PBPK 360
The State of The Science
Industry Perspective

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Eli Lilly and Co.

INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

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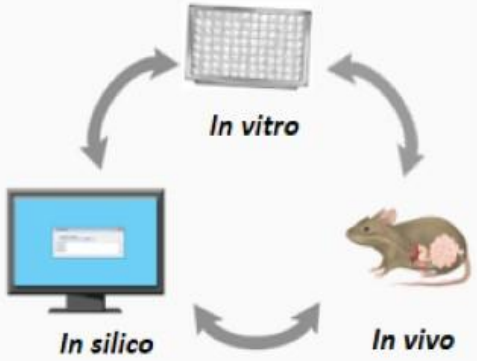
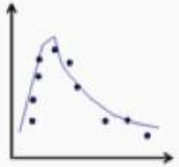
PBPK Modelling Strategies and Approaches in Industry

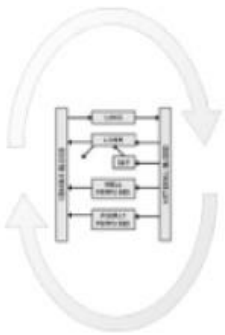
Discovery

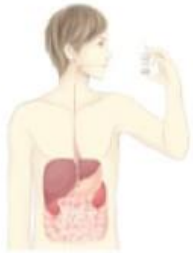


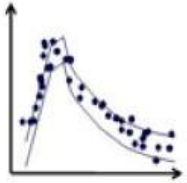


Early risk assessment,
Early first in human dose projection,
Toxicokinetic dose projection,
Early formulation assessment

Early Development



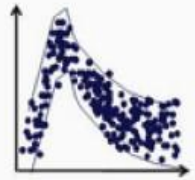




'Learn and confirm' through data integration

First in human, single/multiple ascending dose exposure or efficacy modeling,
Drug-Drug interaction, Food effect,
Formulation/Absorption modeling
Healthy subjects & patients

Late Development



Phase I-IV trials
Patient trials,
Special populations,
Label requirements

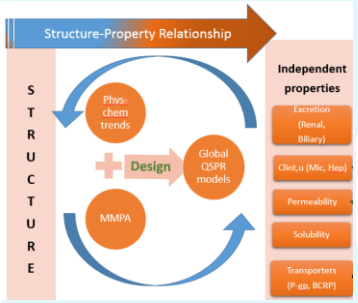
Continuous Model Refinement & Verification

Jones et al., Clin Pharmacol Ther. 2015 Mar;97(3):247-62.

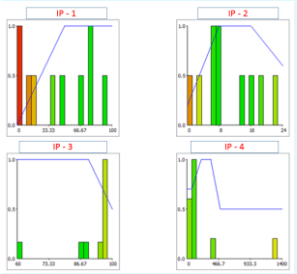
Discovery PK Learning Cycle

Property optimization

Identification of compounds that score high on MPS

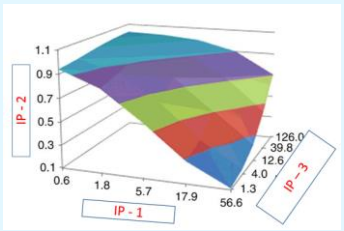


Drive design, synthesis and testing based on the MPS



potency

Derive MPS^ based primarily on 'independent' **human** parameters (Clint,u, Sol, perm, P-gp etc)



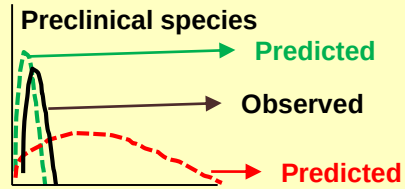
Sensitivity analysis* to identify gaps

Model building

Preclinical PK (mostly rodents)

Bottom up MPK for preclinical species

Observed vs Predicted PK aligned?



Yes

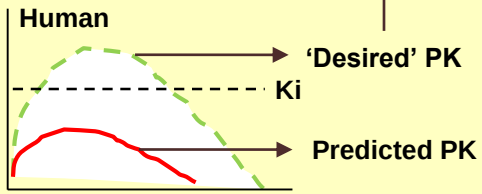
No

eMPK guidance to conduct additional mechanistic investigation

PD Model

Human MPK using the same strategy

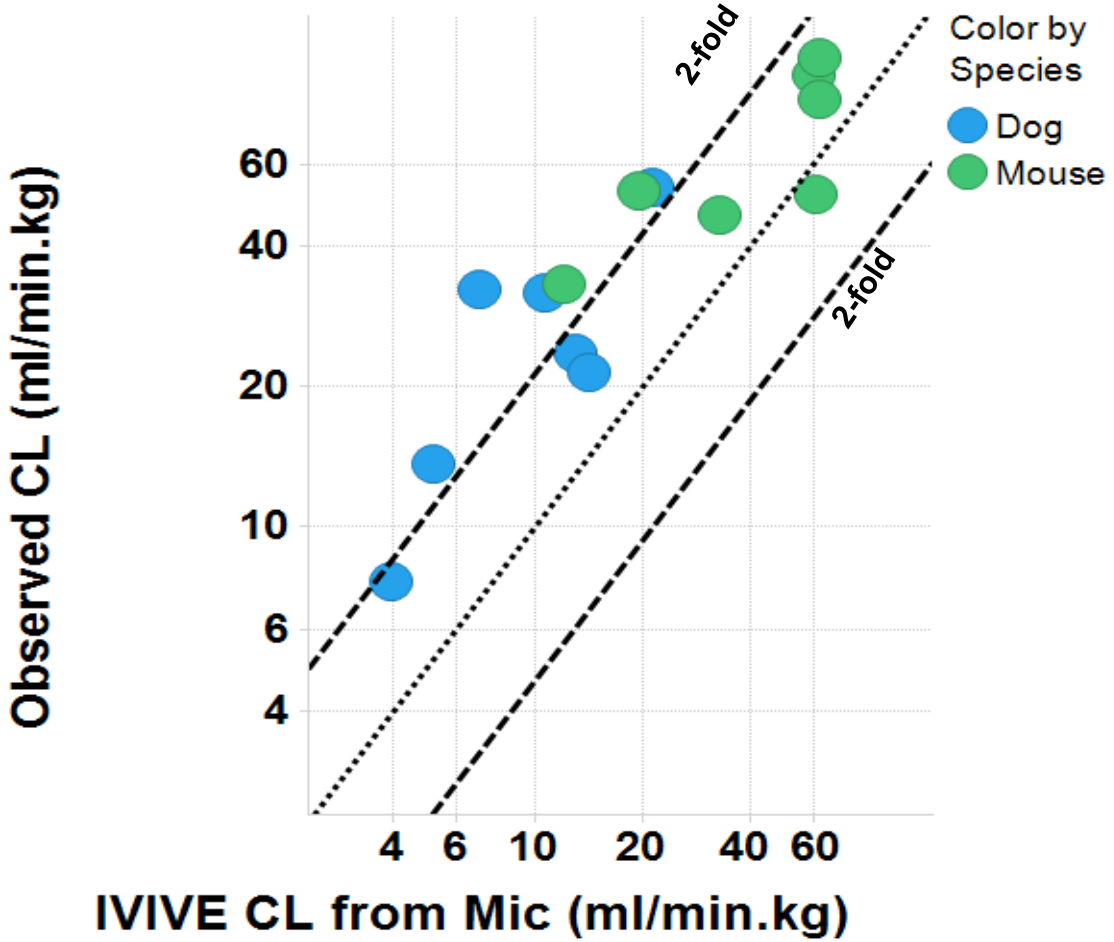
Factors informing the 'desired' PK

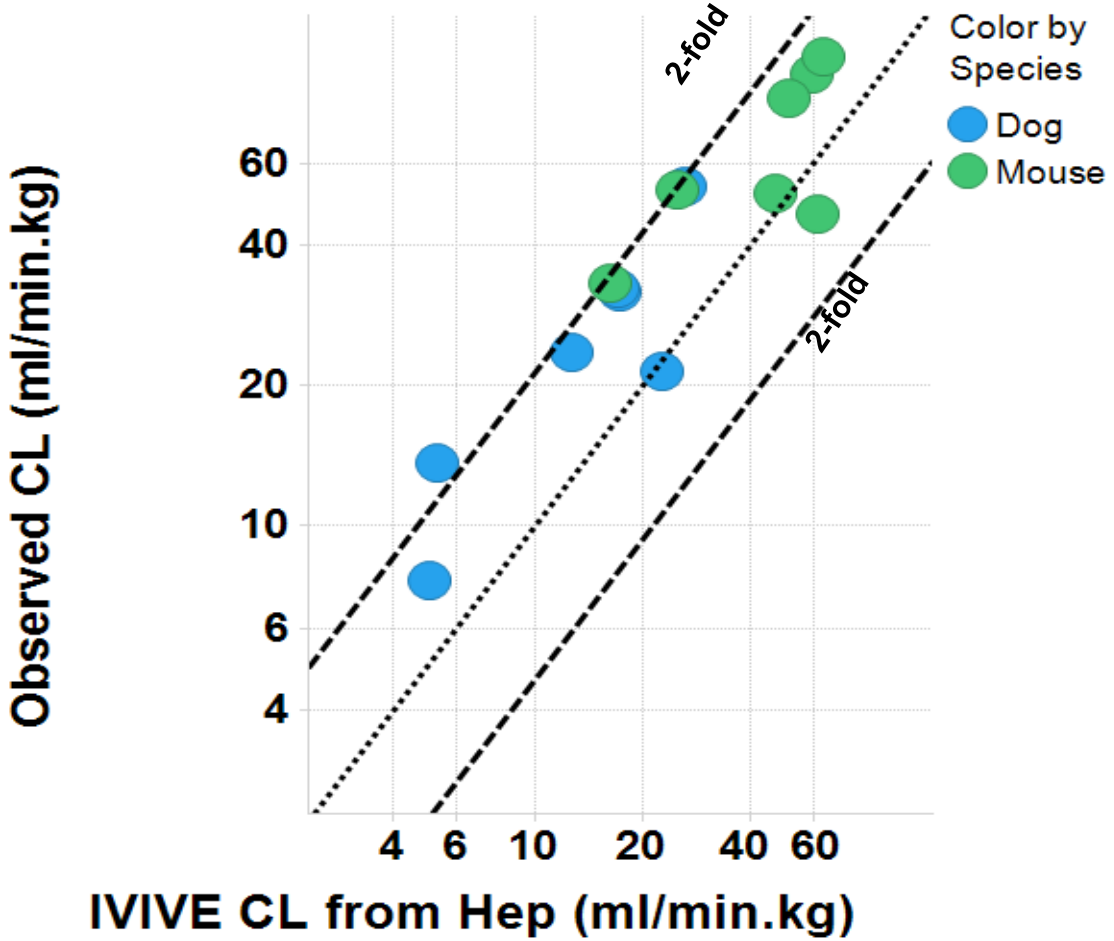


Compare the 'desired' human PK vs predicted

*Sensitivity analysis – Exhaustive search across multiple '**independent**' **human** properties; ^MPS – Multi-property based scoring function

IVIVE CL in Mouse and Dog Based on Microsomes and Hepatocytes

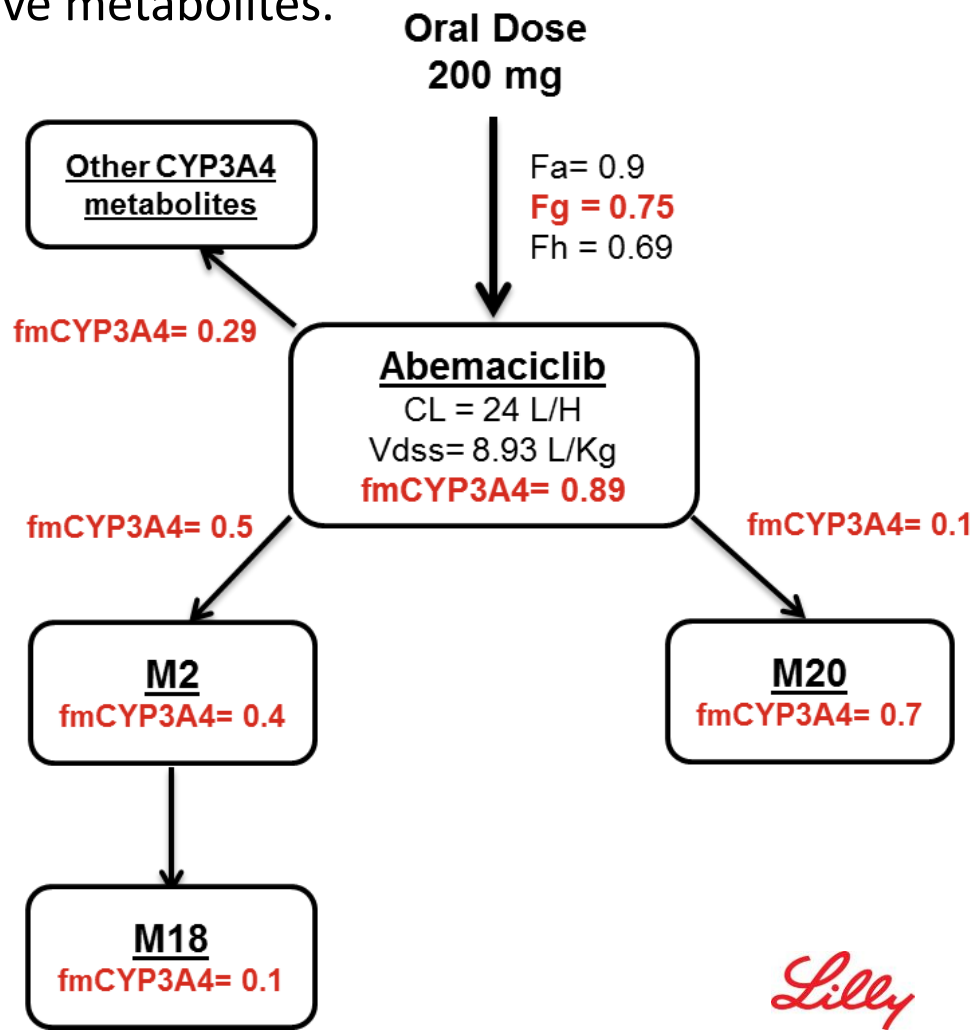




Strategy for estimating human CL – human Hep-IVIVE CL

Abemaciclib Case Study

- Abemaciclib is an oral CDK4 and 6 inhibitor approved for the treatment of hormone receptor (HR+) positive, human epidermal growth factor 2 (HER2)-negative advanced or metastatic breast cancer.
- Abemaciclib is extensively metabolized via CYP3A4 to multiple active metabolites.
- Active metabolites are present in significant concentrations and accounted for approximately 45% of total plasma radioactivity in the human mass balance study.
- Absolute bioavailability 0.45
  - Clearance = 24 L/h
  - Vdss = 8.93 L/kg
- CYP3A4 substrate (Clarithromycin and Rifampin Studies)
  - fmCYP3A4 = 0.89
  - Fg = 0.75



Posada et al., ASCPT 2019

Potency-corrected Unbound Active Species

$$AUC_{\ parent\ \ adjusted} = AUC_{parent} * fu_{parent}$$

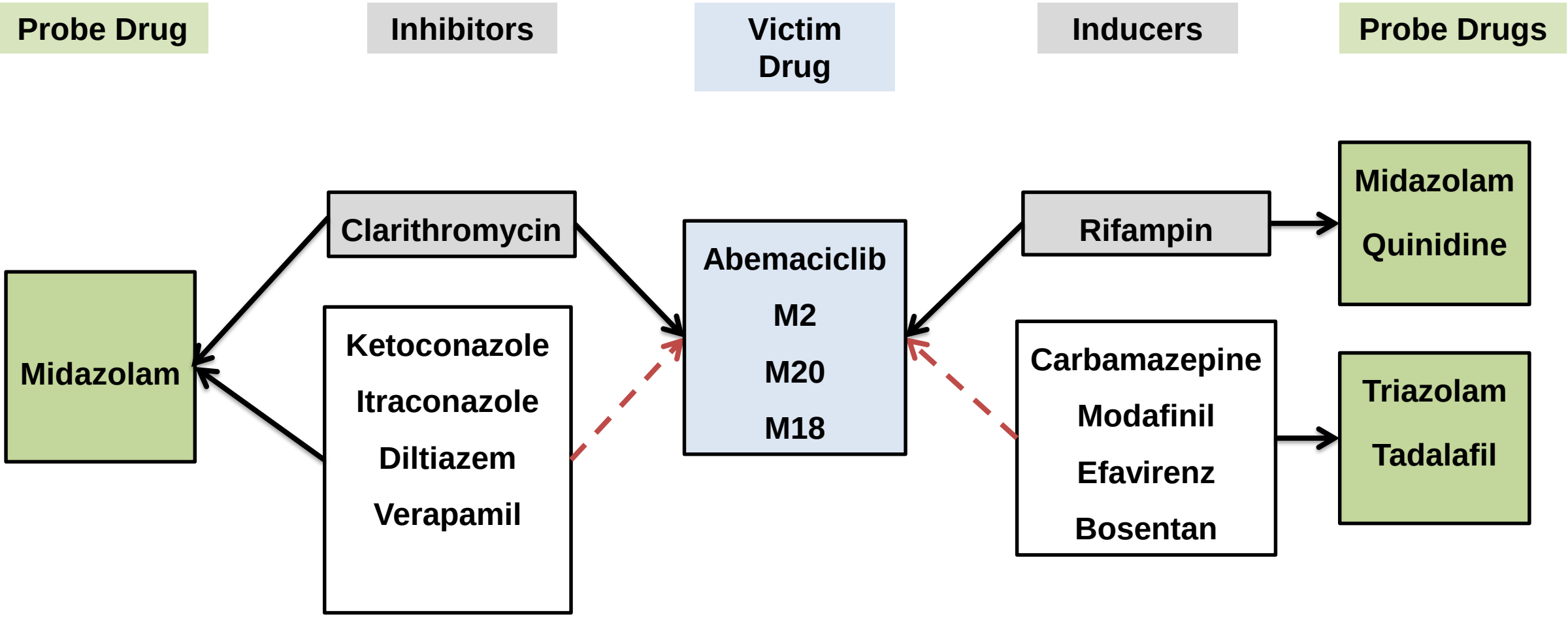
$$AUC_{\ metabolite\ adjusted} = AUC_{metabolite} * fu_{metabolite} * \frac{IC_{50}\ Parent}{IC_{50}\ Metabolite}$$

$$AUC\ ratio\ active\ species = \frac{AUC_{parent,i} + AUC_{M2,\mathrm{i}} + AUC_{M20,\mathrm{i}} + AUC_{M18,\mathrm{i}}}{AUC_{parent} + AUC_{M2} + AUC_{M20} + AUC_{M18}}$$

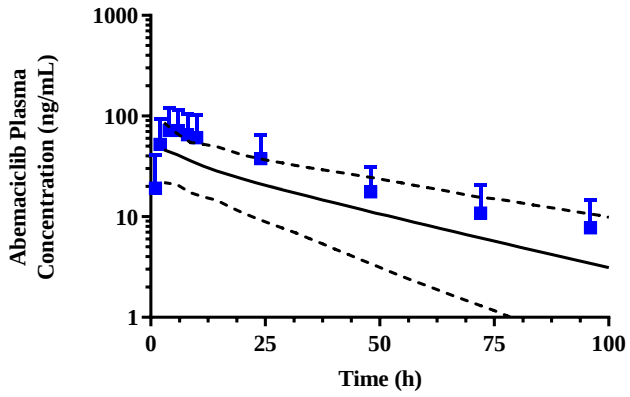
Compound	Potency CDK4/Cyclin D1		Fraction Unbound in Plasma (fu)	
	Abs IC_{50} (μM)	SD	Mean	SE
Abemaciclib	0.00157	0.0006	0.0557	0.0035
M2	0.00124	0.0004	0.0814	0.0045
M18	0.00146	0.0002	0.0340	0.0024
M20	0.00154	0.0002	0.0206	0.0029

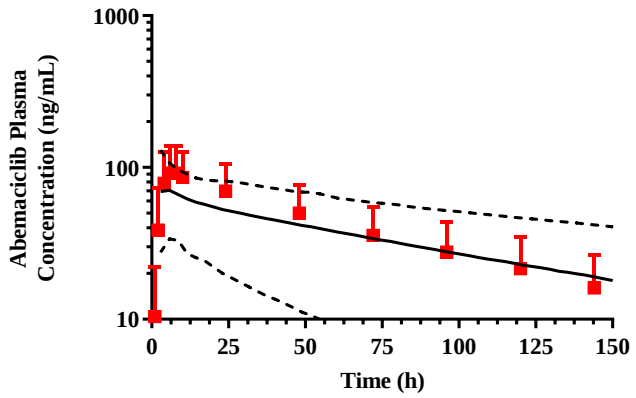
Posada et al., ASCPT 2019

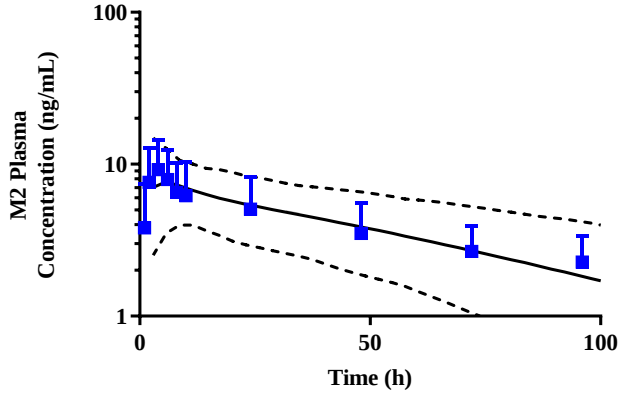
Model Qualification for DDI Prediction

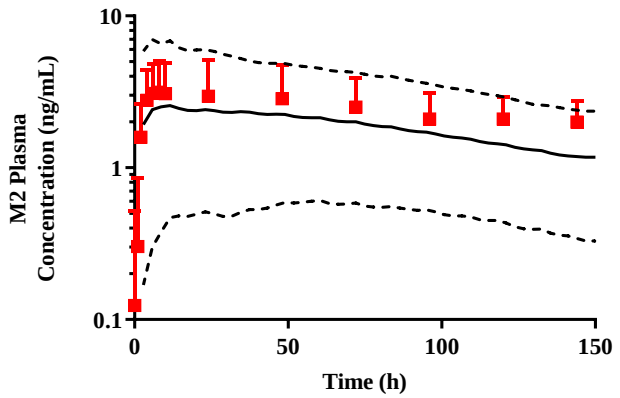


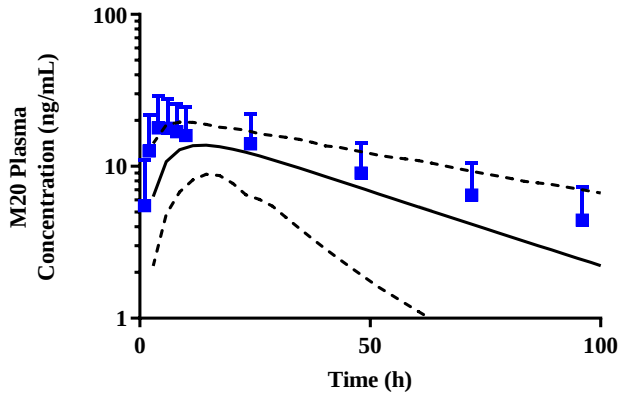
Posada et al., ASCPT 2019

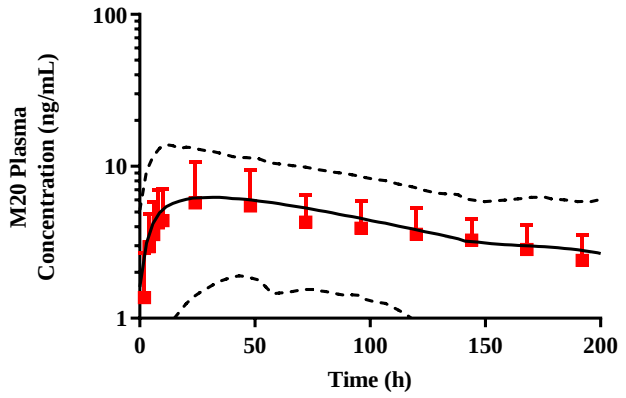










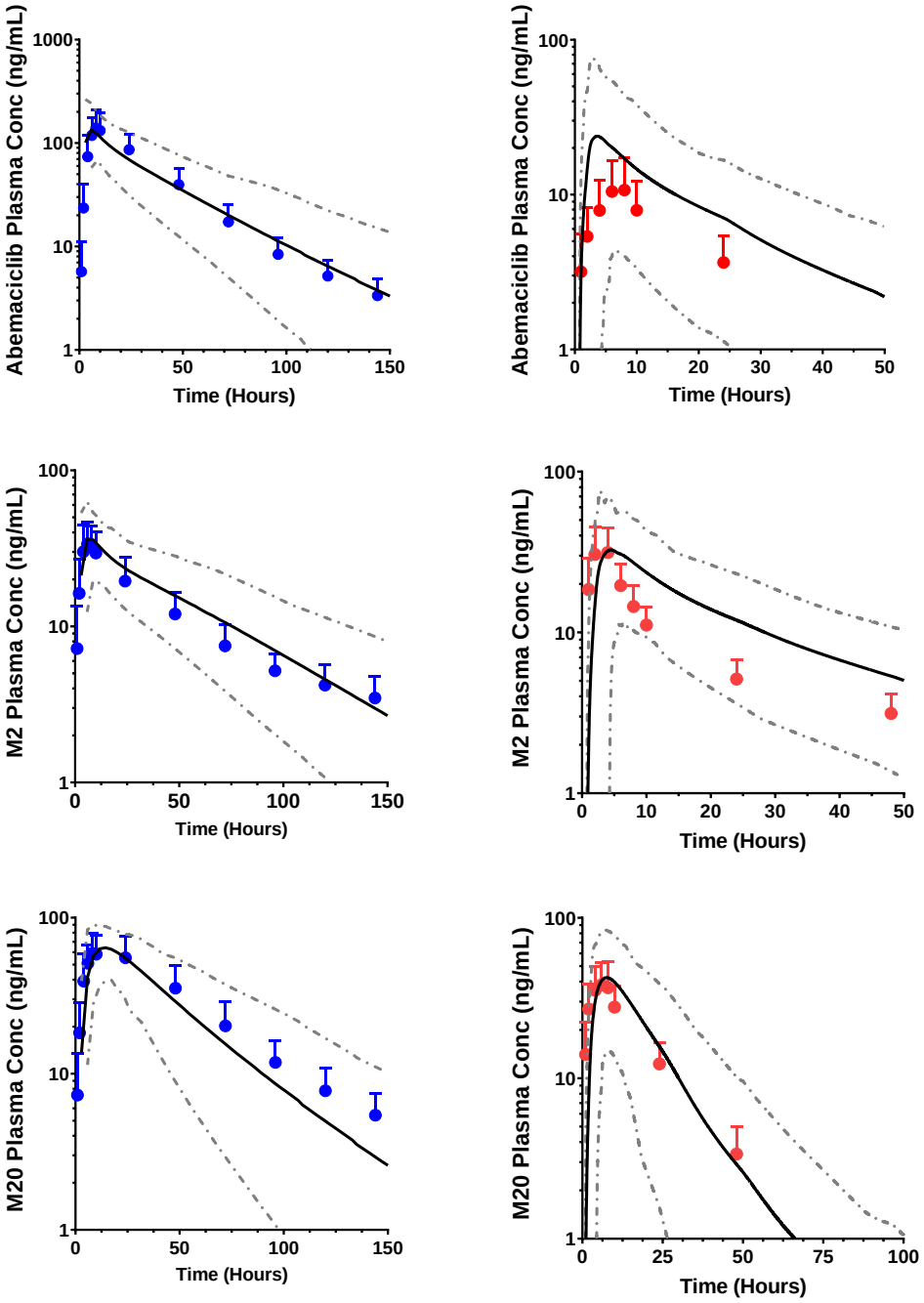


Observed and Predicted Plasma Concentrations for Abemaciclib and Active Metabolites after a 50-mg Dose of Abemaciclib Before (blue) and After (red) Treatment with Clarithromycin

Lines represent the predicted mean concentrations and the 5th and 95th percentiles. The solid squares represent the observed mean and standard deviation.

Posada et al., ASCPT 2019

Observed and Predicted Plasma Concentrations for Abemaciclib and Active Metabolites after a 200-mg Dose of Abemaciclib Before (blue) and After (red) Treatment with Rifampin



The lines represent the predicted mean concentrations and the 5th and 95th percentiles. The solid squares represent the observed mean concentrations and standard deviation.

Posada et al., ASCPT 2019

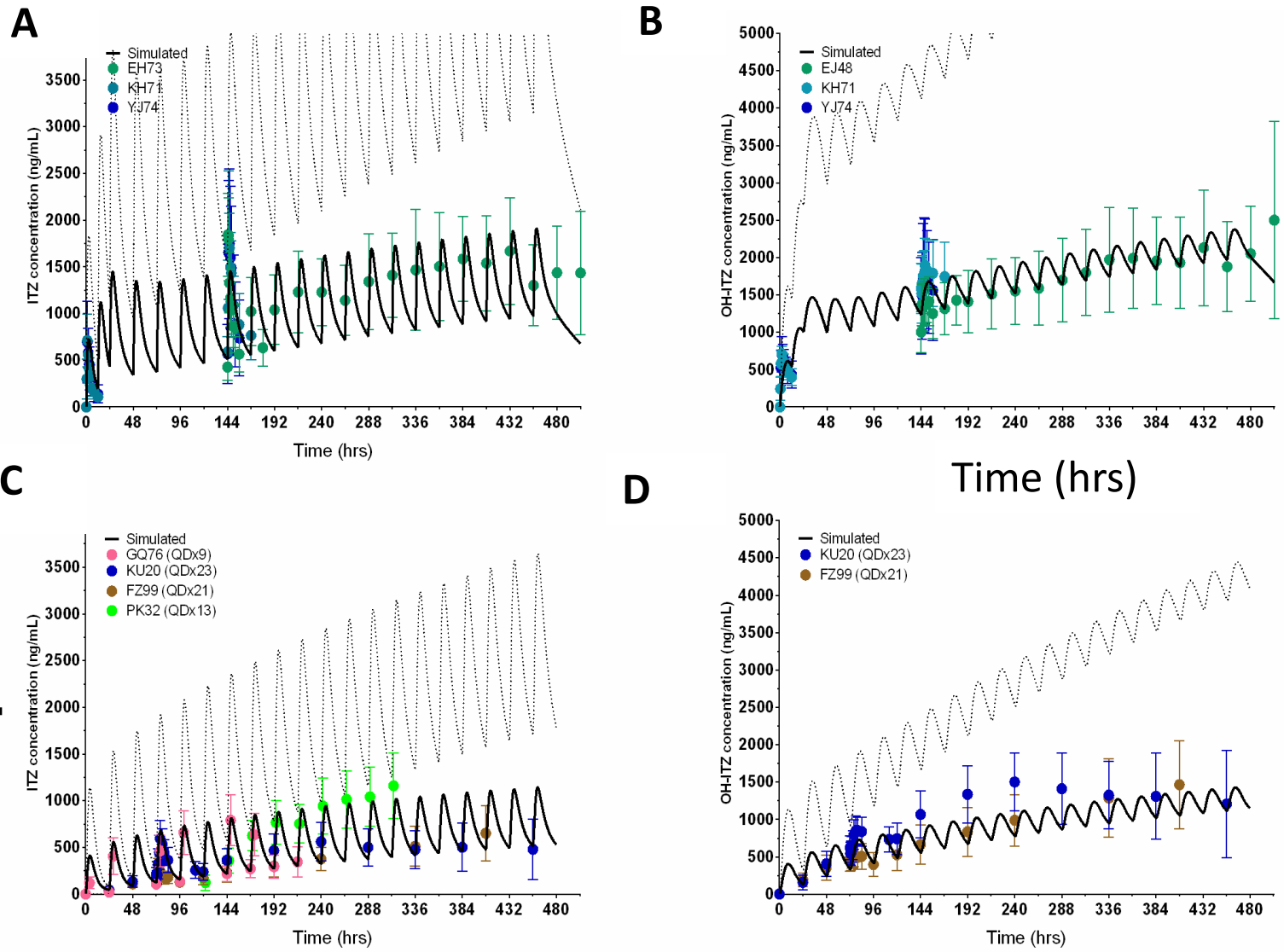
Simulated vs Observed Plasma Concentration–Time Profiles

Itraconazole (ng/ml)

Hydroxyitraconazole (ng/ml)

1st Order Solution

ADAM Capsule



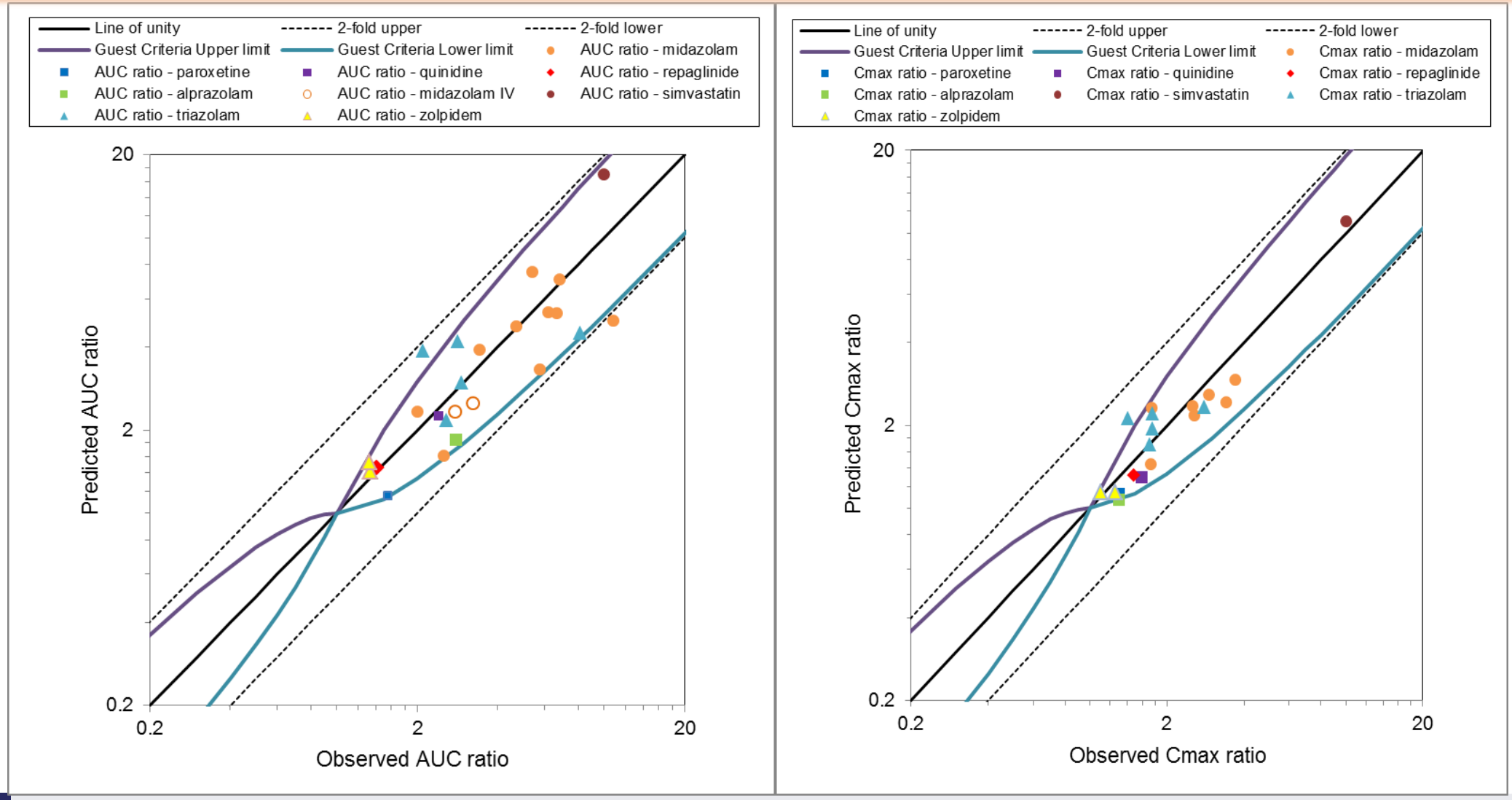
A & B: First order model after 200 mg BID on day 1 followed by 200 mg QD dosing of ITZ solution under fasted condition (3 studies).

C & D: ADAM model after 200 mg QD dosing of ITZ capsules under fed condition (4 studies, 2 with OH-ITZ).

Line represents mean ± SD of 100 individuals (10 trials of 10 subjects).

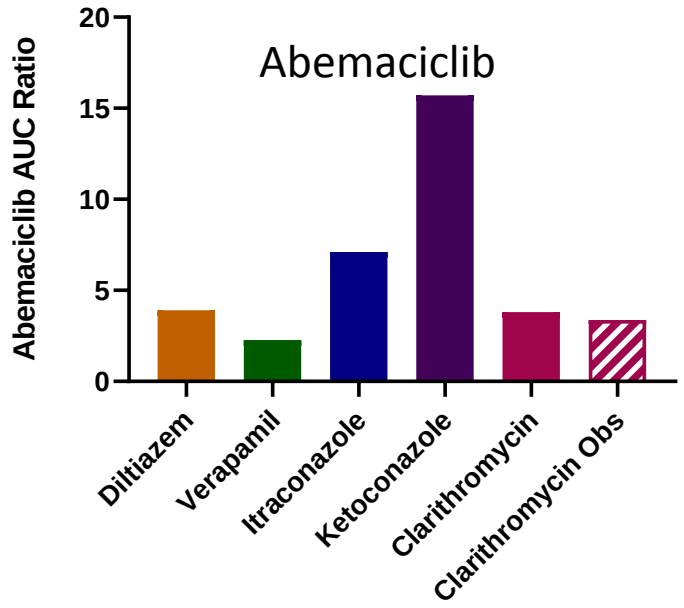
Chen et al., CPT Pharmacometrics Syst Pharmacol. 2019 Sep;8(9):685-695.

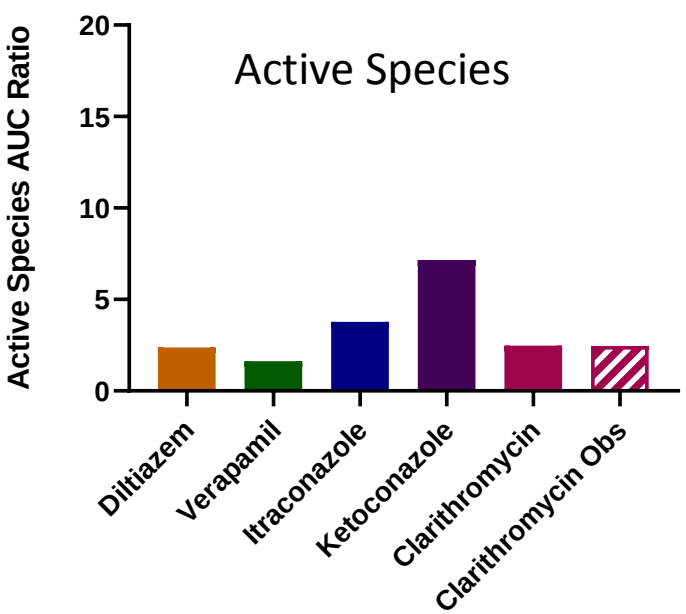
Observed versus Predicted AUC (a) and Cmax (b) Ratios of CYP3A4 Substrates in the Presence and Absence of Itraconazole



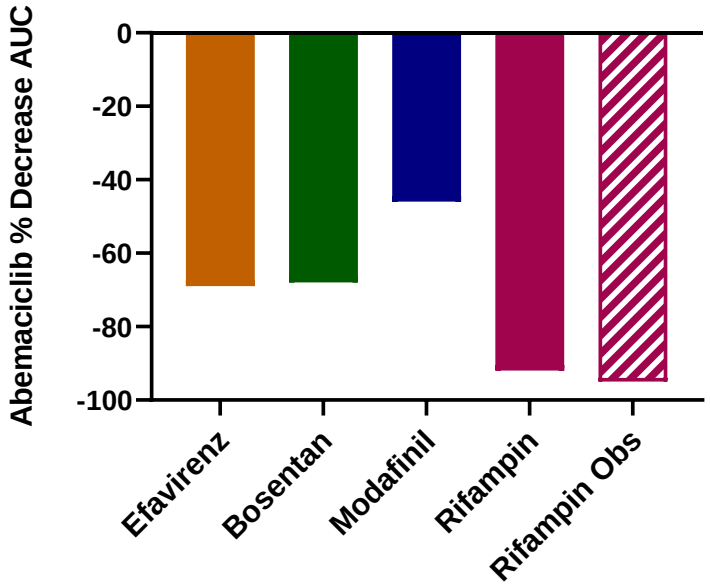
Chen et al., CPT Pharmacometrics Syst Pharmacol. 2019 Sep;8(9):685-695.

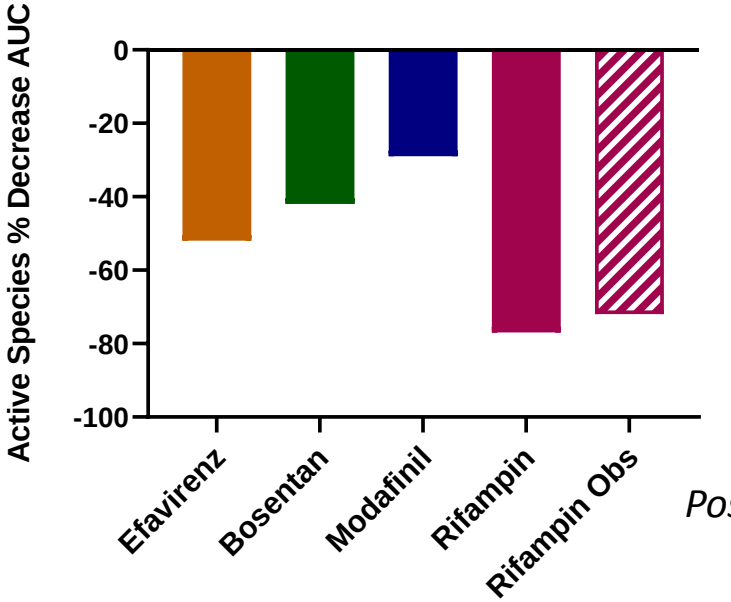
Predicted AUC Ratios for Abemaciclib and Active Species after Coadministration Moderate and Strong CYP3A4 Inhibitors and Inducers





Inhibitors





Inducers

Posada et al., ASCPT 2017 and 2019

Lilly

Effect of Hepatic Impairment: Can PBPK Models Reproduce Complex Disease Effects Pharmacokinetics?

- Functional liver mass reduced
- Enzymatic activity reduced
- Portal blood flow reduced

} Decrease systemic clearance

- Hepatic shunting

} Increase hepatic bioavailability

- Serum albumin reduced

} Increase fu plasma and total clearance

- Renal blood flow reduced

} Decrease renal clearance

- Inflammation

} Increase in serum AAG : Decrease in fraction unbound and total clearance

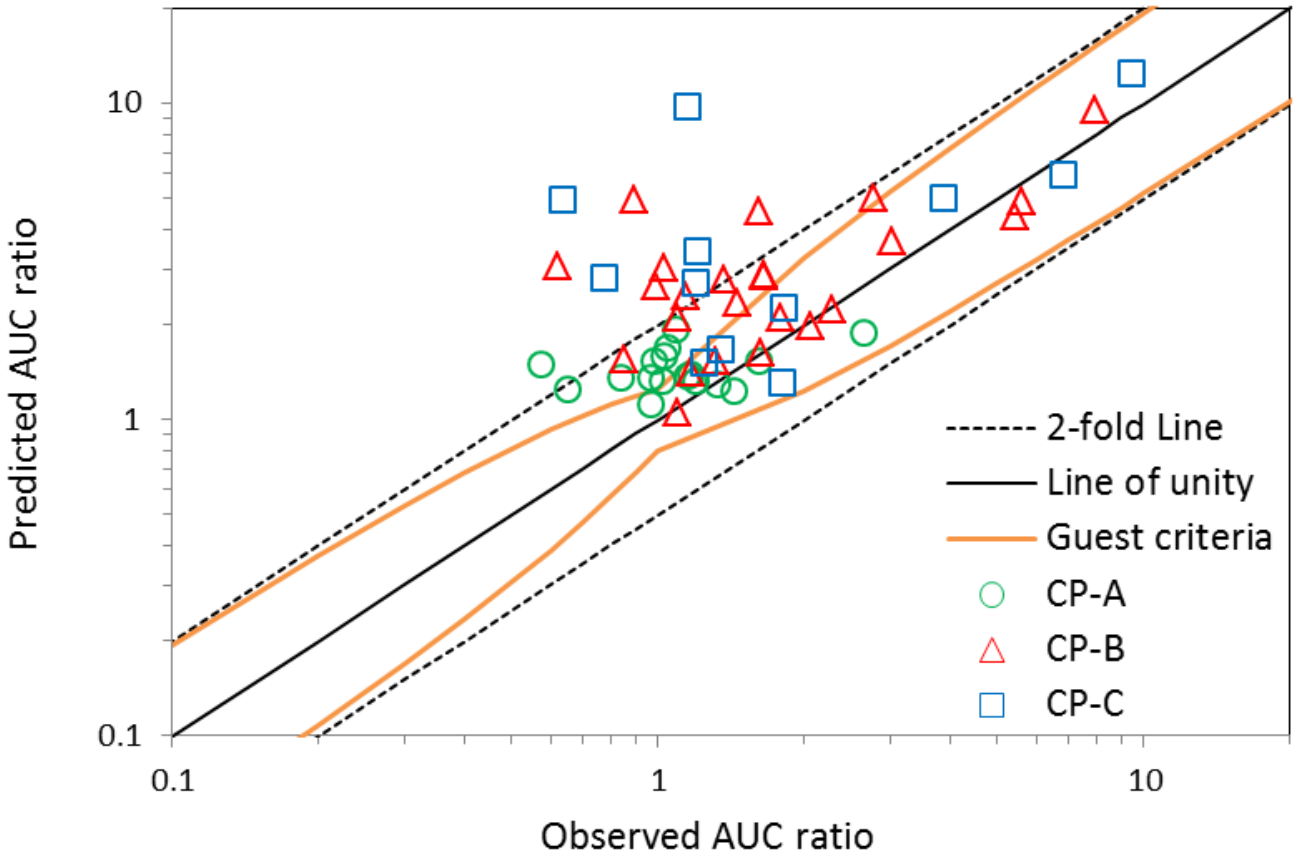
Changes in Potency-Adjusted Unbound Active Species for Abemaciclib in Hepatic Insufficiency Patients

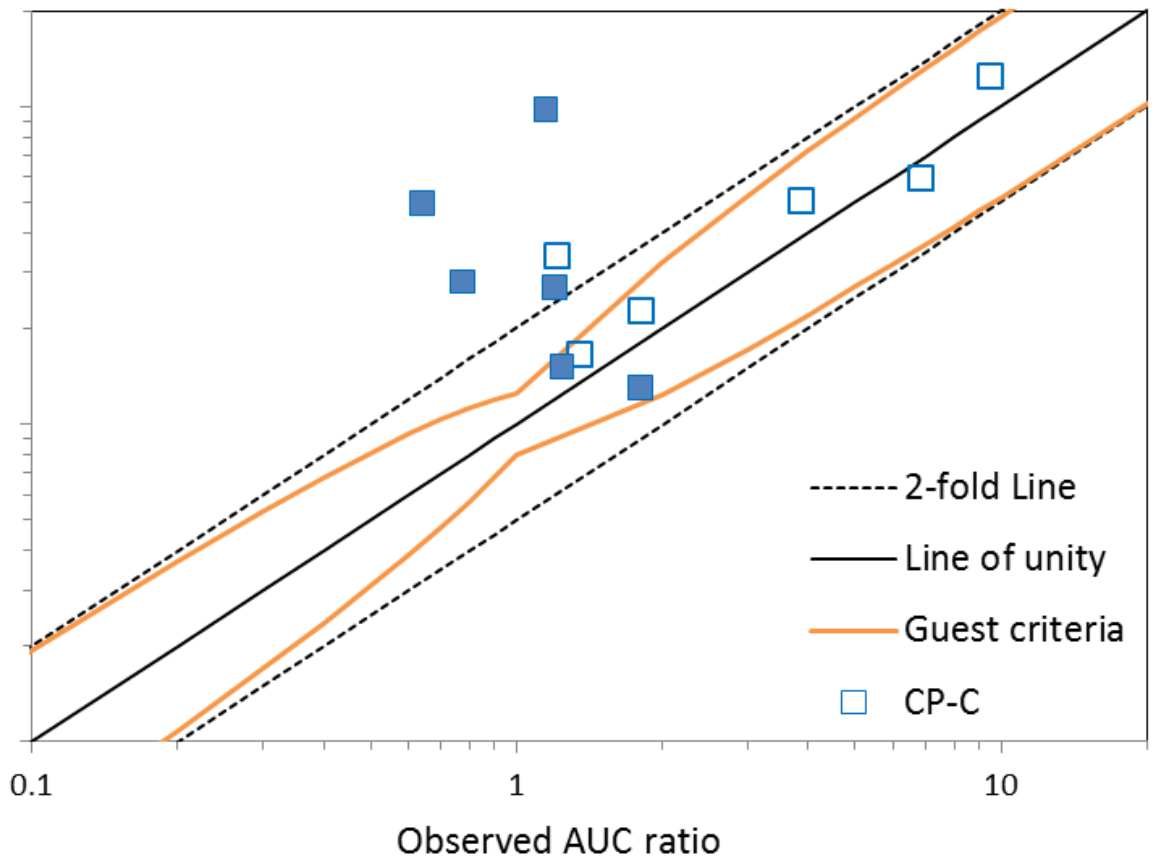
	Predicted $AUC_{0\text{-}inf}$ Ratio Potency-Adjusted Unbound Active Species	Observed $AUC_{0\text{-}}$ Ratio Potency-Adjusted Unbound Active Species	Predicted/ Observed
Child-Pugh A (Mild) /Healthy Volunteers	1.2	1.2	1
Child-Pugh B (Moderate) /Healthy Volunteers	2.5	1.1	2.3
Child-Pugh C (Severe) /Healthy Volunteers	4.0	2.4	1.7

Verzenio Product Monograph Canada 2019

Lilly

Effect of Hepatic Insufficiency (Child-Pugh Classification A, B and C) on the AUC of 35 Compounds Collected by the IQ Working Group





Unpublished Data: IQ Organ Impairment Working Group

Does Food Impact Abemaciclib PK?

Abemaciclib exhibits reasonable solubility and permeability. These properties suggest that a clinically meaningful food effect is not possible. A high confidence prediction with extensive verification.

"A high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) administered to healthy subjects increased the AUC of abemaciclib plus its active metabolites by 9% and increased Cmax by 26%." (*Verzenio FDA Label*)

- **Higher confidence for FE predictions via PBPK modeling for food effect related to GI Lumen Physiology Changes**
  - *in vitro* assays readily available and generally standardized
  - Model verification against clinical data may be required to confirm confidence in some cases

- **Lower confidence for FE predictions via PBPK modeling for food effect related to Intestinal Transport and Metabolism Mechanisms**
  - Low confidence for FE predictions via PBPK modeling especially for transporter interactions
  - Fully accounting for metabolism non-linearity may be challenging (but possible with sufficient data)

- Insufficient examples or straightforward translation to a PBPK model for **food effect related to distribution mechanisms** (e.g. lipoprotein binding, lymphatic transport) - not frequently encountered

DDI Prediction

Application	Confidence	Comments
Reversible CYP inhibition or induction alone	High - Moderate	Accurate fm when non-P450 involved challenging. IV CL and mass balance not available at early stages. Must account for experimental variability in Ki.
Time dependent CYP inhibition	Moderate - Low	Trend to over-prediction from in vitro data
Combined reversible, TDI & induction	Low	Difficult to evaluate mechanisms
Involving active transport	Low to Moderate	Predicting transport inhibition possible but intracellular concentrations challenging

Special Population PK Prediction

Application	Confidence	Comments
Pediatrics, ethnic variations, smokers, pregnancy, obese, elderly	Moderate - Low	Abundance of enzymes and transporters limited or lacking. Changes in gut physiology limited.
Organ impairment (renal and hepatic)	Low	Limited verification vs clinical data. Impact of renal/hepatic impairment on CYP expression and transporter activities not fully clear.

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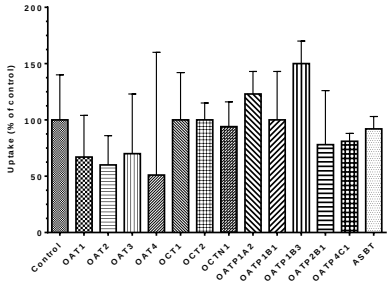
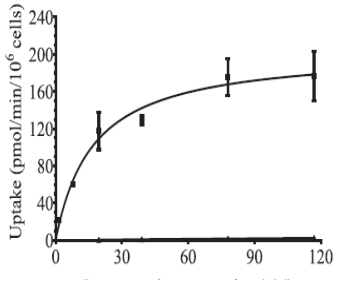
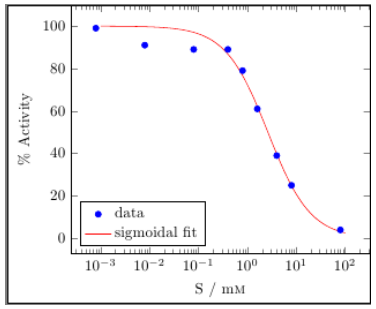
Jones et al., Clin Pharmacol Ther 2015 Mar;97(3):247-62.

Can we predict OAT-mediated DDI's using in vitro data?

IVIVE Strategy







Inhibitor	Iu/IC_{50}
Probenecid	8.5
Ibuprofen	0.38
Diclofenac	0.03
Naproxen	0.01
Celecoxib	0.004

Iu = C_{max} unbound for Inhibitor

Transporter Screen → Uptake Kinetics → Inhibition → Risk Assessment DDI Index = I_u/IC_{50} → **DDI Predictions**

Substrates
Transporter Identification
HEK PEAK cells

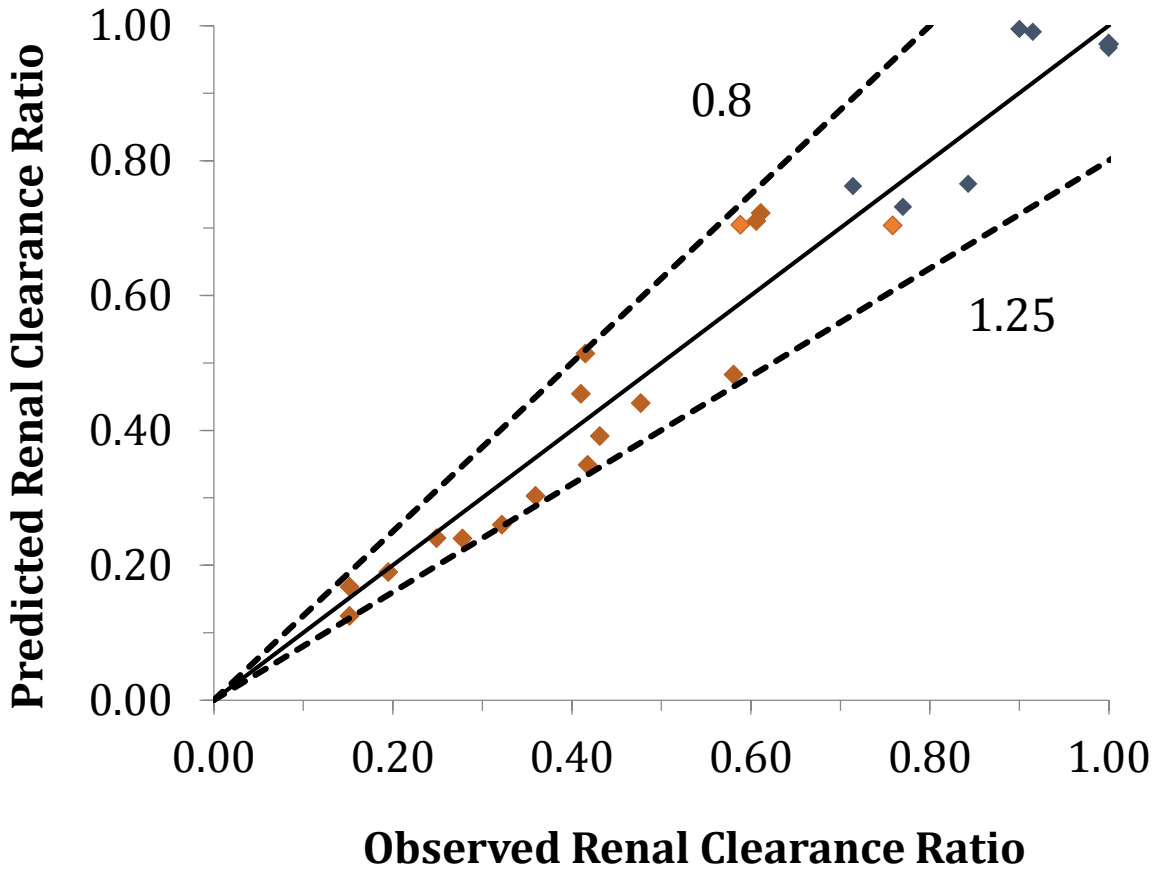
Substrates
- K_m
- V_{max}
- CL_{int}

Inhibitors: (IC_{50})
- Probenecid
- Co-medications
- NSAIDS

Posada et al., ASCPT 2017

Prediction of Renal Clearance Ratio for OAT Substrates

$$CL_{renal}\ Ratio = \frac{Renal\ Clearance\ Inhibited}{Renal\ Clearance}$$



Inhibitors

Probenecid

Ibuprofen

Diclofenac

Naproxen

Aspirin

Substrates

Acyclovir
Adefovir
Baricitinib
Cephradine
Cidofovir
Benzylpenicillin
Bumetanide
Cefamandole
Cefmenoximine
Cinoxacin
Ciprofloxacin
Enalaprilat
Fexofenadine
Furosemide
LY1
Moxalactam
Methotrexate
Nafcilin
Pemetrexed
Oseltamavir
Zalcitabine

Posada et al., ASCPT 2017

The Key is Verification

To enable the development of PBPK modeling in our regulated environment we aspire to move away from stationary opinions about the scope of acceptable PBPK modeling

We need to replace the status quo with verification based limits

Define adequate verification and the user community will be able to define appropriate applications

Verification will be challenging in many evolving applications

Pan industry approaches, such as those undertaken by IQ, may be the only way to collect sufficient verification data for some applications

Conclusions

A mechanistic modelling framework is essential for extrapolation of prior knowledge to new molecules

PBPK modeling has had a major impact in discovery

Increased decision quality has lead to better drugs and resource saving

Acceleration of development has occurred as uncertainty has been reduced by the models

Labelling impact is clear and this is based on highly verified approaches. Recently reviewed by FDA (*J Pharm Sci 108: 21-25, 2019*)

Acknowledgements

Abemaciclib Development Team and PBPK Group at Lilly

IQ Working Groups:

- White Paper
- Organ Impairment
- Itraconazole Model
- Food Effect