Building Encorafenib Physiologically Based Pharmacokinetic Model and its Qualification to Predict Drug-Drug Interaction with Posaconazole

February 16th, 2023

MIDD+

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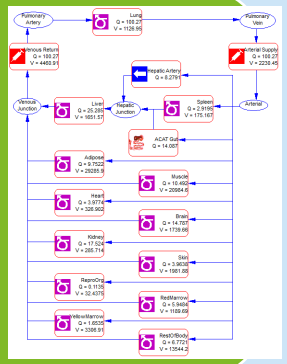
Encorafenib

Building a PBPK model to predict interaction with posaconazole

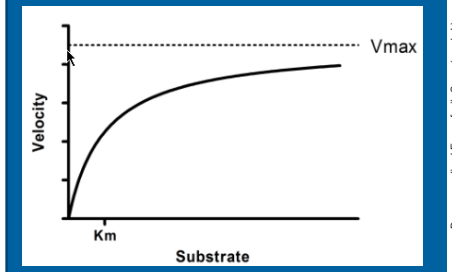


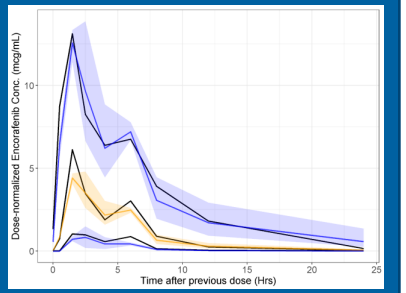
Prediction to support recommendations in labels

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on encorafenib

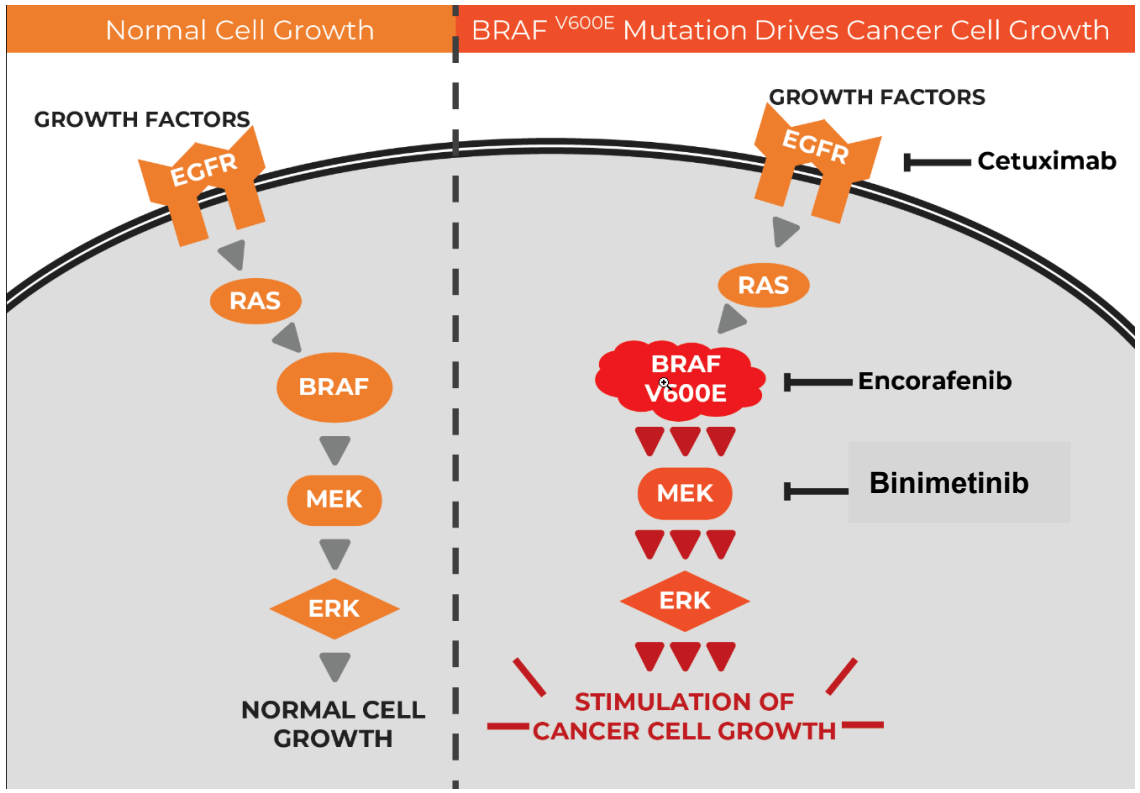
In vitro and *in vivo* data





Specific Challenge: Time-dependent PK and prediction of interaction after multiple doses

Background



https://learn.colontown.org/

Encorafenib

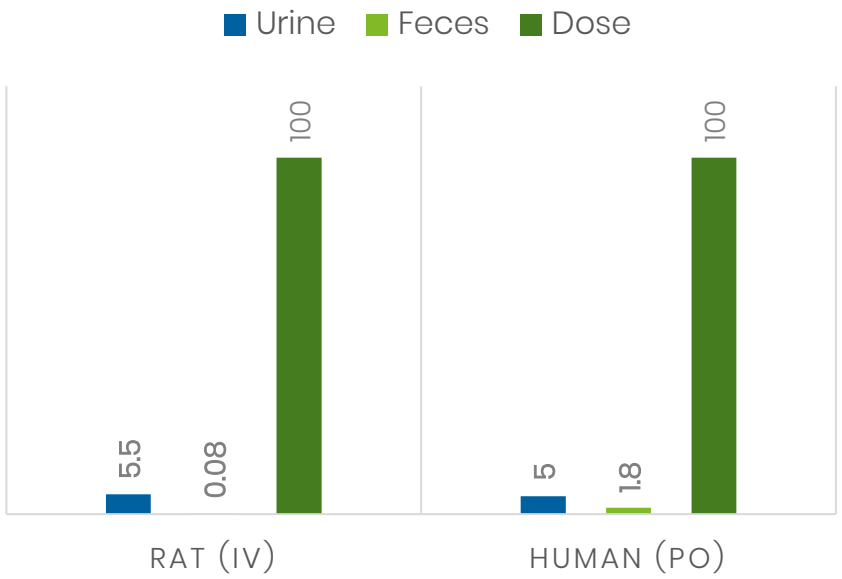
- Potent and highly selective ATP-competitive small molecule RAF kinase inhibitor
- Suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K)
- Indicated in:
  - combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation (2018)
  - combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation (2020)
- Co-developed and Co-marketed, Partnership with Pfizer

Pfizer

Pierre Fabre

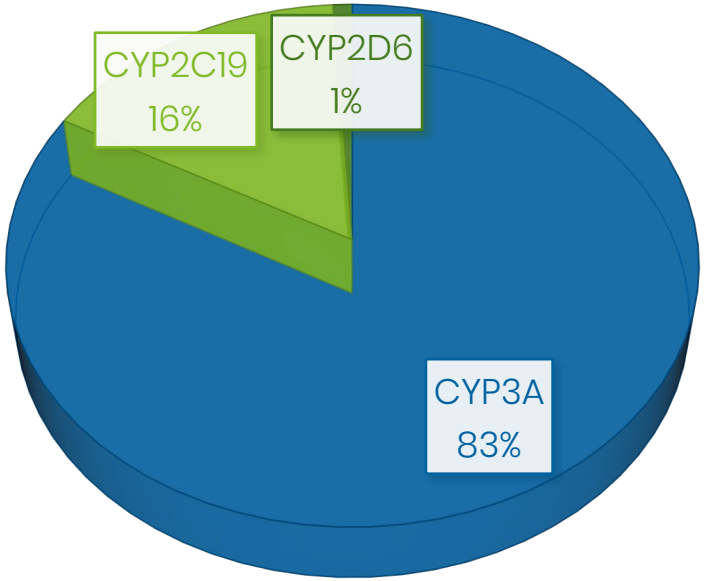
Encorafenib Elimination and *in vitro* Drug Drug Interaction

UNCHANGED ENCORAFENIB (%)



Mass balance studies

METABOLISM PATHWAYS



In vitro Studies

IN VITRO DRUG DRUG INTERACTION

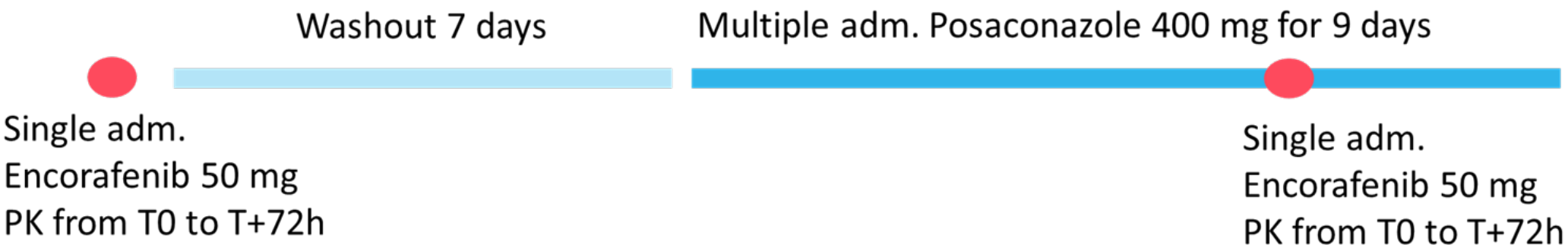
- Reversible and weak time-dependent CYP3A4 inhibitor
- CYP3A4 inducer

Source: FDA Drug Approval Package Multidiscipline Review, European Public Assessment Report

Drug Drug Interaction Clinical Study
encorafenib + posaconazole (strong CYP3A inhibitor)

Design

- Healthy Subjects:
  - Acceptable safety profile
  - Single dose
  - Sub-therapeutic dose (50 mg rather than 450 mg) anticipating a drug interaction with posaconazole
- Posaconazole: well characterized strong CYP3A inhibitor



Drug Drug Interaction Clinical Study encorafenib + posaconazole : Results

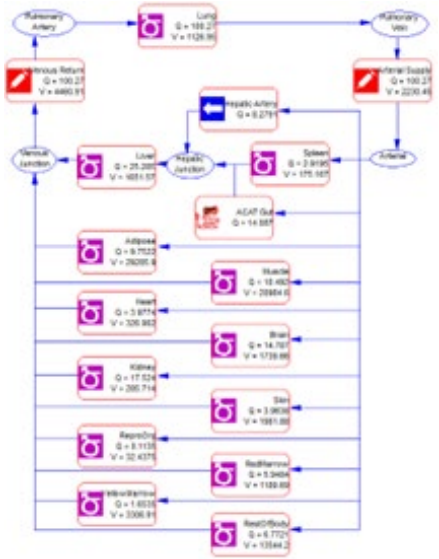
	Geometric Mean (%CV)		
Exposure parameter	**Encorafenib alone (50 mg)**	**Encorafenib (50 mg) with posaconazole (400 mg BID for 7 days)**	**Geometric Mean Ratio* (90% CI)**
$AUC_{0\text{-}72h}$ (ng·hr/mL)	2035 (40%) n=16	5785 (38%) n=16	2.84 (2.55, 3.17)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	2051 (40%) n=16	5812 (38%) n=16	2.83 (2.54, 3.16)
C_{max} (ng/mL)	553.5 (33%) n=16	932.1 (31%) n=16	1.68 (1.54, 1.85)

* Posaconazole 400 mg BID for 7 days and a single encorafenib 50 mg dose vs. a single encorafenib 50 mg dose alone.

Source: FDA Drug Approval Package Multidiscipline Review, European Public Assessment Report

PBPK Modeling: Strategy

- Performed using GastroPlus version 9.0



In vitro data

Phase I studies

Encorafenib PBPK model

Model Qualification

Prediction of posaconazole DDI

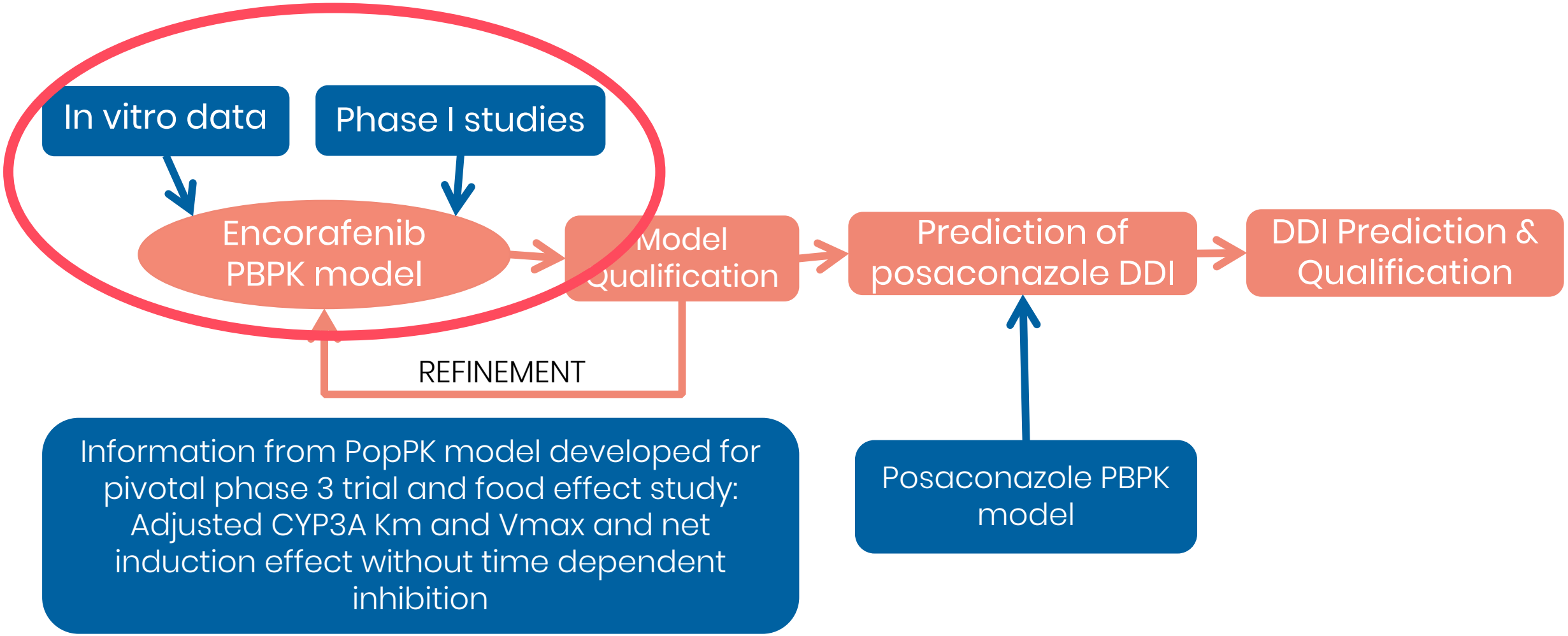
DDI Prediction & Qualification

REFINEMENT

Information from PopPK model developed for pivotal phase 3 trial and food effect study: Adjusted CYP3A Km and Vmax and net induction effect without time dependent inhibition

Posaconazole PBPK model

Step 1 : Initial model development using *in vitro* and Phase I data



Initial Model Development using *in vitro* and Phase I data

1. Use of *in vitro* data
   - ➢ rCYP data (CYP3A, 2C19), CYP2D6 ignored
   - ➢ In vitro quantification of CYP3A4 induction and inhibition
2. Use of Phase I data

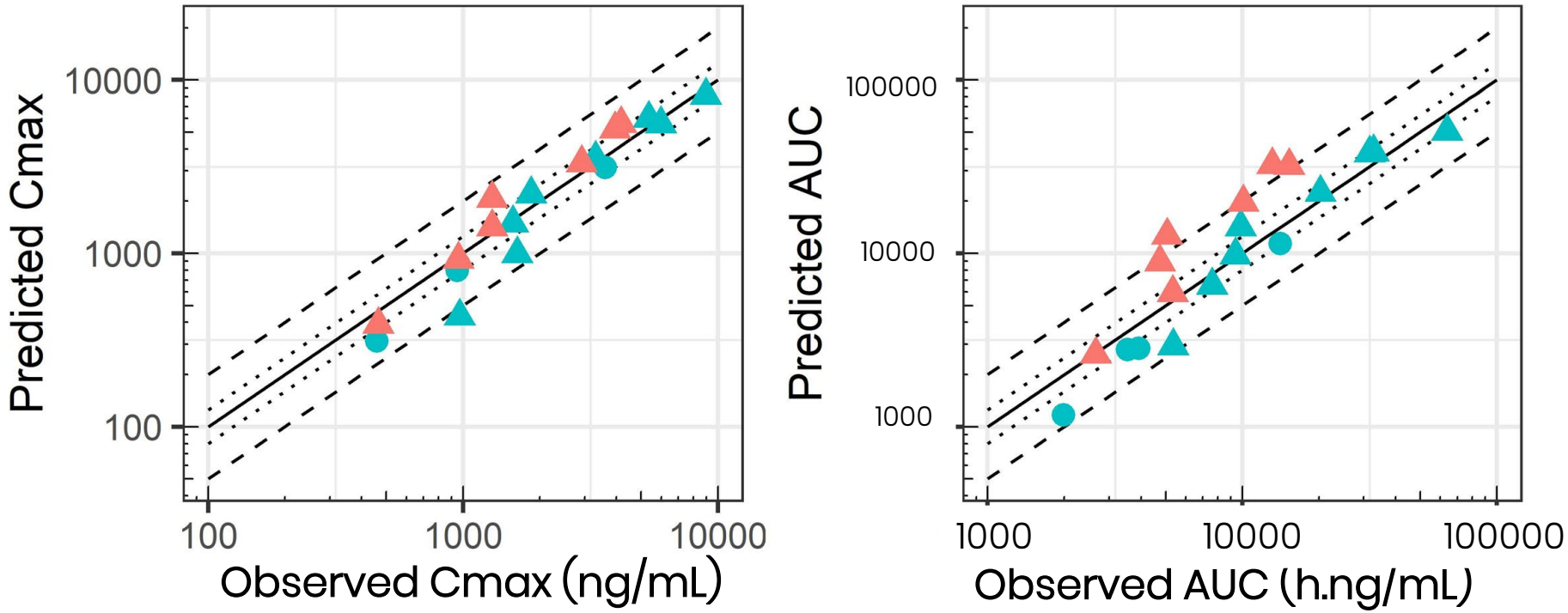
Accumulation ratio ~ 0.5

1. Metabolism-mediated elimination
2. Estimation of absorption

Rich profiles at 2 doses

Study	Encorafenib Dose	Regimen	N/ Study Population
Dose-escalation	50 to 700 mg	Once daily	54 patients
Mass Balance	100 mg	Single dose	4 healthy subjects
DDI with PPI	100, 300 mg	Single dose	15 healthy subjects

Initial Model Qualification



The solid line represents the identity line and the dashed lines show margins for 0.8-1.25 limits and 2-fold errors. AUC corresponds to AUCinf for single dose data and AUCtau for multiple dose data.

Most of the errors expressed as ratio predicted /observed are in 2-fold range ➔ Can be considered qualified/validated

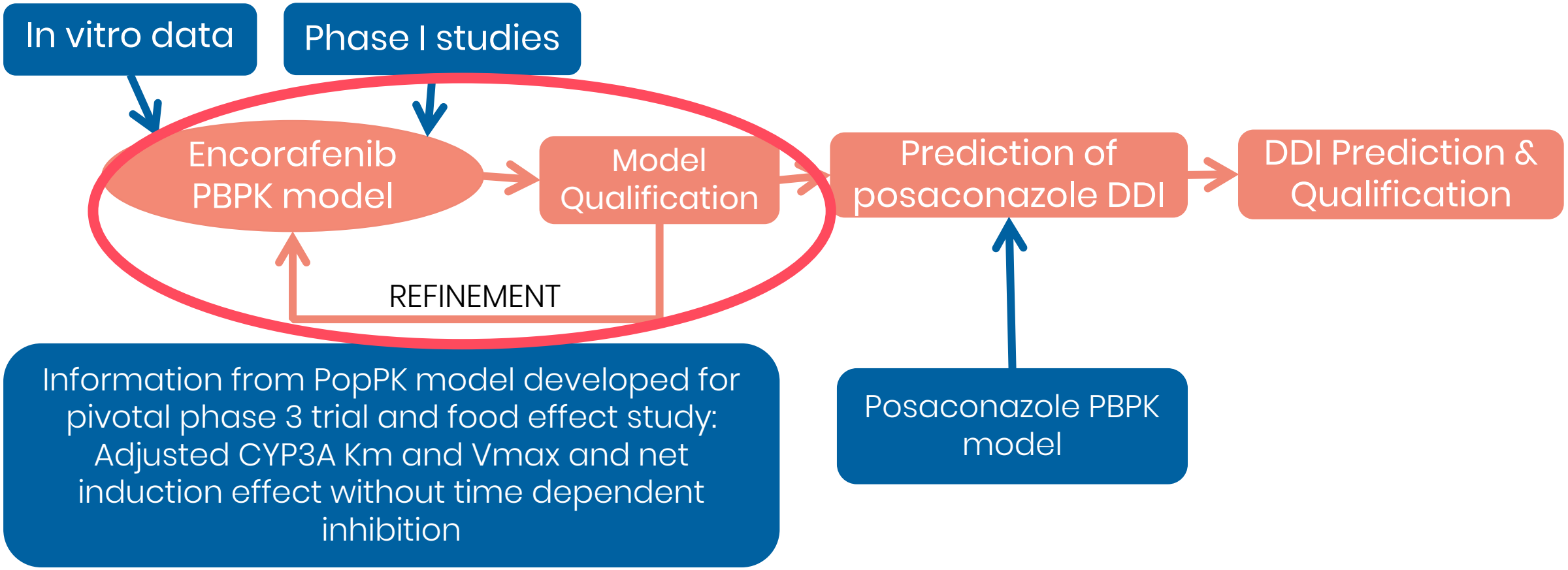
But…

- Auto-induction is predicted but can be improved: under-estimation of auto-induction
- Over-estimation of food effect
  - Predicted: Significant decrease in AUC fasted vs fed
  - Observed: no effect with high fat meal ~ 3-4 % decrease in AUC

  ▶ Not explained by the absorption model (good prediction of the absorbed fraction in fasted and fed conditions)

  ▶ But parameters regarding CYP3A4 in the gut should be improved

Step 2: Model Refinement



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Information :
- PopPK model developed and validated on Phases I, II and III data
- Clinical food effect study

ADME	Adjustments
Time-dependent inhibition	Removed. Net induction = auto-inhibition + auto-induction
Auto-induction	No or negligible dose effect
CYP3A4 Metabolism	Lower saturation of CL -> Km increased (estimated) Aligned with dose escalation study
Volume of distribution	Adjust Kp with LogP
CL in healthy subjects	CYP3A4 et CYP2C19 Vmax adjusted (estimated)

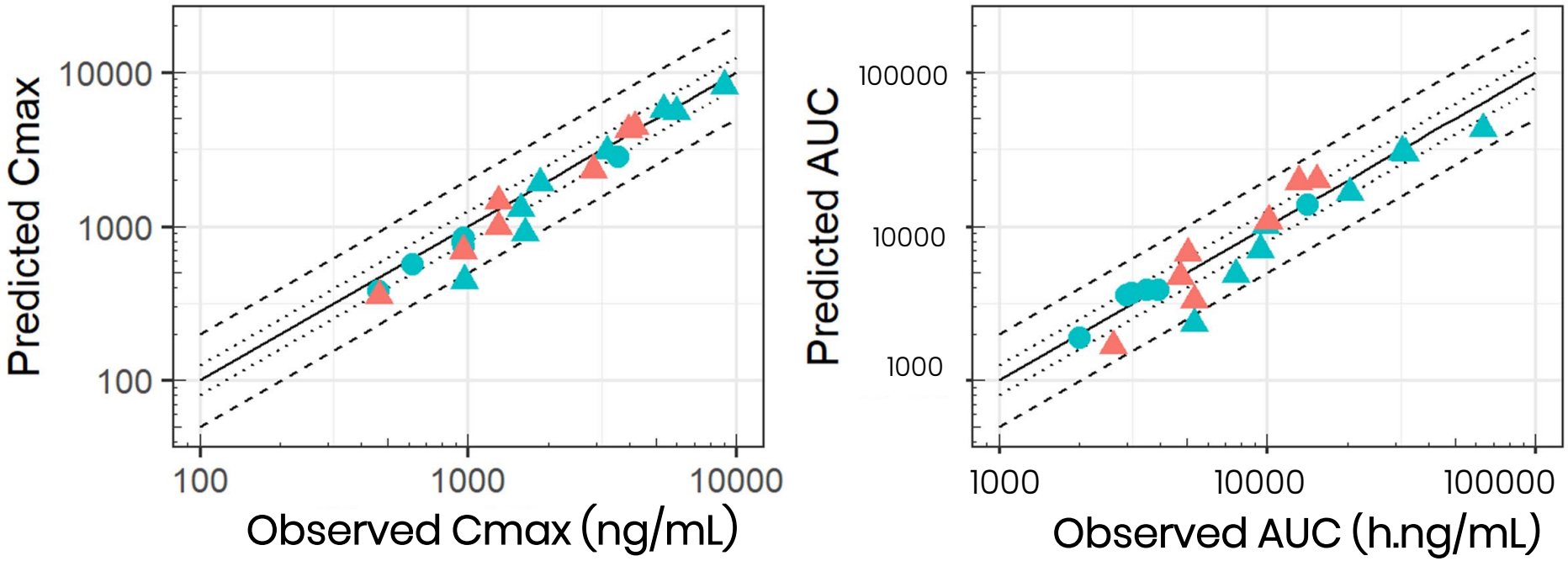
Model Refinement using *in vivo* Information

Food effect Check

Study	Encorafenib Dose	Regimen	N/ Study Population
Food effect	100 mg	Single dose	31 healthy subjects
Pop PK model Pivotal Phase 3	300, 450 mg	Once daily	383 patients and 15 healthy subjects

Clearance adjustment regarding net auto-induction and Vmax

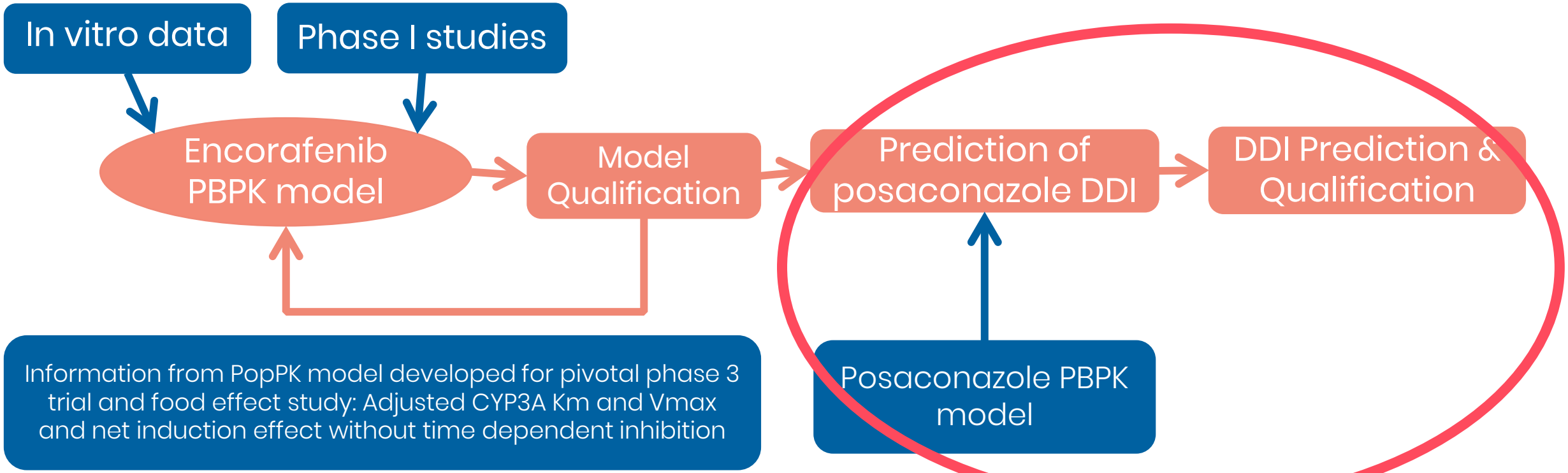
Final Model Qualification



Prediction errors expressed as ratio predicted/observed were improved

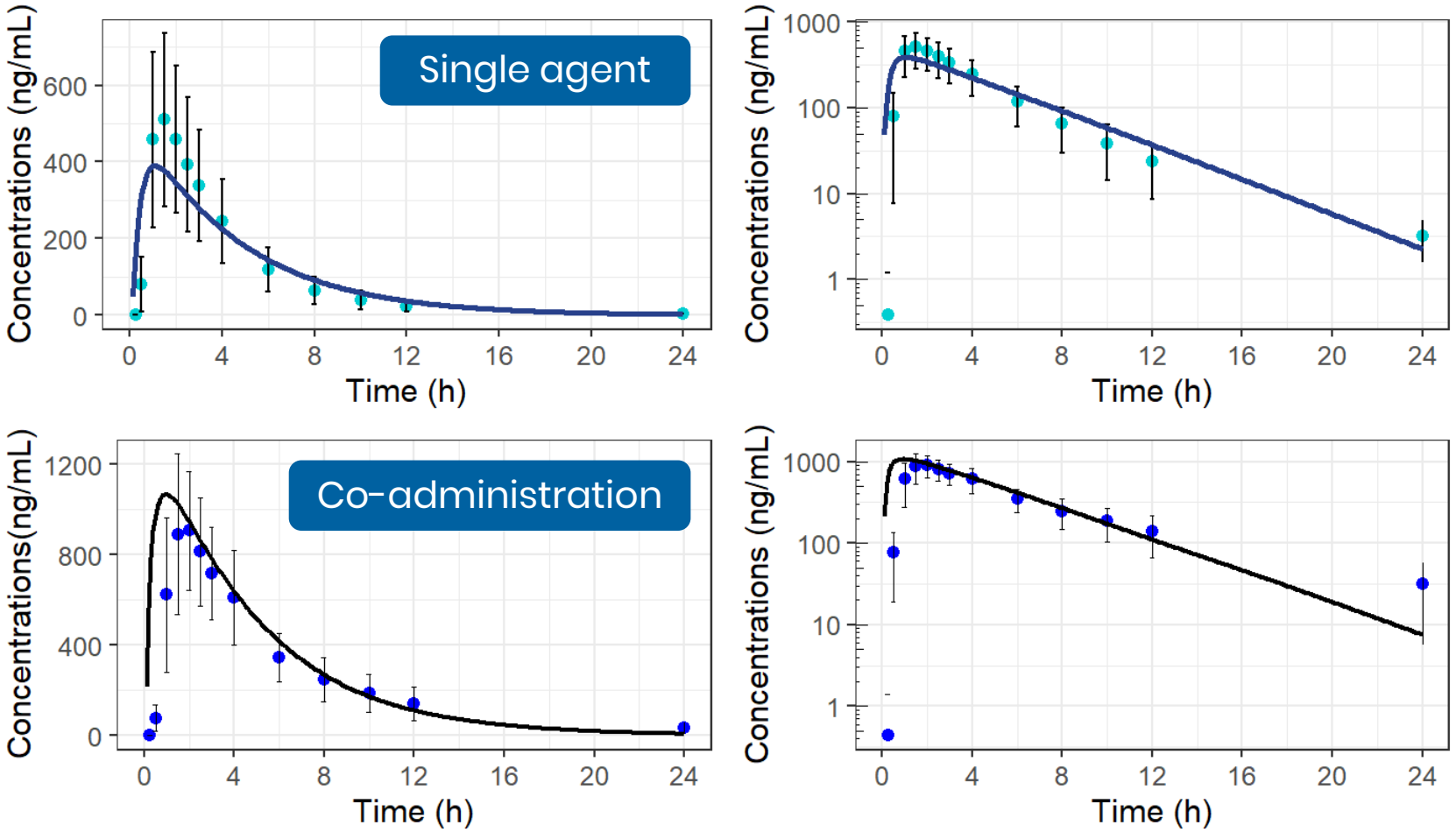
➔ **The model can be used for DDI prediction**

Step 3: Drug Drug Interaction Prediction



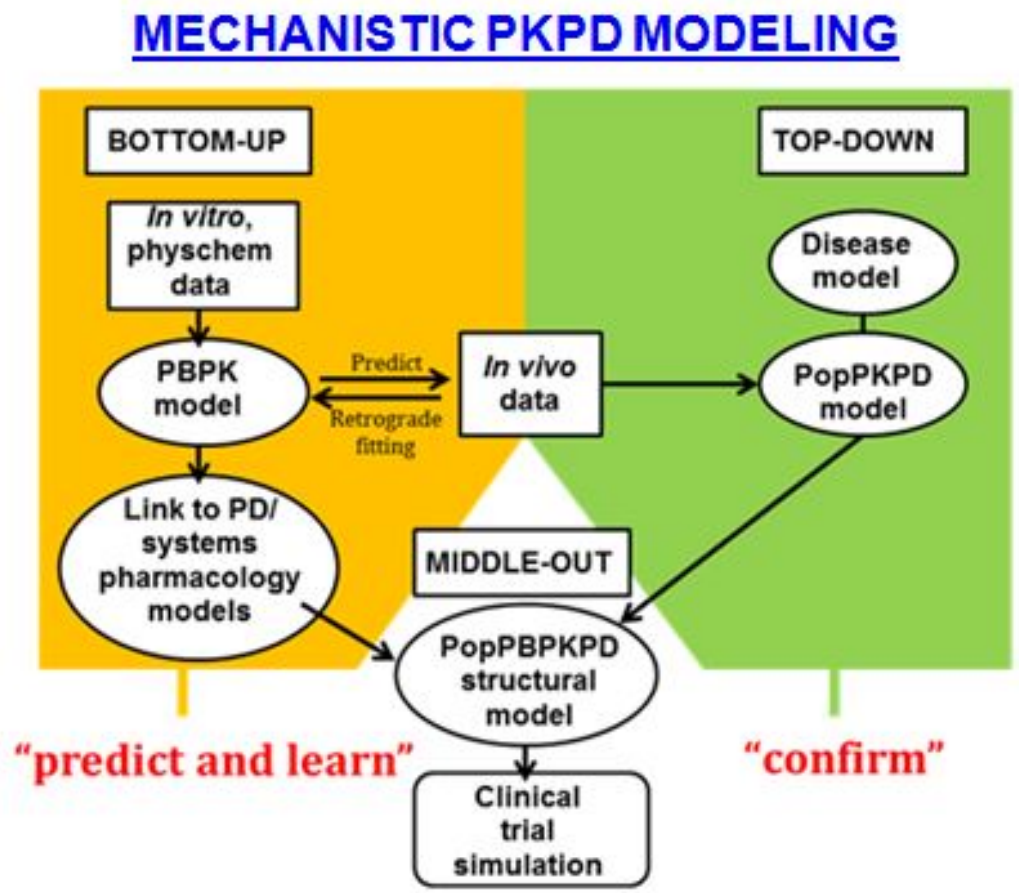
Posaconazole model: The model was validated by comparing simulated and observed oral PK data for posaconazole dose levels ranging from 50 to 1200 mg (5 studies in healthy subjects). The posaconazole PBPK-DDI model successfully predicted the increase in midazolam exposures.

Prediction of Drug Drug Interaction with Posaconazole



Ratio, co-administered single agent	Observed Cmax	Observed AUC	Simulated Cmax	Simulated AUC	Sim/ Obs Cmax	Sim/Obs AUC
	1.90	2.88	2.88	3.30	1.52	1.14

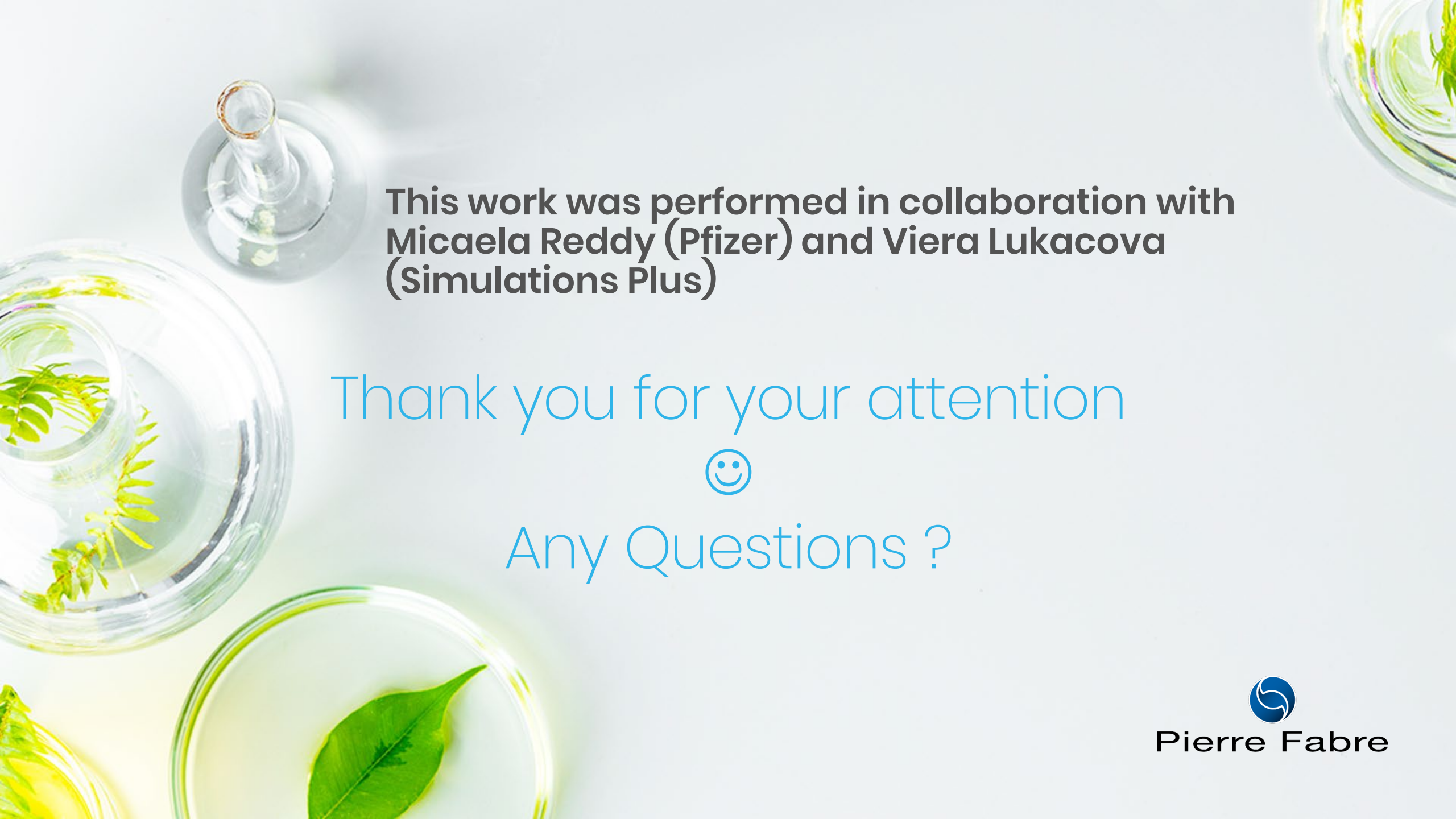
Conclusion and perspectives



G. Tucker 2013 Middle-Out'–Joined-Up Thinking For Pharmacokinetic–Pharmacodynamic Model-Based Learning And Confirming In Drug Development

Combined bottom-up and middle-out approaches

- PBPK encorafenib model validated and reliable for DDI prediction
- Enable DDI predictions at therapeutic dose and regimen (QD)
- Simulations with other strong inhibitors
- Model was used to support recommendations in labels
- Model was used to predict DDI with encorafenib as a victim



This work was performed in collaboration with Micaela Reddy (Pfizer) and Viera Lukacova (Simulations Plus)

Thank you for your attention

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Any Questions ?

Pierre Fabre