Introduction/Objectives

An eight week dose-finding study was planned:
- 3 treatment arms and a placebo arm with 120 patients in each.
- one test dose as an immediate release tablet followed by twice daily extended release tablet.
- The planned PK sampling schedule included 18 samples per patient (reference design).

The aim of the project was to optimize the PK sampling times and particularly to reduce the number of samples, while retaining the possibility to estimate the parameters from a PK model earlier developed (Fig 1).

Material and Methods

Population PK-model
- Developed based on pooled Phase I-Ia data (healthy subjects and patients).
- 3-CMT model with linear elimination and non-linear distribution and absorption.
- Diurnal variation in bioavailability for the ER-formulation was included in the model.
- Day-to-day variability (IOV) was included in clearance.
- Each scenario was optimised separately.
- The design setup with reduced (left) and full (right) clinical restrictions. The sample times were fixed (red) or allowed to move in the shaded area (green). The blue samples were allowed to move within its shaded area but were also allowed to be omitted.

Optimization setup
- Number of samples/patient fixed to either: 18, 16, 14, 12 or 10
- Each scenario was optimized without and with clinical restrictions.
- D-optimization using PopED v. 2.10 (http://poped.sourceforge.net/)
- Efficiency was calculated as:
  Efficiency = \frac{OFF_{Efficiency}}{OFF_{ref}}

Evaluation of the designs using SSE
- Simulation (n=40) and re-estimations (SSE) in NONMEM ver 6.2.
- The precision (RSE%) relative to the mean and the mean absolute error (MAE) were calculated.

Conclusions

Optimal design theory allowed identification of a design for a complex population PK model that is more informative than the original design, despite fewer samples. Thereby, the study cost could be significantly reduced.

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