

Population pharmacokinetics and exposure-response of BTZ-043 for the treatment of tuberculosis.

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Introduction

- BTZ-043 is a first-in-class benzothiazinone for the treatment of TB with demonstrated early-bactericidal activity.^{1,2}
- BTZ-043 is metabolized into two main metabolites: M1 and M2.
- It is unknown if BTZ-043, M2 or both drives the antimicrobial effect.

Objective: Develop a pharmacokinetic-pharmacodynamic model to characterize the exposure-response relationship for BTZ-043 and its main metabolites in a phase 1b/2a trial.

Methods and results

Pharmacokinetics

- A phase 1b/2a randomized, controlled, clinical trial was performed.¹
- BTZ-043 monotherapy with doses administered ranging from 250mg to 1750mg.
- PK-profiling was done on day
 - 1, 12 and 14 at stage 1.
 - 1 and 14 in stage 2.
- Doses >1250mg decreased the bioavailability by 29% (95% CI: 2.0%- 49%).
- Food effects on the bioavailability (vs. standard food):
 - High-fat food: +41% (95% CI: 5.0%- 78%).
 - No food: - 54% (95% CI: 43%- 65%).
 - Late food: -27% (95% CI: 12%- 42%).
- M2 clearance decreased over time on treatment by 27% (95% CI: 24%- 29%).

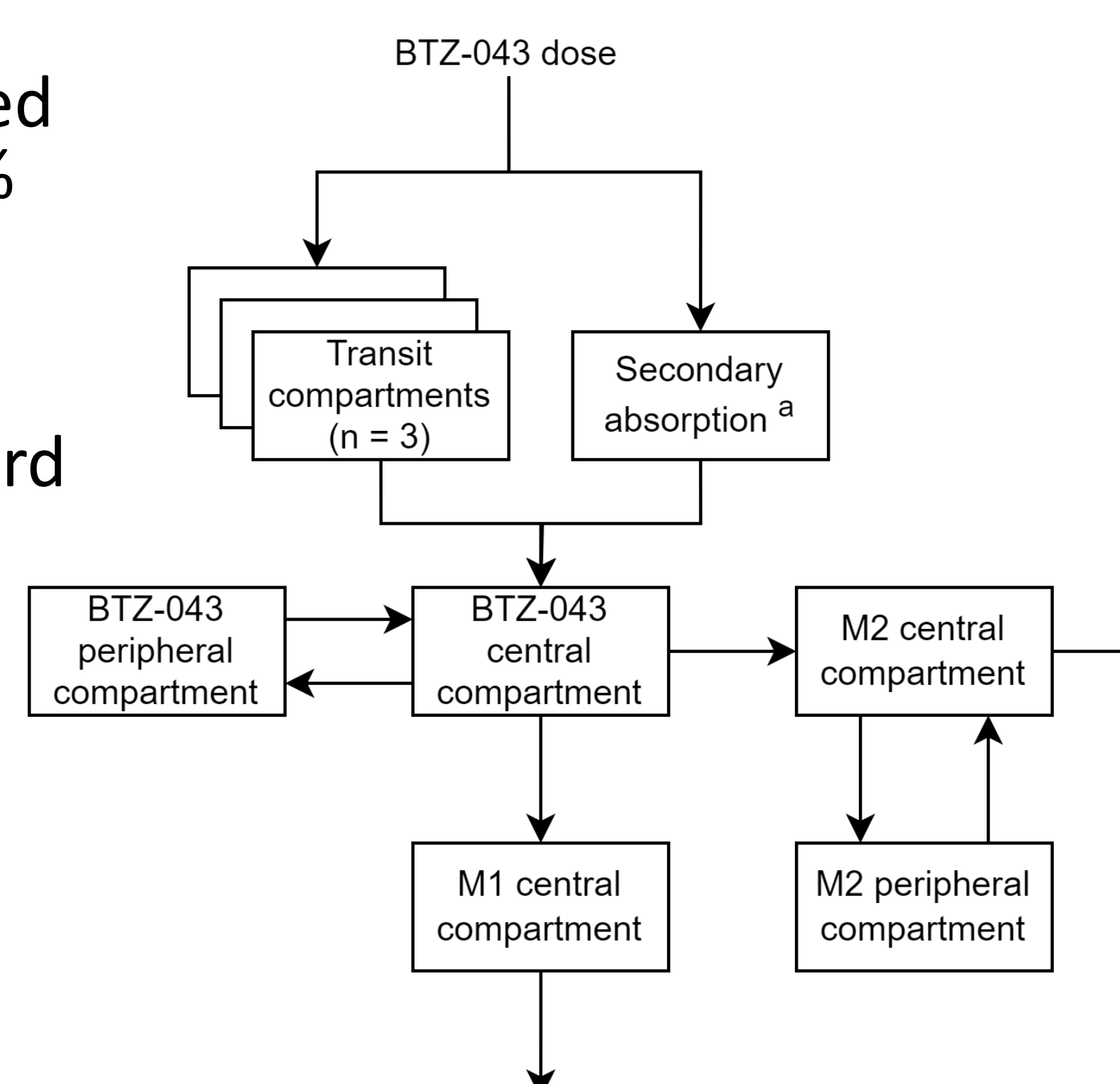


Figure 1: Schematic representation of the PK model. a: Parallel absorption only when administered together with food.

Pharmacodynamics

- Day 0-14 overnight sputum samples cultured using
 - Colony-forming units (CFU).
 - Time-to-positivity (TTP).³
- Bi-linear model with estimated node parameter was selected as structural model.⁴
 - Node estimated at 48 hours.
- M3 method for censored observations.⁵
 - Included baseline negative culture chance.

Exposure-response

- Evaluated based on individual PK-model-derived exposure metrics at steady-state.
- Exposure-response
 - Emax relationship driven by BTZ-043 + M2 AUC₀₋₂₄ (dOFV=-12.1).
 - Only identified between day 0-2.
 - EC₅₀: 19600 (mg/L*h) (95% CI: 5930- 49100).
 - Similar to exposure following 500mg QD together with a standard breakfast.

- Model parameter estimates and PK VPCs stratified on food-type are available here:

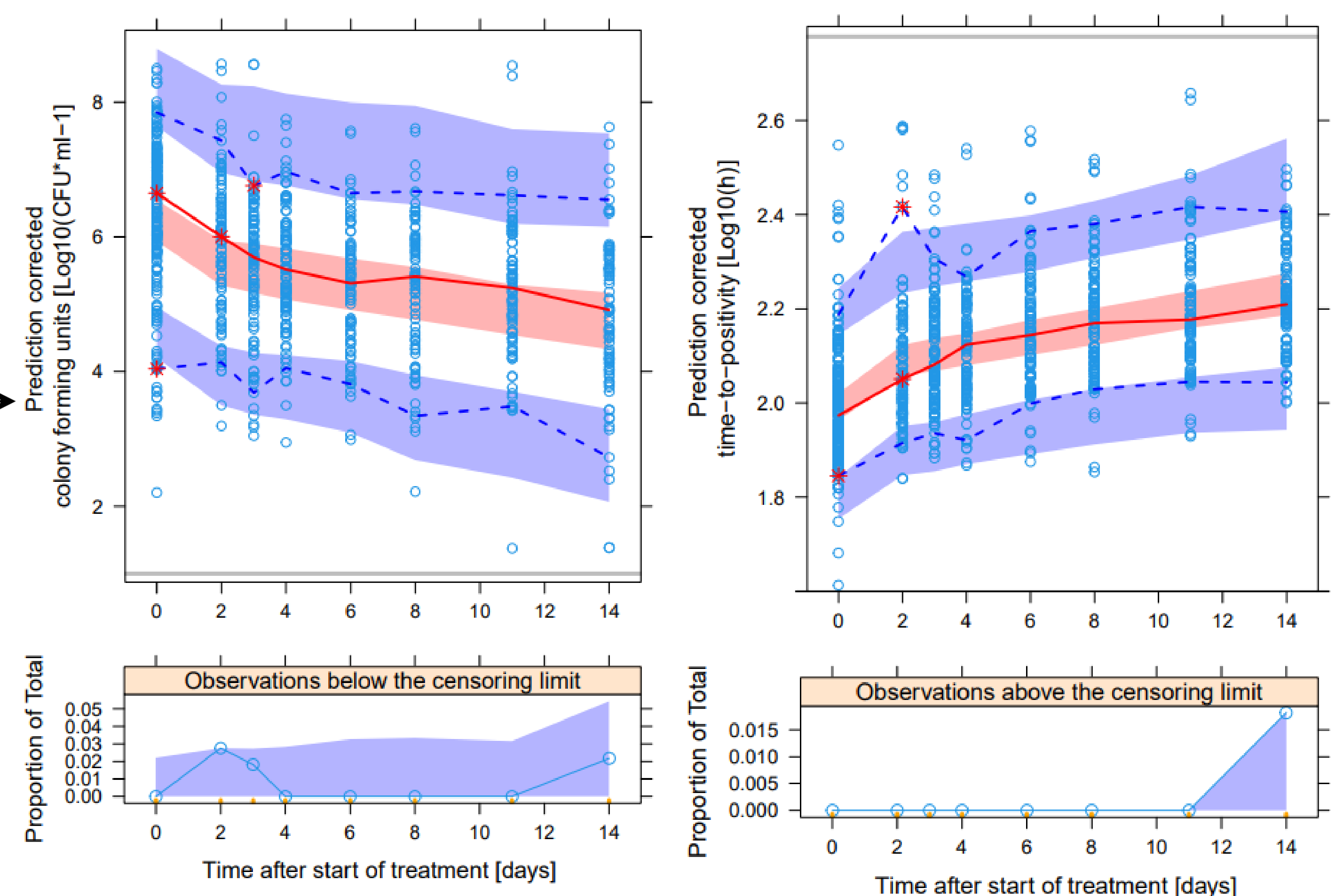


Figure 3 Left: Prediction corrected VPC for CFU. Right: Prediction corrected VPC for TTP. The lines and shaded areas represent the 2.5th, 50th, and 97.5th percentiles.

Conclusion and discussion

- An Emax relationship driven by BTZ-043 + M2 AUC₀₋₂₄ was identified for the first two days after the start of treatment, but not thereafter.
- The EC₅₀ was comparable to the exposure achieved after a 500mg dose following a standard breakfast.
- This supports the 500 – 1500 mg QD doses selected in follow-up trial DECISION (NCT05926466).

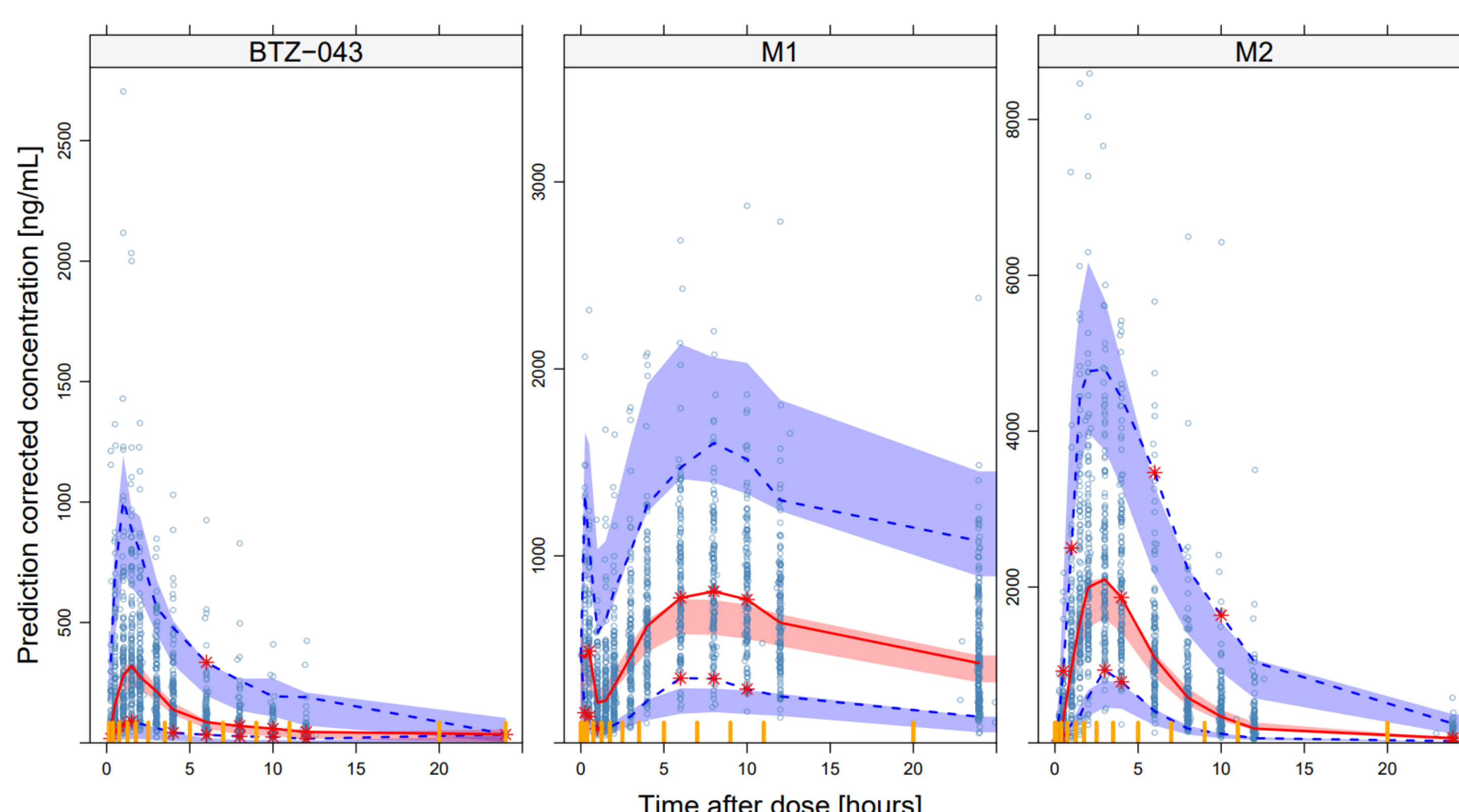


Figure 2: Prediction corrected visual predictive check (VPC) for BTZ-043 (left), M1 (middle), and M2 (right). The lines and shaded areas represent the 2.5th, 50th, and 97.5th percentiles.

1. Hoelscher *et al.* Union conference Paris, 2023.
2. Kloss *et al.* Angewandte Chemie International Edition, 2017.
3. Diacon *et al.* Clin Microbiol Infect, 2012
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5. Beal. Pharmacokinetic Pharmacodyn, 2001.

