Standards for model-based early bactericidal activity analysis and sample size determination in tuberculosis drug development

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Introduction

A critical step in tuberculosis (TB) drug development is the Phase 2a early bactericidal activity (EBA) study which informs if a new drug or treatment has short-term activity in humans. Despite EBA trials being conducted for many years, the amount of information about the best practices for EBA trial conduct and analysis is limited, including model-based sample size estimation and analysis.

The aim of this work was to present a standardized pharmacometric model-based EBA analysis workflow and determine sample sizes needed to detect EBA or a difference between treatment arms.

Methods

A mono-exponential time-to-positivity (TTP) simulation model with parameter estimates for two meropenem-containing treatments [1, 2] was used to generate data (Fig 2 and 3). Two replicates per time point per participant were simulated. TTP observations were simulated for days 0, 1, 2, 3, 4, 5, 8, 10, 12 and 14. Sample size determinations were performed using the Monte-Carlo Mapped Power method to detect EBA and to detect a difference between two arms.

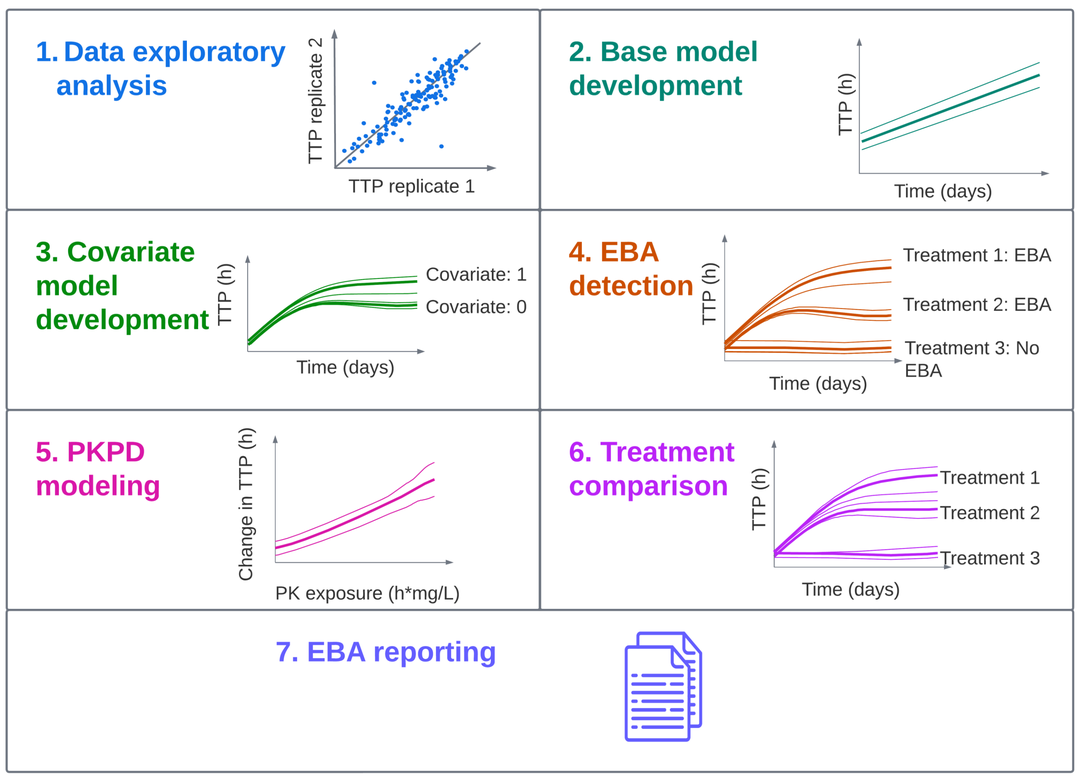

Fig 1. Standardized pharmacometric model-based EBA analysis approach

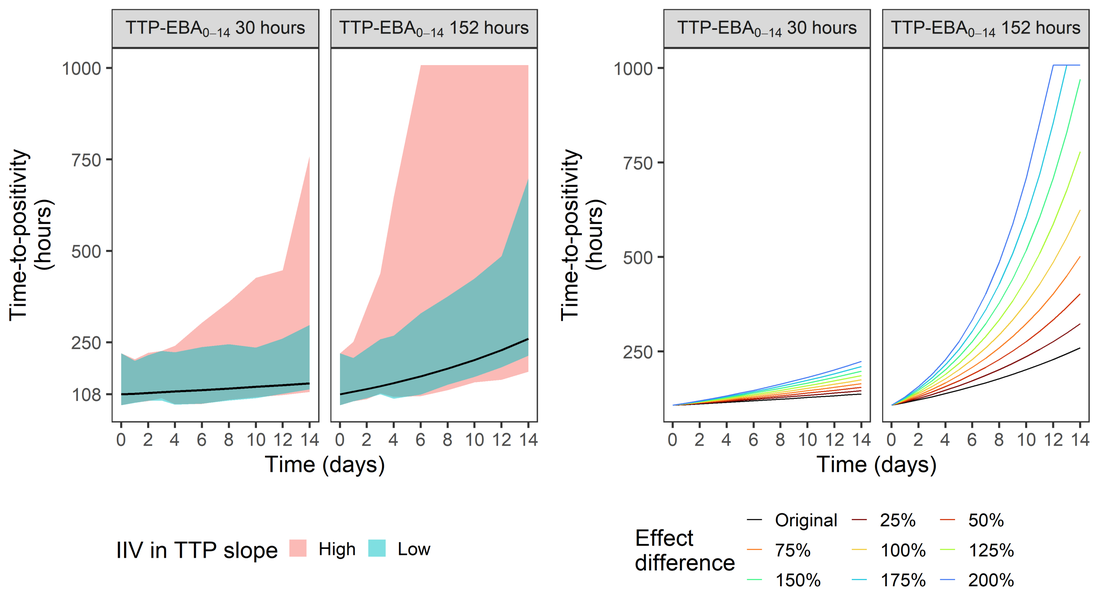

Fig 2. Typical profiles and variability in TTP over time for high (104% CV) and low (22% CV) IIV in EBA

Fig 3. Typical profiles of TTP over time for different effect difference values

Results

To detect EBA with 80% power and at a 5% significance level, 13 and 8 participants per arm were required for a treatment with a change in TTP between day 0 and day 14 (TTP-$EBA_{0\text{-}14}$) as low as 11 hours when accounting for variability in pharmacokinetics and when inter-individual variability (IIV) in TTP slope was 104% (coefficient of variation [CV]) and 22%, respectively (Figure 4). Higher sample sizes were required for smaller EBA and when pharmacokinetics were not accounted for.

To detect a difference between two treatment arms, a decrease in IIV in TTP slope was required to decrease the sample size needed (Figure 5). TTP-$EBA_{0\text{-}14}$ of 152 hours and low IIV in the TTP slope required the lowest sample size of all assessed combinations, followed by TTP-$EBA_{0\text{-}14}$ of 30 hours and low IIV, then TTP-$EBA_{0\text{-}14}$ of 30 hours and high IIV. The highest sample sizes were required for TTP-$EBA_{0\text{-}14}$ of 152 hours and high IIV in the TTP scenario (Figure 6).

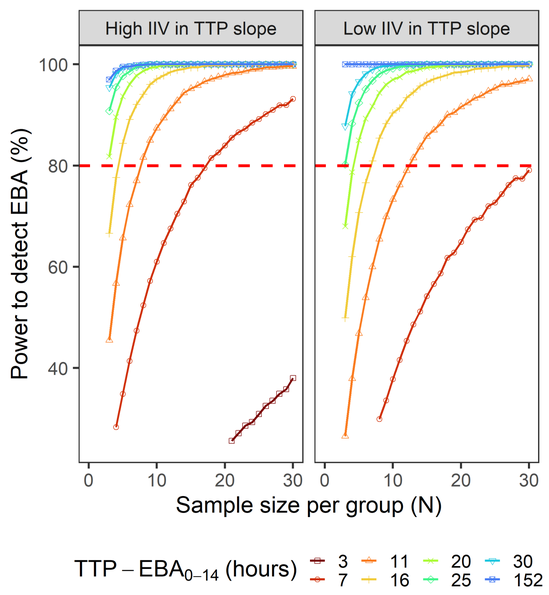

Fig 4. The impact of TTP slope (reported as TTP-$EBA_{0\text{-}14}$) on sample size per arm and power to detect EBA

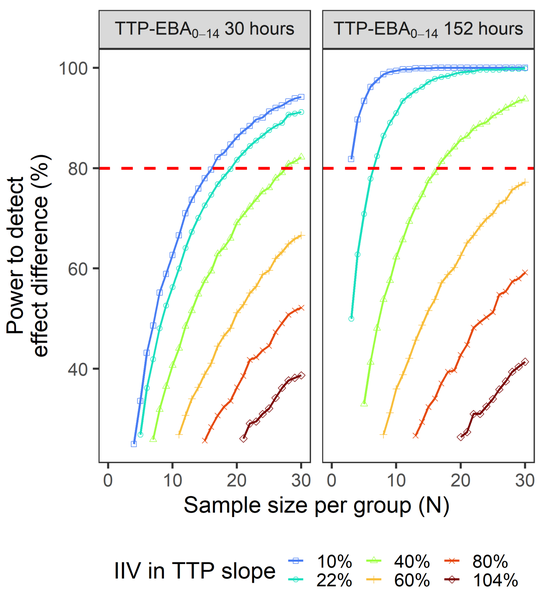

Fig 5. The impact of IIV in TTP slope on sample size per arm and power to detect a difference between two treatment arms

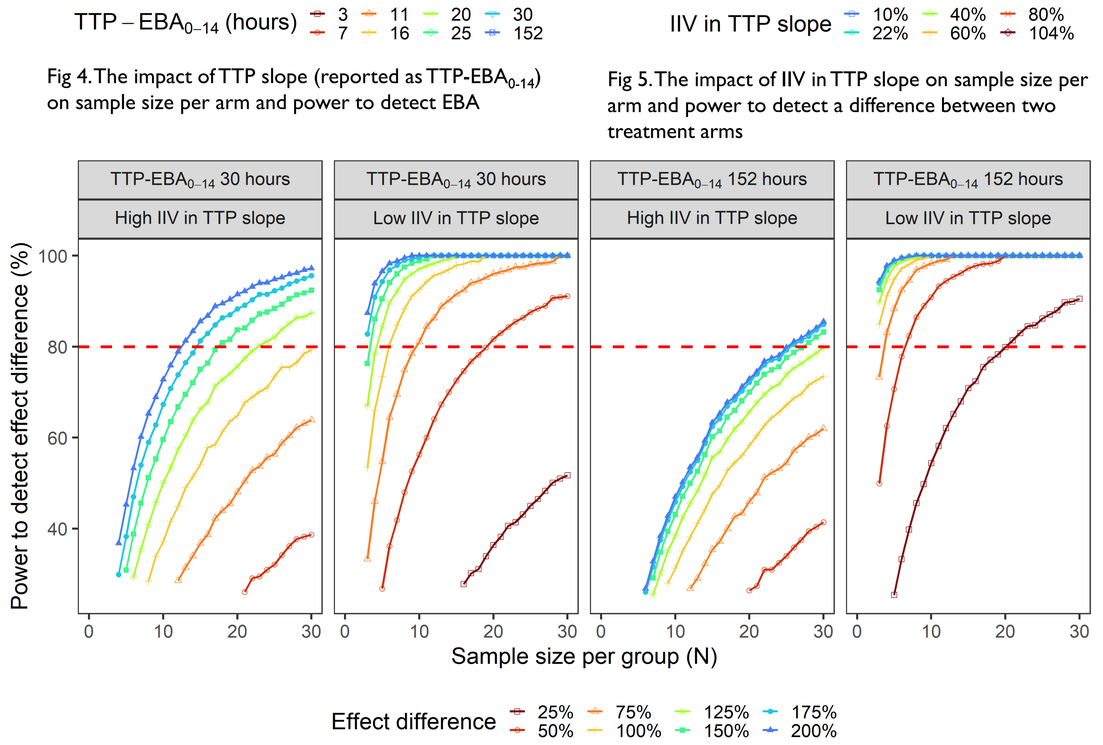

Fig 6. The impact of effect difference on the sample size and power to detect a difference between two treatment groups

Conclusions

The work illustrates the standardized pharmacometric model-based EBA analysis approach and the importance of accounting for covariates and drug exposure in EBA analysis in order to increase the power of detecting EBA as well as differences in EBA between treatments arms.

Acknowledgments

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[2] Unpublished data, ClinicalTrials.gov Identifier: NCT04629378

Publication

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