Evaluation of the Bias and Precision of Bayesian Parameter Estimates When Applying a Phase I Model to Sparse Patient Data

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ABSTRACT

Purpose. A simulation study was conducted to assess the use of a Phase 1 population PK model to estimate Bayesian parameters in Phase 2/3 patients. Specifically, the bias and precision of the Bayesian parameter estimates was examined after applying a Phase 1 model to sparse patient data with varying estimates of mean parameter values and interindividual variability (IIV).

Methods. A 1-CMT model with 1st-order absorption and elimination was used to simulate full-profile steady-state data in Phase 1 subjects for a drug with an elimination half-life ($t_{1/2}$) of 20 hr. Twelve patient populations were simulated (and replicated 100 times) using combinations of population mean $t_{1/2}$ values (ranging from 20-40 hr), increased magnitudes of IIV for CL and V (10-60% higher than Phase 1), and sparse sampling schemes (2-6 samples/ patient). The model was fit to the Phase 1 data using NONMEM's FOCE method with interaction, and applied to each patient dataset to obtain Bayesian PK parameters using the Phase 1 estimates as priors. Bias and precision (median PE% and |PE|%, respectively) were assessed for CL, V and C_{max}.

Results. Reasonable Bayesian parameter estimates (PE% ± 15 and |PE|% < 30) were obtained for patient populations with a $t_{1/2}$ within 25% and magnitudes of IIV for CL and V within 35% of priors. Although bias and imprecision increased as patient PK diverged from priors (PE% ± 45%), this was minimized when there were at least 4 strategic samples per patient.

Conclusions. Reasonably unbiased and precise Bayesian PK estimates can be obtained from sparse patient data using Phase 1 model estimates as priors under the conditions described above. The impact of PK differences from the priors can be mitigated by attending to the quality and quantity of the sparse patient data.

INTRODUCTION

- Due to time constraints, it is sometimes necessary to rapidly assess drug exposures from sparse PK samples collected from patients in Phase 2/3 trials.
- This information can then be used to assess the influence of covariates on PK variability and to investigate exposure-response analyses of safety and efficacy in support of dose selection at End-of-Phase 2 meetings with the FDA.
- Time constraints may make it onerous to conduct a comprehensive population PK analysis appropriate for estimating individual patient PK.
- We investigated the impact of using a structural population PK model and its attendant parameters estimated from a Phase 1 dataset to generate Bayesian PK parameter estimates from sparse patient PK data collected in a Phase 2/3 milieu.
- Use of this approach may lead to biased and imprecise Bayesian estimates of patient PK parameters due to factors such as:
  - insufficient data to move the posthoc parameter from the prior;
  - potential PK differences between patients and healthy subjects; and
  - interindividual variability (IIV) of Phase 1 subjects is small relative to patients.

OBJECTIVES

This simulation study was conducted to assess the bias and precision of Bayesian PK parameter estimates and predicted exposure measures when a Phase 1 model was applied without estimation to sparse patient data.

METHODS

Simulation

- All data simulations were conducted using SAS® Version 8.2.
- PK modeling was performed using NONMEM® Version 5.1.1 with FOCE Interaction via batch processing on a dedicated grid engine of Sun Microsystems servers.

METHODS (Continued)

- Individual PK parameters were simulated for a Phase 1 trial with 200 subjects:
  - population mean clearance (CL), volume of distribution (V), and absorption rate constant (k_a) for an oral drug with t_{max} = 2 hr and $t_{1/2}$ = 20 hr (**Table 1**); and
  - the magnitude of the IIV for parameters (ω^2) and the residual variability (σ^2) were typical of Phase 1 populations.
- Individual PK parameters were also simulated for 12 patient populations (**Table 1**):
  - 100 trials of 200 patients (total of 20,000) for each population;
  - CL and V varied such that $t_{1/2}$ ranged from 20-40 hr;
  - ω^2_{CL} and ω^2_V were increased (10-60 %CV) relative to Phase 1 subjects; and
  - ω^2_{ka} and σ^2 were increased modestly by 10%.
- The PK parameters were assumed to be log-normally distributed.
- A moderate covariance between the interindividual errors (η) for CL and V was assumed (r^2 = 0.36); all other η pairs were assumed to be uncorrelated.

Table 1: Population Mean PK Parameters

Population	Symbol Used in Plots	k_a (hr^{-1})	CL (L/hr)	V (L)	ω^2_{CL} (%CV)	ω^2_V (%CV)	ω^2_{ka} (%CV)	σ^2 (%CV)
Healthy Subjects with Mean $t_{1/2}$ = 20 hr								
1		2.00	2.50	100	20%	35%	45%	10%
Patient Populations with Mean $t_{1/2}$ = 20 hr								
2		2.00	3.50	100	30%	45%	55%	20%
3		2.00	3.50	100	55%	70%	55%	20%
4		2.00	3.50	100	80%	95%	55%	20%
Patient Populations with Mean $t_{1/2}$ = 25 hr								
5		2.00	3.00	105	30%	45%	55%	20%
6		2.00	3.00	105	55%	70%	55%	20%
7		2.00	3.00	105	80%	95%	55%	20%
Patient Populations with Mean $t_{1/2}$ = 30 hr								
8		2.00	2.50	110	30%	45%	55%	20%
9		2.00	2.50	110	55%	70%	55%	20%
10		2.00	2.50	110	80%	95%	55%	20%
Patient Populations with Mean $t_{1/2}$ = 40 hr								
11		2.00	2.00	115	30%	45%	55%	20%
12		2.00	2.00	115	55%	70%	55%	20%
13		2.00	2.00	115	80%	95%	55%	20%

- Simulated CL, V, and k_a values were used to compute individual concentration (Cp) versus time (t) profiles using a 1-CMT model (**Eq. 1**).

$$Cp = \frac{k_a \cdot Dose}{V(\frac{CL}{V} - k_a)} \left[\left(\frac{1 - e^{-n k a \cdot \tau}}{1 - e^{-k a \cdot \tau}} \right) e^{-k a \cdot t} - \left(\frac{1 - e^{-\frac{n CL \cdot \tau}{V}}}{1 - e^{-\frac{CL \cdot \tau}{V}}} \right) e^{-\frac{CL}{V} t} \right] \quad \text{Eq. 1}$$

- Cp were determined over the 24-hour dosing interval (τ) at each time within 3 strategic time windows (**Table 2**) following 100 mg QD dosing for 14 days (n).
- Residual error was simulated and incorporated into each Cp using a proportional error model.

Table 2: Window-Based PK Sampling Strategy

Window	Sample Collection Times
1	0.25, 0.5, 0.75 and 1 hr post-dose
2	1.5, 2, 3 and 4 hr post-dose
3	6, 12, 18 and 24 hr post-dose

- For each population, 5 sparse PK sampling schemes were evaluated (**Table 3**).
  - Uniform sampling in each dataset (2 to 6 samples per individual), with 1 to 2 samples randomly selected from within each time window
  - 5 schemes • 1 trial = 5 sparse PK datasets for Phase 1 subjects
  - 5 schemes • 100 trials • 12 populations = 6000 sparse PK datasets for patients

Table 3: Algorithm Used to Create Sparse Sampling Datasets

Total Number of Samples Per Patient	Number of Samples Randomly Selected (Time Windows 1, 2, 3)
6	2, 2, 2
5	2, 1, 2
4	1, 1, 2
3	1, 1, 1
2	0, 1, 1

Modeling Methods

- A 1-CMT model with first-order absorption and elimination was fit to the full-profile Phase 1 data.
  - ω^2_{CL}, ω^2_V, and ω^2_{ka} were described using an exponential error model;
  - σ^2 was described using a proportional error model; and
  - covariance between η_{CL} and η_V was estimated.
- The model was then applied (e.g., $EST MAXEVAL=0) to each sparse sampling dataset to obtain Bayesian PK parameters using Phase 1 estimates as priors.
- To determine a steady-state C_{max} for each individual, the time of the maximum drug concentration (t_{max}) was calculated as shown in **Eq. 2** and substituted for t in **Eq. 1**.

$$t_{max} = \ln\left(\frac{k_a (1 - e^{-\frac{CL}{V}\tau}) / \frac{CL}{V} (1 - e^{-k_a \cdot \tau})}{k_a - \frac{CL}{V}} \right) \quad \text{Eq. 2}$$

Evaluation of Model Performance

- In order to assess the bias and precision for each parameter, prediction error percents (PE%) and absolute prediction error percents (|PE|%) were computed for CL, V, and C_{max} for each individual (**Eq. 3** and **4**).

$$PE\% = \frac{True\,Parameter - Bayesian\,Estimate}{True\,Parameter} \cdot 100\% \quad \text{Eq. 3}$$

$$|PE|\% = |PE\%| \quad \text{Eq. 4}$$

- The median PE% and |PE|% for each parameter was calculated for:
  - the dataset overall (200 individuals); and
  - the 0-25 and 75-100th %tiles of the true parameter values (50 individuals each)
- The median of the above statistics was calculated across trials for each population.
- The median PE% and |PE|% for both CL and C_{max} across trials was plotted versus the number of samples per individual in the dataset (**Figures 1** and **2**); V and AUC (inversely proportional to CL) are not shown.

RESULTS

PK Analysis

- The fit of the model to the Phase 1 data resulted in parameter estimates that were in general agreement (±3%) with the values used to simulate the data.
- Using these parameter estimates as population priors, Bayesian estimates of CL, V, and k_a were successfully obtained for all sparse sampling datasets.
- By utilizing grid engine technology, all 6005 NONMEM® runs submitted were able to be processed in approximately 10 hours.

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Figure 1: Bias for CL and C_{max} (Refer to Table 1 for Legend)

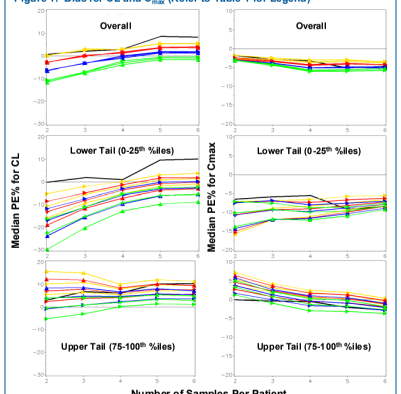
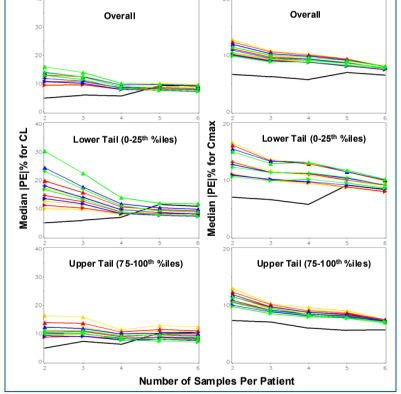


Figure 2: Precision for CL and C_{max} (Refer to Table 1 for Legend)



RESULTS (Continued)

Evaluation of Model Performance

Clearance

- For Phase 1 subjects, CL overall was generally unbiased (median PE% ± 8%) and reasonably precise (median |PE|% < 10%) across sampling schemes.
- For patients, CL overall was generally unbiased (median PE% ± 12%) and acceptably precise (median |PE|% < 15%) across sampling schemes.
- Bias was generally greater in the tails of the true CL distribution but was minimized to an acceptable range (median PE% ≤ 10%) for populations with:
  - $t_{1/2}$ within 25% and both ω^2_{CL} and ω^2_V within 35% of priors, regardless of the amount of PK data; or
  - ≥ 4 strategic PK samples per patient.

Volume of Distribution

- For Phase 1 subjects, V was generally unbiased (median PE% ± 10%) but slightly less precise than CL (median |PE|% ~15%) across sampling schemes.
- For patients, V overall was generally under-predicted and was less precise:
  - populations with a $t_{1/2}$ within 25% and both ω^2_{CL} and ω^2_V within 35% of priors had a median PE% ± 15% and median |PE|% < 30% across sampling schemes; and
  - bias and imprecision could not be reduced to this range for all other populations despite increasing the amount of PK data.
- Bias and imprecision for V was greater in the upper tail of the true V distribution (median PE% and |PE|% ranged from 20-60%).

C_{max}

- C_{max} overall was slightly over-predicted but was reasonably precise in all populations:
  - median PE% ranged from -2% to -5% across sampling schemes; and
  - median |PE|% < 10% for datasets with ≥ 4 PK samples/individual.
- Bias was generally greater in the lower tail of the true C_{max} distribution but was minimized to an acceptable range (median PE% ≤ 10%) for populations with:
  - ω^2_{CL} and ω^2_V within 35% of priors, regardless of the amount of PK data; or
  - ≥ 5 PK samples collected per patient.

DISCUSSION AND CONCLUSIONS

- Since the PK of a drug are similar for healthy subjects and patients in a number of therapeutic areas, it was hypothesized that a Phase 1 population PK model may reasonably predict individual PK parameters in patients.
- To evaluate the robustness of this method, a simulation study was conducted to assess bias and precision of PK parameters when applying a 1-CMT Phase 1 model to sparse patient data with varying mean parameter estimates and IIV.
- The findings from this study show that reasonable estimates of AUC and C_{max} (PE% ± 10 and |PE|% < 15) can be obtained when applying the Phase 1 model to sparse data from patients with a $t_{1/2}$ within 25% and both ω^2_{CL} and ω^2_V within 35% of priors.
- Bias and imprecision increased as patient PK diverged from priors but was minimized when there were ≥ 4 strategic samples per patient. This suggests that the impact of differences from priors can be mitigated by attending to the quality and quantity of data collected using sparse sampling strategies.
- This simulation methodology can be modified (e.g., PK properties of the drug, sampling strategy, etc.) to determine the feasibility of using a Phase 1 model to estimate patient PK under a variety of experimental conditions.