

**Title:** The exposure-response driven development program, application to an anti-inflammatory compound

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**Objectives:** The objective of the presentation is to provide a model for early clinical development with exposure-response serving as the unifying basis. An example using an anti-inflammatory compound in clinical development will demonstrate how assessment of exposure-response using pharmacometric approaches was applied to drive early phase clinical development.

**Methods:** Three key applications of pharmacometric exposure-response evaluation will be highlighted. First, a population approach to allometry coupled with a simulation of human exposures accounting for uncertainty in the allometric parameters was used to predict healthy subject drug exposures. The predicted distribution of exposures was integrated with in vitro pharmacodynamic (PD) data, toxicology data, and animal disease model results to design and choose doses for a First-Time-In-Human (FTIH) study. Second, implementation of near real-time modeling and simulation supported adaptation of the FTIH study. Third, FTIH PK and PD modeling results were used to design a Phase II proof of concept study in patients undergoing percutaneous coronary intervention for acute coronary syndrome.

**Results:** The observed healthy subject exposure data agreed reasonably well with the predicted exposure data. Linkage of predicted human exposures with in vitro PD models and animal disease model PD resulted in selection of a FTIH study dose range that provided ex vivo PD results spanning the desired range. Population PK and PD modeling of FTIH PK/PD data aided optimal dose selection for the Phase II proof of concept study. Biomarker responses in the ACS study established proof of concept and guided dose selection in another study in an alternate indication.

**Conclusions:** A commitment to exposure-response analysis in the nonclinical and early clinical stage of development formed the basis for optimal design of a series of clinical studies. Decisions were more quantitatively-informed and rapid. Observed data validated the approaches employed, thus enhancing support for continued application of pharmacometric approaches to exposure-response-guided drug development.