

Characterization of oral esketamine absorption kinetics in healthy volunteers

Marjie E. Otto^{1,2}, Laura G.J.M. Borghans¹, Joost van Mechelen^{1,3}, Gabriel E. Jacobs^{1,3}, J. G. Coen van Hasselt², Linda B.S. Aulin^{1,2}

¹Centre for Human Drug Research (CHDR), Leiden, The Netherlands

²Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands

³Leiden University Medical Centre (LUMC), Leiden, The Netherlands

LinkedIn

motto@chdr.nl



INTRODUCTION

Oral (PO) esketamine administration is **more clinically feasible** as antidepressant treatment compared to intravenous or nasal administration [1,2]

Extensive first-pass metabolism of esketamine presents to be a challenge for its clinical development [3]

The available **population pharmacokinetic (popPK) model** does not cover the therapeutic range and lacks quantification of variability [4,5]

Aim: Characterize the absorption PK and related variability of PO esketamine in healthy volunteers over a therapeutic dose range, by extension of a previously developed IV esketamine popPK model

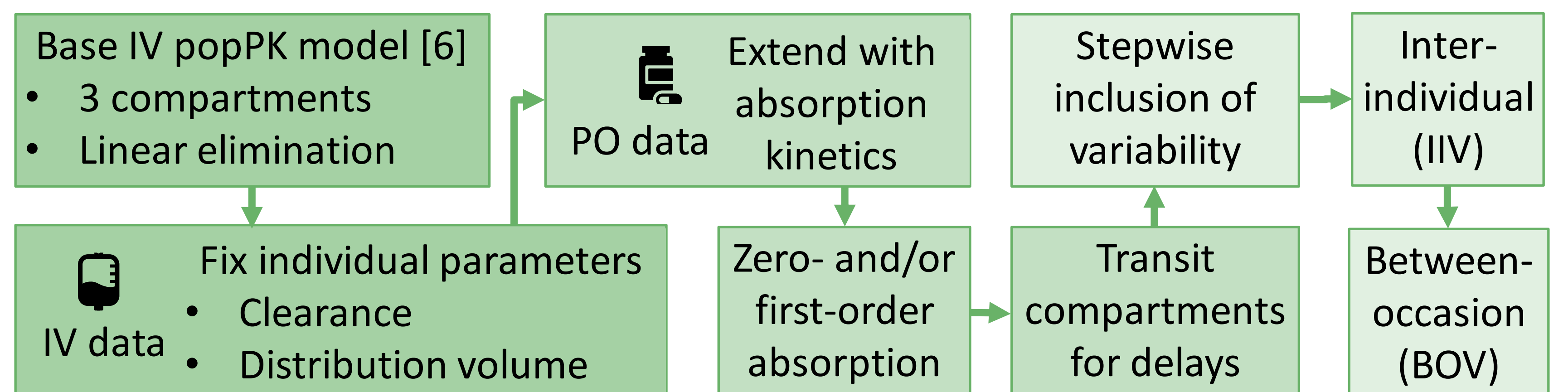
METHODS

Data

Placebo controlled cross-over clinical trial

- 17 healthy volunteers
- 0.4 mg/kg IV in 40 min (t: 0 min)
- 0.2 mg/kg (Low PO) (t:+15 min)
- 0.45 mg/kg (High PO) (t:+15 min)
- 0.25, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 24h
- 571 samples, 17.5% <1.00 ng/mL

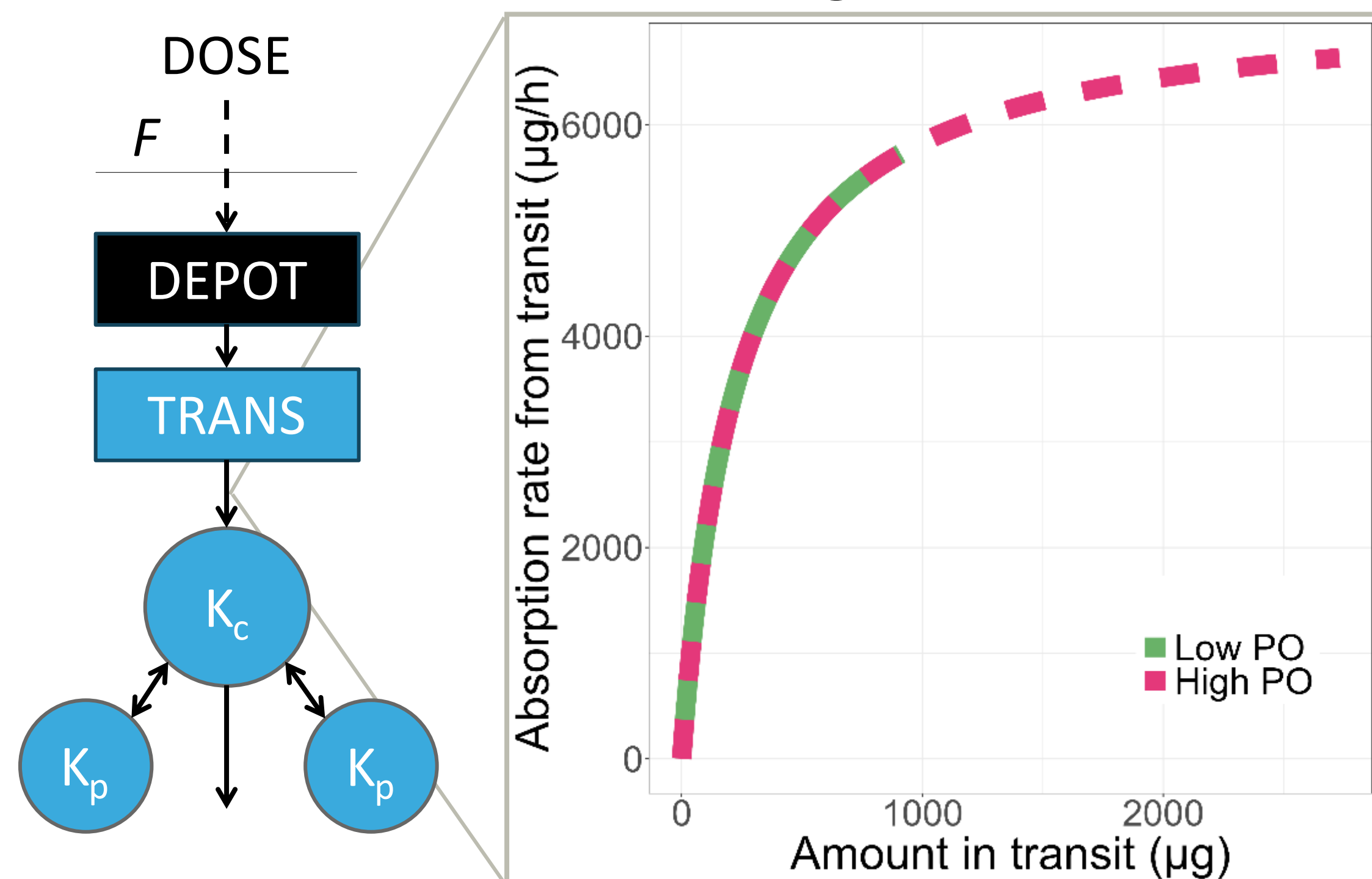
Model development



RESULTS

Saturable absorption kinetics

→ Later Tmax for higher doses



High IIV and BOV for F

→ Correlated with IIV of K_a Max

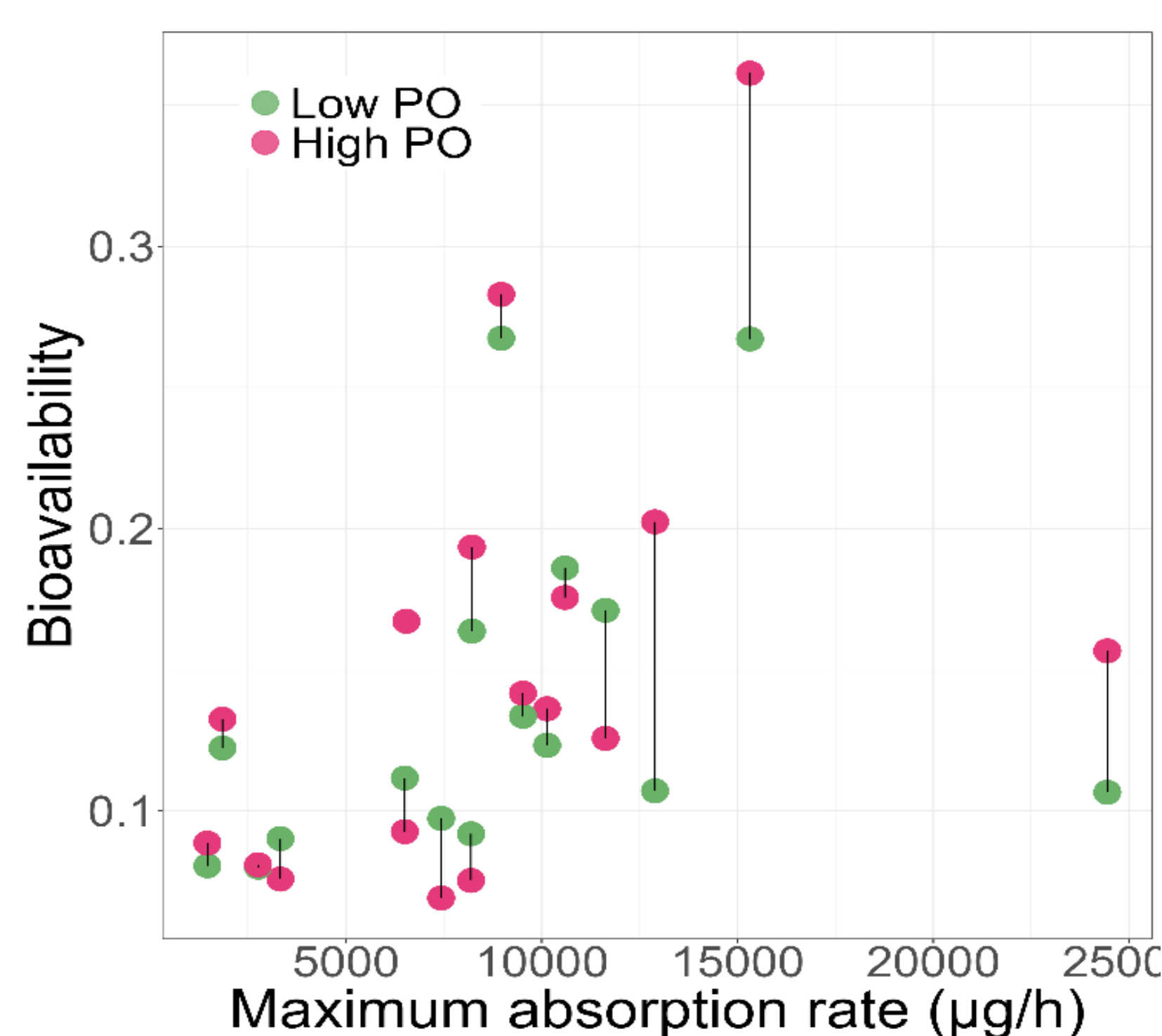
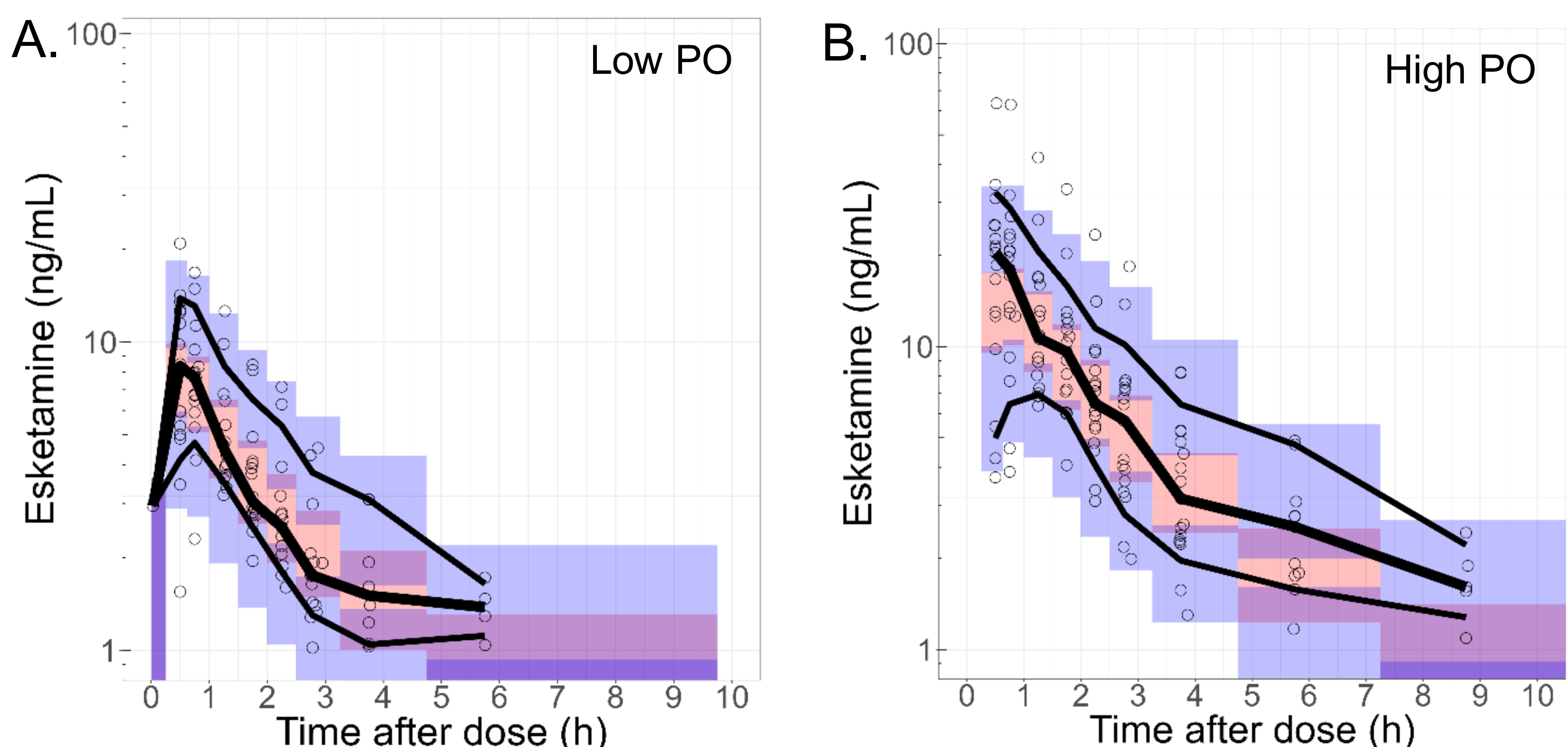


Table 1: PopPK model parameters

Parameter	Estimate [RSE%]
F	0.13 [18]
K_t (h^{-1})	15.0 [54]
K_a Max ($\mu g/h$)	7205 [35]
K_a 50 (μg)	234.9 [35]
IIV F (var)	0.22 [56]
IIV K_a Max (var)	0.59 [62]
BOV F (var)	0.05 [20]
Proportional RUV (CV%)	17.3 [8.0]

RSE: relative standard error, F: bioavailability, K_t : transit rate, K_a Max: maximum absorption rate, K_a 50 amount at which 50% of the maximum absorption rate is reached, IIV: inter-individual variability, BOV: between-occasion variability, RUV: residual unexplained variability, CV: coefficient of variation

Small underprediction during absorption phase of high dose



References:

- [1] Johnston et al. *Neuropsychopharmacology* 49, 23–40 (2024).
- [2] Dutton et al. *Psychopharmacology*. 240, 2483–2497 (2023).
- [3] Zanos et al. *Pharmacol. Rev.* 70, 621–660 (2018).
- [4] Smith-Apeldoorn et al. *BMC Psychiatry* 19, (2019).
- [5] Ashraf et al. *CPT:PSP*. 7, 687–697 (2018).
- [6] Otto et al. *PAGE* 31, Abstr 10594 (2023) Abstr 10594

LACDR



CONCLUSION

- Study designs of future clinical trials with PO esketamine should **take saturable kinetics for high doses into account.**
- A **more semi-mechanistic approach** may be required to account for the interlink between absorption and metabolism kinetics, especially if metabolites will be studied.