UPPSALA UNIVERSITET

Model-Integrated Methods and Innovative Study Designs for Generic LAI Product Development and Regulatory Assessment

Andrew C. Hooker, Ph.D.
Professor of Pharmacometrics

Dept. of Pharmacy, Uppsala University
Uppsala, Sweden

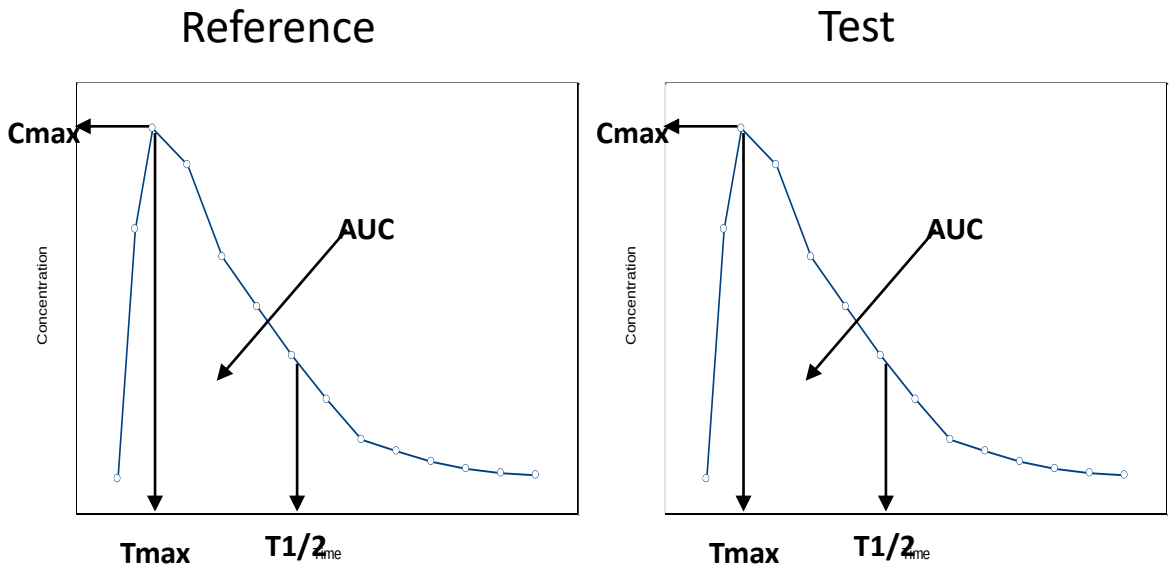
Xiaomei Chen

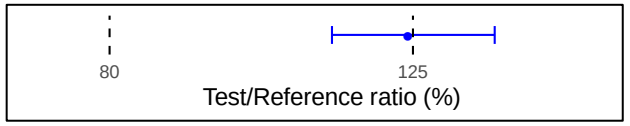
Piyanan Assawasuwannakit

Mats O. Karlsson

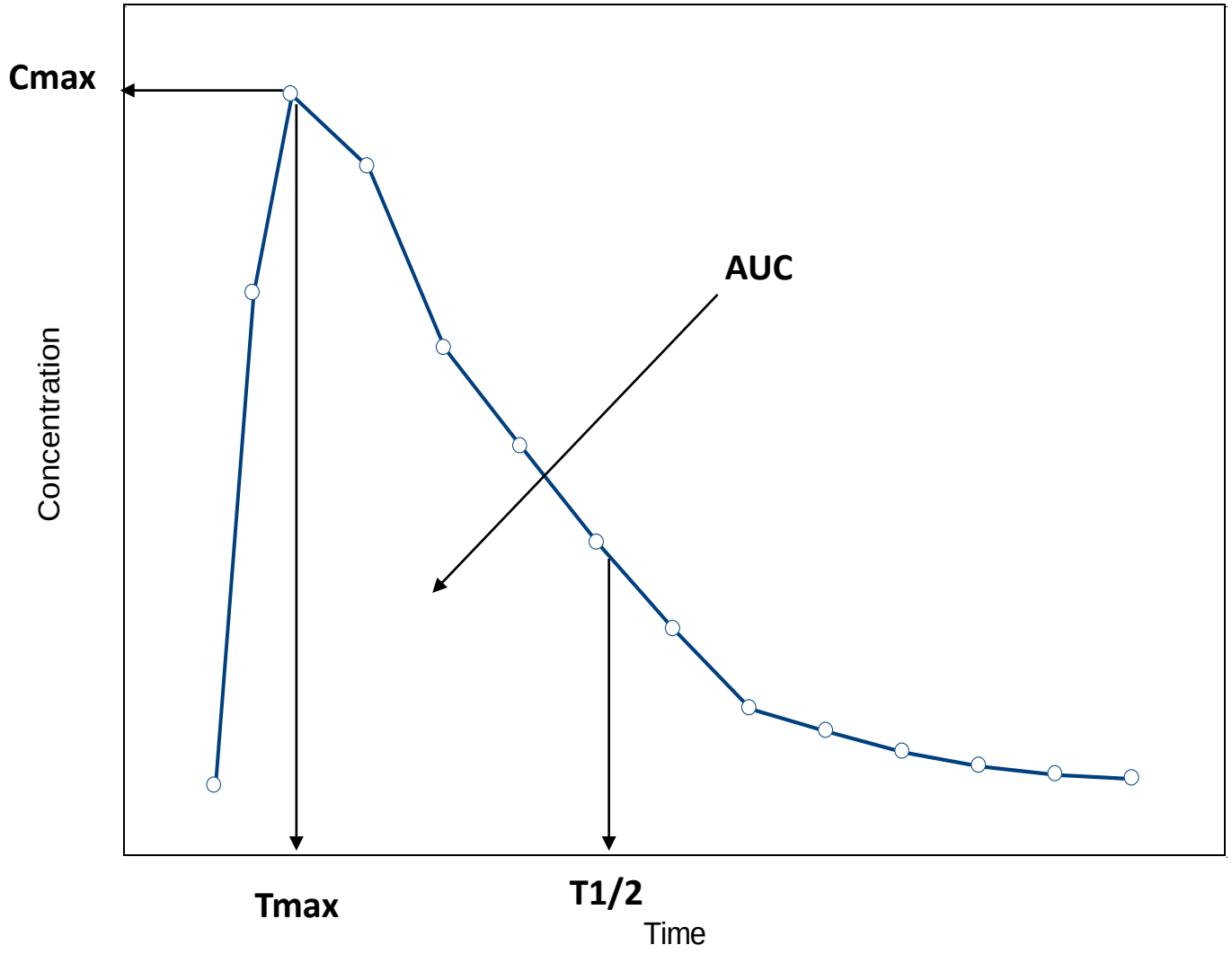
Standard bioequivalence (BE) studies

- 2x2 crossover designs
- Non-compartmental analysis (NCA) based summary PK metrics (e.g., AUC, Cmax)
- BE determined by comparing the 90% confidence interval of the geometric mean ratio of NCA metrics compared to predetermined limits.





Problems with NCA calculations



- Sparse data problems
- Assume equal weight for all observations
- Sensitivity to missing data
- Sensitivity to data below the limit of quantification
- Interpolation problems from the last observation to ∞
- Hard to separate variability sources (BSV/IOV/RUV)
- Ad hoc design of sampling times

NCA analysis can give biased estimates

The AAPS Journal, Vol. 18, No. 1, January 2016 (© 2015)
DOI: 10.1208/s12248-015-9829-2

Research Article

Pharmacokinetic Interactions for Drugs with a Long Half-Life—Evidence for the Need of Model-Based Analysis

Elin M. Svensson,[1,3] Chayan Acharya,[1] Björn Clauson,[1] Kelly E. Dooley,[2] and Mats O. Karlsson[1]

Received 30 June 2015; accepted 12 September 2015; published online 13 October 2015

Abstract. Pharmacokinetic drug-drug interactions (DDIs) can lead to undesired drug exposure, resulting in insufficient efficacy or aggravated toxicity. Accurate quantification of DDIs is therefore crucial but may be difficult when full concentration-time profiles are problematic to obtain. We have compared non-compartmental analysis (NCA) and model-based predictions of DDIs for long half-life drugs by conducting simulation studies and reviewing published trials, using antituberculosis drug bedaquiline (BDQ) as a model compound. Furthermore, different DDI study designs were evaluated. A sequential design mimicking conducted trials and a population pharmacokinetic (PK) model of BDQ and the M2 metabolite were utilized in the simulations where five interaction scenarios from strong inhibition (clearance fivefold decreased) to strong induction (clearance fivefold increased) were evaluated. In trial simulations, NCA systematically under-predicted the DDIs' impact. The bias in average exposure was 29–96% for BDQ and 20–677% for M2. The model-based analysis generated unbiased predictions, and simultaneous fitting of metabolite data increased precision in DDI predictions. The discrepancy between the methods was also apparent for conducted trials, *e.g.*, lopinavir/ritonavir was predicted to increased BDQ exposure 22% by NCA and 188% by model-based methods. In the design evaluation, studies with parallel designs were considered and shown to generally be inferior to sequential/cross-over designs. However, in the case of low inter-individual variability and no informative metabolite data, a prolonged parallel design could be favored. Model-based analysis for DDI assessments is preferable over NCA for victim drugs with a long half-life and should always be used when incomplete concentration-time profiles are part of the analysis.

KEY WORDS: drug-drug interactions; long half-life; model-based analysis; non-compartmental analysis; pharmacokinetics.

Model based assesment

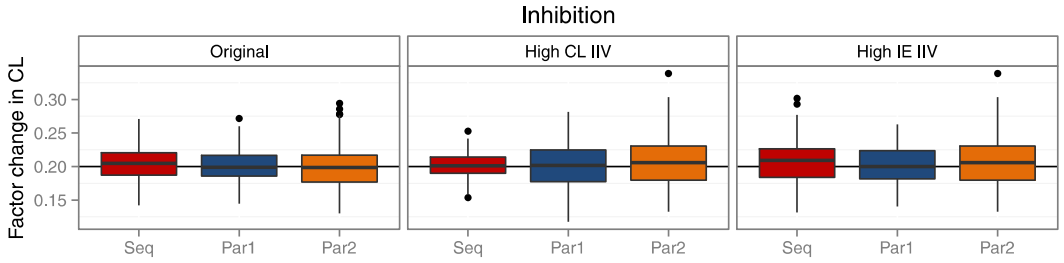


Fig. 4. Box plots of model-based estimation of interaction effect (factor change in CL) for the different designs (*Seq* sequential, *Par1* parallel 1, *Par2* parallel 2), the different PK scenarios (original, high CL IIV, and high IE IIV), and the different interaction effect scenarios (induction, no interaction, and inhibition)

NCA analysis

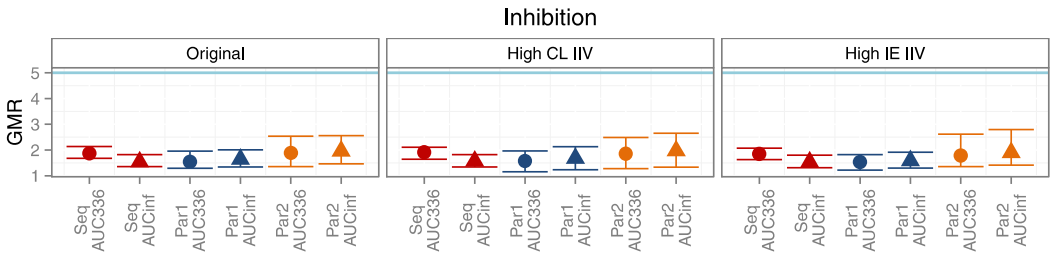


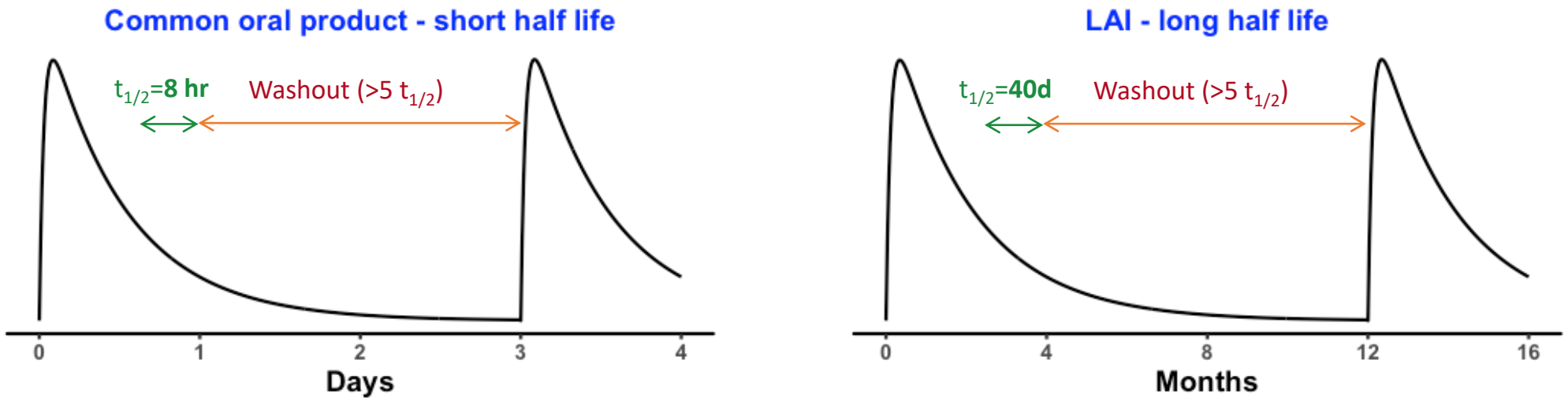
Fig. 5. Median and 90% non-parametric CI for NCA-derived GMRs for the different designs (*Seq* sequential, *Par1* parallel 1, *Par2* parallel 2), the different PK scenarios (original, high CL IIV, and high IE IIV), and the different interaction effect scenarios (induction, no interaction, and inhibition). True impact of the simulated DDI shown as the *light blue line*

Problems for standard BE studies

- Drugs with long half-life (e.g. LAI)
  - Long-term BE trial
  - Crossover steady-state studies may be needed in patients
- Sparse data
- Highly variable drugs (HVD)
  - BE design needs 3- or 4-way crossover study
  - Estimation of between occasion variability can be biased/imprecise
- Steady-state BE studies
  - Methods for establishing steady state can be inaccurate
- Other
  - Designs can be inefficient
  - Special formulations, e.g. local drug product needs clinical endpoint BE study
  - …

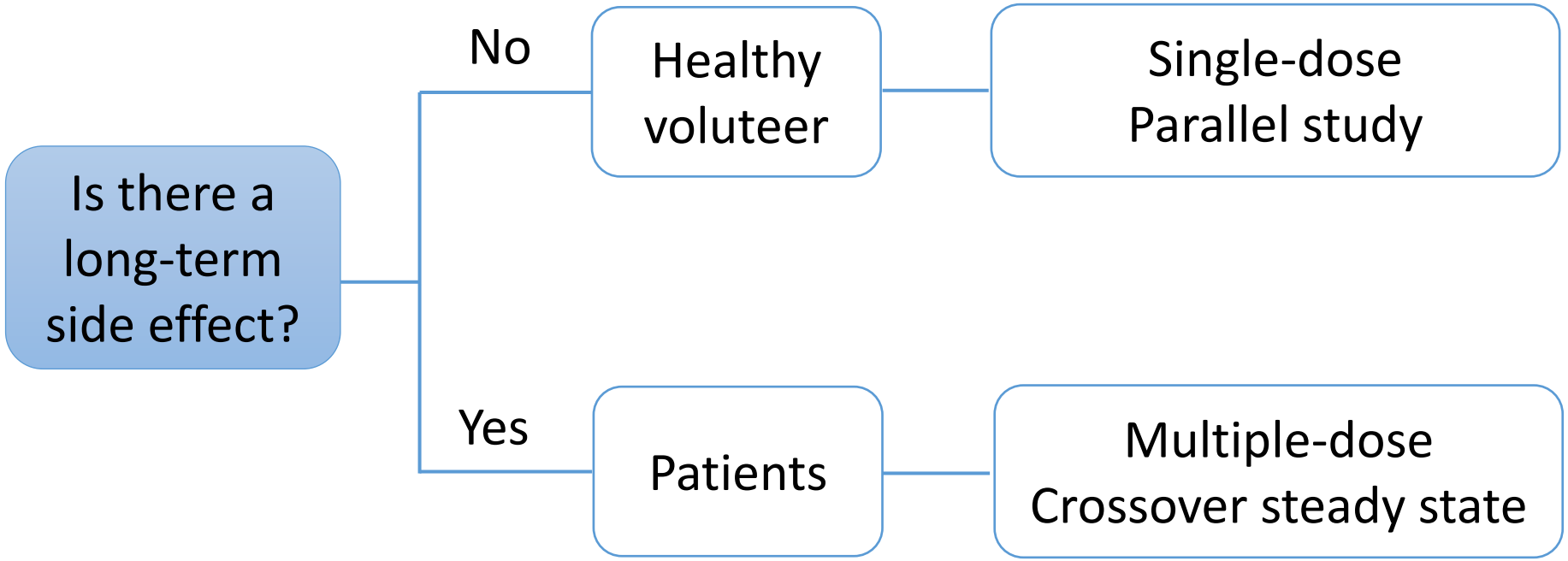
Challenges of performing BE studies for LAI - Long half-life ($t_{1/2}$)

Single dose crossover BE study



It is not practical to perform a single-dose crossover BE study for LAI.

Two types of BE study designs for LAI



- **Contraceptive**
  - Medroxyprogesterone acetate
- **To treat alcohol/drug dependence**
  - Naltrexone

- **Antipsychotic**
  - Paliperidone palmitate
  - Aripiprazole
  - Risperidone
  - Olanzapine Pamoate

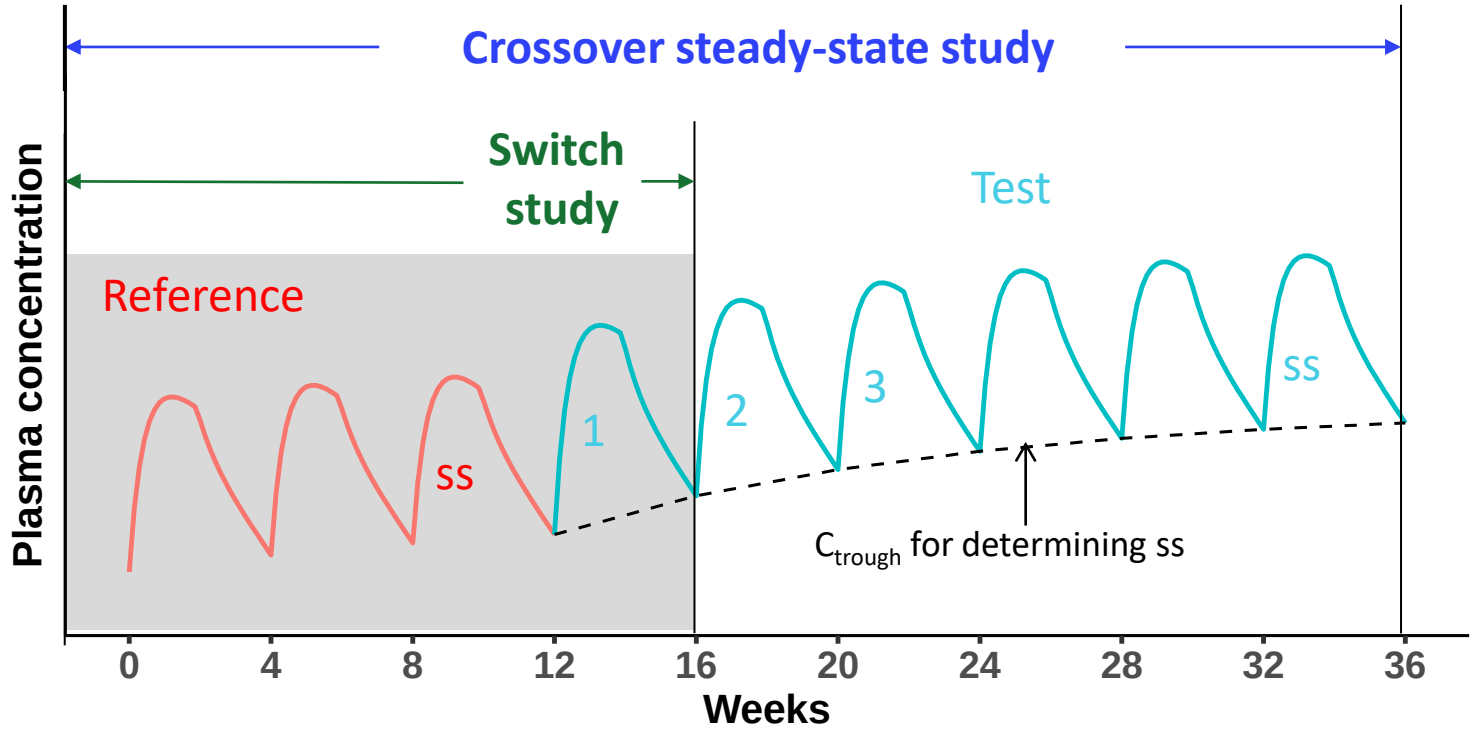
Long $t_{1/2}$ → Dropout, Increased variation

How modeling can help with BE problems and method improvements

UPPSALA UNIVERSITET

- Model-informed BE approach
  - Use pharmacometric models to understand and optimize the operating characteristics of standard BE methods and designs
- Model-integrated BE analysis
- Optimal design approaches for better BE study design

One solution to reduce BE study duration for LAI: use a switch study instead of crossover steady-state

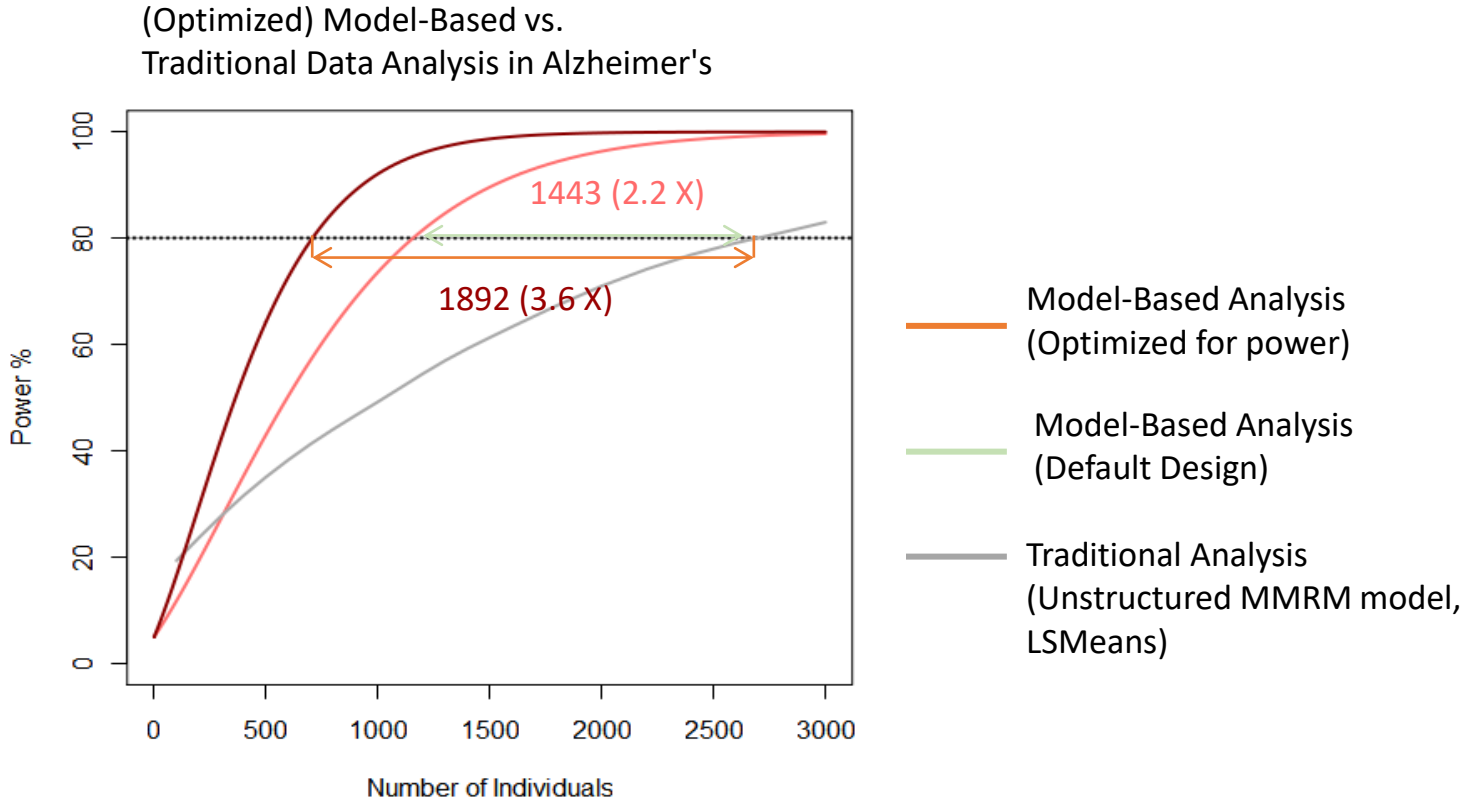


Model-assisted approach: Use models to simulate studies to determine new BE limits.

Model-integrated approach: allows you to separate the superposition of test from reference in first period after switch.

Optimal design approaches for better BE study design

Pharmacometric approaches will typically have **higher power** than standard methods



- Hooker *et al.*, Model-based Trial Optimization for Phase II and III designs in Alzheimer's Disease, ACOP, 2011
- Ueckert *et al.*, Optimizing disease progression study designs for drug effect discrimination, JPKPD, 2013

UPPSALA UNIVERSITET

Previous work

Journal of Pharmacokinetics and Pharmacodynamics, Vol. 31, No. 4, August 2004 (© 2004)

Statistical Issues in a Modeling Approach to Assessing Bioequivalence or PK Similarity with Presence of Sparsely Sampled Subjects

Chuanpu Hu,[1,*] Katy H. P. Moore,[2] Yong H. Kim,[2] and Mark E. Sale[2]

Statistics in Medicine

Research Article

Received 29 April 2010, Accepted 12 April 2011 Published online 26 July 2011 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.4286

Model-based analyses of bioequivalence crossover trials using the stochastic approximation expectation maximisation algorithm

Anne Dubois,[a*†] Marc Lavielle,[b] Sandro Gsteiger,[c] Etienne Pigeolet[c] and France Mentré[a]

Special Issue Paper

Statistics in Medicine

Received 20 October 2010, Accepted 4 August 2011 Published online 3 October 2011 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.4390

Design evaluation and optimisation in crossover pharmacokinetic studies analysed by nonlinear mixed effects models

Thu Thuy Nguyen,[*†] Caroline Bazzoli and France Mentré

Standard analysis

$$\log(\text{Cmax}_{ik}) = \theta_{Cmax} + \beta_{Cmax,TRT}TRT_{ik} + \beta_{Cmax,SEQ}SEQ_i + \beta_{Cmax,PER}PER_k + \eta_{Cmax,i} + \varepsilon_{Cmax,ik}$$

$$\log(\text{AUC}_{\infty,ik}) = \theta_{\text{AUC}\infty} + \beta_{\text{AUC}\infty,TRT}TRT_{ik} + \beta_{\text{AUC}\infty,SEQ}SEQ_i + \beta_{\text{AUC}\infty,PER}PER_k + \eta_{\text{AUC}\infty,i} + \varepsilon_{\text{AUC}\infty,ik}$$

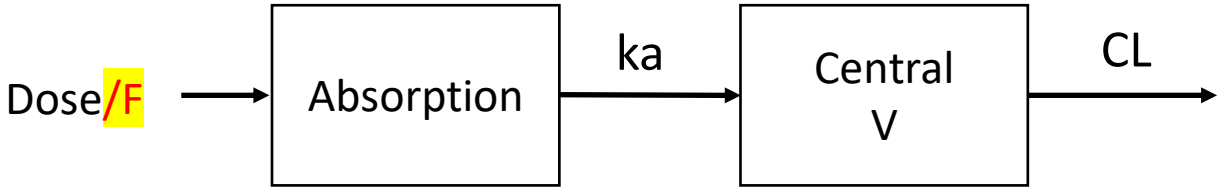
$$\log(\text{AUC}_{tlast,ik}) = \theta_{\text{AUC}t} + \beta_{\text{AUC}t,TRT}TRT_{ik} + \beta_{\text{AUC}t,SEQ}SEQ_i + \beta_{\text{AUC}t,PER}PER_k + \eta_{\text{AUC}t,i} + \varepsilon_{\text{AUC}t,ik}$$

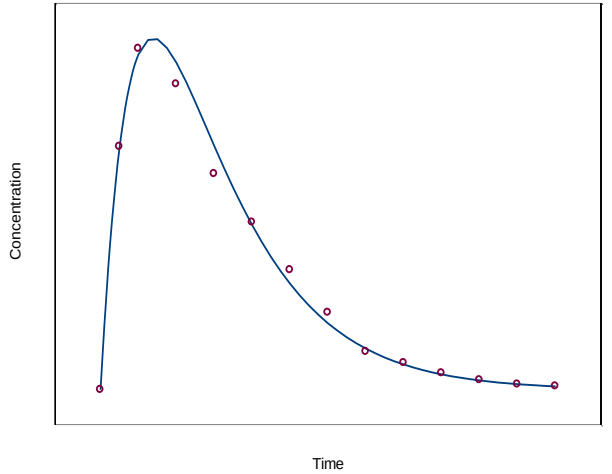
H0 (not bioequivalent) is rejected if:

$$\log(0.8) < CI_{90\%}(\beta_{Cmax,TRT}) < \log(1.25)$$
$$\log(0.8) < CI_{90\%}(\beta_{\text{AUC}\infty,TRT}) < \log(1.25)$$
$$\log(0.8) < CI_{90\%}(\beta_{\text{AUC}t,TRT}) < \log(1.25)$$

Equivalent to testing if the geometric mean ratios of Cmax, AUC_{∞}, AUC_{tlast} fall within 80% - 125%

Model additions used for BE analysis





$$CL_{ik} = \theta_{CL} \cdot e^{\eta_{CL}+\kappa_{CL}}$$

$$V_{ik} = \theta_{V} \cdot e^{\eta_{V}+\kappa_{V}}$$

$$\mathrm{k}a_{ik} = \theta_{ka} \cdot e^{\eta_{ka}+\kappa_{ka}} \cdot \beta_{ka,TRT} \cdot \beta_{ka,SEQ} \cdot \beta_{ka,PER}$$

$$F = 1 \cdot \beta_{F,TRT} \cdot \beta_{F,SEQ} \cdot \beta_{F,PER}$$

$$y_{ijk} = f(\Theta)+\mathrm{h}(\Theta, \varepsilon_{ij})$$

$\beta_{ka,TRT}$: treatment effect on ka (test/ref)

$\beta_{ka,SEQ}$: sequence effect on ka

$\beta_{ka,PER}$: period effect on ka

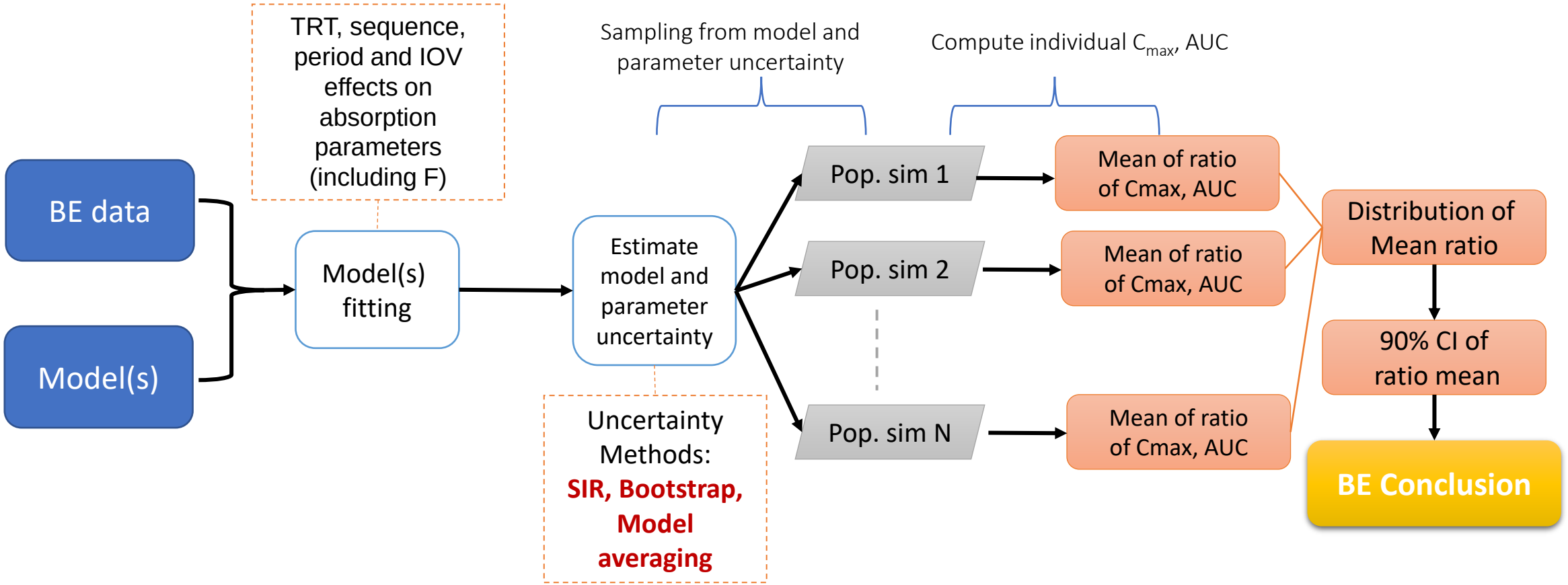
$\beta_{F,TRT}$: treatment effect on in F (test/ref)

$\beta_{F,SEQ}$: sequence effect on F

$\beta_{F,PER}$: period effect on F

Note: if IOV not present in model then it should be added/investigated (for crossover designs)

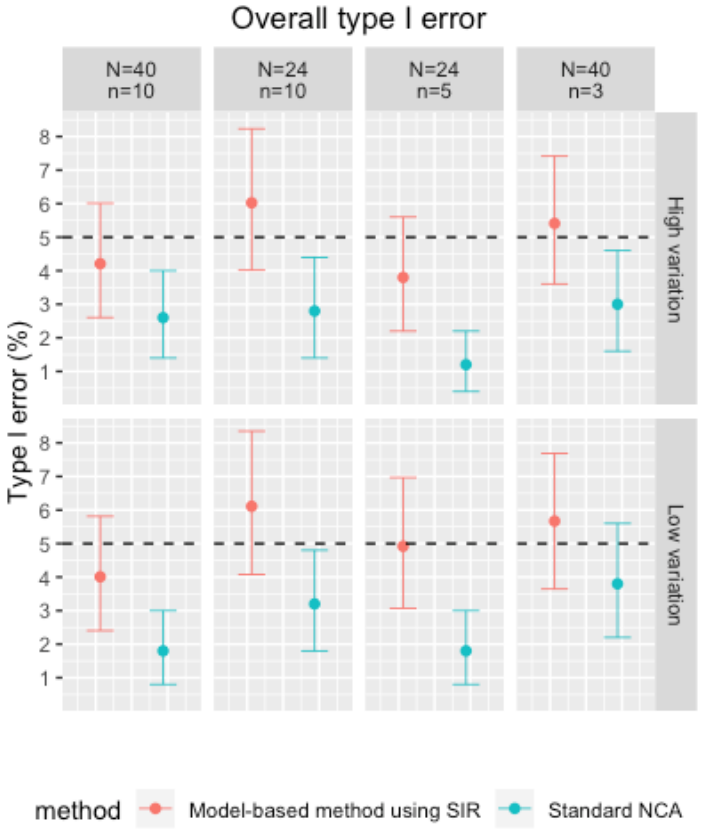
Our developed model-integrated BE method

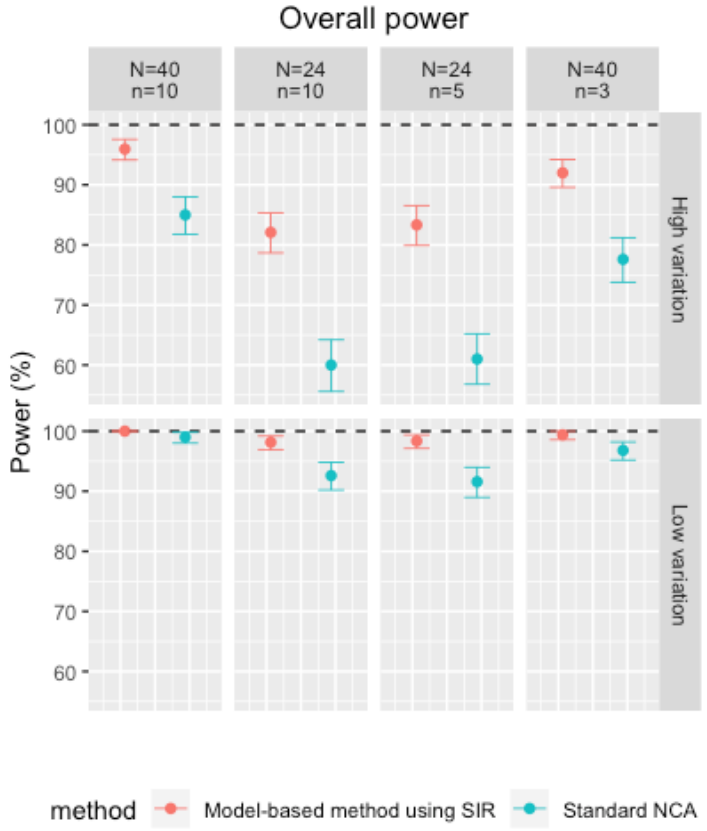


Modeling → **Uncertainty estimation** → **Simulation** → **Conclusion**

- ACOP 2019, Andrew Hooker, Development and comparison of model-based bioequivalence analysis methods on sparse data.
- ACOP 2019, Xiaomei Chen, Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches.
- ACCP 2019, Mats Karlsson, Development of model-informed bioequivalence evaluation strategies for long-acting injectable products (LAI).

Type I error is controlled for this model-integrated BE method and power is higher (especially with high variation and sparser data)





- **ACOP 2019, Andrew Hooker, Development and comparison of model-based bioequivalence analysis methods on sparse data.**
- **ACOP 2019, Xiaomei Chen, Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches.**

Situations where no single PK model may be appropriate for BE analysis

- No prior model
- Identifiability issues
- If IOV not present in model and should be added/investigated

Model Averaging

Avoid estimation/selection bias and overestimation of precision

J Pharmacokinet Pharmacodyn (2017) 44:581–597
DOI 10.1007/s10928-017-9550-0

ORIGINAL PAPER

Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection

Yasunori Aoki[1,2] · Daniel Röshammar[3,4] · Bengt Hamrén[3] · Andrew C. Hooker[1]

Received: 30 June 2016 | Revised: 22 May 2017 | Accepted: 11 June 2017
DOI: 10.1002/sim.7395

RESEARCH ARTICLE

WILEY Statistics in Medicine

Model averaging for robust assessment of QT prolongation by concentration-response analysis

A.G. Dosne[1] | M. Bergstrand[1] | M.O. Karlsson[1] | D. Renard[2] | G. Heimann[2]

The AAPS Journal (2018) 20: 56
DOI: 10.1208/s12248-018-0205-x

Research Article

Comparison of Model Averaging and Model Selection in Dose Finding Trials Analyzed by Nonlinear Mixed Effect Models

Simon Buatois,[1,2,3,5] Sebastian Ueckert,[4] Nicolas Frey,[1] Sylvie Retout,[1,2] and France Mentré[3]

Model qualification

- Models should be identifiable given the study design (test using optimal design software, like PopED). https://andrewhooker.github.io/PopED/

- Use the models to predict (simulate) summary PK metrics (e.g. geometric mean of C_{max} and AUC_{last}). Simulations should, at the least, predict data that results in similar metrics compared to the real data.

Non-compartmental analysis posterior predictive check (NCAPPC)

COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 127 (2016) 83–93

ELSEVIER

journal homepage: www.intl.elsevierhealth.com/journals/cmpb

A diagnostic tool for population models using non-compartmental analysis: The *ncappc* package for R

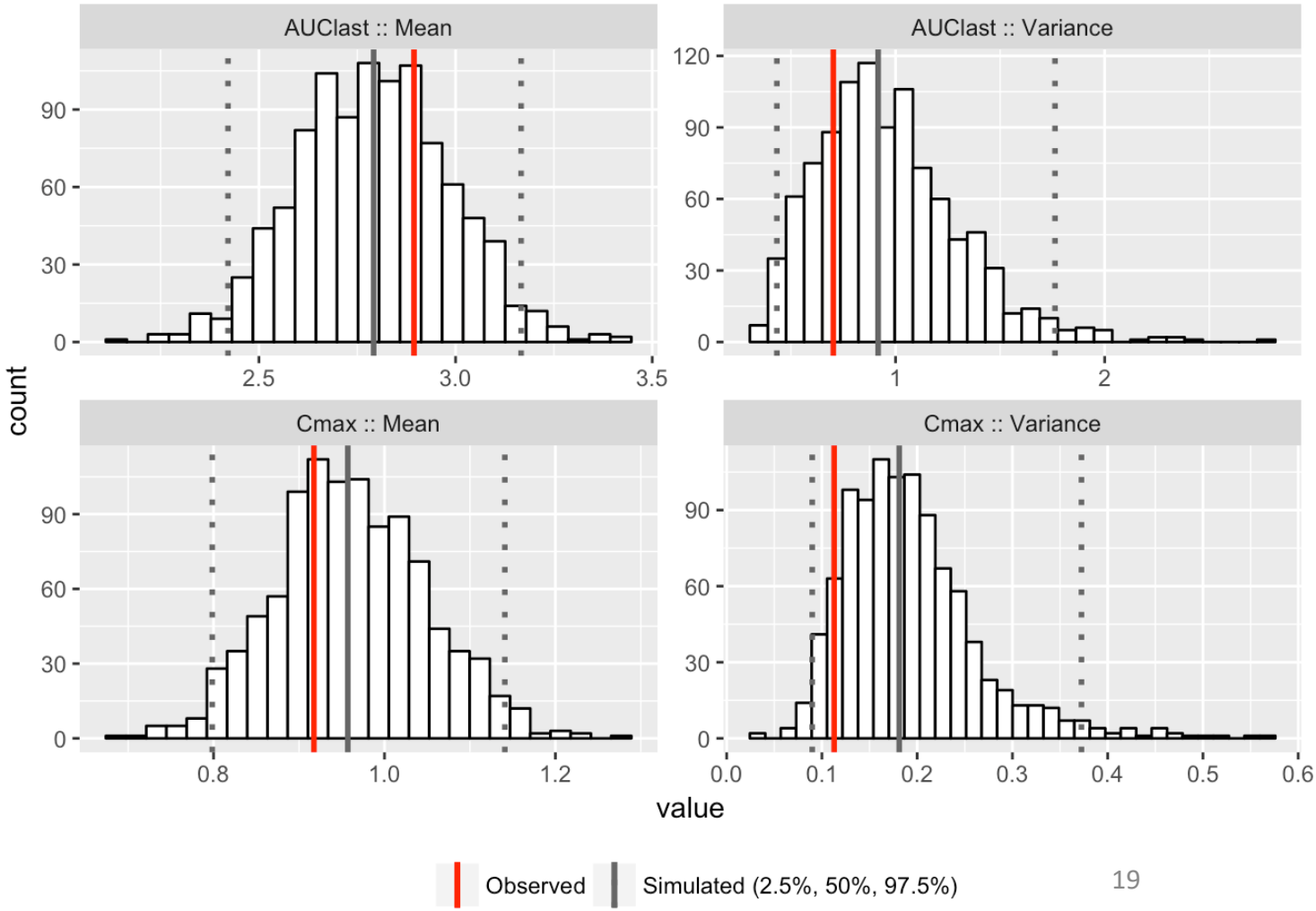
Chayan Acharya[a,*], *Andrew C. Hooker*[a], *Gülbeyaz Yıldız Türkyılmaz*[a,b], *Siv Jönsson*[a], *Mats O. Karlsson*[a]

[a] *Department of Pharmaceutical Biosciences, Uppsala University, P.O. Box 591, SE-751 24 Uppsala, Sweden*
[b] *Ege University, Faculty of Pharmacy, Department of Biopharmaceutics and Pharmacokinetics, 35100 İzmir, Turkey*

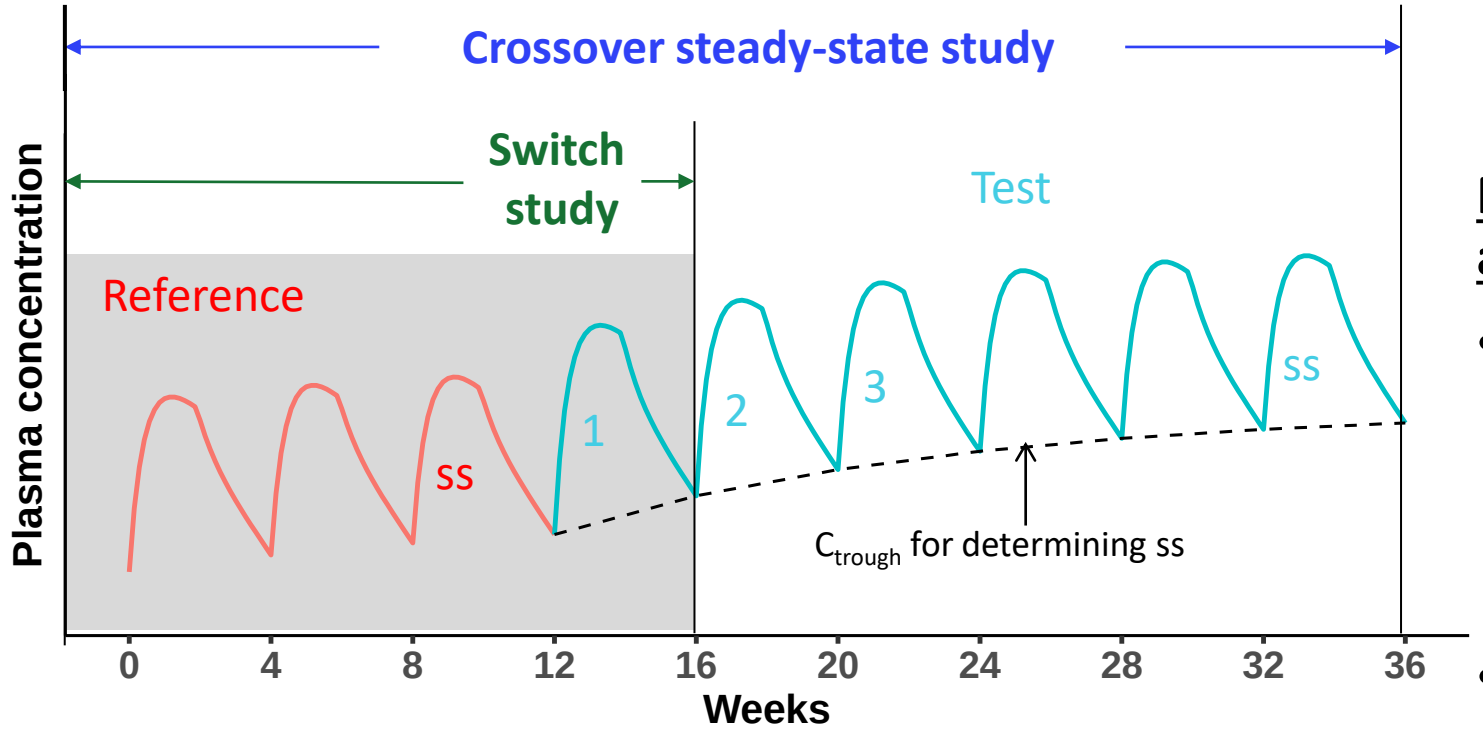
- available on CRAN https://cran.r-project.org/package=ncappc

Comparison of the population mean and variance of NCA metrics

- Histogram of the simulated population mean and variance of the NCA metrics.
- Uncertainty in simulations (model and parameter uncertainty) Possible with rich and sparse data.
- Adjusted confidence intervals so that 5% of all simulations lie outside intervals in all tests.



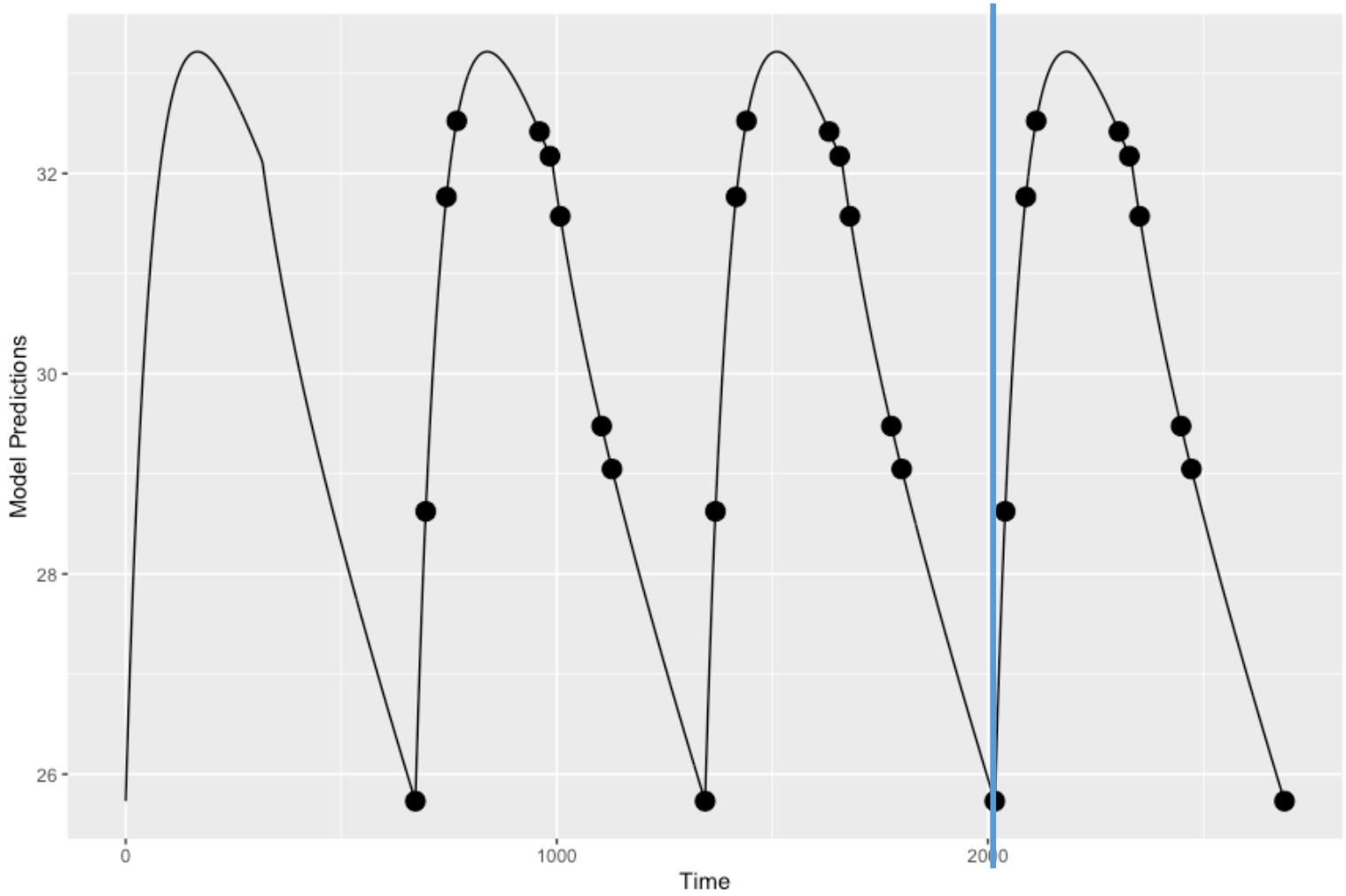
One solution to reduce BE study duration for LAI: use a switch study instead of crossover steady-state



Model-assisted and Model-integrated approaches:

- Research shows that the approach controls type 1 error, but will require more individuals in the study (compared to crossover steady-state studies using NCA metrics)
- Model-integrated more powerful than model-assisted approaches.

Even more innovative designs



Model-integrated OD study
n ~ 10% less for 80% power on AUC compared to standard switch study.

Biostatistics (2020) **0**, 0, *pp.* 1–14
doi:10.1093/biostatistics/kxaa026

Efficient model-based bioequivalence testing

KATHRIN MÖLLENHOFF*

Department of Mathematics, Ruhr-Universität Bochum and Institute of Medical Statistics and Computational Biology, Faculty of Medicine, University of Cologne, Cologne, Germany

kathrin.moellenhoff@rub.de

FLORENCE LOINGEVILLE

Faculty of Pharmacy, University of Lille, EA 2694: Public health: Epidemiology and Healthcare Quality, 59000 Lille, France

JULIE BERTRAND, THU THUY NGUYEN

IAME INSERM, Université de Paris, 75018 Paris, France

SATISH SHARAN, LIANG ZHAO, LANYAN FANG

Division of Quantitative Methods and Modeling, Office of Research Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, USA

GUOYING SUN, STELLA GROSSER

Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, USA

FRANCE MENTRÉ

IAME INSERM, Université de Paris, 75018 Paris, France

HOLGER DETTE

Department of Mathematics, Ruhr-Universität Bochum, Germany

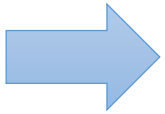
Conclusion

Model-integrated approach

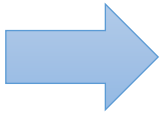
Use M&S in BE analysis procedure

Model-informed approach

Modify NCA-based BE methods



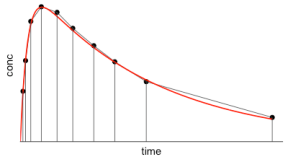
Reduce sample size
and/or
Reduce study duration



Make BE studies more feasible
(especially in currently challenging situations like LAI)

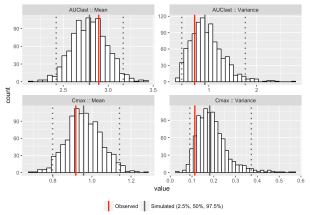
Software

bemod



- Model based BE testing
- To be released on CRAN

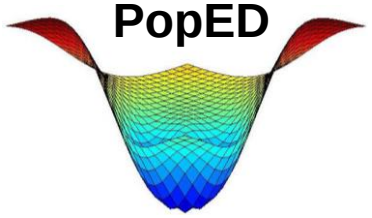
ncappc



- NCA Calculation and Population PK Model Diagnosis
- https://github.com/UUPharmacometrics/ncappc

PsN 4 Perl speaks NONMEM

- SIR
- Bootstrap
- https://uupharmacometrics.github.io/PsN/



- Optimal experimental design software
- https://andrewhooker.github.io/PopED/

Acknowledgements

Funding from FDA

Contracts: HHSF223201710015C, 75F40119C10018

Colleagues at FDA:

Liang Zhao
Lanyan (Lucy) Fang
Satish Sharan
Mark Donnelly
… Many more!

PM group, Uppsala University