Model-based tests of bioequivalence: impact of a model misspecification

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Context

- Pharmacokinetic (PK) bioequivalence can be established by ensuring that the 90% confidence interval of the ratio of drug exposures remains within predetermined limits through two one-sided tests (TOST) [1]
- Parameters of interest: area under the curve AUC and maximal concentration C_{max}
- A model-based approach (MB-TOST) has been advocated to test for similarity in sparse PK studies but questions about its performance in the presence of model misspecification remain un-addressed [2]

Objectives

- Evaluate performances of MB-TOST on data extracted from phase 1 studies of gantenerumab (Roche, Switzerland)
- Investigate the **impact of design and model misspecification**, by comparing it to the traditional non-compartmental approach (NCA-TOST) on simulations

Methods

PK bioequivalence:

- Computation of treatment effects:

$$\beta^T_{AUC} = \mathbb{E}(log(AUC_T)) - \mathbb{E}(log(AUC_R))$$

- Geometric mean ratio: $GMR = e^{\beta^T}$

Two One Sided Tests (TOST)[1]:

$$H_0 : \{\beta^T \leq -\delta \text{ or } \beta^T \geq \delta\}$$

H_0 is rejected if :

$$Z_{-\delta} = \frac{\beta^T + \delta}{SE(\beta^T)} \geq q_{1-\alpha} \text{ and } Z_{\delta} = \frac{\beta^T - \delta}{SE(\beta^T)} \leq q_{\alpha}$$

Guidelines (FDA/EMA) [3] : $\boldsymbol{\delta = log(1.25)}$

Non-compartmental approach (NCA-TOST):

- Recommended by the regulatory authorities
- Computation of individual AUC using the trapezoidal rule and the observed C_{max}
  - → No model assumption
  - → Not appropriate in case of sparse sampling
- Linear mixed effects models
- Asymptotic standard errors from the estimated Fisher Information Matrix (FIM)

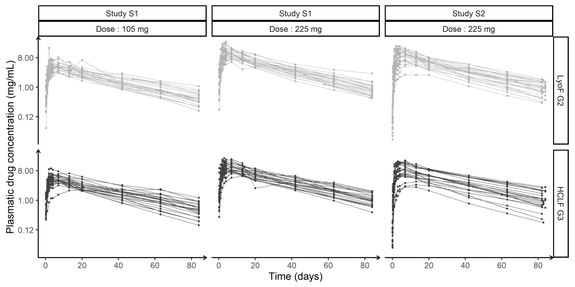
Model-based approach (MB-TOST):

- Structural PK model
- Non linear mixed effects models
- Asymptotic standard errors from the estimated FIM

Real case study

Data

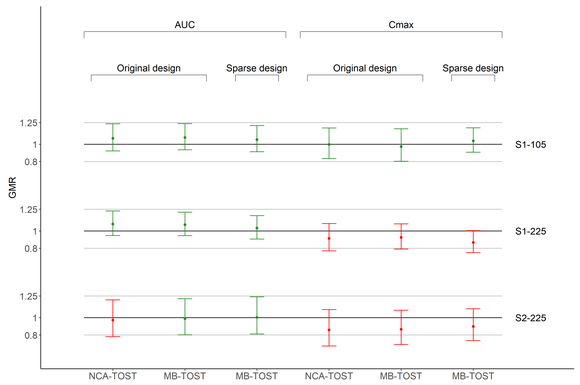
- Subsets of two phase I randomized parallel clinical trials (S1 and S2)
- High concentration liquid formulation (HCLF G3) versus reference lyophilised formulation (LyoF G2) at doses 105 and 225 mg
- Healthy subjects, N=24 subjects per arm, n=11 sampling points per subject (original design)



Methods

- Separate analysis per dose/study groups: S1-105, S1-225 and S2-225
- Creation of fictitious sparse datasets with n=5 (sparse design), by design optimization [3]
- On each of 6 datasets (3 rich, 3 sparse), selection of PK structural model using BIC on reference data (8 PK models tested: one/two-cpt, zero/first order absorption, absorption delay)
- Inter-individual variability structure selected with a second criteria of a relative SE (RSE) below 50% for all parameters
- Treatment effects estimated on all apparent parameters
- MB-TOST
- Comparison to NCA-TOST on original design

Results



- Selected model: two-compartment with first order absorption and absorption delay
- Concordant results with NCA-TOST and MB-TOST on original design
- Although the studies were not designed for this, the AUC for the two formulations were found to be equivalent, using the MB-TOST; C_{max} were found to be equivalent by MB-TOST in S1-105 only
- MB-TOST is robust to sparse design, though the model selected is different on sparse data (one-compartment)

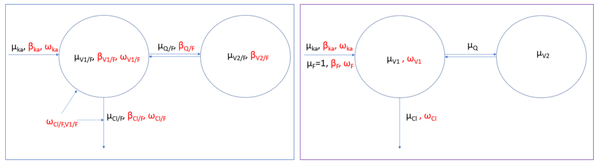
Simulation study

Settings

- Two-compartment PK model, first order absorption, without delay
- 5 scenarios of rich parallel design (N=24,n=11): GMR on AUC and C_{max} at 0.8 and 1.25 to evaluate type I error, and at 0.9, 1 and 1.11 to evaluate power
- Creation of sparse subsets (N=24,n=5)

Methods

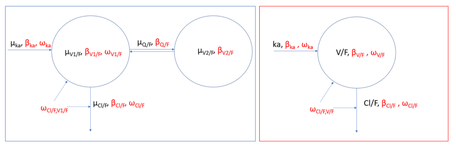
PK models fitted on rich design:



- 2cpt_par: two-cpt model with treatment effects estimated on all parameters
- 2cpt_F: two-cpt model with treatment effects estimated only on ka and F

→ Comparison of MB-TOST and NCA-TOST
→ Evaluation of a model selection step

PK models fitted on sparse design:



- 2cpt_par:two-cpt model with treatment effects estimated on all parameters
- 1cpt_par: one-cpt model with treatment effects estimated on all parameters

→ MB-TOST
→ Evaluation of a model selection step

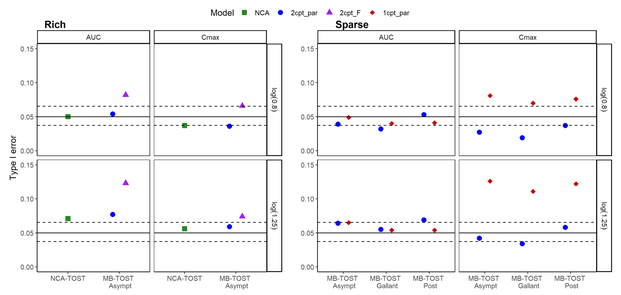
Results

On rich simulations:

- NCA-TOST and MB-TOST, using 2cpt_par, gave consistent results, i.e. type I error close to the nominal value
- 2cpt_F led to an inflated type I error on AUC
- A model selection step prior to MB-TOST selected the simulated model in 85% cases and thereby ensured a type I error at the nominal level

On sparse simulations:

- MB-TOST gave controlled type I error with 2cpt_par
- Type I error was inflated on C_{max} when using 1cpt_par
- A model selection step prior to MB-TOST selected the simulated model in 99% cases and thereby ensured a type I error at the nominal level



Dotted lines: prediction interval of the nominal value 0.05

Conclusion

MB-TOST appears to be a robust alternative to NCA, provided that the PK model is well specified, and the two treatment arms have the same PK structural models. Model selection is key to maintaining an appropriate type I error for similarity testing using MB-TOST.

[1] Schuirmann. *J. Pharmacokinet. Biopharm.* 1987; [2] Dubois et al.*Statistics in Medicine* 2011; [3] FDA *Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA* 2013

Acknowledgements: This work was supported by the U.S. Food and Drug Administration (FDA) under contract 75F40119C10111. The authors thank FDA for this funding. The views expressed in this abstract do not necessarily reflect the views or policies of the FDA.