Population Pharmacokinetic Analysis and Model-Based Simulations of Aripiprazole for a 1-Day Initiation Regimen for the Long-Acting Antipsychotic Aripiprazole Lauroxil

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Electronic Supplementary Material

MODEL DEVELOPMENT

Bioanalytical Methods and Data Retrieval

Plasma samples were analyzed for aripiprazole lauroxil, N-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole (DHA) concentrations using 2 validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) methods. The lower limit of quantification (LLOQ) was 1 ng/mL for all analytes, and the higher limit of quantification was 1000 ng/mL. All concentrations below the quantifiable limit (<LLOQ) were assigned a value of 0.5 ng/mL (ie, LLOQ/2) and were used in the analysis when M3 methodology was used. NONMEM (ICON, Gaithersburg, MD, USA) input files containing dosing and observation records and relevant covariates were created from source data for each of the studies. Elapsed time (h) from the time of the first dose was computed for individual event records for each patient based on dates and times reported for the relevant observations (ie, doses, pharmacokinetic (PK) samples, and time-dependent covariates). Disparate units for all variables were converted to a common unit as necessary to ensure consistency throughout the NONMEM input data file.

The population pharmacokinetic (PopPK) model was developed for aripiprazole only. For modeling, doses of aripiprazole lauroxil (AL) and a nano-crystalline milled dispersion of AL (AL_{NCD}) were expressed as aripiprazole equivalents. The data set was created to be as similar as possible to the existing PopPK data set for AL[1].

Pharmacokinetic Analyses Methods

NONMEM program version 7.3.0 was used in this analysis (ICON)[2]. NONMEM was run through PDx-Pop (version 5.2). Monte Carlo simulations were performed using Pharsight Trial Simulator (version 2.2.2; Certara, Princeton, NJ, USA) and NONMEM (version 7.3.0).

The data analysis consisted of the following major steps:

- Data were explored graphically to gain an understanding of the time course of aripiprazole and DHA appearance in plasma.
- Data from Study 1 were used to develop the base PopPK model.
    - A base PopPK model was developed for aripiprazole accounting for IM absorption of AL_{NCD} and conversion to aripiprazole.
    - The influence of formulation, body weight, and cytochrome P450 isoform 2D6 (CYP2D6) genotype was assessed as part of base model development.
- Final data from Study 3 were added to the data set and used to re-estimate model parameters.
- Final data from Study 2 were added to the data set and used to expand the base PopPK model to include input functions for both oral aripiprazole and intramuscular (IM) AL in addition to AL_{NCD}, estimate final model parameters, and perform a full covariate analysis.
- Data from Study 4 were added to the data set, and final model parameters were updated based on the data from 4 studies.

Overall PopPK Model Development

A base model was initially selected that appropriately described the time course of aripiprazole plasma concentrations in Study 1. The previously developed model for AL[1] served as the starting point for model development. The effect of body weight on clearance (CL) and volume (V) terms was incorporated using a fixed allometric exponent of 0.75 and 1, respectively, scaled to 70 kg[3]. The influence of both AL_{NCD} formulation and CYP2D6 genotype on relevant structural parameters was also assessed as part of the initial base model development. Structural and variance model parameters were estimated for the initial base model. Initially, base model development was performed using untransformed data. As a first step, interindividual variability (IIV) was included on all structural parameters, but the number of random interindividual error terms (ηP) could have been reduced to ensure that the model was minimized successfully and that all parameters were adequately estimated.

Plots of weighted residuals were evaluated for homoscedasticity with respect to predictions and time since dose. The structure of the base model was expanded as necessary to best reflect the characteristic shape of the observations over time. The initial base model was then expanded following the inclusion of final data from Study 3 and was used to re-estimate model parameters. On receipt of the final data from Study 2, the model was updated to include input functions for both oral aripiprazole and IM AL, existing parameters were re-estimated, and full covariate analysis was performed (Section 2).

Modeling Approach

Monte Carlo Importance Sampling EM Assisted by Mode a Posteriori (IMPMAP), used for the previous analyses[1,4], was the starting method of parameter estimation. Alternative methods, including First-Order (FO), First-Order Conditional Estimation (FOCE), Iterative Two-Stage (ITS), Monte Carlo Importance Sampling Expectation Maximization (IMP), and Stochastic Approximation Expectation Maximization (SAEM), were available if IMPMAP failed to converge on reliable parameter estimates. All estimation methods used the interaction option on the $EST record. Composite methods may have been created by using multiple $EST statements so that final estimates

from one method serve as initial estimates for the next. Mu referencing[2] was used to improve the efficiency of computations when ITS, IMP, IMPMAP, and SAEM methods were used.

Both IIV and interoccasion variability (IOV) in model parameters were regarded as random quantities and were modeled in terms of eta (η) variables. The etas across individuals (η_{i_P}) for each model parameter (P) were generally assumed to have a mean of zero and a variance of ω_P^2, which were estimated. This variance described the IIV and IOV of P and, hence, the expected distribution of the individual parameter values (P_i) around the typical population value (TVP).

While the distribution of η_{i_P} was assumed to be normal, the distribution of P_i depended on the mathematical expression relating the two.

In the present modeling activities, IIV was initially incorporated exponentially, where

$$\ln(P_i) = \ln(TV_P) + \eta_{i\_P}$$

where P_i, TV_P, and η_{i_P} are defined above, and ln is the natural logarithm function.

This form for incorporating IIV and IOV ensures that TV_P and P_i always have the same sign, correspond to the commonly observed log-normal distribution for PK parameters, and have the convenient property that the square root of ω_P^2 (ω_P) is an approximation of the coefficient of variation (CV) of TV_P when ω_P^2 is reasonably small (ie, <0.15).

When ω_P^2 exceeds 0.15, the interindividual CV for TVP was computed as $CV_{TV_P} = \sqrt{e^{\omega_P^2} - 1}$

For FOCE, the variance-covariance matrix (Ω) for all parameters with modeled IIV first took the diagonal form.

$$\Omega = \begin{bmatrix} \omega_{P_1}^2 & & & \\ & \omega_{P_2}^2 & & \\ & & \ddots & \\ & & & \omega_{P_n}^2 \end{bmatrix}$$

where Ω is the variance-covariance matrix and $\omega^2_{P1,}$ ω^2_{P2} and ω^2_{Pn} represent the variances of the η_{i_P} associated with parameters *P1*, *P2*, through *Pn*, respectively.

After accounting for the influence of covariates, the covariance between pairs of random IIV parameters (eg, η_{i_P1} and η_{i_P2} for parameters P_1 and P_2, respectively) was examined graphically by plotting η_{i_P1} versus η_{i_P2}, and off-diagonal elements were added to Ω as appropriate to account for observed correlations. Decisions regarding the inclusion of off-diagonal elements in Ω were based on the goodness-of-fit (GoF) criteria. Preference was given to models with off-diagonal elements when the GoF criteria demonstrated no clear difference and when the addition of these elements did not introduce numerical instability to the estimation process. A full-block Ω, or groups of full-block Ω, were preferred when these methods were applied.

GoF was assessed by a variety of plots and computed metrics. GoF plots included data points for observed and/or predicted data, reference lines (eg, identity, zero line), and smooth lines through the data. The following GoF plots were used for graphical model evaluation: plots of population and individual predictions versus observations and versus time, plots of conditional/individual weighted residuals versus predictions and versus time, histograms and quartile-quartile plots of conditional/individual weighted residuals and of the etas, scatter plots of eta pairs and eta versus modeled covariates, and plots overlaying observed and predicted values versus time. The relative standard error (RSE) of the parameter estimates was also used to evaluate GoF, and the 95% confidence interval (CI) for each estimated parameter was constructed based on its RSE. Mean and median η values were examined to ensure they were centered at zero and showed no obvious bias.

COVARIATE EVALUATION

Baseline covariates were obtained from observations on the first day of dosing or at screening if that value was not available. Covariates available for evaluation included continuous covariates (age and body weight [kg] at baseline) and categorical covariates (injection site [gluteal or deltoid], formulation, CYP2D6 genotype [evaluated in base model], ethnicity, sex, and race). CYP2D6 genotype was pooled into phenotypes (eg, extensive metabolizers [EMs] and intermediate

metabolizers [IMs]) in the source data sets. Body weight, formulation, and CYP2D6 genotype were evaluated as part of the initial base model development with Study 1. All other covariates were evaluated once final data from Study 3 and interim data from Study 2 were available. The covariate model was re-evaluated after receipt of the final data from Study 2. The effect of body weight on CL and V terms was incorporated using a fixed allometric exponent of 0.75 and 1, respectively, scaled to 70 kg.

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 versus 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 previous 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 0 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 to avoid confounding in the estimation of covariate effects. Backward deletion was carried out at the $p = 0.001$ (increased objective function value [OFV], <10.83 points; degrees of freedom [df] = 1) significance level where the relative influence of each covariate on the model was re-evaluated by deleting it from the full model on an individual basis. Critical values for the difference in the OFV required for a given probability was adjusted when stochastic estimation methods (eg, SAEM and IMP) were used. The order of removal could be based on:

• RSE and 95% CI of the parameter estimate

• Results of univariate analysis of variance or regression analysis

• Physiological or pharmacological rationale

Where significant covariate effects were identified, assessment of effect magnitude over a relevant range (eg, range within the data set), along with CI, were provided.

FINAL MODEL EVALUATION

The predictive performance of the final models was assessed by applying a posterior prediction-corrected visual predictive check (pcVPC)[5] and calculating the percentage of the observations outside the 90% prediction intervals (PIs)[6].

BASE MODEL DEVELOPMENT (STUDIES 1, 2, AND 3)

The base model was parameterized to describe aripiprazole after single IM administration of AL_{NCD}, single IM administration of AL, and oral aripiprazole administration from 3 Phase 1 studies (Studies 1, 2, and 3). The model contained central and peripheral compartments for aripiprazole. After AL_{NCD} administration, conversion of IM AL_{NCD} to aripiprazole was described by a double Weibull function. After AL administration, conversion of IM AL to aripiprazole was described by a zero-order process with AL IM duration of absorption (Dur) estimated and the first-order absorption of aripiprazole from the dosing depot defined as 1/Dur. Additionally, a lag time from the IM AL depot to the appearance of aripiprazole in the central compartment (ALAG) was also included in the model. First-order processes described the absorption of aripiprazole after oral dosing and the movement between central and peripheral compartments.

The model contained 16 structural parameters: first-order rate of oral absorption (Ka), apparent volume of aripiprazole central compartment (VC/F), apparent clearance of aripiprazole (CL/F), apparent volume of aripiprazole peripheral compartment (VP/F), intercompartmental clearance of aripiprazole (Q/F), AL Dur, ALAG, AL_{NCD} Weibull mean dissolution time 1 (MDT1), AL_{NCD} Weibull slope factor 1 (GAM1), AL_{NCD} Weibull mean dissolution time 2 (MDT2), AL_{NCD} Weibull slope factor 2 (GAM2), estimated AL_{NCD} Weibull fraction parameter (FRAC), predose aripiprazole concentration (Ari [0]), bioavailability after IM AL administration (FIM AL), bioavailability after IM AL_{NCD}

administration (FIM AL_{NCD}), and oral aripiprazole bioavailability ($F_{po,}$ assumed to be 1.0). Two of the bioavailability parameters were fixed. F_{po} was fixed to 1.0 as the reference route of administration, and FIM AL was fixed to 57.1% that of PO, which had been previously estimated[4]. Individual estimates of FIM AL were subsequently used to estimate the fractional change in IM bioavailability after AL_{NCD} administration.

The model contained IIV for 14 of the structural parameters with correlation between 13 of the terms estimated in an Ω block. The IIV for Ari (0) was estimated but was not included in the block nor was the IIV for F_{po}, which was fixed to 0 per the previous final model[4]. The model estimated 1 proportional residual error term, and M3 methodology was used to allow concentrations <LLOQ to be included in the analysis. The model was mu referenced and was fitted using IMPMAP with ISAMPLE of 1000. The model converged using CTYPE = 3, CITER = 10, and CINTERVAL = 1 after 101 iterations.

Model parameters were well estimated. Many %RSE were <10% and the highest was 44%; estimates of IIV were 11 to 25 %RSE. Estimates of IIV in parameters ranged between 33.6% for GAM2 and 511% for Q/F. Reflecting the low number of subjects with predose quantifiable aripiprazole concentrations, the estimate of Ari (0) was well below the LLOQ (0.0380 ng/mL vs 1.0 ng/mL) but was associated with a very high estimate of IIV.

Shrinkage for estimates of IIV ranged between 7.5% for MDT1 and 26% for Ari (0). Of the 8948 aripiprazole (ARI) concentrations included in the analysis, only 1 resulted in individual weighted residuals (IWRES) > 6, and it was retained in the PopPK analysis. Correlations between parameters in the base model ranged between –0.769 and 0.844, and the majority of the correlations were expected. Only 6 strong correlations were > ±0.7; the highest was that between CL/F and FIM AL (0.844). The model estimated the residual variability to be low at 18.9%.

DHA data was not included in the final structural model as addition of this data caused the model to become complex, resulting in instability. Hence, the model was ultimately constructed for a single analyte (aripiprazole) to produce the desired reproducibility within the model and in parameter estimates.

COVARIATE MODEL DEVELOPMENT

The previous PopPK model for ARI after the administration of AL and oral aripiprazole included covariate terms to describe an increase in VC/F with body weight (power model fixed at allometric exponent of 1.0) alongside a reduction in CL/F for CYP2D6 poor metabolizers (PMs)[4]. For CYP2D6, the data set contained EMs and IMs along with subjects whose phenotype was inconclusive, but PMs were absent. The box plot eta for CL/F versus CYP2D6 phenotype did not indicate any notable difference for non-EMs. As indicated in the analysis of Study 1 data alone, there was an insignificant change in OFV when CL/F for non-EMs was evaluated. Consequently, the CYP2D6 phenotype was not evaluated for the current data set. Based on the eta versus covariate plots, in addition to testing weight on VC/F (power model fixed at allometric exponent of 1.0), weight was evaluated on CL/F (identified for the analysis of Study 1 alone as a significant covariate) (power model fixed at allometric exponent of 0.75), AL Dur, and ALAG for AL. Additionally, age on CL/F was evaluated alongside injection site effects for potential changes in FRAC (based on AL_{NCD} injection site), AL Dur, and ALAG (both based on AL injection site). For injection site effects, the change in parameter after IM administration in the deltoid was estimated with IM administration in the gluteal used as the reference. Only the 2 injection sites were evaluated because there were insufficient numbers to estimate differences between right and left sides within an injection site. Given the limited number of Hispanic or Latino subjects (5%) in the data set, ethnicity was not included in the covariate analysis. Additionally, there were no apparent differences in model parameter estimates based on sex or race.

The base model developed from Studies 1, 2, and 3 was updated to include 8 covariate effects in a full model. Inclusion of these 8 effects resulted in a reduction in the OFV by 91 points after correction for standard deviation (SD) in OFV. Supplementary Table S2 presents the estimates of covariate effects for the 8 covariates contained within the full model. Of the 8 effects in the model, 2 of the estimated

injection site effects included the null value (AL_{NCD} injection site on FRAC and AL injection site on ALAG).

Starting with the AL_{NCD} injection site on FRAC, the covariate effects in the full model were removed one by one. Effects that included the null value were the first to be removed. Removal of the AL_{NCD} injection site on FRAC and the AL injection site on ALAG, when individually removed from the model, resulted in nonsignificant changes in the OFV. Consequently, these effects were removed from the model. Removal of the AL injection site on AL Dur with the 4 weight effects and 1 age effect retained in the model resulted in a significant increase in the OFV. Consequently, this effect was retained. Subsequent removal of age on CL/F, weight on ALAG, and weight on AL Dur resulted in nonsignificant changes in the OFV. These effects were removed from the model, which left a model with weight on VC/F and CL/F and AL injection site on AL Dur. Because weight on VC/F was present in a previous AL model and weight on CL/F was identified for Study 1 data to be significant, the model was further reduced with the removal of the AL injection site on AL Dur. This time, with only the 2 weight effects in the model, removal of the effect resulted in a nonsignificant change in OFV. Consequently, this effect was removed. The model was reduced for the last time by removal of the weight on CL/F effect, which was found to be nonsignificant and which provided the model with only weight on VC/F as the reduced full model. The model resulting from backward elimination contained just the single covariate effect of increasing VC/F with weight, a power model fixed at an allometric exponent of 1.0. For completeness, rather than using a fixed value for the effect, the impact of estimating it was evaluated. The estimated weight effect on VC/F was 1.15 (0.940, 1.36); therefore, the 95% CIs included the allometric value of 1.0, to which it was previously fixed. Consequently, the fixed covariate effect was retained.

FINAL PopPK MODEL (STUDIES 1, 2, AND 3)

The final PopPK model was the base model (as described in base model development [Studies 1, 2, and 3]; Supplementary Fig. S1) with the addition of the covariate effect of VC/F to increase weight (fixed at allometric exponent). Therefore, the model contained 17 parameters, 14 of which were

estimated. AL FIM (fixed at 57.1% from previous analysis[6]), oral bioavailability (fixed at 1.0 as reference route of administration), and weight on VC/F (fixed at allometric value 1.0) were fixed, and IIV was estimated in 14 parameters, 13 of which were in a full Ω block. The model estimated 1 proportional residual error term, and M3 methodology was used allowing concentrations <LLOQ to be included in the analysis. The model was mu referenced and fitted using IMPMAP with ISAMPLE of 1000, and it converged after 95 iterations.

Inclusion of the single covariate effect resulted in an 89-point reduction in the OFV (after correction for stochastic noise in OFV). Model parameters were well estimated, with many %RSE <10% and the highest 34%, as were estimates of IIV (12%-30%). Therefore, the 91-point reduction in the full model appears to be related to the presence of this single covariate. There was a 3.9% reduction in IIV on VC/F with the covariate included, and through the full Ω block and correlations there were reductions in 8 of the IIV estimates compared with the base model.

Estimates of IIV in parameters ranged between 34.6% for GAM2 and 631% for Q/F. As seen throughout, reflecting the low number of subjects with predose quantifiable ARI concentrations, the estimate of Ari (0) was well below the LLOQ (0.0400 ng/mL vs 1.0 ng/mL) but was associated with a very high estimate of IIV: 69,924%. As mentioned, this IIV term was estimated separately without correlation with other model parameters, and, though having a parameter with such a high IIV is not desirable, it did enable concentration-time data from IDs with quantifiable concentrations to be included in the analysis.

Shrinkage for estimates of IIV ranged between 6.8% for MDT1 and 28% for Ari (0). GoF plots from the final PopPK model were carried out. Of the 8948 aripiprazole concentrations included in the analysis, only 1 resulted in an IWRES value > 6. The observed concentrations were well described by model predictions, and no apparent study administration route or dose effect on prediction bias was observed. Distribution of etas from the final model and correlation between etas from the base PopPK model were assessed. Correlations between parameters in the final model ranged between –0.768 and 0.839, and most of the correlations were expected. Only 7 strong correlations were > ±0.7; the highest

was that between CL/F and FIM AL (0.839). The model estimated the residual variability to be low at 18.9%, the same as in the base model.

The final PopPK model was evaluated by generating pcVPCs per study and also by regimen within Study 2. The pcVPCs indicated that within and across studies for Study 1 and 3 and by regimen within Study 2, the majority of observed concentrations were contained within the final PopPK model-predicted 90% PIs.

The pcVPCs indicated the PopPK model was robust and was a good predictor of aripiprazole exposure. The occasionally high predose quantifiable aripiprazole concentrations in some studies resulted in some high variability early in the profile, as reflected by the IIV estimate around the fixed estimate of Ari (0), which is reflected at the start of some pcVPC plots.

Although simulated concentrations from the current final model showed good similarity with those from the previous final models[1,4], there appeared to be a slightly lower central tendency. This could potentially affect the simulation objectives of the study if the current final model predicts slightly lower concentrations after AL administration compared with previous models. Subsequently, to optimize the AL model parameters in the current model, data from single and repeat administration of IM AL every 4 weeks (q4wk), q6wk, and q8wk in Study 4–also part of the previous analysis[4]–were included and modeled alongside those of the 3 current AL_{NCD} studies.

FINAL PopPK MODEL UPDATE (STUDIES 1, 2, 3, AND 4)

The existing final model was updated to be compatible with the additional study (Study 4) data. Because this study had up to 7 IM administrations of AL, the model was expanded by adding an additional 6 IM dosing depot for AL, consistent with prior analyses. AL Dur, ALAG, and FIM AL were consistent across depots as per the previous final model fitting Study 4[4]. The model also included IOV on AL Dur, allowing variability between AL IM dosing occasions in Study 4 to be quantified, as done previously. The updated model ran successfully using the updated data set for 4 studies. When rerun 2 more times, the model returned to within ±SD of the OFV, indicating model

stability. It also provided good descriptions of the observed aripiprazole concentrations in all 4 studies, suggesting the 3 aripiprazole inputs were well captured.

Inclusion of a separate proportional error term for Study 4 resulted in nonoverlapping estimates and a 411-point reduction in the OFV, which reflected a lower residual variability for that study (14.4%) than for the 3 AL_{NCD} studies (18.9%).

Accompanying the reduction in OFV was a reduction in the estimated interindividual variability (IIV) of several model parameters with a 25% reduction in AL ALAG, > 40% reductions in VP/F, Q/F, and Ka, respectively, and a 93% reduction in Ari (0).

Most model parameters that included Study 4 data were consistent with those of previous analyses and also from fitting just the 3 AL_{NCD} studies. With more supporting AL data from Study 4, the AL ALAG estimate was reduced from 185 to 104 or 106 hours, which lies between 129 and 78 hours in previous final models. With the Study 4 data included, AL Dur was increased by 103 or 45 hours relative to previous models.

With the exception of a separate proportional residual error term for Study 4 and of 6 additional AL IM dosing depots, the final PopPK model for the updated data set, which included data from Study 4, is identical to that described in Section 6 as the final model for the 3 studies in which AL_{NCD} was administered.

Given the reduction in OFV and the marked reduction in the IIV with a separate residual error term for Study 4, and comparable parameter estimates to the single error model, this model was selected as the final model. Subsequently, this model was used for the simulation aspects of the analysis.

Parameters of the final model are presented in Supplementary Table S3. Estimates of IIV in parameters ranged between 35.9% for GAM2 and 353% for Q/F. The estimate for IIV in Ari (0) was 870%, reflecting the low number of subjects with predose quantifiable aripiprazole concentrations overall. Shrinkage for estimates of IIV ranged between 10.5% for CL/F and 25.3% for Ka oral aripiprazole. Correlations between parameters in the base model ranged from –0.779 to 0.834; most were expected. Only 6 strong correlations were > ±0.7, and the highest was that between CL/F and

FIM AL (0.834). The model estimated the residual variability to be low at 18.9% for the 3 AL_{NCD} studies (as in the final model for these 3 studies) and 14.4% for Study 4.

When rerun 2 additional times, the model returned to within ±SD of the OFV and exhibited the required stability for formal covariate evaluation. The previous analysis using Study 4 data contained only the covariate effects of weight on VC/F and an effect on CL/F for CYP2D6 PMs. Given that only 2 PMs were included in the data set, it was not possible to re-evaluate the CYP2D6 PM effect. Therefore, the only relevant covariate was the same weight on VC/F (fixed to the allometric exponent of 1.0) identified for the 3 studies with AL_{NCD} administered. No further covariate analysis was performed on the expanded data set that included Study 4.

GoF plots from the final ARI PopPK model demonstrated that the observed concentrations were well described by model predictions, and no apparent study, administration route, or dose effect on prediction bias was observed. pcVPCs were created per study and also by regimen within Studies 2 and 4. They indicated that within and across studies for Study 1 and Study 3 and by regimen in Studies 2 and 4, most observed concentrations were contained within the final PopPK model-predicted 90% PIs.

MODEL REFINEMENT FOR SIMULATIONS: MIXTURE MODEL

Although the GoF and pcVPC plots indicated that the model-predicted concentrations fit the observed data well, initial simulations for 15 mg oral aripiprazole for 21 days suggested that the final PopPK model might have overpredicted the exposure to aripiprazole with multiple oral doses. After some evaluation, it was noted that the variability after oral aripiprazole administration in Study 2 was high but consistent with what was observed in the previous pivotal Phase 3 study[7] and that there appeared to be 2 groups, 1 with higher and 1 with lower aripiprazole exposure with the oral initiation regimen. The distinction between the 2 groups was more visible when the 2 groups who received the oral initiation regimen in Study 2 were split by the AL dose received. Additional models were tested that included data from patients who received oral aripiprazole only in previous AL studies, but parameter

estimates were not impacted and no improvement was made in describing the observed concentrations from the oral initiation regimen treatment groups in Study 2.

Given that there appeared to be a subgroup of patients whose profiles reflected a lower exposure after multiple oral aripiprazole administrations, a mixture model was evaluated to determine whether a subpopulation could formally be identified. This subpopulation was visible only during the first 28 days of dosing in 2 treatment arms in 1 of the 4 studies in the final PopPK data set (Study 2). Thus, the mixture model could be applied only to this subset of the data set (ie, only data from the first 28 days after the initiation of AL [441 mg or 882 mg] with the 21-day initiation regimen were assessed). Because the estimated input of aripiprazole from AL—with its long duration and lag time—in this first month was minimal, it was assumed that all input of aripiprazole was due to the 21 days of 15 mg oral aripiprazole co-administered with AL.

Briefly, fitting a mixture model to only the AL 441 mg/21-day initiation treatment group in Study 2 successfully identified a subpopulation with a lower F_{po}. Application of the same model to the AL 882 mg/21-day initiation treatment group and both treatments combined did not provide a satisfactory estimate of the subpopulation in that the mixture model identified some, but not all, of the subpopulation of patients with a lower F_{po} for both treatments. However, applying the estimated proportion of patients in the subpopulation from the AL 441 mg/21-day initiation treatment group (37.4%) for both treatments and allowing the mixture model to estimate the change in F_{po}, the model identified most patients perceived to be in the subpopulation. The reduction in F_{po} in the subpopulation was estimated to be 44.6% (95% CI, 40.9–48.3%). A NONMEM simulation was performed using the mixture model to assess the change in simulated aripiprazole concentrations after 21 days of 15 mg oral aripiprazole. The mixture model gave a more accurate representation of the range of observed concentrations after the initiation of oral treatment in Study 2 than the final PopPK model. Therefore, in order for the formal simulations involving oral treatment initiation to reflect the observed concentrations in Study 2, the results of the mixture model were overlaid on the final PopPK model. Estimates of the reduction in F_{po} and the proportion of patients in the subpopulation from the mixture model were applied to the final PopPK model used for simulations.

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