

Translational tool-based phase 2 clinical outcome predictions of the novel diarylquinoline TBAJ-587 for the treatment of tuberculosis, compared to bedaquiline and TBAJ-876

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BACKGROUND

Bedaquiline (BDQ, first-in-class diarylquinoline), has shortened treatment duration with pretomanid and linezolid (BPaL) in drug-resistant tuberculosis, but is challenged by emerging resistance. TBAJ-587 is a novel diarylquinoline with greater preclinical efficacy than BDQ [1].

Here, we leveraged our preclinical-to-clinical translational platform [2-4] to predict the clinical efficacy of TBAJ-587, both as monotherapy and in a combination regimen with pretomanid and linezolid (TBAJ-587-PaL), compared to BDQ and another novel diarylquinoline in Phase 2, TBAJ-876.

METHODS

- Data:** BALB/c mouse pharmacokinetic (PK) and pharmacodynamic (PD) data for TBAJ-587 monotherapy and TBAJ-587-PaL regimen were integrated (Fig. 1).
- Model Development:** A mouse PK-PD model, incorporating bacterial dynamics, was developed for TBAJ-587 monotherapy and TBAJ-587-PaL regimen, respectively, using NONMEM v.7.5.1 (Figs 2 and 3, Table 1).
- Translational Predictions:** Clinical EBA under TBAJ-587 monotherapy and clinical TTCC under TBAJ-587-PaL regimen were simulated by linking mouse PK-PD model with population PK model [5]. Translational predictions of clinical outcomes of BDQ and TBAJ-876 were also conducted using in-house models [3].

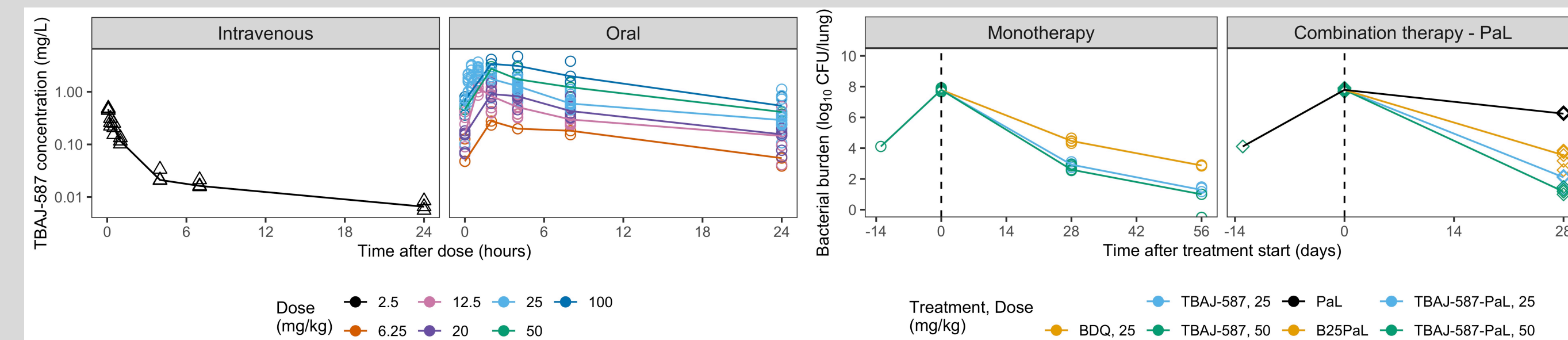


Figure 1. Compilied mouse PK (left) and PD (right) data for TBAJ-587.

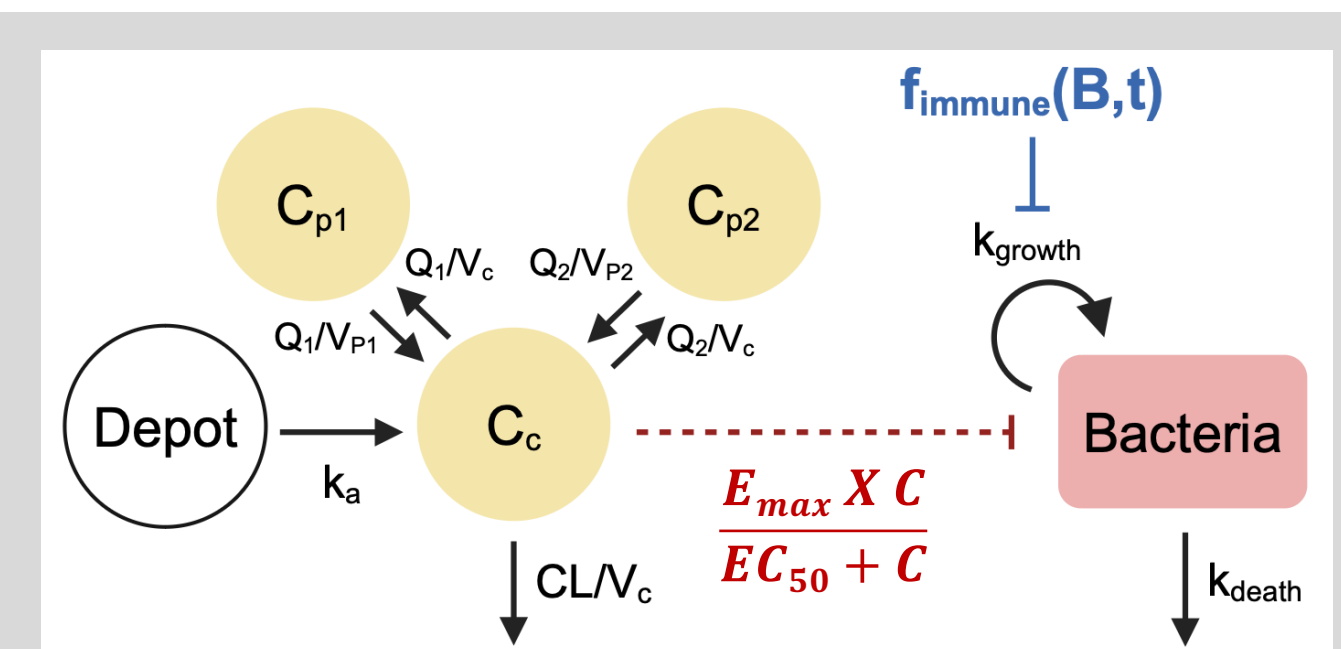


Figure 2. TBAJ-587 PK-PD model structure for clinical translation.

Table 1. TBAJ-587 PK-PD model parameters.

Parameter	Estimate (%RSE)
Monotherapy PK-PD	
EC ₅₀ (mg/L)	0.0264 (0.1)
E _{max} (day ⁻¹)	0.559 (0.05)
Combination Therapy PK-PD	
EC ₅₀ (mg/L)	0.0665 (0.01)
E _{max} (day ⁻¹)	0.736 (0.001)
f _h human/mouse	1

RSE, relative standard error; EC₅₀, half-maximum effective concentration; E_{max}; maximum efficacy; f_h, fraction unbound

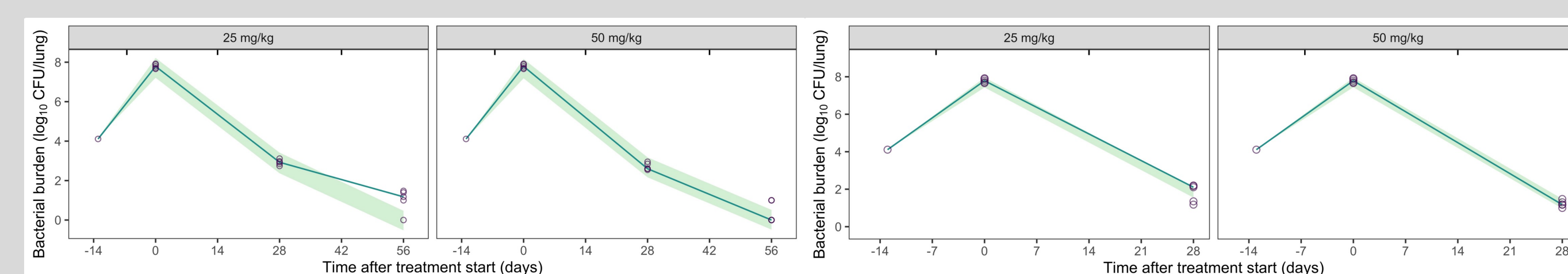


Figure 3. Visual predictive check plots of mouse PK-PD models for TBAJ-587 monotherapy (left) and TBAJ-587-PaL regimen (right).

RESULTS

Monotherapy

TBAJ-587 monotherapy has potency superior to BDQ and comparable to TBAJ-876 (Fig. 4). TBAJ-587 at 50 mg daily would match EBA response for BDQ at the labeled dose or TBAJ-876 at 50 mg daily (Fig. 4).

Combination Therapy

In combination with PaL, TBAJ-587 was predicted to exert TTCC similar to TBAJ-876 but shorter than BDQ, with 95% of converting within 5 weeks, compared to 7 weeks under the approved BPaL regimen (Fig. 5).

Lesion Penetration

In our validated translational site-of-action modeling platform [7], TBAJ-587 and TBAJ-876 reach caseum efficacy targets faster while also being eliminated faster compared to BDQ, reducing the chance of resistance.

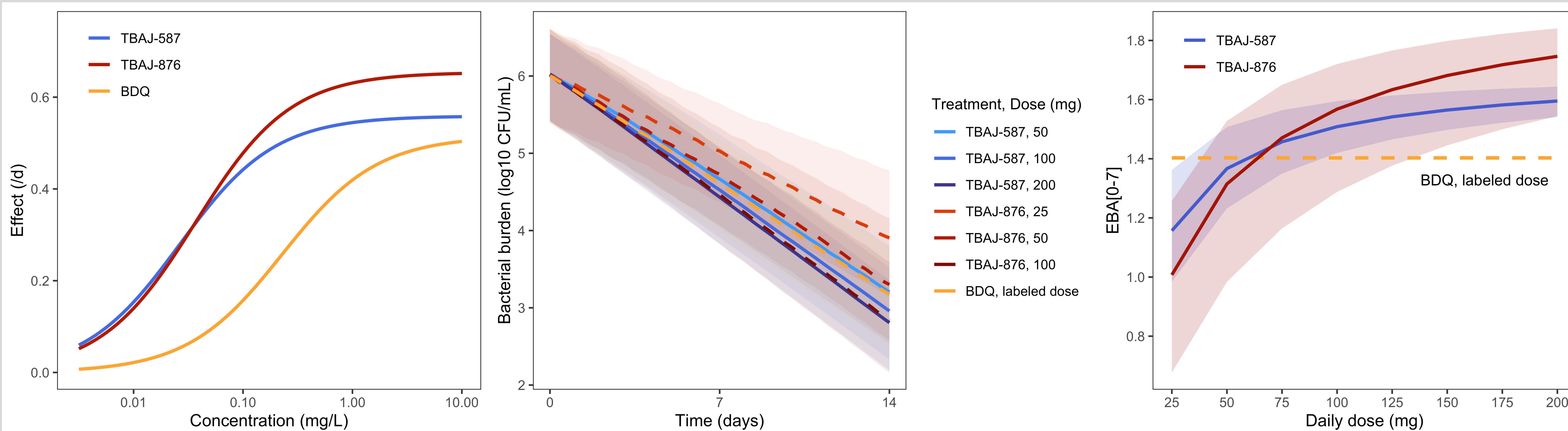


Figure 4. TBAJ-587 monotherapy exposure-response (left), predicted EBA (middle), and dose-response of EBA[0-7] (right), compared to BDQ and TBAJ-876.

EBA was simulated in 500 virtual patients with the distribution of baseline bacterial burden utilized in our translational platform [3].

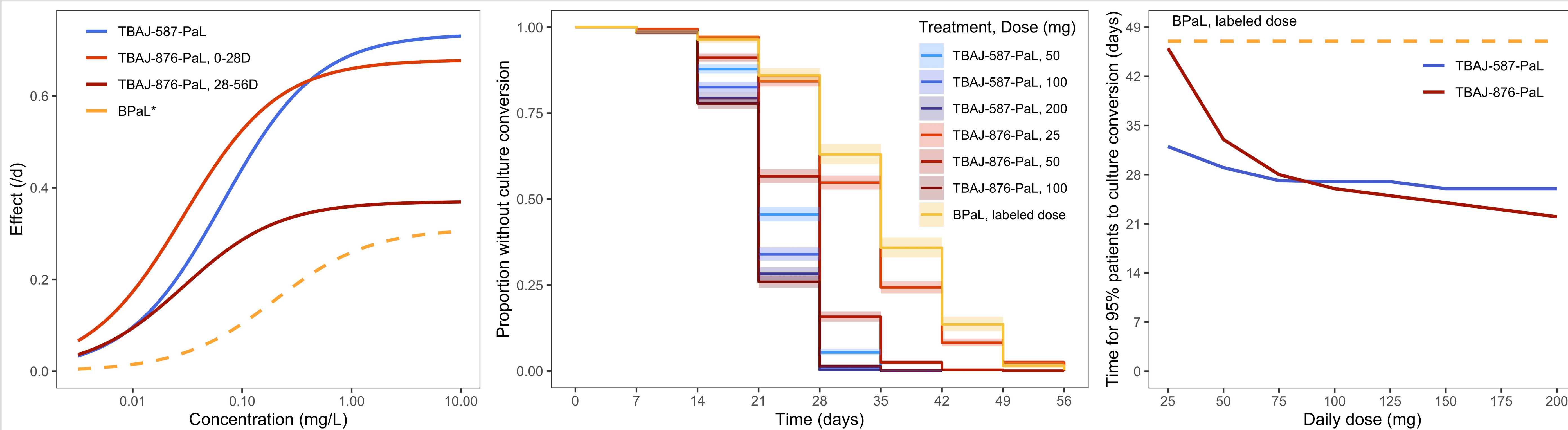


Figure 5. TBAJ-587-PaL regimen exposure-response (left), predicted TTCC (middle), and dose-response of time to 95% patients to culture conversion (right), compared to BPaL and TBAJ-876-PaL regimens.

*BPaL regimen exposure-response was based on linezolid concentrations. TTCC was simulated in 2,278 patients with individual-level baseline bacterial burden obtained from Phase 3 Study 31/A5349 [6].

CONCLUSION

- We predict Phase 2 outcomes of TBAJ-587 monotherapy and in the PaL regimen.
- TBAJ-587, like TBAJ-876, seems more potent with shorter treatment duration and lower risk of resistance development, compared to BDQ.**
- Our integrated translational approach will provide a valuable rationale for dose selection and regimen optimization of TBAJ-587 for future Phase 2/3 clinical trials.

REFERENCES AND ACKNOWLEDGMENTS

[1] Xu, J. et al. AAC. 2021;65(4):e02418-20. [2] Zhang, N. et al. AAC. 2020;64(3):e01727-19.[3] Ernest, J. P. et al. ERJ. 2023;62(2):2300165. [4] PAGE 31 (2023) Abstr 10551. [5] PAGE 31 (2023) Abstr 10347. [6] Dorman, S. E. et al. NEJM. 2021;384(18):1705-1718. [7] PAGE 31 (2023) Abstr 10621