

Semi-mechanistic population pharmacokinetic modeling of the novel antituberculosis drug TBAJ-876 and its metabolite M3 in healthy volunteers

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Background and objectives

Tuberculosis (TB) remains one of the leading causes of death from infectious diseases.¹

TBAJ-876 is a novel oral anti-tuberculosis compound with favorable safety and efficacy profiles. Both TBAJ-876 and its active metabolite, M3, are CYP3A4 substrates,² making them susceptible to first-pass metabolism and potential drug-drug interactions (DDIs).

Human pharmacokinetic data for TBAJ-876 are limited, and no joint parent-metabolite models have been reported.

We developed a population pharmacokinetic parent-metabolite model using data from healthy volunteers.

Methods

This pharmacokinetic study included data from two clinical trials—Study CL-001, which consisted of three cohorts, and Study CL-002.¹

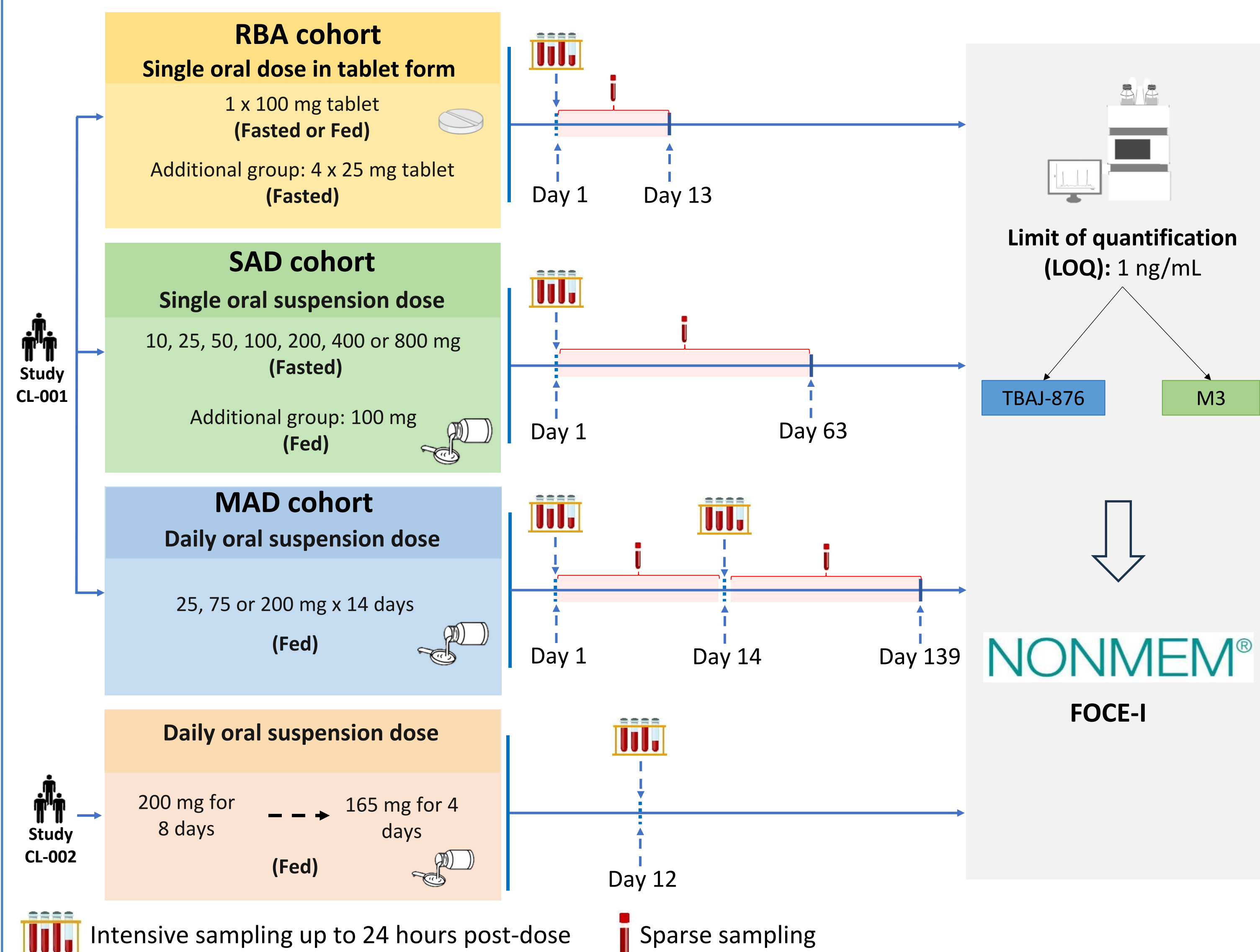


Figure 1. Study protocol.

Analysis started with RBA cohort data, followed by addition of remaining cohorts. A sequential approach was used: parent modeled first, then metabolite, assuming full conversion of TBAJ-876 to M3.

Samples below the LOQ were imputed as zero, with the additive error inflated by 100% of the LOQ, following the M7+ method suggested by Wijk et al.³

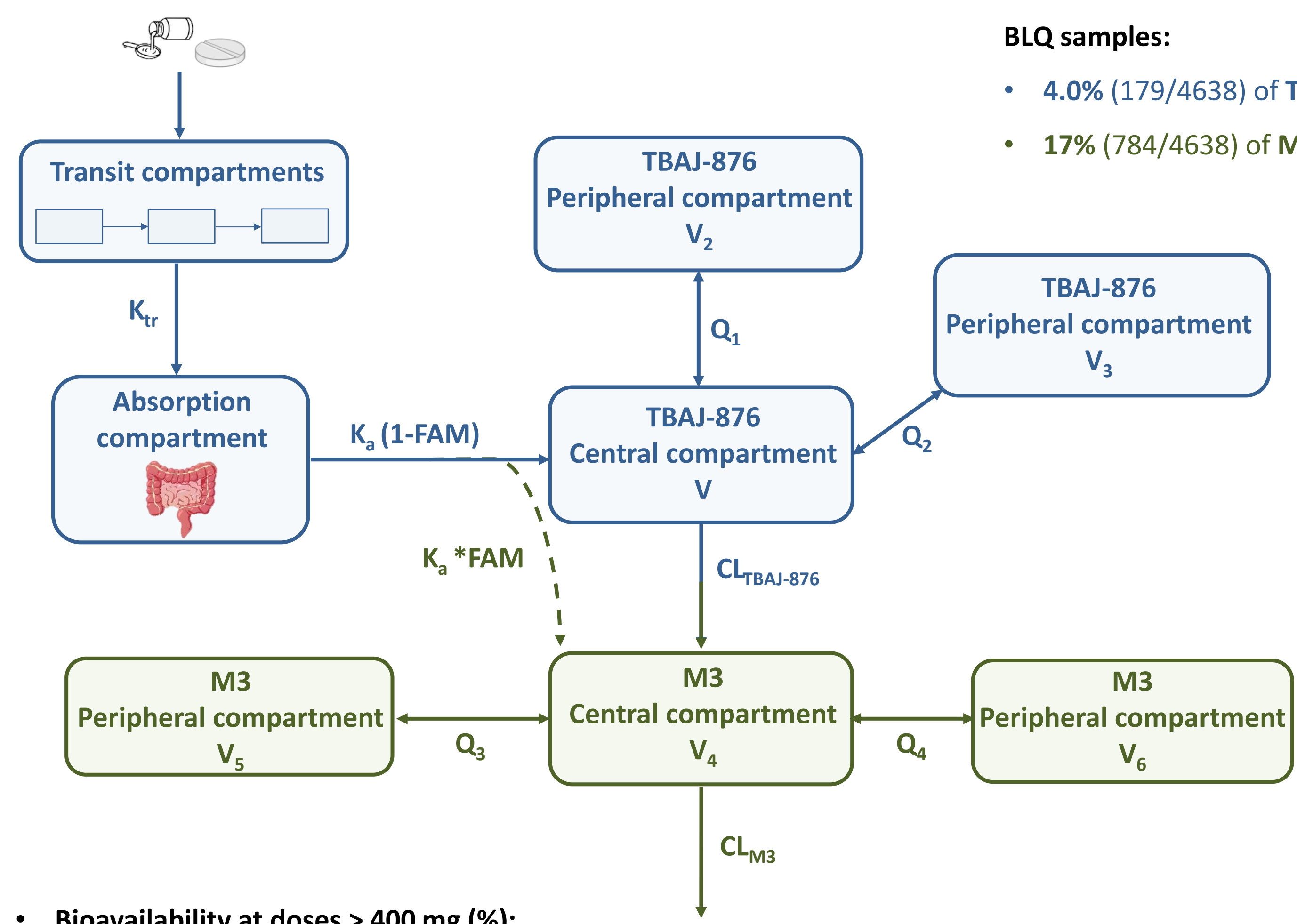
Results

Table 1. Participants characteristics.

	CL-001 study			CL-002 study	Total
	RBA cohort	SAD cohort	MAD cohort		
n	30	55	27	26	138
Female	23 (77)	22 (40)	14 (52)	13 (50)	72 (52)
Age (years)	36 (19–50)	34 (19–50)	35 (19–48)	34 (20–55)	35 (19–55)
Weight (kg)	78 (57–94)	76 (52–100)	77 (56–115)	76 (49–153)	77 (49–153)
Height (cm)	174 (152–192)	166 (148–187)	167 (154–198)	170 (149–185)	169 (148–198)
Fat-free mass (kg) ^a	60 (36–69)	44 (34–72)	49 (37–82)	54 (33–70)	53 (33–82)

Data are presented as median (range: min–max) or n (%).

^a Fat-free mass was calculated by applying the formula from Janmahasatian et al.⁴



• Bioavailability at doses ≥ 400 mg (%):

-46.7 (95%CI: -60.6 - -32.3)

• Bioavailability in Study CL002 (%):

+47.2 (95%CI: +36.2 - +61.2)

Scan for full model parameter estimates



Results - Diagnostic plots

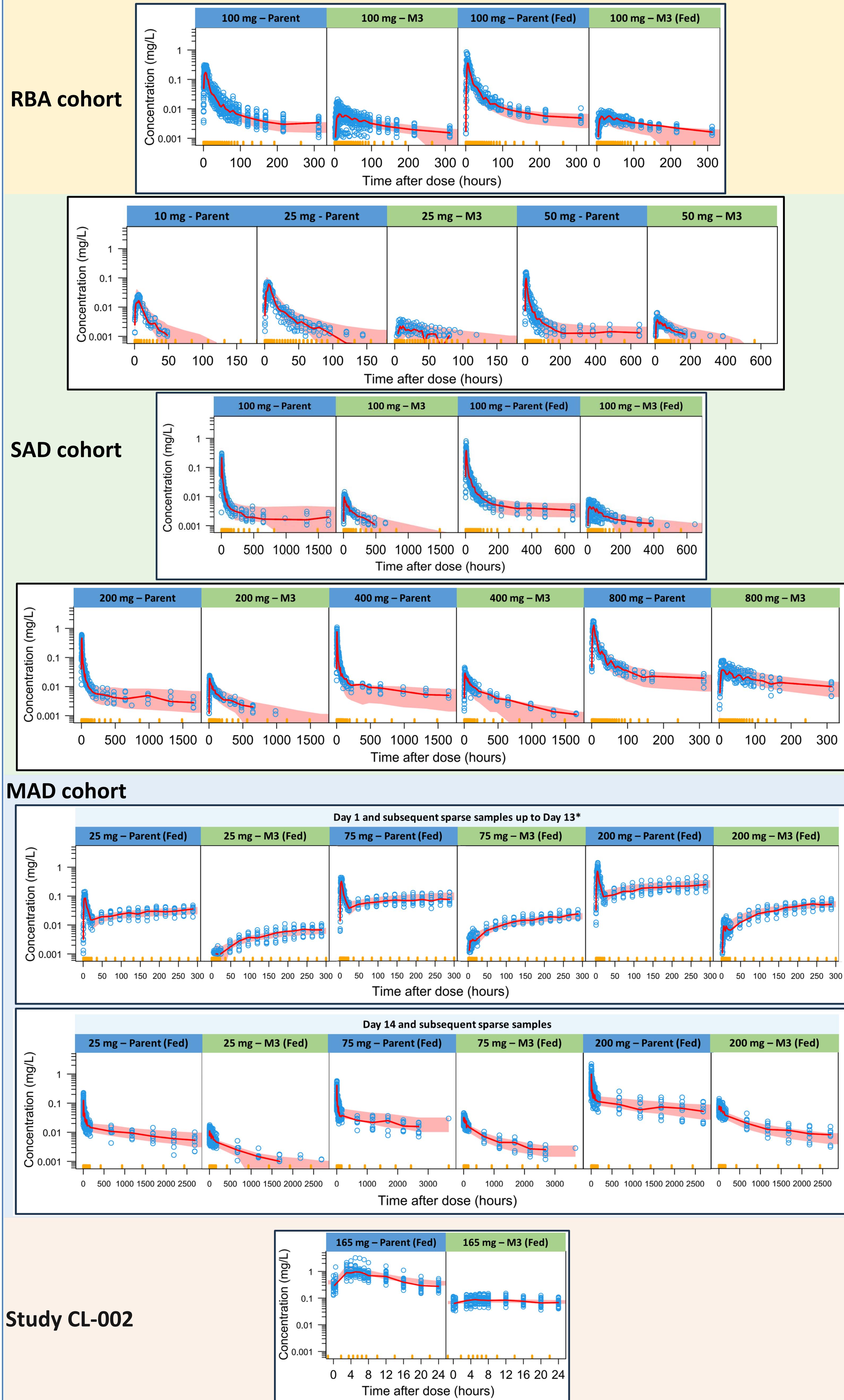


Figure 3. Visual predictive check (VPC) for TBAJ-876 and M3 versus time after dose. Dots represent observed concentrations, the solid red line indicates the median of the observations, and the red shaded area shows the 95% predicted confidence interval. *For MAD cohort data between Day 1 and Day 14, time after dose reflects time since the first dose.

Conclusion

We developed a joint model that semi-mechanistically characterizes the pharmacokinetics of TBAJ-876 and M3.

Our findings suggest that food reduces first-pass metabolism, likely by enhancing drug solubility at the absorption site, which accelerates absorption and limits gut metabolism.

The observed reduction in bioavailability at higher doses may result from saturation of absorption mechanisms.

This model provides a tool for future PK/PD analyses and DDI evaluations.

Acknowledgments

We acknowledge the participants and the whole study team. Computations were performed using facilities provided by the University of Cape Town's ICTS High Performance Computing team: <https://ucthpc.uct.ac.za/>.

References

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- Antonio L, et al. Available from: <https://doi.org/10.1128/aac.00613-24>.
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Figure 2. Schematic representation of the model. MTT: mean transit time; K_{tr}: transit rate constant; K_a: absorption rate constant; FAM: fraction absorbed as metabolite via gut metabolism. Disposition parameters were allometrically scaled to a typical individual with a fat-free mass of 53 kg.