Background

TAK-831 is a highly selective and potent inhibitor of \( T2 \) and \( T5 \). All population PK/PD parameters were estimated with acceptable precision. 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.

Methods

Data from 4 phase 1 studies with single (0-750 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 in plasma and CSF were modeled. The population PK/PD analyses were performed by \( b \). PK/PD Model Building: The exposure of TAK-831 in plasma increased less than dose proportionally with increasing TAK-831 dose. For TAK-831 given as suspension or tablets, 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 additive errors.

Results

A total of 81 subjects contributed to both PK and PD observations. 1. The empirical best characterization using a 3-compartment model with first-order absorption and elimination processes. The complex absorption phase for various TAK-831 oral formulations was modeled 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 validated by postprocessing of NONMEM output, and simulations were performed using R (v3.3.2).

Conclusions

All population PK/PD parameters were estimated with acceptable precision. Daily dosing of TAK-831 resulted in an exposure-dependent \( T2 \) increase in plasma and CSF, with steady-state levels reaching constant over 24 h. The simulation results showed 90% of subjects will achieve measurable EO (90%) at the peak concentration of 125 mg as shown daily dosing each as an apparent plateau in a non-linear relationship.


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