

# Evaluation of Model-Based Bioequivalence approach for one single sample pharmacokinetic studies

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## Introduction

- Bioequivalence (BE) studies are key to the development and approval of generic drugs
- Traditionally, BE studies with pharmacokinetic (PK) endpoints are conducted using a two-way crossover study design and the two one-sided test (TOST) is performed using estimates of area under the concentration-time curve (AUC) and maximal concentration (C<sub>max</sub>) obtained by non-compartmental analysis (NCA).
- In a typical PK BE studies for ophthalmic drug products, only one sample of aqueous humor is collected from one eye per patient.
- Parallel (P) design studies
  - subjects assigned to one pre-specified sampling times  $t_j$  with  $j = 1, \dots, J$
  - $C_{ij}$  the concentration of subject  $i = 1, \dots, N_j$  at  $t_j$
  - total number of samples ( $n_{tot}$ ) =  $\sum_{j=1}^J N_j$  = study sample size ( $N$ )
- Crossover (C) design studies
  - subject with bilateral cataracts randomly assigned one of two treatments to one of two eyes and one sample collected from each eye at the same  $t_j$
  - $C_{ijk}$  the concentration of subject  $i = 1, \dots, N_{kj}$  at each period/in each eye  $k = 1, 2$
  - $n_{tot} = \sum_{k=1}^2 \sum_{j=1}^J N_{kj}$  and  $N = n_{tot}/2$

## Methods

### TOST<sup>1</sup>

- $\beta^T$  = the treatment effect, i.e., the difference in  $\mu_T$  and  $\mu_R$ , which are the average means of the test and reference products for  $\log(AUC)$  or  $\log(C_{max})$
- $H_0 : \beta^T = \mu_T - \mu_R \geq \delta$  or  $\beta^T = \mu_T - \mu_R \leq -\delta$  with  $\delta$  a pre-specified BE margin.

$$\frac{\hat{\beta}^T + \delta}{SE(\hat{\beta}^T)} \geq u_{1-\alpha} \quad \text{and} \quad \frac{\hat{\beta}^T - \delta}{SE(\hat{\beta}^T)} \leq -u_{1-\alpha}$$

where  $\hat{\beta}^T$  and  $SE(\hat{\beta}^T)$  are the  $\beta^T$  estimate and its standard error and  $u_{1-\alpha}$  is the  $1 - \alpha$  quantile of a reference distribution.

- $\delta = \log(1.25) = -\log(0.8)$  and the significance level  $\alpha = 0.05$  according to regulation authorities → The typical BE acceptance criteria is for the 90% confidence interval (CI) around the geometric mean ratio (GMR) of AUC or C<sub>max</sub> to be included in the [80; 125]% interval.

### Model-based (MB) TOST<sup>2</sup>

- Based on a nonlinear mixed effect model (NLMEM) analysis of the data
- Crossover (C) design studies

$$C_{ijk} = f(t_j, \phi_{ijk}) + g(t_j, \phi_{ijk})\epsilon_{ijk}$$

$$\log(\phi_{ijkl}) = \log(\lambda_i) + \beta_1^T T_{ijk} + \beta_1^P P_k + \beta_1^S S_{ij} + \eta_{ijl} + \kappa_{ijkl}$$

- $f(\cdot)$  the structural model and  $g = a + bf(\cdot)$  the error model
- $\phi_{ijkl}$  is the  $l^{\text{th}}$  element of the PK parameter  $n_p$ -vector of individual  $i$  at time  $t_j$  and occasion  $k$
- $\lambda_i$  the  $l^{\text{th}}$  element of the fixed effect  $n_p$ -vector for the covariate reference class
- $T_{ijk}$ ,  $P_k$  and  $S_{ij}$  the treatment, period and sequence covariate vectors
- $\beta_1^T$ ,  $\beta_1^P$  and  $\beta_1^S$  the coefficients of treatment, period and sequence effect vector for the  $l^{\text{th}}$  individual parameter
- $\eta_{ijl}$  the  $l^{\text{th}}$  element of the random effect vector  $\eta_{ij}$  for subject  $i$  at time  $t_j$  capturing the between subject variability (BSV)
- $\kappa_{ijkl}$  the  $l^{\text{th}}$  element of the vector of random effects  $\kappa_{ijk}$  for subject  $i$  at time  $t_j$  and period  $k$ , capturing the within subject variability (WSV)
- $\eta_{ij} \sim N(0, \Omega)$  and  $\kappa_{ijk} \sim N(0, \Gamma)$  independent with  $\omega_i^2$  and  $\gamma_i^2$  the  $l^{\text{th}}$  diagonal element of  $\Omega$  and  $\Gamma$
- $\epsilon_{ijk} \sim N(0, \sigma^2)$  the independent residual errors

- Parallel (P) design studies

$$C_{ij} = f(t_j, \phi_{ij}) + g(t_j, \phi_{ij})\epsilon_{ij}$$

$$\log(\phi_{ijl}) = \log(\lambda_i) + \beta_l^T T_{ij} + \eta_{ijl}$$

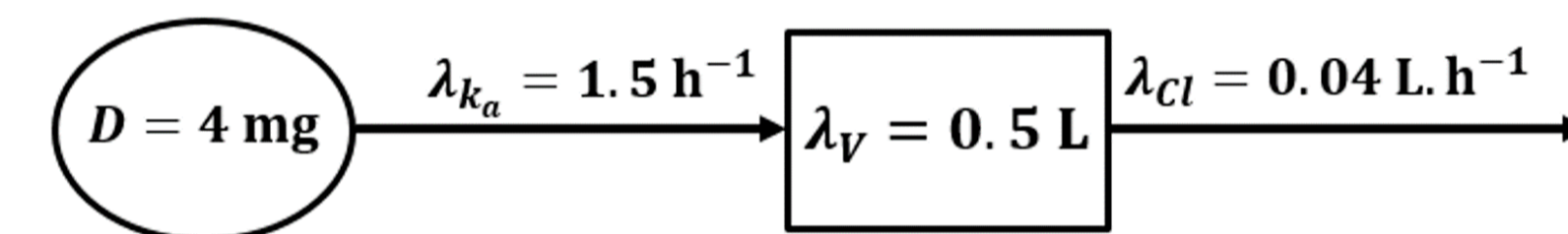
- $\beta_{AUC}^T$  and  $\beta_{C_{max}}^T$  derived from functions of the  $\lambda$  and  $\beta^T$
- $VAR(\beta_{AUC}^T)$  and  $VAR(\beta_{C_{max}}^T)$  are derived using the delta-method using the inverse of the observed Fisher Information Matrix (FIM) with 90% CI =  $\pm u_{1-\alpha} SE$
- NLME modeling was performed using Monolix 2018R2

## Objective

To evaluate MB-TOST, by clinical trial simulation, for the analysis of BE crossover (C) and parallel (P) design 1 single point pharmacokinetic studies

## Simulation study

- PK model of concentrations of the anti-asthmatic drug theophylline, a narrow therapeutic index, however conventional BE limits are used for the analysis



- Limit of Quantification at 0.2 mg/L
- Designs
  - each of the N subjects provides one sample in one (parallel, P) or both (crossover, C) eyes at one sampling time chosen among a set of 10 or 5 possible sampling times:

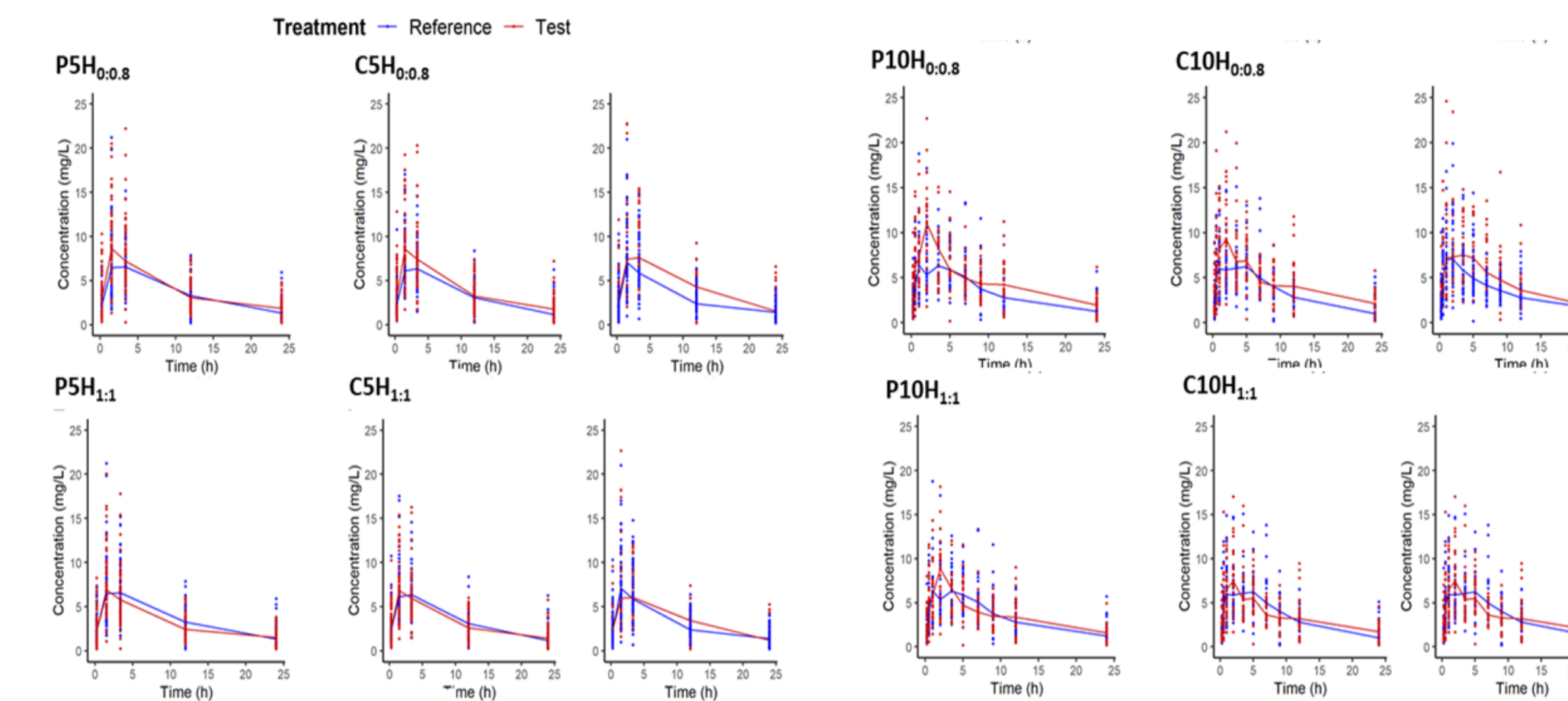
Design	N	Total sample size	Sampling times (h)	Subjects per sampling time
Parallel	500	500	{0.25, 0.5, 1, 2, 3.5, 5, 7, 9, 12, 24}	50
	500	500	{0.25, 1.5, 3.35, 12, 24}	100
Crossover	500	1 000	{0.25, 0.5, 1, 2, 3.5, 5, 7, 9, 12, 24}	50
	500	1 000	{0.25, 1.5, 3.35, 12, 24}	100

	BSV			WSV			Error model	
	$\omega_{ka}$ (%)	$\omega_{V/F}$ (%)	$\omega_{Cl/F}$ (%)	$\gamma_{ka}$ (%)	$\gamma_{V/F}$ (%)	$\gamma_{Cl/F}$ (%)	$a$ (mg/L)	$b$ (%)
Parallel	52	52	52	-	-	-	0.1	10
Cross-over	50	50	50	15	15	15	0.1	10

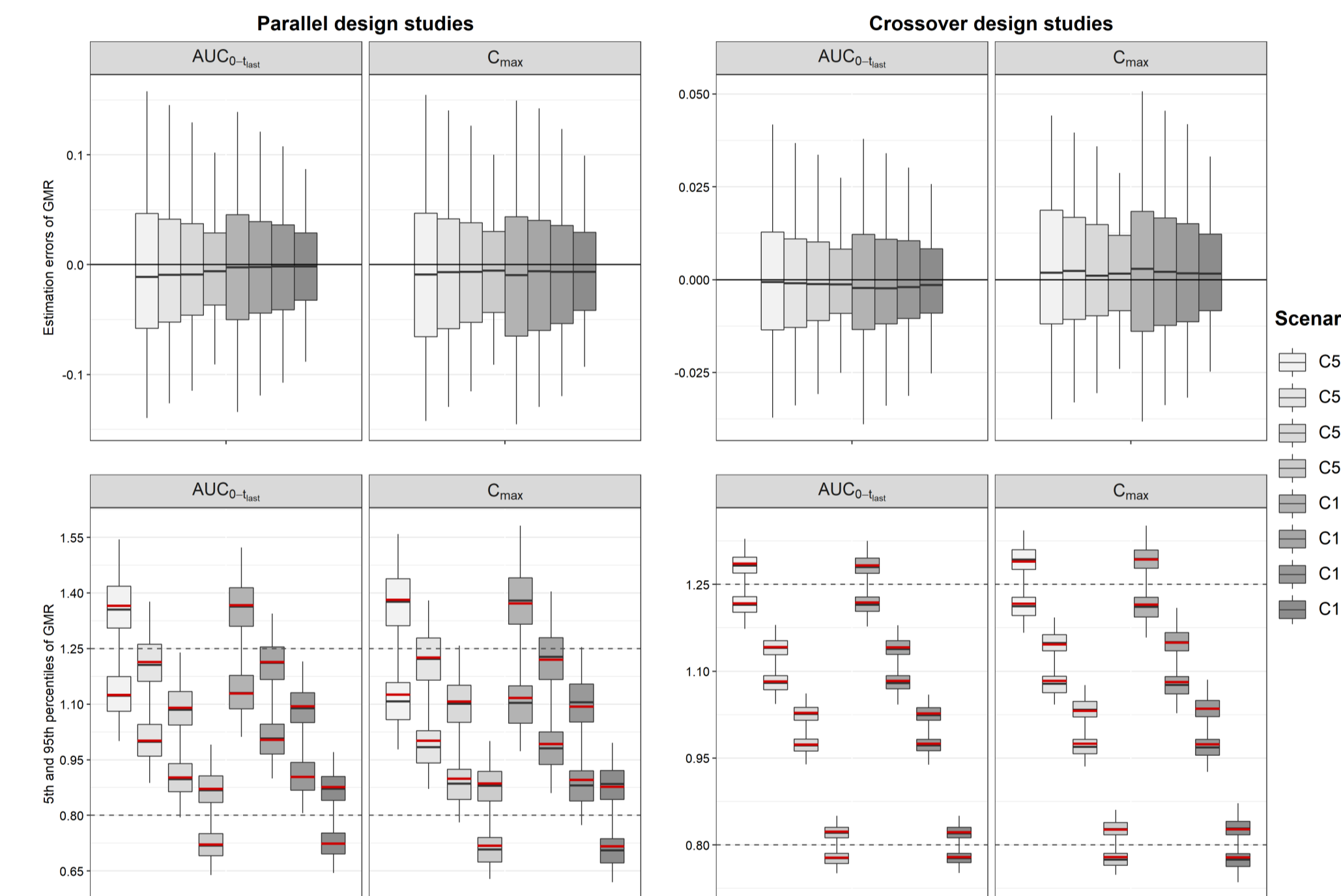
- Under  $H_0 : \beta^T = \log(0.8)$  and  $\beta^T = \log(1.25)$  to assess type I error
- Under  $H_1 : \beta^T = \log(0.9)$  and  $\beta^T = \log(1)$  to assess the power
- 16 scenarios evaluated with 500 simulated data sets for each scenario → 95% prediction interval around 0.05 = [0.033-0.073]

## Results

### SIMULATED DATA SET

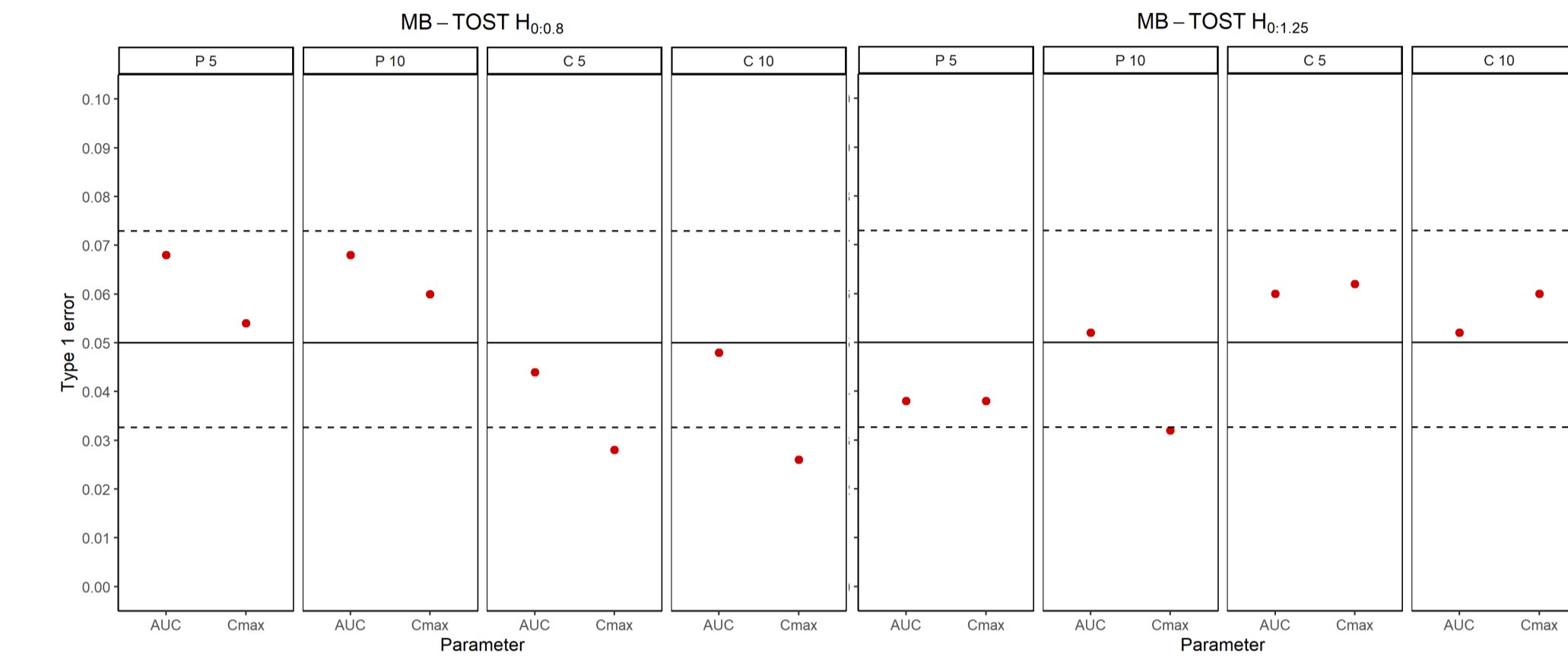


### ESTIMATION



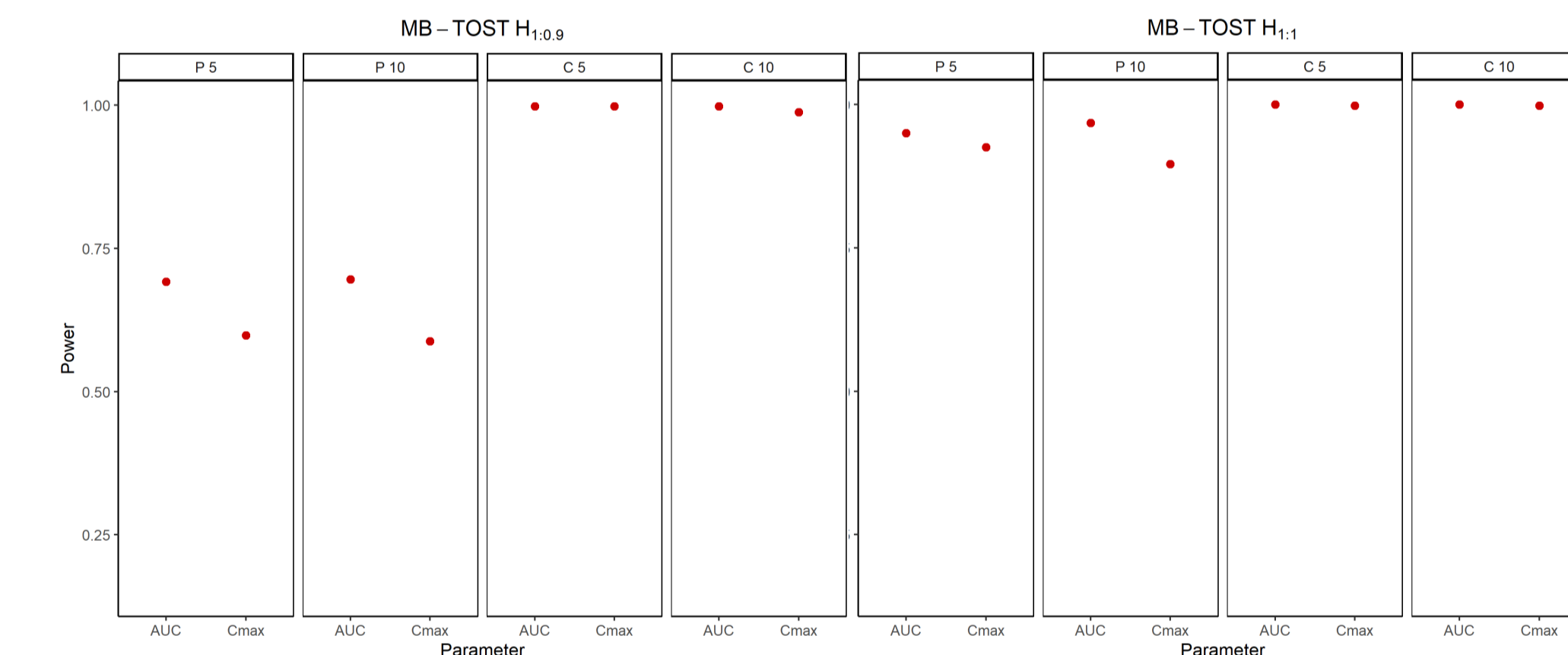
- Model-based GMR for  $AUC_{0-t_{last}}$  and  $C_{max}$  were unbiased and precise
- validation of the parameter estimation step
- Overestimation of 90% CI for  $C_{max}$
- Crossover studies, as expected, resulted in smaller 90% CI

### TYPE I ERROR



- Controlled type 1 errors for  $AUC$  under 0.07 on parallel (P) and crossover (C) study designs
- Significantly conservative type 1 errors for  $C_{max}$  for scenarios  $C5H_{0.0.8}$  and  $C10H_{0.0.8}$

### POWER



- High power estimates close to 100% on crossover studies
- rather low simulated WSV → small 90% CIs

## Conclusion

Simulation study shows that MB approaches, when the PK model is accurately specified, can be a good alternative approach for BE studies with only one-time point measured drug concentration.

## References

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