Population Pharmacodynamic and Markov Modeling Approach for Clinical Trial Outcome Predictions in Anti-obesity Drug Development
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Objectives: Development of anti-obesity drugs is continually challenged by high dropout rates during clinical trials [1]. The objective of this analysis was (i) to develop a population pharmacodynamic (PopPD) model to describe time-courses of bodyweight (BW) changes, accounting for disease progression (DP), lifestyle intervention (LSI) and drug effects; and (ii) to predict, using a Markov Model (MM), Responder (R), Non-responder (NR) and Dropout (D) rates during clinical trials based on longitudinal % BW changes.

Methods: Subjects (n=4591) from 6 Contrave® trials were included in this analysis. An indirect-response model, developed by van Wart et al. [2] was used as a starting point. Inclusion of drug effect was dose driven using a Kinetic-Pharmacodynamic (KPD) model. Additionally, a Population-PK Parameters and Data (PPPD) model was developed using the final KPD model structure and final parameter estimates from a Pharmacokinetic (PK) model based on available Contrave® PK concentrations. Lastly, MM was developed to predict transition rate probabilities between R, NR and D states driven by the PD effect resulting from the KPD or PPPD model.

Results: The developed KPD and PPPD models described the BW changes over time adequately well. Some of the covariates included in the models were diabetes (on Kout, Kpro, BW, and Emax) and race (on LSI). The linked KPD-MM and PPPD-MM models were able to predict transition rates between R, NR and D states well. The PPPD-MM model had slightly better predictions as compared to KPD-MM model.

Conclusions: In this study, BW change is an important factor influencing dropout rates and the MM model has depicted that overall a KPD model driven approach is as good in predicting clinical trial outcome probabilities as a PK driven approach such as the evaluated PPPD model.

References:
2. Van Wart S, et al. ACOP, 2011, San Diego, CA, USA