Designing Sparse-Sampling Schemes for Population PK Study of a Highly Variable Drug

Larisa Reyderman, PhD\textsuperscript{1}, Amrik Shah, ScD\textsuperscript{2}, and Paul Statkevich, PhD\textsuperscript{1}

\textsuperscript{1}Department of Drug Metabolism and Pharmacokinetics; \textsuperscript{2}Department of Statistics

Schering-Plough Research Institute, Kenilworth, NJ, USA

OBJECTIVE

Design a sparse sampling scheme for a population PK component of an efficacy trial of an anti-tumor drug. Due to predisposition to bleeding of the study patient population, the optimal sampling scheme should incur a minimal number of blood draws per patient. The data collected will augment available PK data to allow for identification and testing of covariates for this highly variable drug.

STUDY DESIGN

Population PK Model:

- A population PK model was developed based on the data from 7 Phase I clinical trials, wherein patients (n=88, 40% female, 60% male) were given twice-daily oral doses of 200, 250 or 300 mg. A total of 727 plasma steady-state concentrations (n=7-14/patient) were available for up to 12 or 24 hr post-dose (Day 7, 14 or 15 of dosing) (Figure 1).

- A steady-state one-compartment oral model was fitted to the data which was based on rich data (Table 1, Figure 6).

Sparse Sampling Scenarios:

- Sparse sampling scenarios were selected by splitting the PK profile into 2 segments: 0.5-4 hr – defines “Ka” segment, 6-12 hr – defines “Ke” segment (Figure 3).

- For each sparse sampling scenario, individual patient PK profiles were bootstrapped to generate 100 datasets. The population PK model was fit to each bootstrapped dataset (Figure 4).

- Accuracy and precision of resulting parameter estimates were compared to those from the original model which was based on rich data (Figure 5).

- The likelihood of a successful model fit to the bootstrapped datasets was related to the number of sampling points in the design. The percentage of datasets with successful model fits ranged from 70%-95% for the different sampling scenarios. For the designs under consideration, the scaled mean squared error (MSEs) for the population model parameters ranged from 0.0056 to 0.0195 (Table 1, Figure 6).

RESULTS

Table 1. Prediction Performance

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Ka</th>
<th>Ke</th>
<th>V</th>
<th>Design Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 points</td>
<td>-0.0056</td>
<td>0.0092</td>
<td>-6.3</td>
<td>0.0158</td>
</tr>
<tr>
<td>5 points</td>
<td>-0.00058</td>
<td>0.0080</td>
<td>-5.8</td>
<td>0.0118</td>
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<tr>
<td>6 points</td>
<td>0.00051</td>
<td>0.0028</td>
<td>-2.9</td>
<td>0.00576</td>
</tr>
</tbody>
</table>

Mean Prediction Error: \( me = \frac{1}{n} \sum_{i=1}^{N} p_{ei} \)

Prediction Error (%): \( pe = \frac{\theta - \theta_{true}}{\theta_{true}} \times 100\%

Design Efficiency: \( \frac{1}{n} \sum_{i=1}^{N} MSE_{ei}(\theta) \)

Scaled Mean Squared Error: \( MSE = \frac{MSE_{ei}}{\theta^2} \) (Parameter Efficiency)

Sustained Mean Squared Error: \( MSE = me^2 + \frac{1}{N} \sum_{i=1}^{N} (pe_i - me)^2 \)

CONCLUSIONS

The ease and flexibility of the proposed methodology allowed for evaluation of various sampling scenarios which were subsets of the original design. The estimates of each model fit were used for computation of standard metrics of model prediction errors and design efficiency.