Model-based approach for group sequential and adaptive designs in parallel and cross-over bioequivalence studies

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Introduction

Background

- Bioequivalence (BE) studies are performed to compare pharmacokinetics (PK) of drug formulations with, traditionally, the two one-sided test (TOST) using estimates of area under the curve (AUC) and maximal concentration (Cmax) obtained by non-compartmental analysis (NCA).
- Assumptions on the expected variability of AUC and Cmax are needed for sample size calculation (between subject (ω) and within subject (γ) standard deviation), and in case of uncertainty, it has been recently proposed to perform two-stage studies considering group sequential and adaptive designs for NCA-based BE [1].
- In a previous work [2], we proposed a model-based TOST as an alternative to NCA-based TOST.

Objectives

- To extend model-based statistical approaches for BE assessment to two-stage group sequential and adaptive designs and evaluate them by clinical trial simulation.

Methods

Two one-sided test (TOST):

- The null hypothesis of BE on the treatment effect on log(AUC) or log(Cmax), β^{Tr}, is decomposed into $H_{0,-\delta}$: $\{\beta^{Tr} \leq -\delta\}$ and $H_{0,\delta}$: $\{\beta^{Tr} \geq \delta\}$ where δ=log (1.25) ≈0.22.
- $\boldsymbol{Z_{-\delta}} = \left(\widehat{\beta^{Tr}} + \delta\right)/SE\left(\widehat{\beta^{Tr}}\right)$ and $\boldsymbol{Z_{\delta}} = \left(\widehat{\beta^{Tr}} - \delta\right)/SE\left(\widehat{\beta^{Tr}}\right)$ with rejection at level α if $Z_{-\delta} \geq z_{1-\alpha}$ and $Z_{\delta} \leq -z_{1-\alpha}$ where SE denotes standard error and $z_{1-\alpha}$ the 1-α quantile of a Gaussian.

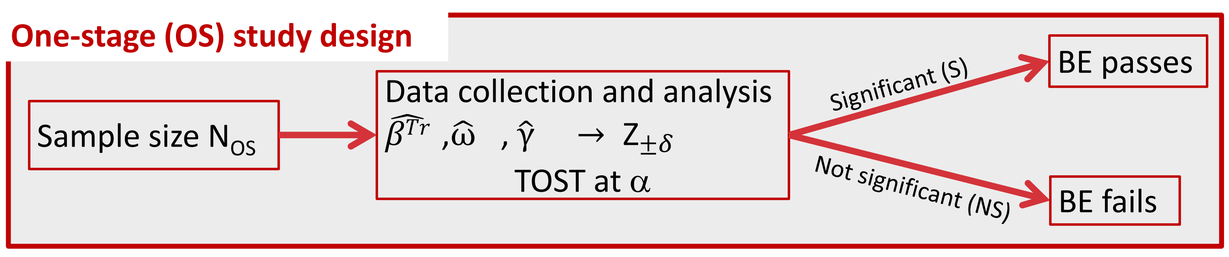
Model-based (MB) TOST

- Estimation using Nonlinear mixed effects models in saemix R package [3] for parallel design studies and the Monolix software [4] for crossover design studies.
- AUC and C_{max} are secondary parameters of the PK model, such that β^{Tr} is a nonlinear function of PK parameters fixed effects and their associated treatment effect coefficient.
- $SE(\widehat{\beta^{Tr}})$ are determined from the observed Fisher information matrix, by the delta method [5].

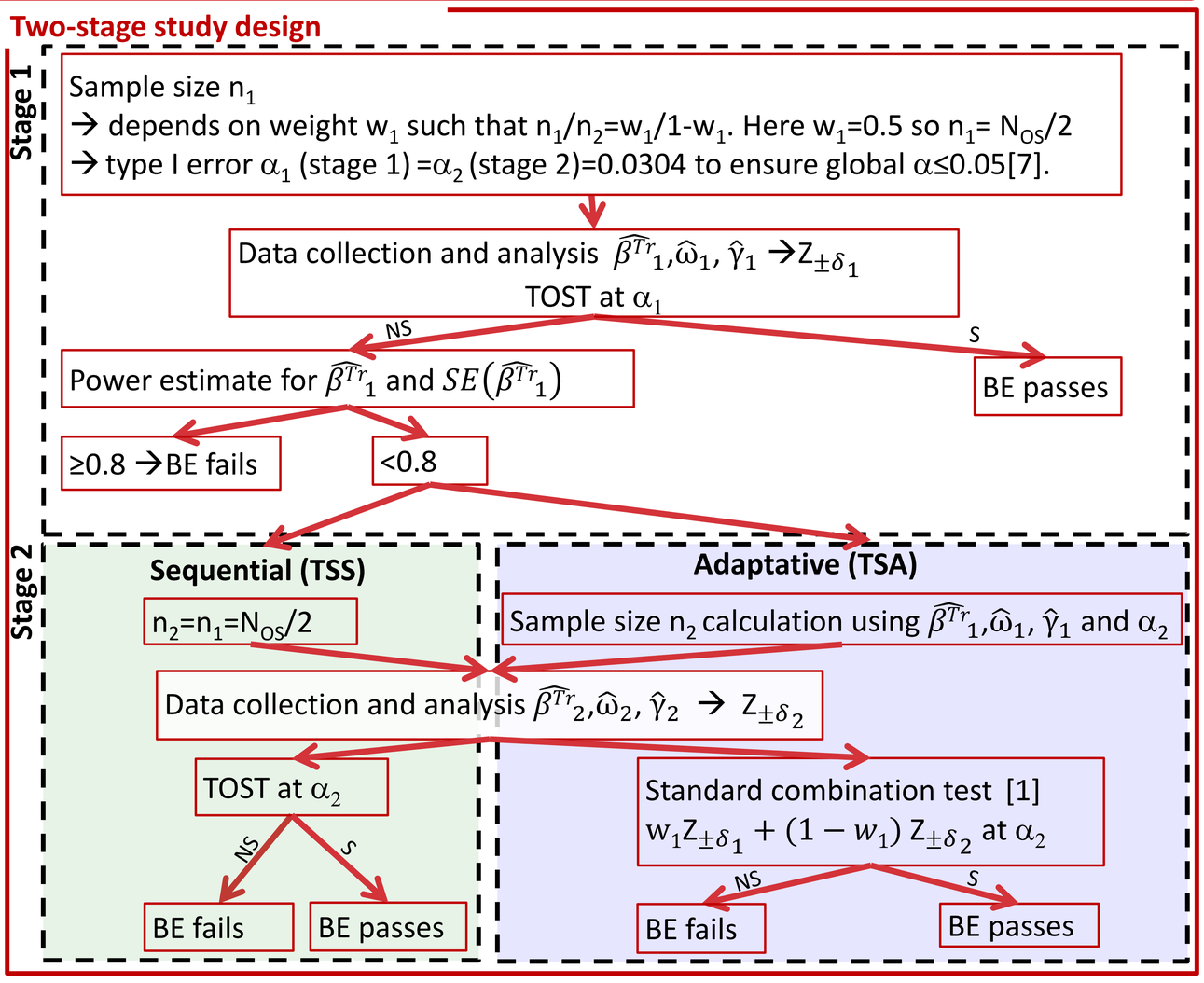
Sample size calculation

- Depends on the PK parameters fixed effects, the residual error, the assumed ω, γ (for crossover studies) and β^{Tr} as well as the type I error α (0.05) and the power 1-β (0.8).
- Derived using the expected population Fisher Information Matrix [6].

One-stage (OS) study design



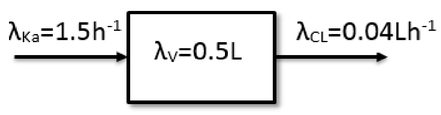
Two-stage study design



Simulation study

Settings

- PK model of concentrations of theophylline [2]
- Dose=4 mg



- n=10 sampling times *t* =(0.25, 0.5, 1, 2, 3.5, 5, 7, 9, 12, 24)
- **Parallel study design**

ω_{ka} (%)	ω_v (%)	ω_{Cl} (%)	$\sigma_{intercept}$ (mg/L)	σ_{slope} (%)
22	11	22	0.1	10

- **Two-sequence two-period crossover study design**

ω (%)	γ (%)	$\sigma_{intercept}$ (mg/L)	σ_{slope} (%)
50	15	0.1	10

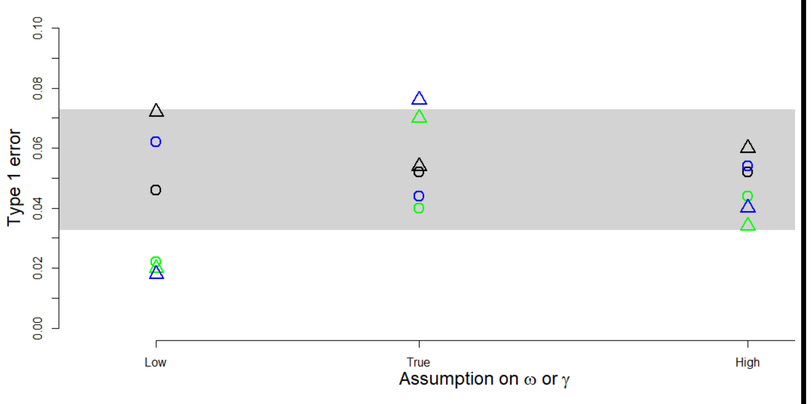
Same ω and γ for all PK parameters

$\beta^{P=}\beta^{S}=0$

- 500 data sets under H_0: β^{Tr} =log(0.8) and H_1: β^{Tr}=log(1)=0
- Evaluation on **AUC** with **varying assumptions on ω and γ at the planning stage**

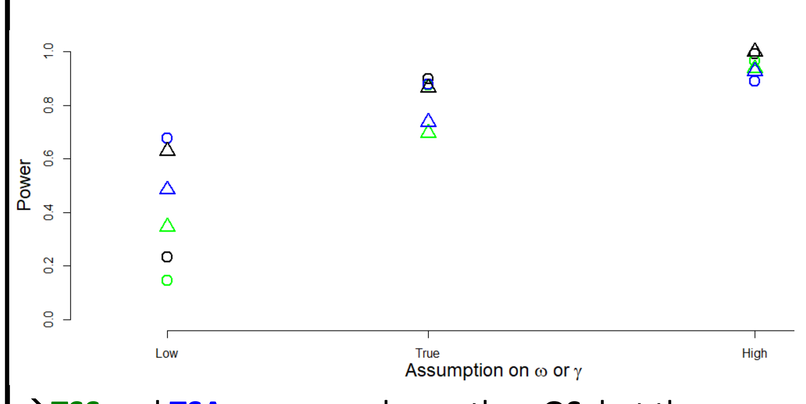
ω (%)			γ (%)		
Low	**True**	**High**	**Low**	**True**	**High**
10	22	30	5	15	25

Type 1 error for parallel (o) and crossover (Δ) designs for **OS**, **TSS** and **TSA**



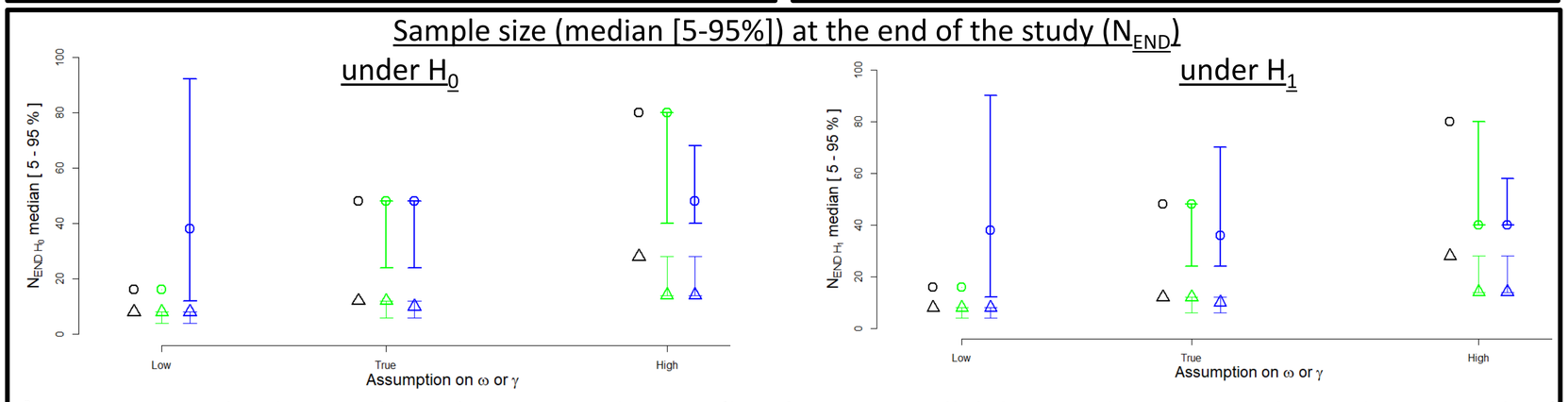
→ In most cases **TSS** and **TSA** type 1 error estimates are within the 0.05 prediction interval [0.0326-0.0729]

Power for parallel (o) and crossover (Δ) designs for **OS**, **TSS** and **TSA**



→**TSS** and **TSA** power are lower than **OS**, but the difference reduces when assumed ω and γ get close or higher than the true ω and γ

Sample size (median [5-95%]) at the end of the study (N_{END})



→ **TSS** and **TSA** lead to similar or lower N_{END} than **OS** (but for **TSA** parallel design when assumed ω and γ are too low)

→ Under H_1, **TSS** and **TSA** stop at stage 1 half of the time, when assumed ω and γ are too high

Conclusion

- We showed that BE assessment is feasible using a model-based approach, which is an extension of these designs for NCA BE [1]
  - with preserved type I errors in most cases and N_{END} similar or reduced compared to **OS** design
  - **TSA** is of interest when a higher variability was assumed at the planning stage than the one actually obtained from the first stage
- Further extensions are needed for sparse design where asymptotic standard errors can be too small [2]

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