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# Model integrated methods for generic LAI product development and regulatory assessment:

## *current status and future research directions*

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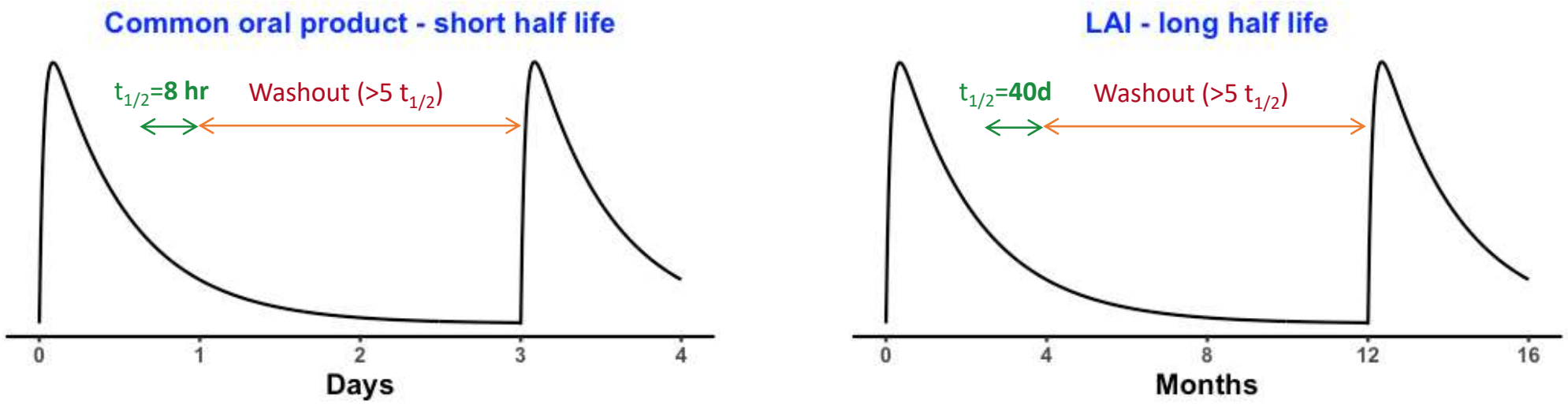
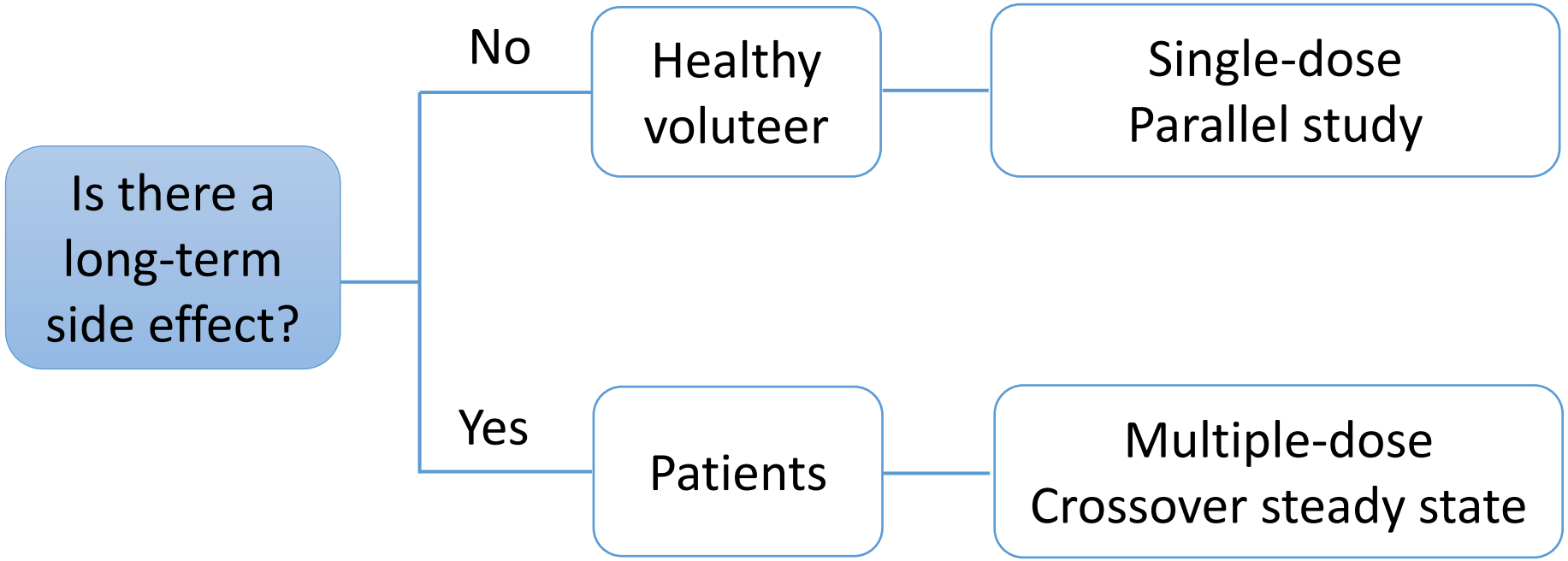
# Challenges of performing BE studies for LAI - Long half-life ($t_{1/2}$)

## 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

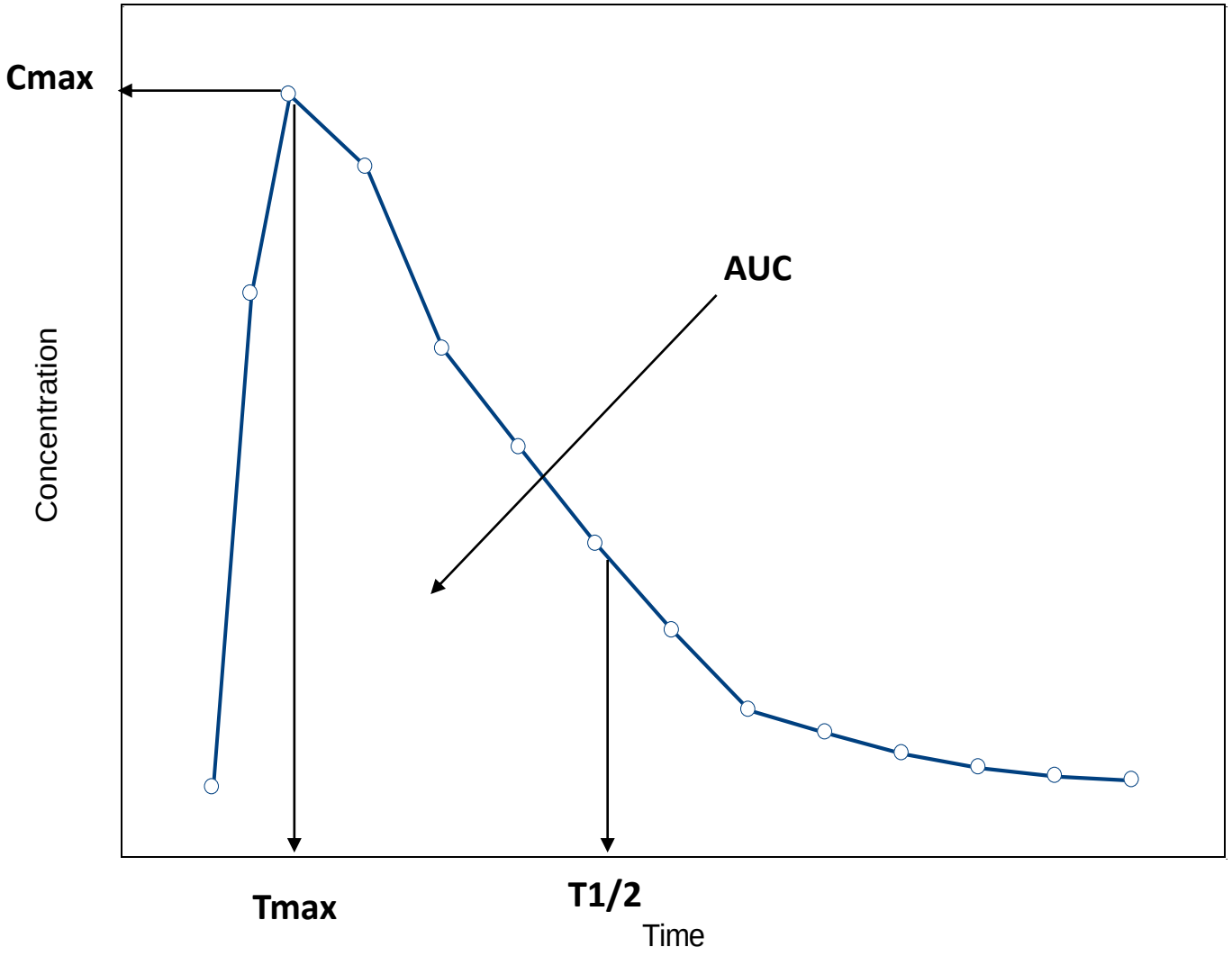



- **Contraceptive**
  - Medroxyprogesterone acetate
- **To treat alcohol/drug dependence**
  - Naltrexone

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

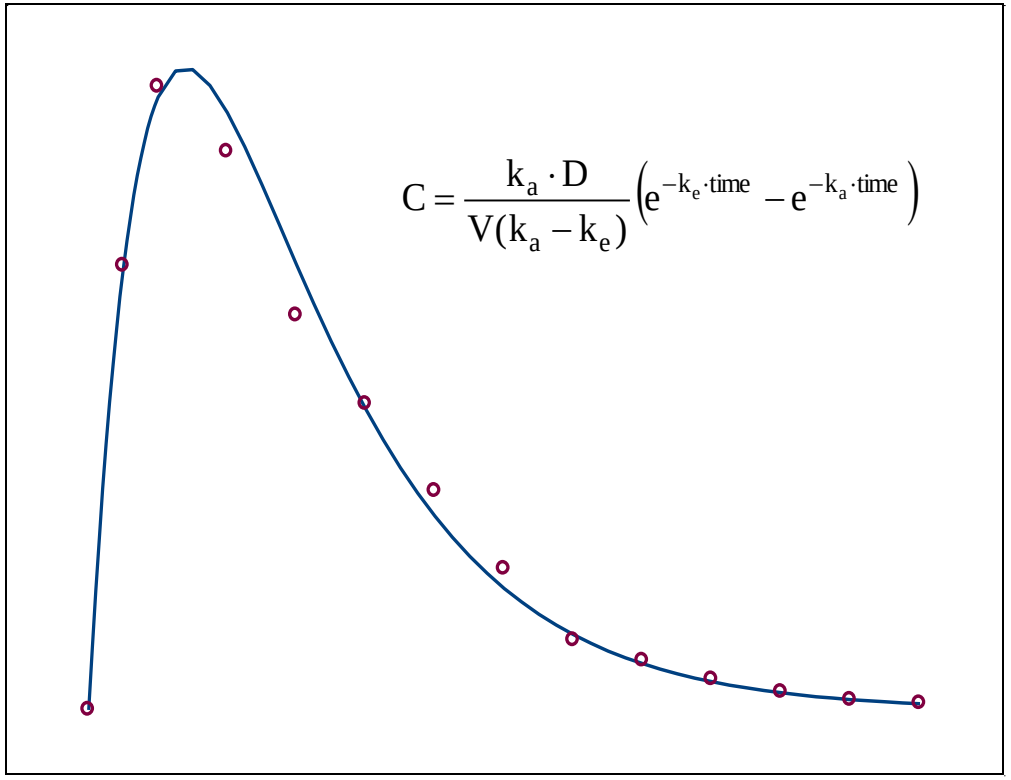
**Long $t_{1/2}$** → Dropout, Increased variation

# Potential problems with standard BE approaches: Problems with NCA calculations



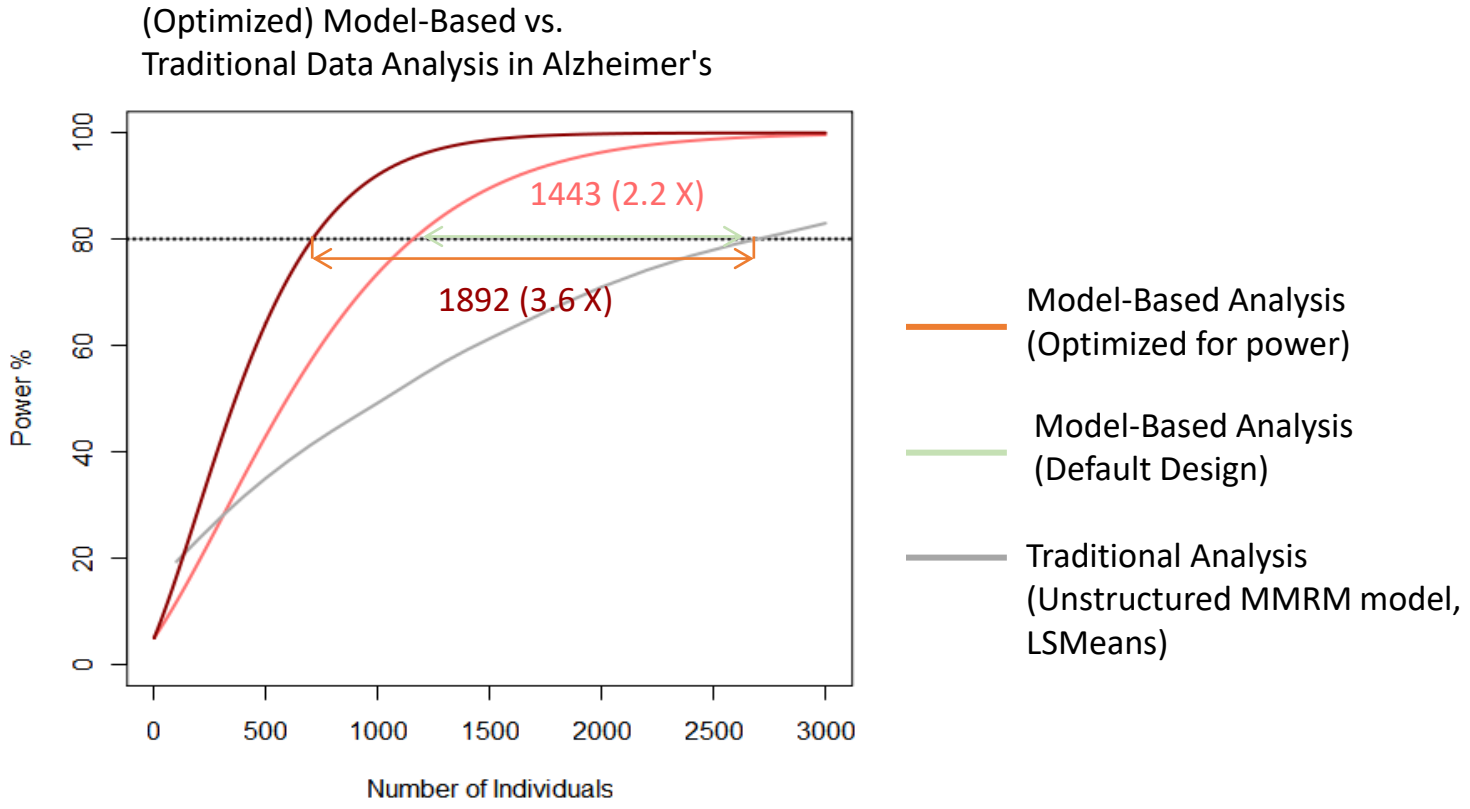

- Sparse data problems
- Assume equal weight for all observations
- Sensitivity to missing data
- Sensitivity to data below the limit of quantification
- Interpolation problems from the last observation to ∞
- Hard to separate variability sources (BSV/IOV/RUV)
- Ad hoc design of sampling times

# Population (NLME) model based approaches in general can handle these problems




- Built to handle sparse data and works well with parallel-group studies
- Higher power to identify differences/similarity
  - Can optimize design (for even higher power)
- Can better separate different types of variation
  - Between subject variation (BSV) on PK parameters
  - Occasion variation (IOV) on PK parameters
  - Residual error on concentration
- NCA Problems solved:
  - assumption about equal weight of all observations
  - sensitivity to missing data
  - sensitivity to data below the limit of quantification
  - interpolation problems from the last observation to ∞
  - Sparse data problems

# 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

# 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

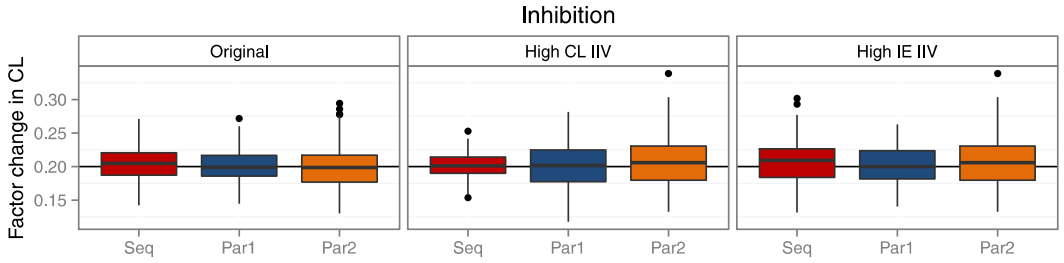



**Fig. 4.** Box plots of model-based estimation of interaction effect (factor change in CL) for the different designs (*Seq* sequential, *Par1* parallel 1, *Par2* parallel 2), the different PK scenarios (original, high CL IIV, and high IE IIV), and the different interaction effect scenarios (induction,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

## NCA analysis

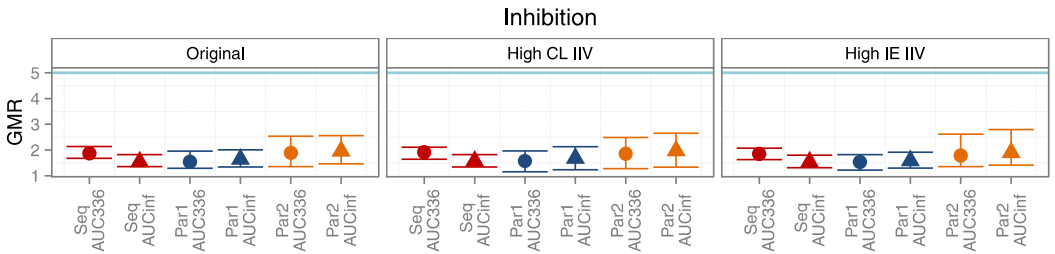
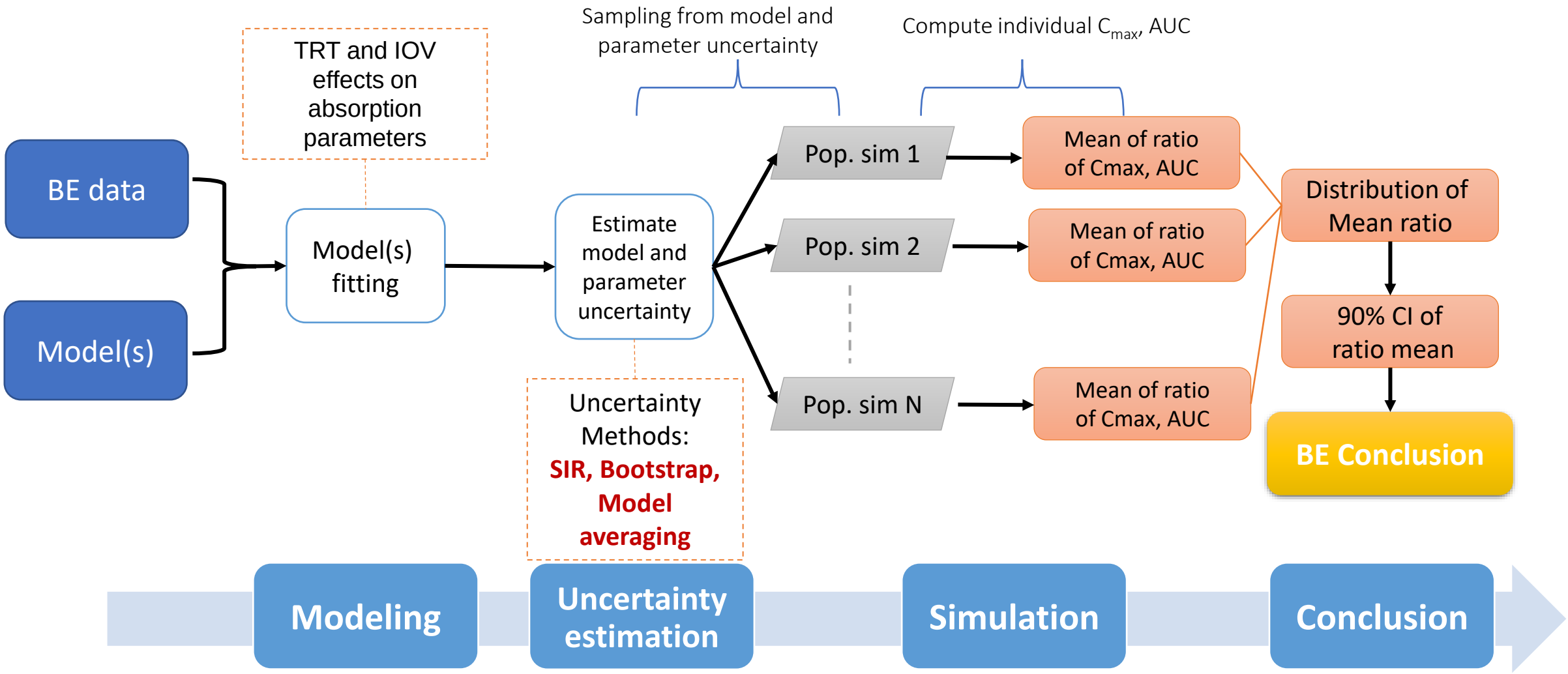



**Fig. 5.** Median and 90% non-parametric CI for NCA-derived GMRs for the different designs (*Seq* sequential, *Par1* parallel 1, *Par2* parallel 2), the different PK scenarios (original, high CL IIV, and high IE IIV), and the different interaction effect scenarios (induction, no interaction, and inhibition).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

# Our developed model-integrated BE method




- 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
- Can not assume true model
- Identifiability issues
- Avoid estimation/selection bias and overestimation of precision

Model Averaging

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]

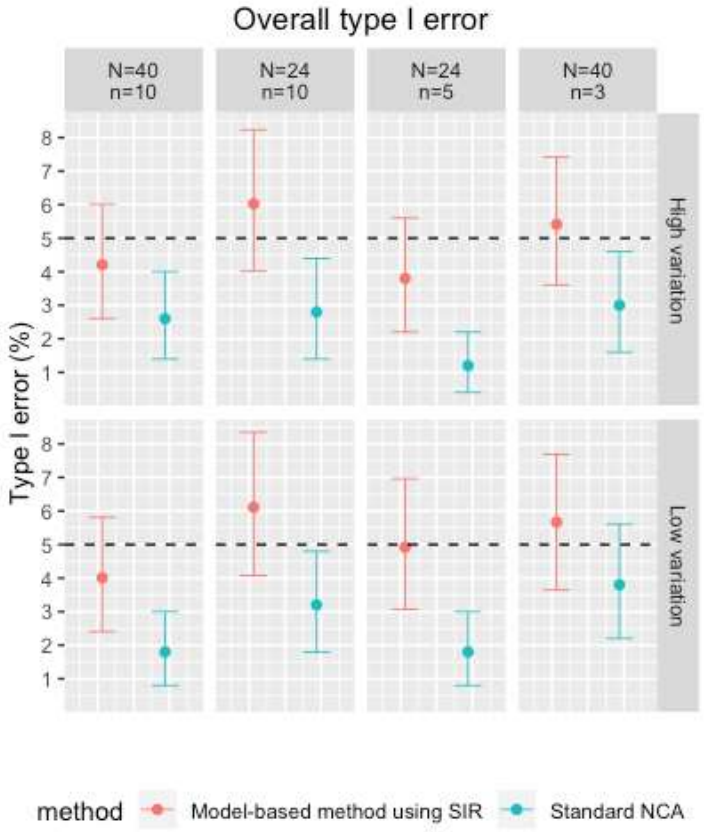
*The AAPS Journal (2018) 20: 56*
DOI: 10.1208/s12248-018-0205-x

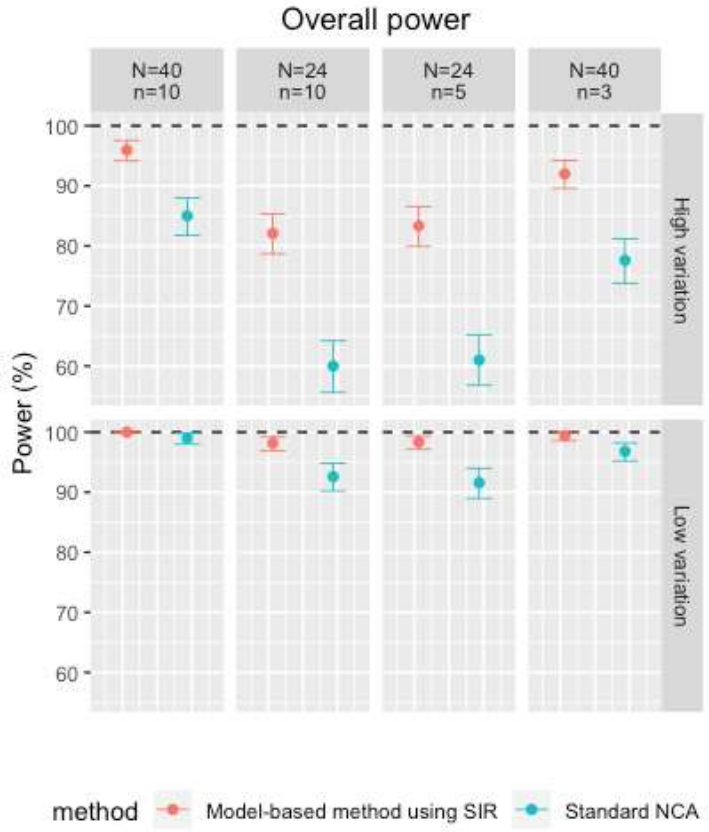
*Research Article*

**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]

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

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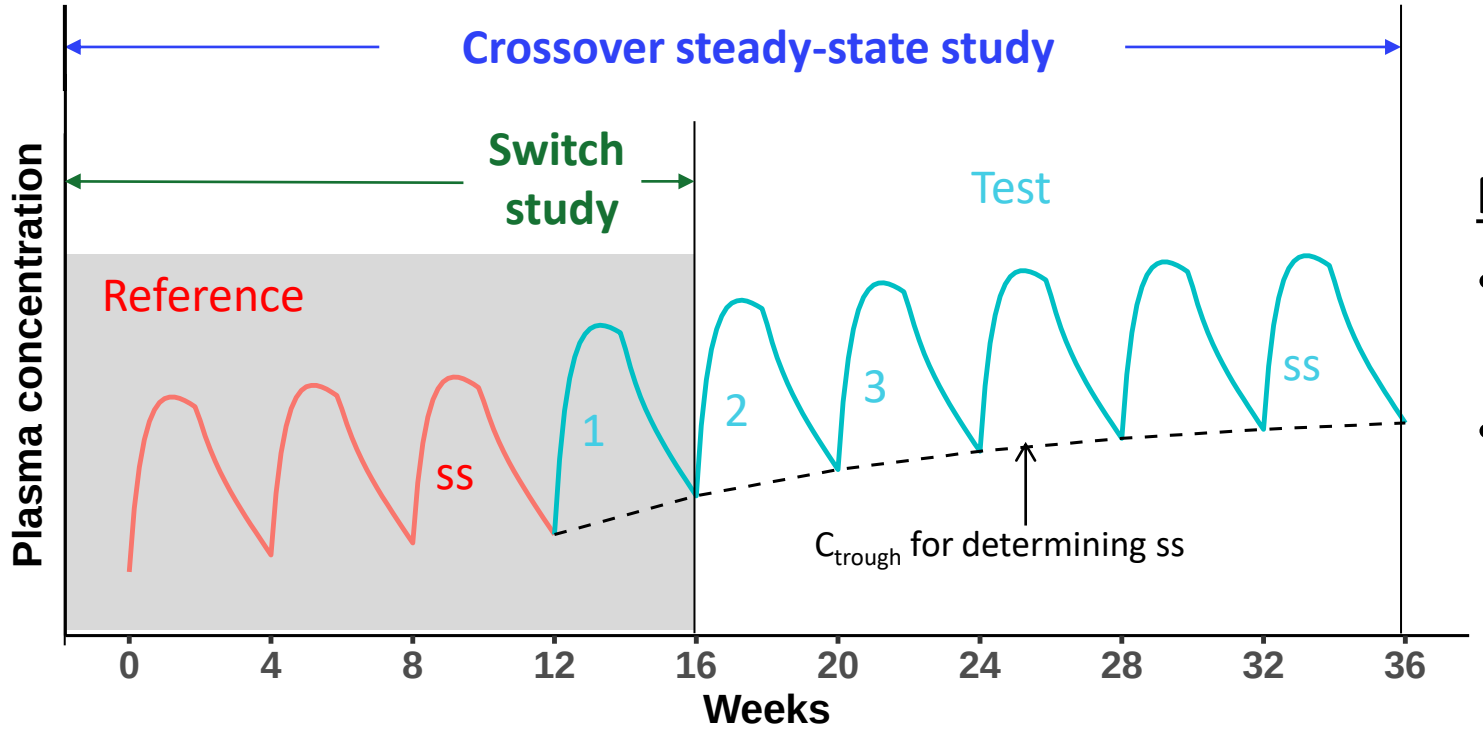
- **ACOP 2019, Xiaomei Chen, Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches.**

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

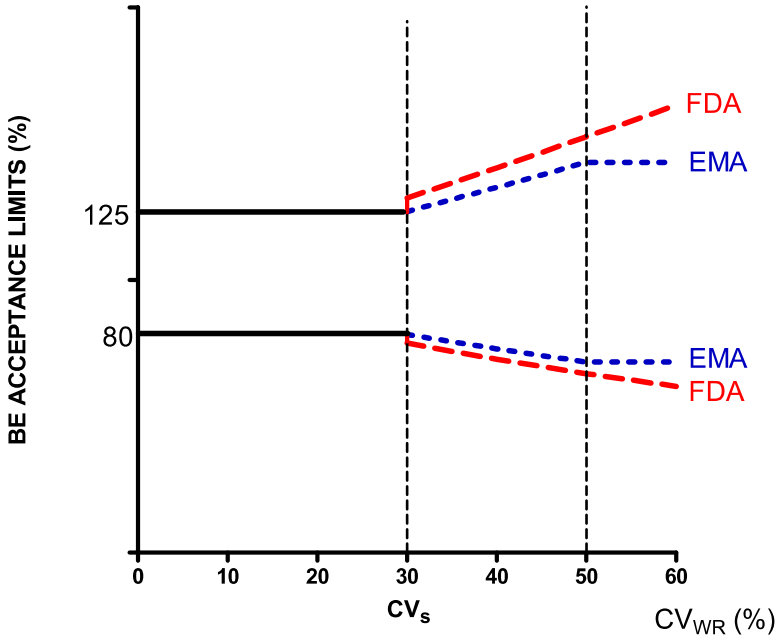



**Model-integrated approach:**

- allows you to separate test from reference in first period after switch.
- Research shows that the approach controls type 1 error, but will require more individuals in the study (compared to crossover steady-state)

# BE for LAI highly variable drugs (HVD)

- RSABE: when IOV of the reference product is > 30% CV




- FDA draft guidance on Progesterone, 2011
- Verbeeck, Musuamba, 2012
- AAPS J. 2012 Dec; 14(4): 915–924, BM Davit, et.al Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration

**Standard reference-scaled average bioequivalence (RSABE) studies**

- Study design
  - 4-way study with sequences of (TRTR, RTRT)
  - 3-way study with sequences of (TRR, RTR, RRT)

**Model based RSABE**

- Shorter studies?
- Smaller studies?
- Better evaluation of IOV?

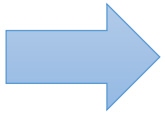
# Conclusion

**Model-integrated approach**

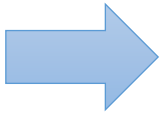
Use M&S in BE analysis procedure

**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)

# Topics for further investigation

- Other innovative BE study designs for LAI using model-integrated methods
  - Incomplete washout designs for highly variable drugs
  - Optimal designs
  - Adaptive optimal (response adaptive) designs?
- Model-integrated improvements
  - Uncertainty in the weights for model averaging
  - How to build models? Which models to include?
- Model informed methods
  - Use the model to asses when SS will be reached
  - Fixed covariates in the standard approach based on NLME model