterize the Safety and Tolerability of

Orally Administered Ziprasidone in Children and Adolescent Subjects (10-17 years of age) with Bipolar I Disorder. Dosing was for group 1 (low dose; 10-40 mg BID;10-day titration) and for group 2 (high dose; 20-80 mg BID) . Thirty-eight subjects completed the study. Only the oral suspension was dosed. Subjects with a body weight ≤45 kg received half the designated doses of ziprasidone, but were titrated within the same 10-day regimen.

A pharmacokinetic model derived previously (see Section 4.2.1) was applied to the dataset to obtain individual estimates of pharmacokinetic parameters, as well as individual and typical predicted concentration-time profiles. This was performed using the NONMEM command MAXEVALS=0 (maximum *a posteriori* Bayesian assessment). The typical and individual concentration predictions were graphically compared to the actual observed concentrations.
The individual estimates of clearance were compared to those obtained previously in the retrospective pooled assessment.

The equations for the typical values of the parameters in the final model are given below and the parameter estimates and their associated standard deviations are given in Table 2.

$$\frac{CL}{F} = \theta_1 \bullet \left(\frac{WT}{70}\right)^{\theta 4} \bullet \left(\frac{AGE}{50}\right)^{\theta 5} \bullet \exp(\eta_1)$$

$$\frac{V2}{F} = \theta_2 \bullet \exp(\eta_2)$$

$$Ka = \theta_3 \bullet \left(\frac{AGE}{50}\right)^{\theta 6} \bullet \exp(\eta_3)$$

$$Ka_{OralSuspnsion} = \theta_7 \bullet \exp(\eta_4)$$

$$ALAG1 = \theta_8^{Formulatin}$$

$$F1 = \theta_9^{Formulatin}$$

In these equations, "Formulation" was set to 0 for the capsule and 1 for the oral suspension.

Source page 1515 supplemental report A1281123
\\cdsesub1\evsprod\NDA020825\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-bipolar-mania\5352-stud-rep-uncontr\a1281123

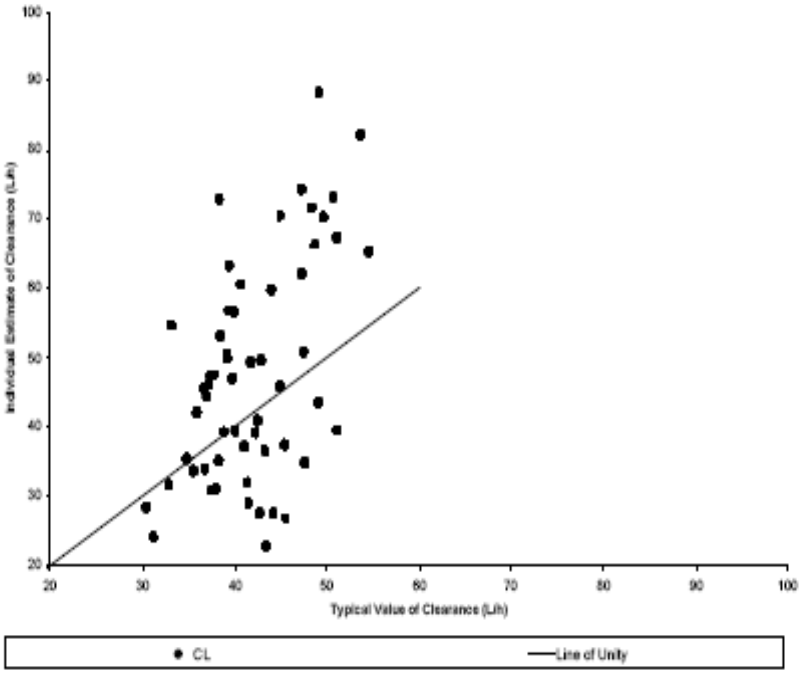
Table 1. Ziprasidone Best Pharmacokinetic Model Parameters for Oral Suspension

Parameter (Units)		Population Mean
CL/F (L/h)	T_1	49.3
Effect of Weight	T_2	0.46
Effect of Age	T_3	0.0747
V/F (L)	T_4	68.1
Ka Capsule (h-1)	T_5	0.065
Effect of age	T_6	-0.253
Ka Oral Suspension (h-1)	T_7	0.109
ALAG1 Oral Suspension (h)	T_8	1.41
F1 Oral Suspension (%BA)	T_9	0.889
CCV Residual Error (%CV)		
Additive Residual Error (ug/L)		

* - given as %CV NE – not estimated

Source page 1515 supplemental report A1281123

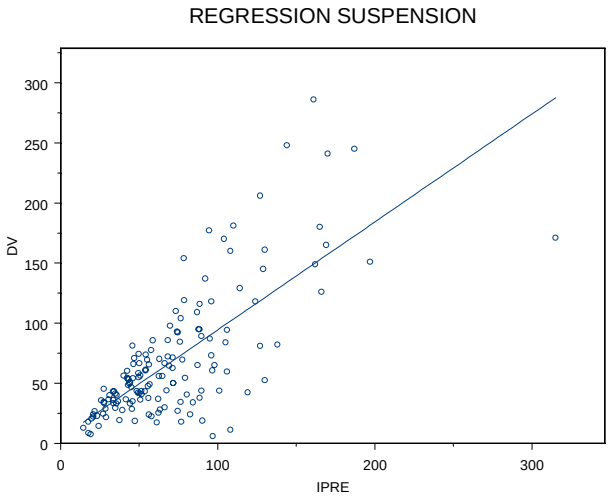
Figure 1. Empirical Bayesian Estimated Clearance versusTypical Predicted Clearance



Source page 1519 supplemental report A1281123

In the final model, the remaining inter-individual variability was relatively low although the residual error was still pronounced. In this model, the clearance of ziprasidone increases as body weight increases and also increases slightly as age increases. However, the absorption of ziprasidone decreases as age increases.

Figure 2. Plot of DV vs IPRE for oral suspension used in Study A1281123 showing that the overall predictions are a bit high for the higher concentrations (graph prepared by FDA).



Reviewer's Comments:

3. The post-hoc fits by the firm show a definite trend towards the individual values overpredicting the typical values for clearance Figure 1.
4. Figure 2 shows the suspension values were overpredicted especially at the higher concentrations. Since most of the values for solution were below 150 the data is acceptable. Better results may have been obtained if this data had been independently modeled.

3.3 Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone

OBJECTIVES

The primary objectives of this analysis were:

- To characterize the population pharmacokinetic behavior of ziprasidone in schizophrenic patients; and
- To identify any population characteristics, that may influence the pharmacokinetic behavior of ziprasidone, e.g., patient age or weight; and

The secondary objective of this analysis was:

- To use the pharmacokinetic model to determine pharmacokinetic changes that may occur as a consequence of formulation changes to an oral suspension

Database

Data were available from 1 Phase 1 study and 1 Phase 2 study in pediatric patients (Study 128-044 and Study 128-122 respectively). There were also data from two Phase 2 studies in adult patients with schizophrenia (Studies 128-109 and 128-303) and two Phase 3 studies in adult patients with schizophrenia (Studies 128-114 and 128-115). For the investigation of the pharmacokinetics of the oral suspension, data from a Phase 1 study in adults (Study A1281037) were added to the database. Final database for the evaluation of oral suspension formulation of 496 subject contributing 2199 concentration-time samples.

Table 1. Covariates Assessed in Population Pharmacokinetic Analysis

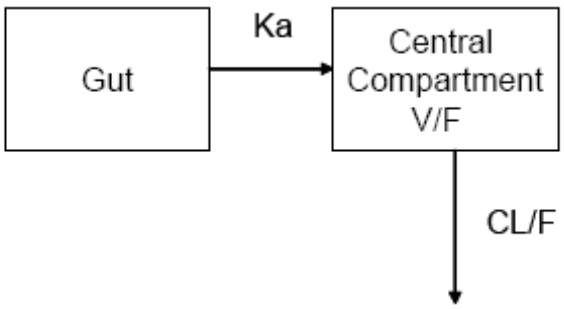
Covariate	Abbreviation	Unit	Value	Type
Demography				
Age	AGE	Yr	Numeric	Continuous
Weight	WT	Kg	Numeric	Continuous
Height	HT	Cm	Numeric	Continuous
Subject Gender	SEX	---	0=female 1=male	Categorical

Source Page 16 Retrospective Population PK Report

Structural Model

The structural model best suited to describe the pharmacokinetics of ziprasidone was a one-compartment model with first order absorption and linear clearance. This model was parameterized in terms of apparent oral clearance (CL/F), the volume of distribution of the central (V/F) compartments and first order absorption rate constant (KA). The residual error model was a combined constant coefficient of variation (CCV) and additive model. Inter-individual variability was described for CL/F, V/F and KA. The FOCE method with the
INTERACTION and SLOW options was employed in NONMEM.

Figure 1. General Schematic Diagram of Ziprasidone Final Pharmacokinetic Model used for the retrospective analysis.



$$\frac{CL}{F} = \theta_1 \bullet \left(\frac{WT}{70}\right)^{\theta 4} \bullet \left(\frac{AGE}{50}\right)^{\theta 5} \bullet \exp(\eta_1)$$

$$\frac{V}{F} = \theta_2 \bullet \exp(\eta_2)$$

$$Ka = \theta_3 \bullet \left(\frac{AGE}{50}\right)^{\theta 6} \bullet \exp(\eta_3)$$

Covariate Models

Continuous covariates such as age or weight were modeled using a general power function:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} cov_i^{\theta_i}$$

Continuous covariates were also assessed using a linear or an intercept slope function:

$$TVP = P_{pop} + \sum_{i=1}^{n} \text{cov}_i \cdot \theta_i$$

Body weight was correlated with other predictors so it was fixed to a known (theoretically and empirically) relationship as an allometrically scaled function. Categorical covariates (e.g., gender and dose of concomitant medication) were modeled using the general equation:

$$TVP = P_{pop} \cdot (1 + \text{cov}_i \cdot \theta_i)$$

In this equation, covi is either 0 (for the standard or reference subject), or 1 for the comparative subject. TVP is the typical value of the parameter, *Ppop* represents the value for the pharmacokinetic parameter when covi is 0, and θ*i* represents a scale factor for the influence of that covariate such that if θ*i* is less than 0, the net effect is a decrease in the typical value, and if θ*i* is greater than 0, the net effect is an increase in the typical value of the parameter.

Inter-Individual Variability

Inter-individual variability for the pharmacokinetic model was described using the following error model:

$$P_j = TVP \cdot e^{\eta_j}$$

Residual Variability

The residual variability for the pharmacokinetic data was described using a combined additive and constant coefficient of variation (CCV) model

$$Cp_{ij} = \hat{C}p_{ij} \bullet \exp(\varepsilon_{ij_1}) + \varepsilon_{ij_2}$$

Source Pages 20-23 Retrospective Population PK Report

Model Qualification

Several methods were used. This review will only report on limited predictive check. 1500 replicate steady state profiles were simulated without parameter uncertainty and the 5th and 95th quantile values were drawn as the approximate 90% prediction intervals. The observed data were overlaid on the prediction intervals and were graphically compared to the simulated data. The 20 and 40 mg BID dose groups were simulated for this exercise.

RESULTS

Table 2. Parameter Estimates and Associated Standard Errors for Final Pharmacokinetic Model

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL/F (L/h)	θ_1	49.3 (2.70)	33.7 (13.4)
Effect of WT	θ_4	0.460 (21.0)	
Effect of AGE	θ_5	0.0747 (72.7)	
V/F (L)	θ_2	68.1 (12.6)	34.9 (165)
KA (h-1)	θ_3	0.0638 (11.4)	52.6 (19.2)
Effect of AGE	θ_6	-0.253 (87.4)	
CCV Residual Error (as %CV)		49.5 (10.3)	
Additive Residual Error (ug/L)		7.65 (81.0)	

* - SE given as %CV

Table 3. Effect of Age and Weight on Apparent Clearance
Final Pharmacokinetic Model

Weight (kg)	Age (yr)	Apparent Clearance (L/h)	Percent Change from Reference
25	8	26	54.31
40	12	34	69.49
55	20	41	83.58
70	35	48	97.37
70	50	49	100.00
85	50	53	109.34
100	50	58	117.83
115	50	61	125.65
130	50	65	132.94
145	50	68.9	139.79
160	50	72.1	146.27

Table 2. Parameter Estimates and Associated Standard Errors for Final Pharmacokinetic Model

Source Page 33 Retrospective Population PK Report

Goodness of Fit for Final Pharmacokinetic Model

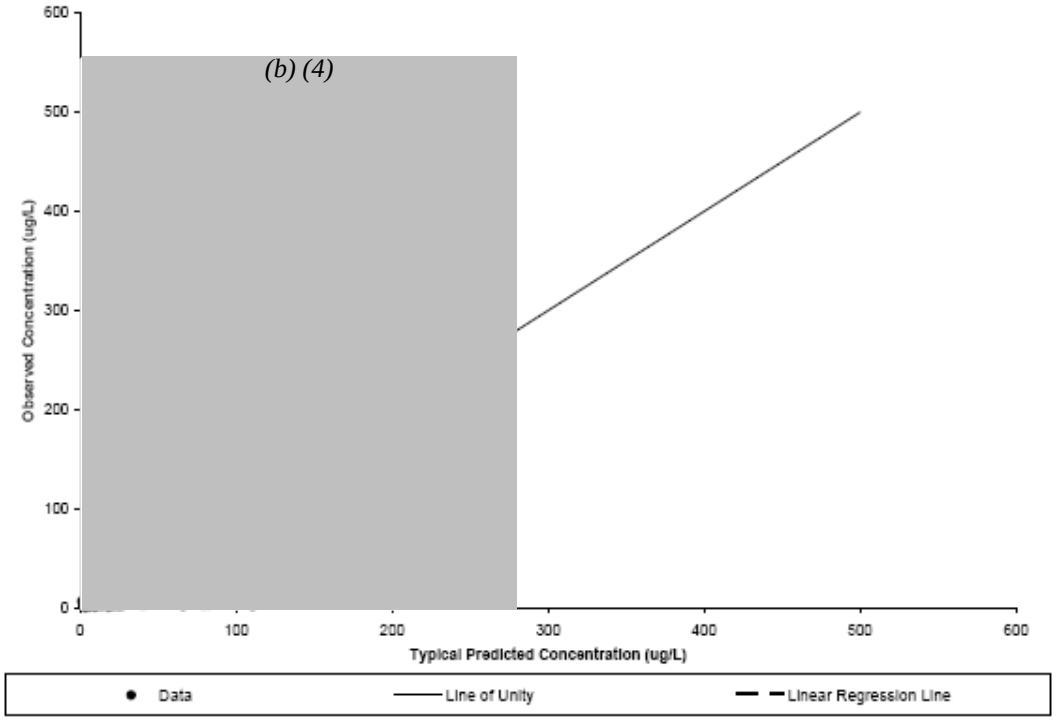
A plot of the observed versus typical predicted ziprasidone concentrations is given in Figure 2. This plot shows that the final model predicts a somewhat higher range of concentrations (250 ug/L) than does the base model (200 ug/L).

Covariate Influences on Pharmacokinetic Parameters

Age and body weight were found to significantly (e.g. the objective function for the single covariate models were reduced by more than 10 points as compared to the base model) impact the pharmacokinetics of ziprasidone.

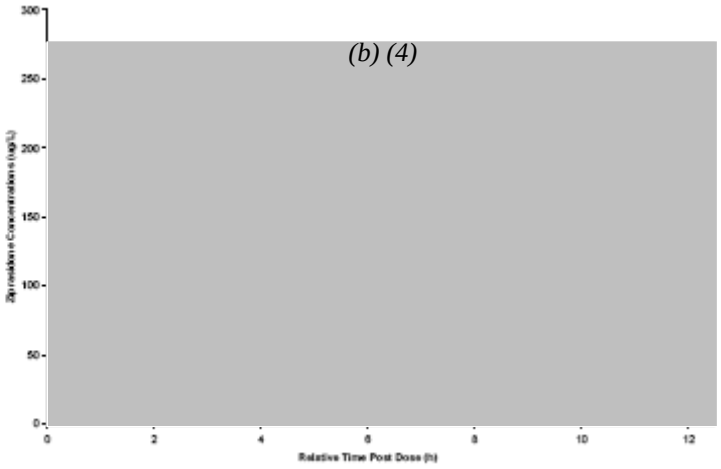
The objective function value was reduced by approximately 55 points as compared to the base pharmacokinetic model when the three covariate factors were added, although the estimates of inter-individual variability for all parameters were not impacted.

Figure 2. Observed versus Typical Predicted Concentrations –
Final Pharmacokinetic Model



Source Pages 38 Retrospective Population PK Report

Model qualification:
Figure 3. Simulated and Observed Concentrations of Ziprasidone 40 mg BID



Source page 41 Retrospective population PK report

Comment :
This plot shows that the final model predicts a somewhat higher range of concentrations (250 ug/L) than does the base model (200 ug/L) the reviewer has concluded that the model adequately describes the data.

\\cdsesub1\evsprod\NDA020825\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-bipolar-mania\5353-rep-analys-data-more-one-stud\retrospective-poppk

Comparison of Study 32 results to the results from the Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone Studies.

Pharmacokinetic Analysis of Ziprasidone which consisted of studies 128-044- and 128-122-children and adolescents- Tourette's syndrome
Five studies conducted in adult subjects (A1281037, 128-109, 128-114, 128-115, and 128-303).
The best pharmacokinetic model that was identified in the retrospective pooled analysis was a one-compartment disposition model with first order absorption and first order elimination.
The model was parameterized for apparent oral clearance (CL/F), the apparent volume of distribution of the central (V/F) compartment and the absorption rate constant (KA) describing drug input into the system. Inter-individual variability was described for all pharmacokinetic parameters which were found to be independent (e.g. no BLOCK structure for the OMEGA matrix was identified). Weight and age were included as covariates on CL/F, and age was included on KA.

Table 1. Parameter Estimates and Associated Standard Errors for Final

Pharmacokinetic Model From Retrospective Evaluation of Pooled Adult and Pediatric Data

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL/F (L/h)	θ_1	49.3 (2.70)	33.7 (13.4)
Effect of WT	θ_4	0.460 (21.0)	
Effect of AGE	θ_5	0.0747 (72.7)	
V/F (L)	θ_2	68.1 (12.6)	34.9 (165)
KA (h-1)	θ_3	0.0638 (11.4)	52.6 (19.2)
Effect of AGE	θ_6	-0.253 (87.4)	
CCVResidual Error (as %CV)		49.5 (10.3)	
Additive Residual Error (ug/L)		7.65 (81.0)	

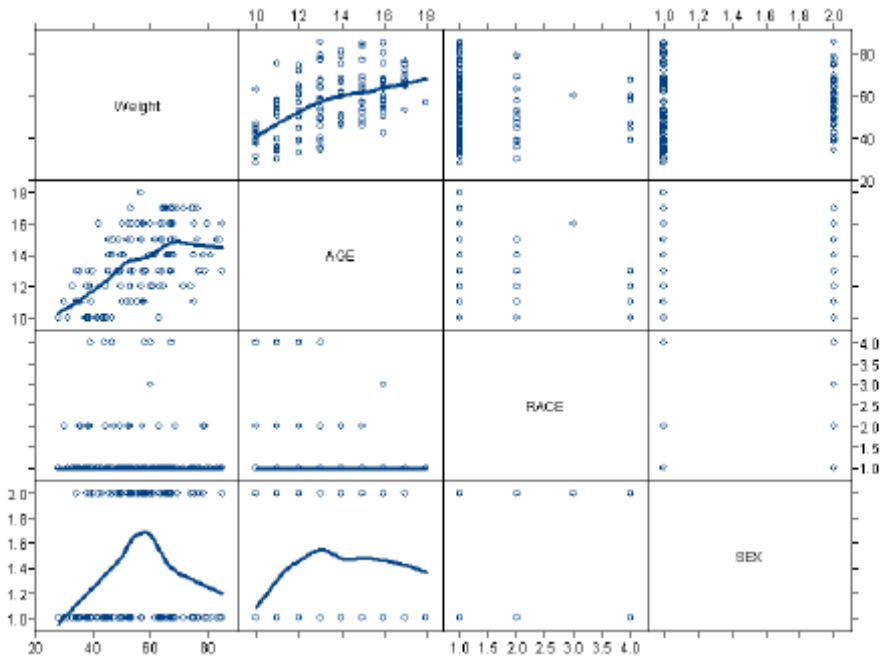
* - SE given as %CV

Source:Page 60 Report A1281132

The results from the current analysis are generally in agreement with the previous analysis. Both models had the same structure except the bipolar pediatric model included an absorption lag time which the pooled analysis did not. Both models used an additive plus proportional residual variability model. The clearance estimates were nearly the same at 49.3 L/hr for the pooled model and 55.1 L/hr for the bipolar pediatric model.

The covariates identified in the previous analysis are different from the current analysis. Age had an effect on both CL/F and KA, although the variability on these parameters was quite high (72.7%CV). This was not found in the current analysis but is most likely due to the much smaller range of ages in the bipolar pediatric study (10-18 year of age) compared to the pooled data model (7-82 years of age) and the correlation between body size and age. Body size was a significant covariate of clearance in both models. The addition of an allometric body weight effect on CL/F and V/F decreased the objective function by greater than 12 units with no additional parameters added to the model.

Fig 1. Matrix Plots of Categorical Covariates with Age and Weight for the Final Analysis Dataset



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An allometric effect of body weight on clearance and volume of distribution were included in the final model. To assess the clinical significance of the covariate influence identified in this analysis, the final population model was used to calculate typical pharmacokinetic parameter values for patients that are representative of the approximate range of body weights observed in this study. The effects of these covariates on CL/F and V/F compared to a 45 kg subject are given below in Table 2.

Table 2. Effect of Body Weight on Apparent Clearance and Volume of Distribution

Body Weight	Clearance (L/hr)	% Change From 45 kg Subject	Volume (L)	% Change From 45 kg Subject
25	28.6	-36	183	-44
30	32.8	-26	220	-33
35	36.8	-17	256	-22
40	40.7	-8	293	-11
45	44.4	0	329	0
50	48.1	8	366	11
55	51.6	16	402	22
60	55.1	24	439	33
65	58.5	32	476	45
70	61.9	39	512	56
75	65.1	47	549	67
80	68.4	54	585	78
85	71.5	61	622	89
90	74.7	68	659	100

Source: BW_CL_V_effect.xls

Source:Page 73 Report A1281132
\\cdsesub1\evsprod\NDA020825\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-bipolar-mania\5351-stud-rep-contr\a1281132

Reviewer's Comments:

The sponsor's approach is acceptable and I agree with the results except they have not included the results from Study A1281123 which was done in adolescents ages 10-17 with an N=38. Although the total N for the retrospective study was 511 it would have been a good idea to include the study A1281123 subjects since it is always a good practice to use all available data.

Reviewer's Analysis

Introduction

An independent analysis was conducted for the data for two reasons:
1. To determine if the sponsors proposed labeling language for dosing and administration is supported by the data and pharmacokinetic analysis submitted by the sponsor?

2. To determine if there was an exposure response relationship for Ziprasidone in children since the dosing was based indirectly on weight:

(a) 20mg/day with dose increases of 20 mg/day every 2nd day up to a target dose of 120-160 mg/day for subjects weighing ≥45 kg.
(b) 20 mg/day with dose increases of 20 mg/day every 2nd day up to a target dose between 40–80 mg/day for subjects weighing <45 kg
(c) subjects requiring a more rapid onset of action based on their clinical history and symptoms, the dose was titrated more rapidly with daily dose increase from 20 mg/day.

Objectives

Analysis objectives are:

a. To determine if there is a dose-response relationship for clinical effect stratified by body weight.

b. To assess if the exposure in children, adolescents and adults are similar when ziprasidone is administered following the sponsor's proposed dosing regimen.

c. To identify if there is a trend for the incidence of dose reduction due to severe adverse effects in different body weight, and age and different titration groups (low or high).

4.3 Methods

4.3.1 Data Sets*

Data sets used are summarized in Table 2.

Table 1. Analysis Data Sets

Study Number	Name	Link to EDR
A1281132	Final Pharmacokinetic Model Study A1281132-Four week Placebo controlled efficacy, safety and pharmacokinetic	\\cdsesub1\evsprod\NDA020825\0030\m5\datasets\a1281132\tabulations

	study with flexible doses-Capsule dosage form	
A1281123	A 27 week safety study to explore tolerated doses-oral suspension	\\cdsesub1\evsprod\NDA020825\0030\m5\datasets\a1281123\tabulations
Meta Analysis	Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone	\\cdsesub1\evsprod\NDA020825\0030\m5\datasets\retrospective-poppk\analysis\programs \\cdsesub1\evsprod\NDA020825\0030\m5\datasets\retrospective-poppk\tabulations

4.3.2 Software

NONMEM VI was used to duplicate the firm's results.
SAS was used for analysis of the data.

4.3.3 Models

The pharmacokinetic models developed by the firm for studies A1281132, A1281123 and the Retrospective population pk study that were discussed in the firm's submission section of this review were used for this analysis.

4.3.4 Exposure response relationship

The exposure response relationship between the YMRS (Young Mania Ratings Score) and dose was determined for subjects <45 kg and subjects ≥ 45 kg by comparing the YMRS over time for each dosing group in the respective weight group.
The primary efficacy endpoint for the studies was (change from baseline to Week 4 in Young Mania Rating Score, YMRS total score). A longitudinal analysis of the data based upon body weight was done using SAS Proc Mixed. The model used to analyze the data was:

```
proc mixed
class  weightclas  trt
model change=trt baseline /solution;
by weightclas time;
```

4.3.5 Comparison of Ziprasidone exposure in children, adolescents and adults

The models developed by the firm were used to estimate the individual clearances for each subject in studies 32, 23 and the retrospective pop pk study.
The individual clearance and volume values were then used to calculate the Cmin values for the low and high dose for subjects <45 kg (i.e., 20 mg and 40 mg) and subjects ≥ 45 kg (i.e., 40 mg and 80 mg) based upon label recommendations. Cmin values were

calculated using the multiple dose equations for a one-compartment model. A lag time was not used in the calculations since delayed absorption would have no impact on the steady-state Cmin value. Cmin was calculated after dosing for 6 half-lives.
AUC was also calculated using the equation based upon the individual subject clearance values:
AUC= Dose/Clearance

4.3.6 Data qualification

Data qualification for the calculations was investigated by comparing the distributions for the calculated Cmin values to those observed experimentally based upon time after dose for study A1281132.

4.3.7 Serious Adverse effects

The number of severe adverse events were summarized for study A1281132 to determine if the events were related to dose, subjects weight or age

Results

No dose-response relationship for clinical effectiveness (YMRS) in subjects with different body weight ($\geq$ 45 kg and < 45 kg) were identified (Figure 1 and Figure 2). In addition, no exposure (i.e., trough concentration) effectiveness relationship was shown for patients on Day 28 (i.e., primary endpoint evaluation).

Figure 1. Effect of dose on the Young Mania Rating Scale for subjects with weights equal to or greater than 45 kg as a function of time of day of dose administration in study A1281132.

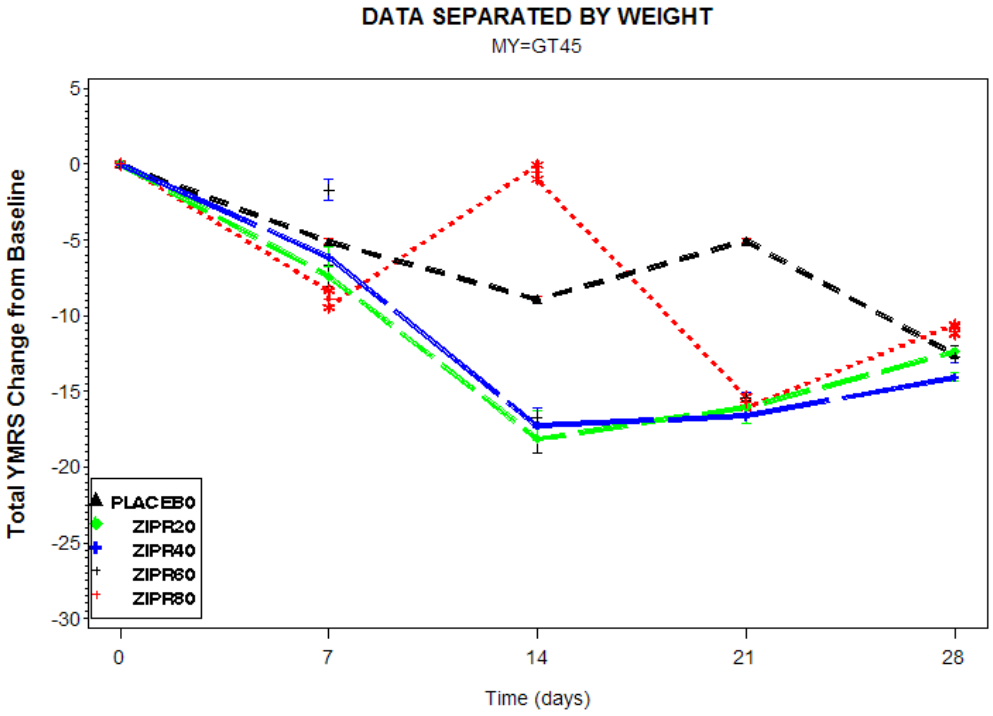


Figure 2. Effect of dose on the Young Mania Rating Scale for subjects with weights less than 45 kg as a function of day of dose administration in study 1281132

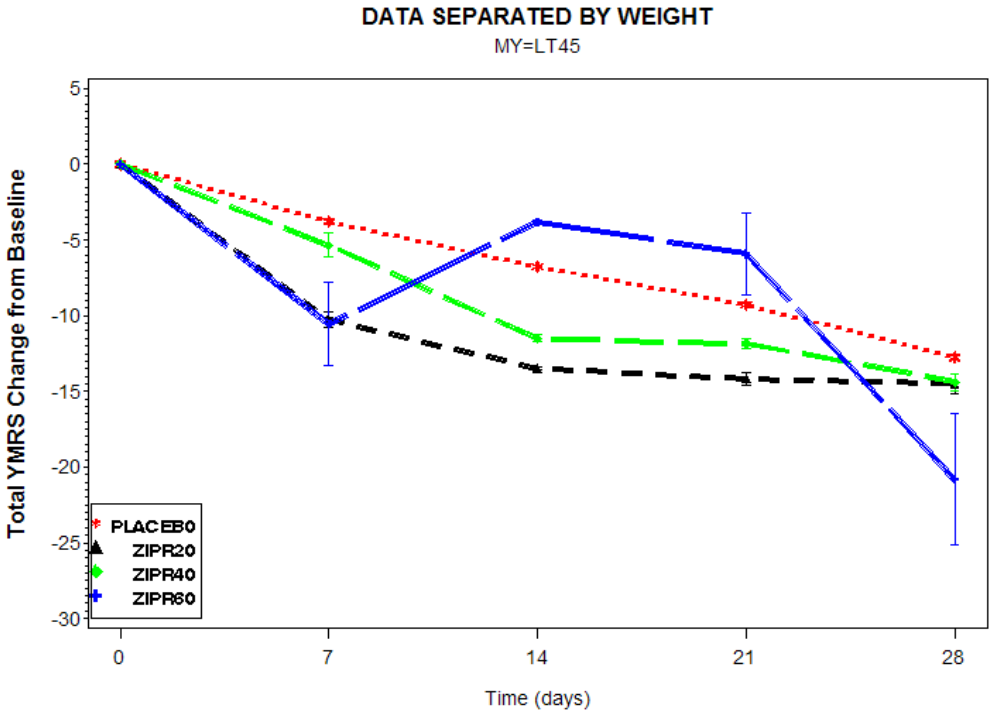
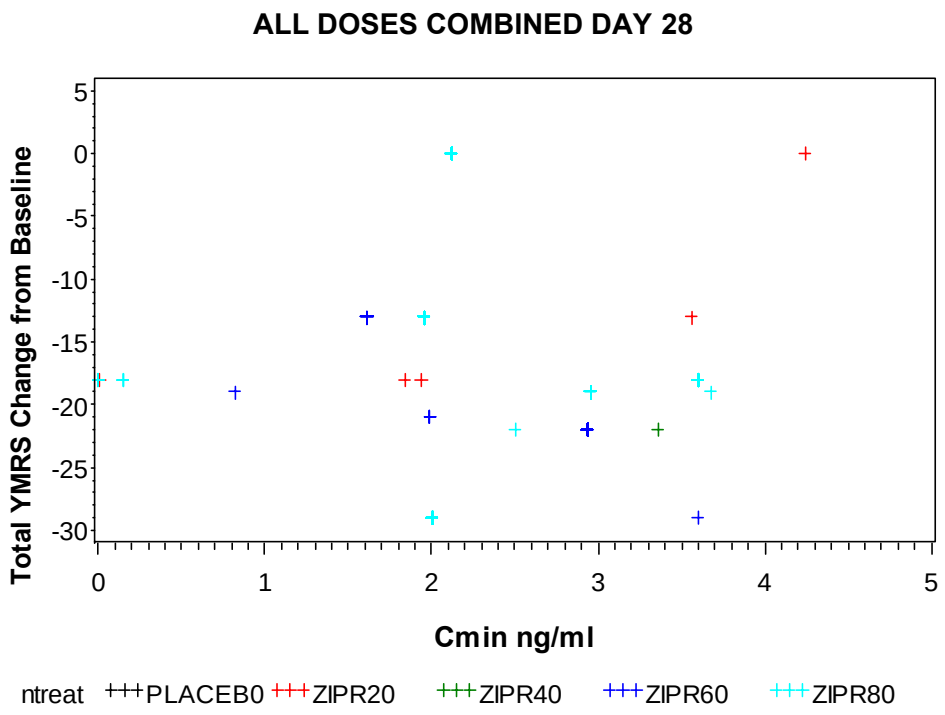


Figure 3. Comparison of the Cmin values from study A1281132 versus the total YMRS score.



The exposure distributions for the calculated Cmin values for high and low doses for the ≥ 45 kg and for the < 45 kg show a distribution pattern similar to that observed in the experimental data. This supports the fact that the calculated Cmin values are representative of the observed values.

Figure 4. Qualification of the calculations for Cmin. Distribution of calculated Cmin values for study A1281132 for the high and low labeled doses for subjects greater than or equal to 45 kg.

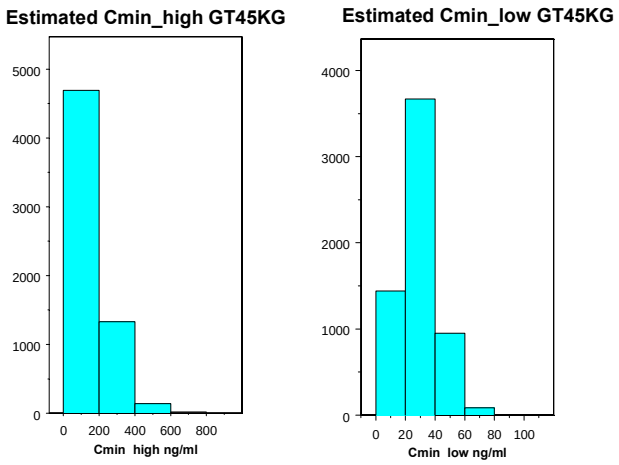


Figure 5. Qualification of the calculations for Cmin. Distribution of calculated Cmin values for study A1281132 for the high and low labeled doses for subjects less than 45 kg.

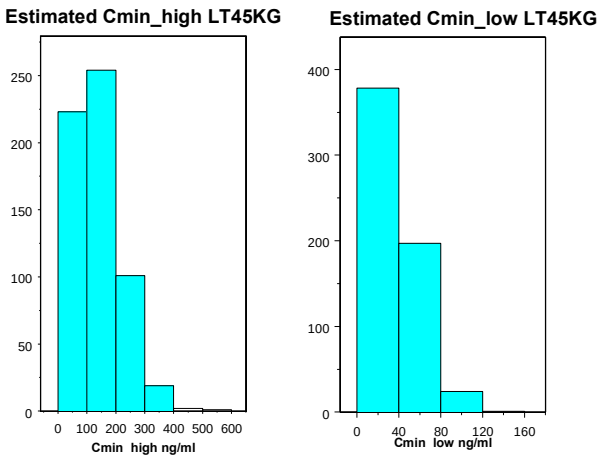
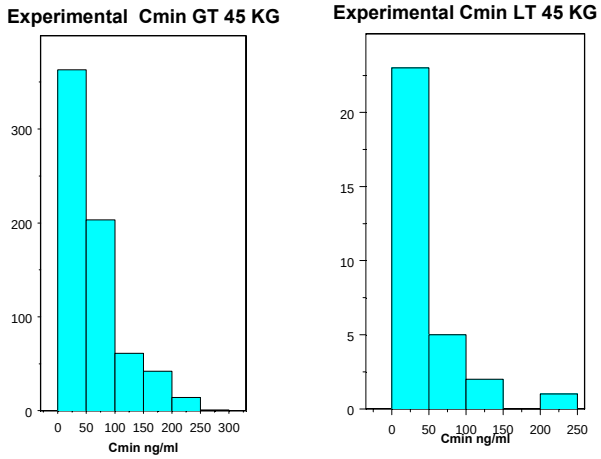


Figure 6. Qualification of the calculations for Cmin. Distribution of experimental observed Cmin values for study A1281132 for the high and low labeled doses combined for subjects less greater than or equal to 45 kg and those subjects less than 45 kg.



The calculated Cmin and AUC values for the high dose for all subjects and the low dose for all subjects show similar exposure in children, adolescents and adults.

Figure 7.

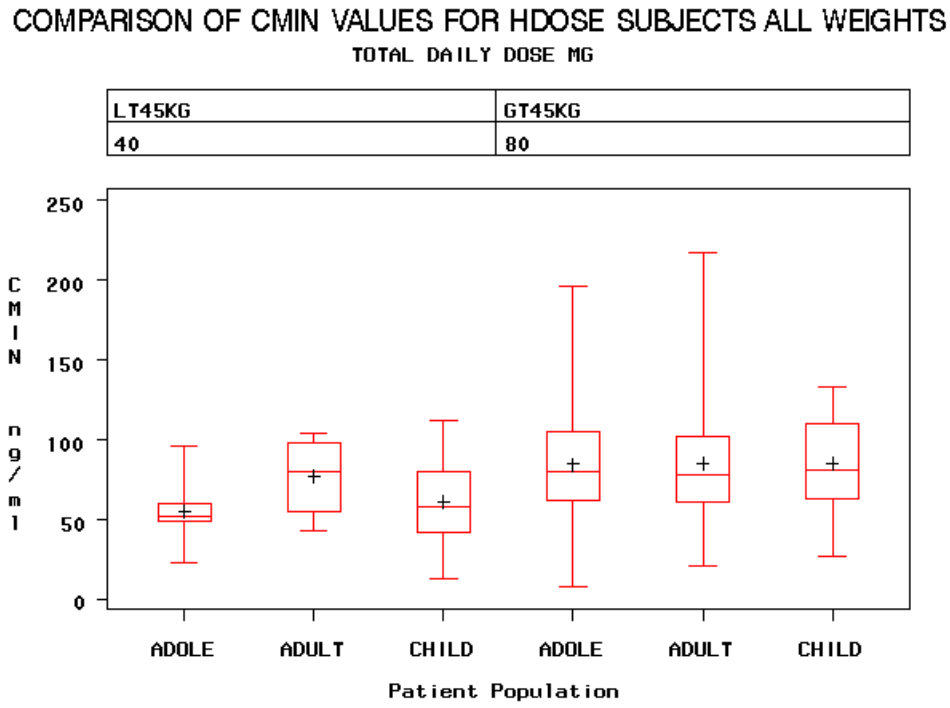


Figure 8.

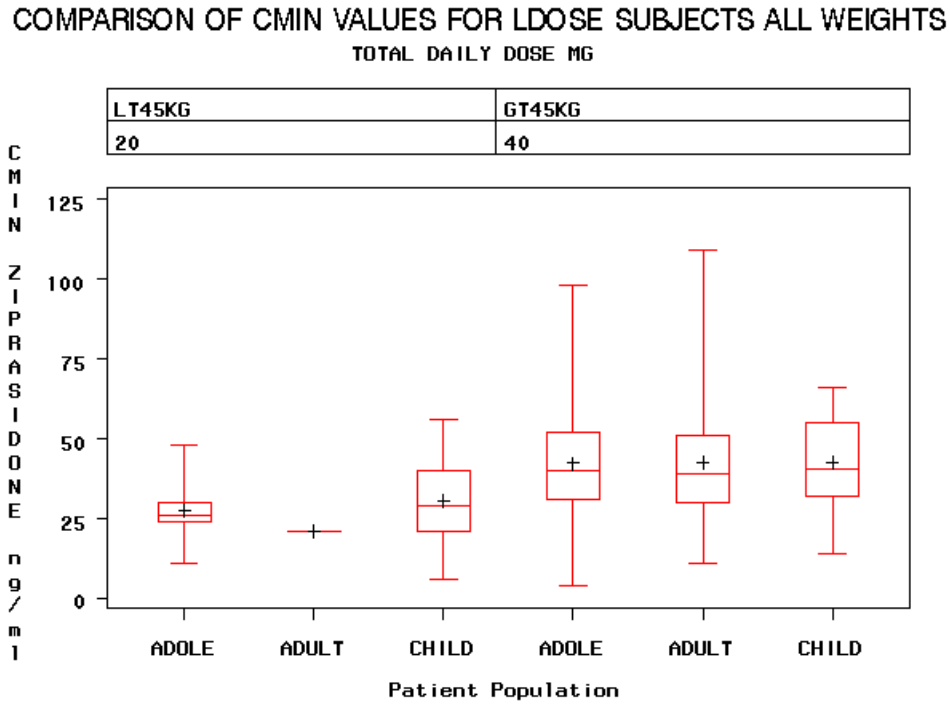


Figure 9.

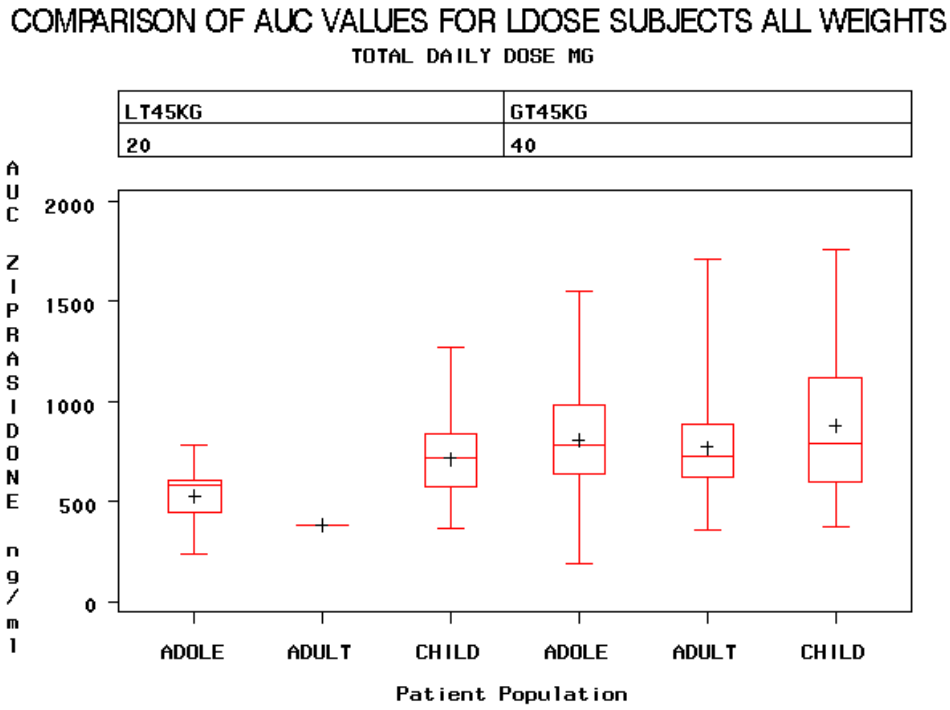
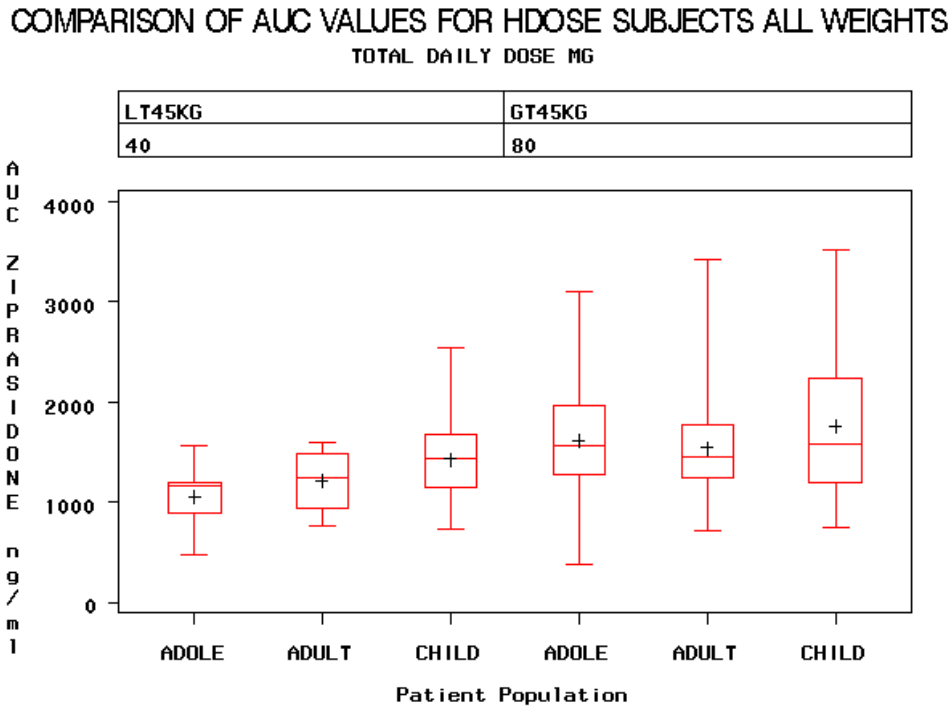


Figure 10.



The results indicate that there is no apparent trend of the incidence of dose reduction due to severe adverse effects in different body weight, age or titration rate (i.e., fast or slow) groups. There were 8/61 subjects (13%) that had severe reactions which led to a reduction in dose (Table 1). Two of those subjects are not listed since they discontinued from the study without any PK samples being collected.

Table 1. Subjects from study A1281132, active drug arm, that had to have the dose reduced due to a severe adverse reaction.

Subject #	ADVERSE	Dose	Weight	F titration	S titration	Gender	Age
10161020	Sedation	80 mg/day	47 kg		Yes	Male	14
10161014	Sedation	80 mg/day	42 kg		Yes	Female	16
10401024	Nausea	80 mg/day	35 kg	Yes		Male	11
11141007	Sedation	100 mg/day	57.6 kg		Yes	Female	16
11241009	Fatigue	150 mg/day	65.83		Yes	Female	14
11321004	Somnolence	120 mg/day	67.2 kg		Yes	Female	15

Listing of Analyses Codes and Output Files

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
GEODON_YMRS.sas	Calculates Dose Response	\\cdsnas\pharmacometrics\Geodon\Analysis\SAS
GEODON_LABELSIM.sas	Calculates Exposure in children, adolescents and adults per label dose	\\cdsnas\pharmacometrics\Geodon\Analysis\SAS
STUDY32.CTL	Control stream study 32	\\cdsnas\pharmacometrics\Geodon\Analysis\NONMEM
CONTROLSTY_23E1.ctl	Control stream study 23	\\cdsnas\pharmacometrics\Geodon\Analysis\NONMEM
METASTDY.CTL	Control stream meta study	\\cdsnas\pharmacometrics\Geodon\Analysis\NONMEM

Office of Clinical Pharmacology:

Pharmacometric review-QT

Summary of Findings

Key Review Questions

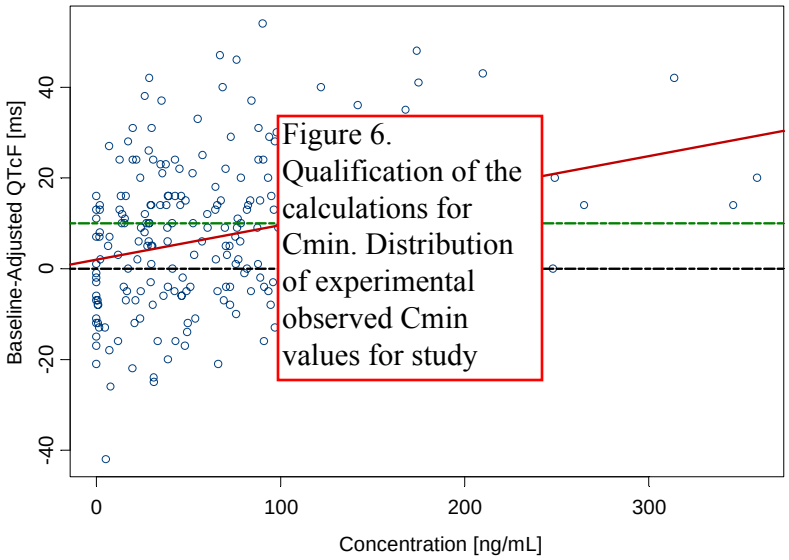
The purpose of this review is to address the following key questions.

Is there concentration-QTc relationship following ziprasidone treatment in pediatric patients 10 -17 years of age?

Yes, a statistically significant zaprasidone concentration-QTcF relationship was established ($P < 0.0001$) by using the observations from the pivotal study (Study A1281132) (Figure 1). Under the mean Cmax (defined as concentrations collected between 5-7 hr post dose) of 20 mg, 40 mg, and 60 mg BID dosing at steady state, the mean predicted QTcF were 8.1, 11.3, 14.2 ms respectively (Figure 2). Because ziprasidone prolongs QTc interval in a concentration-dependant manner, any intrinsic and extrinsic factors that potentially change ziprasidone exposure can affect the risk for QTc interval prolongation.

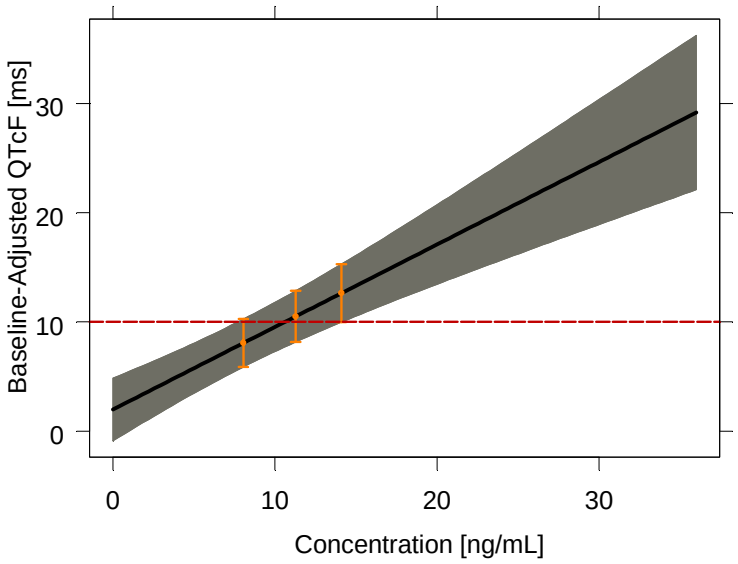
The exposure-QTcF analyses were conducted using baseline corrected QTcF value. In Study A1281132, baseline QTcF was obtained at one time point for each subject. Thus the same baseline value was used to correct the QTcF observations at various time points post dose for each subject. Because there were no time-matched ECGs collected from the placebo group and the ziprasidone group, it is impractical to derive the placebo-adjusted, baseline-corrected QTcF ($\Delta\Delta$QTcF). The time-matched ziprasidone concentrations were included in the analyses. Figure 1 demonstrated that a larger QTc interval prolongation is associated with higher ziprasidone concentration.

Figure 1. Ziprasidone Concentration-QTcF Relationship



Note: Red line = Mean prediction,
Dots with open circle = observation

Figure 2 Model Predicted QTcF Values



Black line = Mean prediction Shaded area = 90% Confidence Interval
Dots with error bar (from right to left) = Mean prediction and 90% confidence interval under mean maximum concentration under the doses of 20 mg, 40 mg, and 60 mg BID dosing

Recommendations

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

In the placebo-controlled pediatric bipolar mania clinical trial, ziprasidone caused a modest increase in the QTc interval. At the time of maximum plasma concentration, the mean placebo-adjusted increase from baseline was 12.4 msec; at the time of steady-state trough plasma concentration, the mean placebo-adjusted increase from baseline was 7.4 msec. **[A1281132 Clinical Study Report: Table 13.9.1]**

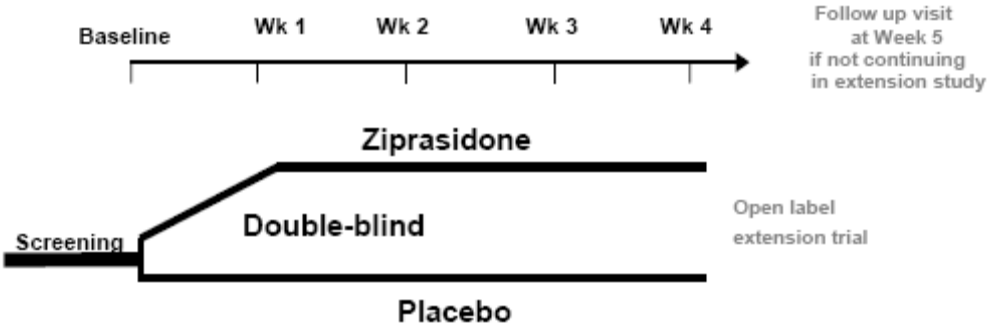
Reviewer's Comments:
Subjects received different doses ranging from 30 mg to 80 mg BID in the treatment group. The QTc observation in zipasidone group is associated with different dose levels.

Results of Sponsor's Analysis

The sponsor's placebo-adjusted, baseline corrected QTc analysis was based on the clinical observations from the study A1281132. This was a four week, double-blind, placebo controlled phase III trial to evaluate the efficacy, safety and pharmacokinetics of flexible doses of oral ziprasidone in children and adolescents with bipolar I disorder (manic or mixed). Approximately 222 subjects were recruited in the study and were assigned randomly into the treatment group and the placebo group at 2: 1 ratio (148 ziprasidone, 74 placebo). Ziprasidone was titrated over the first 1-2 weeks of treatment, and flexibly dosed through Weeks 3 and 4 (Figure 3). The starting dose was 20 mg/day, with dose increases of 20 mg/day every second day up to a target dose of 120 – 160 mg/day for subjects weight over 45 kg. The target dose was obtained by day 14. The dose was to increase above 120 mg/day only in subjects who tolerated 120 mg/day. The target dose for children less than 45 kg was 60 – 80 mg/day. Electrocardiograms were taken during the screening phase (Day -10 to Day -1), at the baseline (Day 0), on Day 7, 14, 21, 28 during the treatment. If abnormal ECGs were observed on Day 28, Additional ECGs were taken on Day 35 during the follow-up phase. Baseline ECGs were taken in triplicate (no less than 2 minutes apart). All ECGs were administered at least 3 hours after food intake. At the Week 4 visit, subjects were to take their morning medication at the visit. An ECG was performed before dosing (trough), as well as between 0.75 and 3 hours and again between 5 and 7 hours after dosing (ie, T_{max}). ECGs showing a QTcF of 460 msec or greater or an increase from baseline of 60 msec or greater were to be repeated within the same visit. Based on the observed data, the mean change from baseline of QTcF was summarized

in Table 2. Table 3 demonstrated the categorical increases in QTcF stratified by gender.

Figure 3 Study Design for A1281132



(Source: Figure S1: Clinical Study Report for A1281132)

Table 2 Mean Baseline and Mean Change from Baseline for QTcF

	Ziprasidone		Placebo	
QTcF, msec	N	Mean (SD)	N	Mean (SD)
Mean baseline	147	396.1 (18.6)	87	399.6 (12.6)
Change from baseline				
Week 1	131	7.1 (15.3)	83	-2.9 (14.0)
Week 2	112	10.1 (17.0)	69	-4.3 (16.2)
Week 3	99	6.7 (15.6)	54	-5.4 (15.8)
Week 4/predose	93	5.9 (16.9)	50	-0.9 (18.0)
Week 4/0.75-3[a]	90	5.1 (17.3)	50	-3.0 (16.8)
Week 4/5-7[b]	84	8.3 (15.0)	48	-2.9 (16.1)
ET/predose	27	4.7 (19.2)	27	-3.4 (16.9)
ET/0.75-3[a]	16	10.3 (17.9)	19	-2.3 (12.2)
ET/5-7[b]	17	10.8 (16.4)	21	-5.5 (12.5)
Week 4/ET/predose	120	5.6 (17.4)	77	-1.8 (17.6)
Week 4/ET/0.75-3[a]	106	5.9 (17.4)	69	-2.8 (15.6)
Week 4/ET/5-7[b]	101	8.7 (15.2)	69	-3.7 (15.1)

Source: Table 13.9.1
[a]0.75-3 hours post dose
[b]5-7 hours post dose
ET = end of treatment, SD = standard deviation

(Source: Table 32, Clinical Study Report for A1281132)

Table 3 Categorical Increase of QTcF, by Gender

	Ziprasidone		Placebo	
QTcF, msec	N	Mean (%)	N	Mean (%)
Male				
≥450 msec	79	1 (1.3)	44	1 (2.3)
≥460 msec	79	1 (1.3)	44	0 (0)
≥480 msec	79	0 (0)	44	0 (0)
≥30 msec increase[a]	79	18 (22.8)	44	4 (9.1)
≥60 msec increase[a]	79	0 (0)	44	0 (0)
Female				
≥450 msec	61	4 (6.6)	41	0 (0)
≥460 msec	61	1 (1.6)	41	0 (0)
≥480 msec	61	0 (0)	41	0 (0)
≥30 msec increase[a]	61	13 (21.3)	41	5 (12.2)
≥60 msec increase[a]	61	1 (1.6)	41	0 (0)
All				
≥450 msec	140	5 (3.6)	85	1 (1.2)
≥460 msec	140	2 (1.4)	85	0 (0)
≥480 msec	140	0 (0)	85	0 (0)
≥30 msec increase[a]	140	31 (22.1)	85	9 (10.6)
≥60 msec increase[a]	140	1 (0.7)	85	0 (0)

Source: Table 13.9.2
[a]from baseline where baseline was defined as the mean of the predose triplicate at the Baseline visit
msec = milliseconds

(Source: Table 33, Clinical Study Report for A1281132)

The sponsor preformed additional analyses to establish the PK-QTc relationship (Please refer to study report: Four-week, double-blind, placebo controlled phase III trial evaluating the efficacy, safety and pharmacokinetics of flexible doses of oral ziprasidone in children and adolescents with bipolar disorder). The ziprasidone concentration-QTcF observations were analyzed using mixed-effects modeling method (FOCE method with SLOW option) as implemented in NONMEM. A linear model with between-subject variabilities on both intercept and slope was applied as base model. Major parameter estimates for the base model were listed in Table 4. The sponsor also identified that body weight is a significant covariate on intercept (Equation 1). The final model parameter estimates were shown in Table 5.

$$Intercept = \theta_1 \cdot BodyWeight^{\theta_3} \qquad \text{(Equation 1)}$$

Where θ_1 represents the typical value for intercept and θ_3 represents body weight effect on intercept.

Table 4 Summary of the Parameter Estimates for Base Model

Parameter (Units)		Population Mean (SE*)	SD Inter-Individual Variance
Intercept (msec)	θ_1	-0.692 (166.2)	12.4 (23.6)
Slope (msec/(ng/mL)	θ_2	0.0884 (15.2)	0.0383 (135.4)
Additive Residual Error (msec, as SD)		9.89 (9.0)	

* - SE expressed as %CV
Source: base_qtcf_zip_con1_blk.smr

Table 5 Summary of the Parameter Estimates for the Covariate Model

Parameter (Units)		Population Mean (90% CI)	SD Inter-Individual Variance (90% CI)
Intercept (msec)	θ_1	$-2.6e^{-7}$ (-0.325 to $2.75e^{-9}$)*	10.9 (9.42 to 13.56)
Slope (msec/(ng/mL)	θ_2	0.0852 (0.067 to 0.106)	0.0223 (0.0018 to 0.0620)
Weight Effect on Intercept	θ_3	42.8 (-0.526 to 51.8)	NA
Additive Residual Error (msec, as SD)			96 (9.19 to 10.583)

Source: final_model_qtcf_zip_boot.csv
* intercept parameter estimate divided by

Figure 3 Study Design for A1281132

(Source: Table 4 and Table 6 in st k, double-blind, placebo controlled phase III trial evaluatin and pharmcokinetics of flexible doses of oral ziprasidone in childr ith bipolar I disorder (manic or mixed))

Reviewer's Comments:
We preformed concentration-QTcF analysis using the similar modeling approach that IRT-QT applies in the review. Please refer to section 4.

Reviewer's Analysis

Introduction

The reviewer's analyses were performed to establish the ziprasidone concentration-QTcF relationship by applying similar modeling approach used in IRT-QT review for thorough QT studies.

Objectives

Analysis objectives are:

d. To characterize ziprasidone concentration-QTcF relationship in children and adolescents with bipolar I disorder (manic or mixed).

e. To estimate the magnitude of unexplained variability in ziprasideon concentration-QTcF relationship in children and adolescents with bipolar I disorder (manic or mixed).

Methods

Data Sets

Datasets used were summarized in
Table 1.

Table 6. Analysis Data Sets

Study Number	Name	Link to EDR

ecglst	ECG singles by patient ID, Visit, and Treatment	\\cdsnas\PHARMACOMETRICS\ Geodon\Dataset
A1281132_PKECG_28APR08_analysis_qtci.csv	Concentration-QTcF Analysis	\\cdsnas\PHARMACOMETRICS\ Geodon\Dataset

Software

The analyses were mainly conducted by using SAS (Version 9.1, SAS Institute) and S_Plus (Version 7.0, Insightful, Inc.)

Models

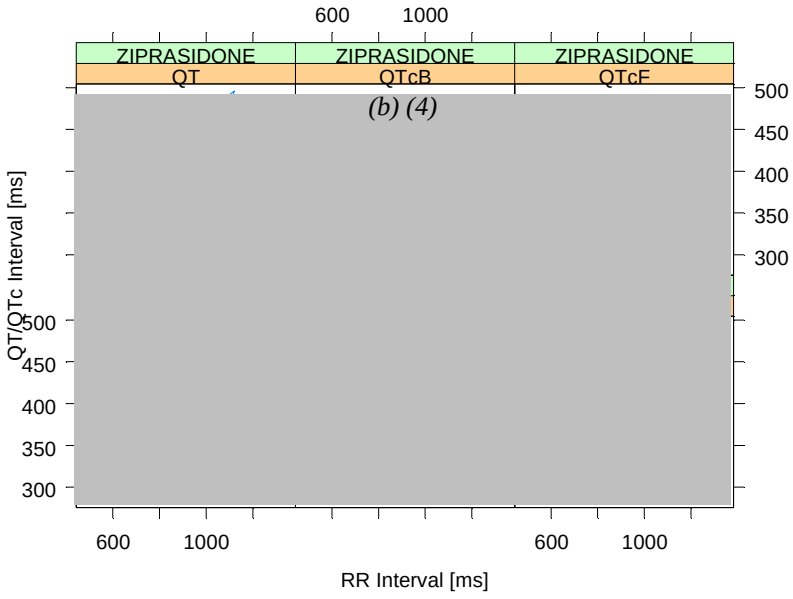
We explored the concentration-QTcF relationship by using the mixed effects linear model.

Results

The observed QT-RR interval relationship was presented in Figure 4 together with the Bazett's (QTcB) and Fridericia (QTcF) stratified by different treatment groups. It appeared that QTcF was the best correction method to remove the heart rate effect. Therefore it was chosen for the reviewer's analyses.

Figure 4 QT, QTcB, QTcF, and QTcS vs. RR, by Treatment Group

(Each Subject's Data Points are Connected with a Line)



(Note: based on the dataset ecglst)

The exposure-QTcF analyses were conducted using baseline corrected QTcF value. In Study A1281132, baseline QTcF was obtained at one time point for each subject. Thus the same baseline value was used to correct the QTcF observations at various time points post dose for each subject. Because there were no time-matched ECGs collected from the placebo group and the ziprasidone group, it is impractical to derive the placebo-adjusted, baseline-corrected QTcF (ΔΔQTcF). The time-matched ziprasidone concentrations were included in the analyses.

Three different ziprasidone concentration- QTcF models were tested: linear models with or without an intercept and a linear model with mean intercept fixed to zero (with between-subject variability). Based on -2 log-likelihood and AIC values (Table 7), the linear model with an intercept best described the observed data. Table 8 summarized the model parameters. The results demonstrated a significant concentration-QTc relationship ($P < 0.0001$). The concentration-QTcF relationship was shown in Figure 5. Based on our concentration-ΔQTcF analysis, body weight is not a statistically significant covariate ($P = 0.20$).

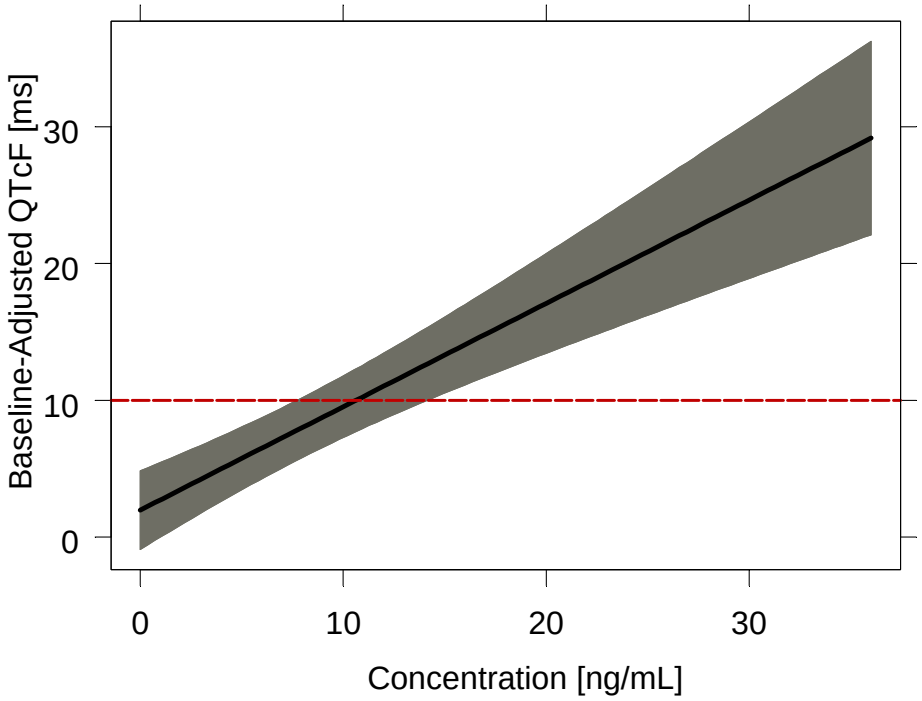
Table 7 Summary of Model Selection

Model	AIC	-2Loglikelihood
Linear Model with an intercept	2133.2	2125.2
Linear Model without an intercept	2196.5	2192.5
Linear Model with intercept fixed to zero	2137.4	2129.4

Table 8 Summary of the Model Parameters

	Estimate (90% CI); P-value	Between-subject variability (SD)
Model 1		
Model1: ΔΔQTcF = Intercept + slope*concentration		
Intercept, msec	1.98 (-0.89 – 4.86) P = 0.25	12.3
Slope, msec per 10 ng/mL	0.76 (0.52 – 0.99) P < 0.0001	0.43
Residual Variability, msec	9.38	---

Figure 5 Ziprasidone Concentration-QTcF Relationship



Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
	CQT Analysis	\\cdsnas\PHARMACOMETRICS\ Geodon\Script

SIGNATURES

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

RD/FTinitialized by Yanning Wang, Ph.D._____
Team Leader Pharmacometrics 1
Office of Clinical Pharmacology

RD/FTinitialized by Christine Garnett, Pharm.D._____
Scientific Lead, Interdisciplinary Review Team for QT Studies
Office of Clinical Pharmacology

RD/FTinitialized by Raman Baweja, Ph.D._____
Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology

cc: NDA 20825, HFD-860(Jackson, Wang, Garnett, Baweja)
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APPENDIX

Pharmacokinetic Control Stream for Study 1281132

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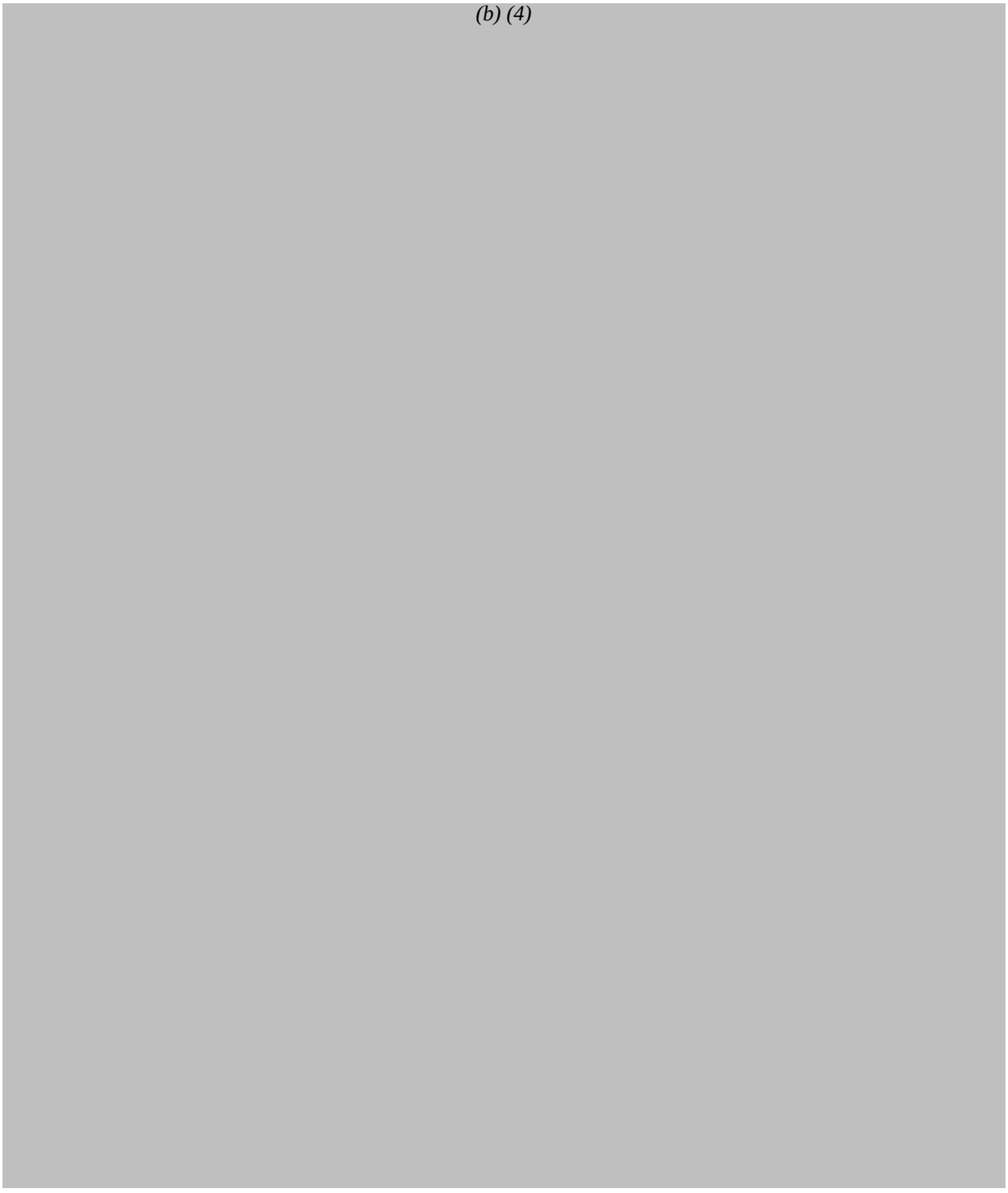

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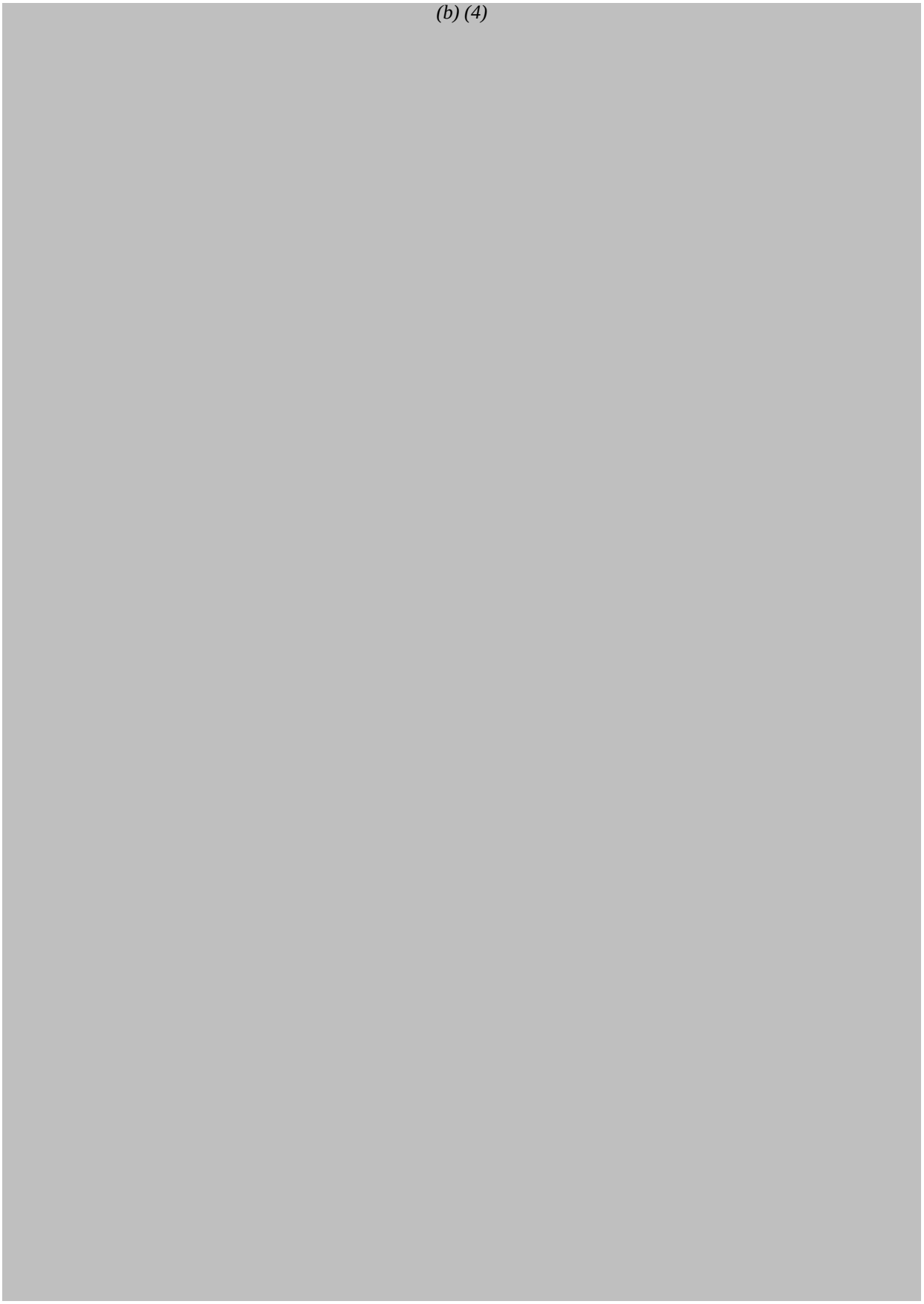

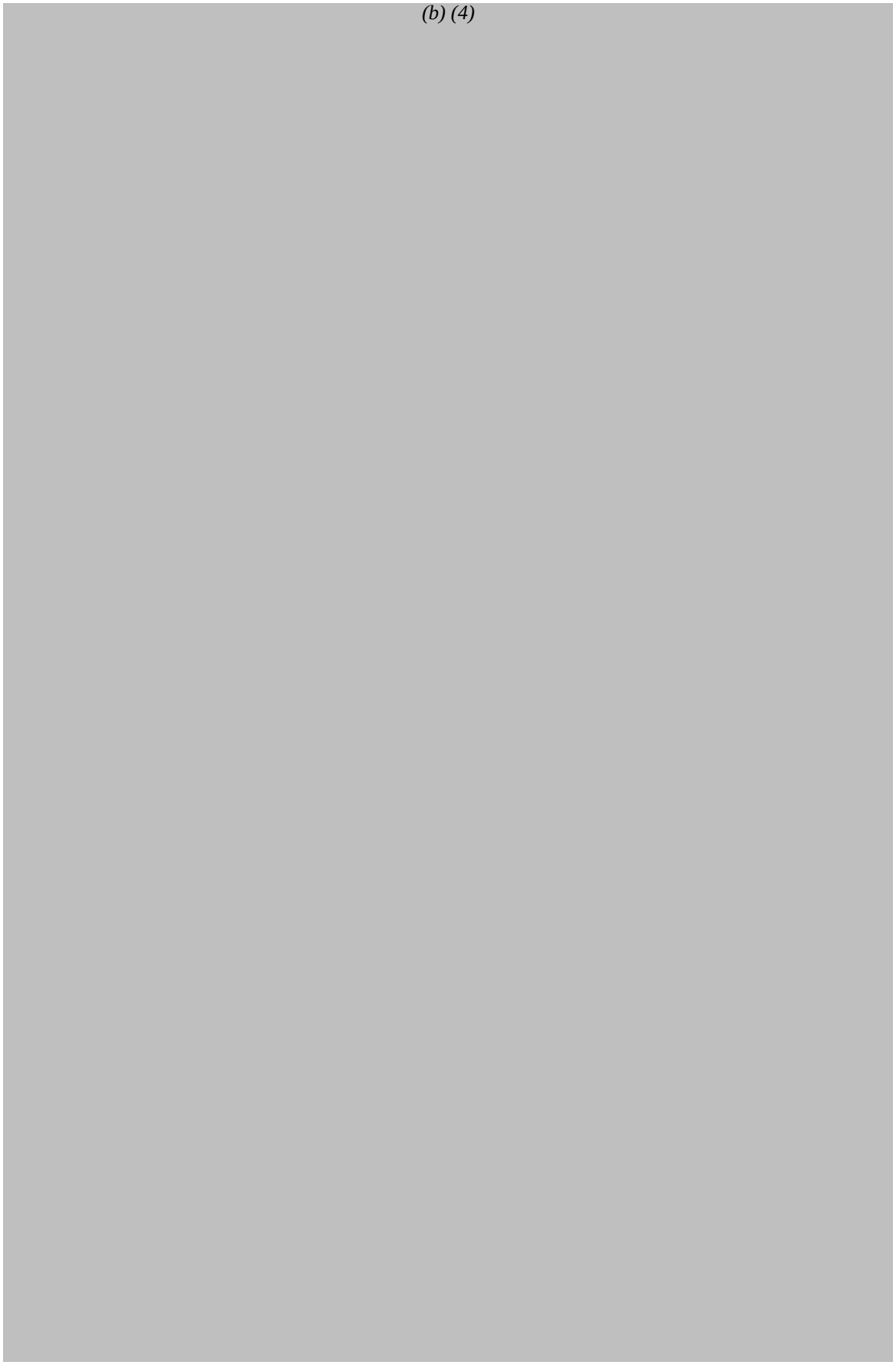
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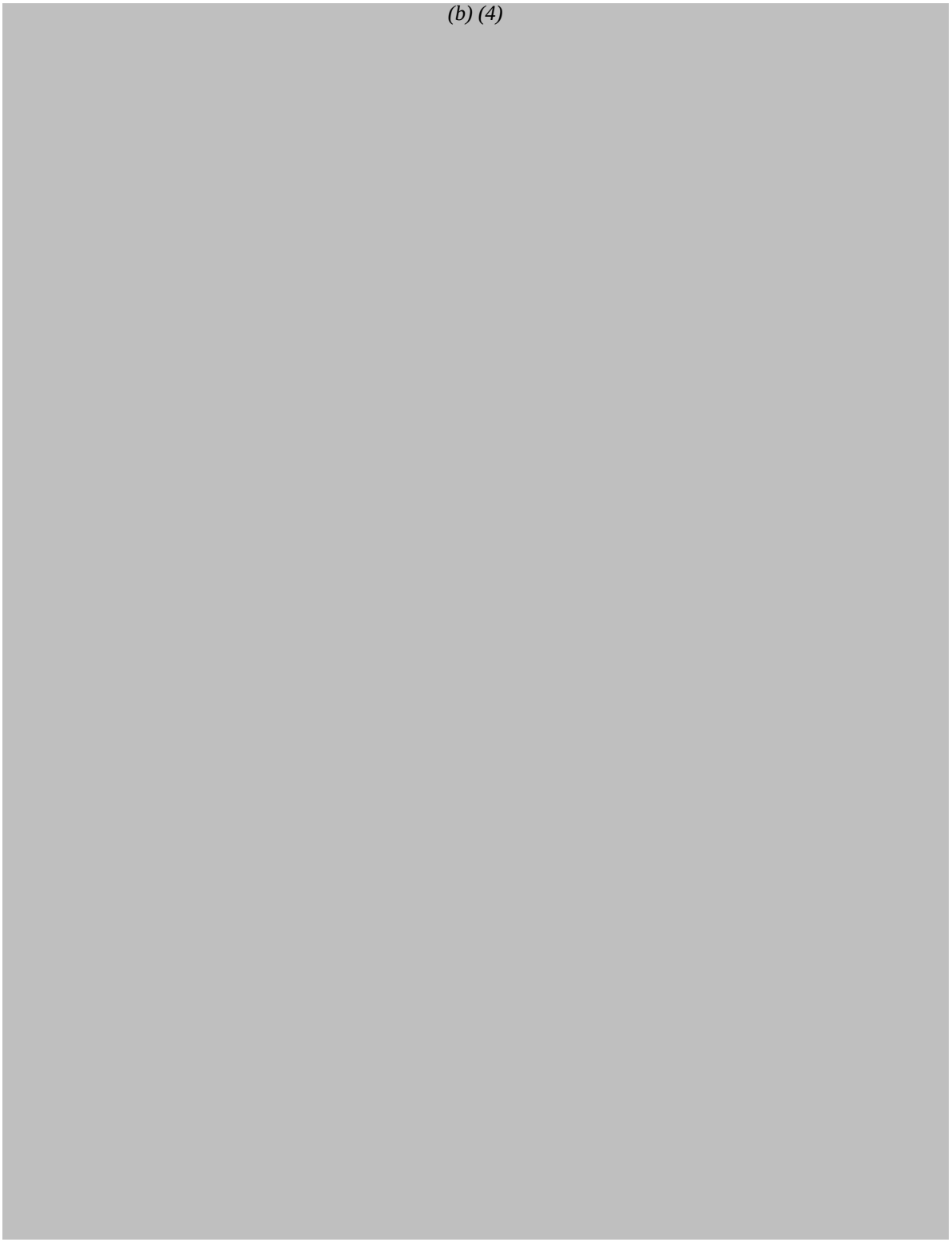
(b) (4)

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/s/

Andre Jackson
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Yaning Wang
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Christine Garnett
4/8/2009 10:15:48 AM
BIOPHARMACEUTICS

Raman Baweja
4/8/2009 10:54:59 AM
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