

Assessment of S65487 PK differences from therapeutic doses to microdose : exploring linear and nonlinear processes



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Introduction

S65487 is a **selective inhibitor of Bcl2**, administered intravenously to treat **hematological malignances** in 3 clinical trials. It is referred as a small molecule.

Microdose study, include in Phase 0 approaches, allows to evaluate subtherapeutic exposures of new drugs in first-in-human studies with the administration of a small dose in order to investigate basic drug properties [1].

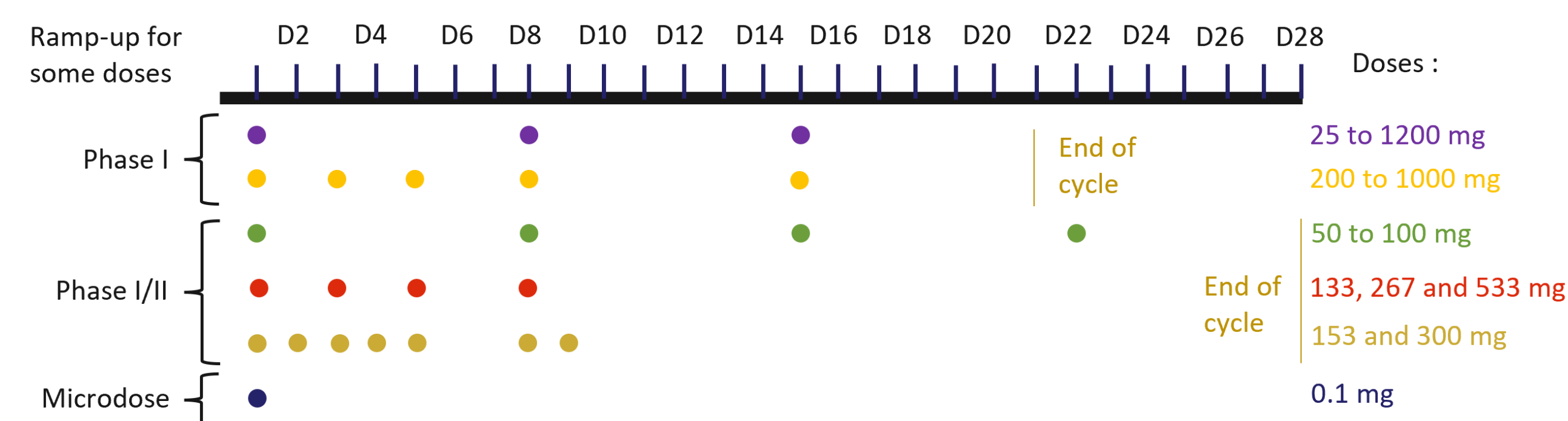


Figure 1: Administration schedule and doses from the various clinical trials used in the study

Model-independent data exploration

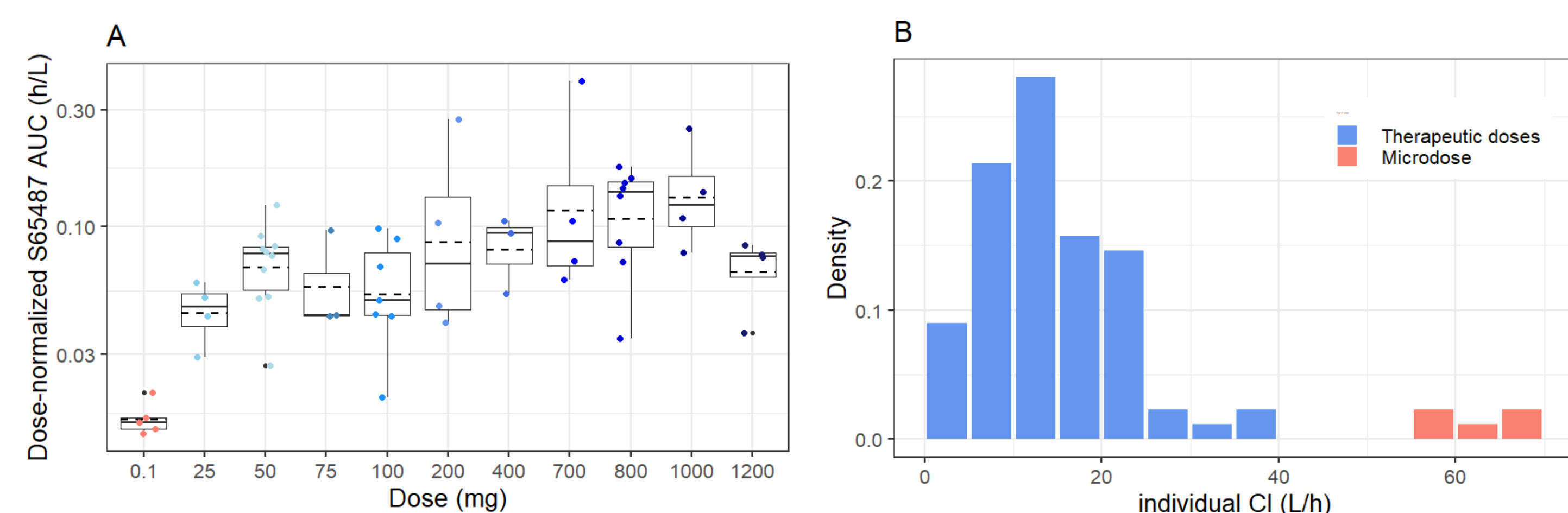


Figure 2: A: Dose-normalized S65487 AUC; B: clearance distribution estimated with non-compartmental approach
→ **Non-linearity between microdose and therapeutic doses, Cl estimates is dose-dependent** [2]

Objective

- To **reconcile PK data** from microdoses and therapeutic doses in a single popPK model by **characterizing non-linearity**

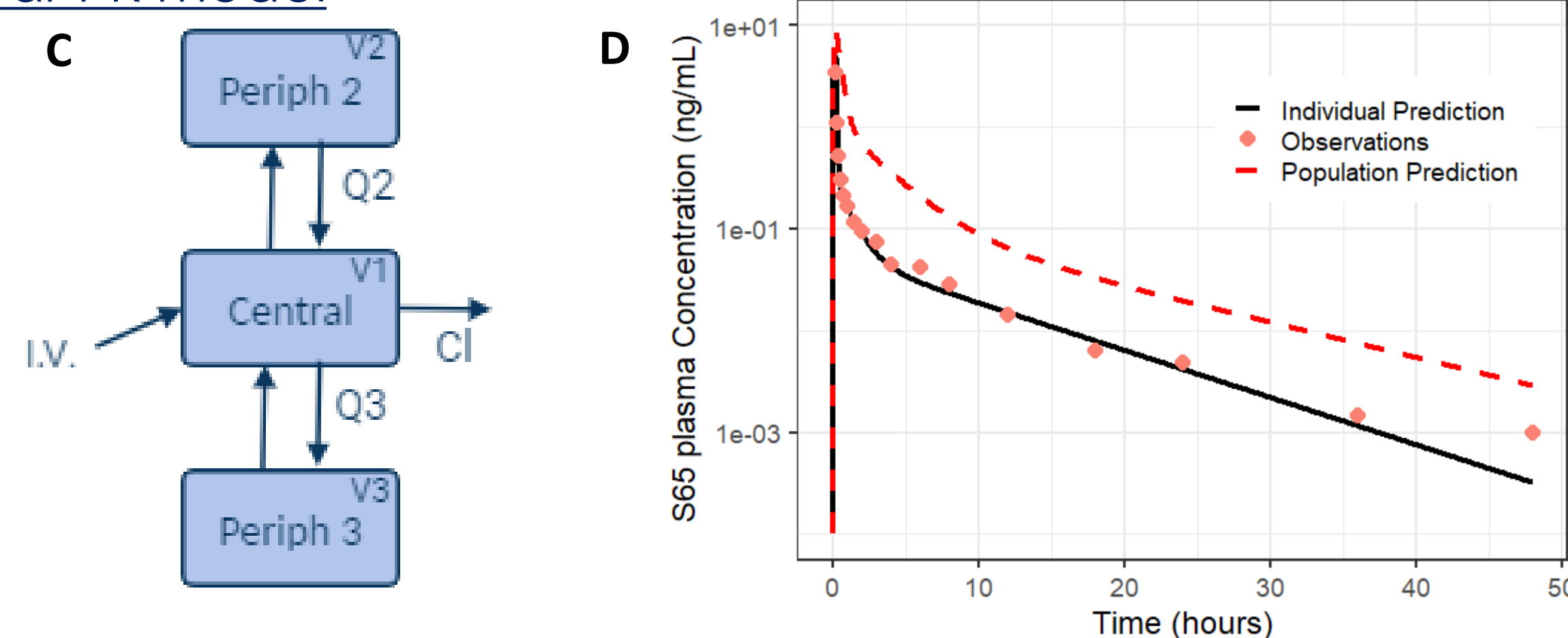
Model evaluation

- Goodness-of-fits
- Parameters estimation (RSE)
- Likelihood estimation (BIC : Bayesian Information Criterion)
- **Model evaluation by its ability to estimate population predicted exposure** [3] → $\frac{\text{population predicted AUC}}{\text{observed AUC}}$

Results

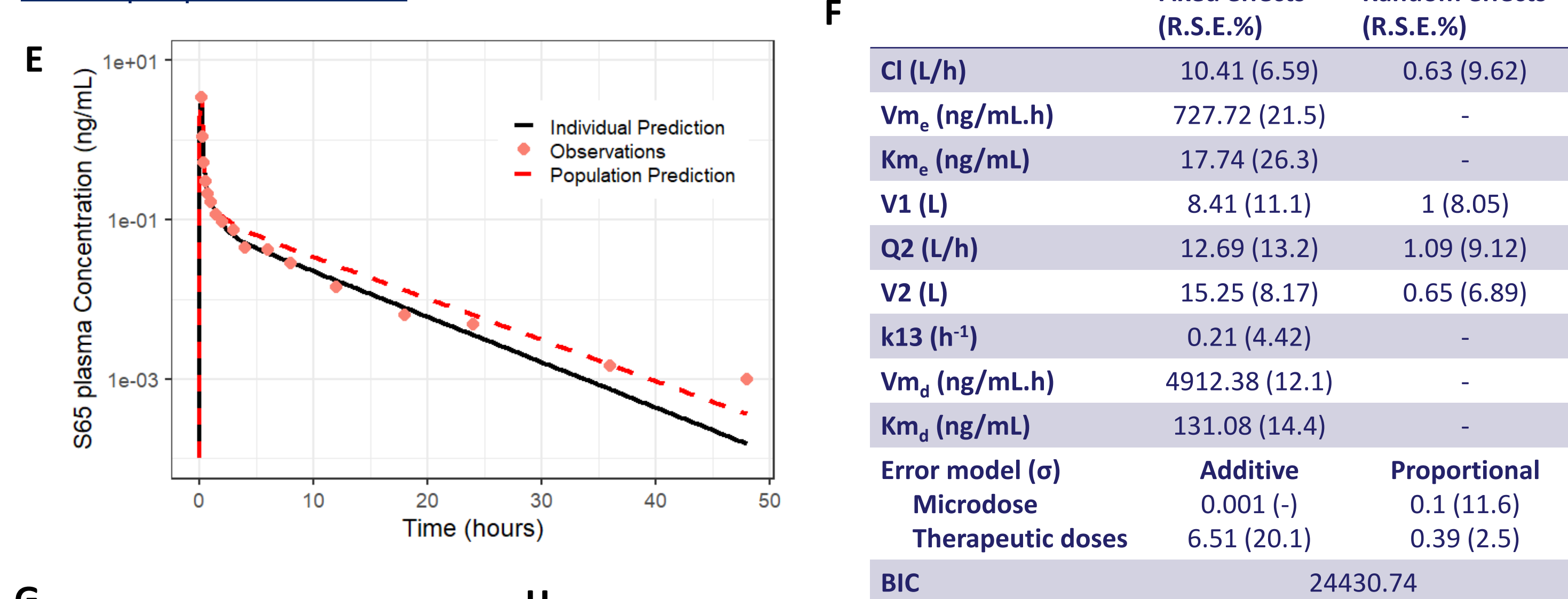
Modelling part

Linear PK model



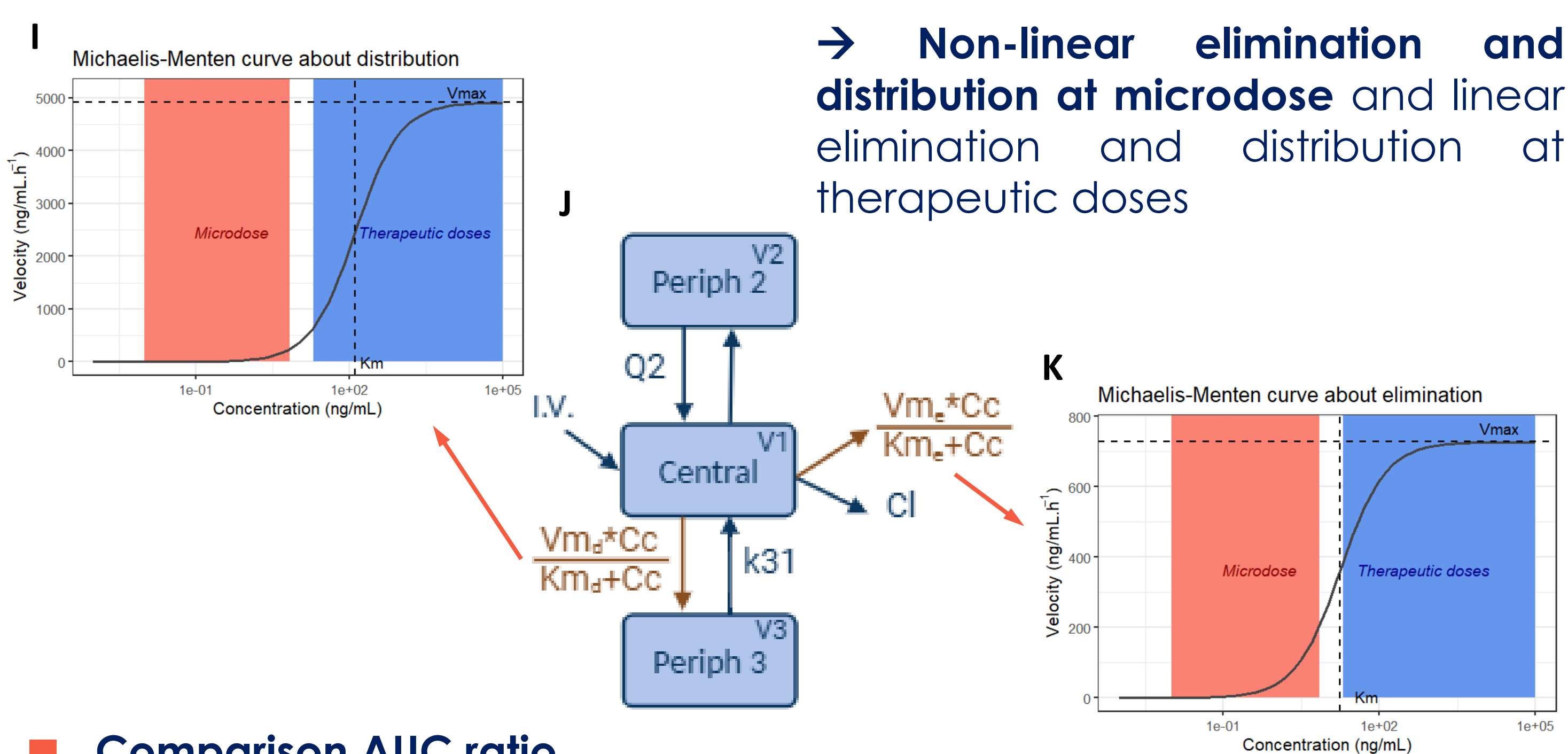
- + Saturable elimination and distribution, using Michaelis-Menten equations
- + 2 errors models

Final popPK model



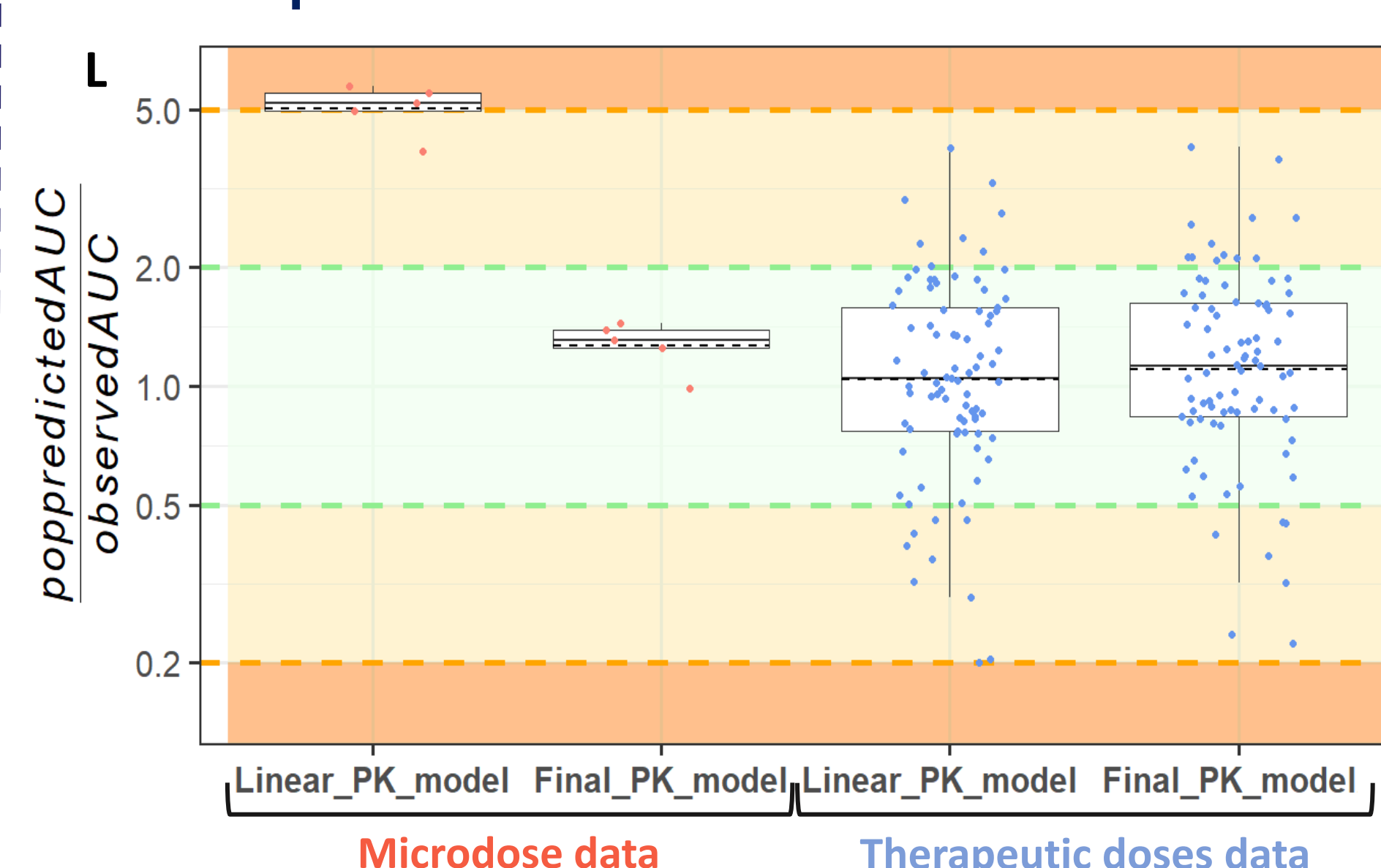
→ **Reconciliation of PK at microdose and therapeutic doses in a popPK model**

Saturable elimination and distribution



→ **Non-linear elimination and distribution at microdose and linear elimination and distribution at therapeutic doses**

Comparison AUC ratio



→ **Improve the S65487 predicted population exposure at microdose, compared with a simple linear PK model.**

Figure 3: C: Initial popPK model schema; D: Individual S65 concentration profile with microdose modeling with the Initial model; E: Individual S65 concentration profile with microdose modeling with the Final model; F: Estimation of final model parameters; G: pcVPC with microdose; H: pcVPC with therapeutic doses; I: Michaelis-Menten curve about distribution; J: Final popPK model schema; K: Michaelis-Menten curve about elimination; L: comparison of AUC ratios
V_m and V_m_d : Maximum elimination and peripheral distribution capacity; K_m and K_m_d : Concentration at half maximum elimination and peripheral distribution capacity; pcVPC : prediction corrected Visual Predictive Check

Conclusion

- Due to potential nonlinearity, the use of microdosing for extrapolation to therapeutic doses should be approached with caution. Various mechanisms need to be explored to accurately predict the pharmacokinetics at therapeutic doses, such as saturation of elimination and distribution or interaction with drug target.
- Bridging micro- and therapeutic doses in a unified population PK model will be useful for future drug candidates in order to take the most from microdose studies.

References

- [1] T. Burt *et al.*, « Microdosing and Other Phase 0 Clinical Trials: Facilitating Translation in Drug Development », *Clin. Transl. Sci.*, vol. 9, n° 2, p. 74-88, avr. 2016, doi: 10.1111/cts.12390
- [2] T. Burt *et al.*, « Phase 0/microdosing approaches: time for mainstream application in drug development? », *Nat. Rev. Drug Discov.*, vol. 19, n° 11, p. 801-818, nov. 2020, doi: 10.1038/s41573-020-0080-x.
- [3] N. Wu, D. A. Katz, et G. An, « A Target-Mediated Drug Disposition Model to Explain Nonlinear Pharmacokinetics of the 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitor SPI-62 in Healthy Adults », *J. Clin. Pharmacol.*, vol. 61, n° 11, p. 1442-1453, nov. 2021, doi: 10.1002/jcph.1925.