

Pharmacokinetic Profile of a 2-Month Dose Regimen of Aripiprazole Lauroxil: A Phase 1 Study and a Population Pharmacokinetic Model

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Supplemental Information

1. Model Development

Aripiprazole (ARI) plasma concentration–time data were used for non-linear mixed-effect modeling with NONMEM[®] program version 7.3.0. PDx-Pop version 5.1 was used as the NONMEM interface.

Untransformed data were used to test three residual error models (additive error model, multiplicative error model, and combination additive and multiplicative error model). M3 methodology [1] was used to allow the inclusion of post-dose below the lower limit of quantification concentrations. Plots of weighted residuals were evaluated for homoscedasticity relative to the predicted concentrations and time after dosing.

As used in the prior population pharmacokinetic (PopPK) model [2], Monte Carlo Importance Sampling with maximum a posteriori (IMPMAP) was the starting method of parameter estimation. Alternative methods, including first-order (FO), first-order conditional estimation (FOCE), iterative two stage (ITS), IMP expectation-maximization, and stochastic approximation expectation-maximization (SAEM), were to be applied if IMPMAP failed to converge on reliable parameter estimates. All estimation methods used the interaction option on the \$EST record. More efficient methods (e.g., FO and ITS) were used for exploratory purposes and to obtain initial estimates for alternative methods if run times were an issue. Composite methods were created by using multiple \$EST statements so that final estimates from one method served as initial estimates for the next. “Mu Referencing [3]” was used to improve the efficiency of computations when ITS, IMP, IMPMAP, and SAEM methods were used.

Both inter-individual variability (IIV) and inter-occasion variability (IOV) were regarded as random quantities and were modeled in terms of eta (η) variables. The etas across individuals ($\eta_{i,p}$) for each model parameter (P) were generally assumed to have a mean of zero; the variance of ω_p^2 described in IIV and IOV for each model parameter identified the expected distribution of the individual parameter values (P_i) around the typical population value (TV_P). In the present modeling, IIV was incorporated exponentially, where $\ln(P_i) = \ln(TV_P) + \eta_{i,p}$. By taking the square root of the variance, this approach allowed for an approximation of the coefficient of variation (CV) of TV_P when the variance was small (<0.15). When the variance exceeded 0.15, the CV for TV_P was computed from $\sqrt{e^{\omega_p^2} - 1}$.

The variance-covariance matrix (Ω) for all parameters with modeled IIV first took a diagonal form. After accounting for the influence of covariates, off-diagonal elements were added to Ω as appropriate to account for observed correlations. Decisions regarding the inclusion of off-diagonal elements were based on the goodness-of-fit criteria. Preference was given to models with off-diagonal elements when the goodness-of-fit criteria demonstrated no clear difference, and when the addition of these elements did not introduce numerical instability to the estimation process. SAEM, IMP, and MAP estimation methods are more robust than FOCE for estimating off-diagonal elements in Ω . A full-block Ω , or groups of full-block Ω , was preferred when these methods were applied.

The goodness-of-fit for a model was assessed by a variety of plots and computed metrics, including plots of population and individual predictions vs observations and vs time, plots of conditional/individual weighted residuals vs predictions and vs time, histograms and quartile–quartile plots of conditional/individual weighted residuals and of the etas, scatter plots of eta pairs and eta vs modeled covariates, and plots overlaying observed and predicted values

vs time. The relative standard error of the parameter estimates was also used to evaluate goodness-of-fit. Mean and median η values were examined to ensure that they were centered at zero and showed no obvious bias. The structure of the base model was expanded as necessary to best reflect the characteristic shape of the observations over time. Characterization of treatment-specific drug input functions were explored as necessary to accommodate alternative dosing conditions represented in the data (e.g., oral vs intramuscular [IM] absorption, and lag time to represent delayed absorption for the long-acting formulation). When a base model had been identified, the influence of covariates was assessed.

2. Covariate Evaluation

Baseline covariates were obtained from observations on the first day of dosing or, if not available, from screening. They included continuous (dose, age, body weight) and categorical covariates (race, ethnicity, gender, particle size of the 1064 mg dose, CYP2D6 phenotype, route of administration, dose regimen). CYP2D6 genotyping for alleles was primarily gel based, although TaqMan was the primary method used for CYP2D6*2 with sequencing as a backup method. The classification system for determining CYP2D6 metabolizer status is shown in Supplemental Tables 5 and Supplemental Table 6. CYP2D6 genotypes for the dataset were: poor metabolizers (PM, $n = 25$), extensive metabolizers ($n = 416$), intermediate metabolizers ($n = 183$), or inconclusive ($n = 3$) or missing ($n = 73$). No CYP2D6 ultra-rapid metabolizers were in the dataset. The available covariates were evaluated and selected for inclusion in the full covariate model based on one or more of the following criteria: if plots of individual estimates vs covariates demonstrated a trend; a statistically significant covariate effect was found by univariate analysis of variance for categorical covariates or by regression analysis for continuous covariates; physiological or pharmacological rationale; or information from prior analyses or published sources. Continuous covariates were centered at their typical values, and categorical covariates were tested and incorporated in the model as a series of index variables taking on values of zero or 1.

The full model with backward deletion approach was used for covariate modeling. All covariate-parameter relationships of interest were entered in the model simultaneously. Highly correlated covariates may have been tested in separate models in order to avoid confounding in the estimation of covariate effects. A backward deletion was performed where the relative influence of each covariate on the model was re-evaluated by deleting it from the full model on an individual basis. A finite number of iterations that produced a stable objective function value

(OFV) and minimal movement in proportional error terms for the base model was used for the covariate analysis. For any covariate to have a significant influence, the OFV must have decreased by >2 times the standard deviation of the OFV compared with the model without the covariate. The changes in OFV were considered in conjunction with other goodness-of-fit plots and metrics. Significant differences in OFV that were not associated with improvements in goodness-of-fit were critically reviewed for indications of model misspecification.

3. Final Model Evaluation

The predictive performance of the final model was assessed by applying a posterior visual predictive check (VPC), and by calculating the percentage of the observations outside the 90% prediction intervals (PIs). The VPCs were presented by study and by regimen within study A105. The final model and associated dataset were used to simulate 250 datasets based on the covariates, sampling times, and the dosing histories contained in the original dataset. The median, 5th, and 95th percentiles of the original concentration data were then compared with the 95% confidence interval (95% CI) of the median, 5th, and 95th percentiles of the simulated data for each time point; this comparison was used to evaluate whether the derived model and associated parameters were consistent with the data.

4. Description of the Base Model

The population pharmacokinetics (PopPK) model [2] was a complex model that described ARI concentration–time data containing four IM dosing compartments and one oral ARI dosing compartment, one central compartment, and one peripheral compartment each for ARI and dehydro-aripiprazole described by 15 parameters, of which correlations between 12 of them were estimated in a full OMEGA block. As A105 had up to seven IM administrations of aripiprazole lauroxil, the 2MPopPK model was expanded by adding an additional three IM dosing depots (with input duration [D1] and absorption lag time [ALAG] consistent across depots) in order to perform a stationary assessment using the PopPK final model parameter estimates. As A105 data were modeled in the absence of any oral ARI administration, the oral aspects of the model (first-order rate of absorption [Ka] and bioavailability following IM administration [FIM]) were fixed to the estimates from the PopPK final model. The bioavailability of oral ARI (FPO) was fixed to 1.0 as the reference treatment, and FIM was expressed relative to oral ARI. The previous covariate effects of the central apparent volume of distribution for ARI (VC/F) increasing with weight (fixed at allometric scaling value of 1.0) and lower apparent clearance of ARI (CL/F) in CYP2D6 PMs were

retained. Attempts to model the A105 data alone or in combination with data from the previous studies suggested that the prior final model was over-parameterized; in particular, the number and correlation of IIV terms in the full OMEGA block. As a result, modeling only the ARI concentration–time data was evaluated.

The base model contained 10 structural parameters: D1 (the duration of zero-order input), ALAG, Ka, VC/F, CL/F, FIM (bioavailability of the IM injection relative to oral ARI), peripheral apparent volume of distribution for ARI (VP/F), inter-compartmental clearance for ARI (Q/F), baseline concentration of ARI (ARI(0)), and FPO, which was fixed to 1.0 as the reference treatment. Q/F and VP/F were fixed to estimates from the PopPK model and ARI(0) was fixed to a value estimated during base model development (0.915 ng/mL). As in the PopPK model, FPO was fixed to 1.0 and used as the reference route of administration. The model contained IIV for all structural parameters with correlation between eight of the terms estimated in an OMEGA block. The IIV for ARI(0) was not included in the block nor was the IIV for FPO, which was fixed to 0 as per the previous final model. The model contained IOV on duration, allowing variability between IM dosing occasions to be quantified. Rather than excluding patients or applying a baseline correction to quantifiable predose concentrations, all data were used unchanged in the analysis using the baseline term.

5. Description of the Covariate Model

Two covariate effects from the PopPK model (VC/F increase with weight and for lower CL/F in CYP2D6 PMs) were retained and five additional covariate effects were included in the base model – surface area on FIM, ALAG and D1, and race and gender on CL/F – for a total of seven in the full model (Supplemental Table 3). Given the limited number of Hispanic/Latino patients (18/682 [2.6%]) in the dataset, ethnicity was not included in the covariate analysis.

Supplemental Table 3 presents the estimates of covariate effects for the seven covariates contained within the full model. For two of the five additional covariates, the 95% CIs did not include the null value of 1.0 for no effect. These were an estimated 25% decrease in ALAG for the formulation with lower surface area and a 16% decrease in CL/F for females in comparison with males. The effect of race on CL/F and surface area on both D1 and FIM included 1.0 in the 95% CIs. As in the base model, the effect of PM CYP2D6 on CL/F did not include the null value for no effect with a 24% reduction in PMs estimated. The full model converged after 187 iterations and returned to within $\pm$ SD in OFV. Inclusion of the five additional covariates resulted in a slight increase 48-point (or

51-point using the rerun model) in OFV from the base model. As expected with such a similar OFV between base and full models, the structural parameter estimates were comparable between base and full models. Inclusion of the five additional covariates resulted in minimal reduction in estimates of IIV with between a 0.2, 1.4, and 6% reduction in IIV for CL/F, D1 and ALAG, respectively, and a 1.7% increase in IIV for FIM observed. Despite two of the five covariate effects not including the null value, inclusion of these new covariates did not result in a decrease in OFV. Therefore, all of the five additional covariates were deemed to be non-significant on the PopPK of aripiprazole.

Analysis of ETA vs covariates did not indicate any strong trends for relationships between etas for base model parameters and the covariates evaluated other than that seen in the prior model. In case there were some correlations between the covariates not evident in the ETA vs covariate plots, individual tests of the two covariates that did not contain the null value were performed. The base model with surface area on ALAG included and the base model with gender on CL/F included returned OFV ($\pm$ SD) values of 90,502 ($\pm$ 9) and 90,581 ($\pm$ 23), respectively. Although these values were slightly higher than the base model, the differences were not statistically significant.

The effect of weight on VC/F was statistically significant in the PopPK model and was retained in this model (2MPopPK), along with the effect of a reduction in CL/F for CYP2D6 PMs. There were 25 CYP2D6 PM patients in this analysis (23 in the PopPK analysis) and the estimate of the reduction in CL/F (23–24% from base or full model, respectively) was comparable with that estimated in the PopPK analysis (23%). Consequently, this clinically relevant covariate was retained in the 2MPopPK model.

6. Final 2MPopPK Model

The final 2MPopPK model retained the structure of the base model (Supplemental Figure 1), and the parameter estimates are reported in Supplemental Table 7. Model stability was tested by re-running the model several times with different initial estimates to confirm reproducibility of the OFV. Furthermore, the models without the first-order rate constant would not converge and thus were not suitable for formal statistical comparisons. Analysis of goodness-of-fit plots from the final model showed that ARI concentrations were well described by model predictions and no apparent study, administration route, or dose effect on prediction bias was observed. Evaluation of VPCs of the final model indicated that, across studies and by regimen within A105, the majority of observed

concentrations were contained within the predicted 90% PIs. Using a dose-normalized, non-prediction-corrected VPC, the percentage of observed ARI concentrations that were outside the final 2MPopPK model-predicted 90% PIs ranged from 3.1% to 16%. With the exception of the every 4 weeks regimen in A105 (16%), less than 10% of observed ARI concentrations were outside the final 2MPopPK model-predicted 90% PIs.

The steady state was determined using the prior PopPK model [2] and as indicated in the aripiprazole lauroxil label [4]. Steady state was assessed using both visual check and serial linear regression in individual simulated patients. Therefore, the prior calculations to determine time to steady state informed the simulation durations for the 2MPopPK model.

Supplemental Tables and Figures

Supplemental Table 1 Inclusion and exclusion criteria for the phase 1 study

Inclusion criteria	• Between 18 and 65 years of age • A Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia or schizoaffective disorder at screening, and clinically stable as evidenced by: ○ No psychiatric hospitalizations 3 months prior to screening ○ Clinical Global Impression – Severity (CGI-S) score of ≤ 3 (mild) at screening • On a stable antipsychotic medication regimen without any antipsychotic treatment regimen changes for at least 2 months prior to screening • Demonstrated ability to tolerate aripiprazole, either by history or by establishing tolerability with test doses during the screening period
Exclusion criteria	• Had received aripiprazole lauroxil or IM depot aripiprazole within 6 months, or other long-acting, injectable antipsychotic medication within 3 months prior to screening • Had received oral aripiprazole within 28 days prior to randomization • Patients receiving or anticipating treatment with known potent oral inducers or inhibitors of cytochrome P450 (CYP) 3A4 or inhibitors of CYP2D6, including prescription medications, over-the-counter medications, or dietary supplements within the 30 days prior to screening

Supplemental Table 2 Clinical trials included in the population-pharmacokinetic analysis

Study	Population	Study Design and Dosing
002 (phase 1)	Chronic stable schizophrenia (N = 84; 77% male; median age, 46 years)	Multicenter, randomized, double-blind, placebo-controlled, multiple-dose study; oral aripiprazole 10 mg QD on days 1–5; randomized to receive aripiprazole lauroxil (441 mg, 662 mg, or 882 mg) or placebo IM on Days 34, 62, 90, and 118 (gluteal injection site). PK samples were collected on Days –1, 8, 13, 24, 29, 30, 33, 35 through 47, 55, 61, 69, 76, 83, 89, 97, 104, 111, 117, 119 through 132, 139, 146, 153, 160, 167, 174, 202, and 230. A total of 7888 aripiprazole and dehydro-aripiprazole measurements were included in the dataset
101 (phase 1) [5]	Chronic stable schizophrenia (N = 46; 70% male; median age, 45.5 years)	Multicenter, randomized, open-label, single-dose study; aripiprazole lauroxil 441 mg IM on Day 1 (gluteal or deltoid injection site) ^a . PK samples were collected Days 1, 2 through 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 28, 31, 38, 45, 52, 59, 70, 80 and 89. A total of 2546 aripiprazole and dehydro-aripiprazole measurements were included in the dataset
102 (phase 1)	Chronic stable schizophrenia (N = 39; 64% male; median age, 47 years)	Multicenter, randomized, double-blind, placebo-controlled, multiple-dose study; aripiprazole lauroxil 441 mg IM on Days 1, 29, 57, and 85 (deltoid injection site; injections alternating between left and right side). PK samples were taken on Days 1, 7, 14, 29, 43, 57, 71, 85, 92, 106, 113, 141 and 169. A total of 838 aripiprazole and dehydro-aripiprazole measurements were included in the dataset
A105 (phase 1)	Stable schizophrenia (N = 140; 73% male; median age, 47 years)	Multicenter, randomized, open-label study; patients were randomized (1:1:1:1) to 1 of 4 aripiprazole lauroxil regimens: 441 mg q4wk, 882 mg q6wk, 1064 mg q8wk, or an alternate formulation of 1064 mg q8wk; oral aripiprazole was prohibited for the study duration; however, patients on other antipsychotics could continue their medication. PK samples were taken on Days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 43, 46, 50, 53, 57, 71, 85, 99, 113, 127, 141, 155, 169, 172, 176, 180, 183, 186, 190, 193, 197, 200, 204, 207, 211, 214, 217, 221, 225, 228, 232, 239, 246, 253, 281, and 309. A total of 10149 aripiprazole and dehydro-aripiprazole measurements were included in the dataset

003 (phase 3) [6]	Acute exacerbation of schizophrenia (N = 407; 69% male; median age, 40 years)	Multicenter, randomized, double-blind, placebo-controlled study; randomized to aripiprazole lauroxil (441 mg or 882 mg) or placebo IM on days 1, 29, and 57; patients in the aripiprazole lauroxil group received daily oral aripiprazole (15 mg), and those in the placebo group received oral placebo on days 1–21 under double-blind conditions (gluteal injection site). PK samples were taken on Days 1, 2, 5, 8, 15, 22, 29, 43, 57, 71, 85, 113 and 141. A total of 7615 aripiprazole and dehydro-aripiprazole measurements were included in the dataset
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^aTwo sentinel patients received aripiprazole lauroxil 221 mg in the deltoid muscle.

IM = intramuscular; QD = daily; q4wk = every 4 weeks; q6wk = every 6 weeks; q8wk = every 8 weeks.

Supplemental Table 3 Covariate effects estimated with the full model

Parameter	Parameter Estimates		
	Point Estimate	% RSE	95% CI
WT on VC/F ^a	1.00	–	–
CL/F PMs ^b	0.763	10.7	0.603, 0.923
Surface area on Duration	1.15	7.08	0.994, 1.31*
Surface area on ALAG	0.745	15.9	0.513, 0.978
Surface area on FIM	0.921	13.3	0.681, 1.16*
CL/F Females ^c	0.842	7.56	0.717, 0.967
CL/F Black/African Americans ^d	0.991	3.72	0.918, 1.06*

^aFixed as 1.0 (allometric value for WT on VC/F)

^bIn reference to non-PMs

^cIn reference to males

^dIn reference to non-Black/African Americans

*Null included in 95% CI. Despite two of the five covariate effects not including the null value, inclusion of these new covariates did not result in a decrease in OFV. Therefore, all of the five additional covariates were deemed to be non-significant.

ALAG = intramuscular lag time; CI = confidence interval; CL/F = apparent clearance of aripiprazole; FIM = bioavailability following intramuscular administration; PM = CYP2D6 poor metabolizer; RSE = relative standard error; VC/F = central apparent volume of distribution for aripiprazole; WT = body weight.

Supplemental Table 4 Simulated median aripiprazole pharmacokinetic parameters at steady state after administration of aripiprazole lauroxil at 4- to 8-week intervals

Dose (mg)	Statistic	Steady State		
		$C_{\min}$ (ng/mL)	$C_{\max}$ (ng/mL)	C_{avg} (ng/mL)
441 mg q4wk	Median	109	129	119
	25 th percentile	79	94	85
	75 th percentile	152	183	166
662 mg q4wk	Median	166	196	183
	25 th percentile	122	139	131
	75 th percentile	231	274	250
882 mg q4wk	Median	229	268	249
	25 th percentile	165	190	178
	75 th percentile	298	349	321
882 mg q6wk	Median	142	186	165
	25 th percentile	105	138	121
	75 th percentile	189	256	219
1064 mg q8wk	Median	125	182	154
	25 th percentile	92	139	115
	75 th percentile	173	255	214

A total of 500 individual aripiprazole concentration–time profiles were generated for each simulation. C_{avg} = average steady-state plasma concentration, calculated as area under the curve over the dosing interval ($\text{AUC}_{\tau/\tau}$); $C_{\max}$ = maximum steady-state plasma concentration; $C_{\min}$ = minimum steady-state plasma concentration; q4wk = every 4 weeks; q6wk = every 6 weeks; q8wk = every 8 weeks.

Supplemental Table 5 Enzyme activity associated with CYP2D6 alleles

CYP2D6 allele	Enzyme activity	Priority
*3	No activity	1
*4	No activity	2
*5	No activity	3
*6	No activity	4
*7	No activity	5
*8	No activity	6
*11	No activity	7
*15	No activity	8
*16	No activity	9
*21	No activity	10
*9	Reduced activity	11
*17	Reduced activity	12
*19	Reduced activity	13
*20	Reduced activity	14
*29	Reduced activity	15
*35	Reduced activity	16
*36	Reduced activity	17
*40	Reduced activity	18
*41	Reduced activity	19
*10	Reduced activity	20
Gene duplication	Ultrarapid activity	21
*2	Normal activity	22
*1 (wild-type)	Normal activity	23

Supplemental Table 6 Summary of gene result/phenotype association for CYP2D6

Gene result combination	Predicted phenotype
Ultrarapid activity/Normal activity	Ultrarapid metabolizer
Ultrarapid activity/Reduced activity	Extensive metabolizer
Ultrarapid activity/No activity	
Normal activity/Normal activity	
Normal activity/Reduced activity	
Normal activity/No activity	Intermediate metabolizer
Reduced activity/Reduced activity	
Reduced activity/No activity	
No activity/No activity	Poor metabolizer
Inconclusive	

Supplemental Table 7 Parameter estimates in the final population-pharmacokinetic model

Parameter	Parameter Estimates			Inter-individual Variability			
	Value	% RSE	95% CI	Value	% RSE	95% CI	CV%
Ka (h ⁻¹)*	0.803	29.9	0.333, 1.27	2.67	25.4	1.34, 4.00	367% ^d
VC/F (L)*	317	2.25	303, 331	0.182	9.34	0.149, 0.215	44.7% ^d
CL/F (L/hr)*	1.898	2.57	1.80, 1.99	0.366	8.91	0.302, 0.430	66.5% ^d
VP/F (L) ^{a,*}	2122**	—	—	2.99	14.7	2.13, 3.85	435% ^d
Q/F (L/hr) ^{a,*}	0.423**	—	—	1.13	10.6	0.895, 1.37	145% ^d
D1 (hr)*	1043	2.09	1000, 1086	0.318	10.8	0.250, 0.386	61.2% ^d
ALAG (hr)*	77.5	4.07	71.3, 83.7	0.344	10.0	0.276, 0.412	64.1% ^d
ARI(0) (ng/mL)*	0.915**	—	—	5.89	7.69	5.00, 6.78	1898% ^d
FIM*	0.571	2.55	0.542, 0.599	0.104	11.6	0.0803, 0.128	32.2%
FPO ^{b,*}	1.00**	—	—	—	—	—	—
WT ON VC/F ^b	1.00**	—	—	—	—	—	—
CL/F PMs ^{c,*}	0.767	10.2	0.614, 0.921	—	—	—	—
				Inter-occasion Variability			
D1	—	—	—	0.125	5.23	0.112, 0.345	35.4
				Residual Variability			
σ^2_{prop} ARI Non-A105	—	—	—	0.0565	1.98	0.0543, 0.0587	23.8
σ^2_{prop} ARI A105	—	—	—	0.0238	2.30	0.0227, 0.0249	15.4

*Indicates parameter was estimated on log-scale and subsequently estimates exponentiated and CIs calculated using SE

** Indicates a fixed value

^aFixed at estimate from previous final model

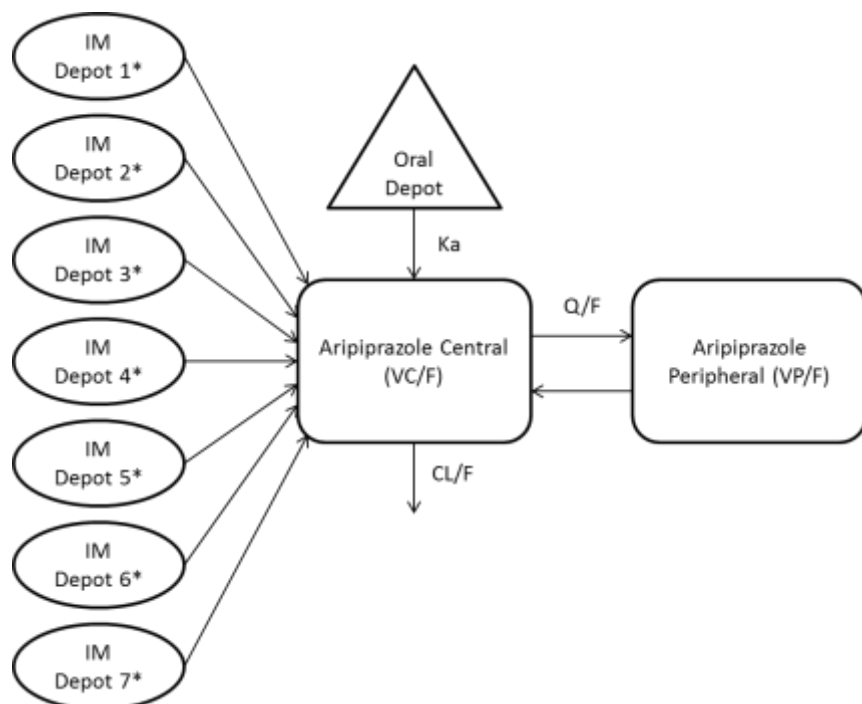
^bFixed as 1.0 (as reference for FPO and at allometric value for WT on VC/F)

^cIn reference to non-PM

^dCV calculated as $CV_{TV_P} = \sqrt{e^{\omega_P^2} - 1} * 100$ rather than square root of $\omega_P^2 * 100$

ALAG = intramuscular lag time; ARI(0) = initial amounts of aripiprazole; CI = confidence interval; CV = coefficient of variation; D1 = intramuscular duration of absorption; CL/F = apparent clearance of aripiprazole; FIM = bioavailability following intramuscular administration; FPO = oral bioavailability; Ka = oral rate of absorption; PM = CYP2D6 poor metabolizer; Q/F = intercompartmental CL for aripiprazole; RSE = relative standard error; SE, standard error; VC/F = central apparent volume of distribution for aripiprazole; VP/F = peripheral apparent volume of distribution for aripiprazole; WT = body weight.

Supplemental Fig 1 Aripiprazole PopPK model structure for aripiprazole lauroxil



*Input from each IM depot described by duration (including IOV) and ALAG, which were consistent across depots. As a result of prolonged duration of absorption of aripiprazole following IM administration, a new IM depot was added for each injection. Seven IM depots were included to accommodate the maximum number of AL injections in the clinical studies (seven in study A105) included in the analysis.

AL = aripiprazole lauroxil; ALAG = absorption lag time; CL/F = apparent total body clearance; IM = intramuscular; IOV = inter-occasion variability; Ka = oral rate of absorption; PopPK, population pharmacokinetics;

Q/F = intercompartmental CL for aripiprazole; VC/F = central volume of distribution; VP/F = peripheral volume of distribution.

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