

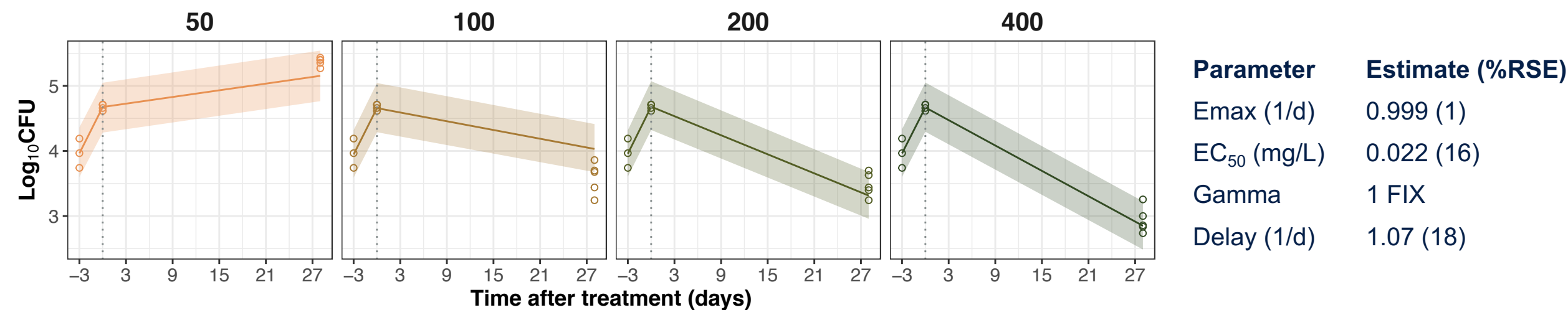
Background

Tuberculosis (TB) is one of the world's deadliest infectious diseases, causing 1.3 million deaths in 2022. Current treatments include a combination of three drugs: bedaquiline (B), pretomanid (Pa), and linezolid (L) in individuals with drug-resistant disease.¹ However, linezolid, a key component of this regimen, has demonstrated toxicities resulting in dose reductions and interruptions.² Given this, there is interest in finding an alternative to linezolid. Sutezolid and TBI-223 are newer oxazolidinones that have shown a better safety profiles while maintaining efficacy in early studies.^{3,4} Here, an integrated translational pharmacokinetic-pharmacodynamic (PK-PD) modeling approach was applied to predict early clinical efficacy and site-of-disease exposures of sutezolid and evaluated against previous results of TBI-223 and linezolid to assess best-in-class.

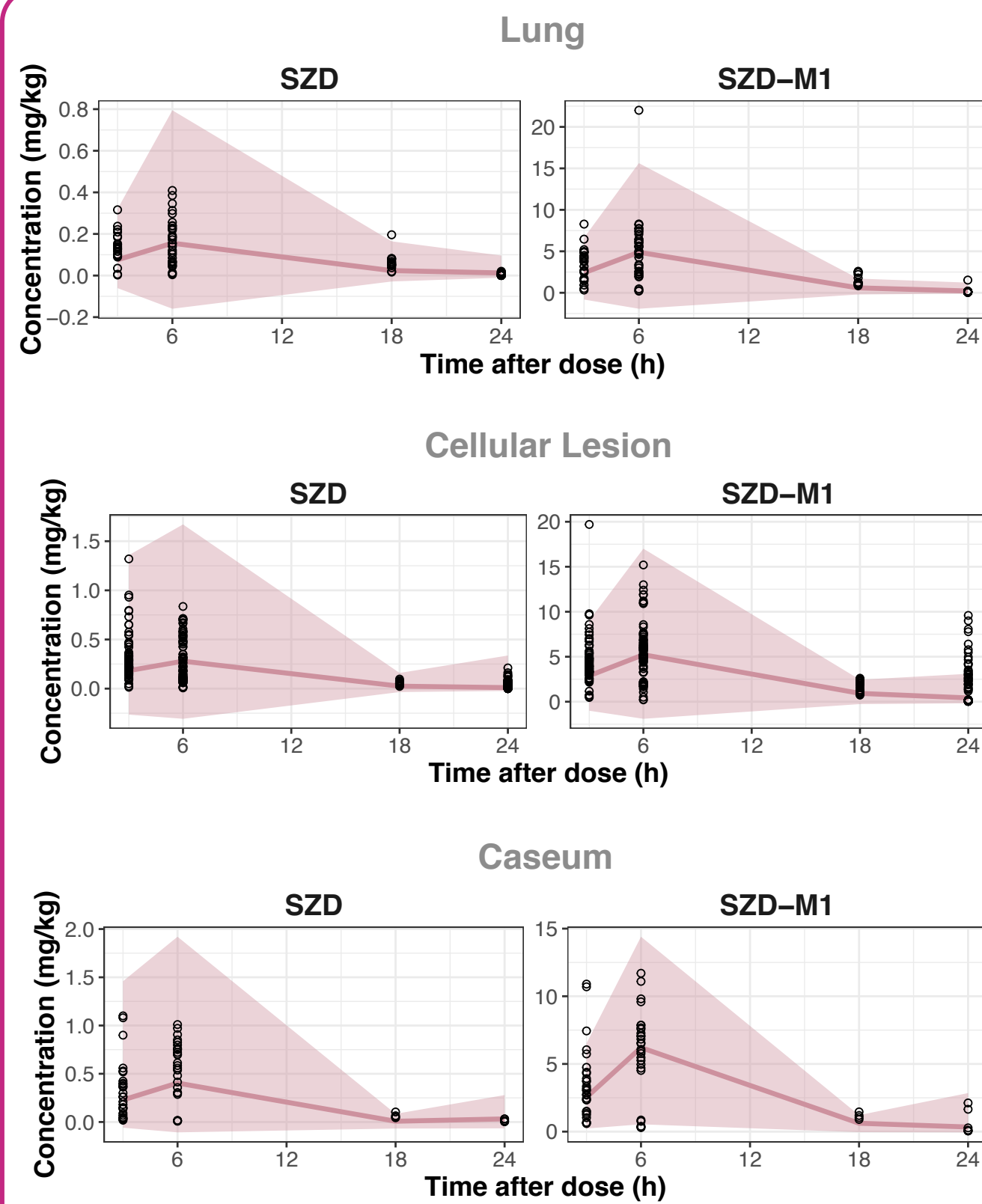
Results

Model parameters and diagnostics

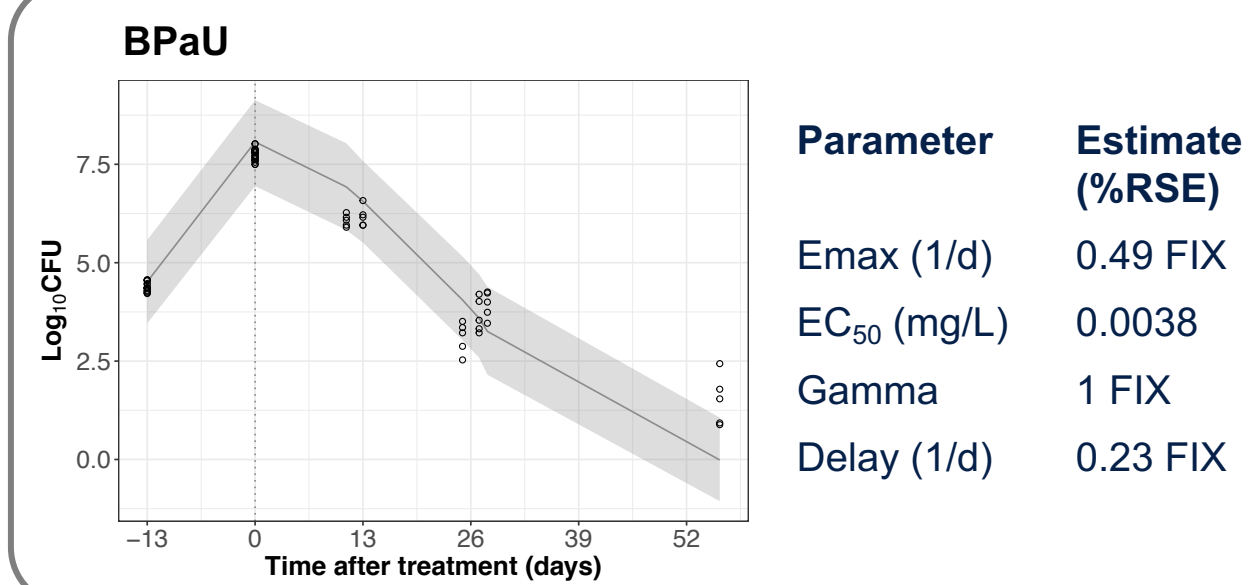
Mouse acute infection monotherapy PK-PD



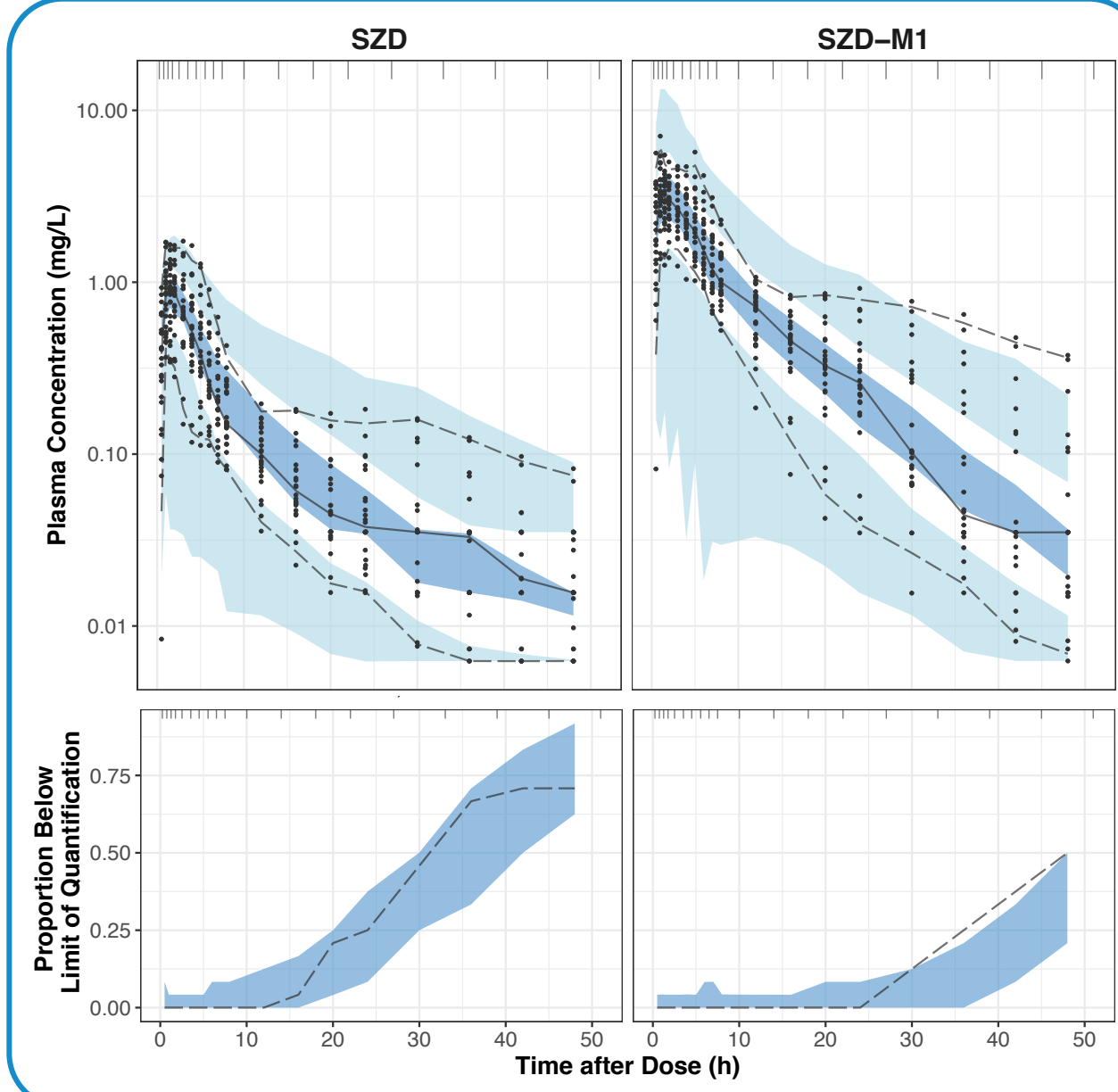
Rabbit site-of-action PK



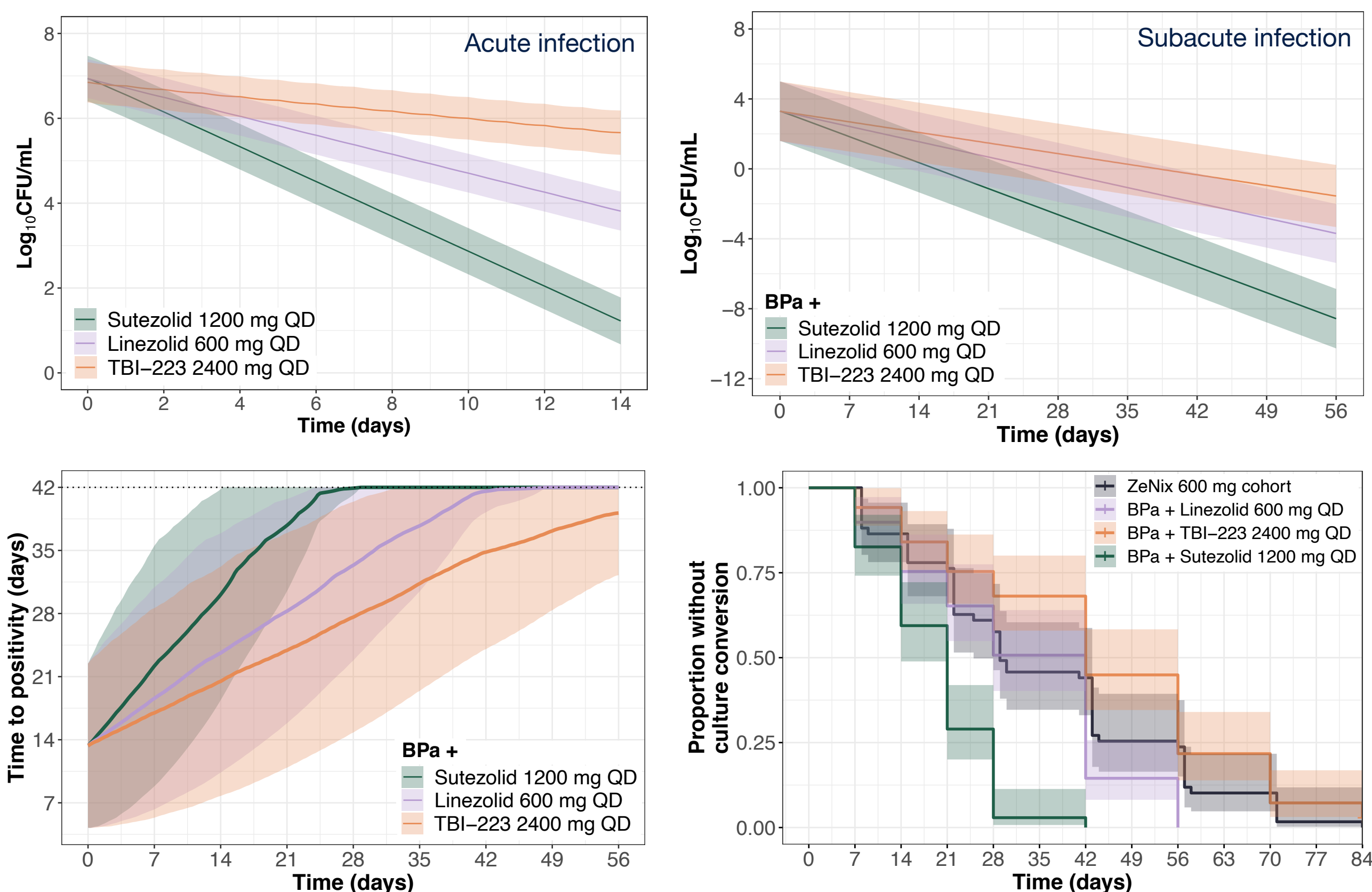
Mouse subacute infection combination PK-PD



Clinical PK



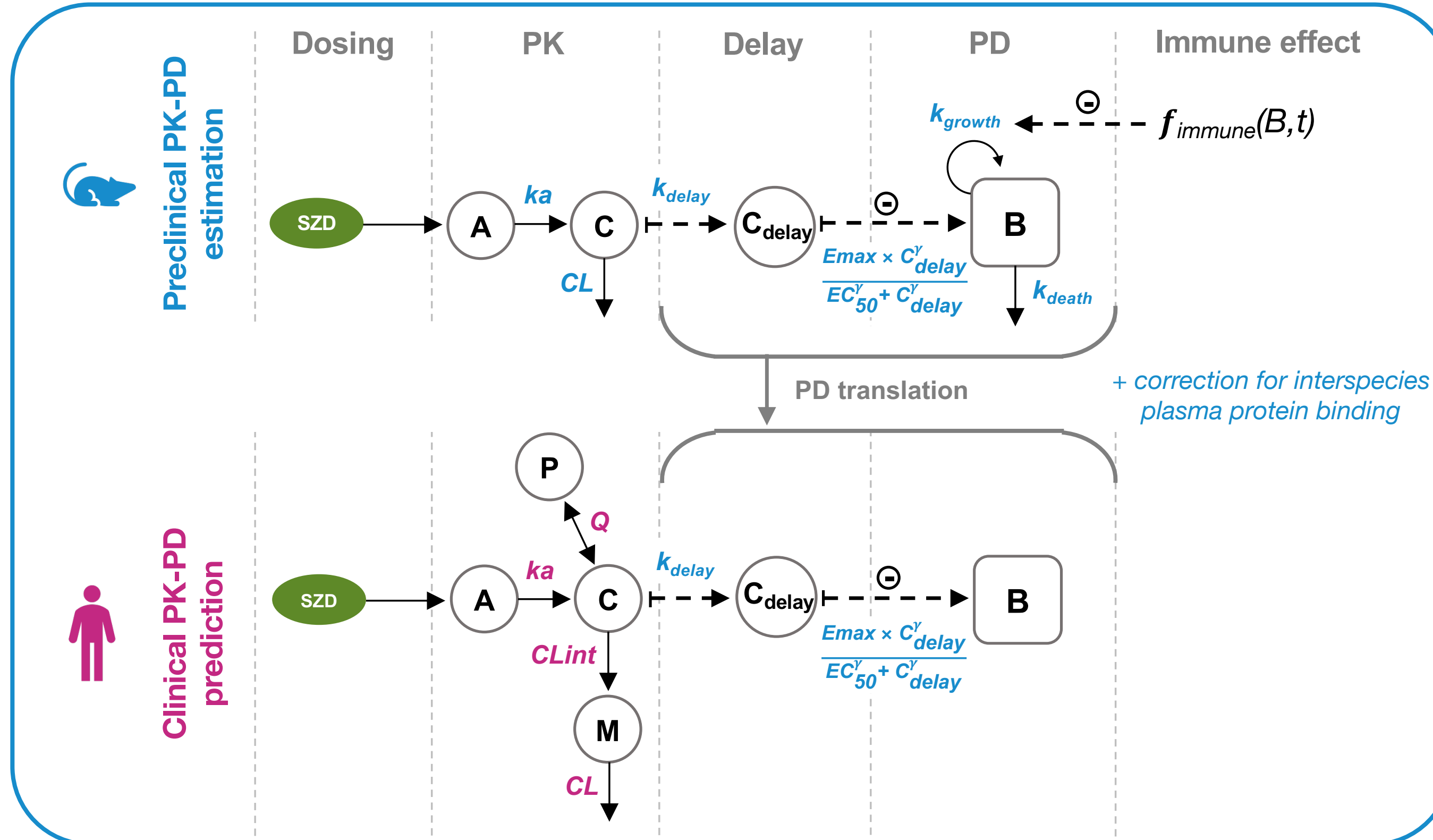
Clinical simulations



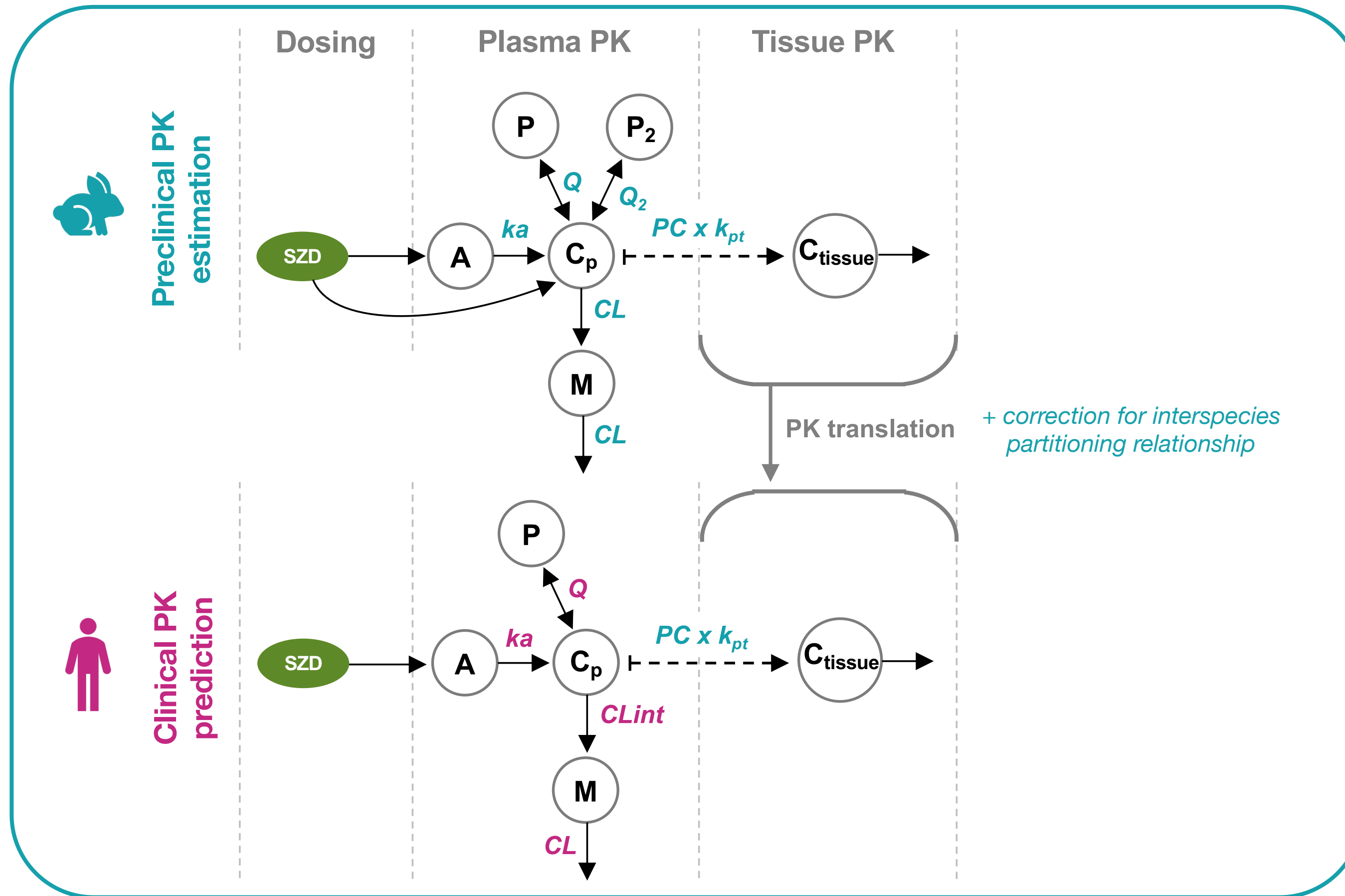
Methods

First, preclinical PK and PD data of sutezolid monotherapy and in combination with BPa were collected from BALB/c mice and New Zealand White rabbits. PD was measured as bacterial colony-forming units (CFU) over time. Clinical PK data was utilized from a Phase 1 single ascending dose trial.⁵ Clinical CFU measurements were taken from a Phase 2a early bactericidal activity trial for comparison to predictions.⁶ Clinical simulations of all oxazolidinones using similar conditions (i.e., baseline bacterial burden distribution, number of virtual subjects) were done for comparison. As PK and PK-PD relationships were assumed to be translatable across species, clinical exposures and outcomes were simulated by fixing parameters derived from the preclinical models and utilizing clinical PK as the driver.

Translational PK-PD model



Translational site-of-disease PK model



Conclusion

Preclinical-to-clinical translation of sutezolid exposure-response validated a previously developed tool⁷ and provided relevant predictions to inform current drug development. Direct comparisons of sutezolid to TBI-223 and linezolid showed superior therapeutic potential of sutezolid in both bactericidal activity and in patients with lung lesions present. These results can later be compared to the observations of the future trials to assess prediction accuracy and potentially provide insight into trial outcomes. Overall, this data-driven modeling approach provides a path for accelerated development of new treatments for TB, with utility in dose selection, rank-ordering of drug candidates, and regimen prioritization.

References

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