Clinical Pharmacokinetics

Quantitative Assessment of Elagolix Enzyme-Transporter Interplay and Drug-Drug Interaction Using Physiologically-Based Pharmacokinetics Modeling

Manoj S. Chiney[1], Juki Ng[1], John P. Gibbs[1], Mohamad Shebley[1]

[1]*Clinical Pharmacology and Pharmacometrics*, AbbVie, North Chicago, IL, USA

AUTHOR ORCID NUMBERS

Manoj S. Chiney: 0000-0003-3679-9363
Juki Ng: 0000-0002-8402-3271
John P. Gibbs: 0000-0001-8892-7318
Mohamed Shebley: 0000-0002-0147-8933

Corresponding Author:
Mohamad Shebley, PhD
AbbVie Inc.

Clinical Pharmacology and Pharmacometrics
Department R4PK, Building AP31-3
1 North Waukegan Road
North Chicago, IL 60064
Email: mohamad.shebley@abbvie.com

Supplemental Table 1: Demographic information of the population representative used for the simulations.

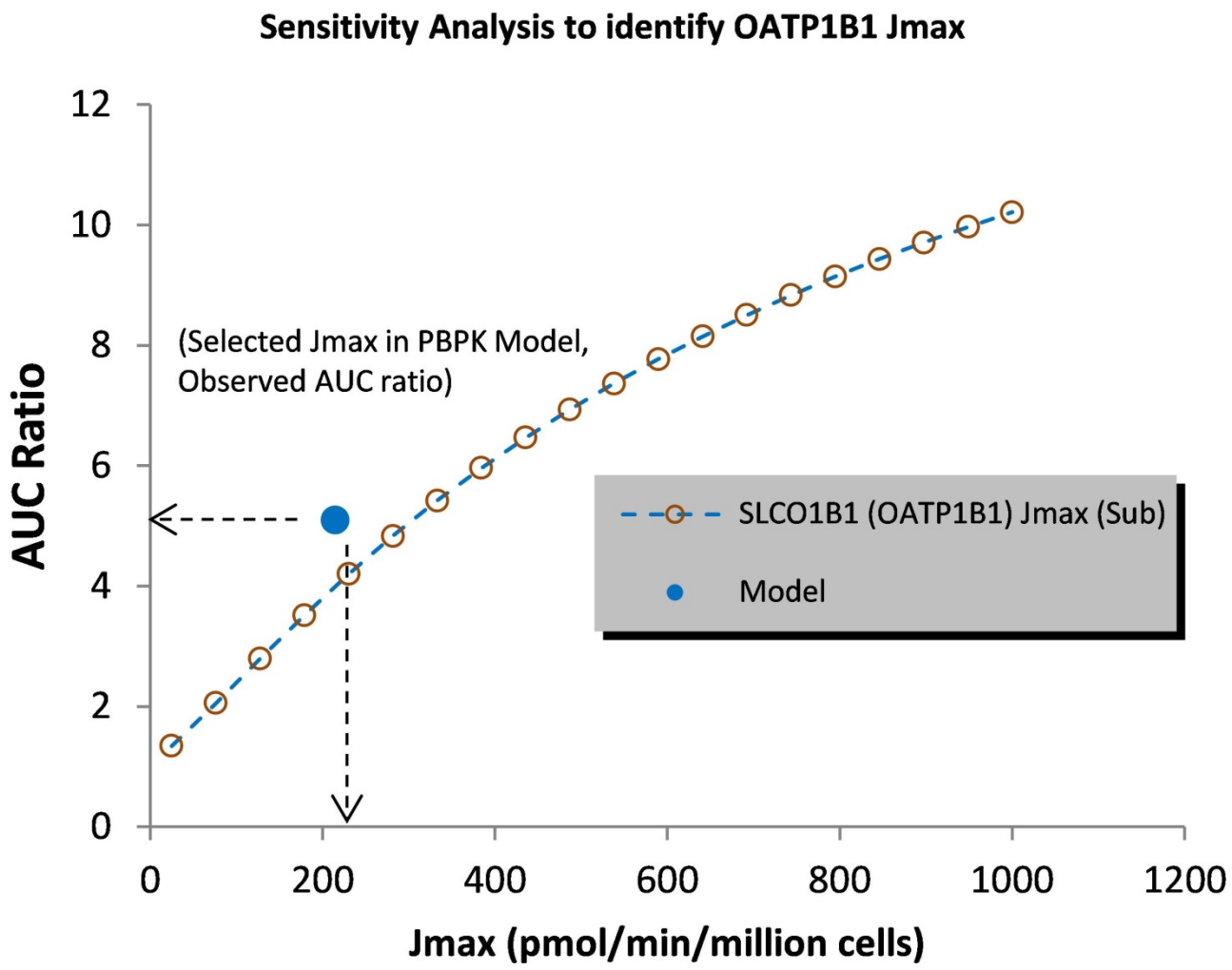
Sex	Male
Age (Years)	20
Weight (kg)	81
Height (cm)	177
BSA (m^2)	1.98
BMI (kg/m^2)	25.9
Haematocrit (%)	43.0
HSA (g/L)	47.3
Serum Creatinine (µmol/L)	76.5
GFR ($mL/min/1.73m^2$)	136
Renal Function	1.13
OATP1B1 Status	Extensive transporter
CYP P450 Status	Extensive metabolizer

Supplemental Table 2: Simulation Design for PK and DDI studies

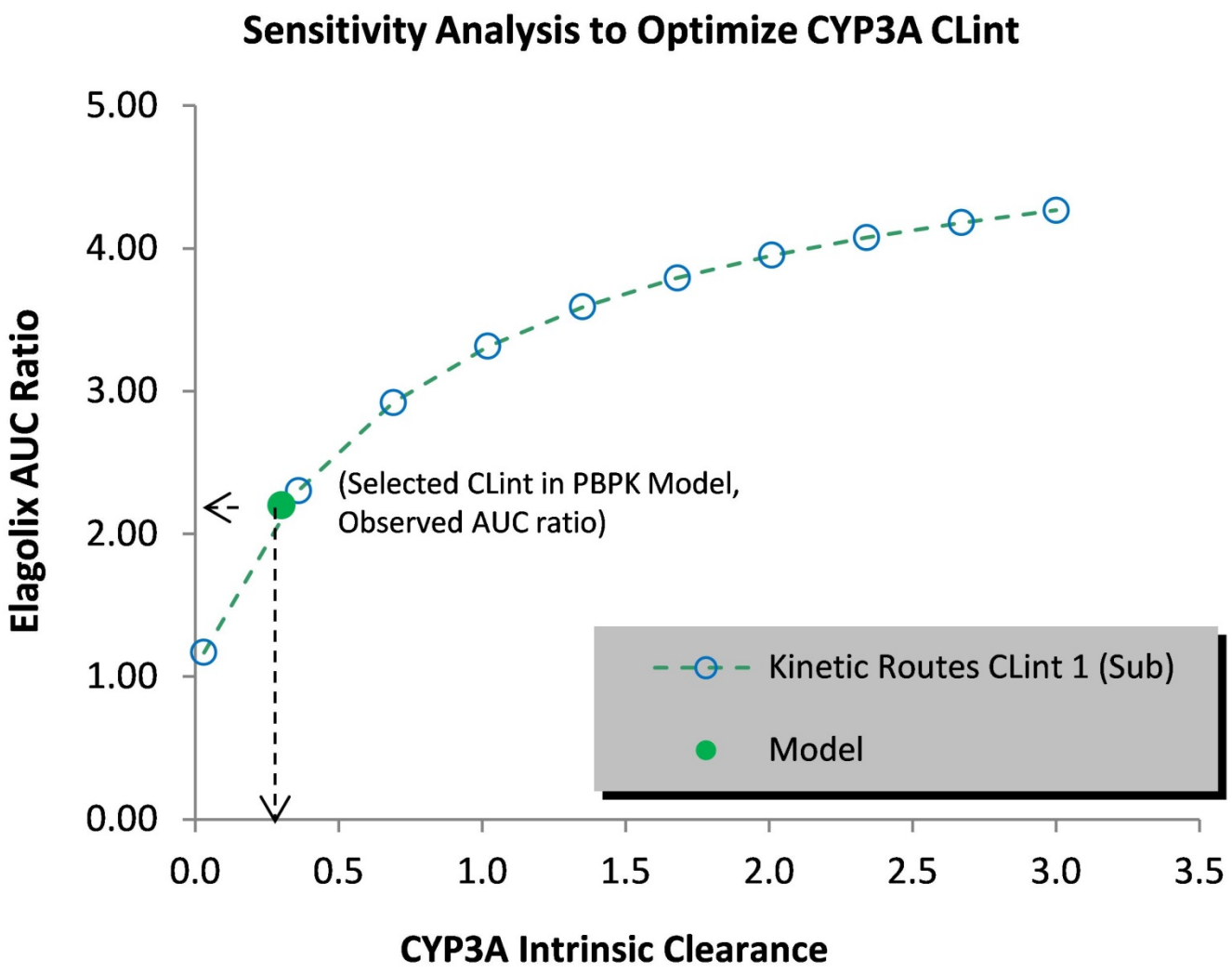
Study	Drug	Route	Dose	Time of Administration	Fasting/Fed	Duration	Simulation Population
Multiple Ascending Dose	Elagolix	PO	150 mg	QD for 21 days	Fasting	23 days	Population Representative
Multiple Ascending Dose	Elagolix	PO	200 mg	BID for 21 days	Fasting	23 days	Population Representative
Rifampin DDI Study	Elagolix (Victim)	PO	150 mg	SD on Day 1 and Day 10	Fasting	13 days	Population Representative
	Rifampin (Perpetrator)	PO	600 mg	QD 12 days	Fasting	13 days	Population Representative
Ketoconazole DDI Study	Elagolix (Victim)	PO	150 mg	SD on Day 4	Fasting	8 days	Population Representative
	Ketoconazole (Perpetrator)	PO	400 mg	QD for 6 days	Fasting	8 days	Population Representative
Midazolam DDI Study	Midazolam (Victim)	PO	5 mg	SD Day 14	Fasting	17 days	Population Representative
	Elagolix (Perpetrator)	PO	150 mg	QD for 16 days	Fasting	17 days	Population Representative
Digoxin DDI Study	Digoxin (Victim)	PO	0.5 mg	QD Day 1 and Day 10	Fasting	13 days	Population Representative
	Elagolix (Perpetrator)	PO	200 mg	BID for 13 days	Fasting	13 days	Population Representative
Midazolam DDI Study	Midazolam (Victim)	PO	5 mg	SD Day 14	Fasting	17 days	Population Representative
	Elagolix (Perpetrator)	PO	200 mg	BID for 16 days	Fasting	17 days	Population Representative
Digoxin DDI Study	Digoxin (Victim)	PO	0.5 mg	QD Day 1 and Day 10	Fasting	13 days	Population Representative
	Elagolix (Perpetrator)	PO	150 mg	QD for 13 days	Fasting	13 days	Population Representative

BID twice daily, *DDI* drug-drug interaction, *PO* orally, *QD* once daily, *SD* single dose.

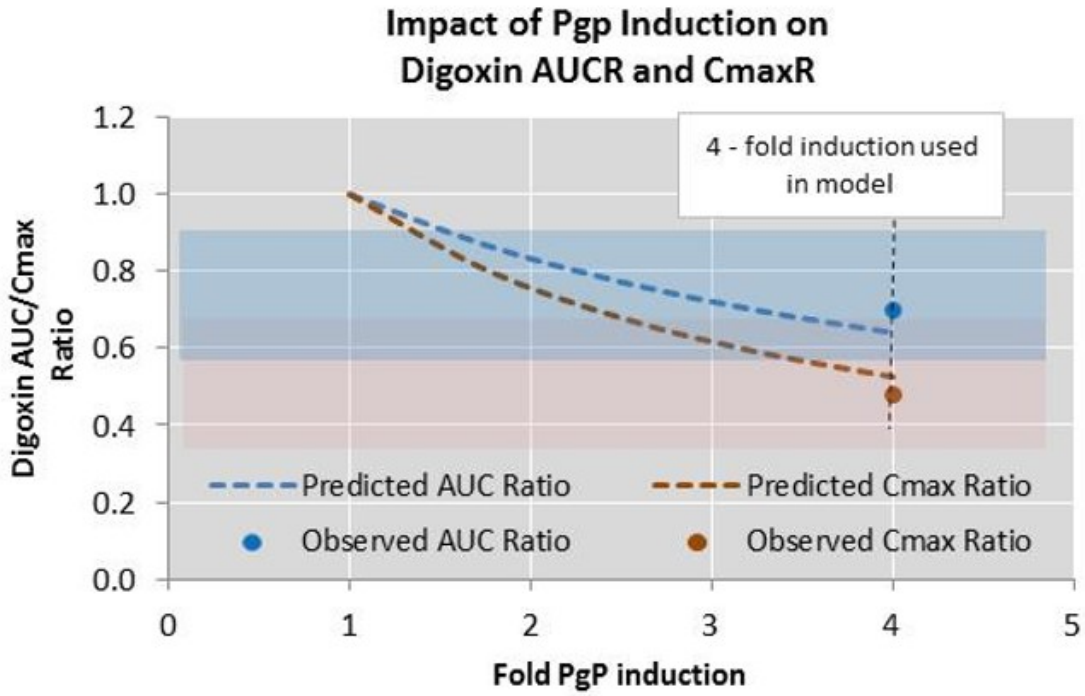
Supplemental Figure 1: Sensitivity Analysis to assess the impact of choice of OATP1B1 Jmax parameter on the predicted elagolix AUC ratio following co-administration with single dose of rifampin.



Supplemental Figure 2: Sensitivity Analysis to assess the impact of choice of CYP3A4 CLint parameter on the predicted elagolix AUC ratio following co-administration with single dose of ketoconazole



Supplemental Figure 3: Sensitivity Analysis to identify the P-gp fold induction that captures the observed DDI of Digoxin with Rifampin.



Shaded regions (blue and red) indicate the range of acceptance criteria based on Guest et. al.