Streamlined Pathways to Clinical Success through Integrated Modelling

Jake Dickinson

Internal

Objectives

1. Identify opportunities within different stages of development projects where MIDD can be advantageous

2. Understand applications of a translational semi-mechanistic PK-PD-TGI model to predict clinical Objective Response Rate and efficacious dose to support dose selection

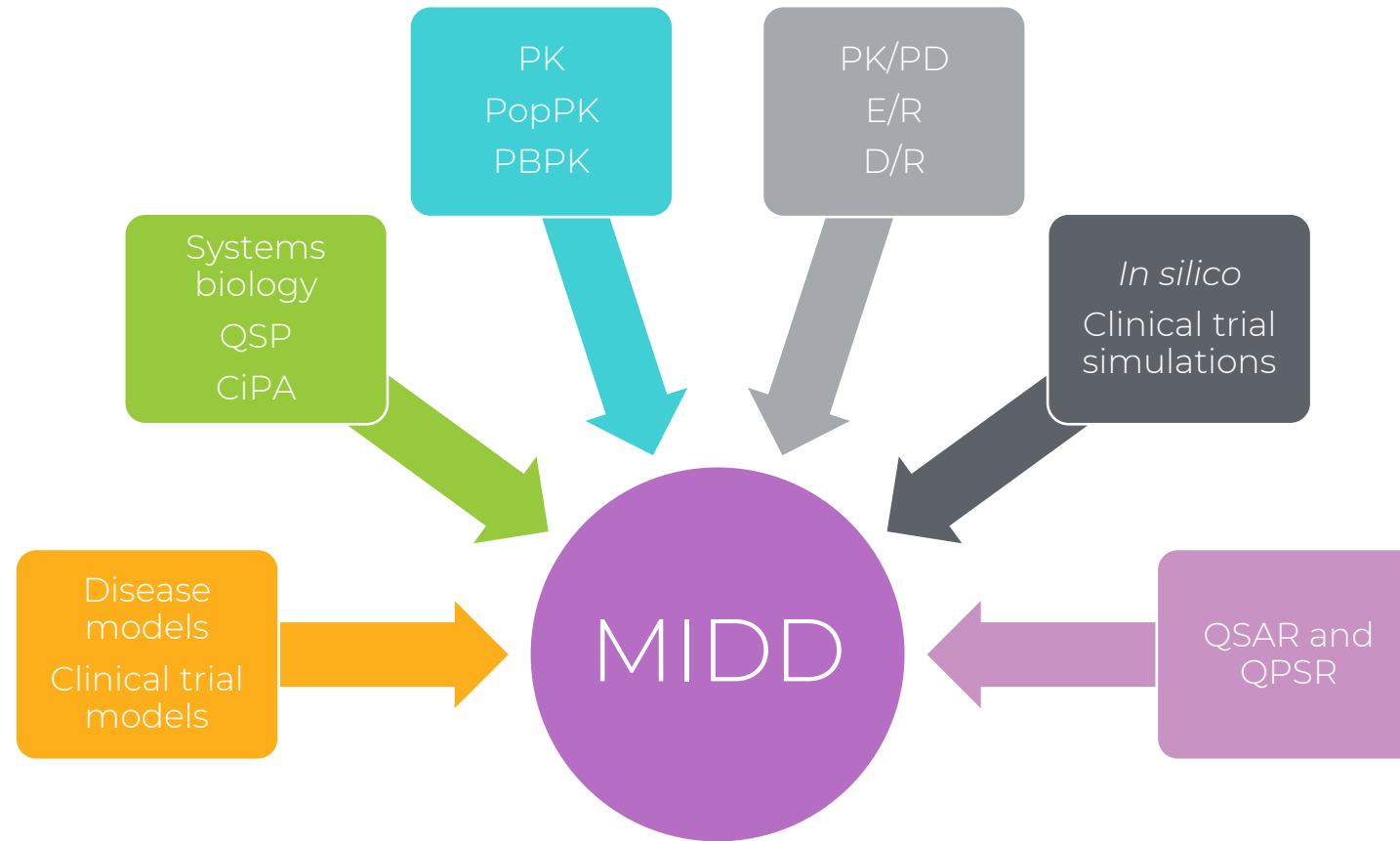3. Explore how modelling approaches may result in new methodologies

MIDD overview

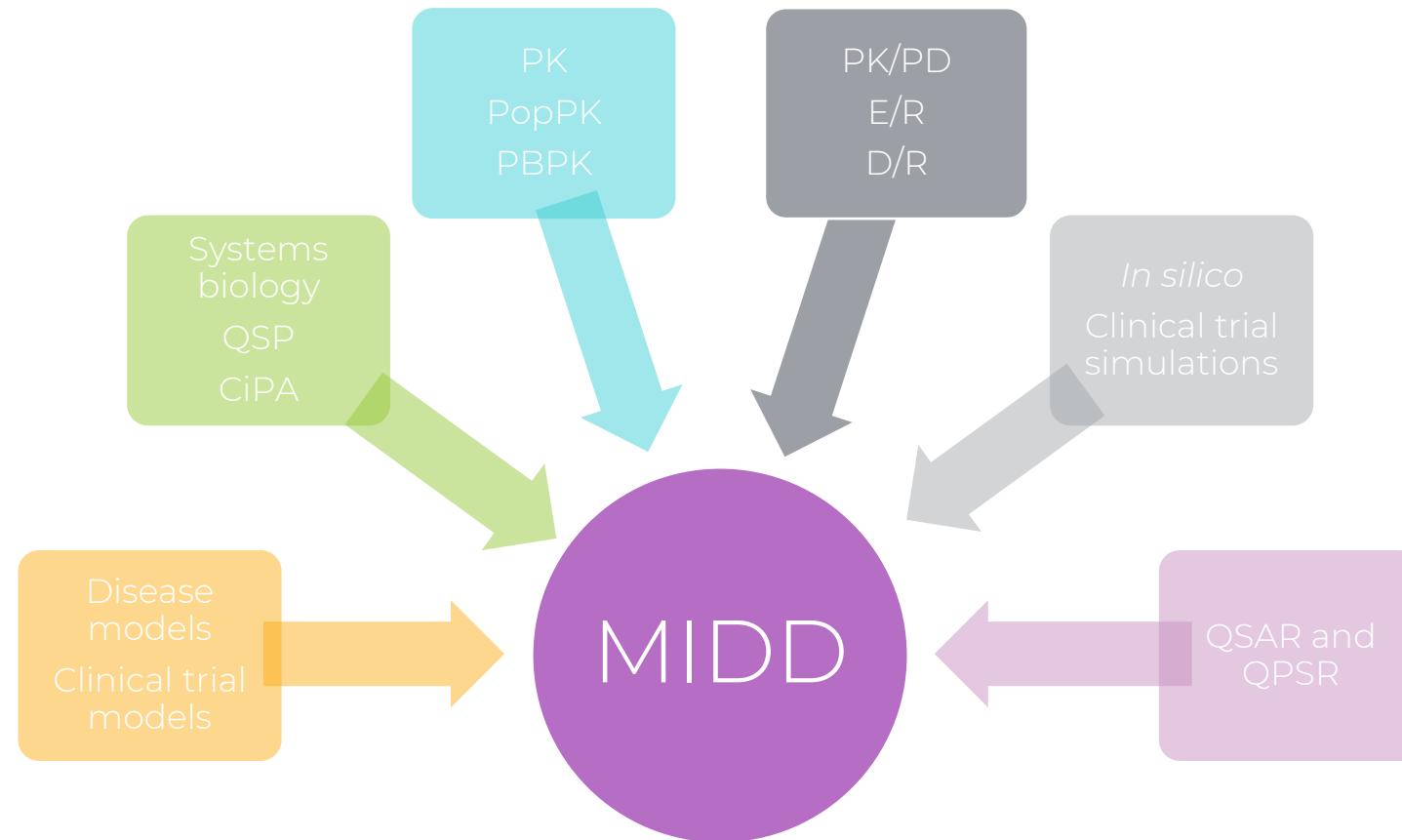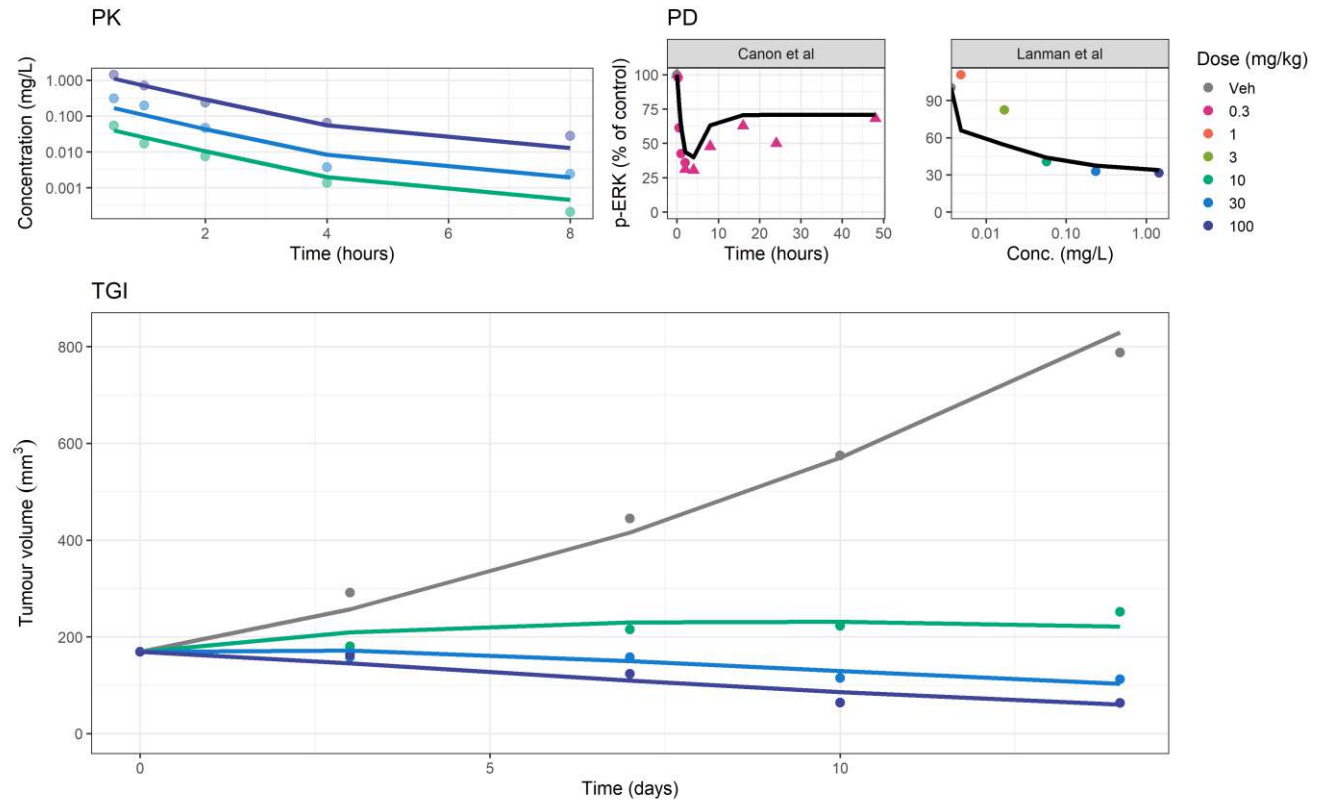Figure adapted Huang SM 2019 AAPS

MIDD overview

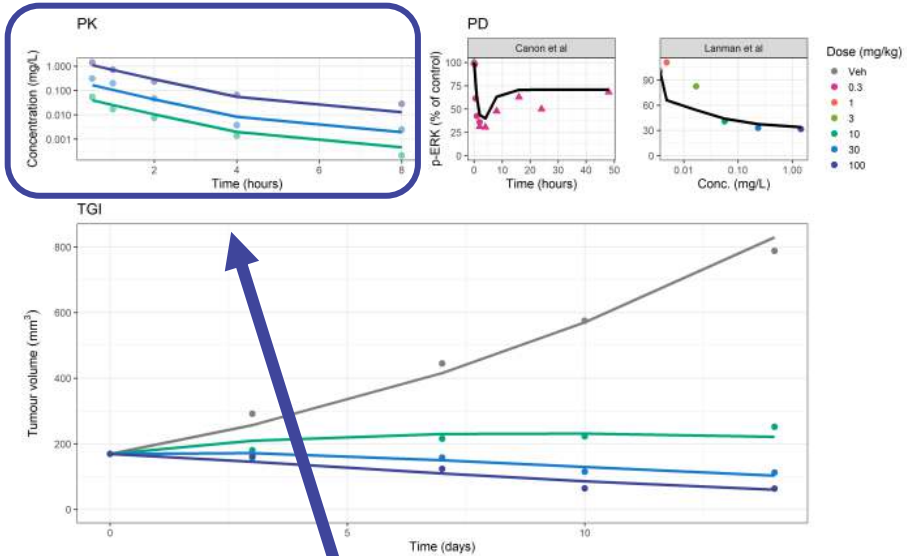

Figure adapted Huang SM 2019 AAPS

Translational PK/PD/TGI modelling of KRAS G12C inhibitors

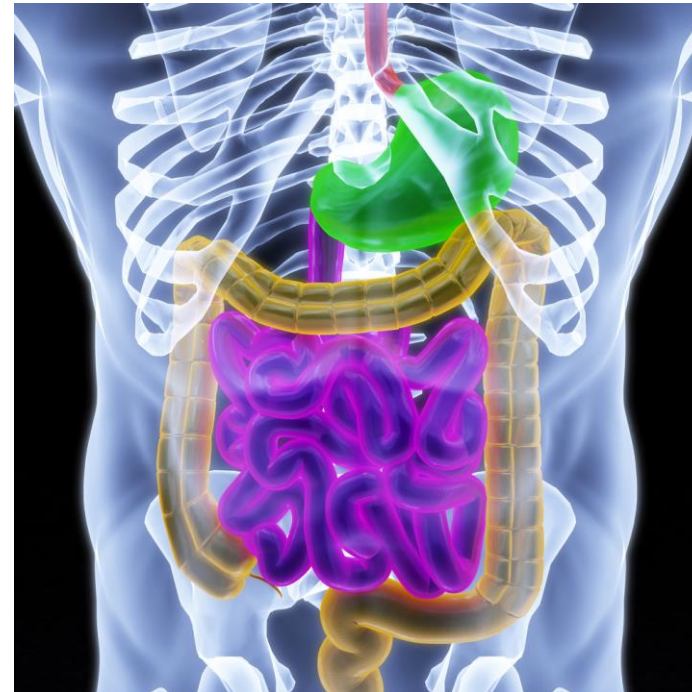Step 1: Establish a preclinical PK-PD-TGI model for compound (Sotorasib)

Dickinson et al 2022 AAPS

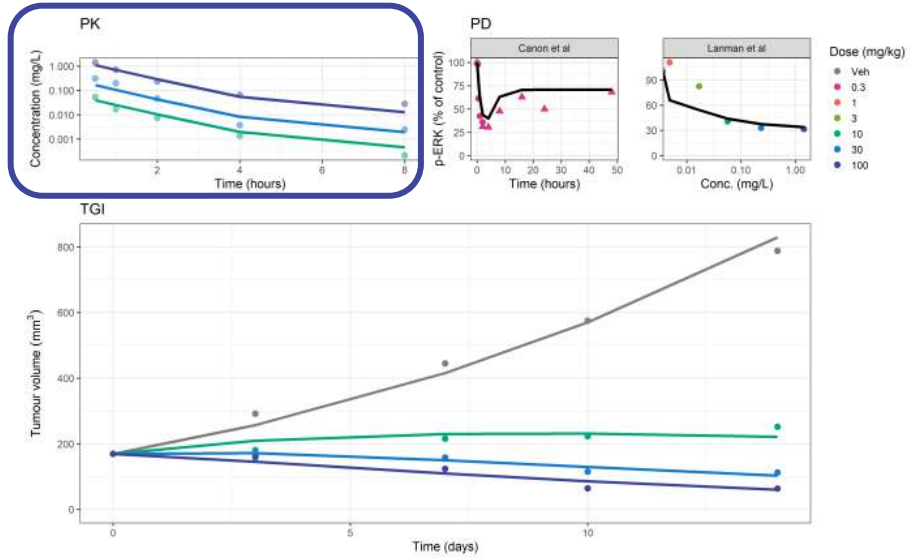# Translational PK/PD/TGI modelling of KRAS G12C inhibitors

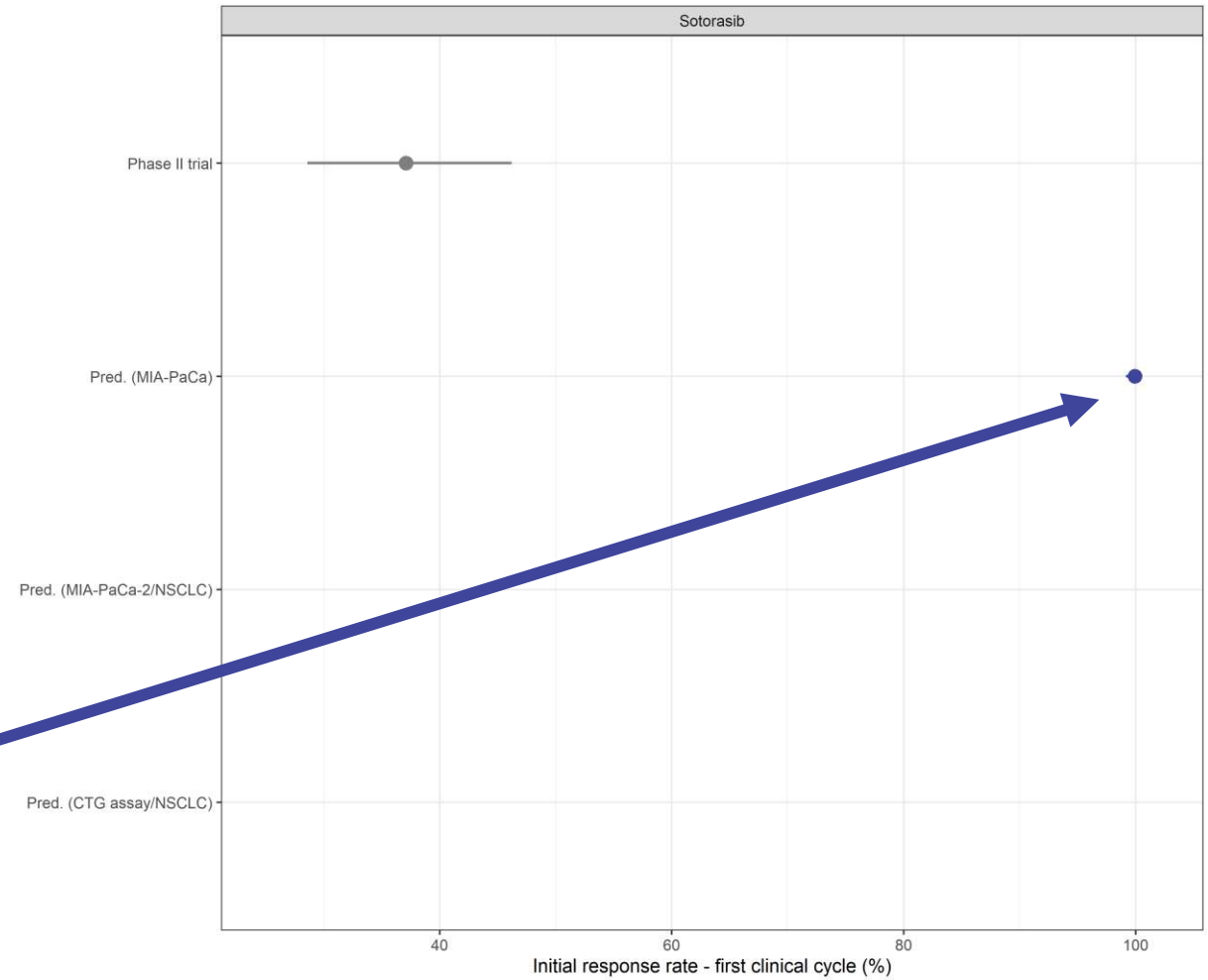Accepted single cell-line translational approach

Step 2: Mouse PK model replaced by human PK model

Dickinson et al 2022 AAPS

SEDA
Pharmaceutical Development Services

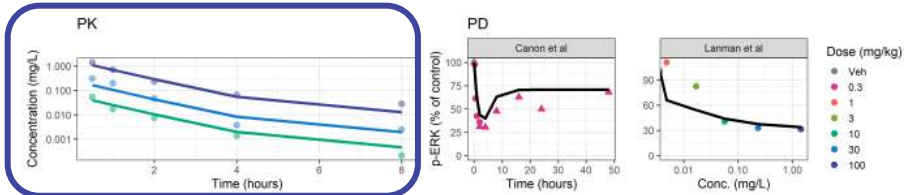# Translational PK/PD/TGI modelling of KRAS G12C inhibitors

Single, sensitive cell-line can lead to overprediction.
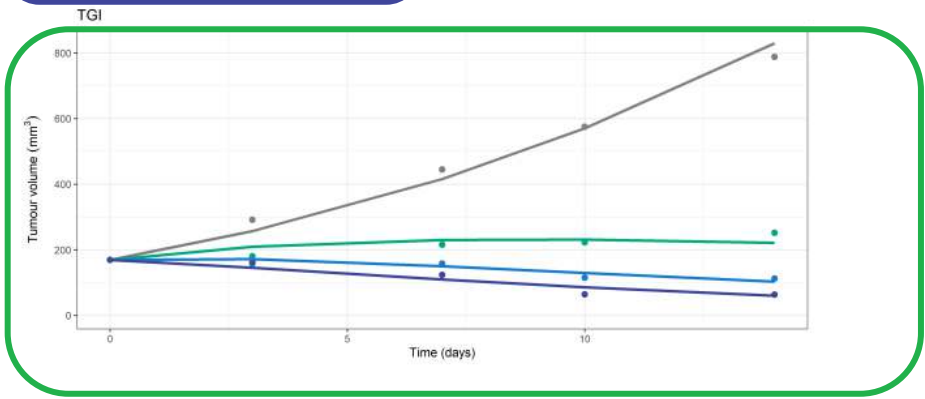Heterogeneity not captured

Dickinson et al 2022 AAPS

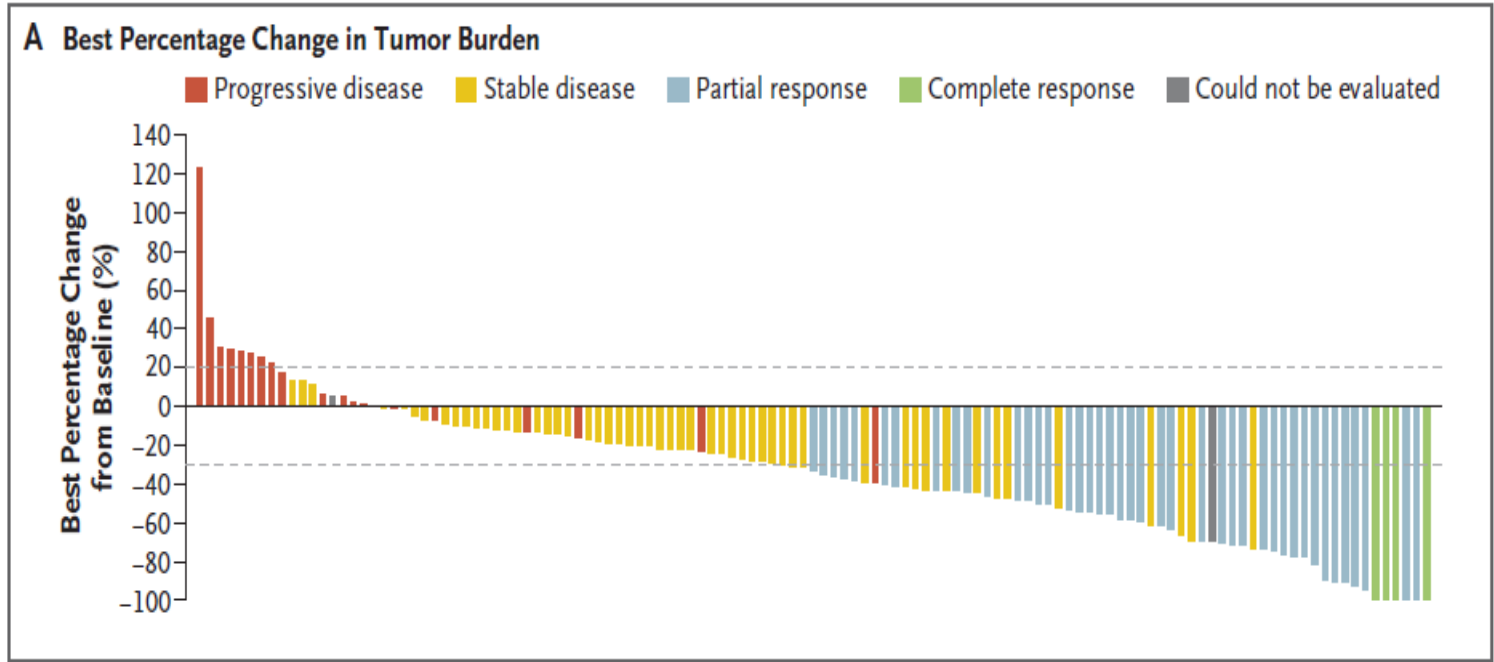# Translational PK/PD/TGI modelling of KRAS G12C inhibitors

Novel translational approach

Skoulidis et al 21 NEJM

Step 3: Clinical tumour growth kinetics back-translated

Dickinson et al 2022 AAPS

SEDA
Pharmaceutical Development Services

Translational PK/PD/TGI modelling of KRAS G12C inhibitors
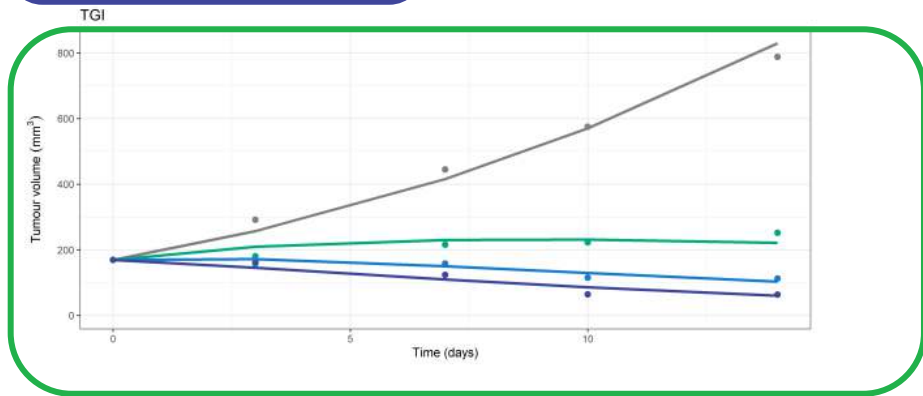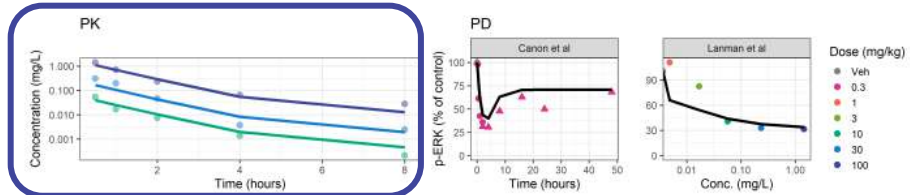
Correlation to reported clinical ORR greatly improved

Dickinson et al 2022 AAPS

SED/\
Pharmaceutical Development Services

Translational PK/PD/TGI modelling of KRAS G12C inhibitors
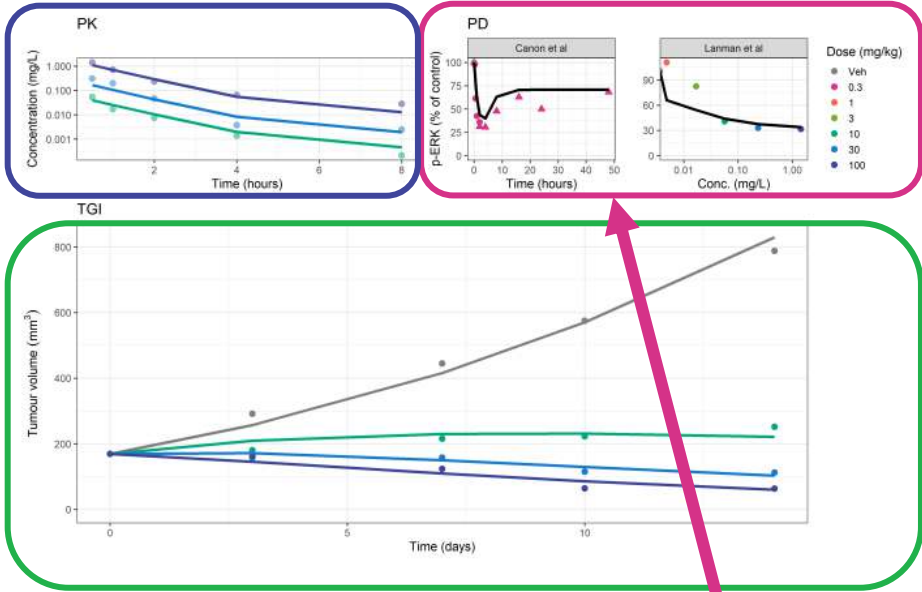
Novel translational approach

Arbitrary representation of in vitro IC50 screening
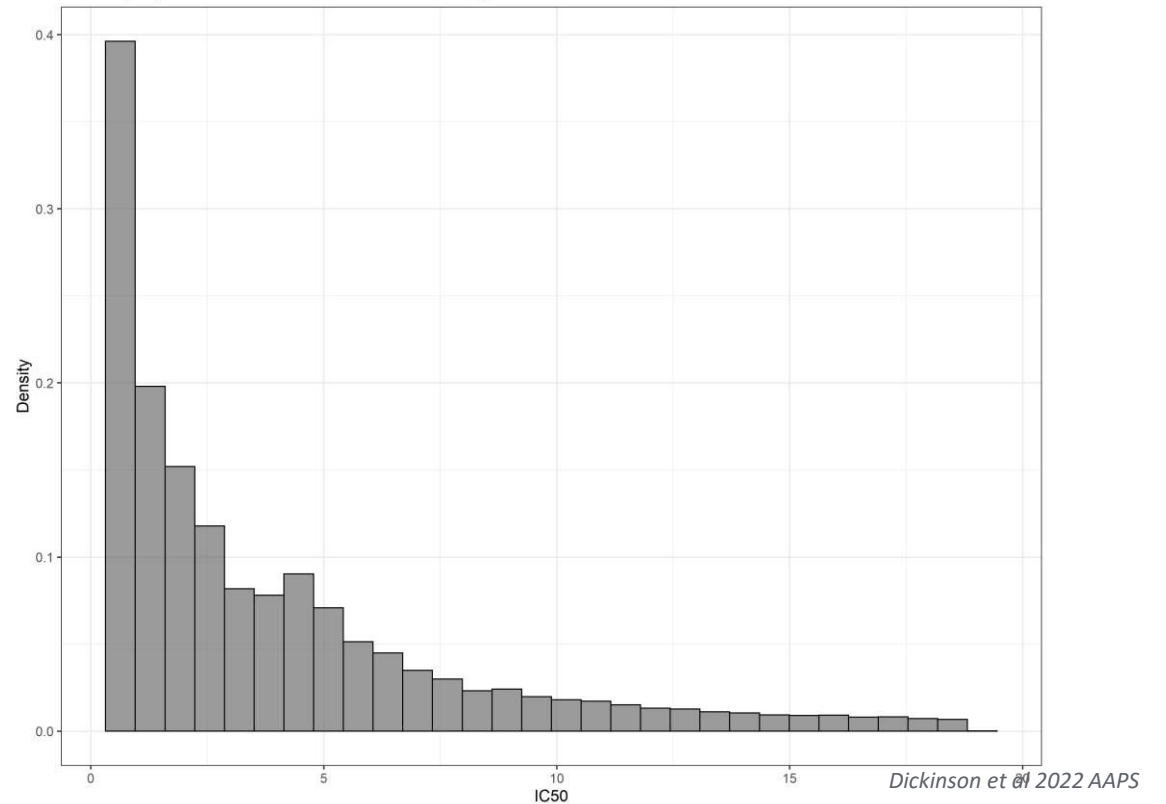
Step 4: IC50 distribution derived from *in vitro* cell-line screening

Dickinson et al 2022 AAPS

SEDA
Pharmaceutical Development Services

Translational PK/PD/TGI modelling of KRAS G12C inhibitors
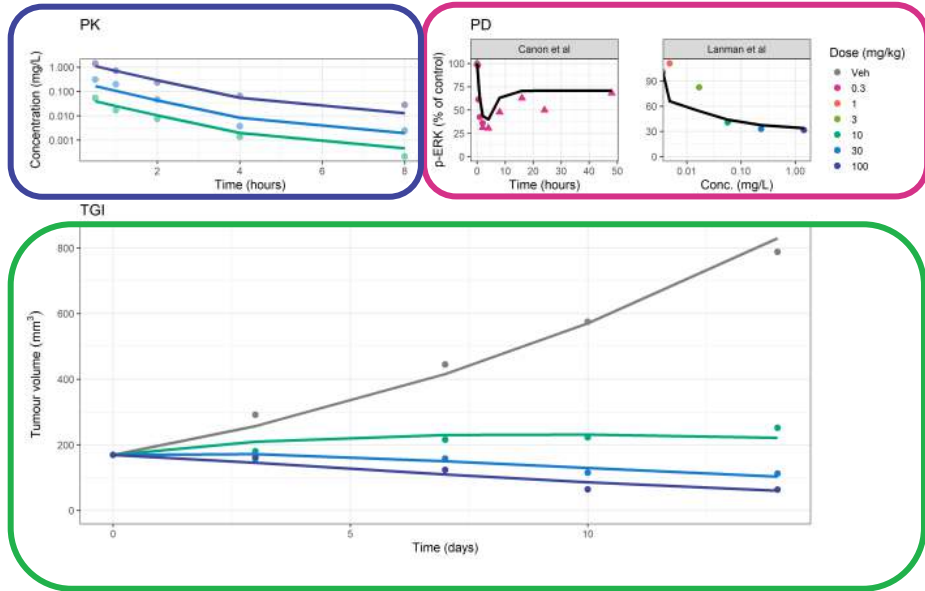
Clinical ORR captured well by model.
Heterogeneity has been explained
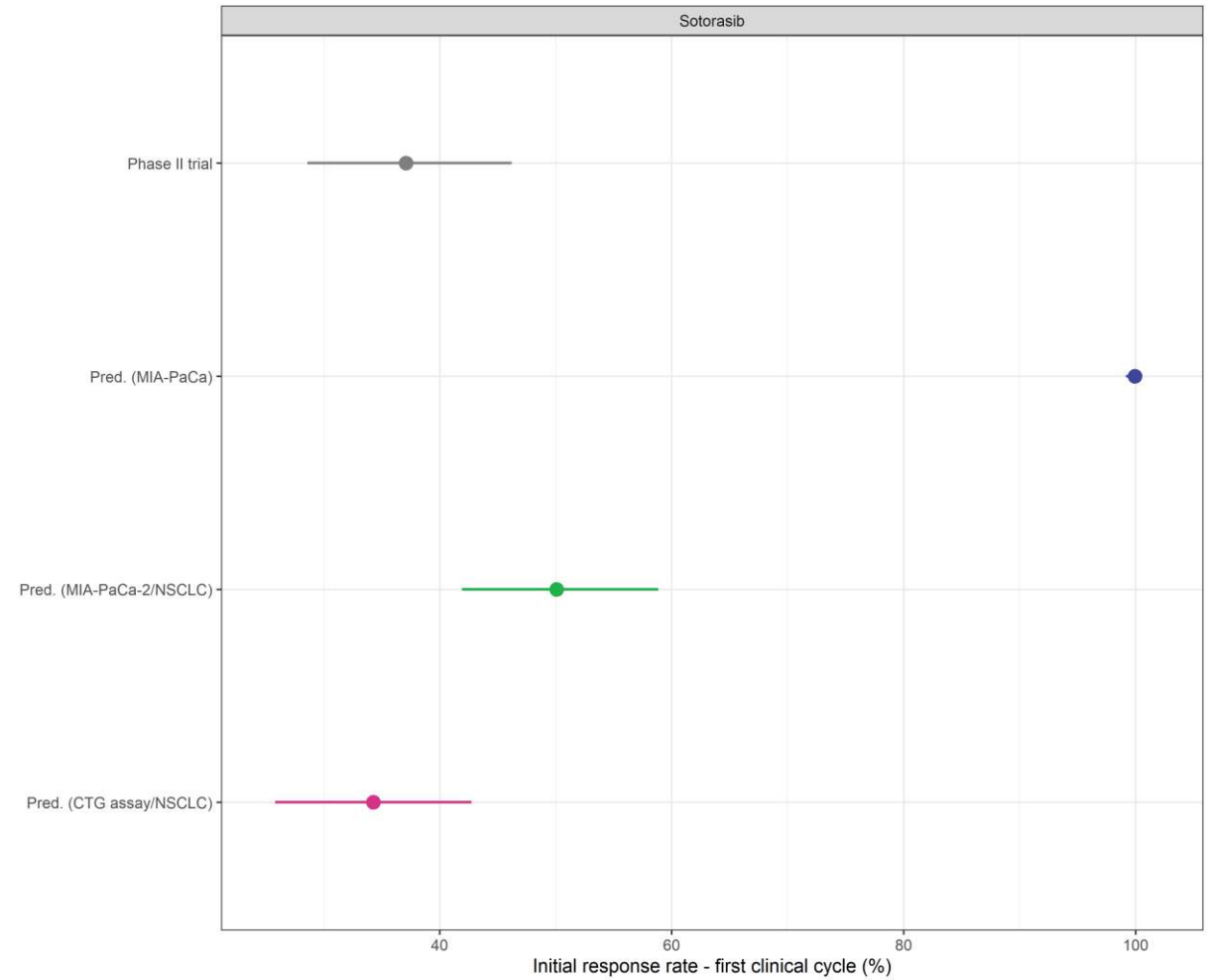
Dickinson et al 2022 AAPS

Translational PK/PD/TGI modelling of KRAS G12C inhibitors
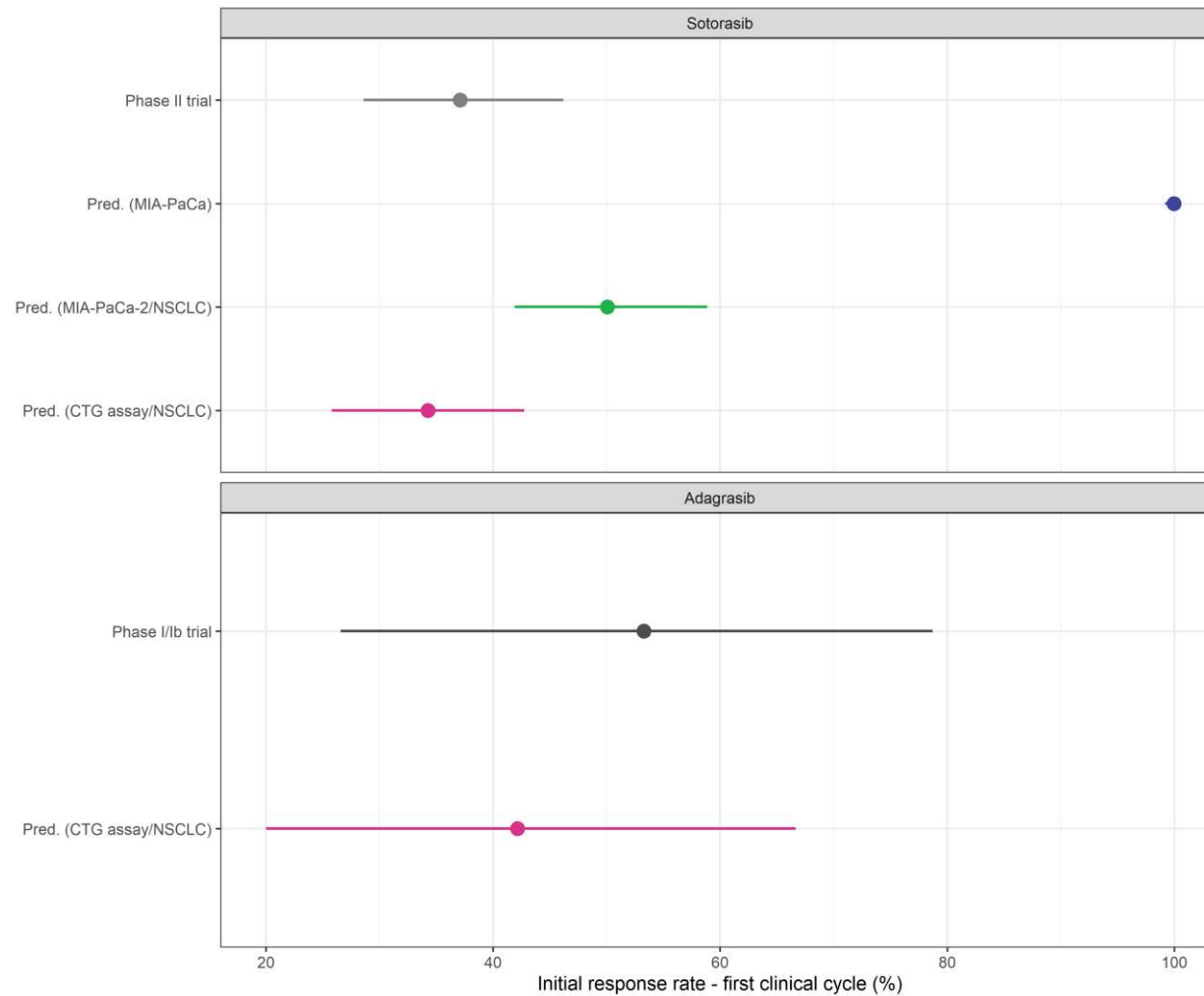
Modelling approach qualified on Adagrasib

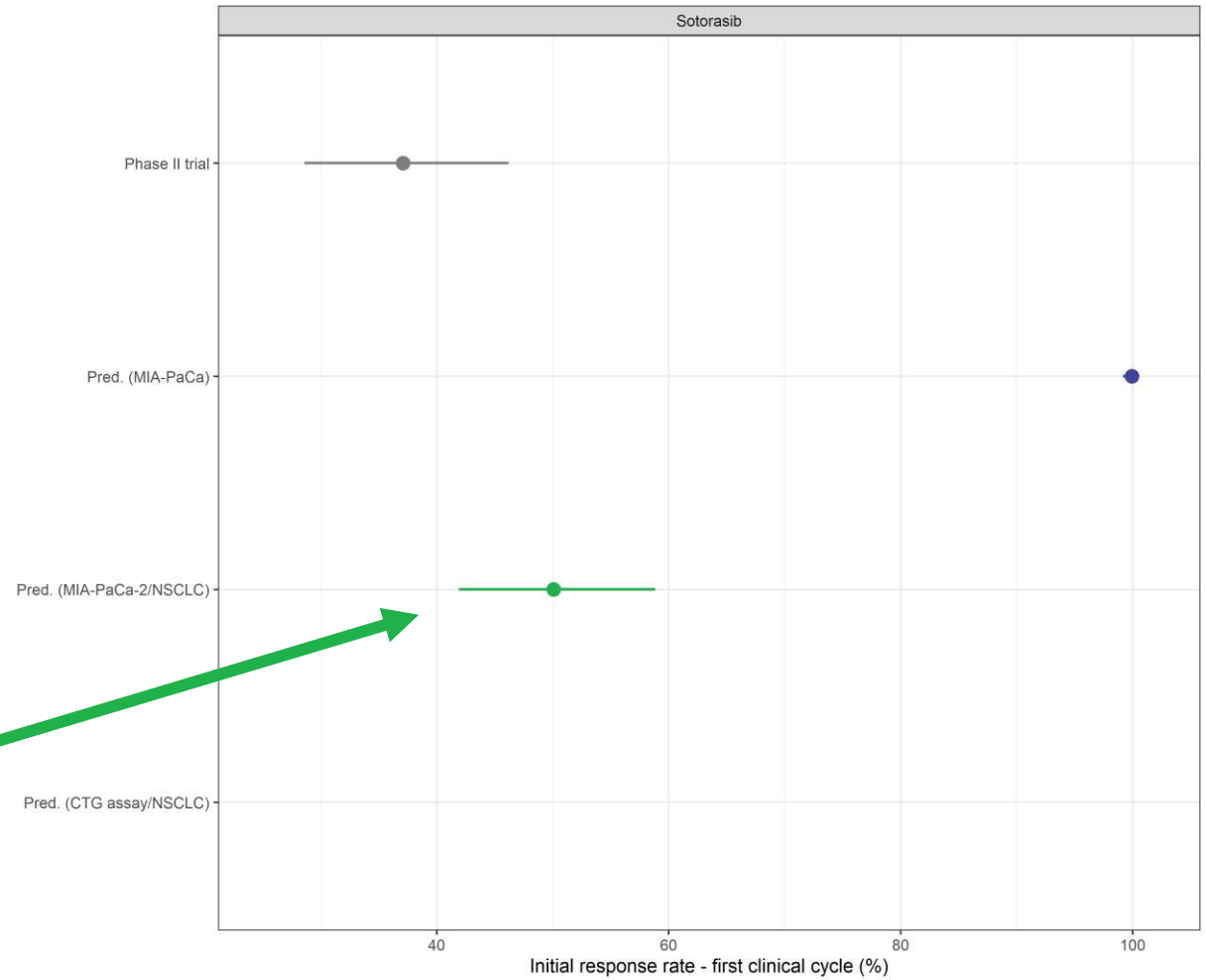*Dickinson et al 2022 AAPS*

MIDD overview
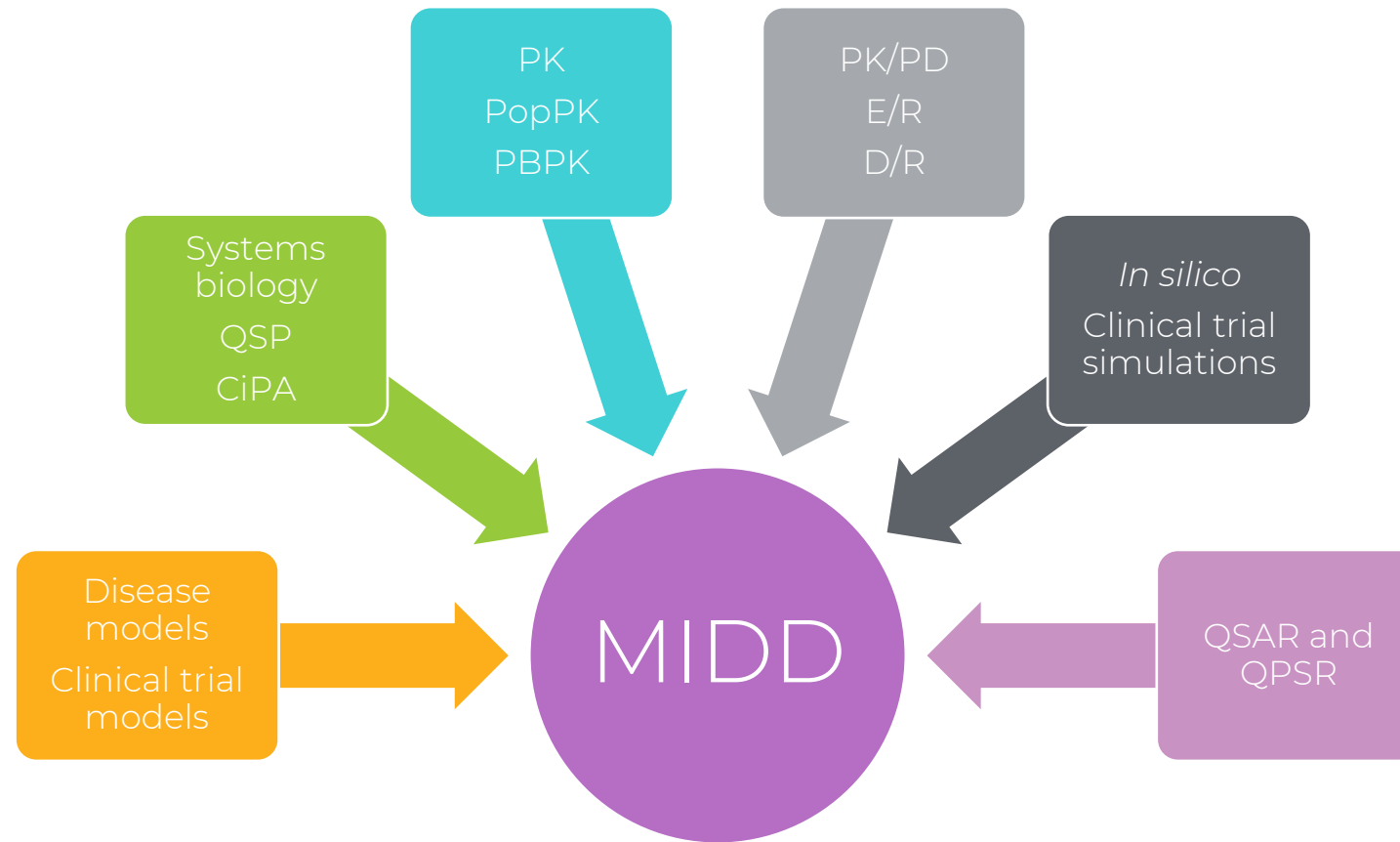
PK
PopPK
PBPK

PK/PD
E/R
D/R

Systems
biology
QSP
CiPA

In silico
Clinical trial
simulations

Disease
models
Clinical trial
models

MIDD

QSAR and
QPSR

Figure adapted Huang SM 2019 AAPS

SEDA
Pharmaceutical Development Services

MIDD overview

Use PopPK as a tool for *in silico* clinical trial simulations

Systems biology
QSP
CiPA

PK
PopPK
PBPK

PK/PD
E/R
D/R

In silico
Clinical trial simulations

Disease models
Clinical trial models

MIDD

QSAR and QPSR

Figure adapted Huang SM 2019 AAPS

SED∧
Pharmaceutical Development Services

Challenge of clinical studies

Very long half life

Terminal phase is due to slow absorption

Concentration (ng/ml)

Time (days)
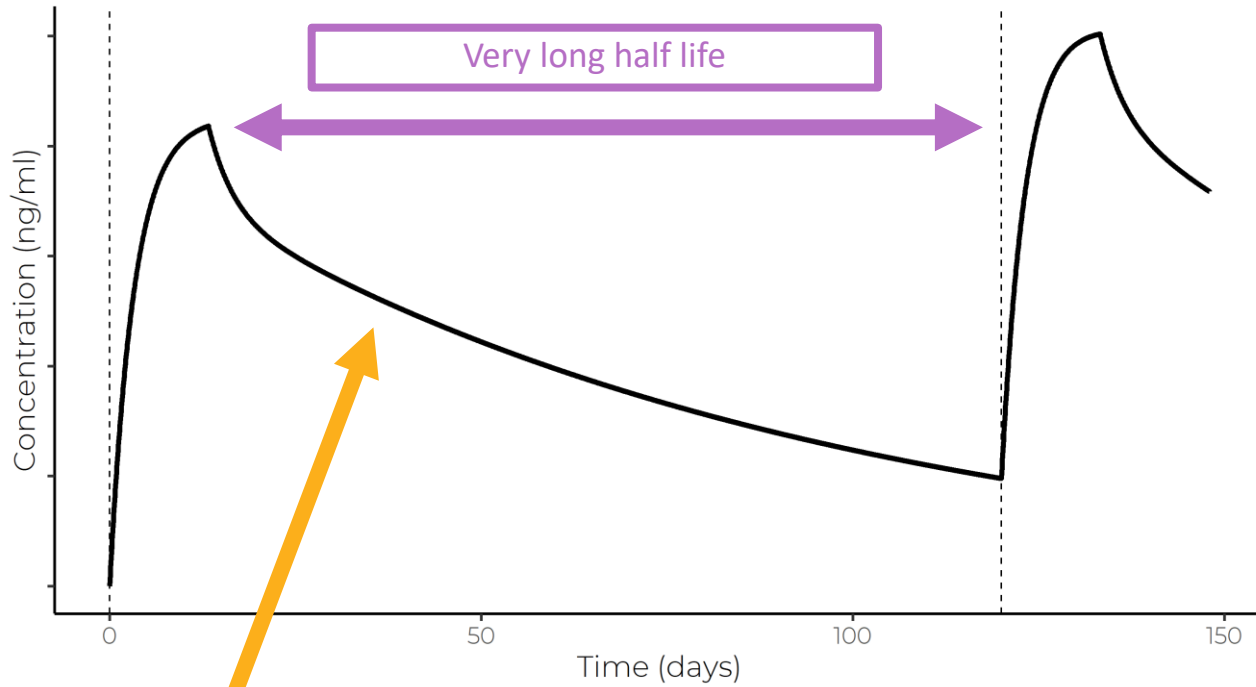
Completion rates for Paliperidone Palmitate
Clinical study NCT00590577

placebo
43% / 57%

25mg
52% / 48%

100mg
54% / 46%

150mg
55% / 45%

Label
Completed
Not Completed
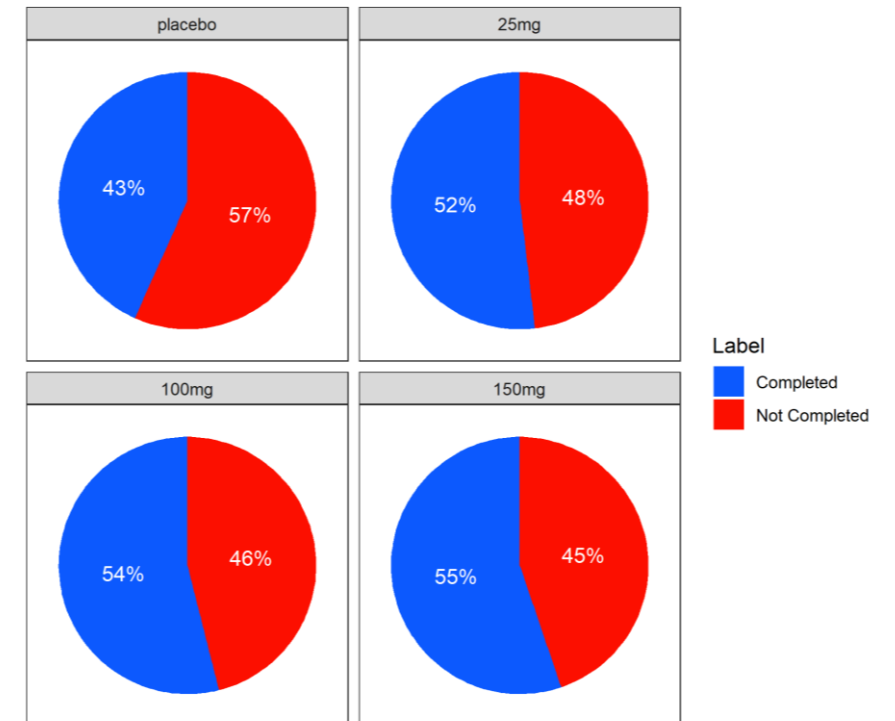
High clinical drop out rates

SEDA
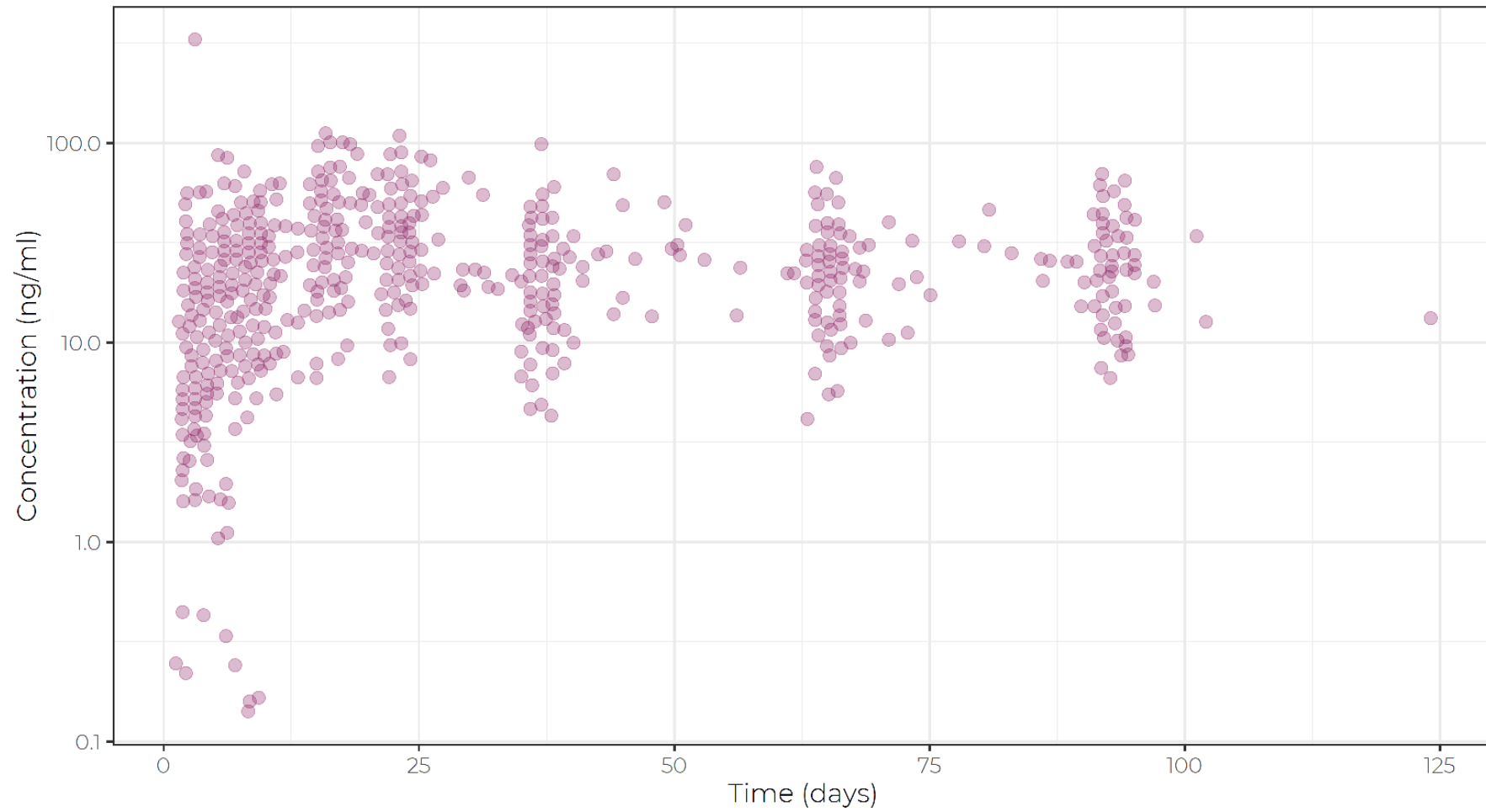Pharmaceutical Development Services

Pharmacokinetic variations

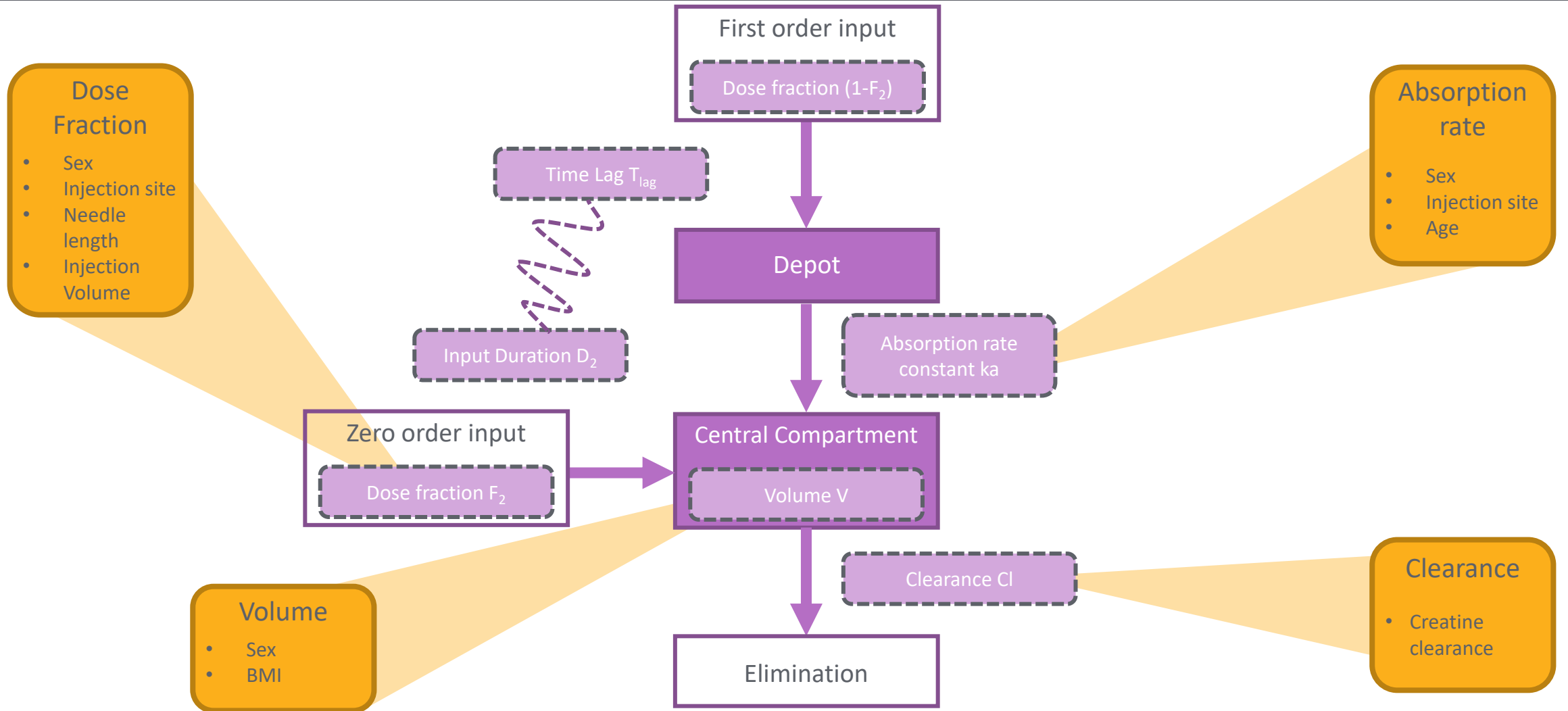
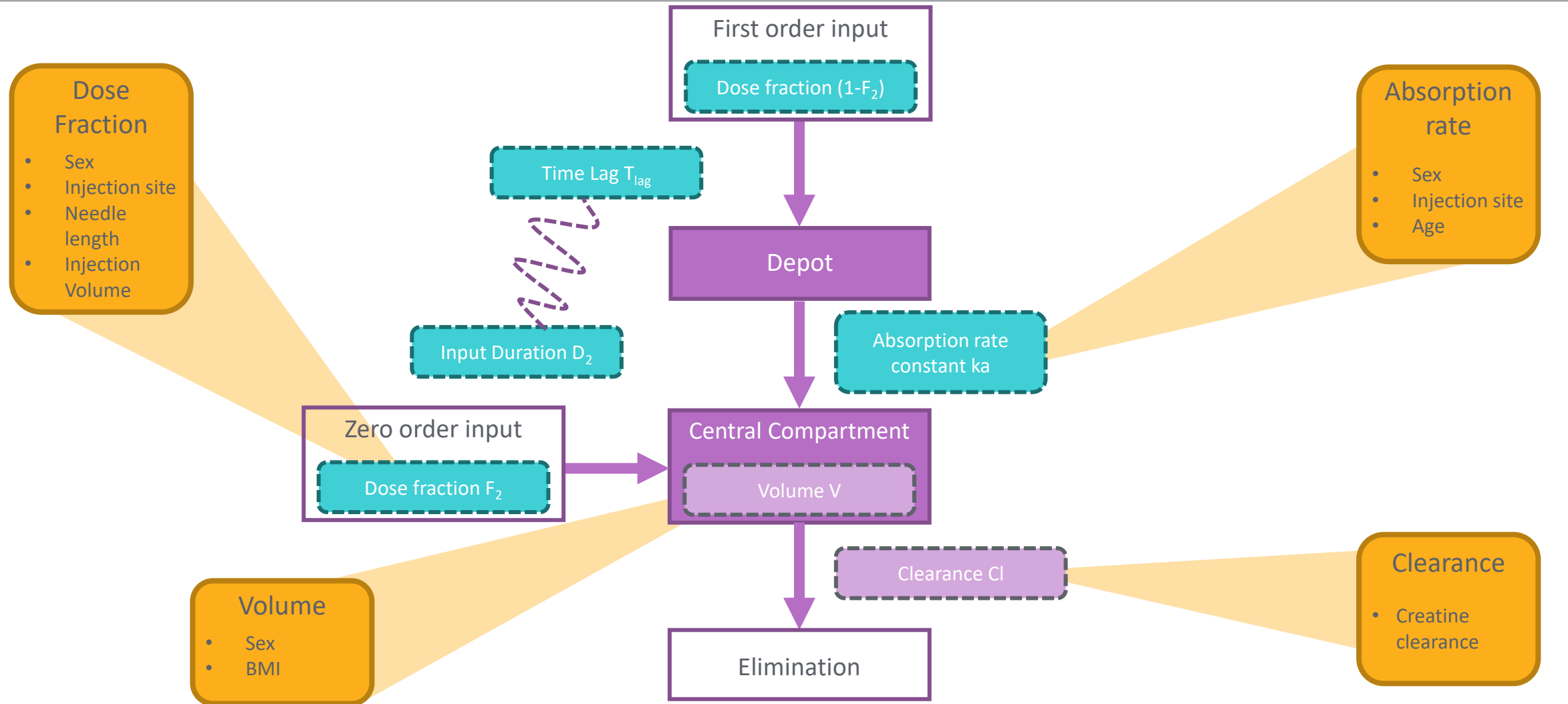Figure adapted from Paliperidone Palmitate FDA Clinical Pharmacology Review

Capturing pharmacokinetic variations

Streamlined Pathways to Clinical Success through Integrated Modelling

Modelling different products

MIDD going forward

Paliperidone Palmitate popPK simulation
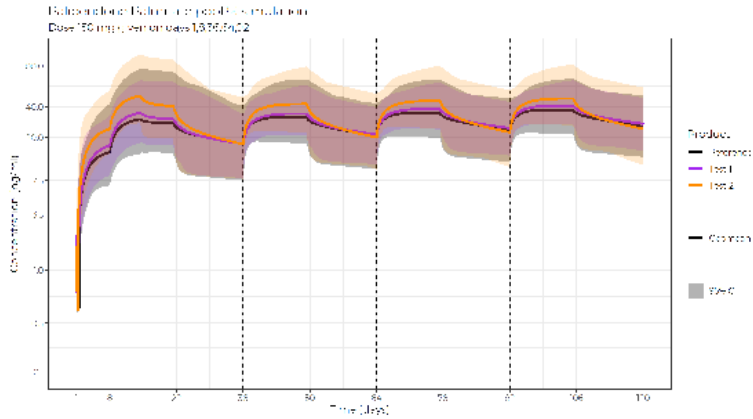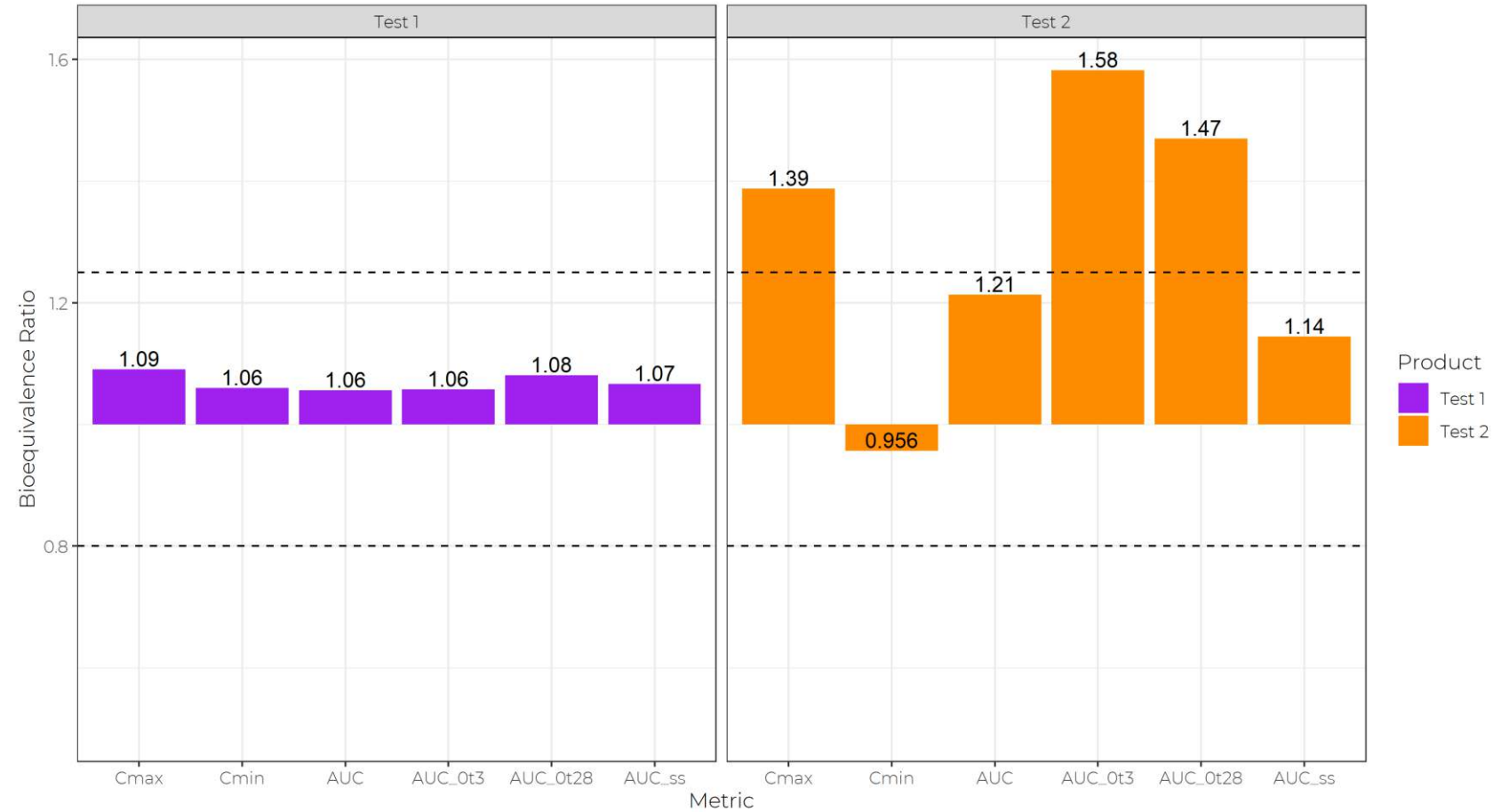Dose 150 mg given on days 1,8,36,64,92
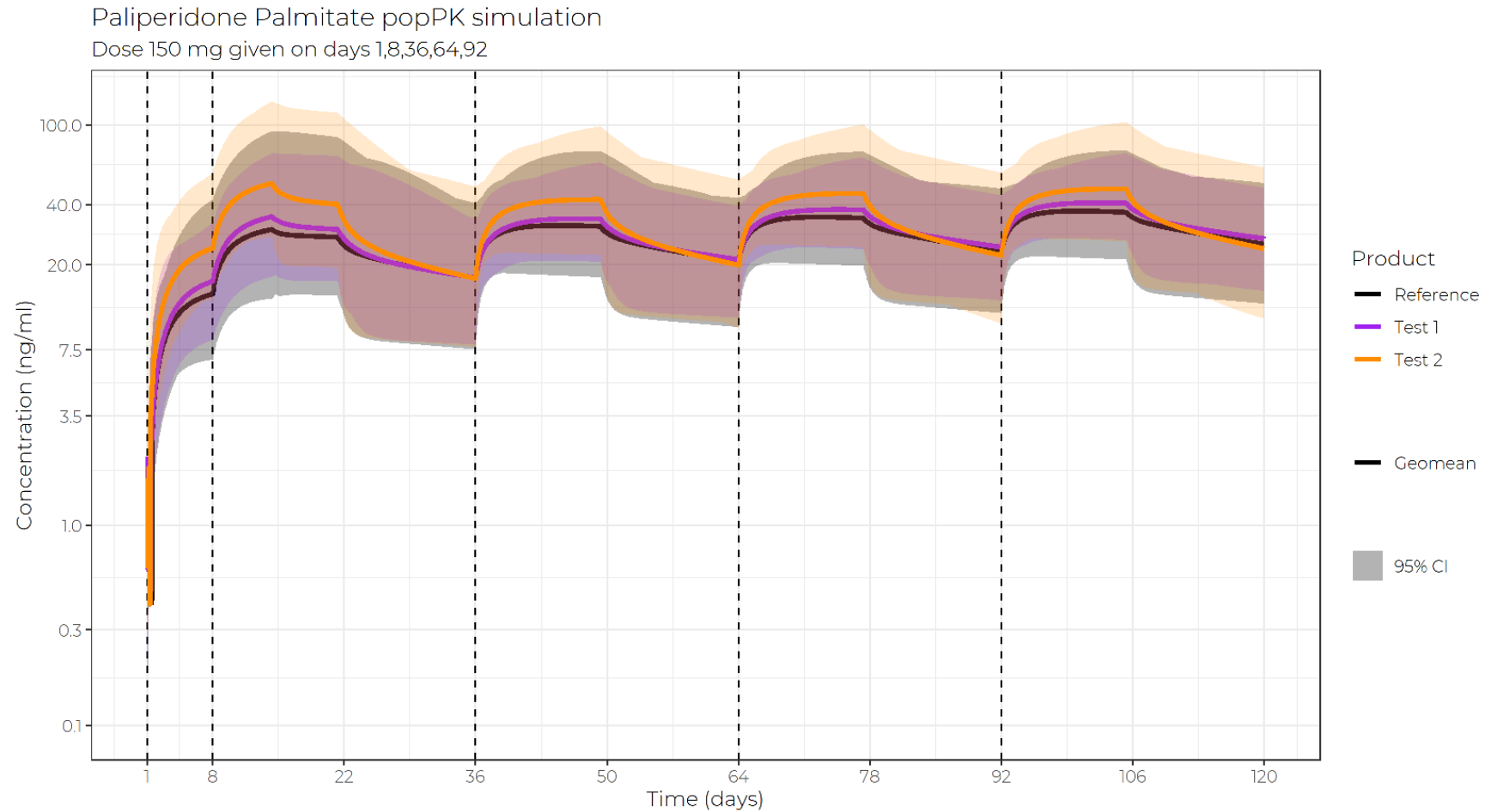
Gajjar et al 2022 EJPS

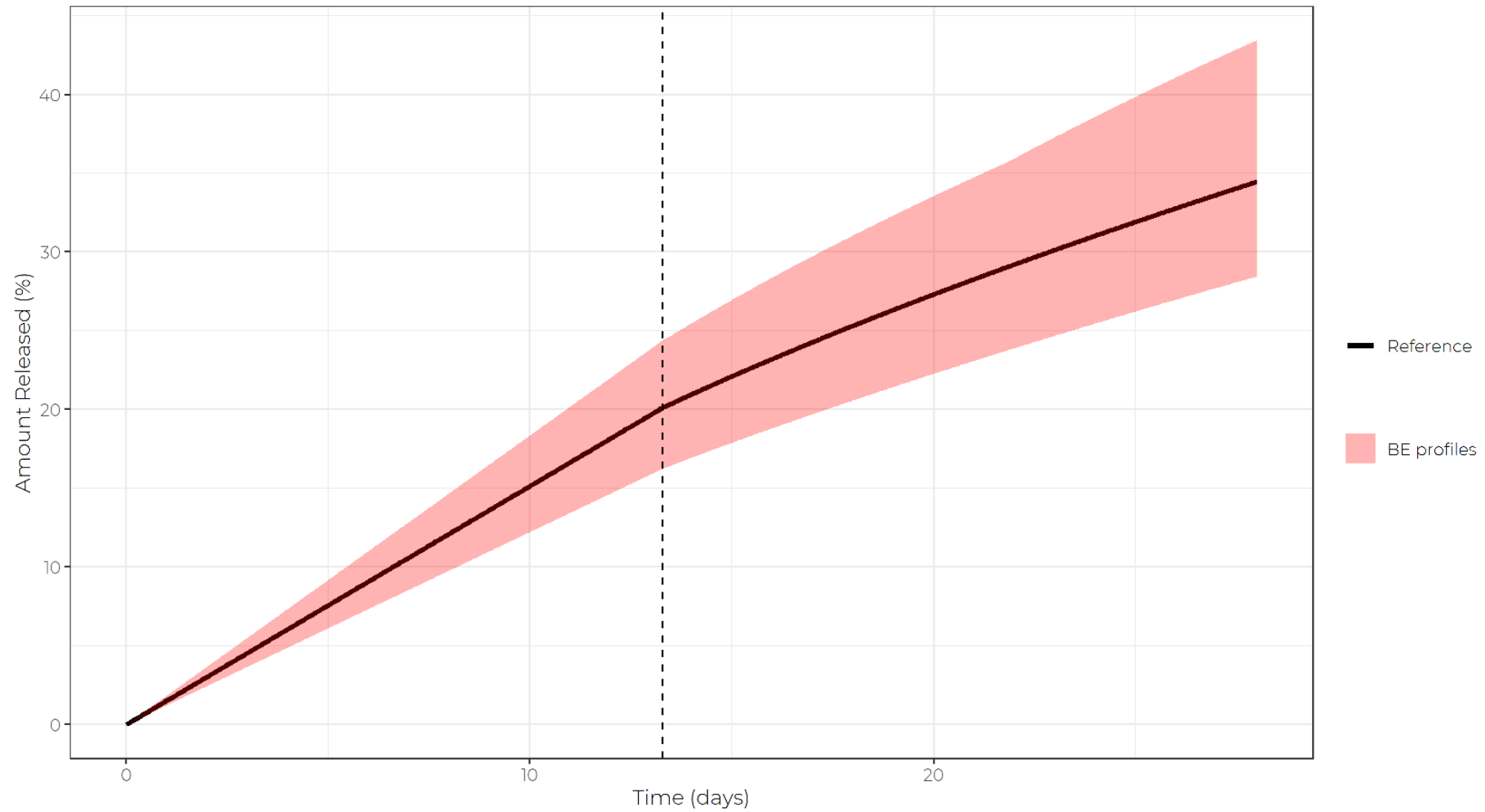# MIDD going forward

Gajjar et al 2022 EJPS

MIDD going forward

MIDD going forward
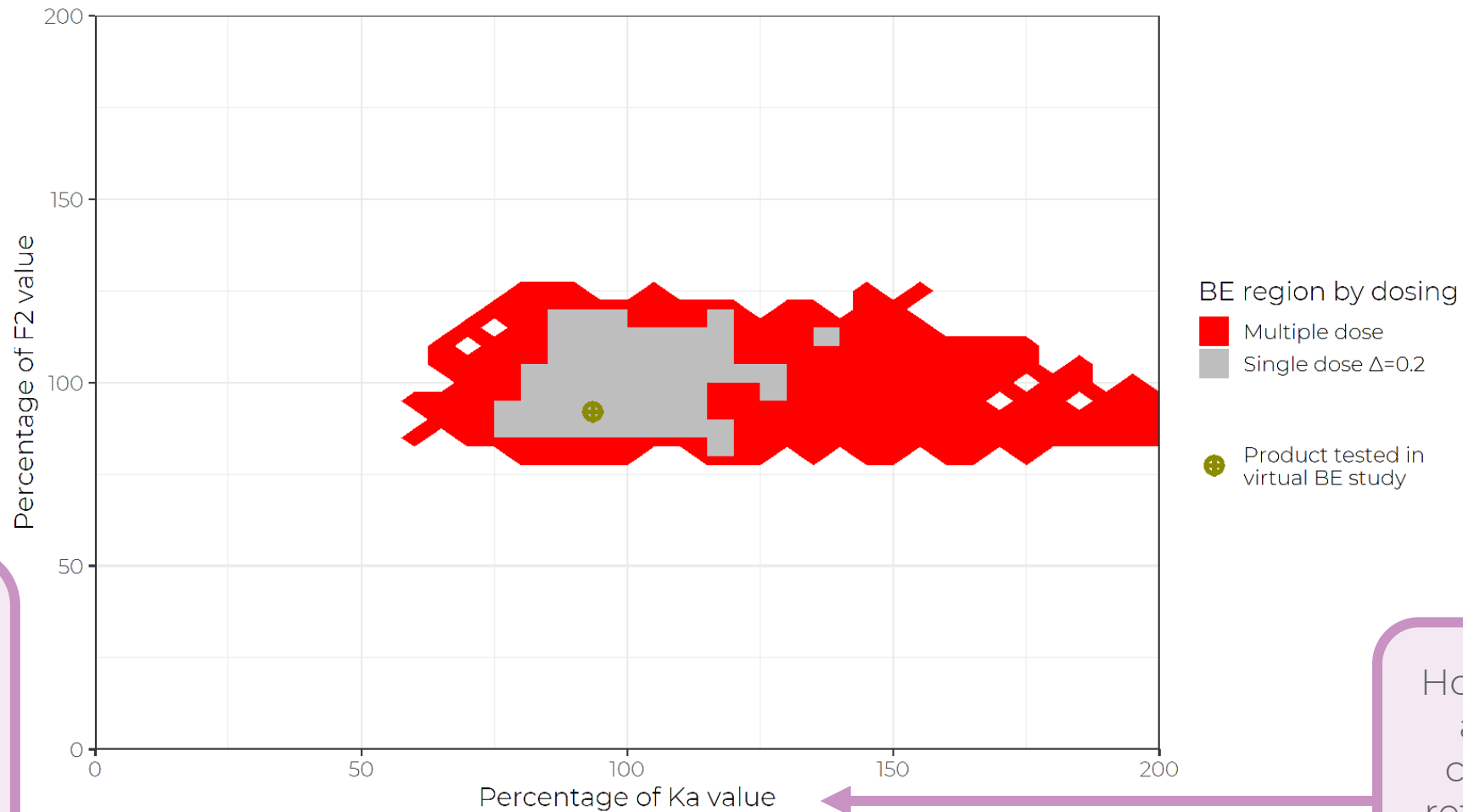
How different is the relative fraction of zero order input compared to the reference product?

How different is the absorption rate compared to the reference product?

Percentage of F2 value

Percentage of Ka value

BE region by dosing
- Multiple dose
- Single dose Δ=0.2

Product tested in virtual BE study

Gajjar et al 2022 EJPS

SEDA
Pharmaceutical Development Services

MIDD going forward

Integrate modelling approach with **shorter**/**smaller** Clinical trials for streamlined development
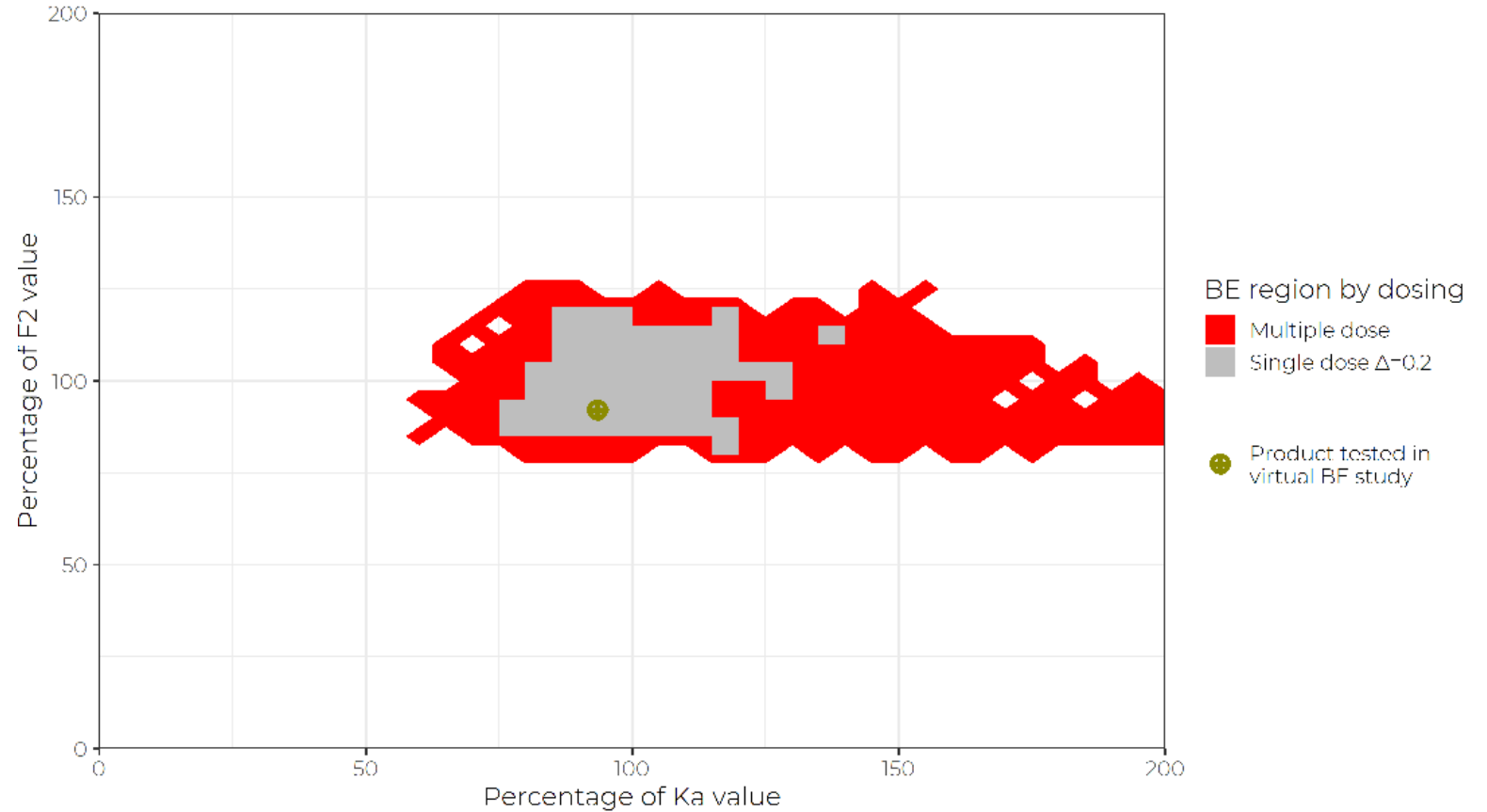
Gajjar et al 2022 EJPS

Acknowledgments

- The author greatly appreciates comments, helpful suggestions from and valuable discussion with the following colleagues:
- Boehringer-Ingelheim:
    - Dr Jens. Quant
    - Dr. Heinrich Huber
    - Dr. Otmar Schaaf
    - Dr. Fabio Savarese
    - Dr. Jan Elias
    - Dr. Lu Vivian Tan
    - Mr. Matthias Klemencic
    - Dr. Johannes Popow
    - Dr. Karl- Heinz Liesenfeld
- Seda Pharmaceutical Development Services:
    - Dr. Hitesh Mistry
    - Dr. Paul Dickinson
    - Dr. Parmesh Gajjar
    - Mr. Harri Dickinson
    - Dr. Linette Ruston
    - Dr. Claire Patterson

SEDA
Pharmaceutical Development Services