II-05

Model Based Bioequivalence: A Promising Tool for the Assessment of Complex PK Profiles ?

Is Model-Based Approach Robust Against Sparse Sampling Design and Model Misspecification in Bio-similarity Assessment?

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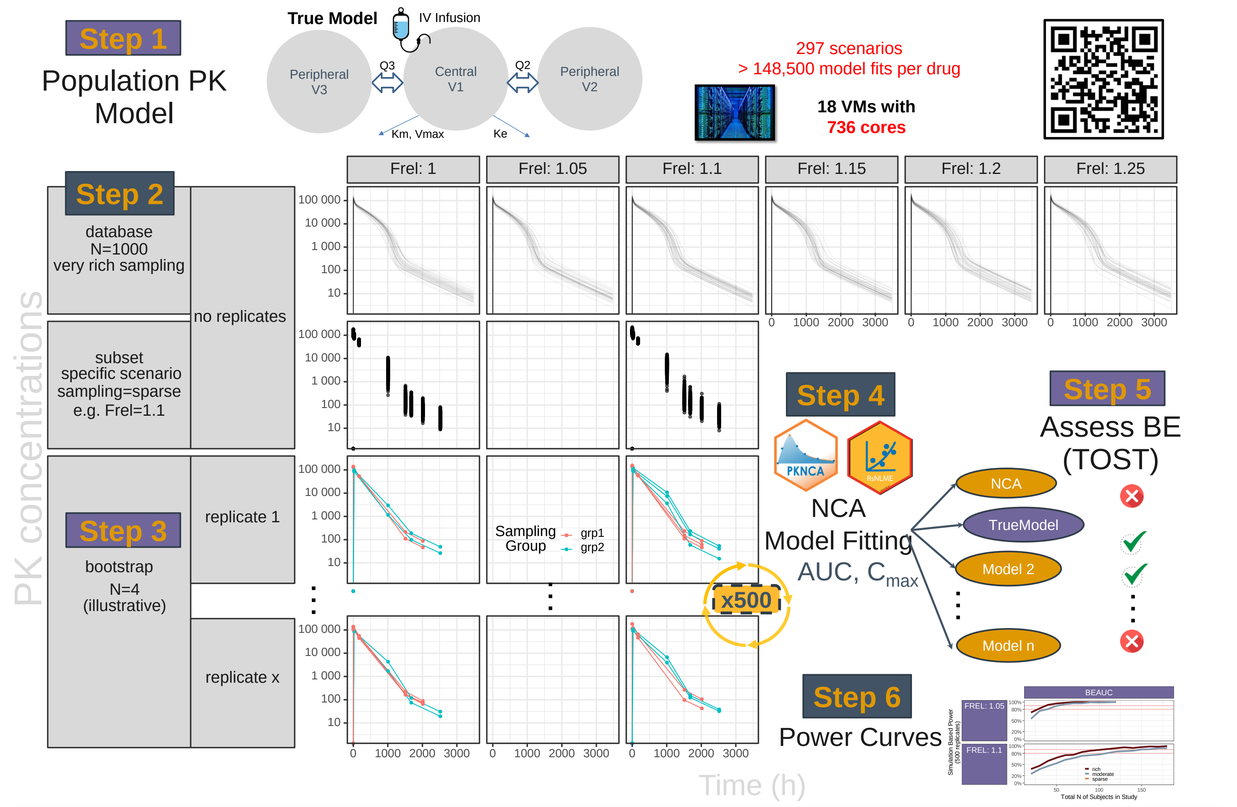
Introduction

Regulatory approval of biosimilars includes comparison of the pharmacokinetic (PK) profiles of the biosimilar and the innovator reference product [1]. The classical non-compartmental analysis (NCA) approach mandates rich sampling which increases the overall costs of biosimilar clinical development, while assessing biosimilarity using sparse sampling designs is known to be difficult and frequently inaccurate [2]. Previous reports indicate that the model-based methods have sufficient power to evaluate bioequivalence [2]. However, it is unclear how robust these approaches are against sparse sampling and model misspecification.This is a simulation-based study to assess the robustness of model-based bioequivalence (MBBE) method against sparse sampling designs and model misspecification using trastuzumab, and clenoliximab as a case studies.

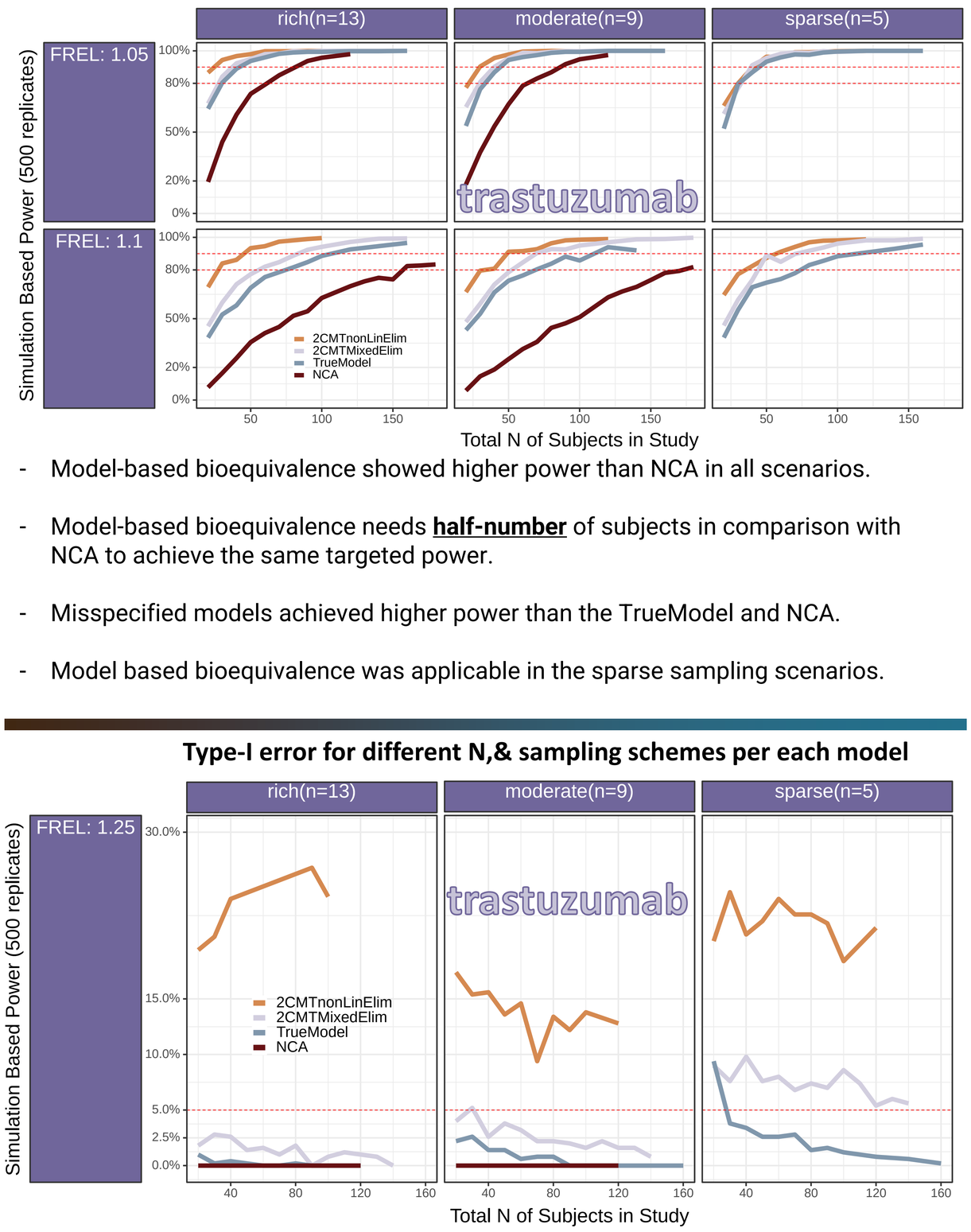
Methodology

Studied scenarios including various combinations of different N-subjects (to reach 90% Power), Frels (1.05, 1.1, & 1.25), and Sampling schedules (rich, moderate, sparse; optimized using **popED**) using published models for trastuzumab & clenoliximab [3,4].



Results

Power to capture the bioequivalence for different N, frels, & sampling scenarios per each model

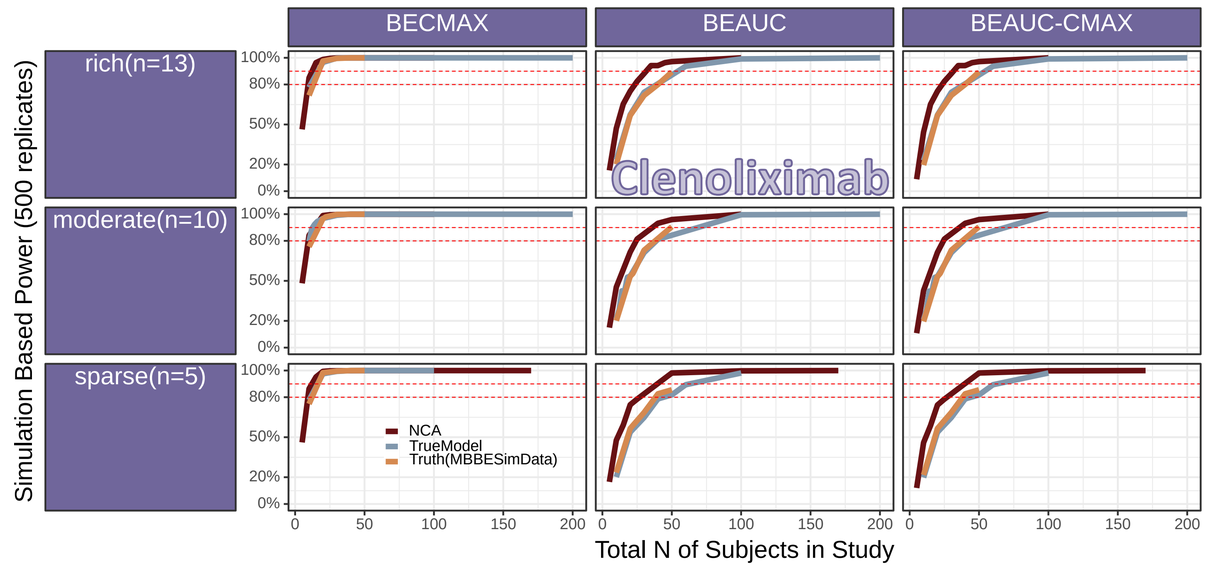


- Model-based bioequivalence showed higher power than NCA in all scenarios.
- Model-based bioequivalence needs **half-number** of subjects in comparison with NCA to achieve the same targeted power.
- Misspecified models achieved higher power than the TrueModel and NCA.
- Model based bioequivalence was applicable in the sparse sampling scenarios.

Type-I error for different N,& sampling schemes per each model

- TrueModel showed similar control on type-I error like NCA.
- Misspecification in the TrueModel by decrease the number of compartments to two instead of three compartments, still shows control on type-I error in all scenarios except the sparse design.
- Big inflation in type-I error after adding more misspecification on the misspecified model (nonlinear elimination only instead of mixed linear and non-linear elimination).

Low variability scenario ($CV\%_{AUC}$ ~ 17%, $CV\%_{CMAX}$~ 14%):



- Clenoliximab is highly variable drug according to the definition of all health authorities.
- We intended to test it in two scenarios: high (**in progress**), and low interindividual variability (**presented**).
- By using low variability, model-based bioequivalence (TrueModel) was superimposed over the PK metrics extracted from the simulated data (the exact true value).
- On the other hand, NCA showed higher biased power in comparison with PK metrics extracted from the simulated data with all sampling scenarios including the rich design.
- Clenoliximab showed high nonlinearity between the AUC and dose, that is why it was the main pillar for determining the bioequivalence. (example for Frel =1.05 the AUC ratio was 1.1)

Conclusion: The MBBE method showed good performance with sparse sampling designs and a reduced number of subjects. We noted inflation of Type-I error with model misspecification that might be mitigated by model averaging or careful model selection. We conclude that MBBE is a promising tool for bioequivalence assessment especially for biosimilarity assessment where data or a model from the innovator product would be available or more generally in situations where NCA is not feasible. More information about the APT program can be found at this poster which details the various contributions and successes of the APT fellows. [5]

Next Steps:

1- The high variability scenario of clenoliximab will be finalized and presented
2- The same methodology will be tested on other biosimilars (panitumumab, and sibrotuzumab).
3- Application of model averaging techniques and recent advances in this specific emerging research area

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