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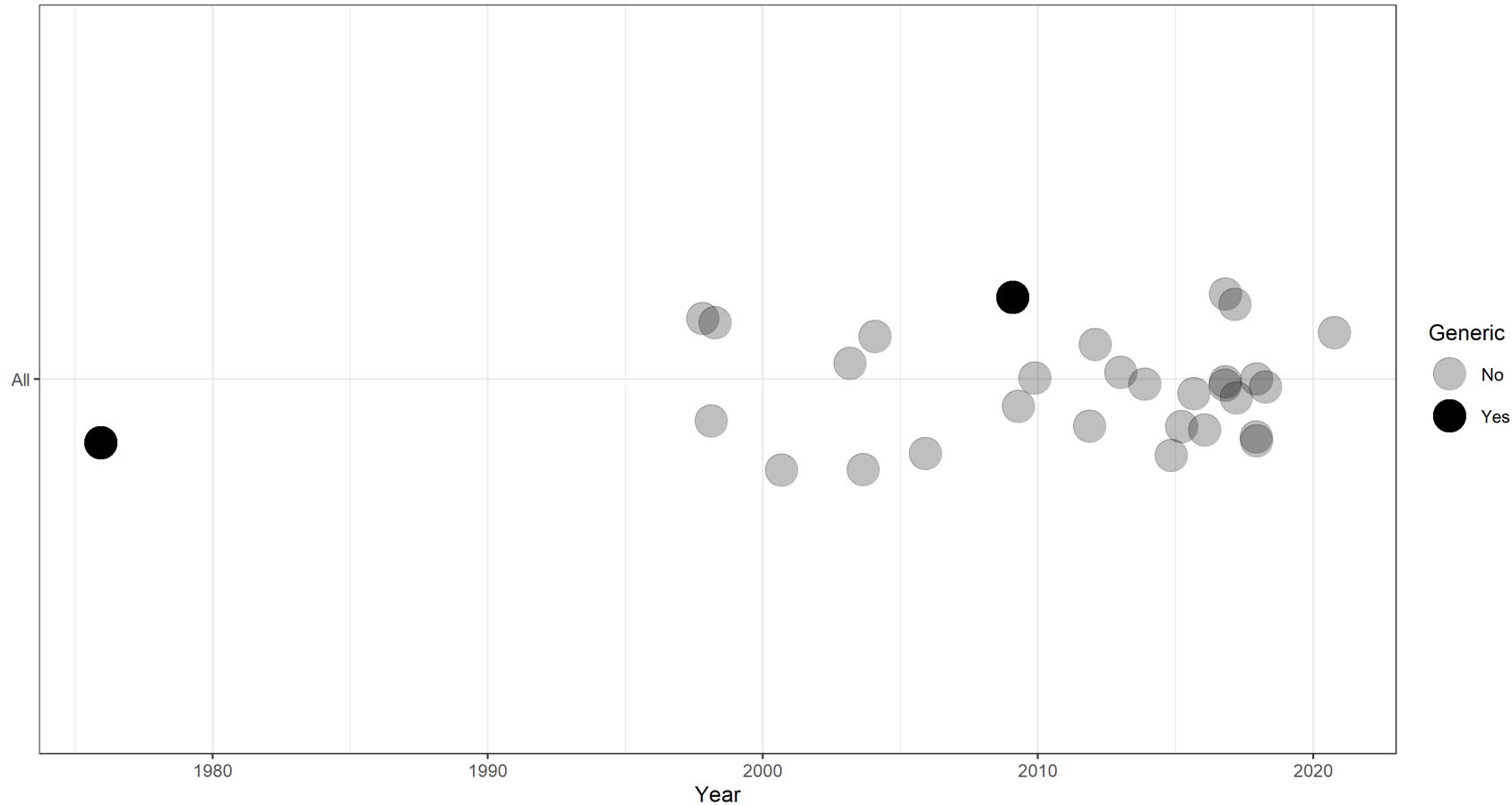
A model integrated pathway to explore
bioequivalence of LAI products:
Studies using Paliperidone Palmitate

Parmesh Gajjar | parmesh.gajjar@sedapds.com

Jake Dickinson, Harri Dickinson, Linette Ruston,
Hitesh Mistry, Claire Patterson, Paul Dickinson

Introduction \

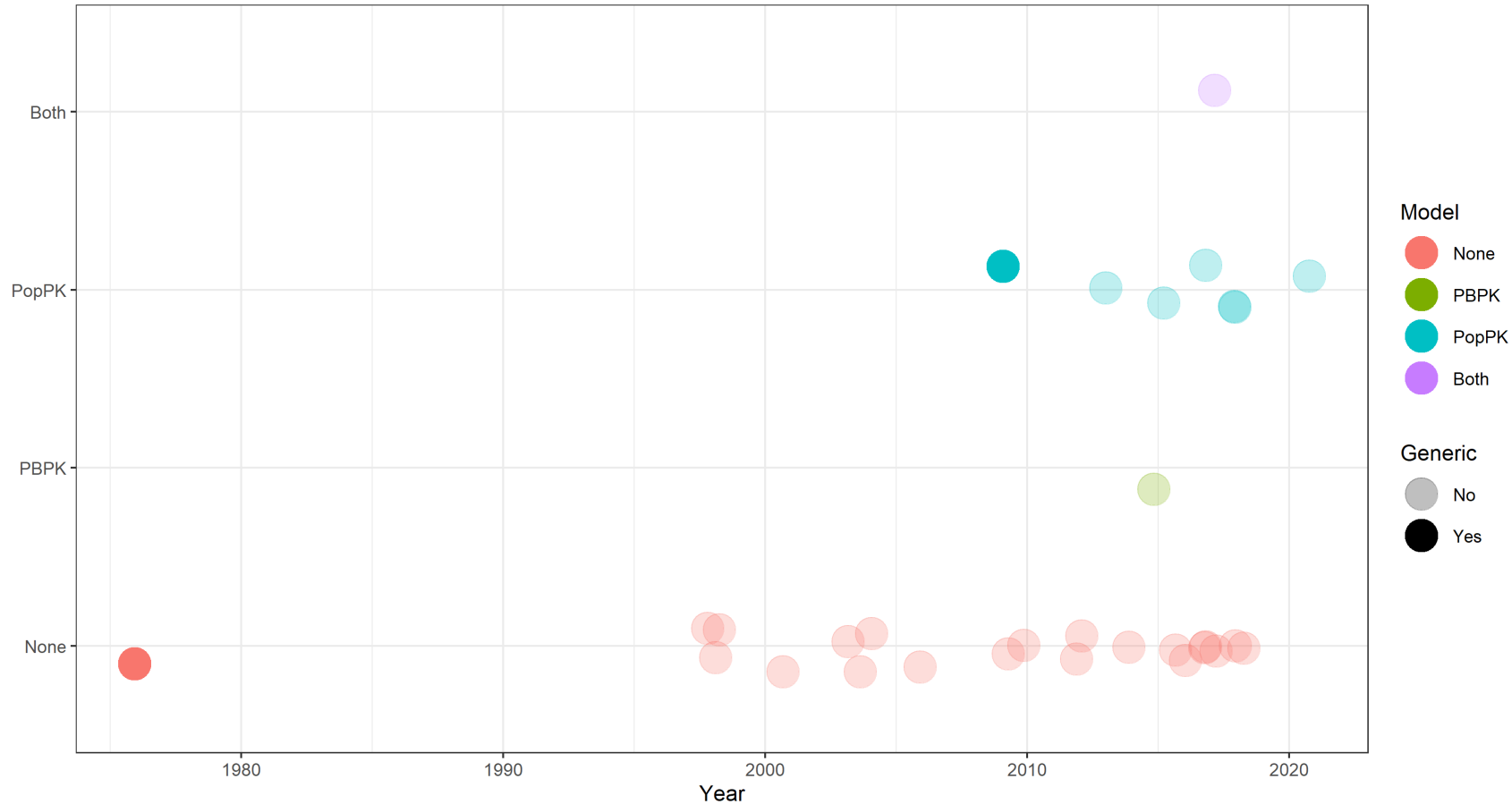
FDA approved LAI products



- Schizophrenia
- Bipolar disorder
- Opioid use
- HIV
- Periodontitis
- Type II Diabetes
- Uveitis
- Endometriosis
- Breast Cancer
- Prostate Cancer
- Endometriosis
- Pregnancy prevention

Introduction \

FDA approved LAI products



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- Pregnancy prevention

A model integrated pathway to explore bioequivalence \

Use Population PK modelling to explore

- HOW to identify which products are bioequivalent after multiple-dosing?
- WHETHER we need multiple-dosing?
- HOW risk can be reduced in BE testing through modelling?

... deliberately radical to drive new thinking

Paliperidone Palmitate \

- Well established Population PK model in the literature
- E.g. Samtani et al (2009)
<https://doi.org/10.2165/1316870-000000000-00000>

Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic

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² Clinical Pharmacology, Advanced PK-PD Modeling & Simulation, Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium

Abstract

Objectives: To characterize the population pharmacokinetics of paliperidone after intramuscular administration of its long-acting palmitate ester at various doses and at two different injection sites (deltoid and gluteal muscle).

Methods: The retrospective analysis included pooled data from 1795 subjects from six phase I trials and five phase II and III trials. A total of 18530 pharmacokinetic samples with valid concentration timepoints were available for this analysis. Nonlinear mixed-effects modelling of the pooled data was conducted using NONMEM[®] software. The full dataset was divided into an index dataset (model development) and a validation dataset. After validation both the index and validation datasets were combined and the final model was re-run on the full dataset.

Results: The concentration-time data for paliperidone following intramuscular administration of its palmitate ester were best fitted to a one-compartment model with first-order elimination. The absorption component of the model allowed a fraction of the dose (f_2) to enter relatively quickly into the central compartment via a zero-order process. After a lag time, the remaining fraction then entered the systemic circulation via a first-order process. Interindividual variability (IIV) in clearance (CL), central volume of distribution (V_d) and the absorption rate constant (k_a) were estimated at a 40%, 69% and 59% coefficient of variation (CV), respectively. The IIV on f_2 for paliperidone absorption via the dual-input process was fitted through logit transformation, and its standard deviation (SD) was 0.064. Similarly, the interoccasion variability (IOV) on CL, V_d and f_2 was 26% CV, 14% CV and 0.07 SD, respectively. An additive-error model with log-transformed data was used to describe the residual variability (RV), and its SD was 0.22. The final covariate model indicated that the following variables had a significant influence on k_a : sex, age, injection volume (IVOL) and injection site (INJS). Similarly, the following variables had a significant influence on f_2 : sex, body mass index (BMI), needle length (NDLL), INJS and IVOL. In addition, CL was related to creatinine clearance (CL_{CR}), whereas V_d was related to BMI and sex.

Conclusions: A dual-absorption pharmacokinetic model best described the complex pharmacokinetics of paliperidone after intramuscular administration of its palmitate ester. These results suggest that the pharmacokinetics of paliperidone palmitate are mostly influenced by BMI, CL_{CR} , INJS, IVOL and NDLL.

Background

Atypical antipsychotic agents represent a treatment option for many patients with schizophrenia.^[1,2] Compliance with oral antipsychotic medications is particularly problematic for patients with schizophrenia and can correlate with poor out-

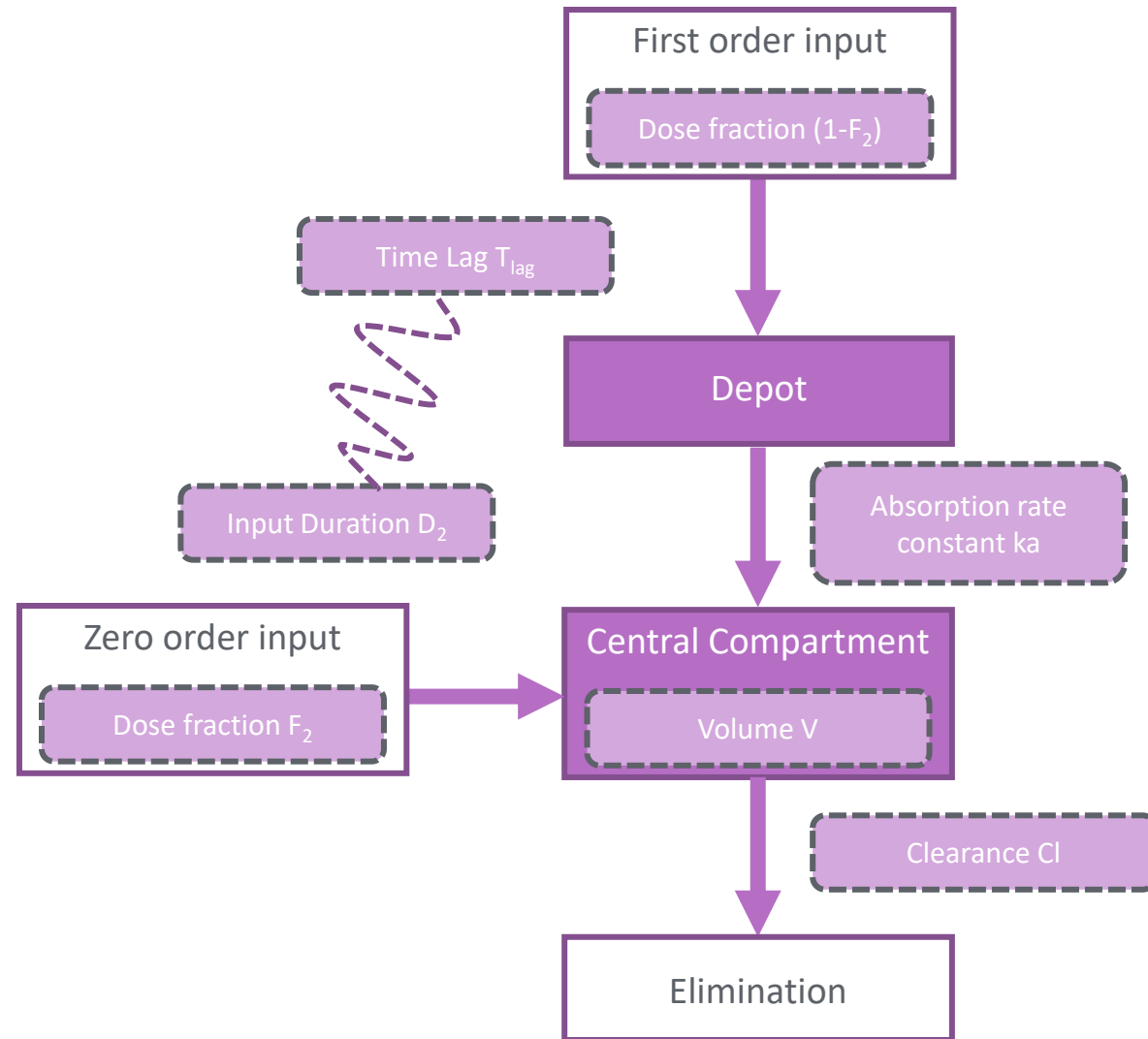
comes.^[1,3-6] In part, to address this problem, sustained-release intramuscular formulations of older 'typical' antipsychotics, such as haloperidol and fluphenazine, were developed.

Paliperidone (9-hydroxy-risperidone) is an atypical antipsychotic agent and is the major active metabolite of risperidone with a receptor-binding profile similar to that of risperidone.

What is a population PK model? \

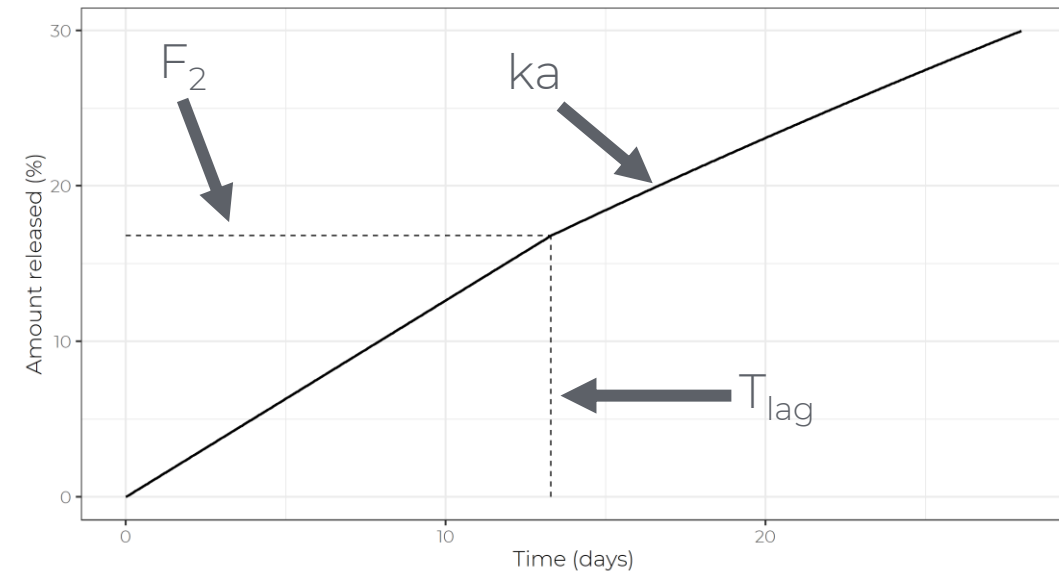
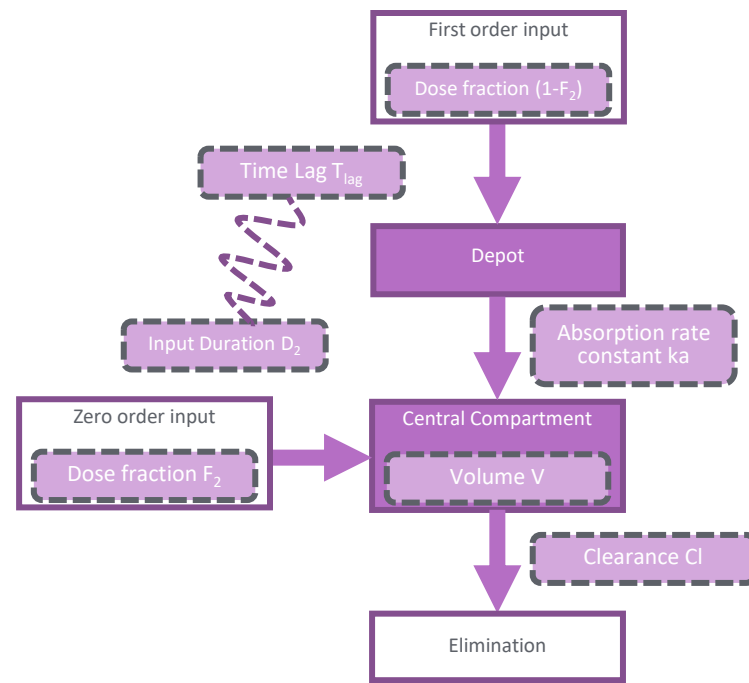
Mathematical model \

- One compartment model with linear absorption and linear elimination
- 5 parameters:
 - Volume V
 - Clearance Cl
 - Absorption rate k_a
 - Dose fraction F_2
 - Duration D / Time lag T_{lag}



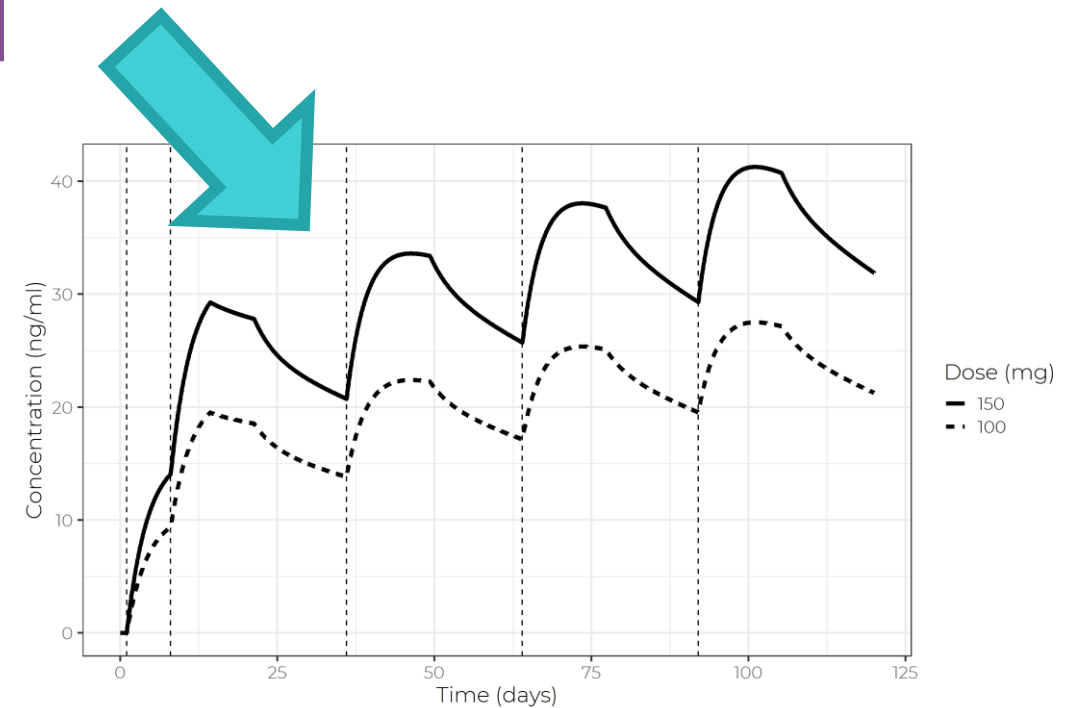
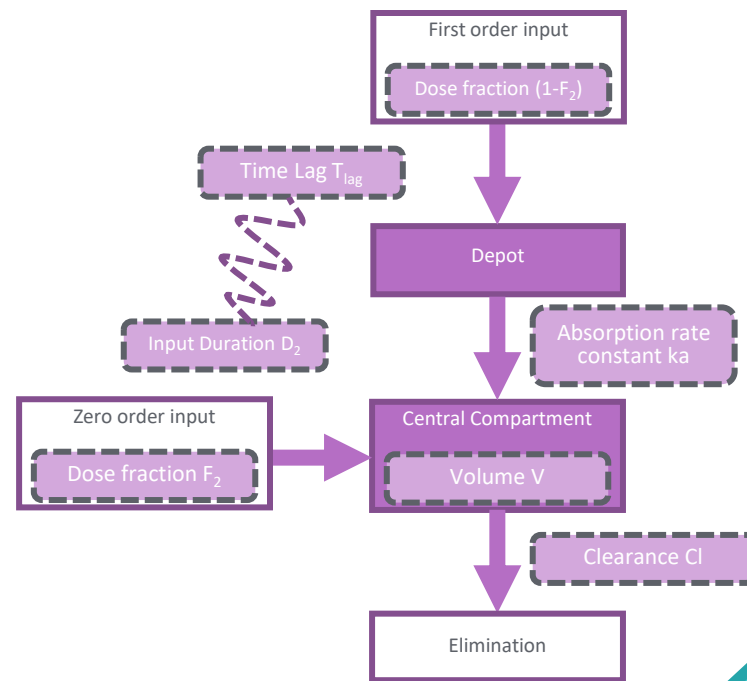
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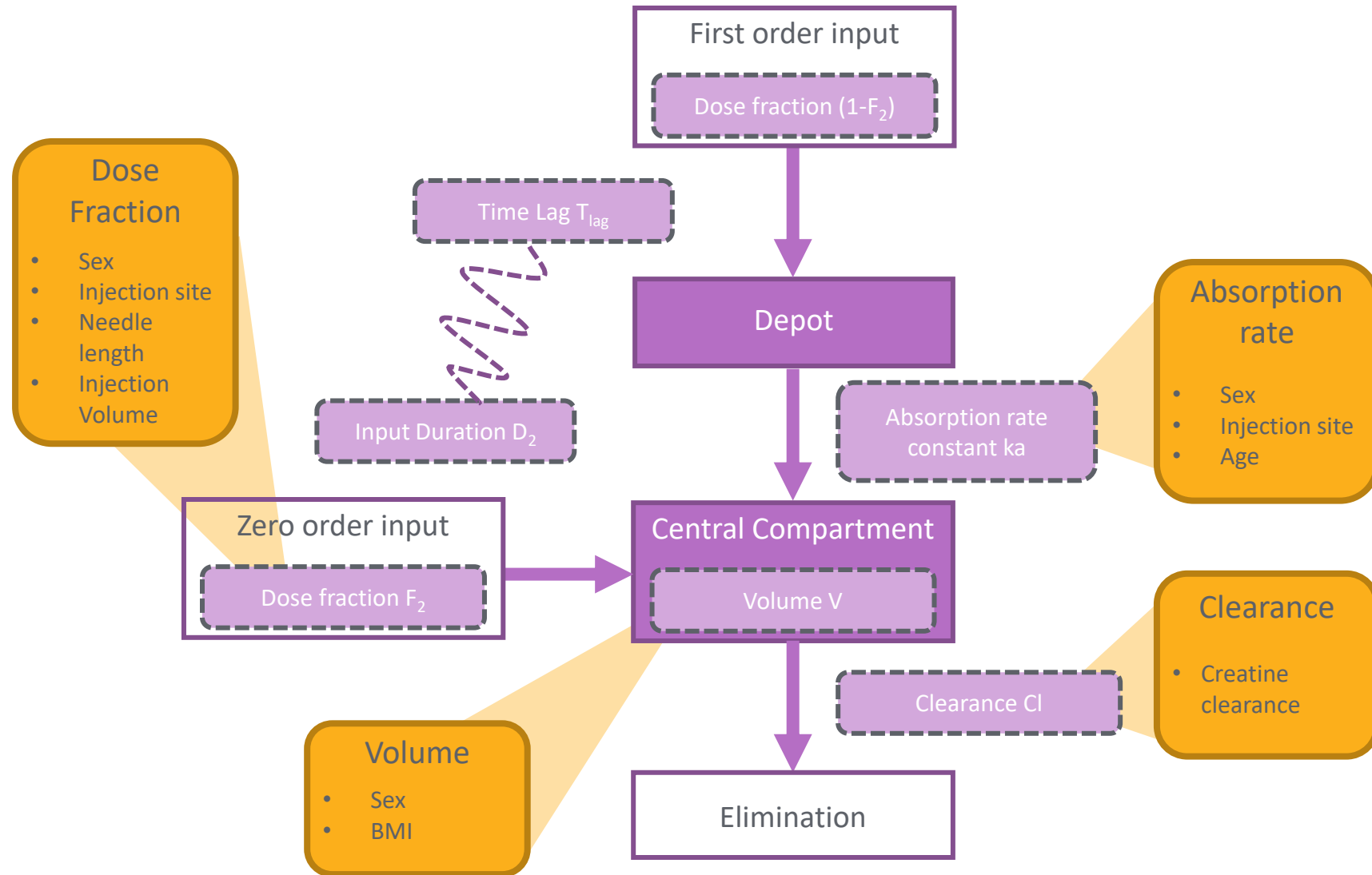
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Mathematical model \

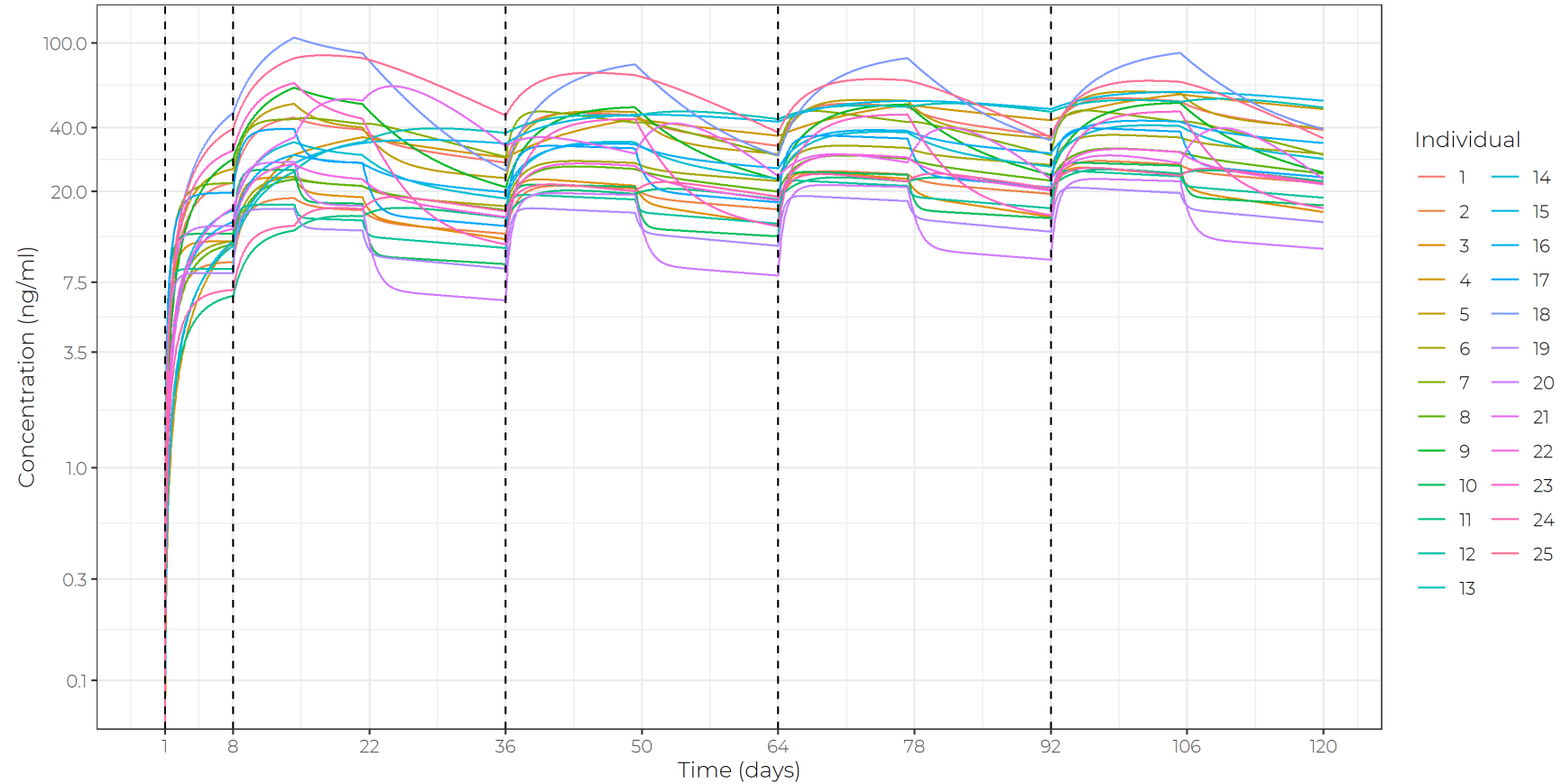
- One compartment model with linear absorption and linear elimination
- 5 parameters:
 - Volume V
 - Clearance Cl
 - Absorption rate k_a
 - Dose fraction F_2
 - Duration D / Time lag T_{lag}
- Including between subject variability



Simulating PK profiles \

- Reference product given to 25 virtual individuals based on the USA population
- Each individual has a unique age, BMI, height and ethnicity, giving them a unique set of PK parameters

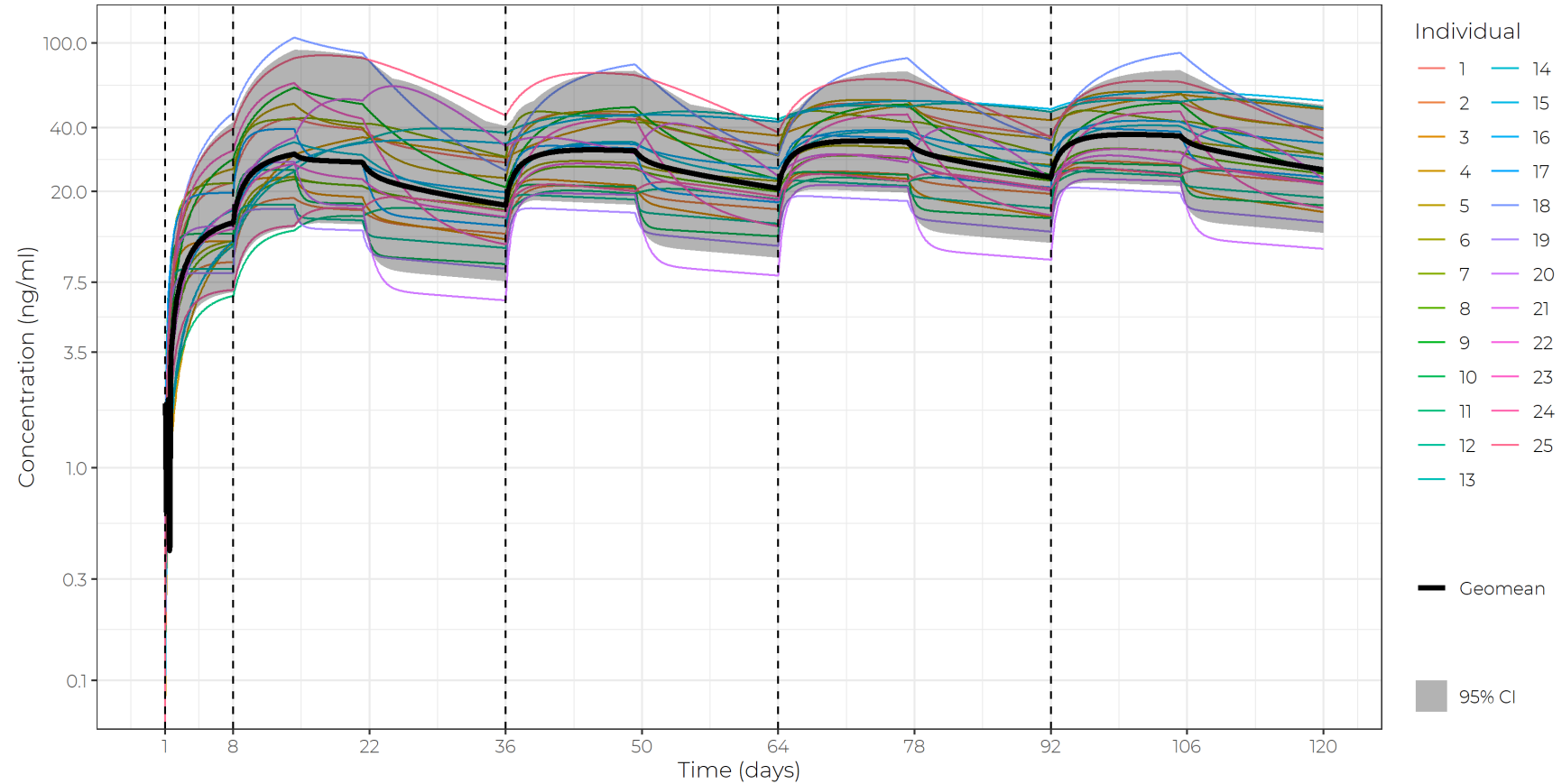
Paliperidone Palmitate popPK simulation
Dose 150 mg given on days 1,8,36,64,92



Simulating PK profiles \

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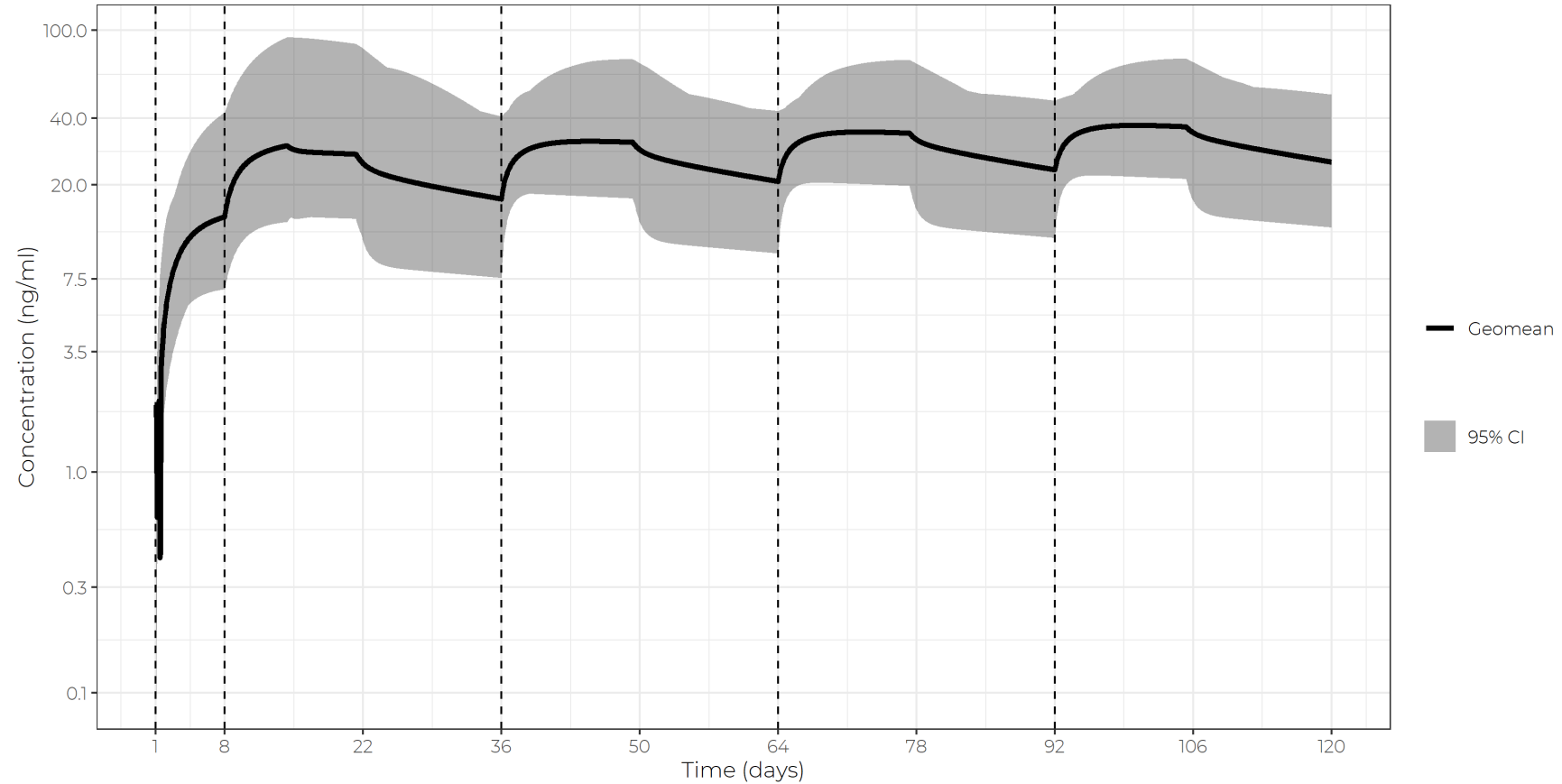
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Simulating PK profiles \

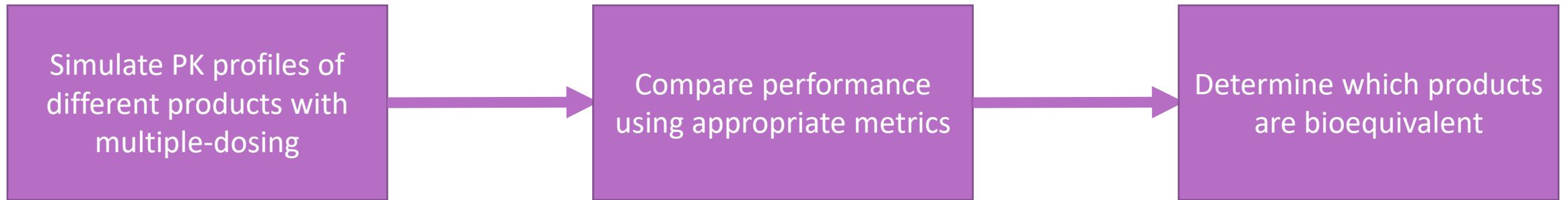
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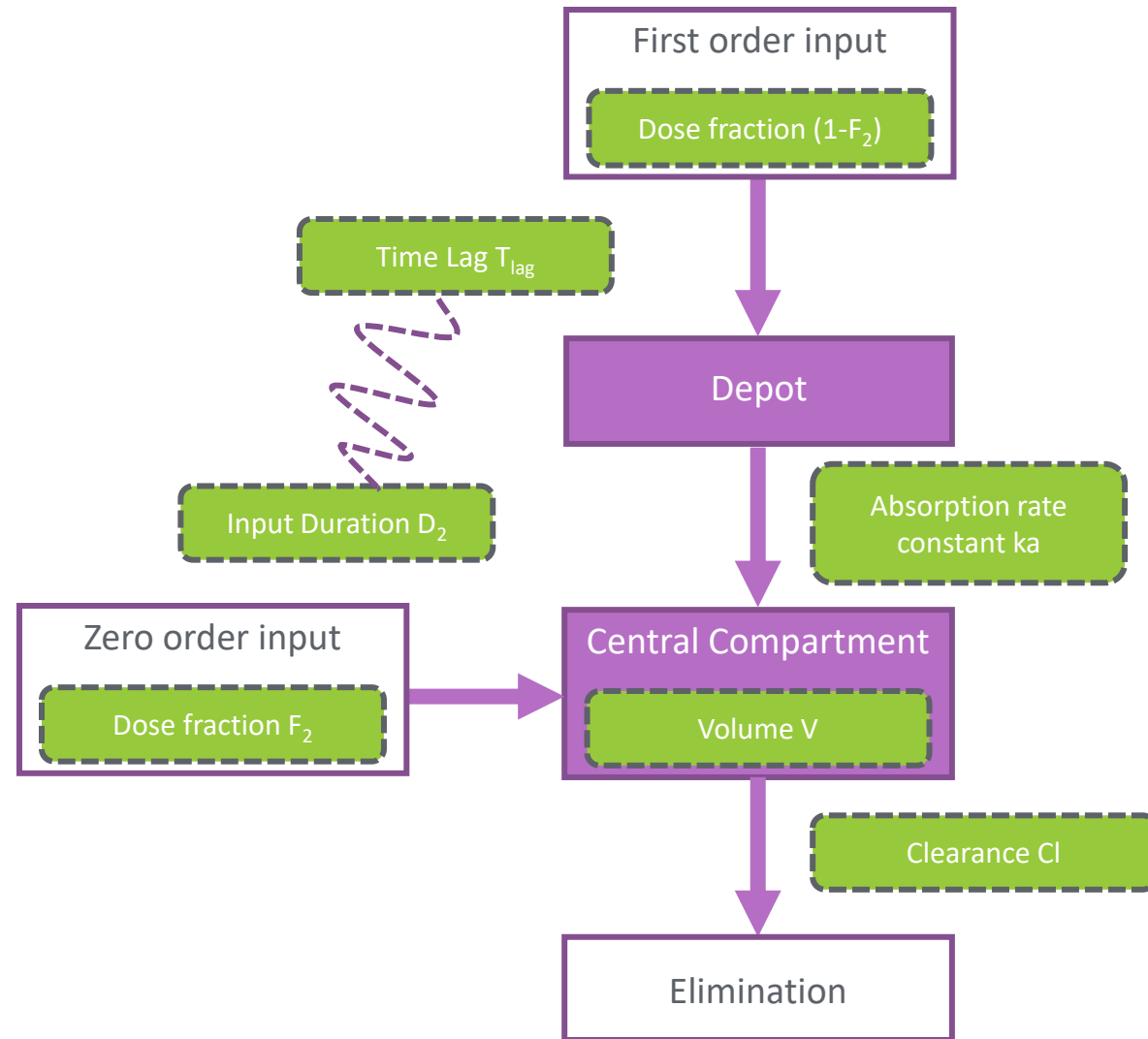
1) How to identify bioequivalent LAI products after multiple dosing ? \

Multiple-dosing bioequivalence \



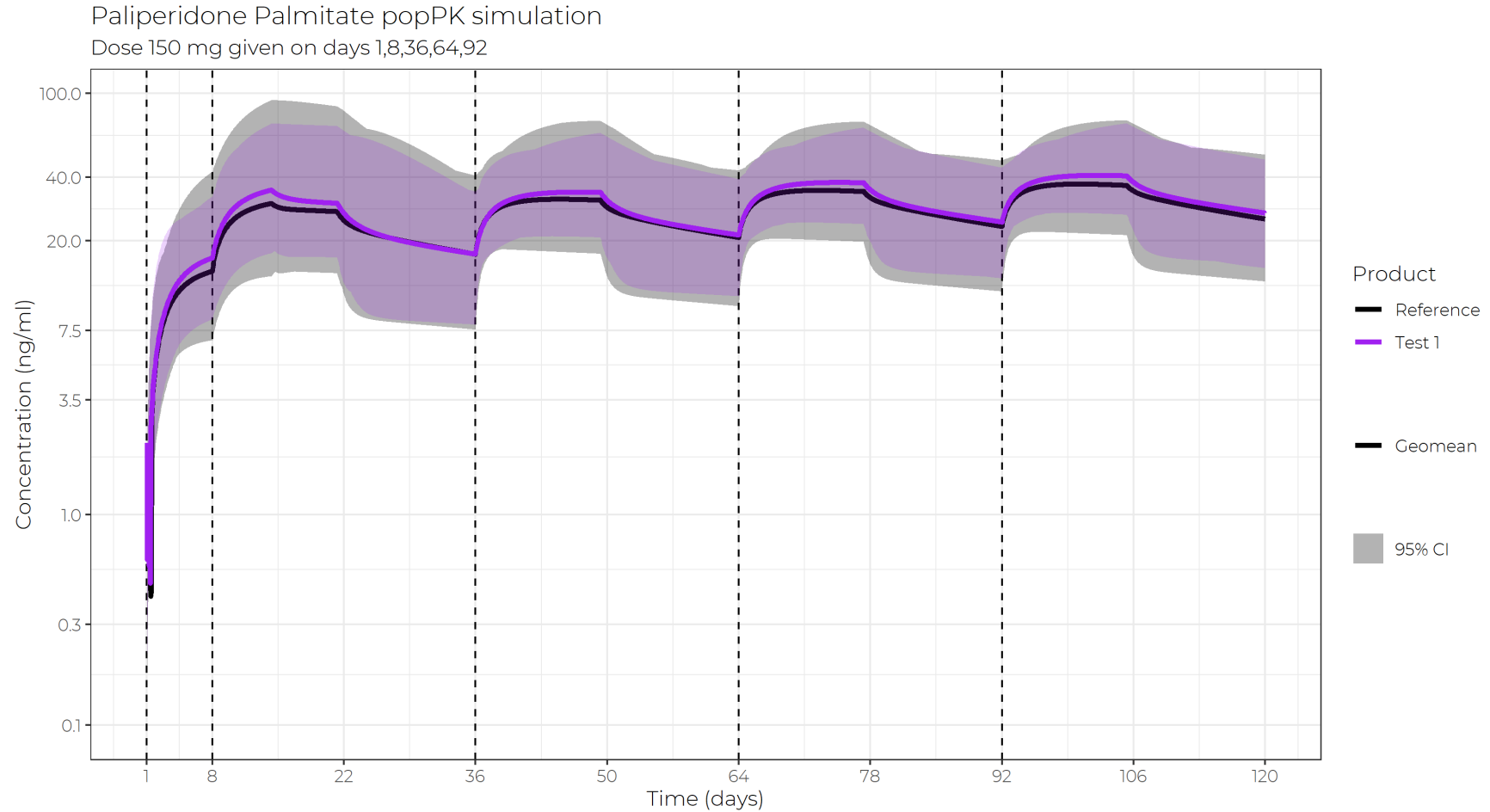
Mathematical model \

- Can easily change values of any of the parameters (shown in green)
 - Volume V
 - Clearance Cl
 - Absorption rate k_a
 - Dose fraction F_2
 - Duration D / Time lag T_{lag} (one variable)
- Both zero-order input and first order input are controlled by one parameter F_2



Simple cross-over study \

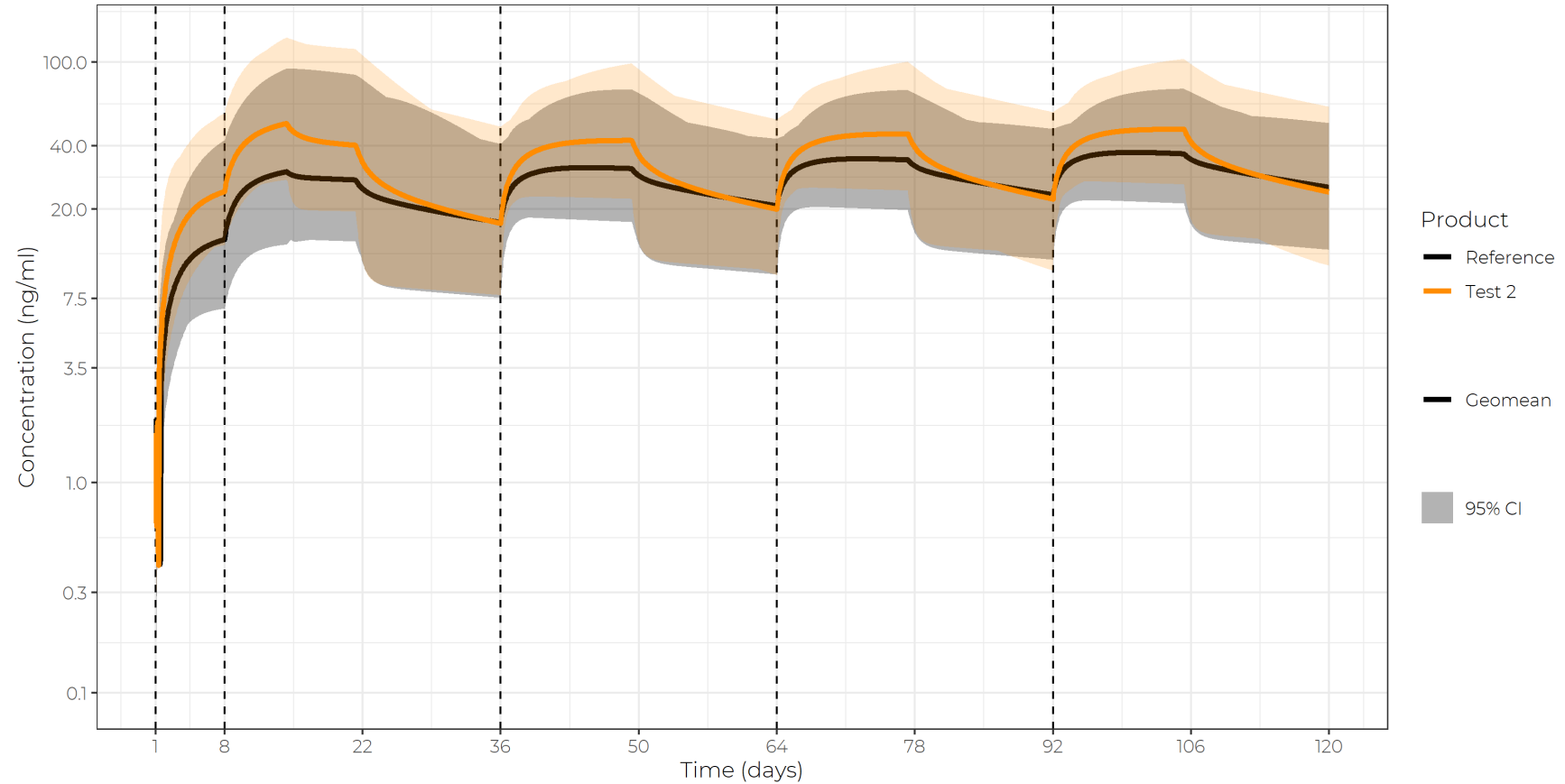
- Same individuals given both reference and test 1 products
- Test 1 has 80% K_a value of reference



Simple cross-over study \

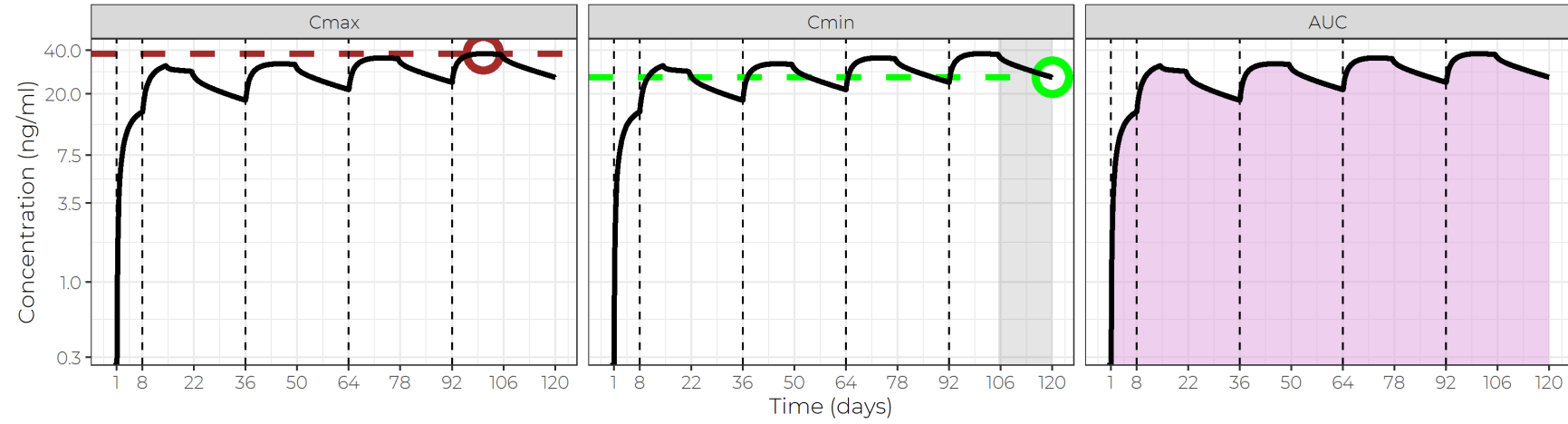
- Same individuals given both reference and test 2 products
- Test 2 has 150% F2 value of reference

Paliperidone Palmitate popPK simulation
Dose 150 mg given on days 1,8,36,64,92



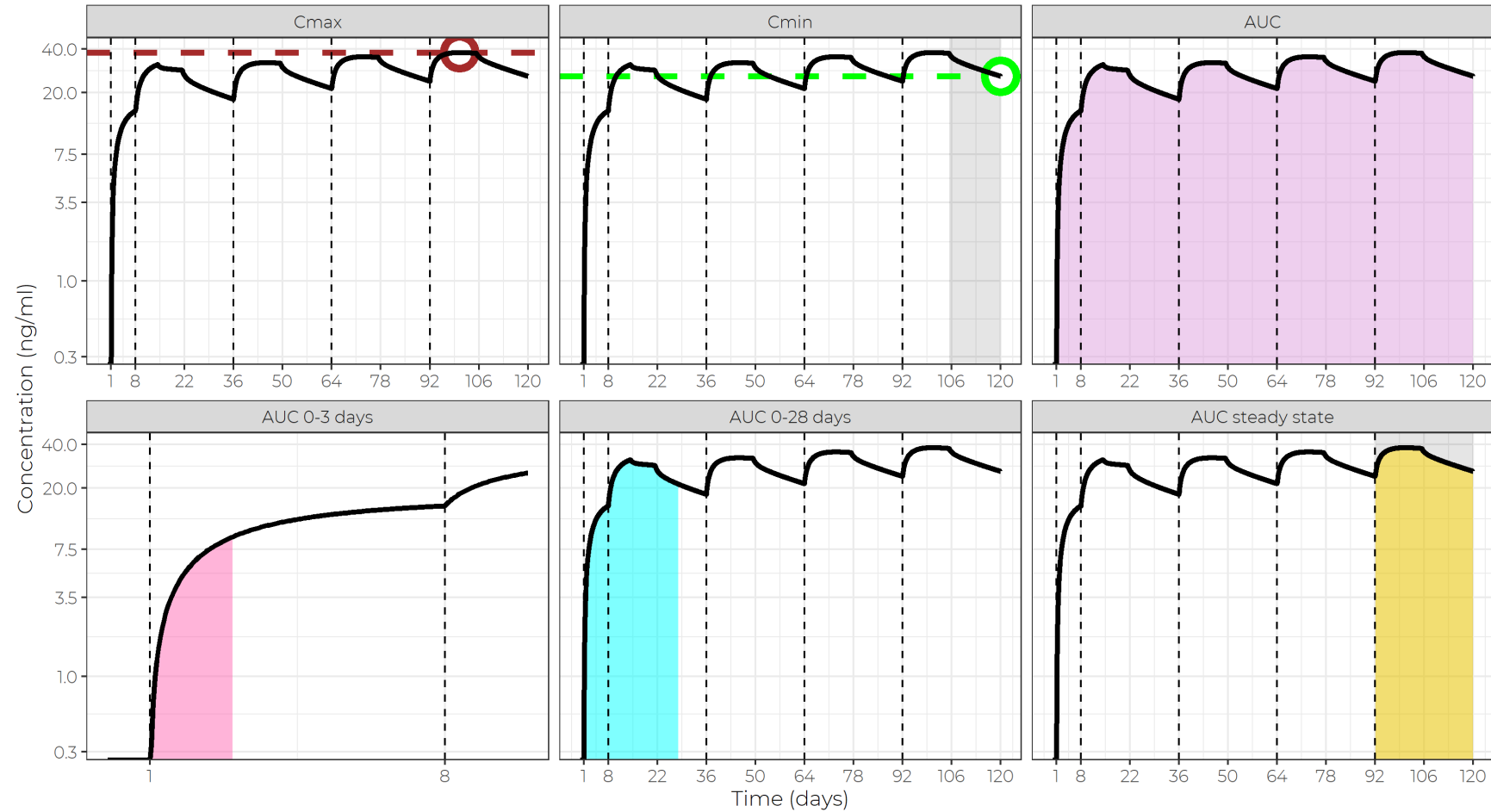
Comparing products \

- Standard metrics of C_{max} , C_{min} and AUC



Comparing products \

- Standard metrics of C_{max} , C_{min} and AUC
- Also add partial AUC's

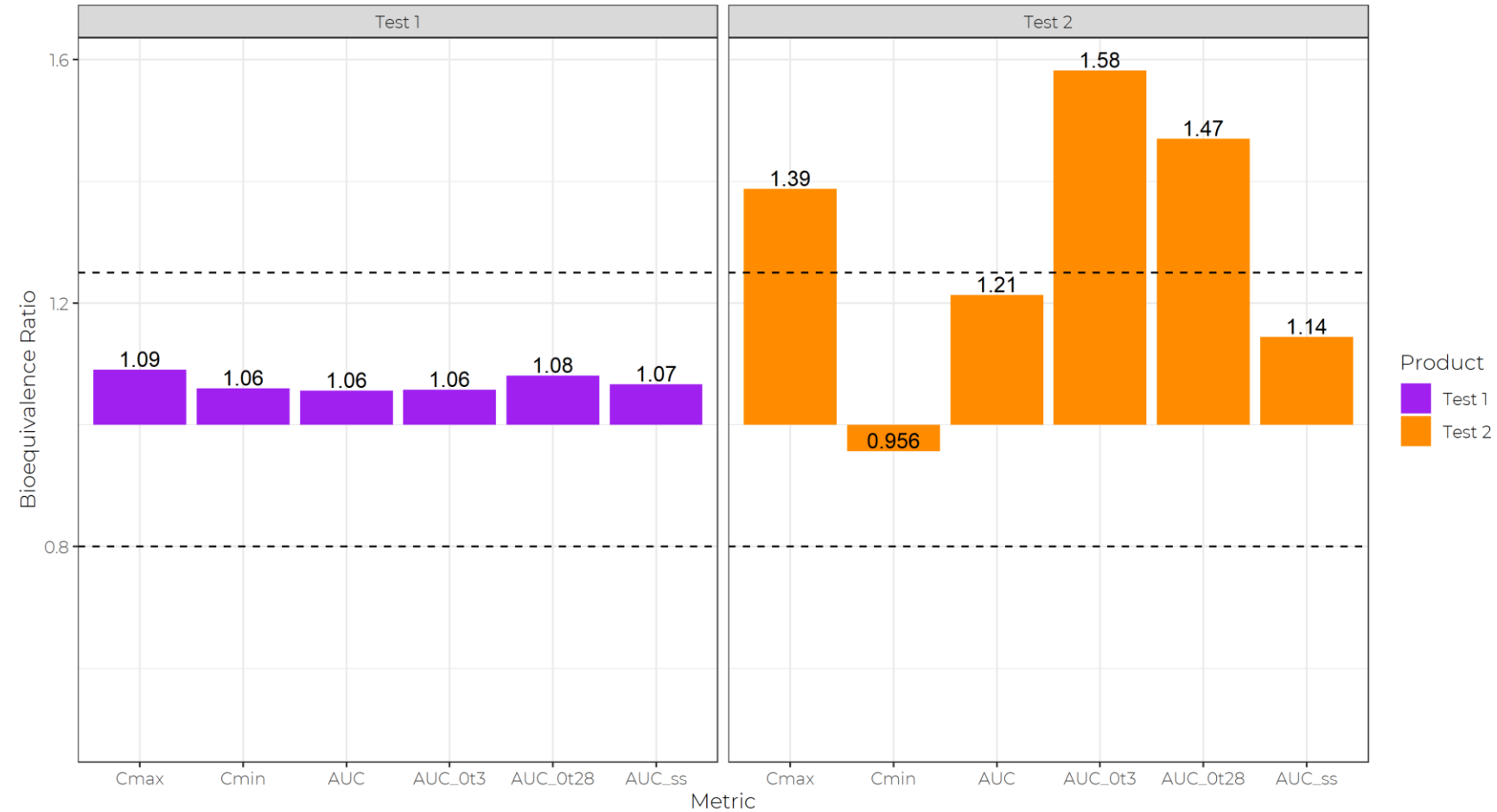


Comparing products \

- Bioequivalence ratio of test/reference between (0.8, 1.25)
- Point ratios have been used for simplicity (i.e. no CI, but analysis can be extended)
- Test 1 is bioequivalent
- Test 2 is not bioequivalent

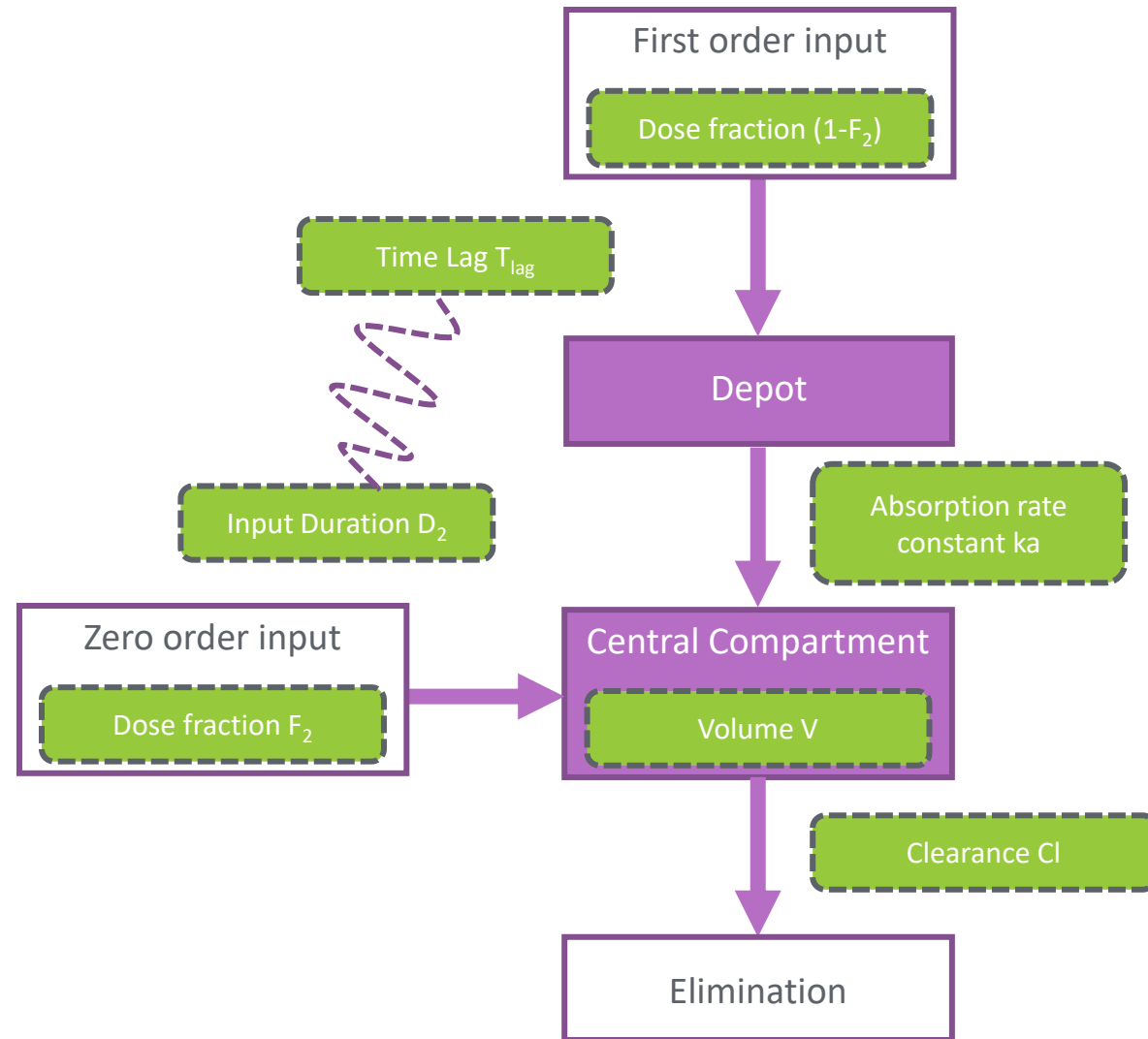
Test 1: Ka is 80% of reference

Test 2: F2 is 150% of reference



Mathematical model \

- Can easily change values of any of the parameters (shown in green)
 - Volume V
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 - Absorption rate k_a
 - Dose fraction F_2
 - Duration D / Time lag T_{lag} (one variable)
- Both zero-order input and first order input are controlled by one parameter F_2

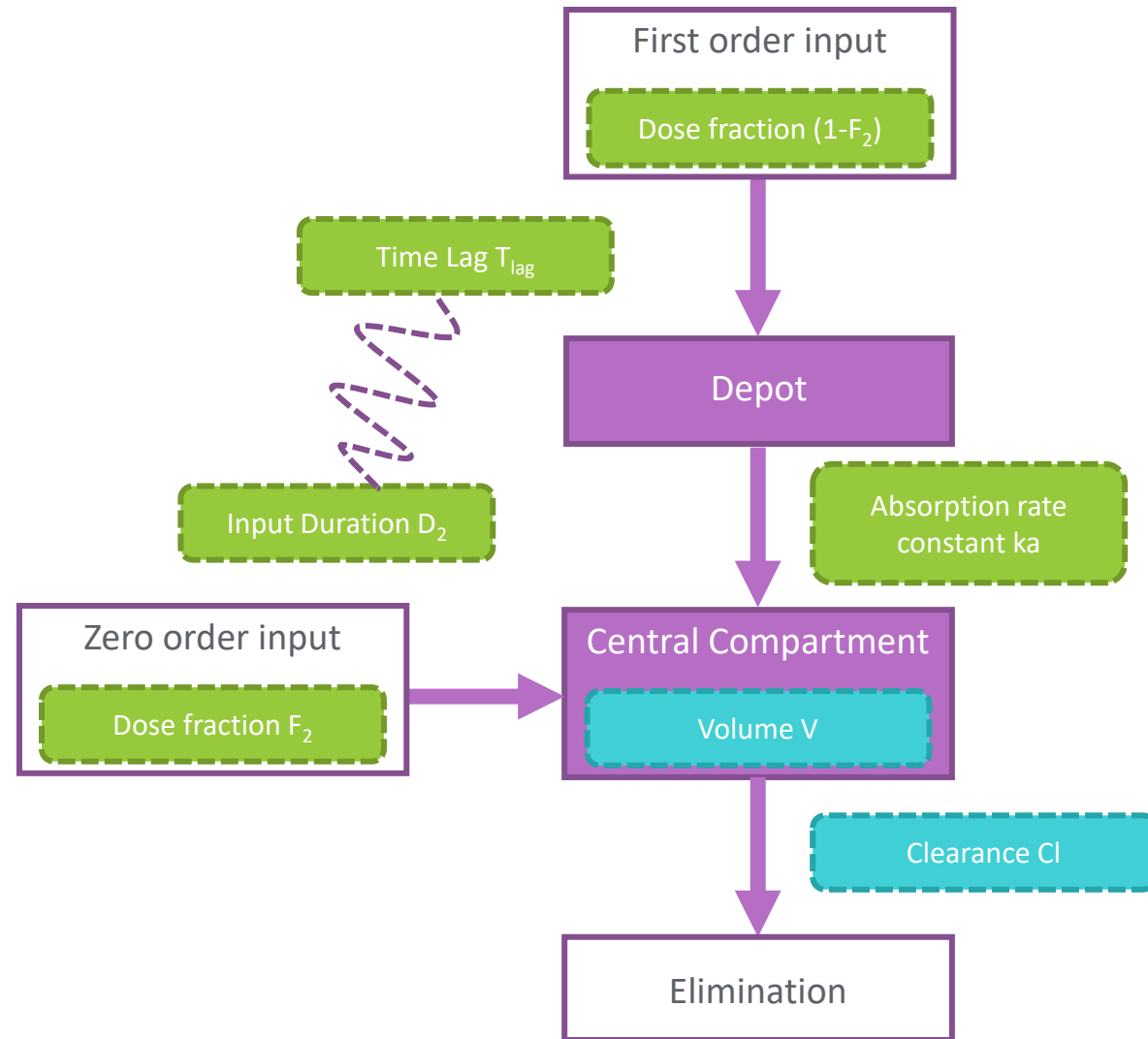


Mathematical model \

Assume Volume (V) and Clearance (Cl) are properties of the drug (blue)

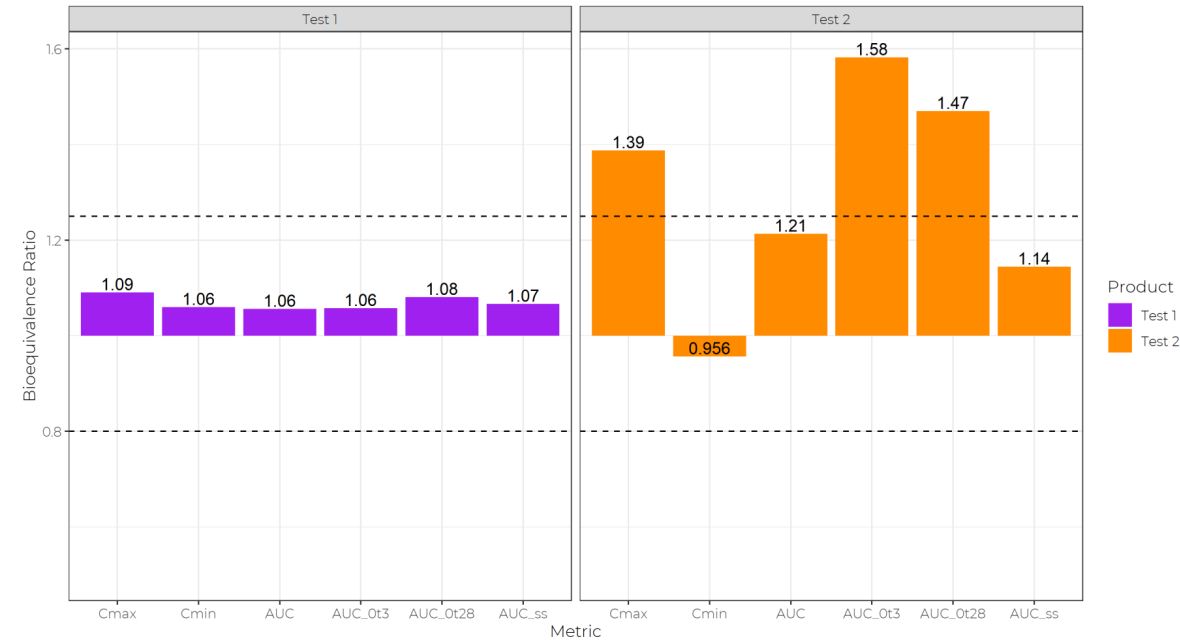
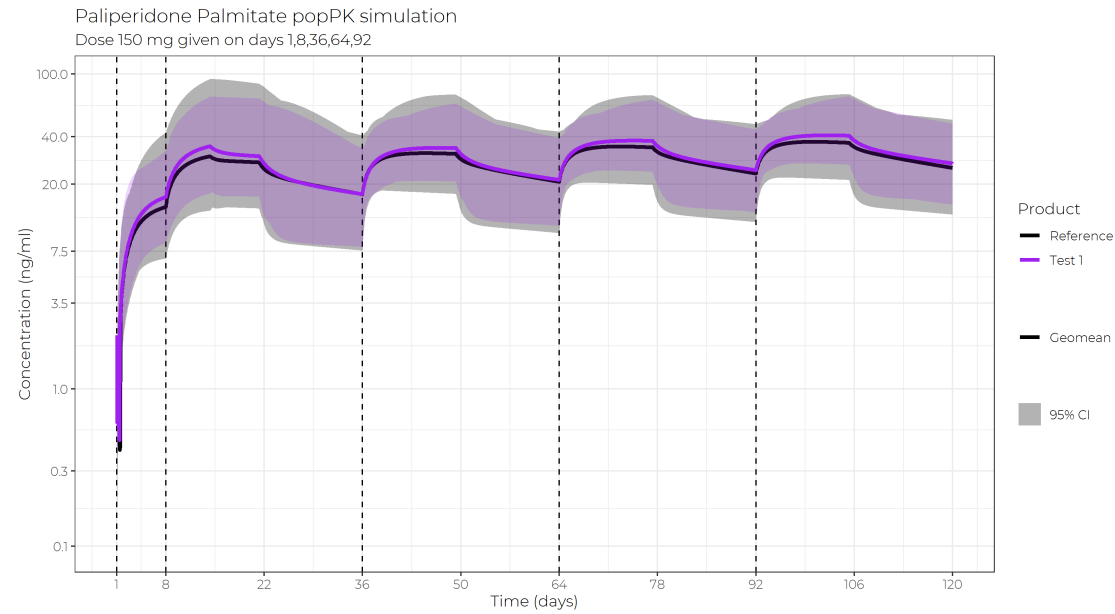
All other parameters are properties of the formulation (green)

Test different products with different F_2 , T_{lag} , k_a values



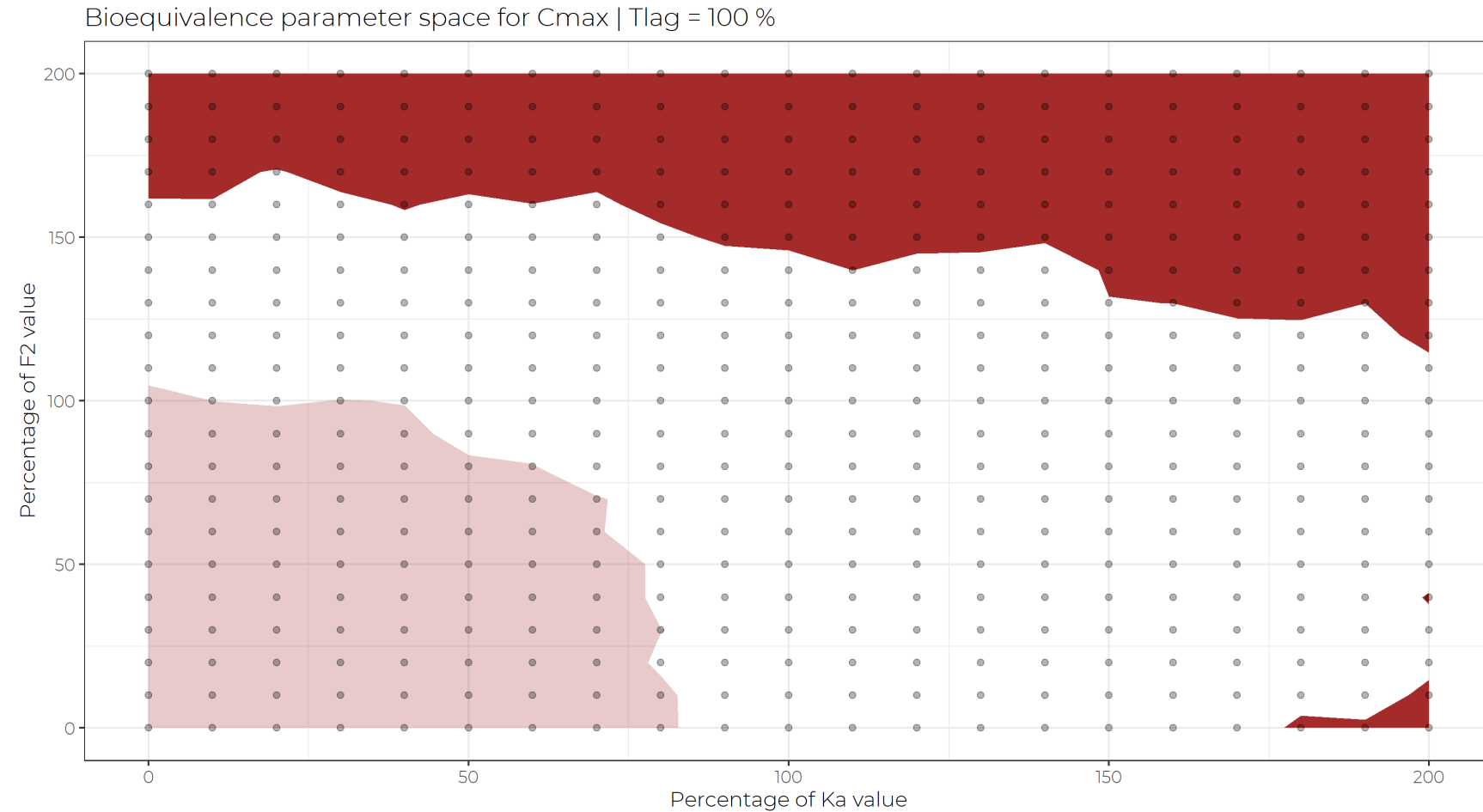
Simple cross-over study

- Same individuals given all products



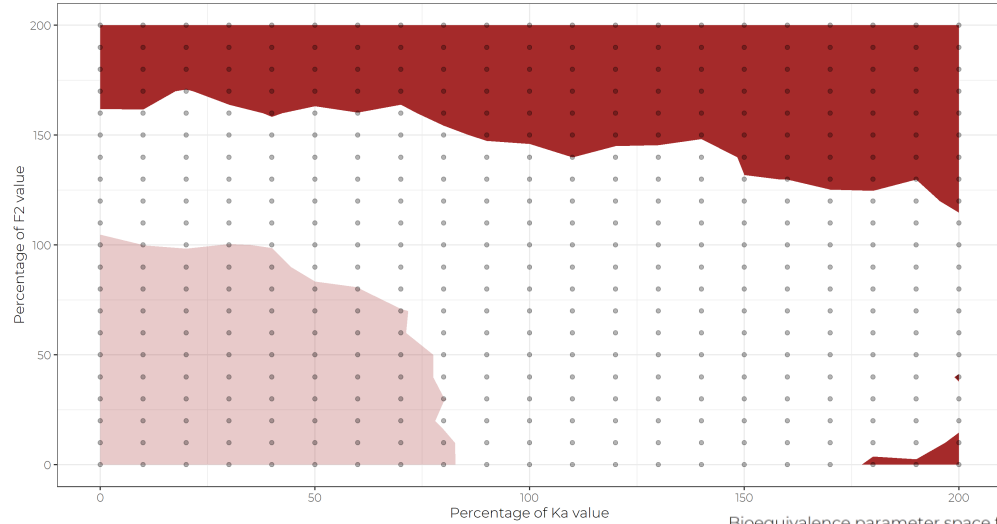
Comparing products \

- 9261 different product combinations (each shown by a grey dot)
- 25 individuals, who have 3 clinical studies of each product
- Over ½ million simulations

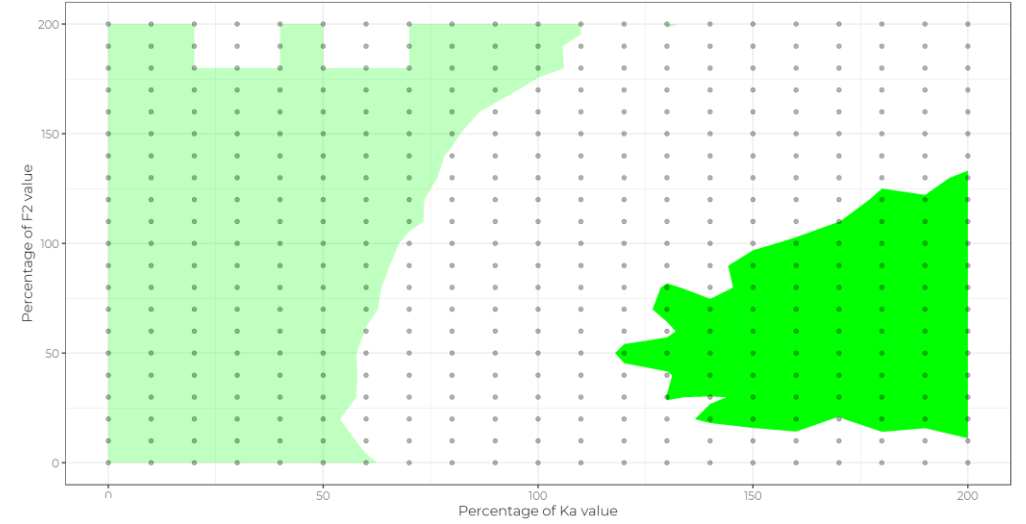


Comparing products \

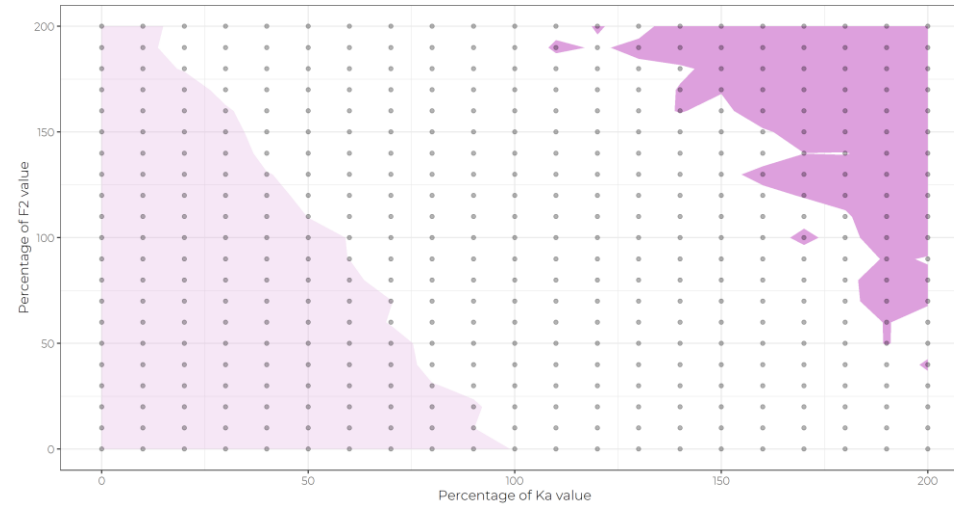
Bioequivalence parameter space for Cmax | Tlag = 100 %



Bioequivalence parameter space for Cmin | Tlag = 100 %

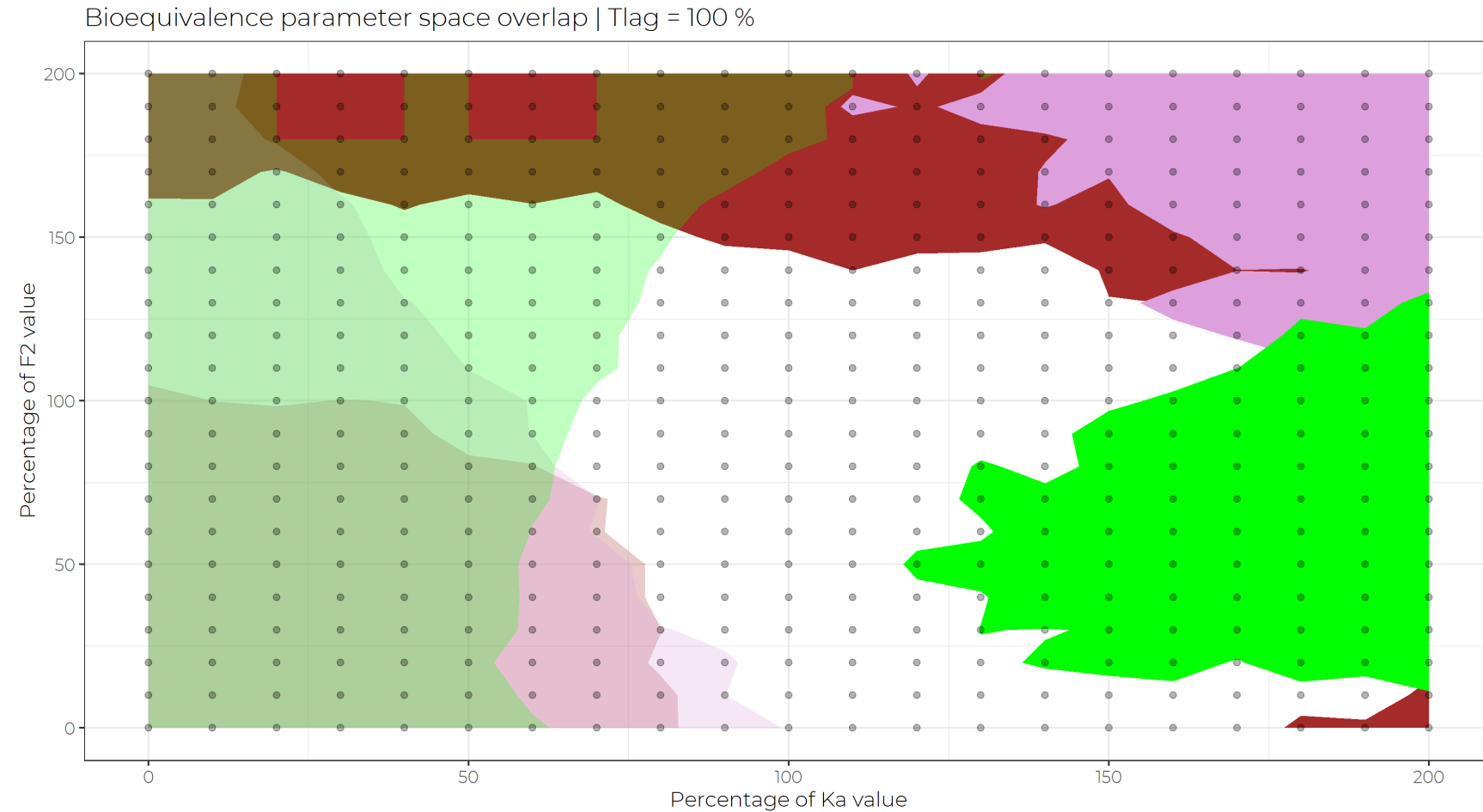


Bioequivalence parameter space for AUC | Tlag = 100 %



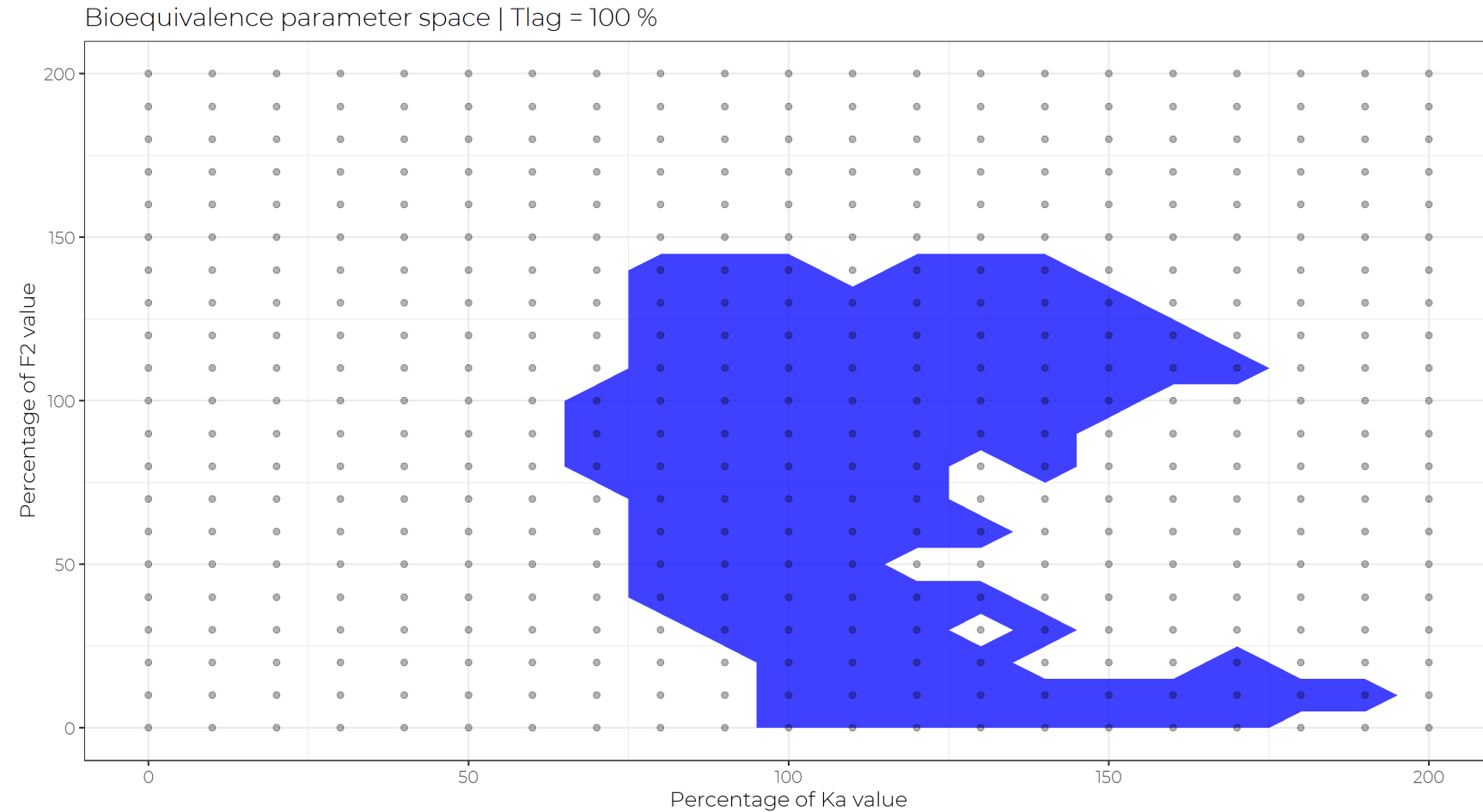
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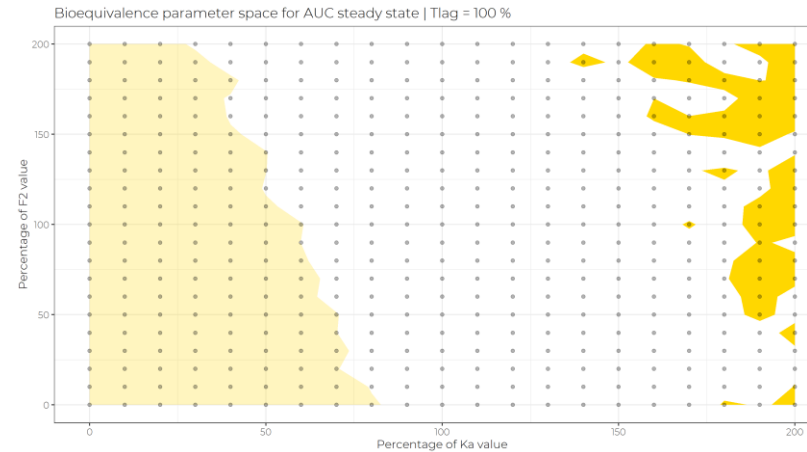
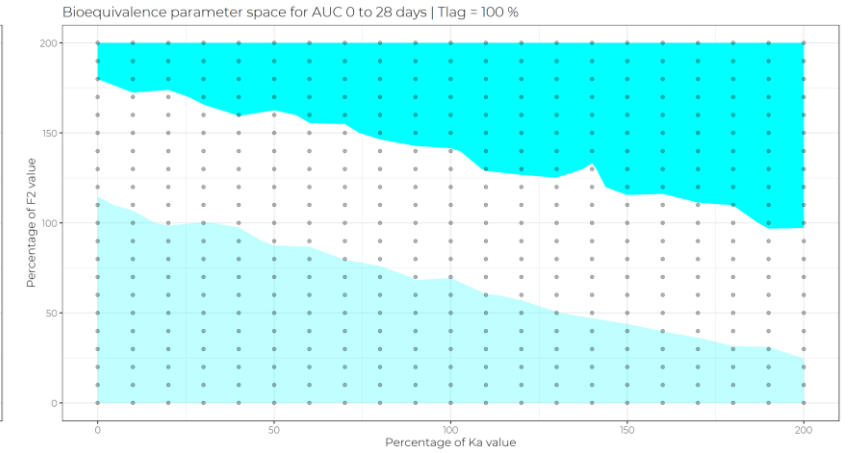
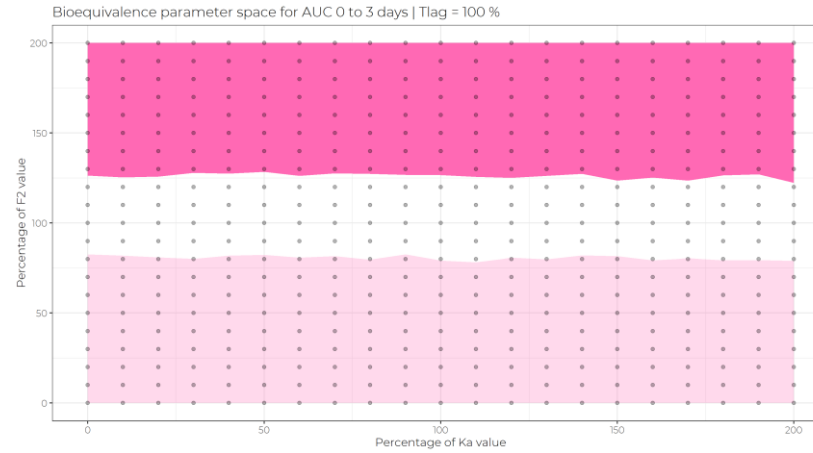
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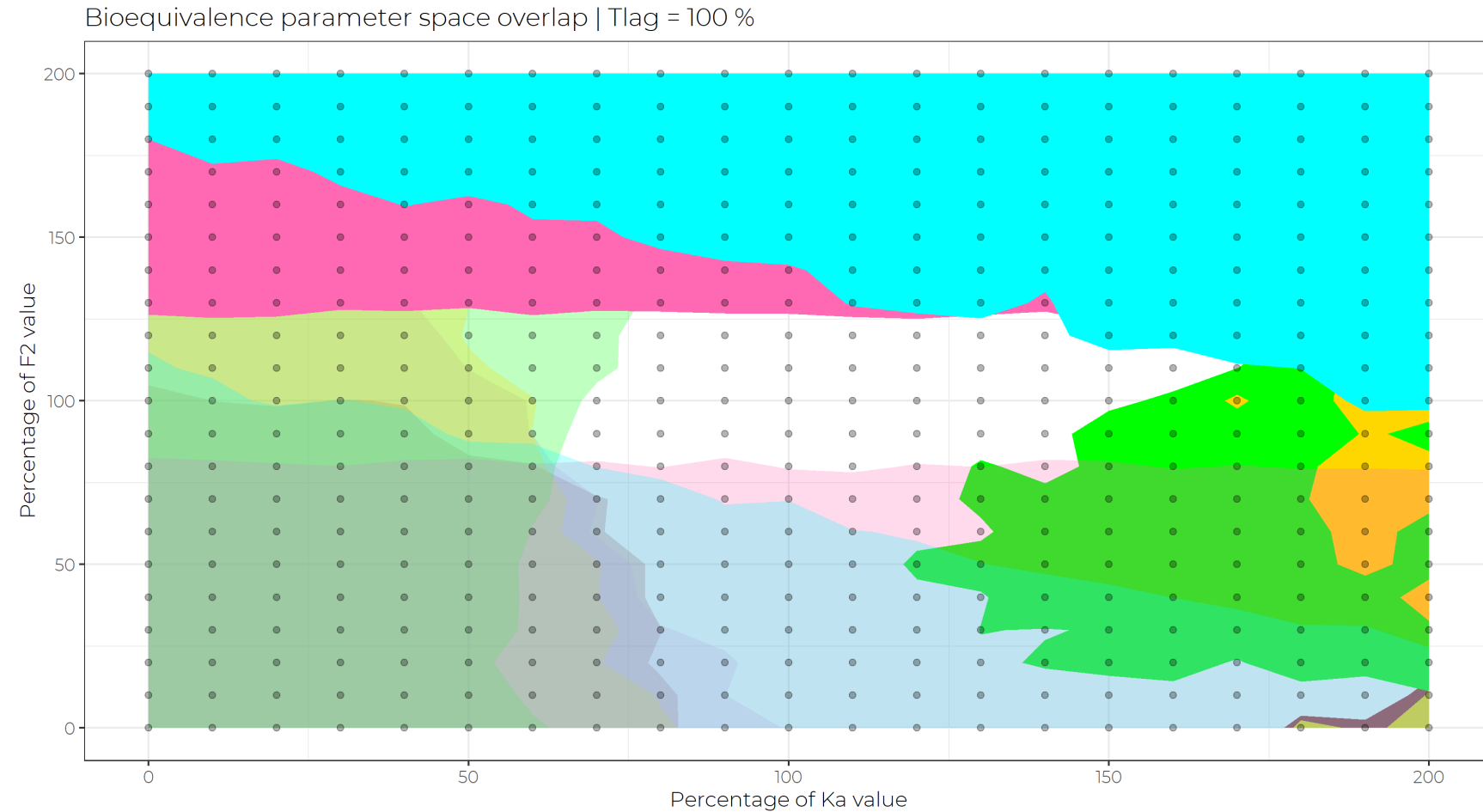
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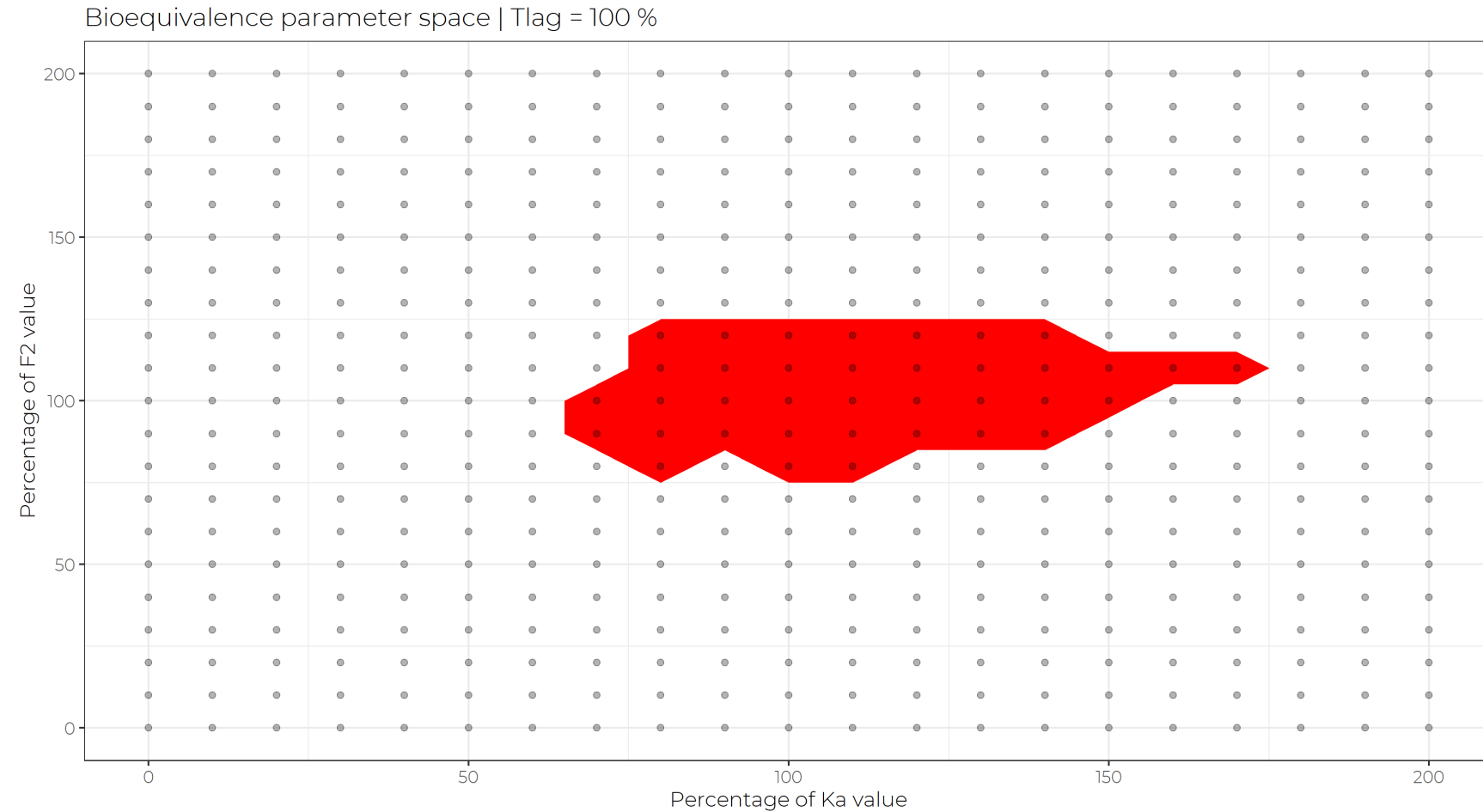
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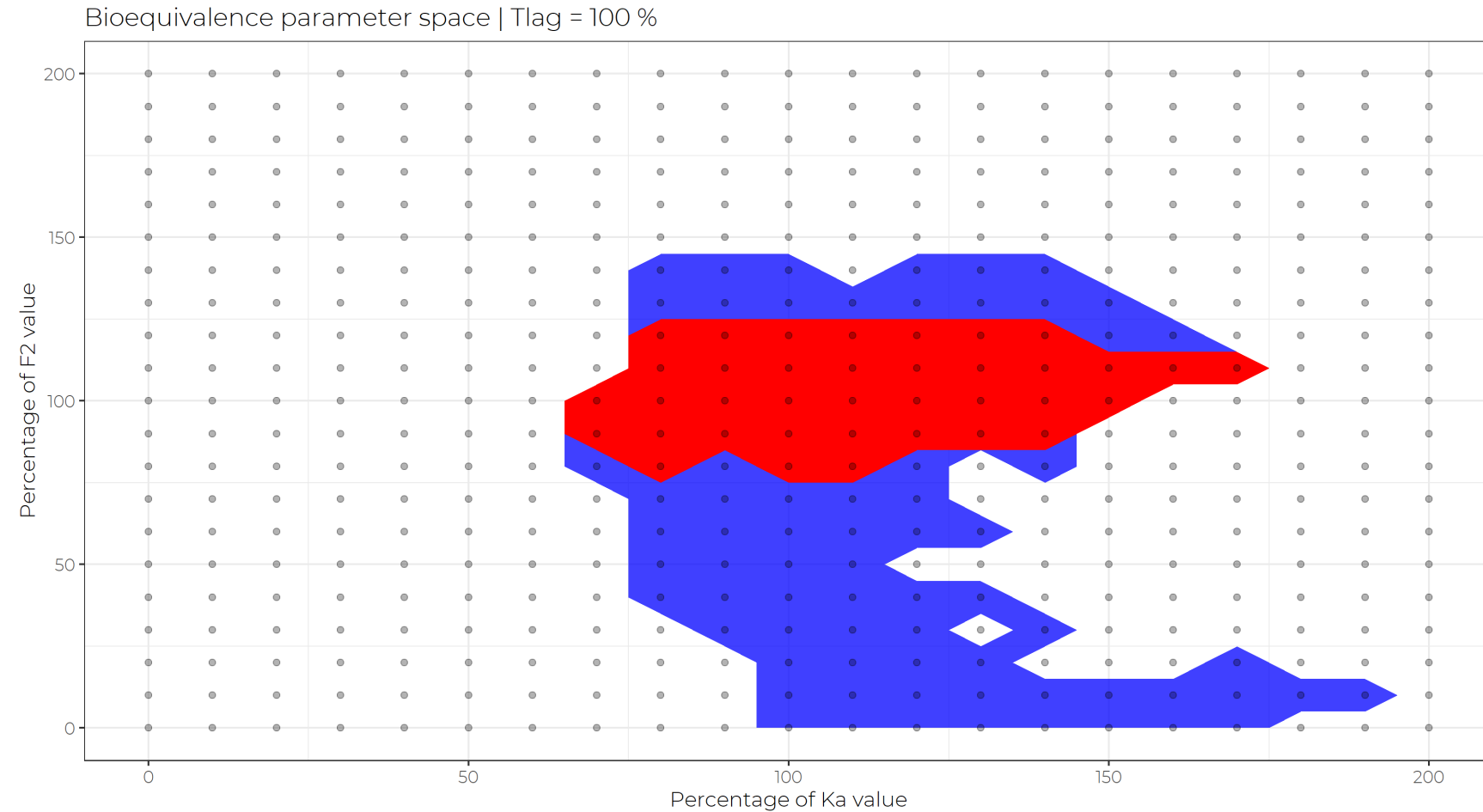
Comparing products \

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- Over ½ million simulations



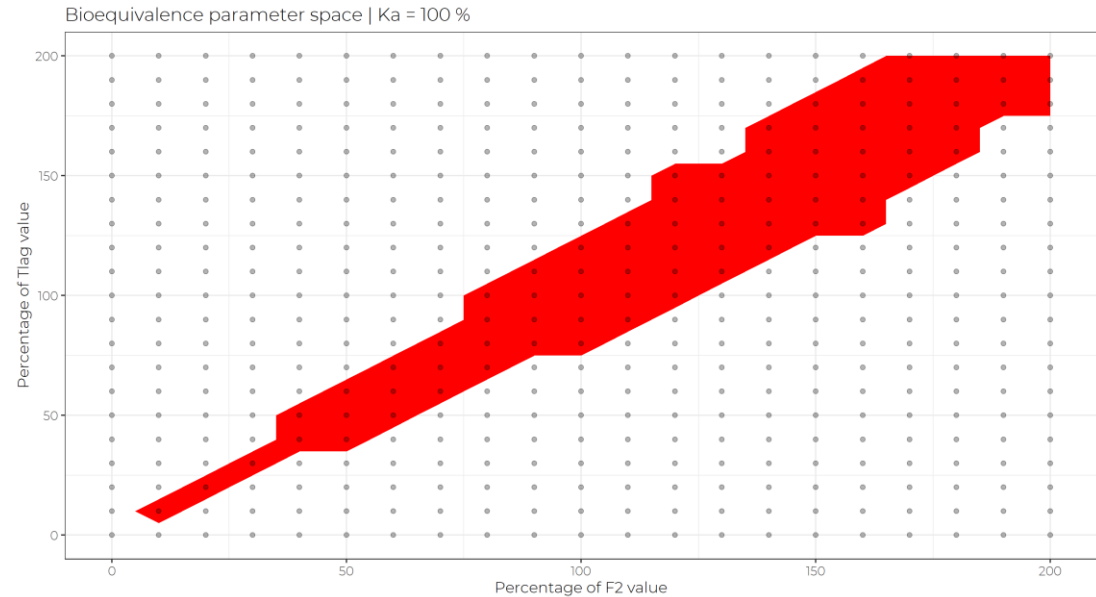
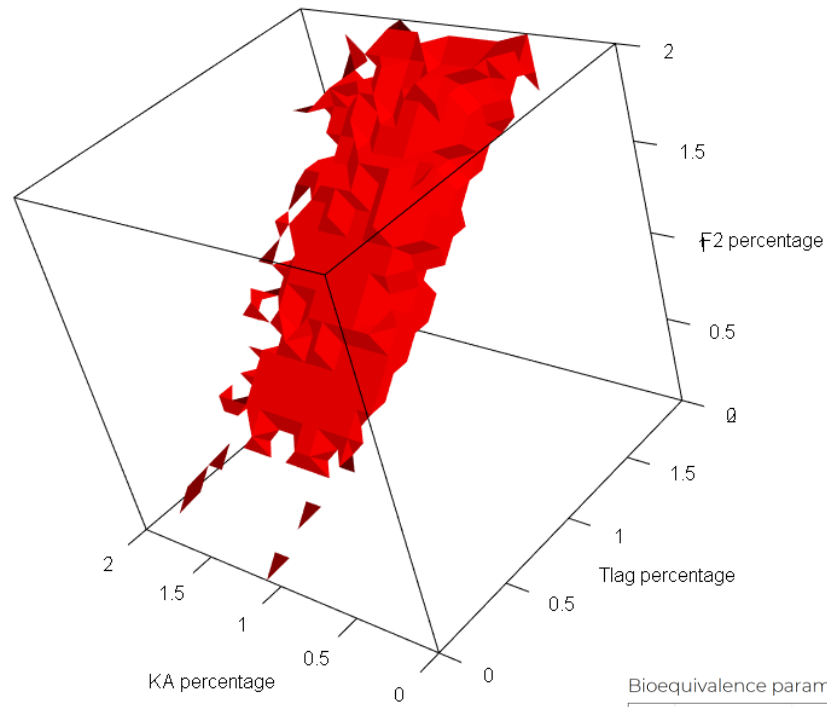
Comparing products \

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- 25 individuals, who have 3 clinical studies of each product
- Over ½ million simulations



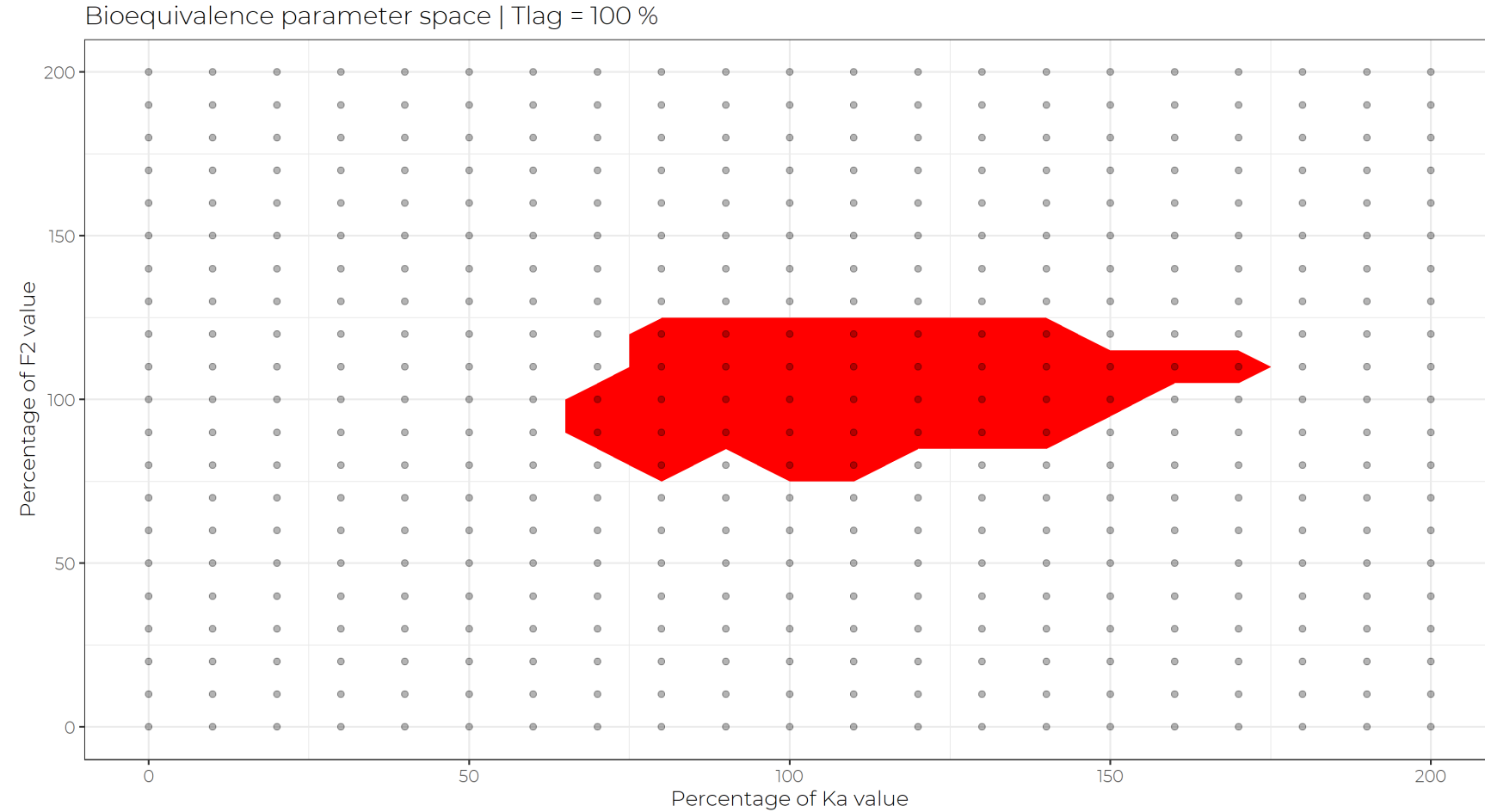
Comparing products \

- 9261 different product combinations (each shown by a grey dot)
- 25 individuals, who have 3 clinical studies of each product
- Over 1/2 million simulations



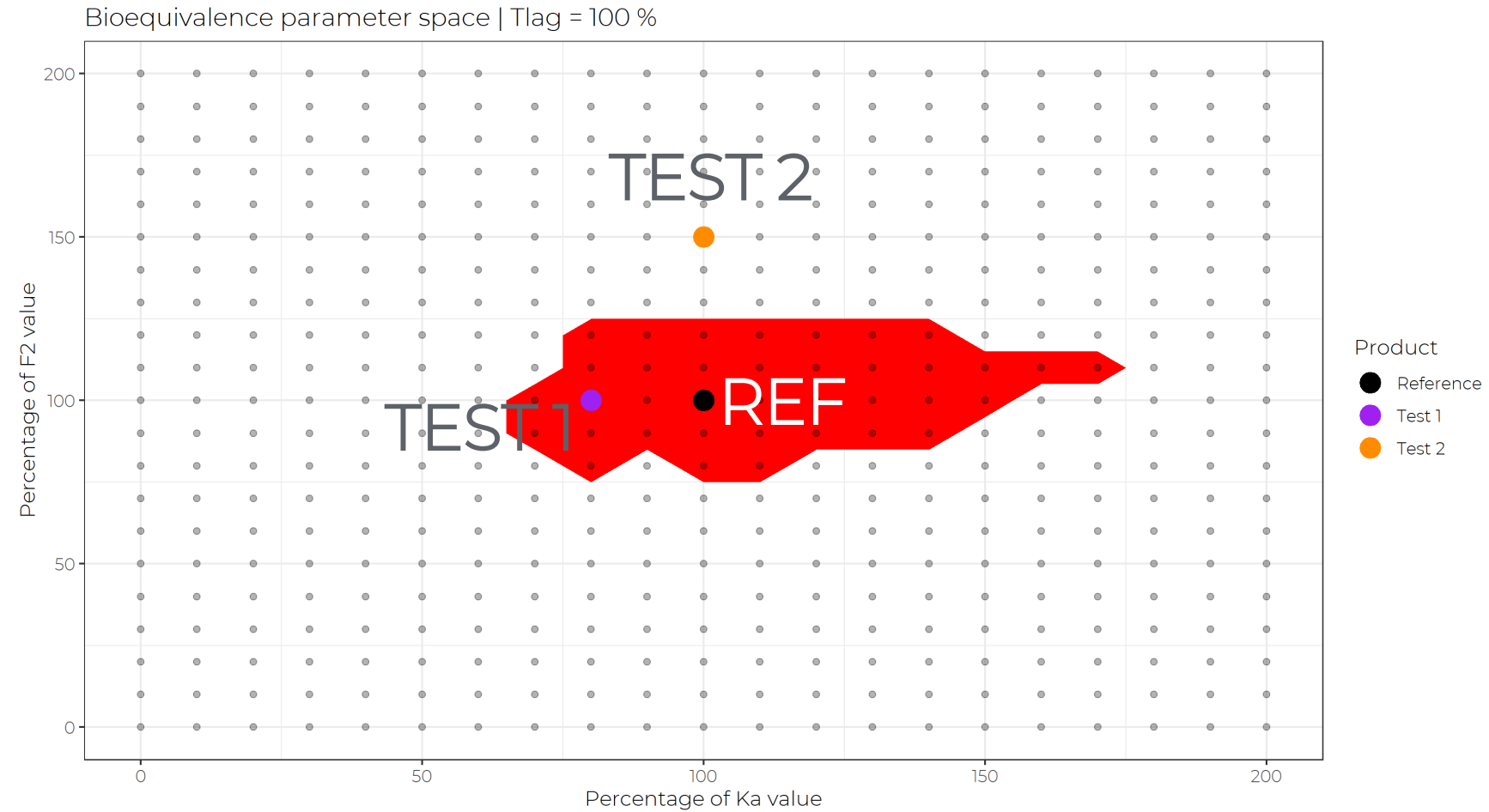
Comparing products \

- Compare bioequivalent and non-equivalent profiles



Comparing products \

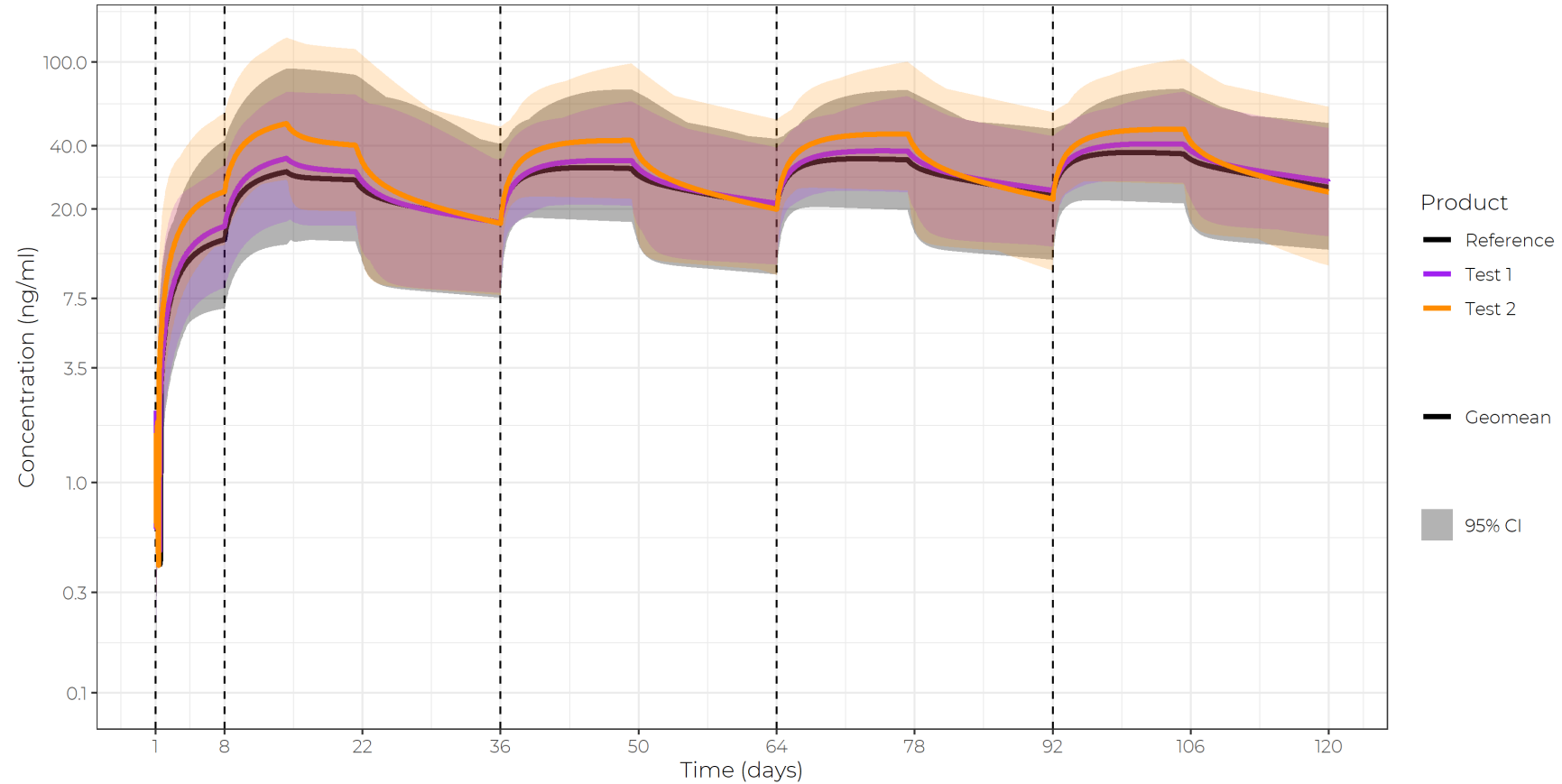
- Compare bioequivalent and non-equivalent profiles



Comparing products \

- Compare bioequivalent and non-equivalent profiles

Paliperidone Palmitate popPK simulation
Dose 150 mg given on days 1,8,36,64,92



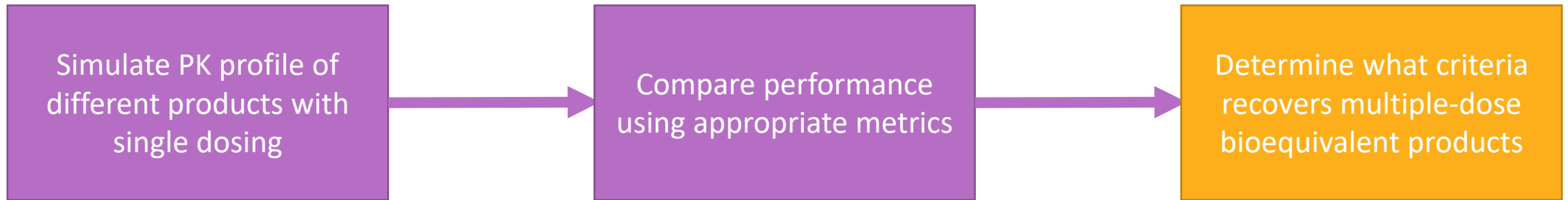
1) Multiple-dose bioequivalence: What have we learnt? \

Population PK modelling has allowed us to

- Simulate PK profiles for different products
- Examine how the choice of BE metrics affects which products are considered bioequivalent
- Discover a range of products (formulation parameter space) which are bioequivalent after multiple-doses

2) Do we need multiple doses? \

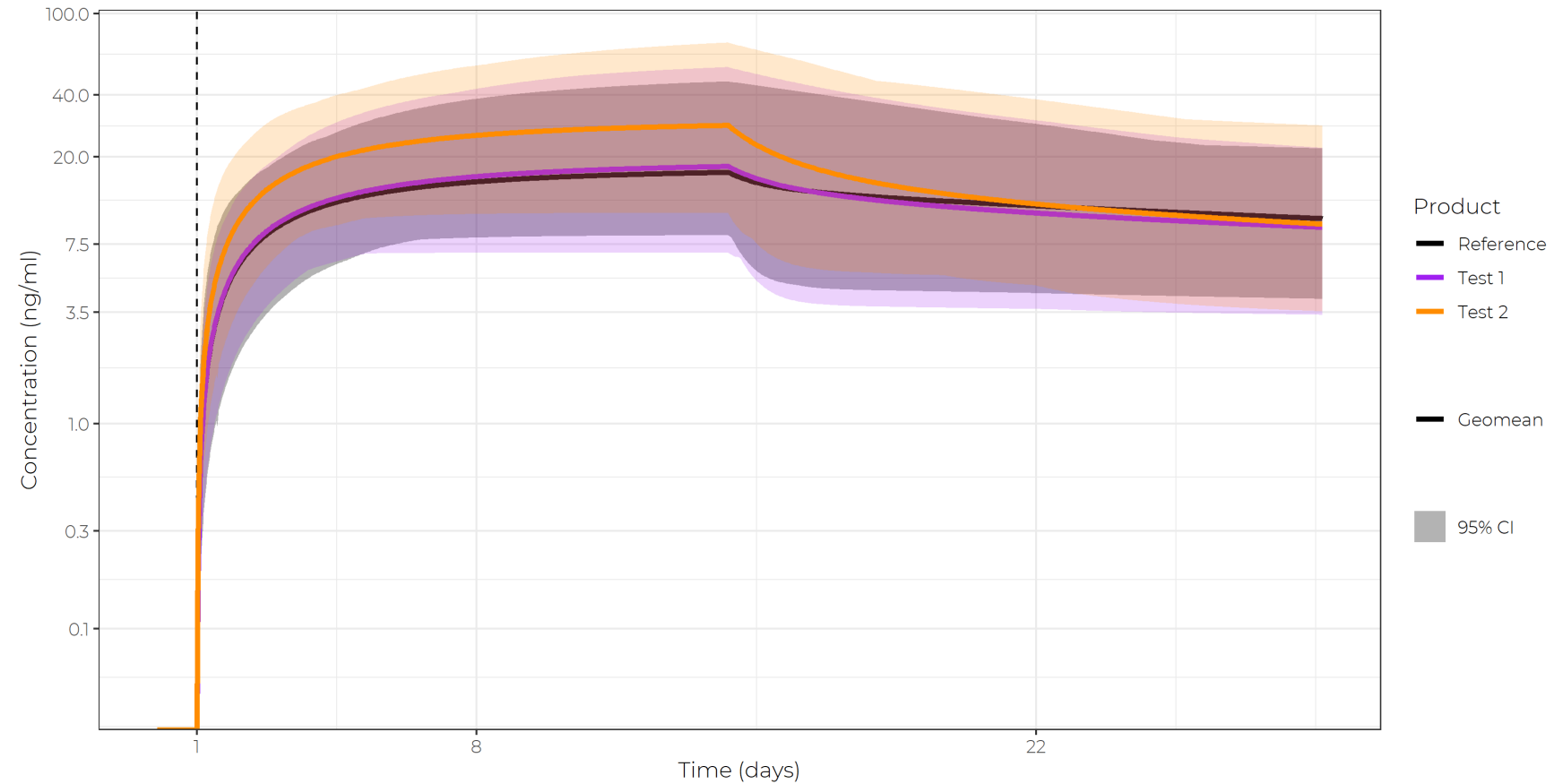
Single-dose bioequivalence \



Comparing products \

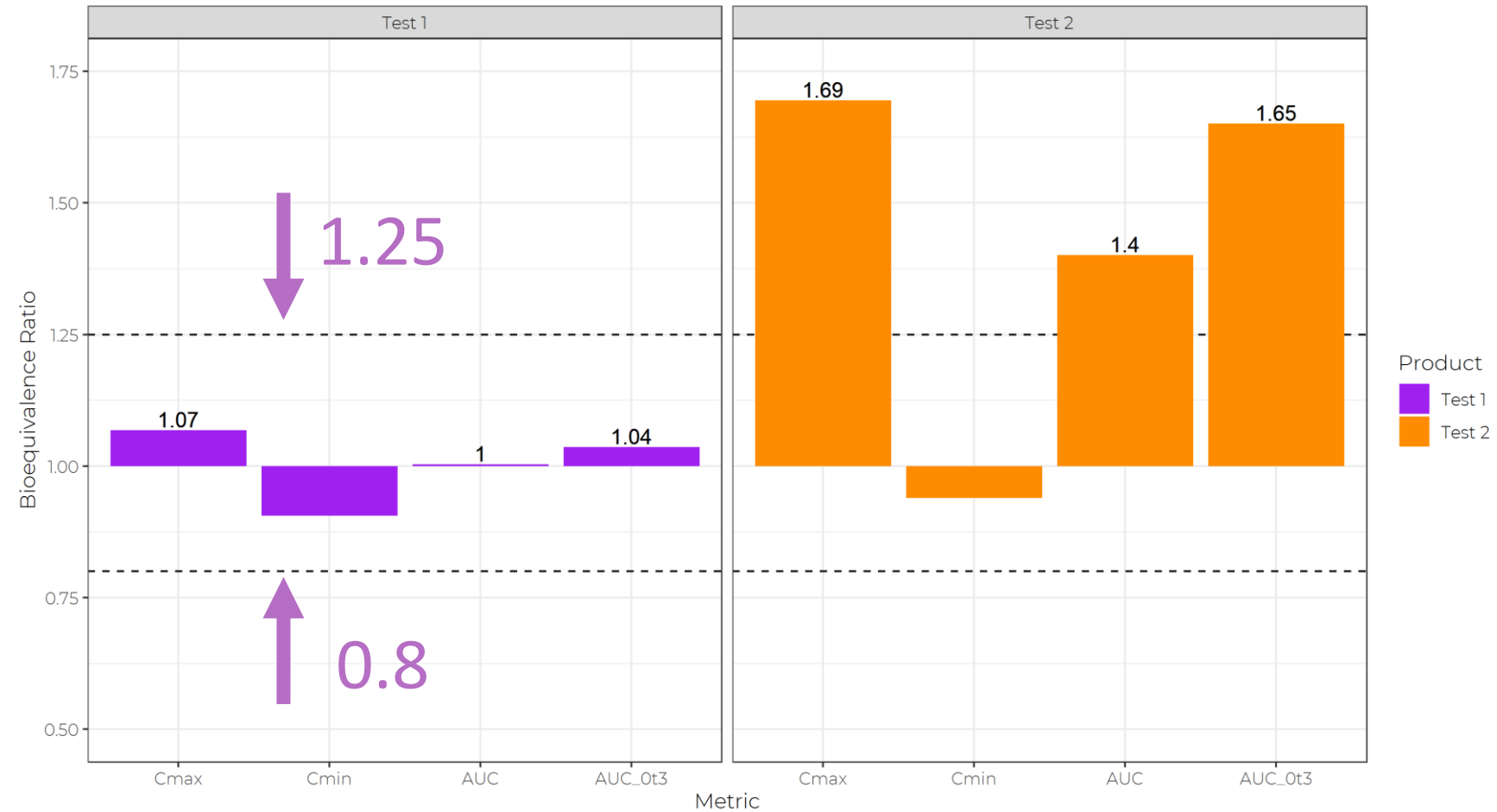
- 1681 different product combinations
- 25 individuals, each receiving 3 schedules of single-dose administration of each product

Paliperidone Palmitate popPK simulation
Dose 150 mg given on days 1



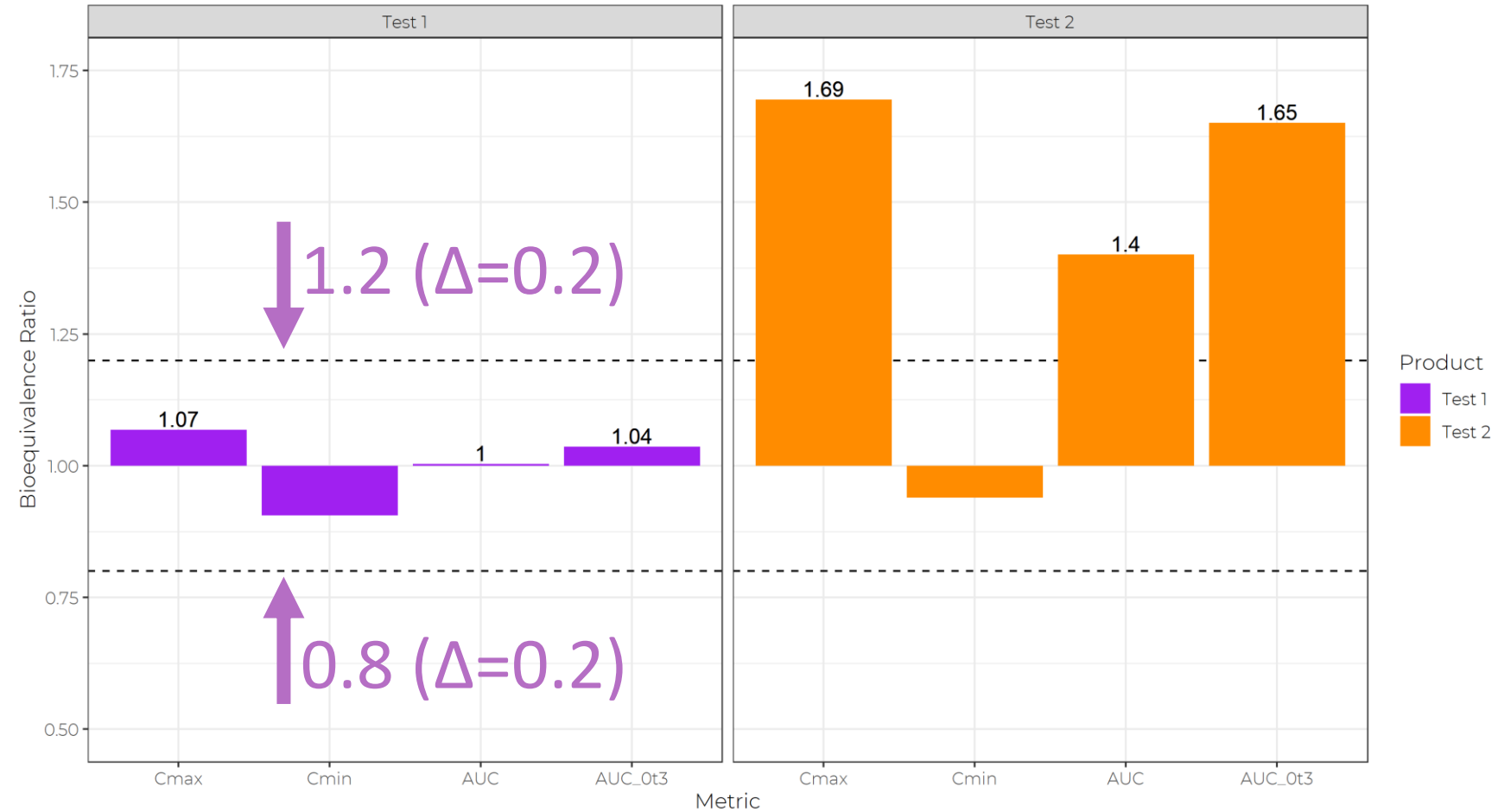
Comparing products \

- What is the necessary bioequivalent ratio?



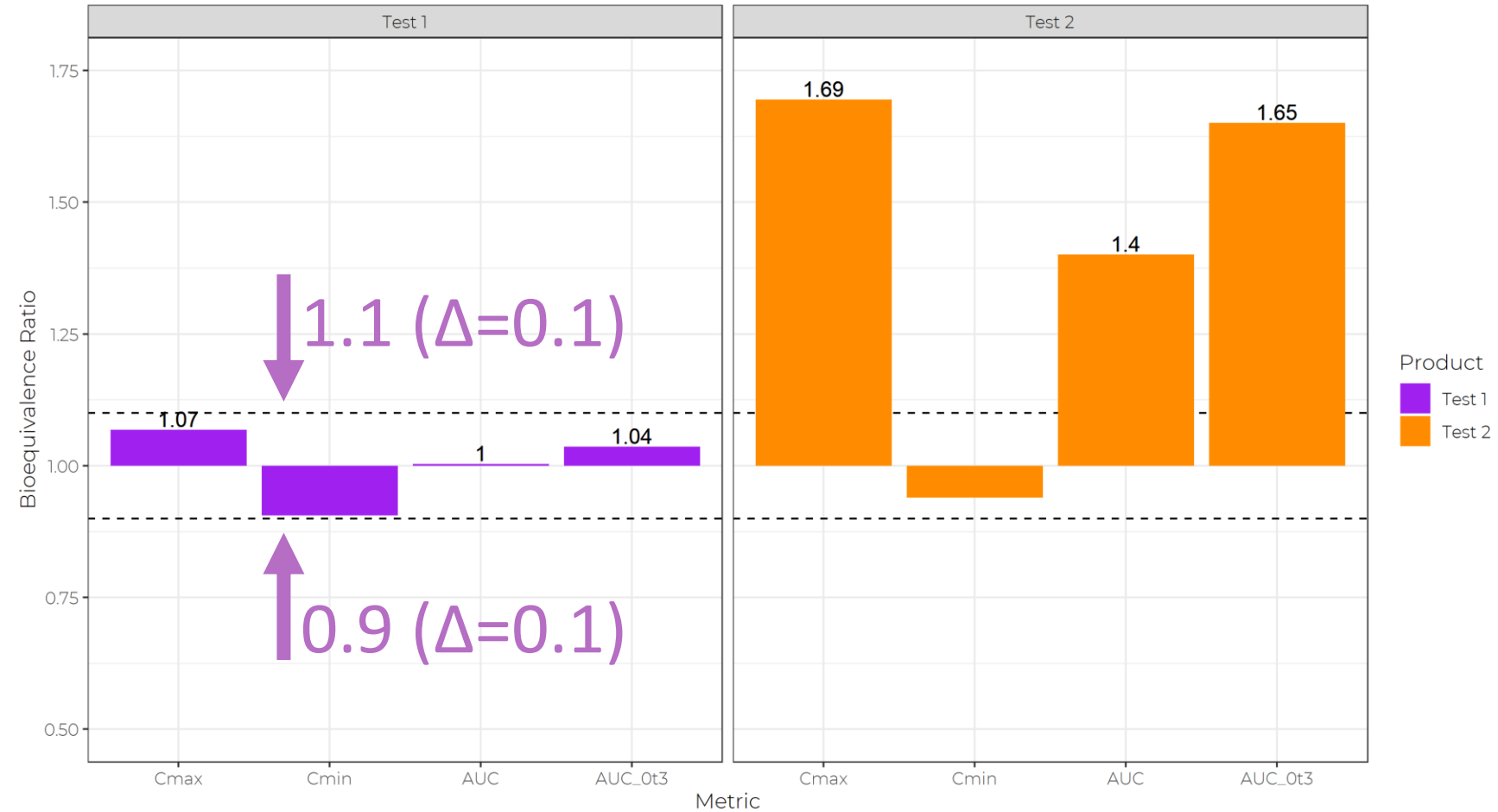
Comparing products \

- What is the necessary bioequivalent ratio?
- For illustration, Δ is symmetric



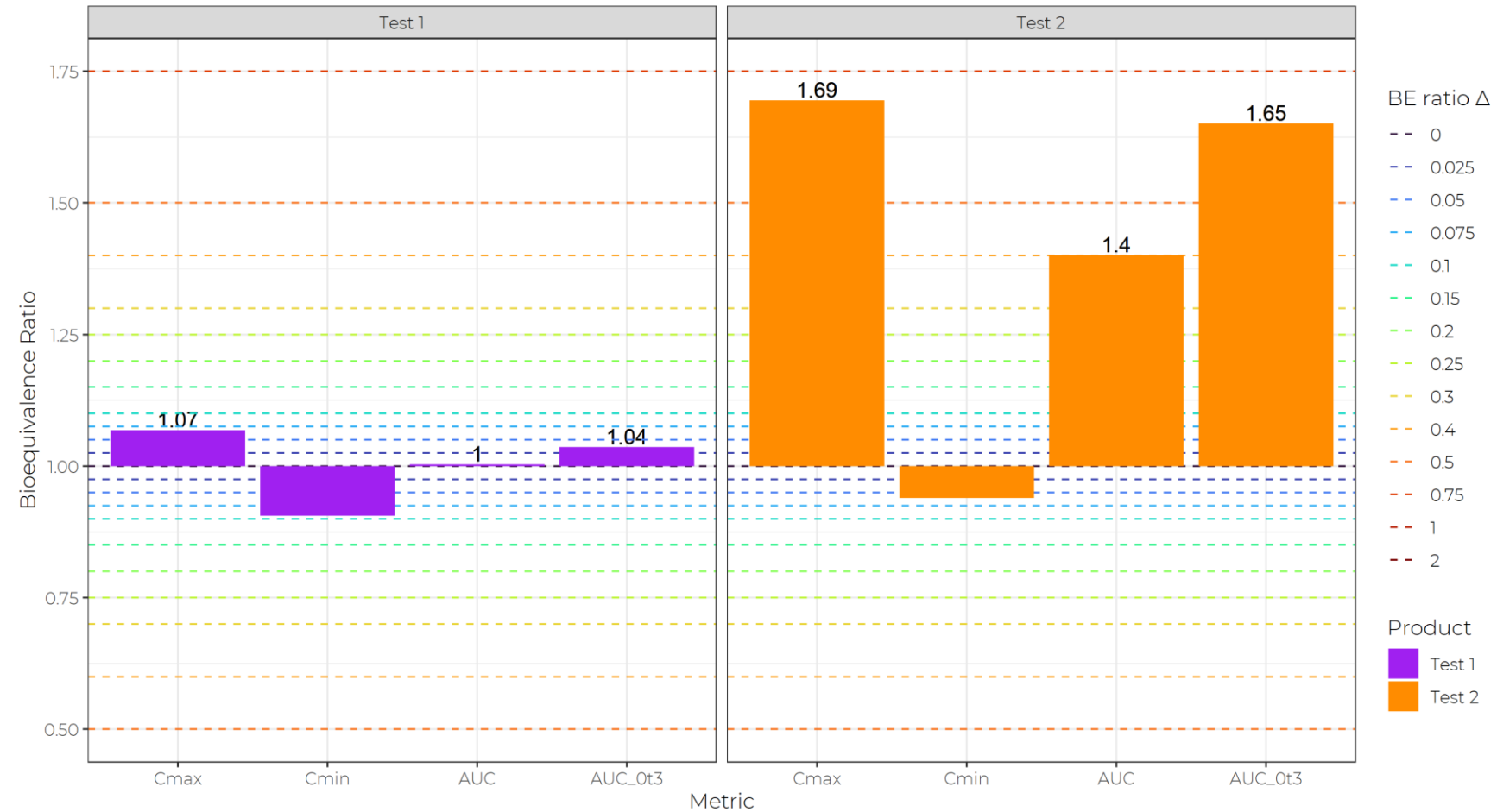
Comparing products \

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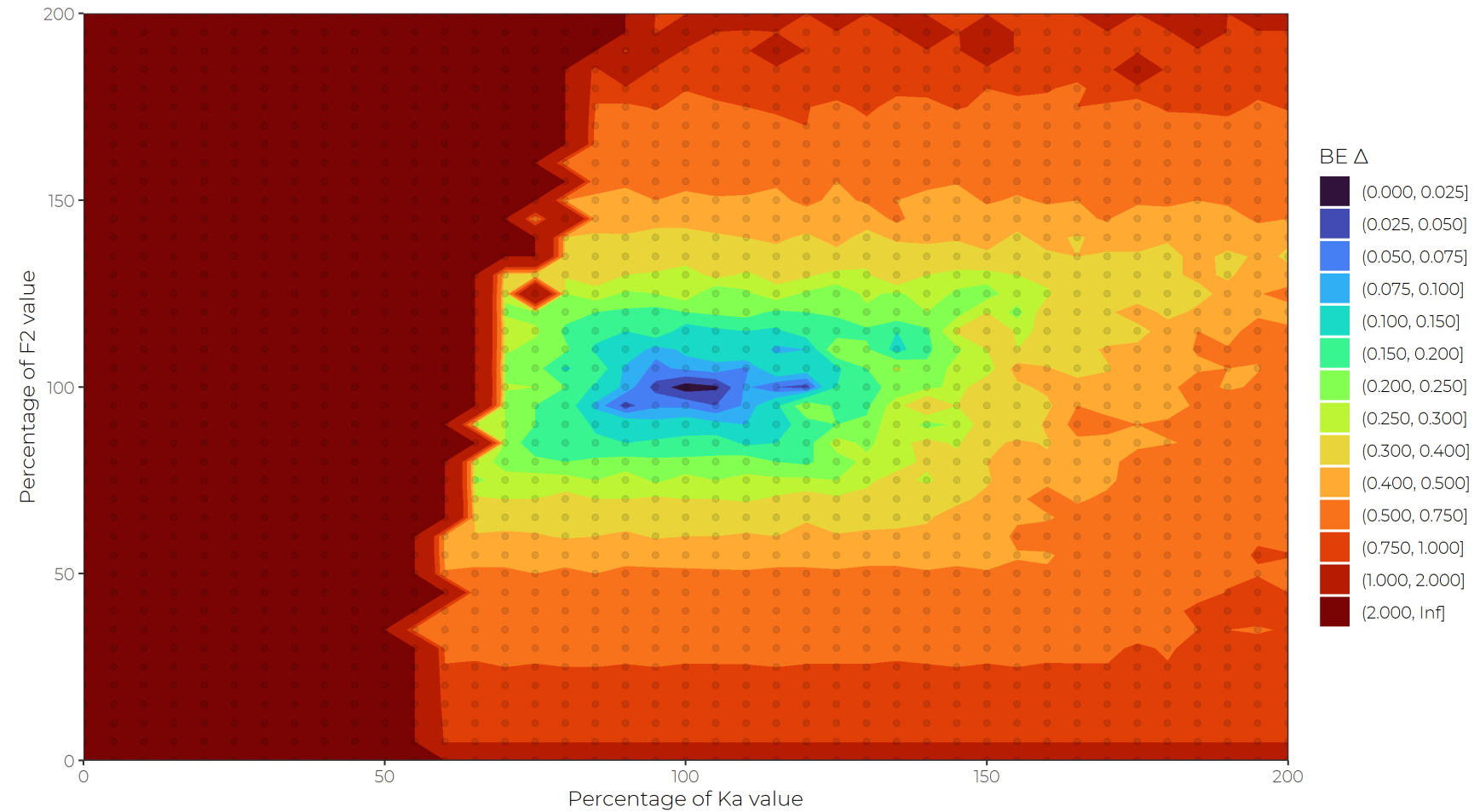
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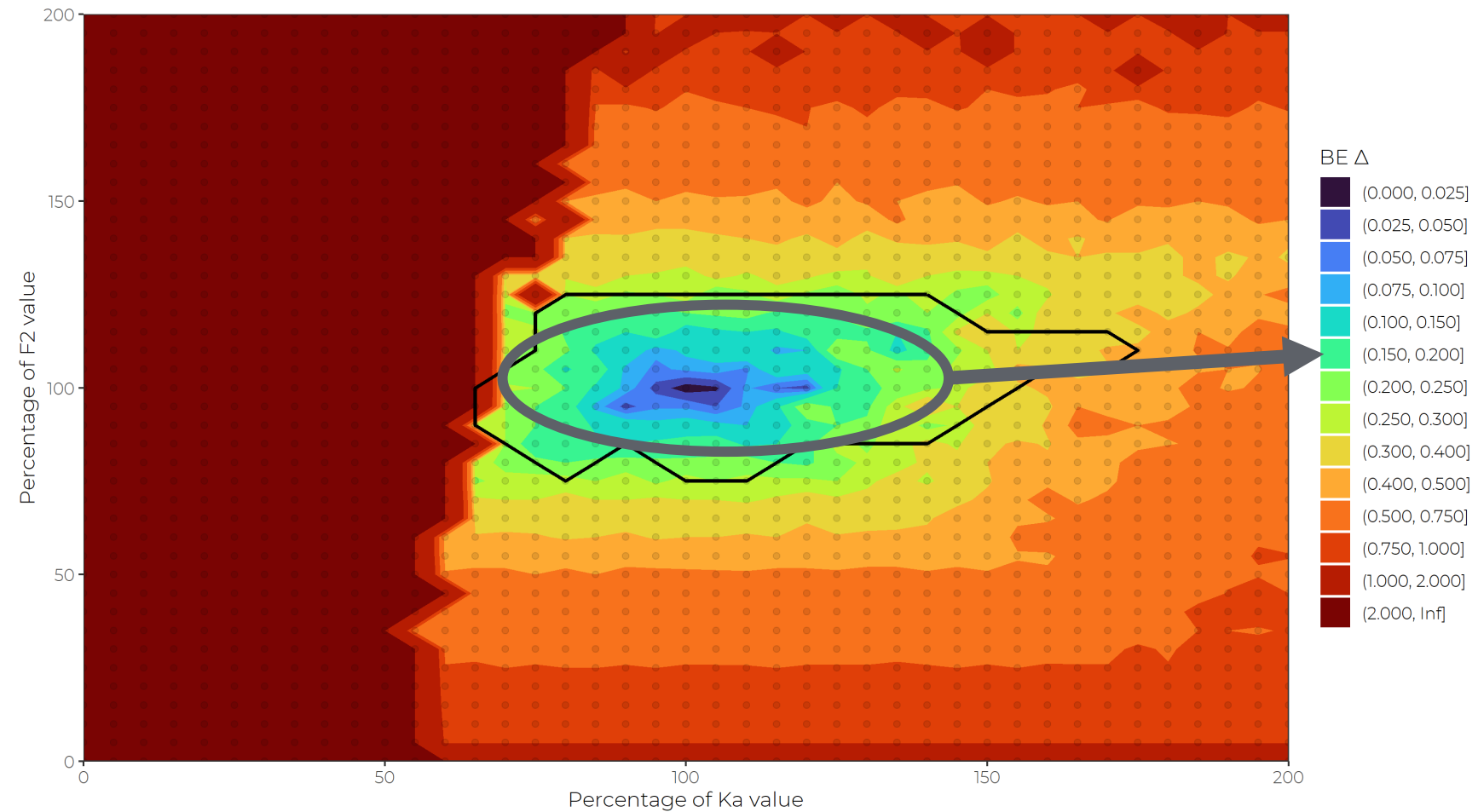
Comparing products \

- 1681 different product combinations
- 25 individuals, who have 3 clinical studies of each product



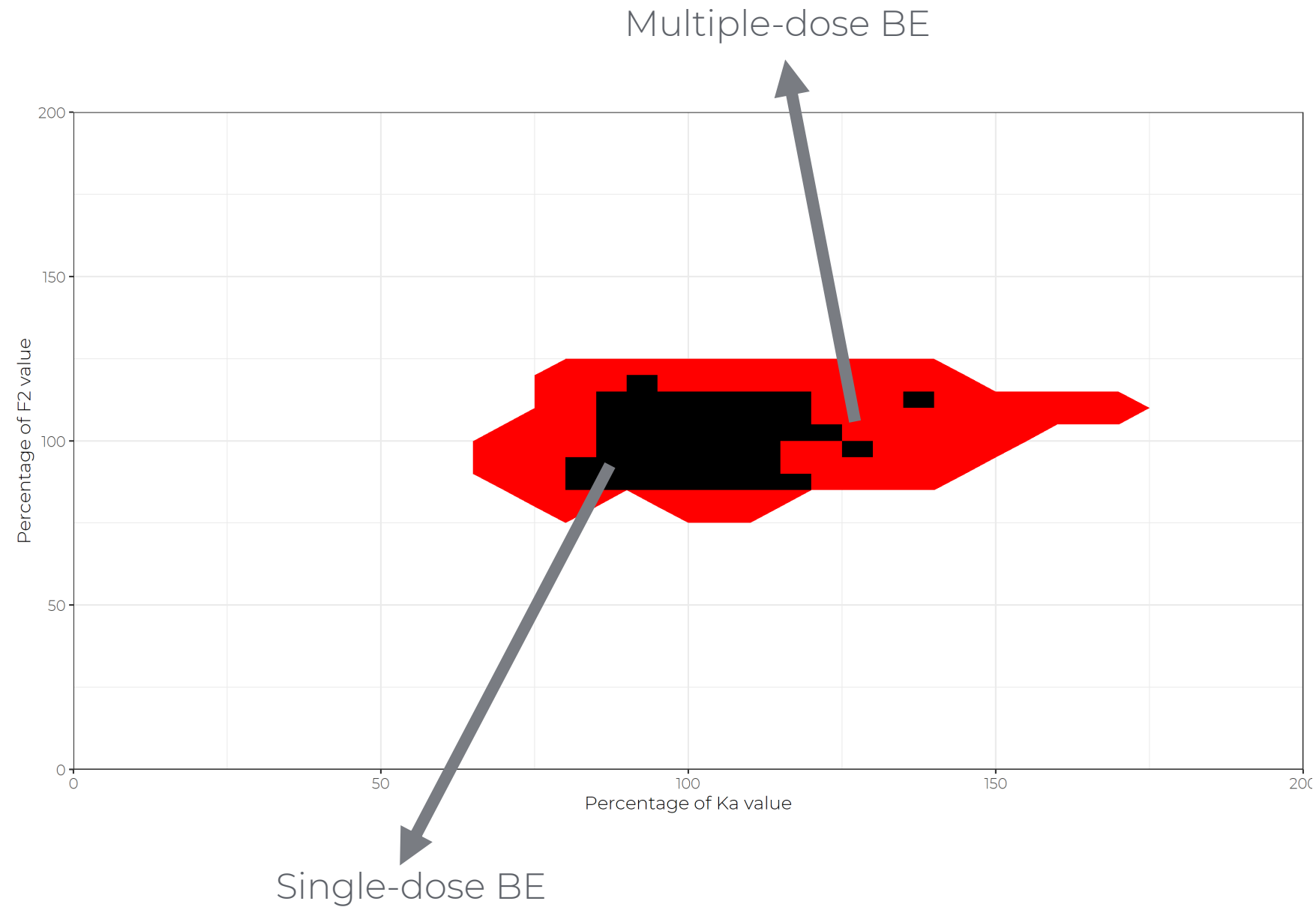
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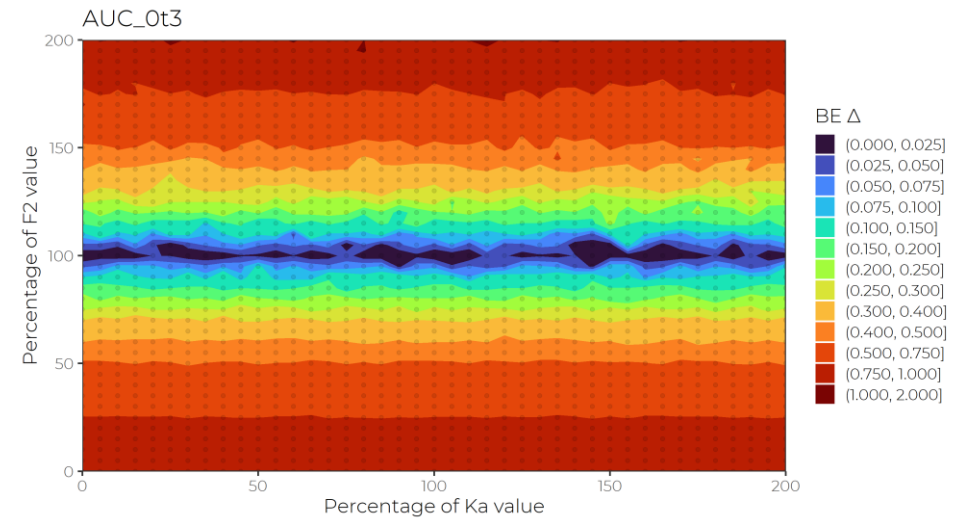
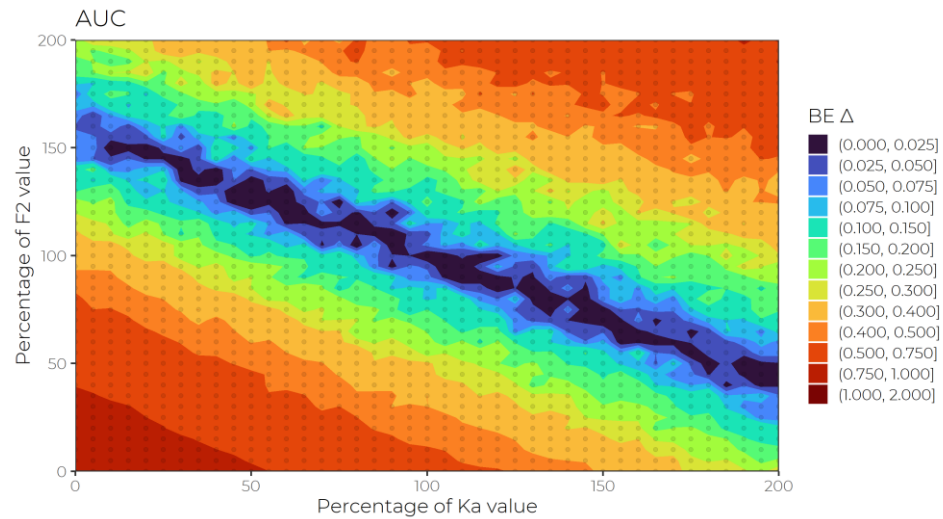
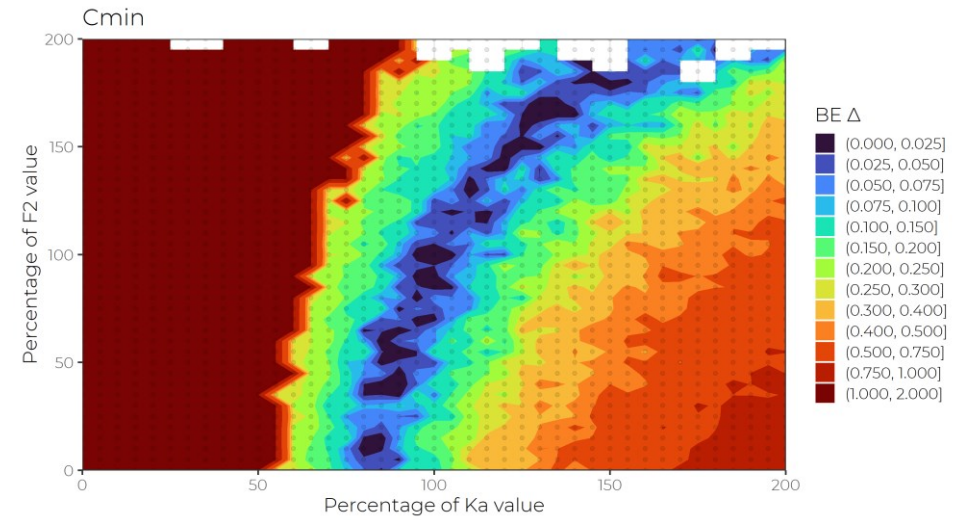
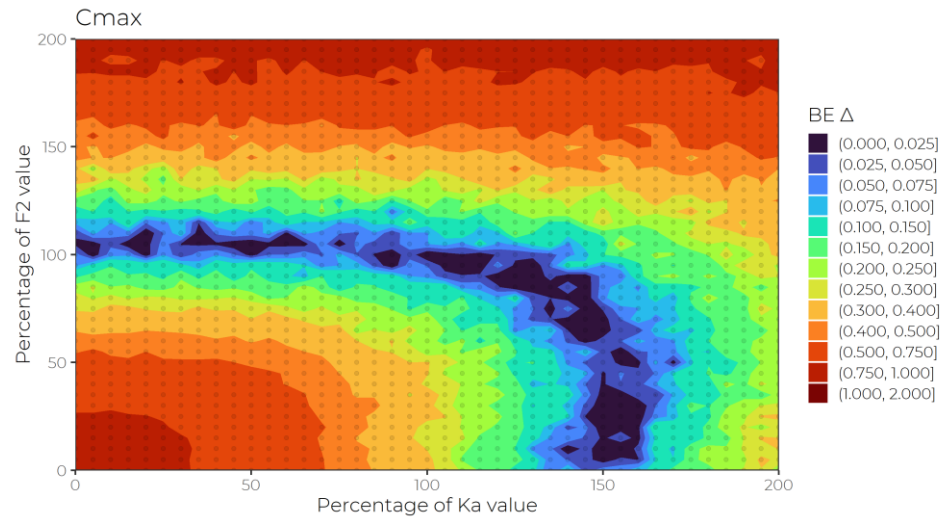


Comparing products \

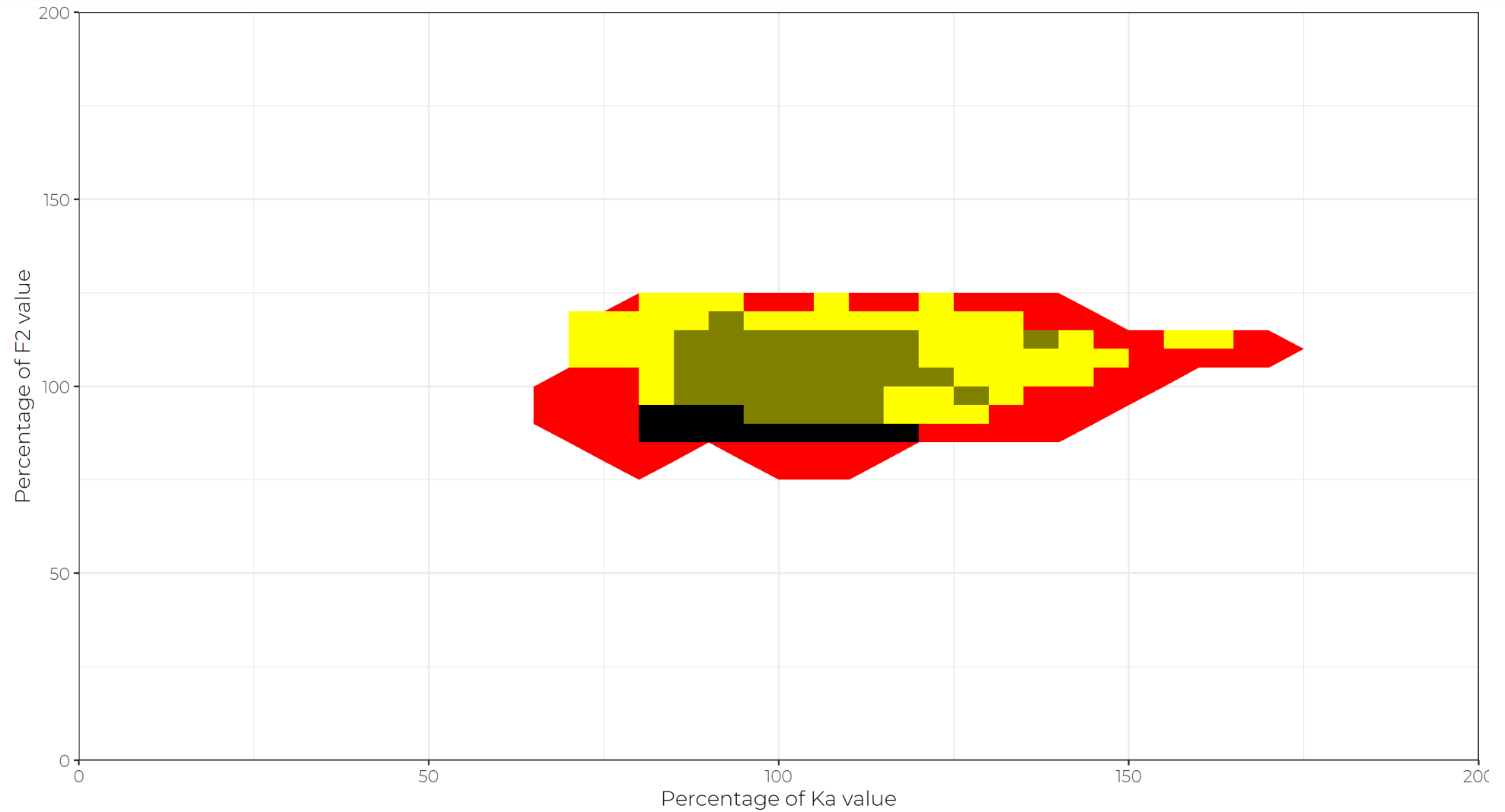
- 1681 different product combinations
- 25 individuals, who have 3 clinical studies of each product
- $\Delta=0.2$
- Single dose studies are more sensitive than multiple dose studies



Comparing products \



Comparing products \



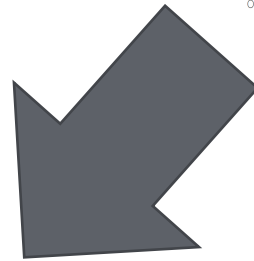
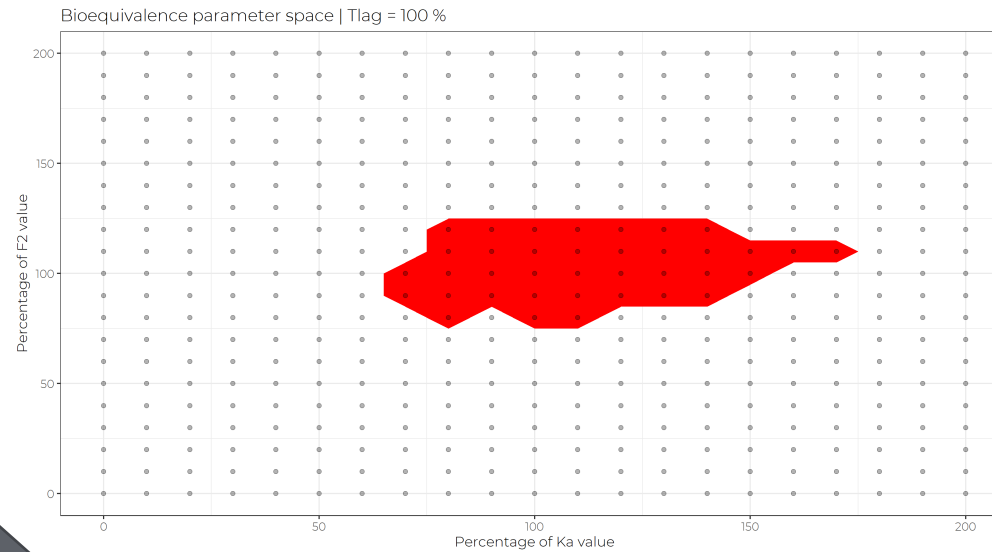
2) Single dose bioequivalence: What have we learnt? \

Population PK modelling has allowed us to

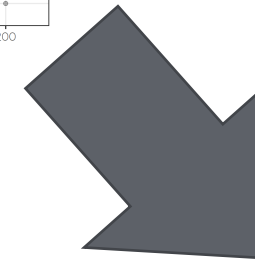
- Determine a criteria on single dose studies that gives products which are multiple-dose bioequivalent

3) How does this modelling integrate into product development and testing? \

Modelling & LAI product development \

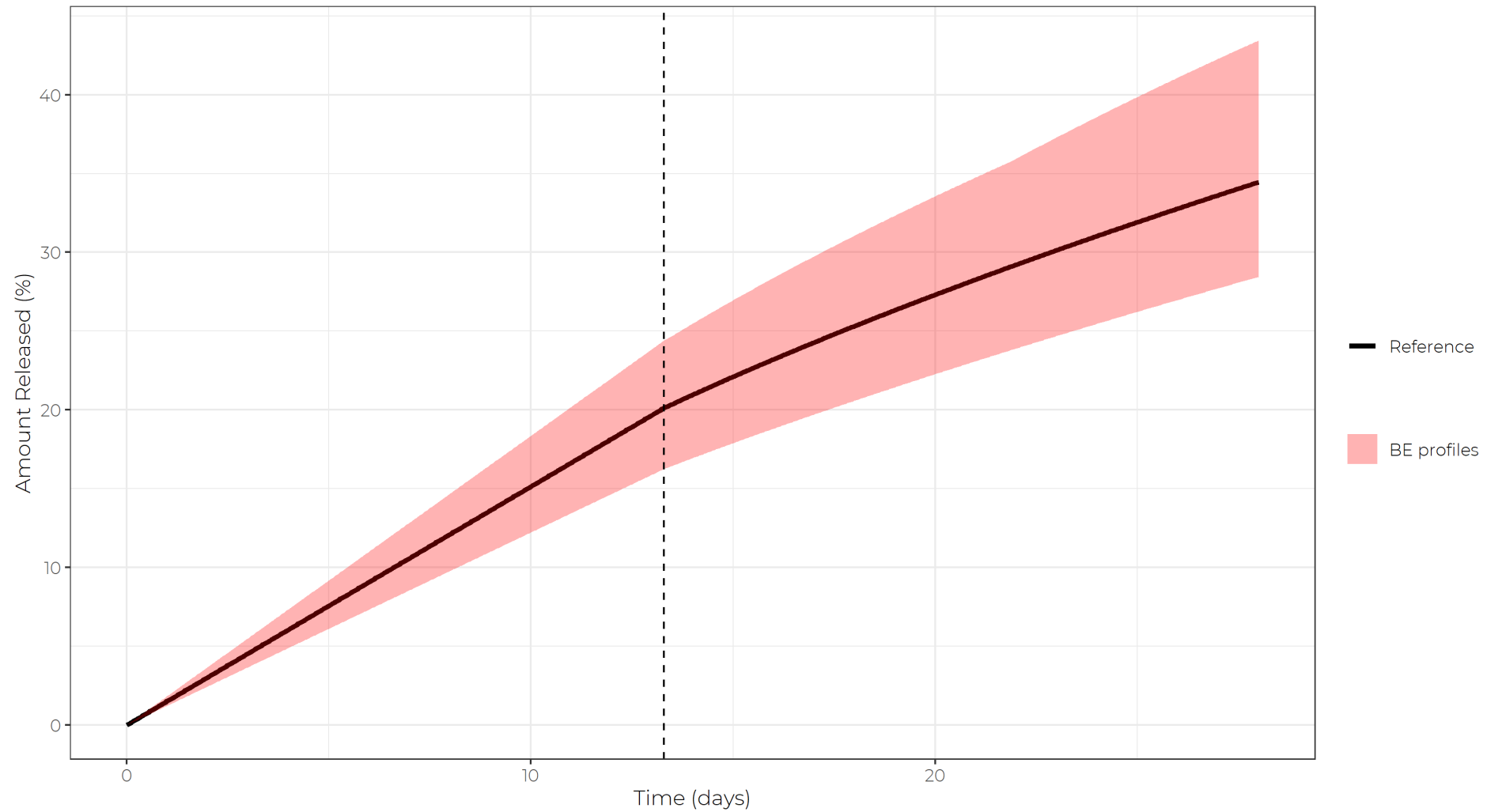


Guide product
development

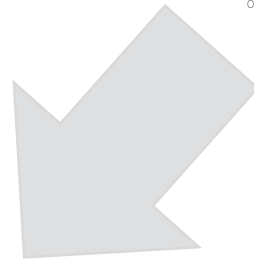
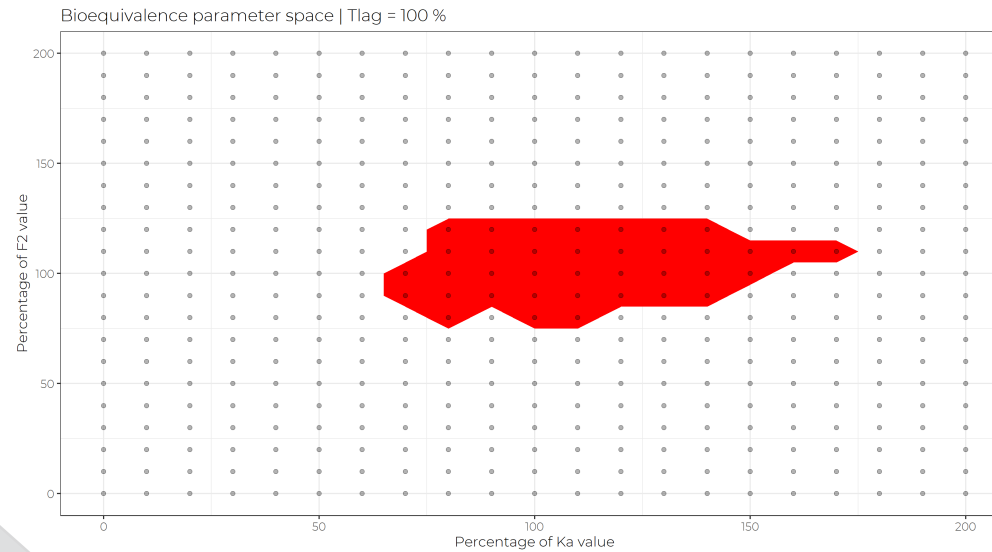


Integrate with
bioequivalence assessment

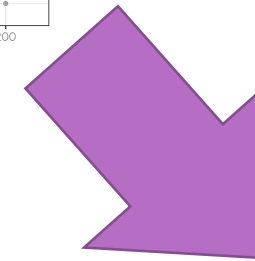
Guide product development \



Modelling & LAI product development \

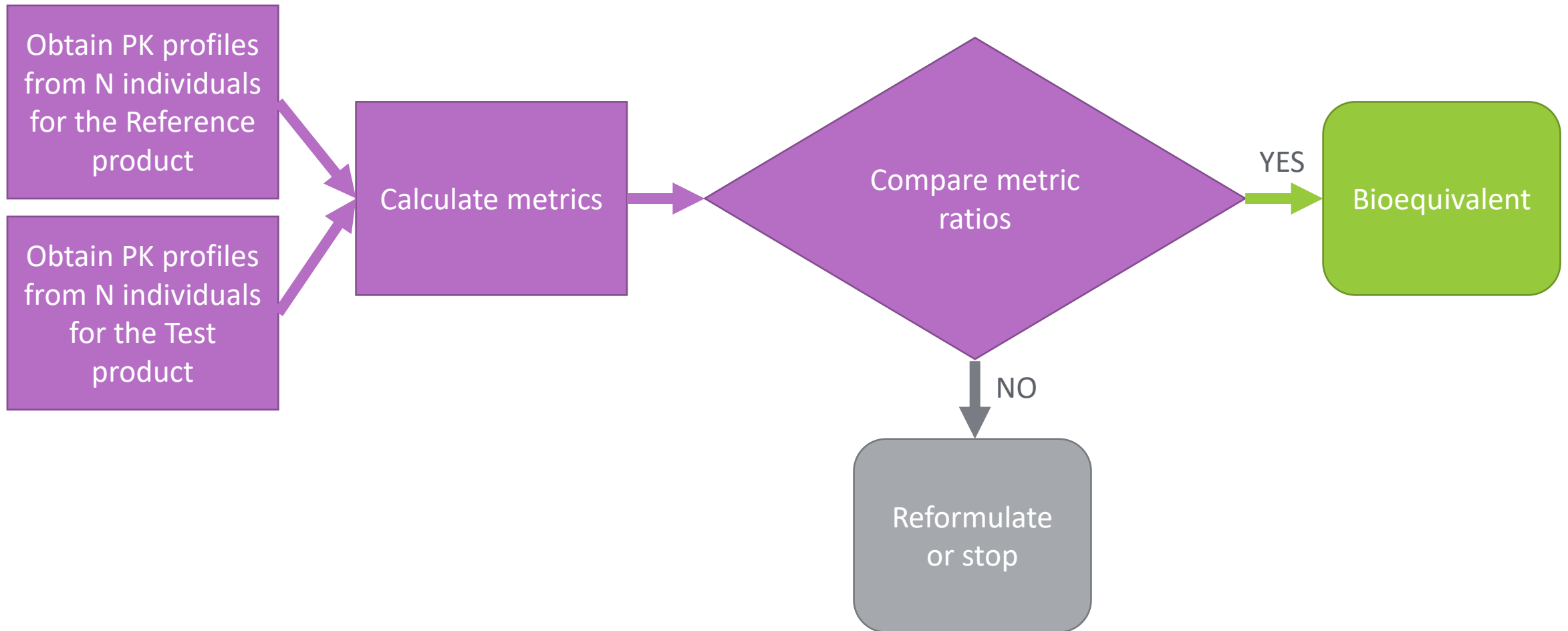


Guide product
development



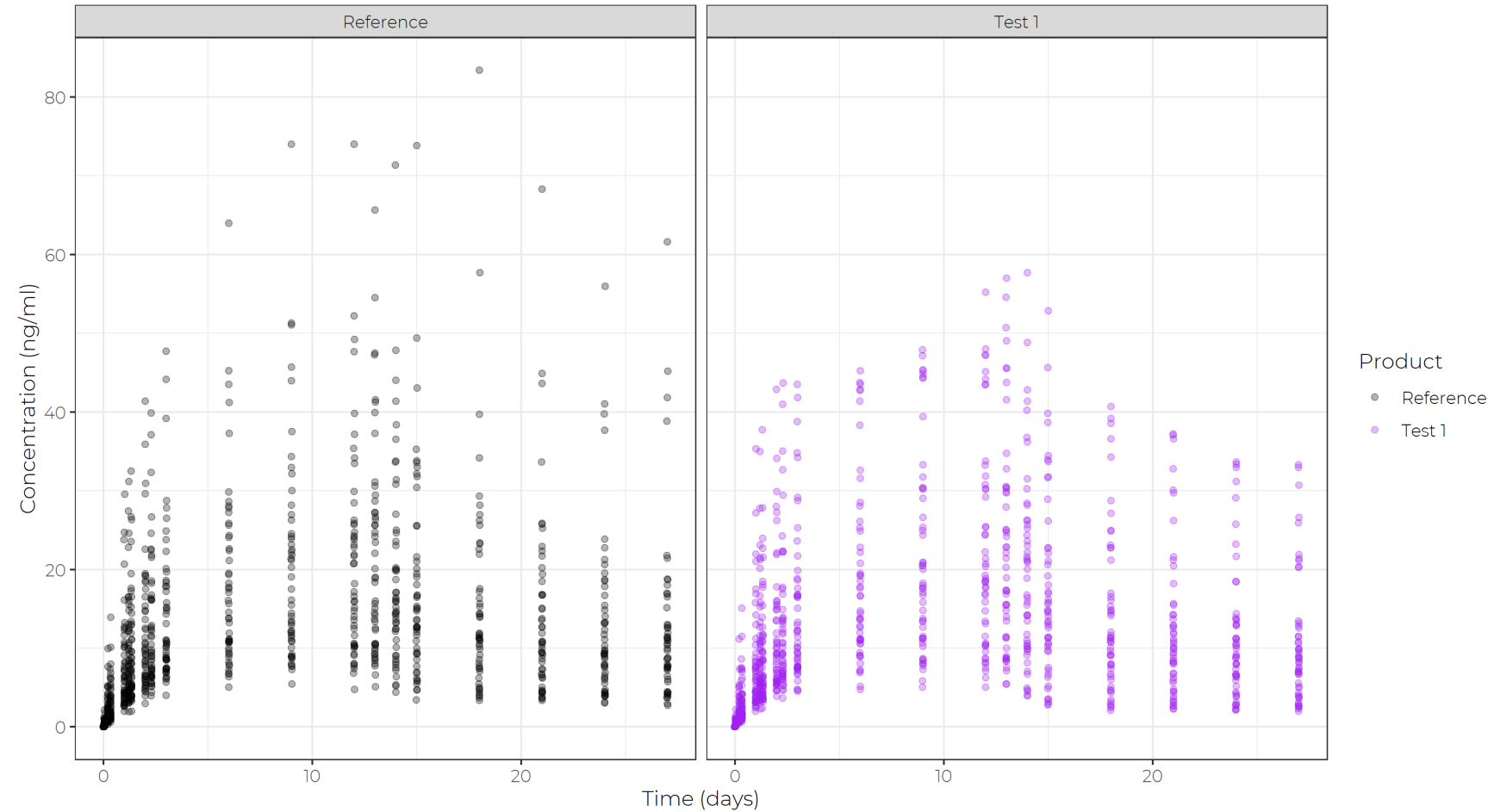
Integrate with
bioequivalence assessment

BE Study \



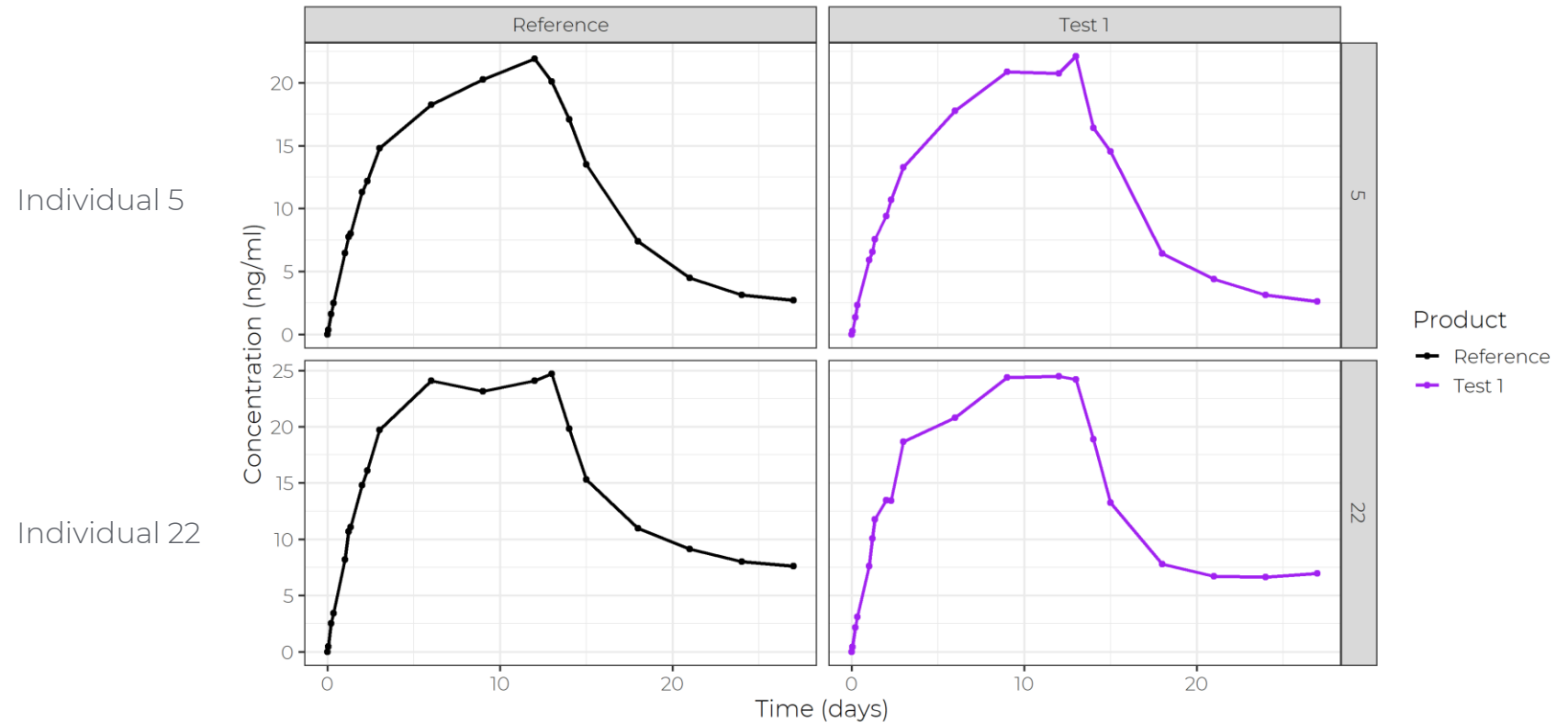
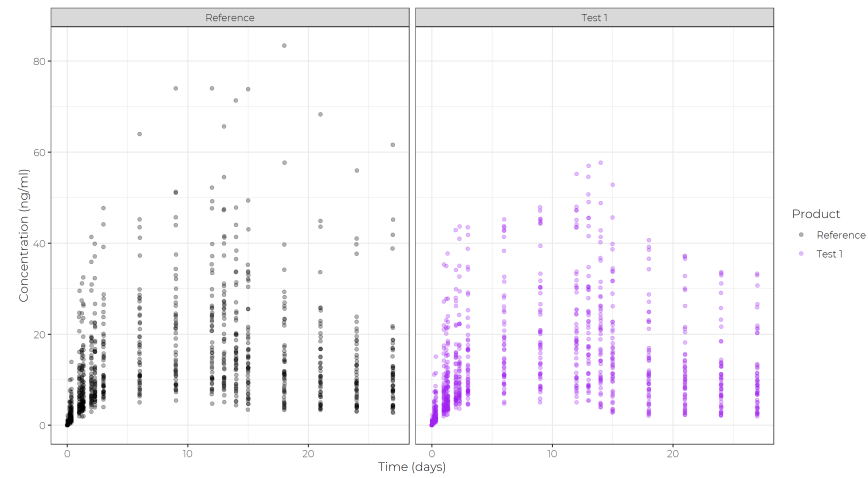
Comparing products \

- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Reference & Test 1



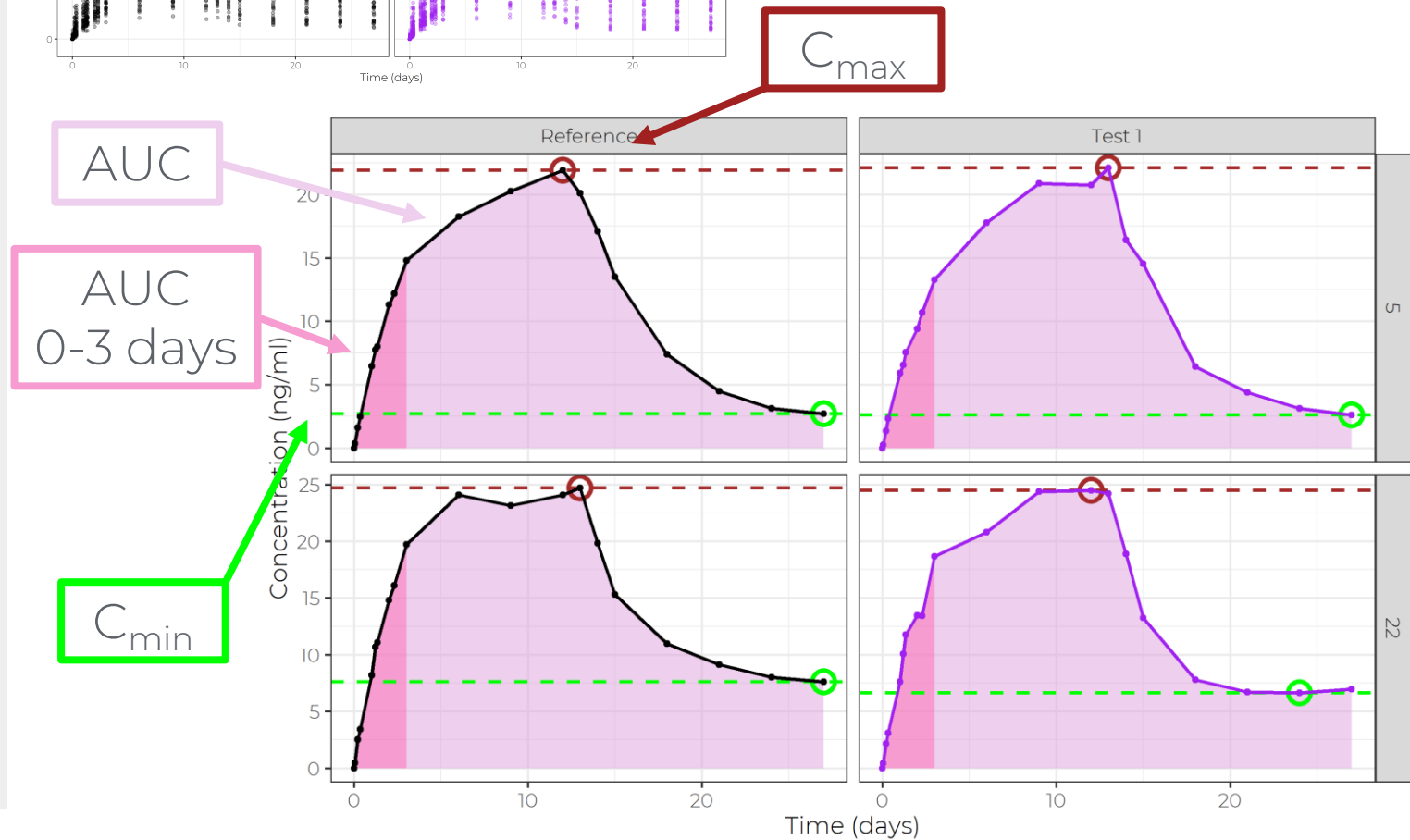
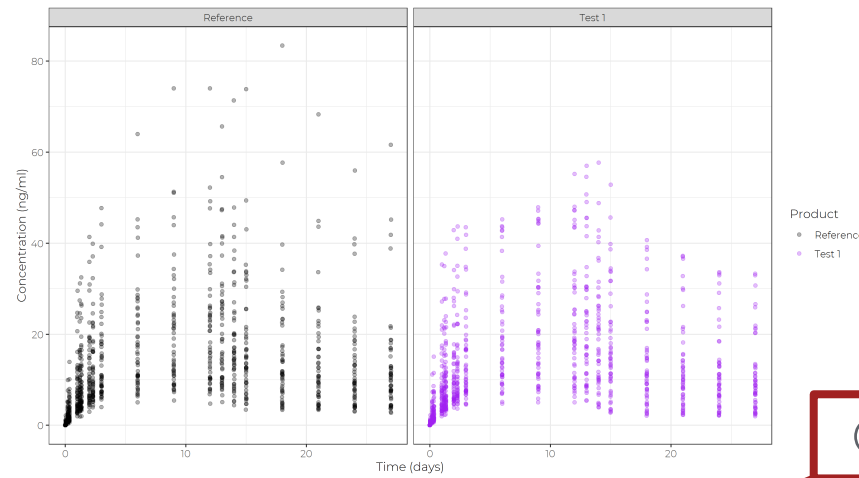
Comparing products \

- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Reference & Test 1



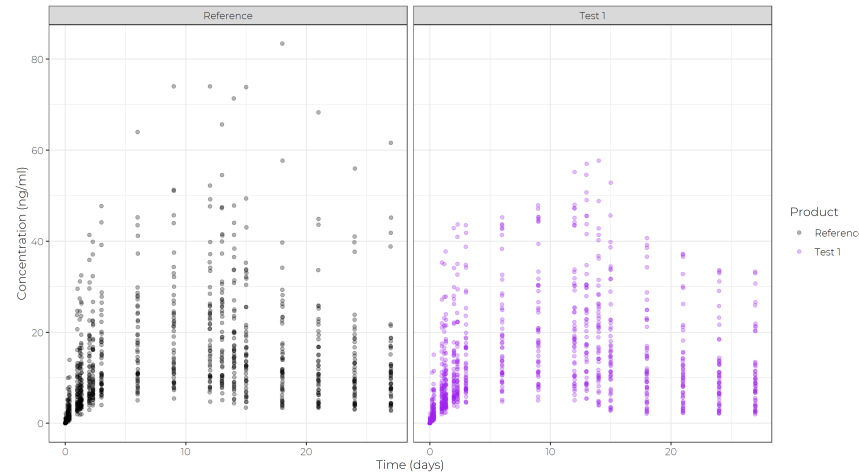
Comparing products \

- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Reference & Test 1
- Calculate PK metrics

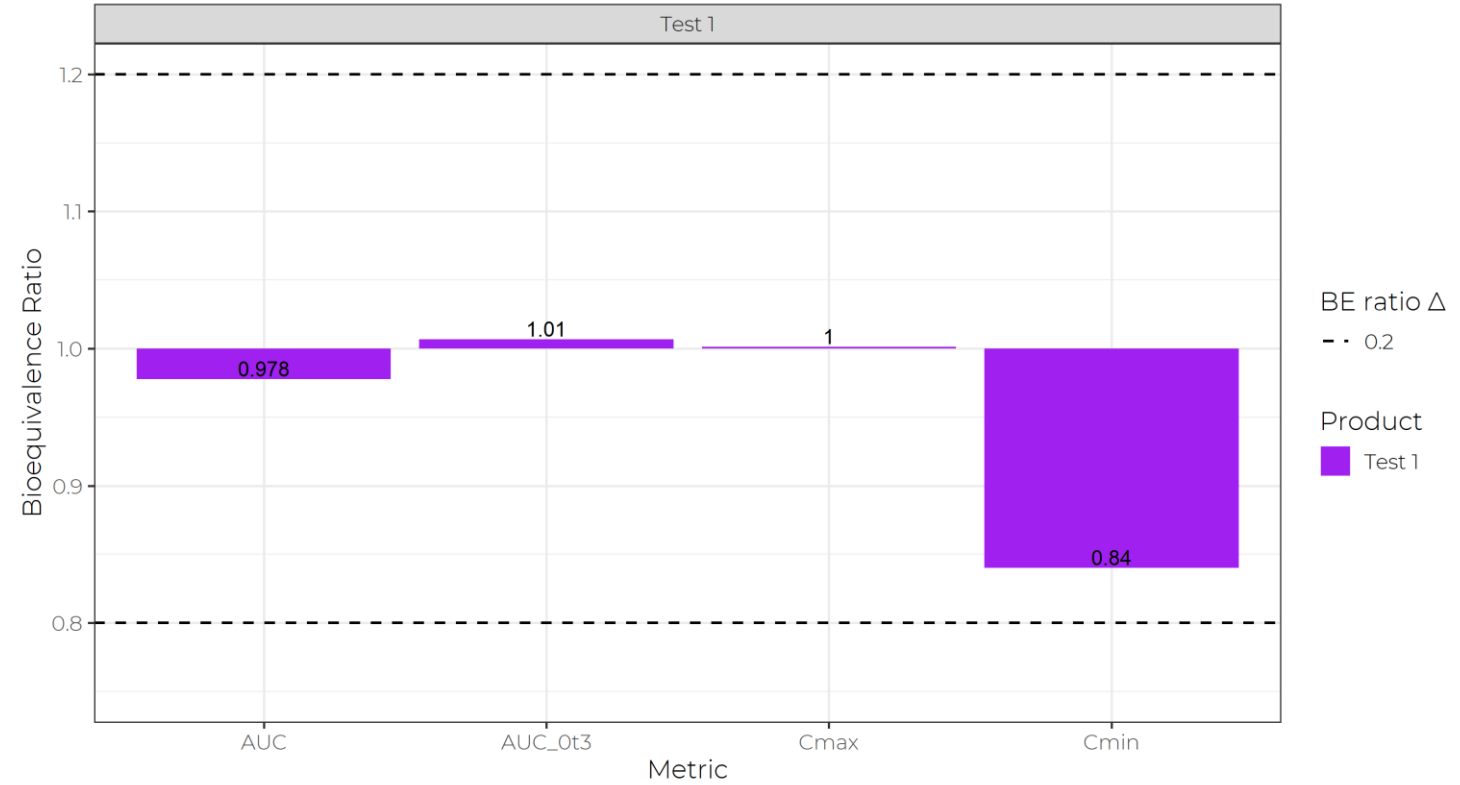


Comparing products \

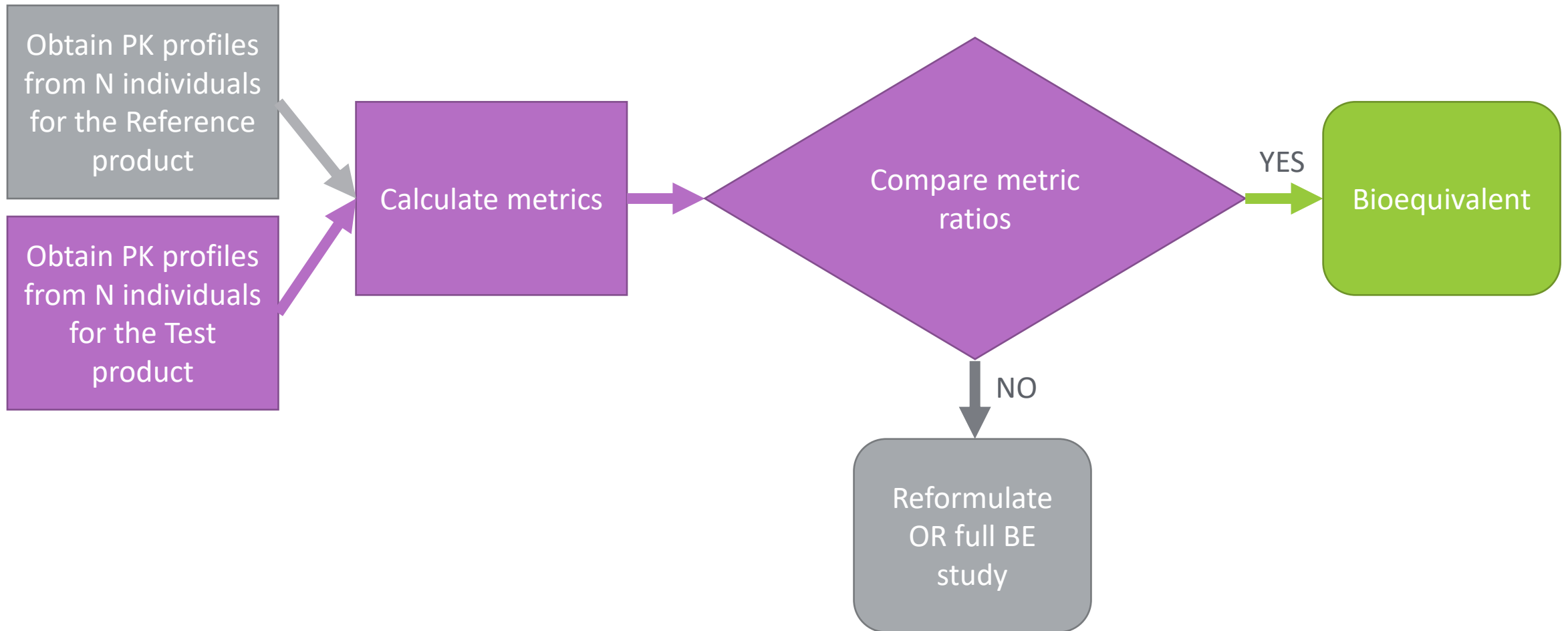
- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Reference & Test 1
- Calculate PK metrics



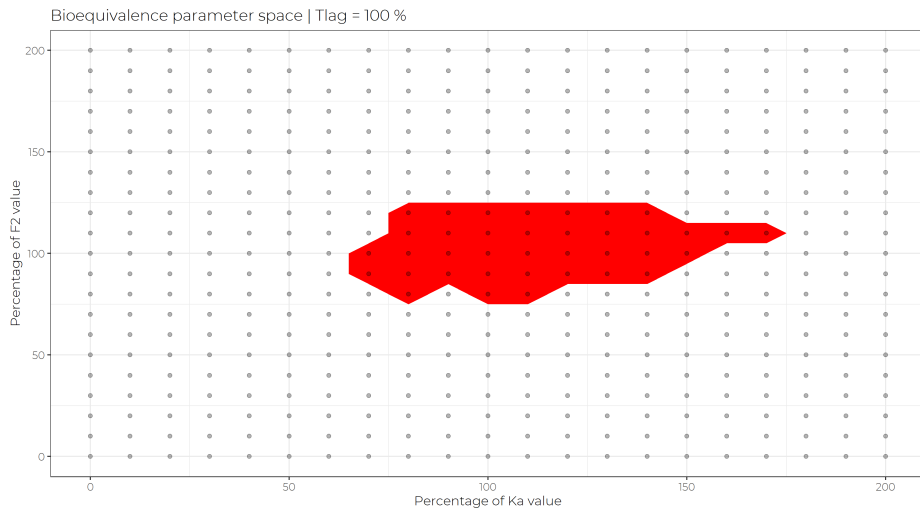
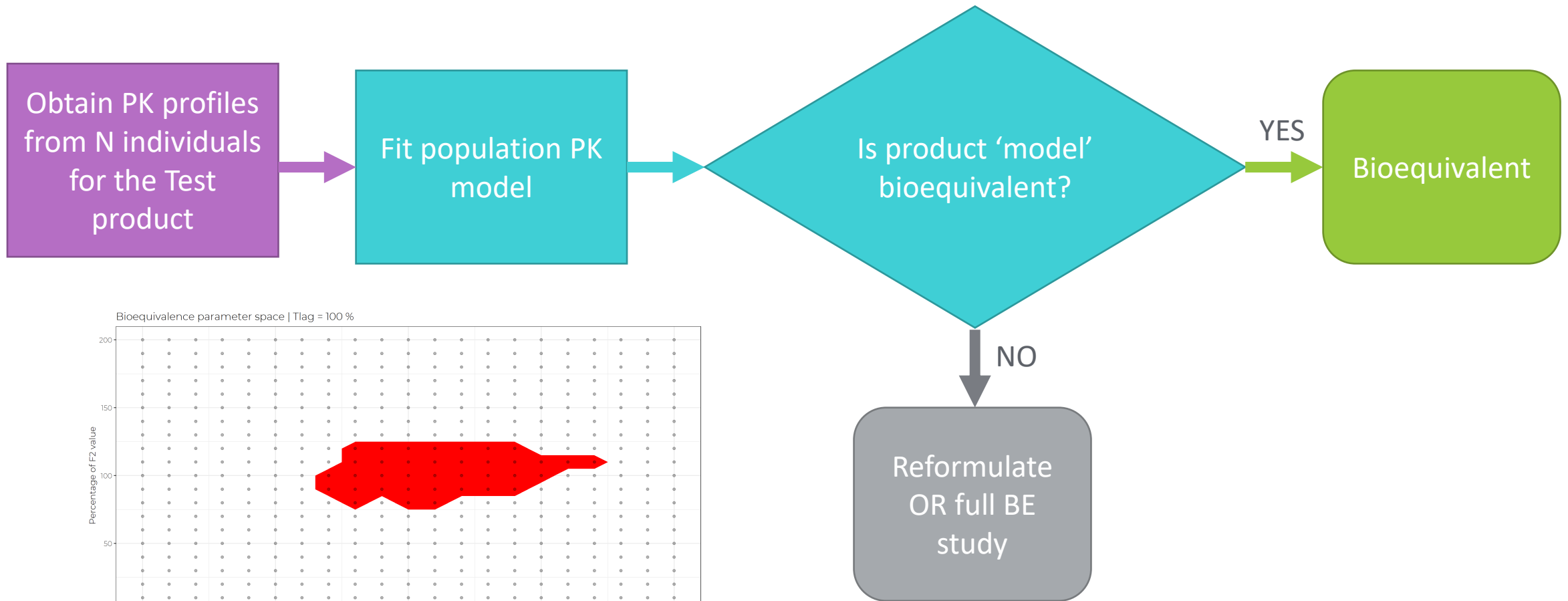
- Need for each individual to take 2 products (Cross-over study)
- High inter-individual and inter-occasion variability



BE Study \

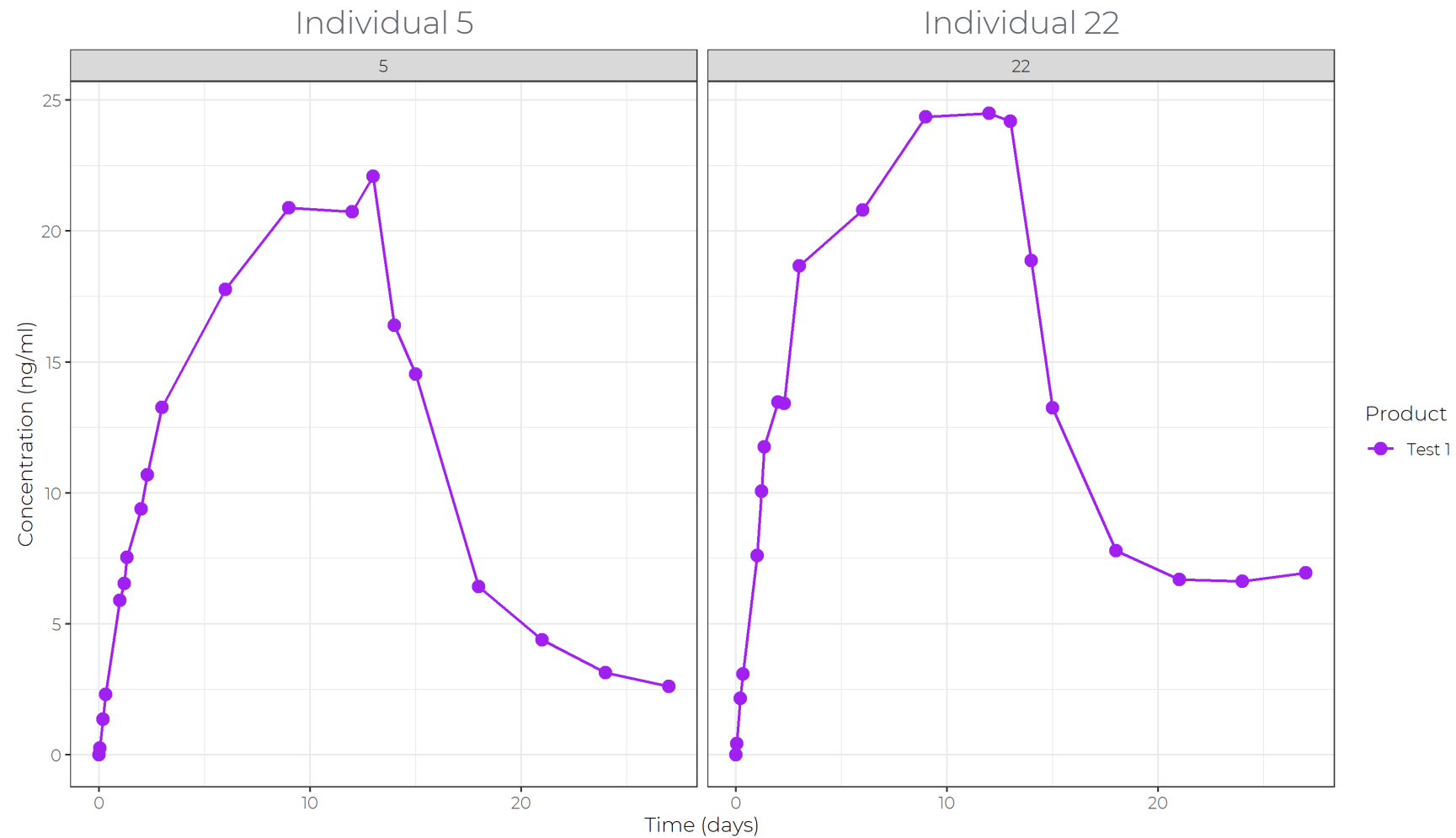


Model integrated BE Study \



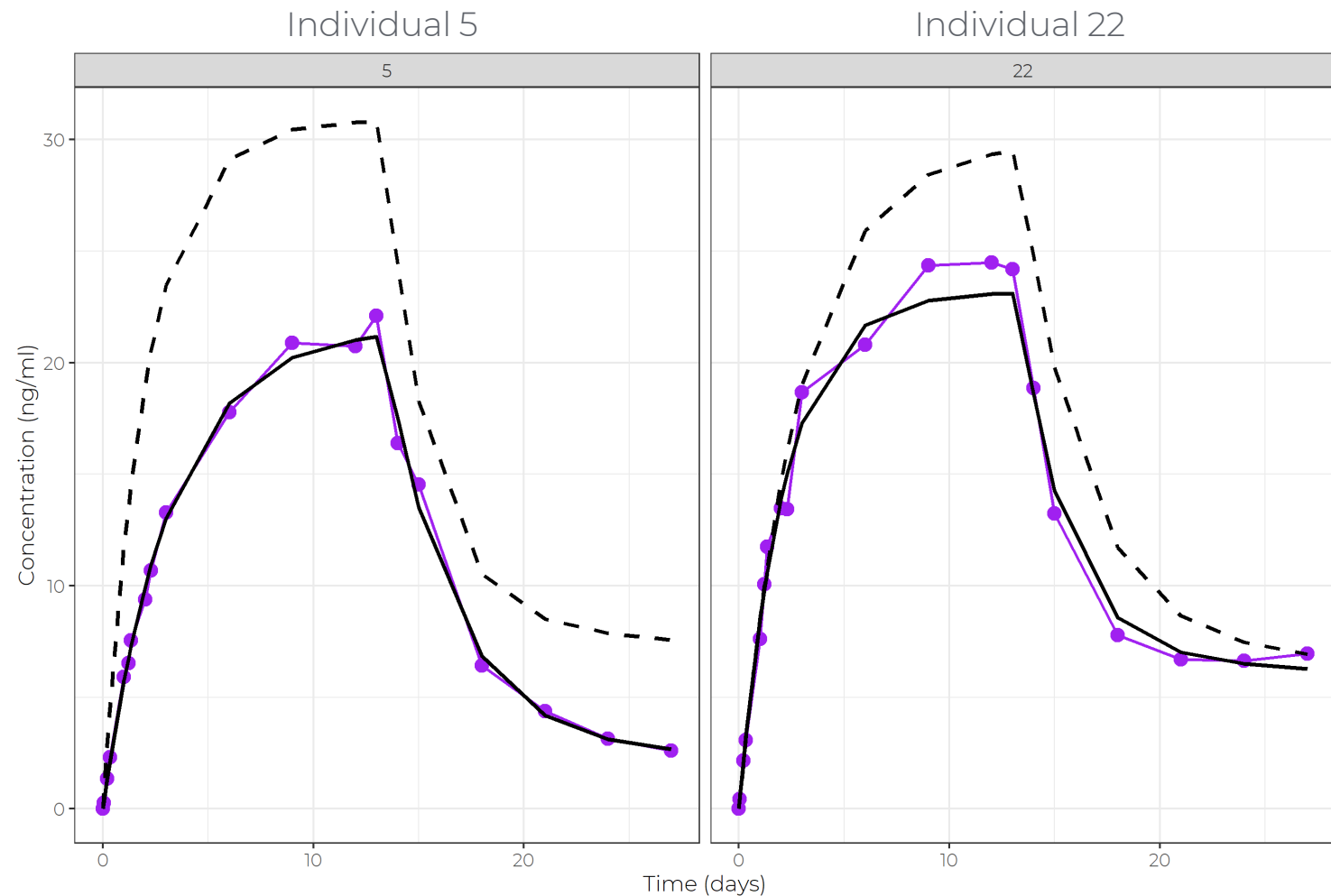
Model-integrated comparison

- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Test 2



Model-integrated comparison

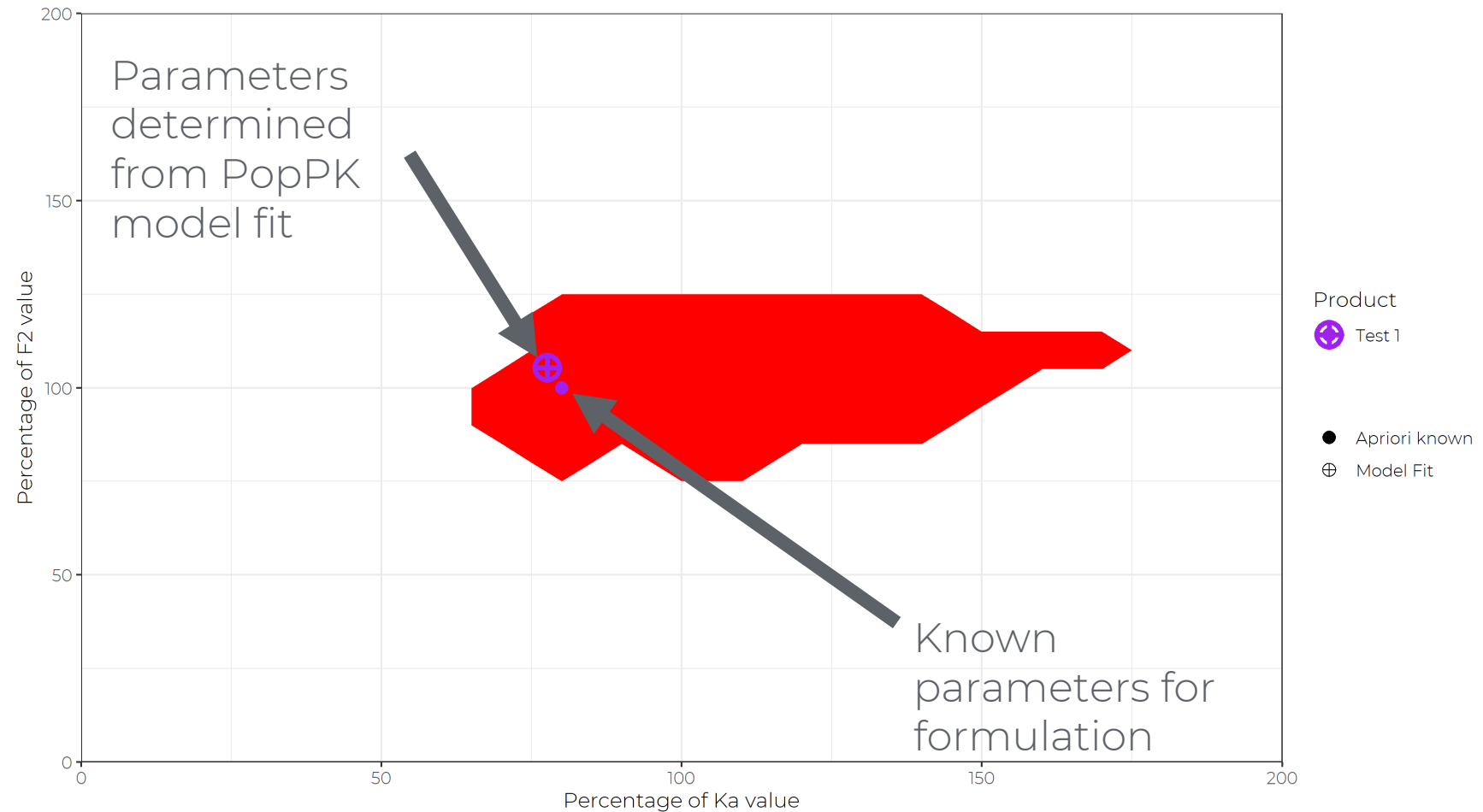
- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Test 1
- Population PK model fitted to the data



Model parameters
 $K_a = 4.5E-4$ (1/hr) (79%)
 $F_2 = 0.179$ (107%)

Model-integrated comparison

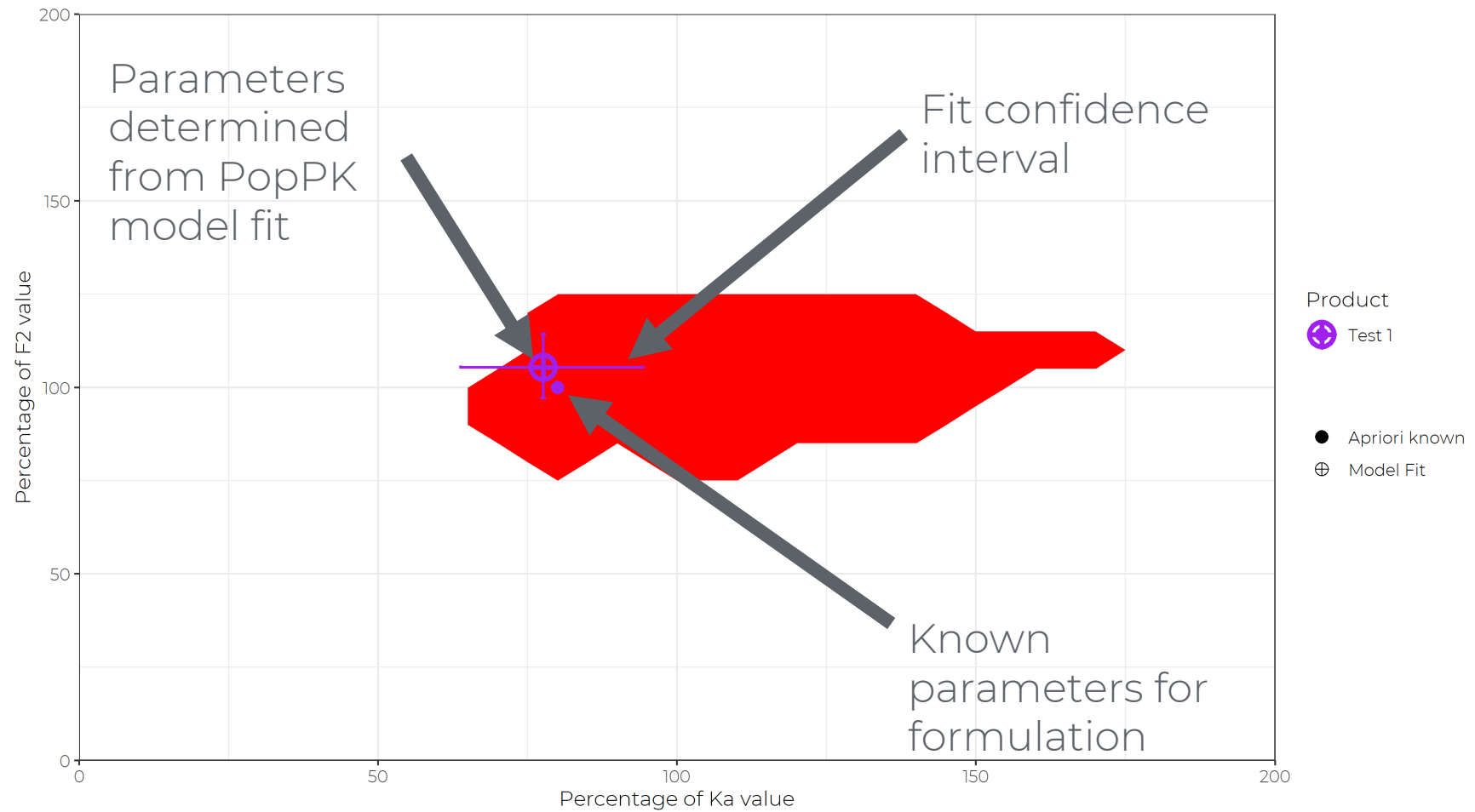
- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Test 1
- Population PK model fitted to the data



Model parameters
Ka = 4.5E-4 (1/hr) (79%)
F2 = 0.179 (107%)

Model-integrated comparison

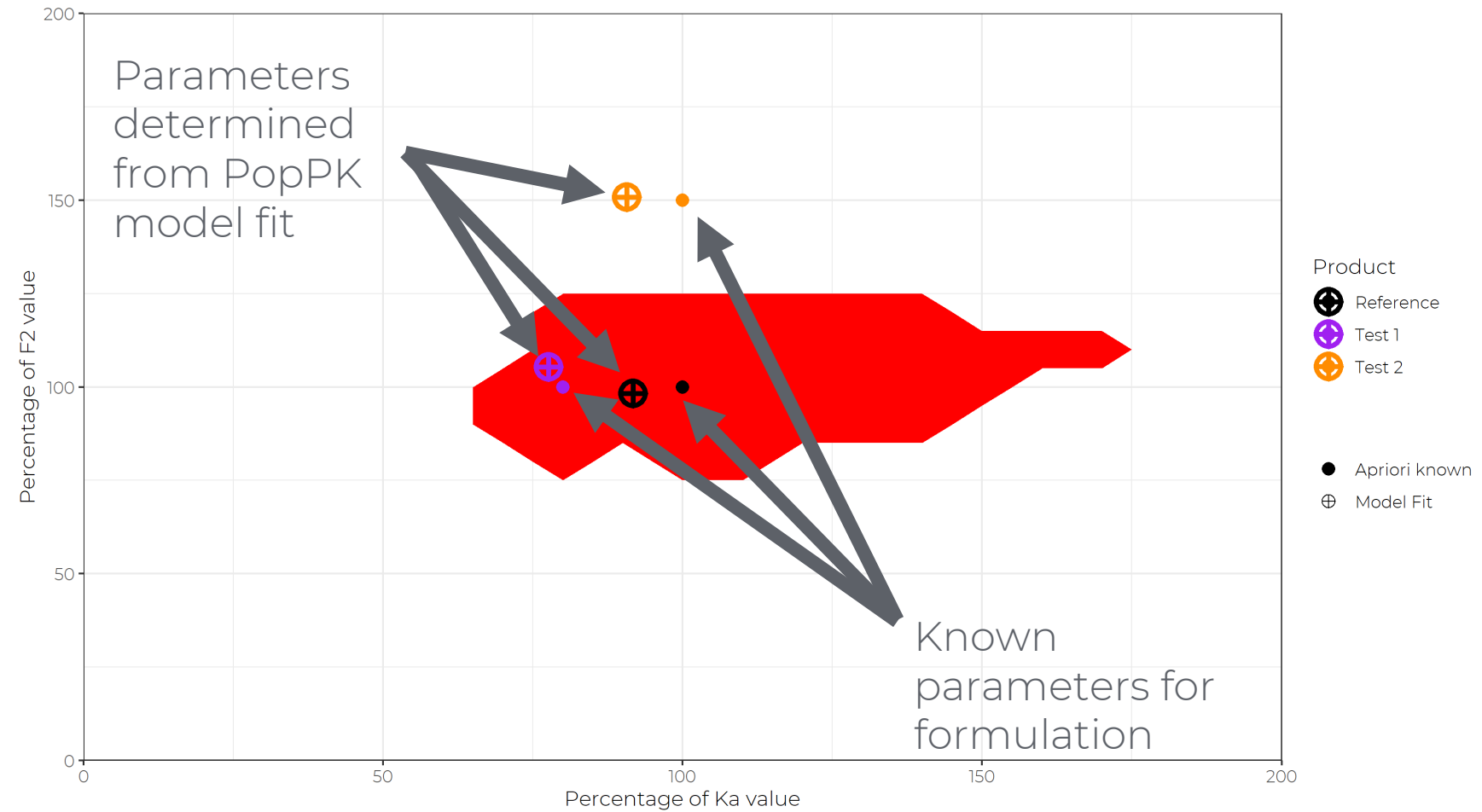
- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Test 1
- Population PK model fitted to the data



Model parameters
 $K_a = 4.5E-4$ (1/hr) (79%)
 $F_2 = 0.179$ (107%)

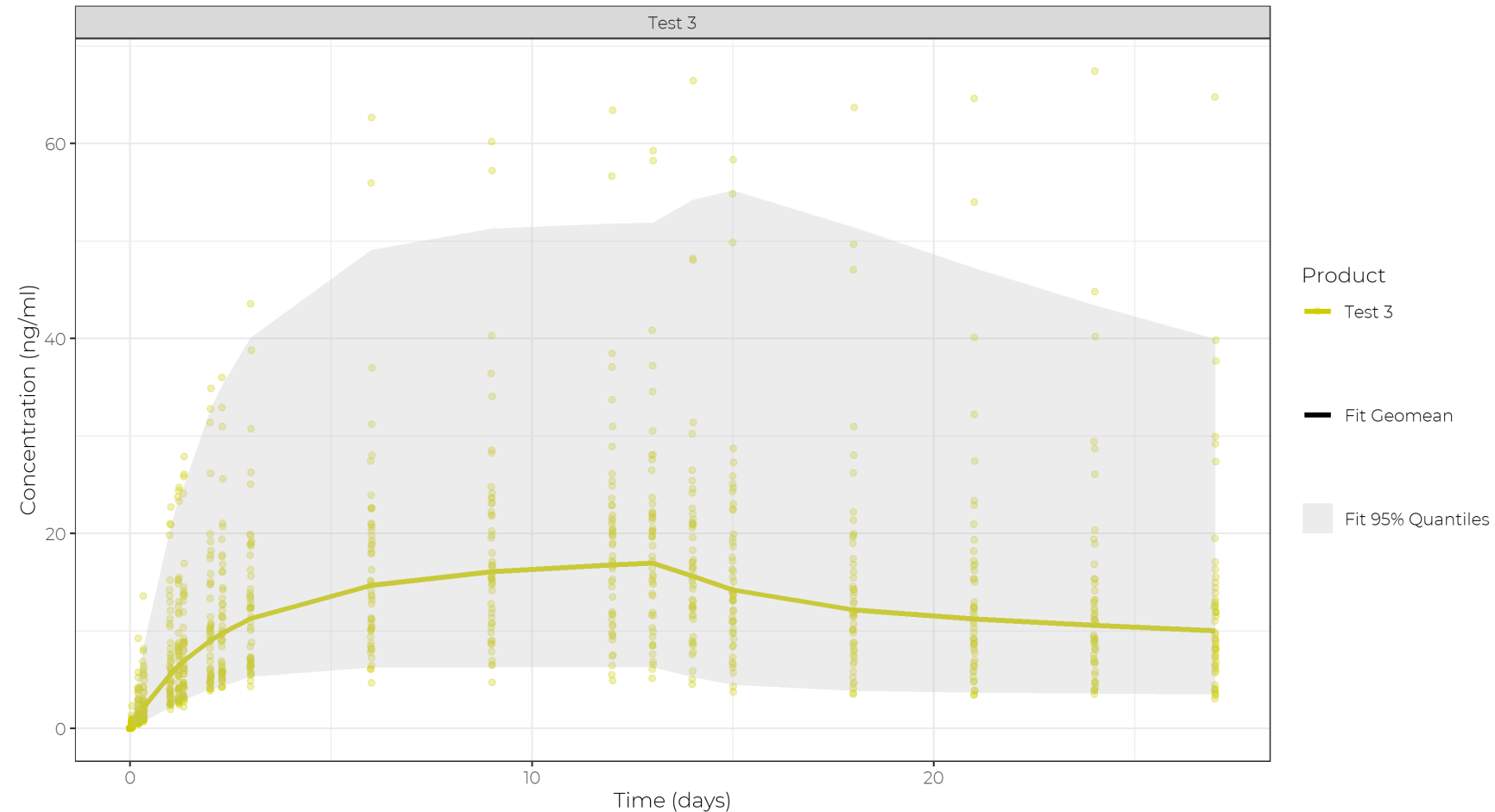
Model-integrated comparison

- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of all products
- Population PK model fitted to the data



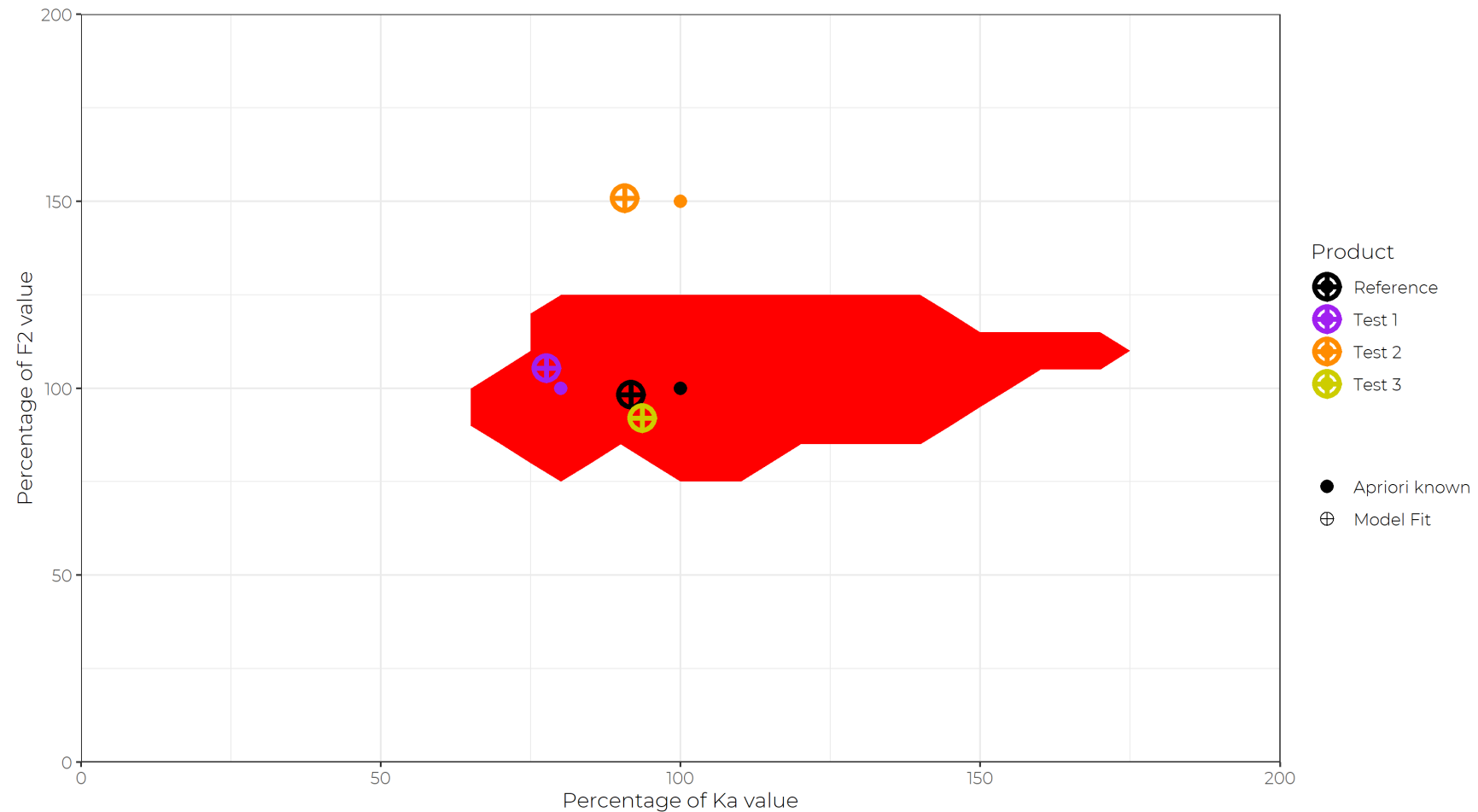
Model-integrated comparison

- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of Test 3
- Formulation parameters of Test 3 are unknown
- Population PK model fitted to the data

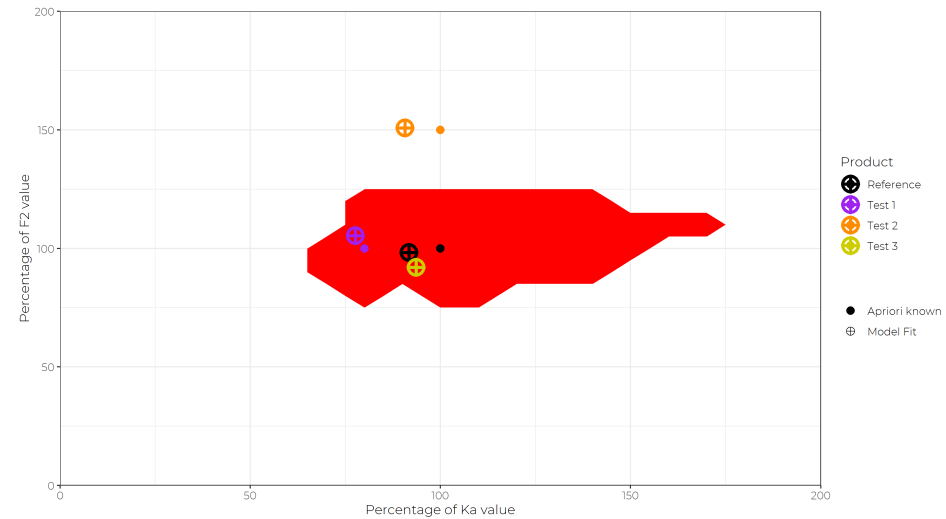


Model-integrated comparison \

- PK data from a virtual population of 50 individuals (based on USA census)
- Virtual crossover study, with each individual receiving a single dose of all products
- Population PK model fitted to the data

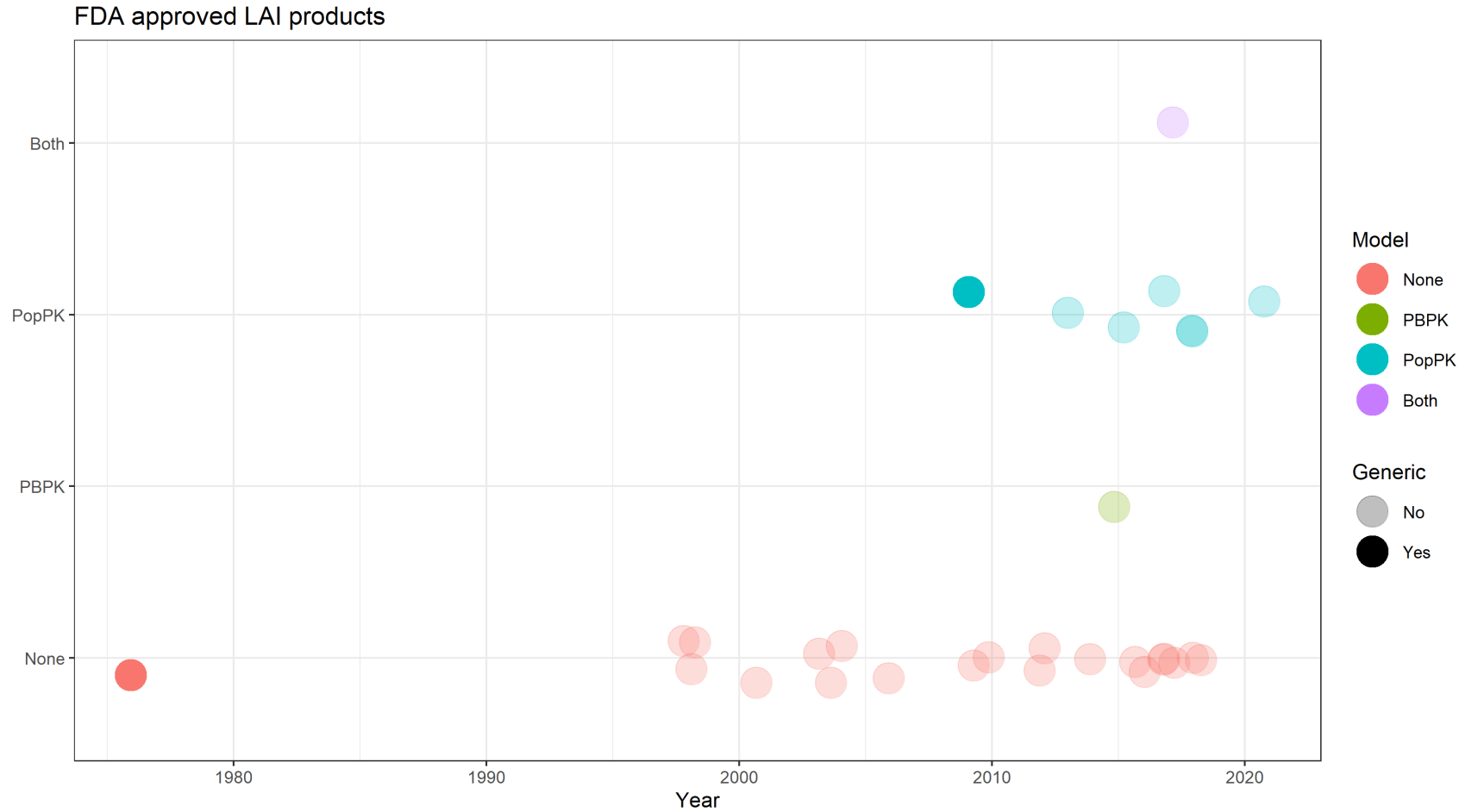


Model-integrated comparison



- Removes need to trial both reference and test products, making clinical trials more streamlined
- Models allow both inter-individual and inter-occasion variability to be accounted for

The power of models \



Conclusion \

- Determine a range of products which are bioequivalent after multiple dosing
- Determine what criteria can be used to recover bioequivalent products after only a single dose
- Create an integrated process with a PK study to prove BE with lower inherent risk



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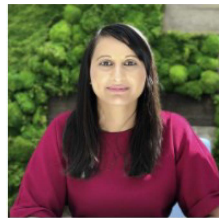
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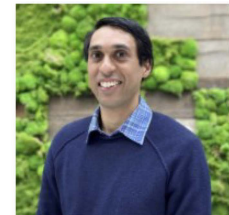
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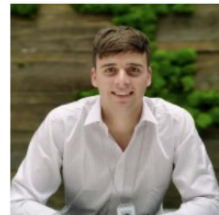
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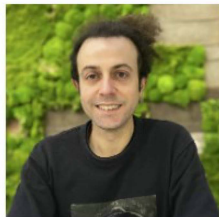
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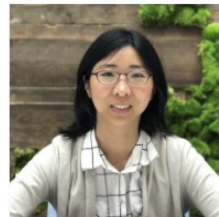
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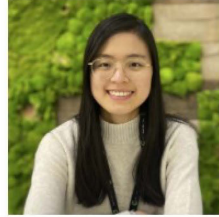
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