Model Informed Dose Evaluation for Aticaprant in Adolescent Patients Following the Adult Dose Regimen

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BACKGROUND AND OBJECTIVES

Aticaprant is a small molecule, high-affinity, selective kappa receptor antagonist, under development by Janssen Research & Development for the adjunctive treatment of major depressive disorder (aMDD). An aticaprant dose of 10 mg QD dose has been selected in adult patients in on-going Phase 3 studies based on the safety and efficacy results observed in the adult Phase 2a study.

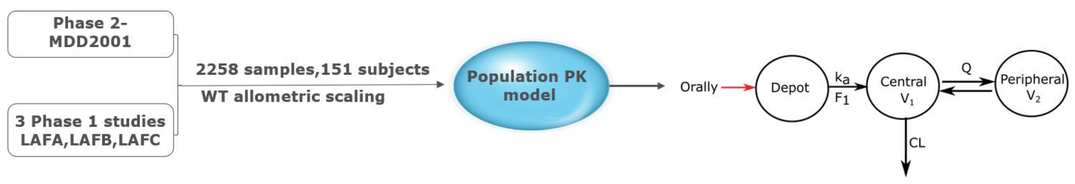
The current exercise aimed to determine whether the aticaprant dose of 10 mg QD for adults is appropriate in adolescents (12 to <18 years).

METHODS

Population Pharmacokinetic Modeling

The adult population pharmacokinetic model was developed using aticaprant plasma concentrations from 4 clinical studies [I2Z-MC-LAFA (single-ascending dose study), I2Z-MC-LAFB (multiple-ascending dose study), I2Z-MC-LAFC (PET receptor occupancy study), and MDD2001 (efficacy, safety, and pharmacokinetics study in subjects with aMDD)] (**Figure 1**), using nonlinear mixed-effects modeling (NONMEM 7.4.1)[1]. Covariates were evaluated in the popPK model. Exploratory analysis, diagnostic graphics, and post-processing of NONMEM analysis results were carried out using R. Model evaluation was based on acceptable parameter precision, goodness-of-fit and visual predictive checks.

Figure 1. Adult Population Pharmacokinetic Model Development



Simulation of Aticaprant Exposures in Adult and Adolescent Populations

Virtual adult and adolescent subject database

For adults, a dataset containing 10,000 virtual adults was generated by sampling the demographic distribution (i.e., body weight and race) from the adult study MDD2001. For adolescent, a dataset of 69,574 virtual adolescents (12 to <18 years) was generated across age and gender with body weight simulated for each year in age group and gender based on CDC growth charts weight-for-age statistical tables[2].

Simulations of adult aticaprant exposures using a dose of 10 mg QD

Model-based simulations were performed to predict aticaprant exposure metrics (i.e., steady-state $AUC_{0\text{-}24h}$ and trough concentration (C_{trough})) for each adult subject among 10,000 virtual adult patient population, using the aticaprant dose of 10 mg QD. The median value and 5th and 95th percentiles of the simulated aticaprant exposures in the full virtual adult patient population were summarized and served as reference for comparison with adolescent simulations.

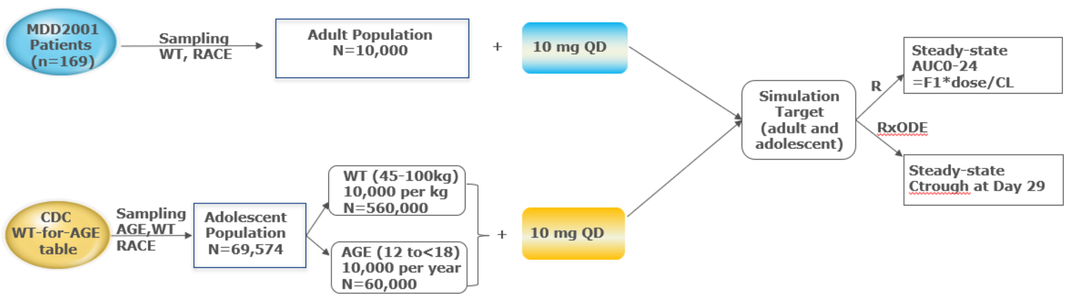
The steady-state $AUC_{0\text{-}24h}$ was calculated with equation ($AUC_{0\text{-}24h}$ =F1*Dose/CL) by sampling random effects on F1 and CL from a log-normal distribution using model parameter estimates and omega estimates. The steady-state C_{trough} was predicted using the aticaprant plasma concentration at day 29 predose (23.99h).

Simulations of adolescent aticaprant exposures using a dose of 10 mg QD

The aticaprant exposure in the adolescent subjects were simulated using the same approach as in the adult population and investigated by body weight or age category. For age category, a total of 60,000 virtual adolescent subjects (12 to <18 years) were sampled from the virtual adolescent subject database. For body weight category, a total of 560,000 virtual adolescent subjects (45 to 100 kg) were sampled. The race distribution of adolescents was sampled from the adult study MDD2001.

The model-based simulations were performed to predict the steady-state $AUC_{0\text{-}24h}$ and trough concentration (C_{trough}) in adolescents, following the aticaprant dose of 10 mg QD. The aticaprant dose for adolescents was considered appropriate if ≥ 80% of the adolescent subjects would have aticaprant exposures (i.e., $AUC_{0\text{-}24h}$ and C_{trough} at steady state) within the 5th and 95th percentiles of the corresponding adult exposure after 10 mg QD dose. **Figure 2** represented the workflow for simulation.

Figure 2. Workflow for Simulation of Aticaprant Exposures in Adult and Adolescent Populations



RESULTS & DISCUSSION

Population Pharmacokinetic Modeling

The popPK model in adult was based on 2,258 aticaprant plasma concentrations from 151 healthy subjects and patients. Observed data were well described by an open two-compartment model with first-order absorption (Ka: 5.20 1/h) and linear clearance (CL: 31.0 L/h). Body weight was a covariate, with the allometric scaling exponent of 0.75 for CL and Q, and 1 for V2 and V3[3]. Race (Black and Hispanic) was a covariate on relative bioavailability (F1: fixed as 1). The interindividual variability in CL, V2, F1, and Ka was assumed to be log normally distributed. The coefficient of variation of CL was 34.4 %. The residual error was described by a proportional error model.

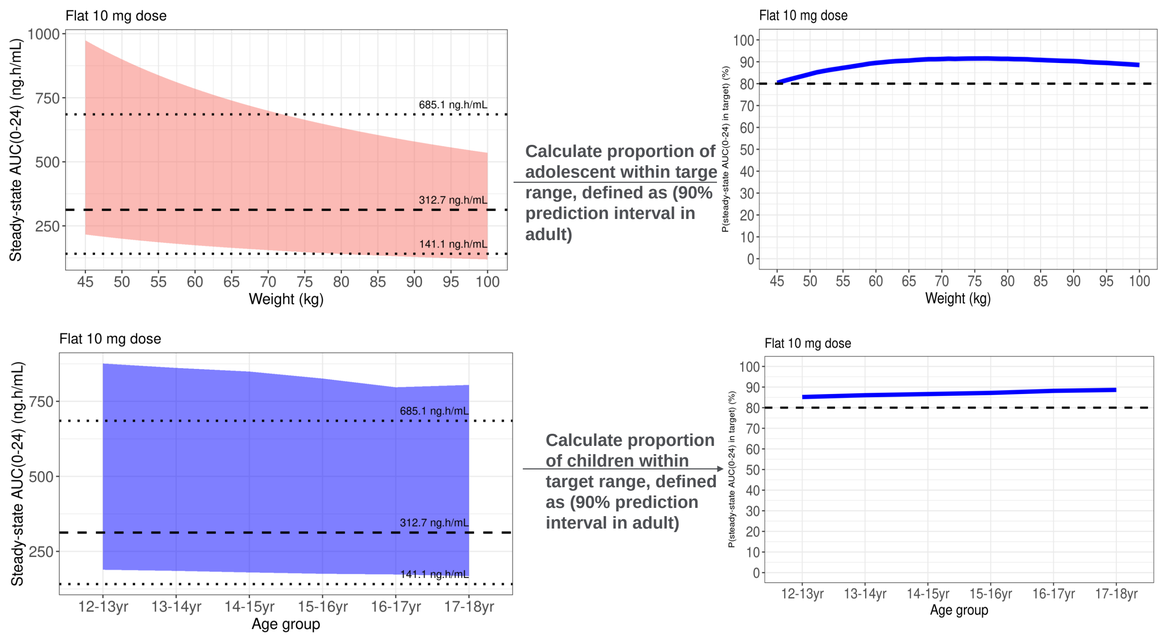
Reference aticaprant exposure values in adults

The model-based simulations in the 10,000 virtual adults receiving aticaprant 10 mg QD, resulted in median (5th and 95th percentiles) steady-state $AUC_{0\text{-}24h}$ and C_{trough} of 312.7 (141.1-685.1) ng*h/ml and 7.6 (3.0-17.7) ng/ml, respectively, which served as reference for comparison with adolescent simulations.

Dose selection for adolescent subjects

The model-based simulations in virtual adolescents demonstrated that the aticaprant dose of 10 mg QD resulted in ≥ 80% of the adolescents with aticaprant exposures within the adult reference exposure for both steady-state $AUC_{0\text{-}24h}$ and C_{trough}, across both body weight and age category, shown in **Figure 3**.

Figure 3. Matching Aticaprant Exposures in Adolescent and Adult Populations



Left figures: 90% prediction interval of simulated aticaprant steady-state AUC(0-24h) in adolescents (shaded areas) as function of body weight (upper left) and age (lower left), compared to the adult simulated median exposure value (dashed line) and 5th and 95th percentiles (dotted lines), following the aticaprant dose of 10 mg QD.

Right figures: Proportion of adolescents within the 5th and 95th simulated percentiles of steady-state AUC(0-24h) in adults as function of body weight (upper right) and age (lower right), for the proposed aticaprant dose of 10 mg QD.

CONCLUSION

The adult clinical dose of aticaprant 10mg QD is expected to achieve systemic aticaprant exposures in the simulated virtual adolescent population comparable to those in adult population. The dose currently proposed will be further updated based on emerging data from adult Phase 3 clinical studies.

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