Application of Optimal Design to Reduce the Sample Costs of a Dose-finding Study

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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 (Fig1).

Material and Methods

Population PK-model

- Developed based on pooled Phase I-IIa 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.

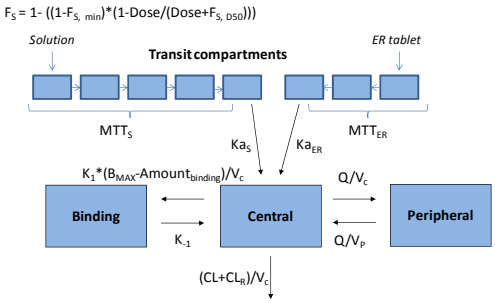

Figure 1: *The population PK model for oral solution and extended release tablet.*

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:
  where p = number of parameters in the model $Efficiency = \left(\frac{OFV}{OFV_{ref}}\right)^{\frac{1}{p}}$

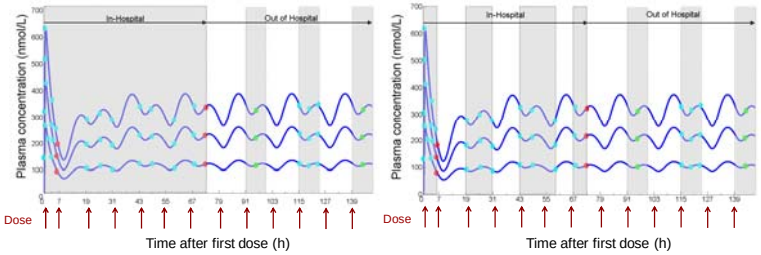

Figure 2: *The design setup with reduced (left) and full (right) clinical restrictions. The sample times were were fixed (red) or allowed to move in the shaded area (green). The blue samples were allowed to move within its shaded area but were also allowed to be omitted.*

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.

Results

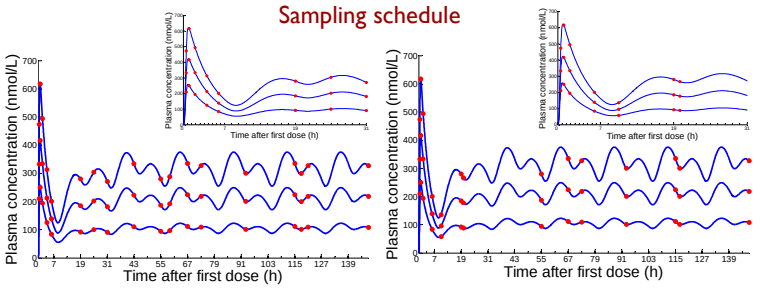

Figure 3: *Sampling schedule for the reference design (left) and proposed design (right).*

- The optimized design for the 18 samples per patient scenario increased the efficiency with 70%, (Fig 4a) compared to with the reference design, which may be translated into 150 fewer patients needed for PK sampling (Fig 4b).
- The proposed optimal design incorporating clinical restrictions had a similar efficiency as the reference design, but included only 14 samples per patient (Fig 4a). Thereby the study cost could be reduced by ~100 000 Euro.

a)

b)

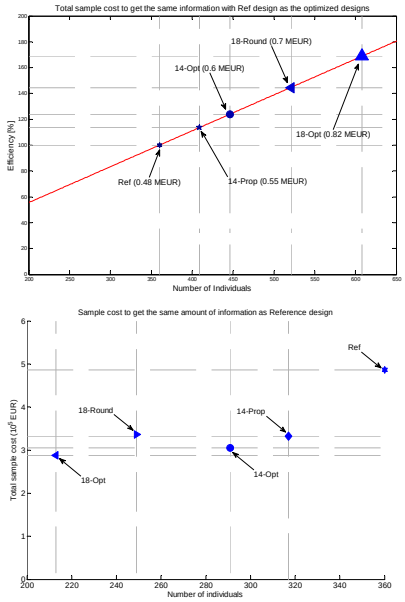

Figure 4: a (top): *Efficiency of optimized designs describe how many patients are needed in the study with the reference design to gain the same information as the optimized designs do with 360 patients.*
b (bottom): *Shows how many patients are needed with the optimized designs to gain the same information as a study with 360 patients and the reference design. The decrease of patients may be translated into reduction of study costs.*

- The SSE showed comparable RSE% on average per parameter as was predicted by the optimal design for both the reference and proposed design (Fig 5). The MAE was <25% on average per parameter and was similar between the two designs.

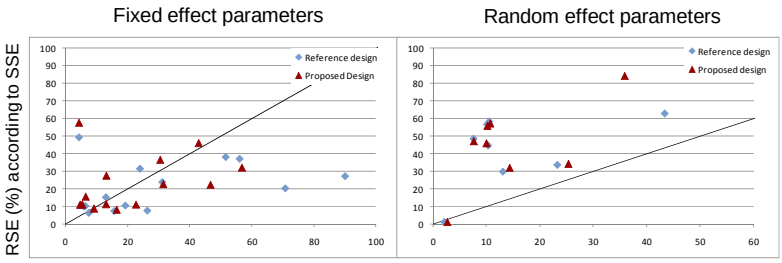

Figure 5: *The precision for each parameter in the model for the reference design and the proposed design.*

Acknowledgement

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