

A novel model-integrated design for bioequivalence of long acting injectables

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BACKGROUND INFORMATION

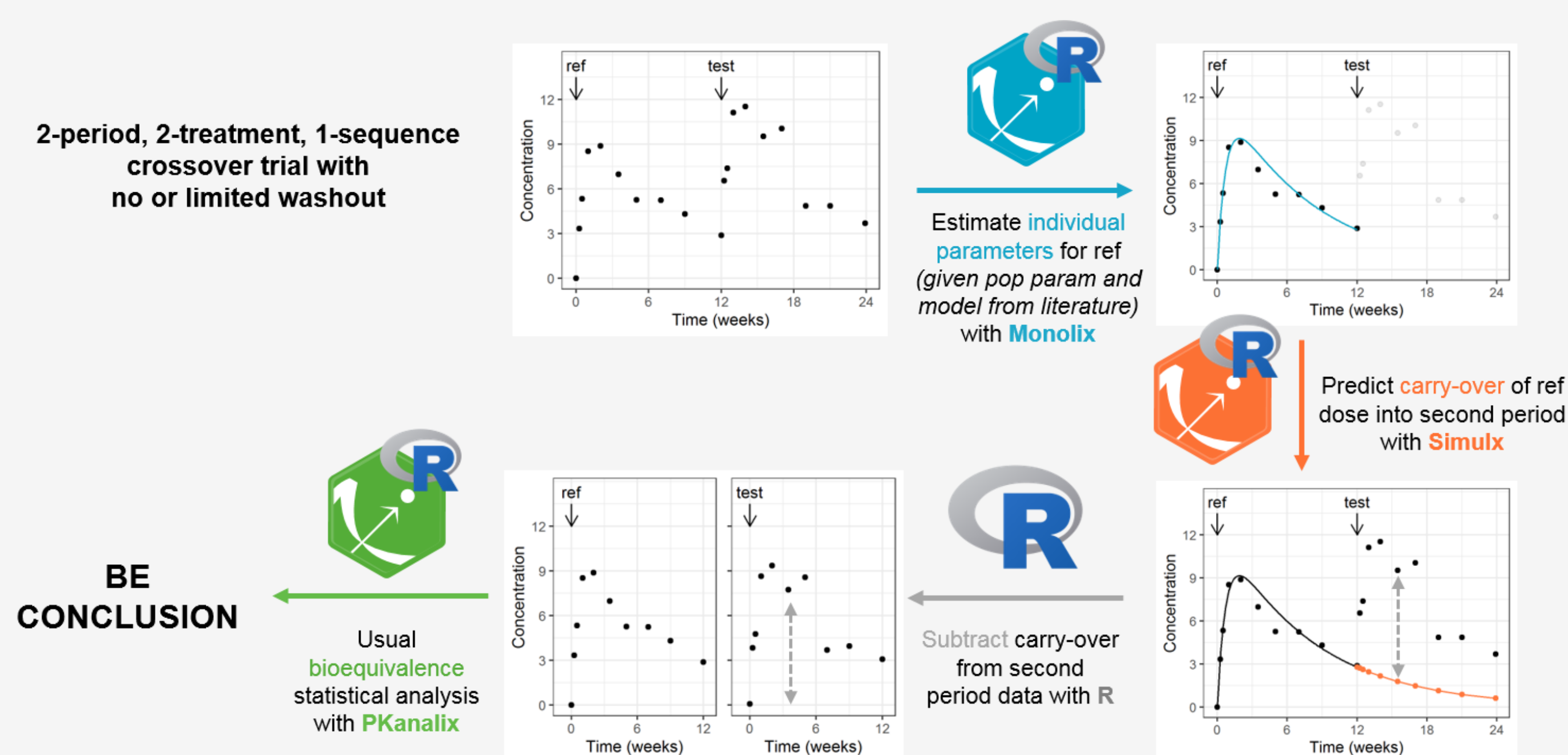
Long-acting injectables (LAI) have been developed to offer prolonged drug release and thus improve treatment adherence. Approximately 30 LAI drug products are currently approved by the FDA. However, only one of these has an approved generic formulation. This is because the long terminal half-life and high inter-individual variability result in risky bioequivalence (BE) trials with long durations and low power.

We propose a novel BE design combined with a model-integrated approach to reduce the duration of bioequivalence trials for LAIs.

Example: for Buprenorphine LAI [1]

- A parallel design would require a sample size of 500 (costly) to achieve 80% power
- A crossover design would require a washout period of at least 1 year (very long)

NOVEL “REDUCED CROSSOVER” BIOEQUIVALENCE DESIGN



The data of the second period takes into account the second dose and the carryover from the first dose and can thus not be directly compared to the data of the first period. Thus, we apply a **model-based correction of the data of the second period**. To do so, **individual parameters are estimated** on the data of the first period (reference formulation, for which a population model is usually available) and used to **predict the carryover concentration into the second period**. The predicted carryover concentration is then **subtracted from the second period data** before **usual BE analysis**.

Requirements:

- Linear PK (superposition principle needed)
- Single dose design (i.e non-toxic drug given to healthy volunteers)

VALIDATION OF THE PROPOSED REDUCED CROSSOVER DESIGN

Does the proposed model-integrated design “work”?

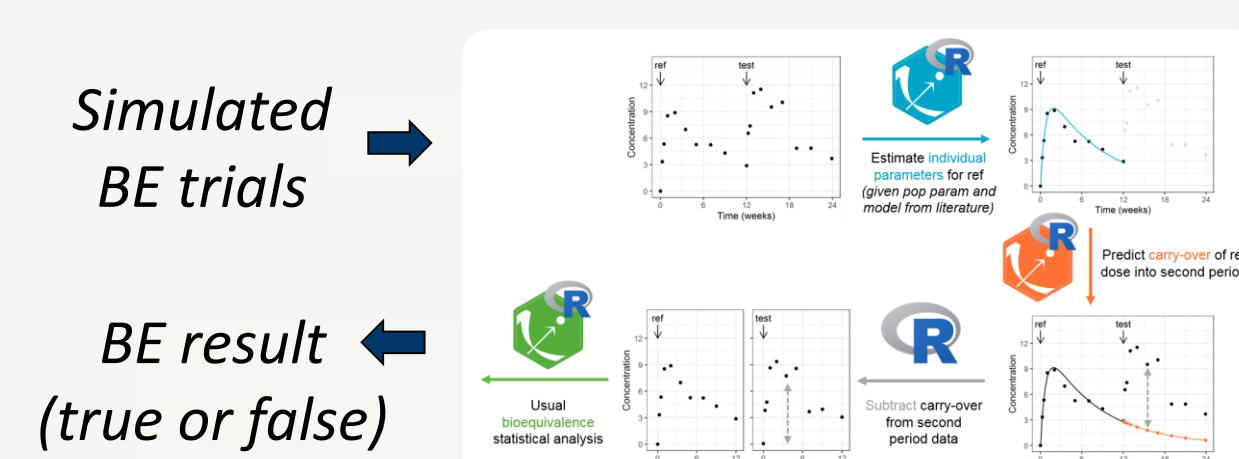
- Do we achieve a **sufficient power with a reasonable number of individuals** (and reasonable study duration)?
- And at the same time do we have a properly **controlled type I error**?

Proposed validation procedure (exemplified on Buprenorphine LAI):

1) Simulate BE reduced crossover trials using model and pop param from literature [1]

- o For several relative bioavailabilities (i.e true ratios between test and ref for NCA param.)
- o For several inter-dose intervals
- o For several number of individuals
- o For many replicates

2) Apply proposed analysis procedure for each simulated trial



3) Calculate the power and type I error as:

$$\text{power} = \frac{\# \text{ trials with BE=true}}{\# \text{ trials}}$$

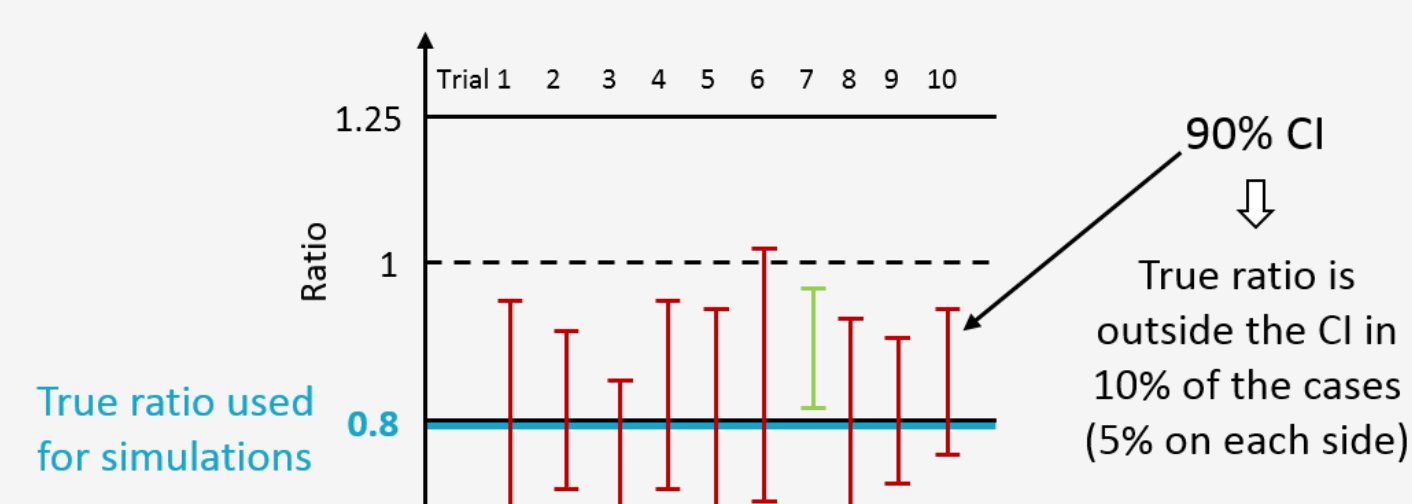
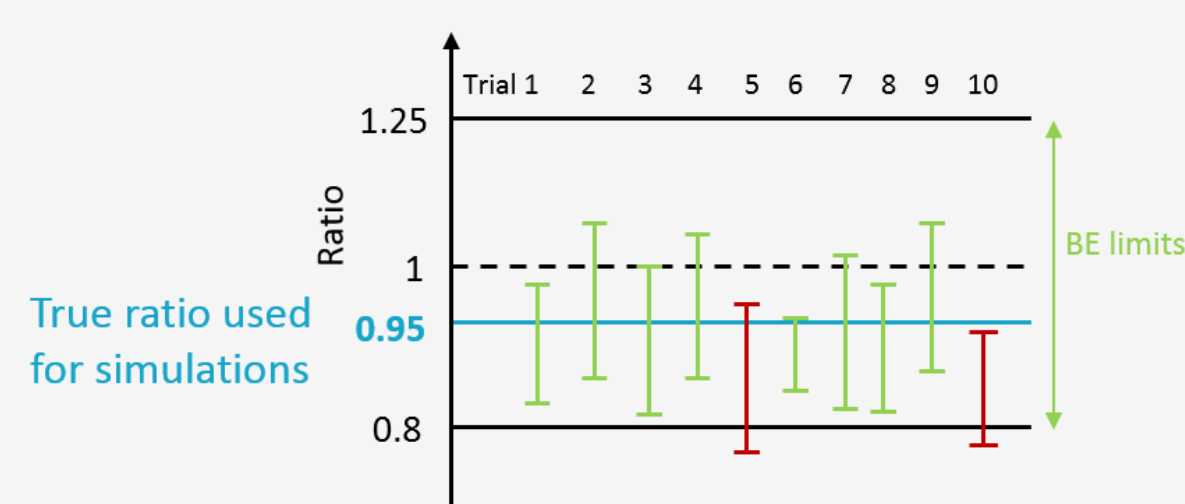
Power: Probability of correctly concluding bioequivalence when formulations are indeed bioequivalent.

Goal: as high as possible

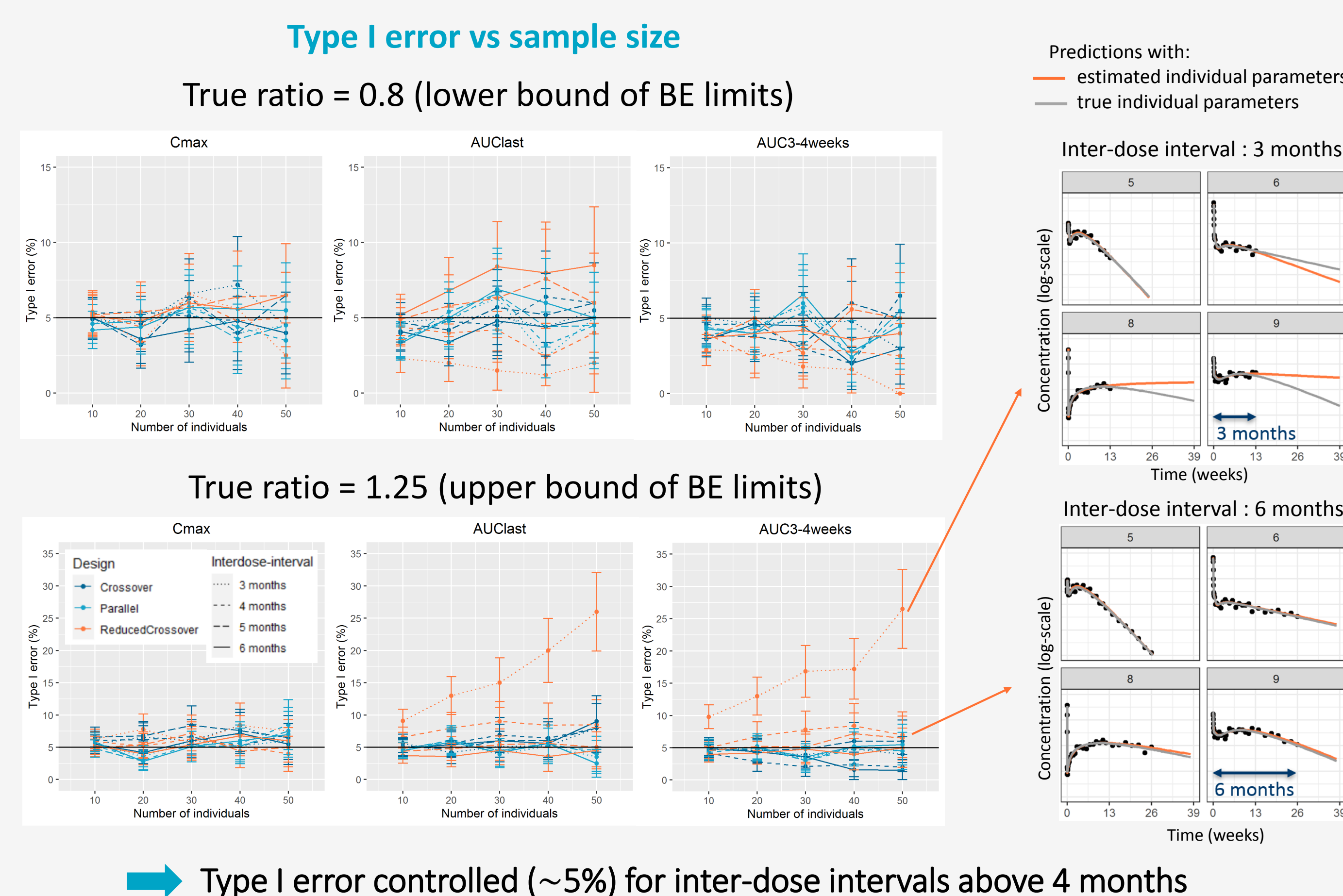
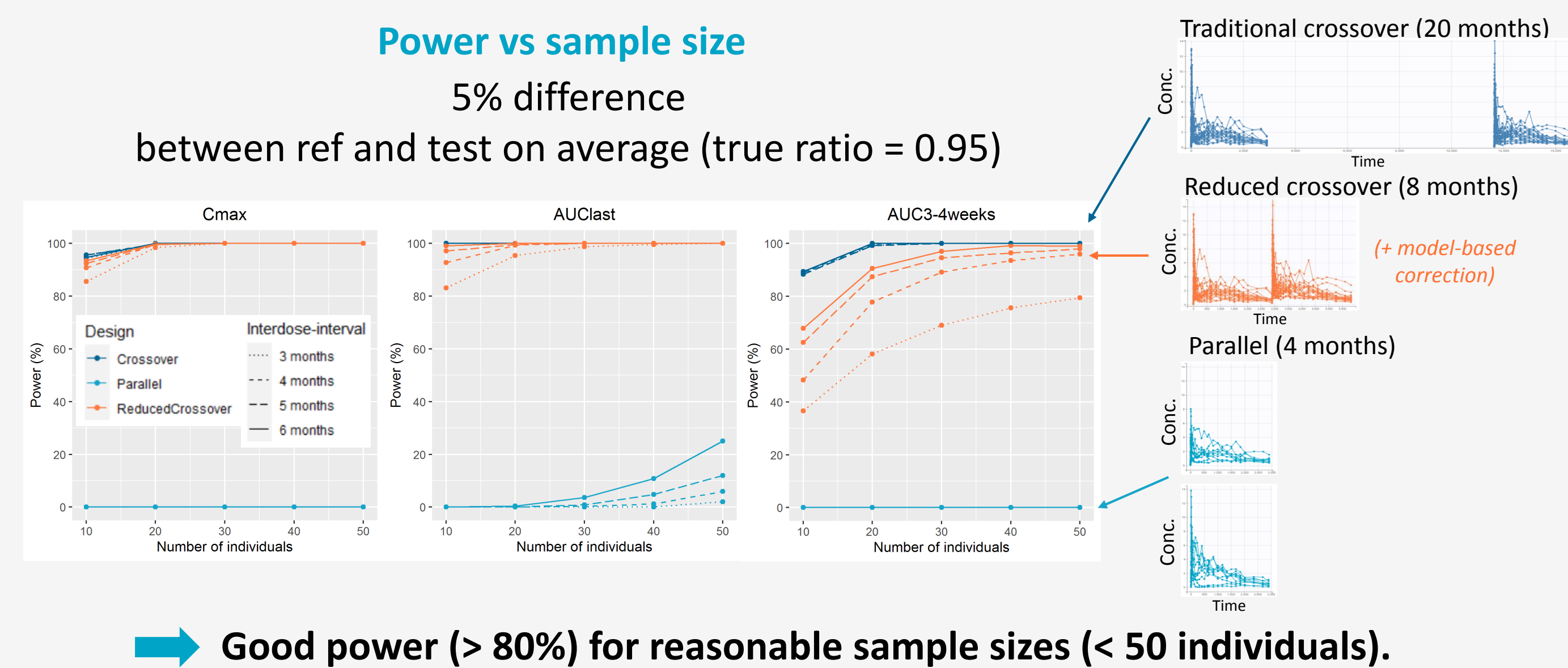
$$\text{type I error} = \frac{\# \text{ trials with BE=true}}{\# \text{ trials}}$$

Type I error: Probability of incorrectly concluding bioequivalence when formulations are not bioequivalent.

Goal: keep under control (5%)



POWER AND TYPE I ERROR RESULTS FOR BUPRENORPHINE



CONCLUSION

With the proposed reduced crossover design with an inter-dose interval of 4 months, a trial bioequivalence trial becomes possible for buprenorphine.

- **Type I error properly controlled**
- **Power > 90%** for AUC3-4weeks, AUClast and Cmax with 30 individuals, assuming a 5% difference between test and ref
- ✓ **Trial duration 3 times shorter** compared to traditional crossover with usual washout
- ✓ **Power much higher** for a given sample size compared to parallel design

The procedure can be applied to any drug product with linear PK and which can be given as a single dose.

IMPLEMENTATION AND USAGE WITH MONOLIXSUITE

- Implemented as two flexible R functions
- Requires a MonolixSuite installation and license (free for academia)
- Uses the R package lixoftConnectors to use Monolix, Simulx and PKanalix from R

Power and type I error assessment (for trial planning)

Input:

- Monolix project with model definition and population parameters for ref
- Sampling times
- Sample size, inter-dose interval, true ratio, and number of replicates

Output:

- Percentage of BE=true over the replicates (i.e power or type I error)

BE analysis (analysis of actual trial data)

Input:

- Monolix project with model definition and population parameters for ref
- Data from BE trial with reduced crossover design

Output:

- CI for each NCA metric
- BE conclusion

REFERENCES

[1] Jones, A. K. *et al.* (2021) 'Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase II and Phase III Trials'

Learn more in this video!

