

Model based estimation of posaconazole tablet and suspension oral bioavailability using real world electronic health record (EHR) and therapeutic drug monitoring (TDM) data in children

Zoe Kane (1,4), Iek Cheng (1,2), Mario Cortina-Borja (1,3), Nigel Klein (1,4), Orlagh McGarrity (2), Robert Chiesa (1,2), Joseph Standing (1,4), Silke Gastine (1,4).

(1) Great Ormond Street and University College London Institute of Child Health, London, UK (2) Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom (3) Department of Population Policy and Practice (4) Department of Infection, Immunity and Inflammation



Background

- Invasive fungal infections (IFIs) are a major cause of morbidity and mortality for immunocompromised patients.
- Posaconazole (PCZ) is approved for treatment and prophylaxis in adult patients with an injection (IV), oral suspension (SUS) and gastro-resistant/delayed-released tablet (DRT) available.
- PCZ is lipophilic (logP=4.6), di-basic, poorly soluble and highly plasma protein bound (97-99%) [1].
- PCZ's ADME properties are complex [2,3] and CL after IV dose escalation (50-300mg) in healthy adults is saturable [4].
- In Europe PCZ is used off license in children. In the US a 'new' SUS was approved in May 2021 for use in children > 2years.

Objectives

- Estimation of PCZ bioavailability (F) for the DRT and 'old' SUS formulations using PopPK analysis of PCZ TDM data in children.

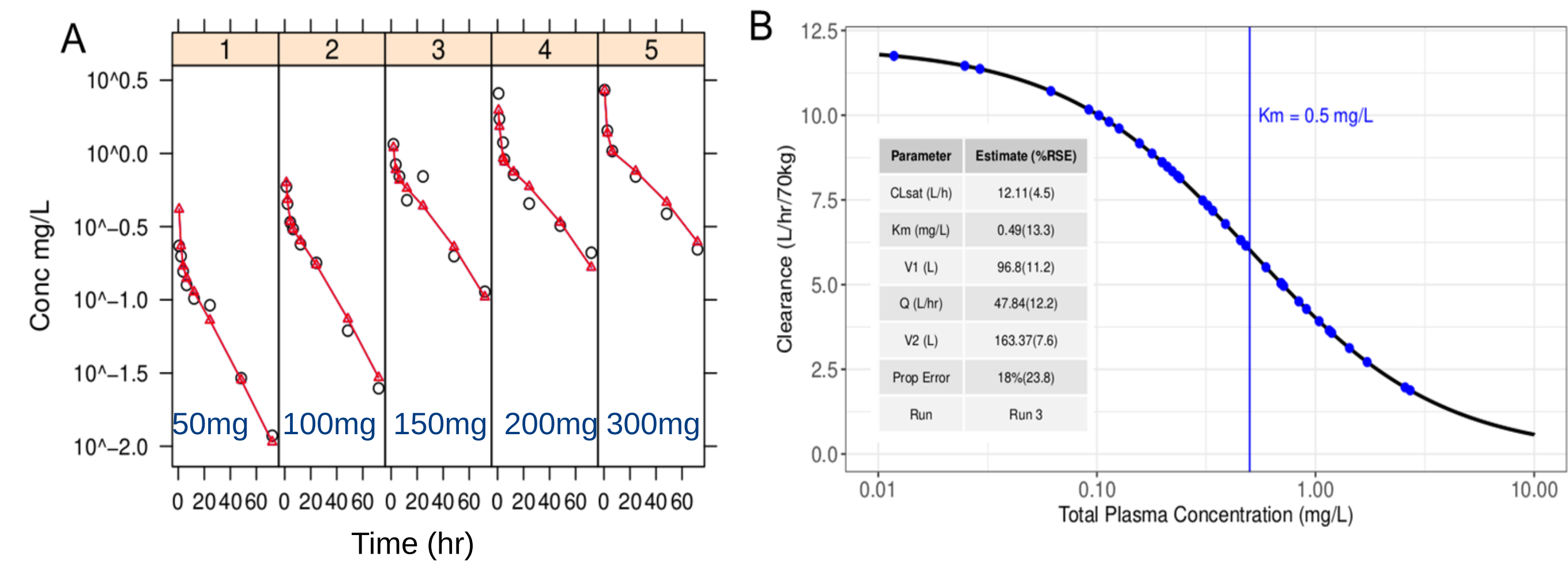
Methods

- Retrospective analysis of PCZ in-patient TDM data from a single specialist paediatric hospitals; Jan 2017 - July 2021.
- CL, V and Ka; fixed based on scaling of prior adult data [4,5,6].
- Covariate effects evaluated for: dose, alanine aminotransferase (ALT), Albumin (ALB), diarrhoea (DIAR) and concomitant dosing of proton-pump inhibitors (PPI).
- BLOQ plasma levels were handled using the M3 method.
- Population PK modelling used the FOCEI algorithm in NONMEM 7.4. Other software: PSN, Xpose4 and R.

Results and Discussion

- Modelling of IV dose escalation in healthy adults [4] shows that a saturable CL model is preferable for PCZ. (-ΔOFV=35 for 1df).

Fig 1. Modelling of published adult PCZ IV dose escalation PK data [4]



- Observed paediatric data: 298 plasma levels; 16:14:70 IV:DRT:SUS. 6% of levels are BLOQ. IV/PO crossover in 7 children, DRT/SUS crossover in 3 children. Total n=104.

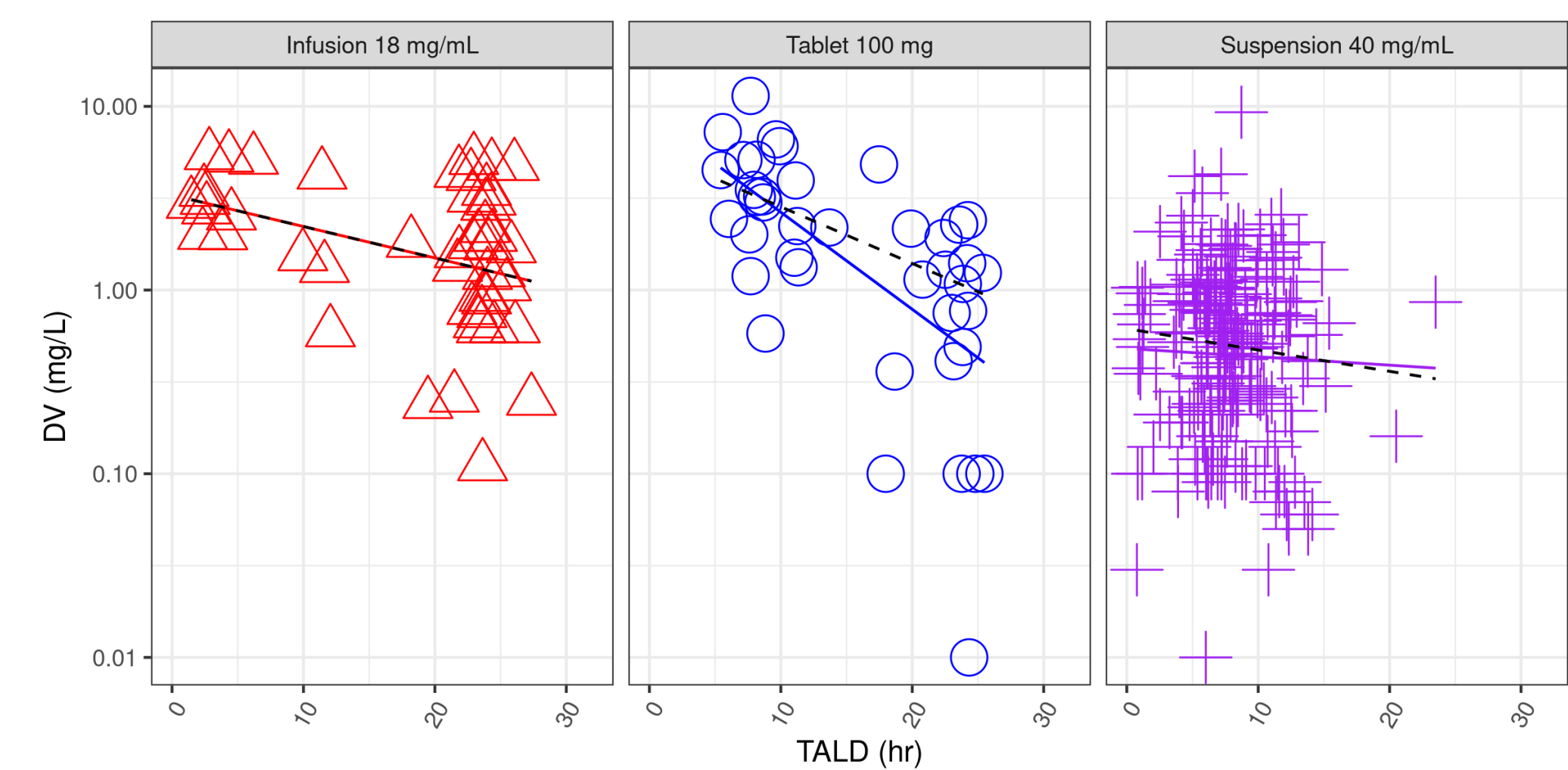


Fig. 2. Observed plasma concentrations versus time after last dose (TALD). Linear regression shown with and without inclusion of BLOQ levels

Results and Discussion

- Median age/weight; 6.2 years/19.5 kg. Diarrhoea 49%, PPI 69%.

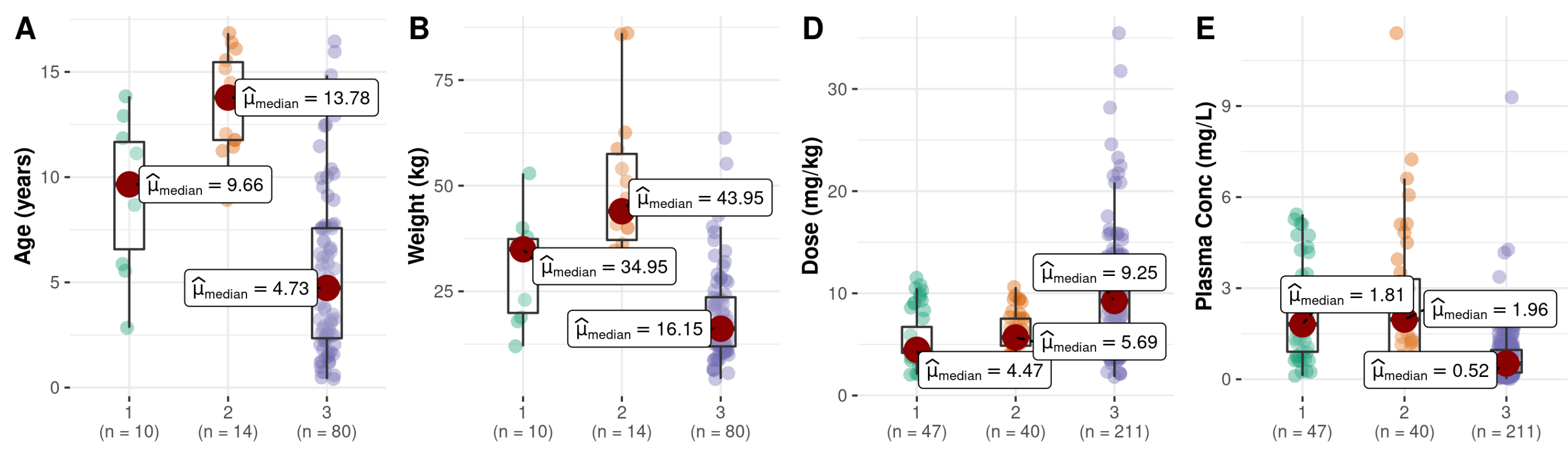


Fig. 3. Age, WT, dose and plasma conc by formulation 1 = IV, 2= DRT, 3= SUS

- Base model: 1-comp, 1st order absorption, saturable CL, IIV on CL and V with ADD plus PROP residual error. WT included *a priori*.
- Parameter sensitivity to Km was performed using the paediatric data and an optimised value utilised; 2 mg/L.

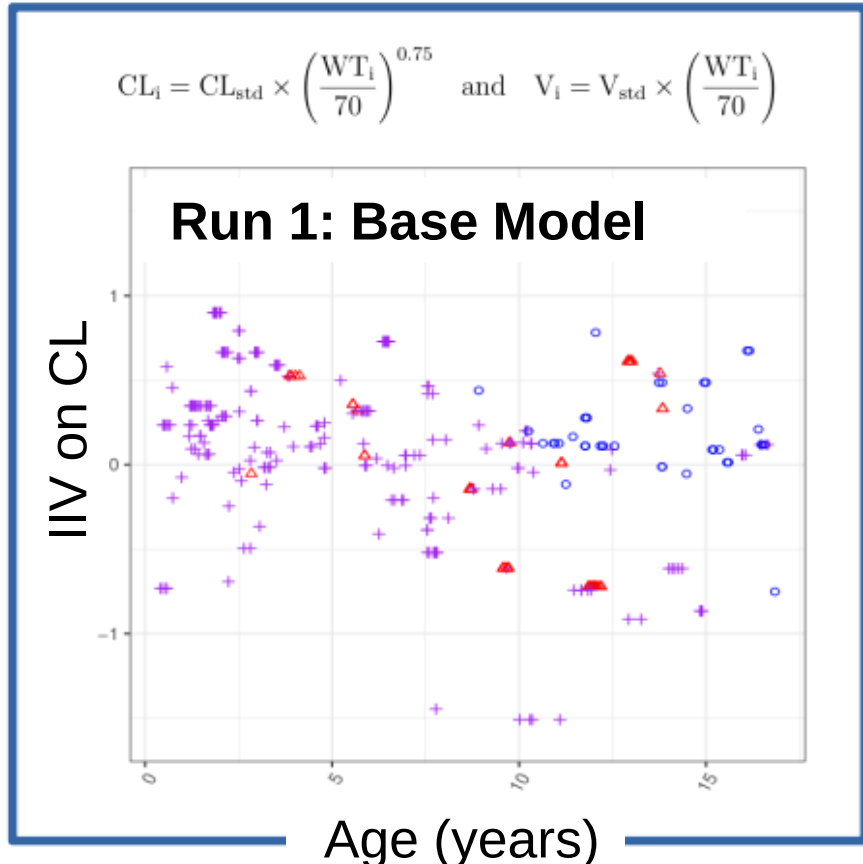


Table 1. Covariate selection

Run	Description	OFV	deltaOFV	df	Pvalue
1	Base Model	251.81	na	na	na
2	Dose on Faus	217.21	34.6	0	na
3	PPI on Faus	234.38	17.43	1	< 0.001
4	DIAR on Faus	246.49	5.32	1	0.021
5	DIAR on CLsat	248.36	3.45	1	0.063
6	Albumin on V	251.28	0.53	1	0.467
7	ALT on CLsat	240.99	10.82	1	0.001
8	PPI on Ftab	248.26	3.55	1	0.060
9	Dose on Ftab	245.01	6.8	1	0.009
10	WT on Ka	249.76	2.05	1	0.152
11	Albumin on Km	251.28	0.53	1	0.467
12	Combined Covariates p<0.05	190.38	61.43	3	< 0.001
13	minus Dose on Ftab	192.69	2.31	0	na
14	minus DIAR on Faus	194.37	3.99	1	0.046
15	minus ALT on CLsat	197.94	7.56	1	0.006
16	minus PPI on Faus	199.71	9.33	1	0.002
17	minus Dose on Faus	225.21	34.83	0	na
18	Final Saturable CL model p<0.01	196.68	55.14	2	< 0.001

Table 2. Final model parameters

Parameter	Estimate (%RSE)	IIV %CV (%RSE)
CLmax (L/h/70kg)	12 (fixed)	48% (37.5)
Km (mg/L)	2 (fixed)	—
V (L/70kg)	250 (fixed)	71% (fixed)
KaTAB (/hr)	0.59 (fixed)	—
KaSUS (/hr)	0.2 (fixed)	—
F1 TAB	0.8 (22.1)	—
D50 SUS (mg/BSA)	39.04 (14.1)	—
FPPI on Faus	-0.31 (-33.1)	—
ALT on CLmax	0.17 (75.7)	—
Add Error (mg/L)	0.41 (57.4)	—
Prop Error (%)	46 (28)	—
OFV	196.68	—

- Final model: includes ALT on CL, dose and PPI on Faus.
- With a linear CL model (data not shown here) F1 TAB is estimated to be > 1.0, this has also been reported preclinically [7].

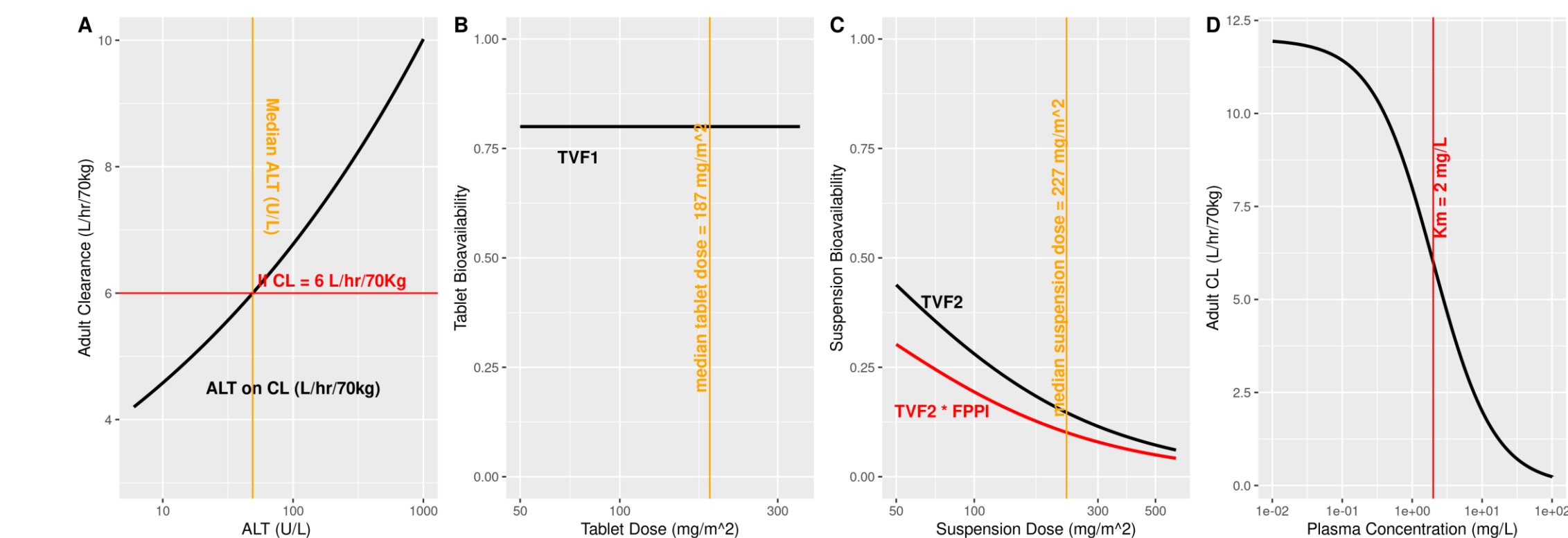


Fig. 4. Visualisation of covariate effects and non-linearity in clearance

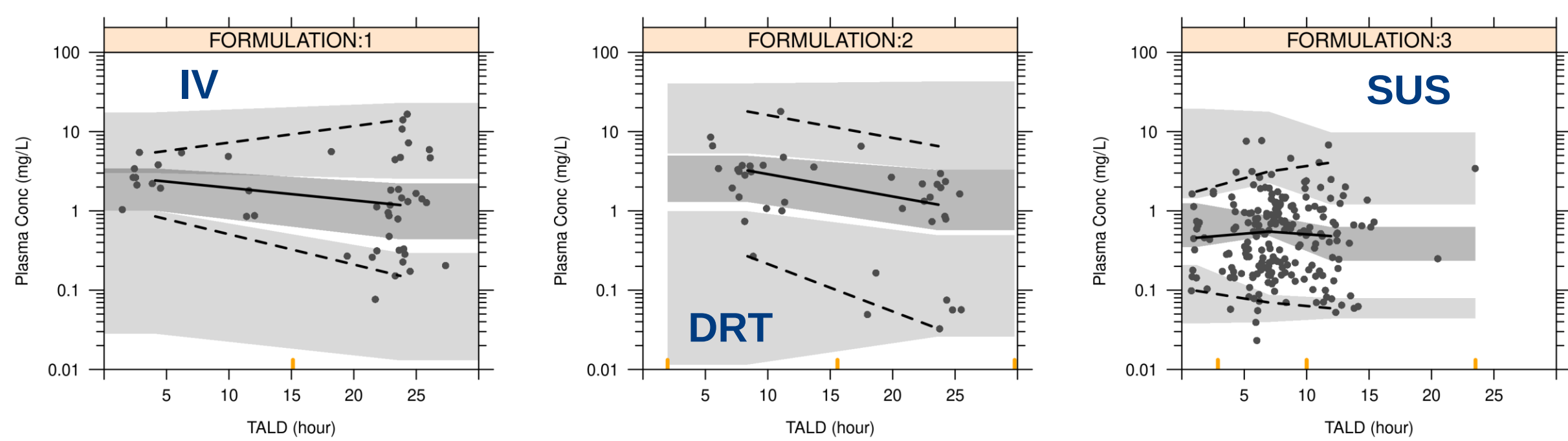


Fig. 5. Prediction corrected VPCs by formulation

Conclusions

- From real-world TDM data, more understanding of PCZ PK in immunocompromised children can be generated.
- Due to the sparse nature of PCZ TDM data extrapolation of PK in adult populations informed the base model.
- Covariate analysis confirmed previously reported dose and PPI effects on the "old" suspension F. An influence of hepatic impairment was also detected with this data.
- This model is currently being used alongside published PD targets to evaluate typical paediatric dosing regimens [8].

References:
[1] Hens et al., Mol Pharm 2017; 14: 4321-33.
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