

P-gp DDI Qualification

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This qualification report is filed at:

<https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports>

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1 Introduction

1.1 Objective

This **qualification report** evaluates for the PBPK platform **PK-Sim** (as part of the open systems pharmacology (OSP) suite) the ability to perform simulations with the intended purpose to predict Permeability-glycoprotein (**P-gp**)-mediated drug-drug interactions (**DDI**).

To demonstrate the level of confidence, the predictive performance of the platform for this indented purpose is assessed via a network of PBPK models of selected P-gp DDI perpetrators, and a respective sensitive P-gp victim drug (digoxin) and a comprehensive dataset from published clinical DDI studies. All PBPK models represent whole-body PBPK models, which allow dynamic DDI simulations in organs expressing P-gp.

The respective *qualification plan* to produce this *qualification report* is transparently provided open-source (<https://github.com/Open-Systems-Pharmacology/Qualification-DDI-P-gp>). The same applies for all presented PBPK models including *evaluation reports* on model building and evaluation of each model (<https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library>).

Evaluation reports including descriptions on model building and detailed evaluations of the included models are documented separately (see [Section 1.2](#)).

Please refer to the [Appendix](#) to learn more details:

- An overview over the Open Systems Pharmacology Suite is given in chapter [Section 5.1](#)
- [Section 5.2](#) shows the implementation of the underlying mathematical equations for drug-drug interactions in the OSP suite.
- A detailed general description of the performed qualification workflow (*qualification plan*, *qualification report*, etc.) can be found in chapter [Section 5.3](#).

1.2 Pgp DDI Network

To qualify the OSP suite for the prediction of the P-gp DDI potential of new drugs, a set of verified PBPK models of perpetrators, and respective P-gp DDI victim drugs is specified to set up a P-gp-mediated DDI modeling network.

The following perpetrator compounds were selected:

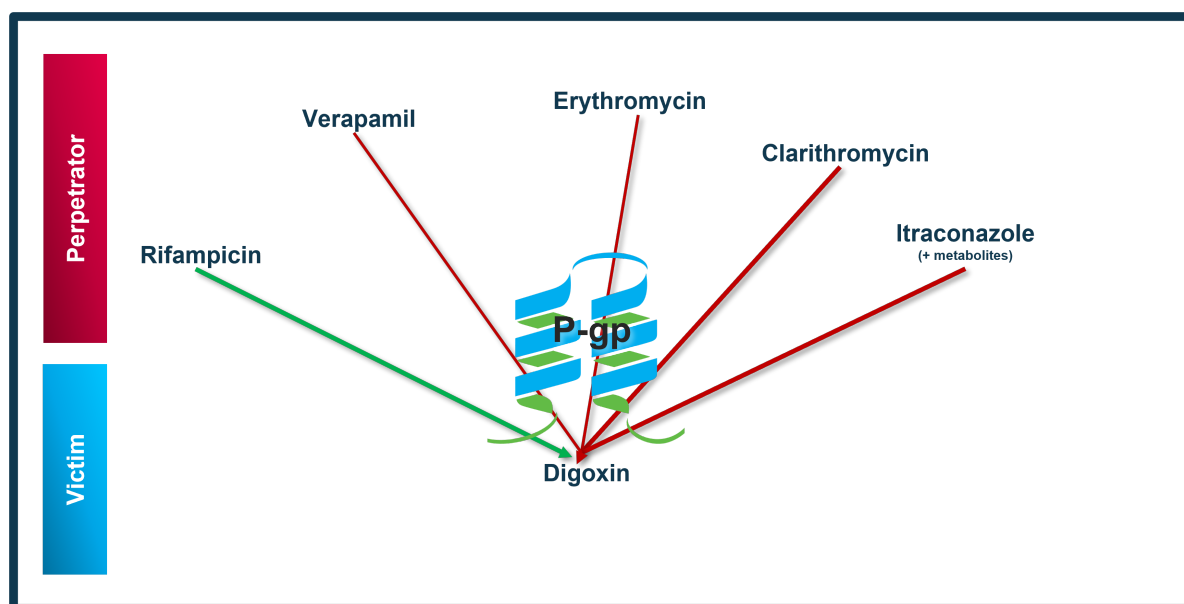
- **Rifampicin** Model snapshot and evaluation plan (*release v2.0*): <https://github.com/Open-Systems-Pharmacology/Rifampicin-Model/releases/tag/v2.0>
- **Verapamil** Model snapshot and evaluation plan (*release v2.1*): <https://github.com/Open-Systems-Pharmacology/Verapamil-Model/releases/tag/v2.1>
- **Erythromycin** Model snapshot and evaluation plan (*release v2.0*): <https://github.com/Open-Systems-Pharmacology/Erythromycin-Model/releases/tag/v2.0>
- **Clarithromycin** Model snapshot and evaluation plan (*release v2.0*): <https://github.com/Open-Systems-Pharmacology/Clarithromycin-Model/releases/tag/v2.0>
- **Itraconazole** including metabolites Model snapshot and evaluation plan (*release v2.0*): <https://github.com/Open-Systems-Pharmacology/Itraconazole-Model/releases/tag/v2.0>

The following sensitive P-gp substrates as victim drugs were selected:

- **Digoxin** Model snapshot and evaluation plan (*release v2.0*): <https://github.com/Open-Systems-Pharmacology/Digoxin-Model/releases/tag/v2.0>

Figure 1 shows the prespecified and developed DDI modeling network of interacting perpetrator and victim drugs for the OSP suite qualification of predicting P-gp-mediated DDI.

Figure 1: P-gp DDI modeling network



The arrows indicate where at least one clinical DDI study between the two connected substances was available and included in the model network. Red indicates inhibition and green indicates induction as the primary type of interaction. Thin arrows indicate weak, mid-thick arrows moderate and thick arrows strong P-gp modulation by the perpetrator.

The published DDI studies between the respective perpetrators and victim drugs were simulated and compared to observed data. The following sections give an overview of the clinical studies being part of this qualification report. The respective data identifier (DataID) refers to the **ID** of the dataset in the OSP PK database, version 1.7 (<https://github.com/Open-Systems-Pharmacology/Database-for-observed-data/releases/tag/v1.7>).

1.2.1 Clarithromycin - Digoxin DDI

The release of the snapshot containing the respective simulations can be found here: <https://github.com/Open-Systems-Pharmacology/Clarithromycin-Digoxin-DDI/releases/tag/v1.0>

The Clarithromycin / digoxin interaction was evaluated using 6 clinical DDI studies including 21 different clinical settings (Gurley 2006, Gurley 2007, Gurley 2008b, Kurata 2002, Rengelshausen 2003, Tsutsumi 2002).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
16324	P-gp	Clarithromycin / digoxin	Clarithromycin: 500 mg po twice daily (14 doses) Digoxin: 0.4 mg po single dose, simultaneous with 12th clarithromycin dose		Gurley 2006
16328	P-gp	Clarithromycin / digoxin	Clarithromycin: 500 mg po twice daily (14 doses) Digoxin: 0.5 mg po single dose, simultaneous with 12th clarithromycin dose		Gurley 2007
229	P-gp	Clarithromycin / digoxin	Clarithromycin: 500 mg po twice daily (14 doses) Digoxin: 0.25 mg po single dose, 2 hours after 12th clarithromycin dose		Gurley 2008b
16305	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg po single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16307	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg iv single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16309	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg po single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16311	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg iv single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16313	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg po single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16315	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg iv single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16333	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg po single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16334	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg iv single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16335	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg po single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16336	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg iv single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
16337	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg po single dose, simultaneous with 10th clarithromycin dose		Kurata 2002

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
16338	P-gp	Clarithromycin / digoxin	Clarithromycin: 400 mg po twice daily (16 doses) Digoxin: 0.25 mg iv single dose, simultaneous with 10th clarithromycin dose		Kurata 2002
3025	P-gp	Clarithromycin / digoxin	Clarithromycin: 250 mg po twice daily (6 doses) Digoxin: 0.75 mg po single dose, 0.5 hours after 3rd clarithromycin dose		Rengelshausen 2003
16409	P-gp	Clarithromycin / digoxin	Clarithromycin: 250 mg po twice daily (6 doses) Digoxin: 0.01 mg/kg iv single dose, 2 hours after 3rd clarithromycin dose		Rengelshausen 2003
16411	P-gp	Clarithromycin / digoxin	Clarithromycin: 250 mg po twice daily (6 doses) Digoxin: 0.75 mg po single dose, 0.5 hours after 3rd clarithromycin dose		Rengelshausen 2003
16413	P-gp	Clarithromycin / digoxin	Clarithromycin: 250 mg po twice daily (6 doses) Digoxin: 0.75 mg po single dose, 0.5 hours after 3rd clarithromycin dose		Rengelshausen 2003
3029	P-gp	Clarithromycin / digoxin	Clarithromycin: 200 mg po twice daily (10 doses) Digoxin: 0.5 mg iv single dose, simultaneous with 3rd clarithromycin dose		Tsutsumi 2002
3032	P-gp	Clarithromycin / digoxin	Clarithromycin: 200 mg po twice daily (10 doses) Digoxin: 0.5 mg iv single dose, simultaneous with 3rd clarithromycin dose		Tsutsumi 2002

1.2.2 Erythromycin - Digoxin DDI

The release of the snapshot containing the respective simulations can be found here: <https://github.com/Open-Systems-Pharmacology/Erythromycin-Digoxin-DDI/releases/tag/v1.1>

The erythromycin-digoxin interaction was evaluated using one clinical DDI study ([Tsutsumi 2002](#)).

DataID	Transporter	Perpetrator / victim	Study design	Clinical study
3028	P-gp	Erythromycin / digoxin	Erythromycin: 200 mg po QID for 5 days Digoxin: 0.5 mg iv, concomitantly with erythromycin on the 2 nd day	Tsutsumi 2002

1.2.3 Itraconazole - Digoxin DDI

The release of the snapshot containing the respective simulations can be found here: <https://github.com/Open-Systems-Pharmacology/Itraconazole-Digoxin-DDI/releases/tag/v1.0>

The itraconazole-digoxin interaction was evaluated using 2 clinical DDI studies including 3 different clinical settings ([Jalava 1997](#), [Partanen 1995](#)).

DataID	Transporter	Perpetrator / victim	Study design	Comment	Clinical study
271	P-gp	Itraconazole / digoxin	Itraconazole: 200 mg po once daily (5 doses) Digoxin: 0.5 mg po single dose, 1 h after the 3rd itraconazole dose		Jalava 1997
16329	P-gp	Itraconazole / digoxin	Itraconazole: 200 mg po once daily (10 doses) Digoxin: 0.25 mg po once daily (20 doses), 2 hours after 12th itraconazole dose		Partanen 1995
16330	P-gp	Itraconazole / digoxin	Itraconazole: 200 mg po once daily (10 doses) starting with the 11th digoxin dose Digoxin: 0.25 mg po once daily (20 doses), simultaneous with 10th itraconazole dose		Partanen 1995

1.2.4 Verapamil - Digoxin DDI

The release of the snapshot containing the respective simulations can be found here: <https://github.com/Open-Systems-Pharmacology/Verapamil-Digoxin-DDI/releases/tag/v1.1>

The verapamil-digoxin interaction was evaluated using a 11 clinical DDI studies including 12 different clinical settings ([Belz 1981](#), [Belz 1983](#), [Doering 1983](#), [Johnson 1987](#), [Klein 1982](#), [Pedersen 1981](#), [Pedersen 1982](#), [Pedersen 1983](#), [Rodin 1988](#), [Schwartz 1982](#), [Wiebe 2020](#)).

DataID	Transporter	Perpetrator / victim	Study design	Comment	Clinical study
16635	P-gp	Verapamil / digoxin	Verapamil: 80 mg po TID for 14 days Digoxin: 0.125 mg po TID for 14 days		Belz 1981
16165	P-gp	Verapamil / digoxin	Verapamil: 80 mg po TID for 14 days Digoxin: 0.125 mg po TID for 14 days		Belz 1983
16167	P-gp	Verapamil / digoxin	Verapamil: 120 mg po TID for 14 days Digoxin: 0.125 mg po TID for 14 days		Belz 1983
16169	P-gp	Verapamil / digoxin	Verapamil: 80 mg po TID for 14 days Digoxin: 0.125 mg po TID for 14 days		Doering 1983
16159	P-gp	Verapamil / digoxin	Verapamil: 80 mg po BID for 4 days followed by TID for 10 days Digoxin: 1.0 mg iv (15 min) on day 13		Johnson 1987
16174	P-gp	Verapamil / digoxin	Verapamil: 80 mg po TID for 14 days Digoxin: 0.25 mg PO OD for 28 days		Klein 1982
16638	P-gp	Verapamil / digoxin	Verapamil: 80 mg po TID for 10 days Digoxin: 0.75 mg IV SD at day 10		Pedersen 1981
16163	P-gp	Verapamil / digoxin	Verapamil: 80 mg po TID followed by 120mg TID Digoxin: initial dose of 1mg PO followed by 0.0625 mg po BID followed by 0.125mg BID		Pedersen 1982
16162	P-gp	Verapamil / digoxin	Verapamil: 120 mg po TID for 12 days Digoxin: 1.0 mg iv (bolus) on day 8		Pedersen 1983
3063	P-gp	Verapamil / digoxin	Verapamil: 80mg BID for 4 days followed by 80mg TID for 10 days Digoxin: 0.25 mg PO BID for 14 days		Rodin 1988
16175	P-gp	Verapamil / digoxin	Verapamil: 80 mg po QID for 70 days Digoxin: 0.46 mg PO OD for 85 days	Daily dose of digoxin varied between patients between 0.25 and 1 mg/day. 0.46 is the arith. mean of all dose levels.	Schwartz 1982
16172	P-gp	Verapamil / digoxin	Verapamil: 120 mg po SD Digoxin: 0.25 mg PO SD 1h after verapamil dosing		Wiebe 2020

1.2.5 Rifampicin - Digoxin DDI

The release of the snapshot containing the respective simulations can be found here: <https://github.com/Open-Systems-Pharmacology/Rifampicin-Digoxin-DDI/releases/tag/v1.0>

The rifampicin-digoxin interaction was evaluated using 9 clinical DDI studies including 11 different clinical settings (Drescher 2003, Gurley 2006, Gurley 2007, Gurley 2008b, Greiner 1999, Kirby 2012, Larsen 2007, Reitmann 2011, Wiebe 2020).

DatalD	Transporter	Perpetrator / victim	Study design	Comment	Clinical study
191	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (16 doses) Digoxin: 1 mg po single dose, simultaneous with 11th rifampicin dose		Greiner 1999
193	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (16 doses) Digoxin: 1 mg iv single dose, simultaneous with 11th rifampicin dose		Greiner 1999
227	P-gp	Rifampicin / digoxin	Rifampicin: 300 mg po twice daily (16 doses) Digoxin: 0.25 mg po single dose, 2 hours after 13th rifampicin dose		Gurley 2008b
314	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (14 doses) Digoxin: 0.5 mg po single dose, 12 hours after 14th rifampicin dose		Kirby 2012
316	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (14 doses) Digoxin: 0.5 mg iv single dose, 12 hours after 14th rifampicin dose		Kirby 2012
337	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (6 doses) Digoxin: 0.5 mg po single dose, simultaneous with 7th rifampicin dose		Larsen 2007
396	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (28 doses) Digoxin: 0.5 mg po single dose, 1 h after the 28th (last) rifampicin dose		Reitmann 2011
397	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (28 doses) Digoxin: 0.5 mg po single dose, 169 h (1 week +1 h) after the 28th (last) rifampicin dose		Reitmann 2011
398	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (28 doses) Digoxin: 0.5 mg po single dose, 337 h (2 weeks +1 h) after the 28th (last) rifampicin dose		Reitmann 2011
16301	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po single dose Digoxin: 0.25 mg po single dose, simultaneous with rifampicin dose		Wiebe 2020
16319	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (14 doses) Digoxin: 1 mg iv single dose, 12 h after the 10th rifampicin dose		Drescher 2003
16322	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (14 doses) Digoxin: 0.4 mg po single dose, simultaneous with 7th rifampicin dose		Gurley 2006
16326	P-gp	Rifampicin / digoxin	Rifampicin: 600 mg po once daily (14 doses) Digoxin: 0.5 mg iv single dose, simultaneous with 7th rifampicin dose		Gurley 2007

2 Qualification of Use Case Pgp-mediated DDI

The following section shows the correlations between observed and model-predicted AUC and $C_{\max}$ ratios, respectively.

Specifically, the PBPK model performance for the PK parameters **AUC ratio (AUCR)** and **$C_{\max}$ ratio (CMAXR)** is assessed via:

- predicted (*Pred*) vs. observed (*Obs*) plots
- *Pred/Obs* vs. *Obs* plots
- geometric mean fold error (GMFE):

$$10^{\frac{\sum |\log(\frac{Pred}{Obs})|}{n}}$$

- number of AUCR and CMAXR falling within 2-fold error range and within the limits as suggested by [Guest et al. 2011](#)
- detailed table of results for each study

In the plots,

- the dotted lines denote 0.50–2.00 (2-fold) criterion,
- the solid lines denote the limits as suggested by [Guest et al. 2011](#),
- the bold solid line denotes the unity line,
- each color represents one combination of drugs,
- squares represent studies with intravenous administration of the victim drug and circles represent studies with oral administration of the victim drug.

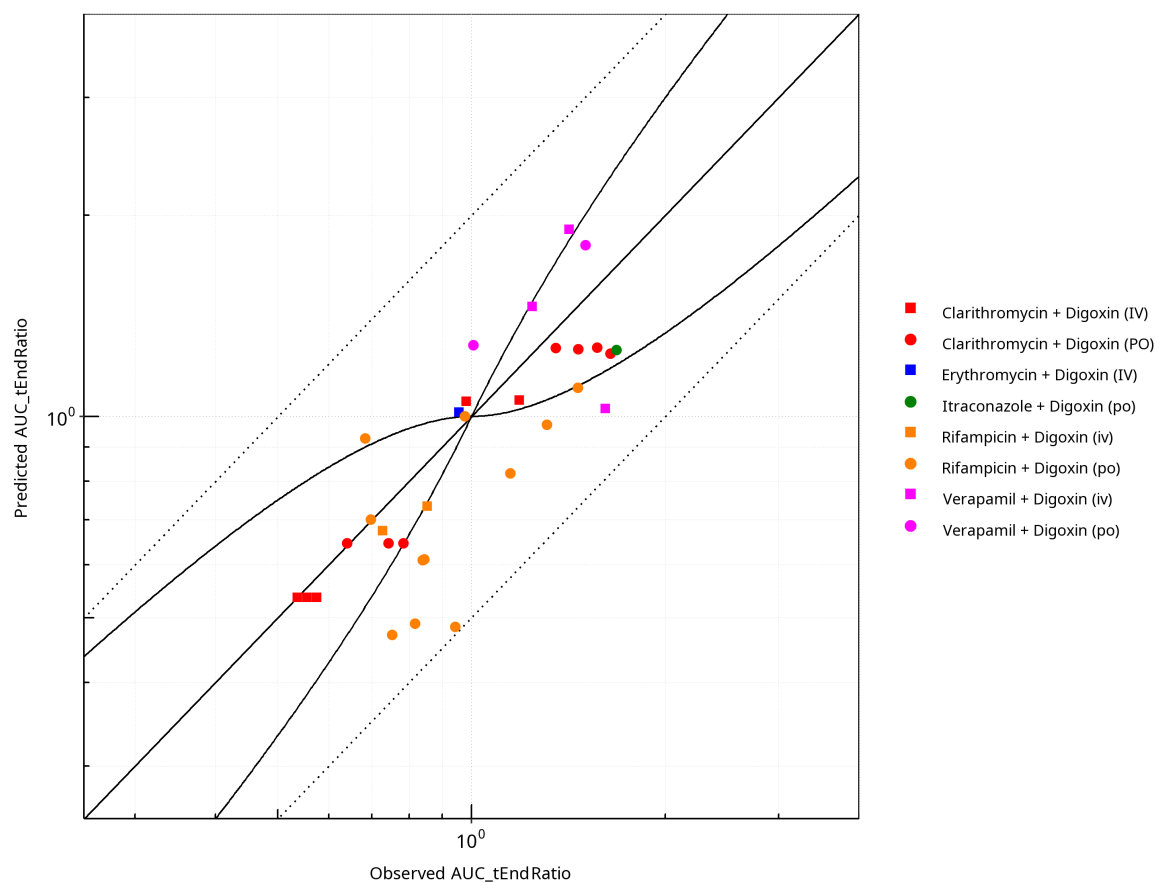


Figure 2-1: Pgp DDI. Predicted vs. Observed AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

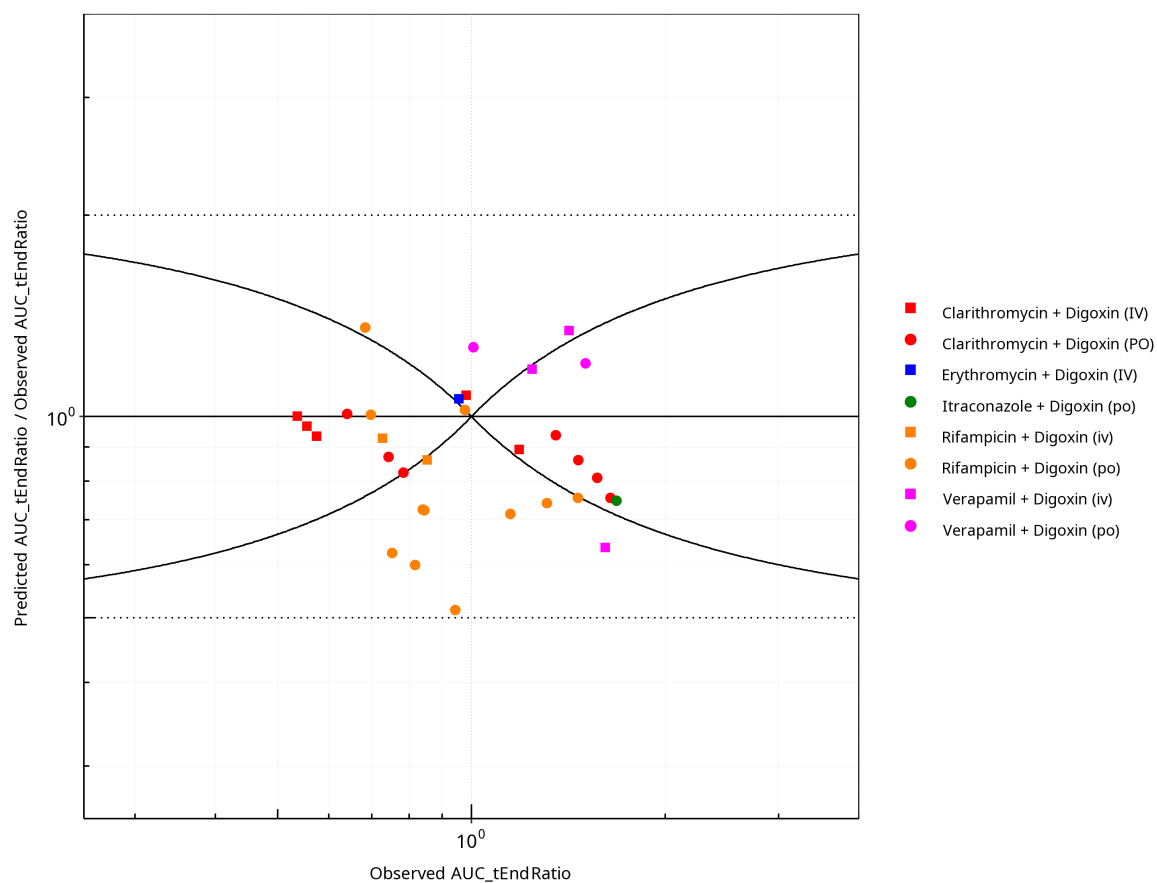


Figure 2-2: Pgp DDI. Predicted/Observed vs. Observed AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

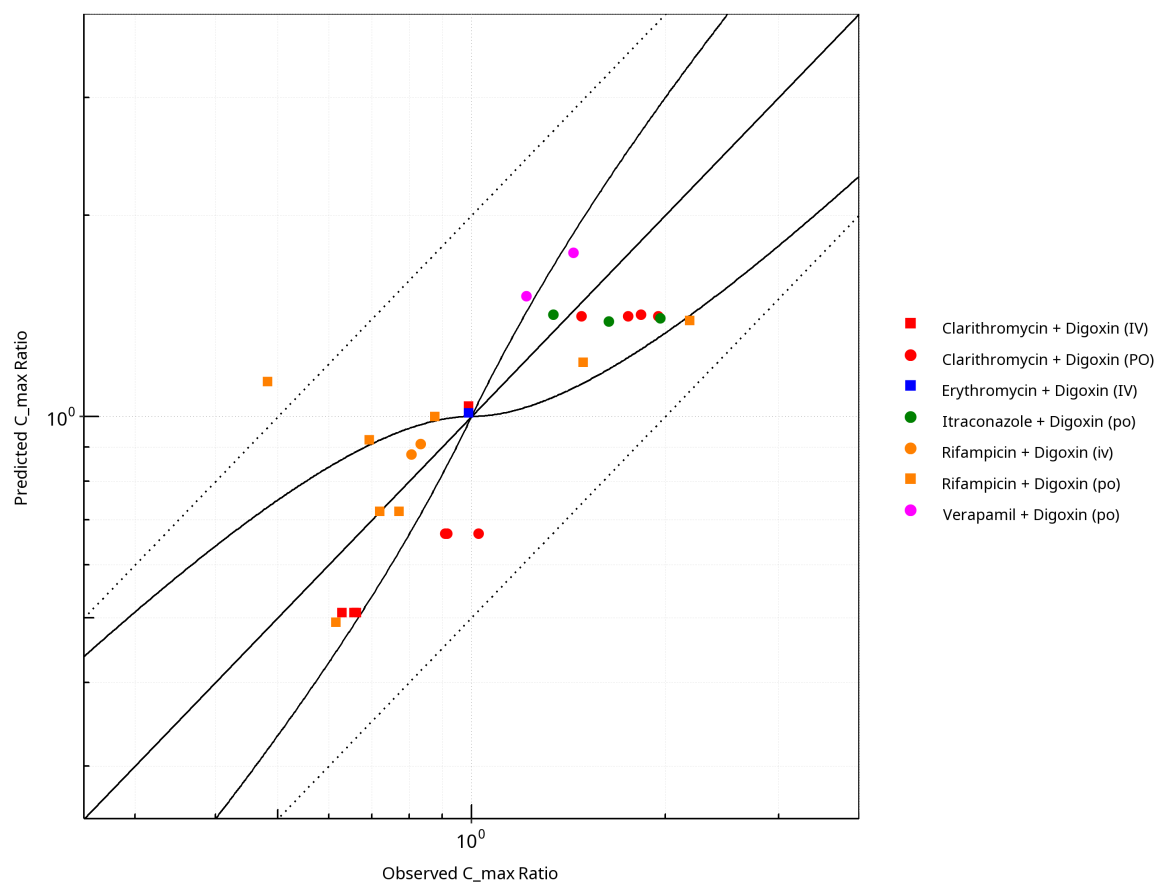


Figure 2-3: Pgp DDI. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

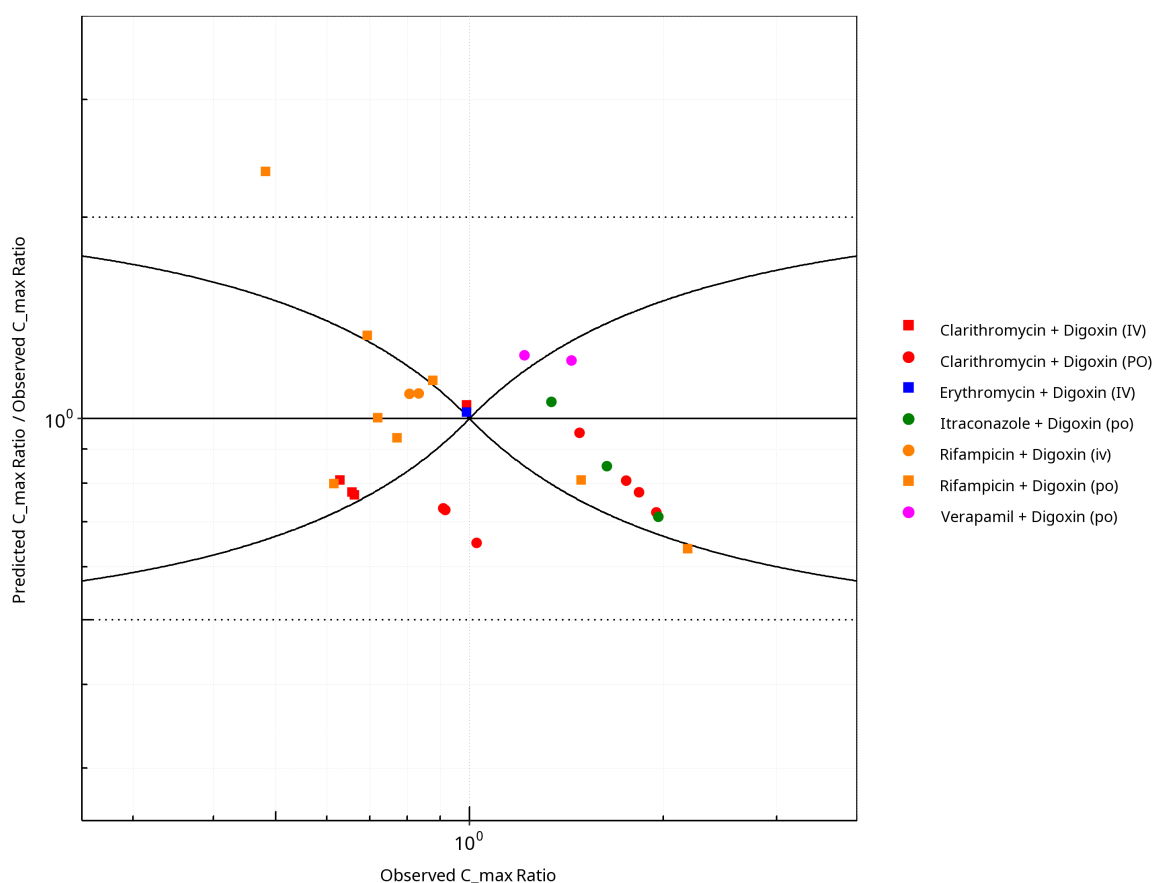


Figure 2-4: Pgp DDI. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-1: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC _{tEnd}	1.24
C _{max}	1.25

Table 2-2: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	32	-
Points within Guest <i>et al.</i>	16	50
Points within 2 fold	32	100

Table 2-3: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	27	-
Points within Guest <i>et al.</i>	17	62.96
Points within 2 fold	26	96.30

Table 2-4: Summary table for Pgp DDI

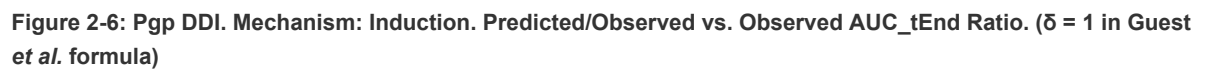
DataID	Perpetrator	Victim	Predicted AUC_tEnd Ratio	Observed AUC_tEnd Ratio	Pred/Obs AUC_tEnd Ratio	Predicted C_max Ratio	Observed C_max Ratio	Pred/Obs C_max Ratio	Reference
191	Rifampicin, 600 mg, PO, MD OD (16 days)	Digoxin, PO	0.70	0.70	1.01	1.13	0.48	2.34	Greiner 1999
193	Rifampicin, 600 mg, PO, MD OD (16 days)	Digoxin, IV	0.73	0.85	0.86	0.91	0.83	1.09	Greiner 1999
227	Rifampicin, 300 mg, PO, MD BID (7 days)	Digoxin, PO	0.47	0.75	0.63	0.49	0.62	0.80	Gurley 2008b
229	Clarithromycin, 500 mg, PO, MD BID (7 days)	Digoxin, PO	1.26	1.47	0.86	1.42	1.75	0.81	Gurley 2008b
271	Itraconazole, 200 mg, PO, MD OD (5 days)	Digoxin, PO	1.26	1.68	0.75	1.42	1.34	1.06	Jalava 1997
314	Rifampicin, 600 mg, PO, MD OD (14 days)	Digoxin, PO	0.49	0.94	0.51	0.52	-	-	Kirby 2012
316	Rifampicin, 600 mg, PO, MD OD (14 days)	Digoxin, PO	0.82	1.15	0.72	1.13	-	-	Kirby 2012
337	Rifampicin, 600 mg, PO, MD OD (6 days)	Digoxin, PO	0.49	0.82	0.60	0.52	-	-	Larsen 2007
396	Rifampicin, 600 mg, PO, MD OD (28 days)	Digoxin, PO	1.11	1.46	0.76	1.21	1.49	0.81	Reitman 2011
397	Rifampicin, 600 mg, PO, MD OD (28 days)	Digoxin, PO	0.93	0.68	1.36	0.92	0.69	1.33	Reitman 2011
398	Rifampicin, 600 mg, PO, MD OD (28 days)	Digoxin, PO	1.00	0.98	1.03	1.00	0.88	1.14	Reitman 2011

DataID	Perpetrator	Victim	Predicted AUC_tEnd Ratio	Observed AUC_tEnd Ratio	Pred/Obs AUC_tEnd Ratio	Predicted C_max Ratio	Observed C_max Ratio	Pred/Obs C_max Ratio	Reference
3028	Erythromycin, 200 mg, PO, MD QID (5 days)	Digoxin, IV	1.02	0.95	1.06	1.01	0.99	1.02	Tsutsumi 2002
3029	Clarithromycin, 200 mg, PO, MD BID (5 days)	Digoxin, IV	1.05	0.98	1.08	1.04	0.99	1.05	Tsutsumi 2002
3063	Verapamil, 80 mg, PO, MD: 80mg BID (4 days), 80mg TID (10 days)	Digoxin, PO	1.81	1.50	1.20	1.76	1.44	1.22	Rodin 1988
16159	Verapamil, 80 mg, PO, MD BID 4days, TID 10days	Digoxin, IV	1.46	1.24	1.18	1.05	-	-	Johnson et al. 1987
16162	Verapamil, 120 mg, PO, TID, 7 days pre- treatment	Digoxin, IV	1.91	1.42	1.34	1.01	-	-	Pedersen et al. 1983
16172	Verapamil, 120 mg, PO, SD	Digoxin, PO	1.28	1.01	1.27	1.52	1.22	1.25	Wiebe 2020
16301	Rifampicin, 600 mg, PO, SD	Digoxin, PO	0.97	1.31	0.74	1.39	2.18	0.64	Wiebe 2020
16305	Clarithromycin, 400 mg, PO, MD	Digoxin, PO	0.65	0.74	0.87	0.67	1.02	0.65	Kurata 2002
16307	Clarithromycin, 400 mg, PO, MD	Digoxin, IV	0.54	0.57	0.93	0.51	0.66	0.78	Kurata 2002
16309	Clarithromycin, 400 mg, PO, MD	Digoxin, PO	0.65	0.64	1.01	0.67	0.91	0.74	Kurata 2002
16311	Clarithromycin, 400 mg, PO, MD	Digoxin, IV	0.54	0.54	1.00	0.51	0.66	0.77	Kurata 2002
16313	Clarithromycin, 400 mg, PO, MD	Digoxin, PO	0.65	0.78	0.83	0.67	0.92	0.73	Kurata 2002
16315	Clarithromycin, 400 mg, PO, MD	Digoxin, IV	0.54	0.56	0.97	0.51	0.63	0.81	Kurata 2002

DataID	Perpetrator	Victim	Predicted AUC_tEnd Ratio	Observed AUC_tEnd Ratio	Pred/Obs AUC_tEnd Ratio	Predicted C_max Ratio	Observed C_max Ratio	Pred/Obs C_max Ratio	Reference
16319	Rifampicin, 600 mg, PO, MD	Digoxin, IV	0.68	0.73	0.93	0.88	0.81	1.09	Drescher 2003
16322	Rifampicin, 300 mg, PO, MD	Digoxin, PO	0.61	0.84	0.73	0.72	0.77	0.94	Gurley 2006
16324	Clarithromycin, 500 mg, PO, MD	Digoxin, PO	1.27	1.35	0.94	1.42	1.48	0.95	Gurley 2006
16326	Rifampicin, 300 mg, PO, MD	Digoxin, PO	0.61	0.84	0.73	0.72	0.72	1.00	Gurley 2007
16328	Clarithromycin, 500 mg, PO, MD	Digoxin, PO	1.27	1.57	0.81	1.42	1.95	0.73	Gurley 2007
16329	Itraconazole, 200 mg, PO, MD	Digoxin, PO	1.35	-	-	1.39	1.63	0.85	Partanen 1996
16330	Itraconazole, 200 mg, PO, MD	Digoxin, PO	1.37	-	-	1.40	1.97	0.71	Partanen 1996
16409	Clarithromycin, 250 mg, PO, MD BID (3 days)	Digoxin, IV	1.06	1.19	0.89	1.00	-	-	Rengelshausen 2003
16411	Clarithromycin, 250 mg, PO, MD BID (3 days)	Digoxin, PO	1.24	1.64	0.76	1.42	1.83	0.78	Rengelshausen 2003
16638	Verapamil, 80 mg, PO, TID	Digoxin, IV	1.03	1.61	0.64	0.83	-	-	Pedersen 1981

2.1 Mechanism

2.1.1 Induction



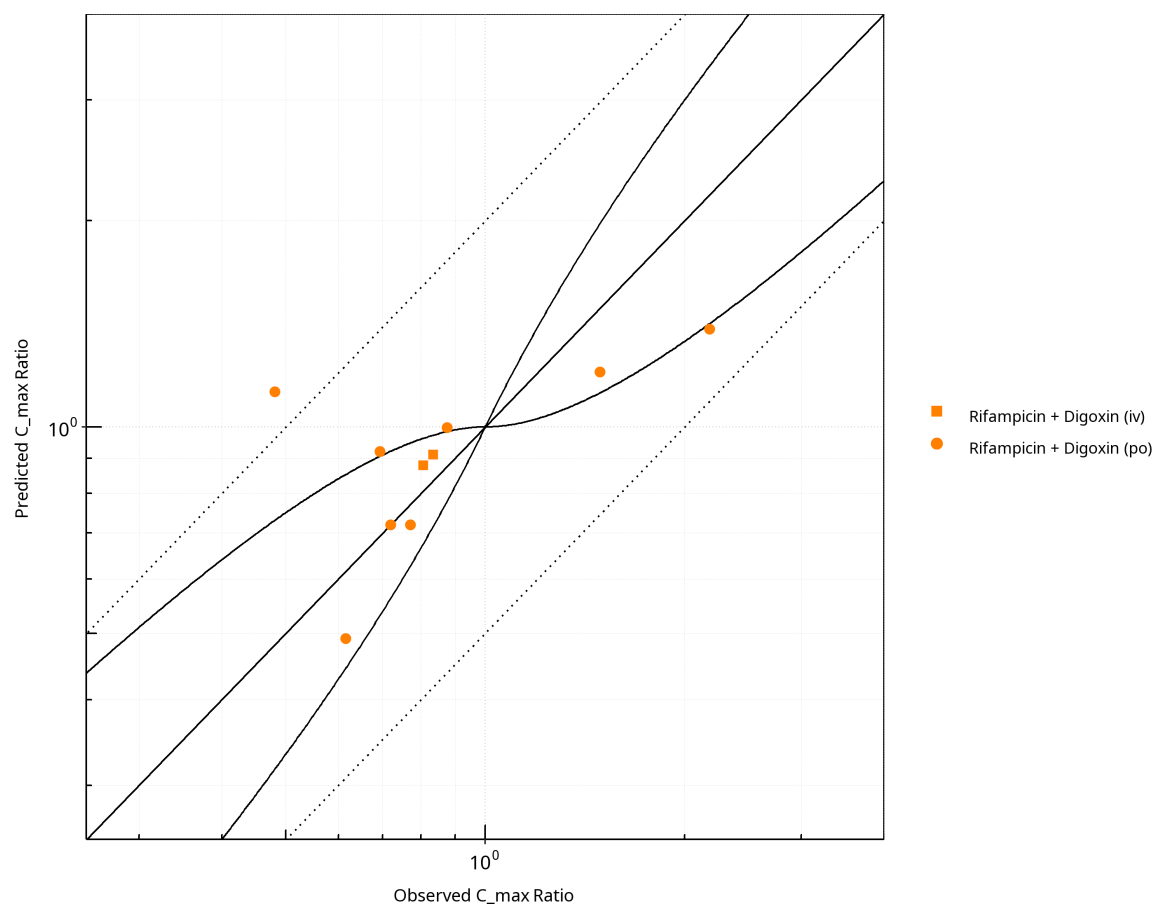


Figure 2-7: Pgp DDI. Mechanism: Induction. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

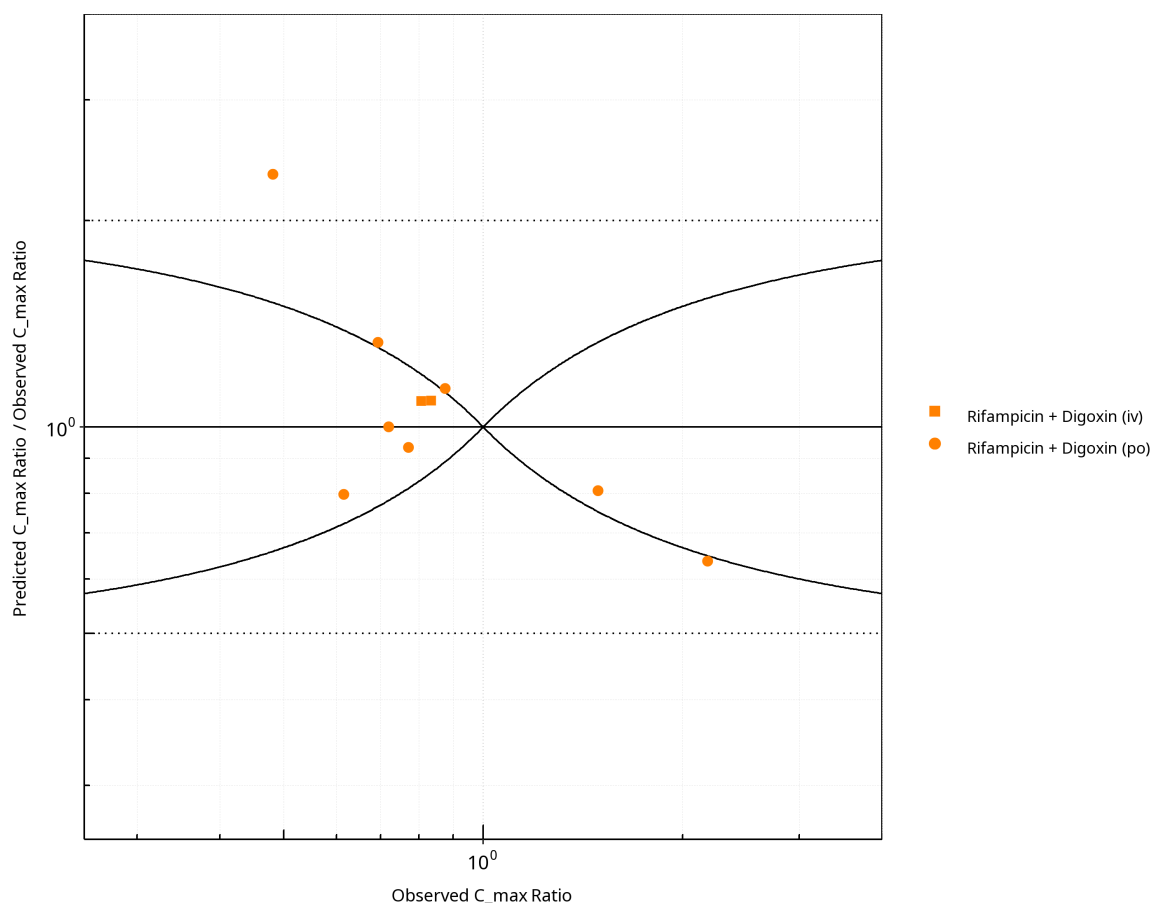


Figure 2-8: Pgp DDI. Mechanism: Induction. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-5: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC _{tEnd}	1.33
C _{max}	1.27

Table 2-6: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	13	-
Points within Guest <i>et al.</i>	2	15.38
Points within 2 fold	13	100.00

Table 2-7: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	10	-
Points within Guest <i>et al.</i>	6	60
Points within 2 fold	9	90

2.1.2 Mechanism-based Inactivation

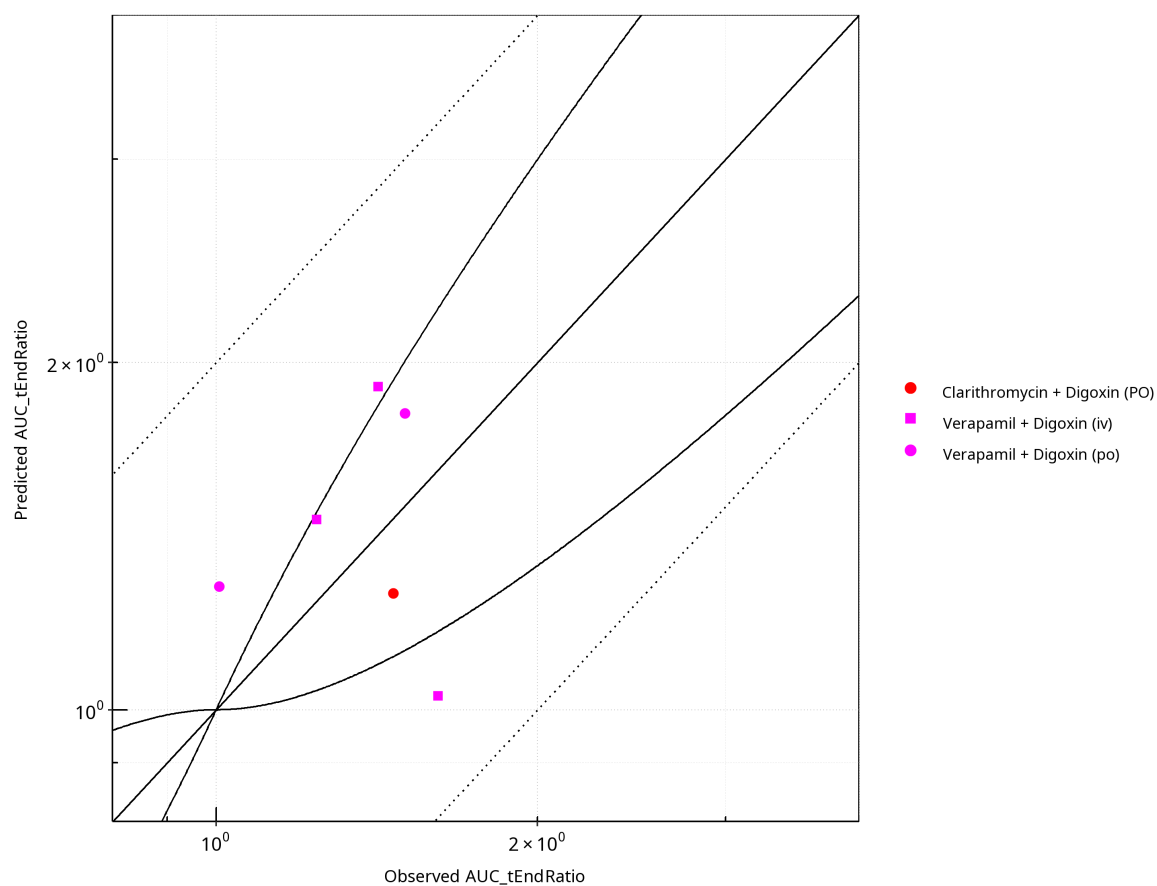


Figure 2-9: Pgp DDI. Mechanism: Mechanism-based Inactivation. Predicted vs. Observed AUC_{tEndRatio}. ($\delta = 1$ in Guest *et al.* formula)

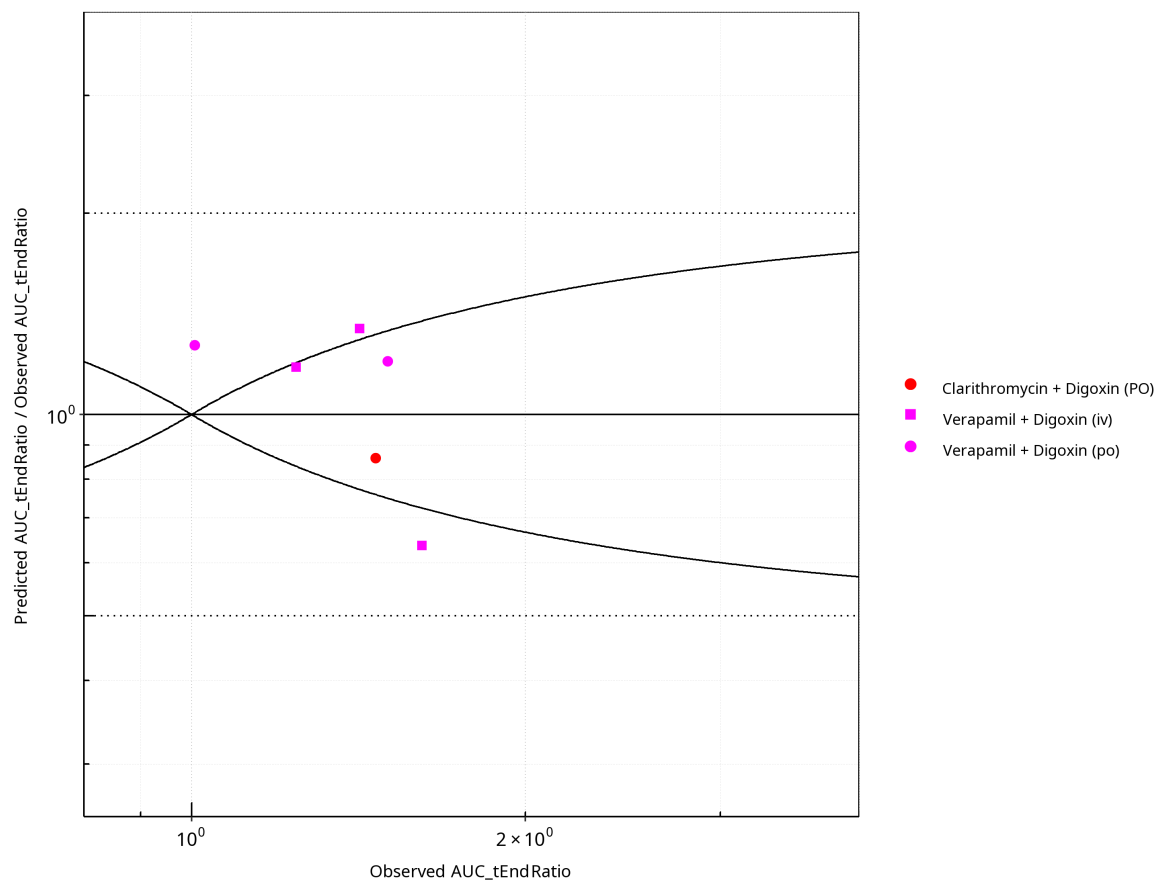


Figure 2-10: Pgp DDI. Mechanism: Mechanism-based Inactivation. Predicted/Observed vs. Observed AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

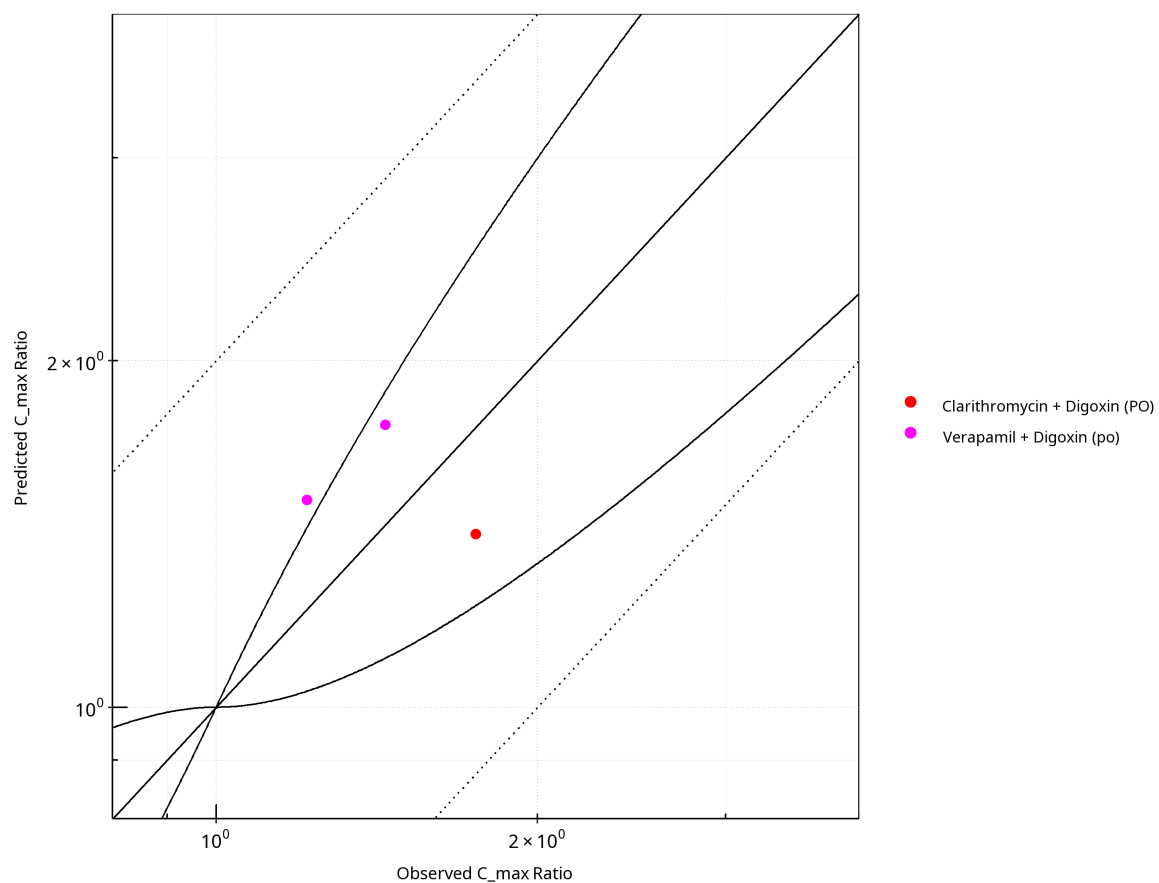


Figure 2-11: Pgp DDI. Mechanism: Mechanism-based Inactivation. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

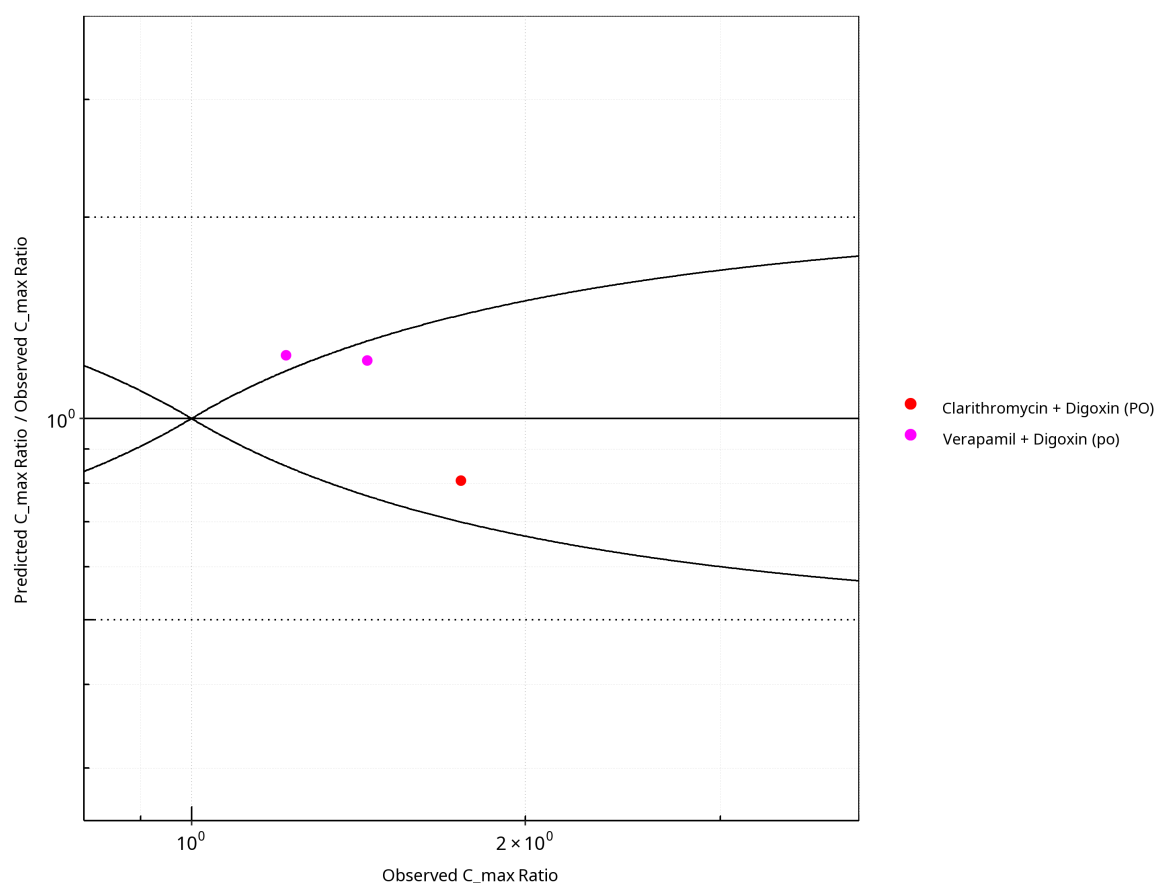


Figure 2-12: Pgp DDI. Mechanism: Mechanism-based Inactivation. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-8: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC _{tEnd}	1.28
C _{max}	1.24

Table 2-9: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	6	-
Points within Guest <i>et al.</i>	3	50
Points within 2 fold	6	100

Table 2-10: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	3	-
Points within Guest <i>et al.</i>	2	66.67
Points within 2 fold	3	100.00

2.1.3 Reversible Inhibition

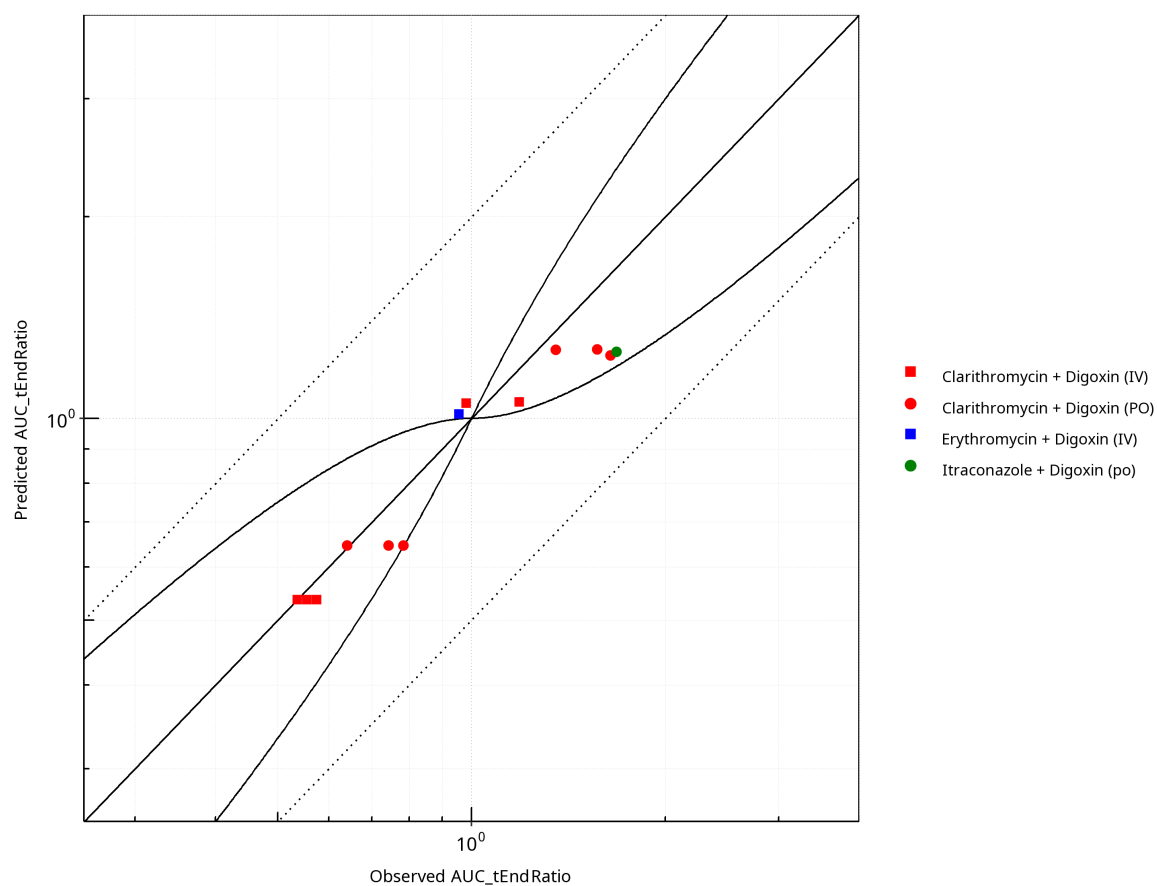


Figure 2-13: Pgp DDI. Mechanism: Reversible Inhibition. Predicted vs. Observed AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

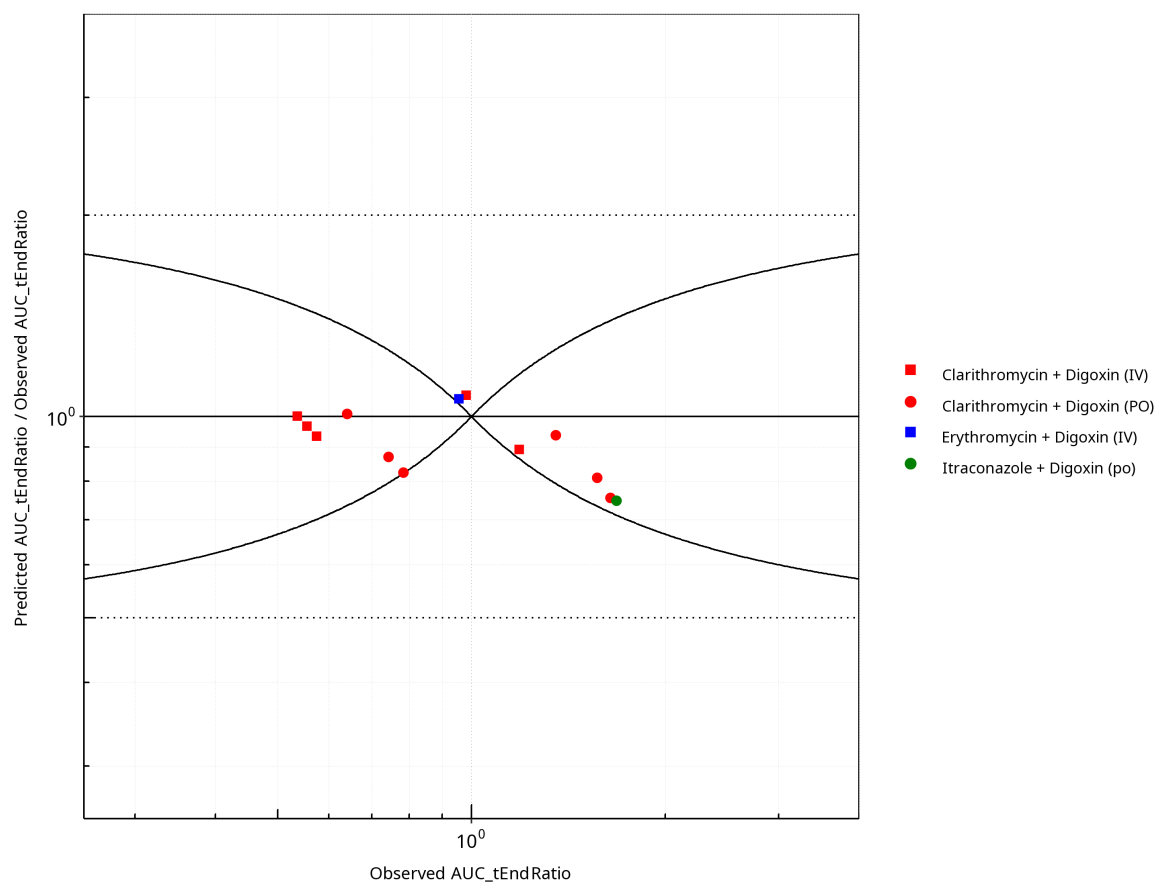


Figure 2-14: Pgp DDI. Mechanism: Reversible Inhibition. Predicted/Observed vs. Observed AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

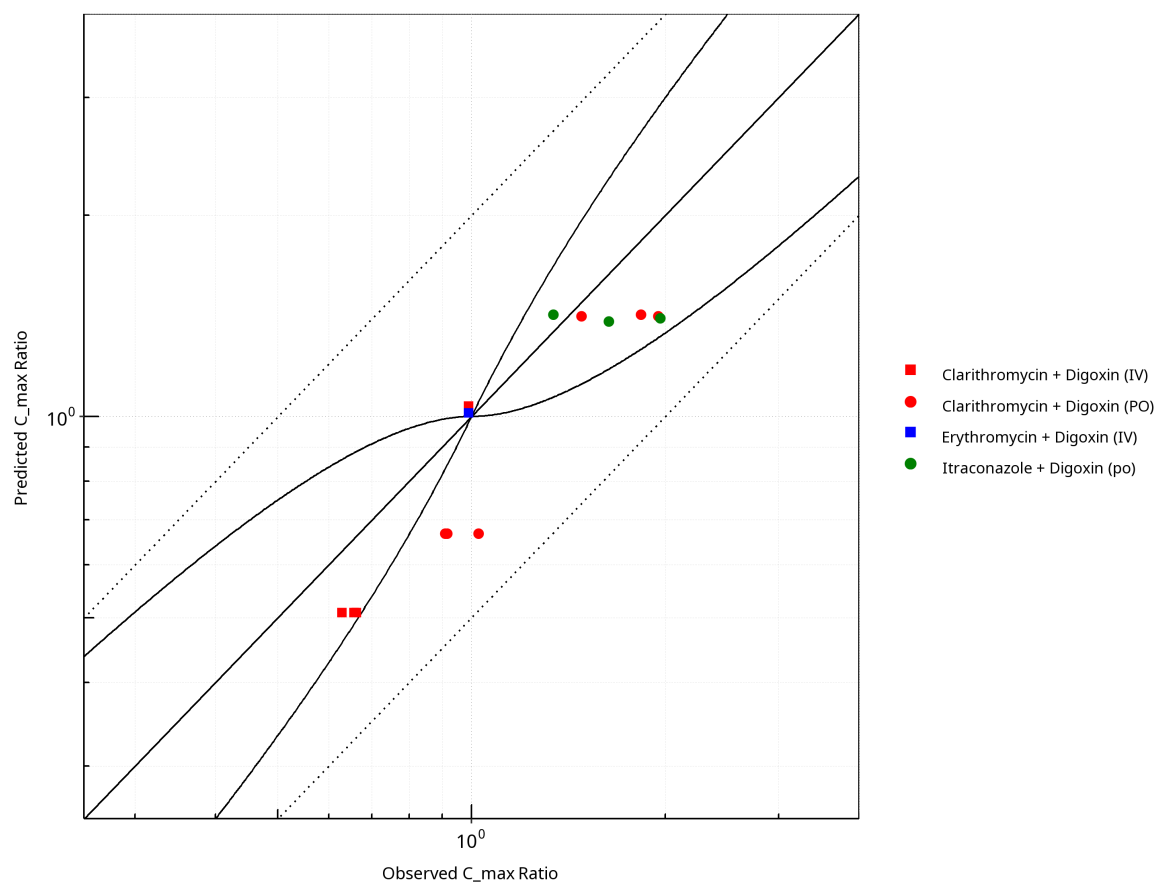


Figure 2-15: Pgp DDI. Mechanism: Reversible Inhibition. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

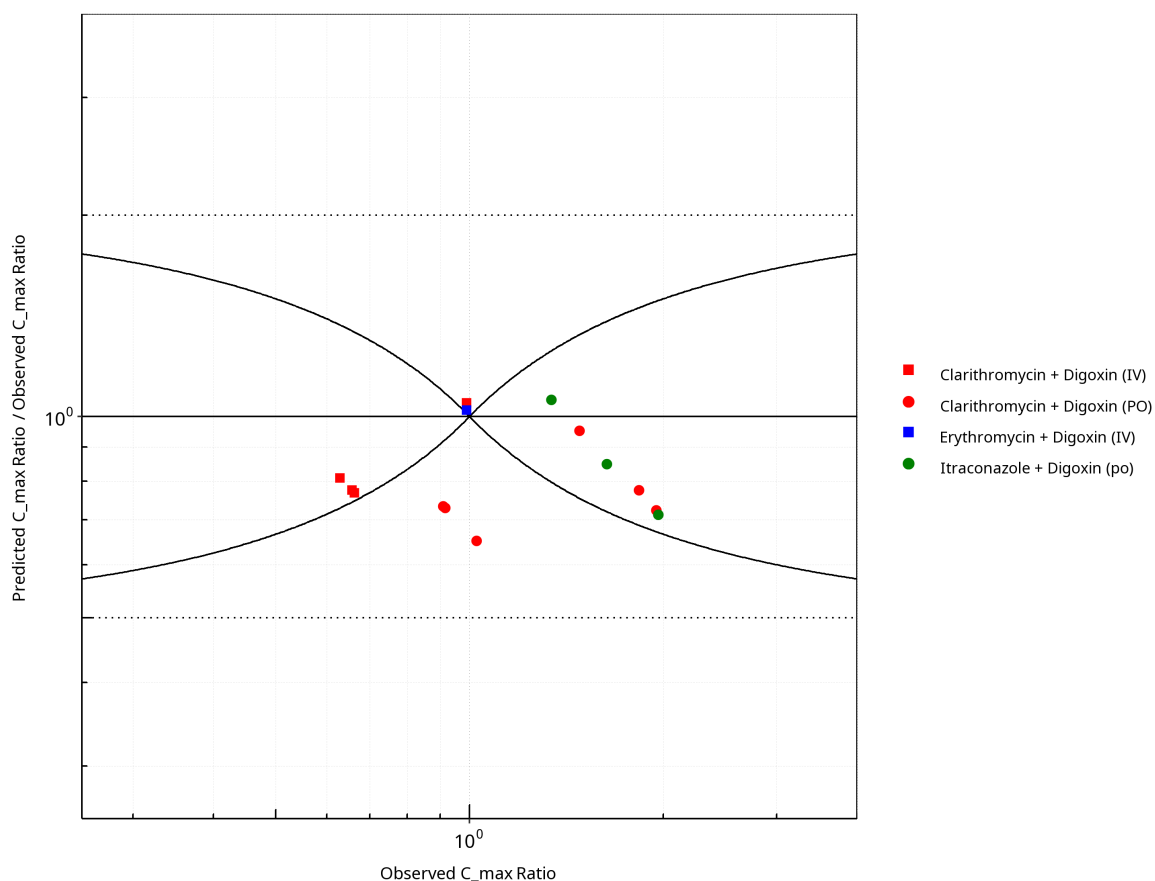


Figure 2-16: Pgp DDI. Mechanism: Reversible Inhibition. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-11: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC _{tEnd}	1.12
C _{max}	1.24

Table 2-12: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	13	-
Points within Guest <i>et al.</i>	11	84.62
Points within 2 fold	13	100.00

Table 2-13: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	14	-
Points within Guest <i>et al.</i>	9	64.29
Points within 2 fold	14	100.00

2.2 Perpetrator

2.2.1 Clarithromycin

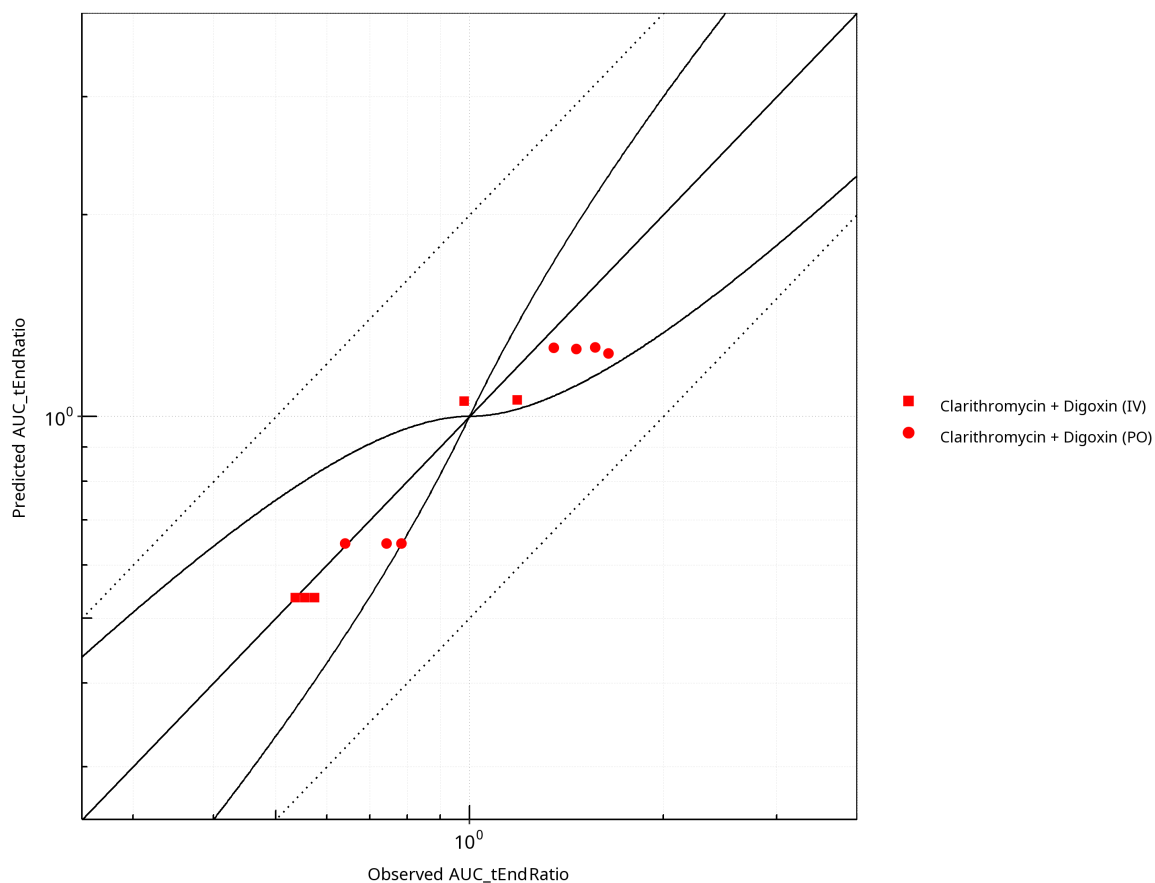


Figure 2-17: Pgp DDI. Perpetrator: Clarithromycin. Predicted vs. Observed AUC_{tEndRatio}. ($\delta = 1$ in Guest *et al.* formula)

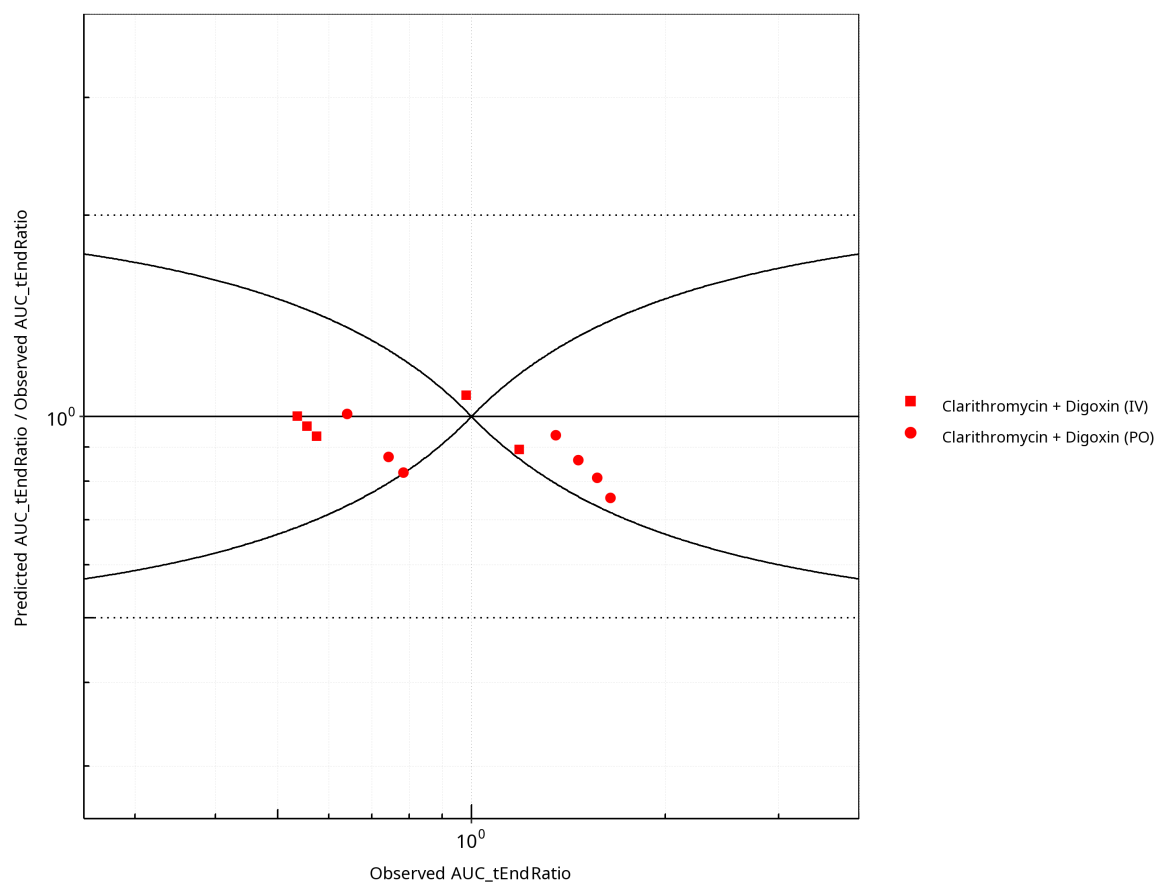


Figure 2-18: Pgp DDI. Perpetrator: Clarithromycin. Predicted/Observed vs. Observed AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

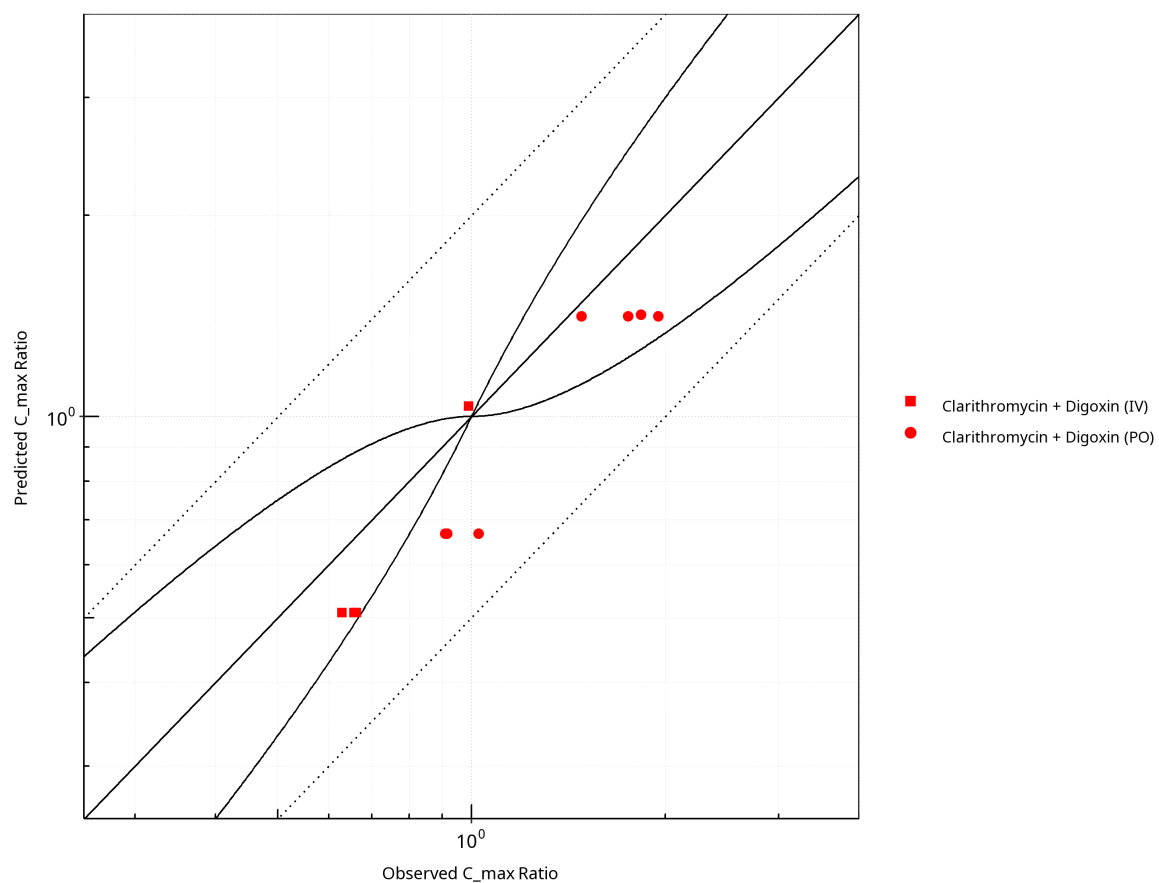


Figure 2-19: Pgp DDI. Perpetrator: Clarithromycin. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

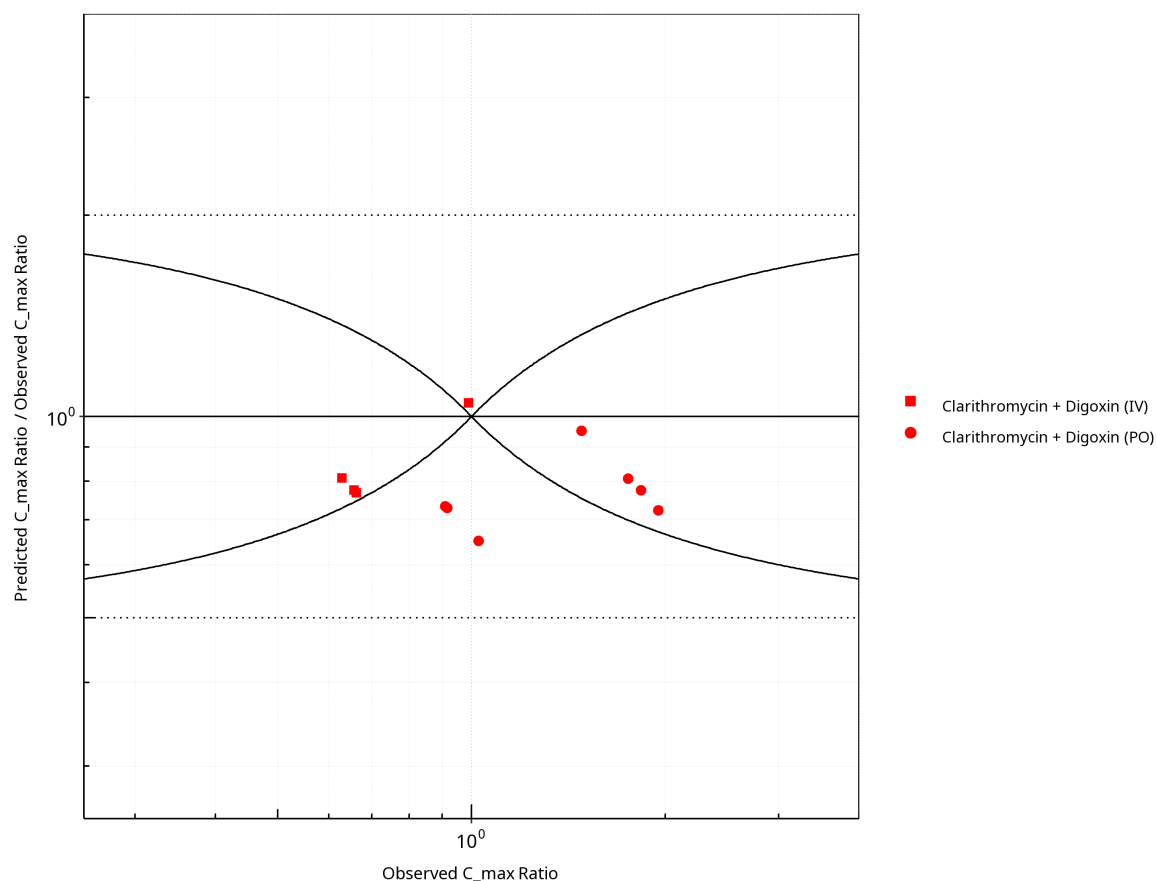


Figure 2-20: Pgp DDI. Perpetrator: Clarithromycin. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-14: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC _{tEnd}	1.12
C _{max}	1.27

Table 2-15: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	12	-
Points within Guest <i>et al.</i>	11	91.67
Points within 2 fold	12	100.00

Table 2-16: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	11	-
Points within Guest <i>et al.</i>	7	63.64
Points within 2 fold	11	100.00

2.2.2 Erythromycin

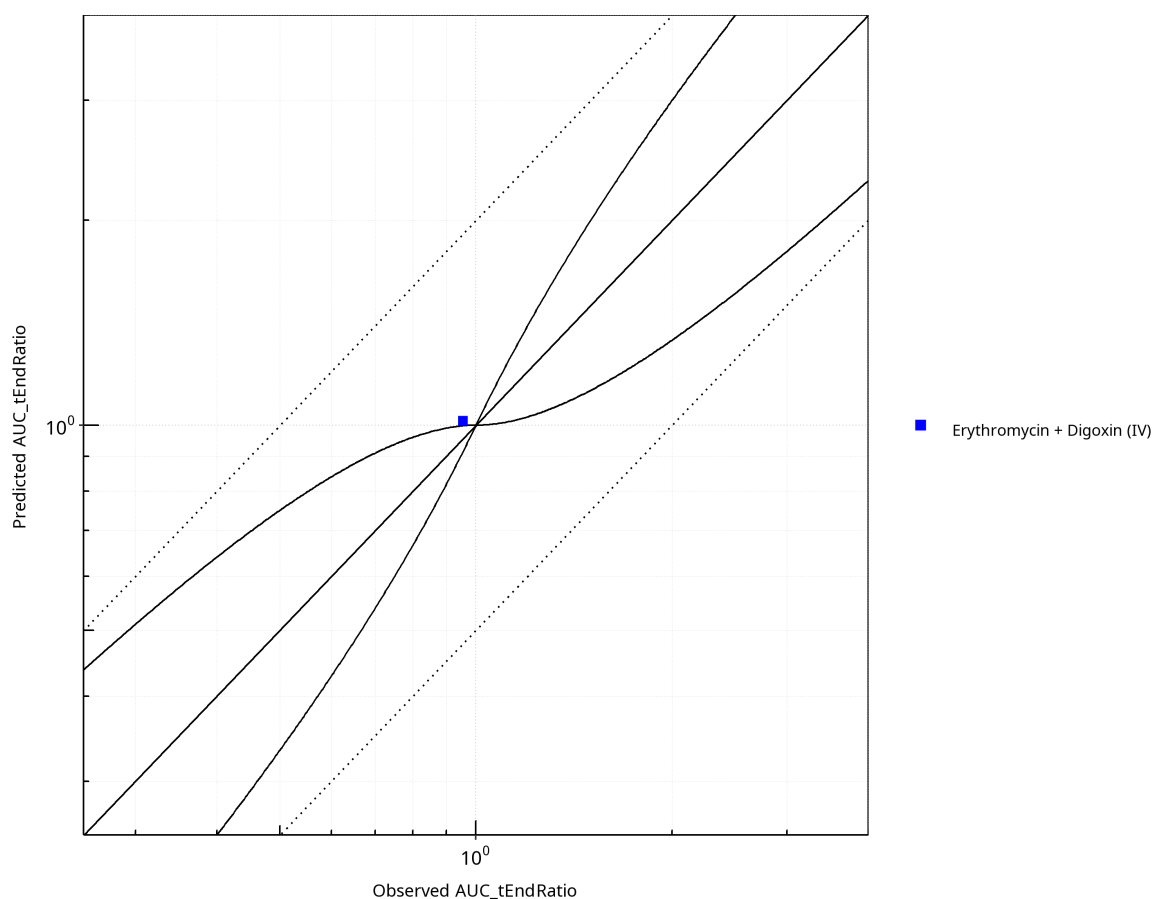


Figure 2-21: Pgp DDI. Perpetrator: Erythromycin. Predicted vs. Observed AUC_{tEndRatio}. ($\delta = 1$ in Guest *et al.* formula)

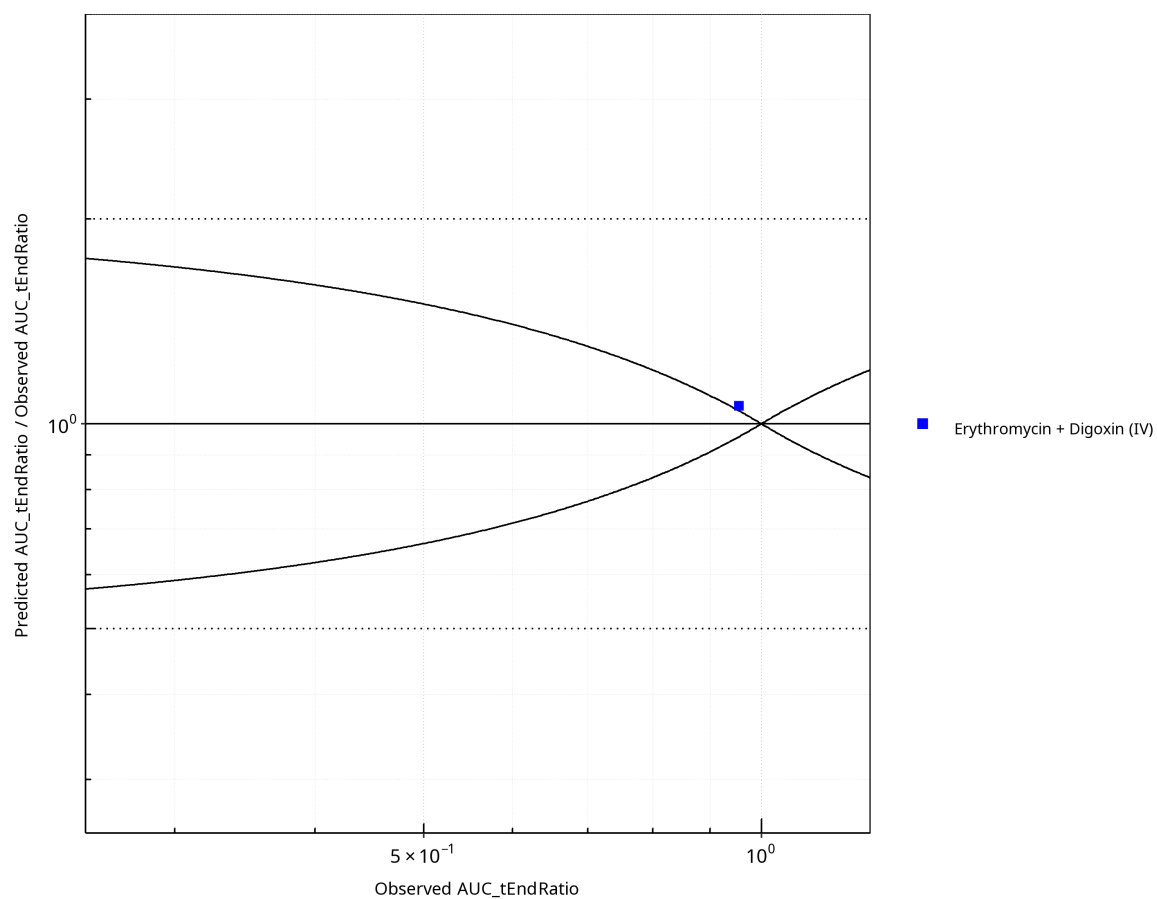


Figure 2-22: Pgp DDI. Perpetrator: Erythromycin. Predicted/Observed vs. Observed AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

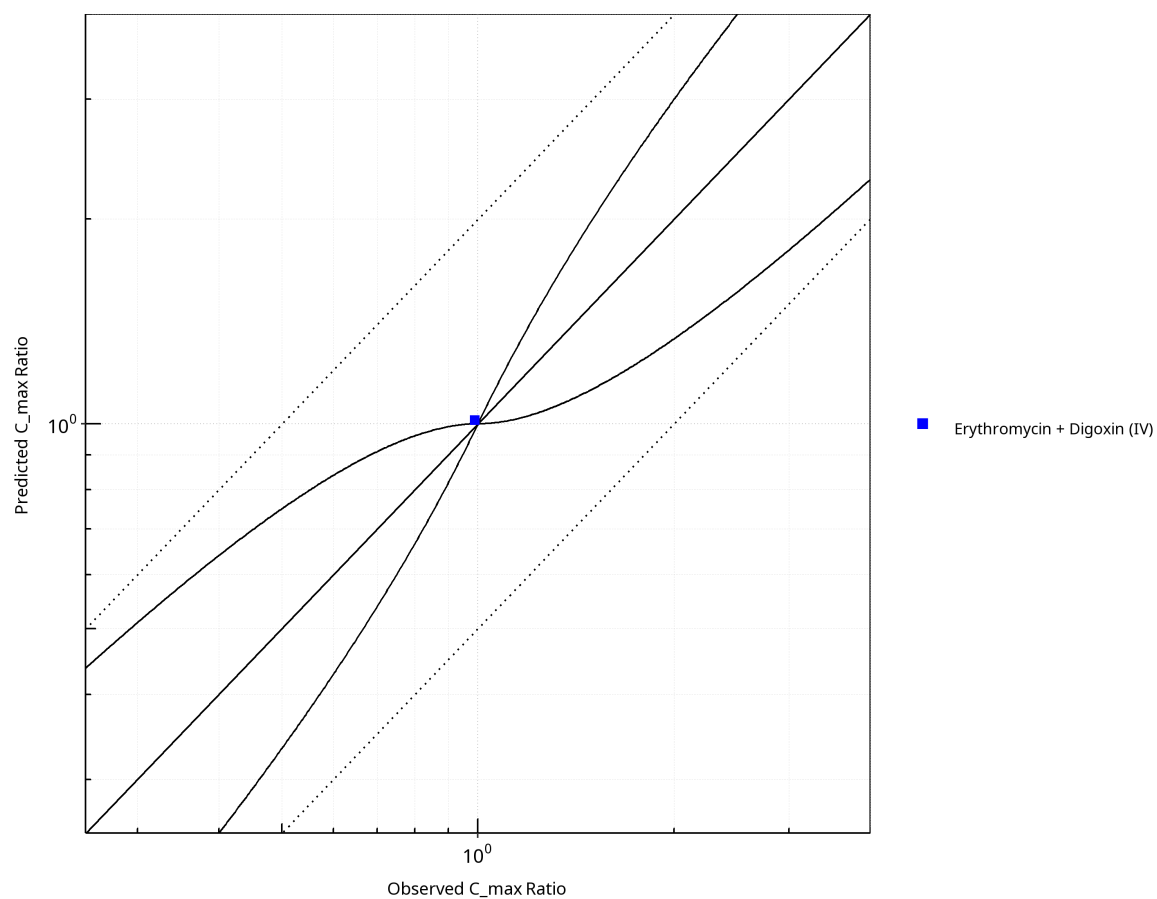


Figure 2-23: Pgp DDI. Perpetrator: Erythromycin. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

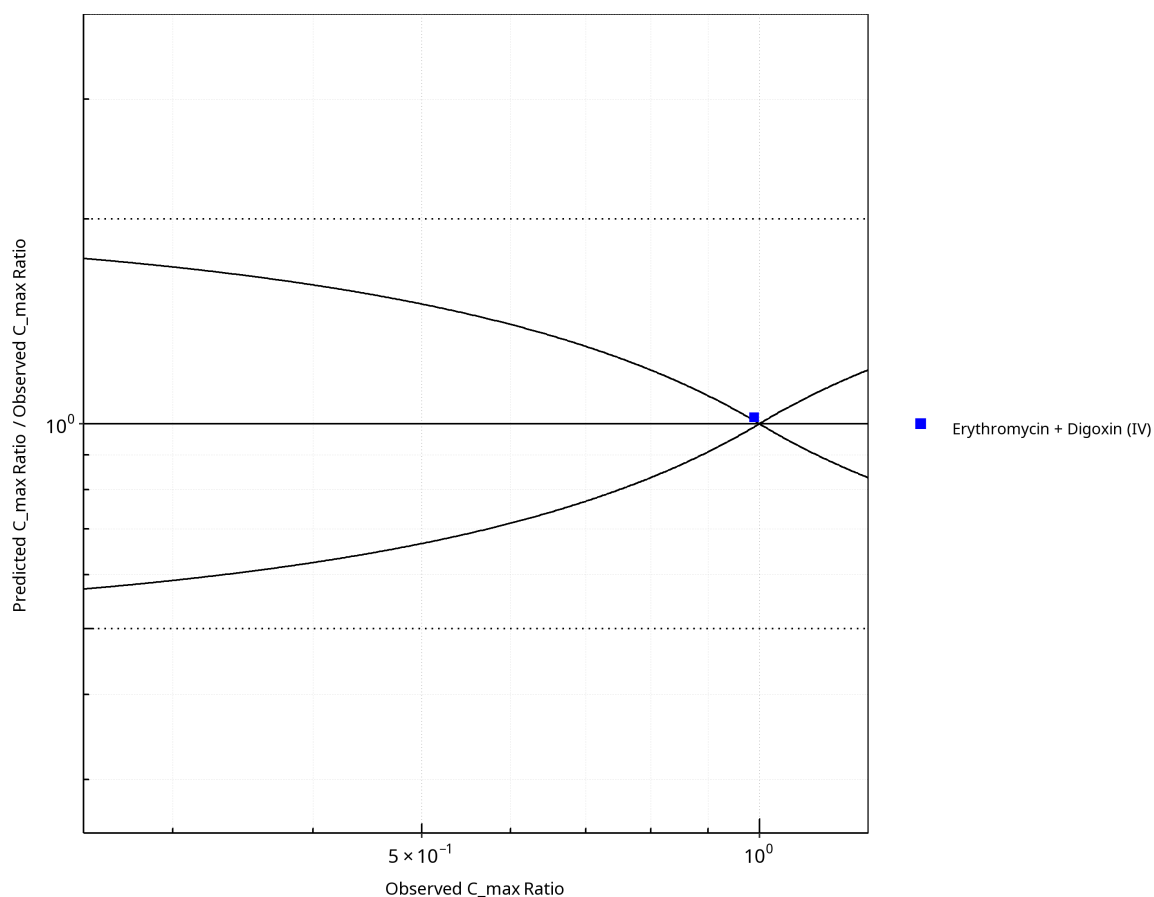


Figure 2-24: Pgp DDI. Perpetrator: Erythromycin. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-17: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC _{tEnd}	1.06
C _{max}	1.02

Table 2-18: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	1	-
Points within Guest <i>et al.</i>	0	0
Points within 2 fold	1	100

Table 2-19: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	1	-
Points within Guest <i>et al.</i>	0	0
Points within 2 fold	1	100

2.2.3 Itraconazole

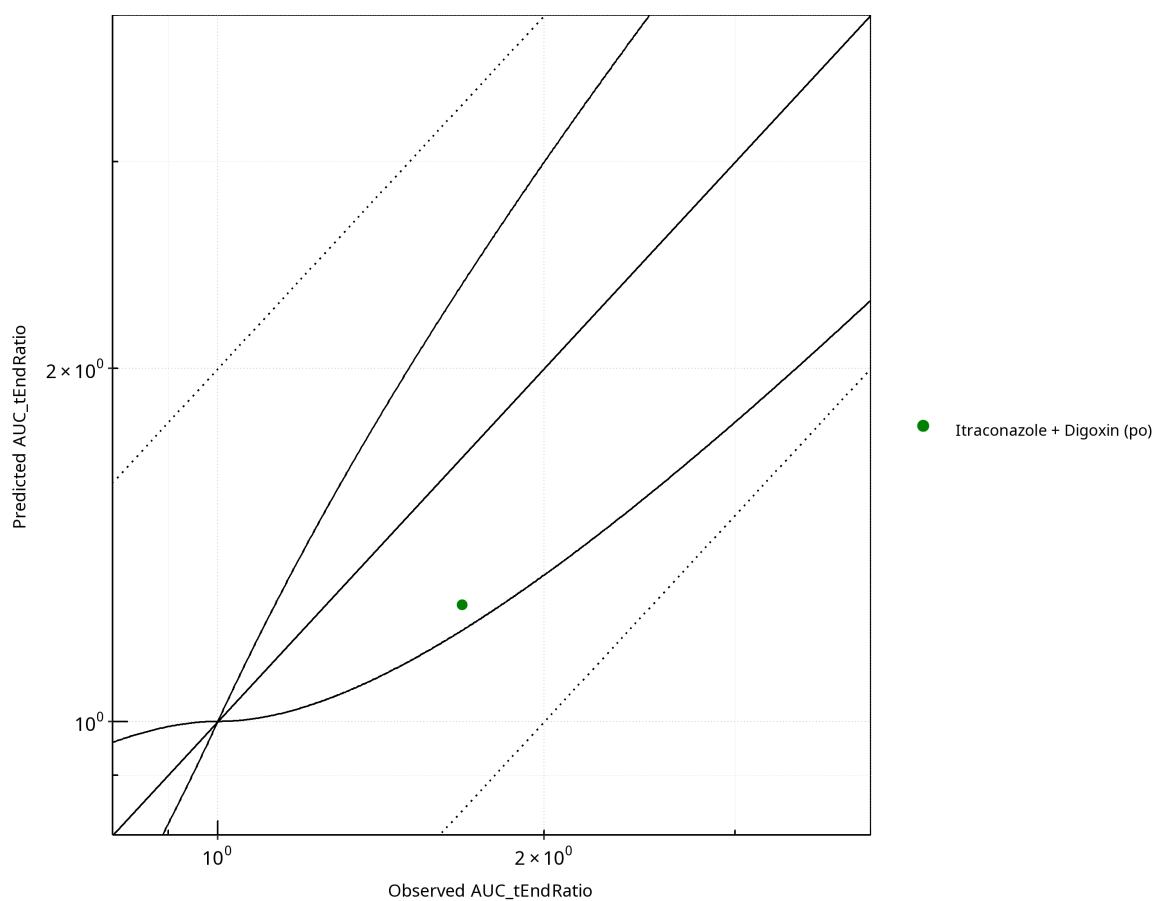


Figure 2-25: Pgp DDI. Perpetrator: Itraconazole. Predicted vs. Observed AUC_{tEndRatio}. ($\delta = 1$ in Guest *et al.* formula)

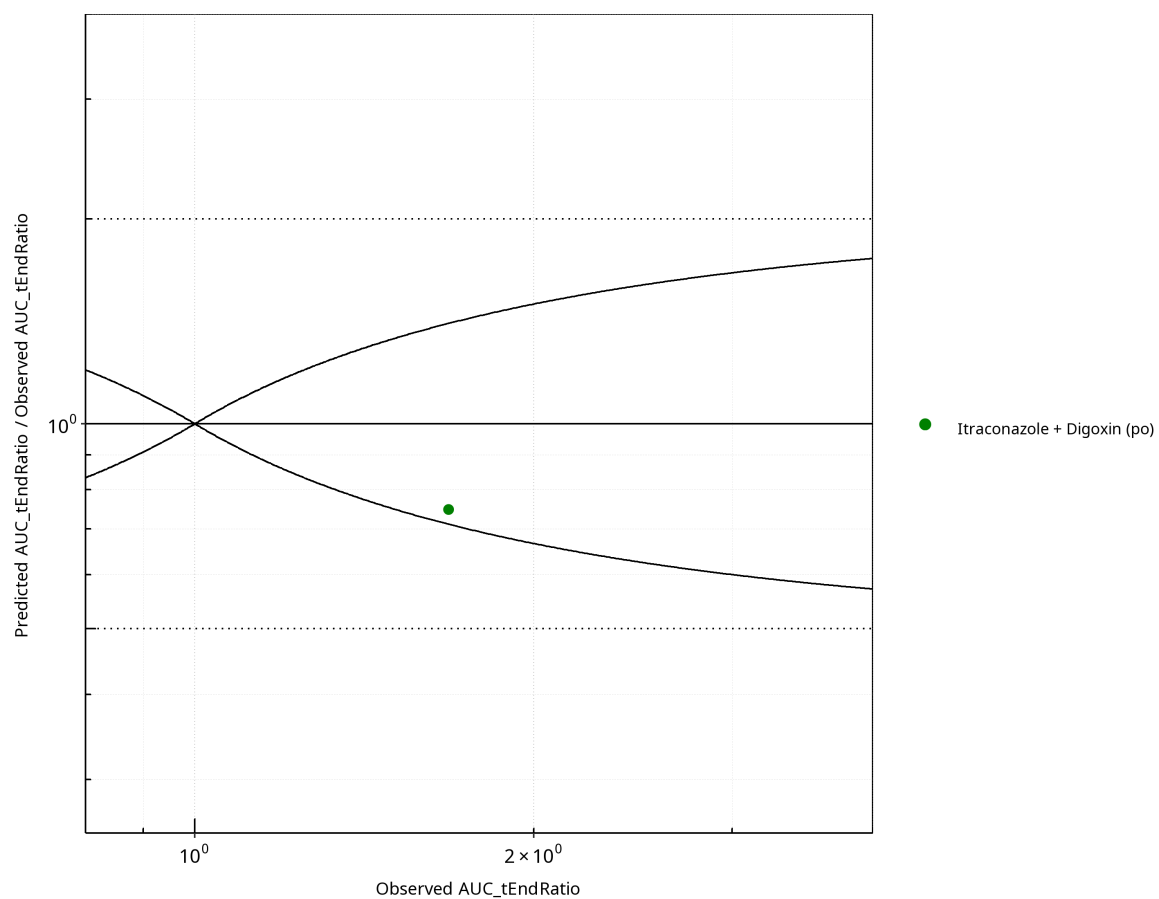


Figure 2-26: Pgp DDI. Perpetrator: Itraconazole. Predicted/Observed vs. Observed AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

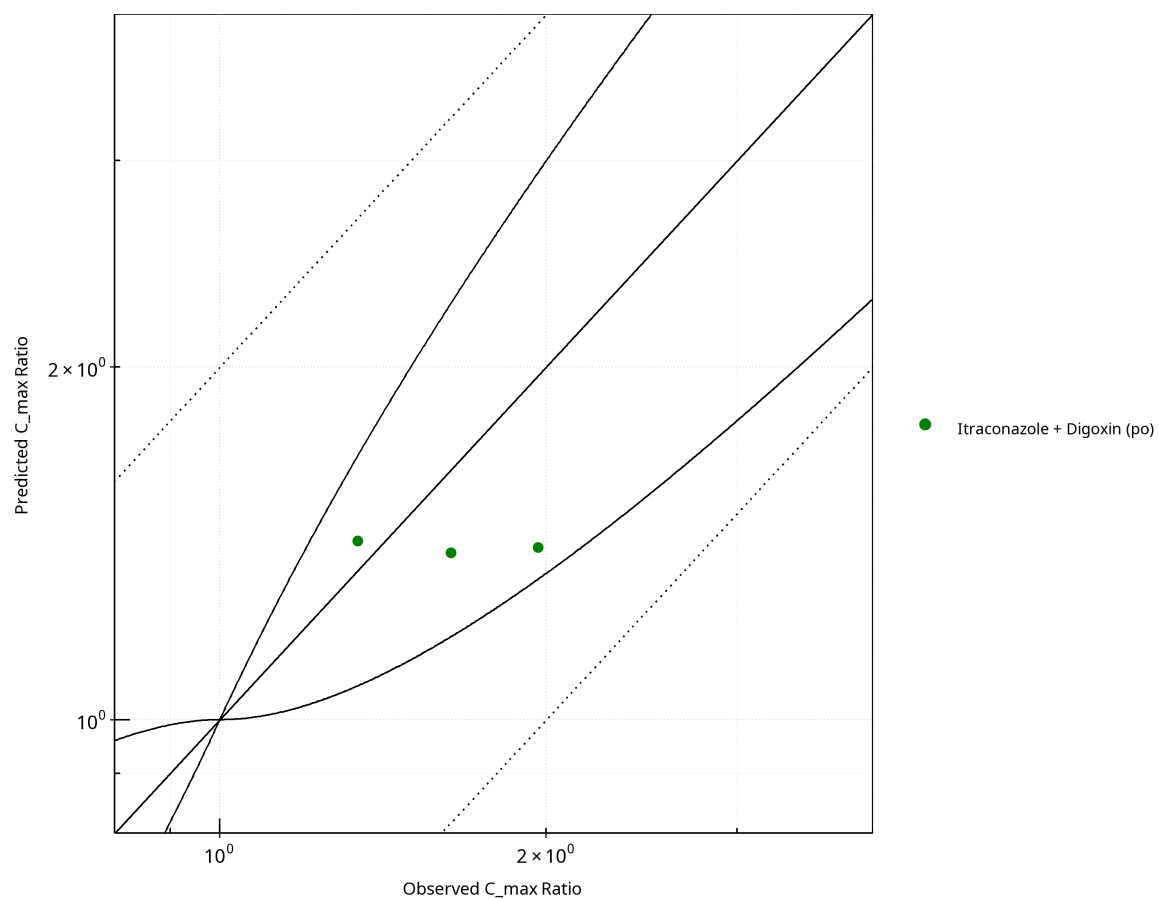


Figure 2-27: Pgp DDI. Perpetrator: Itraconazole. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

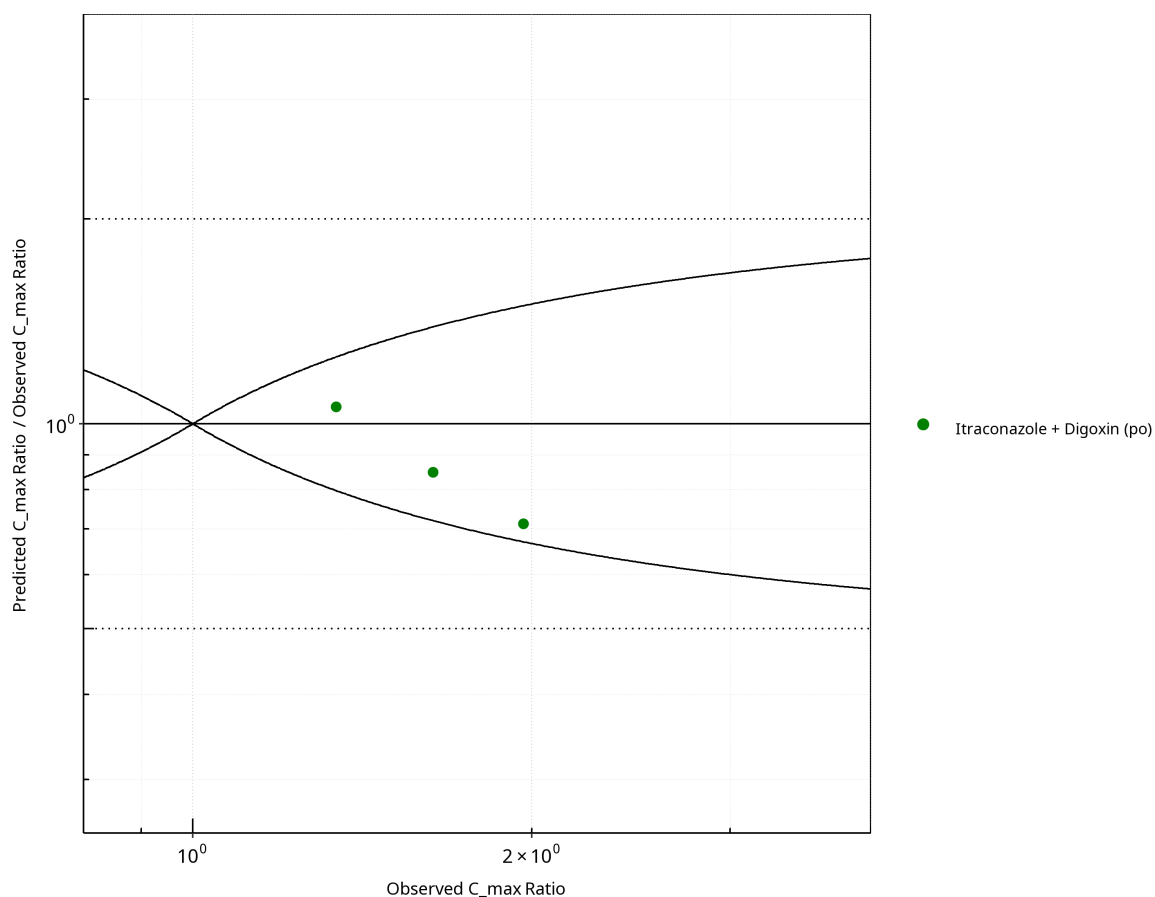


Figure 2-28: Pgp DDI. Perpetrator: Itraconazole. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-20: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC_tEnd	1.33
C _{max}	1.20

Table 2-21: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	1	-
Points within Guest <i>et al.</i>	1	100
Points within 2 fold	1	100

Table 2-22: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	3	-
Points within Guest <i>et al.</i>	3	100
Points within 2 fold	3	100

2.2.4 Rifampicin

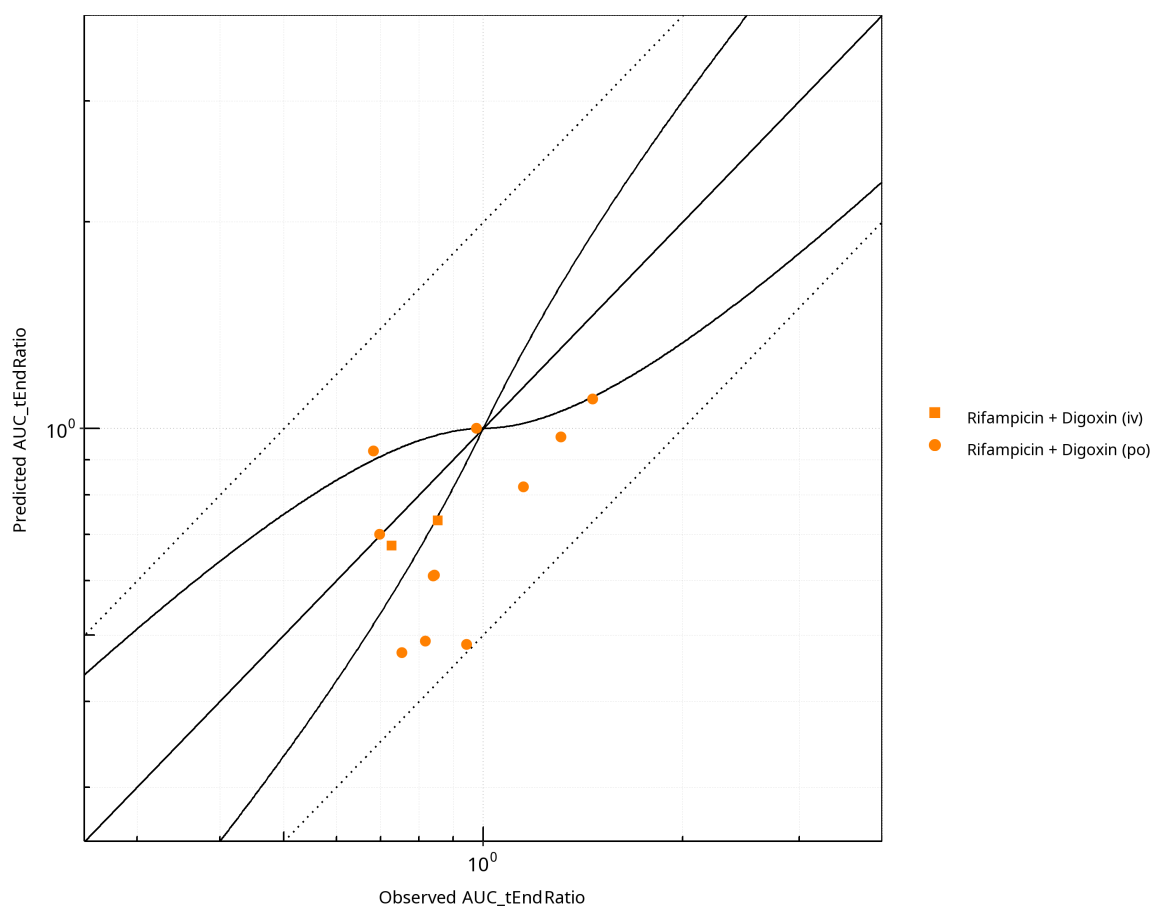


Figure 2-29: Pgp DDI. Perpetrator: Rifampicin. Predicted vs. Observed AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

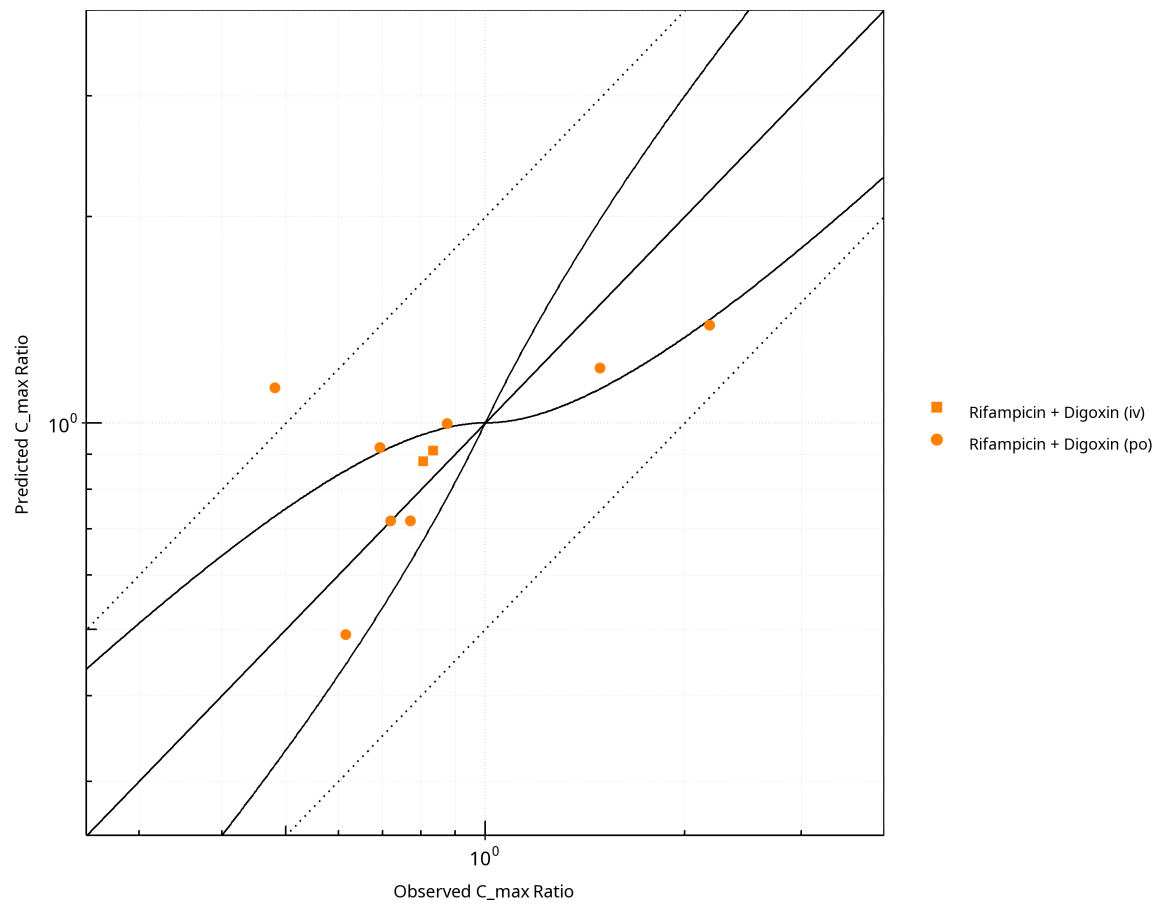


Figure 2-31: Pgp DDI. Perpetrator: Rifampicin. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

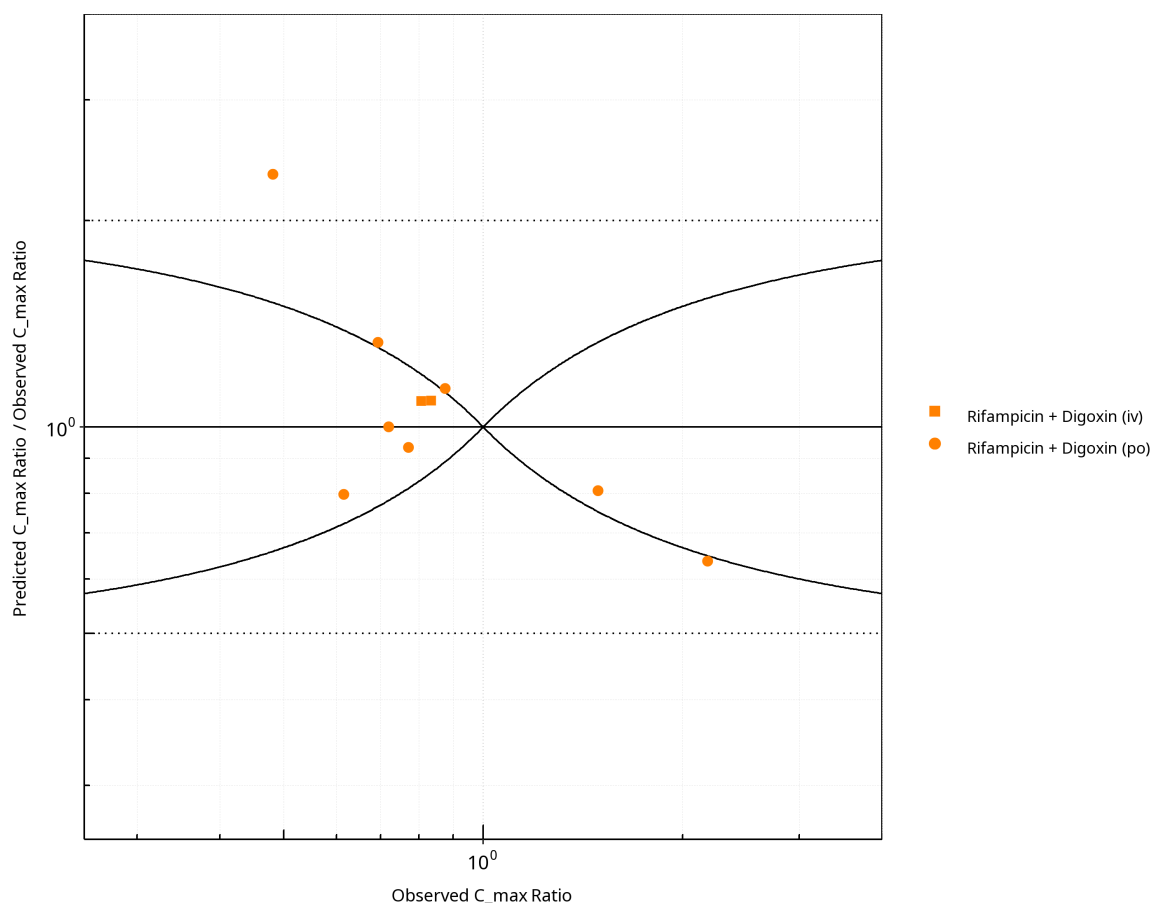


Figure 2-32: Pgp DDI. Perpetrator: Rifampicin. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-23: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC _{tEnd}	1.33
C _{max}	1.27

Table 2-24: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	13	-
Points within Guest <i>et al.</i>	2	15.38
Points within 2 fold	13	100.00

Table 2-25: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	10	-
Points within Guest <i>et al.</i>	6	60
Points within 2 fold	9	90

2.2.5 Verapamil

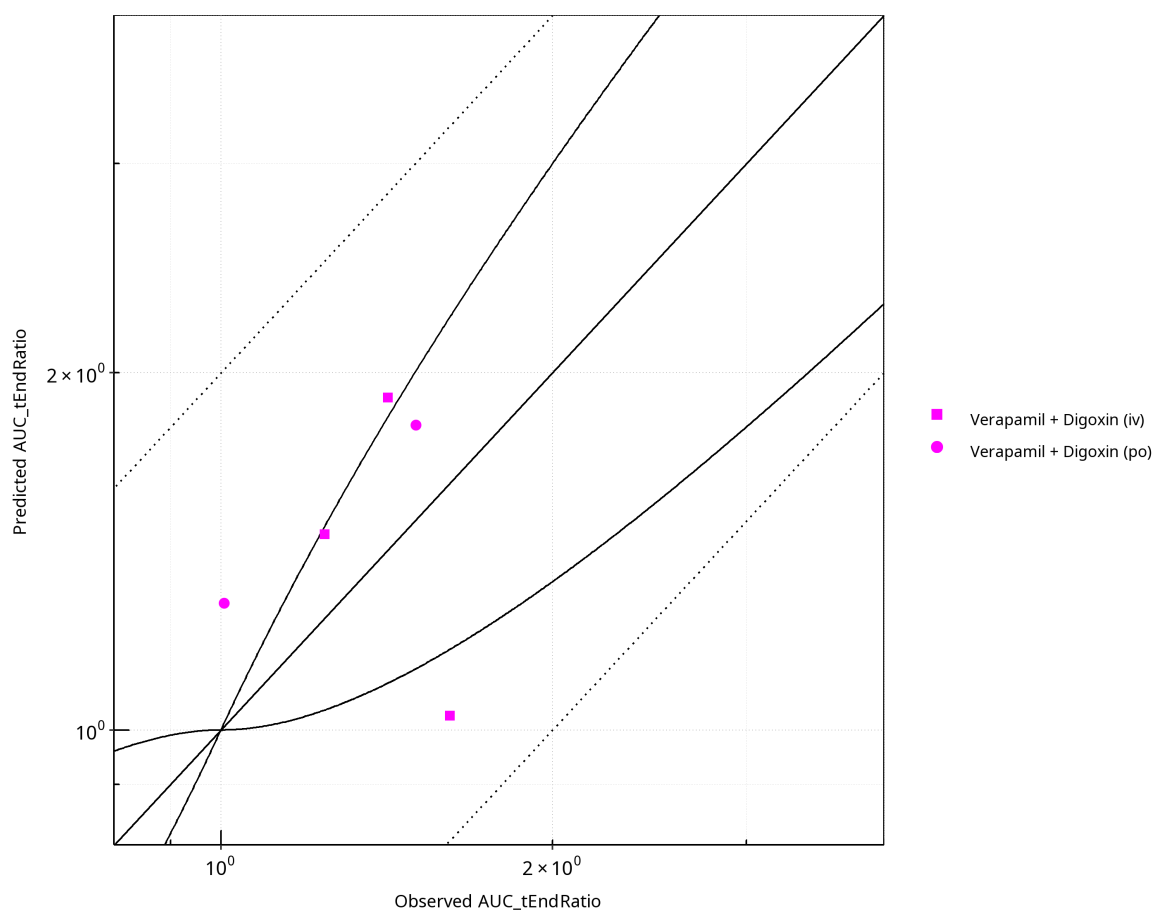


Figure 2-33: Pgp DDI. Perpetrator: Verapamil. Predicted vs. Observed AUC_{tEndRatio}. ($\delta = 1$ in Guest *et al.* formula)

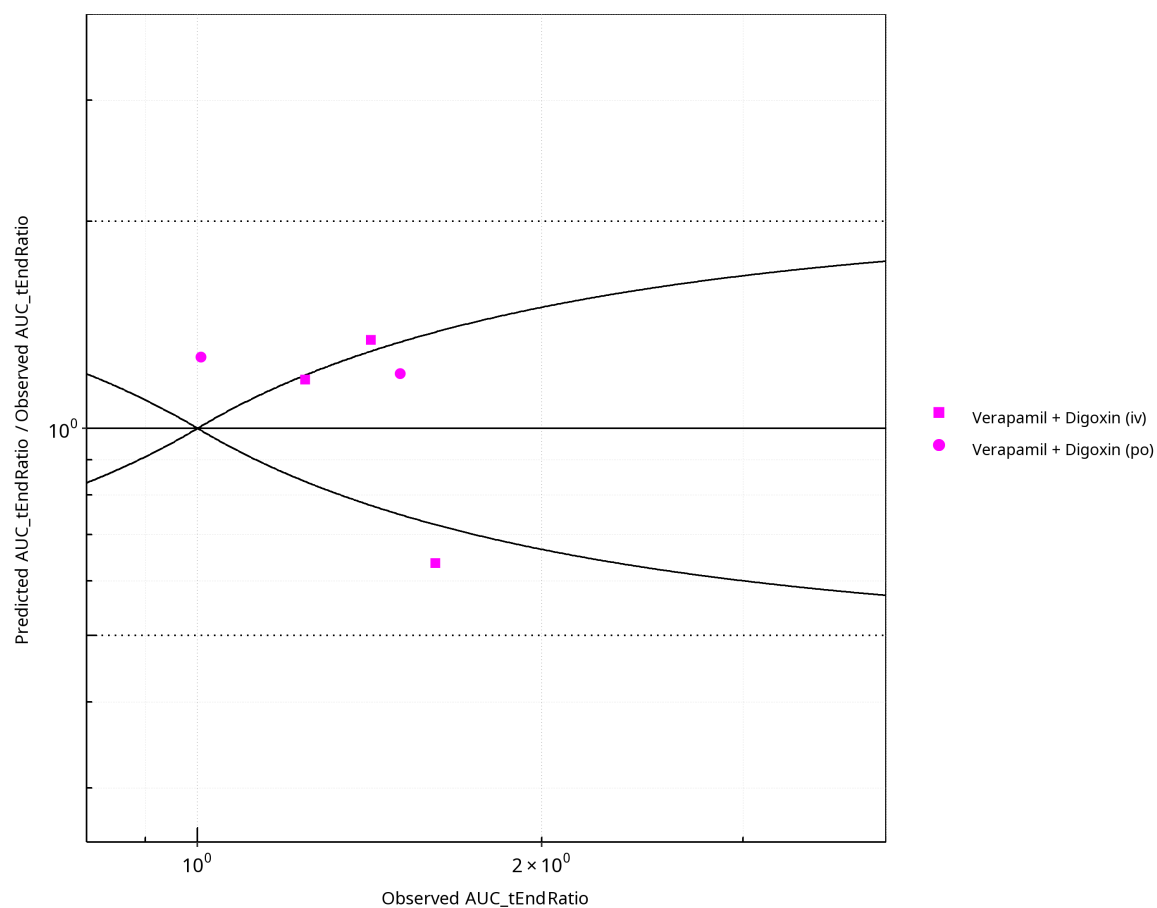


Figure 2-34: Pgp DDI. Perpetrator: Verapamil. Predicted/Observed vs. Observed AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

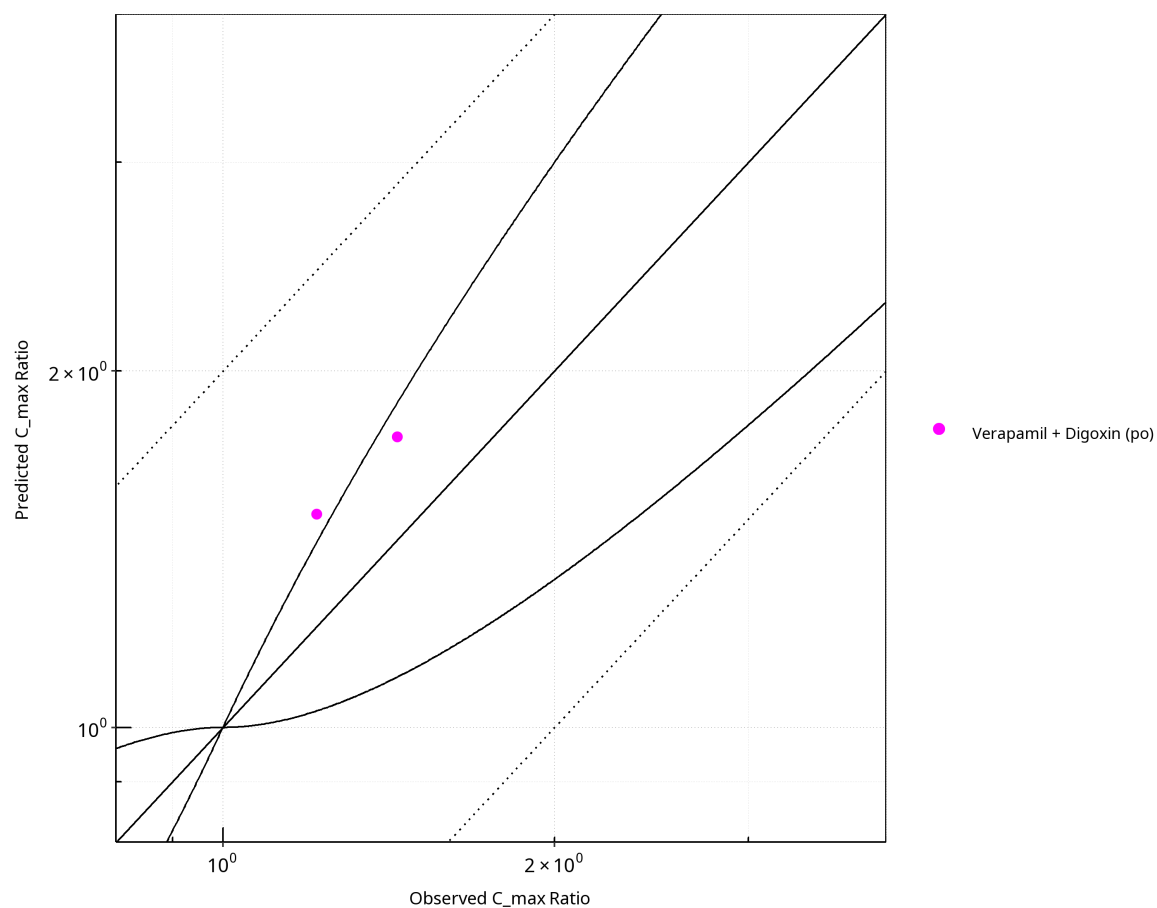


Figure 2-35: Pgp DDI. Perpetrator: Verapamil. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

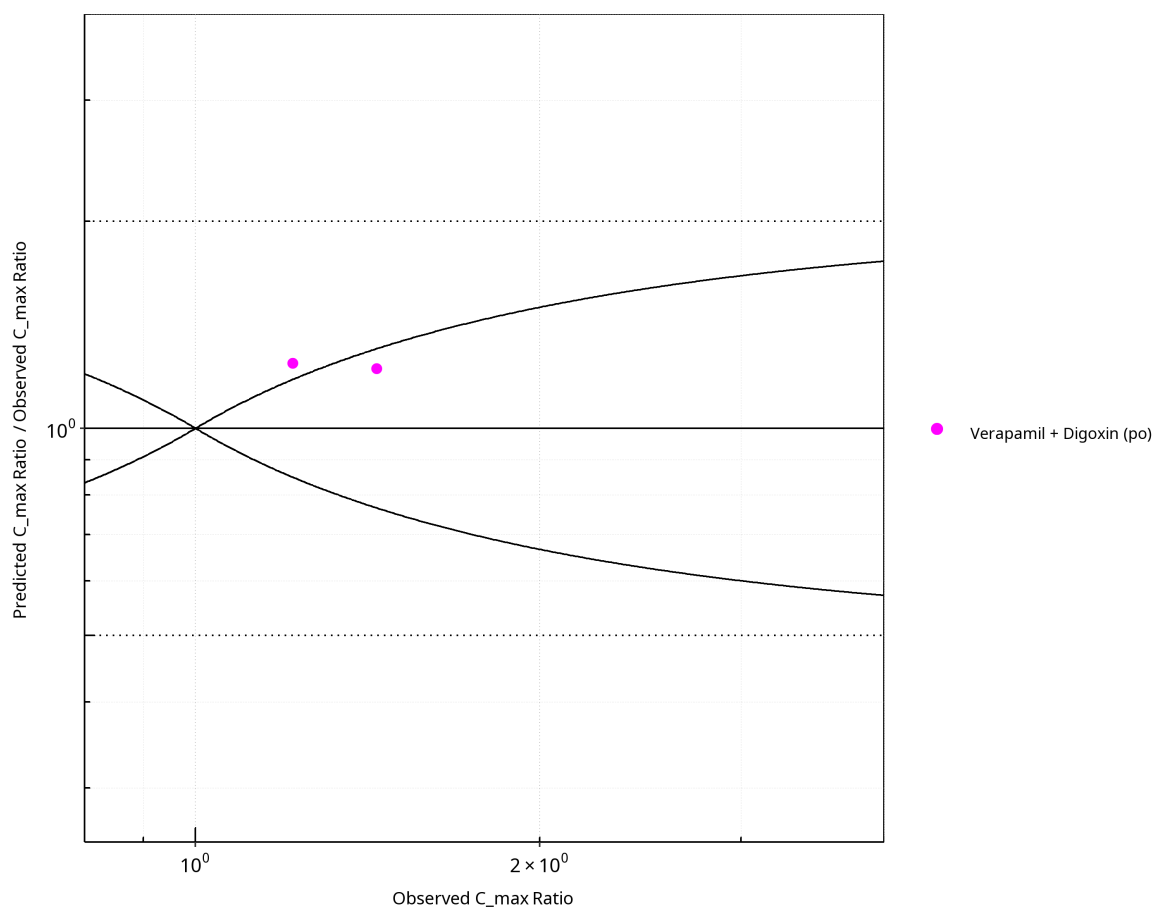


Figure 2-36: Pgp DDI. Perpetrator: Verapamil. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-26: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC_tEnd	1.31
C _{max}	1.23

Table 2-27: Summary table for Pgp DDI - AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC_tEnd	Number	Ratio [%]
Points total	5	-
Points within Guest <i>et al.</i>	2	40
Points within 2 fold	5	100

Table 2-28: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	2	-
Points within Guest <i>et al.</i>	1	50
Points within 2 fold	2	100

2.3 Victim

2.3.1 Digoxin

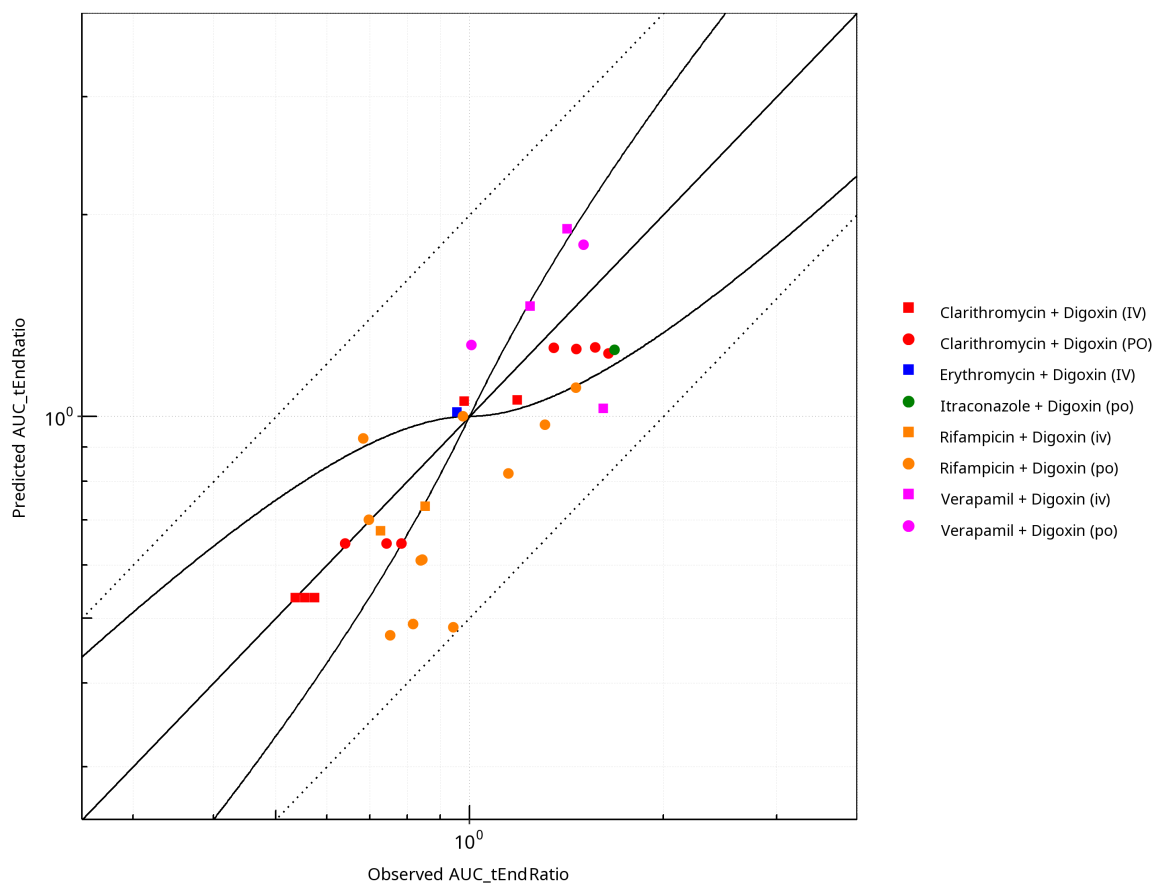


Figure 2-37: Pgp DDI. Victim: Digoxin. Predicted vs. Observed AUC_{tEndRatio}. ($\delta = 1$ in Guest *et al.* formula)

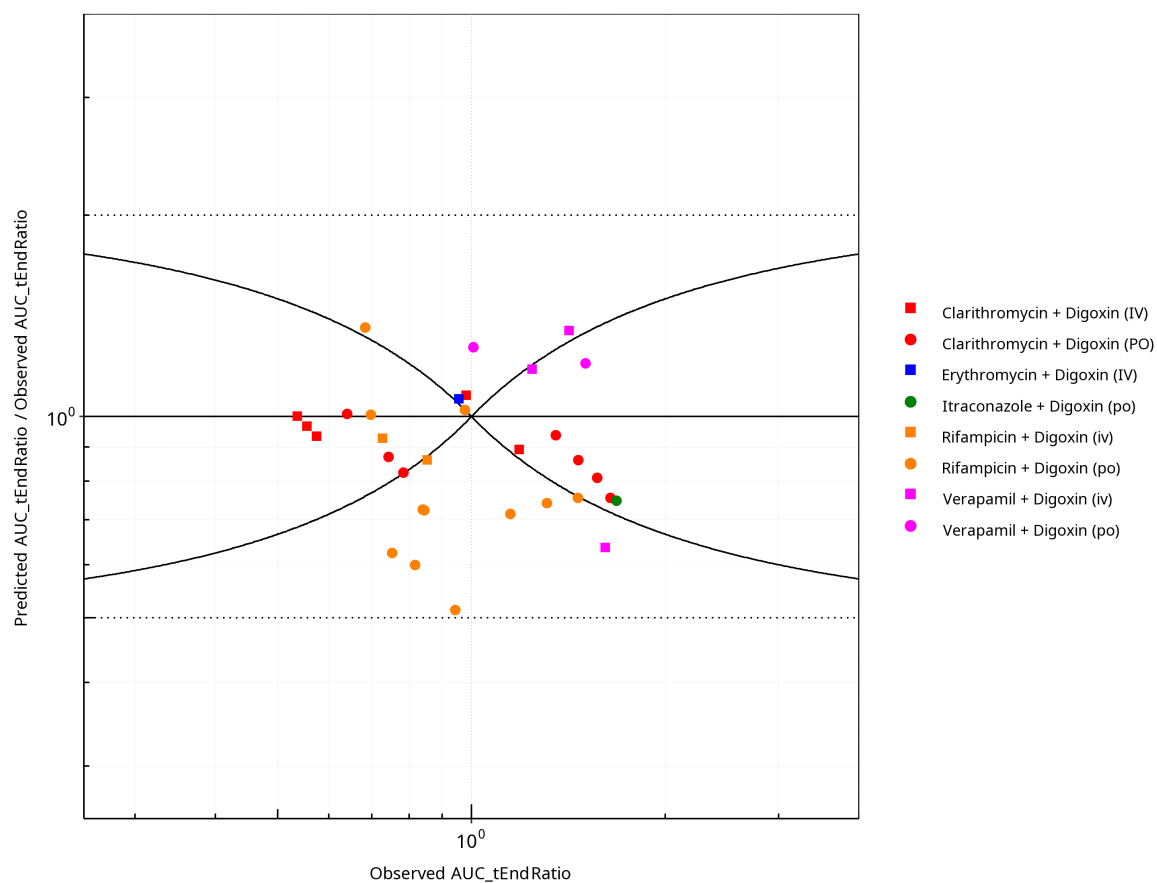


Figure 2-38: Pgp DDI. Victim: Digoxin. Predicted/Observed vs. Observed AUC_tEnd Ratio. ($\delta = 1$ in Guest *et al.* formula)

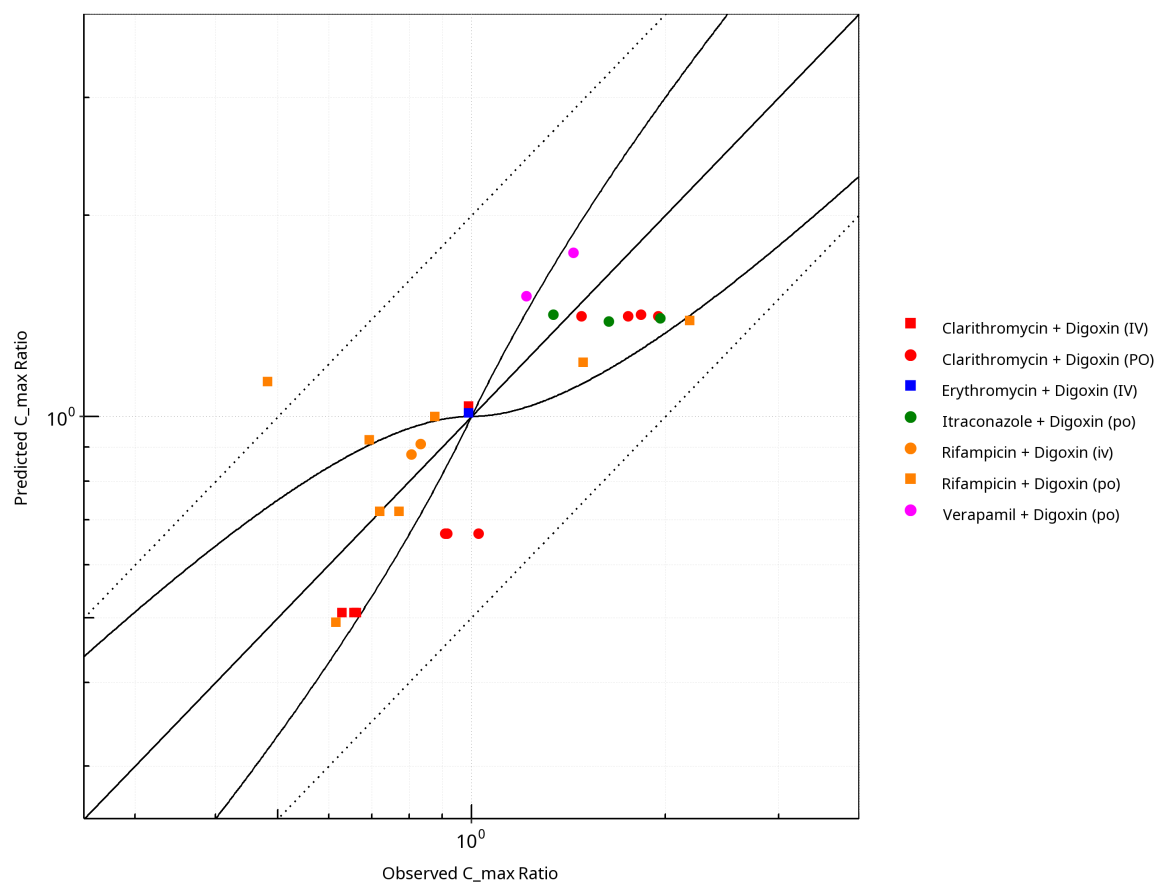


Figure 2-39: Pgp DDI. Victim: Digoxin. Predicted vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

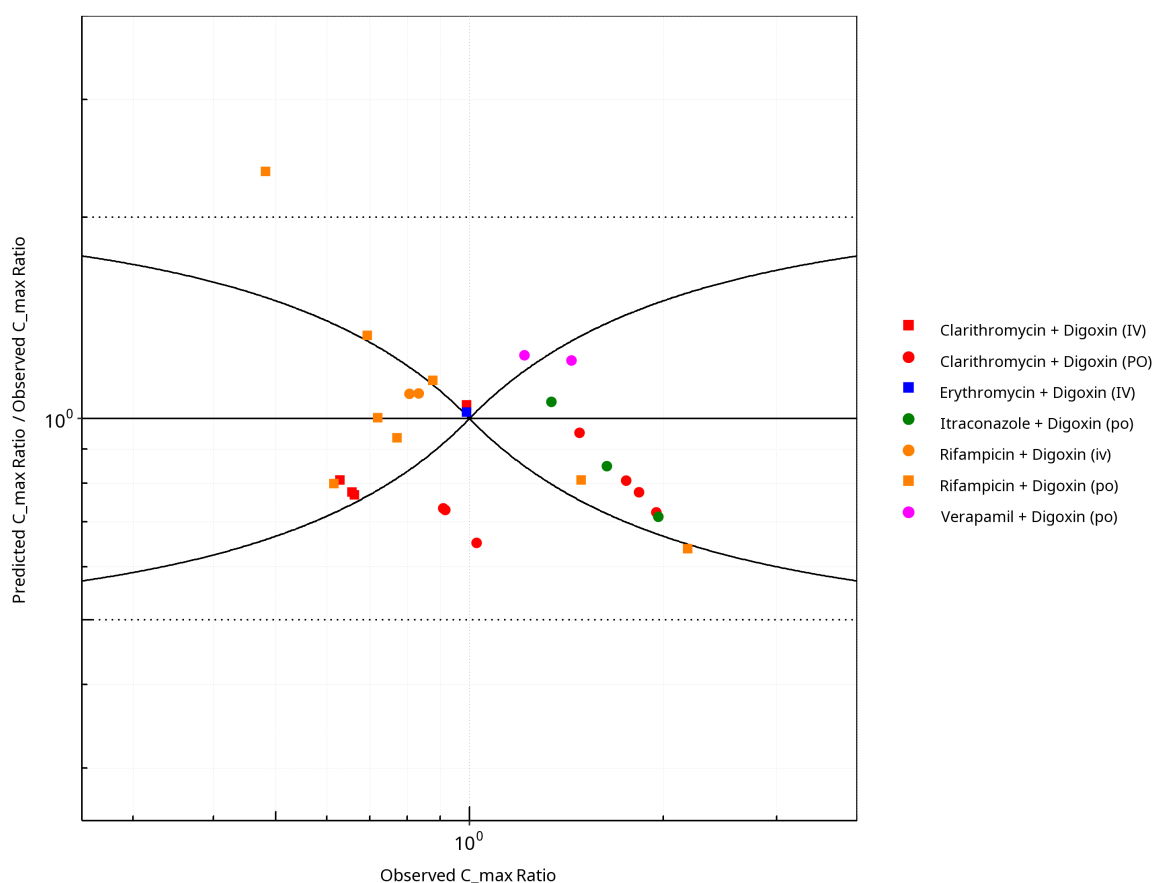


Figure 2-40: Pgp DDI. Victim: Digoxin. Predicted/Observed vs. Observed C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

Table 2-29: GMFE for Pgp DDI Ratio

PK parameter	GMFE
AUC _{tEnd}	1.24
C _{max}	1.25

Table 2-30: Summary table for Pgp DDI - AUC_{tEnd} Ratio. ($\delta = 1$ in Guest *et al.* formula)

AUC _{tEnd}	Number	Ratio [%]
Points total	32	-
Points within Guest <i>et al.</i>	16	50
Points within 2 fold	32	100

Table 2-31: Summary table for Pgp DDI - C_{max} Ratio. ($\delta = 1$ in Guest *et al.* formula)

C _{max}	Number	Ratio [%]
Points total	27	-
Points within Guest <i>et al.</i>	17	62.96
Points within 2 fold	26	96.30

3 Concentration-Time Profiles

The following section shows concentration time profiles of the victim drugs of the simulated DDI studies in comparison to observed data (if available).

3.1 Clarithromycin - Digoxin DDI

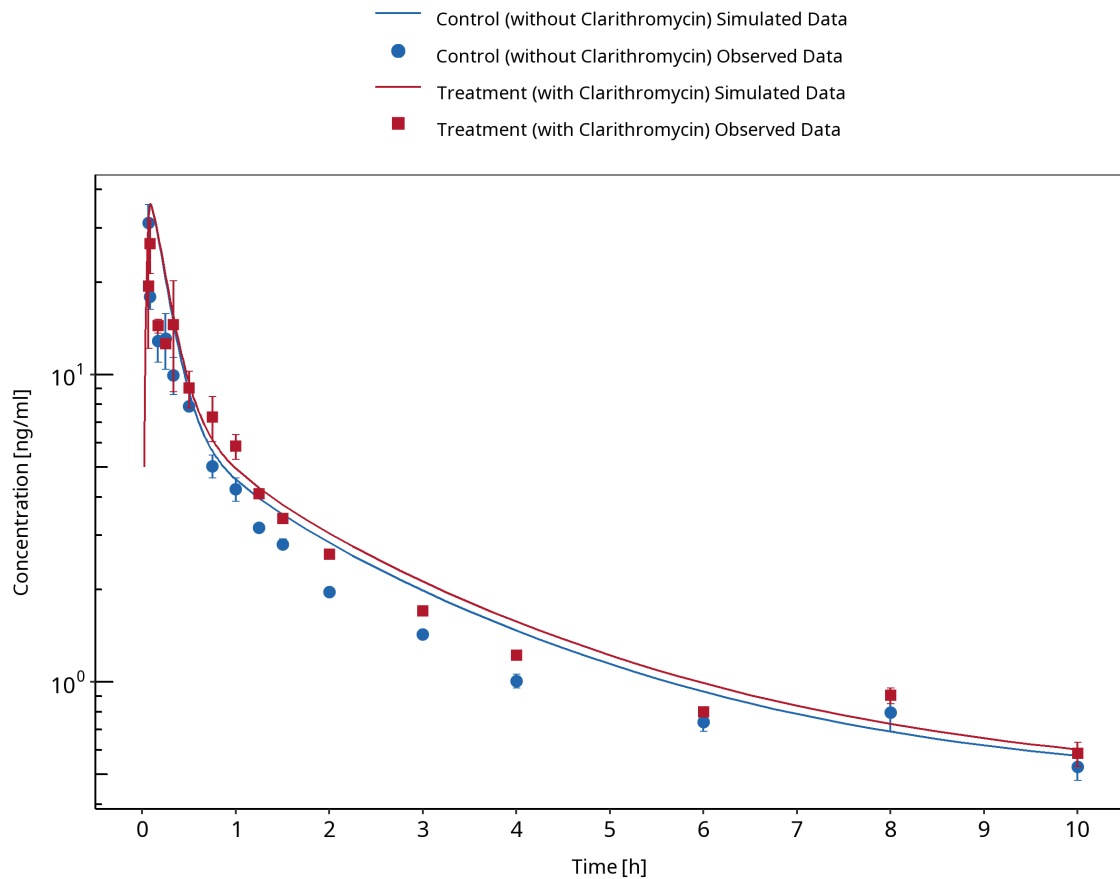


Figure 3-1: Rengelshausen 2003 (0.01 mg/kg IV) - Plasma

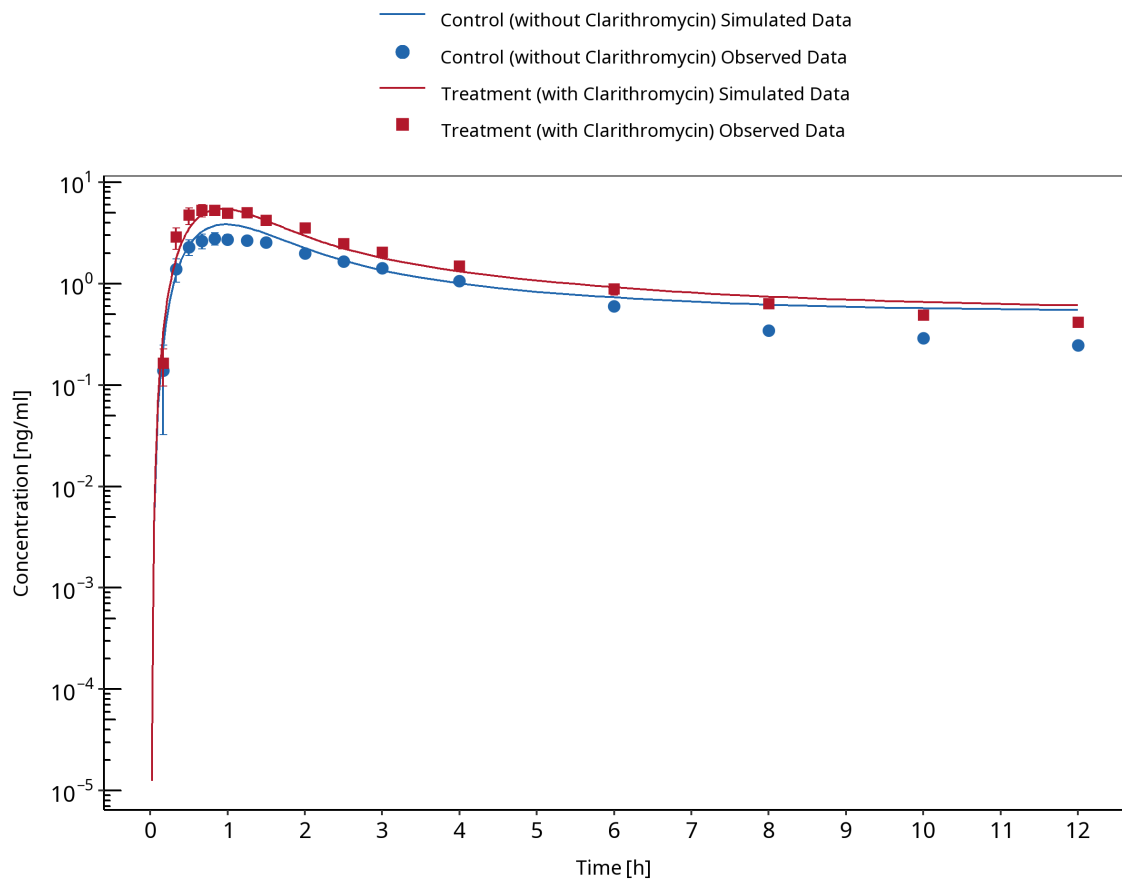


Figure 3-2: Rengelshausen 2003 (0.75 mg PO) - Plasma

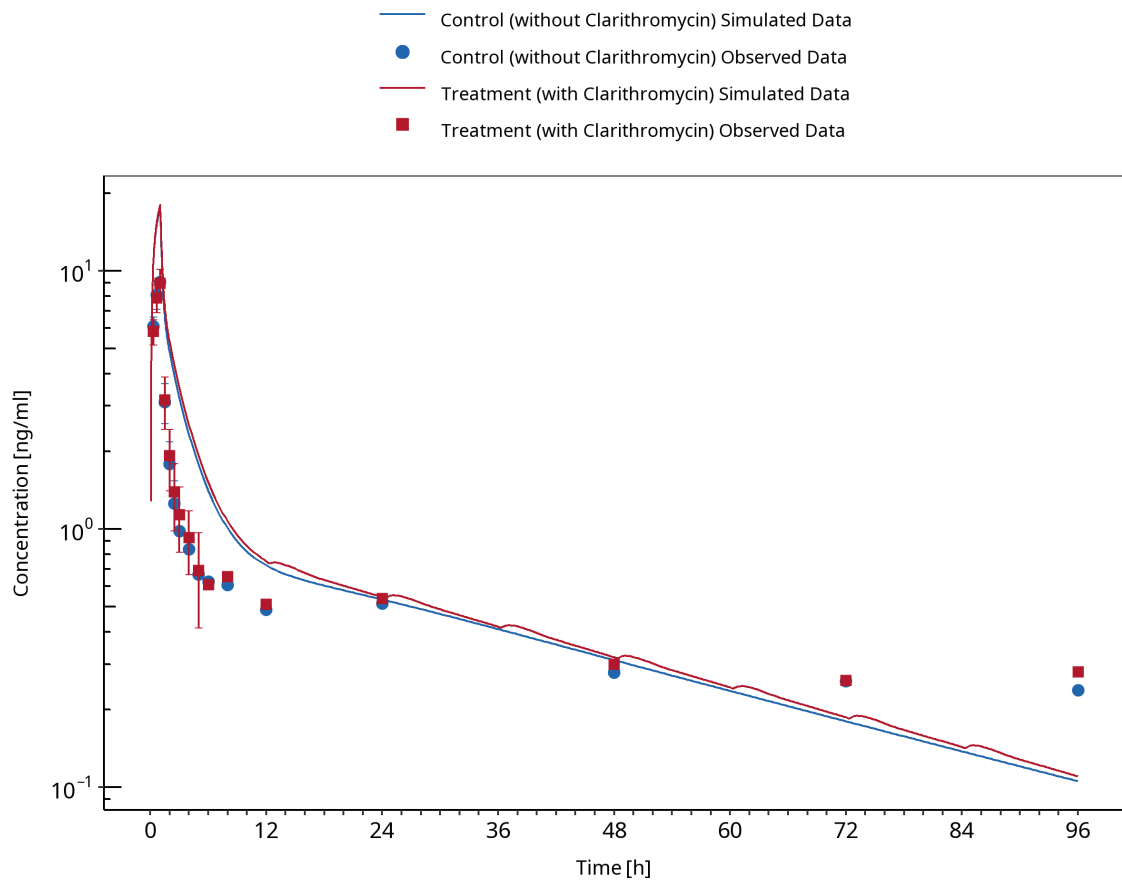


Figure 3-3: Tsutsumi 2002 (0.5mg IV) - Plasma

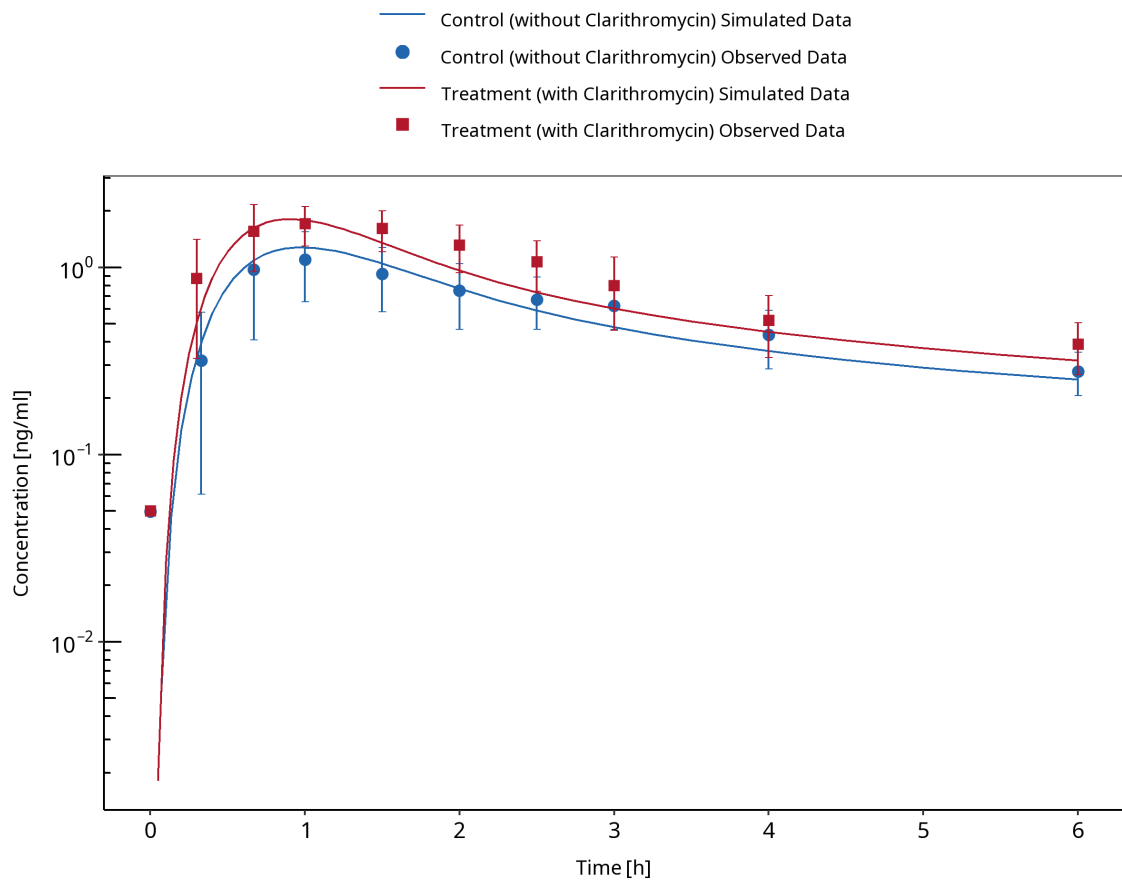


Figure 3-4: Gurley 2008 (0.25 mg PO) - Plasma

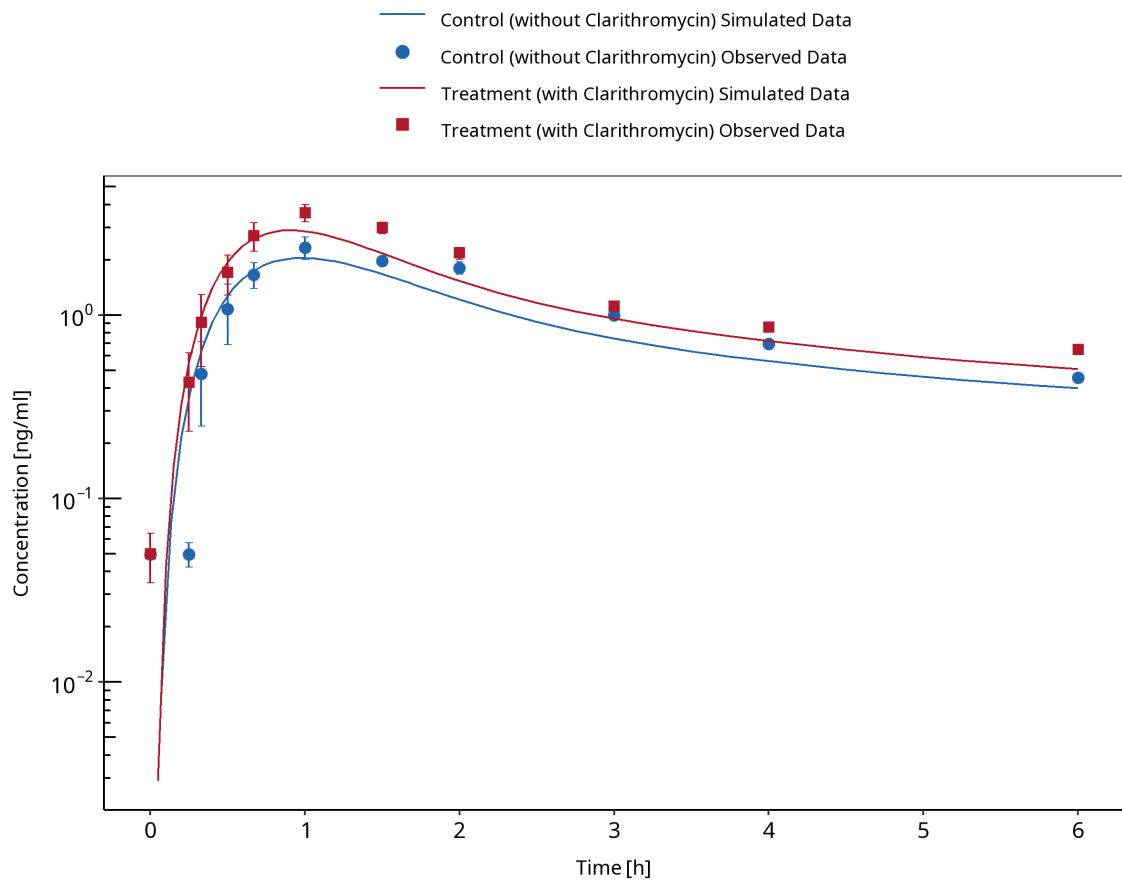


Figure 3-5: Gurley 2006 (0.4 mg PO) - Plasma

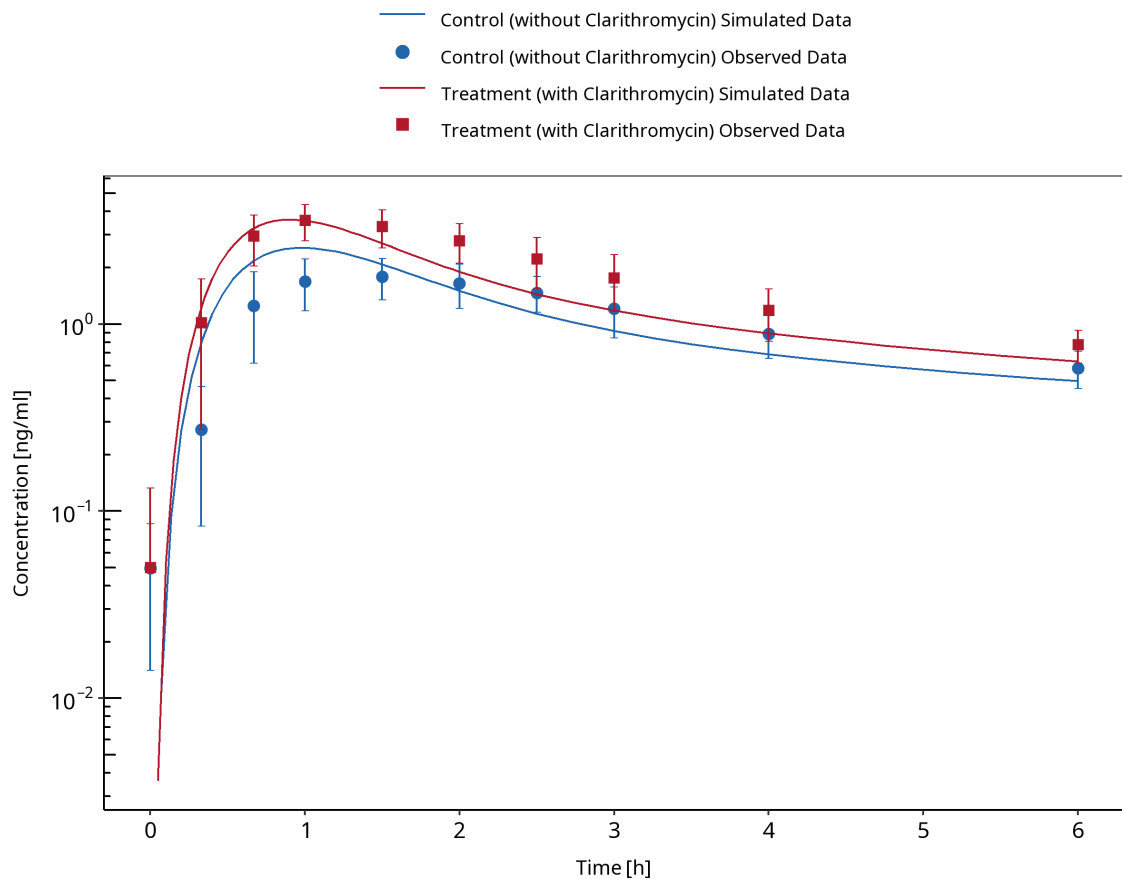


Figure 3-6: Gurley 2007 (0.5 mg PO) - Plasma

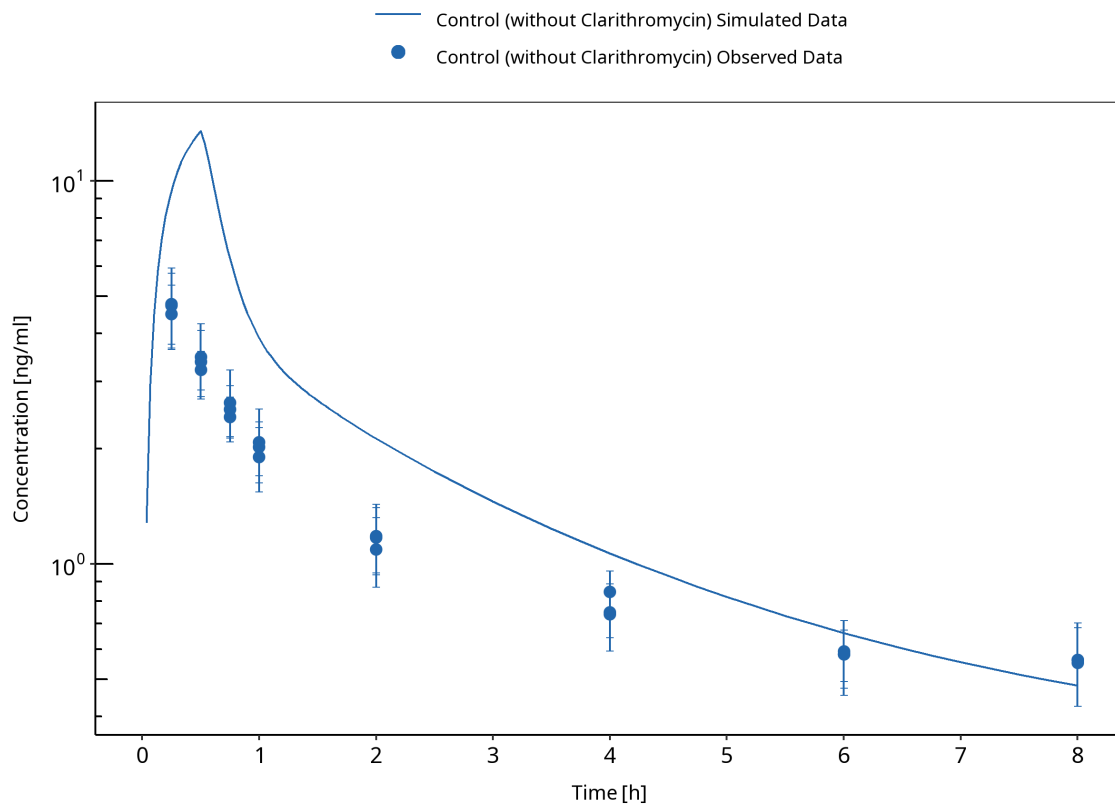


Figure 3-7: Kurata 2002 (0.5 mg IV) - Plasma

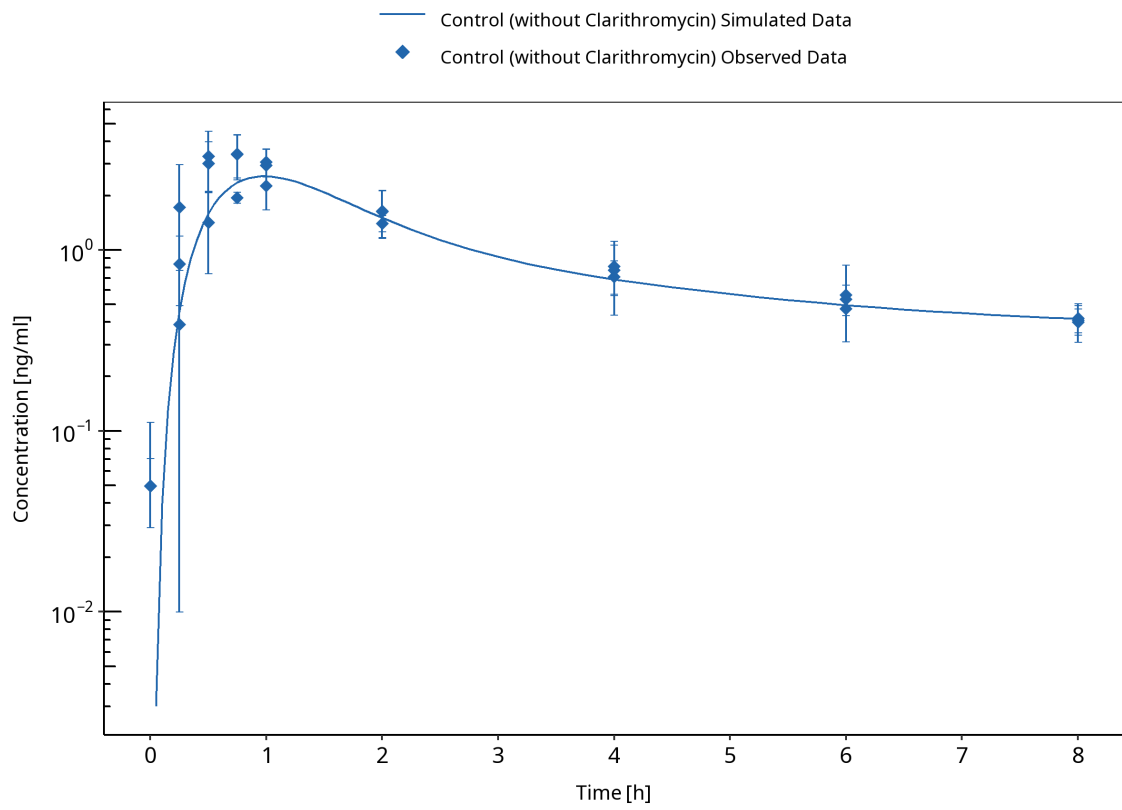


Figure 3-8: Kurata 2002 (0.5 mg PO) - Plasma

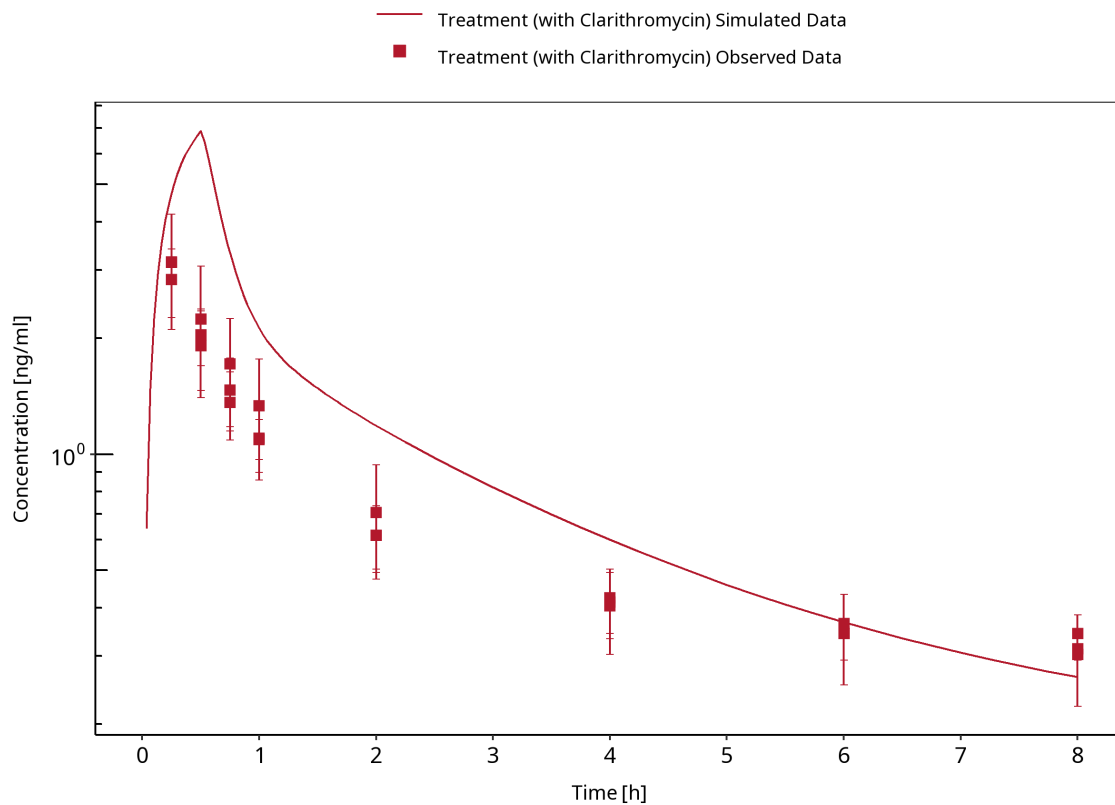


Figure 3-9: Kurata 2002 (0.25 mg IV) - Plasma

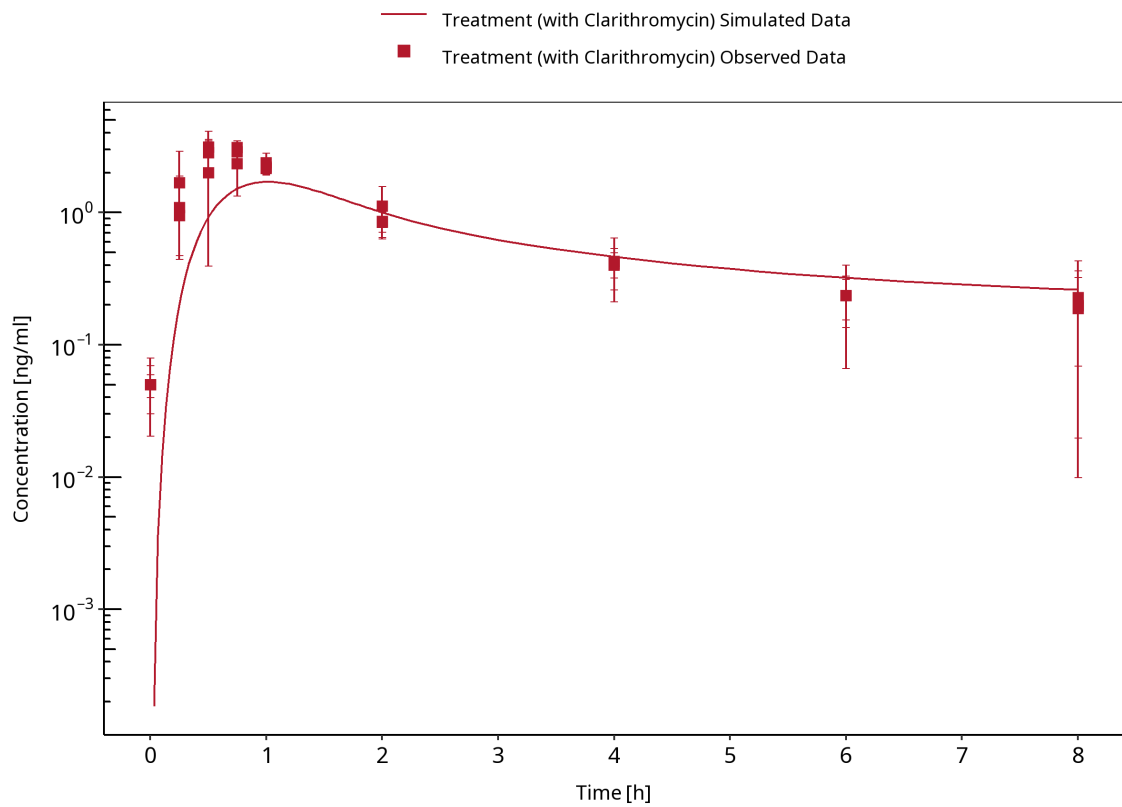


Figure 3-10: Kurata 2002 (0.25 mg PO) - Plasma

3.2 Erythromycin - Digoxin DDI

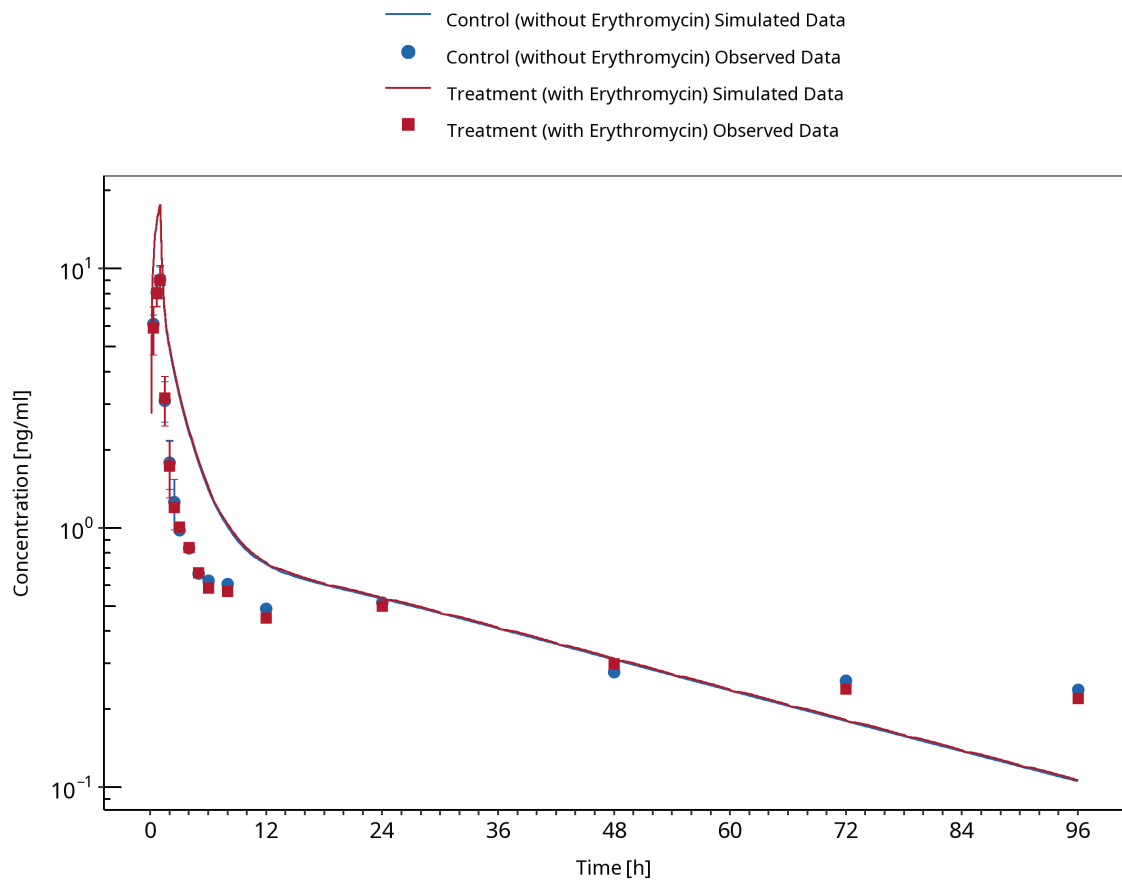


Figure 3-11: Tsutsumi 2002 - Plasma

3.3 Itraconazole - Digoxin DDI

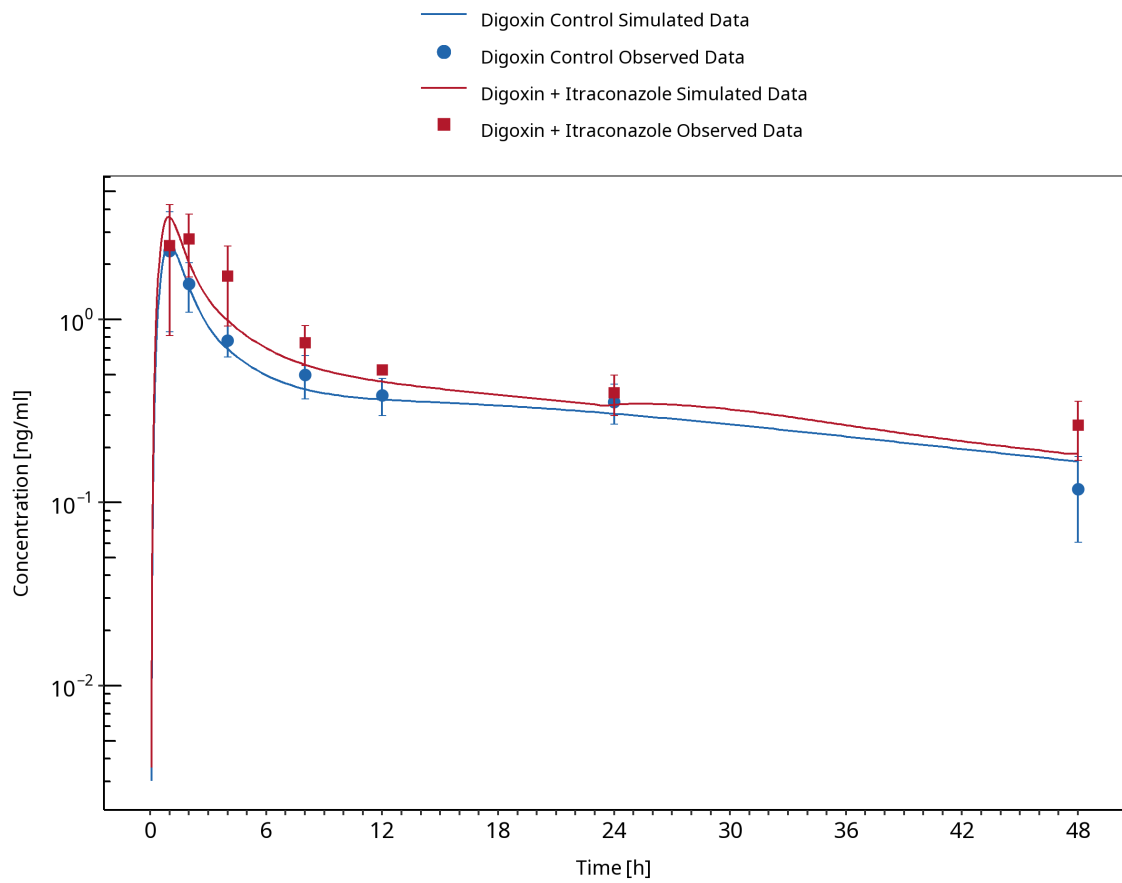


Figure 3-12: Jalava 1997

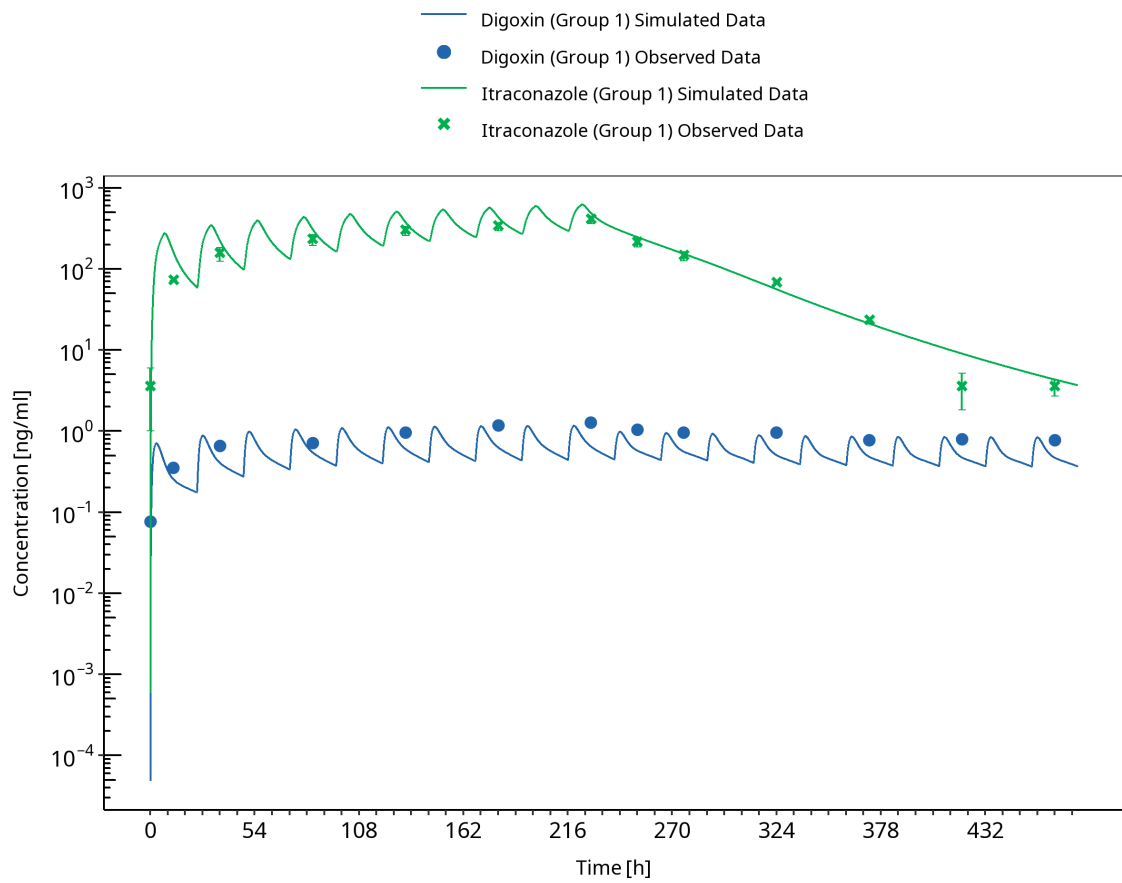


Figure 3-13: Partanen 1996 - Group 1

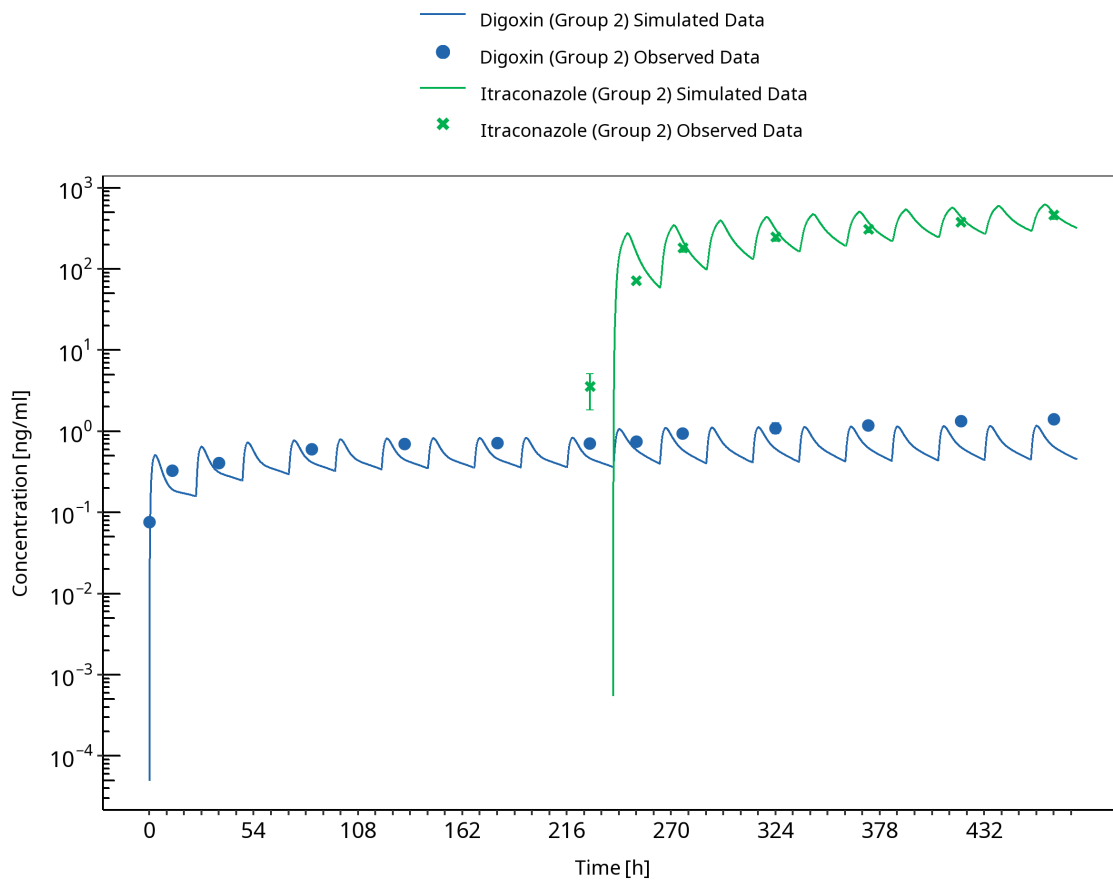


Figure 3-14: Partanen 1996 - Group 2

3.4 Verapamil - Digoxin DDI

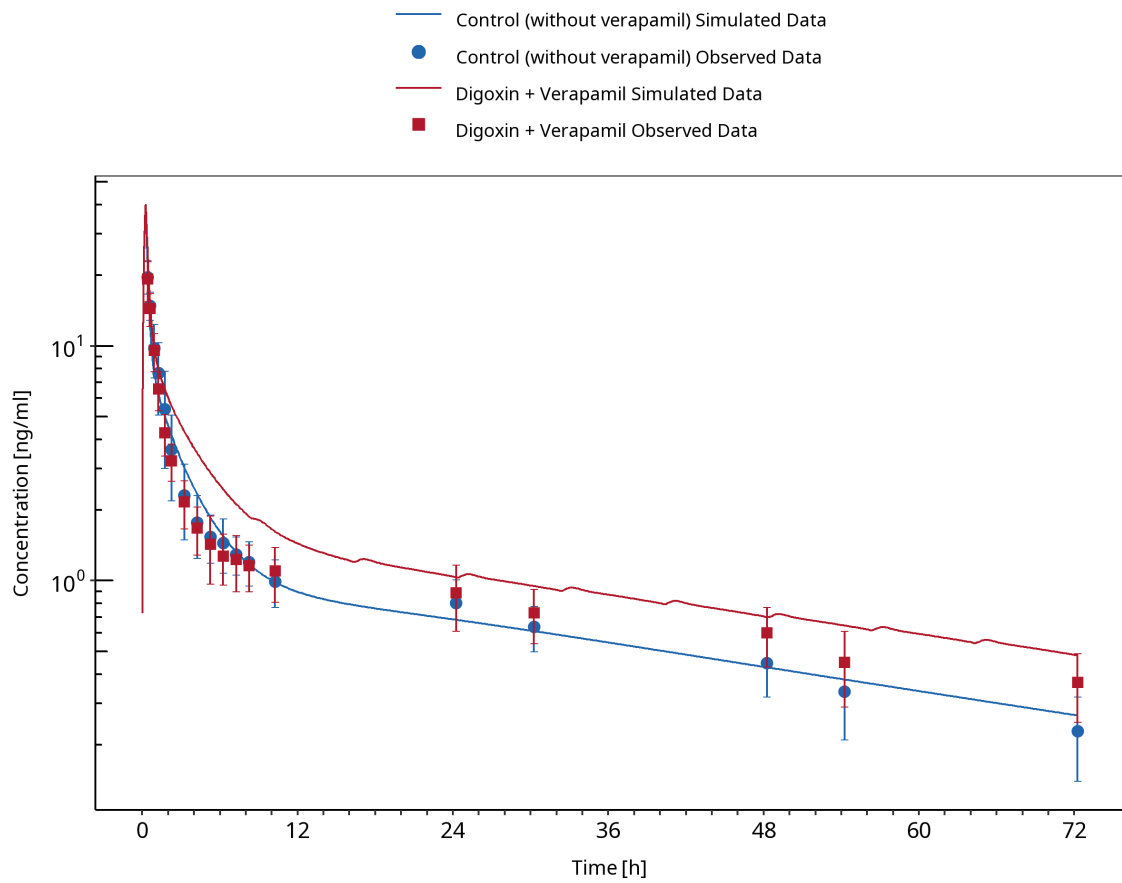


Figure 3-15: Johnson 1987

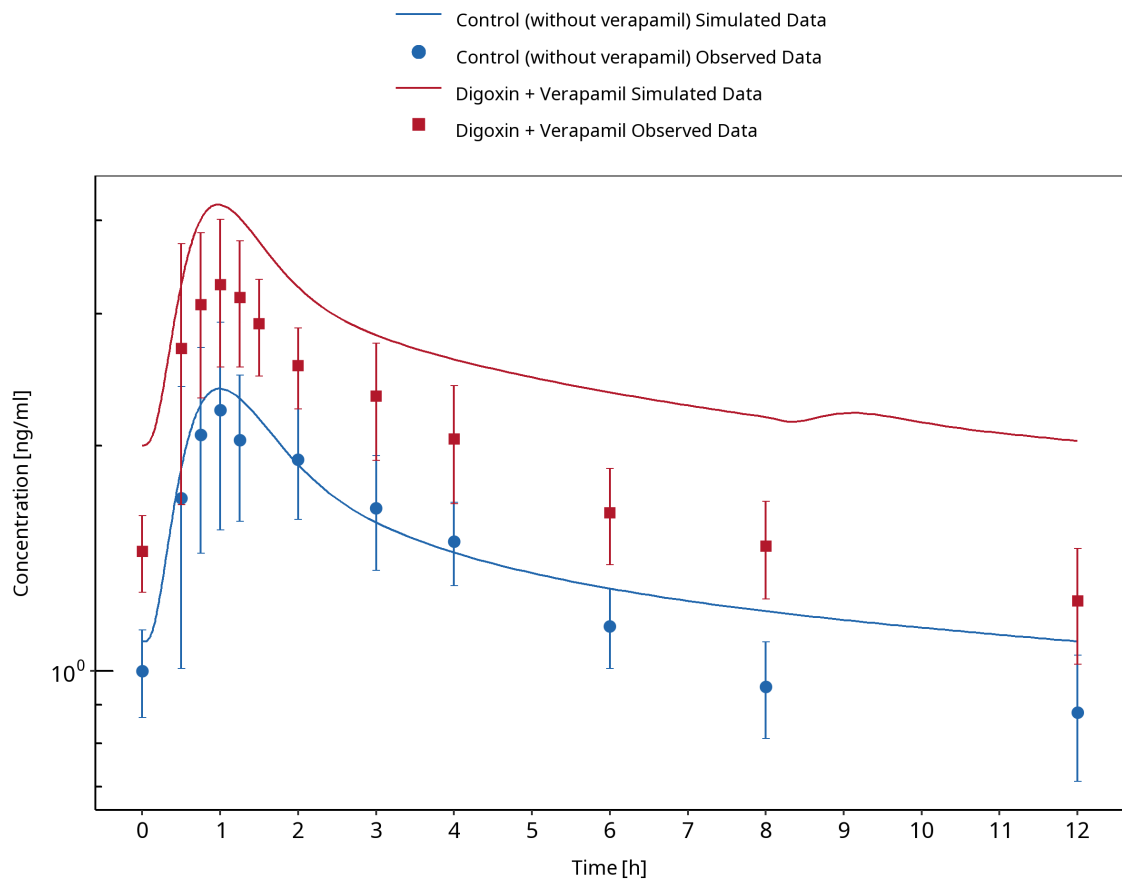


Figure 3-16: Rodin 1988

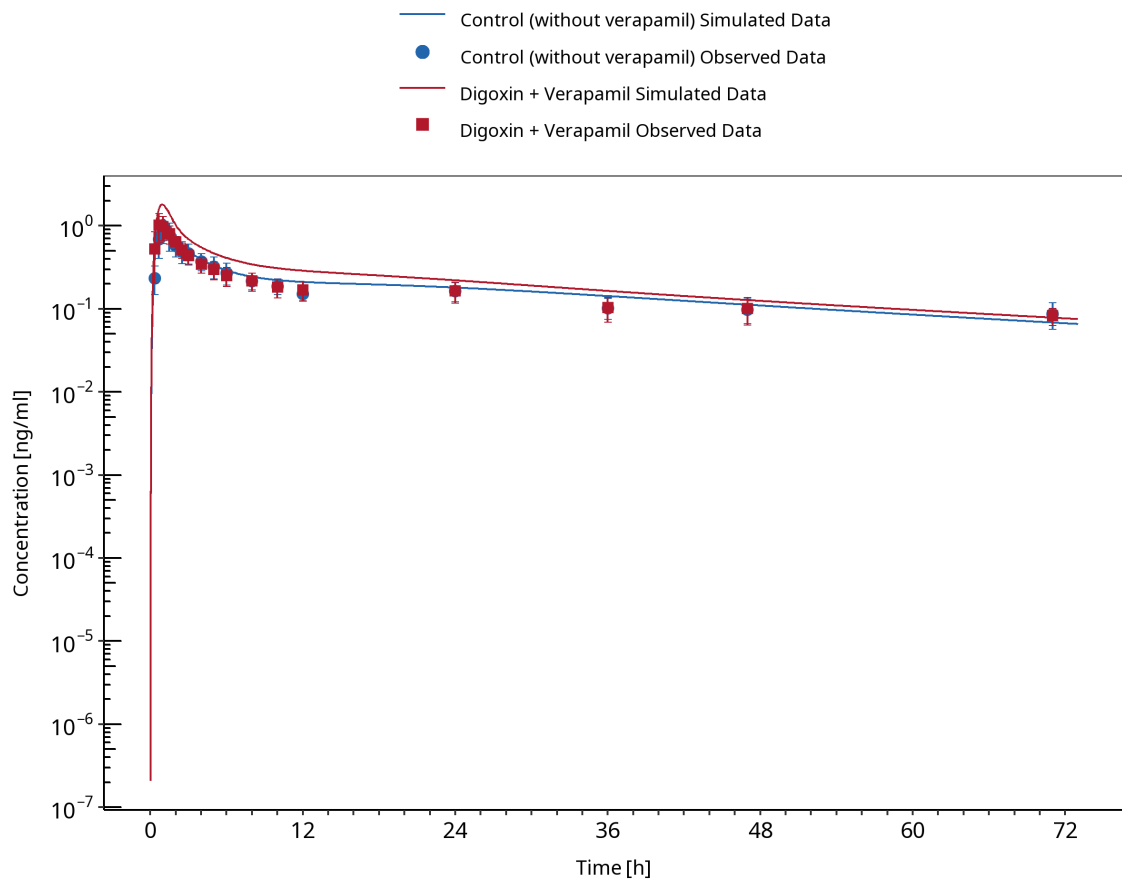


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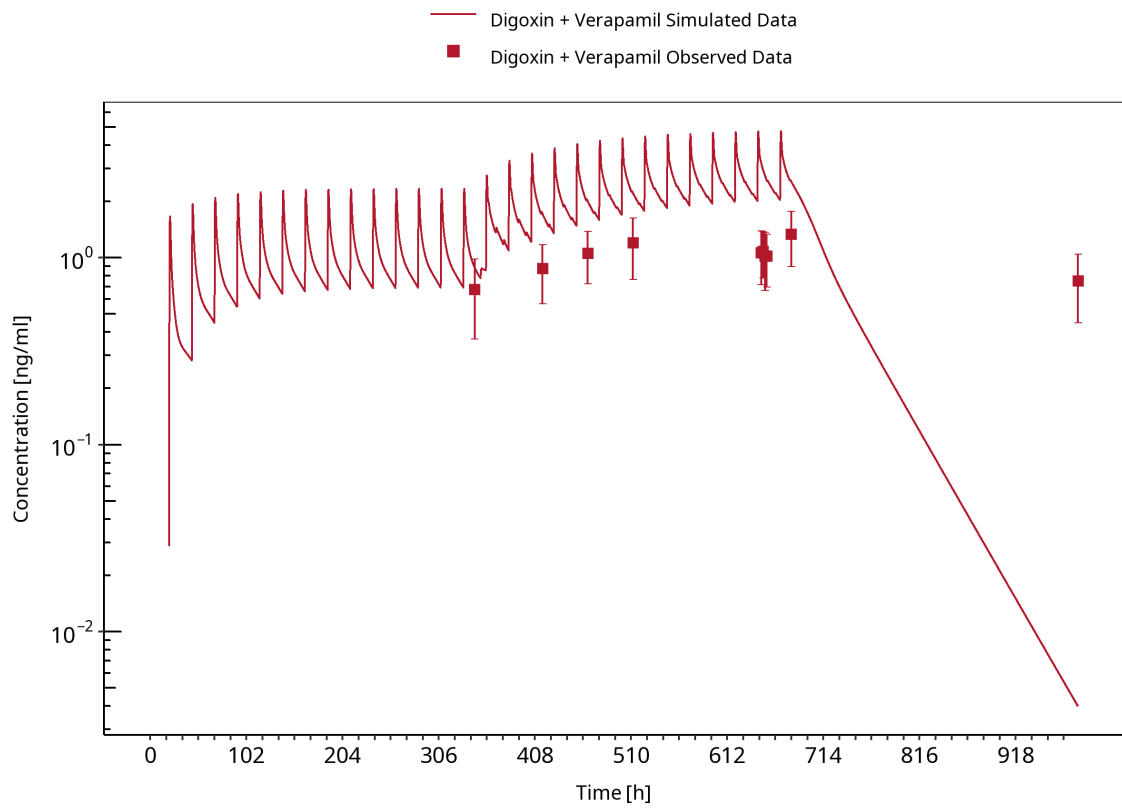


Figure 3-18: Klein 1982

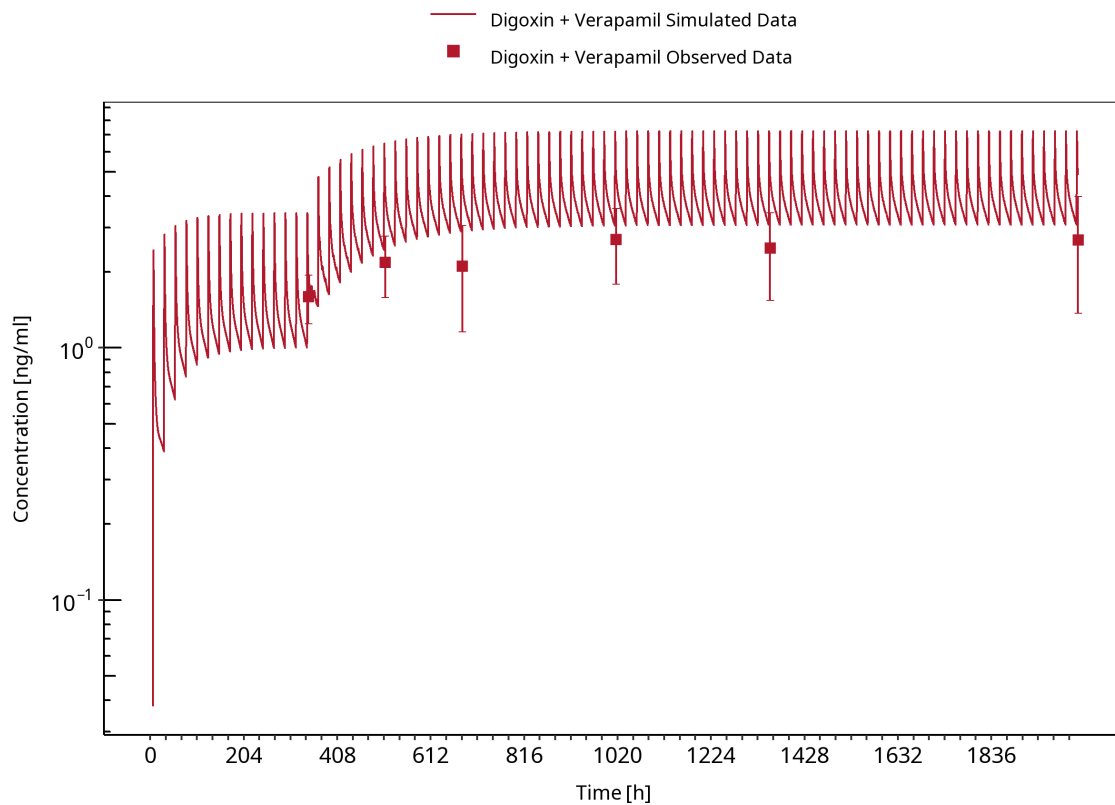


Figure 3-19: Schwartz 1982

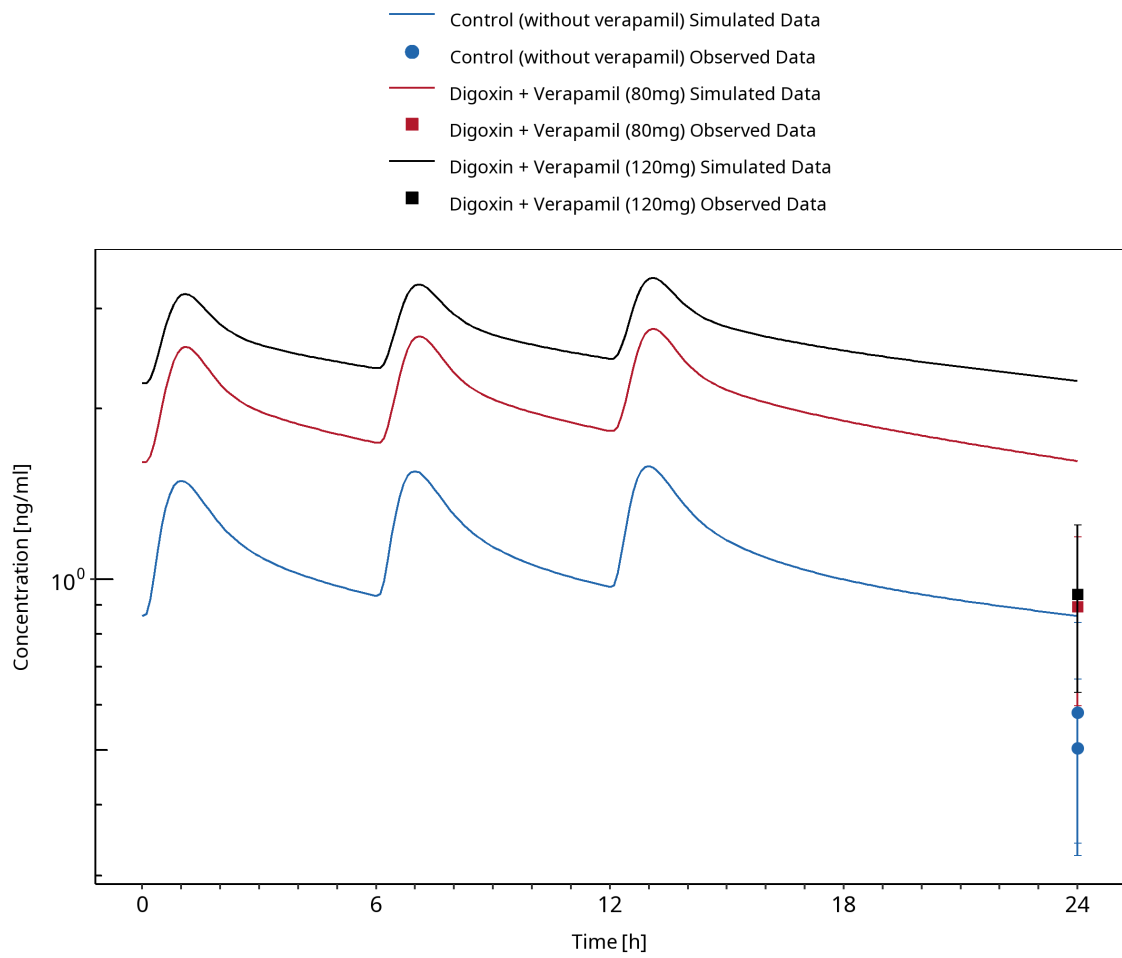


Figure 3-20: Belz 1983

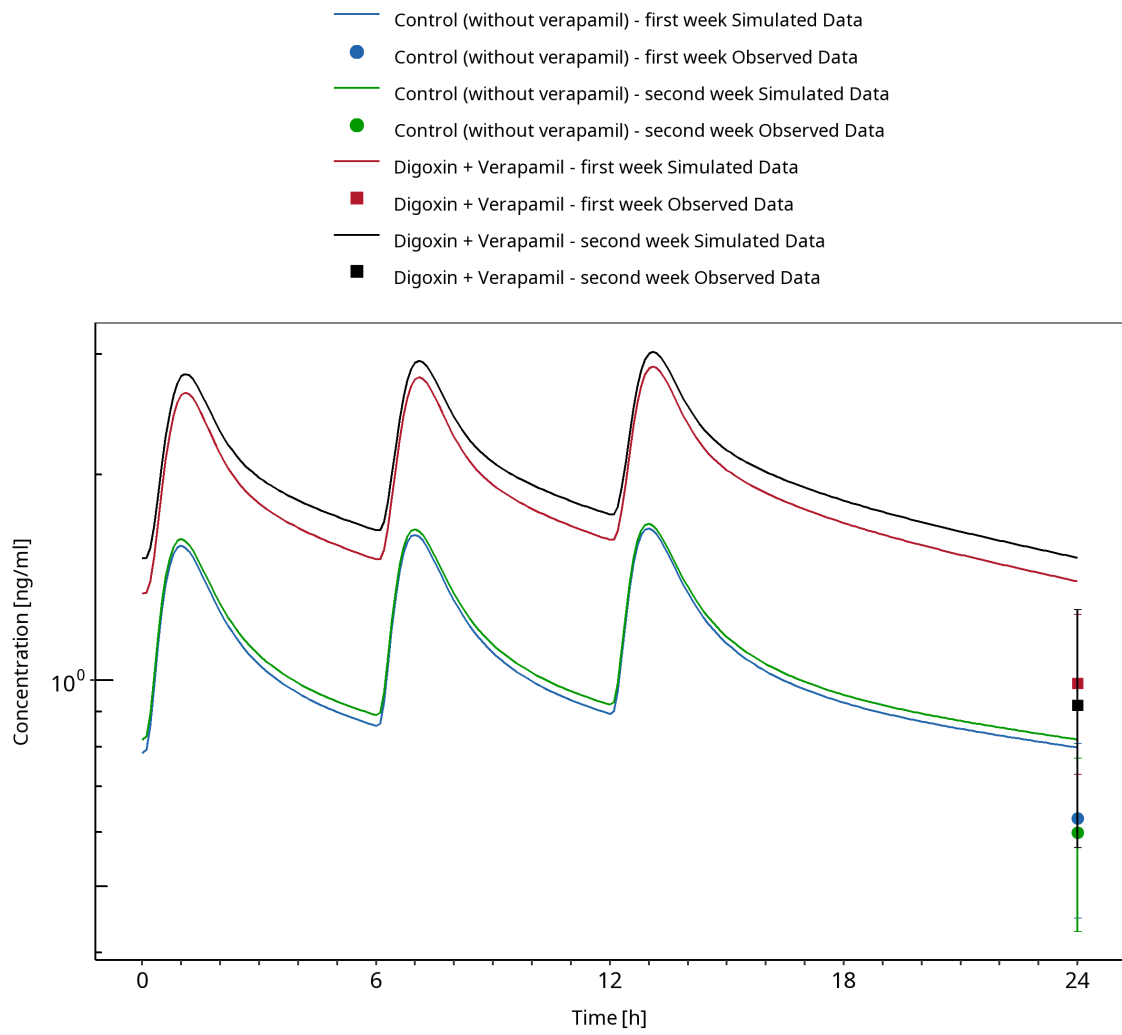


Figure 3-21: Doering 1983

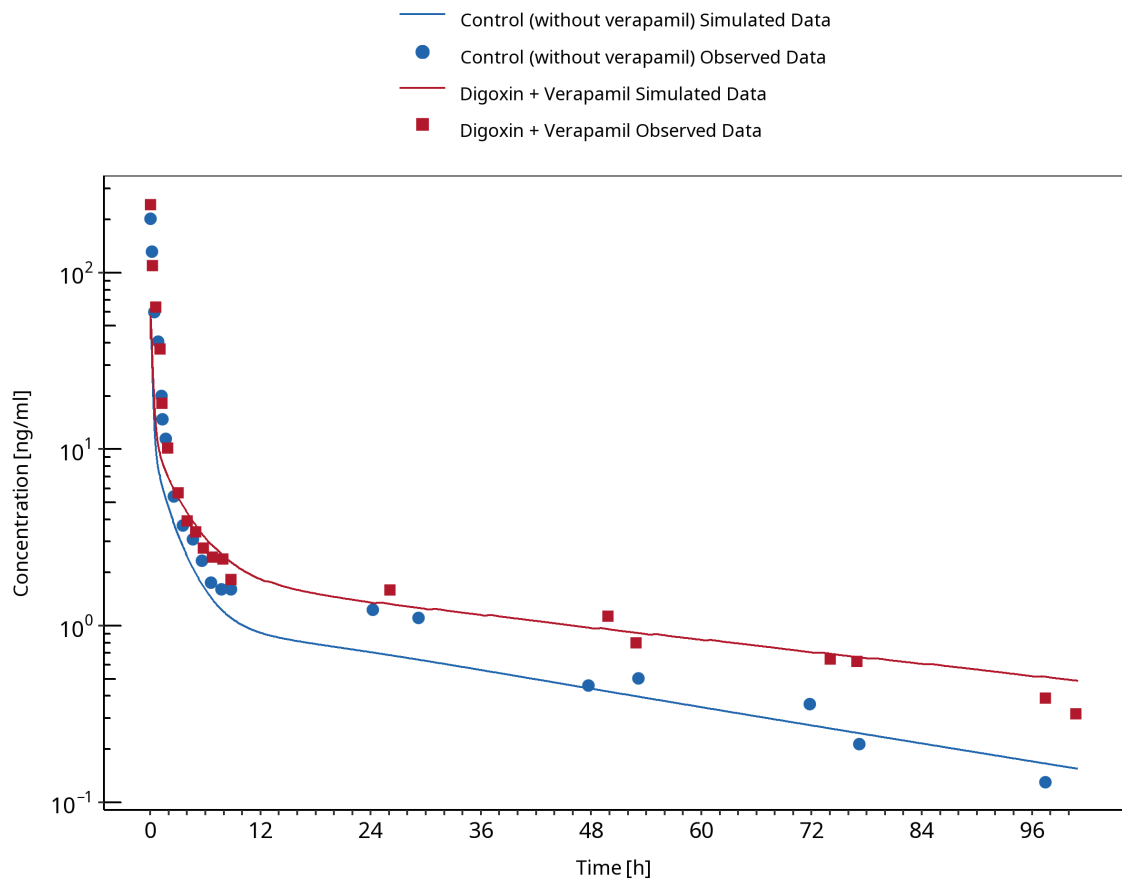


Figure 3-22: Pedersen 1983

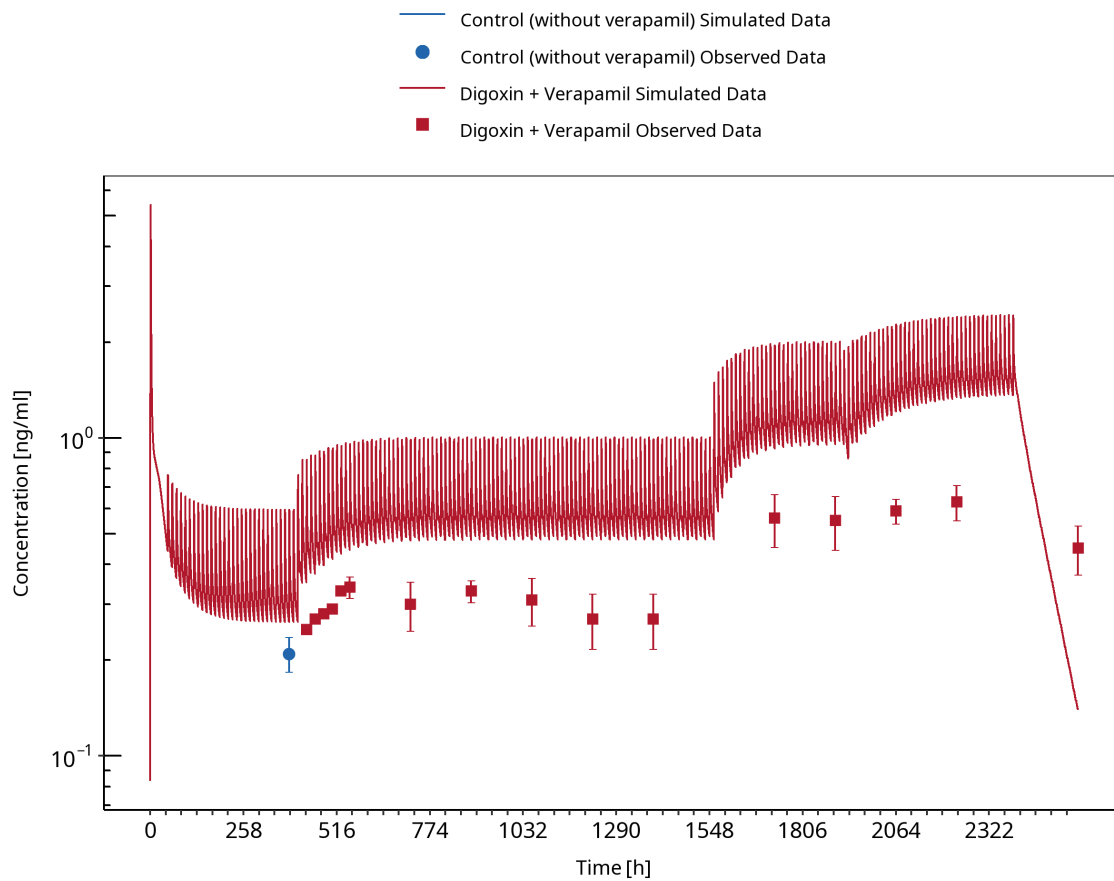


Figure 3-23: Pedersen 1982

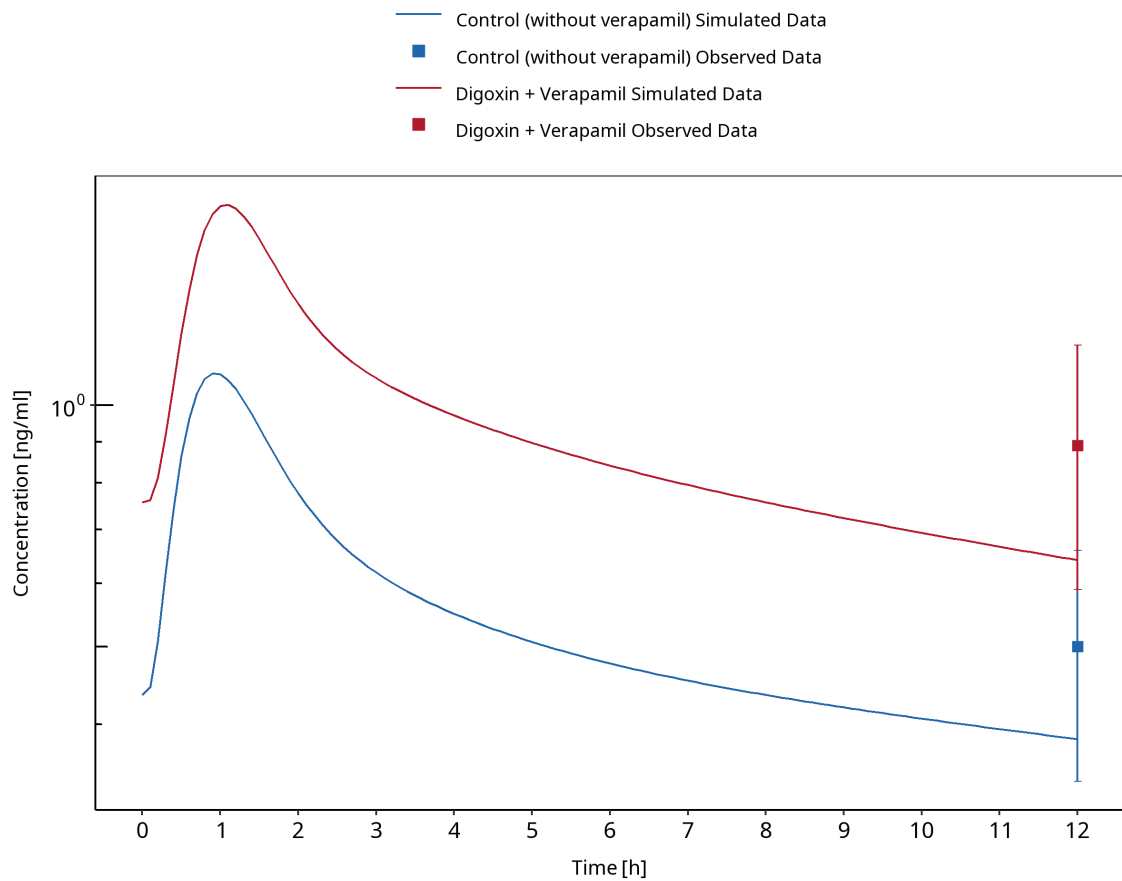


Figure 3-24: Belz 1981

3.5 Rifampicin - Digoxin DDI

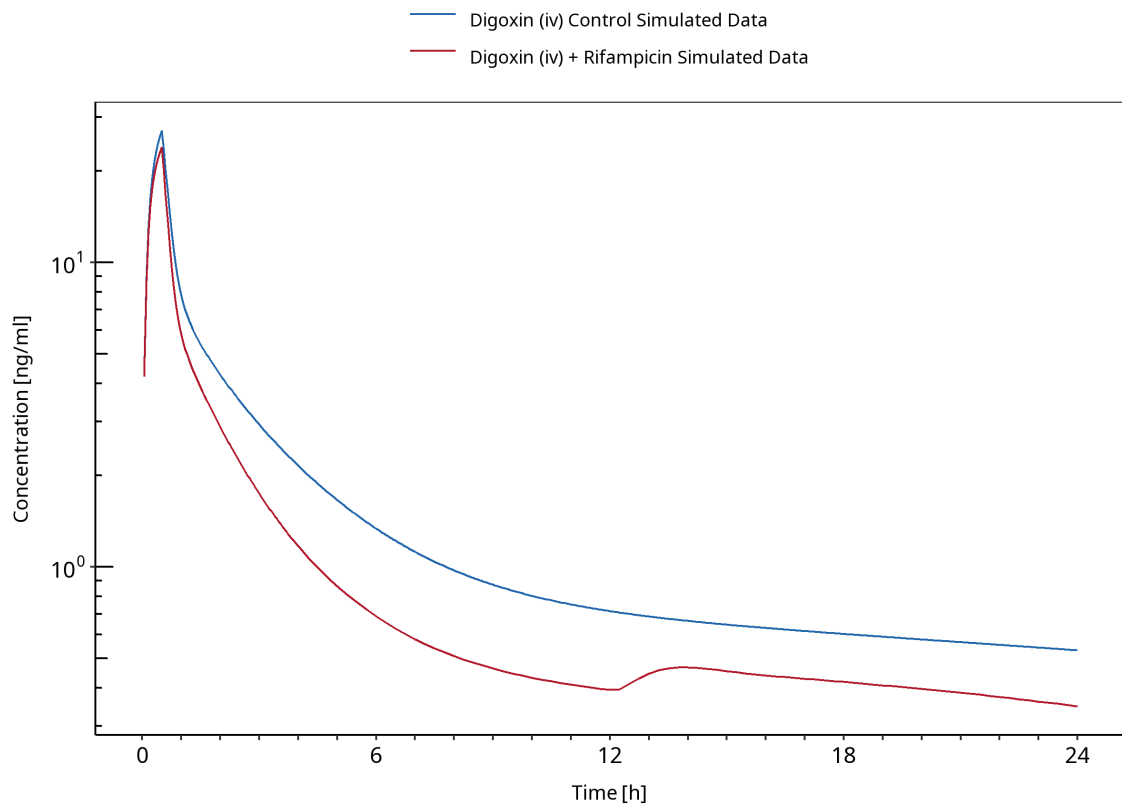


Figure 3-25: Drescher 2003

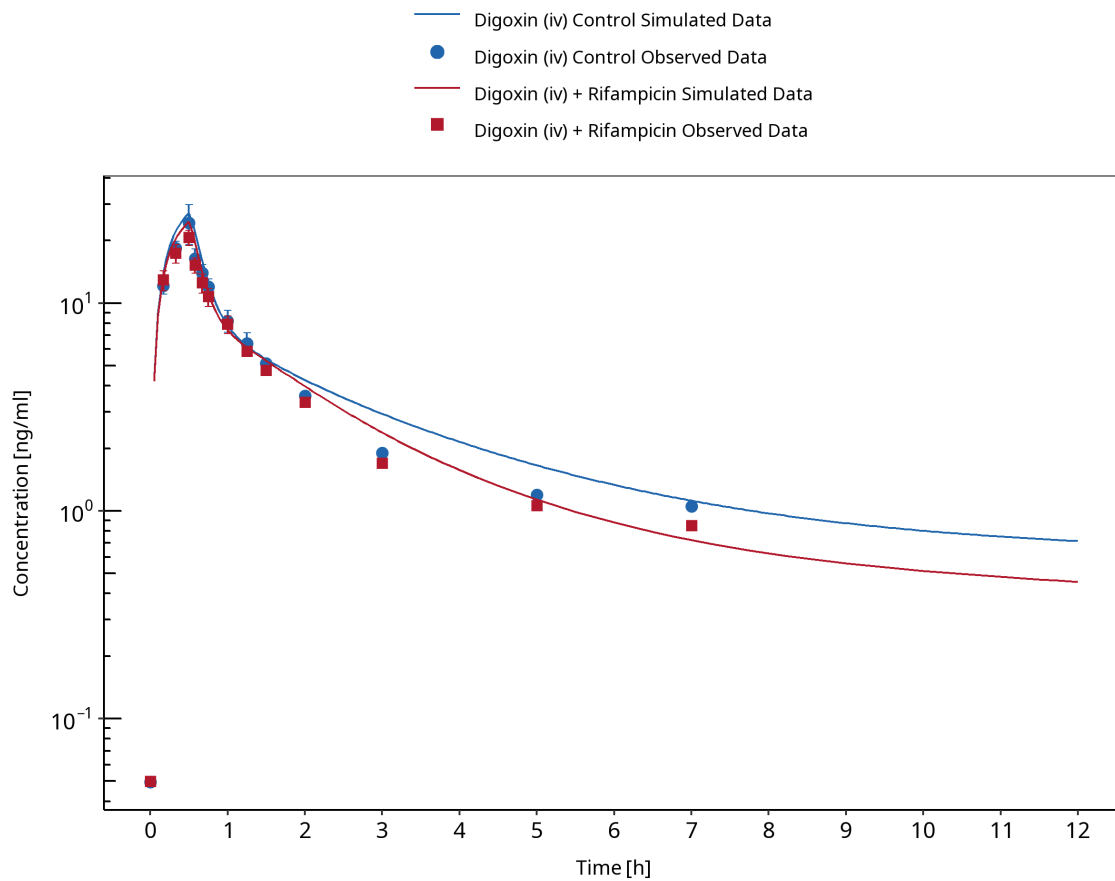


Figure 3-26: Greiner 1999 (iv)

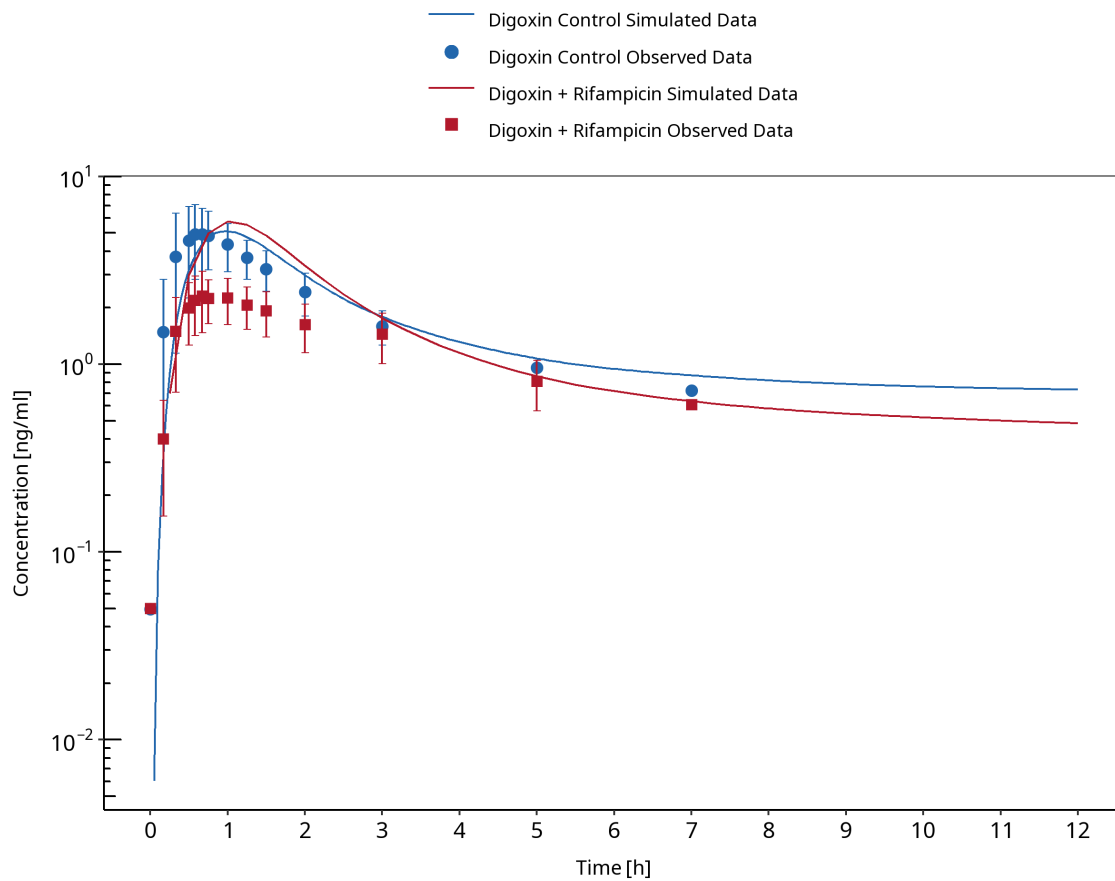


Figure 3-27: Greiner 1999 (po)

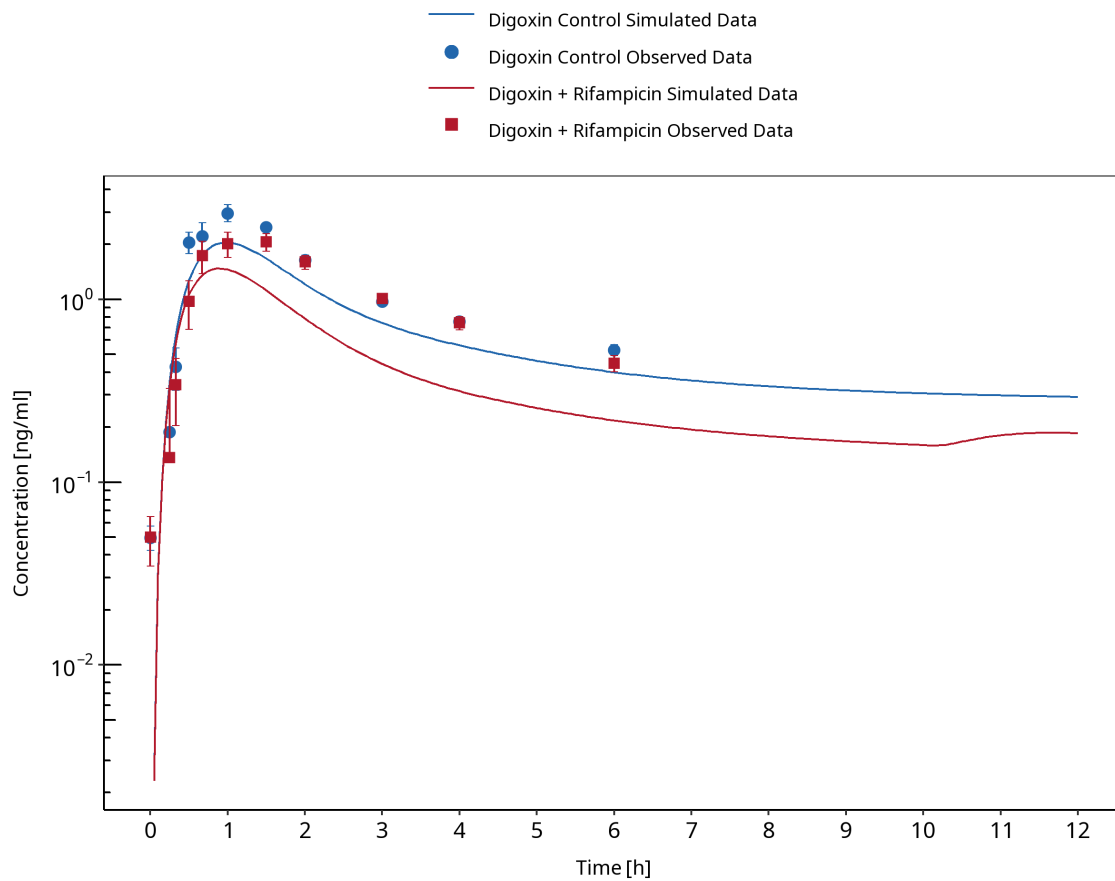


Figure 3-28: Gurley 2006

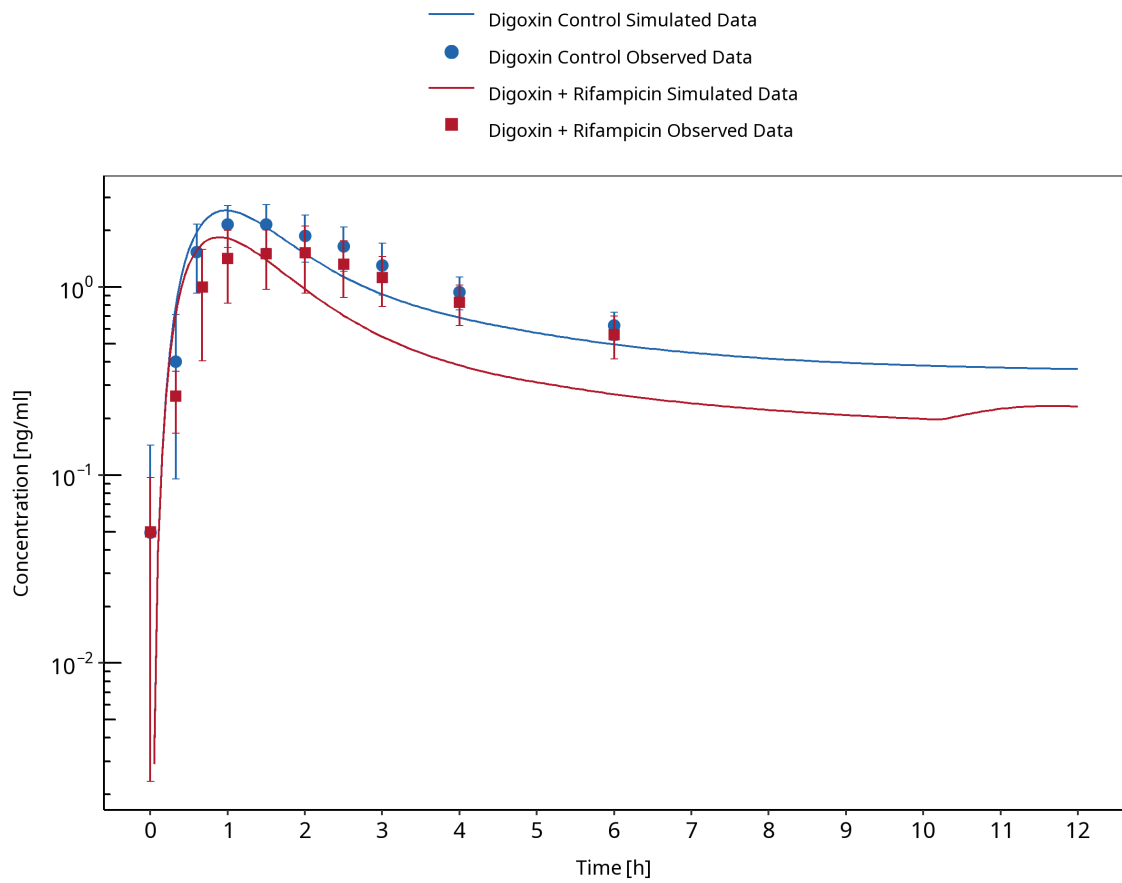


Figure 3-29: Gurley 2007

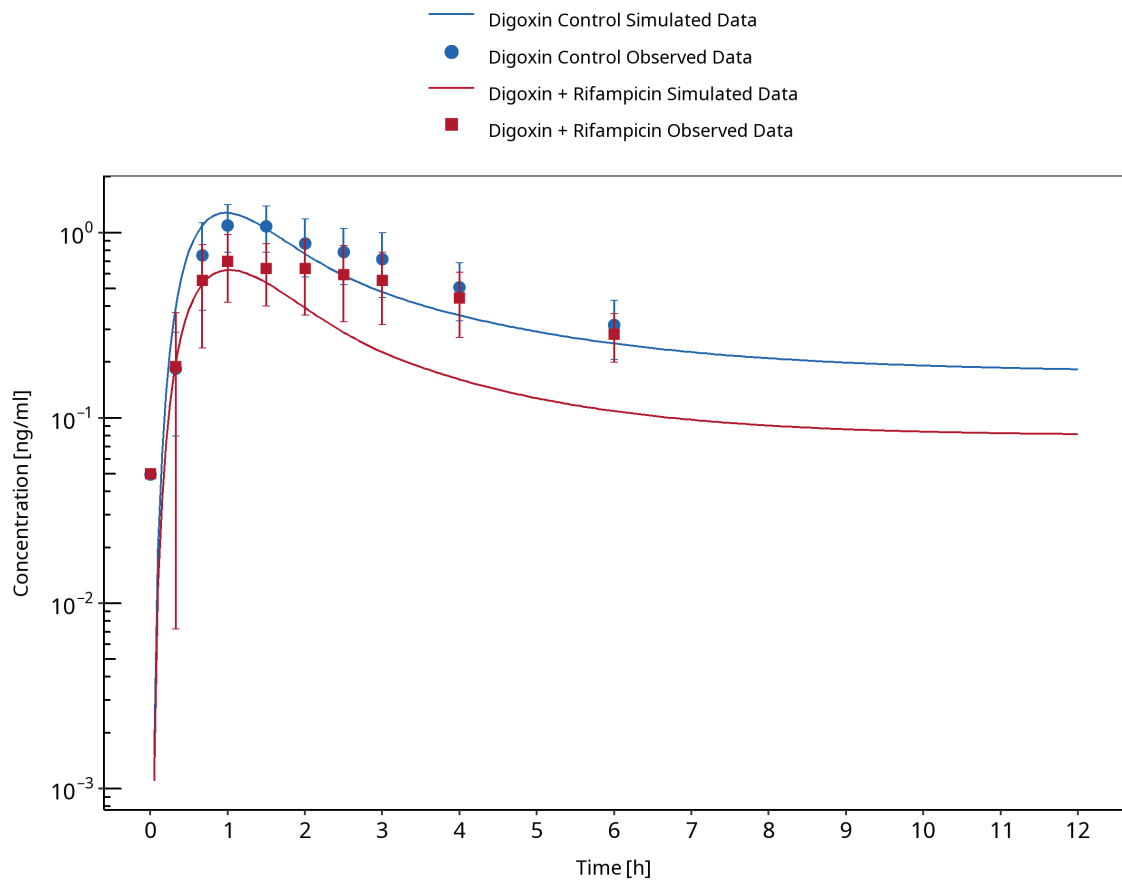


Figure 3-30: Gurley 2008

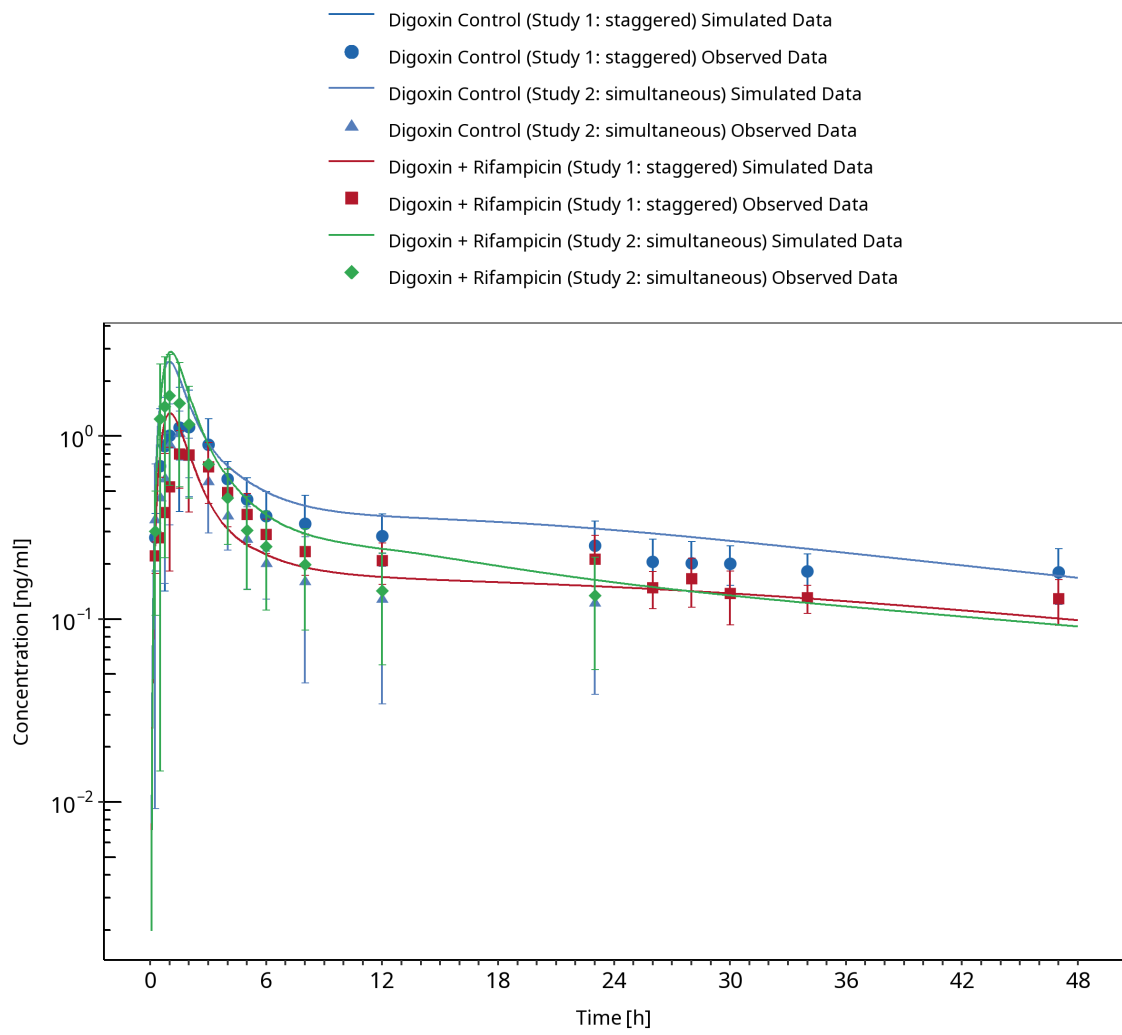


Figure 3-31: Kirby 2012

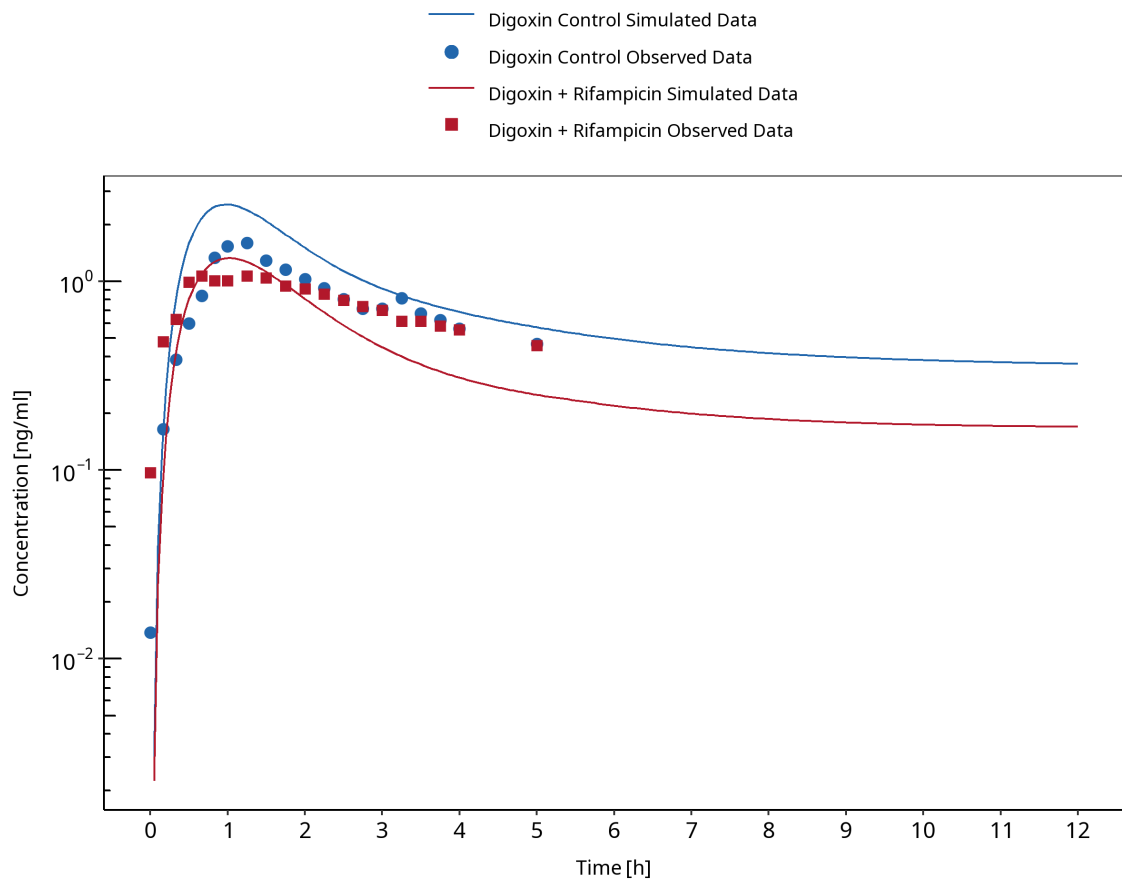


Figure 3-32: Larsen 2007

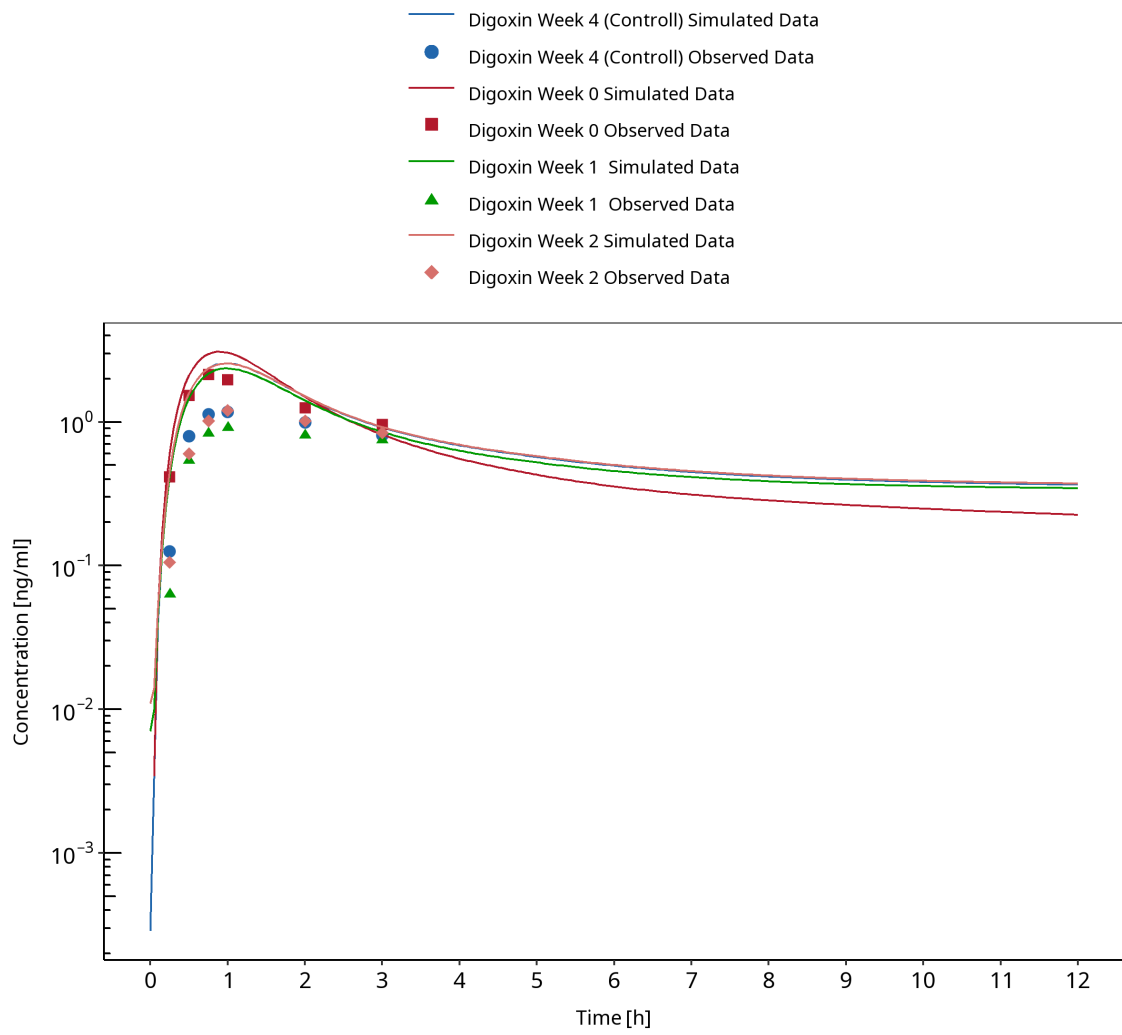


Figure 3-33: Reitman 2011

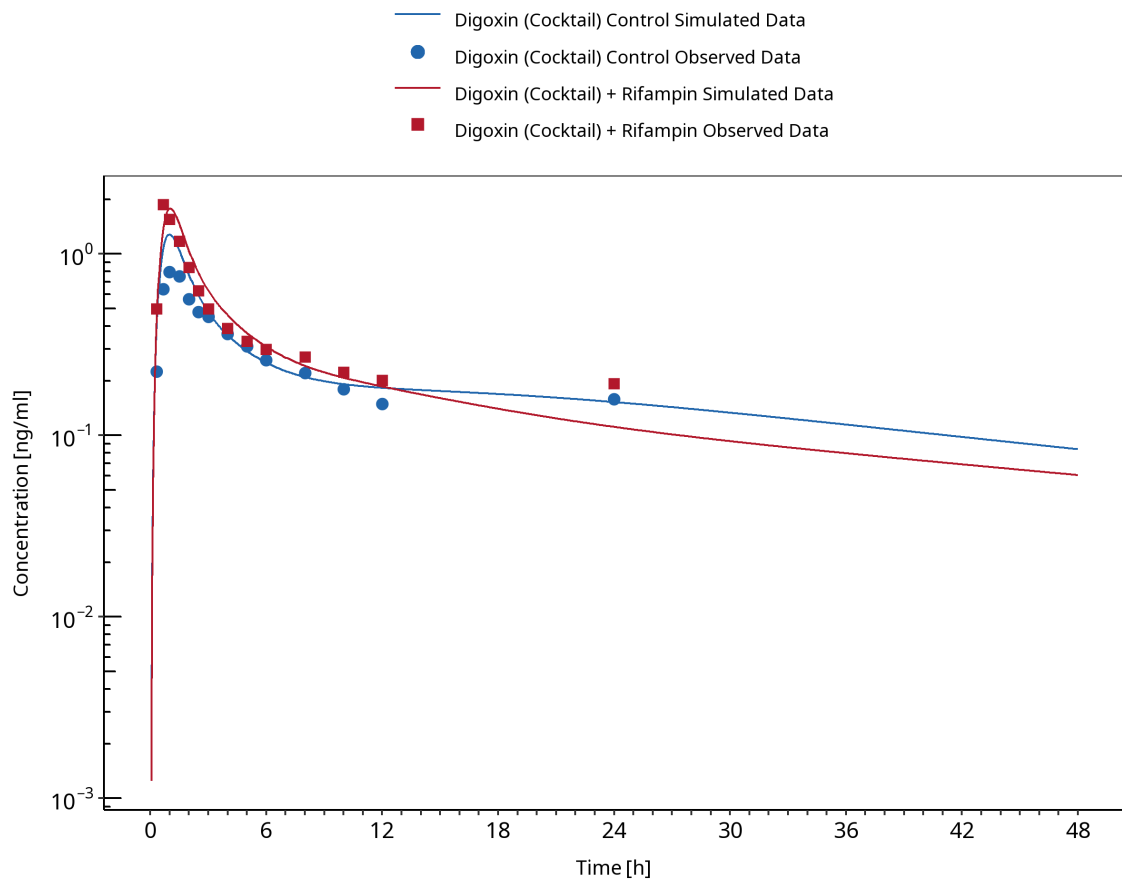


Figure 3-34: Wiebe 2020

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5 Appendix

5.1 Open Systems Pharmacology Suite (OSPS) Introduction

Open Systems Pharmacology Suite (OSP suite) is a tool for PBPK modeling and simulation of drugs in laboratory animals and humans. PK-Sim® and MoBi® are part of the OSP suite [1]. PK-Sim® is based on a generic PBPK-model with 18 organs and tissues. One of the main assumptions is that all compartments are well-stirred. Represented organs/tissues include arterial and venous blood, adipose tissue (separable adipose, excluding yellow marrow), brain, lung, bone (including yellow marrow), gonads, heart, kidneys, large intestine, liver, muscle, portal vein, pancreas, skin, small intestine, spleen and stomach, as shown in [Figure Appendix-1](#).

Each organ consists of four sub-compartments namely the plasma, blood cells (which together build the vascular space), interstitial space, and cellular space. Distribution between the plasma and blood cells as well as between the interstitial and cellular compartments can be permeability-limited. In the brain, the permeation barrier is located between the vascular and the interstitial space. PK-Sim® estimates model parameters (intestinal permeability [2] organ partition coefficients (tissue-to-plasma partition coefficients) [3,4], and permeabilities) from physico-chemical properties of compounds (molecular weight, pKa, acid/base properties) and the composition of each tissue compartment (lipids, water and proteins). Partition coefficients can be calculated using a variety of methods available in PK-Sim®, for example the internal PK-Sim® method [3,4] or that of Rodgers and Rowland [5-7].

Physiological databases included in the software incorporate the dependencies of organ composition, organ weights, organ blood flows and gastrointestinal parameters (gastrointestinal length, radius of each section, intestinal surface area, gastrointestinal transit times, and pH in different intestinal segments [2]), with the user-defined body weight and height and ethnicity of the individual [8]. Thereby, PK Sim® allows generating realistic virtual populations. For a detailed description of the PBPK model structure implemented in PK Sim®, see Willmann et al. [2,4,8,9] or the OSP Suite homepage (<https://docs.open-systems-pharmacology.org/mechanistic-modeling-of-pharmacokinetics-and-dynamics/modeling-concepts>).

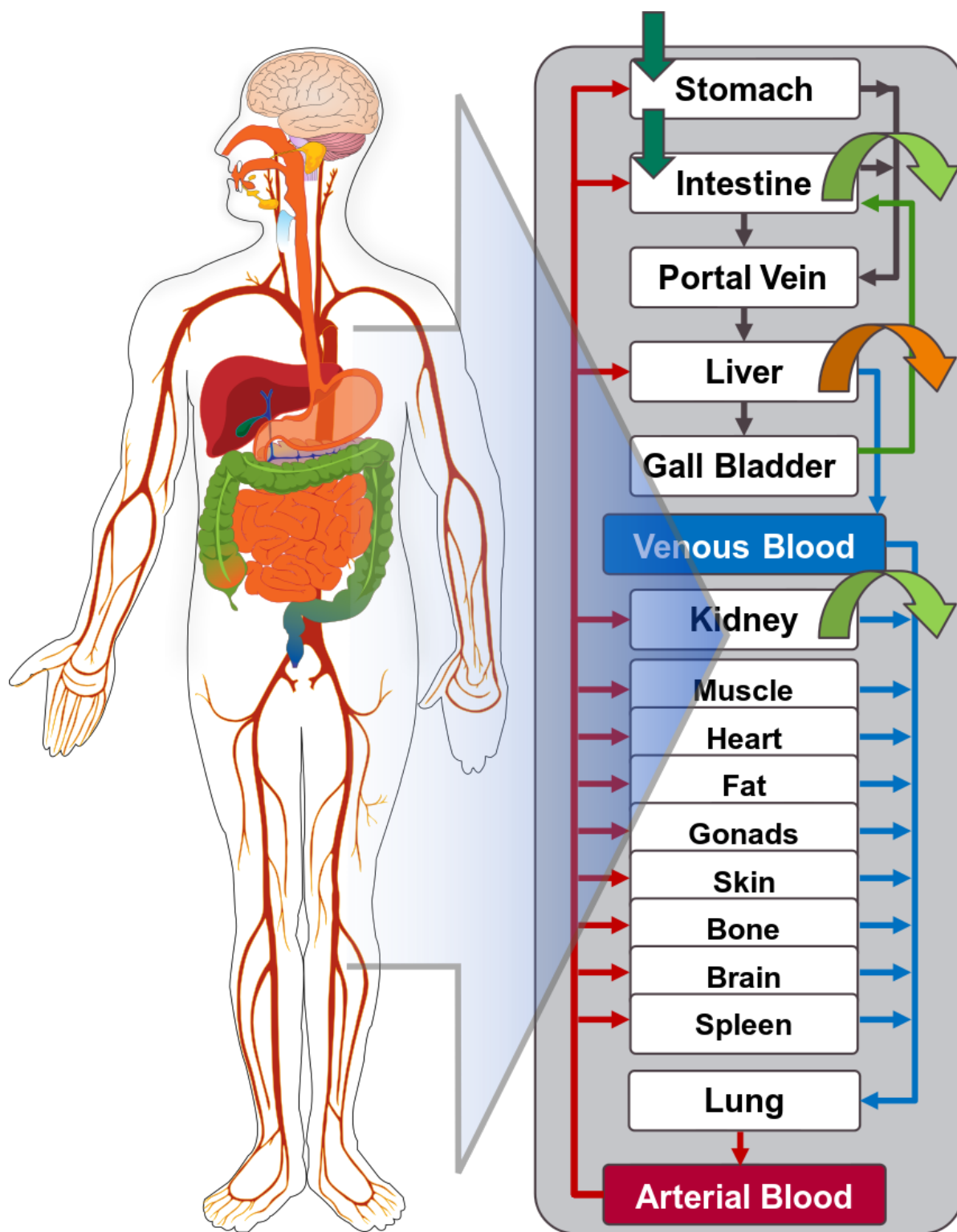


Figure Appendix-1: Structure of the Whole Body PBPK Model integrated in PK-Sim®

References for OSPS introduction

[1] www.open-systems-pharmacology.org

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5.2 Mathematical Implementation of Drug-Drug Interactions

DDI modeling: Competitive inhibition

A detailed representation of the mathematical implementation of competitive enzyme inhibition can be found in the OSP manual (<https://docs.open-systems-pharmacology.org/working-with-pk-sim/pk-sim-documentation/pk-sim-compounds-defining-inhibition-induction-processes#competitive-inhibition-simple-setting-with-one-inhibitor>).

DDI modeling: Mechanism-based inhibition

A detailed representation of the mathematical implementation of mechanism-based enzyme inhibition can be found in the OSP manual (<https://docs.open-systems-pharmacology.org/working-with-pk-sim/pk-sim-documentation/pk-sim-compounds-defining-inhibition-induction-processes#irreversible-inhibition>).

DDI modeling: Induction

A detailed representation of the mathematical implementation of enzyme induction can be found in the OSP manual (<https://docs.open-systems-pharmacology.org/working-with-pk-sim/pk-sim-documentation/pk-sim-compounds-defining-inhibition-induction-processes#enzyme-induction>).

5.3 Automatic (re)-qualification workflow

Open Systems Pharmacology (<https://www.open-systems-pharmacology.org/>) provides a dynamic landscape of model repositories and a database of observed clinical data. Additionally, a technical framework to assess confidence of a specific intended use has been developed (qualification runner and reporting engine). This framework allows for an automatic (re)-qualification workflow of the OSP suite, comprising the following steps **Figure Appendix-2**:

- PBPK model development and verification with observed data,
- Qualification plan generation,
- Qualification plan execution,
- Qualification report generation.

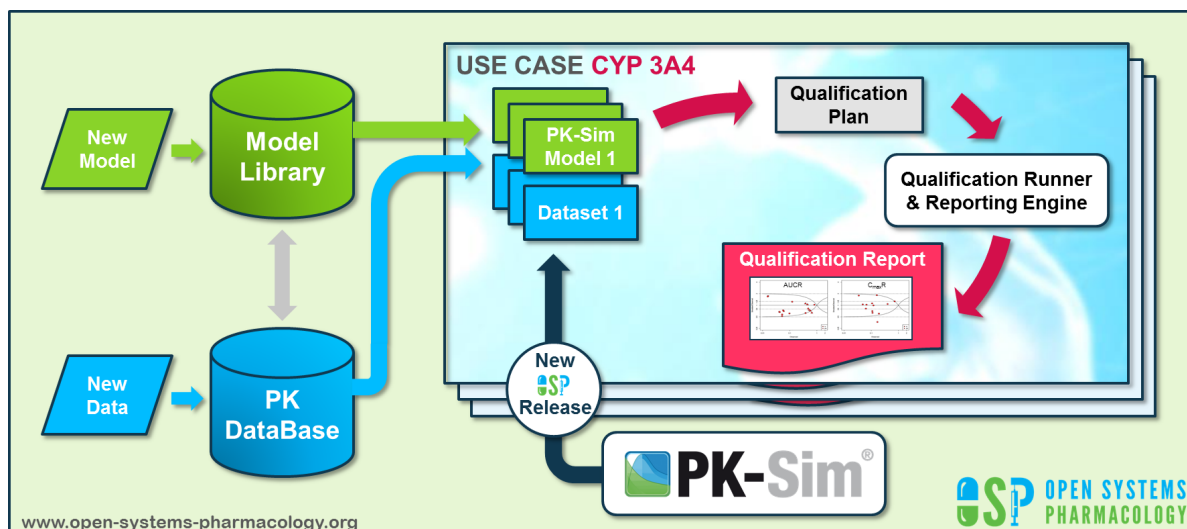


Figure Appendix-2: OSP suite automatic (re)-qualification workflow

In a first step, the respective qualification scenario is saved in a special qualification repository on OSP GitHub (<https://github.com/Open-Systems-Pharmacology/>). This qualification scenario repository contains a detailed qualification plan that links and combines respective models and data to address the use case that shall be qualified. Therefore, the qualification plan consists of:

- PK-Sim project files,
- Additional model building steps (if applicable),
- Description of potential cross-dependencies between PK-Sim project files (if applicable),
- Observed data (needed for model development and verification),
- Qualification scenario description text modules
- Detailed report settings to describe the generation of charts and qualification measures.

PK-Sim projects, observed data sets, and qualification scenario text modules are deposited in distinct repositories and are referenced by the qualification plan (**Figure Appendix-3**).

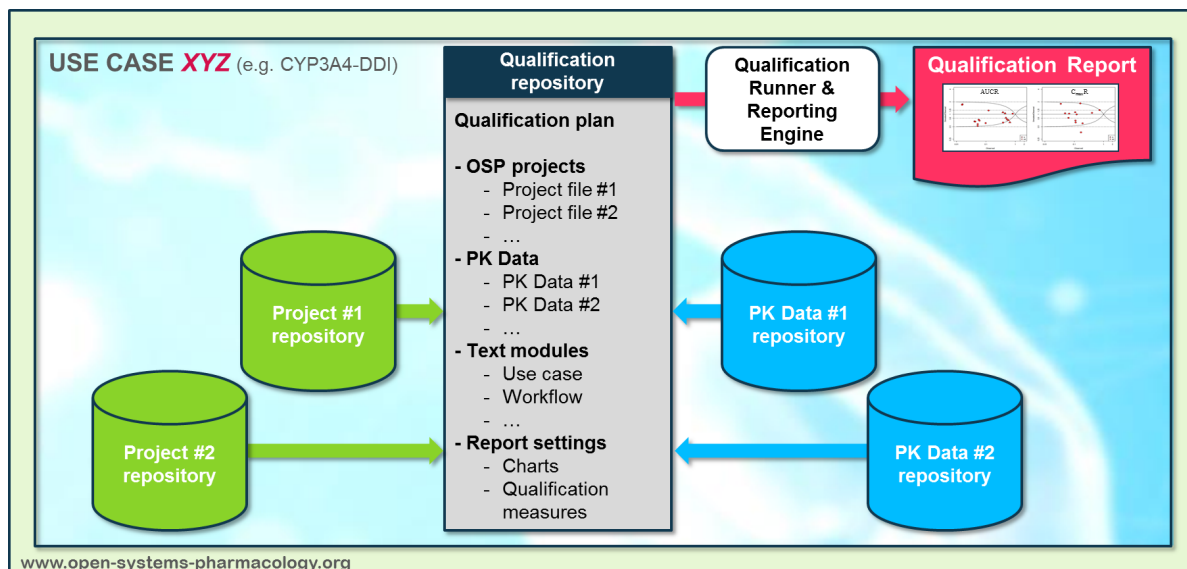


Figure Appendix-3: Qualification scenario repository landscape on GitHub

In a second step the qualification runner (<https://github.com/Open-Systems-Pharmacology/QualificationRunner>) processes the qualification plan, i.e. all project parts are exported and prepared for the reporting engine (<https://github.com/Open-Systems-Pharmacology/Reporting-Engine>). The reporting engine provides a validated environment (implemented in R) for model execution and finally generates the qualification report. This report contains

the evaluation of the individual PBPK models with observed data (i.e. standard goodness of fit plots, visual predictive checks) and a comprehensive qualification of the specific use case assessing the predictive performance of the OSP suite by means of a predefined set of qualification measures and charts.

The automated execution of the described workflow can be triggered to assess re-qualification in case new data, changes in model structure or parameterization, or new OSP suite releases arise.