Model-based bioequivalence approach: robustness to model misspecification for sparse pharmacokinetic bioequivalence studies

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Context

- Pharmacokinetic (PK) bioequivalence (BE) studies compare a reference (R) to a test (T) treatment in terms of exposure, i.e., the area under the curve (AUC) and the maximum plasma concentration (C_{max})
- Regulatory authorities generally recommend estimating AUC and C_{max} on data collected with a two-way, single dose, crossover study using a non-compartmental analysis (NCA) and using a two one-sided test (TOST)[1] on the treatment effect (β^T)[2,3]
- Due to challenges using NCA in PK studies with sparse samples, model-based BE (MBBE) has been proposed[4] however **the choice of the structural PK model remains a major challenge**[5]

Objectives

- **To evaluate the robustness of the MBBE approach to model misspecification in PK BE studies with sparse samples**
- **To investigate the impact of model selection (MS) and model averaging (MA)**

Methods

MBBE

- **Non linear mixed-effects model**
  - Fit of concentrations collected in R and T arms together
  - Treatment (β^T), sequence and period effects on all PK parameters μ
  - Population parameters obtained with the SAEM algorithm (Monolix 2020R1)
  - SE obtained by linearisation
  - Likelihood estimated by importance sampling
  - β^T_{AUC}, β^T_{Cmax} and their SE derived from the μ, β^T and their SE analytically or by Monte Carlo calculations (at least 800 samples)
- **MB-TOST**[4]
  - $H_{0,-\delta} : \{\beta^T_{AUC} \leq -\delta\}$ and $H_{0,\delta} : \{\beta^T_{AUC} \geq \delta\}$ and

$$W_{-\delta} = \frac{\hat{\beta}^T_{AUC} + \delta}{SE(\hat{\beta}^T_{AUC})} \geq z_{1-\alpha} \text{ and } W_{\delta} = \frac{\hat{\beta}^T_{AUC} - \delta}{SE(\hat{\beta}^T_{AUC})} \leq -z_{1-\alpha}$$

    with δ fixed to $\log(1.25)$ by the regulatory guidances[2,3], $SE(\beta^T)$ the standard error (SE) of β^T, $z_{1-\alpha}$ the quantile of a normal distribution at level $(1-\alpha)$ with α=5%
  - BE is concluded if the 90% confidence interval (CI) around the geometric mean ratio ($GMR = \exp(\beta^T)$) is within $[0.8; 1.25]$[2]
- **Extension to handle a set of M candidate models**

MS

  - Selection based on data from treatment R only according to the Akaike Information Criteria (AIC)
  - Fit of the selected model based on data from both treatment arms data and TOST

MA

  - The M models are fit based on data from both treatment arms, then weights are calculated[6]:

$$w_m = \frac{exp(-\Delta AIC_m/2)}{\sum_{m'=1}^{M} exp(-\Delta AIC_{m'}/2)}$$

    with AIC_m the AIC of model m and $\Delta AIC_m = AIC_m - min(AIC_{m=1,\dots,M})$
  - Models with weight under 0.5% are removed and weights are updated
  - Calculation of weighted $\hat{\beta}^T$ and SE($\hat{\beta}^T$)[6,7] and TOST

Real case study

Data

- Phase I, single-dose, two-way crossover BE study from Servier
- $N = 36$ healthy volunteers (i.e. 18 per arms) and $n = 22$ PK samples per period

Method

- Set of $M = 10$ candidate models with varying number of compartments for the distribution (1 or 2-COMPT) and/or absorption types with transit compartments (TRANSIT), delayed (LAG) and zero- or first-order (0/1-order)

Results

- MS: TRANSIT_2-COMPT model selected
- MA: TRANSIT_2-COMPT model with $w = 1$
- BE concluded with MB-TOST on AUC and C_{max}
  - $GMR_{AUC} = 1.00$ and $CI_{90_{AUC}} = [0.97; 1.04] \in [0.8, 1.25]$
  - $GMR_{C_{max}} = 1.04$ and $CI_{90_{C_{max}}} = [0.99; 1.10] \in [0.8, 1.25]$

[1] Schuirmann. *J. Pharmacokinet. Biopharm.* 1987; [2] FDA *Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA.* 2021; [3] EMA *Guideline on the Investigation of Bioequivalence.* 2010; [4] Dubois et al. *Stat. Med.* 2011; [5] Guhl et al. *PAGE 29 abstract 9719.* 2021; [6] Buatois et al. *AAPS J.* 2018; [7] Turek et al. *Comput. Stat. Data Anal.* 2012;

Simulation study

Settings

- Single-dose, two-way crossover study with $N = 20$ patients per sequence (within subject variability = 30%) and $n = 6$ PK samples per period {t=0.3, 3, 6, 12, 72, 144}
- $S = 200$ datasets simulated for each scenario

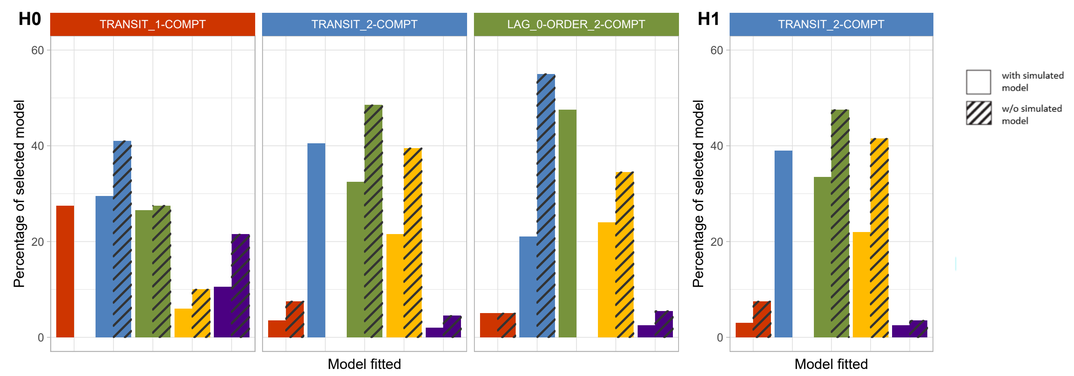
		Simulated model		
		TRANSIT_1-COMPT	TRANSIT_2-COMPT	LAG_0-ORDER_2-COMPT
Data fitted with	TRANSIT_1-COMPT TRANSIT_2-COMPT LAG_0-ORDER_2-COMPT LAG_1-ORDER_2-COMPT LAG_0-ORDER_1-COMPT MS with and w/o simulated model MA with and w/o simulated model	Under H_0 with β^T=log(1.25)	Under H_0 with β^T=log(1.25) and under H_1 β^T=log(0.95)	Under H_0 with β^T=log(1.25)

- Evaluation: proportion of model selected, type I error and power

Results

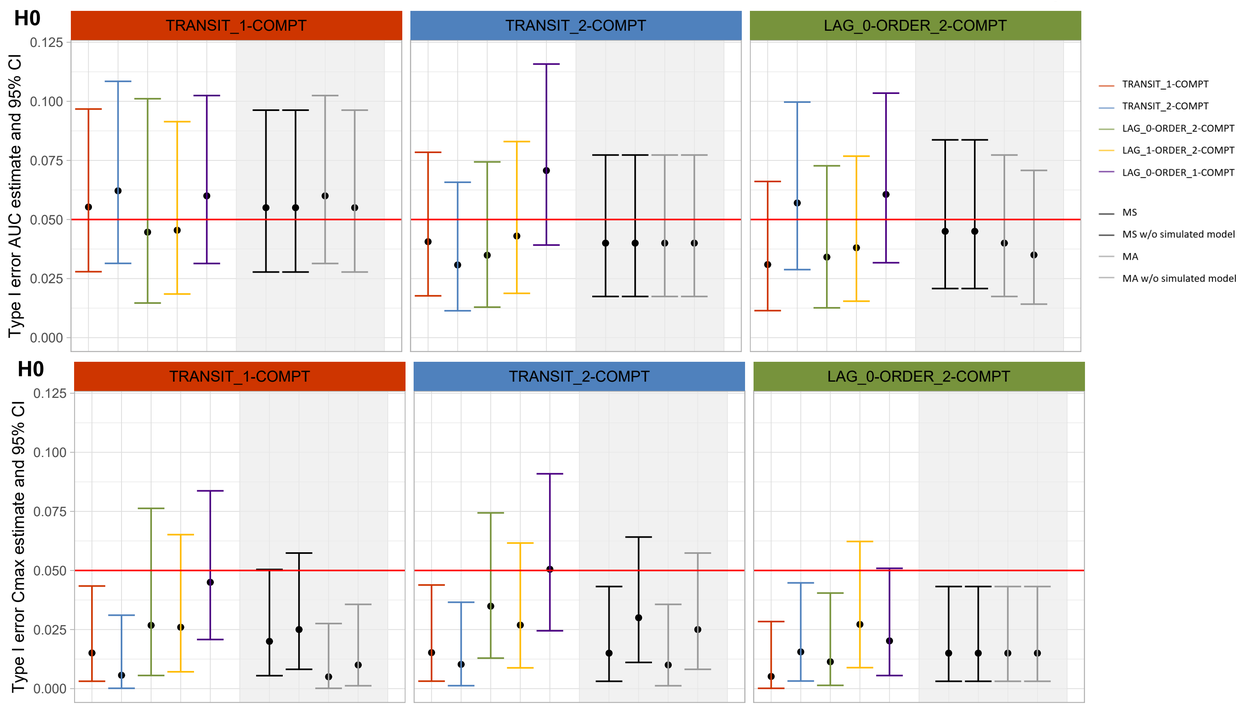
- **MS**

Candidate model selected (%) for each scenario when the simulated model was included or excluded from the candidate pool



  - with simulated model: right model selected in 28%, 41% and 48% cases under H_0 and 39% under H_1 → model not highly identifiable under simulation settings
  - w/o simulated model: selection driven by number of COMPT
- **MA** performs similarly to MS, with one candidate model having $w = 1$ in 68% and 73% of the cases under H_0 and H_1
- **Type I error**

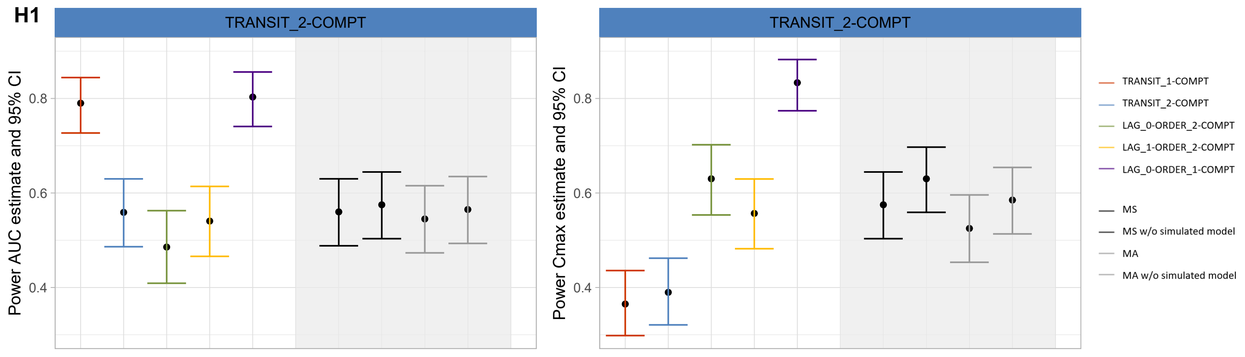
Estimate and 95% CI for AUC and C_{max} using M candidate models, MS and MA when the simulated model was included or excluded from the candidate pool



→ In general, the 95%CI around the type I error estimate includes the 5% target or is just below for C_{max}

- **Power**

Estimate and 95% CI for AUC and C_{max} using M candidate models, MS and MA when the simulated model was included or excluded from the candidate pool



→ MS and MA showed similar power for AUC and higher power for C_{max} when compared to the simulated model

Conclusion

The MBBE approach appears to be robust to model misspecification in our simulation study. MS and MA led to type I errors around or below 5% and ensured a reasonable power. No added value was observed with MA compared to MS. Further work is needed to assess the robustness when R and T have different PK models.