Leveraging Biomarkers, Clinical Endpoints, and Exposure-Response Modeling and Simulation to Optimize Phase 3 Dose Selection

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**Objective:** A key goal of early clinical development programs is to optimize Phase 3 dose selection in order to maximize the benefit-risk of the drug. The main objective of this research is to leverage the relationship between biomarkers, clinical endpoints and exposure response modeling for making go/no-go decisions in early clinical development and improve the selection of target doses.

**Methods:** A simulation based framework [1] is used to evaluate different early biomarker trial designs to improve Phase 3 dose selection. The early development scenario consists of two biomarker trials namely Ph1b-Proof of Concept (PoC) and Ph1b-Dose finding (DF) followed by a Ph2b DF trial. The biomarker levels (BM1, BM2) are measured on days 1 and 14 during the trials and BM3, measured on day 28, is the early clinical endpoint. A linear relationship is assumed between biomarkers and the Ph2b clinical endpoint, observed after 12 weeks of therapy. The biomarker responses are generated using an additive baseline effect-inhibitory Emax model using area under the curves as the exposure metric with underlying pharmacokinetic (PK) variability. A Bayesian tri-variate normal distribution model is assumed for the 3 biomarkers and posterior probabilities are used to make go/no-go decisions regarding the next stage of the trial and for dose selection. The simulations are carried out using a trial version of CytelSim® software.

**Results:** Based on two sequences of trial designs (PoC -> Ph2b & PoC-Ph1bDF-Ph2b), preliminary results assuming moderate PK variability have indicated that the probability of selecting the correct dose is similar between an exposure based metric and a dose metric.

**Conclusions:** A Bayesian modeling framework to leverage the relationship between biomarkers, clinical endpoints and PK exposures for early clinical development decision and optimize phase 3 dose selection has been developed and further investigations are underway.

**Reference:**