Using Dose-Response Modeling to Improve Planning, Study Design, and Decision Making in Early Clinical Development

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Objectives: To design an efficient and informative phase 1 study and clinical decision method, incorporating model based drug development (MBDD), for a monoclonal antibody preparing for first in man studies.

Methods: Based on a paired-comparison design, the project team originally proposed a Phase 1 program with a SAD/MAD design with standard size dose cohorts followed by one expanded dose cohort studied at one of the previous dose levels. The Phase1/2 transition go/no-go decision was originally based on a proof-of-mechanism (POM) of target suppression, with the extended cohort necessary to power the POM decision. The decision criteria used the method suggested in Lalonde¹, with specification of a target value (TV) representing best-expected performance and a lower reference value (LRV) representing minimal acceptable performance. The team then sought to develop a faster and less complex clinical plan through further integration of MBDD.

An updated decision analysis using dose-response modeling integrated with MBDD methods was developed to more fully capture available pre-clinical data and dose response. A modeling approach was applied to preclinical data and response. The SAD study design was then incorporated in a dose-response-model based analysis, which allows use of all measurements in the go/no-go analysis.

Results: The figure shows the performance characteristics of the original design (with extended cohort) and the model-based design (LRV=0.2, TV=0.5, response normalized with maximum of 1). The dose-response model based method showed superior performance at the LRV and TV.

Figure: A: Original analysis (N=15/group in extended cohort) B: Modeling based analysis

Conclusions: As a consequence of the resulting decision criteria and program revisions, the Phase 2 POC study will begin 21 months earlier and cost >$1M USD less than in the original proposal. Incorporating pre-clinical data modeling and dose-response modeling into the formal Phase 1 decision process resulted in shorter time-lines, reduced cost, and improved decision performance.

References:

LaLonde et al, CLINICAL PHARMACOLOGY & THERAPEUTICS, V 82  N1, July 2007