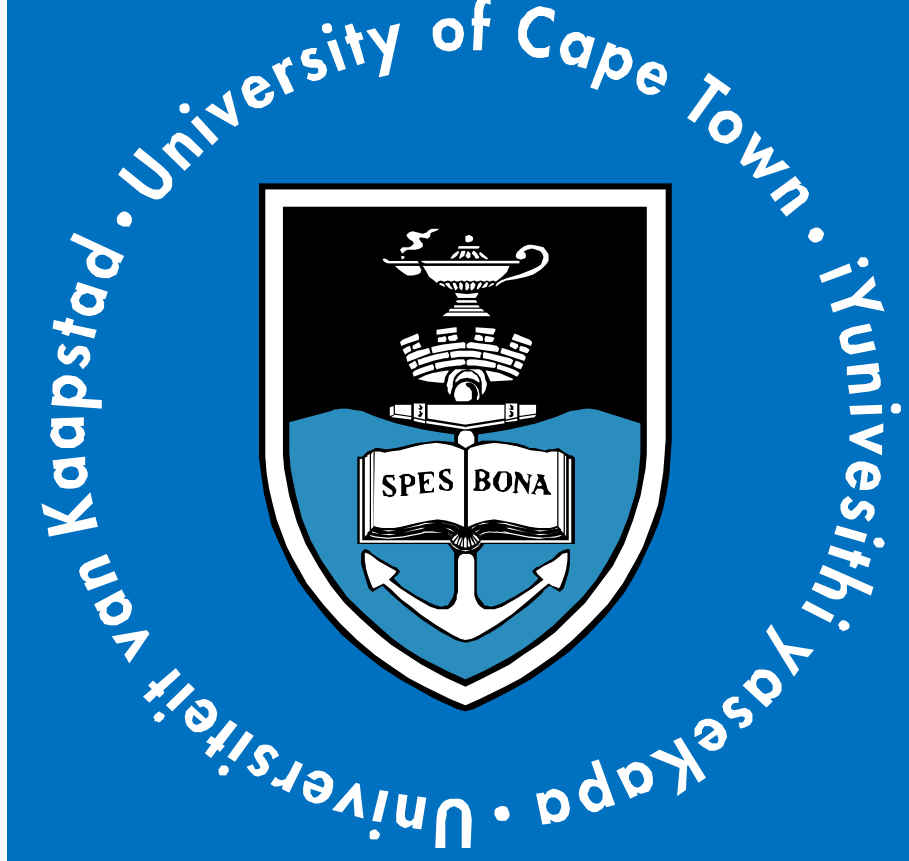




Population Pharmacokinetics of the Novel Antimalarial OZ439

E.K. Phongi(1), M de Kock(1), L Wiesner(1), T. Wells(2), E. Decloedt(1, 3), K.I. Barnes(1), P. Denti(1).

(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; (2) Medicines for Malaria Venture, (MMV), Geneva Switzerland; (3) Department of Clinical Pharmacology, Stellenbosch University, Cape Town, South Africa

email: eddy.phongi@uct.ac.za

Background and Aim

- OZ439 is a novel anti-malarial compound related to the artemisinins, but with a longer elimination half-life.
- In vitro, OZ439 is a potent inhibitor of both CQ-resistant and CQ-sensitive forms of *P. falciparum*.
- The renal excretion of OZ439 and most metabolites was negligible following single dose administration.
- OZ439 is a substrate of CYP3A4, but *in vitro* experiments suggest that hepatic clearance plays a relatively minor role in the total clearance of OZ439.
- OZ439 undergoes blood-mediated degradation.

The aim is to characterise the pharmacokinetics (PK) of single ascending doses of OZ439 in healthy volunteers, and to assess whether any drug interaction with mefloquine was observed.

Methods

Two cohorts of 18 South African healthy volunteers received respectively 100 mg and 400 mg single doses of OZ439 during two periods with and without mefloquine.

Blood samples collected pre-dose, and 1, 2, 3, 4, 6, 8, 10, 16, 24, 36, 48, 72 and 96 hrs post-dose for period 1 and also 168, 240, 336 hrs, Day 28, Day 35 and Day 42 post-dose for period 2.

DOSE
Cohort 1: 100 mg
Cohort 2: 400 mg.

Allometric Scaling Test
WT, FFM, FAT.

Pop – PK analysis, in NONMEM 7.3.

Table 1 Patient info

Covariate	Median (range)
Sex	M = 15 / F = 3
Age (years)	29.9 (19 - 49)
Weight (kg)	66.2 (52.7 – 86.2)
BMI (kg/m ²)	23 (19 – 30.3)
FFM (kg)	51 (37.1 – 61.2)

BLQ imputed to LLOQ/2, only 1st value in a series included in the fit, all values included in VPC

Table 2 Concentration summary

	Cohort 1: 100 mg	Cohort 2: 400 mg	Total
Volunteers	8	10	18
Total samples	278	346	624
# BLQ /No peak	61(21.9%)	23(6.6%)	84(13.5%)
BLQ in Pre-dose	8(13.1%)	10(43.5%)	18(21.9%)

Results

Better fitting with:

- 3-compartment disposition model
- 1st-order elimination and 1st-order absorption with transit.
- FAT to scale the volume for Vper_1 improved the fit
- Effect of Dose on bioavailability and saturable CL (OFV ↓ 330.467)

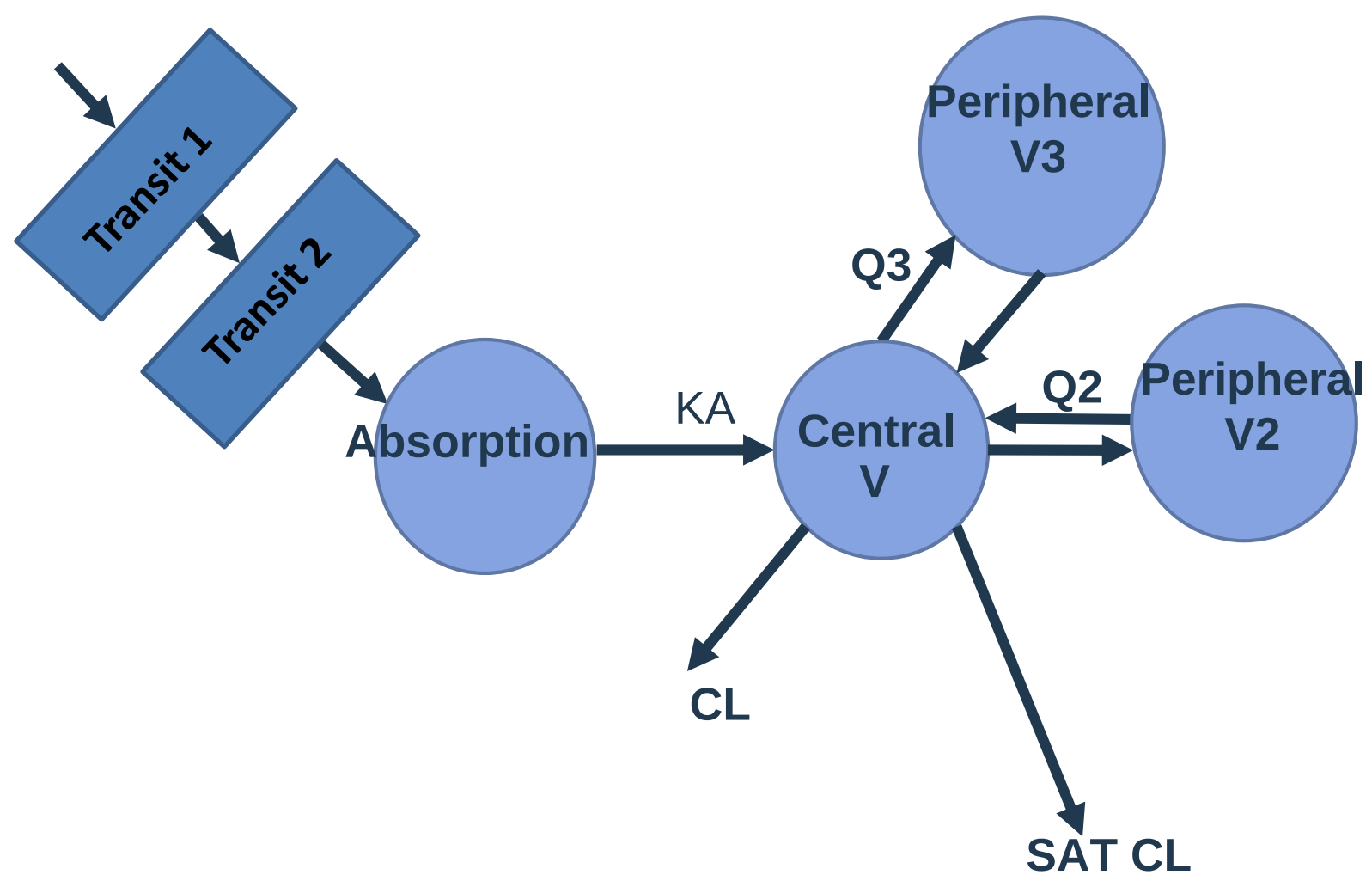


Figure 1 Structural model

Table 3 Final parameter estimates

Parameter	Typical value	BSV (%)	or	*BOV (%)
CL non saturable (L/h)	56.7			1.2
V _{CENTRAL} (L)	468			2.3
KA (1/h)	1.77			
MTT (h)	0.829	26.1		32.2*
NN	0.569			
F	1 FIXED	20.6		15.6*
Q (L/h)	28.9			38.5
V ₂ (L)	5040			
Q2 (L/h)	22.2			
V ₃ (L)	353			
ADD error (ug/L)	0.116			
PROP error (%)	17			
CL _o saturable (L/h)	141			16.4
km (ug/L)	8.14			
Dose effect on F (%)	+51.8			

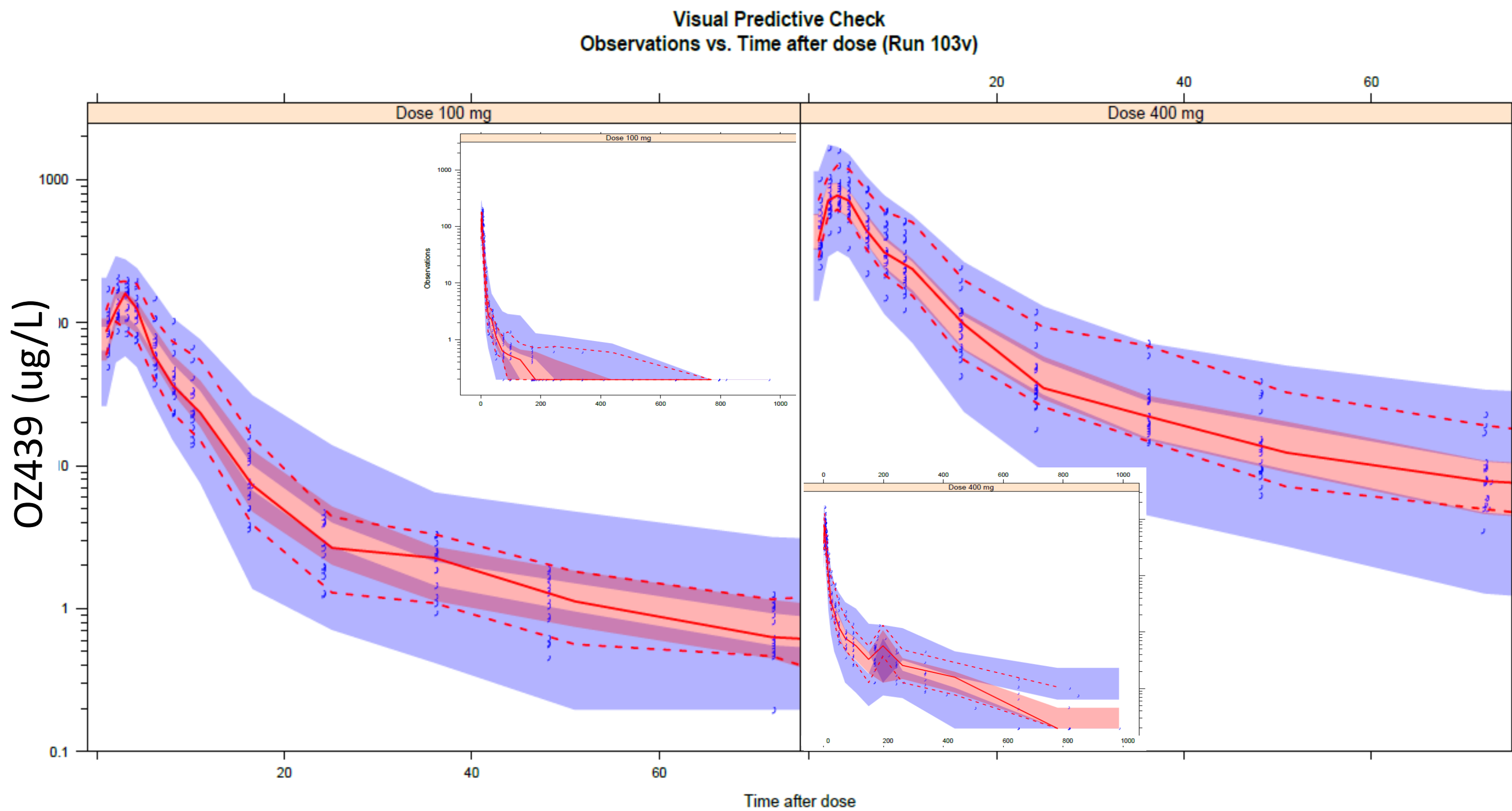
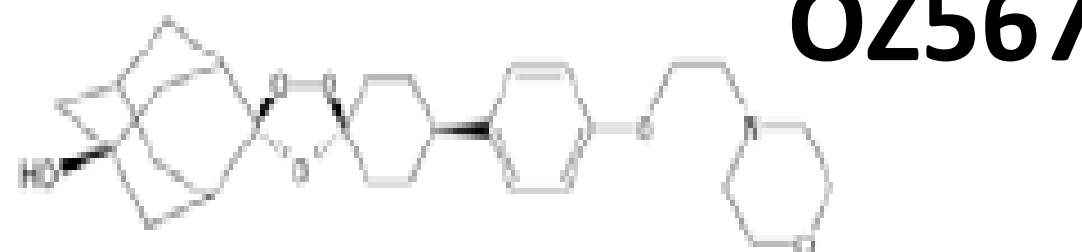


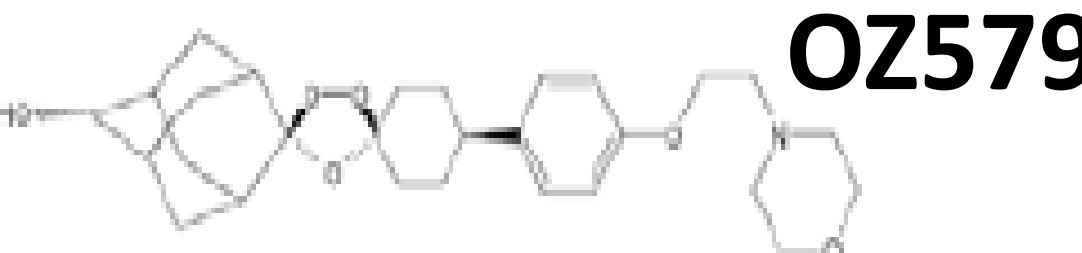
Figure 1. Visual predictive check, stratified by dose. Insert is VPC until last sample

Name	cis-Adamantane-2-spiro-3'-5'-[4'-[2'-(4'-morpholinyl)ethoxy]phenyl]-1'-2'-4'-trioxaspiro[4.5]decane mesylate
Code	OZ439
Drug Class	Anti-malarial
INN	Not applicable
Molecular Formula	C ₂₈ H ₄₀ NO ₅ S
Molecular Weight	565.27 (469.28 as free base)
Structure	

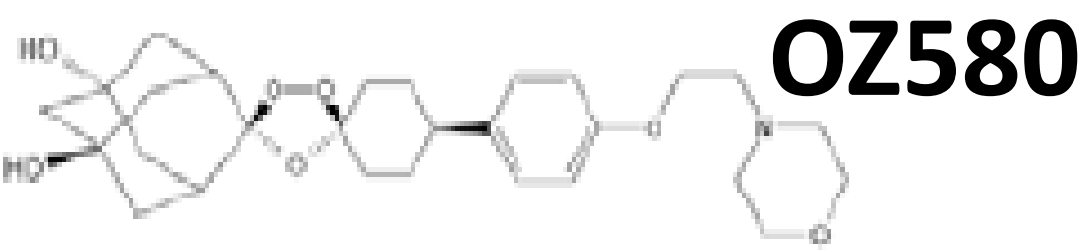
OZ439



OZ567



OZ579



OZ580

Figure 2. OZ439 with its three metabolites; OZ567, OZ579, OZ580

400 mg dose yields ~50% higher bioavailability than 100 mg.

Two clearance processes were identified, one of which saturable already at low concentrations.

No interaction was found with mefloquine on any PK parameter.

From the NCA: Dose exposure relationship for both parent and metabolites were not linear.

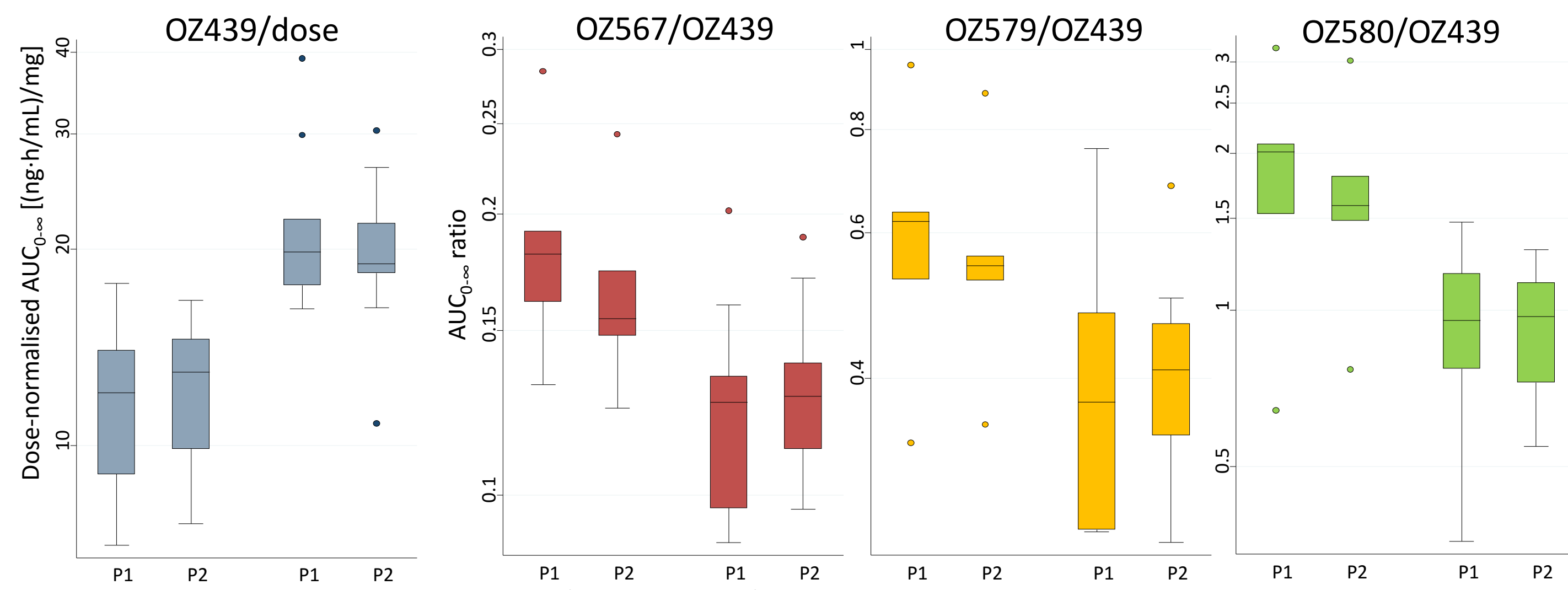


Figure 3. Ratio AUC Metabolites

Table 4 AUC of Parent and Metabolites Per Dose

Compound	AUC (100 mg) h.ug/L	AUC (400 mg) h.ug/L
OZ439	1150	7780
OZ567	189	1000
OZ579	635	3140
OZ580	1900	6940

Conclusions

We described the PK of OZ439

Dose-exposure nonlinearity for parent compound and metabolites:

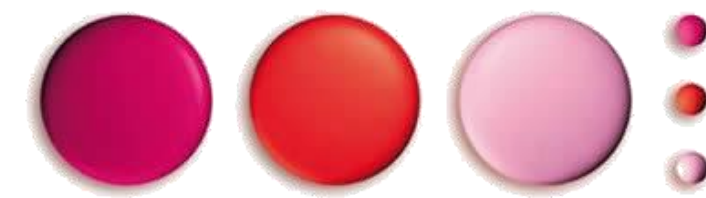
- CL due to several processes, some of which appear saturable.
- Increase in bioavailability with larger doses suggests saturation of intestinal and/or hepatic CYP3A4.
- No significant interaction with mefloquine was found.

Body fat affects distribution.

Integration of metabolite concentrations in the model may help elucidating these findings.

References

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- [2] B. J. Anderson and N. H. G. Holford, "Mechanism-based concepts of size and maturity in pharmacokinetics.," Annu. Rev. Pharmacol. Toxicol., vol. 48, pp. 303–332, 2008.



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