Assessment of expected drug exposure relative maximum safety limits in early phase studies

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Introduction

- During early phase clinical drug development, drug exposure should not exceed the maximum exposure limits.
- Pharmacokinetic models are often used when designing such studies for predicting what doses will render exposure below the maximum exposure limits, and for assessing Go/No-Go based on interim data.
- There are various approaches to perform such simulations with regard to sources of uncertainty and exposure metrics of interest.

Objective: To evaluate different simulation strategies and explore the potential impact on decision making for early PK studies.

Methods

A single ascending dose study was simulated, using a two-compartment population PK model with first-order absorption and elimination (Figure 1, parameter estimates Table 1).

- Doses of 1, 1.5, 3, 6 (and after an interim analysis) 8 mmol
- 6 subjects per dose level cohort
- PK sampling at 1,2,3,4,8,12,24,36,48, and 72h after dose

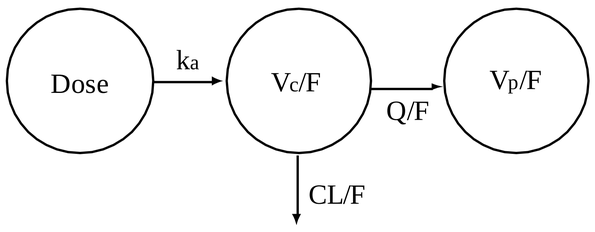

***Figure 1*. Simulation model,** where k_a is the first-order absorption rate constant, V_c/F is the apparent central volume of distribution, CL/F is the apparent clearance/F, V_p/F is the apparent peripheral volume of distribution and Q/F is the apparent inter-compartmental clearance.

An interim analysis was performed after the 6 mmol dose level, whereby the model was updated and used to simulate into the next dose level of 8 mmol.

The study was simulated 300 times under each simulation strategy:

- with the parameter values from the simulation model (TRUE)
- with the parameter estimates from the interim analysis
  - without parameter uncertainty with maximum likelihood estimates (MLE)
  - with parameter uncertainty from the NONMEM covariance step (COV)
  - with parameter vectors from Sampling Importance Resampling (SIR) [1]

The parameter estimates and uncertainties are found in Table 1.

The expected proportion of study replicates and individuals exceeding the maximum exposure limits at the 8 mmol dose level was assessed for calculating:

- The probability a subject may exceed exposure limits
- The probability a study dose level may have average exposure exceeding limits

The stop criterion for not progressing to the 8 mmol dose level was a >5% risk of exceeding the exposure limits of 1200 nM for C_{MAX} and 5500 nM*h for $AUC_{0\ to\ 24}$.

All simulations were performed in NONMEM version 7.3.0 installed on an Intel Xeon-based server and PsN 4.8.1.. Post-processing of simulation results was performed using R version 3.3.3.

				COV	SIR		
Parameter		**TRUE**	**MLE**	**RSE%**	**RSE%**	**2.5th**	**97.5th**
CL/F	(L/h)	10	11.2	11.2%	8.3%	9.4	13.0
V_c/F	(L)	100	69.7	121%	38.9%	18.8	120
V_p/F	(L)	200	214	35.2%	11.3%	165	262
Q/F	(L)	50	52.3	107%	19.5%	35.1	74.7
K_a	(h^{-1})	10	1.48	65.9%	77.1%	0.66	5.28
IIV CL		0.1	0.11	65.9%	48.8%	0.04	0.25
COV CL-V_c		0.05	0.17	27.6%	66.5%	-0.01	0.41
IIV Vc		0.1	0.35	255%	109.4%	0.02	1.36
IIV K_a		0.5	0.15	452%	167.6%	0.00	0.91
Res err		0.1	0.08	18.8%	9.9%	0.07	0.10

MLE : maximum likelihood estimate, RSE: relative standard error

***Table 1.* Parameter estimates** of simulation model (TRUE) and re-estimated parameters values based on simulated data up to the 6 mmol dose level (MLE), as well as the relative standard error (RSE%) of the estimates given by the NONMEM covariance step (COV) or sampling importance re-sampling (SIR) in PsN. The 95% confidence interval of the estimates (2.5^{th} and 97.5^{th} percentiles) are also given by SIR.

Conclusions

- The choice of simulation strategy may have impact when deciding whether to proceed to a next higher dose level or not based on available data during early phase trials.
- We recommend to clearly define upfront how the expected exposure will be assessed relative the maximum exposure limits when exploring the maximum dosing schedule.
- If of particular importance, different simulation strategies can be applied and subsequently the most conservative approach can be chosen.

Results

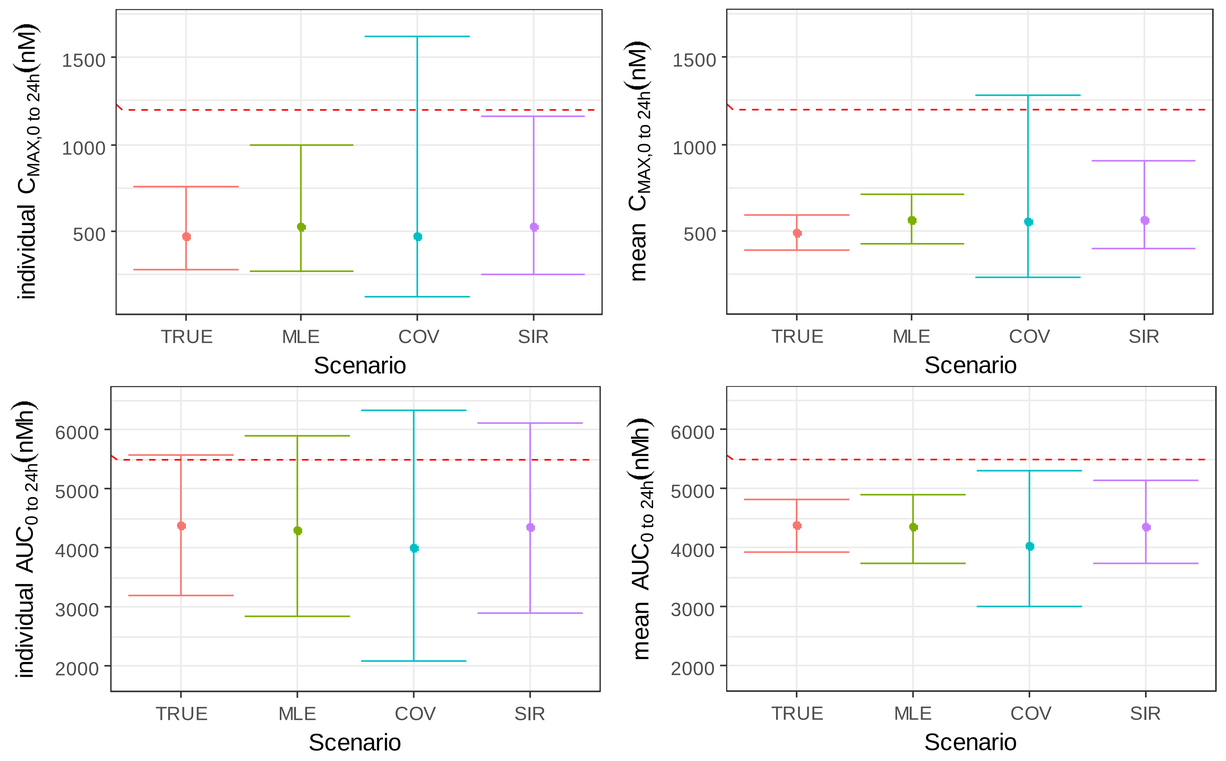

***Figure 2*. Simulation results,** the left panels shows the expected C_{MAX} and $AUC_{0\ to\ 24}$ after a single 8 mmol dose (dot) and the 90% prediction interval in the population (bracket) for the four simulation scenarios. The right panels shows the expected mean of the same metrics for a cohort of 6 subjects (dot) and the 90% confidence interval across simulated cohorts (bracket). The maximum exposure limits are indicated by the dashed red lines (1200 nM for C_{MAX} and 5500 nM*h for $AUC_{0\ to\ 24}$), if the upper edge of the bracket is above the exposure limit a No-Go decision is indicated for the 8 mmol dose level.

The choice of exposure metric, simulation strategy, and if to consider the mean exposure or individual exposure per dose level, all influenced the decision if to progress to the next (8 mmol) dose level (Figure 2).

The C_{MAX} metric had greater variability between simulation strategies than the AUC metric. Whether assessing the exposure limit per subject or the average per dose level had greater impact on decision making for AUC than for C_{MAX}. Based on AUC, progressing to the 8 mmol dose was supported with all simulation strategies when using the mean exposure, but not with any simulation strategy when using individual exposure. For C_{MAX}, the Go/No-Go decision was the same for the average and individual exposure scenarios.

In this study the MLE predictions of AUC and C_{MAX} were close to true, but due to risk of bias the uncertainty of the predictions generally should be included. In all cases the NONMEM COV was simulating wider distributions compared with SIR, and hence a greater proportion of cases were exceeding the exposure limit and would have resulted in a false positive No-Go decision based on the mean C_{MAX}. This was most likely an effect of a poor covariance matrix from NONMEM due to poor design of the simulated study (only MATRIX=S successful).

As expected, the proportion of cases exceeding the exposure limits was much greater for individual subjects compared to for the average exposure in 6 subjects for a dose level, e.g. for the AUC exposure limit simulated from SIR, the fraction of patients exceeding the limit was 13% compared to the fraction of studies where the mean exposure exceeding the limit was 2%.

References

[1] Dosne AG L, Bergstrand M, Karlsson MO. An automated sampling importance resampling procedure for estimating parameter uncertainty. J Pharmacokinet Pharmacodyn 44(6):509-520, 2017.