

Early phase 2a dose recommendation for 2nd generation diarylquinoline TBAJ-587

Albin A.M. Leding (1), Paul Bruinenberg (2), Almari Conradie (2), Jerry Nedelman (2), Antonio Lombardi (2), Dean Hickman (2) and Ulrika S.H. Simonsson (1)

(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden
(2) TB Alliance, New York, NY, USA

Introduction

Diarylquinolines (DARQs) have become essential to treatment regimens against *Mycobacterium tuberculosis*. TBAJ-587 is a 2nd generation DARQ that shows promising efficacy and safety in preclinical studies. This work presents the pharmacokinetic data of TBAJ-587 and its metabolites M2 and M3 with a population pharmacokinetic analysis followed by simulations to explore different doses in relation to efficacy and safety targets as well as the impact of loading doses on exposure levels.



More information of TBAJ-587

Methods

Pharmacokinetic data were available in 42 healthy volunteers from a phase 1 trial¹ with six single oral dose cohorts dosed under fasting conditions and one parallel food effect cohort dosed after a high-fat breakfast (Table 1).

The developed population pharmacokinetic model was utilized to explore different regimens in relation to efficacy and safety. The efficacy target was derived with an exposure-matching strategy to the first-in-class DARQ, bedaquiline. Two safety references were the derived, lowest-observed-adverse-effect level and no-observed-adverse-effect level, from a 3-month dog toxicity study.

Table 1: Overview of oral dose in mg and number of patients (n) for each cohort

Cohort	1	2	3	4	5	6	7*
Dose (mg)	25	50	100	200	400	800	200
Patients (n)	6	4	5	8	4	6	9

* Food effect cohort

Results

The final combined population pharmacokinetic model of TBAJ-587, M2 and M3 is shown in Figure 1. Relative bioavailability increased 68.8% with food, while $f_{m,M3}$ decreased by 47.1%. The estimated terminal half-life was 3.5 – 9 months across dose groups. Some parameters depended on the dose. Prediction-corrected visual predictive check is shown in Figure 2.

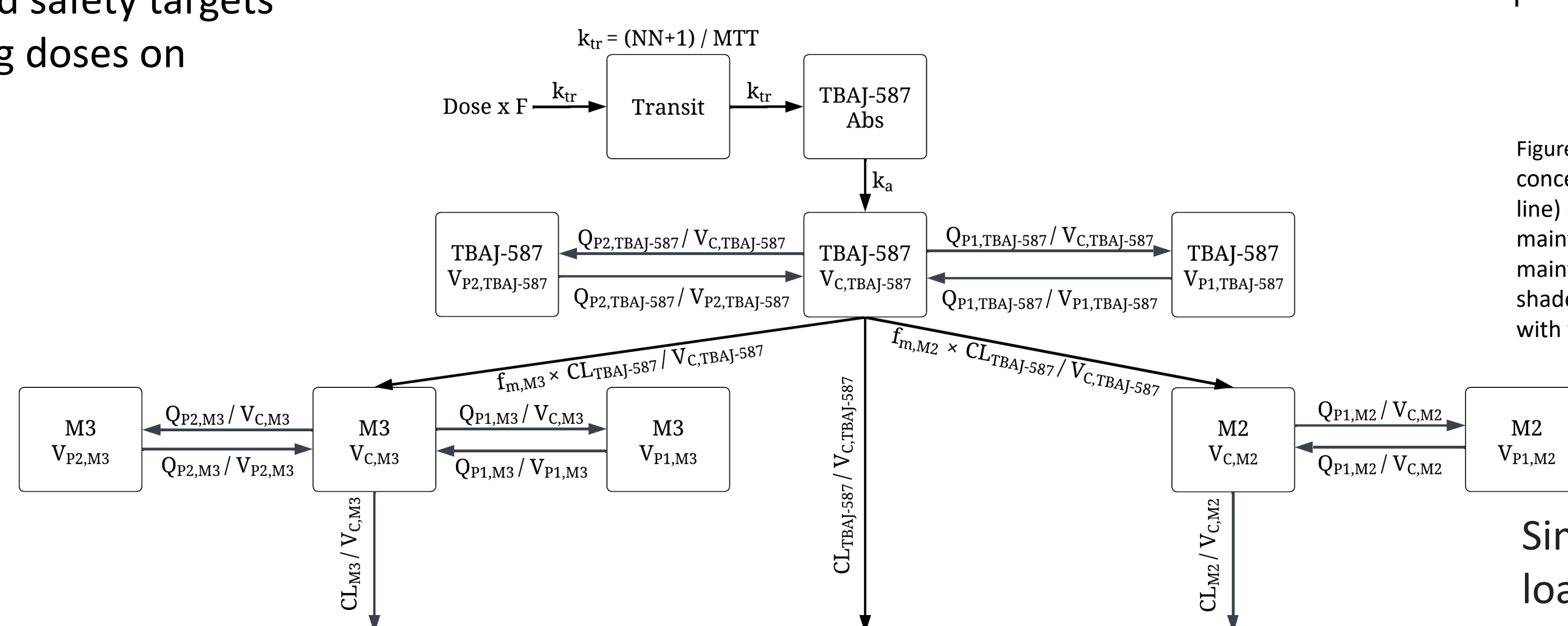


Figure 1: Structural overview of the final population pharmacokinetic model describing TBAJ-587, M2 and M3.

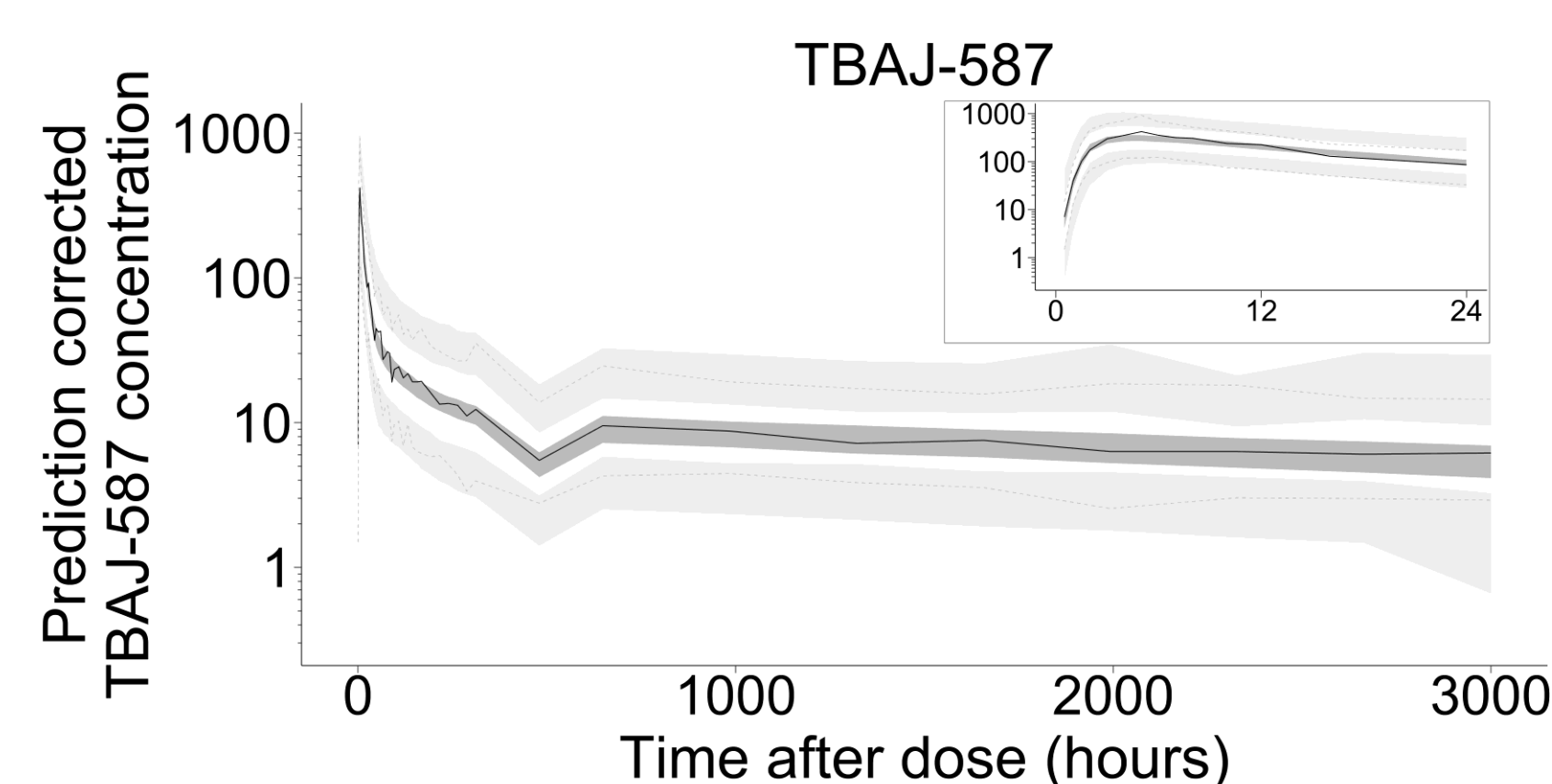


Figure 2: Prediction-corrected visual predictive check (n=1000) of the final TBAJ-587 pharmacokinetic sub-model. The dark grey shaded areas are the 95% confidence interval of the 50th percentiles of the simulated data. The light grey shaded areas are the 95% confidence interval of the 97.5th and 2.5th percentiles of the simulated data. The solid line is the median of the prediction-corrected observations and the upper and lower dashed lines are the 97.5th and 2.5th percentiles of the prediction-corrected observations, respectively.

The predicted daily areas under the curves ($AUC_{0-24 h}$) are shown in Table 2.

Table 2: Predicted area under the concentration versus time curve from 0-24 hours ($AUC_{0-24 h}$) at the end of week 4 for TBAJ-587, M2 and M3 after daily oral dosing in fed condition.

Dose	TBAJ-587 $AUC_{0-24 h}$ ($h \times mg \times L^{-1}$)	M2 $AUC_{0-24 h}$ ($h \times mg \times L^{-1}$)	M3 $AUC_{0-24 h}$ ($h \times mg \times L^{-1}$)
25 mg	2.08	0.139	0.296
50 mg	4.05	0.244	0.532
100 mg	7.83	0.425	0.951
200 mg	15.1	0.734	1.69
400 mg	28.8	1.25	2.98
800 mg	54.4	2.12	5.21

Result cont.

The lowest dosing regimen without a loading dose that exceeded the efficacy target at all times was 100 mg once daily (Figure 3).

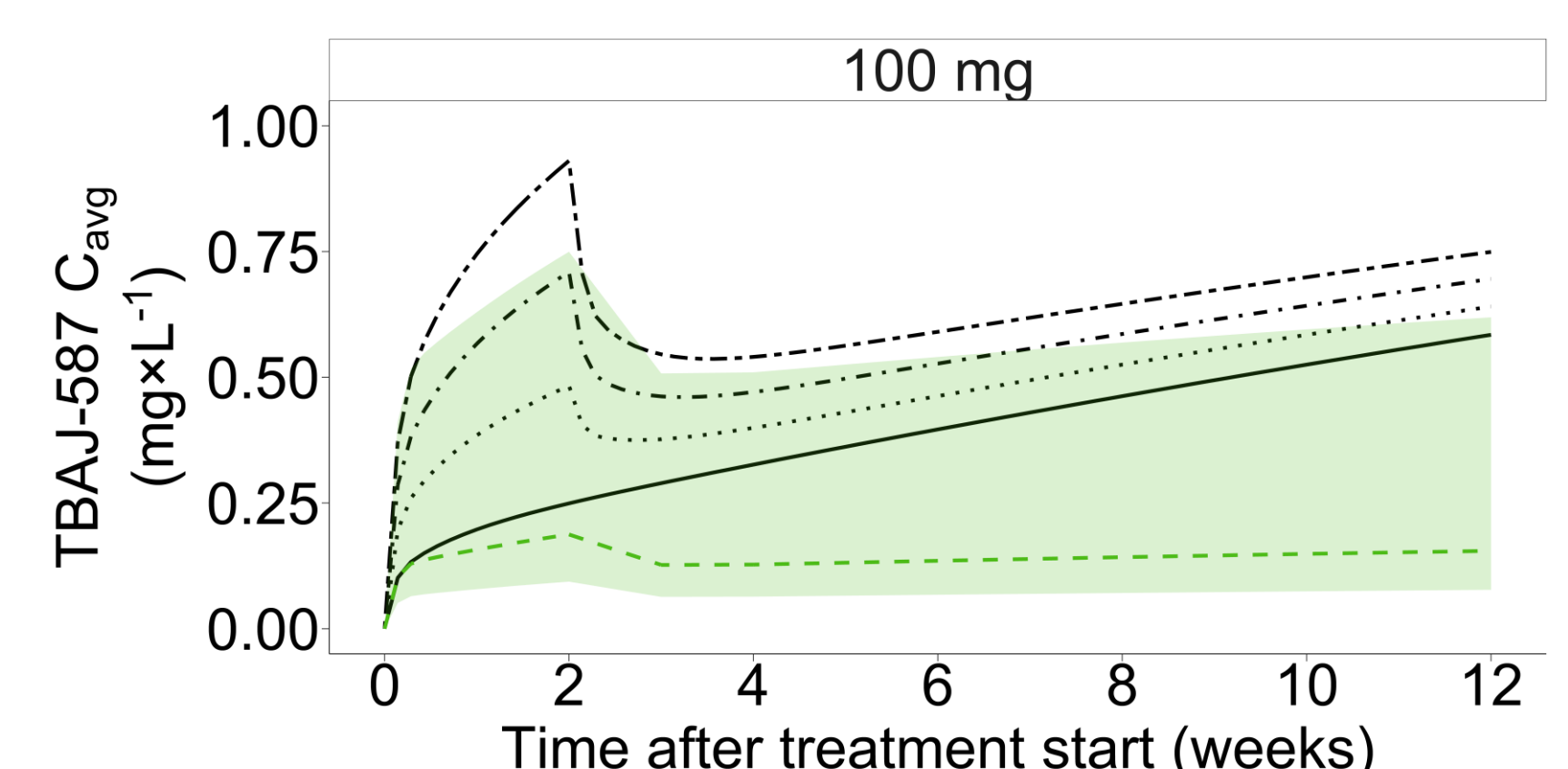


Figure 3: Predicted exposure in relation to efficacy target. Predicted average concentration of TBAJ-587 over time, 100 mg maintenance dose without (solid line) and with different once daily loading doses for two weeks (dotted 2 x maintenance, dot-dashed 3 x maintenance and short-long-dashed lines 4 x maintenance). The dashed green line indicates the efficacy target 1 and the green shaded area represents the 5th and 95th percentile of the efficacy target. Dosing with food was simulated.

Simulations of 200 mg, with and without loading doses, were below both safety references (Figure 4).

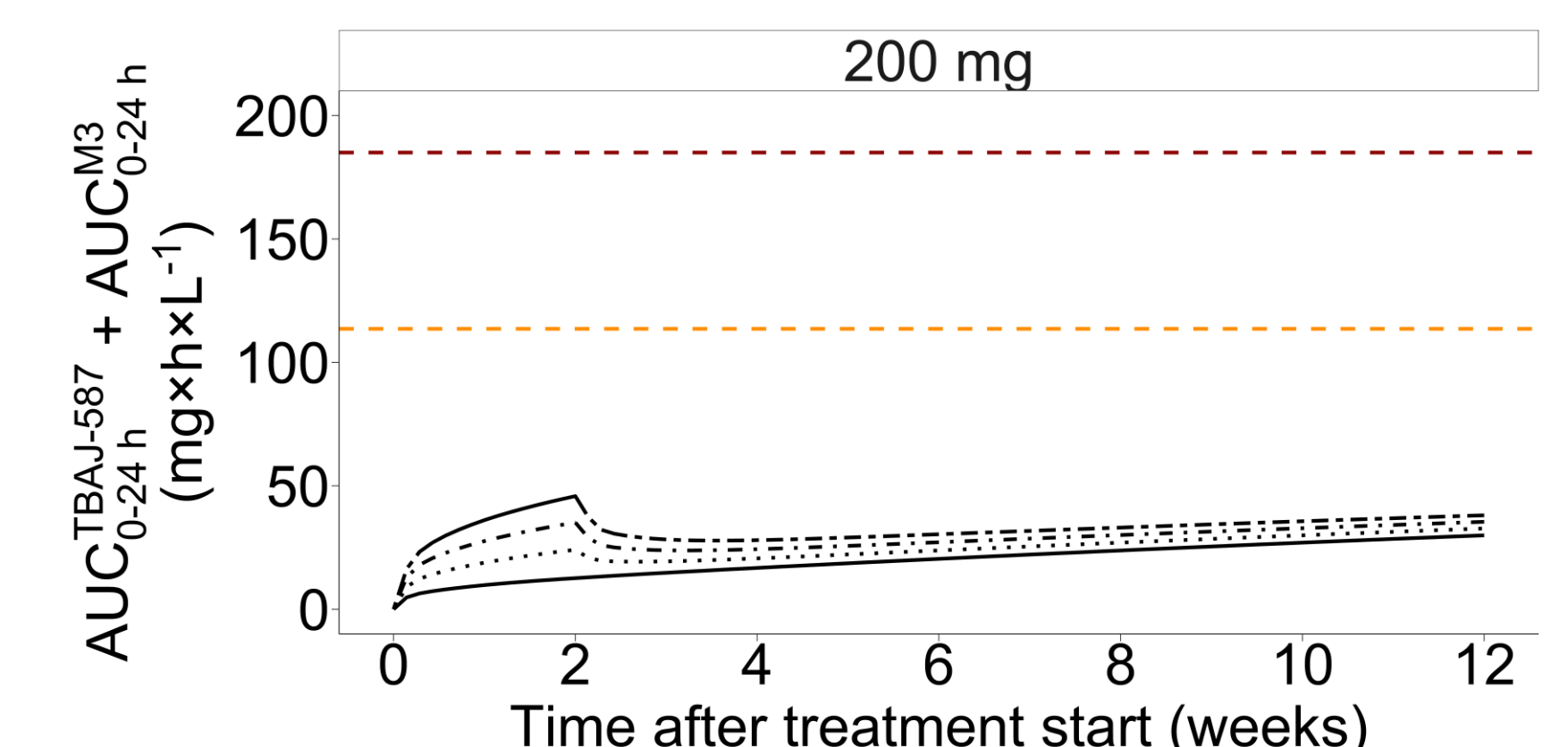


Figure 4: Predicted exposure in relation to safety references. Predicted daily sum of TBAJ-587's and M3's area under the concentration versus time curves after 200 mg maintenance dose without (solid line) or with different once daily loading doses (dotted 2 x maintenance, dot-dashed 3 x maintenance and short-long-dashed lines 4 x maintenance). The horizontal lines lowest-observed-adverse-effect level (LOAEL) and no-observed-adverse-effect level (NOAEL), from a 3-month dog toxicity study. Dosing with food was simulated.

Conclusions

A population pharmacokinetic exposure matching strategy together with efficacy target and safety references identified that:

- At least 100 mg daily regimen, with or without loading doses, reaches the efficacy target
- Doses in the range 25-200 mg daily remain below safety references.
- 100 mg daily regimen, with or without loading doses, can be studied further in combinations in Phase 2a studies.

In collaboration with



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Reference

¹ Global Alliance for TB Drug Development, Evaluation of the Safety, Tolerability, PK of TBAJ-587 in Healthy Adults, clinicaltrials.gov, NIH; 2021, [accessed Jan 27, 2025]. Available from: <https://clinicaltrials.gov/study/NC04890535>



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