Application of Population Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling and Simulation to Inform the Design of a Dose-Finding Study in Patients With Schizophrenia

Jan Berkhout,[1] Teun M. Post,[1] Lin Xu,[2] Liming Zhang,[2] Jens Wendland,[2] Hélène Faessel,[2] Majid Vakilynejad[2]

[1]LAP&P Consultants BV, Leiden, The Netherlands; [2]Takeda Pharmaceuticals International, Inc., Cambridge, MA, USA

Background

- TAK-831 is a highly selective and potent inhibitor of D-amino acid oxidase (DAAO), an enzyme that degrades D-serine and is highly expressed in glia and neurons within the mammalian brain.[1,2] Inhibition of DAAO increases levels of D-serine, a co-agonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors, and may improve NMDA-dependent glutamatergic hypofunction,[1] such as in schizophrenia.
- Clinical studies were performed to assess safety, pharmacokinetics (PK), pharmacodynamics (PD), and brain enzyme occupancy (EO) in healthy volunteers. TAK-831 is being developed as an adjunctive therapy for negative symptoms of schizophrenia.
- The current work describes development of a PK/EO/PD model to quantitatively assess the temporal relationship between TAK-831 PK, EO, and changes in D-serine in plasma and cerebrospinal fluid (CSF) to inform dose selection for a dose-finding study in patients with schizophrenia.

Methods

Data from 4 phase 1 studies with single (10-750 mg) or multiple (15-1200 mg) oral daily (QD) doses of TAK-831 given as suspension or tablets were pooled for analysis. Observed concentrations of TAK-831 and D-serine in plasma and CSF were modeled. The population PK/PD analyses were performed by means of nonlinear mixed effects using NONMEM (v7.3) and PsN (v4.6). Final model selection was based on maximum likelihood criteria and goodness-of-fit plots. The adequacy of the final model was evaluated with a predictive check method. Diagnostic graphics, exploratory analyses, postprocessing of NONMEM output, and simulations were performed using R (v3.3.2).

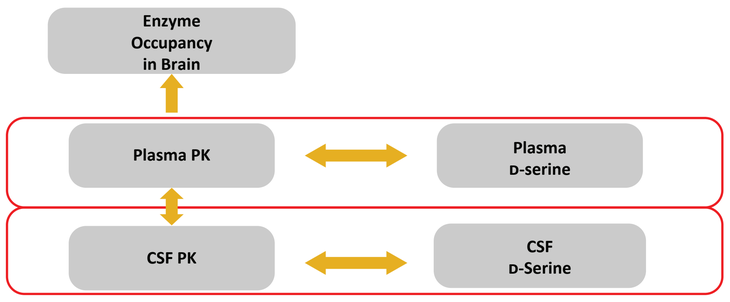
Population PK Model Building:

The exposure of TAK-831 in plasma increased less than dose proportionally with increasing TAK-831 dose from 10-1200 mg. PK modeling was tested with 1-, 2-, and 3-compartment models by a linear and nonlinear process. The differences in the absorption profile when given as an oral suspension or tablet formulation, coadministered with or without food, were modeled via addition of transit compartments to account for absorption delay. Random variability was modeled as an exponential function and residual variability tested as the proportional and residual errors.

Population PK/PD Model Building:

Relationships of imaged EO in brain and plasma TAK-831 concentration were tested as a direct response, indirect response, or an effect compartment model. Relationships of D-serine elevation and TAK-831 exposure in both CSF and plasma were modeled as an indirect response function based on the inhibitory effect of TAK-831 on DAAO and subsequent reduced D-serine degradation. Random variability was modeled as an exponential function and residual variability tested as the proportional and additive errors.

Overview of Modeling Approach

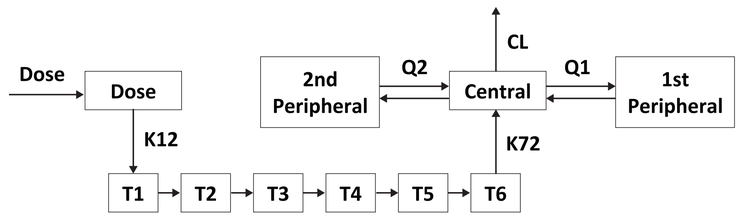


Results

A total of 149 subjects contributed 2647 PK and 2561 PD observations.

1. TAK-831 PK was best characterized using a 3-compartment model with first-order absorption and elimination processes. The complex absorption phase for various TAK-831 oral formulations under fed and fasted conditions was modeled with 6 transit compartments. All model PK parameters were estimated with good precision (coefficient of variation <38%). Population mean clearance (CL) and volume of distribution (V2) were 99 L/h and 150 L, respectively. Median bioavailability of the tablet formulation (F1) under fasted conditions was 0.735 relative to the suspension formulation. Between-subject variability for CL, V2, and F1 was 16.6%, 16.3%, and 30.6%, respectively.

A. Schematic Overview of Plasma TAK-831 PK Model



Interindividual variability in PK parameters (CL, Q1, k12, k72, V2, V3, F1, and lag time) was quantified using an exponential model. Residual variability was modeled separately for each study as a proportional model.

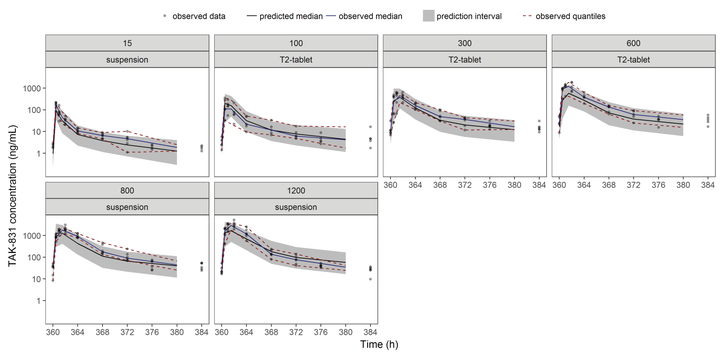


Figure 1. Visual Predictive Check Plot of Plasma PK Model

B. PK/D-Serine Model

2. An indirect-response PK/PD model was used to describe the relationship between PK and D-serine in both plasma and CSF. The drug effect was implemented as an inhibitory effect on the k_{out}, best described as a sigmoidal inhibitory model:
   - Plasma PD (D-Serine) Model

$$k_{in}\ AMP * \cos\left(\frac{2\pi(t+HOR)}{24}\right) \rightarrow \text{D-Serine (Plasma)} \qquad k_{out} \bullet \frac{I_{max} \bullet Cp^{h}}{Cp^{h} + IC_{50}{}^{h}}$$

$Cp \rightarrow$ Plasma concentration TAK-831

   - CSF D-Serine Model

$$k_{in} \rightarrow \text{D-Serine (CSF)} \qquad k_{out} \bullet \frac{I_{max} \bullet Ccsf^{h}}{Ccsf^{h} + IC_{50}{}^{h}}$$

$Ccsf \rightarrow$ CSF concentration TAK-831

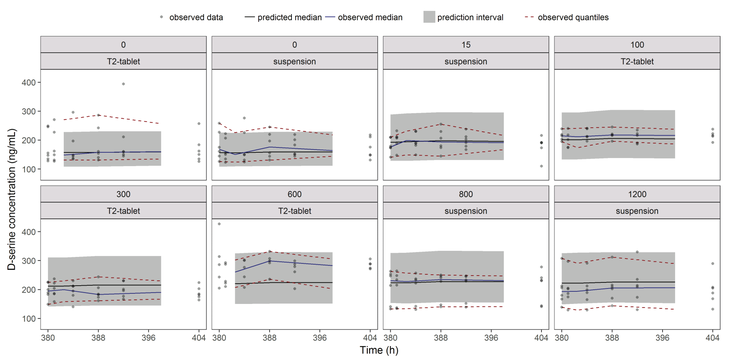
AMP=amplitude (ng/mL); HOR=horizontal shift (h); h=Hill coefficient; I_{max}=maximum possible effect; IC_{50}=half maximal effect.

A cosine function on the kin was used to describe circadian rhythm of D-serine in plasma. The period was fixed to 24 h, the amplitude (AMP) was 4.95 ng/mL, and the horizontal shift (HOR) was -15.3 h.

In the plasma PD model, the population mean values of k_{in} and k_{out} were 9.30 ng/mL/h and 0.0567/h, respectively. The maximal inhibitory effect (I_{max}), IC_{50}, and Hill coefficient values were –0.32, 3.25 ng/mL, and 0.714, respectively.

In the CSF PD model, the population mean values of k_{in} and k_{out} were 14.3 ng/mL/h and 0.0813/h. I_{max} was fixed at –1. The IC_{50} and Hill coefficient values were 0.333 ng/mL and 0.285, respectively.

a: Plasma



b: CSF

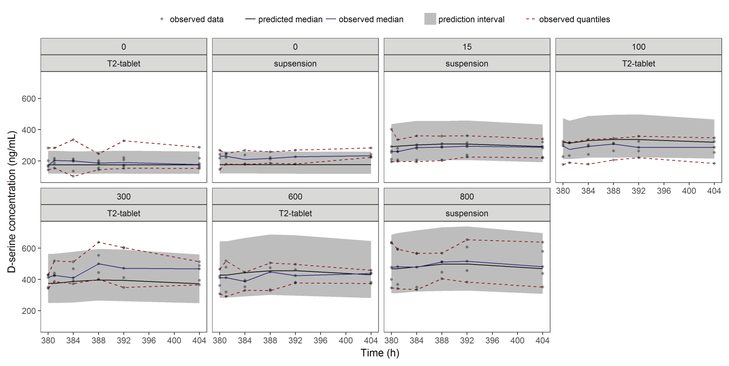


Figure 2. Visual Predictive Check Plot of D-Serine Model

C. PK/Brain EO Model

A direct response model best described the relationship between TAK-831 concentration vs time profile and brain EO vs time profile. No time delay was observed between PK profile and EO. The relationship of EO vs TAK-831 plasma concentration was as described below:

$$Vt = \frac{\text{VSB x Drug (Conc)}}{EC_{50} + \text{Drug (Conc)}} + \text{VND}$$

Conc=concentration; VND=volume of distribution of the nondisplaceable component (nonspecific binding and free radiotracer); VSB=group-level (global) volume of distribution of specific binding in the target region; Vt=volume distribution of the target region.

The population estimate for EC_{50} was 20.8 ng/mL. Interindividual variabilities in VSB and EC_{50} were quantified as an exponential function and were 23.4% and 97.9%, respectively. Residual error was modeled as a proportional function.

D. Simulation

The developed PK/EO/D-serine models were used to simulate a variety of daily doses (N=500) to optimize dose selection in phase II trials.

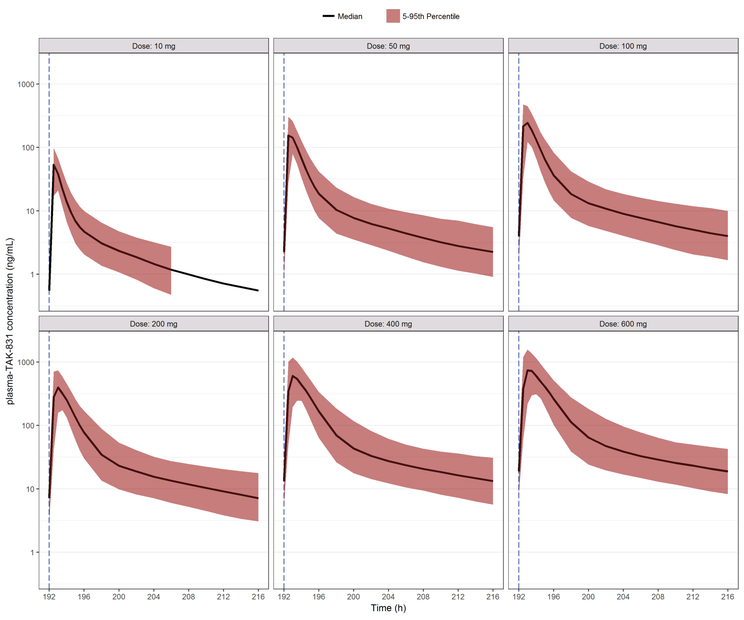
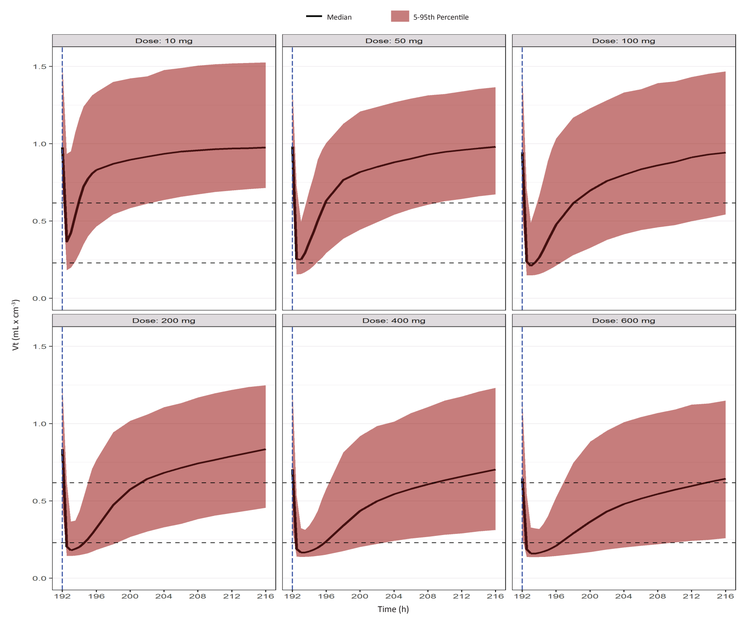


Figure 3. Simulated PK Profiles at Steady State With Various Doses



Note: Dashed lines represent 90% and 50% receptor occupancies.

Figure 4. Simulated EO Profiles at Steady State With Various Doses

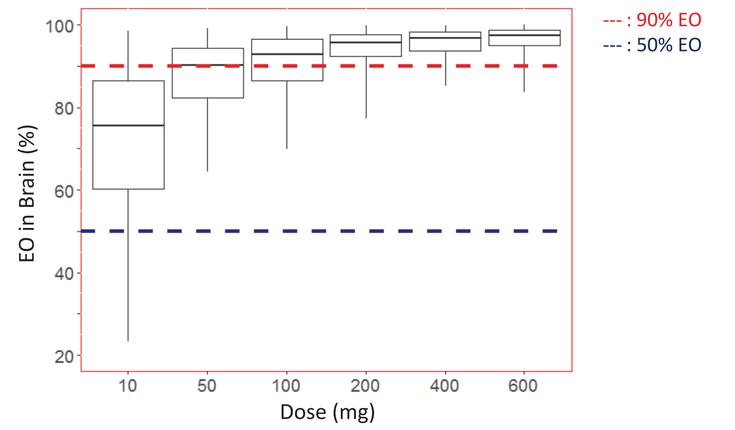


Figure 5. Box Plot of Predicted Maximum EO at Different Doses

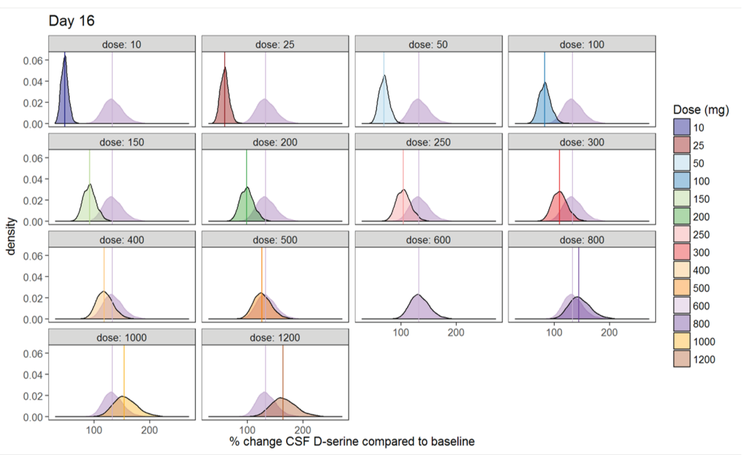
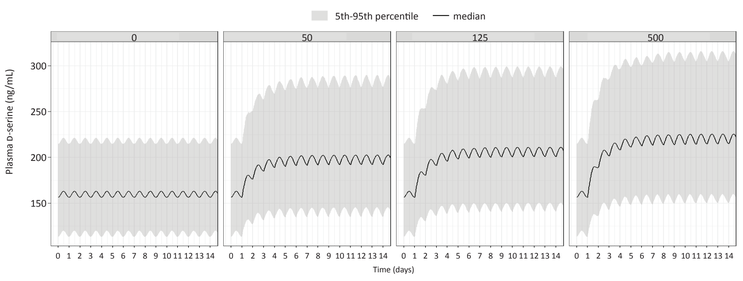


Figure 6. Predicted Percent Change (5th, 95th Percentiles) in CSF D-Serine Relative to Baseline at Steady State (Using 600 mg QD as a Reference)

a: Plasma



b: CSF

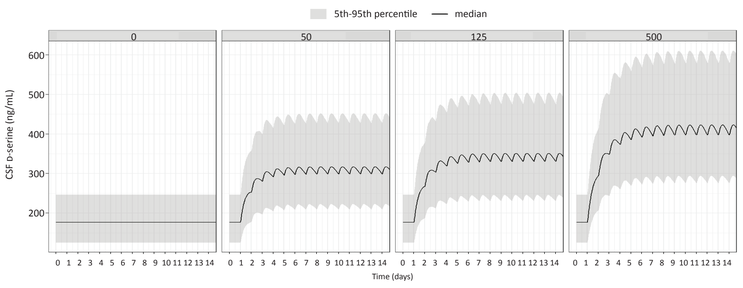


Figure 7. Predicted D-Serine After First 2 Weeks on Daily Dose of 0, 50, 125, and 500 mg of TAK-831

Conclusions

- All population PK/PD parameters were estimated with acceptable precision.
- Daily dosing of TAK-831 resulted in an exposure-dependent D-serine increase in plasma and CSF, with steady-state levels remaining constant over 24 h.
- The simulation results showed 90% of subjects will achieve maximal EO (>90%) at the peak concentration of 600 mg or above daily dosing and reach an apparent plateau in D-serine elevation in plasma and CSF.
- The distribution of D-serine elevation in CSF is fully separated between 50 mg and 500 mg; therefore, these were chosen as the lowest and highest doses in the phase 2 trial. The 125 mg dose was added as a middle dose to investigate and understand the relationship between downstream increases in D-serine and clinical benefit in patients with schizophrenia.
- This integrated PK/PD and PK/EO modeling analysis provided the quantitative basis for model-informed dose selection in early clinical development.

References

1. **Kakegawa W, Miyoshi Y, Hamase K, et al. D-Serine regulates cerebellar LTD and motor coordination through the delta2 glutamate receptor. *Nat Neurosci*. 2011;14(5):603-11.**
2. **Sacchi S. D-Serine metabolism: new insights into the modulation of D-amino acid oxidase activity. *Biochem Soc Trans*. 2013;41(6):1551-6.**
3. **Xu L, DeMartinis N, Wu J, et al. Safety, pharmacokinetics, and pharmacodynamics of TAK-831, a selective D-amino acid oxidase inhibitor, in healthy volunteers (abstr W187). *Neuropsychopharmacology*. Dec 6, 2018. doi: 10.1038/s41386-018-0268-5.**

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