Impact of Model Uncertainty on Phase 2 Diabetes Trial Design

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Objectives: To evaluate the impact of different levels of model uncertainty (due to limited prior data in patients) on the power of Phase 2 trial designs for treatment of T2DM, and the performance of exposure-response versus dose-response models.

Methods: A population PK/PD model was used to simulate exposure-response relationships for HbA1c and glucose in a hypothetical patient population. Although the true underlying model is assumed to be known (an indirect response model, with HbA1c linked to glucose), different levels of uncertainty are simulated as scenarios with varying confidence in the model parameters. The uncertainty in estimates of Emax and EC50, ranging from 0 to 200% CV, reflect the amount of prior knowledge in patients. Doses for the simulations were selected based on the current parameter estimates. 1,000 trial replicates were simulated for each combination of sample size and number of dose levels. Power was calculated for various metrics, including ability to estimate model parameters and the target dose, using both exposure-response and dose-response models. Simulations are visualized using Shiny, an R package.

Results: In general, power increased with sample size and number of dose levels, and decreased with increasing uncertainty. For example, using an exposure-response model for a 5-dose design, the sample size required for at least 80% power to estimate a target dose whose true typical HbA1c response is within 0.15% of the desired response was 39/arm for the lowest uncertainty, and 53/arm for the highest uncertainty (Figure 1). Exposure-response models typically provided slightly greater power than dose-response models. When using the linear model, power was significantly lower due to model misspecification.
**Conclusions:** Model uncertainty has significant impact on the design of a dose-finding Phase 2 study. Thus, leveraging prior data in T2DM patients may have significant cost-saving benefits. Further, Emax models based on exposure and dose performed comparably, while a simple linear regression was extremely poor, suggesting that power is low when using a model that does not well describe the underlying dose-response relationship.