

## **Modeling and Simulation to Quantify the Therapeutic Value of Drug X in A Combination Therapy**

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**Objectives:** The therapeutic effectiveness of Drug X as a single agent has been clinically established and its efficacy in a drug combination was evaluated in a clinical trial with the target patient population. The objective of this modeling and simulation analysis was to quantify the therapeutic value of Drug X in a combined drug regimen.

**Methods:** The contribution of Drug X to the clinical efficacy of a selected drug combination (Group 1) was evaluated by comparison to a treatment without Drug X (Group 2). Pharmacokinetics of Drug X was characterized with a population PK model based on ~1300 plasma concentration data from 230 subjects. Therapeutic effects of two treatment groups were evaluated by three exposure-response modeling approaches: 1) use an inhibitory Emax model to characterize time course of drug effect in which Drug X exposure was incorporated as a covariate of the maximal response; 2) use a binary logistic regression model to estimate the probability of responders who achieved a target effect in a defined treatment period and the probability was described as a function of Drug X exposure, and 3) use a Cox proportional hazards model to assess the time to achieve the target effect, in which probabilities of responders in the two treatment groups were assessed separately.

**Results:** The inhibitory Emax model described the efficacy measures adequately as function of time from baseline to the end of trial for both treatment groups. Time to 50% of the maximal response and magnitude of the maximal response were estimated for each individual. The maximal response exposure was found to be positively associated with Drug X exposure and the estimated Emax at steady state was 23% higher in patients received Drug X (Group 1) than those not received Drug X (Group 2). The estimated probability of responder in Group 2 was 0.67. The probability increased in patients who received Drug X. The model predicted probability at a population average exposure to Drug X was 18 % higher than that in the non-Drug X group at the end of treatment. Inclusion of Drug X significantly shortened time to the target response. For instance, the median time that patients achieved the target response was 4 weeks earlier in Group 1 than in Group 2.

**Conclusions:** The therapeutic value of Drug X was quantified with a modeling and simulation approach providing a scientific rationale for inclusion of Drug X in a combination therapy.