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Novel Model-Integrated Design for Bioequivalence Studies of LAI Products

A Complete Framework with the MonolixSuite

Géraldine Cellière

Challenges for bioequivalence (BE) trials for LAI

- LAI are designed to require infrequent dose administration to improve patient adherence
- LAI have extended drug release, leading to flip-flop kinetics and long apparent half-lives
- Typical BE designs are impracticable:
  - **Parallel:** high variability between individuals → **low power**

Example LAI: Buprenorphine

Trade Names	Ingredient	Indication	Dose Frequency
ABILIFY MAINTENA KIT	ARIPIPRAZOLE	Schizophrenia; bipolar I disorder	Monthly
ARISTADA	ARIPIPRAZOLE LAUROXIL	Schizophrenia	Monthly, 6 weeks, 2 months
ARISTADA INITIO KIT	ARIPIPRAZOLE LAUROXIL	Schizophrenia	One time
SUBLOCADE	BUPRENORPHINE	Opioid use disorder	Monthly
PROBUPHINE	BUPRENORPHINE HYDROCHLORIDE	Opioid Dependence	one time (6 months)
CABENUVA KIT	CABOTEGRAVIR; RILPIVIRINE	HIV-1 treatment	Monthly
ATRIDOX	DOXYCYCLINE HYCLATE	Chronic adult periodontitis	1 week
BYDUREON BCISE	EXENATIDE	Improve glycemic control in type II diabetes	Weekly
BYDUREON...BYDUREON PEN	EXENATIDE SYNTHETIC	Improve glycemic control in type II diabetes	Weekly
YUTIQ	FLUOCINOLONE ACETONIDE	Chronic non-infectious uveitis affecting the posterior segment of the eye	36 months (one time)
ZOLADEX	GOSERELIN ACETATE	carcinoma of prostate, endometriosis, breast cancer	Monthly (4 weeks)
SUSTOL	GRANISETRON	Antiemetics for prevention of acute and delayed nausea and vomiting with chemotherapy	Weekly
LUPRON DEPOT...LUPRON DEPOT-PED	LEUPROLIDE ACETATE	Endometriosis, Fibroids, Advanced prostrate cancer; children with central precocious puberty	1,3,4,6 months
ELIGARD	LEUPROLIDE ACETATE	Palliative treatment of advanced prostate cancer	1,3,4,6 months
LUPANETA PACK	LEUPROLIDE ACETATE; NORETHINDRONE ACETATE	Endometriosis	Monthly
DEPO-PROVERA	MEDROXYPROGESTERONE ACETATE	Prevention of Pregnancy	3 months
DEPO-SUBQ PROVERA 104	MEDROXYPROGESTERONE ACETATE	Prevention of pregnancy, endometriosis-associated pain	3 months
SINUVA	MOMETASONE FUROATE	Nasal polyps who had ethmoid surgery	3 months (one time)
VIVITROL	NALTREXONE	Alcohol/Opioid Dependence	Monthly (4 weeks)
SANDOSTATIN LAR	OCTREOTIDE ACETATE	Acromegaly, Carcinoid Tumors and Vasoactive Intestinal Peptide secreting tumors	Monthly (4 weeks)
ZYPREXA RELPREVV	OLANZAPINE PAMOATE	Schizophrenia	2, 4 weeks
INVEGA SUSTENNA	PALIPERIDONE PALMITATE	Schizophrenia, schizoaffective disorder, mood stabilizers or antidepressants	Monthly
INVEGA TRINZA	PALIPERIDONE PALMITATE	Schizophrenia	3 months
SIGNIFOR LAR KIT	PASIREOTIDE PAMOATE	Acromegaly, Cushing's Disease	4 weeks
PERSERIS KIT	RISPERIDONE	Schizophrenia	Monthly
RISPERDAL CONSTA	RISPERIDONE	Schizophrenia, Bipolar I Disorder	2 weeks
XYOSTED (AUTOINJECTOR)	TESTOSTERONE ENANTHATE	Testosterone replacement therapy	weekly
ZILRETTA	TRIAMCINOLONE ACETONIDE	Osteoarthritis pain of the knee	3 months (one time)
TRIPTODUR KIT	TRIPTORELIN PAMOATE	precocious puberty	24 weeks
TRELSTAR	TRIPTORELIN PAMOATE	Advanced prostrate cancer	4/12/24 weeks

Draft Guidance on Buprenorphine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Buprenorphine

Dosage Form; Route: Solution, extended release; subcutaneous

Recommended Study: One study

1. Type of Study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, randomized, parallel, in vivo
   Strength: 300 mg/1.5 mL
   Subjects: Males and non-pregnant, non-lactating females with moderate or severe opioid use disorder (OUD), 18 to 65 years old

[...]

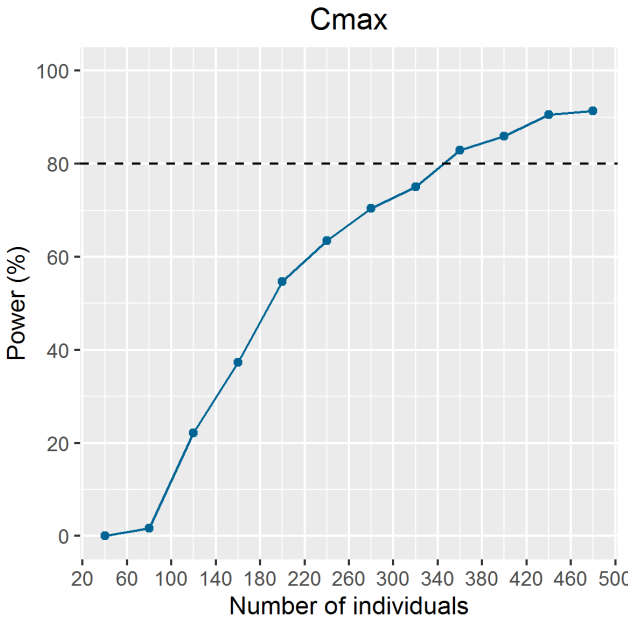
Analytes to measure (in appropriate biological fluid): Buprenorphine in plasma

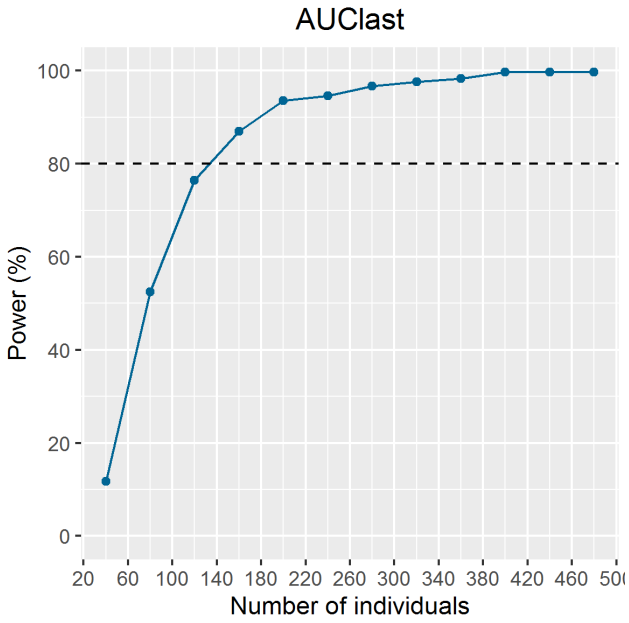
Bioequivalence based on (90% CI): Buprenorphine

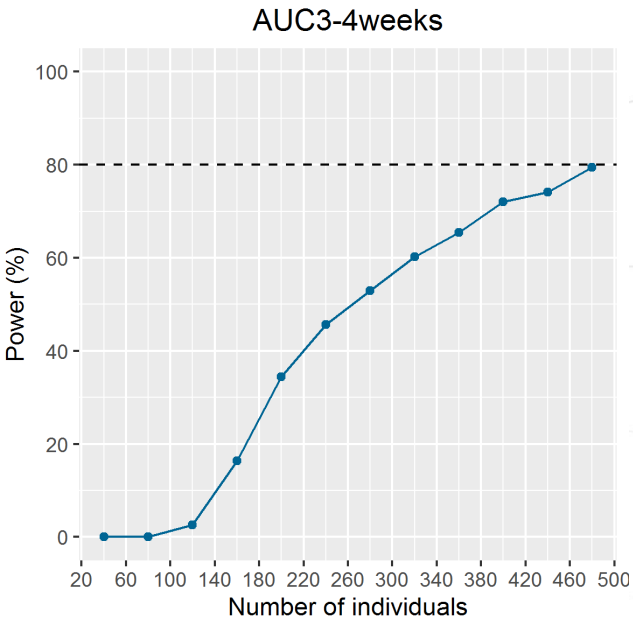
The confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{3week\text{-}4week}$) should fall within the limits of 80.00-125.00%, where C_{max} is the maximum plasma concentration, $AUC_{0\text{-}tlast}$ is the area under the curve from 0 to the last sampling time point, and $AUC_{3week\text{-}4week}$ is the area under the plasma concentration time curve from 3 weeks to 4 weeks. The applicant should submit time to maximum concentration (T_{max}) as supportive data.

LAI Buprenorphine with single dose parallel BE trial

Assuming a 5% difference between test and ref:







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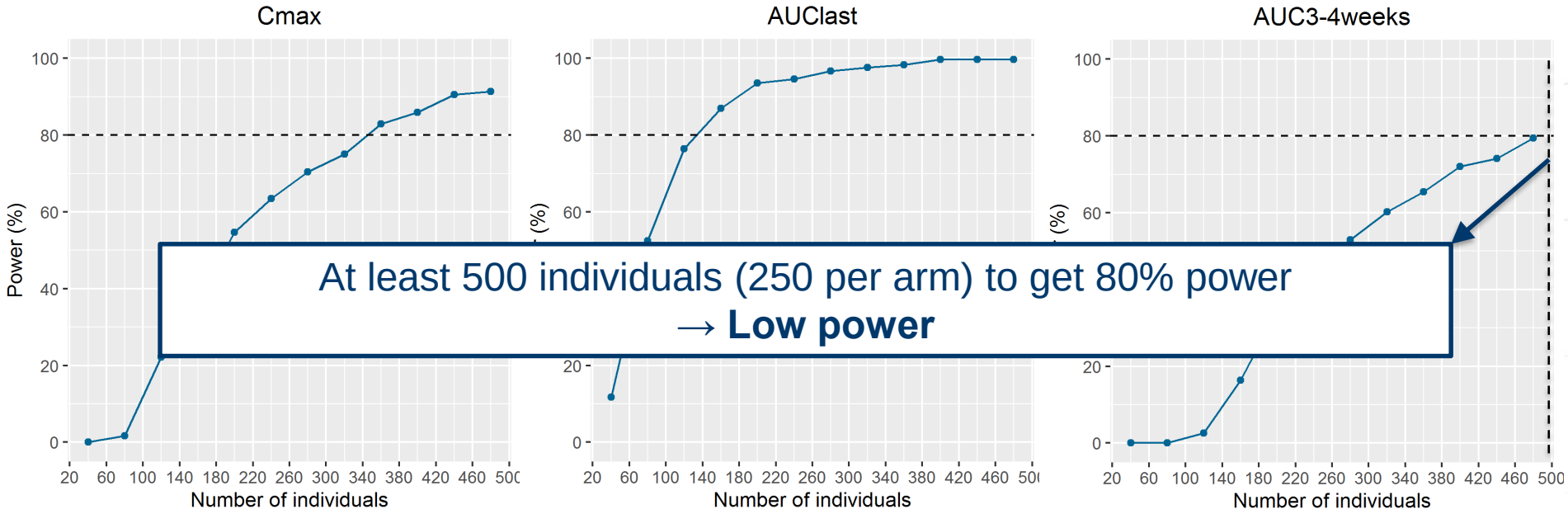

At least 500 individuals (250 per arm) to get 80% power
→ **Low power**

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Challenges for bioequivalence (BE) trials for LAI

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- LAI have extended drug release, leading to flip-flop kinetics and long apparent half-lives
- Typical BE designs are impracticable:
  - **Parallel:** high variability between individuals → **low power**
  - **Crossover**: long half-lives → long wash-out period
    → **long BE trial duration**
    → high dropout rate

LAI Buprenorphine with crossover BE trial

- FDA guidance:
  - *"An adequate washout period (e.g., more than 5 half lives of the moieties to be measured) should separate each treatment"*

- Buprenorphine LAI (SUBLOCADE™):
  - Apparent half-life ≈ 73 days
    => washout period of one year

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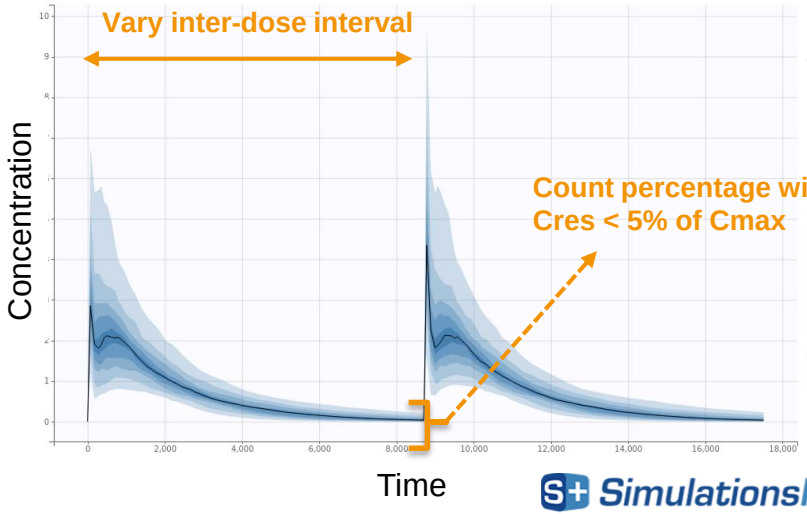

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- Buprenorphine LAI (SUBLOCADE™):
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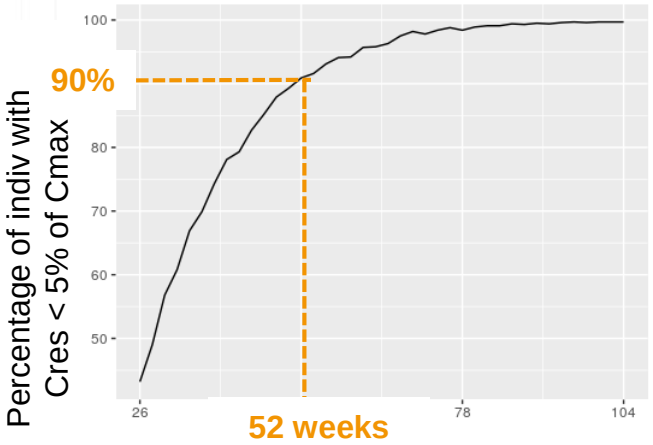
    => washout period of one year
  - One year after the first dose, 90% of individuals have a residual concentration below 5% of their Cmax



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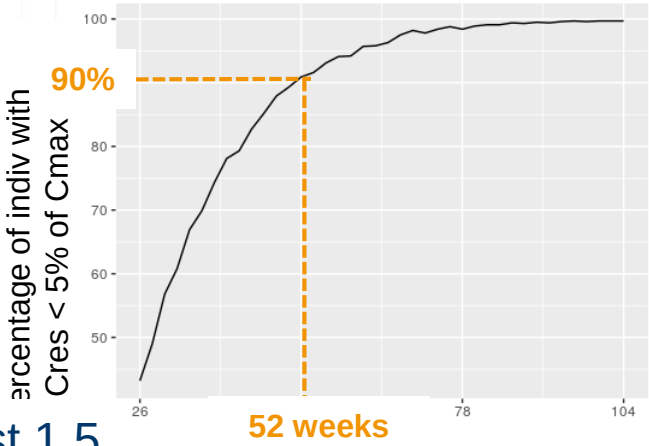


Individuals need to be followed over at least 1.5 years → **Long duration**

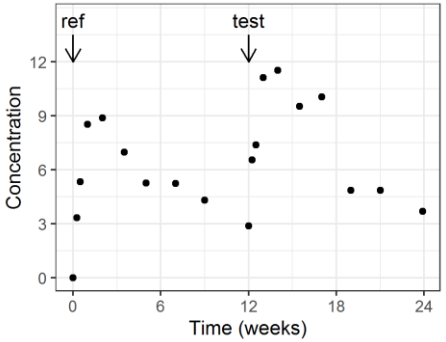
Challenges for bioequivalence (BE) trials for LAI

- LAI are designed to require infrequent dose administration to improve patient adherence
- LAI have extended drug release, leading to flip-flop kinetics and long apparent half-lives
- Typical BE designs are impracticable:
  - **Parallel:** high variability between individuals → **low power**
  - **Crossover**: long half-lives → long wash-out period
    → **long BE trial duration** → high dropout rate
- These challenges have prevented the development of generics (over 30 LAI, only 1 has a generic product)

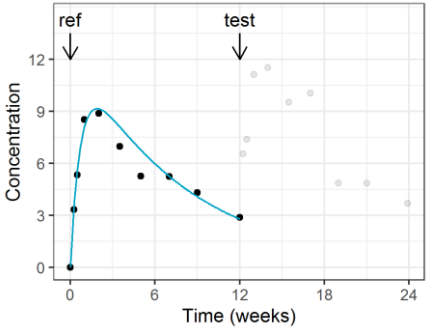
→ **Propose alternative designs based on model-integrated evidence (MIE)**

Alternative design “single dose reduced crossover”

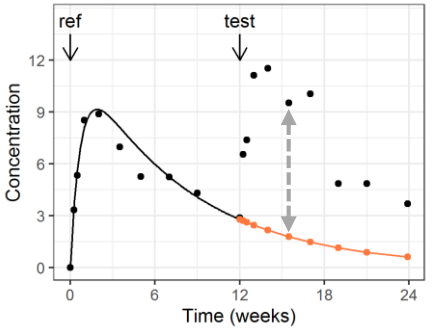
2-period, 2-treatment, 1-sequence crossover trial with no or limited washout



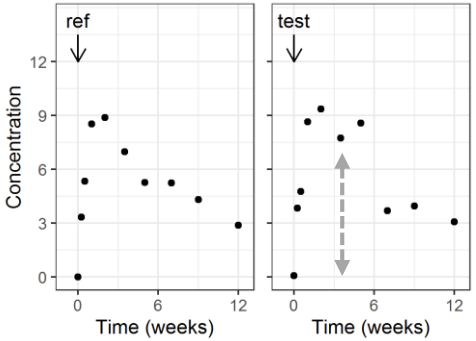
Estimate individual parameters for ref *(given pop param and model from literature)*



Predict carry-over of ref dose into second period



Subtract carry-over from second period data

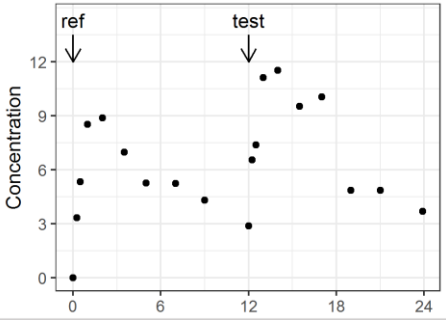


Usual bioequivalence statistical analysis

BE CONCLUSION

Alternative design “single dose reduced crossover”

2-period, 2-treatment, 1-sequence crossover trial with no or limited washout



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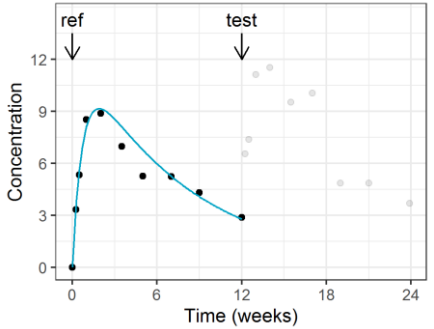

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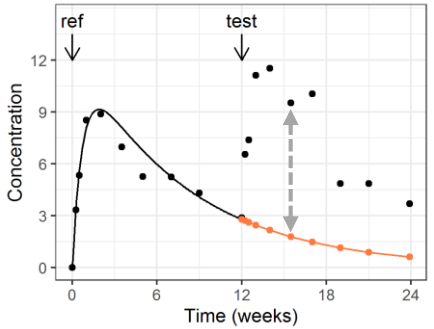

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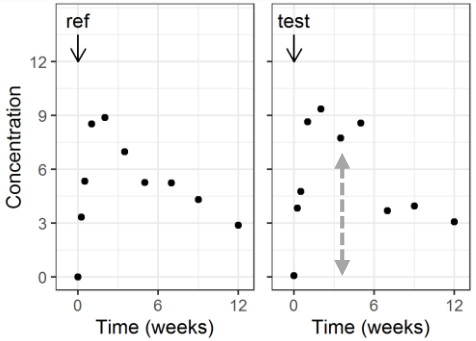


Usual bioequivalence statistical analysis

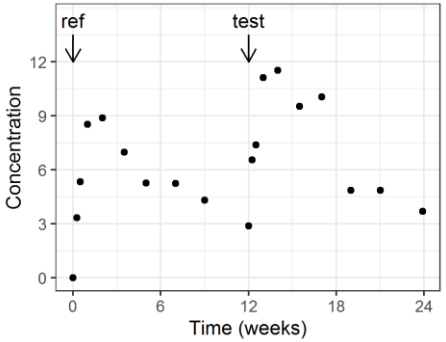
BE CONCLUSION

Requirements:

- LAI can be given to healthy volunteers as single dose (not toxic)
- PK is linear (superposition principle)
- popPK model for reference product is available

Alternative design “single dose reduced crossover”

MonolixSuite with R functions



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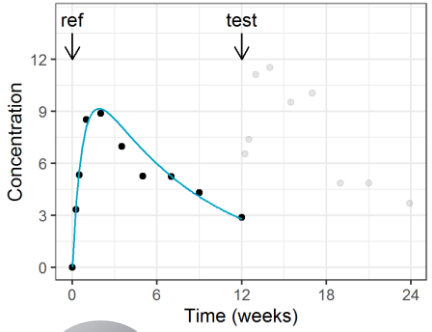

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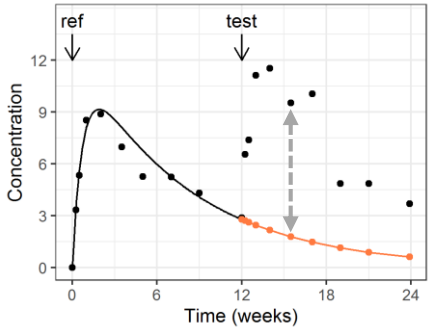

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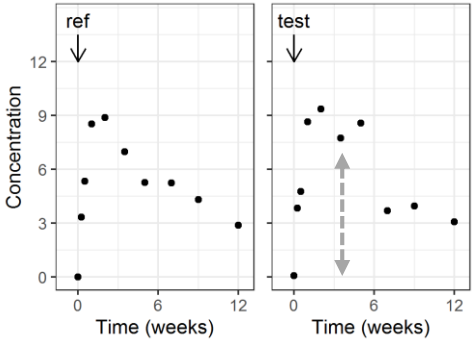


Usual bioequivalence statistical analysis

BE CONCLUSION

R code using the lixoftConnectors: at a glimpse

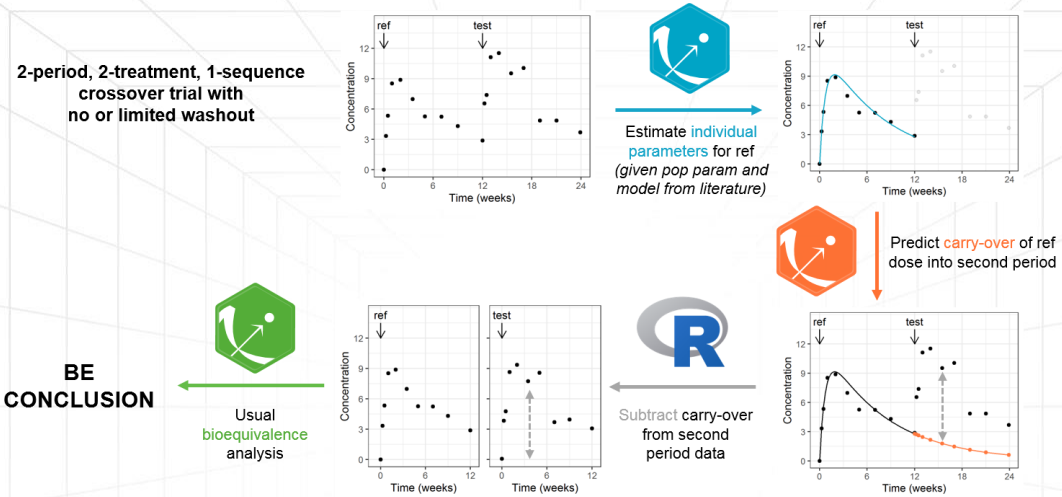
```
initializeLixoftConnectors(software = “monolix”)
loadProject("get_indivparam_template.mlxtran")
setData(dataFile = “trial_data.csv”, headerTypes =c("id","time","observation","amount","contcov"))
runConditionalDistributionSampling()

initializeLixoftConnectors(software = "simulx“)
importMonolixProject("get_indivparam_template.mlxtran")
defineOutputElement(name="sampling2ndPeriod", element=list(data=data.frame(time=samplingTimes), output="Cc"))
setGroupElement(group="simulationGroup1", elements = c("mlx_CondMean","sampling2ndPeriod“,”mlx_trt”))
runSimulation()
exportSimulatedData()

# data correction in R

initializeLixoftConnectors(software = "pkanalix“)
newProject(data = list(dataFile=paste0(“data_corrected.csv"),
                       headerTypes=c('id’,’occ’,'time','observation','amount','ignore','catcov’)
runNCAEstimation()
runBioequivalenceEstimation()
getBioequivalenceResults()$confidenceIntervals$test[,c("Parameter","Ratio","CILower","CIUpper")]
```

Alternative design “single dose reduced crossover”



⇒ Does it work?

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

Bioequivalence analysis: statistics reminder

μ = population average of the NCA parameter for test (T) or ref (R)

$e.g.\ \mu_T = \text{mean}(AUC)_T$

- Bioequivalence analysis in practice:
  - Calculate $\frac{\mu_T}{\mu_R}$
  - Construct a 90% confidence interval for $\frac{\mu_T}{\mu_R}$
  - Bioequivalence is concluded if the confidence interval is within the BE limits [0.8, 1.25]

- Bioequivalence analysis seen as hypothesis testing:
  - Bioequivalence is concluded if the null hypothesis H_0 is rejected
  - **Two one-sided tests** at the 5% level of significance

$$H_0: \ \frac{\mu_T}{\mu_R} \leq 0.8 \ \text{ or } \ 1.25 \ \leq \frac{\mu_T}{\mu_R}$$

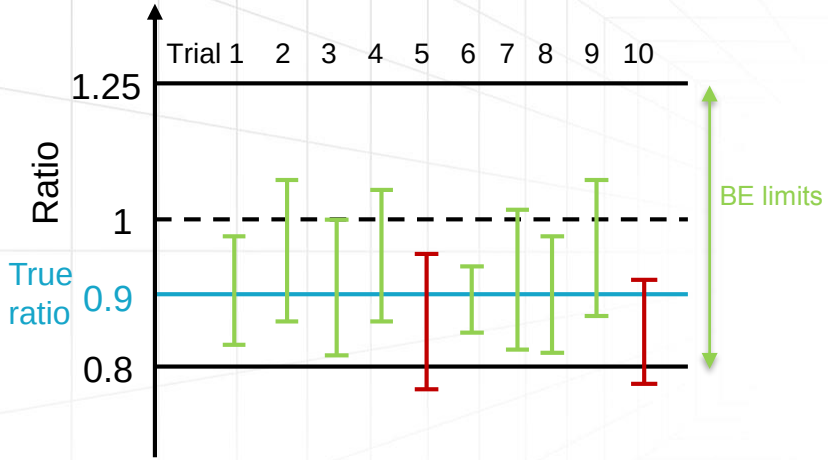
$$H_1: \ 0.8 < \frac{\mu_T}{\mu_R} < 1.25$$

Type I error and power: statistics reminder

	H0 is true: Formulations are not bioequivalent	H0 is false: Formulations are bioequivalent
H0 is not rejected	Correct conclusion $p = 1 - \alpha$	Type II error $p = \beta$
H0 is rejected: Bioequivalence is concluded	Type I error $p = \alpha$	Correct conclusion (Power) $p = 1 - \beta$

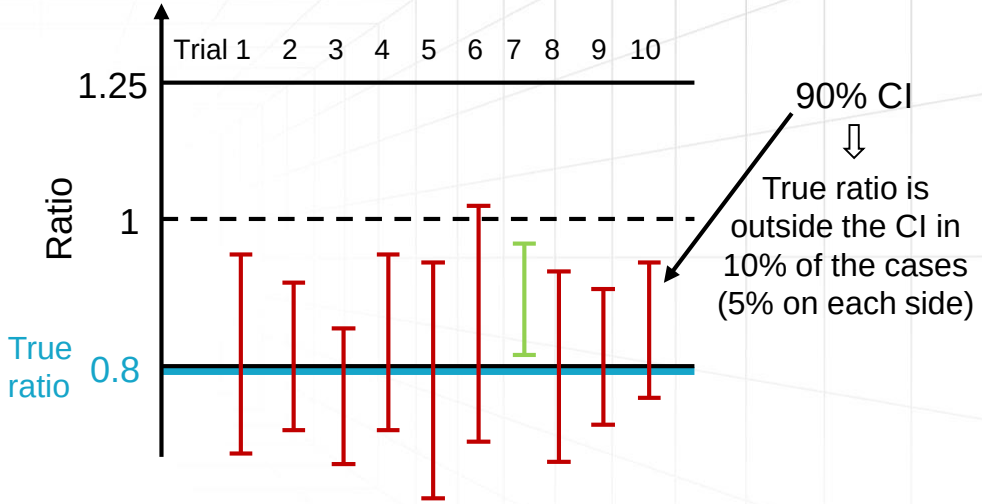
Empirical power and type I error on many trials

Power



$$\text{power} = \frac{\#\text{ trials with BE=true}}{\#\text{ trials}} = 80\%$$

Type I error



$$\text{type I error} = \frac{\#\text{ trials with BE=true}}{\#\text{ trials}} = 10\%$$

Power assessment via simulations

- Simulate a large number of BE clinical trials under the H_1 hypothesis (bioequivalence)

$$H_1: \ 0.8 < \frac{\mu_T}{\mu_R} < 1.25$$

True ratio of AUC is in]0.8, 1.25[

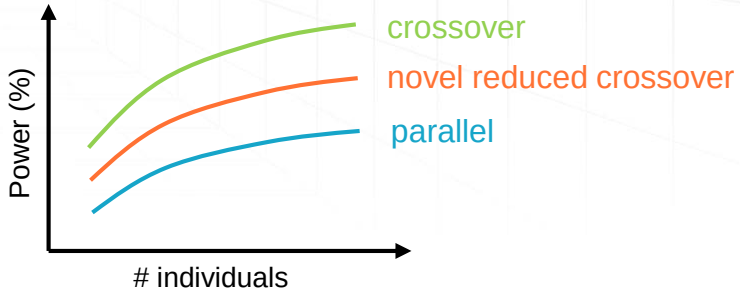
- Apply the BE analysis on each clinical trial simulation and record the BE conclusion
- Calculate the power as:

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

Probability of correctly concluding bioequivalence when formulations are indeed bioequivalent.

- Vary:
  - Number of individuals
  - True AUC ratio between the two formulations
  - Design:
    - crossover (with washout)
    - reduced crossover (with correction), different duration between doses
    - parallel

GOAL: power as high as possible



Type I error assessment via simulations

- Simulate a large number of BE clinical trials under the H_0 hypothesis at the limit

$$H_0: \frac{\mu_T}{\mu_R} \leq 0.8 \text{ or } 1.25 \leq \frac{\mu_T}{\mu_R}$$

True ratio of AUC is 0.8 or 1.25.

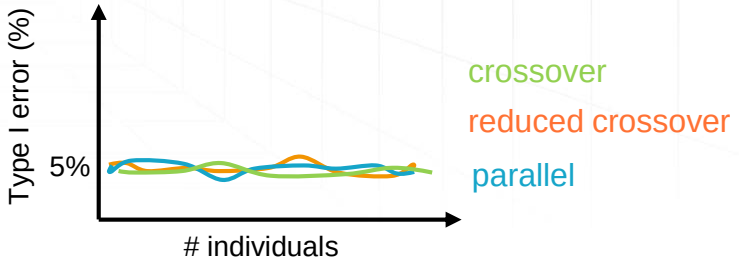
- Apply the BE analysis on each clinical trial simulation and record the BE conclusion
- Calculate the type I error as:

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

Probability of incorrectly concluding bioequivalence when formulations are not bioequivalent.

- Vary:
  - Design:
    - crossover (with washout)
    - reduced crossover (with correction), different duration between doses
    - parallel
  - Number of individuals
  - True AUC ratio of 0.8 and 1.25

GOAL: keep the type I error under control (5% on each side if BE confidence level is 90%)

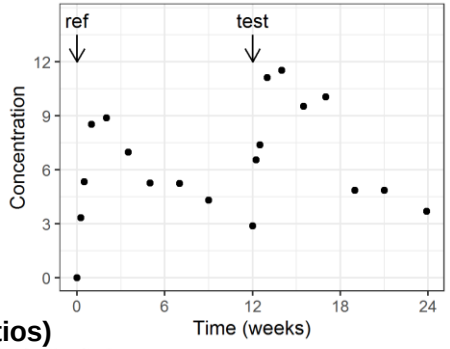


Assessment via simulations

Lit.

Simulate BE reduced crossover trial using model and pop param from literature

- **For several relative bioavailabilities (true ratios)**
  - **For several inter-dose intervals**
    - **For several number of individuals**
      - **For many replicates**



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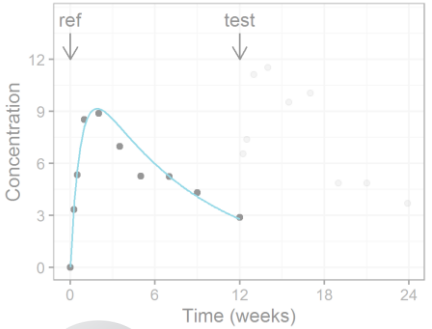
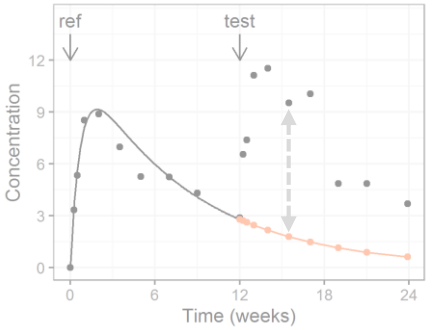
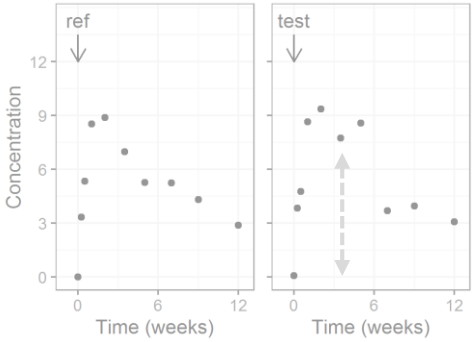


Predict carry-over of ref dose into second period



Subtract carry-over from second period data



Usual bioequivalence statistical analysis

BE CONCLUSION correct ?

Clinical trial simulations

- Monte-Carlo simulation
  - **Model**: from literature
  - **Individual parameters**: sampled from the distributions characterized by the population parameters. Inter-occasion variability included if estimated in the literature.
  - **Treatment**: single dose at max approved amount
  - **Output**: simulated observation (prediction + residual error) on realistic sampling times
  - **Design**: crossover with washout, reduced crossover (without washout), or parallel

- Difference between the two formulations
  - All population parameters are the **same except the (relative) bioavailability**
    => allows to easily choose the value of the true ratio between test and ref

  - Different absorption parameters between ref and test
    => but not possible to simulate with known true ratio
    => only to investigate power but not type I error

Buprenorphine LAI example

- BUP-XR (SUBLOCADE™): extended-release subcutaneous buprenorphine formulation for the treatment of opioid use disorder, with monthly dosing interval

- Published model:

Clinical Pharmacokinetics (2021) 60:527–540
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ORIGINAL RESEARCH ARTICLE

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

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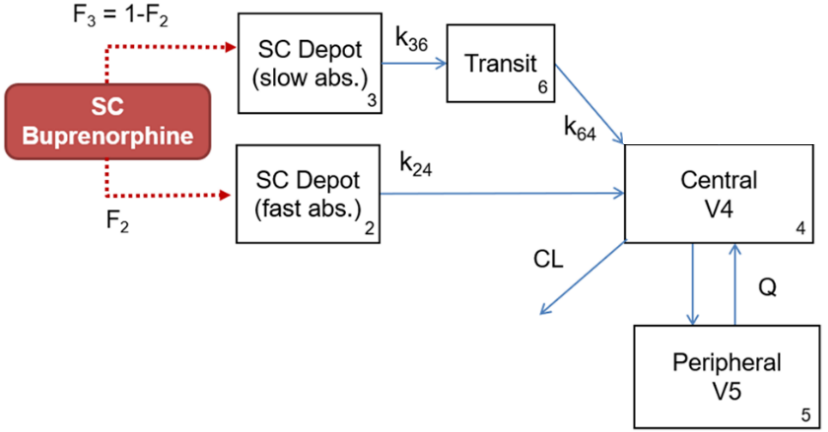


Buprenorphine LAI example

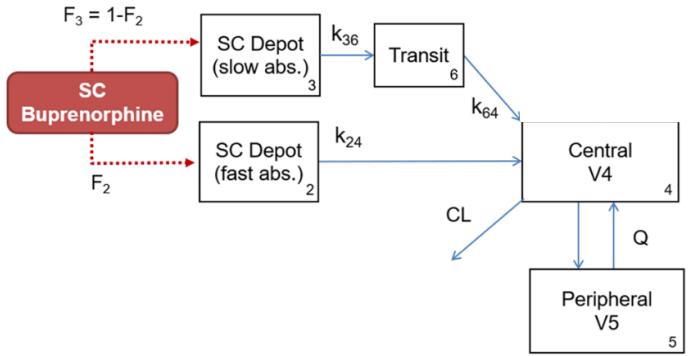
Parameter	Description	Estimate (%RSE)	Variance (%RSE)	Inter-individual variability (%CV)
CL/F	BUP-XR apparent elimination clearance (L/h)	52.2 (1.5)	0.0909 (11)	30.9
V4/F	BUP-XR apparent volume of central compartment (L)	432 (6.1)	0.704 (14)	101
Q/F	BUP-XR apparent distribution clearance (L/h)	79.5 (fixed)	0.334 (fixed)	62.9
V5/F	BUP-XR apparent volume of peripheral compartment (L)	1110 (fixed)	0.941 (fixed)	125
k14	SL absorption rate constant (1/h)	1.17 (fixed)	0.190 (fixed)	45.7
k24	Fast absorption rate constant from SC depot (1/h)	0.0277 (5.0)	0.643 (15)	95.0
k36	Slow absorption rate constant from SC depot (1/h)	0.00392 (7.5)	1.69 (11)	210
k64	Rate constant from transit to central compartments (1/h)	0.000507 (3.5)	0.384 (10)	68.4
F1	Relative bioavailability for SL buprenorphine tablets vs BUP-XR	0.185 (fixed)	0.195 (fixed)	46.4
F2	Fraction of SC dose absorbed by fast process	0.0680 (2.1)	0.194 (11)	NA[a]
FRK14	Relative change in k14 for film vs tablet formulation	0.636 (11)	NA	NA
FRF1	Relative change in F1 for film vs tablet formulation	1.47 (3.5)	NA	NA
F1DOSE	Relative change in F1 for dose ≥ 16 mg compared to < 16 mg	0.765 (fixed)	NA	NA
θ_{BMI} (CL)	Power coefficient for BMI on CL/F	−0.362 (21)	NA	NA
θ_{BMI} (k24)	Power coefficient for BMI on k24	−1.32 (14)	NA	NA
		Residual variability (%RSE)		
PROP	Proportional residual error	0.190 (0.66)		
ADD	Additive residual error (ng/mL)	0.0378 (13)		

$TVk24 = 0.0277 \times (BMI/24.8)^{-1.32}$ and $TVCL = 52.2 \times (BMI/24.8)^{-0.362} \times (Weight/70)^{0.75}$, where $TVk24$ and $TVCL$ are the typical values for k24 and CL/F, and 24.8 kg/m^2 is the median BMIs

BMI body mass index, *CV* coefficient of variation for log-normal distribution calculated as $100 \times \sqrt{\exp(\omega^2) - 1}$, where ω^2 is the variance of the random effect, *NA* not applicable, *RSE* relative standard error, *SC* subcutaneous, *SL* sublingual

[a]Logit-normal distribution

Characteristic		Total
	N	570[a]
BMI (kg/m^2)	Mean (SD)	25.4 (4.2)
	Min–Max	18.0–35.0



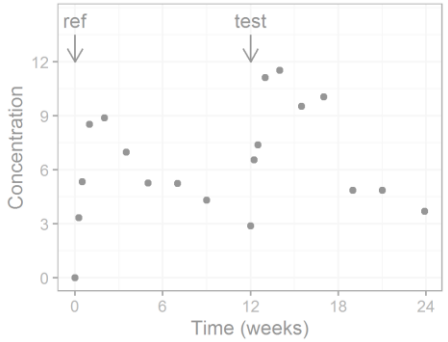
Note: no inter-occasion variability

Assessment via simulations for Buprenorphine

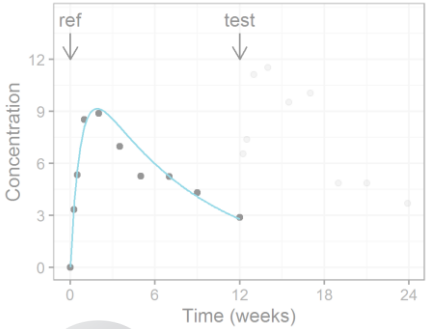
Lit.

Simulate BE reduced crossover trial using model and pop param from literature

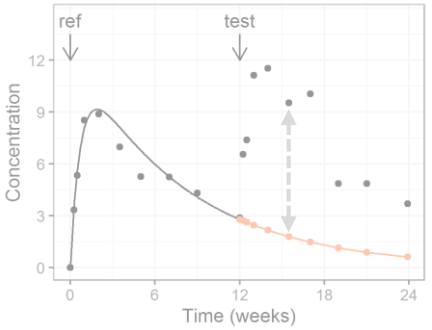
- o For true ratio = 0.8, 0.85, 0.9, 0.95, 1, or 1.25
  - o For duration between doses = 3, 4, 5 or 6 months
    - o For number of individuals = 10, 20, 30, 40, or 50
      - o For replicates = 200



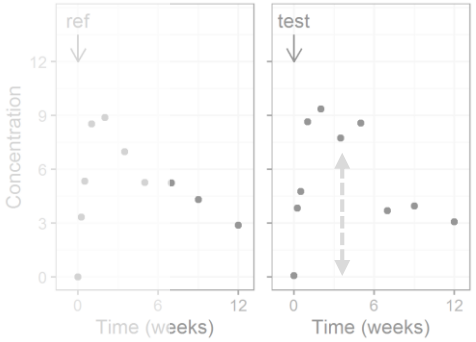
Estimate individual parameters for ref *(given pop param and model from literature)*



Predict carry-over of ref dose into second period



Subtract carry-over from second period data



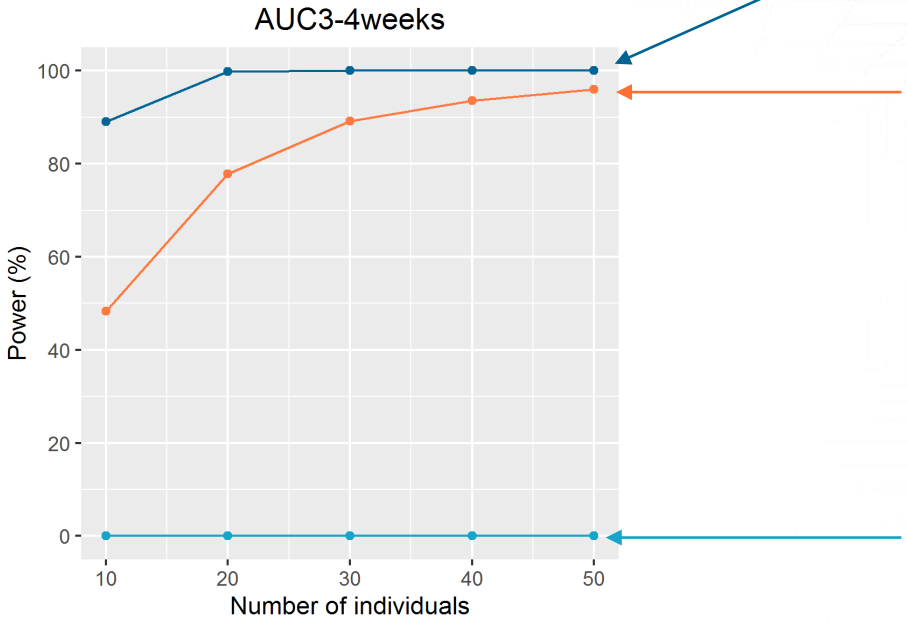
Usual bioequivalence statistical analysis

BE CONCLUSION

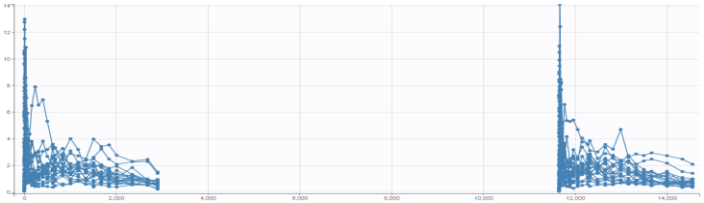
$$\text{power} = \frac{\#\ \text{BE=true}}{\#\ \text{rep}}$$

Buprenorphine: power vs sample size

- 5% difference between ref and test on average (true ratio = 0.95)
- Reduced crossover with 4 months between the ref and test dose



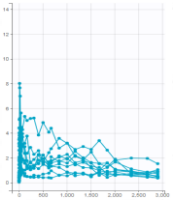
Traditional crossover design (20 months)

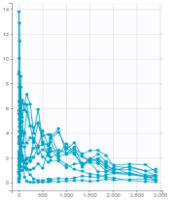


Reduced crossover design (8 months)

(+ model-based correction)

Parallel design (4 months)





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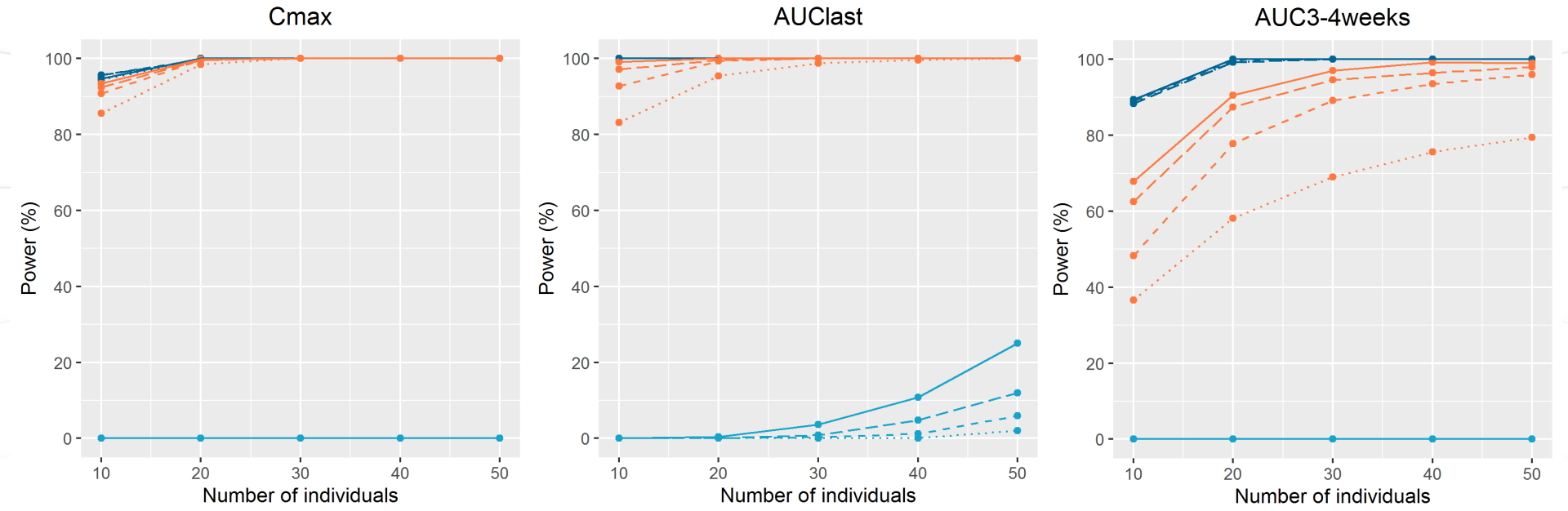
Buprenorphine: power vs sample size

5% difference
between ref and test on average (true ratio = 0.95)



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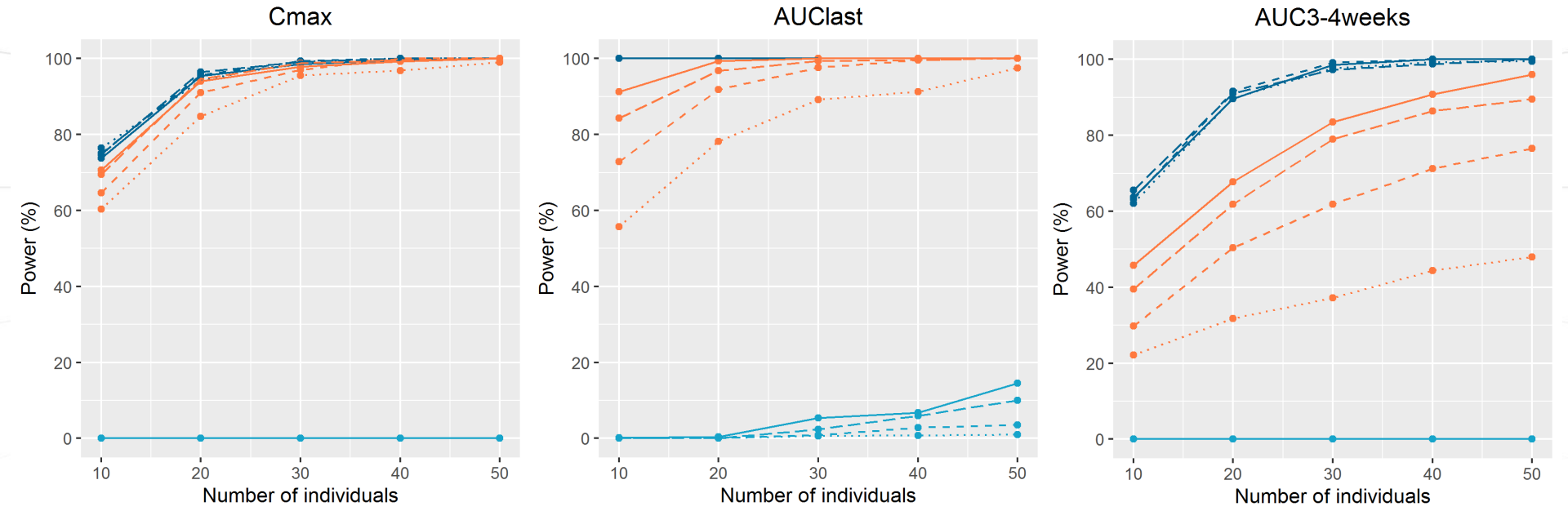
Buprenorphine: power vs sample size

10% difference
between ref and test on average (true ratio = 0.90)



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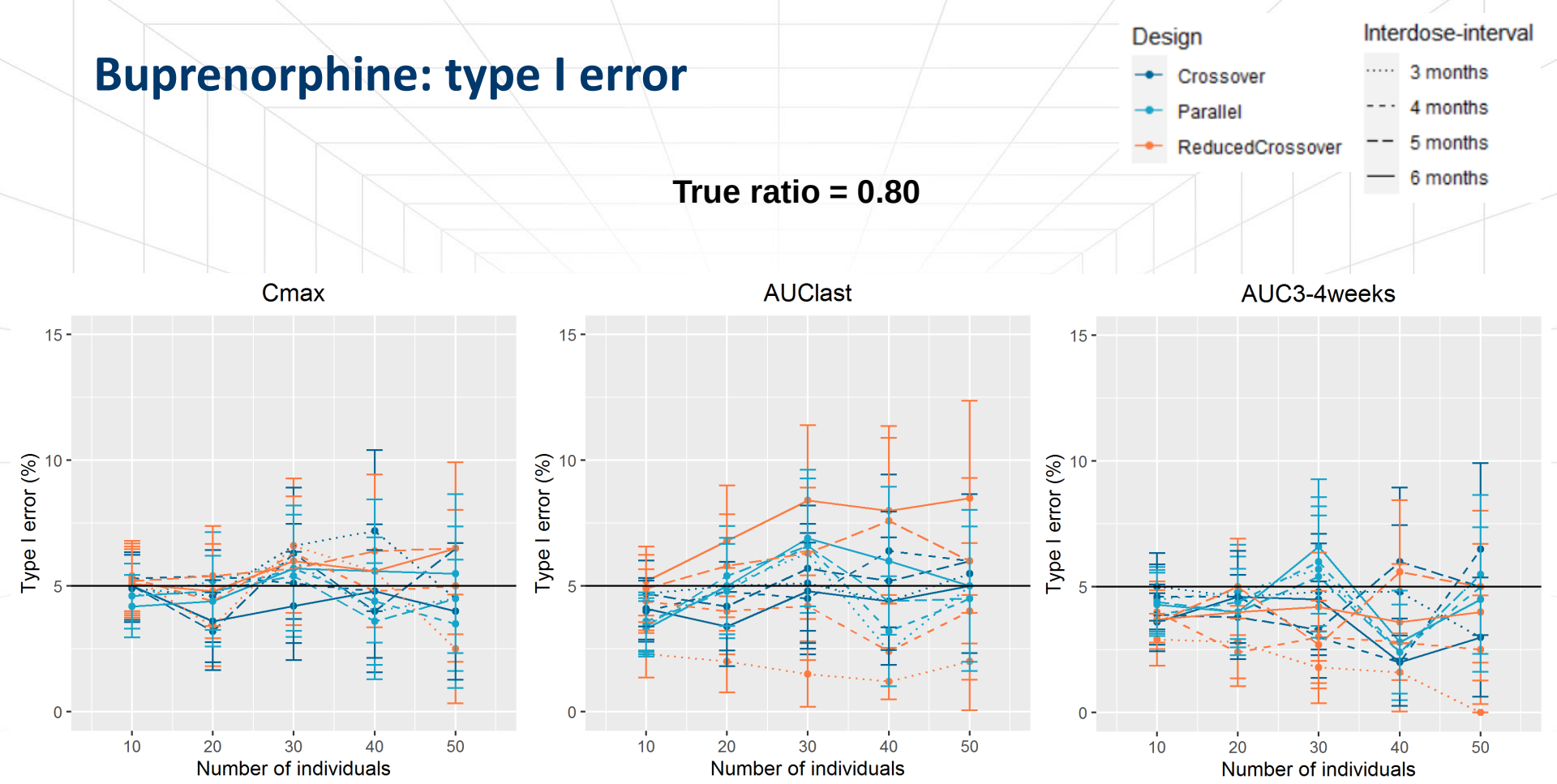
Buprenorphine: type I error

True ratio = 0.80



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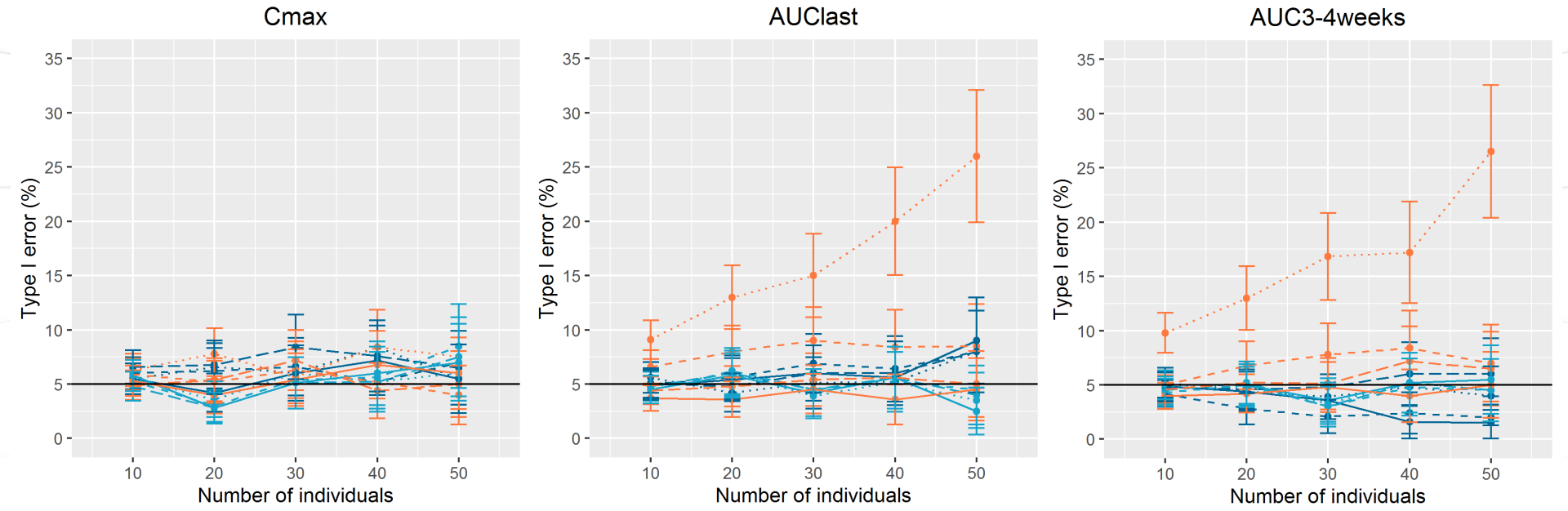
Buprenorphine: type I error

True ratio = 1.25



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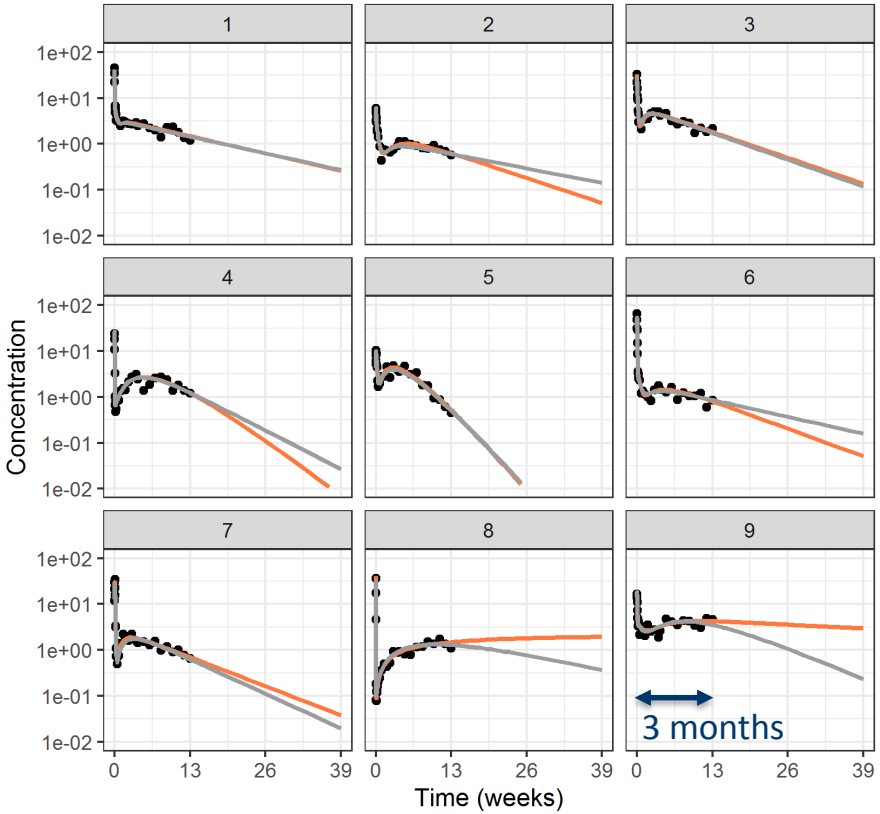
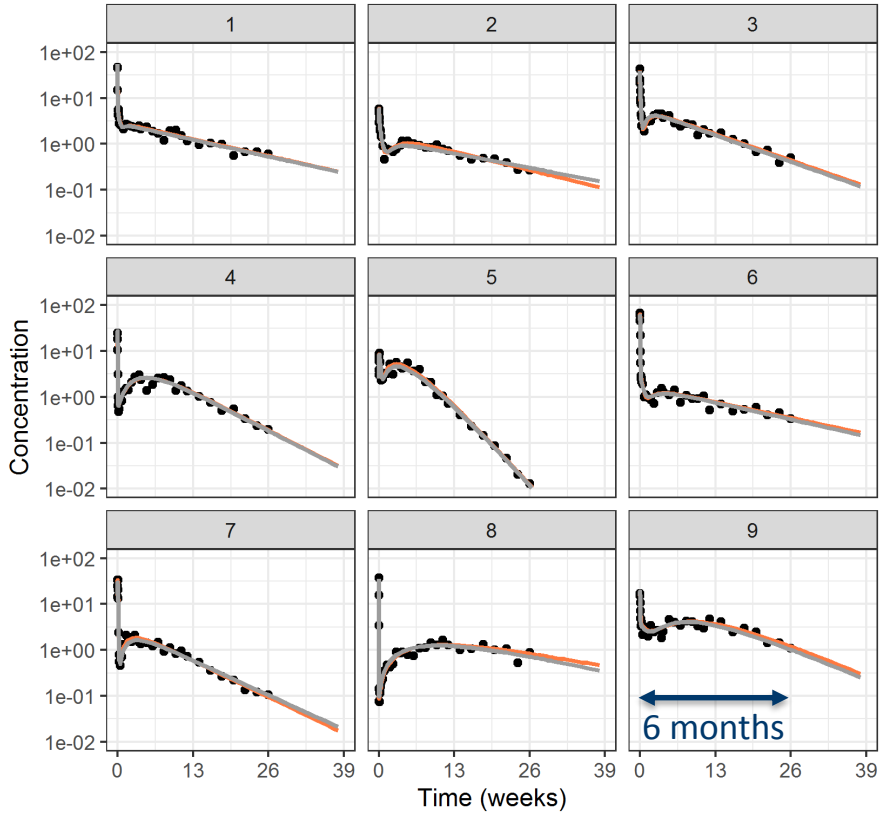
Where does the bias come from?

Predictions with:
- estimated individual parameters
- true individual parameters

Inter-dose interval : 3 months



Inter-dose interval : 6 months



Conclusion on the alternative design for Buprenorphine

Reduced crossover design with inter-dose intervals of 4 months:

- 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 washout
- ✓ Power much higher for a given sample size compared to parallel design

Pros and Cons of the alternative “reduced crossover” design

Requirements:

- PK is linear (superposition principle)
- popPK model for reference product is available
- LAI can be given to healthy volunteers as single dose (not toxic)

Pros:

- Individuals parameters are estimated for the reference formulation only, for which a population model is available
- Data of second period is shifted but residual error remains the same (safer than simulation of BE trial from a model)

Cons:

- Different post-processing for ref and test (1-sequence design)

Implementation and usage

- Implemented as an R script
- Use the R package lixoftConnectors
- Requires a MonolixSuite installation and license (free for academia)

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 depending on the true ratio)

BE analysis of 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

Summary

The model-based bioequivalence analysis of a "reduced crossover" design provides:

- ✓ **good power**
- ✓ **reasonable study duration**
- ✓ **controlled type I error**

Implemented as an R script using the MonolixSuite.