

**Title: Model-based characterization of dose-response relationship in exploratory clinical development – extracting a small signal from noisy response data**

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**Objectives: To characterize the dose response relationship using a model based approach**

**Background:** Exploratory clinical development trials often include biomarker or clinical readouts (for safety or efficacy) that exhibit significant within-subject variability. This variability is in part due to systematic diurnal patterns as well as apparent random changes. Typical examples include steroid, histamine and heart rate. Here we present a model-based analysis of lung function data (FEV<sub>1</sub>) in order to extract a signal from very noisy data; previously, a simple pre-dose baseline-corrected primary statistical analysis had failed to detect a clear monotonic dose-response relationship.

**Data:** Forced expiratory volume in one second (FEV<sub>1</sub>) was measured in patients at pre-dose baseline and a range of time points up to 48 hours post-dose in a Phase I trial. The trial had two parts, and both followed a single dose, randomized, placebo-controlled, crossover design. The first part (Part A) included treatment groups for placebo, positive control, and the MTD of Drug X. The second part (Part B) included treatment with placebo and one of four selected dose levels of Drug X. Thirty-four patients completed both studies, four completed only Part A, and six completed only part B.

**Methods:** A kinetic-pharmacodynamic (K-PD) model [1] was developed, including the following elements:

1. A periodic function to account for systematic changes in baseline
2. A dose-linear longitudinal concave function to account for the waxing and waning of drug input signal over time
3. A nonlinear E<sub>max</sub> function to relate the longitudinal drug input function with the response
4. A mixed effects model (implemented in NONMEM V) which accounted for the between-patient variability, the within-patient between-period variability and the residual variability in the profiles predicted by the model elements 1-3 above.

The model was used to predict the dose-response relationship to help selection of doses in a subsequent dose-finding study.

**Results:** The model described the data reasonably well. A visual predictive check [2] provided further reassurance that the model was appropriately predictive of the data. Applying the model, it was possible to extract dose-response information, which indicated that the drug produced a maximum effect typical for this class of drug.

**Conclusions:** The large between- and within-patient variability typically seen in FEV<sub>1</sub> data can confound a small treatment signal. Standard statistical approaches therefore often fail to characterize dose-response relationships, particularly in small exploratory trials. A model-based approach which accounts for systematic and random sources of variability appears to improve the signal-to-noise ratio of the efficacy signal sufficiently to enable characterization of the dose-response relationship.

**References:**

[1] Jacqmin P., Snoeck E., Schaick van E.A., Gieschke R., Pillai P., Steimer J.-L. and Girard P., Modeling response time profiles in the absence of drug concentrations; definition and performance evaluation of the K-PD model, *Journal of Pharmacokinetics and Pharmacodynamics* 34: 57-85, 2006

[2] Holford N., The Visual Predictive Check – Superiority to Standard Diagnostic (Rorschach) Plots. PAGE 14 Abstr 738 [[www.page-meeting.org/?abstract=738](http://www.page-meeting.org/?abstract=738)], 2005