Appendix 2. Applicant's Data Collected and Data Editing, continued

The below is reproduced from Volume 1.84 p. 71 of the NDA.

ST-10 Levels of dose group and AUC steady state in the PK/PD models that treated them as factor variables.

Variable	Level 1	Level 2	Level 3	Level 4	Level 5
GRP	2	10,15,20,30			
	2,10	15,20,30			
	2,10,15	20,30			
	2,10	15,20	30		
	2	10	15	20	30
AUSS	≤9	>9 and ≤15	>15		

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Appendix 3. Applicant's Pharmacokinetics Model Selection Process

The below is reproduced from Volume 1.84 pp. 29-33 of the NDA. The results of this strategy are presented in a series of Tables which are found on pp. 71-80 of Volume 1.84, these tables are reproduced below (beginning on Page 6. of this appendix).

4 DESCRIPTION OF DATA ANALYSIS PROCEDURE

4.1 POPULATION PK ANALYSIS

The population PK analysis consisted of several major steps:

1. Base PK model building;
2. Covariate model building with the First Order (FO) method;
3. Model reduction with the FO method;
4. Model reduction with the First Order Conditional method (FOCE) with interaction;
5. Model refinement;
6. Evaluation of the final model.

The NONMEM program version V level 1.1, with NM-TRAN version III level 1.1, and PREDPP version IV level 1.1 was used for this analysis [14]. The first-order and first order conditional (with interaction) methods of NONMEM [15] were used to obtain estimates of the population and individual parameters. The ~~~~ NONMEM interface [16] was used to run NONMEM. ~~~~ [17,18] and ~~~~ [19,20] were used for goodness-of-fit diagnostics and visualization of results. SAS version 6.12 [9] was used for data management.

4.1.1 Base pharmacokinetic model

One- and two-compartment linear models parameterized in terms of clearances and volumes of the compartments were fitted to the data and compared in the model building process. FO method was used. Drop in the objective function value as well as diagnostic goodness-of-fit plots guided model selection. Plots of individual and population predictions from one-compartment models versus the predictions from two-compartment models were also used for model comparisons.

4.1.2 Statistical model

The exponential error models were used to describe the inter-patient variability in all pharmacokinetic parameters, e.g., for CL:

$$CL_j = CL_{0j} \exp(\eta_{j\,CL}), \qquad \text{(Eq.1)}$$

where $\exp(\eta_{j\,CL})$ denoted the difference (proportional) between the true individual parameter (CL_j) and the typical value (CL_{0j}) predicted for an individual with covariates equal to those of patient j. In the base model without covariates, CL_{0j} is the same for all individuals, and it was denoted by CL_0. Inter-patient variability was modeled the same way for the other parameters. The individual random effects, η's (e.g., $\eta_{j\,CL}$), are random variables with a mean of zero and variances of ω^2 (e.g., ω^2_{CL}). The models with the

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 30 of the NDA.

diagonal and correlated variance-covariance matrix (Ω) of inter-individual random effects was used.

Random residual variability was modeled using a combined additive and constant CV error model:

$$Y_{ij} = F_{ij} + F_{ij}\varepsilon^{P}_{ij} + \varepsilon^{A}_{ij}. \qquad \text{(Eq. 2)}$$

Y_{ij} and F_{ij} were the i^{th} measured and model predicted plasma concentrations for the j^{th} patient, respectively. The parameters ε^{P}_{ij} and ε^{A}_{ij} denoted the random residual error for the constant coefficient of variation (CV) and additive portion of the error, respectively.

Means of all the residual error terms were assumed to be equal to zero; variances were denoted as σ^2_P and σ^2_A, respectively. The random variables ε^{P}_{ij} and ε^{A}_{ij} were assumed to be independent.

A proportional error model only (without the additive part) was also tested.

4.1.3 Covariate model structure

The following demographic, clinical laboratory values, disease indicators and concomitant medications were considered in the analysis:

Demographic:	gender (SEX), age (AGE), weight (WTB), race (RACE), body surface area (BSA), body mass index (BMI), lean body weight (LBW), smoking (SMOK), and alcohol consumption (ALCO);
Clinical laboratory values:	Baseline values of estimated creatinine clearance (CRCL and CSAL), total protein (PROT), creatine kinase (CPK), total bilirubin (BILI), alkaline phosphatase (ALK), asparate aminotransferase (SGOT), and alanine aminotransferase (SGPT);
Disease indicators:	Baseline values of total PANSS score (BPD) and diagnosis (schizophrenia versus schizoaffective disoder, DIAG);
Concomitant medications:	groups A, B,C, D, E , and G (GRA, GRB, GRC, GRD, GRE, GRG) (See description of the groups in Section 3.1.3.), lorazepam (CF1), ketoconazole (CA1), haloperidol (CB1), ranitidine hydrochloride (CB2), combination antacids and adsorbents (CC1), magnesium hydroxide (CC2), aluminum hydroxide (CC3), famotidine (CD1), omeprazole (CD2), clonazepam (CG1), and temazepam (CG2).

Body surface area (BSA) and lean body weight (LBW) were very highly correlated with weight (WTB); therefore they were not used during model building. They were only explored during model refining stage.

In addition, study (STUD) and dose group (GRP) were also considered. They were not explicitly incorporated in NONMEM models, but were used for diagnostics.

Gender, race, smoking, alcohol consumption, diagnosis, study, and presence of concomitant medications were modeled as categorical covariates. The other covariates

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 31 of the NDA.

were modeled as continuous. Concomitant medications were modeled as time-varying covariates, whereas all the other covariates were modeled as time-independent.

The exponential (proportional) model for covariates was first tried for all the covariates. Continuous covariates were centered about the median (or a value close to the median) of the distribution of the respective covariate in the population. For example, the influence of weight on clearance CL_j was modeled as:

$$CL_{0j} = CL_0 \exp((WT_j - \text{median}(WT_j))/\text{median}(WT_j)) * CL_{WT}), \quad \text{(Eq. 3)}$$

where CL_{0j} was the typical value of clearance predicted for an individual with covariates equal to those of patient j, CL_0 denoted the typical clearance for an individual with the median value of weight, and CL_{WT} was an estimated effect of weight on clearance. The expression

$$\exp((WT_j - \text{median}(WT_j))/\text{median}(WT_j)) * CL_{WT}) \quad \text{(Eq. 4)}$$

represented the proportion by which predicted clearance of the individual with weight WT_j differed from the typical clearance in the population.

Additionally, power models of the form

$$CL_{0j} = CL_0 (WT_j/\text{median}(WT_j))^{\gamma_{WT}}, \quad \text{(Eq. 5)}$$

were tried.

For the covariates with missing values in the population coded as –1 in the data set (SMOK, ALCO, CPK, and BPD), a separate parameter for a missing value was used when modeling the covariate.

For patients with very high estimated creatinine clearance (CRCL or CSAL > 150), creatinine clearance was restricted to be below 150 mg/min, as it is commonly done [21] (the value of 150 was used in NONMEM).

4.1.4 Model building procedure

Model building was performed in several steps:

Step 1: Base model without covariates.
At this step, a compartmental model was chosen. The first order estimation method was used at this step. The objective function value, diagnostic goodness-of-fit plots, and distributions of random effects guided model selection. It was shown [22] that for FO method the actual α level is much higher than the stated nominal level when the

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 32 of the NDA.

likelihood ratio test is used (sometimes as high as $\alpha = 0.4$ for the stated nominal level of $\alpha = 0.05$). Therefore, the likelihood ratio test with the $\alpha = 0.001$ significance level (that corresponded to the drop of $\Delta = 10.83$ in the value of the objective function for one additional parameter) was used for model comparisons with the FO method.

Diagnostic goodness-of-fit plots included plots of population and individual predicted versus observed concentrations (PRED and IPRED versus DV), weighted residuals versus time (WRES versus TIME), absolute individual weighted residuals versus individual predictions (|IWRES| versus IPRED), distributions and a scatter-plot matrix of individual Bayes estimates of inter-patient random effects.

Step 2: Construction of the full covariate model.
At this step, a full covariate model was chosen. As above, the first order estimation method was used. The drop of $\Delta = 10.83$ in the value of the objective function with the addition of one parameter was judged to significantly improve the model fit.

A large portion of the covariates were time-varying covariates. Screening techniques (graphical and GAM [23] analysis) are not effective for this type of covariates and were not used in this analysis. Rather, all the covariates were incorporated into the population model.

Due to the large number of covariates needed to be tested, the model was not constructed by adding one covariate at a time to one parameter. Model building, instead, proceeded as follows. First, one covariate was added to all three parameters CL, V, and Ka. This involved adding three or more parameters to the base model. If the model with the covariate did not decrease the objective function by at least 10.83, the covariate was dropped from further investigation. If the model with the covariate passed this criterion, the models with that covariate in only one pharmacokinetic parameter were tried. If any of the models that significantly improved the fit, involved adding more than one fixed (θ) parameter (this was the case for some categorical covariates with more than two levels), they were further split into submodels with only one additional parameter (for example, a model that tested Race=Asian versus all other races in V).

All the models with one additional parameter (compared with the base model) chosen as significant were incorporated together in the full model.

Step 3: Covariate model reduction with FO method
At this step, covariates were eliminated from the full model using the backward elimination procedure. The first order estimation method was used. As before, the increase of $\Delta = 10.83$ in the value of the objective function with the deletion of one parameter from the model was a criterion for the significance of the parameter.

First, all possible models with one covariate less than in the full model were fitted to the data. The model with the lowest objective function value was compared with the full model. If the increase in the objective function was less than the critical value, the model was adopted as the new starting model. The procedure was repeated with this model

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 33 of the NDA.

serving as the full model. The procedure was repeated several times, every round starting with a model with one less covariate than on the previous round. The procedure stopped when no covariates could be eliminated.

Step 4: Model refinement
This step involved several consecutive sub-steps. First, a number of alternative models were fitted for covariates that were highly correlated in the population. This involved interchanging the covariates in the models, trying some combinations of correlated covariates, and models other than exponential (see section 4.1.3). The first-order method was used.

The differences between some of these models were subtle, so FOCE method had to be used. Also, with the large amount of data used for the analysis, there was a sense that even with the stated α =0.001 significance level, the FO method might keep spurious covariates in the model. Therefore, the model reduction procedure was implemented again using FOCE with interaction method, this time starting from the best model described by the FO method. The significance level α =0.01 was used. This corresponded to the increase of Δ=6.68 in the value of the objective function for one parameter excluded from the model.

Diagnostic plots of inter-individual random effects versus covariates for the reduced model suggested a couple of minor modifications to improve the model. Therefore, a few additional models (described in Section 6.3.4) were fitted before arriving at the final model.

4.1.5 Evaluation of the final population model
The predictive performance of the population model was evaluated through graphical analysis and through fitting the final model to data subsets (leverage analysis).

4.1.5.1 Graphical analysis
The final population model with the final parameter estimates was used to predict the observed concentration levels. Goodness-of-fit plots were evaluated for systematic bias. Plots of individual random effects versus covariates were evaluated to check for unaccounted dependencies on covariates. Scatter plot matrix of individual random effects was used to check the adequacy of their correlation structure.

4.1.5.2 Fitting to data subsets (leverage analysis)
All patients were randomly divided into ten groups, each consisting of roughly 10% of the total number of patients. Excluding patients from one of ten groups from the full data file created ten new data sets. The final pharmacokinetic model was fitted to each of the resulting data files, and the model parameters were compared with the estimates and confidence intervals obtained from the fit of the full data file.

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 71 of the NDA.

ST-11 Summary of NONMEM runs for base pharmacokinetic model

Run[a]	Model	Ω^b/Σ structure	OF[cd]
12	1 compartment: $CL = \theta_1 \exp(\eta_{CL})$, $V = \theta_2 \exp(\eta_V)$, $KA = \theta_3 \exp(\eta_{KA})$	Ω: DIAG(CL,V, KA) Σ:additive + proportional	22409.90
10	Same as 12	Ω: COR(CL,V, KA) Σ:additive + proportional	22400.79
11	Same as 12	Ω: COR(CL,KA), COR(V,KA) Σ:additive + proportional	22400.79
15	Same as 12	Ω: DIAG(CL,V, KA) Σ: proportional	22412.84
13	2compartments: $CL = \theta_1 \exp(\eta_{CL})$, $V2 = \theta_2 \exp(\eta_{V2})$, $KA = \theta_3 \exp(\eta_{KA})$, $Q = \theta_4 \exp(\eta_Q)$, $V3 = \theta_5 \exp(\eta_{V3})$	Ω: DIAG(CL,V2, KA, Q,V3) Σ:additive + proportional	22270.88
14	Same as 13	Ω: DIAG(CL,V2, KA), COR(Q,V3) Σ:additive + proportional	22265.43

a. The data file pk_mod1.csv was used in all the runs
b. DIAG(X,Y,Z) denotes a diagonal variance-covariance matrix of inter-individual random effects X,Y, and Z; COR(X,Y) denotes a correlation between inter-individual random effects X and Y.
c. The first order estimation method (FO) was used in all the runs.
d. OF denotes the minimum value of the objective function.

The below is reproduced from Volume 1.84 p. 72 of the NDA.

ST-12 Parameter estimates of the base pharmacokinetic model (Run 15)

Parameter	Estimate	%RSE	%CV
CL (L/h)	3.22	2.42%	
V (L)	303	4.22%	
KA (1/h)	1.37	16.7%	
Inter-individual variability			
ω^2_{CL}	0.210	7.71%	45.8%
ω^2_V	0.334	19.4%	57.8%
ω^2_{KA}	1.2	77.8%	110%
Intra-individual variability			
σ^2_p	0.0307	9.51%	17.5%

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 73 of the NDA.

ST-13 Summary of NONMEM runs for Stage 1 PK covariate model building

Run[f]	Model[a]	OF	Δ[b]
15	Base model: no covariates	22412.84	NA
20	GRA	22411.75	-1.09
21	DIA	22397.99	-14.85*
22	GRB	22396.76	-16.08*
23	GRC	22381.93	-30.91*
24	GRD	22374.97	-37.87*
25	GRE	22403.77	-9.07
26	ALK	22399.56	-13.28*
27	SGOT	22402.68	-10.16
28	SGPT	22400.16	-12.68*
29	BPD	22356.6	-56.24*
30	CPK	22389.08	-23.76*
31	GRF	22404.16	-8.68
32	GRG	22397.16	-15.68*
33	CA1	22414.48	1.64
34	CB1	22410.15	-2.69
35	CB2	22408.31	-4.53
36	CC1	22384.21	-28.63*
37	CC3	22412.43	-0.41
38	CD1	22409.89	-2.95
39	CD2	22370.17	-42.67*
40	CF1	22404.16	-8.68
41	CG1	22409.46	-3.38
42	CG2	22385.49	-27.35*
43	BILI	22392.15	-20.69*
44	SMOK	22381.87	-30.97*
45	ALCO	22381.26	-31.58*
46	SEX	22350.83	-62.01*
47	AGE	22378.05	-34.79*
48	WTB	22357.53	-55.31*
49	BMI	22403.19	-9.65
50	PROT	22409.28	-3.56
51	CSAL	22351.69	-61.15*
274	RACE(1)[c]	22405.89	-6.95
273	RACE(2,3)[d]	22406.41	-6.43
52	RACE(4,5)[e]	22365.48	-47.36*

a. Stage 1 models: linear regression model for one covariate is added to each of CL, V, and Ka. Covariate name (ex., AGE) denotes a covariate added to the model.
b. Change in the objective function compared to the final base model.
c. Covariates for RACE=1.
d. Covariates for RACE=2 and RACE=3.
e. Covariates for RACE=4 and RACE=5.
f. The data file pk_mod1.csv was used in all the runs
* Significant improvement

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 74 of the NDA.

ST-14 Summary of NONMEM runs for Stage 2 PK covariate model building

Run[a]	Model[a]	OF	Δ[b]
15	Base model: no covariates	22412.84	NA
54	CL(DIA)	22402.07	-10.77
55	V(DIA)	22412.84	0
56	KA(DIA)	22410.08	-2.76
57	CL(GRC)	22383.87	-28.97*
58	V(GRC)	22407.93	-4.91
59	KA(GRC)	22412.84	0
60	CL(GRD)	22410.79	-2.05
61	V(GRD)	22386.03	-26.81*
62	KA(GRD)	22382.6	-30.24*
63	CL(ALK)	22400.53	-12.31*
64	V(ALK)	22411.01	-1.83
65	KA(ALK)	22412.05	-0.79
66	CL(SGPT)	22407.40	-5.44
67	V(SGPT)	22404.53	-8.31
68	KA(SGPT)	22412.68	-0.16
115	CL(BPD)[c]	22403.18	-9.66
275	V(BPD)[c]	22412.45	-0.39
276	KA(BPD)[c]	22411.45	-1.39
277	CL(CPK)[c]	22411.69	-1.15
73	V(CPK)	22409.09	-3.75
74	KA(CPK)	22419.72	6.88
75	CL(GRG)	22407.66	-5.18
76	V(GRG)	22403.69	-9.15
77	KA(GRG)	22412.83	-0.01
78	CL(CC1)	22385.77	-27.07*
79	V(CC1)	22408.46	-4.38
80	KA(CC1)	22412.1	-0.74
81	CL(CD2)	22405.59	-7.25
82	V(CD2)	22376.03	-36.81*
83	KA(CD2)	22412.83	-0.01
84	CL(CG2)	22411.51	-1.33
85	V(CG2)	22397.99	-14.85*
86	KA(CG2)	22390.59	-22.25*
87	CL(BILI)	22406.76	-6.08
88	V(BILI)	22399.31	-13.53*
89	KA(BILI)	22412.84	0
90	KA(BILI)	22412.84	0
91	CL(SMOK)	22393.26	-19.58*
92	V(SMOK)	22404.87	-7.97
93	KA(SMOK)	22419.1	6.26
94	CL(ALCO)	22393.07	-19.77*
95	V(ALCO)	22404.16	-8.68
96	KA(ALCO)	22411.42	-1.42
97	CL(AGE)	22411.74	-1.1
98	V(AGE)	22379.72	-33.12*
99	KA(AGE)	22412.43	-0.41
100	CL(WTB)	22396.07	-16.77*
101	V(WTB)	22378.03	-34.81*

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 75 of the NDA.

Run[c]	Model[a]	OF	Δ[b]
102	KA(WTB)	22412.84	0
103	CL(CSAL)	22351.7	-61.14*
104	V(CSAL)	22412.69	-0.15
105	KA(CSAL)	22412.83	-0.01
106	CL(RACE=4, RACE=5)	22393.75	-19.09*
107	V(RACE=4, RACE=5)	22378.8	-34.04*
108	KA(RACE=4, RACE=5)	22414.98	2.14
109	CL(GRB)	22412	-0.84
110	V(GRB)	22402.56	-10.28
111	KA(GRB)	22409.81	-3.03
112	CL(SEX)	22354.32	-58.52*
113	V(SEX)	22411.14	-1.7
114	KA(SEX)	22410.78	-2.06

a. Stage 2 models: linear regression model for one covariate is added to each of CL, V, and Ka. The parameter name denotes the PK parameter to which a covariate is added.
b. Change in the objective function compared to the final base model
c. The data file pk_mod1.csv was used in all the runs
d. Missing value of the covariate is treated as equal to the median value in the population
* Significant improvement

ST-15 Summary of NONMEM runs for Stage 3 PK covariate model building

Run[b]	Model[a]	OF	Δ[e]	Comparison Model
120	CL(SMOK=MISSING)[c]	22393.87	0.61	91
121	CL(ALCO=MISSING)[c]	22394.09	1.02	94
122	CL(RACE=Asian)[d]	22410.08	-2.76	15
124	V(RACE=Asian)[d]	22380.71	-32.13*	15

a. Stage 3 models: a model with one additional parameter is added to the base model.
b. The data file pk_mod1.csv was used in all the runs
c. A categorical model with a different PK parameter for missing and nonmissing value of the covariate.
d. RACE= Asian versus all others
e. Change in the objective function when compared with the respective model (Comparison model)
* Significant improvement

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Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 76 of the NDA.

ST-16 Summary of NONMEM runs for PK covariate model reduction with FO method

Run[a]	Model[b]	OF[c]	Δ[d]	Comparison Run
126	Full model: CL(CSAL,SEX,GRC,WTB,ALK), V(CD2,BILI,AGE,WTB,RACE=4,CG2), KA(GRD,CG2)	22136.44		
First round: one covariate deleted from Run 126				
127	CL(CSAL)	22157.79	21.35	126
128	CL(SEX)	22160.09	23.66	126
129	CL(GRC)	22159.11	22.67	126
130	CL(WTB)	22137.16	0.72*	126
131	CL(ALK)	22142.00	5.56	126
132	V(CD2)	22149.29	12.85	126
133	V(BILI)	22142.95	6.51	126
134	V(AGE)	22172.01	35.57	126
135	V(WTB)	22169.65	33.22	126
136	V(RACE=4)	22163.28	26.85	126
137	KA(GRD)	22140.49	4.05	126
138	KA(CG2)	22138.82	2.38	126
Second round: one covariate deleted from Run 130				
139	CL(CSAL)	22168.22	31.06	130
140	CL(SEX)	22169.80	32.63	130
141	CL(GRC)	22159.40	22.24	130
142	CL(ALK)	22142.40	5.24	130
143	V(CD2)	22150.66	13.50	130
144	V(BILI)	22143.63	6.47	130
145	V(AGE)	22172.75	35.59	130
146	V(WTB)	22170.42	33.26	130
147	V(RACE=4)	22164.24	27.08	130
148	KA(GRD)	22141.20	4.03	130
149	KA(CG2)	22139.71	2.54*	130
Third round: one covariate deleted from Run 149				
150	CL(CSAL)	22170.93	31.22	149
151	CL(SEX)	22163.91	24.20	149
152	CL(GRC)	22161.65	21.94	149
153	CL(ALK)	22144.79	5.08	149
154	V(CD2)	22150.68	10.97	149
155	V(BILI)	22146.07	6.36	149
156	V(AGE)	22175.35	35.65	149
157	V(WTB)	22172.65	32.95	149
158	V(RACE=4)	22166.77	27.06	149
159	KA(GRD)	22143.79	4.08*	149
Fourth round: one covariate deleted from Run 159				
160	CL(CSAL)	22175.36	31.57	159
161	CL(SEX)	22167.21	23.42	159
162	CL(GRC)	22166.11	22.32	159
163	CL(ALK)	22149.41	5.62*	159
164	V(CD2)	22183.20	39.41	159
165	V(BILI)	22150.41	6.63	159
166	V(AGE)	22179.19	35.41	159

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 77 of the NDA.

Run[a]	Model[a]	OF[b]	Δ[c]	Comparison Run
167	V(WTB)	22176.25	32.47	159
168	V(RACE=4)	22171.16	27.37	159
Fifth round: one covariate deleted from Run 163				
169	CL(CSAL)	22178.55	29.15	163
170	CL(SEX)	22177.85	28.44	163
171	CL(GRC)	22173.41	24.00	163
172	V(CD2)	22189.35	39.95	163
173	V(BILI)	22156.35	6.94*	163
174	V(AGE)	22184.16	34.76	163
175	V(RACE=4)	22177.11	27.71	163
176	V(WTB)	22182.79	33.38	163
Sixth round: one covariate deleted from Run 173				
177	CL(CSAL)	22185.71	29.36	173
178	CL(SEX)	22184.64	28.30	173
179	CL(GRC)	22180.14	23.79	173
180	V(CD2)	22194.65	38.30	173
181	V(AGE)	22190.64	34.29	173
182	V(WTB)	22193.75	37.40	173
183	V(RACE=4)	22188.53	32.18	173

a. Model with one less covariate as compared with the comparison model. P(COV) denotes a PK parameter P for which a relationship with the covariate COV is fixed to zero. For example, CL(SEX) denotes a model without SEX in CL compared to the Comparison Run for the respective round.
b. Objective function value
c. Change in the objective function compared to Comparison Run
d. The data file pk_mod1.csv was used in all the runs
* Model deleted after the respective round

ST-17 Summary of NONMEM runs for PK model refinement: FO method

Run[a]	Model[b]	OF	Δ[c]	ΔNpar[d]
184	Model as in Run 173, but with the data set pk_mod1_subwt.csv: CL(CSAL, SEX, GRC), V(CD2, AGE, WTB, RACE=4)	22077.32		
185	CL(WTB) instead of CL(SEX)	22106.62	29.30	0
186	CL(BSA) instead of CL(SEX)	22103.38	26.05	0
187	CL(POWER WTB) instead of CL(SEX)	22106.23	28.90	0
190	CL(POWER WTB,BMI) instead of CL(SEX,CSAL)	22077.13	-0.20	0
191	CL(POWER WTB, BMI) instead of CL(SEX,GRC)	22093.18	15.85	0
196	CL(LBW) instead of CL(SEX)	22082.52	5.20	0
197	CL(linear LBW) instead of CL(SEX)	22081.24	3.92	0
188	CL(POWER WTB,BMI) instead of CL(SEX)	22066.06	-11.26	1
189	CL(BSA,BMI) instead of CL(SEX)	22067.93	-9.39	1
192	CL(linear WTB,BMI) instead of CL(SEX)	22066.88	-10.44	1
193	As 192, but V linear in WTB	22067.83	-9.50	1
198	CL(linear LBW,BMI) instead of CL(SEX)	22069.86	-7.47	1

a. The data file pk_mod1_subwt.csv was used in all the runs.
b. If not noted otherwise, the description specifies the difference from Run 184.
c. Change in the objective function compared to Run 184
d. Change in the number of estimated parameters compared to Run 184

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 78 of the NDA.

ST-18 Summary of NONMEM runs for PK model refinement: reduction with FOCEI.

Run[a]	Model[b]	Converge	OF[c]	Δ[d]	Comparison Run
199	As 192, but FOCEI method	Y	21972.47		
First round: one covariate deleted from Run 199					
201	CL(GRC)	N	21975.36	2.88*	199
200	CL(CSAL)	N	21977.86	5.39	199
204	CL(WTB)	N	21979.91	7.43	199
205	CL(BMI)	N	21980.13	7.65	199
206	V(CD2)	Y	21972.85	0.38*	199
207	V(AGE)	N	21983.38	10.90	199
208	V(WTB)	N	22005.02	32.55	199
209	V(RACE=4)	Y	21976.70	4.23	199
215	CL(GRC)-V(CD2)	Y	21975.70	3.22*	199
Second round: one covariate deleted from Run 215					
232	CL(CSAL)	Y	21981.15	5.45	215
233	CL(WTB)	N	21983.17	7.47	215
234	CL(BMI)	N	21983.43	7.73	215
235	V(AGE)	N	21985.35	9.66	215
236	V(WTB)	Y	22008.28	32.59	215
237	V(RACE=4)	Y	21979.76	4.07*	215
Third round: one covariate deleted from Run 237					
212	CL(CSAL)	N	21985.07	5.31*	237
238	CL(WTB)	Y	21988.46	8.70	237
239	CL(BMI)	Y	21986.47	6.70	237
240	V(AGE)	Y	21990.29	10.52	237
241	V(WTB)	Y	22013.54	33.78	237
First round: one covariate deleted from Run 212					
217	CL(BMI)	Y	21997.66	12.59	212
224	CL(WTB)	Y	22005.29	20.22	212
226	V(WTB)	Y	22019.41	34.34	212
225	V(AGE)	Y	21994.48	9.41	212
Further refinement					
252	CL(LBW) instead of CL(WTB,BMI)	Y	21982.79	-2.28	212
254	add CL(MILD) to 252	Y	21978.58	-4.21	252
263	As 254, but MILD is based on CRCL, not CSAL	Y	21979.42	0.85	254
260	Final for PK/PD: model as 254, but with pk_mod1_cor1.csv	Y	22056.90		
262	Final PK: as 252, but with pk_mod1_cor1.csv	Y	22063.89		

a. Where not noted otherwise, the data file pk_mod1_subwt.csv was used.
b. Model with one less covariate as compared with the comparison model. P(COV) denotes a PK parameter P for which a relationship with the covariate COV is fixed to zero. For example, CL(GRC) denotes a model without GRC in CL compared to the Comparison Run for the respective round.
c. Objective function value
d. Change in the objective function compared to Comparison Run
* Sub-model deleted after the respective round

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 79 of the NDA.

ST-19 Parameter estimates of the final pharmacokinetic model (Run 262)

Parameter	Parameter estimate	%RSE[a]	95% Confidence interval		CV%
			Lower bound	Upper bound	
CL_0	3.81	2.70%	3.61	4.01	
CL_{LBW}	0.498	25.9%	0.245	0.751	
V_0	293	3.45%	273	313	
V_{AGE}	0.309	28.3%	0.138	0.480	
V_{WT}	0.754	11.7%	0.581	0.927	
KA	1.06	12.2%	0.807	1.31	
Inter-individual variability					
ω^2_{CL}	0.225	7.96%	0.190	0.260	47.4%
ω^2_V	0.159	18.8%	0.100	0.218	39.9%
ω^2_{KA}	1.43	77.6%	0	3.61	120%
Residual variability					
σ^2_P	0.0302	9.50%	0.0246	0.0358	17.4%

a. %RSE is percent relative standard error (100% x SE/EST)

ST-20 Parameter estimates of the pharmacokinetic model used in PKPD (Run 260)

Parameter	Parameter estimate	%RSE[a]	CV%
CL_0	3.84	2.56%	
CL_{CRAL}	-0.150	36.7%	
CL_{LBW}	0.415	28.7%	
V_0	293	2.83%	
V_{AGE}	0.325	19.4%	
V_{WT}	0.748	9.72%	
KA	1.10	5.01%	
Inter-individual variability			
ω^2_{CL}	0.223	7.76%	47.2%
ω^2_V	0.158	15.9%	39.7%
ω^2_{KA}	1.47	20%	121%
Residual variability			
σ^2_P	0.0302	8.77%	17.4%

a. %RSE is percent relative standard error (100% x SE/EST)

Appendix 3. Applicant's Pharmacokinetics Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 80 of the NDA.

ST-21 Dependence of clearance on lean body weight

Lean body weight in the population	Lean body weight LBW (kg)	Typical clearance CL (L/h)	Fraction[a]
Min	20.6	2.51	0.70
10% quantile	45.2	3.23	0.90
Median	57.7	3.60	1.00
90% quantile	70.9	3.98	1.11
Max	84.7	4.39	1.22

a. Fraction of clearance of a typical patient with median LBW.

ST-22 Dependence of volume of distribution on weight and age

Weight in the population	Weight (kg)	Age in the population	Age (years)	Typical volume (L)	Fraction[a]
Min	43	Median	39	206	0.70
10% quantile	62	Median	39	246	0.84
Median	81	Median	39	293	1.00
90% quantile	110	Median	39	383	1.31
Max	153	Median	39	570	1.94
Median	81	Min	18	246	0.84
Median	81	10% quantile	25.3	261	0.89
Median	81	Median	39	293	1.00
Median	81	90% quantile	52	327	1.11
Median	81	Max	68	373	1.27

a. Fraction of volume of distribution of a typical patient with median weight and age.

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Appendix 4. Applicant's QT-interval Model Selection Process

The below is reproduced from Volume 1.84 pp. 40-41 of the NDA. The results of the strategy put forth on pages 40-41 are presented in a series of Tables which are found on pp. 95-97 of Volume 1.84, these tables are reproduced below (beginning on page 2. of this appendix).

4.3 PHARMACOKINETIC/SAFETY ANALYSIS

The objective of the pharmacokinetic/safety analysis was to assess the relationship between patients' aripiprazole plasma concentration and QTc prolongation. Therefore plasma concentration was the independent variable, and change of QTc from baseline was the response variable in the analysis.

Three measures of QTc interval were used in the analysis: Bazett's (QTCB), Fridericia's (QTCF) [24], and the FDA Div of Neuropharm recommended (QTCn) corrected cardiac QT interval (see Section 3.3.1 and Appendix IV). Separate analyses were performed for QTCB, QTCF and QTCn.

For each of the QTc measures, separate analyses were performed for three windows of time difference (2, 12, and 48 hours) between ECG and pharmacokinetic measurements.

In addition, separate analyses were performed for patients on aripiprazole and patients in both aripiprazole and placebo groups.

The following graphical and statistical analysis was performed for each of the response measures and time windows:

1. **Individual plots (spaghetti plots) of QTc change from baseline versus plasma concentration;**
2. **Plots of QTc change from baseline versus plasma concentration for all occasions together (Day 14, Day 28 and Early termination), and for each occasion separately;**
3. **Linear mixed-effects modeling of QTc change from baseline versus plasma concentration.**

The linear mixed-effects regression (appropriate for repeated measures design) models had the intercept and the concentration as fixed effects and patients' ID as the additive inter-individual random effect as follows:

$$\Delta QTc_{ijk} = \mu_k + \alpha_k * Conc_{ij} + \eta_{jk} + \varepsilon_{ijk}.$$

Here ΔQTc_{ijk} denoted change from baseline of the i^{th} measurement from the j^{th} patient for the k^{th} QTc measure ($k = 1,2,3$ for QTCB, QTCF, and QTCn, respectively); μ_k and α_k were the intercept and the slope for the k^{th} QTc measure; η_{jk} was the individual random effect of the j^{th} patient for the k^{th} QTc measure; ε_{ijk} was the residual error; and $Conc_{ij}$ was the i^{th} concentration measurement from the j^{th} patient (independent variable).

Appendix 4. Applicant's QT-interval Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 95 of the NDA.

ST-35 Typical drug effect (on top of placebo effect) after 30 days of dosing according to the final Duration and AUCU models

PKPD run (Model)		AUCU[a]	AUSS	Drug effect (on top of placebo)	
				With concomitant lorazepam	No concomitant lorazepam
334 (Duration)		NA	NA	-11.5	-8.9
385 (AUCU)	Min	8.47	0.319	-4.9	-4.3
385 (AUCU)	1st quartile	86.7	3.65	-12. 7	-9.6
385 (AUCU)	Median	138	5.82	-12.9	-9.4
385 (AUCU)	3rd quartile	198	8.34	-11.6	-8.3
385 (AUCU)	Max	475.0	21.9	-3.2	-2.2

a. AUCU values reached by 26-30 days of dosing

ST-36 Total change[a] from baseline of Total PANSS score in typical patients on aripiprazole after 30 days of dosing

BPD level[b]	BPD	Change from baseline[c]	
		With concomitant lorazepam	No concomitant lorazepam
Min	57	-3.3	-7.1
1st quartile	82	-11.1	-14.8
Median	93	-14.5	-18.2
3rd quartile	107	-18.8	-22.6
Max	146	-30.9	-34.7

a. Includes placebo and drug effect;

b. The first and second columns correspond to distribution of BPD in placebo patients. In patients on aripiprazole the distribution may slightly differ.

c. According to Duration model, PKPD run 334.

ST-37 Parameter estimates and p-values for change in QTCB from baseline for aripiprazole patients according to the linear mixed-effects model.

Time window[a]	Parameter	Estimate	p-value
2-hour window	Intercept	-3.18	0.300
	Conc	0.00122	0.900
12-hour window	Intercept	-2.24	0.301
	Conc	0.00157	0.818
48-hour window	Intercept	-1.51	0.465
	Conc	0.0000560	0.993

a. Maximum time difference between ECG and corresponding blood samples

Appendix 4. Applicant's QT-interval Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 96 of the NDA.

ST-38 Parameter estimates and p-values for change in QTCB from baseline for aripiprazole and placebo patients according to the linear mixed-effects model.

Time window[a]	Parameter	Estimate	p-value
2-hour window	Intercept	-2.70	0.0514
	Conc	-0.000257	0.967
12-hour window	Intercept	-2.57	0.0406
	Conc	0.00244	0.618
48-hour window	Intercept	-2.23	0.0709
	Conc	0.00184	0.704

a. Maximum time difference between ECG and corresponding blood samples

ST-39 Parameter estimates and p-values for change in QTCF from baseline for aripiprazole patients according to the linear mixed-effects model.

Time window[a]	Parameter	Estimate	p-value
2-hour window	Intercept	-4.45	0.0723
	Conc	-0.00126	0.872
12-hour window	Intercept	-4.84	0.00470
	Conc	0.00119	0.832
48-hour window	Intercept	-3.97	0.0147
	Conc	-0.000542	0.918

a. Maximum time difference between ECG and corresponding blood samples

ST-40 Parameter estimates and p-values for change in QTCF from baseline for aripiprazole and placebo patients according to the linear mixed-effects model.

Time window[a]	Parameter	Estimate	p-value
2-hour window	Intercept	-3.40	0.00270
	Conc	-0.00456	0.377
12-hour window	Intercept	-3.79	0.000200
	Conc	-0.00169	0.678
48-hour window	Intercept	-3.46	0.000500
	Conc	-0.00209	0.598

a. Maximum time difference between ECG and corresponding blood samples

ST-41 Parameter estimates and p-values for change in QTCn from baseline for aripiprazole patients according to the linear mixed-effects model.

Time window[a]	Parameter	Estimate	p-value
2-hour window	Intercept	-4.24	0.0928
	Conc	-0.000559	0.944
12-hour window	Intercept	-4.31	0.0134
	Conc	0.00139	0.807
48-hour window	Intercept	-3.52	0.0365
	Conc	-0.000232	0.966

a. Maximum time difference between ECG and corresponding blood samples

Appendix 4. Applicant's QT-interval Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 97 of the NDA.

ST-42 Parameter estimates and p-values for change in QTCn from baseline for aripiprazole and placebo patients according to the linear mixed-effects model.

Time window[a]	Parameter	Estimate	p-value
2-hour window	Intercept	-3.26	0.0045
	Conc	-0.00360	0.489
12-hour window	Intercept	-3.55	0.0006
	Conc	-0.000732	0.858
48-hour window	Intercept	-3.20	0.0016
	Conc	-0.00121	0.762

a. Maximum time difference between ECG and corresponding blood samples.

Appendix 5. Applicant's PANSS Model Selection Process

The below is reproduced from Volume 1.84 pp. 33-40 of the NDA. The results of the strategy put forth on pages 33-40 are presented in a series of Tables which are found on pp. 81-95 of Volume 1.84, these tables are reproduced below (beginning on Page 9. of this appendix).

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 pp. 33-34 of the NDA.

4.2 POPULATION PK/PD ANALYSIS

The population PK/PD analysis consisted of several major steps:

1. Base placebo model development using the data from placebo patients;
2. Covariate placebo model building;
3. Base PK/PD model development using the pharmacokinetic and pharmacodynamic data from patients on aripiprazole;
4. Base PK/PD model development using the individual exposure and pharmacodynamic data from patients on aripiprazole and placebo;
5. Covariate PK/PD model building.

As in the pharmacokinetic analysis, the NONMEM program version V level 1.1, with NM-TRAN version III level 1.1, and PREDPP version IV level 1.1 was used [14]. Throughout the PK/PD analysis, the first order conditional (FOCE) method with interaction was used to obtain estimates of the population and individual parameters. The ——— .NONMEM interface [16] was used to run NONMEM. S-Plus 2000 Professional Release 2 [18] and Xpose 2.0 [19] were used for goodness-of-fit diagnostics and visualization of results. SAS version 6.12 [9] was used for data management.

4.2.1 Placebo model

4.2.1.1 Base and covariate placebo model structure

The dependence of placebo effect (EFF_{PLAC}) on duration of placebo dosing was sought in the following form:

$$SCORE = SCORE_0 + EFF_{PLAC},$$

$$EFF_{PLAC} = SLP_{DUR} * DUR^{**}PWR_{DUR},$$

Here SCORE denotes total PANSS score at the time of measurement; $SCORE_0$ denotes the initial score at duration DUR=0; and SLP_{DUR} and PWR_{DUR} denote the slope and power of the duration term, respectively. The parameters $SCORE_0$, SLP_{DUR}, and PWR_{DUR} were the model parameters to be estimated.

The same covariates as in pharmacokinetic analysis were considered (except for the dose group) in the development of the covariate placebo model. The additive model for covariates was first tried. The covariates were added to the slope of the duration term. As in pharmacokinetic analysis, the continuous covariates were centered in the models. For example, the influence of the baseline score on typical slope was modeled as:

$$SLP_{DUR\,0j} = SLP_0 + SLP_{BPD} * (BPD_j - median(BPD_j)),$$

where $SLP_{DUR\,0j}$ was the typical slope predicted for an individual with BPD equal to BPD of patient j (BPD_j); SLP_0 denoted the typical slope for an individual with the median BPD in the population; and SLP_{BPD} was an estimated effect of BPD on slope.

In addition to the additive covariate models, the exponential models were tried at the model refining stage.

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 35 of the NDA.

4.2.1.2 Statistical placebo model

Since there are no requirements for the parameters of the empirical PD models to be positive and there is no a priori evidence of log-normality of their distributions, the additive error models were used in addition to exponential error models to describe the inter-patient variability, e.g., for SLP_{DUR}:

$$SLP_{DUR\,j} = SLP_{DUR\,0j} + \eta_{j\,SLP},$$

where $\eta_{j\,SLP}$ denoted the difference between the true individual parameter ($SLP_{DUR\,j}$) and the typical value ($SLP_{DUR\,0j}$) predicted for an individual with covariates equal to those of patient j. The models with the diagonal variance-covariance matrix of inter-individual random effects were used.

As in the pharmacokinetic modeling, random residual variability was modeled using an additive, proportional or combined error model.

4.2.1.3 Placebo model building

Development of the placebo model was performed in several steps:

Step 1: Base placebo model without covariates

At this step, models with different sets of inter-individual random effects and different residual models were tried. In addition, models that estimated the initial score with and without use of BPD were compared. The significance α level of 0.05 (Δ=3.84 for one additional parameter) was used for model discrimination.

Diagnostic goodness-of-fit plots included plots of population and individual predicted versus observed concentrations (PRED and IPRED versus DV), weighted residuals versus time (WRES versus TIME), and absolute individual weighted residuals versus individual predictions (|IWRES| versus IPRED).

Step 2: Construction of the full covariate model.

At this step, a full covariate model was chosen. As above, the drop of Δ=3.84 in the value of the objective function with the addition of one parameter was judged to significantly improve the model fit.

Plots of individual random effects versus time-invariant covariates were used to screen the covariates for inclusion in the population model. Time-variant covariates, concomitant medications, were included without pre-screening.

One covariate at a time was added to the base model. All covariates that significantly improved the fit when added alone to the base model were incorporated together in the full model.

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 36 of the NDA.

Step 3: Covariate model reduction
At this step, covariates were eliminated from the full model using the backward elimination procedure (see Section 4.1.4). As in PK section with the FOCE method, the increase of Δ=6.68 in the value of the objective function with the deletion of one parameter from the model was a criterion for the significance (α= 0.01) of the parameter.

Step 4: Model refinement
Estimates for some of the structural model parameters were small or were poorly estimated. Therefore, the models with those parameters eliminated (described in 6.4.1.2) were tried. In addition, a model with a more complex structural dependence on duration and a model with the exponential rather than additive covariate effect were tried before arriving at the final model.

4.2.2 Aripiprazole PK/PD model

4.2.2.1 Base PK/PD model

Drug effect (EFF_{DRUG}) was modeled as an increment above the placebo effect, so that total change of PANSS score from baseline was sum of the placebo and drug effect:

$SCORE = SCORE_0 + EFF_{PLAC} + EFF_{DRUG}$

A model for the drug effect was sought as a function of exposure (or total daily dose) and duration of dosing.

The following exposure and dose measures were investigated:

1.	Cumulative AUC	(AUCU)	Total exposure from start of dosing to the last day before the PANSS measurement
2.	Last AUC	(AUL)	AUC for the 24 hour period ending at the time of last dose before the PANSS measurement
3.	AUCss	(AUSS)	Steady state AUC determined from dose and clearance
4.	GRP		Dose group

The cumulative AUC and the last AUC increased with duration of dosing; the other two measures, AUSS and GRP were time-independent.

The exposure measures were computed as follows (see derivation in Appendix IV):

$$AUL = \frac{D}{V}\frac{Ka}{Ka-K}\left(\frac{1-\left(e^{-24K}\right)^{[DUR]}}{K} - \frac{1-\left(e^{-24Ka}\right)^{[DUR]}}{Ka}\right),$$

$$AUSS = \frac{D}{CL},$$

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 37 of the NDA.

$$AUCU = AUSS \cdot [DUR] + \frac{D}{V}\frac{Ka}{K-Ka}\left(\frac{e^{-24K}}{K}\cdot\frac{1-\left(e^{-24K}\right)^{[DUR]}}{1-e^{-24K}} - \frac{e^{-24Ka}}{Ka}\cdot\frac{1-\left(e^{-24Ka}\right)^{[DUR]}}{1-e^{-24Ka}}\right).$$

Here D denotes the daily dose, Ka is the absorption rate constant, K=CL/V denotes the elimination rate constant, and [DUR] denotes the number of full days of dosing.

In Study 31-93-202 doses were not constant, they were to be escalated from 5 mg to 30 mg a day during the first two weeks of the study. Therefore computations of AUL and AUCU had to be adjusted for this study as described below.

On average, in Study 31-93-202 the dose of 30 mg was attained by 15 days. For computation of AUC, it was assumed that the dose increased linearly with duration from 5 mg on day 0 to 30 mg on day 15, and that it stayed 30 mg after day 15. The adjusted last AUC (AUL_{adj}) on day DUR was assumed to be a fraction of AUL for fixed 30 mg dose, the fraction equal to the ratio of the dose on that day to the 30 mg dose. Thus, this fraction monotonically increased from day 0 to day 15, where it reached the value of 1.

For the cumulative AUC, the adjusted cumulative AUC ($AUCU_{adj}$) was also assumed to be a fraction of AUCU for the fixed 30 mg dose. The fraction was calculated as the ratio of the area under the dose versus duration curve from day 0 to day DUR over the corresponding area for the fixed 30 mg regimen. This fraction increased monotonically with duration, with faster increase in the first 15 days and slower increase thereafter.

Since doses could have been rising non-linearly and since linear approximation for the last and the cumulative AUC is a simplification, the adjustment fractions were allowed to differ from the fraction obtained using the above assumptions. This was attained by raising the fractions in some power that was estimated simultaneously with all the parameters in the PK/PD model. Later in the analysis this power was fixed to 1.

The individual exposures were used in the drug effect model. They were computed in one of two ways (both ways were tried):

1. Both the PK and PD data were kept in the data file (pkpd1_act_mod2.csv), the population PK parameters were fixed to the parameters from the final pharmacokinetic model. In this case individual exposures were computed in NONMEM simultaneously with fitting the PK/PD model.
2. Individual exposures were computed from the final pharmacokinetic model for patients on aripiprazole. For placebo patients they were assigned zero values. These parameters were added to the PD data file (pd_both.csv, with only PANSS scores, no PK data) to be used in the model as independent variables or covariates.

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 38 of the NDA.

Various combinations of functions of exposure and duration were tried for the drug effect model. The structural models and the exposure measures used are summarized in the following table. Several exposure parameters listed in one row of the table denote several separate models of the same structural form with different exposure measures as independent variables, one for each model.

Structural model form		Exposure parameters used (one at a time)
Additive models of exposure and duration		
SLPpar* PAR	+ SLPdur * DUR	AUSS
SLPpar * PAR	+ SLPdur * DUR ** PWRdur	AUSS
SLPpar * PAR**PWRpar	+ SLPdur * DUR	AUSS
SLPpar * PAR** PWRpar	+ SLPdur * DUR ** PWRdur	AUSS
Emax(PAR)	+ SLPdur * DUR ** PWRdur	AUSS
Multiplicative models of exposure and duration		
SLPpar * PAR	* DUR	AUCU, AUSS
SLPpar * PAR	* DUR ** PWRdur	AUCU, AUL, AUSS, GRP
SLPpar * PAR** PWRpar	* DUR ** PWRdur	AUCU, AUL, AUSS, GRP
(SLP_0+ SLPpar * PAR)	* DUR ** PWRdur	AUCU, AUL, AUSS, GRP
Emax(PAR)	* DUR ** PWRdur	AUCU, AUL, AUSS, GRP
Hill(PAR)	* DUR ** PWRdur	AUCU, AUL, AUSS, GRP
Other models of exposure and duration		
(SLP_0+ SLPpar * PAR)	* DUR **($PWRdur_0$+ $PWRdur_{PAR}$*PAR)	GRP
SLPdur * DUR **($PWRdur_0$+ $PWRdur_{PAR}$*PAR)		AUCU, AUL, AUSS
Models with exposure only		
SLPpar * PAR		AUCU
SLPpar * PAR** PWRpar		AUCU
Emax(PAR)		AUCU, AUL, AUSS, GRP
Hill(PAR)		AUCU, AUL, AUSS, GRP
Models with duration only		
SLPdur * DUR		
SLPdur * DUR ** PWRdur		

Here PAR denotes an exposure measure (AUCU, AUL, AUSS, or GRP), DUR denotes the duration of dosing (in days), Emax(PAR) and Hill(PAR) denote Emax and Hill models for the respective exposure measures as:

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 39 of the NDA.

Emax(PAR)=E_{max}par*PAR/(EC_{50}par+PAR),

Hill(PAR) = E_{max}par*PAR**Gamma/(EC_{50}par**Gamma +PAR**Gamma),

and SLPpar, PWRpar, SLPdur, PWRdur, SLP_0, $PWRdur_0$, $PWRdur_{PAR}$, E_{max}par, EC_{50}par, and Gamma denote the estimated parameters.

Estimated structural parameters were modeled both as fixed effects and a sum of fixed effects and additive random effects. Combined additive and proportional error models were used for modeling residual error.

The placebo effect (EFF_{PLAC}) was modeled using the model developed on the placebo data. The model was used in one of the following ways:

1. The structure and the population parameters of EFF_{PLAC} (Placebo model) were fixed to the values from the final model obtained on the placebo patients' data, and individual parameters of the Placebo model were estimated simultaneously with the PD model. This approach was used on the data with both placebo and aripiprazole patients (pd_both.csv) and on the data with aripiprazole patients only (pkpd1_act_mod2.csv).

2. Placebo model was fixed to the model for a typical placebo patient. This means that the population parameters were fixed to the values from the model on the placebo data, except the parameters for inter-individual variability that were fixed to zero. This approach was used only on the data with no placebo patients (pkpd1_act_mod2.csv).

4.2.2.2 Covariate PK/PD model

In addition to the covariates used for building the population PK model, dose (GRP) and the individual estimate of AUC at steady state (AUSS) were also used as the covariates. They were studied both as continuous and factor variables. Several different groupings were used for factors; the groupings are described in table ST-10

Variable	Level 1	Level 2	Level 3	Level 4	Level 5
GRP	2	10,15,20,30			
	2,10	15,20,30			
	2,10,15	20,30			
	2,10	15,20	30		
	2	10	15	20	30
AUSS	≤9	>9 and ≤ 15	>15		

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 40 of the NDA.

The additive regression model was used for covariates. The covariates were added to the power or slope of the duration term (for Duration model) or AUCU term (AUCU model).

4.2.2.3 PK/PD model building
Development of the model was performed in several steps:

Step 1: Base model without covariates
At this step, different structural models (see previous Section) with different exposure parameters, inter-individual random effects and different residual models were compared. The significance α level of 0.05 (Δ=3.84 for one additional parameter) was used for model discrimination. Besides the value of the objective function, the values of the parameter estimates and diagnostic plots greatly influenced the selection process (for example, parameter estimates in some models with both duration and exposure were meaningless).

Step 2: Construction of the full covariate model.
At this step, a full covariate model was chosen. As before, one covariate at a time was added to the base model. The drop of Δ=3.84 in the value of the objective function with the addition of one parameter was judged to significantly improve the model fit. All covariates that significantly improved the fit when added alone to the base model were incorporated together in the full model.

Step 3: Covariate model reduction
At this step, covariates were eliminated from the full model using the backward elimination procedure (see Section 4.1.4). As in the PK section with the FOCE method, the increase of Δ=6.68 in the value of the objective function with the deletion of one parameter from the model was a criterion for the significance (α= 0.01) of the parameter.

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 81 of the NDA.

ST-23 Summary of NONMEM runs for base placebo model

Placebo Run[a]	Model[b]	OF[c]	Δ[d]	Comparison Placebo Run
2	$SCORE_0=\theta_1 \exp(\eta_{PANS})$, $SLP_{DUR}=\theta_2+\eta_{SLP}$, $PWR_{DUR}=\theta_3$, Σ: proportional	7680.45		
3	As Run 2, but $PWR_{DUR}=\theta_3 \exp(\eta_{PANS})$	7677.95	-2.50	2
4	As Run 2, but Σ: additive + proportional	7678.23	-2.22	2
6	As Run 2, but $SCORE_0=(\theta_1+\theta_4*BPD) \exp(\eta_{PANS})$	7034.78	-645.67	2
7	As Run 6, but $SLP_{DUR}=\eta_{SLP}$	7040.02	5.24	6
8	As Run 6, but $SCORE_0=(\theta_1+\theta_4*BPD)$	7034.78	0.00	6
9	As Run 6, but $SCORE_0=\theta_4*BPD$	7038.73	3.95	6

a. The data set pd_plac.csv was used in all the runs
b. Model of the form: $SCORE = SCORE_0 + SLP_{DUR}*DUR^{**}PWR_{DUR}$; diagonal Ω matrix
c. Objective function value
d. Change in the objective function compared to Comparison Run

ST-24 Parameter estimates of the base placebo model (Placebo Run 8)

Parameter	Estimate	%RSE	SD or %CV
$SCORE_{0\ INCPT}$	4.45	31.7%	
$SCORE_{0\ BPD}$	0.945	1.58%	
SLP_{DUR}	-1.04	43.5%	
PWR_{DUR}	0.385	15.8%	
Inter-individual variability			
ω_{SLP}^2 (additive)	44.7	38.5%	SD = 6.69
Intra-individual variability			
σ_P^2	0.00864	8.21%	%CV = 9.30%

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 82 of the NDA.

ST-25 Summary of runs for placebo covariate model building.

Placebo Run[a]	Model[b]	OF[c,d]	Δ[e]
8	Base placebo model	7034.78	
11	ALCO	7031.63	-3.15
12	RACE[f]	7029.82	-4.96*
18	BPD	7026.69	-8.09*
13	GRA	7030.71	-4.06*
14	CG1	7031.78	-2.99
15	GRE	7024.21	-10.57*
17	GRG	7034.56	-0.22
19	CA1	7034.71	-0.06
20	CF1	7017.56	-17.21*
21	CG2	7034.42	-0.36
44	GRB	7034.11	-0.67
45	CB1	7028.66	-6.12*

a. The data file pd_plac.csv was used in all the runs
b. Linear regression model: one covariate is added to the slope of the duration term. Covariate name (ex., ALCO) denotes a covariate added to the model.
c. Objective function value
d. FOCE method with interaction
e. Change in the objective function compared to the base placebo model.
f. Covariate for RACE=4.
* Significant improvement

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Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 83 of the NDA.

ST-26 Summary of NONMEM runs for placebo covariate model reduction and refinement

Placebo Run[a]	Model[b]	OF[cd]	Δ[e]	Comparison Run
46	Full placebo covariate model[f]: RACE, BPD,GRA,GRE,CB1,CF1	6984.00		
First round: models with one less covariate compared to Placebo Run 46				
47	RACE	6989.22	5.22	46
48	BPD	6991.97	7.97	46
49	GRA	6987.87	3.86*	46
50	GRE	6994.06	10.06	46
51	CB1	6989.29	5.29	46
52	CF1	7002.07	18.07	46
Second round: models with one less covariate compared to Placebo Run 49				
53	RACE	6993.16	5.29*	49
54	bpd	6995.92	8.05	49
55	GRE	6997.92	10.05	49
56	CB1	6993.27	5.40	49
57	CF1	7005.86	17.99	49
Third round: models with one less covariate compared to Placebo Run 53				
58	BPD	7001.31	8.15	53
59	GRE	7003.13	9.97	53
60	CB1	6998.32	5.16*	53
61	CF1	7011.09	17.93	53
Fourth round: models with one less covariate compared to Placebo Run 60				
70	BPD	7006.98	8.66	60
71	GRE	7008.21	9.90	60
72	CF1	7016.80	18.48	60
Placebo model refinement				
42	As Placebo Run 60, but intercept PAN0 fixed to 0	6998.87	0.55	60
43	As Placebo Run 42, but GRE fixed to 0	7008.60	9.73	42
62	As Placebo Run 42, but additional decay with time	6996.94	-1.93	42
63	As Placebo Run 42, but exponential model for BPD instead of additive	6997.66	-1.20	42
65	As Placebo Run 43, but $SCORE_0$ fixed to BPD	7009.96	1.36	43

a. The data file pd_plac.csv was used in all the runs
b. Model with one less covariate as compared with the comparison model. Covariate listed denotes a covariate for which a relationship with the slope of the duration term is fixed to zero.
c. Objective function value
d. FOCE method with interaction
e. Change in the objective function compared to Comparison Run
f. Covariates listed are covariates in the slope of the duration term
* Model deleted after the respective round

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 84 of the NDA.

ST-27 Parameter estimates of the final placebo model (Placebo Run 65)

Parameter	Estimate	%RSE	%CV or SD
SLP_0	-2.66	25.6%	
SLP_{BPD}	-0.0878	32.7%	
SLP_{CFI}	1.82	35.9%	
Power	0.371	15.3%	
Inter-individual variability			
ω^2	44.0	36.1%	SD= 6.63 additive
Residual variability			
σ^2_p	0.00859	8.23%	CV = 9.27%

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The below is reproduced from Volume 1.84 p. 85 of the NDA.

ST-28 Summary of NONMEM runs for base PK/PD model with no placebo patients in the data file.

PKPD run[a]	Model form[b,c]	Parameter (PAR)[d]	Random effects[e]	Conv[f]	Bound[g]	OF[h]
Multiplicative models of exposure and duration						
4	SLPpar* PAR * DUR** PWRdur, fixed adjustment[i]	AUCU	EFF	Y	N	31285.11
11	SLPpar* PAR * DUR** PWRdur	AUCU	EFF	Y	N	31283.96
12	SLPpar* PAR * DUR** PWRdur, no adjustment[j]	AUCU	EFF	Y	N	31290.76
13	SLPpar* PAR * DUR** PWRdur	AUCU	EFF	Y	N	31283.96
15	SLPpar* PAR * DUR** PWRdur	AUCU	EFF, PWRdur	Y	N	31276.61
17	SLPpar* PAR * DUR	AUCU	EFF	Y	N	31359.14
18	SLPpar* PAR * DUR** PWRdur	AUCU	PWRdur	Y	Y	31235.19
19	SLPpar * PAR** PWRpar * DUR ** PWRdur	AUCU	PWRpar, PWRdur	N	N	31238.29
20	SLPpar* PAR * DUR** PWRdur	AUCU	SLPpar	Y	N	31283.96
22	SLPpar* PAR * DUR** PWRdur	AUCU	SLPpar, PWRdur	Y	N	31276.61
23	SLPpar * PAR** PWRpar * DUR ** PWRdur	AUCU	SLPpar, PWRdur	N	N	31268.40
24	SLPpar * PAR** PWRpar * DUR ** PWRdur	AUCU	SLPpar, PWRpar, PWRdur	Y	Y	31235.62
122	SLPpar* PAR * DUR** PWRdur, typical placebo effect[k]	AUCU	SLPpar, PWRdur	Y	N	31711.30
124	SLPpar * PAR** PWRpar * DUR ** PWRdur, typical placebo effect[k]	AUCU	SLPpar, PWRpar, PWRdur	Y	Y	31343.31
71	SLPpar* PAR * DUR** PWRdur	AUL	EFF	Y	N	31293.69
72	SLPpar* PAR * DUR** PWRdur	AUL	SLPpar, PWRdur	Y	N	31283.56
73	SLPpar * PAR** PWRpar * DUR ** PWRdur	AUL	SLPpar, PWRpar, PWRdur	N	N	31237.73
9	SLPpar* PAR * DUR** PWRdur	AUSS	EFF, PWRdur	Y	N	31359.69
37	SLPpar* PAR * DUR** PWRdur	AUSS	SLPpar, PWRdur	Y	N	31283.52
38	SLPpar * PAR** PWRpar * DUR ** PWRdur	AUSS	SLPpar, PWRpar, PWRdur	N	N	31435.03

The below is reproduced from Volume 1.84 p. 86 of the NDA.

39	SLPpar * PAR** PWRpar * DUR ** PWRdur	AUSS	SLPpar, PWRdur	N	N	31498.37
PKPD run[a]	Model form[cc]	Parameter (PAR)[d]	Random effects[e]	Conv[f]	Bound[g]	OF[h]
10	SLPpar* PAR * DUR** PWRdur	GRP	EFF, PWRdur	Y	N	31358.33
51	SLPpar* PAR * DUR** PWRdur	GRP	SLPpar, PWRdur	Y	N	31268.26
52	SLPpar * PAR** PWRpar * DUR ** PWRdur	GRP	SLPpar, PWRpar, PWRdur	N	N	31252.34
53	SLPpar * PAR** PWRpar * DUR ** PWRdur	GRP	SLPpar, PWRdur	N	N	31253.83
Models with exposure only						
16	SLPpar* PAR	AUCU	EFF	Y	N	31340.38
25	HILL(PAR)	AUCU	Emaxpar, EC50par, Gamma	N	N	31223.20
26	HILL(PAR)	AUCU	Emaxpar, Gamma	N	N	31227.43
27	HILL(PAR)	AUCU	Emaxpar, EC50par	N	N	31224.54
28	HILL(PAR)	AUCU	EC50par, Gamma	N	N	31217.49
29	HILL(PAR)	AUCU	EC50par	N	N	31218.43
30	HILL(PAR)	AUCU	Gamma	N	N	31224.36
31	HILL(PAR)	AUCU	Emaxpar	Y	N	31217.93
32	HILL(PAR)	AUCU		Y	N	31217.93
36	EMAX(PAR)	AUCU	EC50par	N	N	31223.15
128	HILL(PAR), typical placebo effect[z]	AUCU	EC50par, Gamma	N	N	32844.04
129	HILL(PAR), typical placebo effect[z]	AUCU	EC50par	NR	N	
130	HILL(PAR), typical placebo effect[z]	AUCU	Gamma	NR	N	
131	HILL(PAR), typical placebo effect[z]	AUCU	Emaxpar	Y	Y	31272.98
132	HILL(PAR), typical placebo effect[z]	AUCU		Y	N	32186.60
136	EMAX(PAR), typical placebo effect[z]	AUCU	EC50par	N	N	32184.66
74	HILL(PAR)	AUL		Y	Y	31225.29
75	HILL(PAR)	AUL	Emaxpar	N	Y	31225.29
76	EMAX(PAR)	AUL	EC50par	N	N	31265.25
33	HILL(PAR)	AUSS		Y	Y	31240.05
34	HILL(PAR)	AUSS	Emaxpar, EC50par,	N	N	31233.35

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 87 of the NDA.

PKPD run[a]	Model form[bc]	Parameter (PAR)[d]	Gamma Random effects[e]	Conv[f]	Bound[g]	OF[h]
35	EMAX(PAR)	AUSS	Emaxpar, EC50par	Y	N	31230.93
40	EMAX(PAR)	AUSS	EC50par	N	N	31240.61
41	EMAX(PAR)	AUSS	Emaxpar	Y	N	31230.93
42	HILL(PAR)	AUSS	Emaxpar	Y	Y	31233.34
44	HILL(PAR)	AUSS	EC50par	Y	Y	31233.34
45	HILL(PAR)	AUSS	EC50par, Gamma	N	N	31302.36
46	HILL(PAR)	AUSS	Emaxpar, Gamma	Y	Y	31233.34
133	HILL(PAR), typical placebo effect[i]	AUSS		Y	Y	32220.69
134	HILL(PAR), typical placebo effect[i]	AUSS	Emaxpar, EC50par, Gamma	NR	N	
48	HILL(PAR)	GRP		Y	N	31230.93
49	HILL(PAR)	GRP	Emaxpar, EC50par, Gamma	N	N	31214.81
50	EMAX(PAR)	GRP	Emaxpar, EC50par	N	N	31236.06
54	EMAX(PAR)	GRP	EC50par	N	N	31260.63
55	EMAX(PAR)	GRP	Emaxpar	Y	Y	31234.78
56	HILL(PAR)	GRP	Emaxpar	Y	Y	31214.80
57	HILL(PAR)	GRP	Gamma	Y	N	31246.66
58	HILL(PAR)	GRP	EC50par	N	N	31266.69
59	HILL(PAR)	GRP	EC50par, Gamma	NR	N	
60	HILL(PAR)	GRP	Emaxpar, Gamma	Y	Y	31214.81
61	HILL(PAR)	GRP	Emaxpar, EC50par	N	N	31214.81
Models with duration only						
62	SLPdur * DUR ** PWRdur		SLPdur, PWRdur	Y	N	31230.93
63	SLPdur * DUR ** PWRdur		PWRdur	Y	N	31230.93
162	SLPdur * DUR ** PWRdur, typical placebo effect[i]		SLPdur, PWRdur	N	N	33459.33

a. The data file pkpd1_act_mod2.csv was used in all the runs.

The below is reproduced from Volume 1.84 p. 88 of the NDA.

b. EFF denotes the drug effect (on top of placebo effect), PAR denotes an exposure measure (AUCU, AUL, AUSS, or GRP) specified in the next column, DUR denotes the duration of dosing (in days), Emax(PAR) and Hill(PAR) denote Emax and Hill models for the respective exposure measures; SLPpar, PWRpar, SLPdur, PWRdur, SLP_Δ, $PWRdur_\Delta$, $PWRdur_{PAR}$, E_{max}par, EC_{50}par, and Gamma denote the estimated parameters.
c. Where not noted otherwise, AUCU and AUL are adjusted for Study 31-93-202, and the parameters for adjustment are estimated.
d. The exposure measure used in the model.
e. Estimated parameters that have an additive random component.
f. Convergence;
g. Estimates on the boundary
h. FOCE, minimum objective function value
i. Adjustment parameter is fixed to 1, i.e. linear assumptions are used for adjustment of AUCU and AUL in Study 31-93-202
j. No adjustment of AUCU and AUL in Study 31-93-202
k. Placebo inter-individual random effect is set to zero

The below is reproduced from Volume 1.84 p. 89 of the NDA.

ST-29 Summary of NONMEM runs for base PK/PD model with placebo patients in the data file.

PKPD run[a]	Model form[bc]	Parameter (PAR)[d]	Random effects[e]	Conv[f]	Bound[g]	OF[h]
300	From PK model compute individual exposures, output them to merge with PD information.					
Additive models of exposure and duration						
302	SLPpar* PAR + SLPdur * DUR	AUSS	SLPpar, SLPdur	Y	N	20703.11
306	SLPpar * PAR + SLPdur * DUR ** PWRdur	AUSS	SLPpar, SLPdur	N	N	20685.43
307	SLPpar * PAR**PWRpar + SLPdur * DUR	AUSS	SLPpar, SLPdur	Y	N	20702.08
311	SLPpar * PAR**PWRpar + SLPdur * DUR** PWRdur	AUSS	SLPpar, SLPdur	Y	N	20683.63
312	Emax(PAR) + SLPdur * DUR ** PWRdur	AUSS	Emaxpar, SLPdur	Y	N	20683.74
313	SLPpar * PAR**PWRpar + SLPdur * DUR** PWRdur	AUSS	SLPpar	Y	N	20716.19
Multiplicative models of exposure and duration						
303	SLPpar* PAR * DUR	AUSS	SLPpar	Y	N	20766.02
304	SLPpar * PAR * DUR ** PWRdur	AUSS	SLPpar, PWRdur	Y	N	20730.21
305	Emax(PAR) * DUR ** PWRdur	AUSS	Emaxpar, PWRdur	Y	Y	20679.02
314	(SLP0+ SLPpar * PAR) * DUR ** PWRdur	AUSS	SLP0, PWRdur	Y	N	20696.82
315	(SLP0+ SLPpar * PAR) * DUR ** PWRdur	GRP	SLP0, PWRdur	Y	N	20678.31
316	(SLP0+ SLPpar * PAR) * DUR ** PWRdur	AUL	SLP0, PWRdur	Y	N	20696.16
317	(SLP0+ SLPpar * PAR) * DUR ** PWRdur	AUCU	SLP0, PWRdur	Y	Y	20676.24
318	Same as 317 with less constrain on fraction of AUCcum for 31-93-202	AUCU	SLP0, PWRdur	Y	Y	20675.87
319	(SLP0+ SLPpar * PAR) * DUR ** PWRdur	AUSS	SLP0	Y	N	20699.20
320	SLPpar * PAR * DUR ** PWRdur	AUSS	SLPpar	Y	N	20738.89
322	SLPpar * PAR * DUR ** PWRdur	GRP	SLPpar	Y	N	20735.94
323	SLPpar * PAR * DUR ** PWRdur	GRP	SLPpar, PWRdur	Y	N	20716.40
324	SLPpar * PAR * DUR ** PWRdur	AUCU	SLPpar, PWRdur	N	N	24190.58
332	SLPpar * PAR** PWRpar * DUR ** PWRdur	AUCU	SLPpar, PWRpar	Y	Y	20687.22
Models with duration only						

The below is reproduced from Volume 1.84 p. 90 of the NDA.

308	SLPdur * DUR		SLPdur	Y	N	20713.66
PKPD run[a]	Model form[b,c]	Parameter (PAR)[d]	Random effects[e]	Conv[f]	Bound[g]	OF[h]
309	SLPdur * DUR ** PWRdur		SLPdur	Y	N	20716.82
310	SLPdur * DUR ** PWRdur		SLPdur, PWRdur	Y	N	20678.64
393	SLPdur * DUR ** PWRdur		PWRdur	Y	N	20678.64
Models with exposure only						
330	SLPpar * PAR** PWRpar[i]	AUCU	SLPpar, PWRpar	Y	N	20704.04
331	SLPpar * PAR** PWRpar	AUCU	SLPpar, PWRpar	Y	N	20702.27
394	SLPpar * PAR** PWRpar[i]	AUCU	PWRpar	Y	N	20704.04

a. The data file pd_both.csv was used in all the runs, except PKPD Run 300.
b. PAR denotes an exposure measure (AUCU, AUL, AUSS, or CRP) specified in the next column, DUR denotes the duration of dosing (in days), Emax(PAR) and Hill(PAR) denote Emax and Hill models for the respective exposure measures; SLPpar, PWRpar, SLPdur, PWRdur, SLP_{ss}, $PWRdur_{ss}$, $PWRdur_{PAR}$, E_{max}par, EC_{50}par, and Gamma denote the estimated parameters.
c. Where not noted otherwise, AUCU and AUL are adjusted for Study 31-93-202, and the parameters for adjustment are estimated.
d. The exposure measure used in the model.
e. Estimated parameters that have an additive random component.
f. Convergence;
g. Estimates on the boundary
h. FOCE, minimum objective function value
i. Adjustment parameter is fixed to 1, i.e., linear assumptions are used for adjustment of AUCU and AUL in Study 31-93-202

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 91 of the NDA.

ST-30 Summary of NONMEM runs for covariate PK/PD model building.

PKPD run[a]	Model	Conv[b]	OF[c]	Δ[d]	Comparison run
DURATION MODEL					
393	Base duration model: SLPdur * DUR ** PWRdur	Y	20678.64		
Building full duration model[e]					
326	AUSS	Y	20678.03	-0.61	393
327	GRP	Y	20765.38	86.74	393
328	AUL	Y	20678.01	-0.63	393
329	AUCU	N	20813.87	135.23	393
333	BPD	Y	20678.61	-0.03	393
334	CF1	Y	20670.60	-8.04	393
336	AGE	Y	20675.80	-2.84	393
337	SEX	Y	20678.03	-0.61	393
338	RACE=4	Y	20676.29	-2.35	393
339	BMI	Y	20678.63	0	393
340	DIAG	Y	20678.36	-0.28	393
341	GRE	Y	20675.40	-3.24	393
342	WTB	Y	20678.38	-0.25	393
358	CSAL	Y	20678.57	-0.07	393
359	ALCO	Y	20673.90	-4.73	393
360	SMOK	Y	20673.82	-4.82	393
362	LBW	Y	20678.23	-0.41	393
366	GRB	Y	20677.99	-0.65	393
367	GRG	Y	20678.63	0	393
368	CB1	Y	20675.28	-3.35	393
369	CG1	Y	20678.24	-0.39	393
370	CG2	Y	20678.52	-0.12	393
376	Full duration model. Covariates: CF1, SMOK, ALCO	Y	20665.64	-13	393
Duration model reduction[f]					
377	SMOK,ALCO	Y	20672.77	7.14	376
378	CF1,SMOK	Y	20666.40	0.76	376
379	CF1,ALCO	Y	20666.59	0.96	376
AUCU MODEL					
394	Base AUCU model: SLPper *AUCU**PWRper	Y	20704.04		
Building full AUCU model[g]					
343	BPD	Y	20703.97	-0.06	394
344	CF1	Y	20695.04	-8.99	394
345	AGE	Y	20701.23	-2.81	394
346	SEX	Y	20703.79	-0.25	394
347	WTB	Y	20703.66	-0.38	394
348	RACE=4	Y	20701.82	-2.22	394
349	BMI	Y	20704.03	-0.01	394

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 92 of the NDA.

PKPD run[a]	Model	Conv[b]	OF[c]	Δ[d]	Comparison run
350	DIAG	Y	20704.02	-0.02	394
352	GRB	Y	20700.26	-3.78	394
353	LBW	Y	20703.20	-0.84	394
354	AUSS	Y	20691.74	-12.29	394
355	SMOK	Y	20697.45	-6.59	394
356	ALCO	Y	20698.80	-5.24	394
357	CSAL	Y	20703.93	-0.1	394
371	CG2	Y	20704.02	-0.01	394
372	CG1	Y	20703.25	-0.79	394
373	CB1	Y	20701.41	-2.63	394
374	GRB	Y	20703.83	-0.21	394
375	GRG	Y	20704.02	-0.02	394
384	AUSS in SLPpar[f]	Y	20696.26	-7.78	394
386	Full AUCU model. Covariates: AUSS,CF1,SMOK,ALCO	Y	20674.28	-29.76	394
AUCU model reduction[g]					
387	AUSS,CF1,SMOK	Y	20674.54	0.26	386
391	AUSS,CF1,ALCO	Y	20676.30	2.02	386
399	CF1,SMOK,ALCO	Y	20687.68	13.4	386
400	AUSS,SMOK,ALCO	Y	20696.73	22.44	386
385	AUSS,CF1	Y	20679.58	5.04	387
401	CF1,SMOK	Y	20688.31	13.77	387
402	AUSS,SMOK	Y	20685.98	11.44	387

a. The data file pd_both.csv was used in all the runs;
b. Convergence;
c. Objective function value, FOCE method with interaction;
d. Change in the objective function compared to Comparison Run;
e. Model with one additional covariate as compared with the base (comparison) model.
f. Covariate listed denotes a covariate for which a relationship with power of the duration term is estimated.
g. Model with one less covariate as compared with the comparison model. Covariates listed are the covariates in the model
h. Covariate listed denotes a covariate for which a relationship with power of the AUCU term is estimated.
i. Covariate listed denotes a covariate for which a relationship with the slope of the AUCU term is estimated.

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 93 of the NDA.

ST-31 Summary of additional NONMEM runs for relationships with dose in PK/PD models.

PKPD run[a]	Model	Conv[b]	OF[c]
DURATION MODEL			
335	GRP<15, 15≤GRP<30, GRP=30	Y	20678.17
364	GRP= 2,10,15,20,30	Y	20673.57
365	GRP<15, GRP≥15	Y	20678.32
383	GRP= 2,10,15,20,30 in SLPdur	Y	20676.62
392	AUSS<9, 9≤AUSS≤15, AUSS>15	Y	20673.66
AUCU MODEL			
351	GRP<15, 15≤GRP<30, GRP=30	Y	20698.52
380	GRP= 2,10,15,20,30	N	20689.27
382	GRP= 2,10,15,20,30 in SLPpar	Y	20686.67

a. The data file pd_both.csv was used in all the runs
b. Convergence
c. Objective function value, FOCE method with interaction

ST-32 Parameter estimates of the final Duration PK/PD model (PKPD run 334)

Model form			
$SCORE=BPD+EFF_{PLAC}+I_{ARIP}*EFF$, $I_{ARIP}=0$ for placebo, =1 for aripiprazole patients $EFF=SLPdur*DUR**(PWRdur0+PWRdur_{CFI}*I_{CFI}+\eta)$, I_{CFI}=1, if concomitant lorazepam; =0 otherwise			
Parameter	Estimate	%RSE[a]	%CV or SD
SLPdur	-1.65	Not estimated	
PWRdur0	0.494	Not estimated	
$PWRdur_{CFI}$	0.0778		
Inter-individual variability			
ω^2	0.0558	Not estimated	SD= 0.236 additive
Residual variability			
σ^2_A	38.0	Not estimated	SD = 6.16
σ^2_P	0.00227	Not estimated	CV = 4.76%

a. Covariance step aborted, and standard errors could not be estimated.

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 94 of the NDA.

ST-33 Parameter estimates of the final AUCU PK/PD model (PKPD run 385)

Model form			
SCORE=BPD +EFF0 +I_{ARIP}* EFF , I_{ARIP} = 0 for placebo, =1 for aripiprazole patients EFF= SLPpar *AUCU**PWRpar, PWRpar= PWRpar0+ PWR_{Ass}(AUSS-12)/12+ PWR_{CP1} *I_{CP1} + η, $I_{LORAZEPAM}$=1, if concomitant lorazepam; =0 otherwise			
Parameter	Estimate	%RSE	%CV or SD
SLPpar	-1.59	25.5%	
PWRpar0	0.242	26.4%	
PWR_{Ass}	-0.231	36.5%	
$PWRdur_{CP1}$	0.0635	27.9%	
Inter-individual variability			
ω^2	0.0249	23.0%	SD =0.158 additive
Residual variability			
σ^2_A	39.0	16.1%	SD =6.24 additive
σ^2_P	0.00222	39.7%	CV =4.71%

ST-34 Typical placebo effect after 30 days of placebo dosing according to the final placebo model

BPD level	BPD	Change of total PANSS score from baseline	
		With concomitant lorazepam	No concomitant lorazepam
Min	57	8.2	1.8
1st quartile	82	0.44	-6.0
Median	93	-3.0	-9.4
3rd quartile	107	-7.3	-13.7
Max	146	-19.4	-25.8

Appendix 5. Applicant's PANSS Model Selection Process, continued

The below is reproduced from Volume 1.84 p. 95 of the NDA.

ST-35 Typical drug effect (on top of placebo effect) after 30 days of dosing according to the final Duration and AUCU models

PKPD run (Model)		AUCU[a]	AUSS	Drug effect (on top of placebo)	
				With concomitant lorazepam	No concomitant lorazepam
334 (Duration)		NA	NA	-11.5	-8.9
385 (AUCU)	Min	8.47	0.319	-4.9	-4.3
385 (AUCU)	1st quartile	86.7	3.65	-12.7	-9.6
385 (AUCU)	Median	138	5.82	-12.9	-9.4
385 (AUCU)	3rd quartile	198	8.34	-11.6	-8.3
385 (AUCU)	Max	475.0	21.9	-3.2	-2.2

a. AUCU values reached by 26-30 days of dosing

ST-36 Total change[a] from baseline of Total PANSS score in typical patients on aripiprazole after 30 days of dosing

BPD level[b]	BPD	Change from baseline[c]	
		With concomitant lorazepam	No concomitant lorazepam
Min	57	-3.3	-7.1
1st quartile	82	-11.1	-14.8
Median	93	-14.5	-18.2
3rd quartile	107	-18.8	-22.6
Max	146	-30.9	-34.7

a. Includes placebo and drug effect;

b. The first and second columns correspond to distribution of BPD in placebo patients. In patients on aripiprazole the distribution may slightly differ.

c. According to Duration model, PKPD run 334.

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

66 pages