Cross-Species Scaling of CNS Aβ40 Response to a Gamma Secretase Inhibitor Through Semi-Mechanistic PK/PD Modeling and Application to Early Decision Making

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Background and Objectives

The γ-secretase inhibitor, MK-0752, can acutely and significantly lower CSF Aβ40 concentrations. While the pharmacokinetics (PK) of MK-0752 is well described, PK/PD modeling and animal scaling of CNS Aβ response to MK-0752 is complicated by variation in plasma protein binding across species. This presents challenges in the species scaling of the PK/PD relationship to humans. The objectives of this work were to develop PK/PD models of CNS Aβ40 response to MK-0752 and to establish a meaningful scaling approach for comparing the drug effect on CNS Aβ response across a variety of species including humans.

PK/PD Model Development – Human

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Sigmoid Emax PK/PD Relationship Characterized Tg-Mouse, YAC-Mouse, and Guinea Pig Data Wall

All level = 100% - Emax * (C / CIC50)

Sigmoid Emax PK/PD Relationship Characterized Monkey Data Wall

Native Pool Fit of PK Profiles in Plasma to Model

Cross-Species Scaling Approach

New PK/PD scaling approach allows for comparison of CNS Aβ response to MK-0752 across non-human and human species. The approach is based on a semi-mechanistic PK/PD model where the effect of the drug on Aβ40 is described by a Sigmoid Emax function. The model parameters for Emax, n, and CIC50 are identical across species allowing for direct comparison of Aβ40 response across species.

Example of Application to Early Development Compound Leading to No-Go Decision

Application to Early Decision Making

Conclusions

1. Semi-mechanistic PK/PD modeling allowed for characterization of the drug effect on CN$Aβ$ response across a variety of species including humans.
2. Parameters in the same core equation describing response in brain tissue were used in all models, a cross-species scaling approach for this key PK/PD parameter could be developed despite marked inter-species differences in the time-course of response across the species.
3. Concomitant plasma protein binding was required for successful interspecies scaling of IC50.

Example of Application to Early Development Compound Leading to Go Decision

 Establishment of this inter-species PK/PD scaling approach has allowed for its application in programs targeting Aβ to aid Go/No-Go decisions with regards to early development compounds targeting Aβ.