# Assessing the Adequacy of a Minimal PK Sampling Schedule for Individual Dose Adjustment Decisions in a Proof of Mechanism (PoM) Study in a Special Population

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## Background

Drug A was previously tested in healthy subjects and patients (reference population) and is now being investigated for a new indication in a special population (new population). Sufficient exposure (AUCss) in the PoM study is required to demonstrate whether or not the hypothesized mechanism works for the new indication.

Prior PK information on drug A in the reference population demonstrated linearity over the PoM dose range and was described by a two-compartment population PK model with the peripheral volume of distribution increasing with body size (BMI).

As the new population differs in body size and composition, the PK characteristics could also be different. In the event that CL differs in the new population, individual dose increases may be necessary to reach the minimum AUCss required for the PoM study.

## Objectives

To propose a sparse PK sampling design for the PoM study under the following aspects:

a) What would be an informative sparse PK sampling design to assess the PK characteristics in the new population?

b) What is the minimal PK information required for adequate and timely individual AUCss prediction and dose decision if the CL in the new population is up to two-fold different than expected?

## Methods

### PoM Study Design

The PoM study design (Fig. 1) includes a 3-step dose-escalation phase (1x, 2x and 3x the starting dose, i.e., dose1) over 6 weeks, and a 10-week maintenance phase at the anticipated efficacious target exposure, i.e., dose3.

The dose to achieve target exposure (dose3) was selected based on exposure predictions in the reference population, and the minimum efficacious exposure was defined as the 5$^{th}$ percentile of the predicted AUC at steady-state (AUCss), i.e., the lower limit of the 90% PI.

A dose increase (from dose3 to dose4) may be needed to ensure that each individual subject in the PoM study achieves the minimum efficacious exposure. The individual dose increase decision will be made at week 7 (day 43), based on PK sampling and AUCss predictions during the dose-escalation phase.

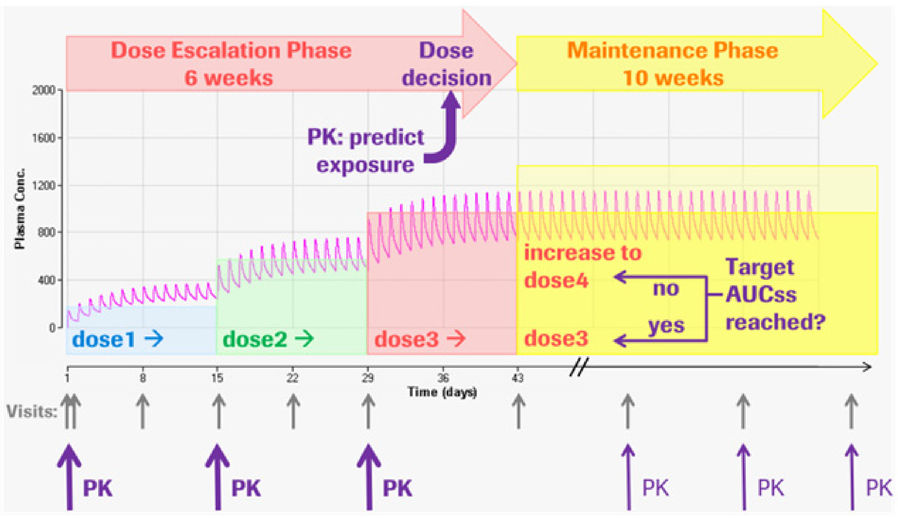


**Figure 1: Illustration of the PoM study design**. The solid purple line illustrates the plasma concentration-time curve for a typical subject in the reference population. Vertical arrows indicate study visits. Drug A is administered orally QD; dose1 is the starting dose, dose2 is 2xdose1, dose3 is 3xdose1, and dose4 is 4xdose1. The decision to stay on dose3 or increase to dose4 for the maintenance phase will be based on the individual AUCss prediction before day 43.

### Optimized PK Sampling Schedule

A number of alternative possible PK sampling schedules were evaluated with PFIM 4.0, using the Bayesian option for empirical Bayes estimates (EBEs) of individual PK parameters [1,2].

The best / optimized PK sampling schedule was selected according to the following criteria:

- A minimum number of blood samples, collected at the most informative time points possible under the study design
- Accurate predictions of each subject's exposure for the maintenance phase
- Correct individual dose adjustment decision before week 7
- Accurate characterization of PK properties in the new population at the end of the study
- Robust, i.e., informative also in case of different PK characteristics in the new population

### Reduced and Minimum PK Sampling Schedules

Simulations were performed to investigate whether the number of PK samples could be further reduced without compromising the dose decision for the maintenance phase of the PoM study.

*Simulation Scenarios*

The reference model was used to simulate 1000 subjects for each of the following scenarios:

1) CL is as expected
2) CL is 50% lower than expected
3) CL is 50% higher than expected
4) CL is 100% higher that expected
5) CL is as expected, 40% variability on KA

| Parameter | Typical Value | Variability (%CV) |
|---|---|---|
| KA (1/h) | 0.570 | 0 Fix |
| CL (L/h) | 4.21 | 40 |
| V2 (L) | 103 | 83 |
| V3 (L) | 262 | 31 |
| Q (L/h) | 29.2 | 0 Fix |
| V3_BMI (power) | 1.76 | |
| Residual error: add. (1.66 ng/mL), prop. (13%) | | |

**Table 1:** Parameters in the reference model

A number of reduced PK sampling schedules (see Table 2) were explored for comparison to the optimized PK sampling schedule derived from PFIM. EBEs of PK parameters were obtained with the reference model and compared with the true (simulated) parameters. The minimum PK sampling scheme was identified that will result in accurate decisions to stay on dose3 or increase to dose4.

## Results

### Optimized PK Sampling Schedule

A PK sampling schedule with a total of 10 samples per individual on study days 1, 2, 15, and 29 was identified as the optimal schedule (Table 2; schedule b) after PFIM evaluations, with respect to the previously defined optimization criteria. PFIM estimates for RSE were 6% on CL and less than 30% on all other PK parameters; shrinkage was 3%, 10% and 29% on CL, V2 and V3, respectively.

| | Day1 | Day2 | Day15 | Day 29 | N | Comment |
|---|---|---|---|---|---|---|
| a) | 1, 4, 12 | pre | pre, 0.5, 3 | | 7 | No 29 day data |
| **b)** | **1, 4, 12** | **pre** | **pre, 0.5, 3** | **pre, 0.5, 3** | **10** | **Optimized** |
| c) | 1, 4, 12 | pre | pre, 0.5, 3 | | 7 | Analyzed assuming 40% variability in KA |
| d) | 2, 12 | pre | pre, 0.5, 3 | | 6 | Reduced (day1) |
| **e)** | **2, 12** | **pre** | **pre, 3** | | **5** | **Minimal sampling** |
| f) | 2, 12 | pre | pre, 3 | pre, 3 | 7 | Minimal & day 29 |

**Table 2:** Optimized (schedule b) and reduced PK sampling schedules used for empirical Bayes analyses of the simulated PK data. pre: pre-dose sample, numbers: hours post-dose.

### Impact of Reduced Sampling on PK Parameter and Exposure Estimates

The impact of the explored sampling schedules on the accuracy of EBEs for CL is presented in Figure 2.

With the optimized PK sampling schedule (b), the bias of EBEs is minimal for all simulated scenarios, and 90% of EBEs are within 20% of the true (simulated) values.

With the reduced sampling schedules, accurate CL estimates are obtained for the simulation scenarios with CL as expected or up to 2-fold higher (scen1, 3-5). However, the scenario with CL 2-fold lower than expected (scen2) results in biased CL estimates towards the reference value, and in wider 90% CIs.

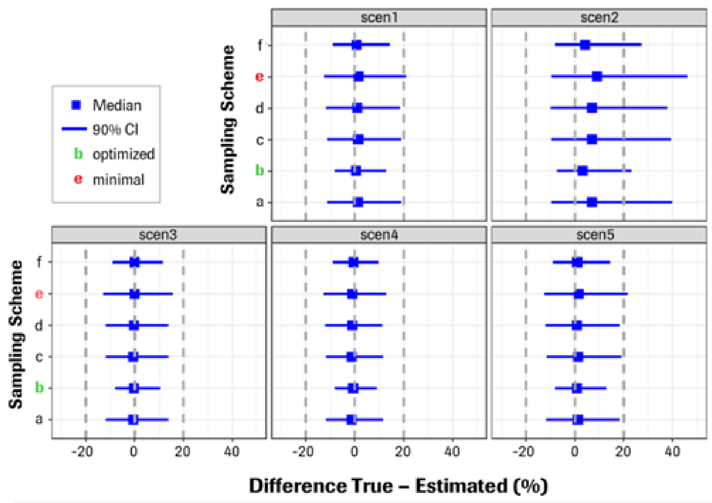


**Figure 2: Impact of PK sampling schedule on EBEs for CL**. Point-ranges represent the median and 90% CI for the difference (%) between true and estimated individual CL for each of the five simulated scenarios (scen1 to 5).

As AUCss is derived from CL, the bias and uncertainty on CL in scen2 result in exposure estimates that tend to be too low, especially in the upper part of the distribution, where the true exposure is above the 90% PI from the reference population, as presented in Figure 3.

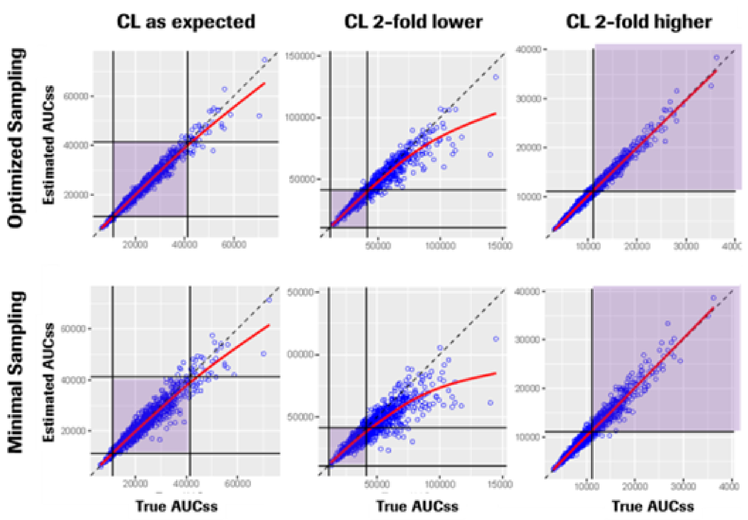


**Figure 3: Impact of PK sampling scheme on exposure prediction**. Results are presented for sampling schemes b (optimized, top row) and e (minimal, bottom row). Symbols: Individual estimated vs. true AUCss. Purple areas: 90% PI from the reference population. Lines: upper and lower limits (5$^{th}$ and 95$^{th}$ percentiles) of the 90% PI. A greater bias is observed with the minimal sampling scheme when CL is 2-fold lower than expected.

### Impact of Sampling Scheme on Dose Adjustment Decisions

Accurate dose increase decisions can be made with minimal PK sampling up to day 15, as demonstrated in Figure 4.

Despite biased AUCss estimates (Figure 3) the dose increase decision is not affected, since the predictions for low exposures, that trigger a dose increase, are unbiased. The risk of missing a true underexposure is less than 5% in all scenarios.

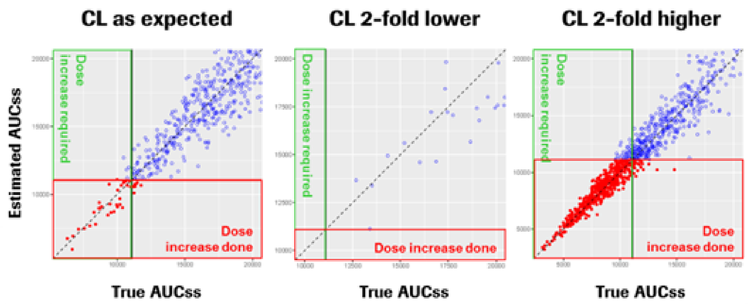


**Figure 4: Accuracy of Dose Adjustment Decisions**. Symbols: Estimated vs. true AUCss with PK sampling schedule e. Green and red rectangles indicate true and estimated AUCss below the minimum efficacious exposure. Red symbols: Dose increase decisions.

## Conclusion

A minimal PK sampling schedule is shown to facilitate adequate and timely dose decisions to ensure sufficient individual exposure in the PoM study even if the true CL in the new population is two-fold different from the prior value. The additional samples recommended by PFIM for precise and accurate PK characterization may be collected later in the study.

### References:

[1] Retout S, Duffull S, Mentré F (2001) Development and implementation of the population Fisher information matrix for the evaluation of population pharmacokinetic designs. Comput Methods Programs Biomed 65: 141–151.

[2] Combes FP, Retout S, Frey N, Mentré F (2013) Prediction of shrinkage of individual parameters using the bayesian information matrix in nonlinear mixed effect models with evaluation in pharmacokinetics. Pharm Res 30: 2355–2367. doi:10.1007/s11095-013-1079-3.