Simulation Approach to Inform Modeling Analysis Plan to Assess Exposure-Response for Cognition Efficacy in an Alzheimer’s Disease Study

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Objectives: Develop modeling analysis plan to characterize the exposure-response (E-R) for cognition from a mild-to-moderate Alzheimer’s Disease study. Use trial simulation to ensure that model-building criteria return a model that reliably reflects underlying truth across a wide-range of potential trial outcomes.

Methods: The clinical trials simulation tool¹ incorporating the ADAS-cog disease progression model developed by CAMD was used to generate 1000 replicate trials (n=570 patients per arm – placebo, 12- or 40-mg daily) for each of 12 E-R truth scenarios (Emax terms relating AUC to rate of change in ADAS-cog). Scenarios were based on 4 potencies and 3 maximal responses. Simulated trial datasets were analyzed using a longitudinal disease progression model similar to CAMD model and incorporating one of 4 E-R terms on rate of change: treatment effect, linear slope, Emax, intercept+slope.

Results: The AIC differences between the structural models were not large (eg, ΔAIC for Emax vs treatment model was 0.66 (90% range -5.25 – 2.21), indicating that AIC provides modest differentiation value. Models selected by AIC only yielded a high likelihood of inconsistency with true E-R, especially for modest effect sizes or low potency. An alternative decision tree was developed that combines criteria of estimated effect size for 12 mg and 40 mg arm from base-drug-effect model and estimated AUC50 from Emax model. The model-estimated drug effects for the tested dose levels and an extrapolation dose are summarized in Figure 1 and indicate more accurate and narrow prediction intervals with the decision tree approach for some scenarios.

Conclusions: The decision tree model selection criteria, as compared to AIC, provides a higher likelihood of selecting a model that accurately describes the true exposure response profile within the expected exposure range and of predicting drug effect upon treatment with 80 mg. Therefore, these criteria were incorporated into the prospective model analysis plan.

References: Clin Pharmacol Ther. 2015 Mar;97(3):210-4
Figure 1. Model-Estimated Drug Effect at 12, 40 and 80 mg based on 1000 Replicate Final Models Selected by Decision Tree vs AIC Criteria Approach for 12 Scenarios Tested Reflecting Simulated Trial Data

Red line = truth; black symbol = median prediction; bar 90% PI

Decision tree

AIC