

CYP3A4 DDI Qualification

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<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 cytochrome P450 3A4 (**CYP3A4**)-mediated drug-drug interactions (**DDI**).

To demonstrate the level of confidence, the predictive performance of the platform for this intended purpose is assessed via a network of PBPK models of selected index CYP3A4 DDI perpetrators (covering the range from strong induction to strong inhibition), and respective sensitive index CYP3A4 victim drugs 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 CYP3A4.

The respective *qualification plan* to produce this *qualification report* is transparently documented and provided open-source (www.open-systems-pharmacology.org). The same applies for all presented PBPK models including *evaluation reports* on model building and evaluation of each model.

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 CYP3A4 DDI Network

To qualify the OSP suite for the prediction of the CYP3A4 DDI potential of new drugs, a set of verified PBPK models of index perpetrators, covering the range from strong CYP3A4 induction to strong inhibition, and respective CYP3A4 DDI victim drugs is specified to set up a CYP3A4-mediated DDI modeling network.

The following perpetrator compounds were selected:

- **Rifampicin** (strong CYP3A4 inducer)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Rifampicin-Model/releases/tag/v1.0>
- **Efavirenz** (moderate CYP3A4 inducer)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Efavirenz-Model/releases/tag/v1.0>
- **Fluvoxamine** (weak/moderate CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Fluvoxamine-Model/releases/tag/v1.0>

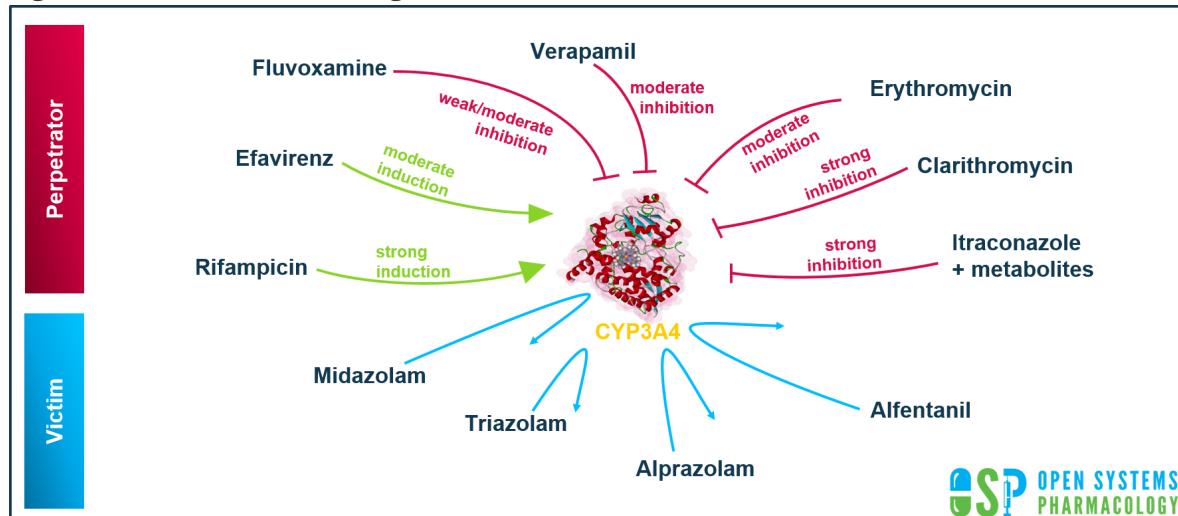
- **Verapamil** (moderate CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Verapamil-Model/releases/tag/v1.0>
- **Erythromycin** (moderate CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Erythromycin-Model/releases/tag/v1.0>
- **Clarithromycin** (strong CYP 3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Clarithromycin-Model/releases/tag/v1.0>
- **Itraconazole** including metabolites (strong CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Itraconazole-Model/releases/tag/v1.1>

The following sensitive CYP3A4 substrates as victim drugs were selected:

- **Midazolam**
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Midazolam-Model/releases/tag/v1.0>
- **Triazolam**
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Triazolam-Model/releases/tag/v1.0>
- **Alprazolam**
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Alprazolam-Model/releases/tag/v1.0>
- **Alfentanil**
Model snapshot and evaluation plan (*release v2.0*): <https://github.com/Open-Systems-Pharmacology/Alfentanil-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 CYP3A4-mediated DDI.

Figure 1: CYP3A4 DDI modeling network



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](#).

Clarithromycin - Midazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Clarithromycin-Midazolam-DDI/releases/tag/v1.0>.

The clarithromycin-midazolam interaction was evaluated using eight clinical DDI studies quantifying the interaction following ten different dosing regimens ([Gorski 1998](#), [Gurley 2006](#), [Gurley 2008a](#), [Markert 2013](#), [Pruksaritanont 2017](#), [Quinney 2008](#), [van Dyk 2018](#), [Yeates 1997](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
175	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 7 days Midazolam: 0.05 mg/kg iv single dose, 2 hours after the 13 th clarithromycin dose		Gorski 1998
173	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 7 days Midazolam: 4 mg po single dose, 2 hours after the 13 th clarithromycin dose		Gorski 1998
217	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 7 days Midazolam: 8 mg po single dose, 2 hours after the 13 th clarithromycin dose		Gurley 2006
223	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 7 days Midazolam: 8 mg po single dose, 2 hours after the 13 th clarithromycin dose		Gurley 2008a
354	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 4 days Midazolam: 3 mg po single dose, 0.25 hours after the 7 th clarithromycin dose		Markert 2013
1099	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 5 days Midazolam: 0.01 mg po single dose, administered simultaneously with the 7 th clarithromycin dose		Pruksaritanont 2017
2027	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 7 days Midazolam: 0.05 mg/kg iv single dose, 2 hours after the 13 th clarithromycin dose		Quinney 2008
2030	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 7 days Midazolam: 3.5 mg po single dose, 2 hours after the 13 th clarithromycin dose		Quinney 2008
2004	CYP3A4	Clarithromycin / midazolam	Rifampicin: 300 mg po QD for 7 days Wash-out phase for 3 days Clarithromycin: 250 mg po BID for 3 days Midazolam: 1 mg po single dose, 12 hours after the last rifampicin dose and again 12 hours after the last clarithromycin dose	Only assessment in Caucasian subjects simulated. AUC _{0-6h} ratio reported and simulated for comparison.	van Dyk 2018
469	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 250 mg po BID for 5 days Midazolam: 15 mg po single dose, 1.5 hours after the 9 th clarithromycin dose		Yeates 1997

Clarithromycin - Triazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Clarithromycin-Triazolam-DDI/releases/tag/v1.0>

The clarithromycin-triazolam interaction was evaluated using one clinical DDI study ([Greenblatt 1998a](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Clinical study
1102	CYP3A4	Clarithromycin / triazolam	Clarithromycin: 500 mg po twice daily at irregular time intervals for 2 days Triazolam: 0.125 mg po single dose, 1 hour after the 3 rd clarithromycin dose	Greenblatt 1998a

Erythromycin - Alfentanil DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Erythromycin-Alfentanil-DDI/releases/tag/v1.0>

The erythromycin-alfentanil interaction was evaluated using one clinical DDI study ([Bartkowski 1989](#)) quantifying the interaction following two different dosing regimens. Additionally, the plasma concentration-time profile of an individual investigated in this study was subsequently reported in a later study ([Bartkowski 1993](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Clinical study
779	CYP3A4	Erythromycin / alfentanil	Erythromycin: 500 mg po single dose (enteric coated tablet containing erythromycin as free base) Alfentanil: 0.05 mg/kg iv single dose, 1.5 hours after erythromycin dose	Bartkowski 1989
780	CYP3A4	Erythromycin / alfentanil	Erythromycin: 500 mg po BID for 7 days (enteric coated tablet containing erythromycin as free base) Alfentanil: 0.05 mg/kg iv single dose, 1.5 hours after the 13 th erythromycin dose	Bartkowski 1989

Erythromycin - Alprazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Erythromycin-Alprazolam-DDI/releases/tag/v1.0>.

The erythromycin-alprazolam interaction was evaluated using one clinical DDI study ([Yasui 1996](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Clinical study
777	CYP3A4	Erythromycin / alprazolam	Erythromycin: 400 mg po TID for 10 days (filmcoated tablet containing erythromycin stearate) Alprazolam: 0.8 mg po single dose, 2 hours after the 22 nd erythromycin dose	Yasui 1996

Erythromycin - Midazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Erythromycin-Midazolam-DDI/releases/tag/v1.0>.

The erythromycin-midazolam interaction was evaluated using five clinical DDI studies quantifying the interaction following nine different dosing regimens ([Carls 2014](#), [Okudaira 2007](#), [Olkola 1993](#), [Swart 2002](#), [Zimmermann 1996](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
828	CYP3A4	Erythromycin / midazolam	Erythromycin: 250 mg po single dose (filmcoated tablet containing erythromycin stearate) Midazolam: 0.03 mg po single dose, 1 hour after erythromycin dose	AUC _{2-4h} ratio reported and simulated for comparison.	Carls 2014
829	CYP3A4	Erythromycin / midazolam	Erythromycin: 1000 mg single dose (filmcoated tablet containing erythromycin stearate) Midazolam: 0.03 mg po single dose, 1 hour after erythromycin dose	AUC _{2-4h} ratio reported and simulated for comparison.	Carls 2014
362	CYP3A4	Erythromycin / midazolam	Erythromycin: 200 mg po four times daily for 7 days (filmcoated tablet containing erythromycin stearate) Midazolam: 2.5 mg po single dose, 1 hour after the 5 th erythromycin dose	Subjects received 5 mg midazolam po in control phase	Okudaira 2007
363	CYP3A4	Erythromycin / midazolam	Erythromycin: 200 mg po four times daily for 7 days (filmcoated tablet containing erythromycin stearate) Midazolam: 2.5 mg po single dose, 1 hour after the 13 th erythromycin dose	Subjects received 5 mg midazolam po in control phase	Okudaira 2007
364	CYP3A4	Erythromycin / midazolam	Erythromycin: 200 mg po four times daily for 7 days (filmcoated tablet containing erythromycin stearate) Midazolam: 2.5 mg po single dose, 1 hour after the 25 th erythromycin dose	Subjects received 5 mg midazolam po in control phase	Okudaira 2007
368	CYP3A4	Erythromycin / midazolam	Erythromycin: 500 mg po TID for 6 days (enteric coated tablet containing erythromycin as free base) Midazolam: 0.05 mg/kg iv single dose, 2 hours after the 17 th erythromycin dose		Olkola 1993
366	CYP3A4	Erythromycin / midazolam	Erythromycin: 500 mg po TID for 6 days (enteric coated tablet containing erythromycin as free base) Midazolam: 15 mg po single dose, 2 hours after the 17 th erythromycin dose		Olkola 1993
420	CYP3A4	Erythromycin / midazolam	Erythromycin: 500 mg po QID for 5 days (filmcoated tablet containing erythromycin stearate) Midazolam: 0.075 mg/kg mg iv single dose, together with the 96 th erythromycin dose		Swart 2002
471	CYP3A4	Erythromycin / midazolam	Erythromycin: 500 mg po TID for 5 days (filmcoated tablet containing erythromycin stearate) Midazolam: 0.8 mg po single dose, 1.5 hours after the 13 th erythromycin dose		Zimmermann 1996

Erythromycin - Triazolam DDI

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

The erythromycin-alprazolam interaction was evaluated using two clinical DDI studies ([Greenblatt 1998](#), [Phillips 1986](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Clinical study
781	CYP3A4	Erythromycin / triazolam	Erythromycin: 500 mg po twice daily for 2 days Triazolam: 0.125 mg po single dose, 1 hour after the 3rd erythromycin dose	Greenblatt 1998
757	CYP3A4	Erythromycin / triazolam	Erythromycin: 333 mg po TID for 3 days Triazolam: 0.5 mg po single dose, together with the last erythromycin dose	Phillips 1986

Fluvoxamine - Alprazolam DDI

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

The fluvoxamine-alprazolam interaction was evaluated using one clinical DDI study quantifying the interaction following the first dose and in steady-state different doses ([Fleishaker 1994](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Clinical study
1104	CYP3A4	Fluvoxamine / alprazolam	Fluvoxamine: 50 mg fluvoxamine maleate QD for 3 days, followed by 100 mg fluvoxamine maleate QD for 7 days Alprazolam: 1 mg po four times daily on Day 7 starting together with the 7 th fluvoxamine dose	Fleishaker 1994
1113	CYP3A4	Fluvoxamine / alprazolam	Fluvoxamine: 50 mg fluvoxamine maleate QD for 3 days, followed by 100 mg fluvoxamine maleate QD for 7 days Alprazolam: 1 mg po four times daily on Days 7 - 10 starting together with the 7 th fluvoxamine dose	Fleishaker 1994

Fluvoxamine - Midazolam DDI

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

The fluvoxamine / midazolam interaction was evaluated using two clinical DDI studies ([Kashuba 1998](#), [Lam 2003](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
2007	CYP3A4	Fluvoxamine / midazolam	Fluvoxamine: titrated to a daily dose of 150 mg (50 mg in the morning (6 a.m.), 50 mg in the evening (8 p.m.)) Midazolam: 0.025 mg/kg iv single dose, 3 hours after a morning fluvoxamine dose	Observed data: Baseline (control) assessment: mean of six measures (every 2 weeks) Phenotyping (fluvoxamine treatment) assessment: mean of two measures (14 days and 28 days after the start of fluvoxamine treatment), midazolam administered at 9 a.m. Simulated: the midazolam dose was administered 3 weeks after the start of fluvoxamine as an approximation of the two observed assessments	Kashuba 1998
1089	CYP3A4	Fluvoxamine / midazolam	Fluvoxamine: titrated to a daily dose of 200 mg (100 mg BID) Midazolam: 10 mg po single dose, 1 hour after a fluvoxamine steady state dose		Lam 2003

Itraconazole - Alprazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Itraconazole-Alprazolam-DDI/releases/tag/v1.0>.

The Itraconazole / alprazolam interaction was evaluated using oneclinical DDI studies ([Yasui 1998](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1026	CYP3A4	Itraconazole / alprazolam	Itraconazole: 200 mg po once daily (6 doses, capsule fasted) Alprazolam: 0.8 mg po single dose, 1 hour after 4th itraconazole dose		Yasui 1998

Itraconazole - Midazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Itraconazole-Midazolam-DDI/releases/tag/v1.0>.

The itraconazole / midazolam interaction was evaluated using seven clinical DDI studies including 12 different clinical settings ([Ahonen 1995](#), [Backman 1998](#), [Olkkola 1994](#), [Olkkola 1996](#), [Pruksaritanont 2017](#), [Templeton 2010](#), [Yu 2004](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
50	CYP3A4	Itraconazole / midazolam	Itraconazole: 100 mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg po single dose, simultaneous with 4th itraconazole dose		Ahonen 1995
58	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg po single dose, 2 hours after 4th itraconazole dose	Midazolam simulated as 15 mg for comparability to control phase, in which a 15 mg dose was given.	Backman 1998
59	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg po single dose, 4 days after 4th itraconazole dose	Midazolam simulated as 15 mg for comparability to control phase, in which a 15 mg dose was given.	Backman 1998
370	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg po single dose, 1 hours after 4th itraconazole dose		Olkkola 1994
377	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (6 doses, capsule fasted) Midazolam: 7.5 mg po single dose, 2 hours after 1st itraconazole dose		Olkkola 1996
378	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (6 doses, capsule fasted) Midazolam: 0.05 mg/kg iv single dose, 2 hours after 4th itraconazole dose		Olkkola 1996
379	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (6 doses, capsule fasted) Midazolam: 7.5 mg po single dose, 2 hours after 6th itraconazole dose		Olkkola 1996
1097	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (5 doses) (solution fasted) Midazolam: 10 µg po single dose, simultaneous with 4th itraconazole dose		Prueksaritanont 2017
424	CYP3A4	Itraconazole / midazolam	Itraconazole: 50 mg po single dose (solution fasted) Midazolam: 2 mg po single dose, 4 hours after itraconazole dose		Templeton 2010

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
425	CYP3A4	Itraconazole / midazolam	Itraconazole: 100 mg po single dose (solution fasted) Midazolam: 2 mg po single dose , 4 hours after itraconazole dose		Templeton 2010
426	CYP3A4	Itraconazole / midazolam	Itraconazole: 400 mg po single dose (solution fasted) Midazolam: 2 mg po single dose , 4 hours after itraconazole dose		Templeton 2010
199	CYP3A4	Itraconazole / midazolam	Itraconazole: 200 mg po once daily (4 doses, capsule fasted) Midazolam: 1 mg iv single dose, simultaneous with 4th itraconazole dose	Only assessment in CYP3A5*3/*3 genotype subjects simulated.	Yu 2004

Itraconazole - Triazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Itraconazole-Triazolam-DDI/releases/tag/v1.0>.

The itraconazole / triazolam interaction was evaluated using two clinical DDI studies including 5 different clinical settings ([Neuvonen 1996](#), [Varhe 1994](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1078	CYP3A4	Itraconazole / triazolam	Itraconazole: 200 mg po single dose (capsule fasted) triazolam: 0.25 mg po single dose , simultaneous with itraconazole dose	3 hours fasting before triazolam/itraconazole administration	Neuvonen 1996
1079	CYP3A4	Itraconazole / triazolam	Itraconazole: 200 mg po single dose (capsule fed) triazolam: 0.25 mg po single dose , 3 hours after itraconazole dose	itraconazole dose was taken after lunch	Neuvonen 1996
1080	CYP3A4	Itraconazole / triazolam	Itraconazole: 200 mg po single dose (capsule fed) triazolam: 0.25 mg po single dose , 12 hours after itraconazole dose	itraconazole dose was taken with a snack, 3 hours fasting before triazolam administration	Neuvonen 1996
1081	CYP3A4	Itraconazole / triazolam	Itraconazole: 200 mg po single dose (capsule fed) triazolam: 0.25 mg po single dose , 24 hours after itraconazole dose	itraconazole dose was taken with a snack, 3 hours fasting before triazolam administration	Neuvonen 1996
1029	CYP3A4	Itraconazole / triazolam	Itraconazole: 200 mg po once daily (4 doses, capsule fasted) triazolam: 0.25 mg po single dose , 1 hour after 4th itraconazole dose		Varhe 1994

Verapamil - Midazolam DDI

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

The itraconazole / midazolam interaction was evaluated using two clinical DDI studies including 3 different clinical settings ([Backman 1994](#), [Wang 2005](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1108	CYP3A4	Verapamil / midazolam	Verapamil: 80 mg po three times a day (5 doses) Midazolam: 15 mg po single dose, 1 hours after 4th verapamil dose		Backman 1994
1111	CYP3A4	Verapamil / midazolam	Verapamil: 240 mg po once daily (7 doses, sustained release) Midazolam: 0.05 mg/kg iv single dose, 24 hours after the 7th verapamil dose		Wang 2005
1116	CYP3A4	Verapamil / midazolam	Verapamil: 240 mg po once daily (7 doses, sustained release) Midazolam: 4 mg/kg po single dose, 48 hours after the 7th verapamil dose		Wang 2005

Efavirenz - Alfentanil-DDI

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

The efavirenz-alfentanil interaction was evaluated using one clinical DDI study that includes iv and oral administration of alfentanil ([Kharasch 2012](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
801	CYP3A4	Efavirenz / alfentanil	Efavirenz: 600 mg po OD for 20 days Alfentanil: 43 µg/kg po single dose, 1/2 hour after the 15 th efavirenz dose		Kharasch 2012
803	CYP3A4	Efavirenz / alfentanil	Efavirenz: 600 mg po OD for 20 days Alfentanil: 15 µg/kg iv single dose, 1/2 hour after the 16 th efavirenz dose		Kharasch 2012

Efavirenz - Midazolam DDI

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

The efavirenz-midazolam interaction was evaluated using two clinical DDI studies, one using single dose and one using one multiple dose administration of efavirenz ([Katzenmaier 2010](#), [Mikus 2017](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
2041	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po OD over 14 days Midazolam: 3 mg po single dose on day 14 together with efavirenz dose		Katzenmaier 2010
2044	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 4 mg po single dose, 12 hours (day 1) after efavirenz dose		Mikus 2017
2045	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 2 mg iv single dose, 18 hours (day 1) after efavirenz dose		Mikus 2017
2047	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 4 mg po single dose, 132 hours (day 6) after efavirenz dose		Mikus 2017
2048	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 2 mg iv single dose, 138 hours (day 6) after efavirenz dose		Mikus 2017
2049	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 4 mg po single dose, 252 hours (day 11) after efavirenz dose		Mikus 2017
2050	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 2 mg iv single dose, 258 hours (day 11) after efavirenz dose		Mikus 2017
2051	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 4 mg po single dose, 372 hours (day 16) after efavirenz dose		Mikus 2017
2052	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 2 mg iv single dose, 378 hours (day 16) after efavirenz dose		Mikus 2017
2053	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 4 mg po single dose, 516 hours (* day 22) after efavirenz dose		Mikus 2017
2054	CYP3A4	Efavirenz / midazolam	Efavirenz: 400 mg po SD on day 1 Midazolam: 2 mg iv single dose, 522 hours (day 22) after efavirenz dose		Mikus 2017

Rifampicin - Alfentanil DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Rifampicin-Alfentanil-DDI/releases/tag/v1.0>.

The rifampicin / midazolam interaction was evaluated using 5 clinical DDI studies including 16 different clinical settings ([Kharasch 1997](#), [Kharasch 2004](#), [Kharasch 2011](#), [Kharasch 2011b](#), [Phimmasone 2001](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
278	CYP3A4	Rifampicin / alfentanil	Rifampicin: 600 mg po once daily (5 doses) Alfentanil: 20 µg/kg IV single dose, 24.5 h after 5th rifampicin dose		Kharasch 1997
283	CYP3A4	Rifampicin / alfentanil	Rifampicin: 600 mg po once daily (6 doses) Alfentanil: 15 µg/kg IV single dose, 9 h after 5th rifampicin dose		Kharasch 2004
288	CYP3A4	Rifampicin / alfentanil	Rifampicin: 600 mg po once daily (6 doses) Alfentanil: 60 µg/kg PO single dose, 9 h after 6th rifampicin dose		Kharasch 2004
299	CYP3A4	Rifampicin / alfentanil	Rifampicin: 5 mg po once daily (6 doses) Alfentanil: 15 µg/kg IV single dose, 13 h after 5th rifampicin dose		Kharasch 2011
300	CYP3A4	Rifampicin / alfentanil	Rifampicin: 10 mg po once daily (6 doses) Alfentanil: 15 µg/kg IV single dose, 13 h after 5th rifampicin dose		Kharasch 2011
301	CYP3A4	Rifampicin / alfentanil	Rifampicin: 25 mg po once daily (6 doses) Alfentanil: 15 µg/kg IV single dose, 13 h after 5th rifampicin dose		Kharasch 2011
302	CYP3A4	Rifampicin / alfentanil	Rifampicin: 75 mg po once daily (6 doses) Alfentanil: 15 µg/kg IV single dose, 13 h after 5th rifampicin dose		Kharasch 2011
309	CYP3A4	Rifampicin / alfentanil	Rifampicin: 5 mg po once daily (6 doses) Alfentanil: 75 µg/kg PO single dose, 13 h after 6th rifampicin dose		Kharasch 2011
310	CYP3A4	Rifampicin / alfentanil	Rifampicin: 10 mg po once daily (6 doses) Alfentanil: 75 µg/kg PO single dose, 13 h after 6th rifampicin dose		Kharasch 2011

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
311	CYP3A4	Rifampicin / alfentanil	Rifampicin: 25 mg po once daily (6 doses) Alfentanil: 75 µg/kg PO single dose, 13 h after 6th rifampicin dose		Kharasch 2011
312	CYP3A4	Rifampicin / alfentanil	Rifampicin: 75 mg po once daily (6 doses) Alfentanil: 75 µg/kg PO single dose, 13 h after 6th rifampicin dose		Kharasch 2011
763	CYP3A4	Rifampicin / alfentanil	Rifampicin: 600 mg po once daily (6 doses) Alfentanil: 1 mg IV single dose, 12 h after 5th rifampicin dose	sequential administration of intravenous unlabeled alfentanil and oral deuterated alfentanil	Kharasch 2011b
771	CYP3A4	Rifampicin / alfentanil	Rifampicin: 600 mg po once daily (6 doses) Alfentanil: 4 mg PO single dose, 15 h after 5th rifampicin dose	sequential administration of intravenous unlabeled alfentanil and oral deuterated alfentanil	Kharasch 2011b
767	CYP3A4	Rifampicin / alfentanil	Rifampicin: 600 mg po once daily (6 doses) Alfentanil: 1 mg IV single dose, 12 h after 6th rifampicin dose	simultaneous administration of intravenous unlabeled alfentanil and oral deuterated alfentanil	Kharasch 2011b
775	CYP3A4	Rifampicin / alfentanil	Rifampicin: 600 mg po once daily (6 doses) Alfentanil: 4 mg PO single dose, 12 h after XXth rifampicin dose	simultaneous administration of intravenous unlabeled alfentanil and oral deuterated alfentanil	Kharasch 2011b
391	CYP3A4	Rifampicin / alfentanil	Rifampicin: 600 mg po once daily (5 doses) Alfentanil: 15 µg/kg IV single dose, 11 h after 5th rifampicin dose		Phimmasone 2001

Rifampicin - Alprazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Rifampicin-Alprazolam-DDI/releases/tag/v1.0>.

The rifampicin-alprazolam interaction was evaluated using two clinical DDI studies quantifying the interaction in three clinical settings ([Gashaw 2003](#), [Schmider 1999](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comments	Clinical study
2009	CYP3A4	Rifampicin / alprazolam	Rifampicin: 450 mg, five doses at irregular times intervals over 4 days Alprazolam: 1 mg po single dose, 14 hours after the last rifampicin dose		Gashaw 2003
2010	CYP3A4	Rifampicin / alprazolam	Rifampicin: 450 mg, five doses at irregular times intervals over 4 days followed by a wash-out phase for 14 days Alprazolam: 1 mg po single dose after the wash-out phase (i.e. 350 hours after the last rifampicin dose)		Gashaw 2003
1001	CYP3A4	Rifampicin / alprazolam	Rifampicin: 450 mg po QD for 4 days Alprazolam: 1 mg po single dose, 24 hours after the last rifampicin dose	Administration time of alprazolam relative to rifampin not reported; it was assumed that alprazolam was administered 24h after the last rifampin dose	Schmider 1999

Rifampicin - Midazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Rifampicin-Midazolam-DDI/releases/tag/v1.0>.

The rifampicin / midazolam interaction was evaluated using 21 clinical DDI studies including 35 different clinical settings ([Backman 1996](#), [Backman 1998](#), [Chung 2006](#), [Eap 2004](#), [Gorski 2003](#), [Gurley 2006](#), [Gurley 2008a](#), [Kharasch 1997](#), [Kharasch 2004](#), [Kharasch 2011](#), [Kim 2018](#), [Link 2008](#), [Phimmasone 2001](#), [Pruksaranant 2017](#), [Reitman 2011](#), [Shin 2013](#), [Shin 2016](#), [Szalat 2007](#), [van Dyk 2018](#), [Wiesinger 2011](#), [Yu 2004](#)).

In the study by [Eap 2004](#), the induction of CYP3A4 by rifampicin was evaluated using first 0.075 mg and one day later 7.5 and orally administered midazolam. The magnitude of the DDI with the low dose was much lower than for the higher dose (AUC ratio 0.44 vs. 0.09), which can actually only be explained by issues with the limit of detection after induction for the small midazolam dose considering the entire set of observed data. Therefore, as well as in [Almond 2016](#), the dataset of the low dose setting was excluded from this analysis.

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
54	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (5 doses) Midazolam: 15 mg PO single dose, 17 h after 5th rifampicin dose		Backman 1996
56	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (5 doses) Midazolam: 15 mg PO single dose, 17 h after 5th rifampicin dose (Phase IV)		Backman 1998
57	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (5 doses) Midazolam: 15 mg PO single dose, 7 days after 5th rifampicin dose (Phase V)		Backman 1998
113	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (9 doses) Midazolam: 0.075 mg/kg PO single dose, 22 h after 7th rifampicin dose		Chung 2006
129	CYP3A4	Rifampicin / midazolam	Rifampicin: 450 mg po once daily (5 doses) Midazolam: 0.075 mg PO single dose, 18 h after 4th rifampicin dose	Dataset excluded (see comment above)	Eap 2004
132	CYP3A4	Rifampicin / midazolam	Rifampicin: 450 mg po once daily (5 doses) Midazolam: 7.5 mg PO single dose, 18 h after 5th rifampicin dose		Eap 2004
179	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (7 doses) Midazolam: 0.05 mg/kg IV single dose, 12 h after 6th rifampicin dose		Gorski 2003
177	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (7 doses) Midazolam: 6 mg PO single dose, 12 h after 6th rifampicin dose	Subjects received a 4 mg midazolam dose in control phase.	Gorski 2003
215	CYP3A4	Rifampicin / midazolam	Rifampicin: 300 mg po twice daily (14 doses, 7 days) Midazolam: 8 mg PO single dose, 2 h after 13th rifampicin dose		Gurley 2006
221	CYP3A4	Rifampicin / midazolam	Rifampicin: 300 mg po twice daily (14 doses, 7 days) Midazolam: 8 mg PO single dose, 2 h after 13th rifampicin dose		Gurley 2008a
276	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (5 doses) Midazolam: 1 mg IV single dose, 24 h after 5th rifampicin dose		Kharasch 1997

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
280	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (6 doses) Midazolam: 1 mg IV single dose, 8 h after 5th rifampicin dose		Kharasch 2004
286	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (6 doses) Midazolam: 3 mg PO single dose, 8 h after 6th rifampicin dose		Kharasch 2004
294	CYP3A4	Rifampicin / midazolam	Rifampicin: 5 mg po once daily (6 doses) Midazolam: 1 mg IV single dose, 12 h after 5th rifampicin dose		Kharasch 2011
295	CYP3A4	Rifampicin / midazolam	Rifampicin: 10 mg po once daily (6 doses) Midazolam: 1 mg IV single dose, 12 h after 5th rifampicin dose		Kharasch 2011
296	CYP3A4	Rifampicin / midazolam	Rifampicin: 25 mg po once daily (6 doses) Midazolam: 1 mg IV single dose, 12 h after 5th rifampicin dose		Kharasch 2011
297	CYP3A4	Rifampicin / midazolam	Rifampicin: 75 mg po once daily (6 doses) Midazolam: 1 mg IV single dose, 12 h after 5th rifampicin dose		Kharasch 2011
304	CYP3A4	Rifampicin / midazolam	Rifampicin: 5 mg po once daily (6 doses) Midazolam: 3 mg PO single dose, 12 h after 6th rifampicin dose		Kharasch 2011
305	CYP3A4	Rifampicin / midazolam	Rifampicin: 10 mg po once daily (6 doses) Midazolam: 3 mg PO single dose, 12 h after 6th rifampicin dose		Kharasch 2011
306	CYP3A4	Rifampicin / midazolam	Rifampicin: 25 mg po once daily (6 doses) Midazolam: 3 mg PO single dose, 12 h after 6th rifampicin dose		Kharasch 2011
307	CYP3A4	Rifampicin / midazolam	Rifampicin: 75 mg po once daily (6 doses) Midazolam: 3 mg PO single dose, 12 h after 6th rifampicin dose		Kharasch 2011
2036	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (10 doses) Midazolam: 2.5 mg IV single dose, simultaneous with 10th rifampicin dose	Only assessment in male subjects simulated. Subjects received a 1 mg midazolam dose in control phase. Observed reported dose-normalized AUCR back-calculated to non dose-normalized AUCR.	Kim 2018

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
342	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (6 doses) Midazolam: 2 mg IV single dose, 24 h after 6th rifampicin dose		Link 2008
344	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (6 doses) Midazolam: 7.5 mg PO single dose, 24 h after 6th rifampicin dose		Link 2008
389	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (5 doses) Midazolam: 1 mg IV single dose, 10 h after 5th rifampicin dose		Phimmasone 2001
1098	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po SD Midazolam: 10 µg PO single dose, simultaneous with rifampicin dose		Prueksaritanont 2017
392	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (4 weeks) Midazolam: 2 mg PO single dose, simultaneous with 28th rifampicin dose	PK data of midazolam admintsered 28 days after the last rifampicin dose served as <i>control</i> (reference)	Reitman 2011
393	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (4 weeks) Midazolam: 2 mg PO single dose, 7 days after 28th rifampicin dose	PK data of midazolam admintsered 28 days after the last rifampicin dose served as <i>control</i> (reference)	Reitman 2011
394	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (4 weeks) Midazolam: 2 mg PO single dose, 14 days after 28th rifampicin dose	PK data of midazolam admintsered 28 days after the last rifampicin dose served as <i>control</i> (reference)	Reitman 2011
1092	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (10 doses) Midazolam: 2.5 mg IV single dose, simultaneous h with 10th rifampicin dose	Subjects received a 1 mg midazolam dose in control phase. Observed reported dose-normalized AUCR back-calculated to non dose-normalized AUCR.	Shin 2013
1095	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (10 doses) Midazolam: 2.5 mg IV single dose, simultaneous h with 10th rifampicin dose	Subjects received a 1 mg midazolam dose in control phase. Observed reported dose-normalized AUCR back-calculated to non dose-normalized AUCR.	Shin 2016
422	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (7 doses) Midazolam: 0.05 mg/kg IV single dose, 12 h after 12th rifampicin dose		Szalat 2007
2002	CYP3A4	Rifampicin / midazolam	Rifampicin: 300 mg po once daily (7 doses) Midazolam: 1 mg PO single dose, 12 h after 7th rifampicin dose	Only assessment in Caucasian subjects simulated. AUC _{0-6h} ratio reported and simulated for comparison.	van Dyk 2018

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
204	CYP3A4	Rifampicin / midazolam	Rifampicin: 10 mg po once daily (11 doses) Midazolam: 1 mg PO single dose, 12 h after 8th rifampicin dose	In the study midazolam was coadministered with either etonogestrel, dienogest, drospirenone, levonorgestrel or norethindrone.	Wiesinger 2020
205	CYP3A4	Rifampicin / midazolam	Rifampicin: 11 doses of 10 mg po once daily, followed by 11 doses of 600 mg po once daily Midazolam: 1 mg PO single dose, 12 h after 8th 600 mg rifampicin dose (after the 19 th overall rifampicin dose)	In the study midazolam was coadministered with either etonogestrel, dienogest, drospirenone, levonorgestrel or norethindrone.	Wiesinger 2020
202	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily (10 doses) Midazolam: 2 mg IV single dose, 24 h after 10th rifampicin dose	Only assessment in CYP3A5*3/*3 genotype subjects simulated. Subjects received a 1 mg midazolam dose in control phase. Observed reported dose-normalized AUCR back-calculated to non dose-normalized AUCR.	Yu 2004

Rifampicin - Triazolam DDI

The release of the snapshot containing the respective simulations can be found here:

<https://github.com/Open-Systems-Pharmacology/Rifampicin-Triazolam-DDI/releases/tag/v1.0>.

The rifampicin-triazolam interaction was evaluated using one clinical DDI study ([Villikka 1997](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comments	Clinical study
1004	CYP3A4	Rifampicin / triazolam	Rifampicin: 600 mg QD for 5 days Triazolam: 0.5 mg po single dose, 17 hours after the last rifampicin dose		Villikka 1997

2 Qualification of Use Case CYP3A4-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:

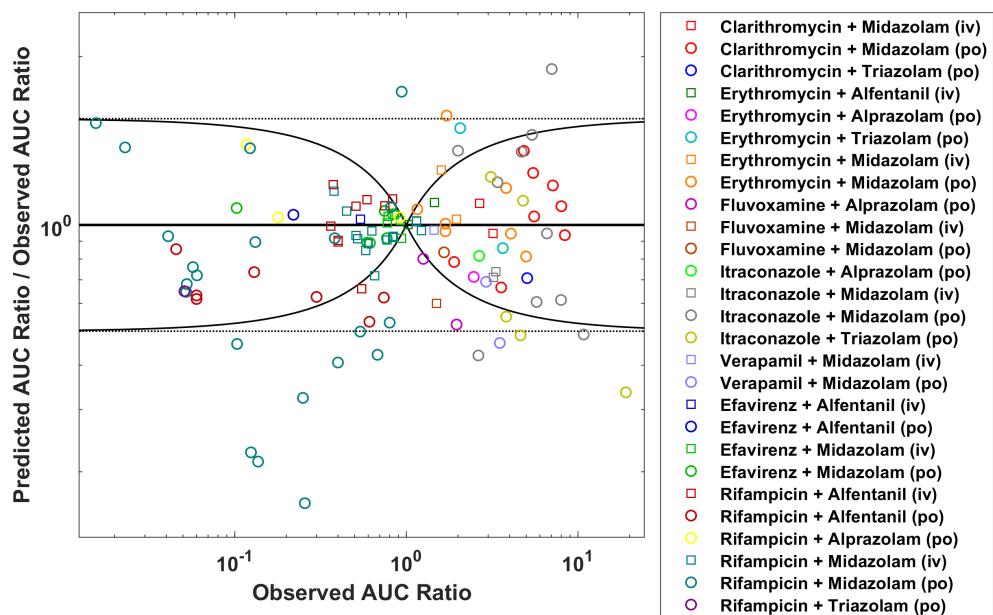
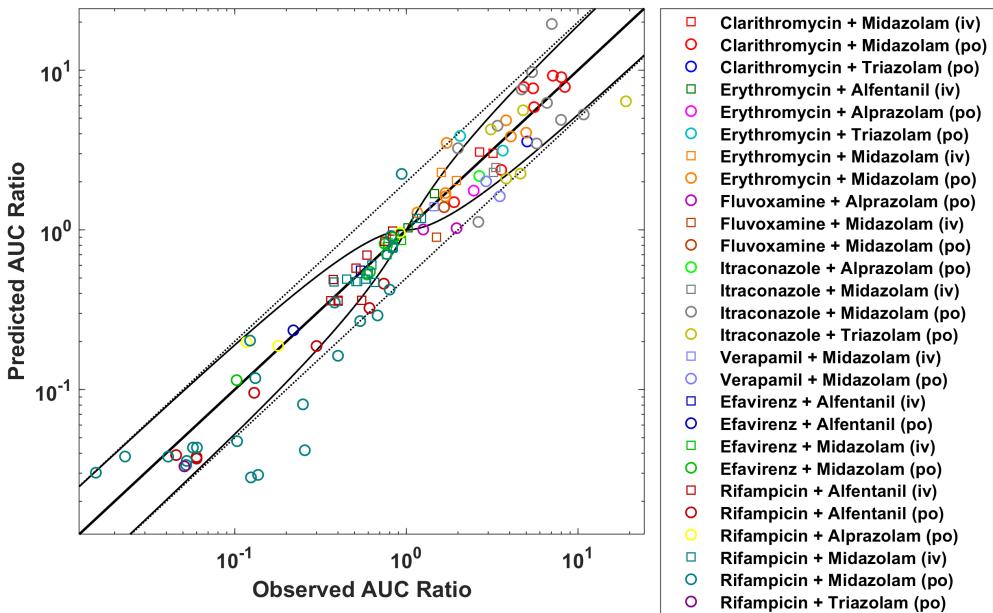
- predicted (*Pred*) vs. observed (*Obs*) plots
- $Pred/Obs$ vs. *Obs* plots
- geometric mean fold error (GMFE):

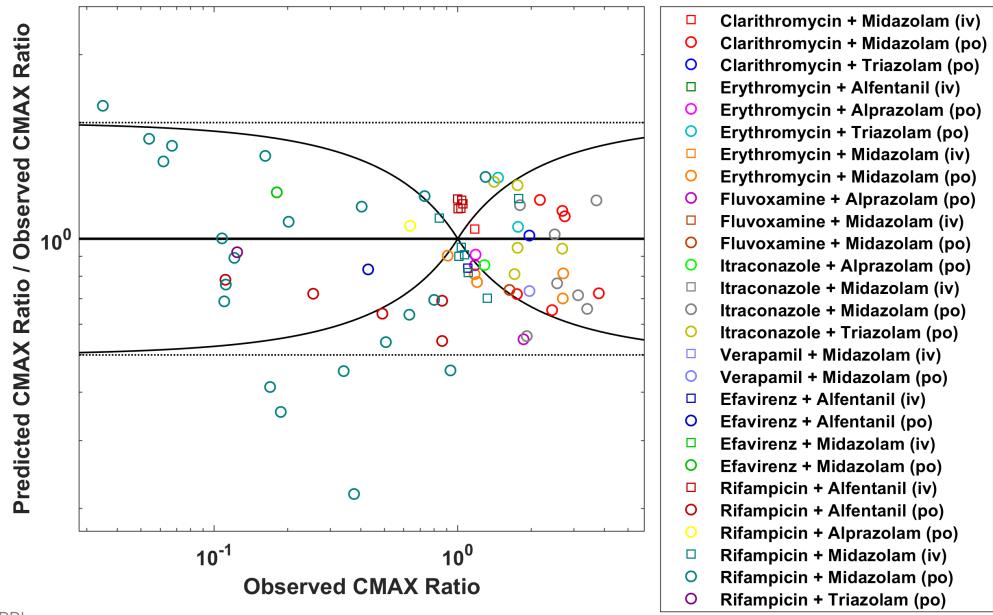
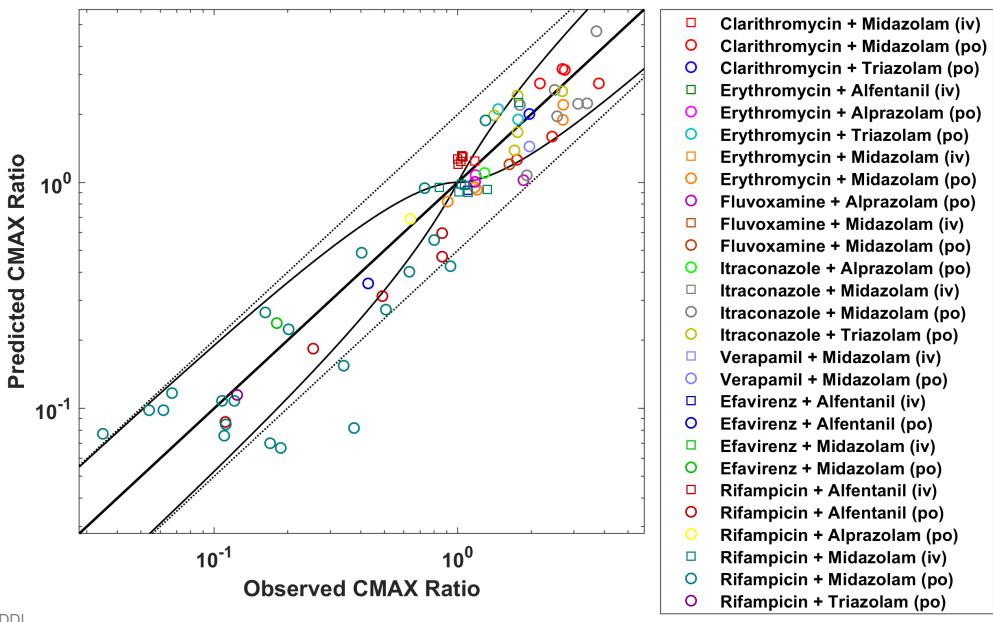
$$10^{\frac{\sum |\log(\frac{Pred}{Obs})|}{n}}$$

- 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.





GMFE (AUC) = 1.398725

GMFE (CMAX) = 1.370608

AUC	Number	Ratio [%]
Points total	118	-
Points within Guest et al.	88	74.5763
Points within 2-fold	102	86.4407

CMAX	Number	Ratio [%]
Points total	76	-
Points within Guest et al.	43	56.5789
Points within 2-fold	70	92.1053

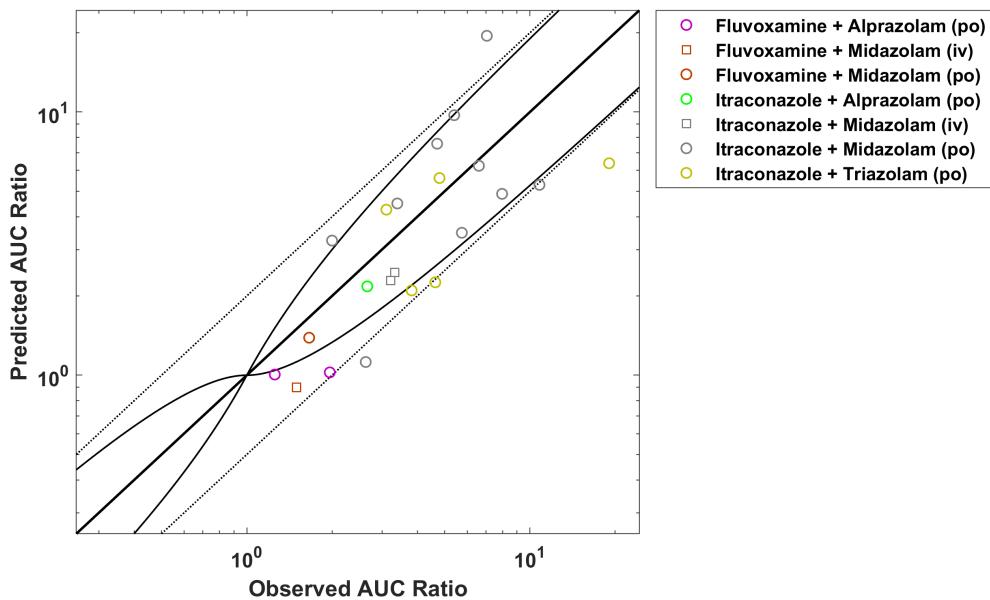
DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
175	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, IV	3.0681	2.6667	1.1506	1.2413	-	-	Gorski 1998
2027	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, IV	3.024	3.2	0.94501	1.2413	1.1724	1.0587	Quinney 2008
173	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	9.241	7.1429	1.2937	3.0765	-	-	Gorski 1998
217	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	7.8536	8.3929	0.93575	2.7414	3.7956	0.72225	Gurley 2006
223	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	7.6974	5.4834	1.4038	2.7414	2.1743	1.2608	Gurley 2008a
354	Clarithromycin, 500 mg, PO, MD BID (4 days)	Midazolam, PO	5.871	5.5556	1.0568	2.6201	-	-	Markert 2013
1099	Clarithromycin, 500 mg, PO, MD BID (5 days)	Midazolam, PO	7.8476	4.84	1.6214	3.177	2.69	1.181	Pruksaritanont 2017
2030	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	9.0373	8	1.1297	3.1442	2.75	1.1433	Quinney 2008
2004	Clarithromycin, 250 mg, PO, MD BID (3 days)	Midazolam, PO	1.4921	1.9	0.78531	1.258	1.75	0.71885	van Dyk 2018
469	Clarithromycin, 250 mg, PO, MD BID (5 days)	Midazolam, PO	2.3757	3.5716	0.66518	1.5939	2.44	0.65325	Yeates 1996
1102	Clarithromycin, 500 mg, PO, MD OD (2 days)	Triazolam, PO	3.5766	5.06	0.70684	2.0063	1.968	1.0194	Greenblatt 1998a
779	Erythromycin, 500 mg, PO, SD	Alfentanil, IV	1.0294	1.0262	1.0031	1	-	-	Bartkowski 1989
780	Erythromycin, 500 mg, PO, MD BID (6 days)	Alfentanil, IV	1.6891	1.4611	1.1561	1.0269	-	-	Bartkowski 1989
777	Erythromycin, 400 mg, PO, MD TID (10 days)	Alprazolam, PO	1.7608	2.4716	0.71239	1.0766	1.1833	0.90984	Yasui 1996
781	Erythromycin, 500 mg, PO, MD OD (2 days)	Triazolam, PO	3.1373	3.65	0.85953	1.8985	1.768	1.0738	Greenblatt 1998a
757	Erythromycin, 333 mg, PO, MD TID (3 days)	Triazolam, PO	3.8729	2.0597	1.8803	2.109	1.4643	1.4403	Phillips 1986
420	Erythromycin, 500 mg, PO, MD QID (5 days)	Midazolam, IV	2.2865	1.5978	1.431	1.027	-	-	Swart 2002
368	Erythromycin, 500 mg, PO, MD TID (7 days)	Midazolam, IV	2.0362	1.9619	1.0379	1.0191	-	-	Olkkola 1993
366	Erythromycin, 500 mg, PO, MD TID (7 days)	Midazolam, PO	3.8438	4.0674	0.94501	1.8908	2.7	0.70029	Olkkola 1993
471	Erythromycin, 500 mg, PO, MD TID (3 days)	Midazolam, PO	4.8518	3.8137	1.2722	2.205	2.7114	0.81322	Zimmermann 1996
362	Erythromycin, 200 mg, PO, MD QID (2 days)	Midazolam, PO	1.2849	1.16	1.1077	0.82212	0.90909	0.90434	Okudaira 2007
363	Erythromycin, 200 mg, PO, MD QID (4 days)	Midazolam, PO	1.6208	1.69	0.95905	0.92675	1.2	0.77229	Okudaira 2007
364	Erythromycin, 200 mg, PO, MD QID (7 days)	Midazolam, PO	1.7031	1.69	1.0077	0.94964	1.1727	0.80977	Okudaira 2007
828	Erythromycin, 250 mg, PO, SD	Midazolam, PO	3.5056	1.7178	2.0407	3.2106	-	-	Carls 2014
829	Erythromycin, 1000 mg, PO, SD	Midazolam, PO	4.0618	4.9912	0.8138	3.6258	-	-	Carls 2014
1104	Fluvoxamine, 50/100 mg, PO, MD OD (10 days), 50 mg day 1-3, then 100 mg	Alprazolam, PO	1.006	1.2551	0.80147	1.005	1.1769	0.85396	Fleishaker 1994
1113	Fluvoxamine, 50/100 mg, PO, MD OD (10 days), 50 mg day 1-3, then 100 mg	Alprazolam, PO	1.025	1.9631	0.52212	1.022	1.8619	0.54891	Fleishaker 1994
2007	Fluvoxamine, 50/100 mg, PO, MD BID (4 weeks), dose titration to 150 mg/day over 7 days: 50 mg in the evening for 3 days, 50 mg in the morning and evening for the next 3 days, then 50 mg in the morning and 100 mg in the evening	Midazolam, IV	0.90009	1.5	0.60006	0.24742	-	-	Kashuba 1998
1089	Fluvoxamine, 50/100 mg, PO, MD OD (12 days), titrated from 50 mg BID to 100 mg BID administered for 6 days	Midazolam, PO	1.3882	1.66	0.83627	1.2013	1.63	0.73701	Lam 2003
1026	Itraconazole, 200 mg, PO, MD OD (6 days)	Alprazolam, PO	2.1755	2.6627	0.81702	1.0999	1.2868	0.85474	Yasui 1998
378	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, IV	2.2908	3.2258	0.71016	1.0117	-	-	Olkkola 1996
199	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, IV	2.4587	3.3333	0.73761	1.0112	-	-	Yu 2004
50	Itraconazole, 100 mg, PO, MD OD (4 days)	Midazolam, PO	3.4762	5.7451	0.60507	1.9613	2.5588	0.7665	Ahonen 1995
58	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	4.8857	7.97	0.61301	2.2277	3.12	0.71402	Backman 1998
59	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	1.1226	2.63	0.42685	1.074	1.92	0.55939	Backman 1998
370	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	5.2845	10.8	0.48931	2.2377	3.4	0.65813	Olkkola 1994
377	Itraconazole, 200 mg, PO, SD	Midazolam, PO	4.4916	3.4	1.3211	2.1997	1.8	1.222	Olkkola 1996
379	Itraconazole, 200 mg, PO, MD OD (6 days)	Midazolam, PO	6.244	6.6	0.94606	2.5665	2.5	1.0266	Olkkola 1996
1097	Itraconazole, 200 mg, PO, MD OD (5 days)	Midazolam, PO	19.4647	7.04	2.7649	4.6651	3.71	1.2575	Pruksaritanont 2017

DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
424	Itraconazole, 50 mg, PO, SD	Midazolam, PO	3.2463	2	1.6232	2.2008	-	-	Templeton 2010
425	Itraconazole, 200 mg, PO, SD	Midazolam, PO	7.5749	4.7	1.6117	3.4395	-	-	Templeton 2010
426	Itraconazole, 400 mg, PO, SD	Midazolam, PO	9.718	5.4	1.7996	3.7303	-	-	Templeton 2010
1078	Itraconazole, 200 mg, PO, SD	Triazolam, PO	4.2543	3.11	1.3679	1.9806	1.41	1.4047	Neuvonen 1996
1079	Itraconazole, 200 mg, PO, SD	Triazolam, PO	5.6094	4.79	1.1711	2.4221	1.76	1.3762	Neuvonen 1996
1080	Itraconazole, 200 mg, PO, SD	Triazolam, PO	2.2531	4.63	0.48663	1.6677	1.76	0.94754	Neuvonen 1996
1081	Itraconazole, 200 mg, PO, SD	Triazolam, PO	2.0999	3.82	0.54971	1.3848	1.71	0.80984	Neuvonen 1996
1029	Itraconazole, 200 mg, PO, MD OD (4 days)	Triazolam, PO	6.3835	19.0287	0.33547	2.5312	2.6854	0.94257	Varhe 1994
1111	Verapamil, 240 mg, PO, MD OD (7 days)	Midazolam, IV	1.4026	1.4524	0.96572	1.1019	-	-	Wang 2005
1108	Verapamil, 80 mg, PO, MD TID (2 days)	Midazolam, PO	2.0133	2.9167	0.69028	1.4415	1.9692	0.732	Backman 1994
1116	Verapamil, 240 mg, PO, MD OD (7 days)	Midazolam, PO	1.6228	3.5056	0.46293	1.3474	-	-	Wang 2005
803	Efavirenz, 600 mg, PO, MD OD (19 days)	Alfentanil, IV	0.56016	0.54	1.0373	0.92176	1.0978	0.83962	Kharasch 2012
801	Efavirenz, 600 mg, PO, MD OD (19 days)	Alfentanil, PO	0.23512	0.22	1.0687	0.35697	0.42857	0.83293	Kharasch 2012
2045	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.83147	0.78538	1.0587	0.93223	-	-	Mikus 2017
2048	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.78703	0.77712	1.0127	0.91054	-	-	Mikus 2017
2050	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.85818	0.9375	0.9154	0.94266	-	-	Mikus 2017
2052	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.91246	0.85377	1.0687	0.96565	-	-	Mikus 2017
2054	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.94941	0.92217	1.0295	0.9806	-	-	Mikus 2017
2041	Efavirenz, 400 mg, PO, MD OD (14 days)	Midazolam, PO	0.11468	0.1027	1.1167	0.23823	0.1806	1.3191	Katzenmaier 2010
2044	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.52615	0.59055	0.89095	0.64634	-	-	Mikus 2017
2047	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.54604	0.61417	0.88907	0.63889	-	-	Mikus 2017
2049	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.70578	0.76968	0.91697	0.77859	-	-	Mikus 2017
2051	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.82	0.74803	1.0962	0.86911	-	-	Mikus 2017
2053	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.89691	0.83661	1.0721	0.92649	-	-	Mikus 2017
278	Rifampicin, 600 mg, PO, MD OD (5 days)	Alfentanil, IV	0.35994	0.36301	0.99152	0.89694	-	-	Kharasch 1997
283	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.48775	0.375	1.3007	1.2012	1.0033	1.1972	Kharasch 2004
299	Rifampicin, 5 mg, PO, MD OD (6 days)	Alfentanil, IV	0.98467	0.83	1.1863	1.3091	1.0392	1.2597	Kharasch 2011
300	Rifampicin, 10 mg, PO, MD OD (6 days)	Alfentanil, IV	0.8489	0.75	1.1319	1.2935	1.049	1.233	Kharasch 2011
301	Rifampicin, 25 mg, PO, MD OD (6 days)	Alfentanil, IV	0.69485	0.59	1.1777	1.2671	1	1.2671	Kharasch 2011
302	Rifampicin, 75 mg, PO, MD OD (6 days)	Alfentanil, IV	0.57591	0.51	1.1292	1.2354	1.0294	1.2001	Kharasch 2011
763	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.36165	0.4	0.90412	0.89854	-	-	Kharasch 2011b
767	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.35775	0.4	0.89439	0.89637	-	-	Kharasch 2011b
391	Rifampicin, 600 mg, PO, MD OD (5 days)	Alfentanil, IV	0.36297	0.55	0.65994	0.89919	-	-	Phimmasone 2001
288	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.038957	0.045631	0.85373	0.087	0.11111	0.783	Kharasch 2004
309	Rifampicin, 5 mg, PO, MD OD (6 days)	Alfentanil, PO	0.46082	0.74	0.62272	0.59606	0.86275	0.69088	Kharasch 2011
310	Rifampicin, 10 mg, PO, MD OD (6 days)	Alfentanil, PO	0.32444	0.61	0.53188	0.46881	0.86275	0.5434	Kharasch 2011
311	Rifampicin, 25 mg, PO, MD OD (6 days)	Alfentanil, PO	0.18757	0.3	0.62522	0.31358	0.4902	0.63971	Kharasch 2011
312	Rifampicin, 75 mg, PO, MD OD (6 days)	Alfentanil, PO	0.095562	0.13	0.73509	0.18365	0.2549	0.72046	Kharasch 2011
771	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.037884	0.06	0.6314	0.083994	-	-	Kharasch 2011b
775	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.037011	0.06	0.61684	0.082592	-	-	Kharasch 2011b

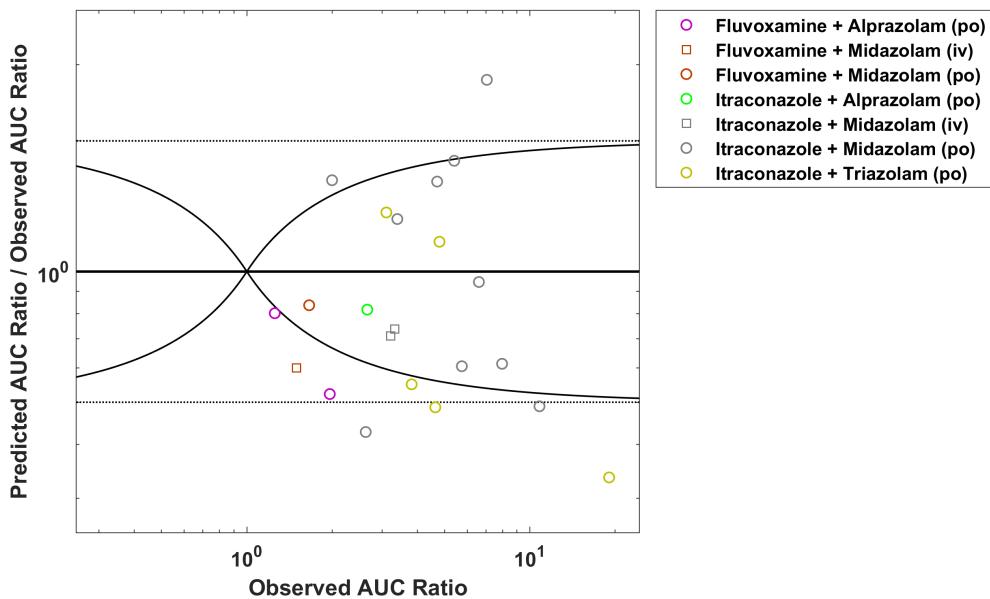
DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
2009	Rifampicin, 450 mg, PO, MD, q.d. for 5 days	Alprazolam, PO	0.18831	0.17935	1.05	0.67772	-	-	Gashaw 2003
2010	Rifampicin, 450 mg, PO, MD, q.d. for 5 days	Alprazolam, PO	0.96233	0.91667	1.0498	0.9951	-	-	Gashaw 2003
1001	Rifampicin, 450 mg, PO, MD OD (4 days)	Alprazolam, PO	0.19839	0.11726	1.6919	0.68932	0.63816	1.0802	Schnider 1999
179	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, IV	0.49099	0.44898	1.0936	0.75209	-	-	Gorski 2003
276	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, IV	0.47342	0.37931	1.2481	0.90482	-	-	Kharasch 1997
280	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, IV	0.4757	0.52113	0.91284	0.90853	1.01	0.89957	Kharasch 2004
294	Rifampicin, 5 mg, PO, MD OD (6 days)	Midazolam, IV	0.78052	0.84	0.9292	0.98019	1.0323	0.94956	Kharasch 2011
295	Rifampicin, 10 mg, PO, MD OD (6 days)	Midazolam, IV	0.69874	0.77	0.90745	0.9682	1.0645	0.90952	Kharasch 2011
296	Rifampicin, 25 mg, PO, MD OD (6 days)	Midazolam, IV	0.60481	0.63	0.96001	0.9493	0.83871	1.1319	Kharasch 2011
297	Rifampicin, 75 mg, PO, MD OD (6 days)	Midazolam, IV	0.53126	0.6	0.88544	0.92855	1.3226	0.70208	Kharasch 2011
2036	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.1815	1.15	1.0274	2.2563	-	-	Kim 2018
342	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, IV	0.47024	0.65501	0.71791	0.90365	1.106	0.81708	Link 2008
389	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, IV	0.47562	0.51	0.93258	0.907	-	-	Phimmasone 2001
1092	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.179	1.15	1.0252	2.2563	-	-	Shin 2013
1095	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.179	1.225	0.96247	2.2563	1.775	1.2712	Shin 2016
422	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, IV	0.491	0.57947	0.84732	0.75222	-	-	Szalat 2007
202	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	0.76842	0.83333	0.92211	1.9391	-	-	Yu 2004
54	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.038093	0.041	0.9291	0.098048	0.061818	1.5861	Backman 1996
56	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.038143	0.023	1.6584	0.098049	0.054	1.8157	Backman 1998
57	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.11806	0.132	0.89436	0.22359	0.202	1.1069	Backman 1998
113	Rifampicin, 600 mg, PO, MD OD (9 days)	Midazolam, PO	0.028231	0.12449	0.22677	0.070021	0.16957	0.41294	Chung 2006
132	Rifampicin, 450 mg, PO, MD OD (5 days)	Midazolam, PO	0.033758	0.052239	0.64622	0.08487	0.11154	0.7609	Eap 2004
177	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, PO	0.047548	0.10335	0.46006	0.11675	0.067039	1.7415	Gorski 2003
215	Rifampicin, 300 mg, PO, MD BID (7 days)	Midazolam, PO	0.043409	0.057161	0.75942	0.10788	0.12092	0.89216	Gurley 2006
221	Rifampicin, 300 mg, PO, MD BID (7 days)	Midazolam, PO	0.043409	0.060317	0.71968	0.10788	0.10762	1.0023	Gurley 2008a
286	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, PO	0.03579	0.052632	0.68001	0.075637	0.10989	0.6883	Kharasch 2004
304	Rifampicin, 5 mg, PO, MD OD (6 days)	Midazolam, PO	0.423	0.8	0.52875	0.55551	0.8	0.69438	Kharasch 2011
305	Rifampicin, 10 mg, PO, MD OD (6 days)	Midazolam, PO	0.29154	0.68	0.42874	0.42549	0.93333	0.45588	Kharasch 2011
306	Rifampicin, 25 mg, PO, MD OD (6 days)	Midazolam, PO	0.16305	0.4	0.40762	0.27343	0.50667	0.53966	Kharasch 2011
307	Rifampicin, 75 mg, PO, MD OD (6 days)	Midazolam, PO	0.080913	0.25	0.32365	0.15436	0.34	0.45399	Kharasch 2011
344	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, PO	0.030212	0.015549	1.943	0.07709	0.034865	2.2111	Link 2008
1098	Rifampicin, 600 mg, PO, SD	Midazolam, PO	2.2421	0.94	2.3853	1.88	1.3	1.4461	Prueksaritanont 2017
392	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.20286	0.123	1.6493	0.26564	0.162	1.6397	Reitman 2011
393	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.35124	0.383	0.91707	0.48815	0.403	1.2113	Reitman 2011
394	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.91664	0.815	1.1247	0.94285	0.731	1.2898	Reitman 2011
2002	Rifampicin, 300 mg, PO, MD OD (7 days)	Midazolam, PO	0.041745	0.25641	0.16281	0.08178	0.375	0.21808	van Dyk 2018
204	Rifampicin, 10 mg, PO, MD OD (22 days)	Midazolam, PO	0.26874	0.539	0.4986	0.40212	0.63265	0.6356	Wiesinger 2020
205	Rifampicin, 600 mg, PO, MD OD (22 days)	Midazolam, PO	0.029266	0.137	0.21362	0.06674	0.18755	0.35585	Wiesinger 2020
1004	Rifampicin, 600 mg, PO, MD OD (5 days)	Triazolam, PO	0.033096	0.051	0.64895	0.11455	0.12414	0.92277	Villikka 1997

Mechanism

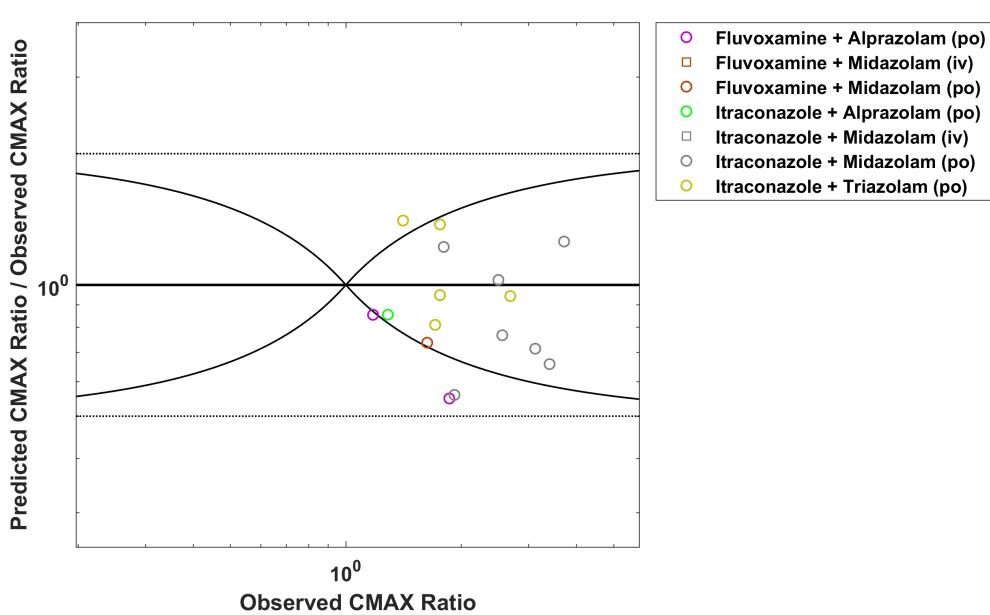
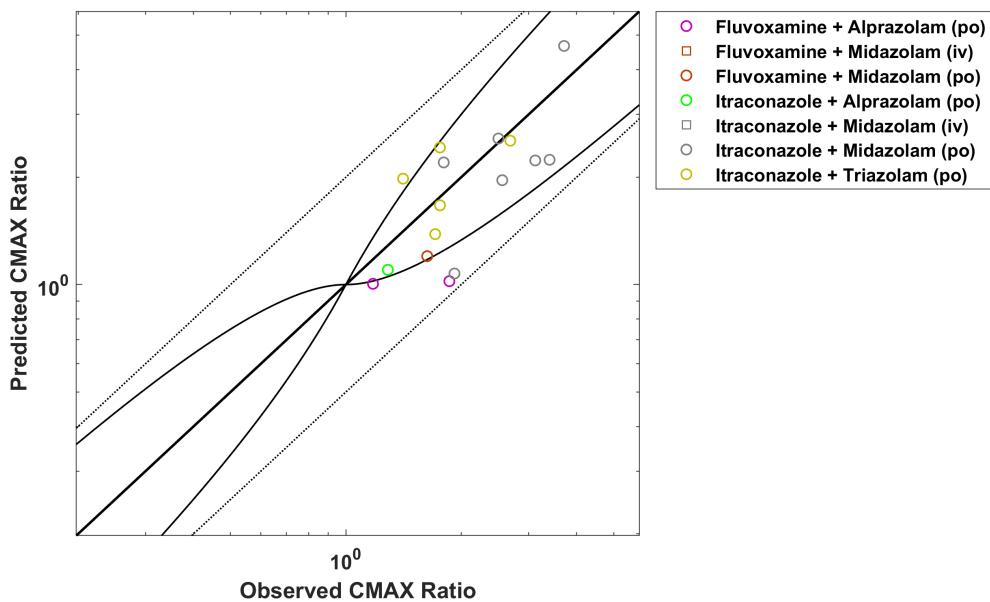
Competitive Inhibition



CYP3A4 DDI Competitive Inhibition



CYP3A4 DDI Competitive Inhibition



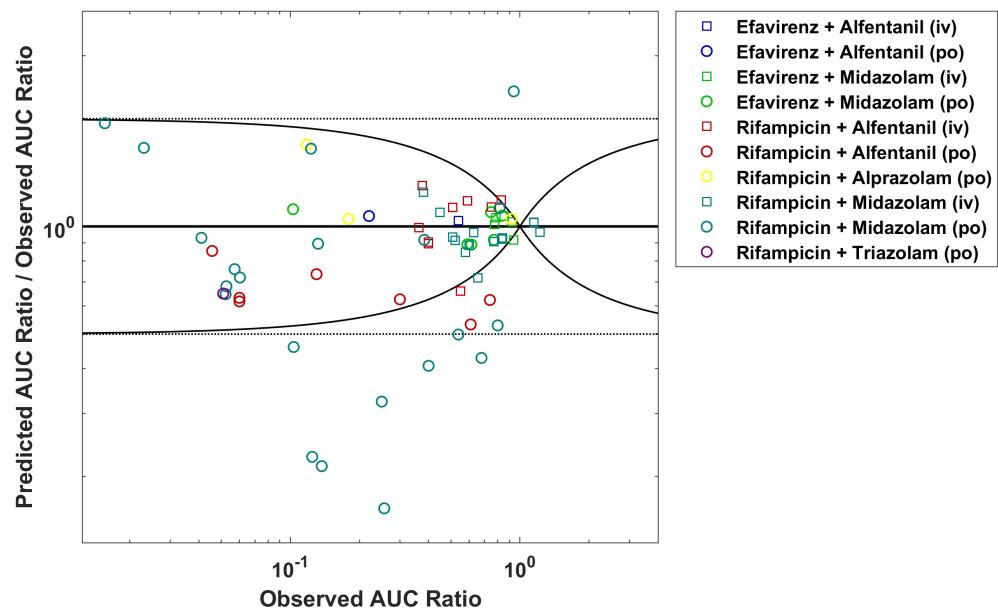
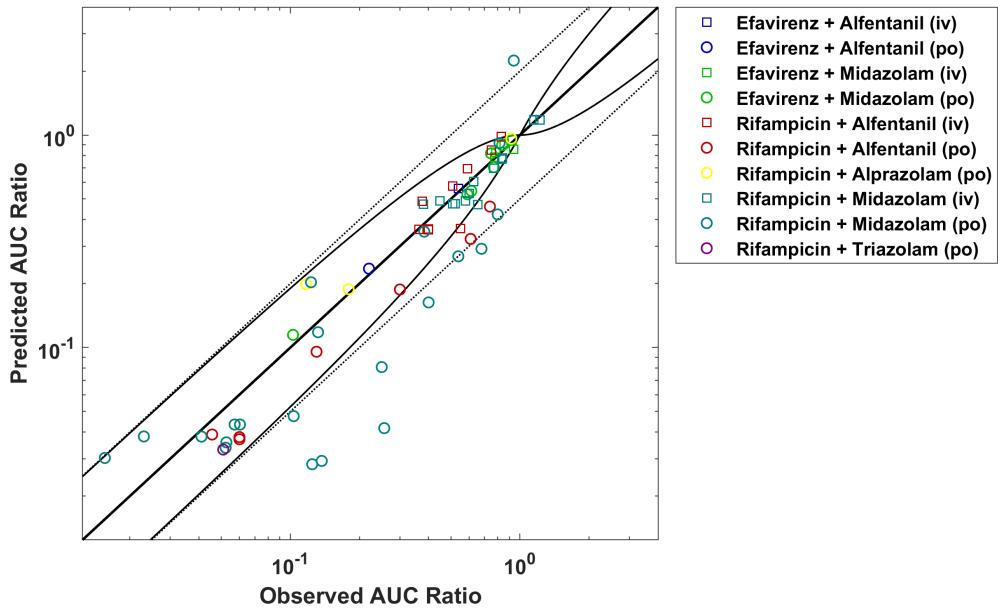
GMFE (AUC) = 1.630053

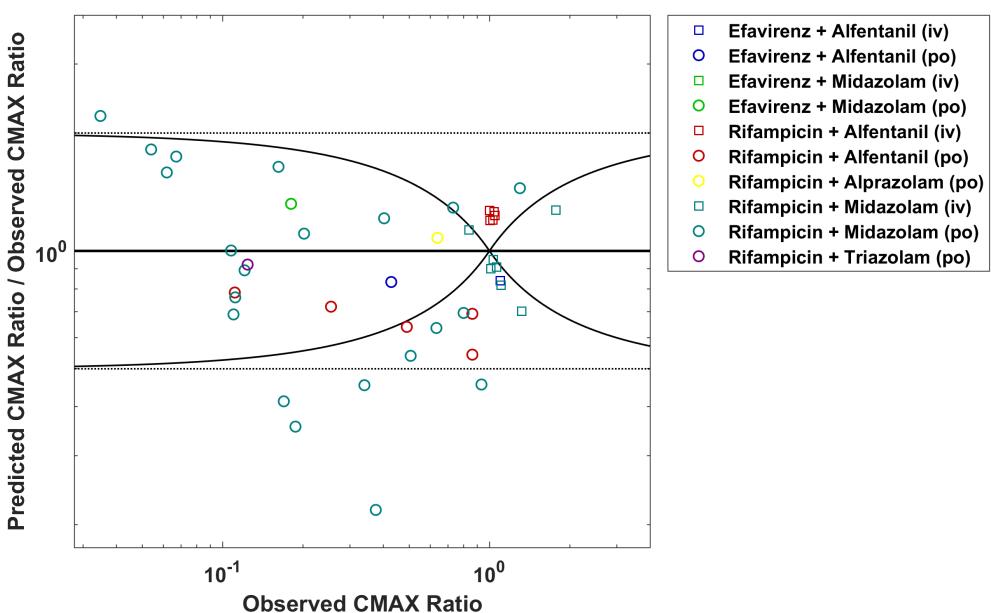
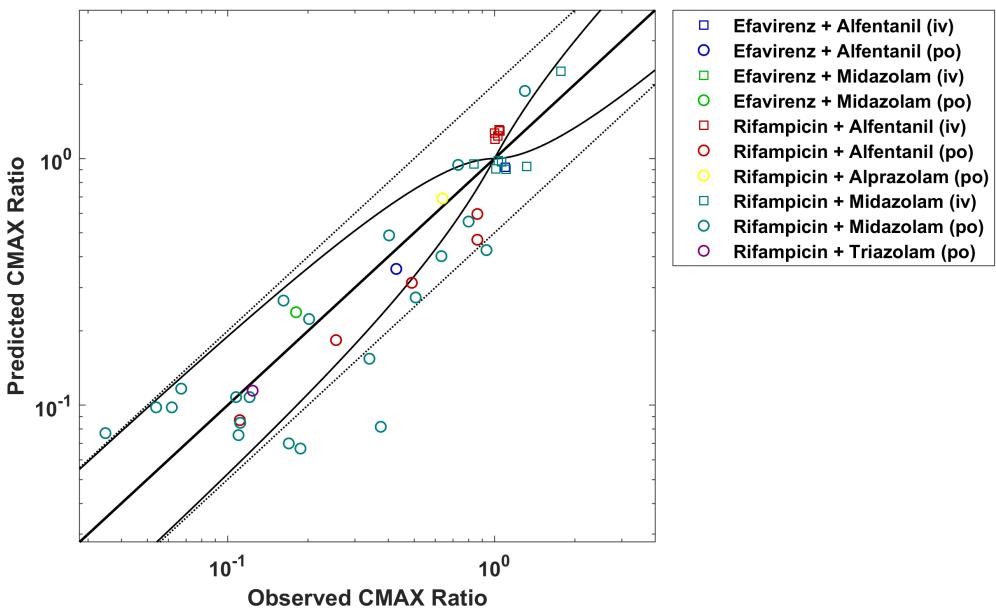
GMFE (CMAX) = 1.305125

	AUC	Number	Ratio [%]
Points total		22	-
Points within Guest et al.		12	54.5455
Points within 2-fold		17	77.2727

	CMAX	Number	Ratio [%]
Points total		16	-
Points within Guest et al.		12	75
Points within 2-fold		16	100

Induction





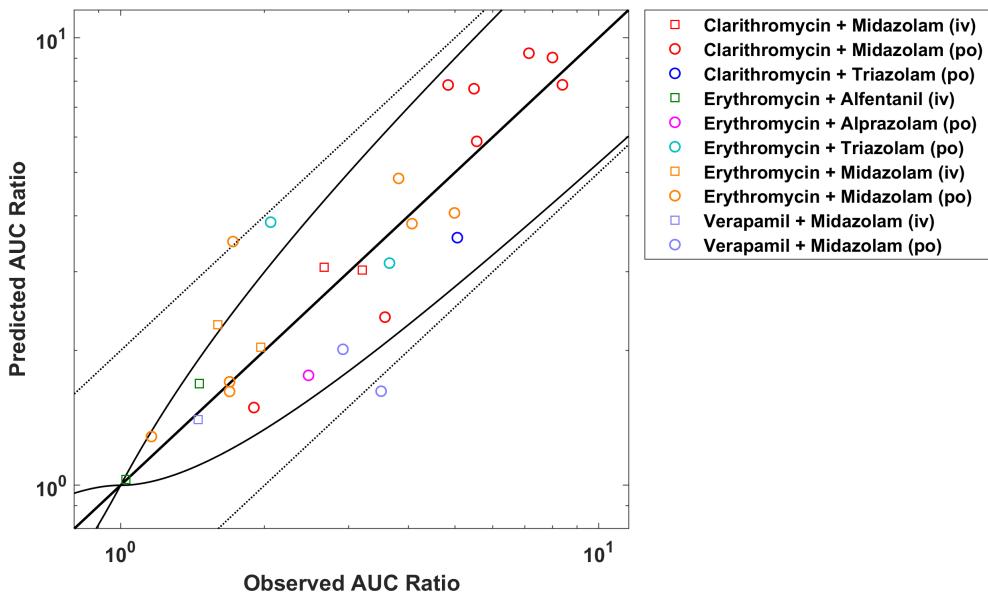
GMFE (AUC) = 1.384442

GMFE (CMAX) = 1.451894

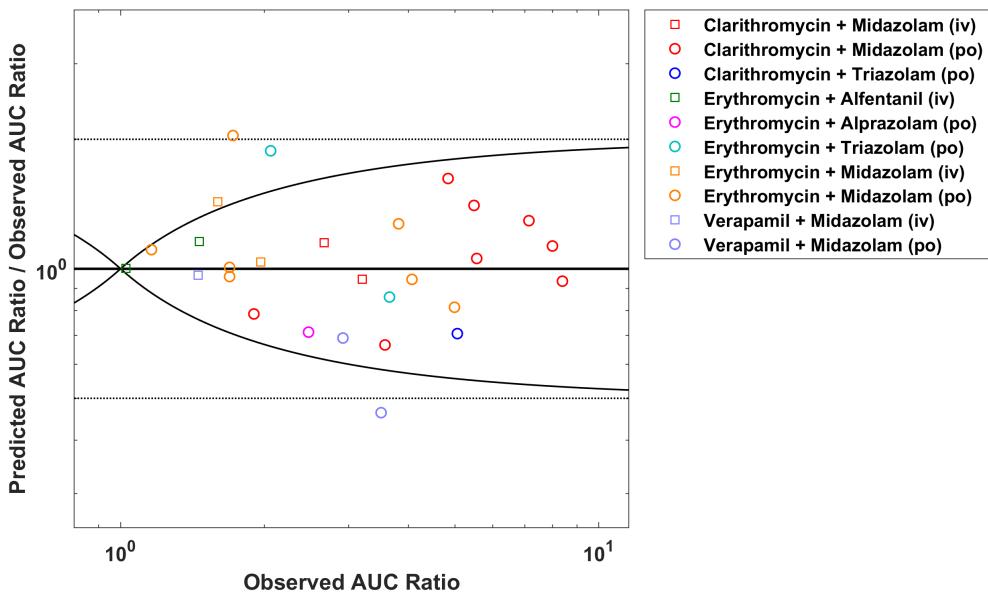
	AUC	Number	Ratio [%]
Points total	68	-	
Points within Guest et al.	52	76.4706	
Points within 2-fold	59	86.7647	

	CMAX	Number	Ratio [%]
Points total	43	-	
Points within Guest et al.	18	41.8605	
Points within 2-fold	37	86.0465	

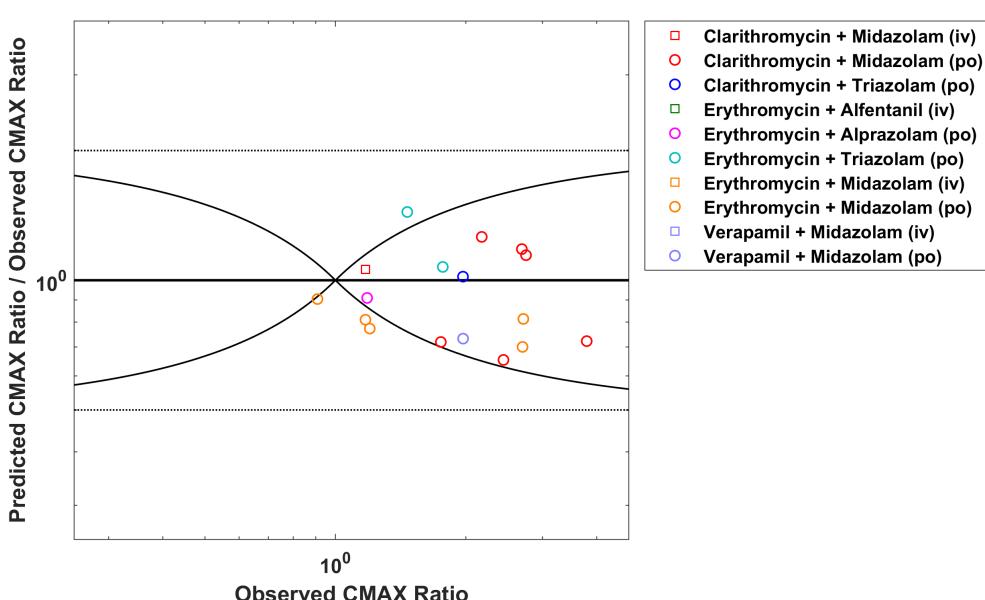
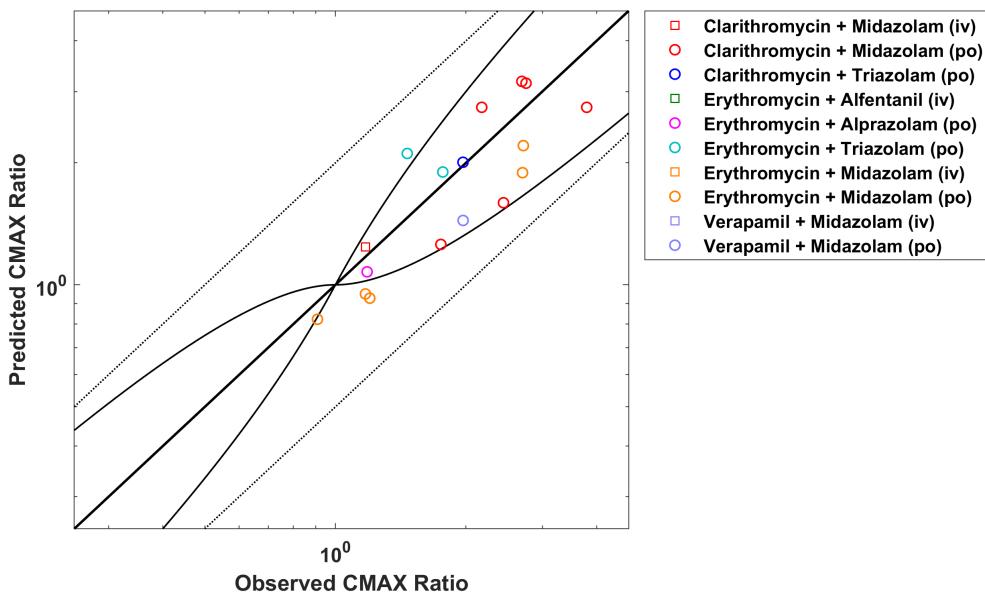
Mechanism based Inactivation



CYP3A4 DDI Mechanism based Inactivation



CYP3A4 DDI Mechanism based Inactivation



GMFE (AUC) = 1.271545

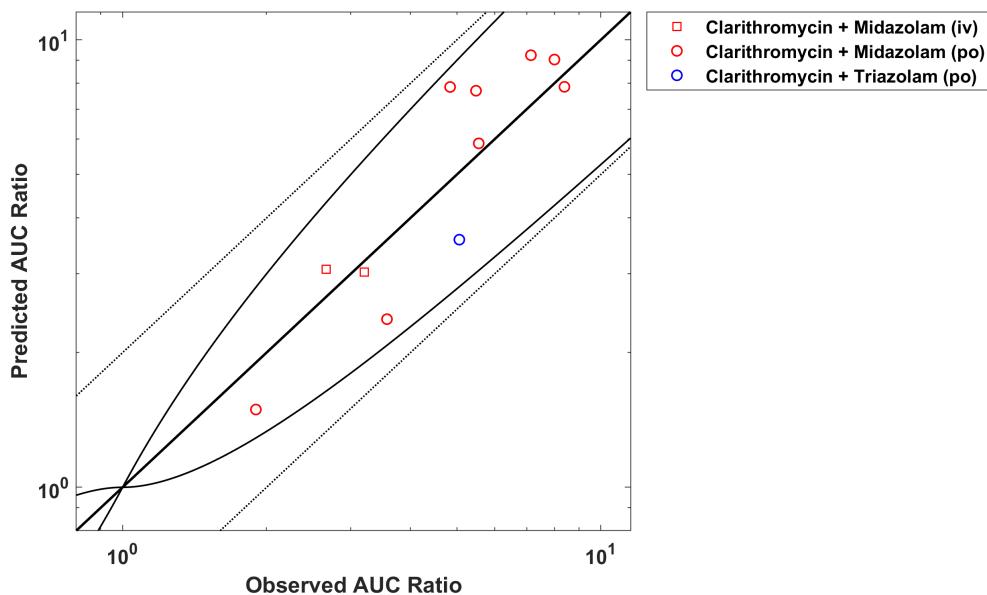
GMFE (CMAX) = 1.240603

	AUC	Number	Ratio [%]
Points total		28	-
Points within Guest et al.		24	85.7143
Points within 2-fold		26	92.8571

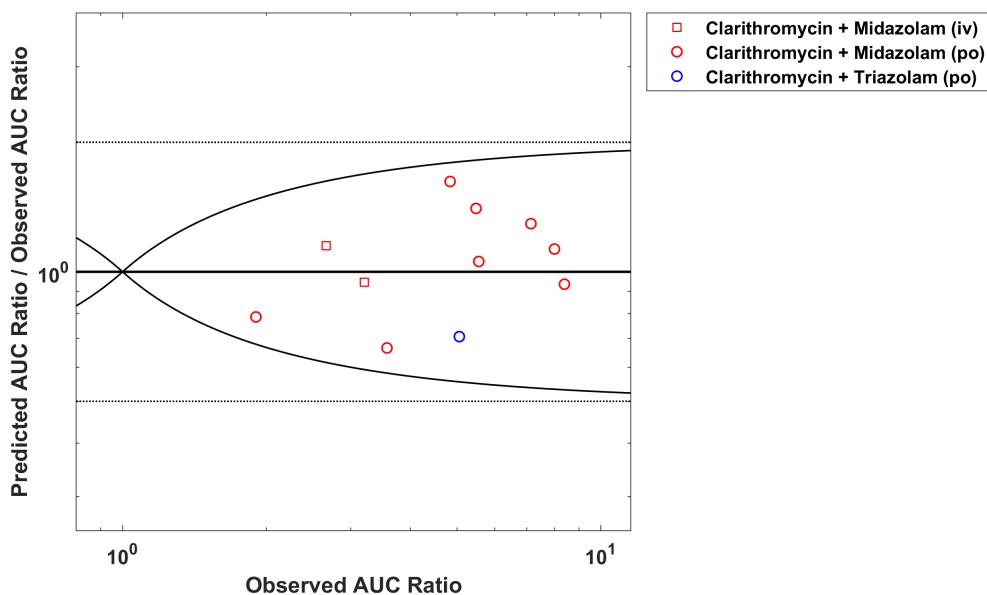
	CMAX	Number	Ratio [%]
Points total		17	-
Points within Guest et al.		13	76.4706
Points within 2-fold		17	100

Perpetrator

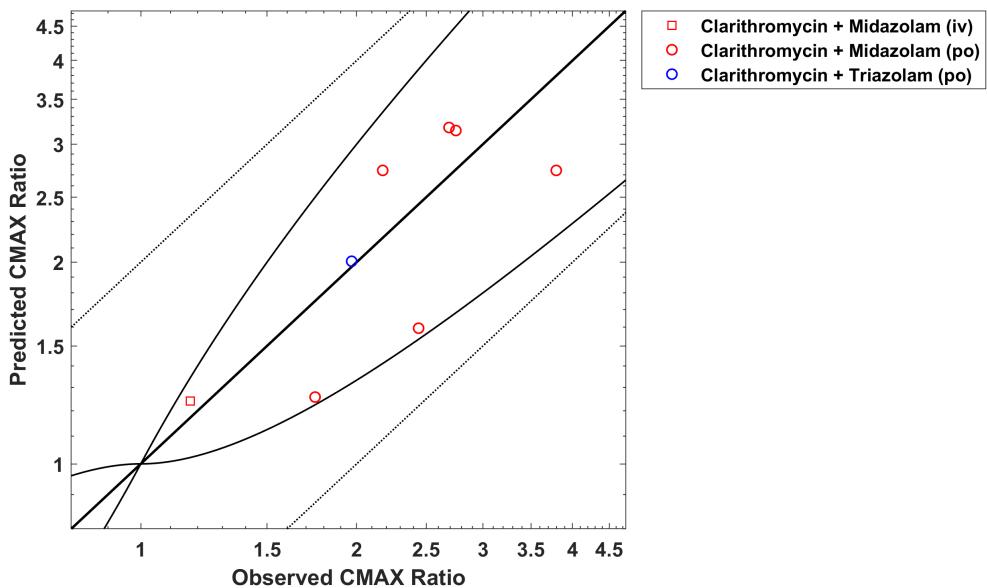
Clarithromycin



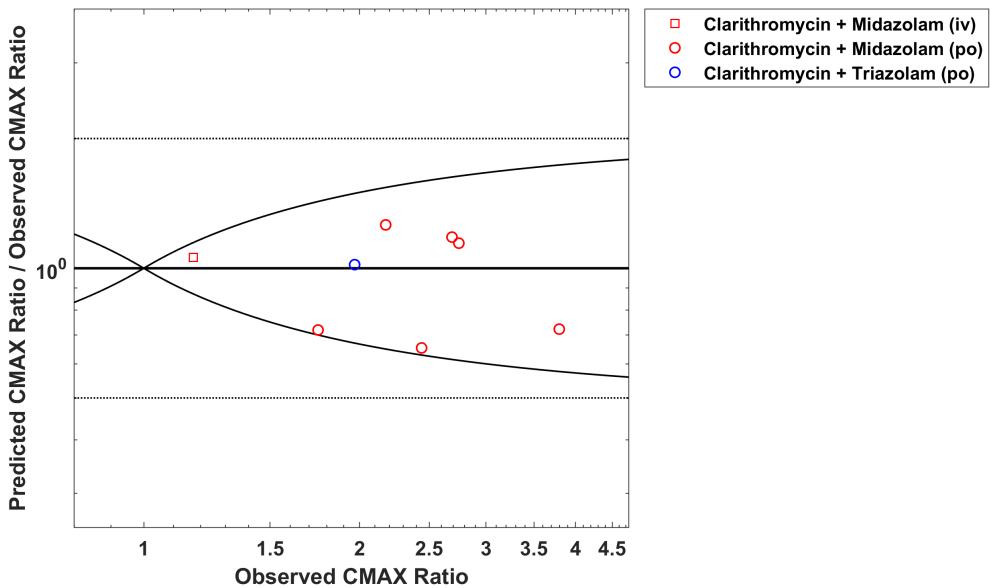
CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin

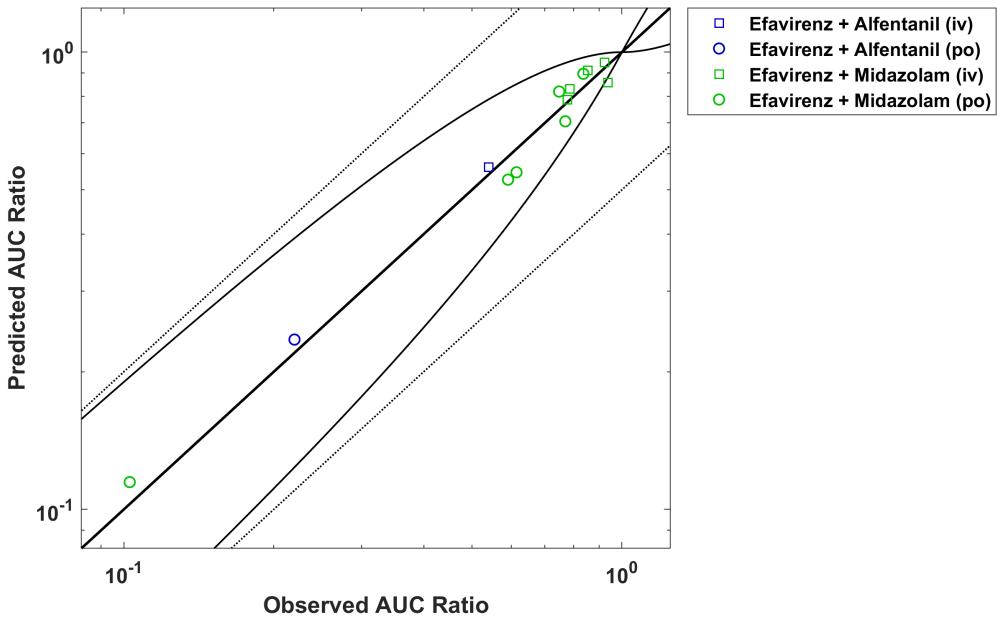
GMFE (AUC) = 1.257076

GMFE (CMAX) = 1.235171

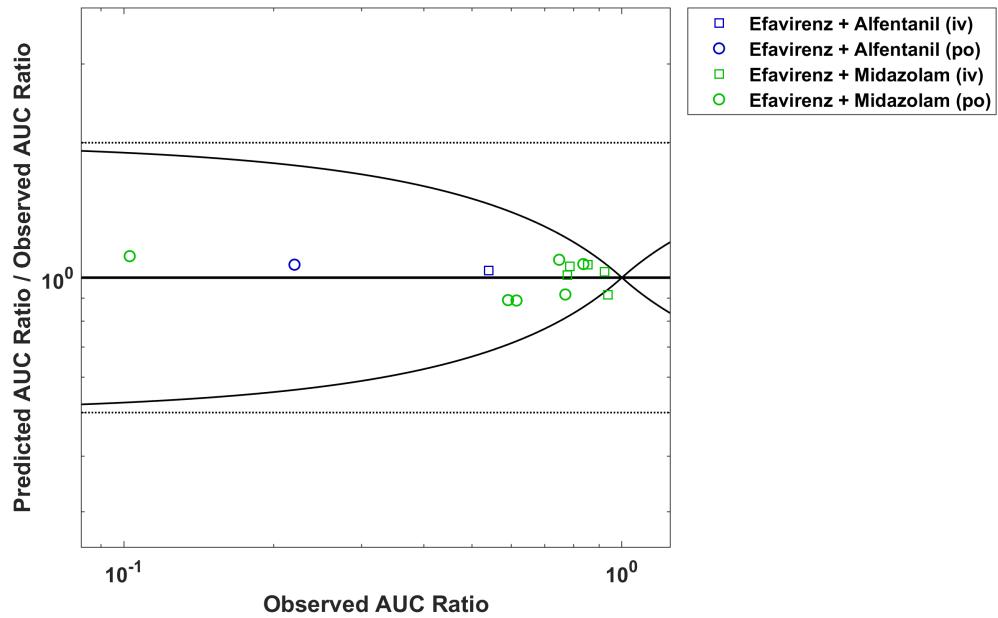
	AUC	Number	Ratio [%]
Points total		11	-
Points within Guest et al.		11	100
Points within 2-fold		11	100

	CMAX	Number	Ratio [%]
Points total		8	-
Points within Guest et al.		8	100
Points within 2-fold		8	100

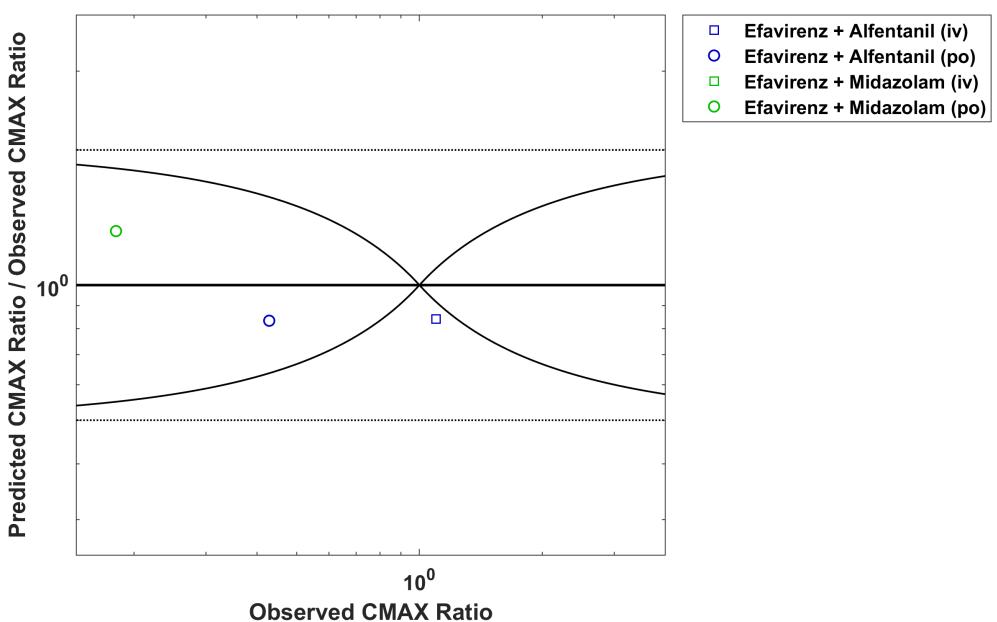
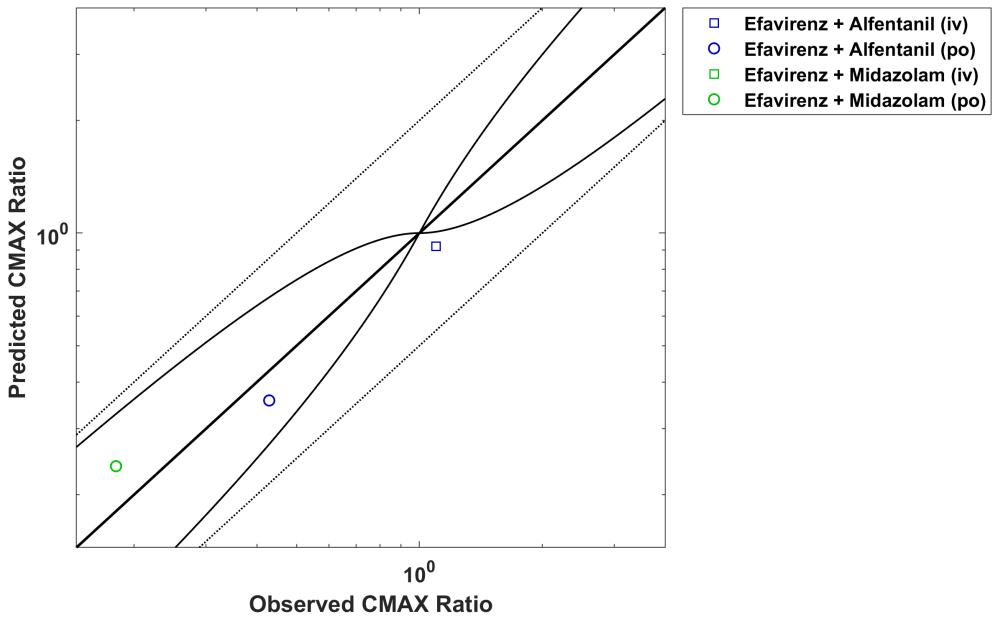
Efavirenz



CYP3A4 DDI Efavirenz



CYP3A4 DDI Efavirenz



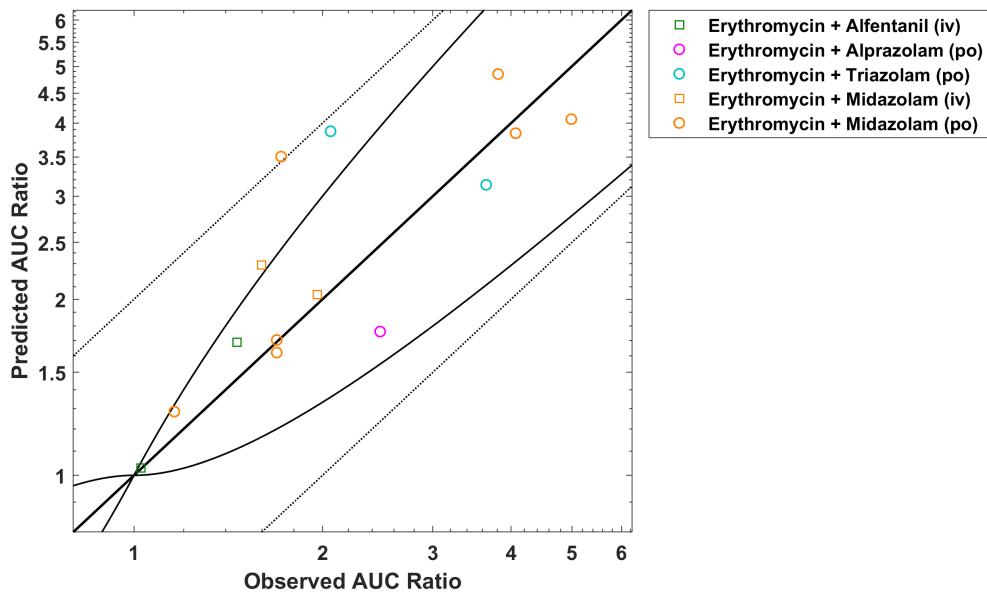
GMFE (AUC) = 1.075674

GMFE (CMAX) = 1.235565

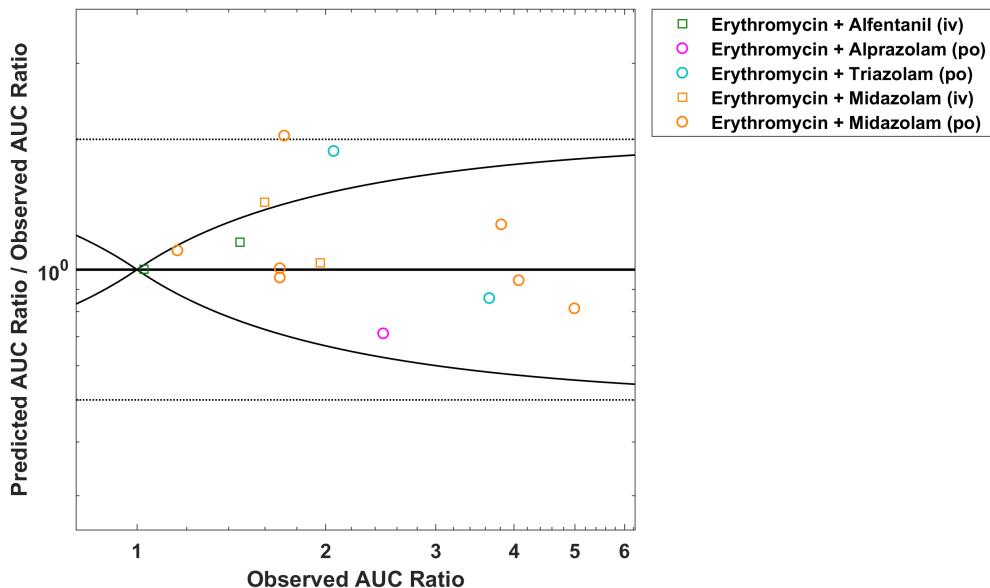
	AUC	Number	Ratio [%]
Points total		13	-
Points within Guest et al.		12	92.3077
Points within 2-fold		13	100

	CMAX	Number	Ratio [%]
Points total		3	-
Points within Guest et al.		2	66.6667
Points within 2-fold		3	100

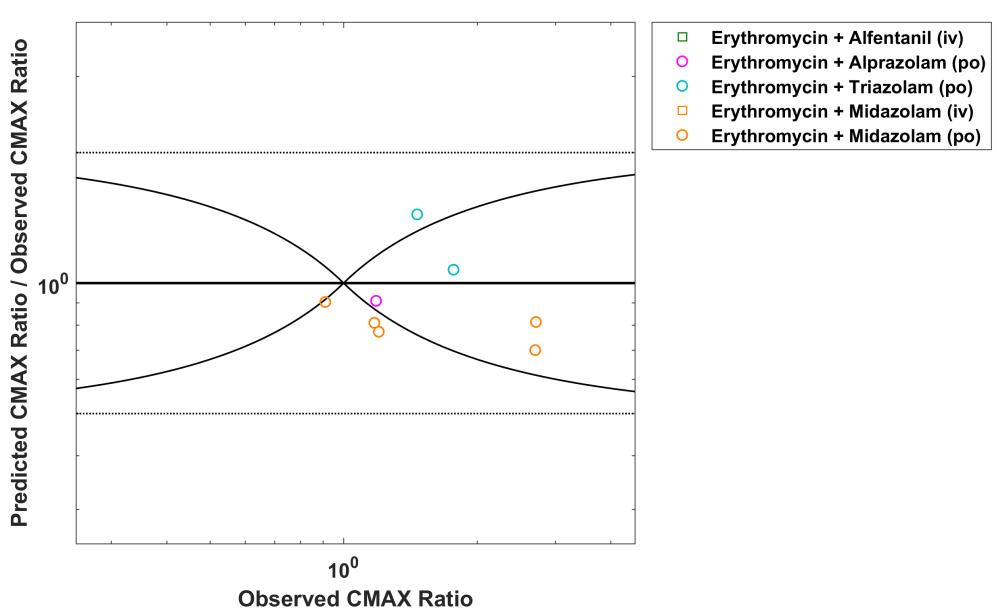
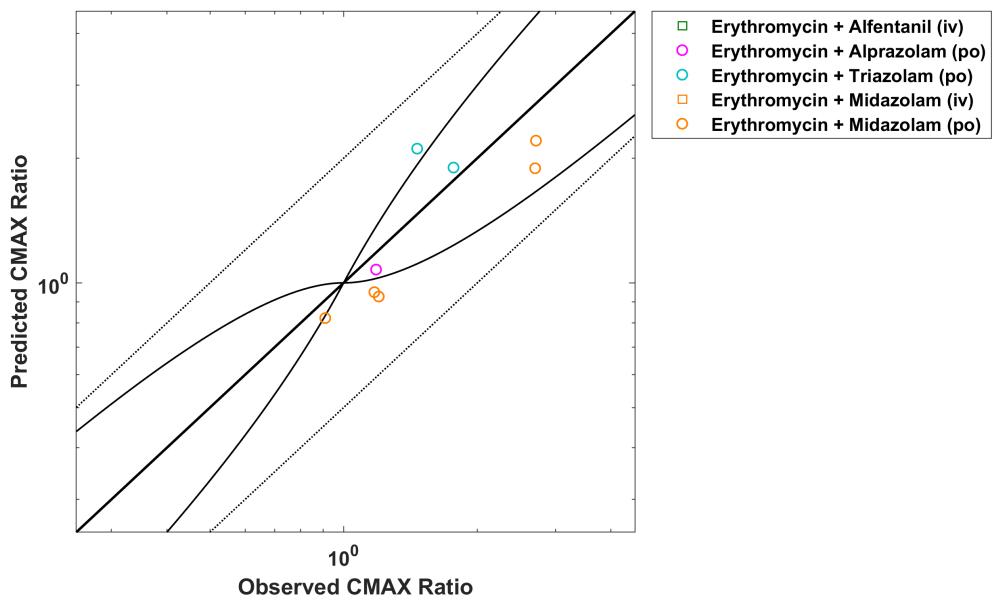
Erythromycin



CYP3A4 DDI Erythromycin



CYP3A4 DDI Erythromycin



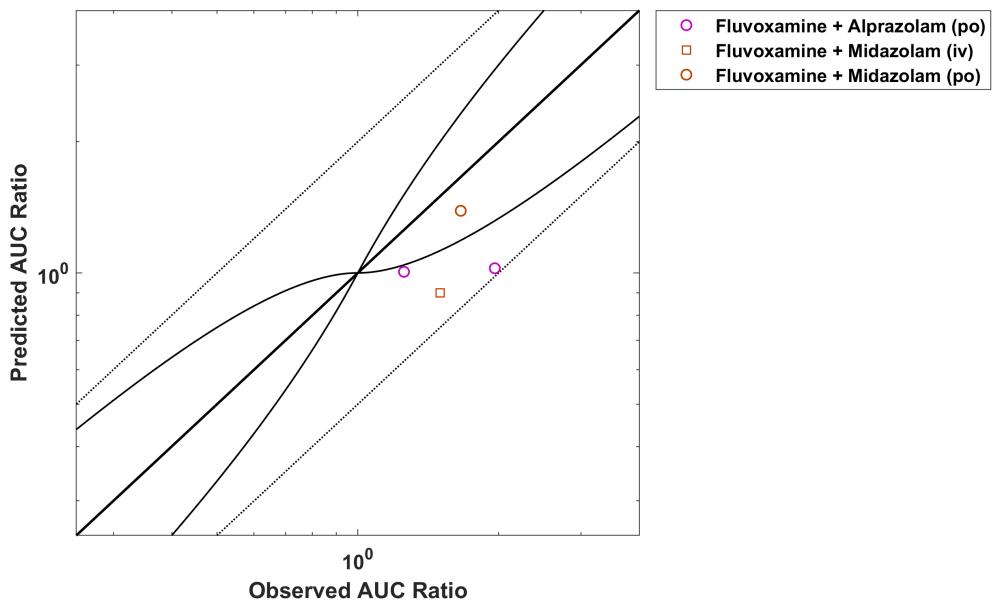
GMFE (AUC) = 1.242000

GMFE (CMAX) = 1.231138

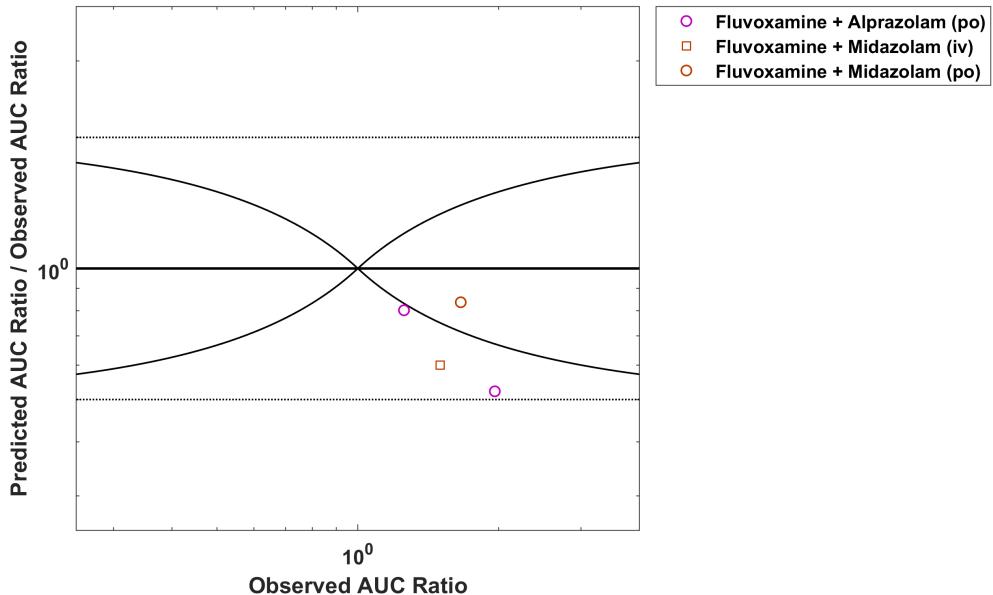
	AUC	Number	Ratio [%]
Points total		14	-
Points within Guest et al.		11	78.5714
Points within 2-fold		13	92.8571

	CMAX	Number	Ratio [%]
Points total		8	-
Points within Guest et al.		4	50
Points within 2-fold		8	100

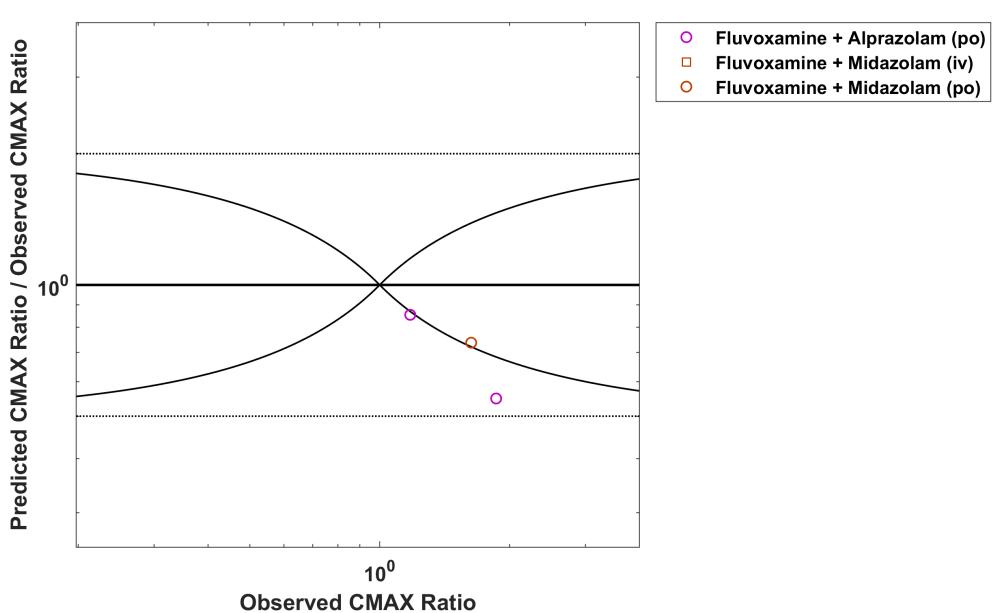
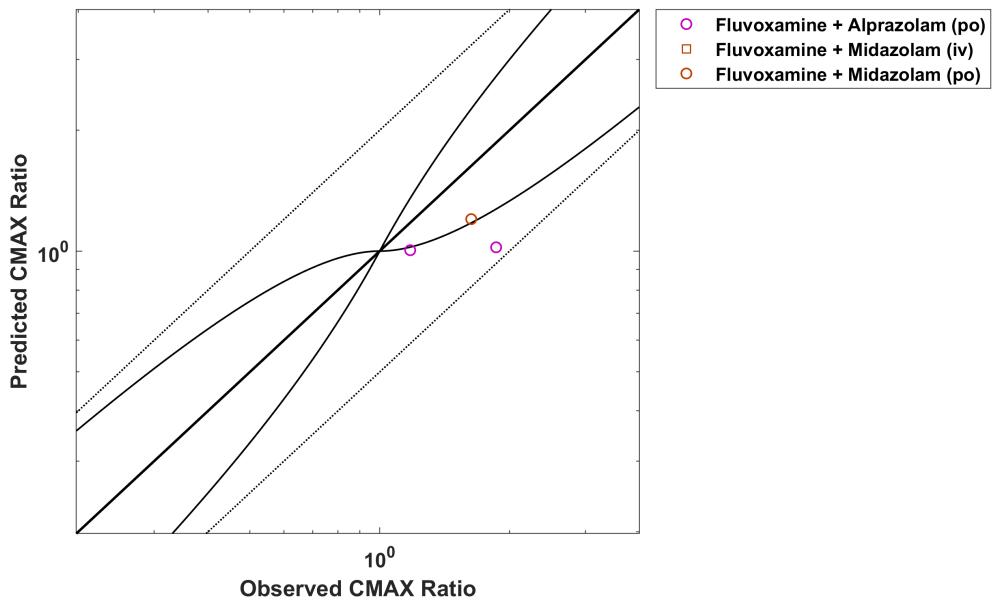
Fluvoxamine



CYP3A4 DDI Fluvoxamine



CYP3A4 DDI Fluvoxamine



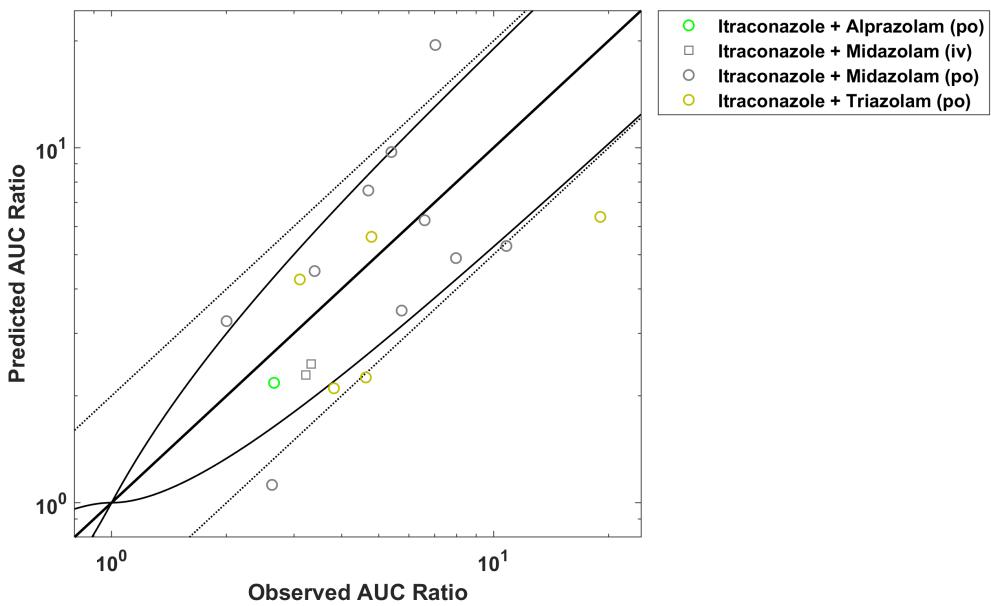
GMFE (AUC) = 1.477241

GMFE (CMAX) = 1.425160

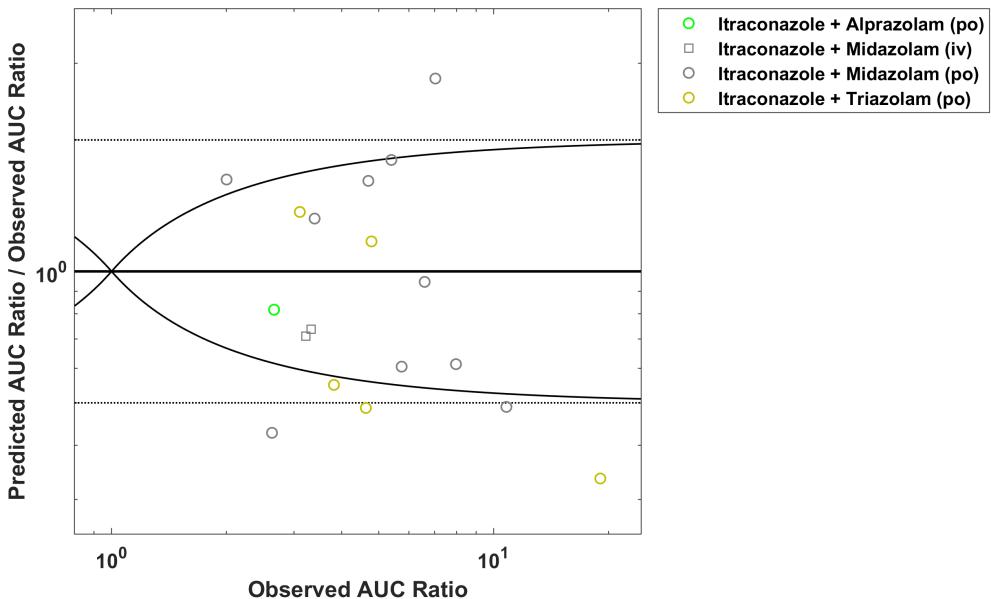
	AUC	Number	Ratio [%]
Points total		4	-
Points within Guest et al.		1	25
Points within 2-fold		4	100

	CMAX	Number	Ratio [%]
Points total		3	-
Points within Guest et al.		1	33.3333
Points within 2-fold		3	100

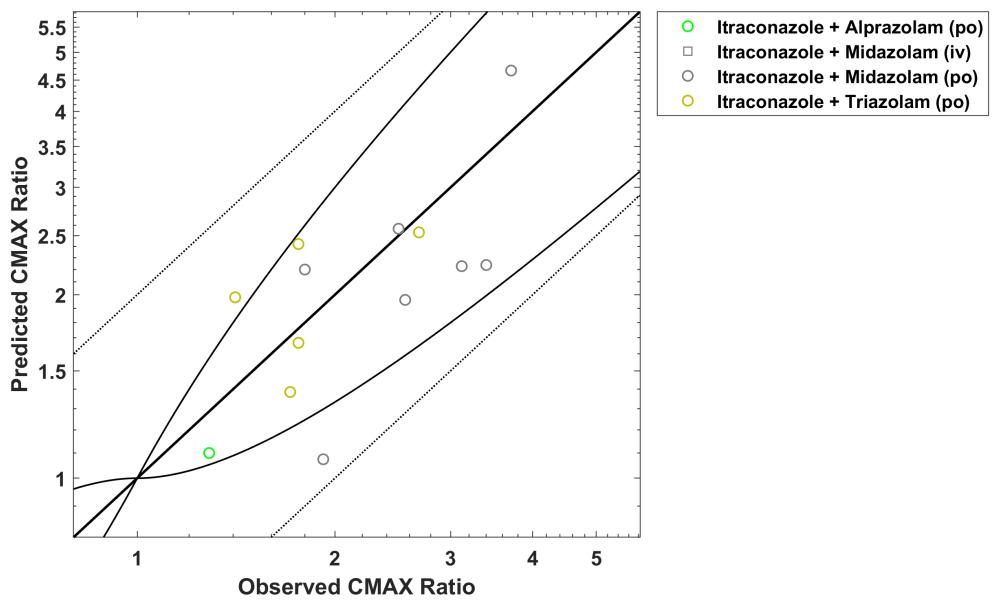
Itraconazole



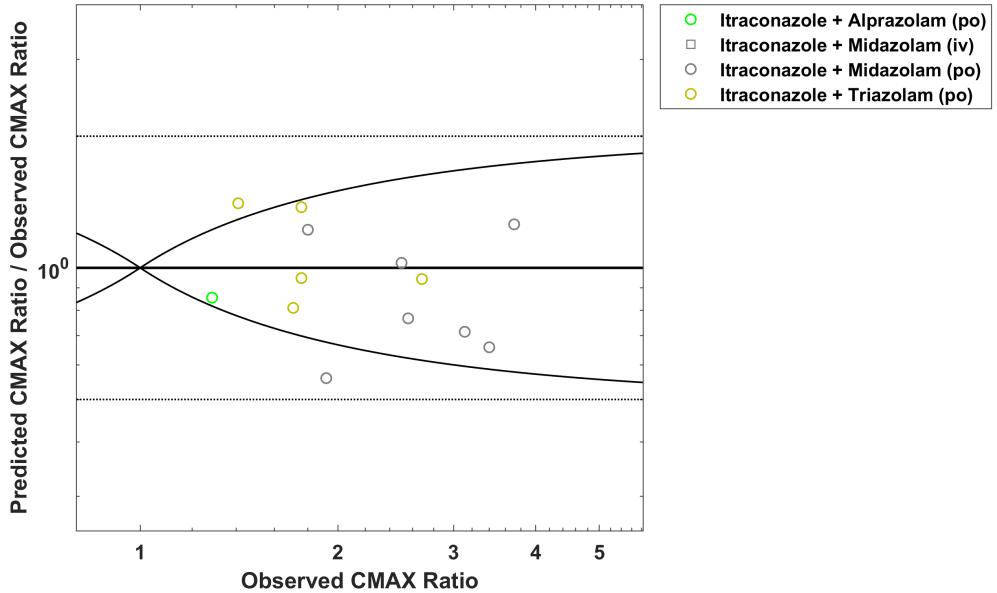
CYP3A4 DDI Itraconazole



CYP3A4 DDI Itraconazole



CYP3A4 DDI Itraconazole



CYP3A4 DDI Itraconazole

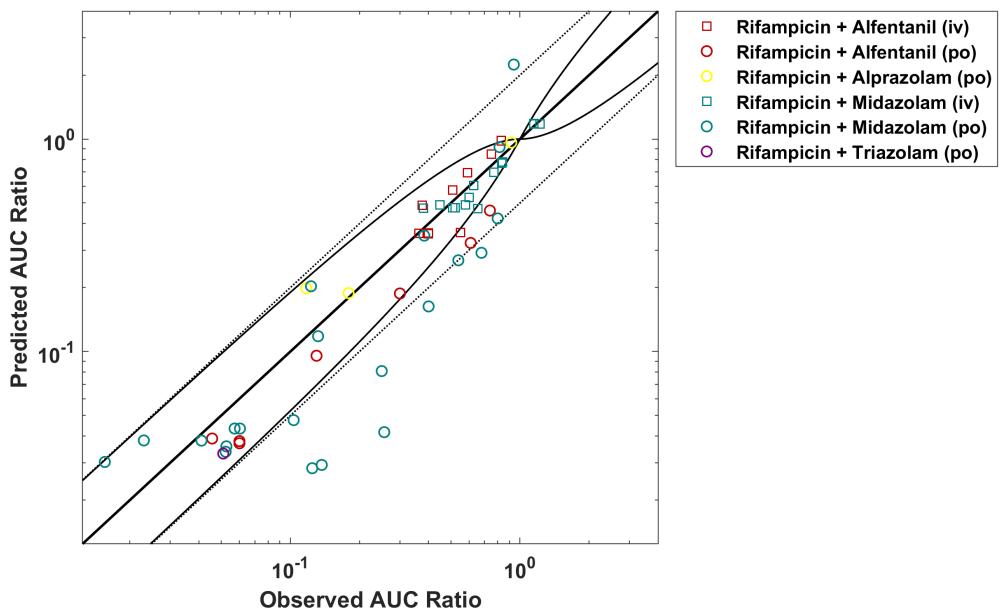
GMFE (AUC) = 1.666102

GMFE (CMAX) = 1.278893

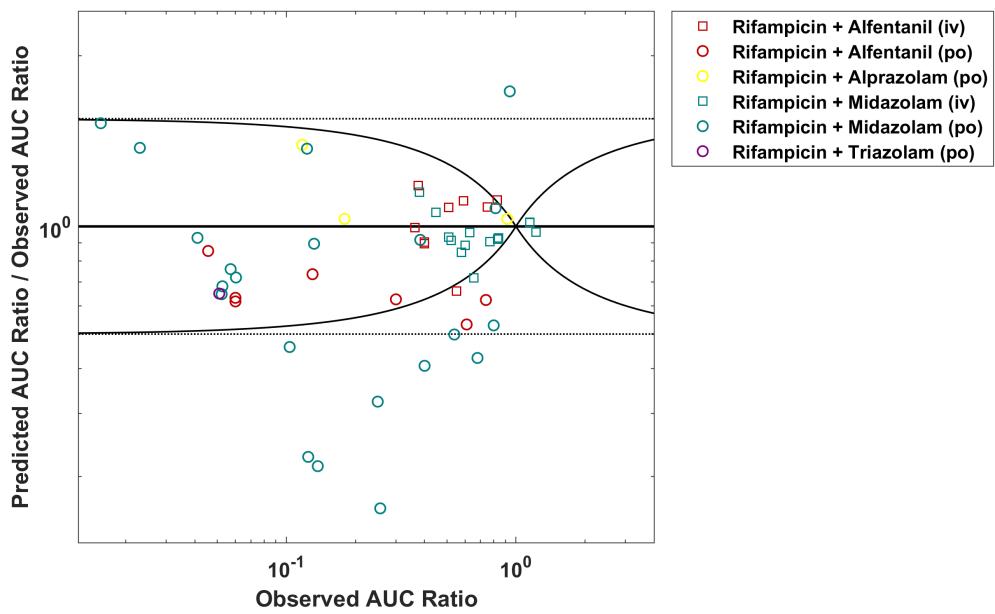
AUC	Number	Ratio [%]
Points total	18	-
Points within Guest et al.	11	61.1111
Points within 2-fold	13	72.2222

CMAX	Number	Ratio [%]
Points total	13	-
Points within Guest et al.	11	84.6154
Points within 2-fold	13	100

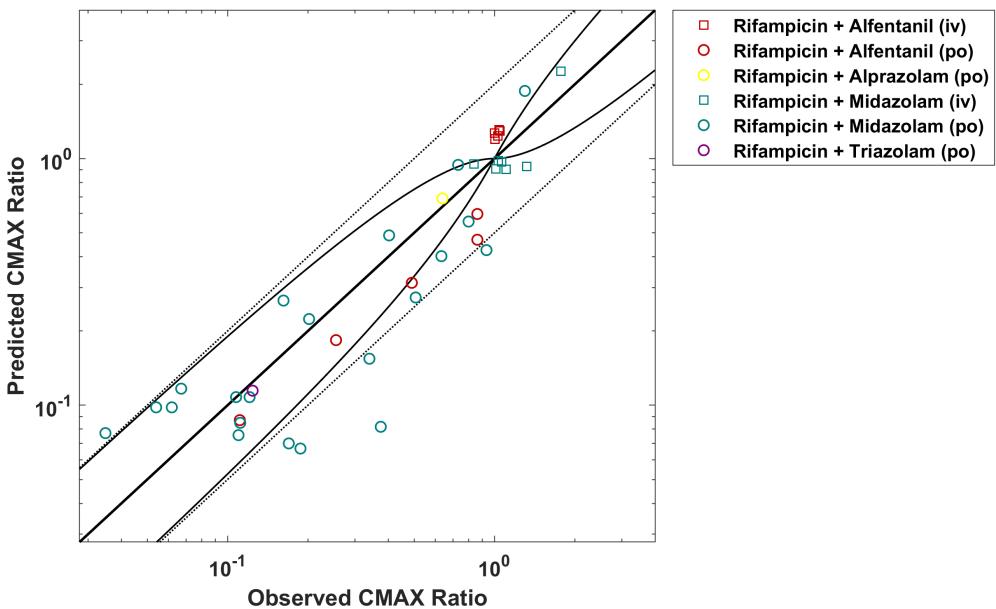
Rifampicin



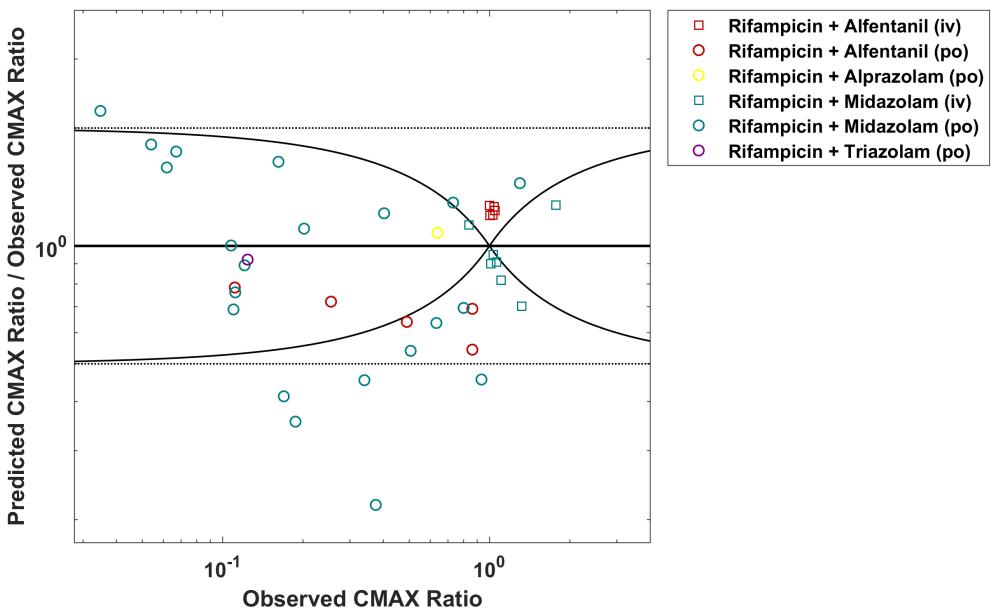
CYP3A4 DDI Rifampicin



CYP3A4 DDI Rifampicin



CYP3A4 DDI Rifampicin



CYP3A4 DDI Rifampicin

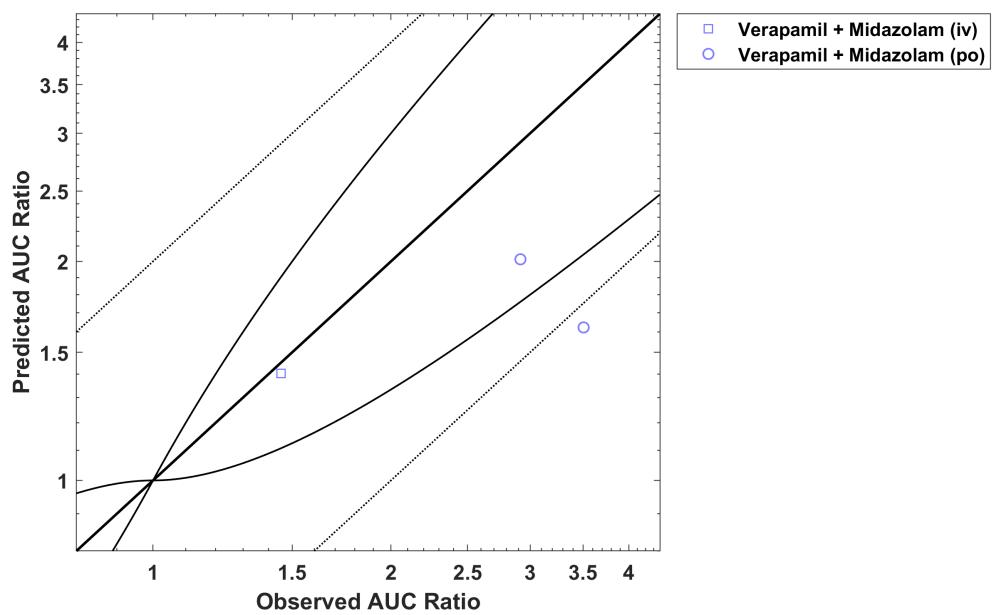
GMFE (AUC) = 1.469532

GMFE (CMAX) = 1.469570

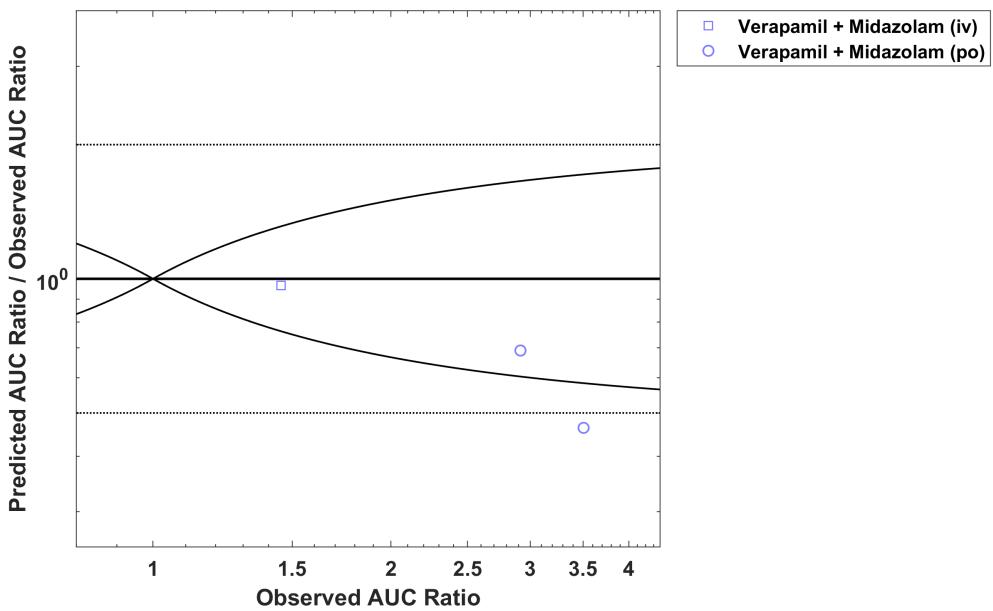
	AUC	Number	Ratio [%]
Points total		55	-
Points within Guest et al.		40	72.7273
Points within 2-fold		46	83.6364

	CMAX	Number	Ratio [%]
Points total		40	-
Points within Guest et al.		16	40
Points within 2-fold		34	85

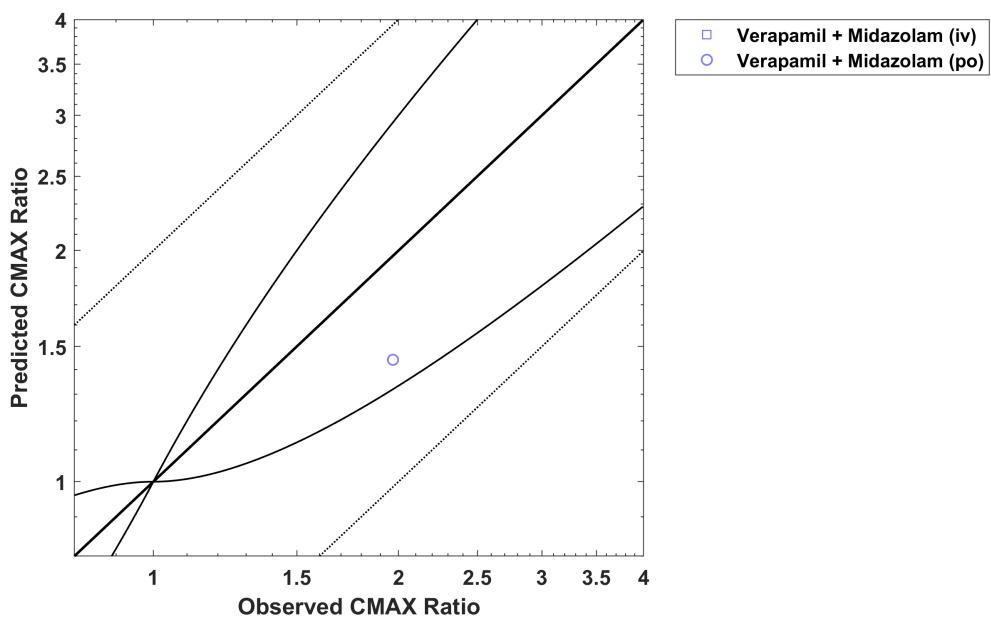
Verapamil



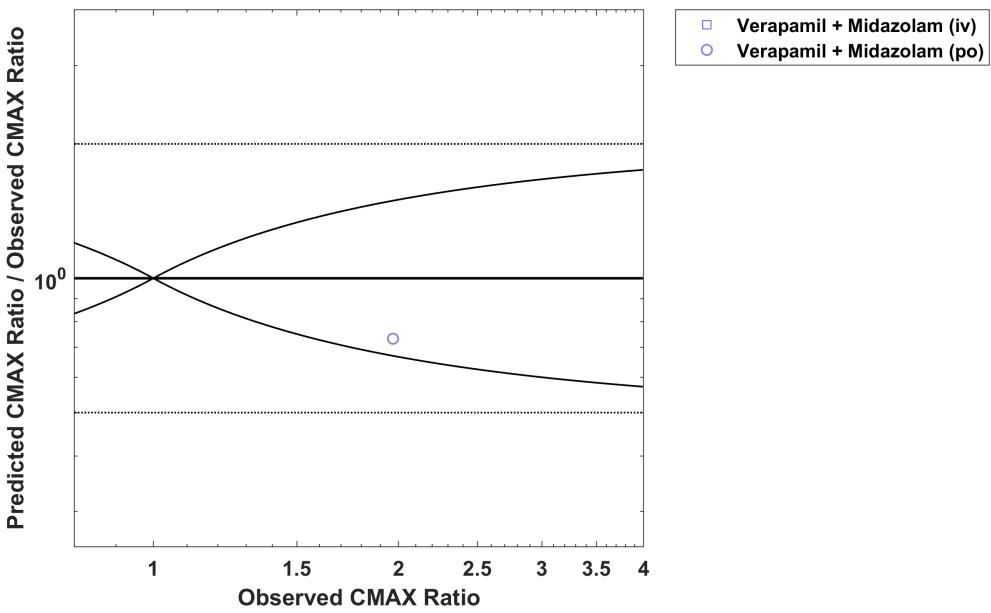
CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil

GMFE (AUC) = 1.479805

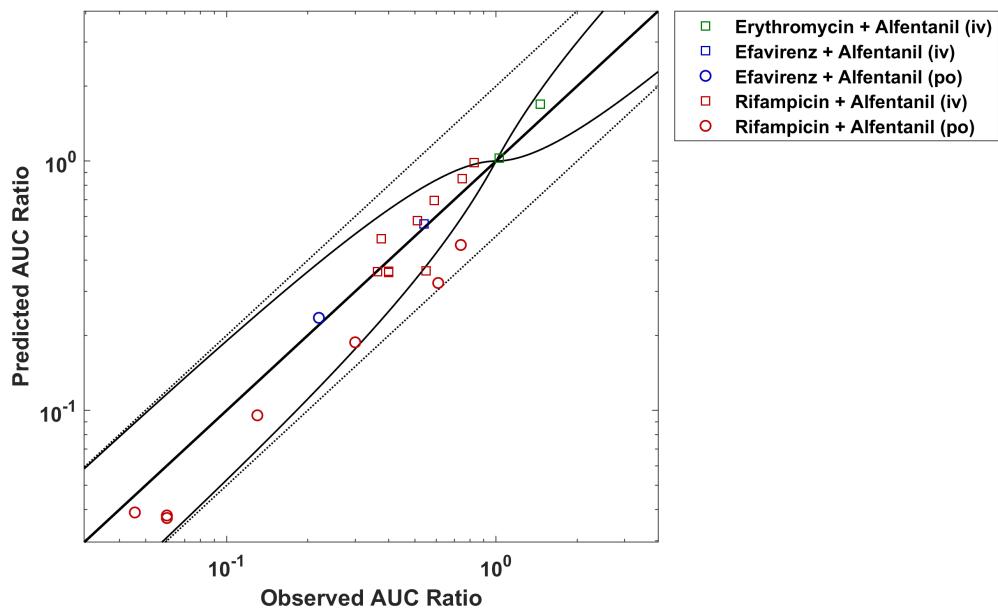
GMFE (CMAX) = 1.366122

	AUC	Number	Ratio [%]
Points total		3	-
Points within Guest et al.		2	66.6667
Points within 2-fold		2	66.6667

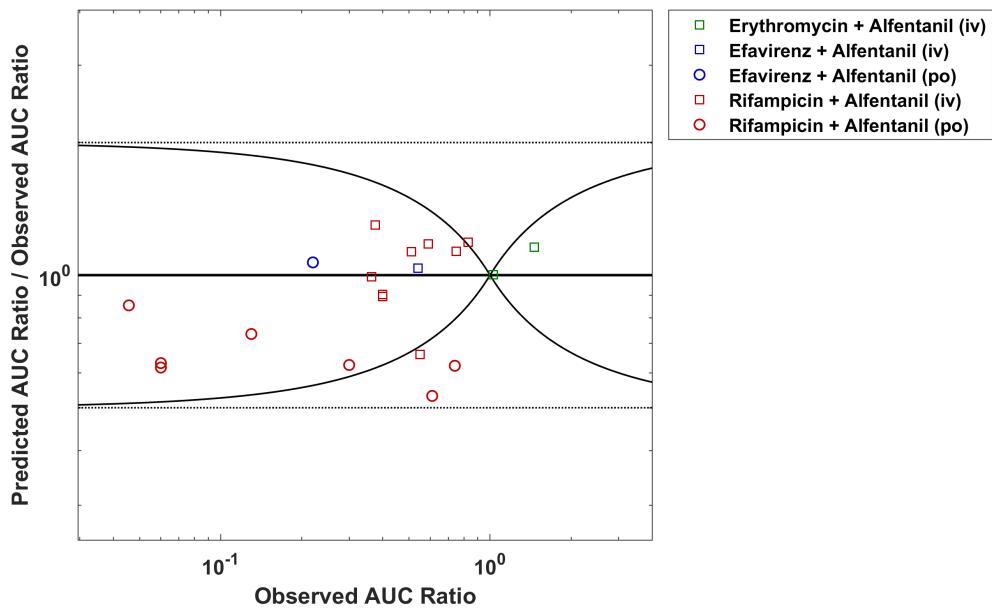
	CMAX	Number	Ratio [%]
Points total		1	-
Points within Guest et al.		1	100
Points within 2-fold		1	100

Victim

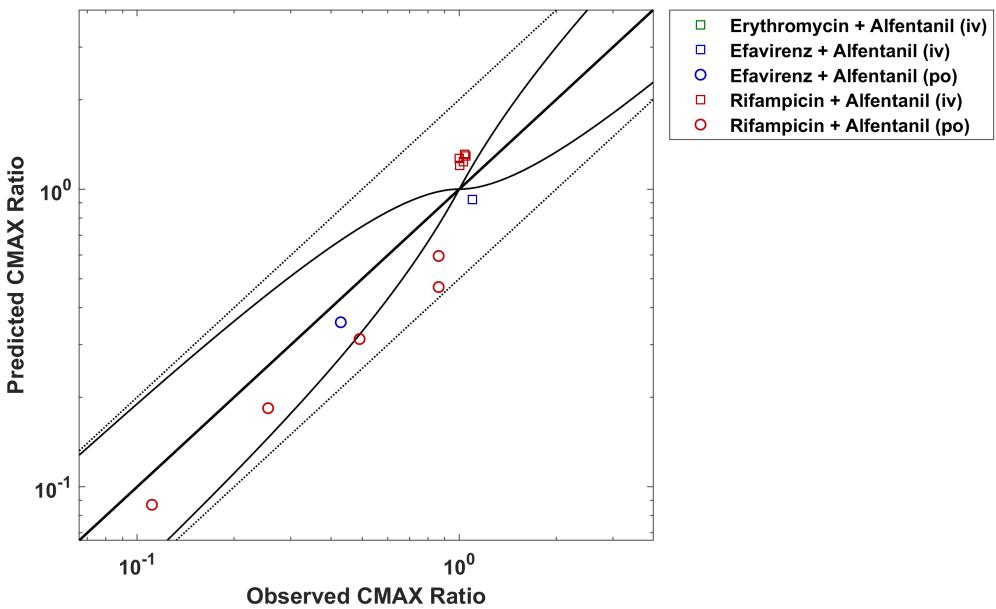
Alfentanil



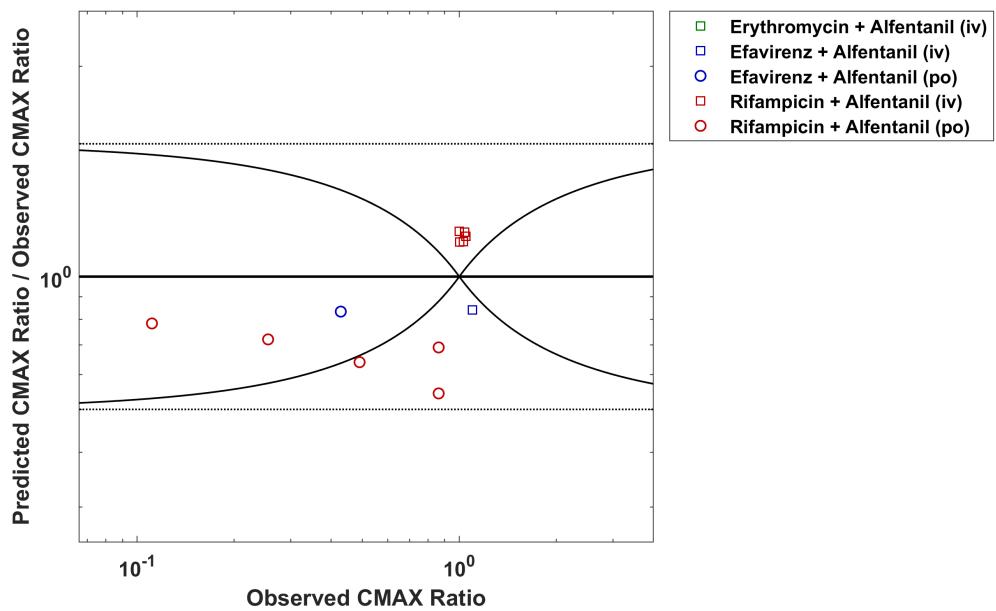
CYP3A4 DDI Alfentanil



CYP3A4 DDI Alfentanil



CYP3A4 DDI Alfentanil



CYP3A4 DDI Alfentanil

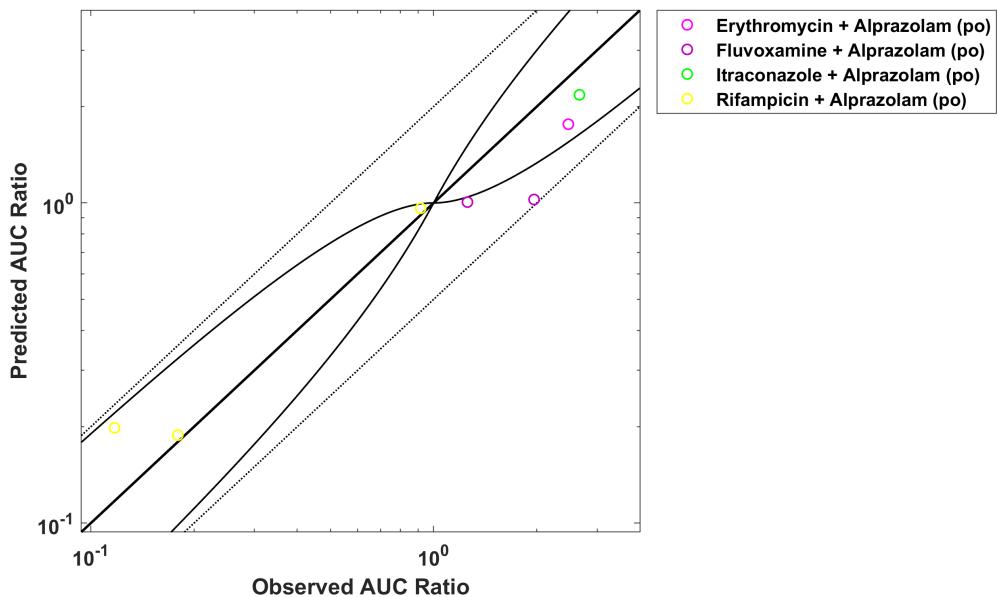
GMFE (AUC) = 1.265796

GMFE (CMAX) = 1.327112

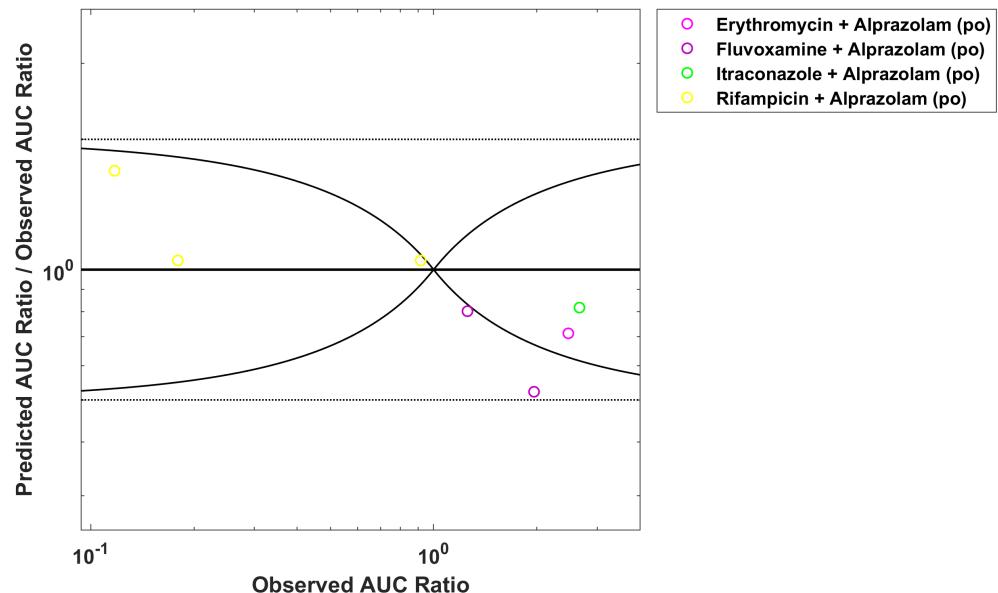
	AUC	Number	Ratio [%]
Points total	20	-	
Points within Guest et al.	16	80	
Points within 2-fold	20	100	

	CMAX	Number	Ratio [%]
Points total	12	-	
Points within Guest et al.	3	25	
Points within 2-fold	12	100	

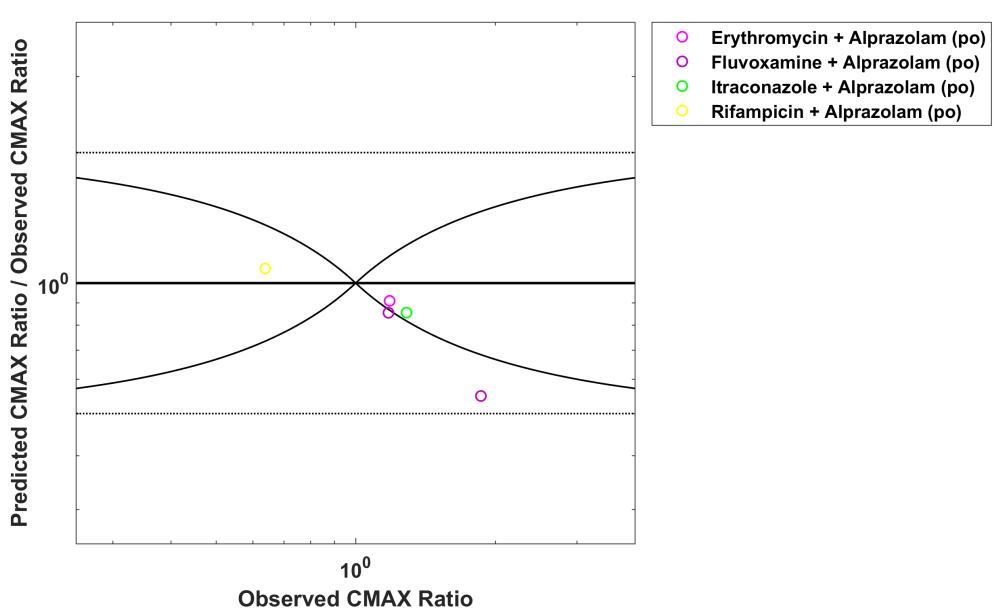
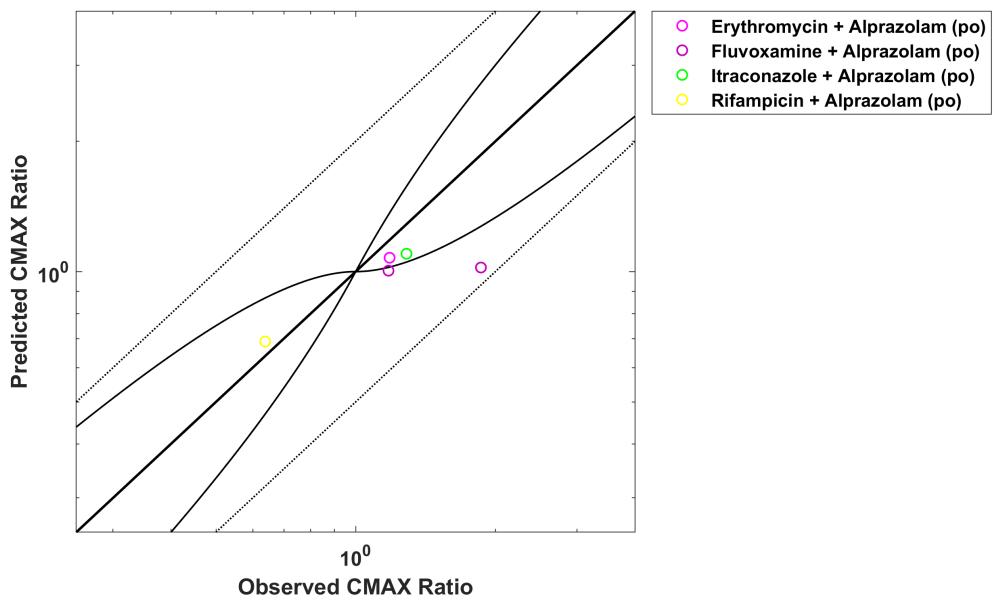
Alprazolam



CYP3A4 DDI Alprazolam



CYP3A4 DDI Alprazolam



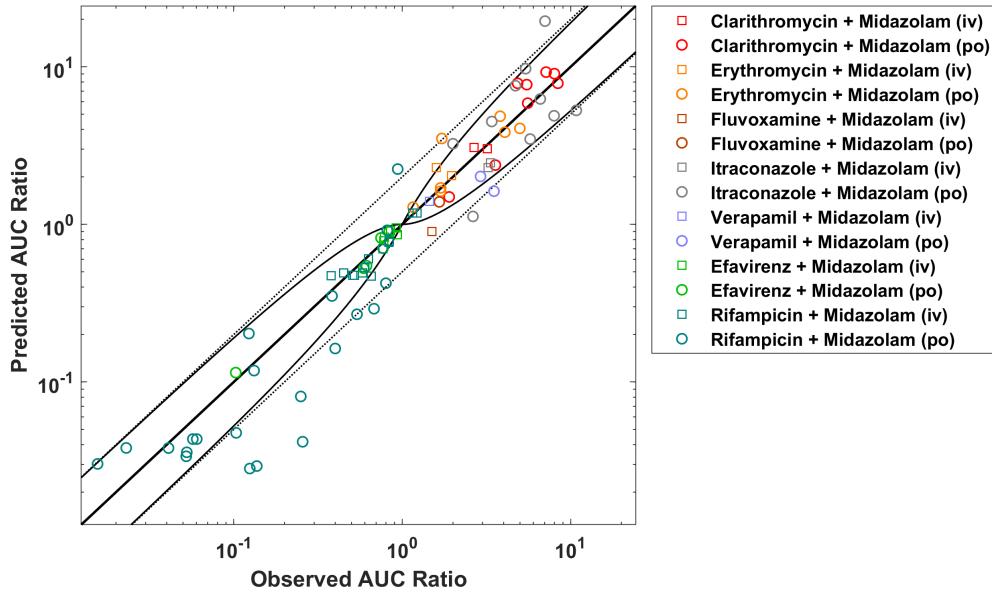
GMFE (AUC) = 1.337497

GMFE (CMAX) = 1.242657

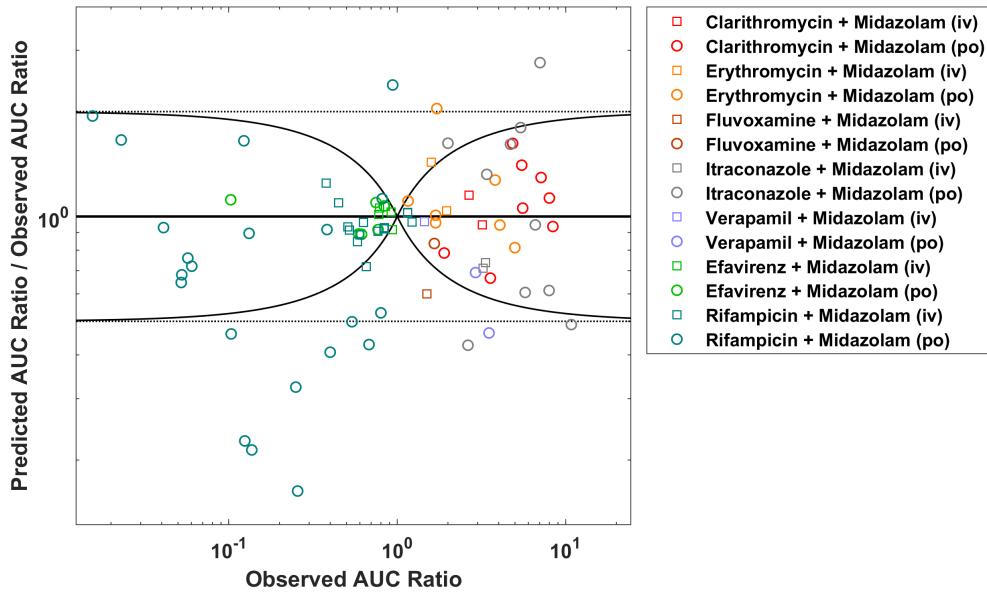
	AUC	Number	Ratio [%]
Points total		7	-
Points within Guest et al.		5	71.4286
Points within 2-fold		7	100

	CMAX	Number	Ratio [%]
Points total		5	-
Points within Guest et al.		3	60
Points within 2-fold		5	100

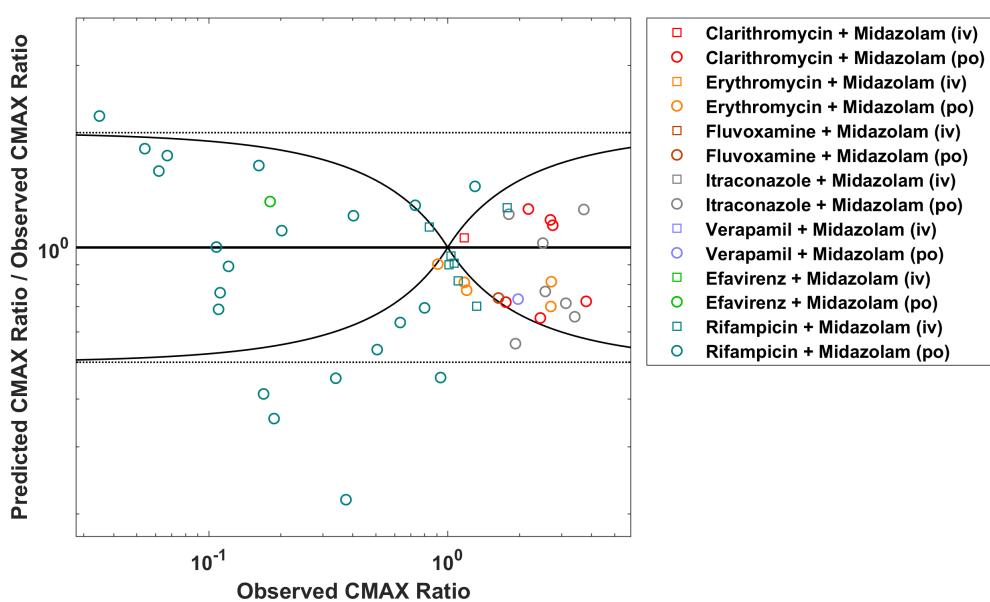
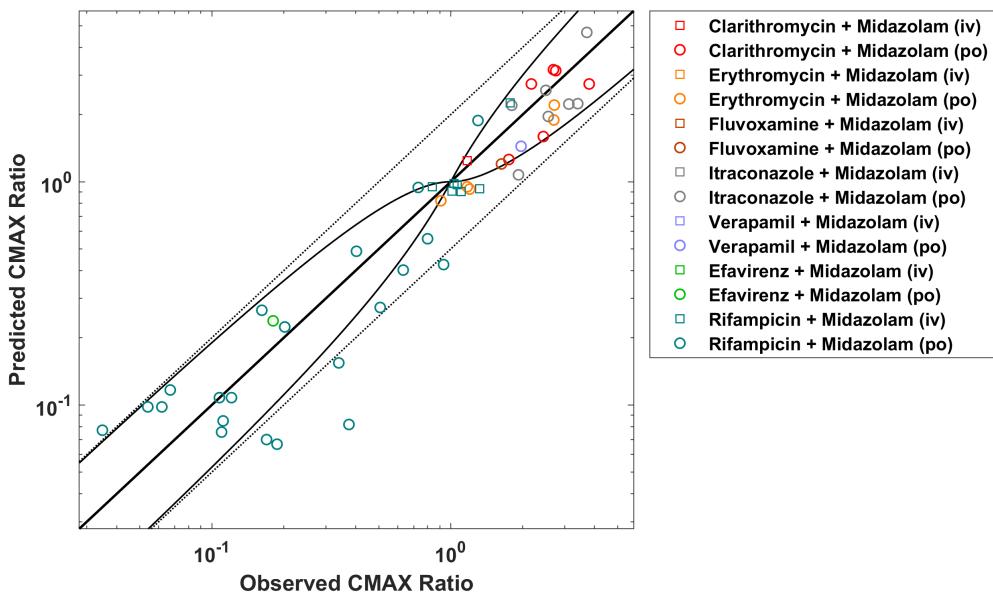
Midazolam



CYP3A4 DDI Midazolam



CYP3A4 DDI Midazolam



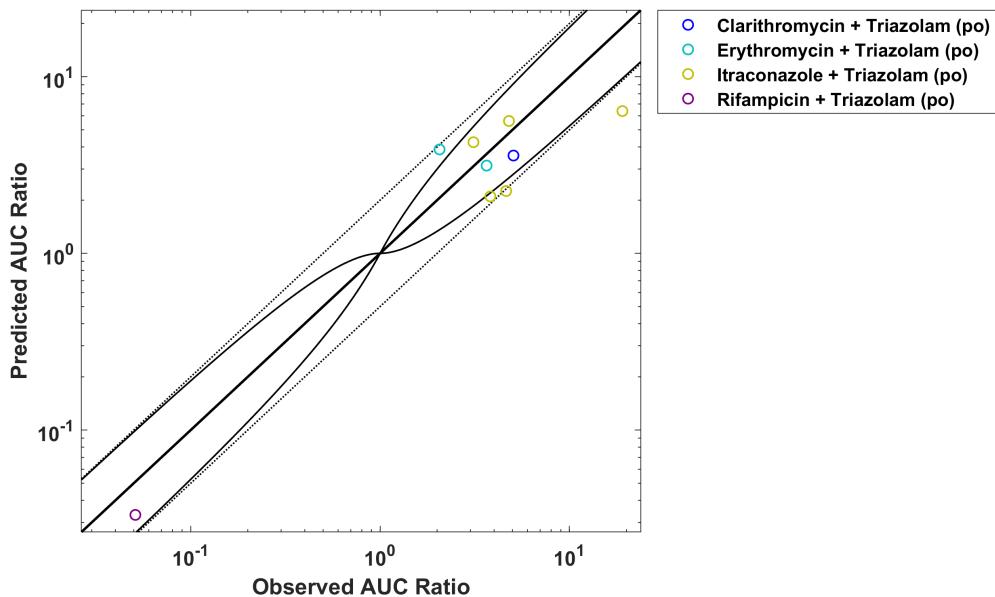
GMFE (AUC) = 1.413926

GMFE (CMAX) = 1.432132

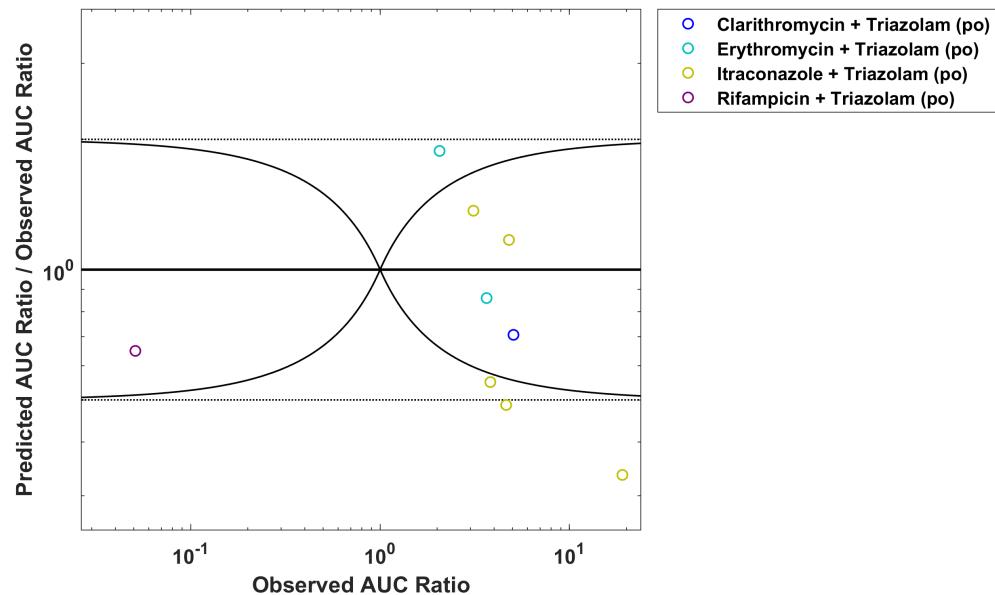
	AUC	Number	Ratio [%]
Points total		82	-
Points within Guest et al.		62	75.6098
Points within 2-fold		68	82.9268

	CMAX	Number	Ratio [%]
Points total		50	-
Points within Guest et al.		30	60
Points within 2-fold		44	88

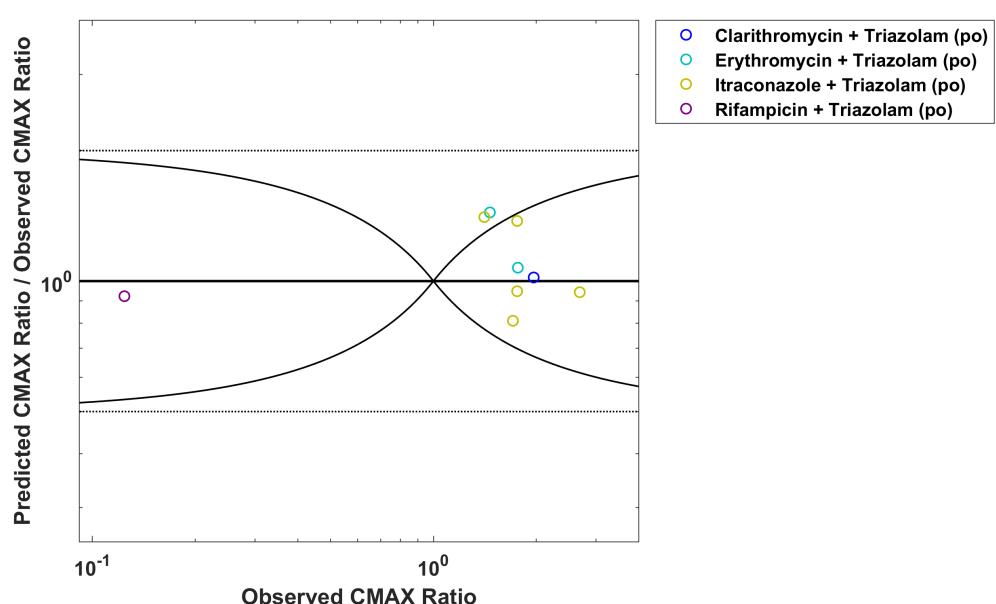
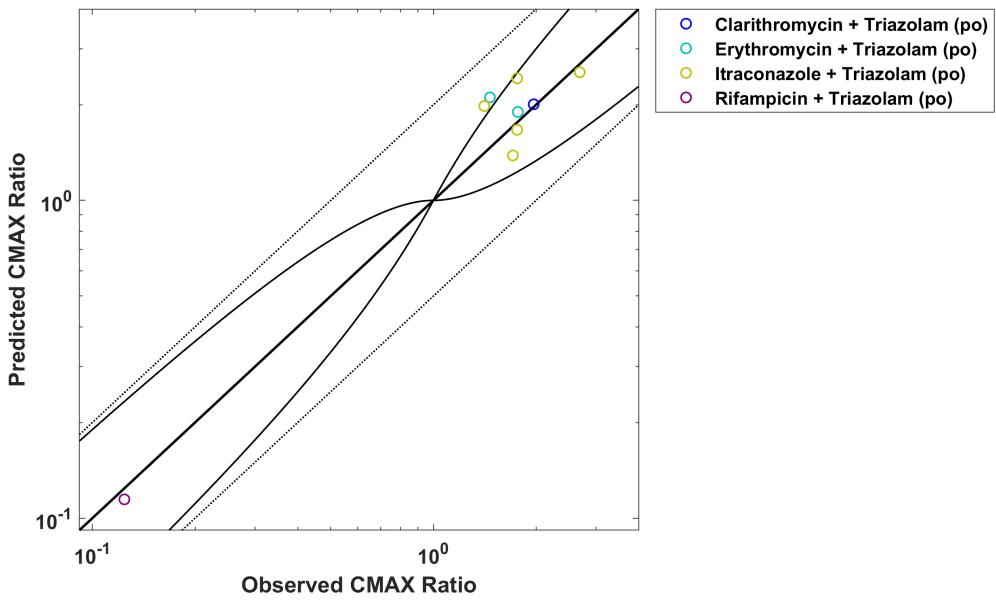
Triazolam



CYP3A4 DDI Triazolam



CYP3A4 DDI Triazolam



GMFE (AUC) = 1.638541

GMFE (CMAX) = 1.183830

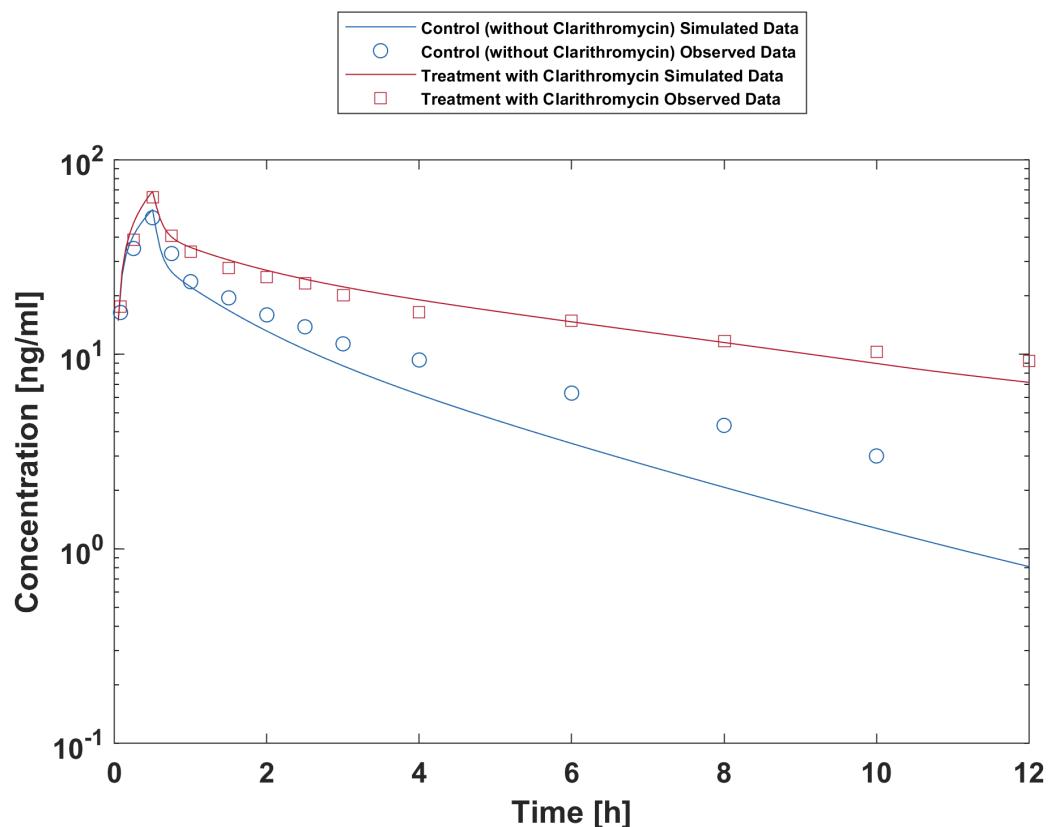
	AUC	Number	Ratio [%]
Points total		9	-
Points within Guest et al.		5	55.5556
Points within 2-fold		7	77.7778

	CMAX	Number	Ratio [%]
Points total		9	-
Points within Guest et al.		7	77.7778
Points within 2-fold		9	100

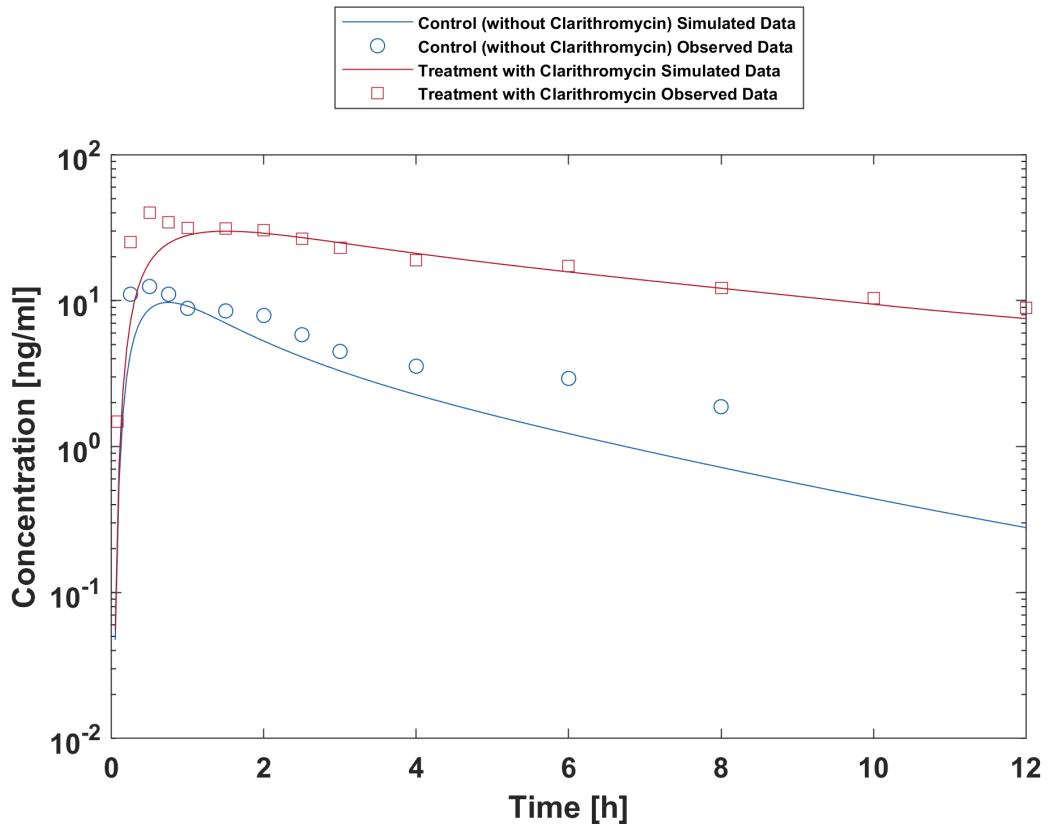
3 Concentration-Time Profiles

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

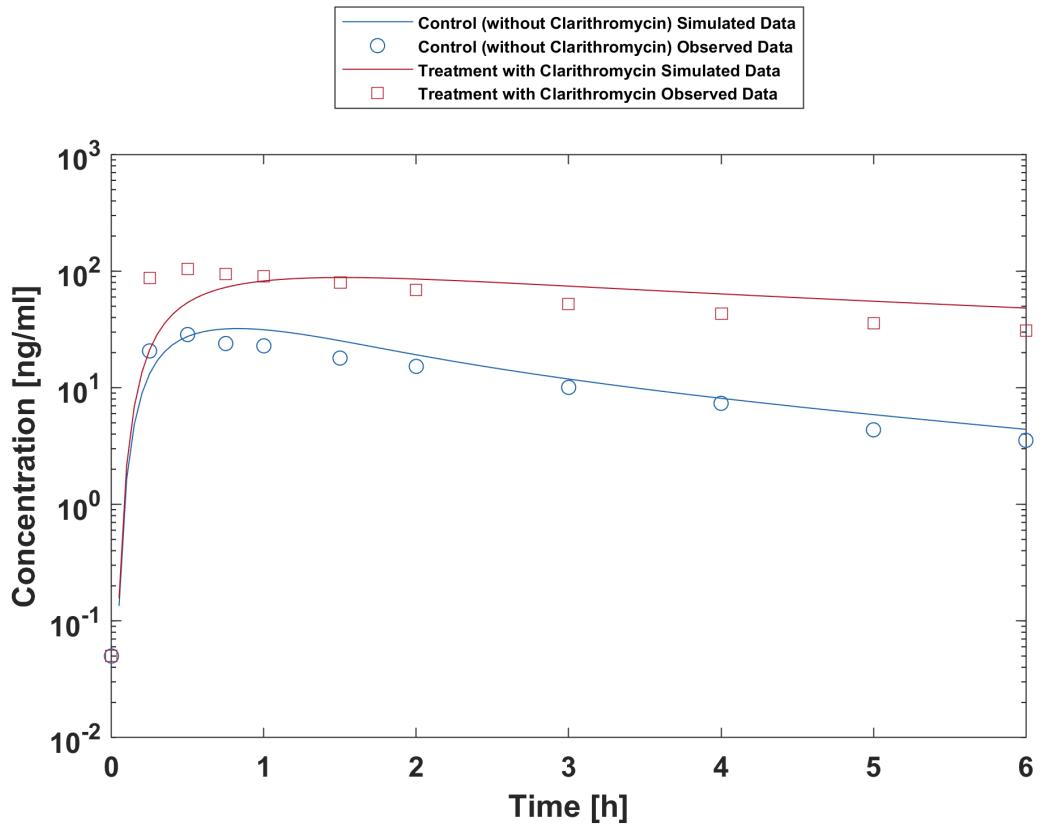
3.1 Clarithromycin - Midazolam DDI



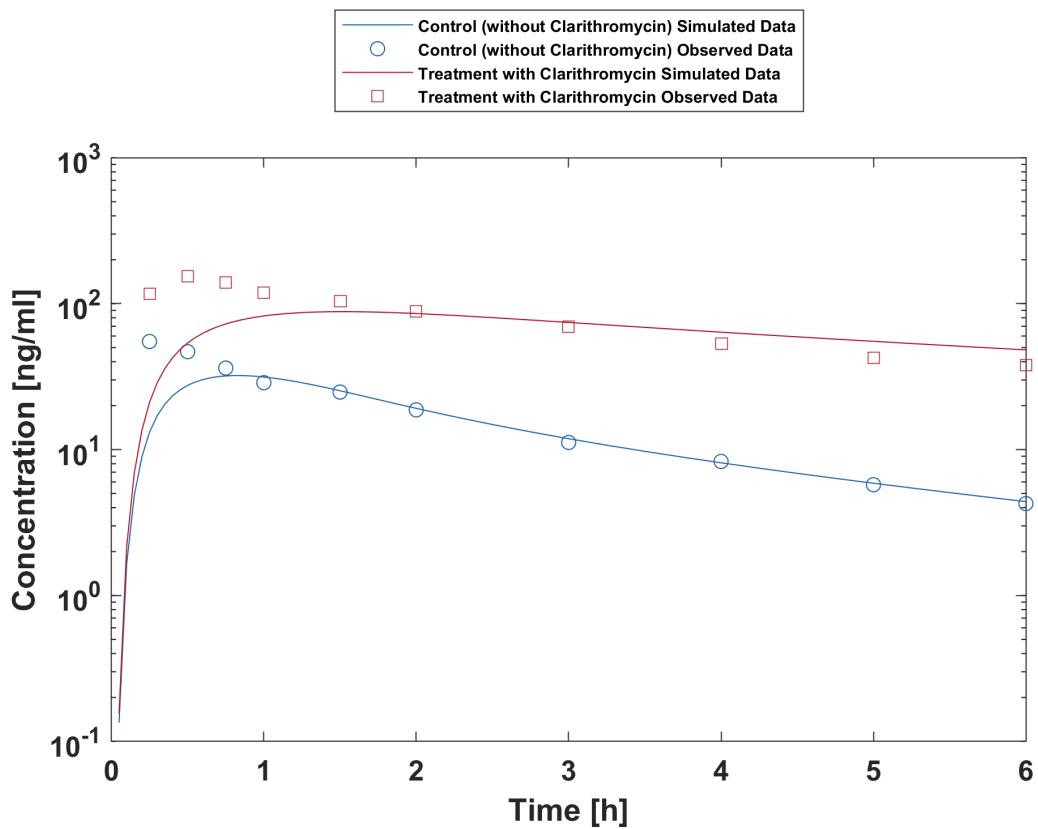
Gorski 1998 (midazolam IV)



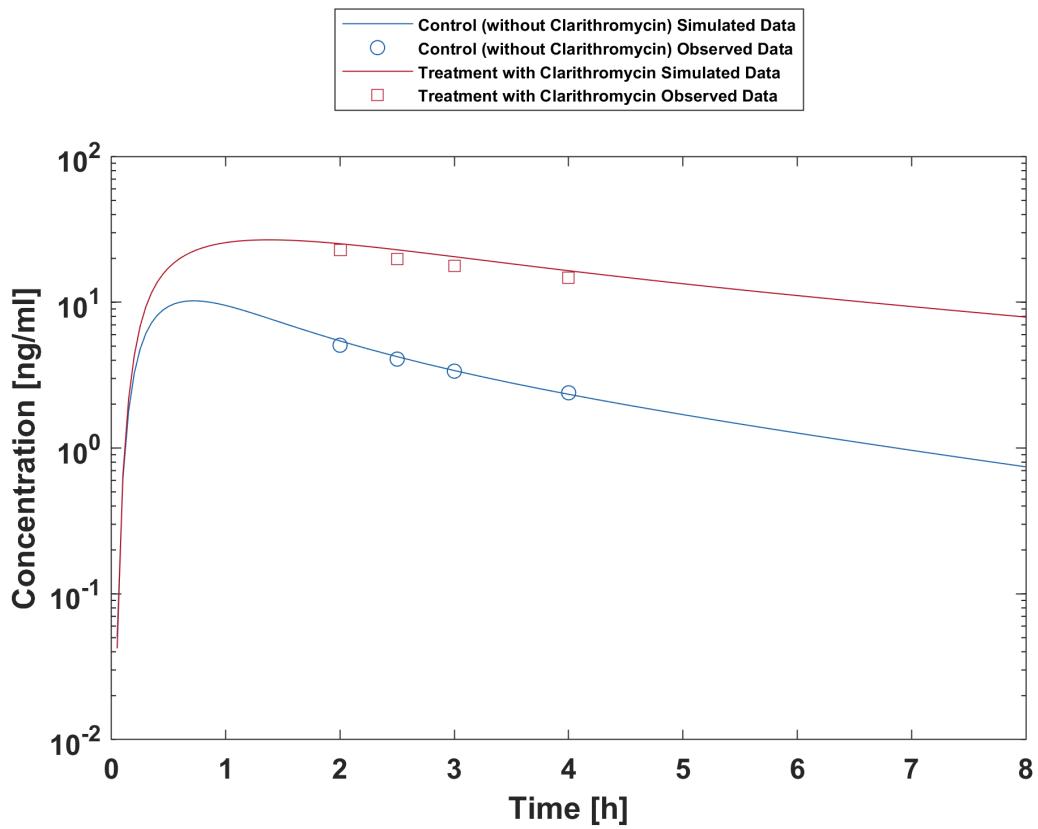
Gorski 1998 (midazolam po)



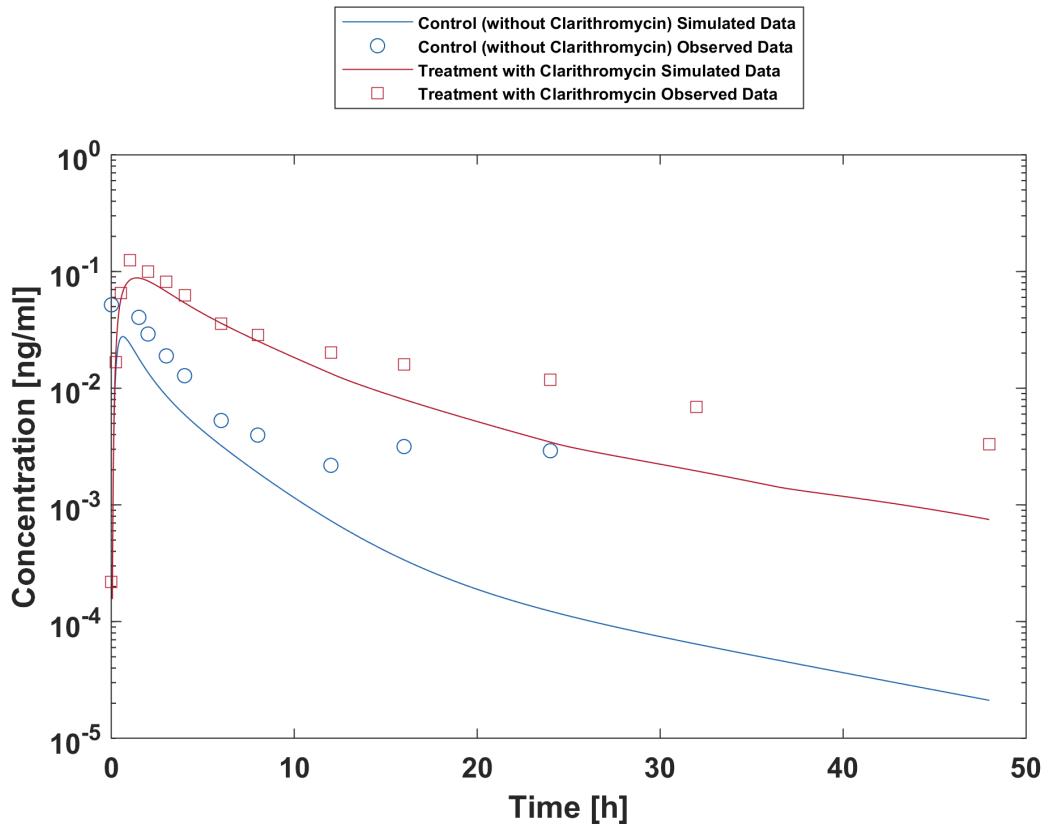
Gurley 2006



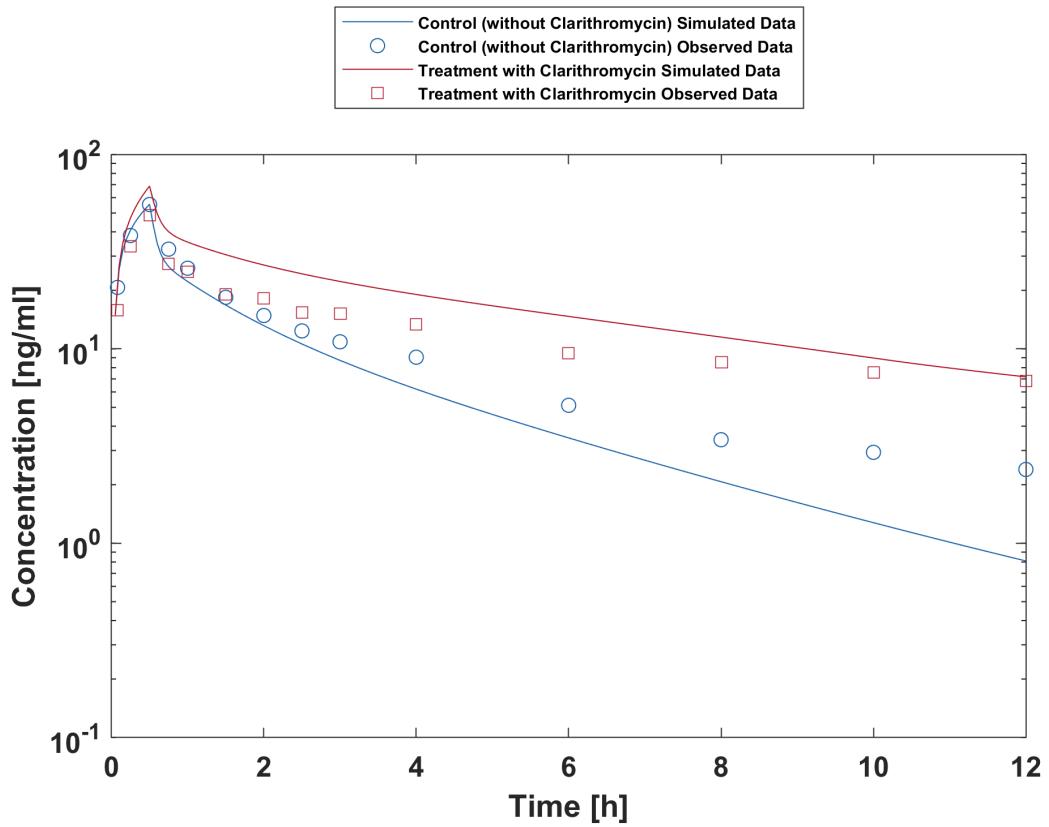
Gurley 2008a



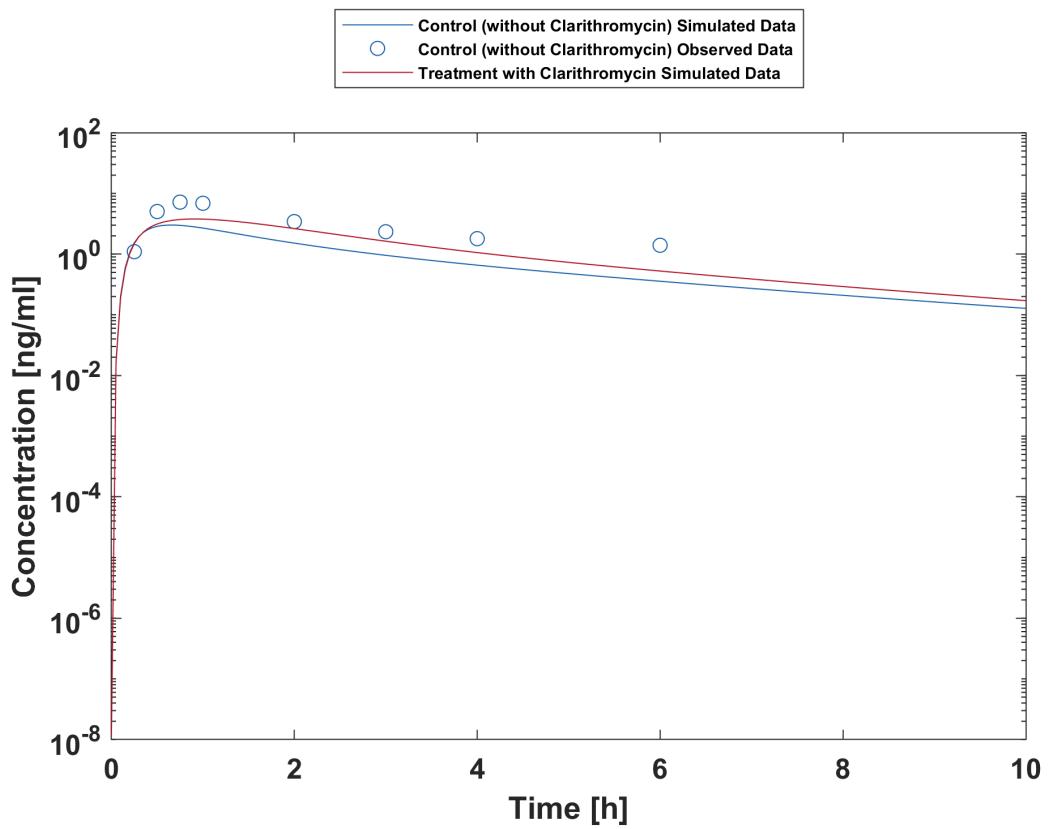
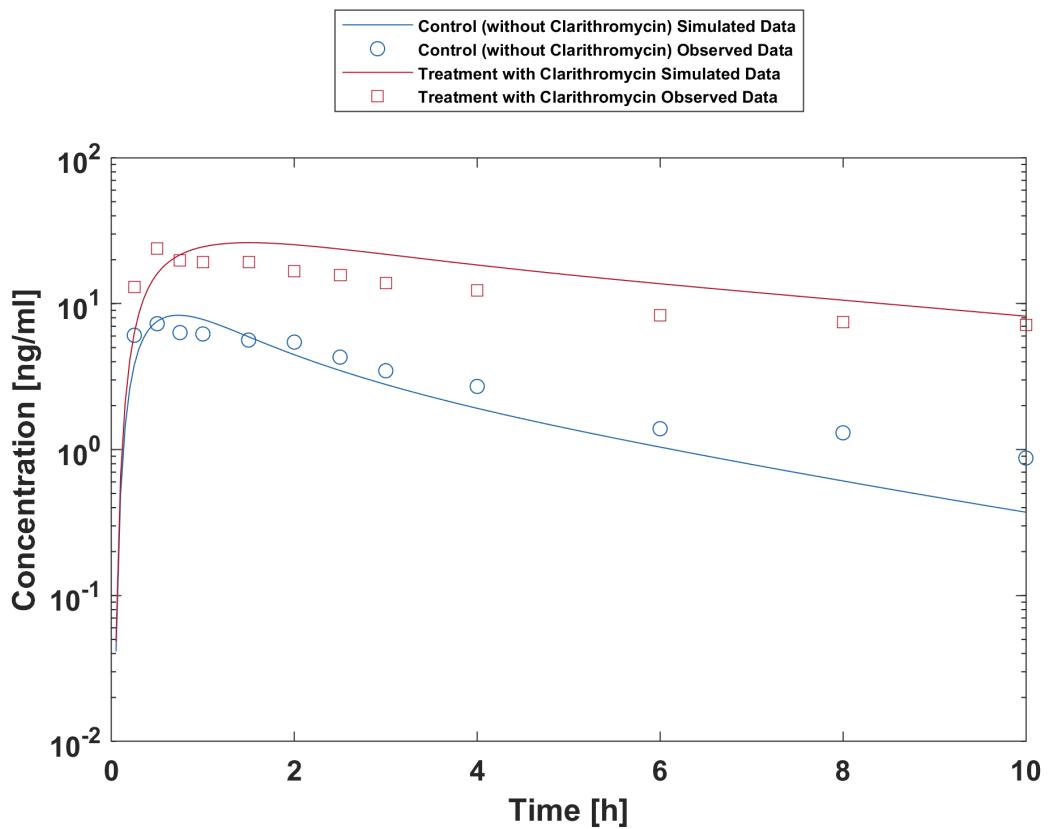
Markert 2013

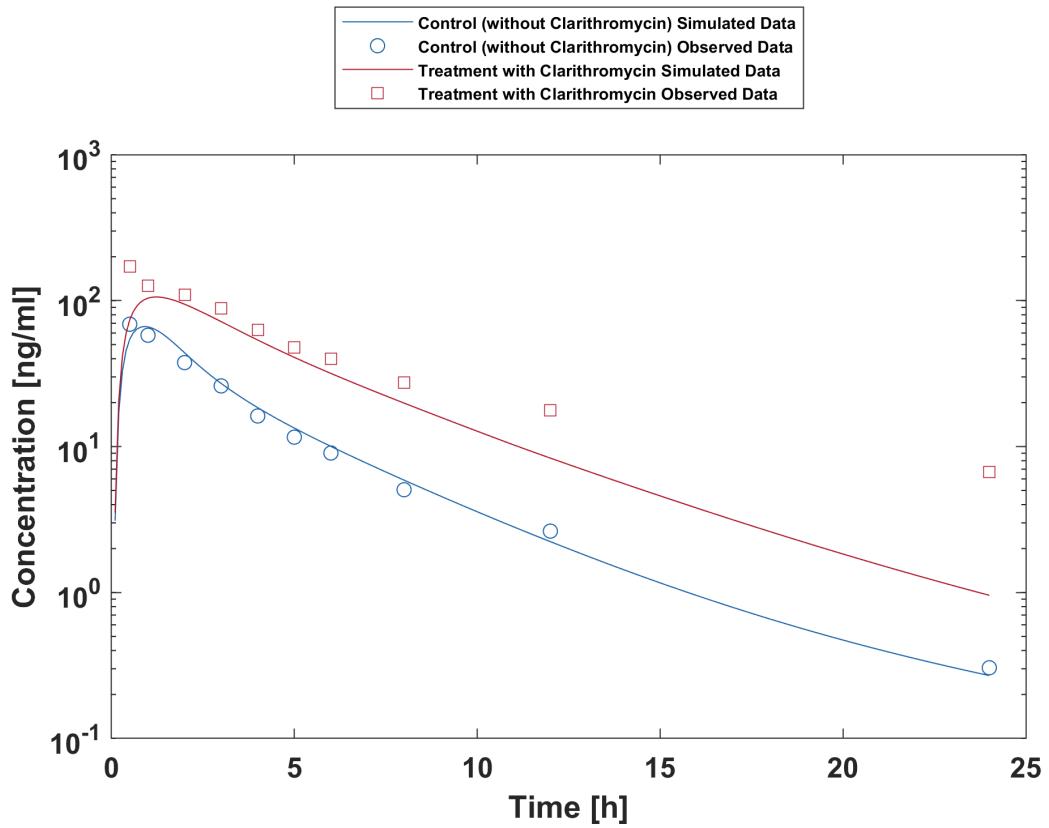


Prueksaritanont 2017



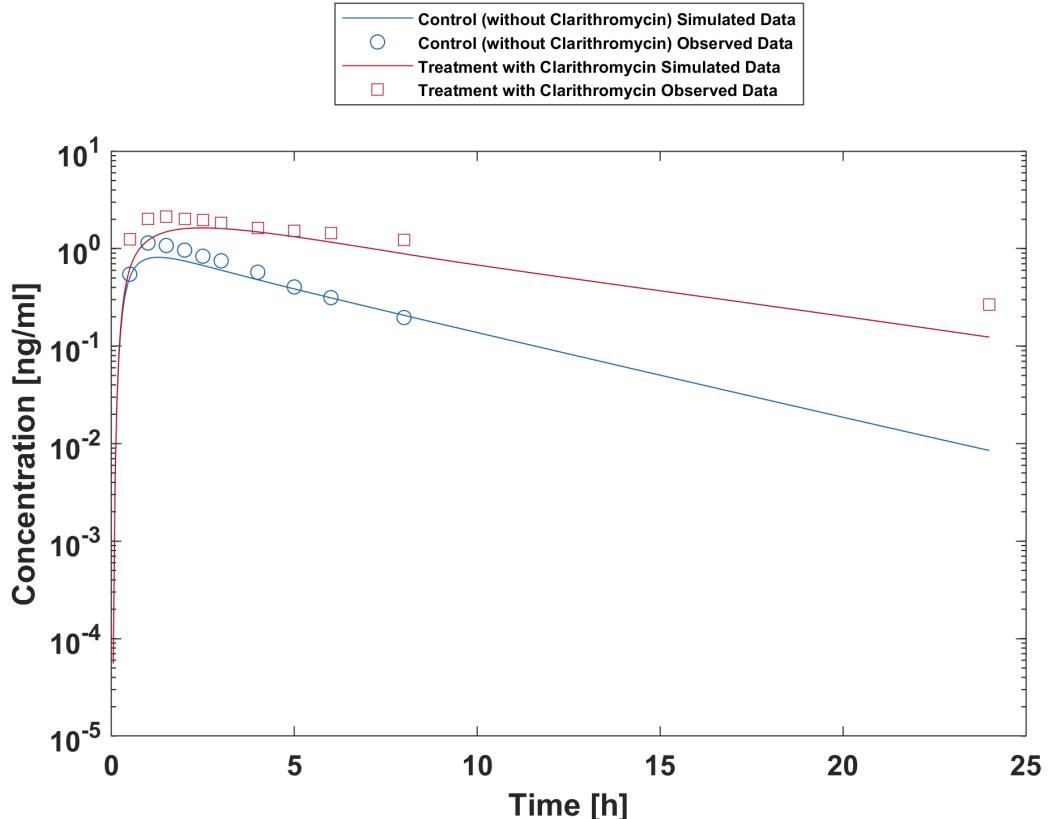
Quinney 2008 (midazolam IV)





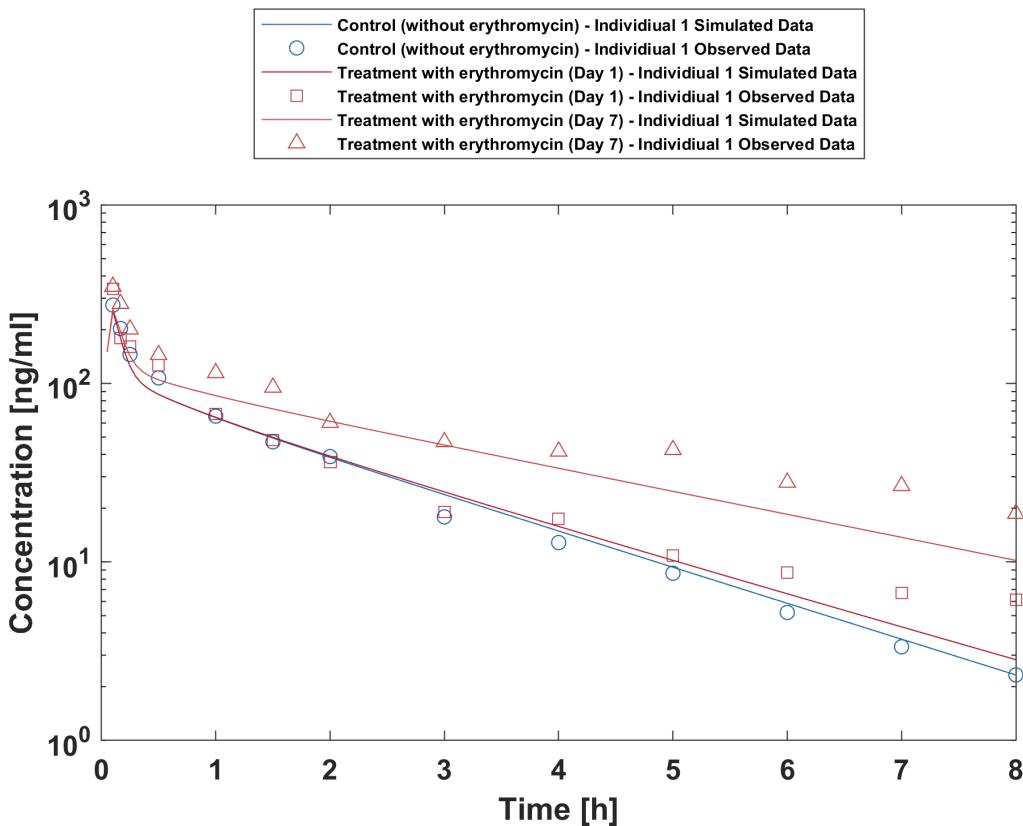
Yeates 1996

3.2 Clarithromycin - Triazolam DDI

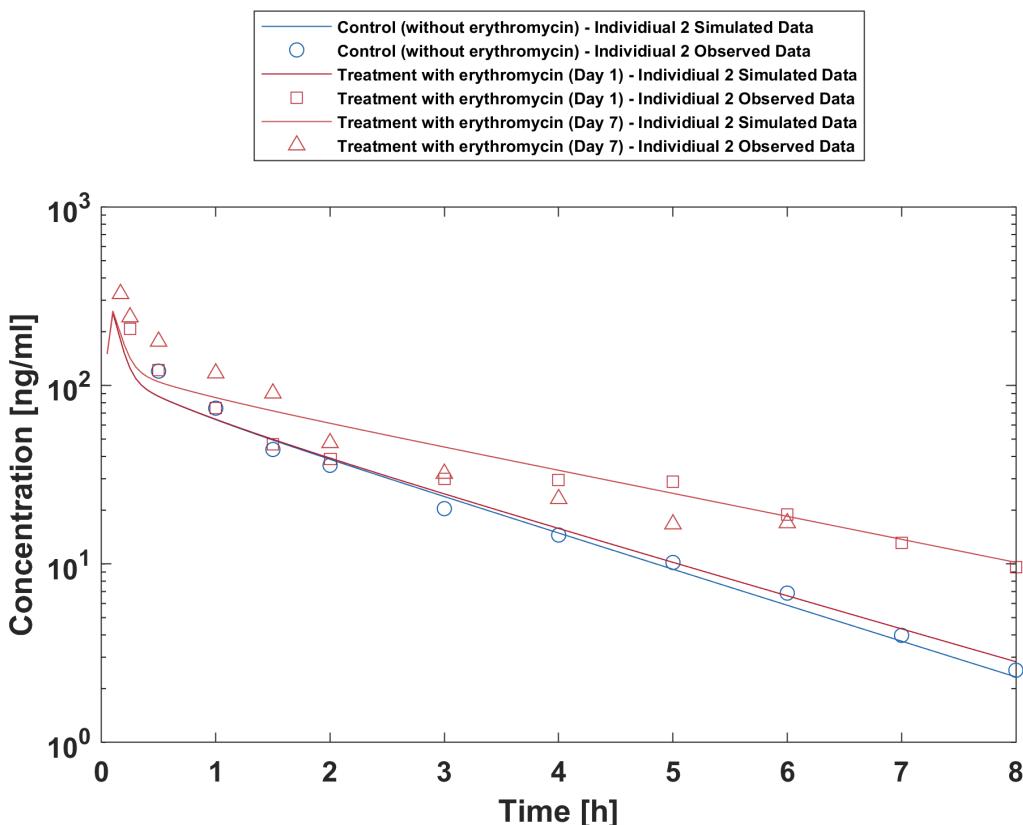


Greenblatt 1998a

3.3 Erythromycin - Alfentanil DDI

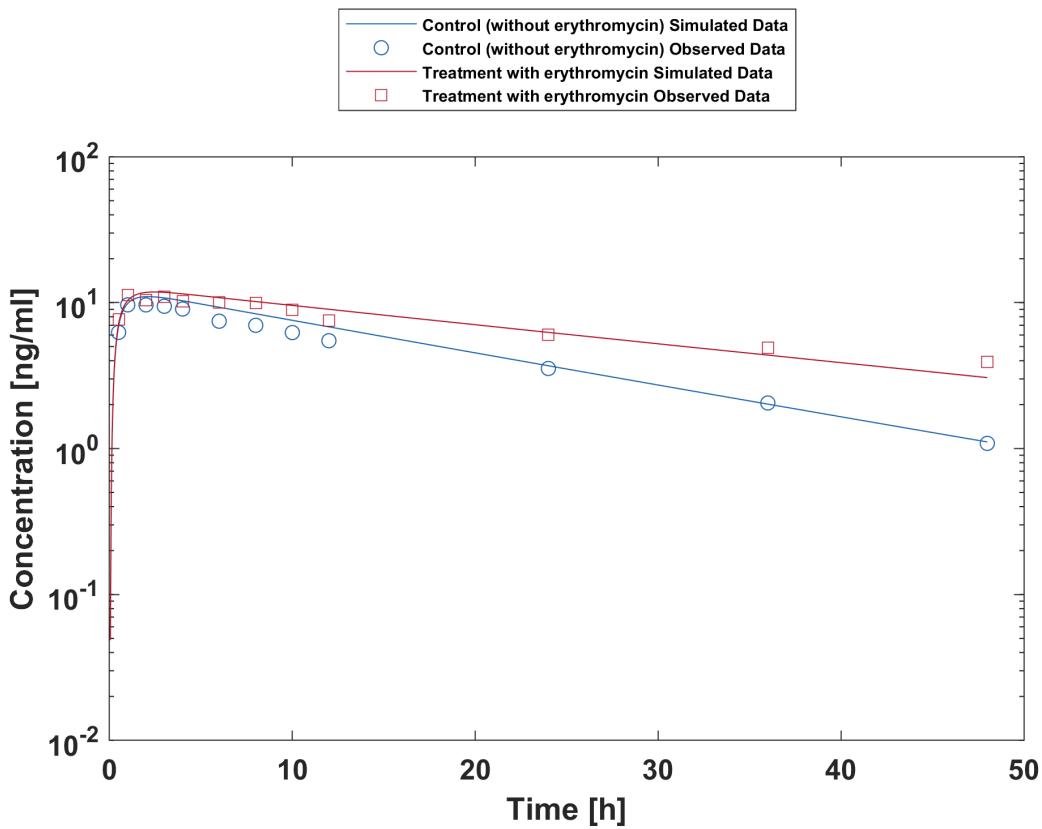


Bartkowski 1989



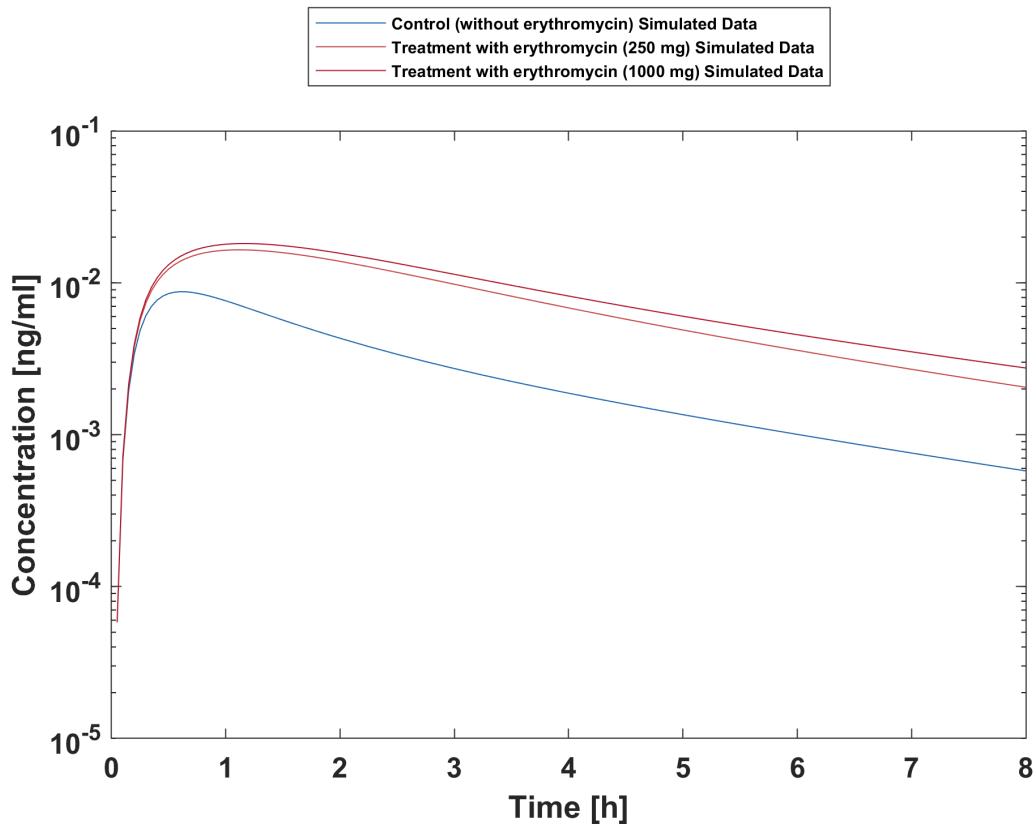
Bartkowski 1993

3.4 Erythromycin - Alprazolam DDI

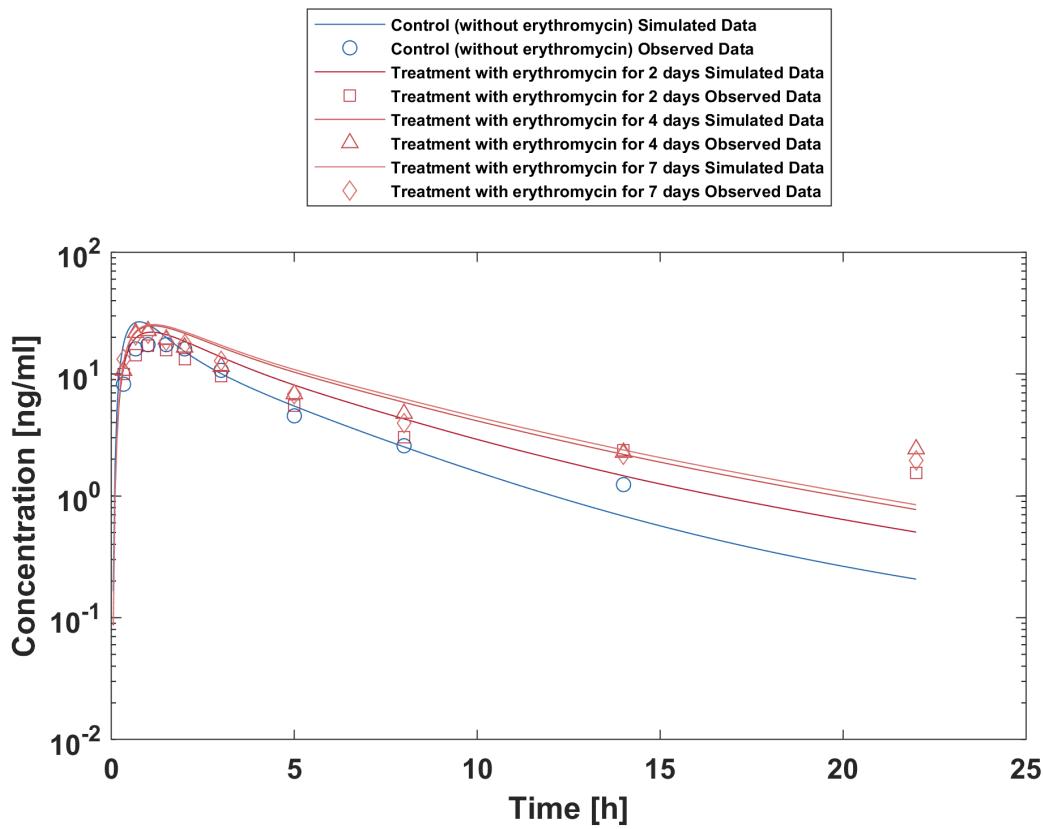


Yasui 1996

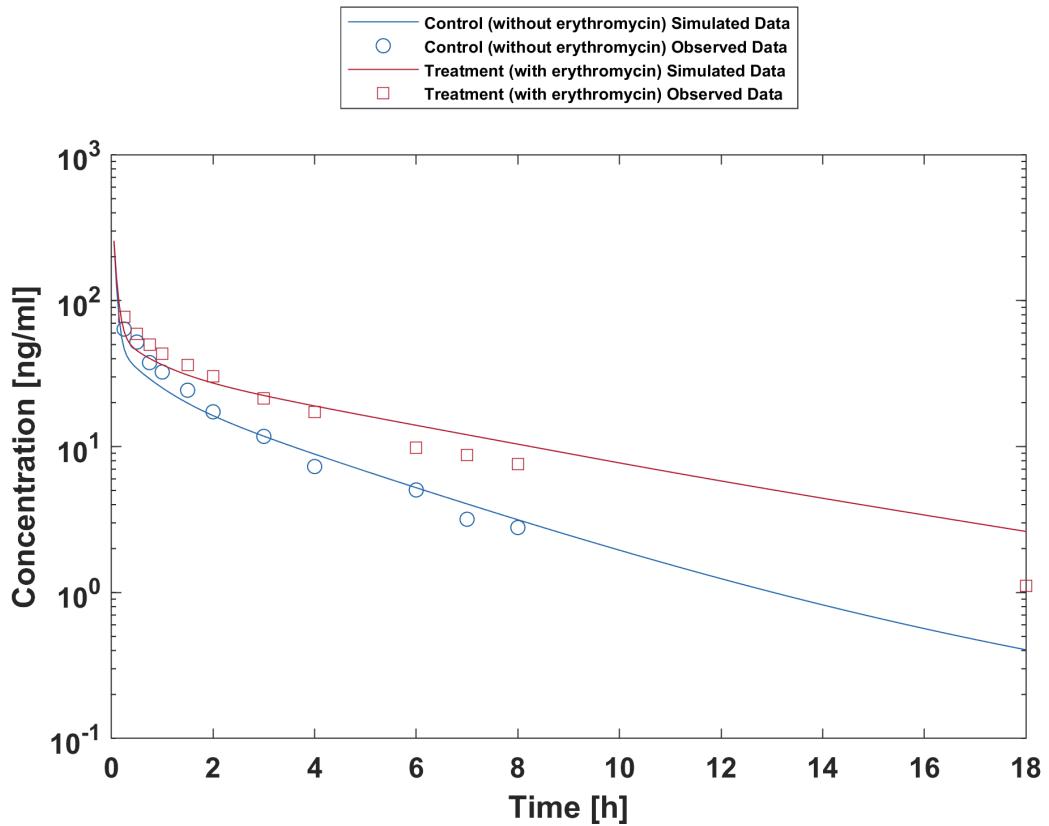
3.5 Erythromycin - Midazolam DDI



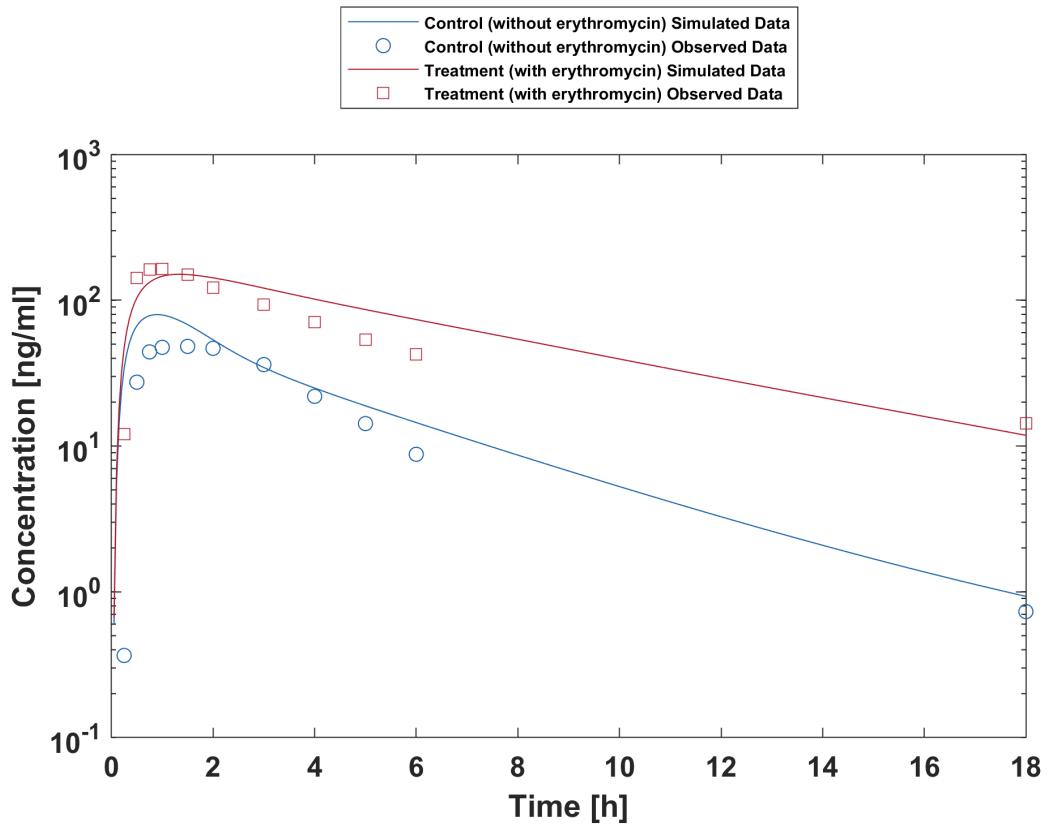
Carls 2014



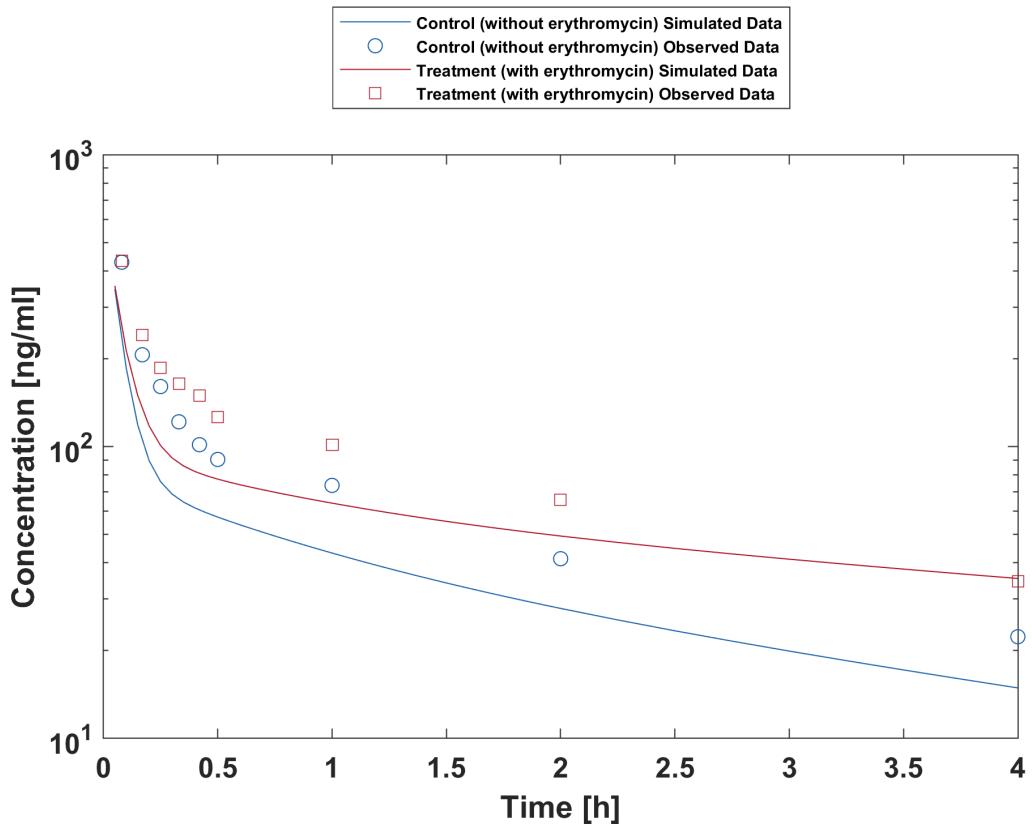
Okudaira 2007



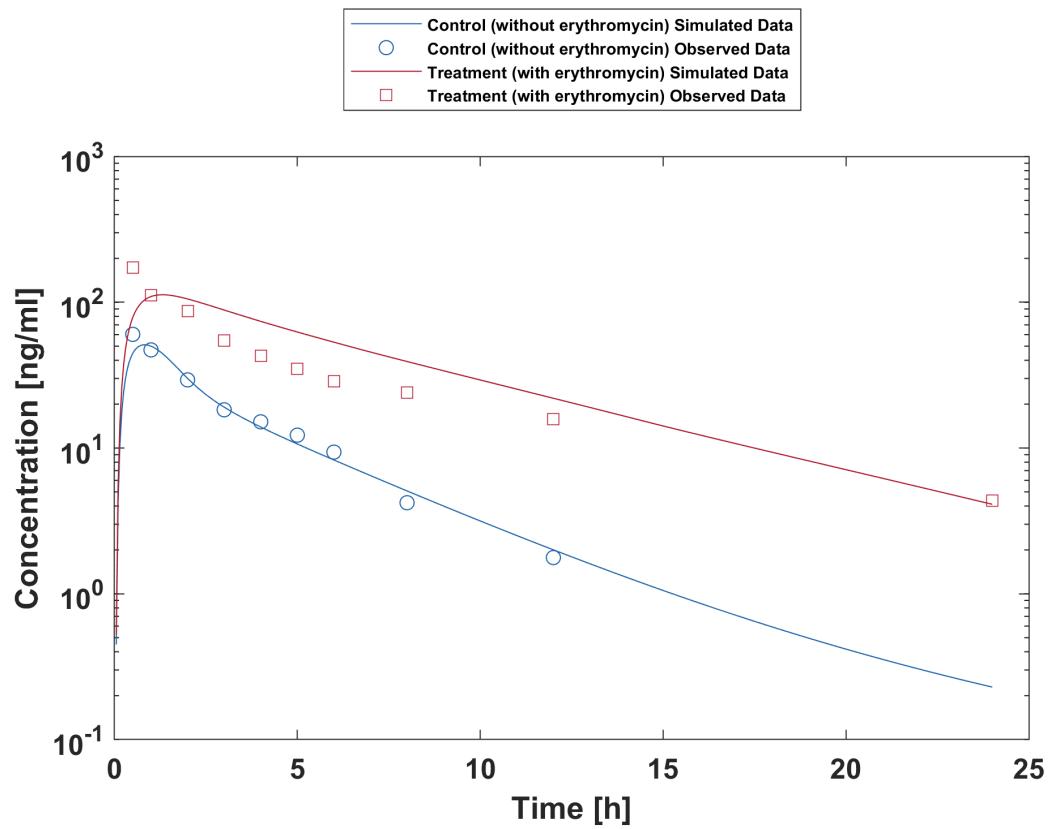
Olkkola 1993 (midazolam IV)



Olkkola 1993 (midazolam po)

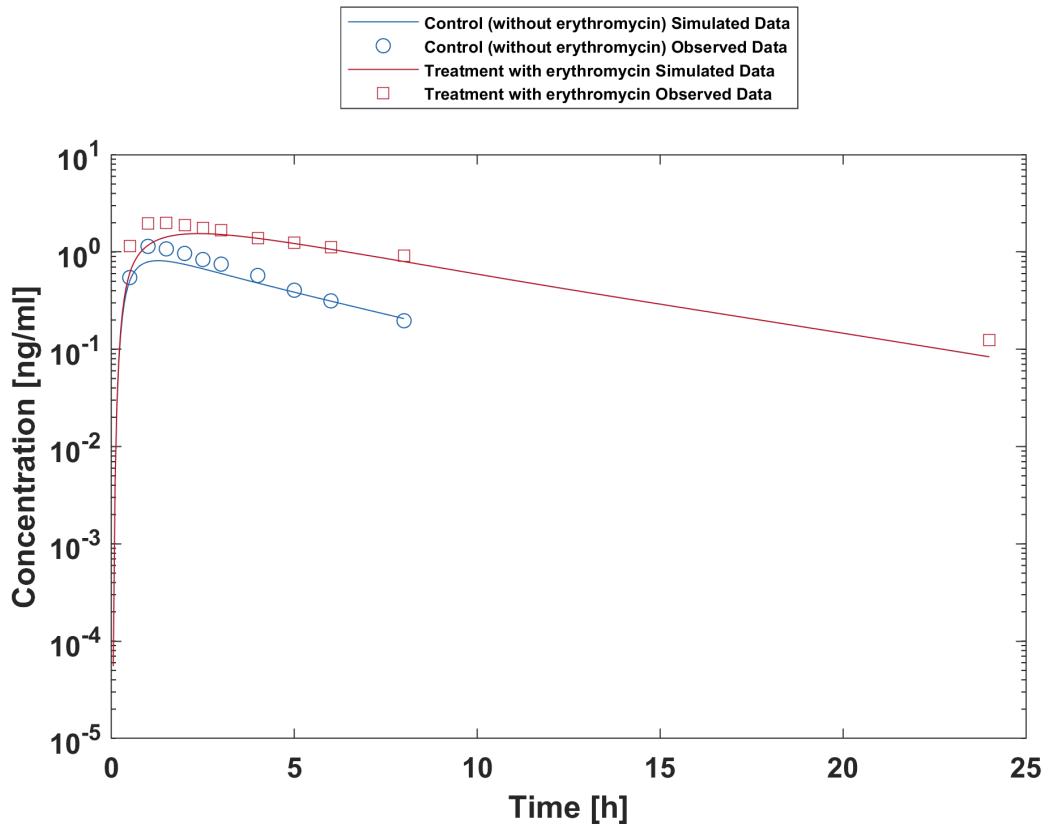


Swart 2002

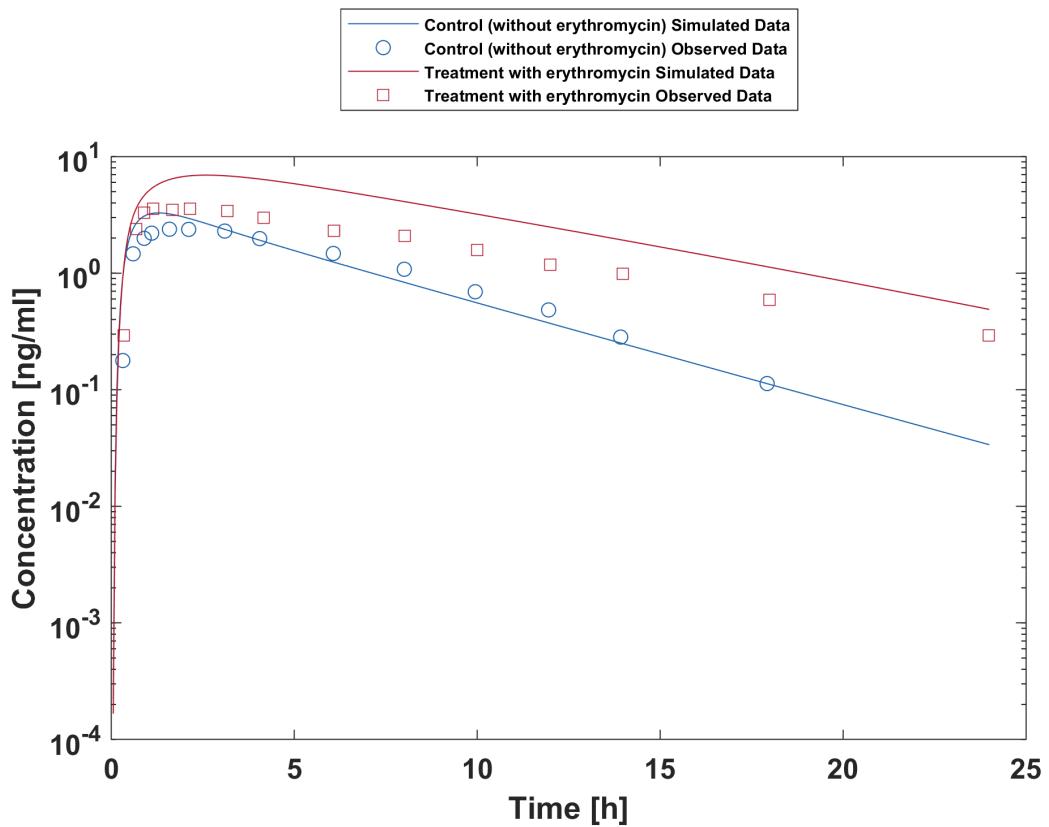


Zimmermann 1996

3.6 Erythromycin - Triazolam DDI

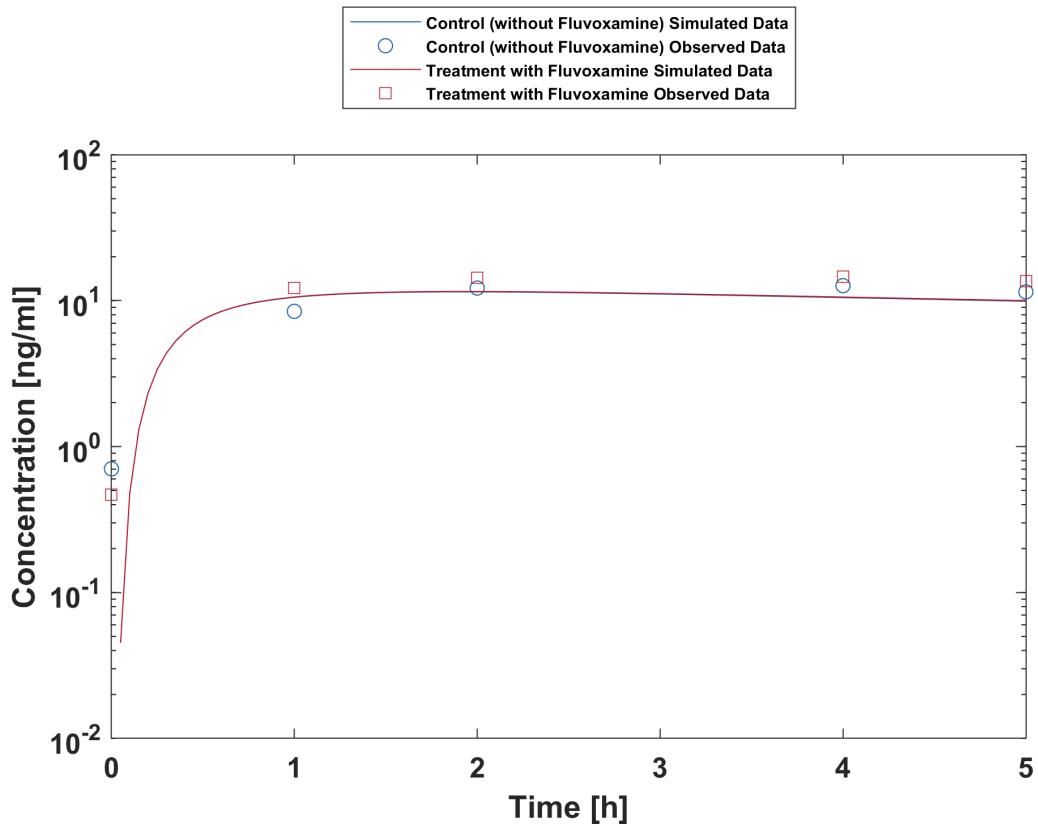


Greenblatt 1998

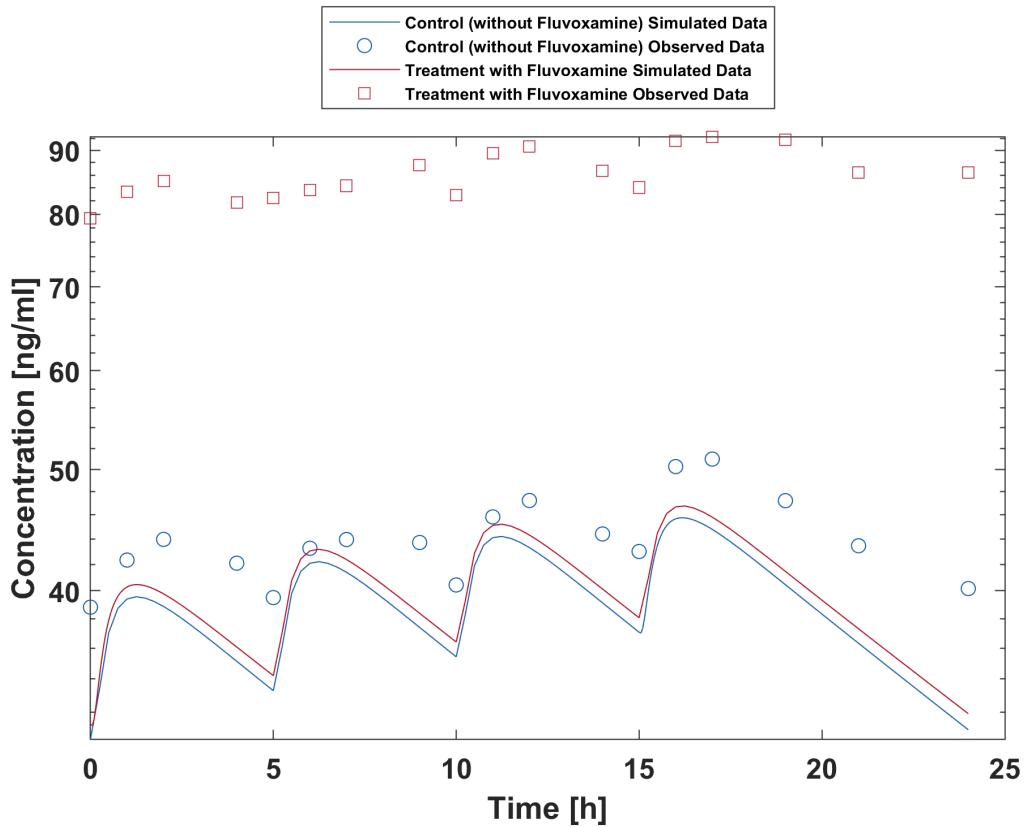


Phillips 1986

3.7 Fluvoxamine - Alprazolam DDI

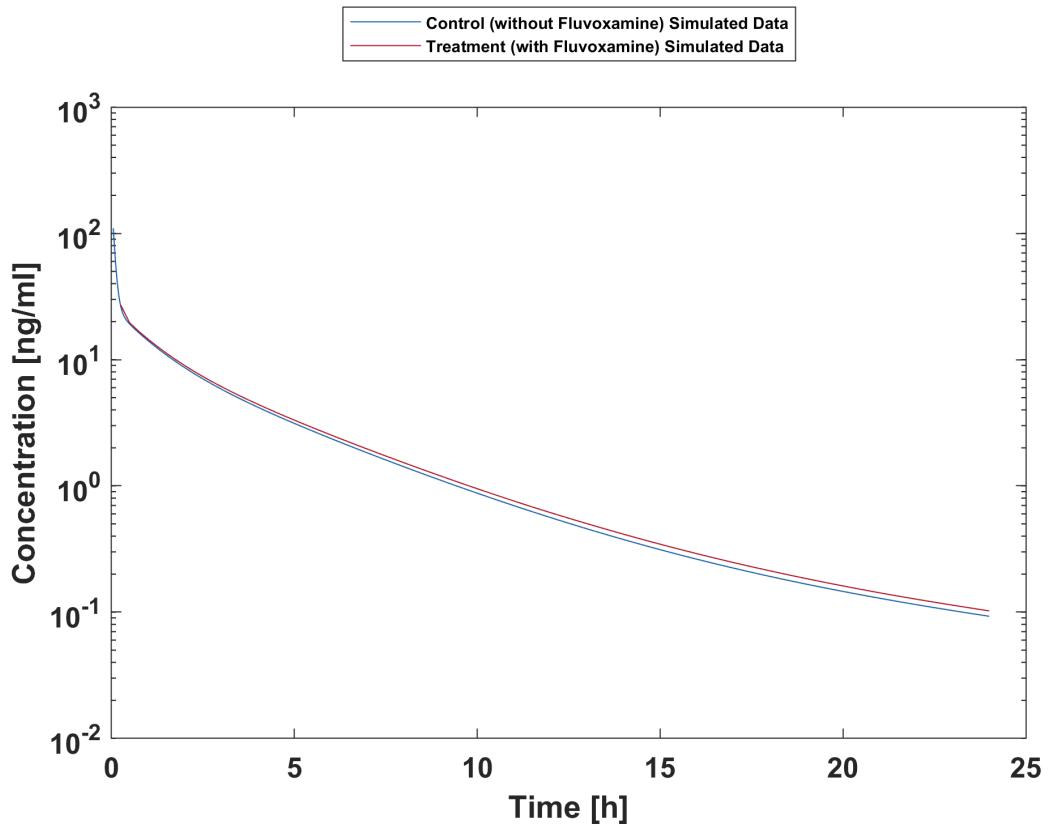


Fleishaker 1994 (Day 1, first dose)

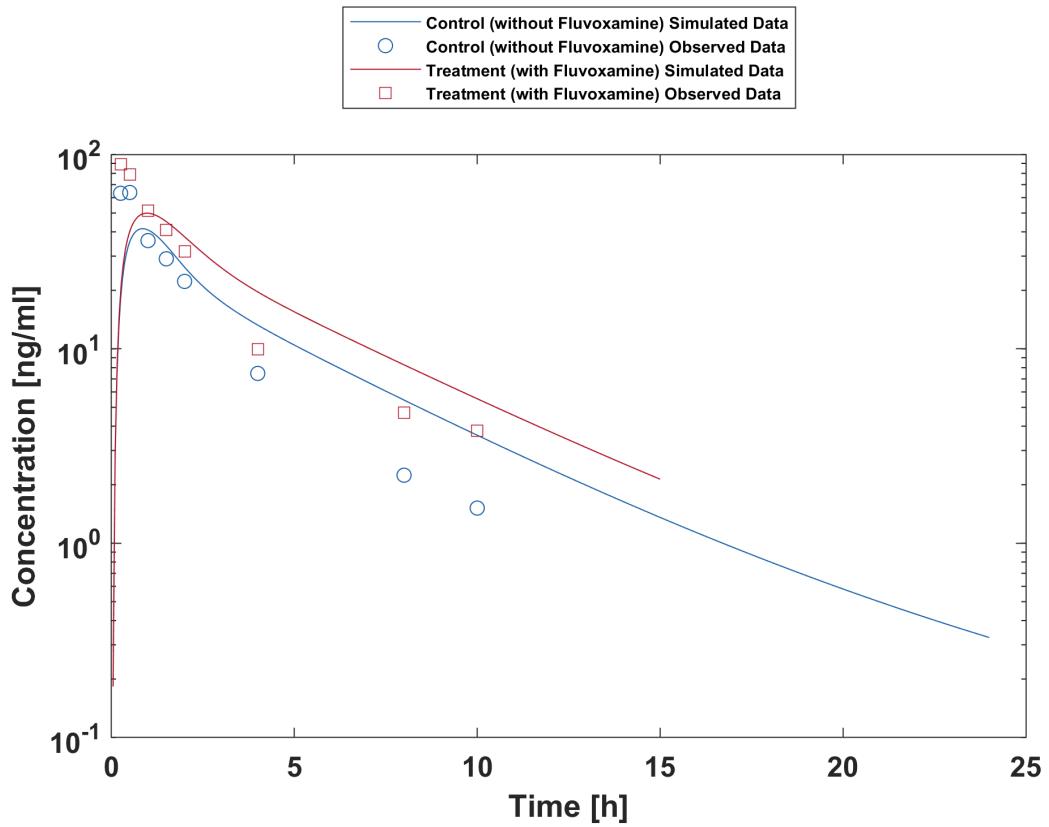


Fleishaker 1994 (Day 10)

3.8 Fluvoxamine - Midazolam DDI

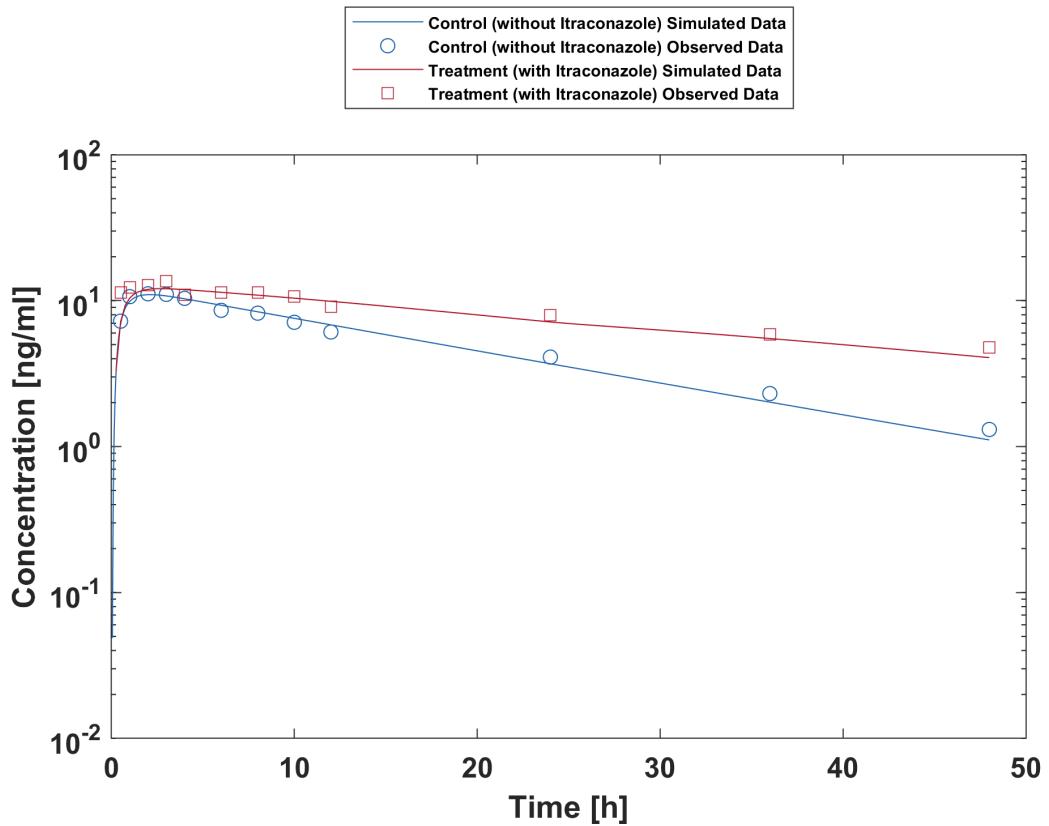


Kashuba 1998

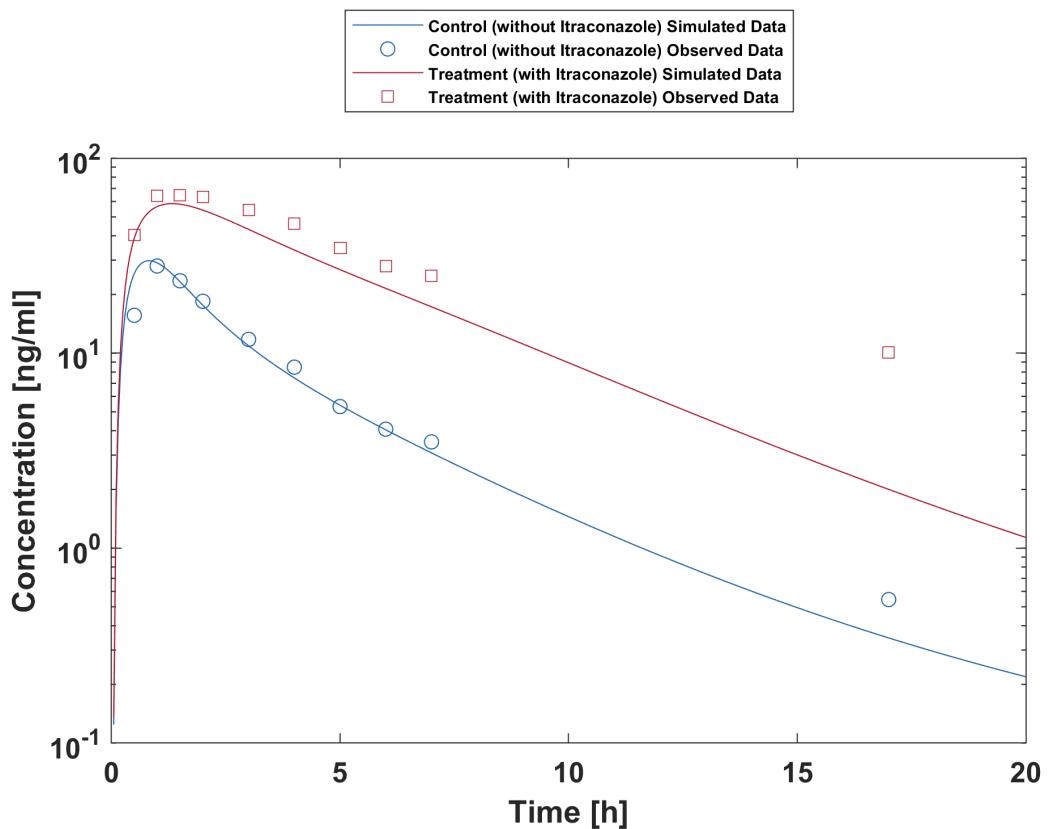


Lam 2003

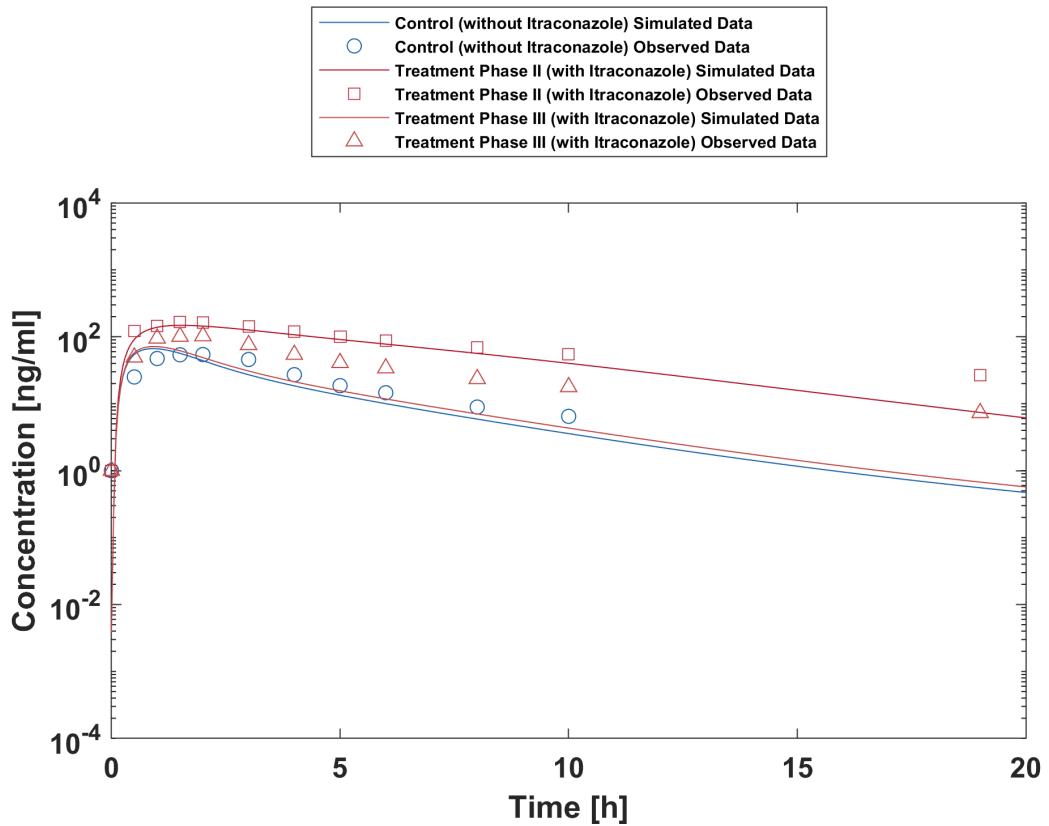
3.9 Itraconazole - Alprazolam DDI



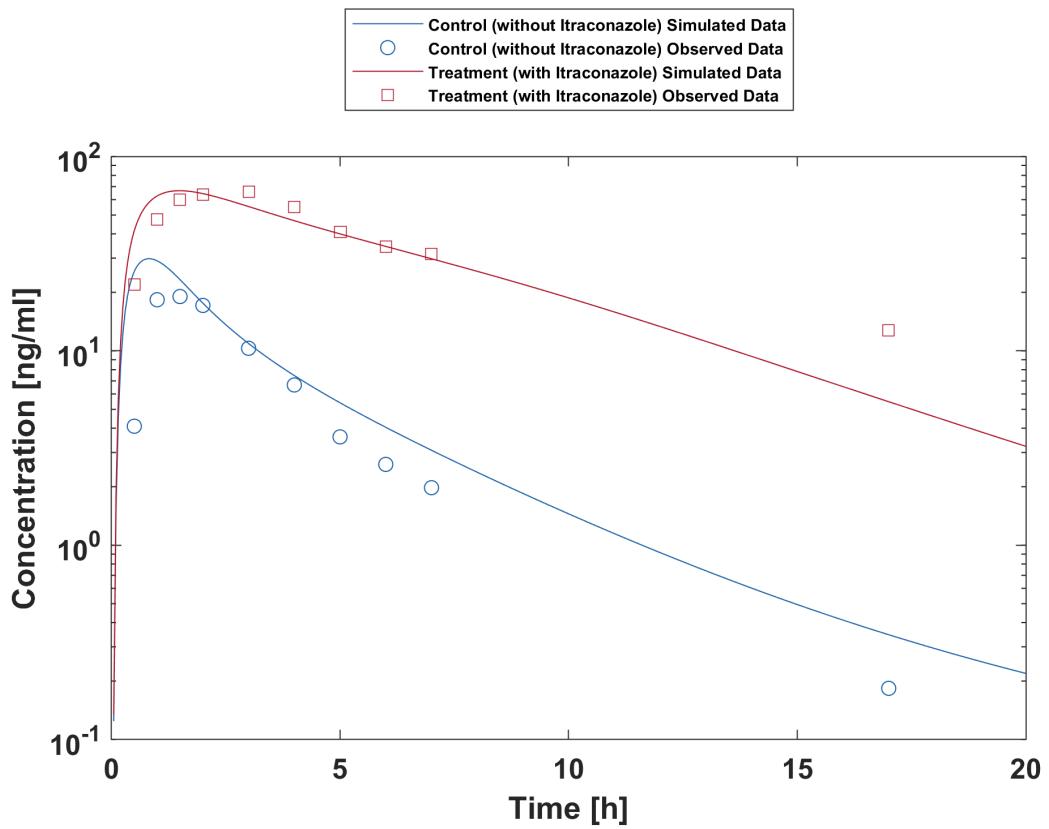
3.10 Itraconazole - Midazolam DDI



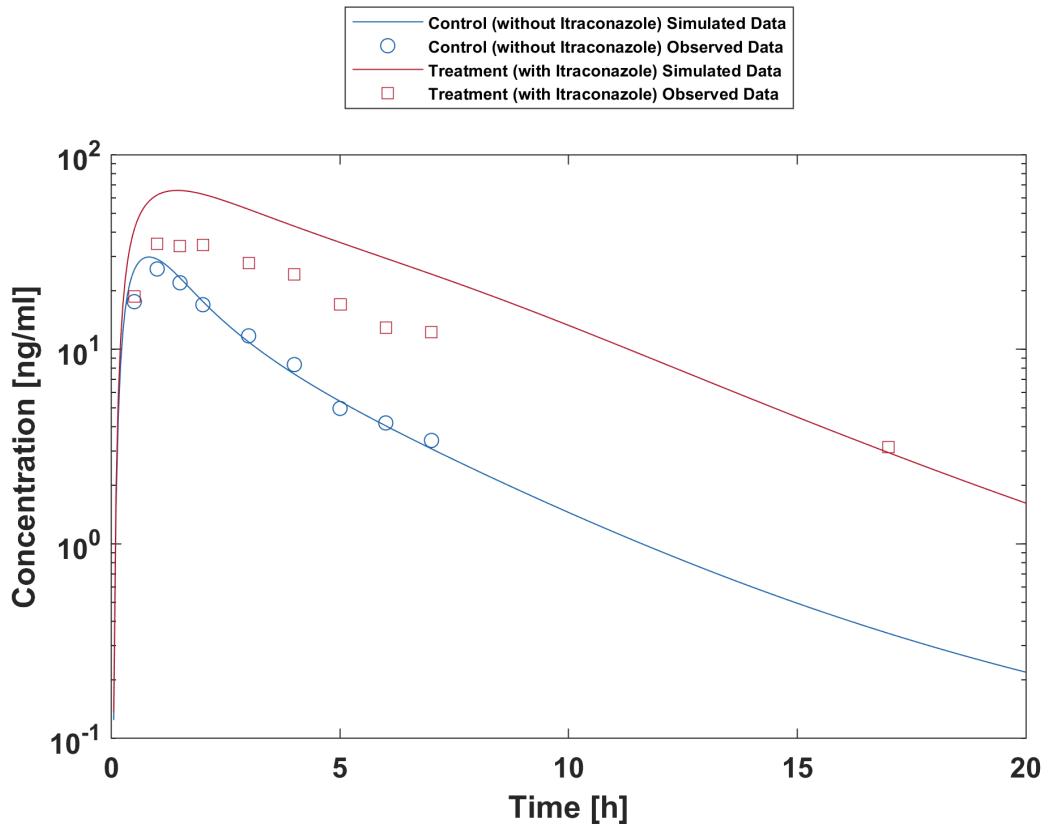
Ahonen 1995



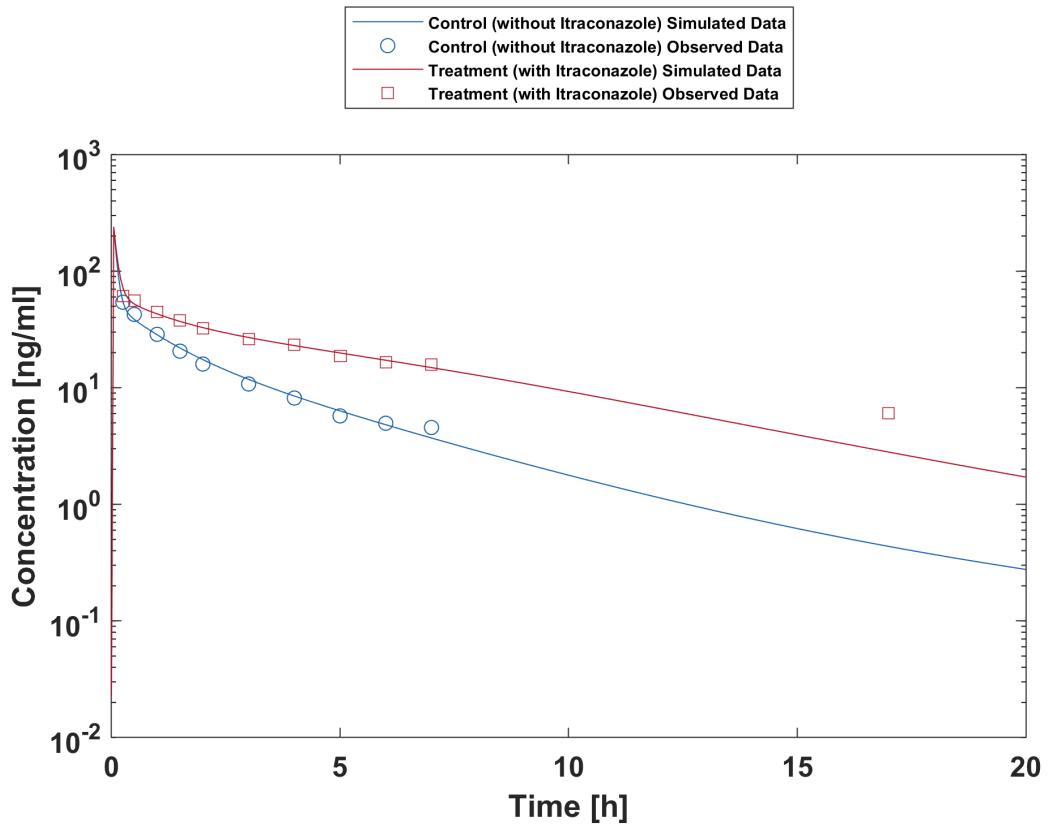
Backman 1998



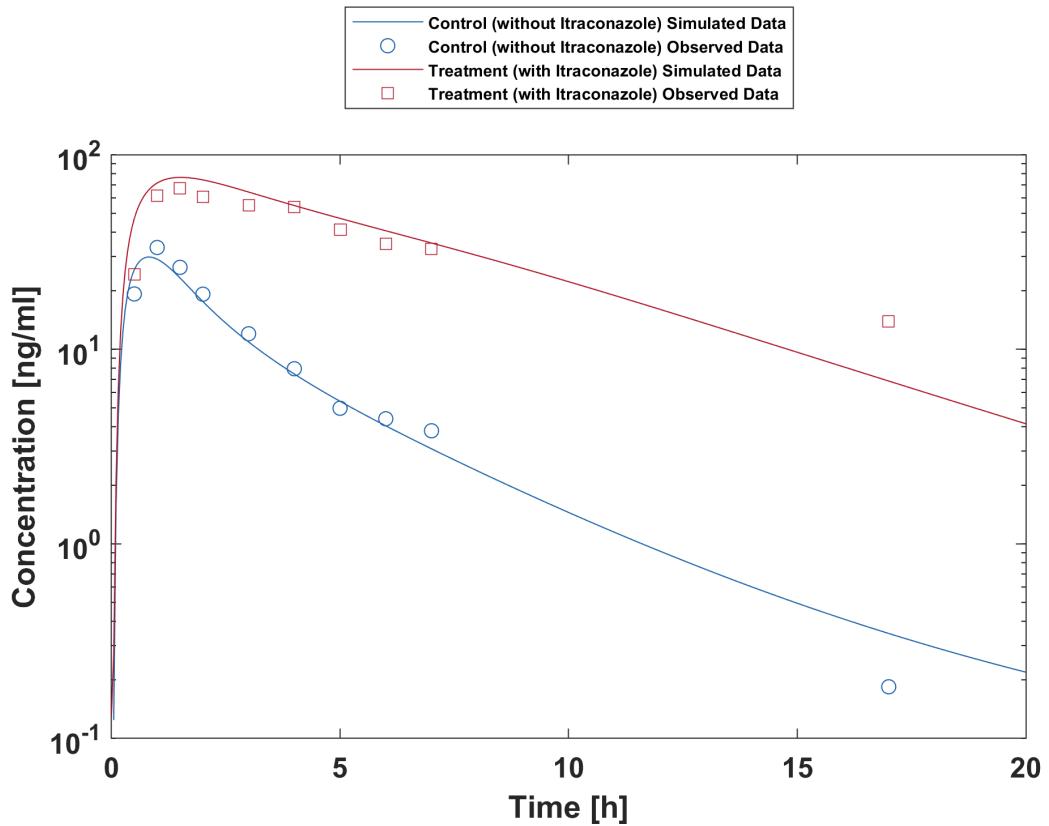
Olkkola 1994



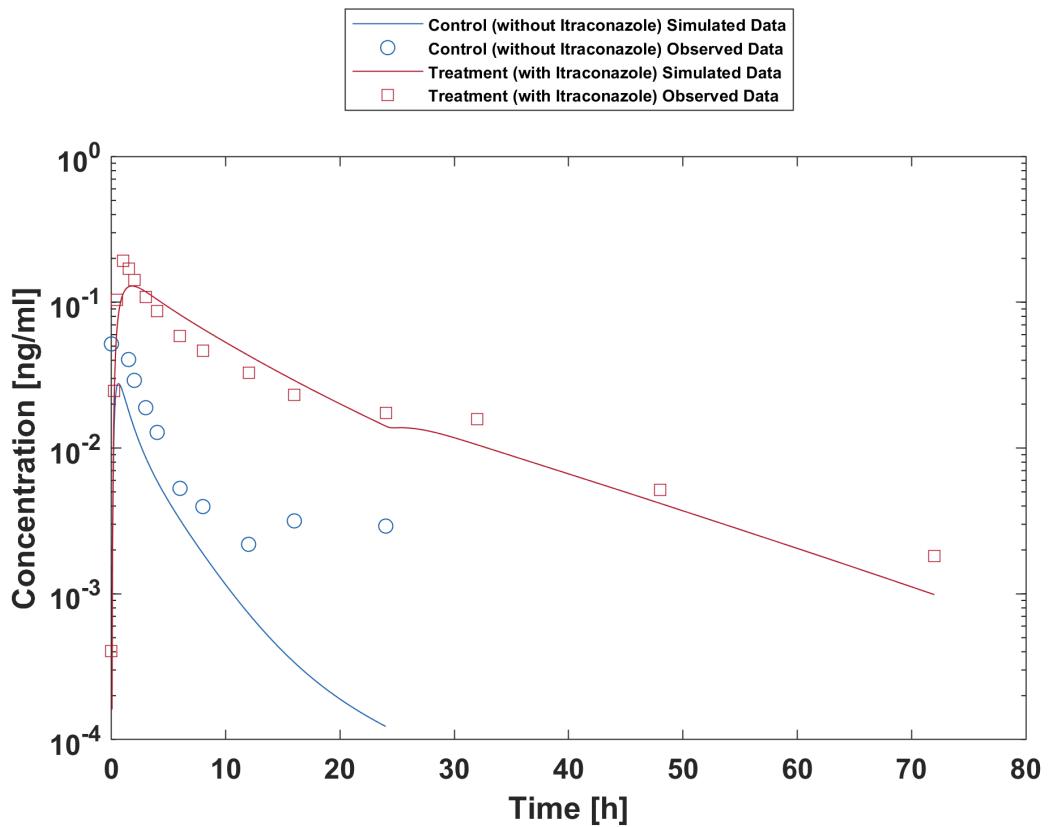
Olkola 1996 (day 1 po)



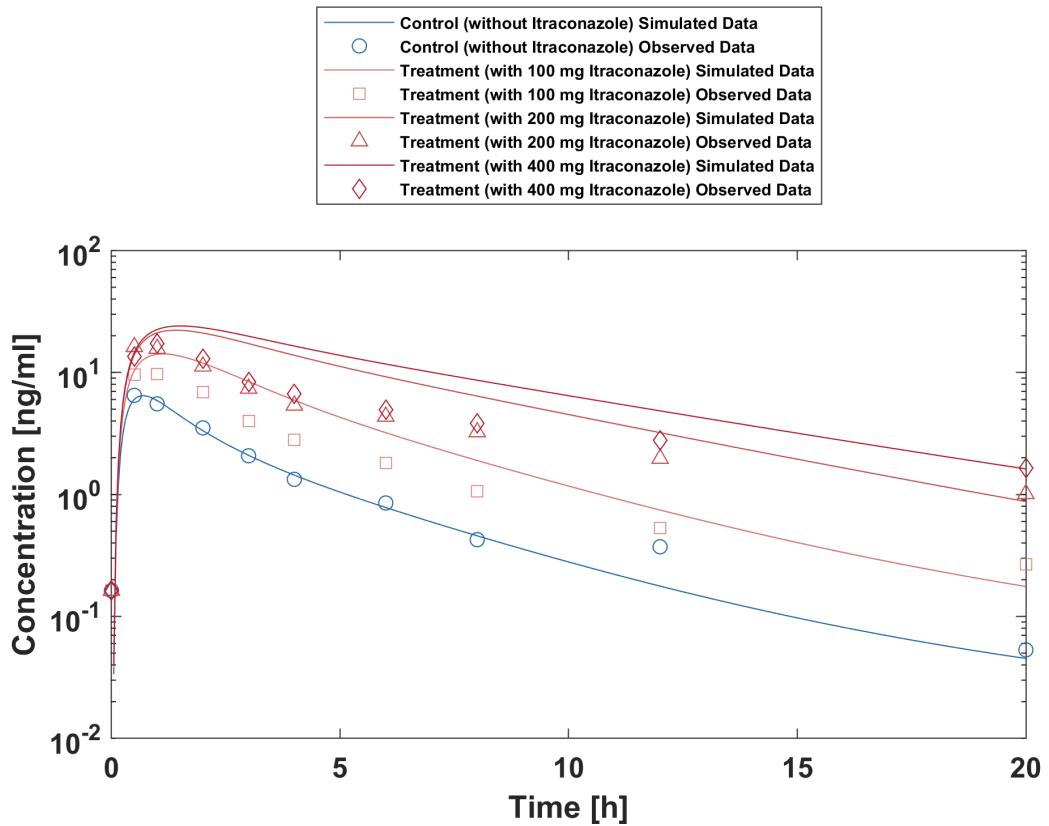
Olkola 1996 (day 4 iv)



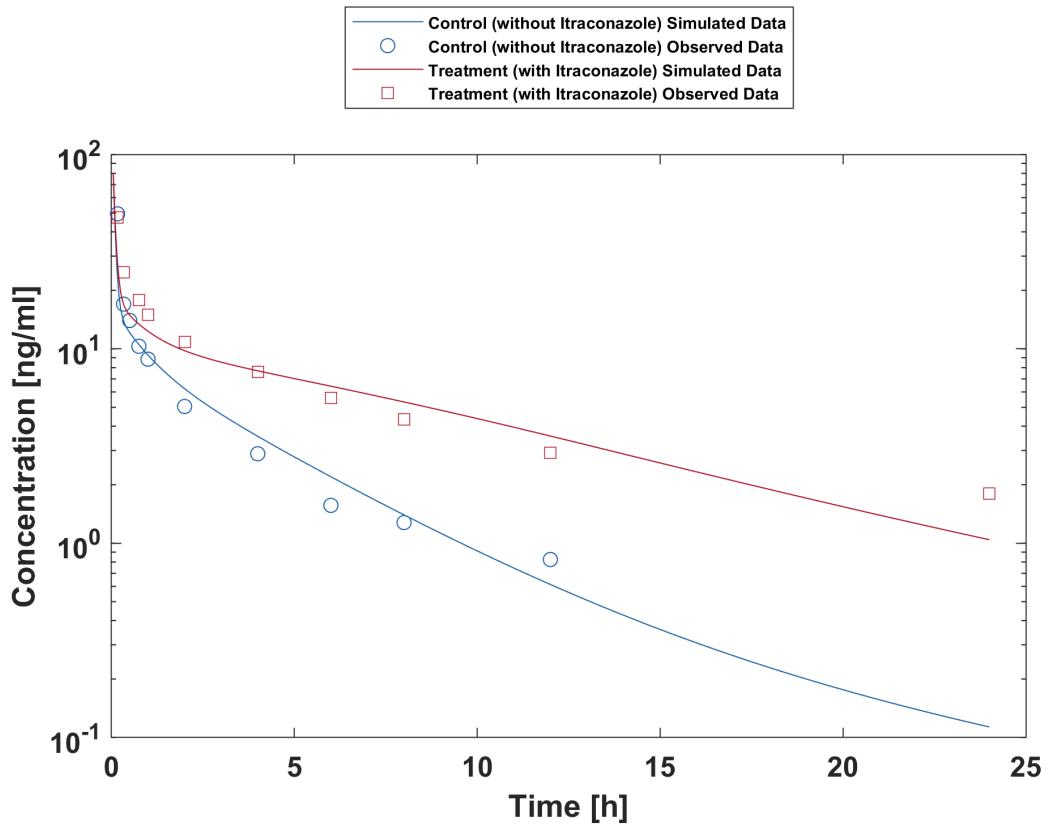
Olkola 1996 (day 6 po)



Prueksaritanont 2017

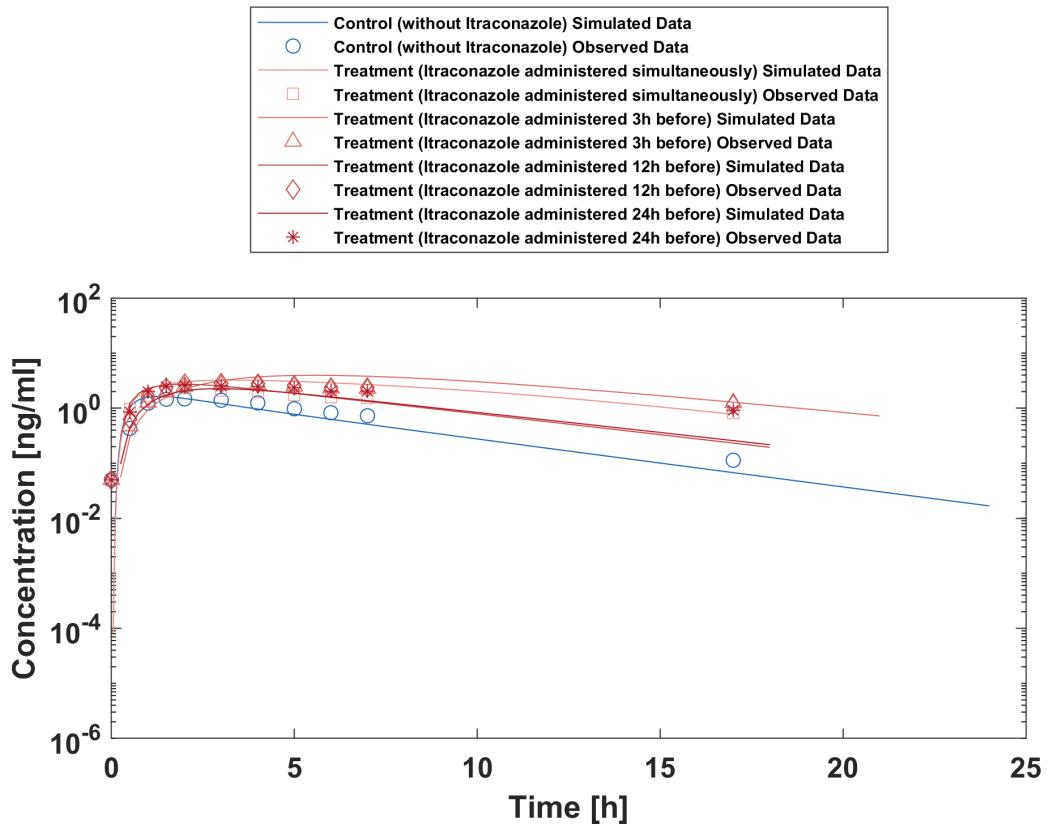


Templeton 2010

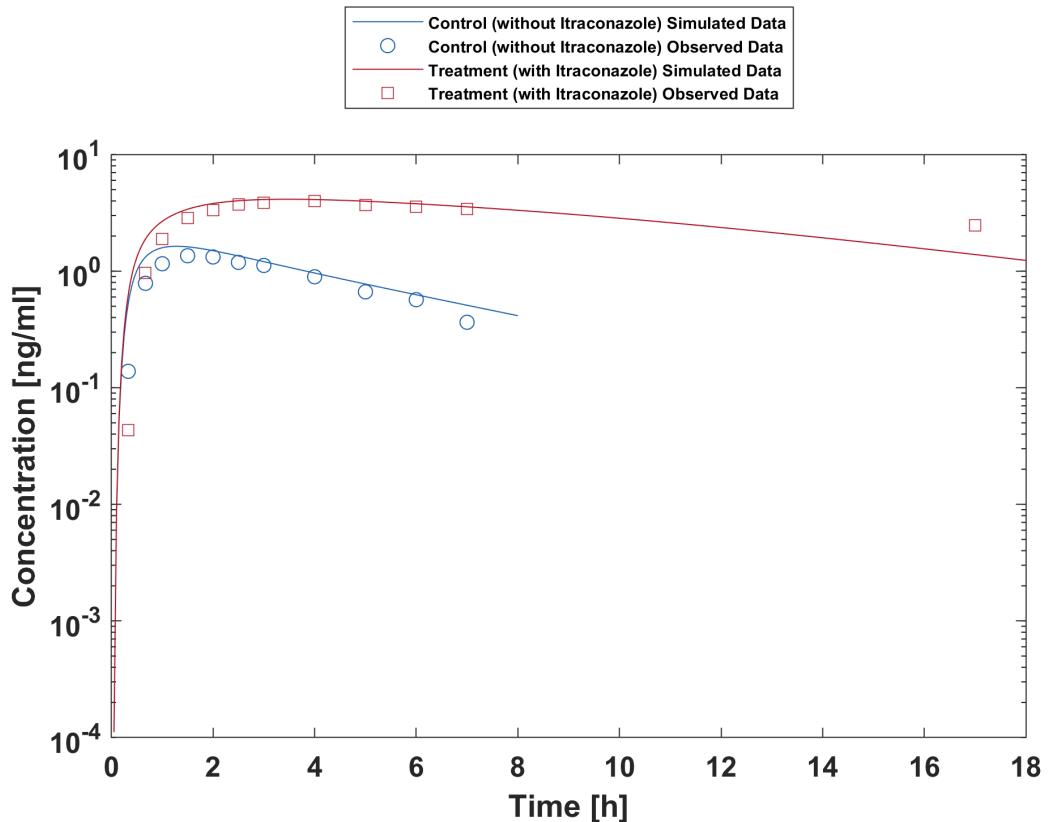


Yu 2004 (CYP3A5*3/*3)

3.11 Itraconazole - Triazolam DDI

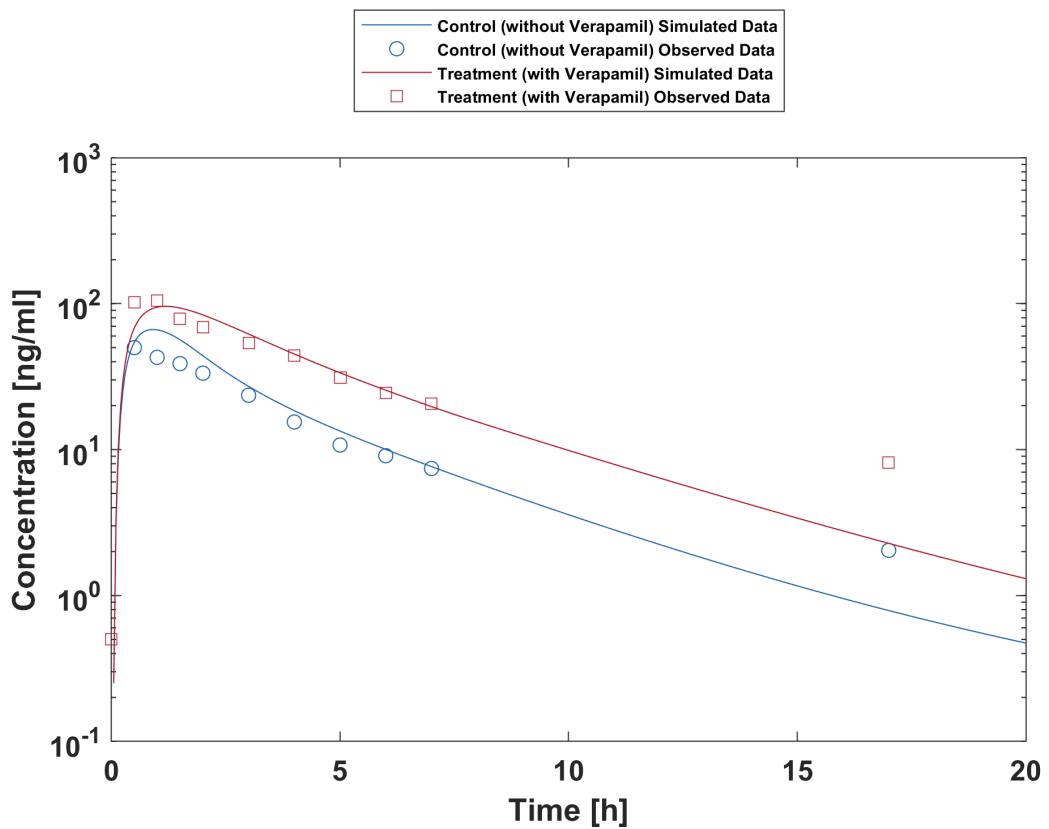


Neuvonen 1996

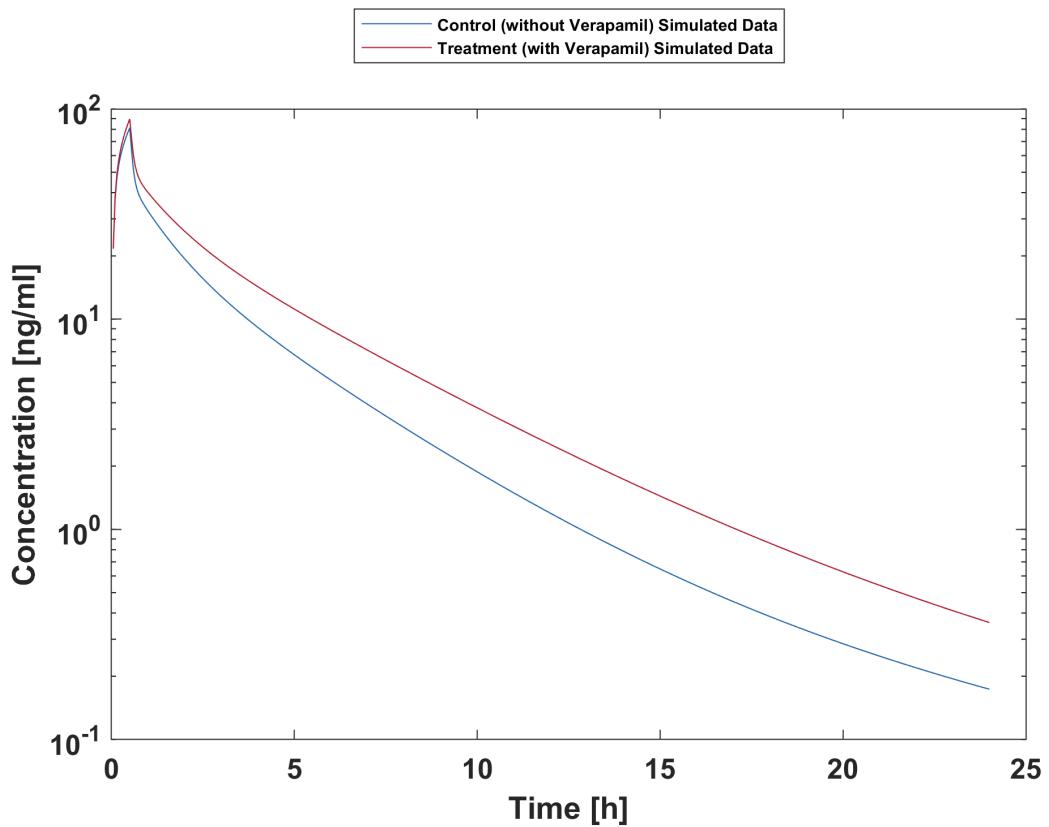


Varhe 1994

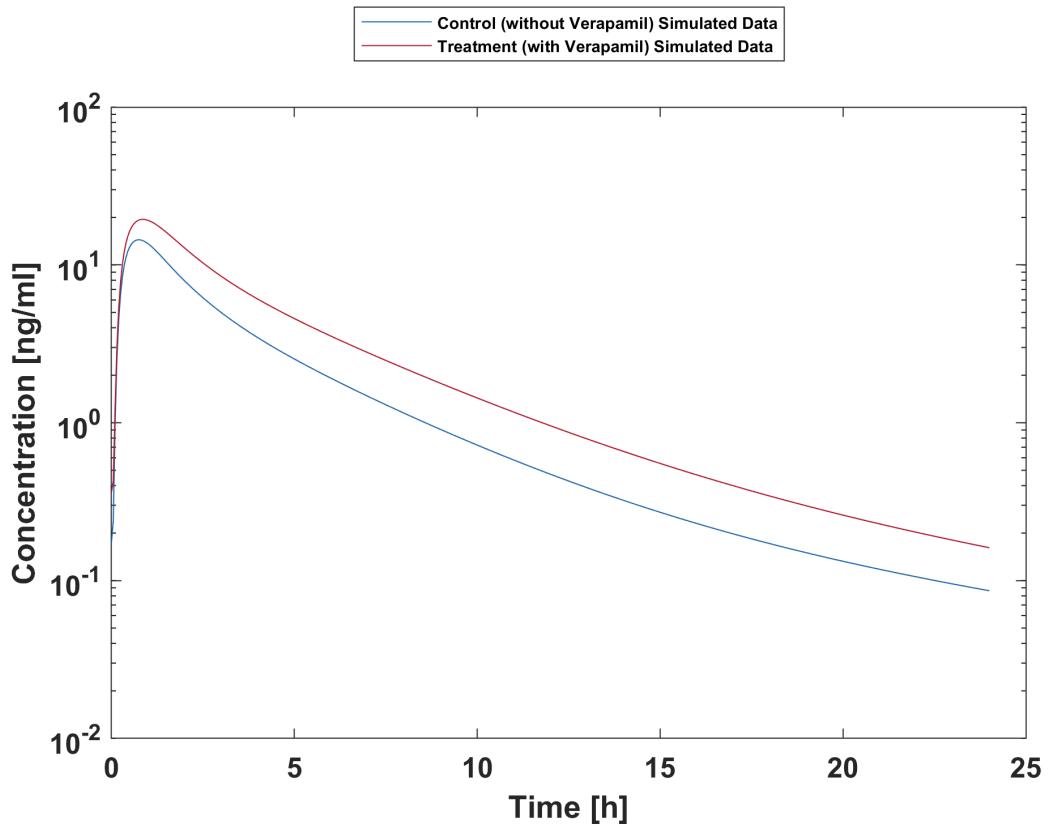
3.12 Verapamil - Midazolam DDI



Backman 1994

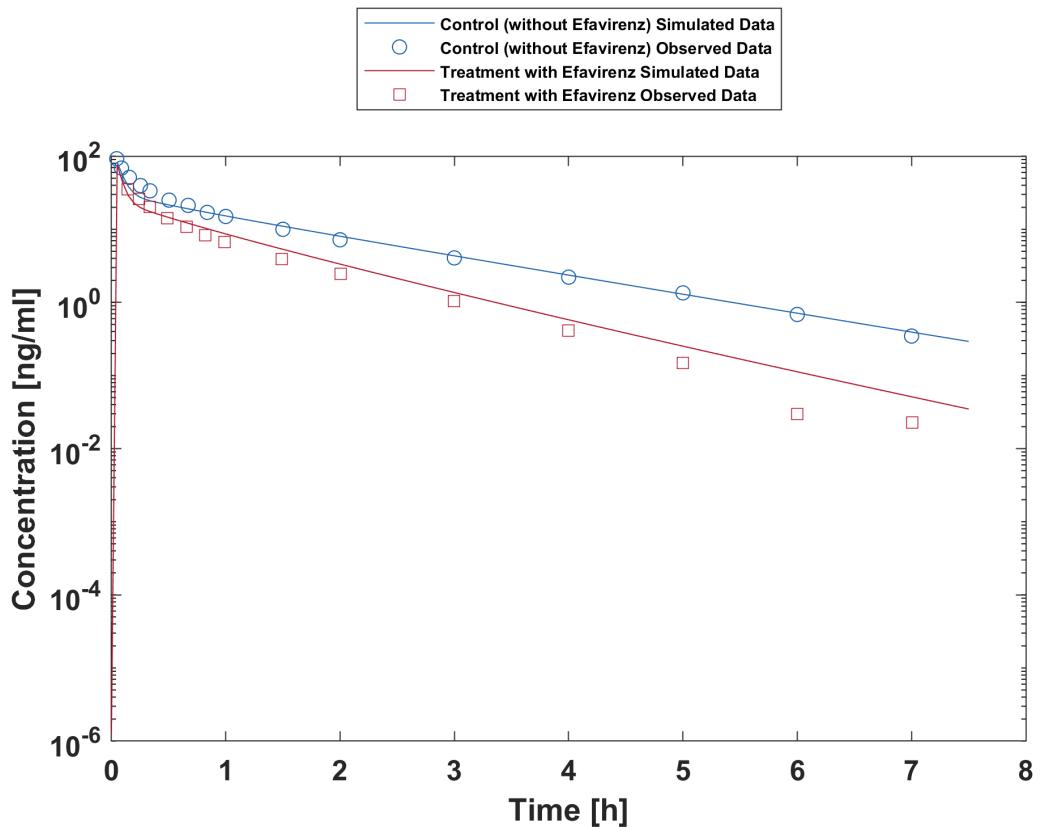


Wang 2005 (iv)

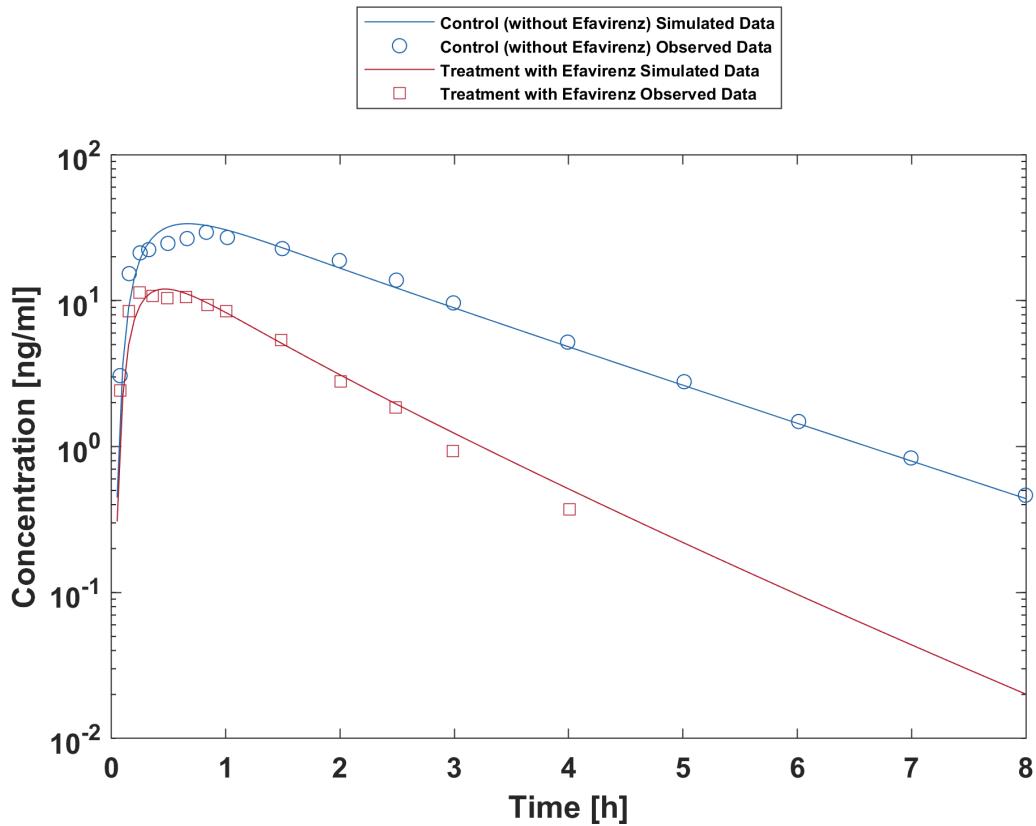


Wang 2005 (po)

3.13 Efavirenz - Alfentanil DDI

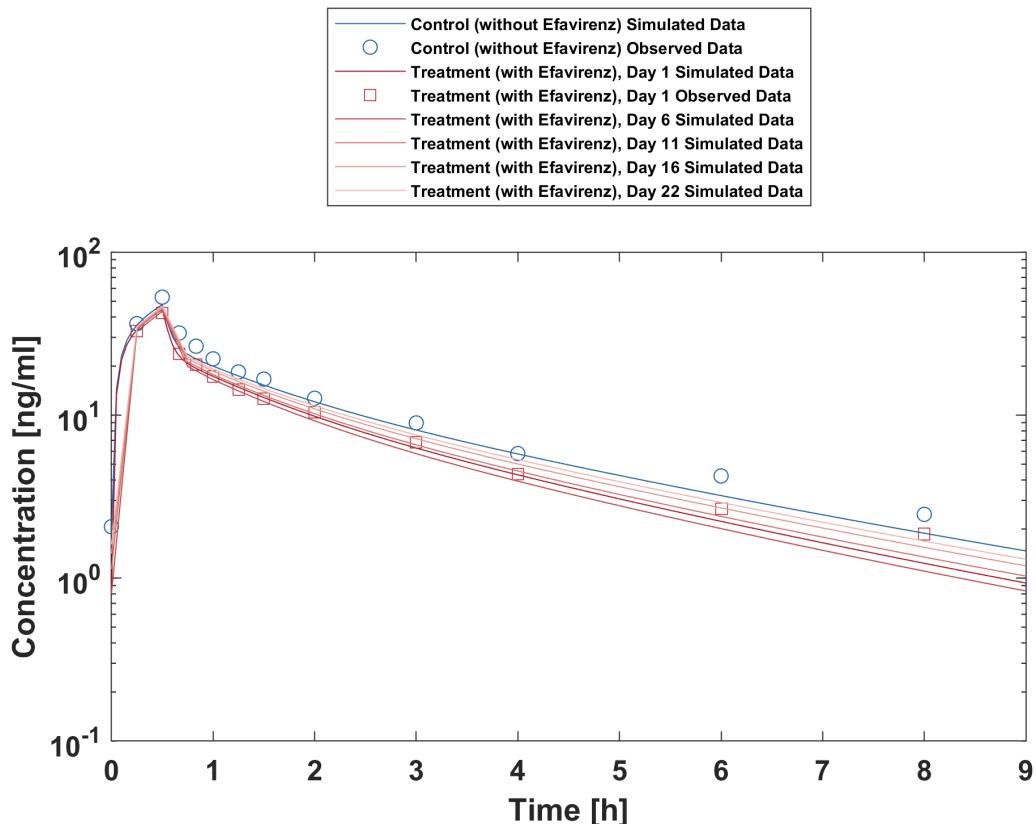


Kharasch 2012 IV

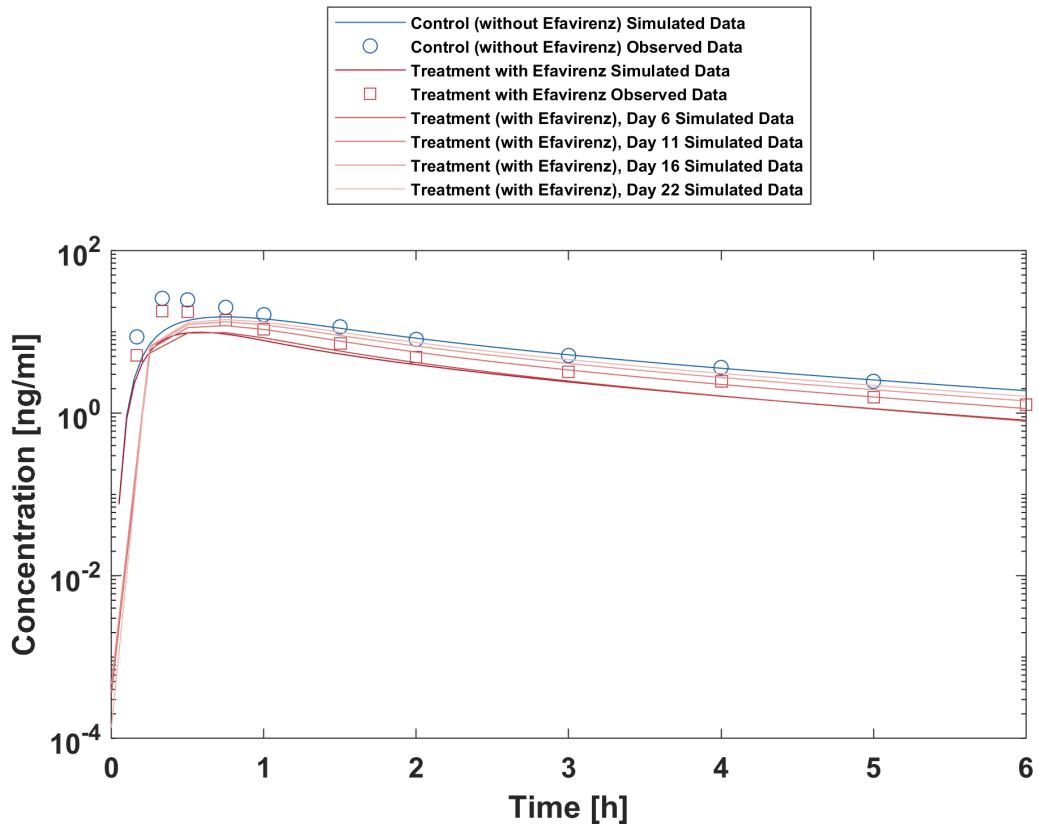


Kharasch 2012 PO

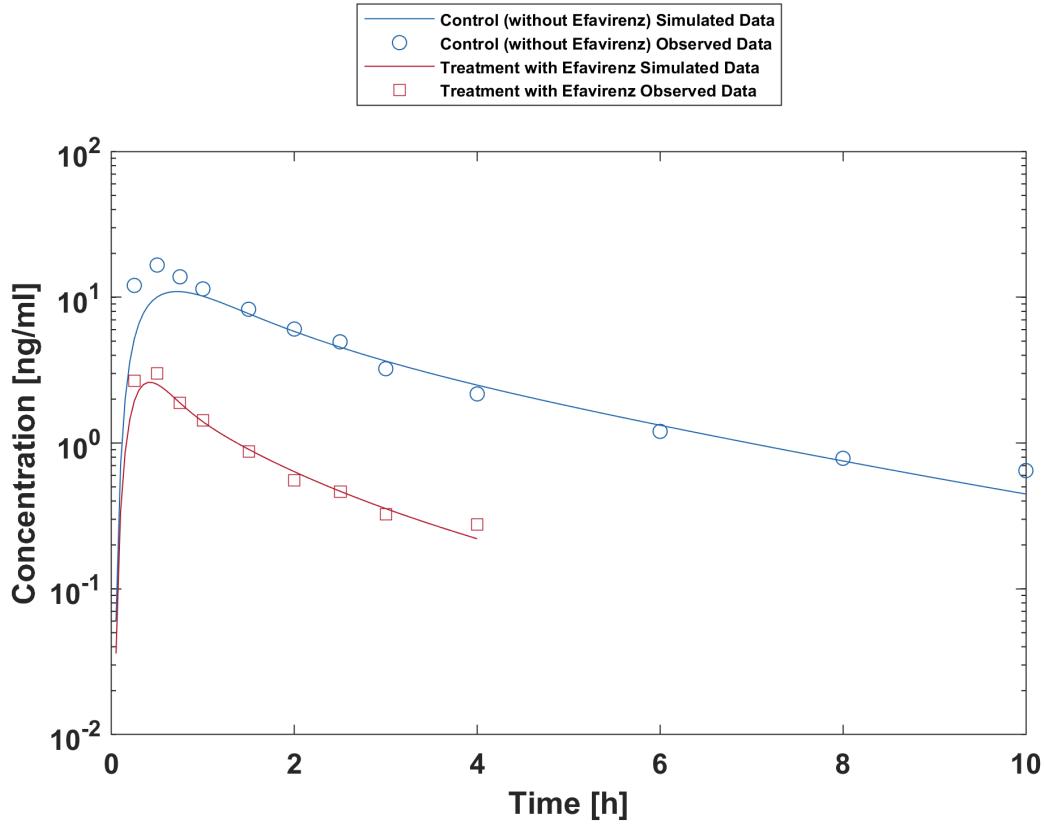
3.14 Efavirenz - Midazolam DDI



Mikus 2017 IV

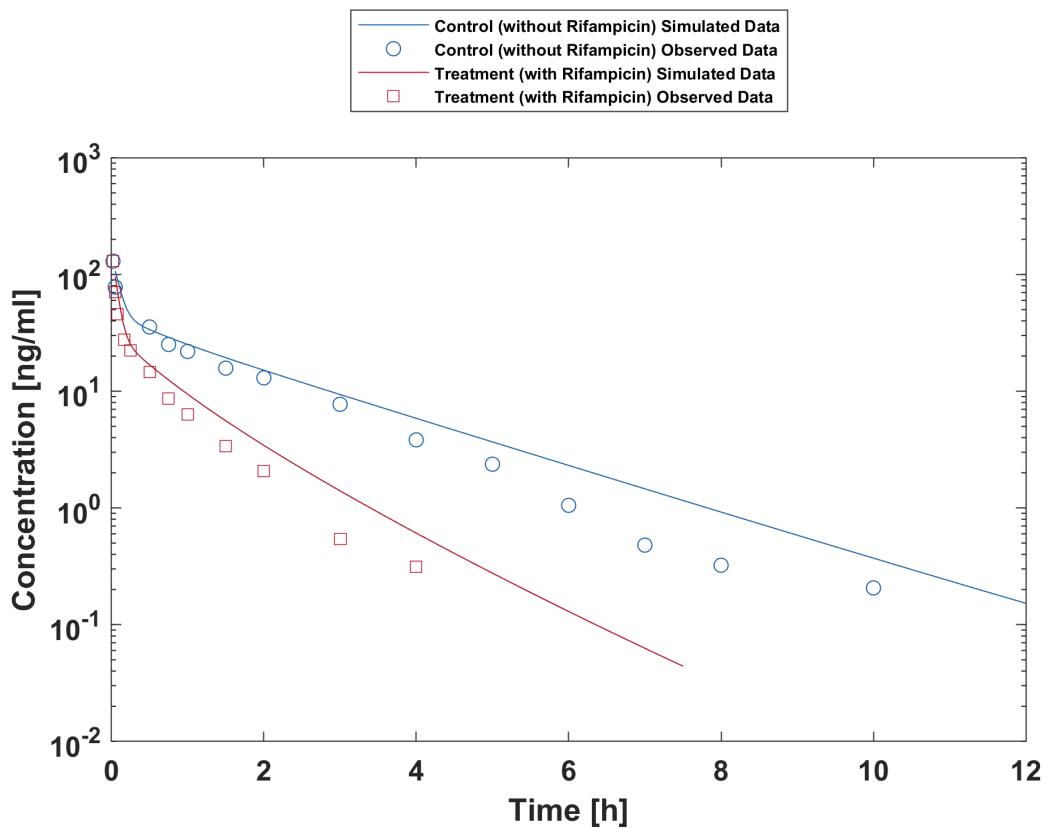


Mikus 2017 PO

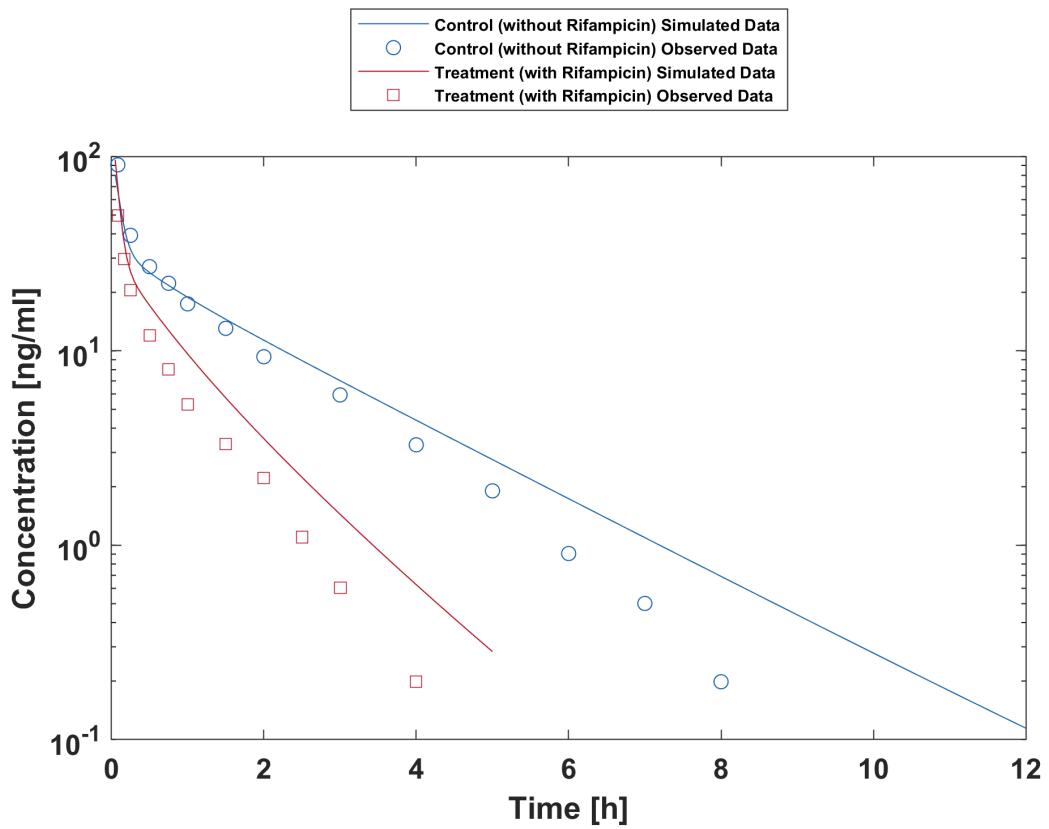


Katzenmaier 2010

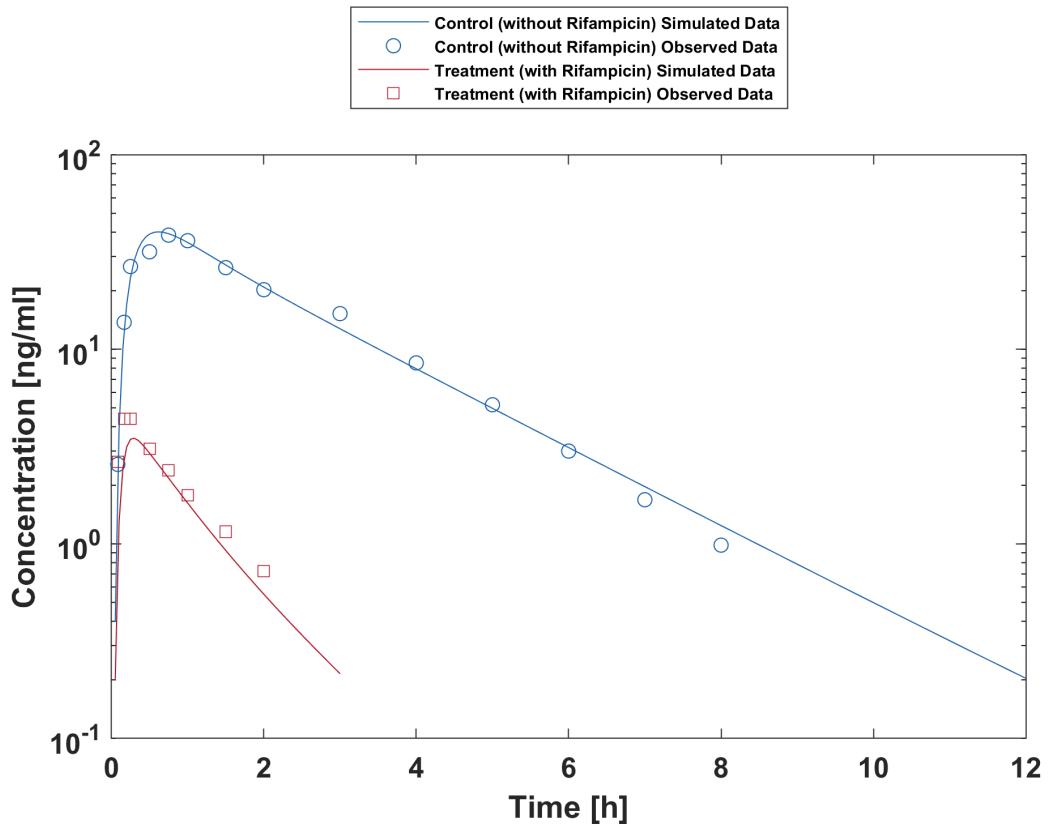
3.15 Rifampicin - Alfentanil DDI



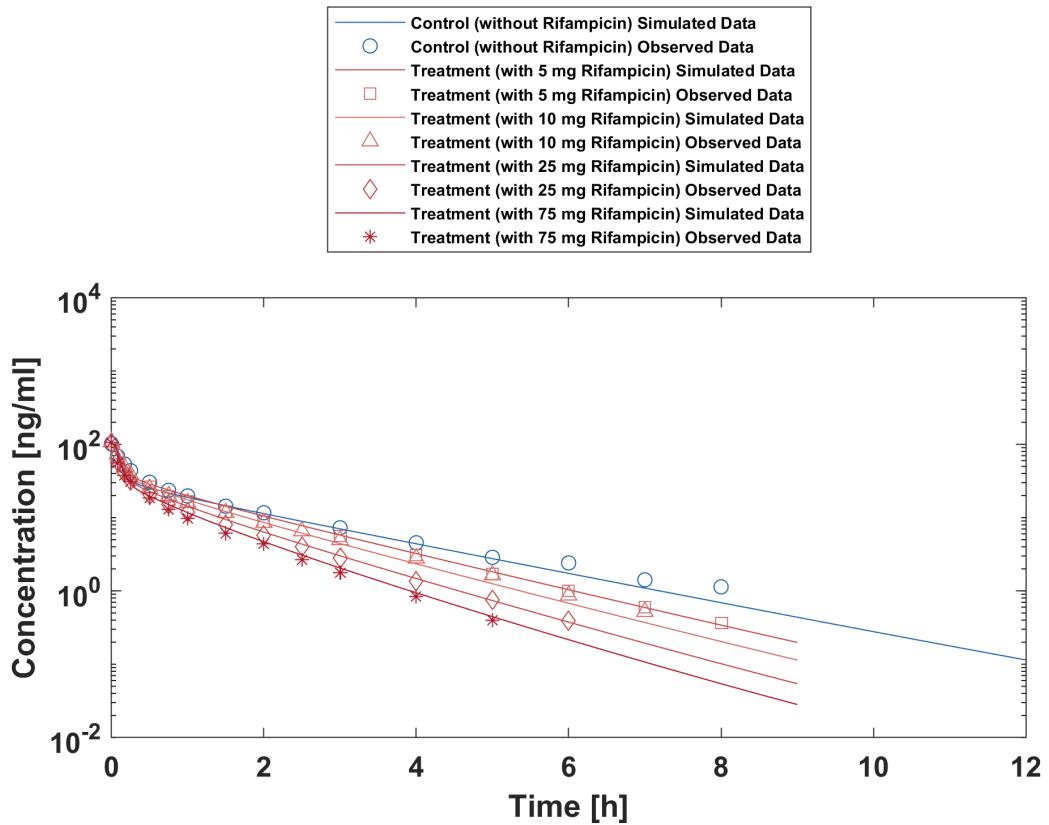
Kharasch 1997



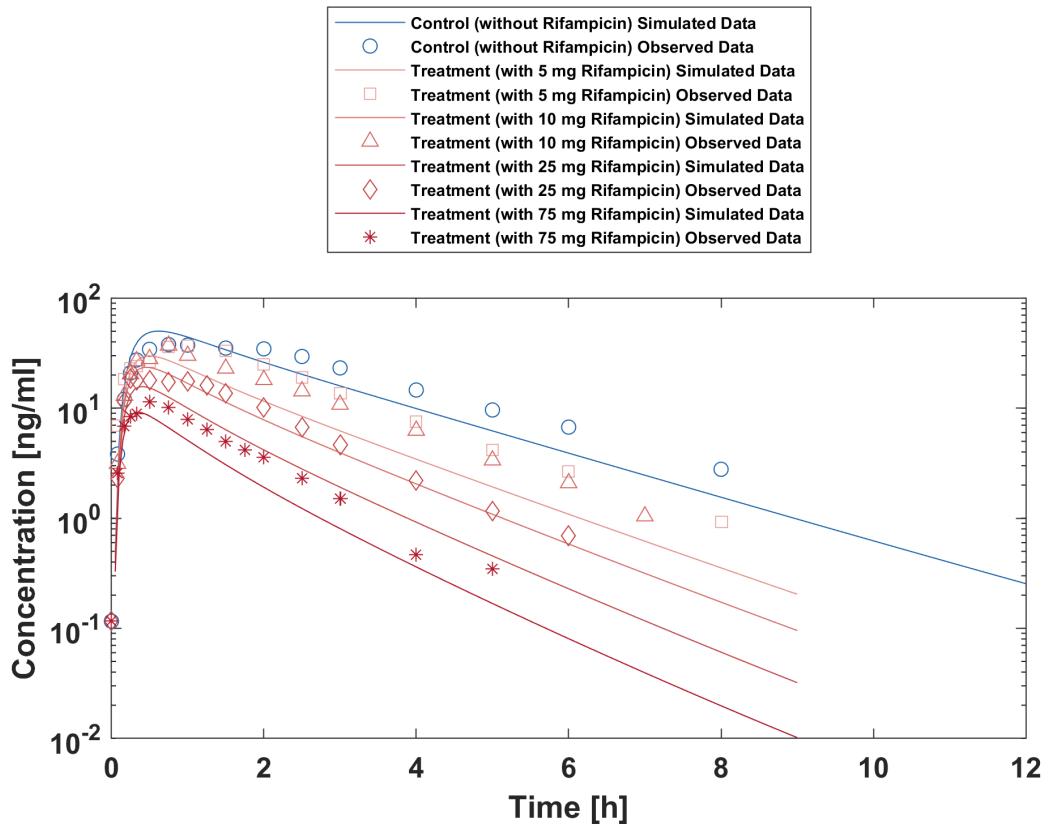
Kharasch 2004 (iv)



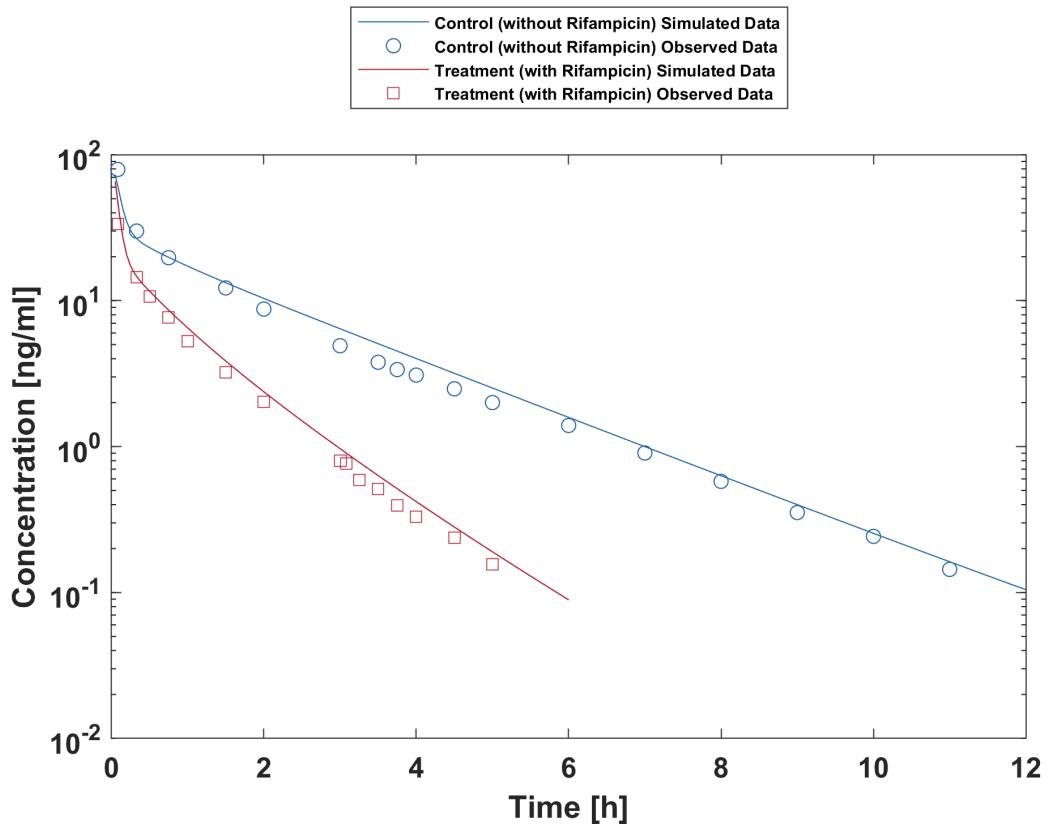
Kharasch 2004 (po)



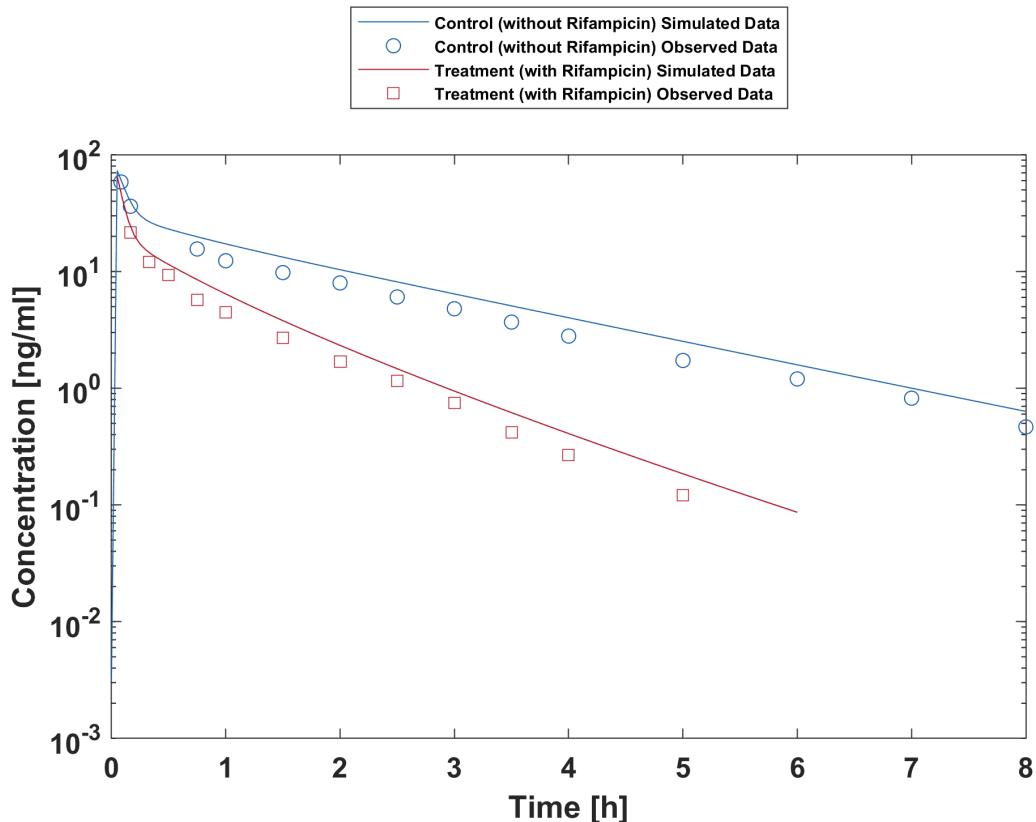
Kharasch 2011 (iv)



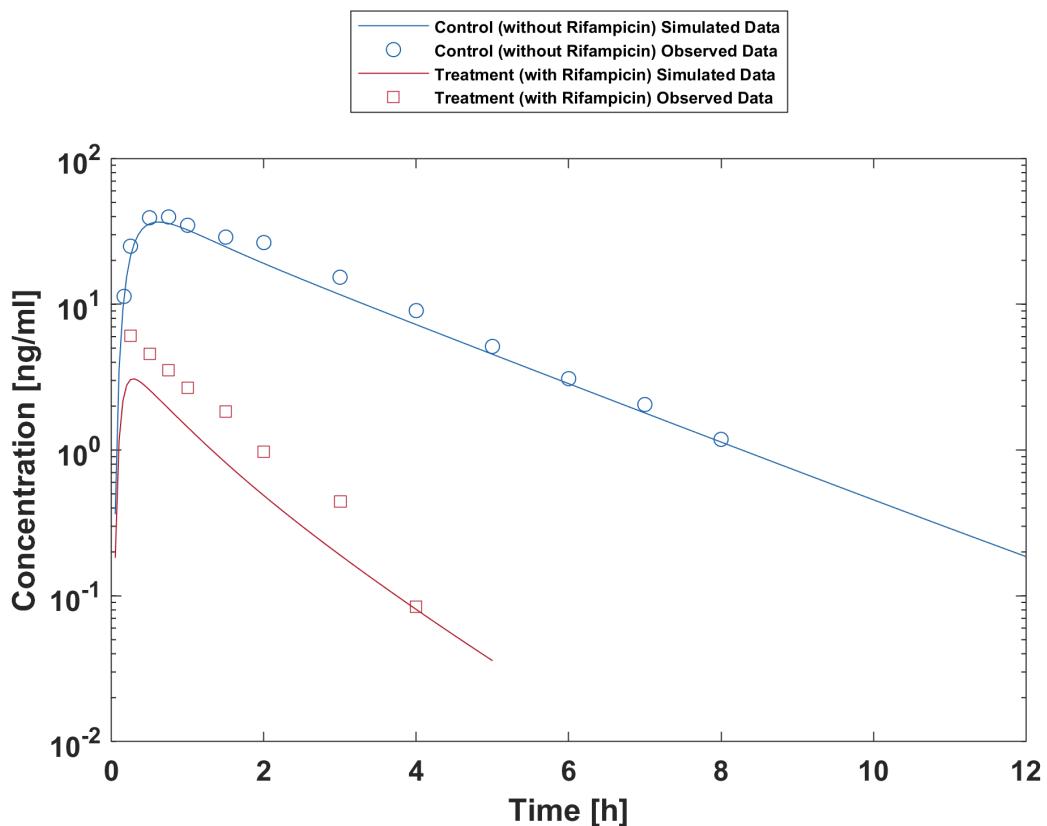
Kharasch 2011 (po)



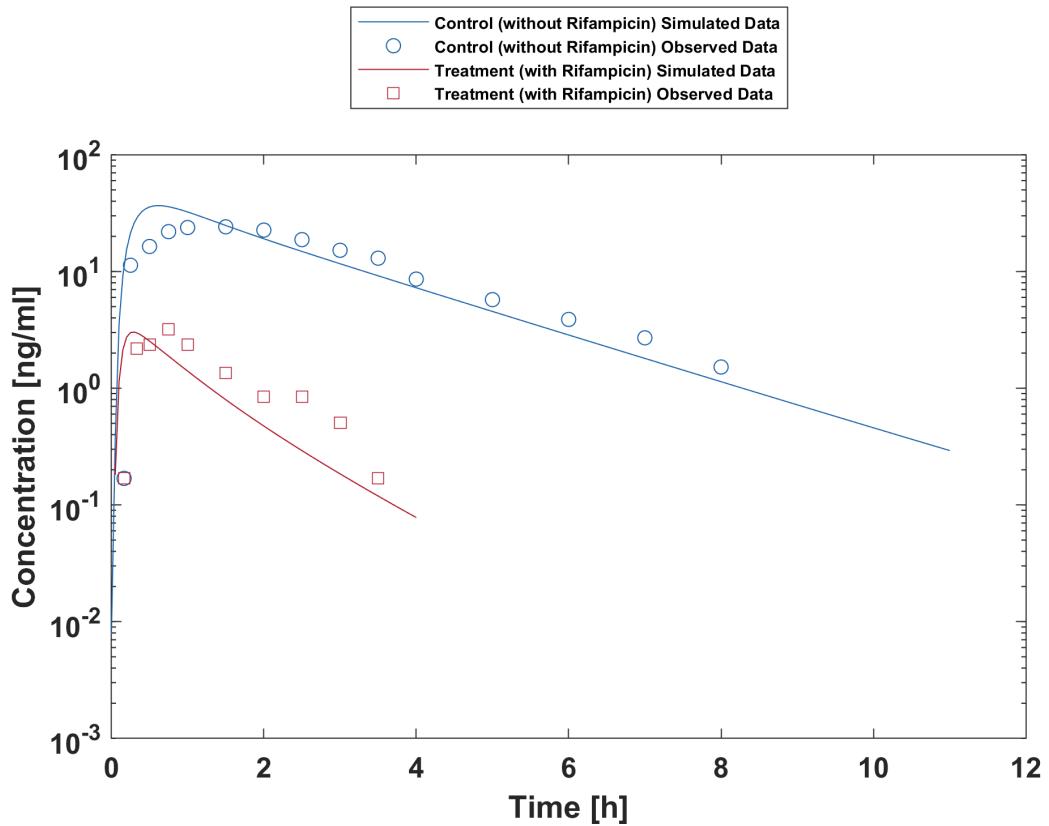
Kharasch 2011b (iv during sequential administration of iv unlabeled alfentanil and oral deuterated alfentanil)



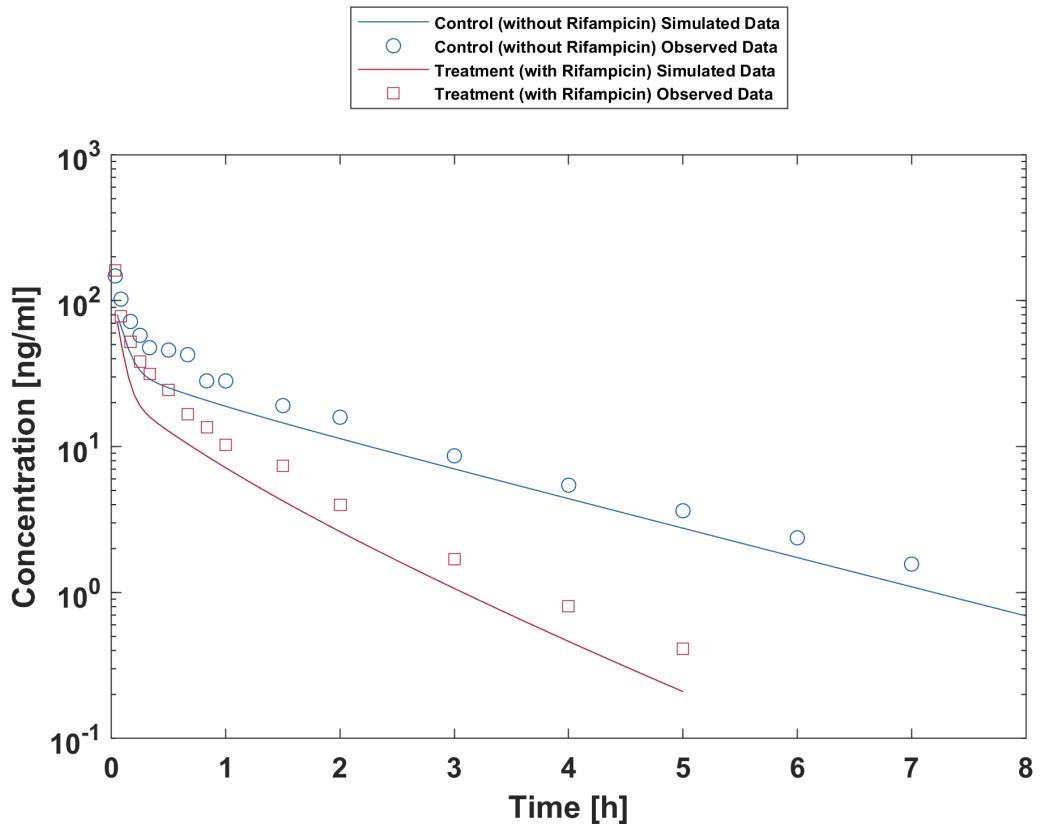
Kharasch 2011b (iv during simultaneous administration of iv unlabeled alfentanil and oral deuterated alfentanil)



Kharasch 2011b (po during sequential administration of iv unlabeled alfentanil and oral deuterated alfentanil)

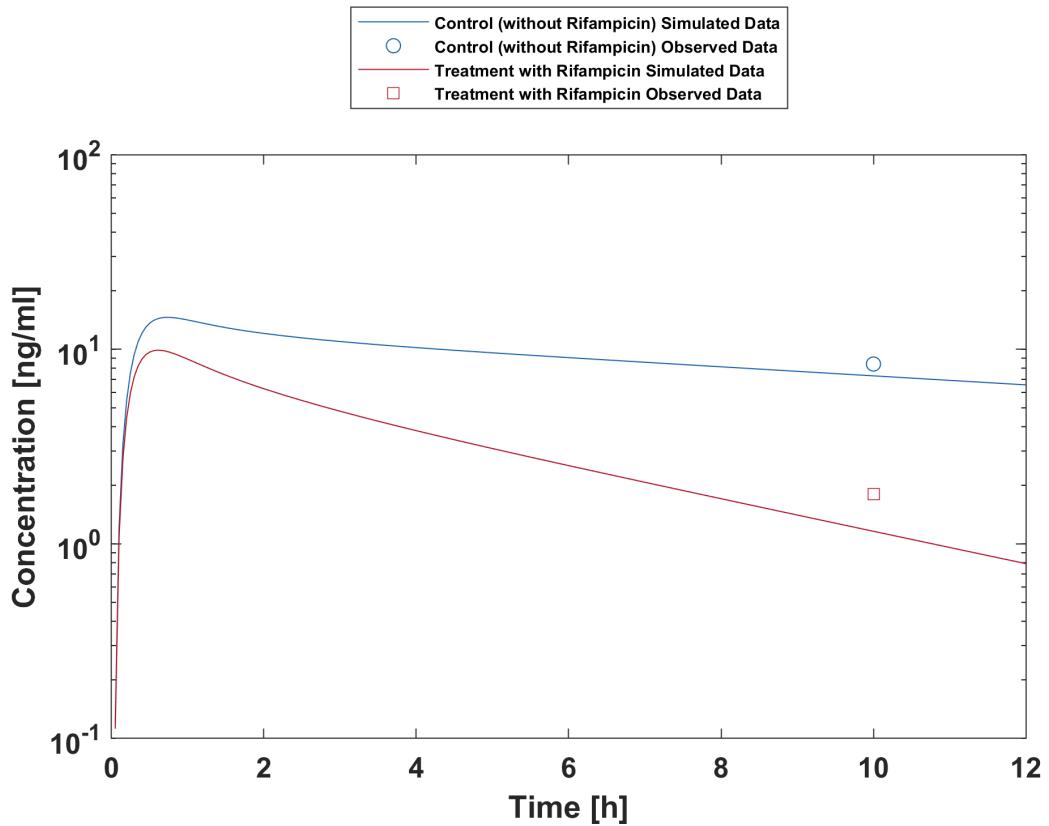


Kharasch 2011b (po during simultaneous administration of iv unlabeled alfentanil and oral deuterated alfentanil)

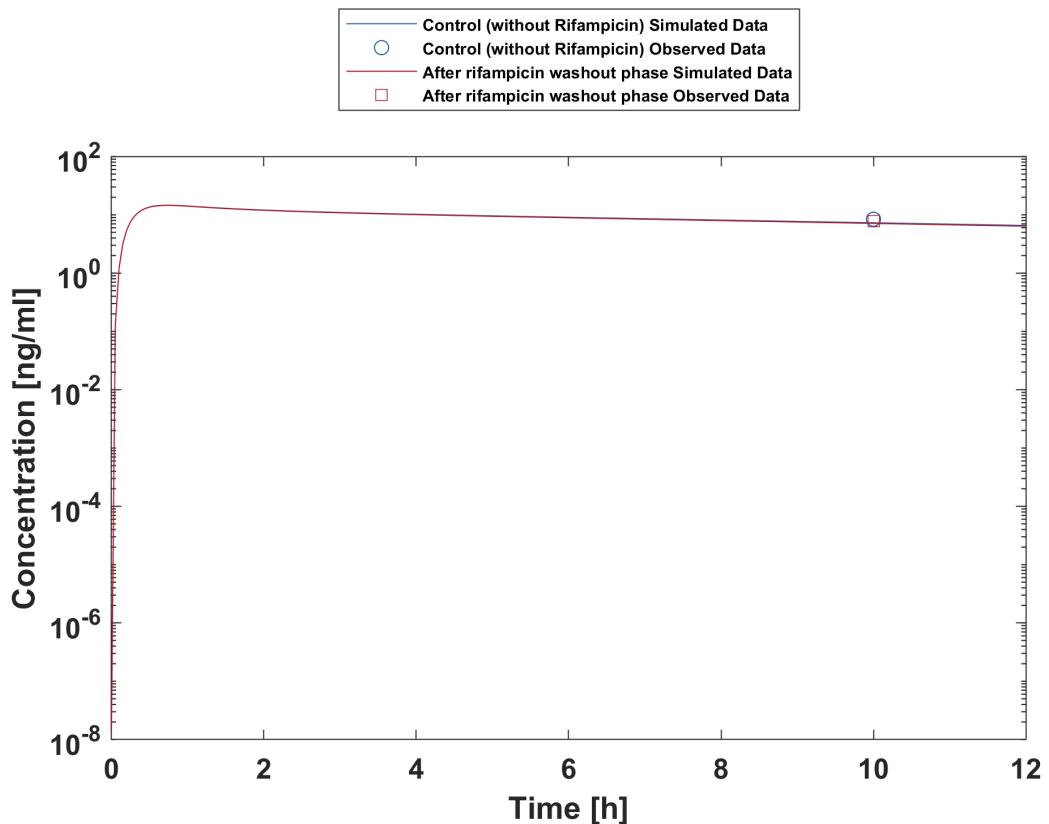


Phimmasonne 2001

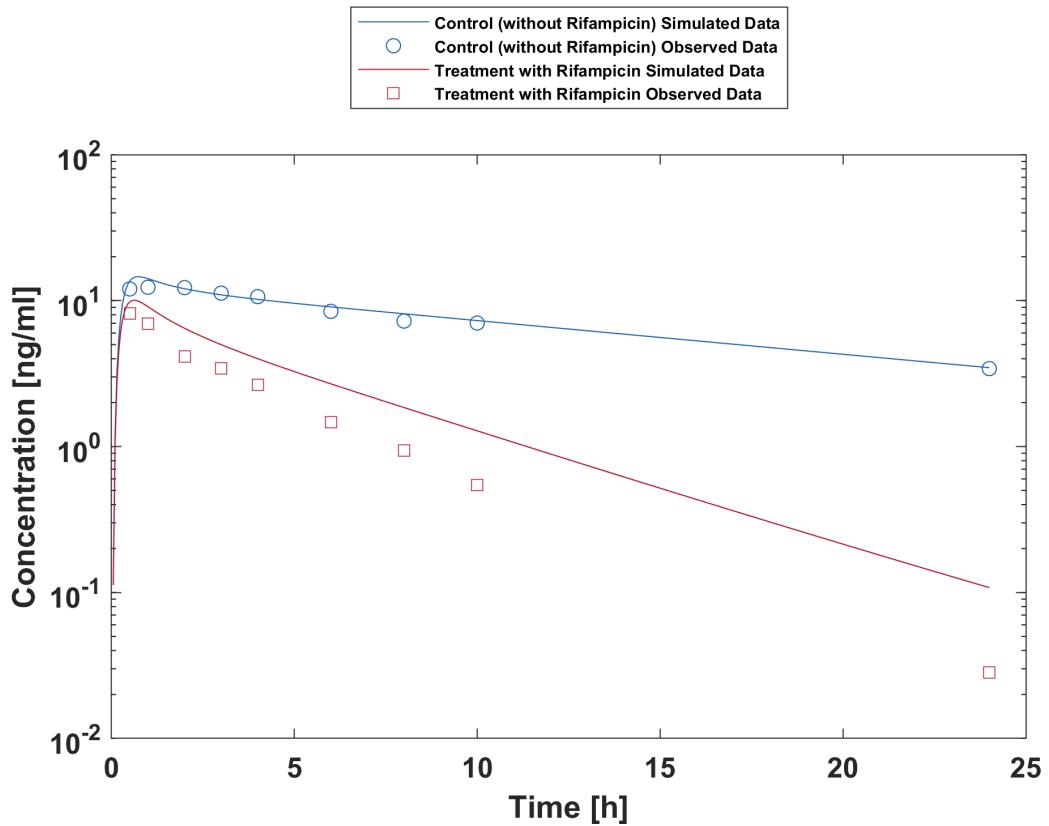
3.16 Rifampicin - Alprazolam DDI



Gashaw 2003 (Day 7)

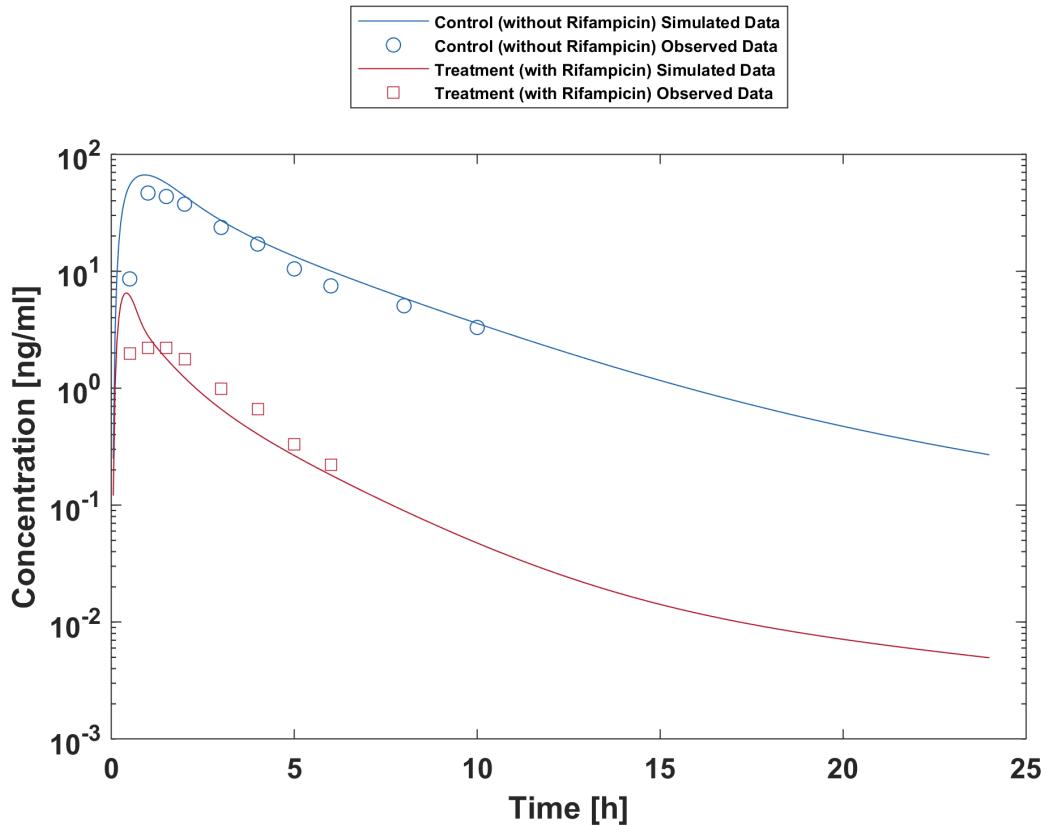


Gashaw 2003 (after washout phase)

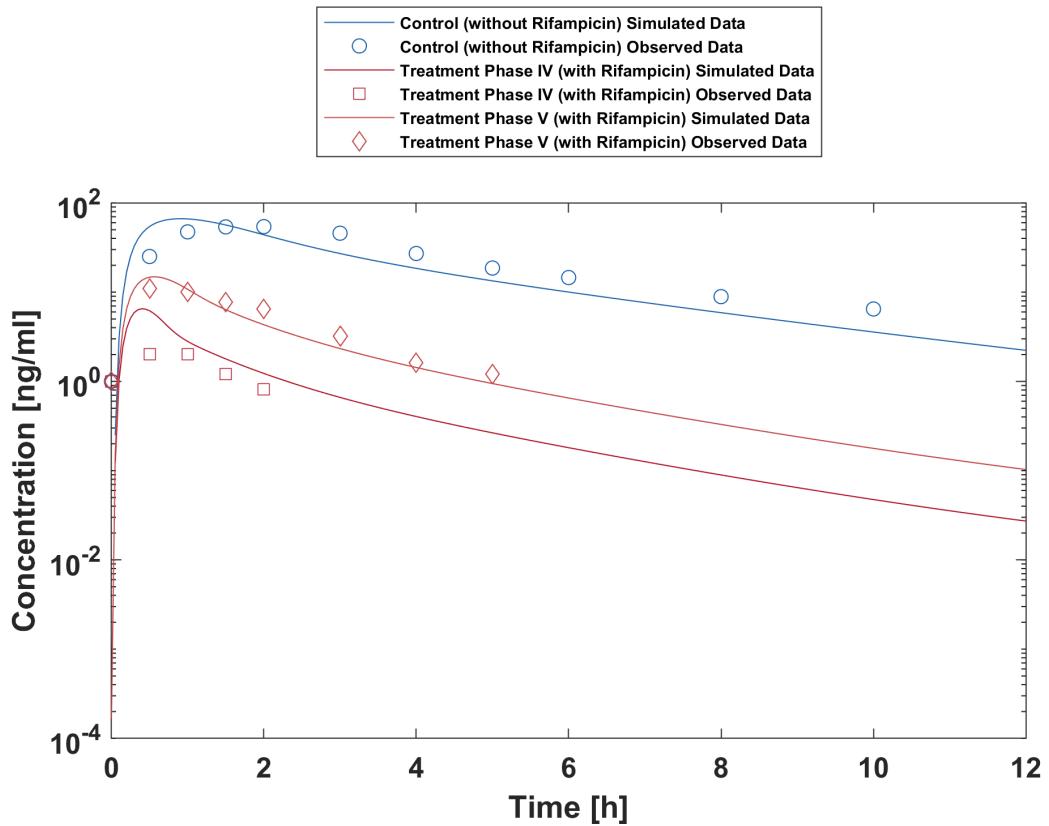


Schmider 1999

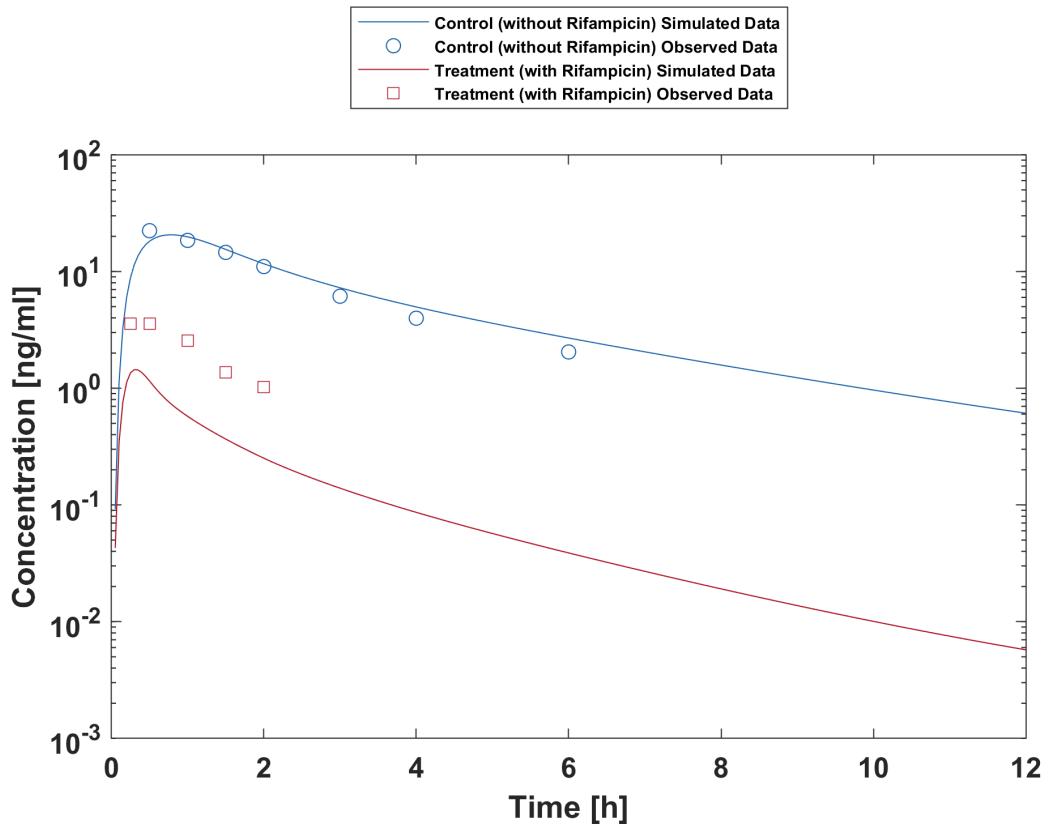
3.17 Rifampicin - Midazolam DDI



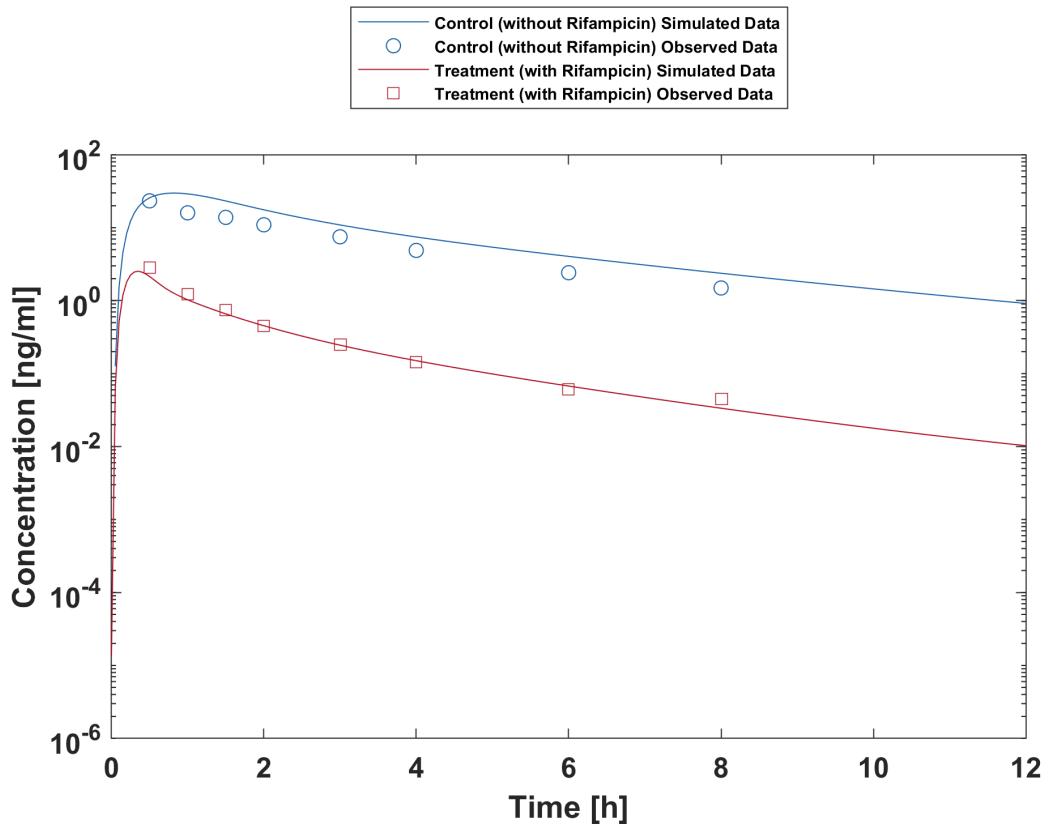
Backman 1996



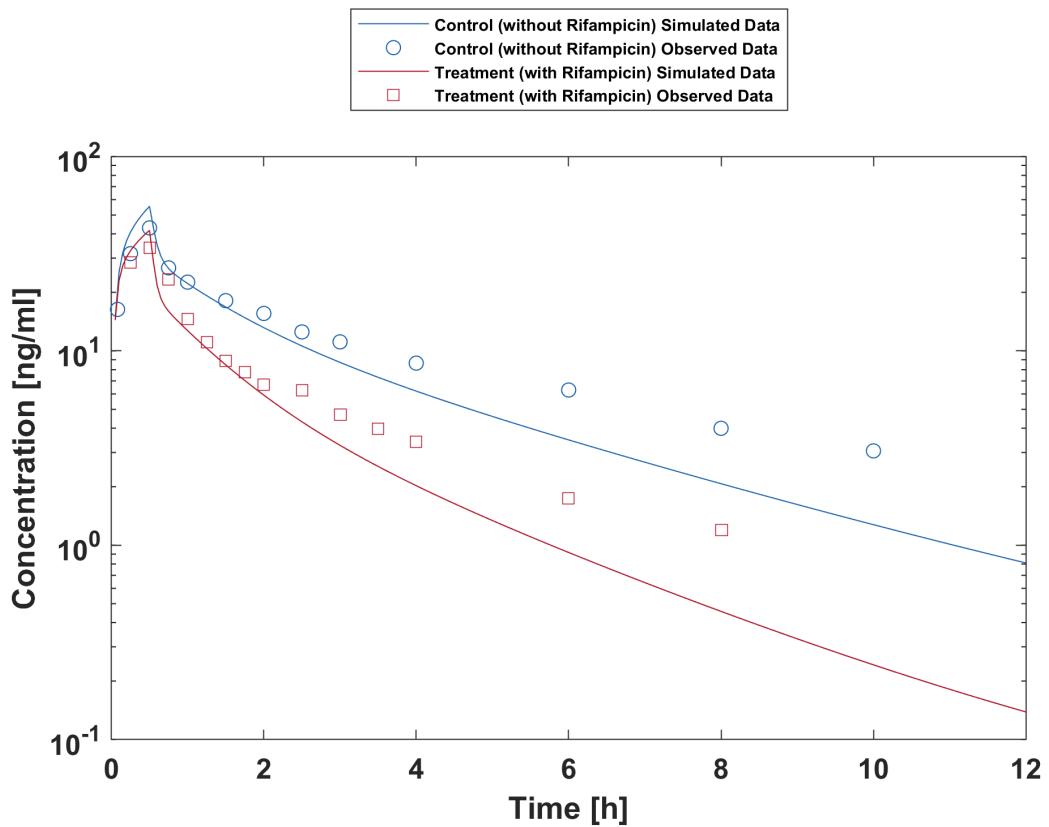
Backman 1998 (Phase IV and V vs. I)



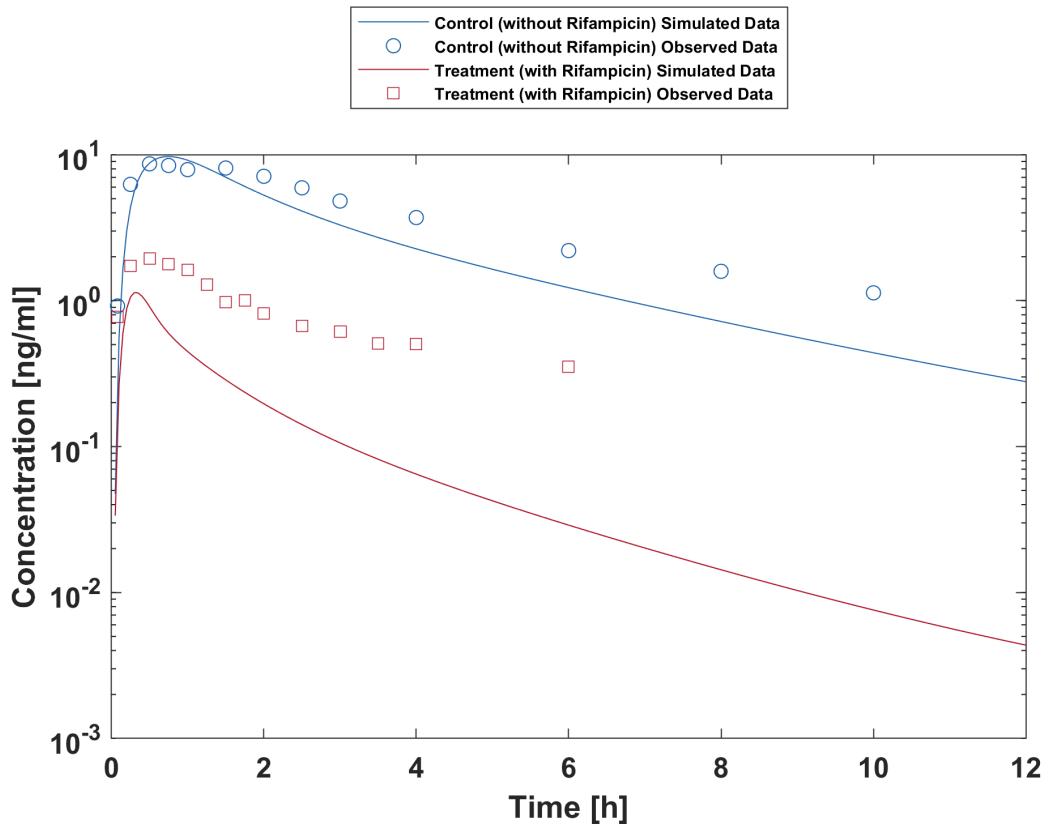
Chung 2006



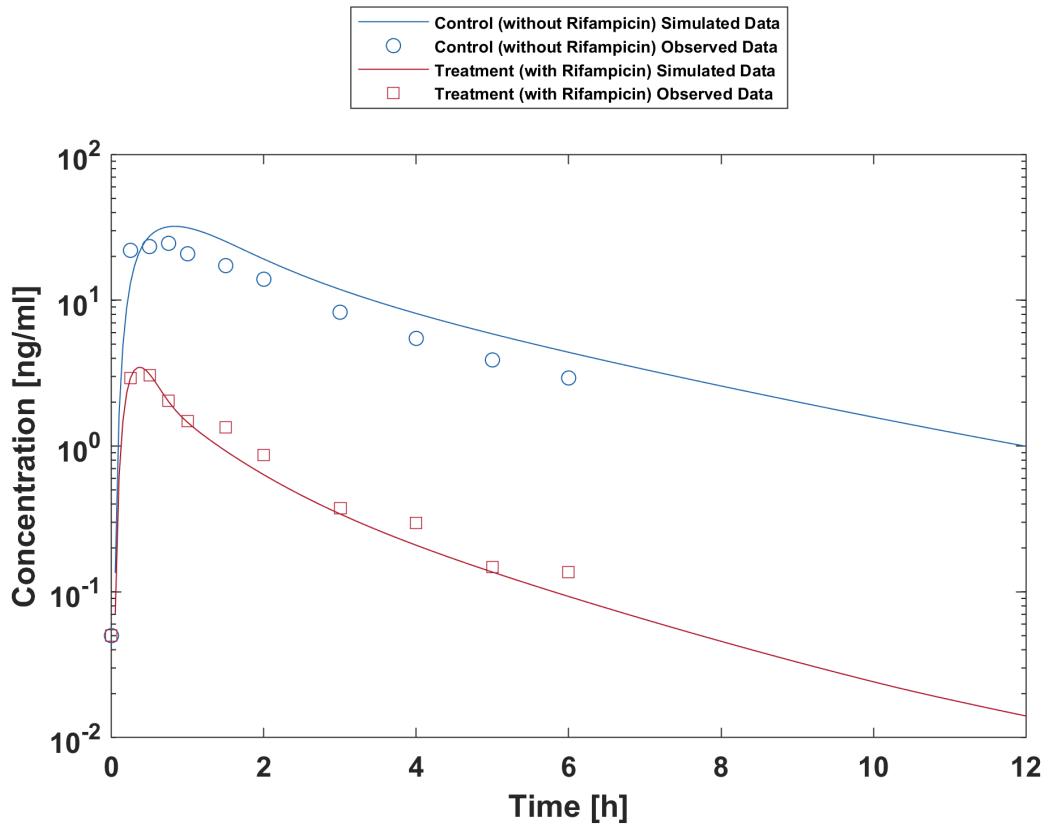
Eap 2004 (7.5 mg)



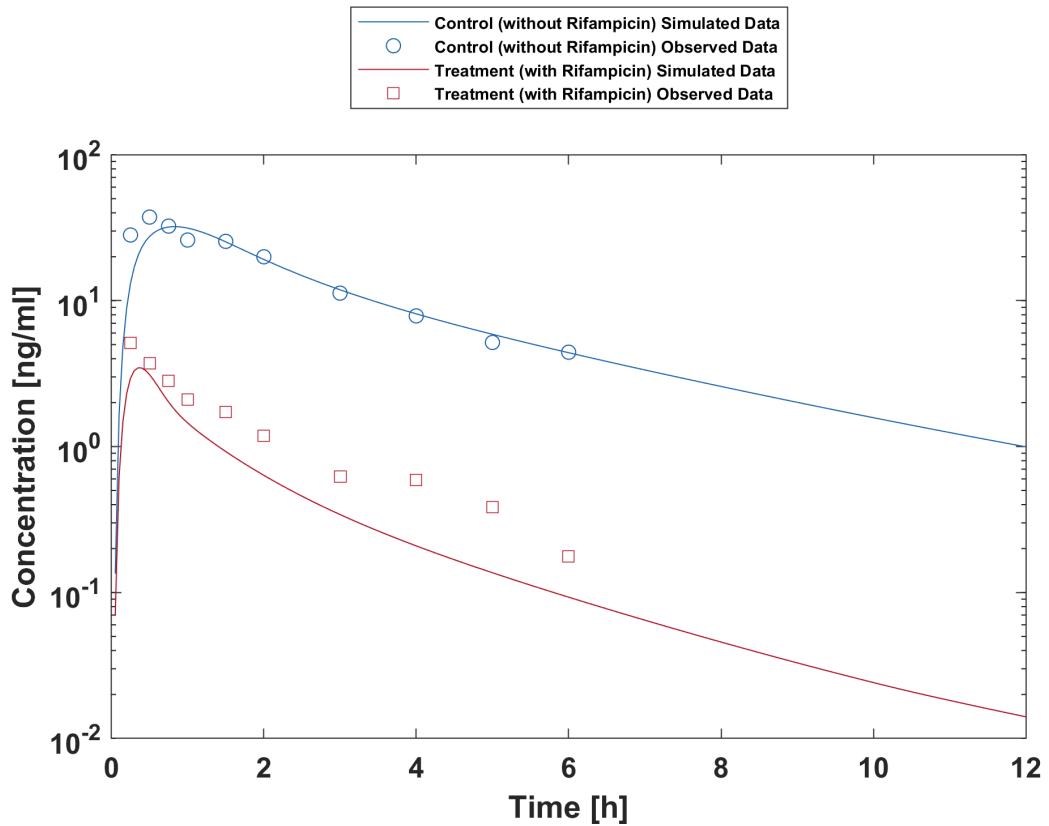
Gorski 2003 (iv)



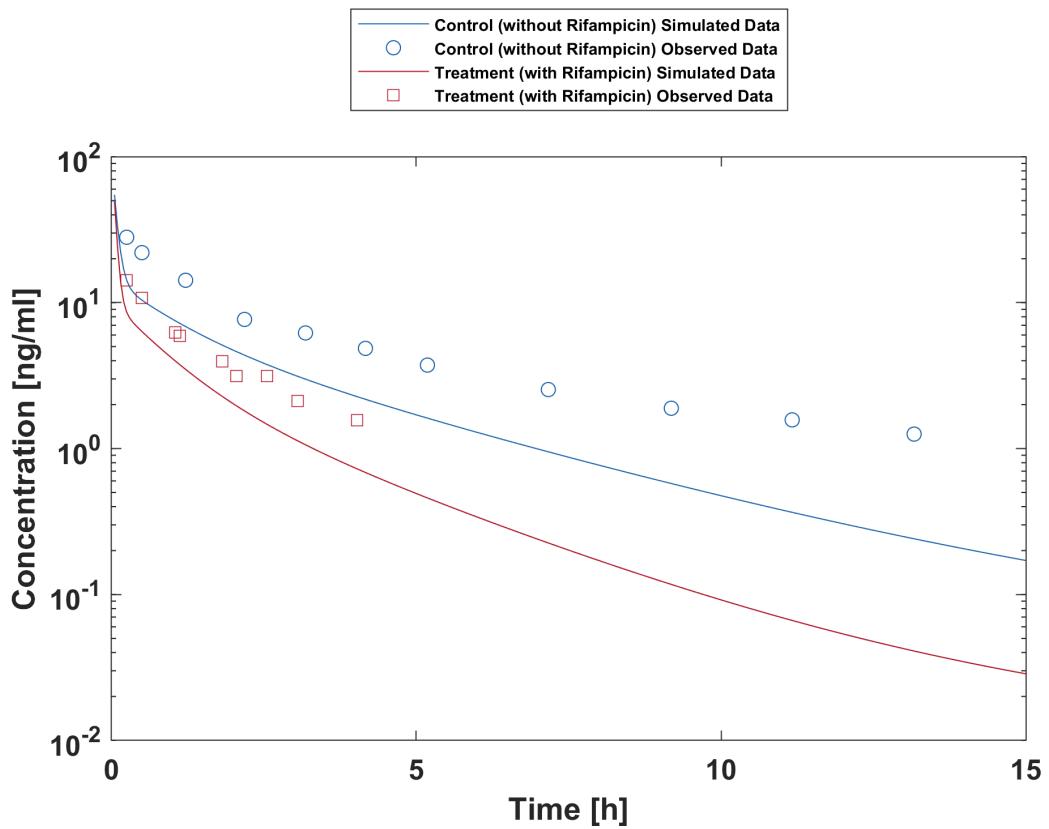
Gorski 2003 (po)



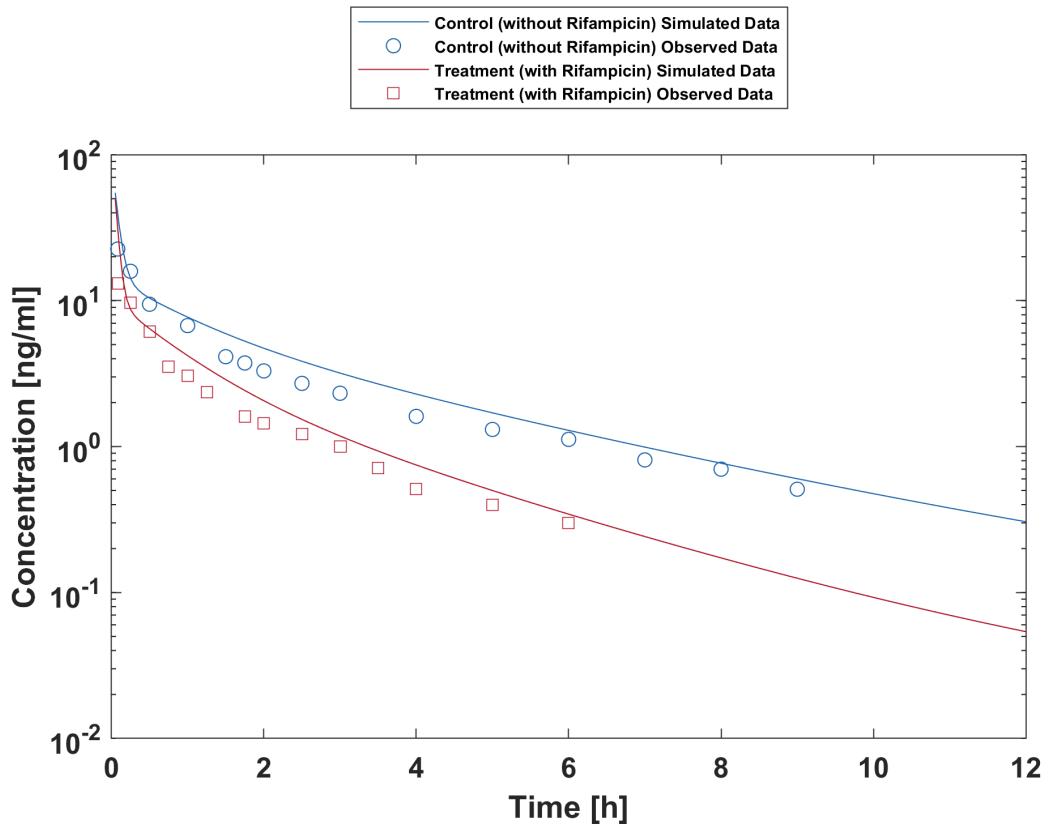
Gurley 2006



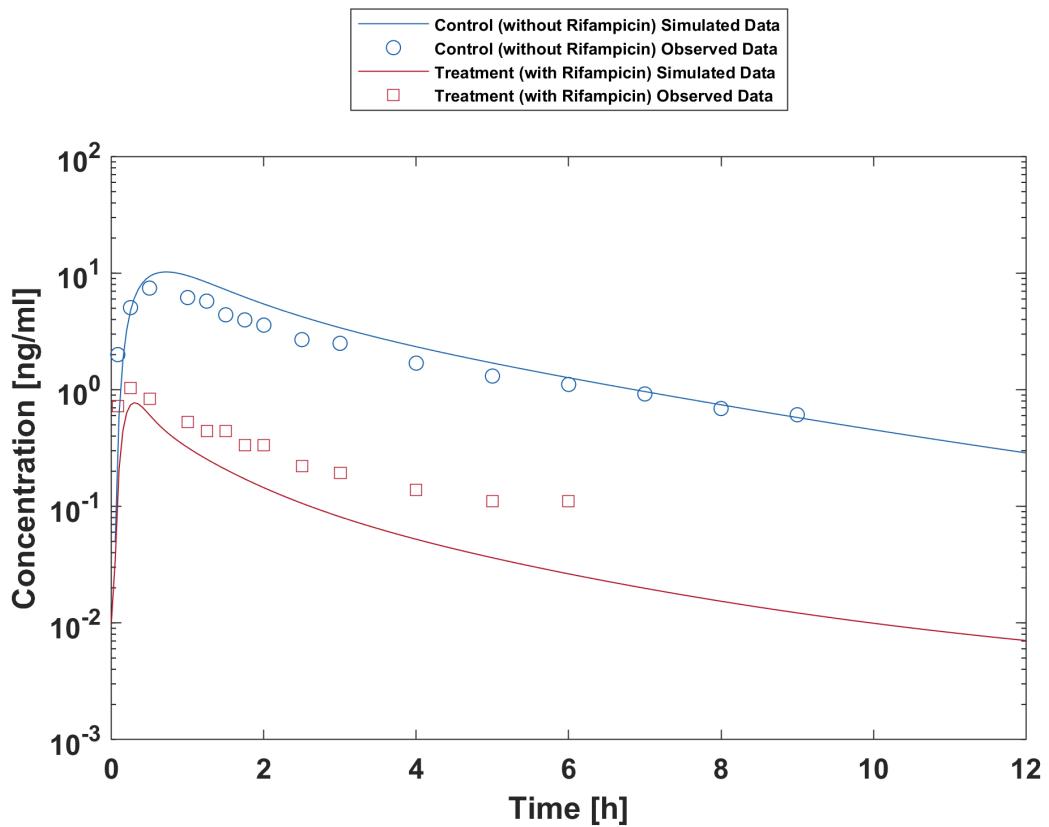
Gurley 2008a



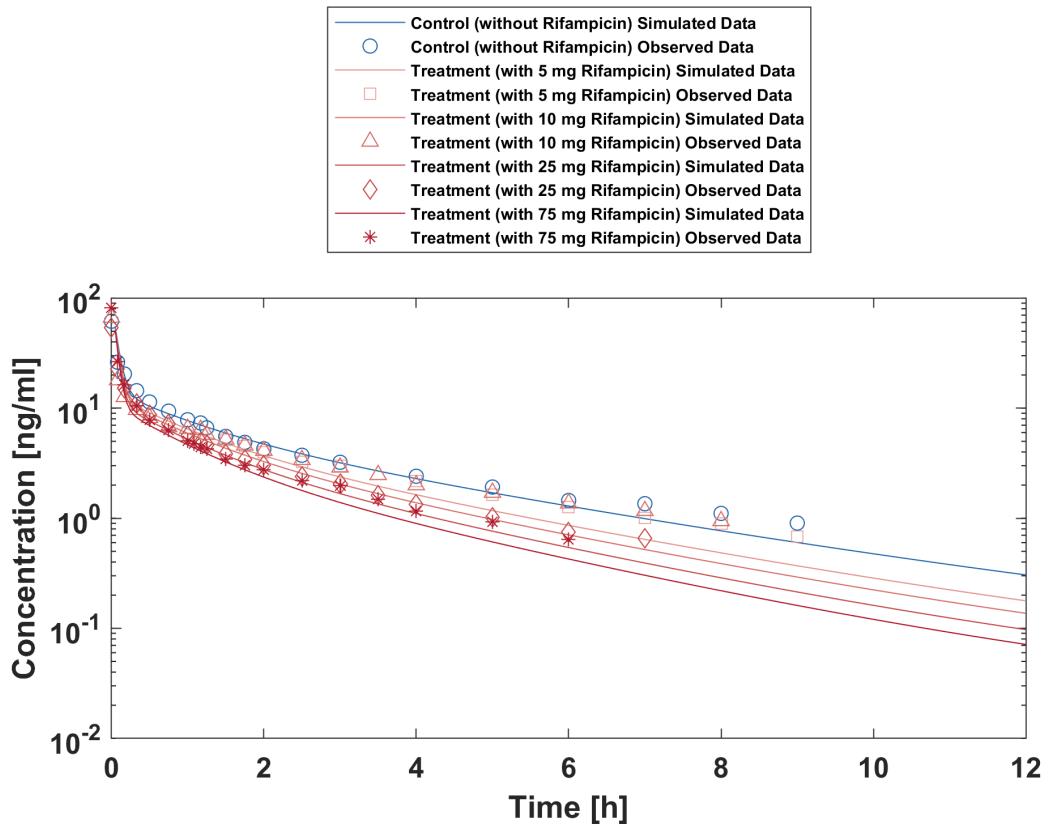
Kharasch 1997



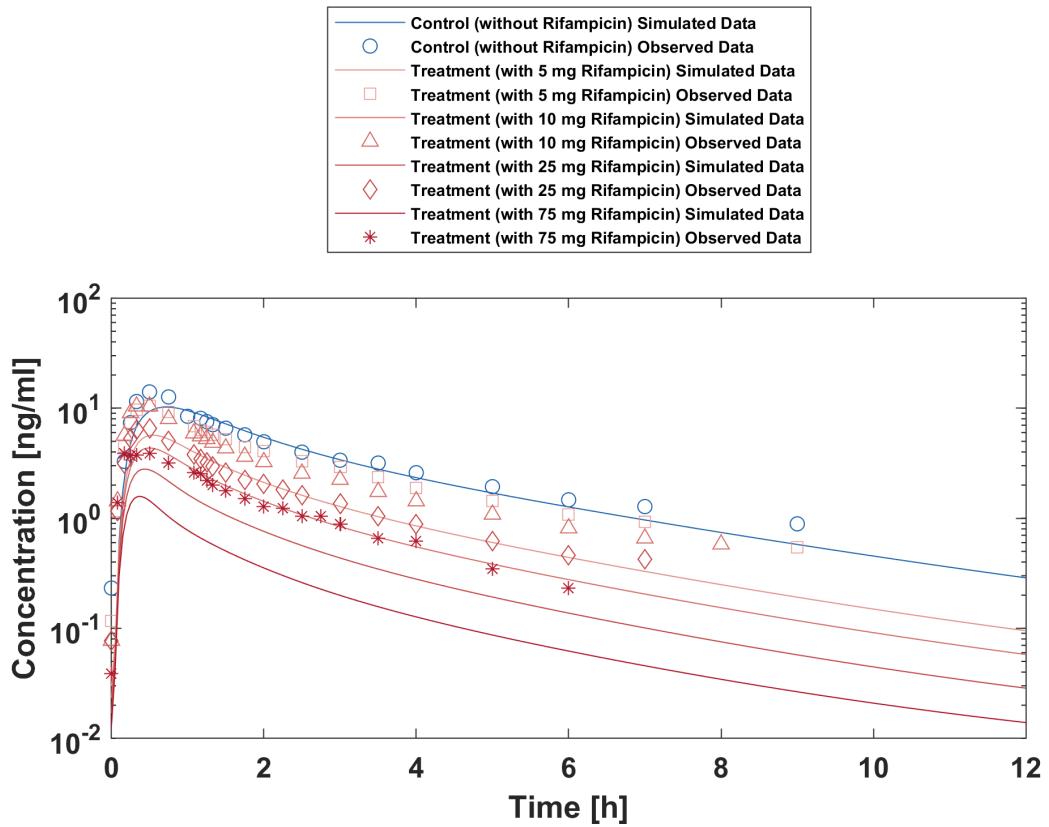
Kharasch 2004 (iv)



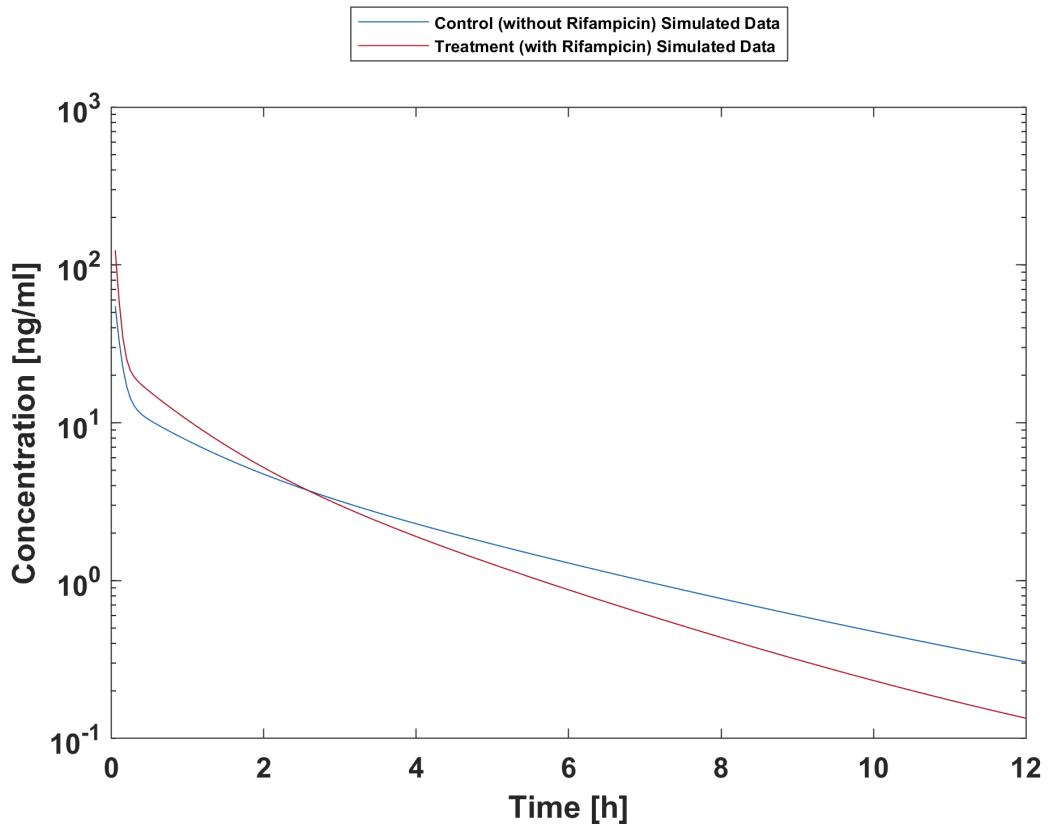
Kharasch 2004 (po)



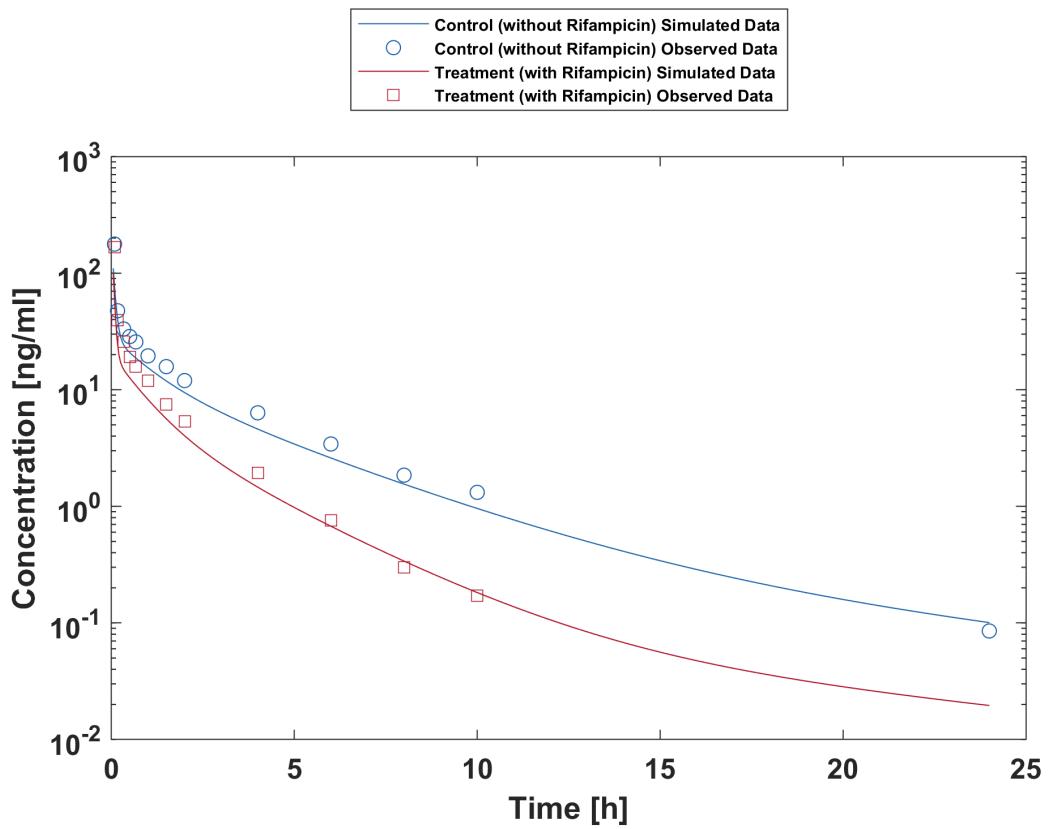
Kharasch 2011 (iv)



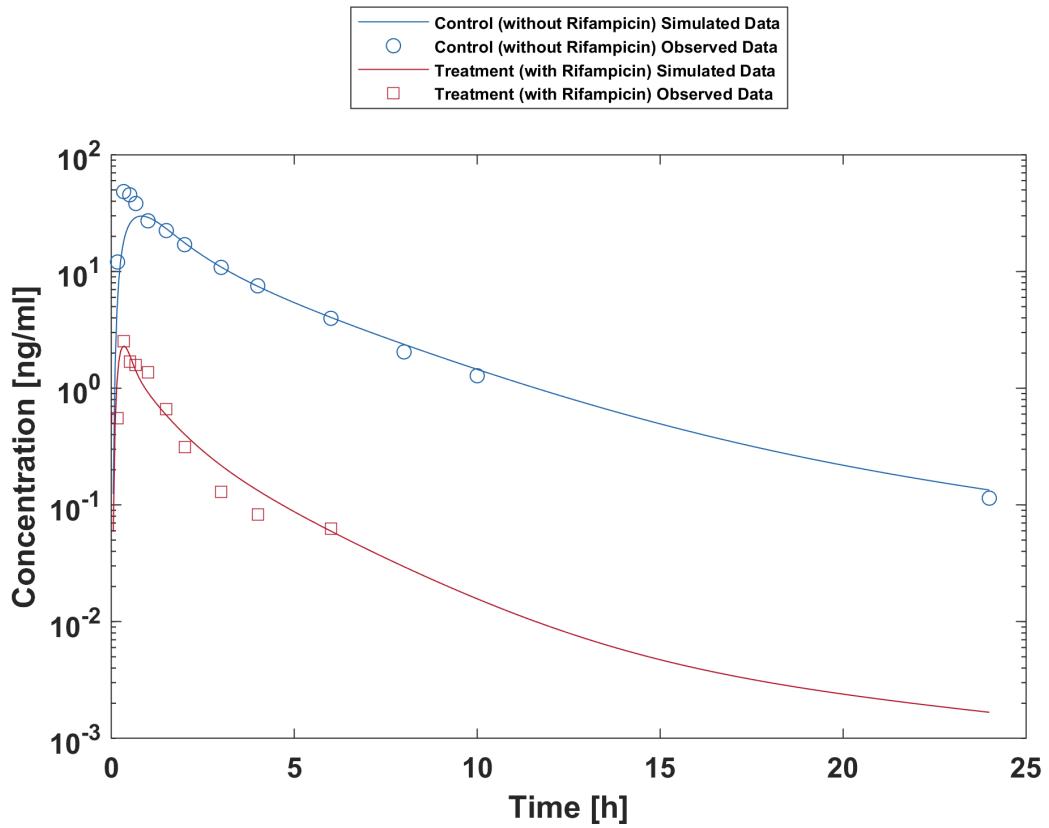
Kharasch 2011 (po)



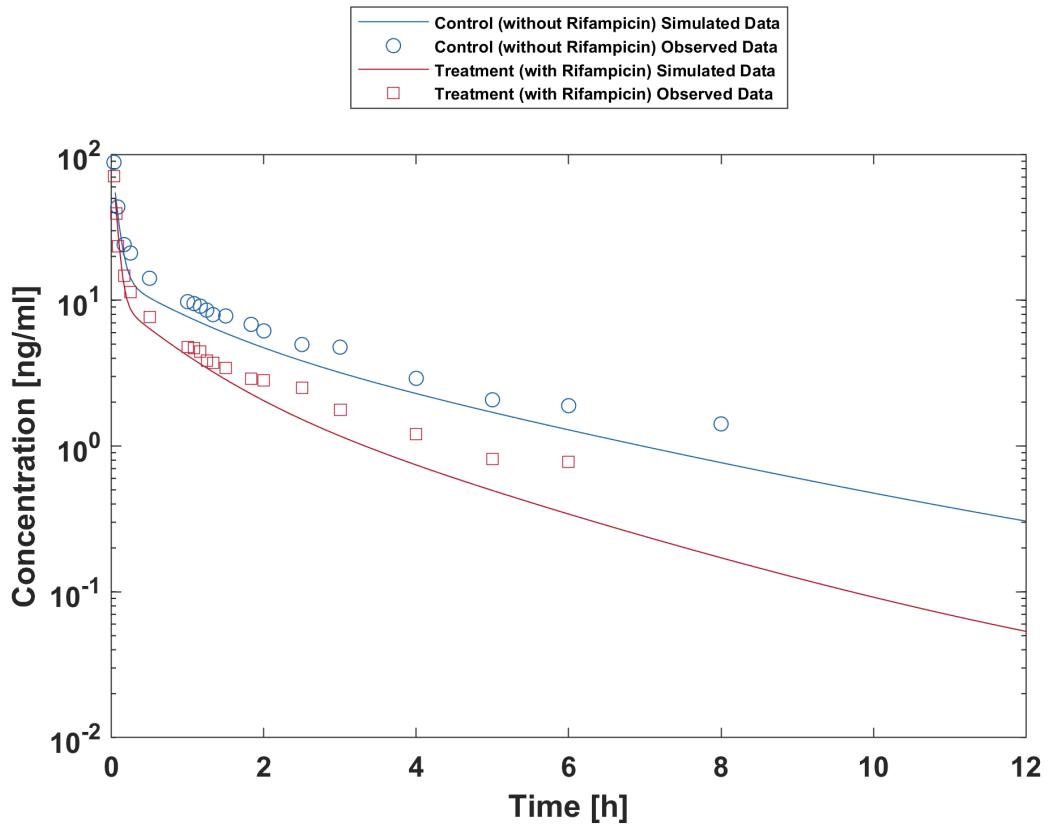
Kim 2018



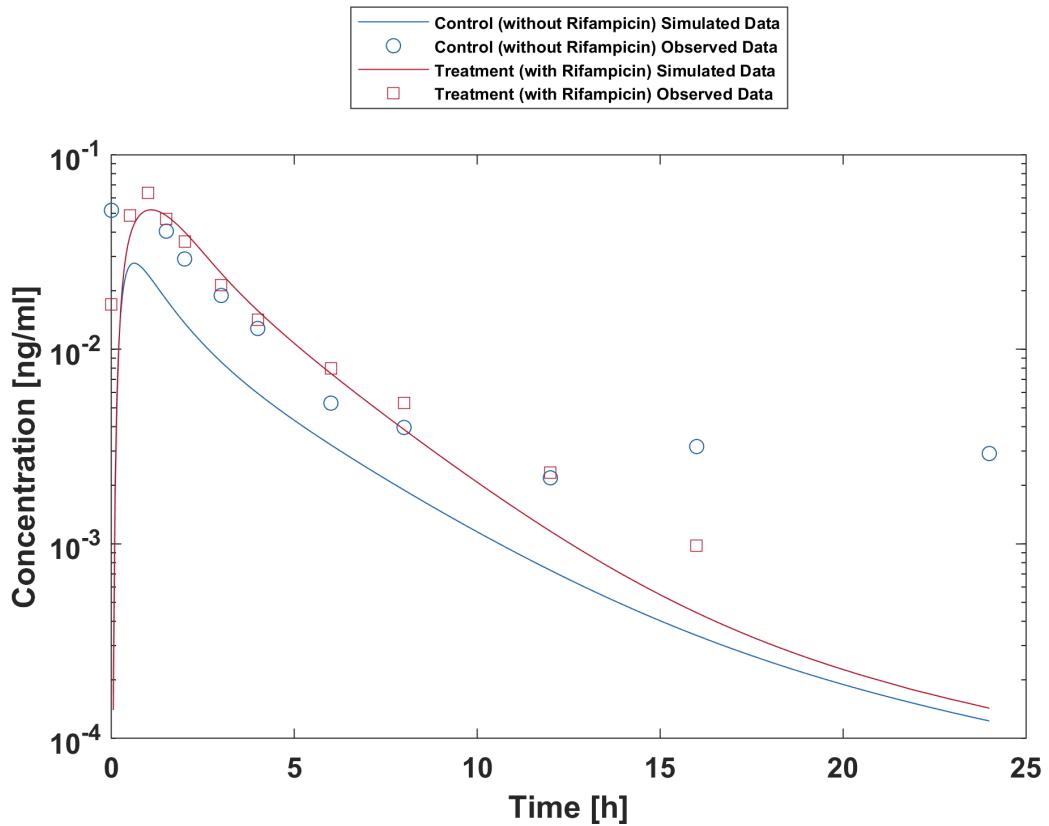
Link 2008 (iv)



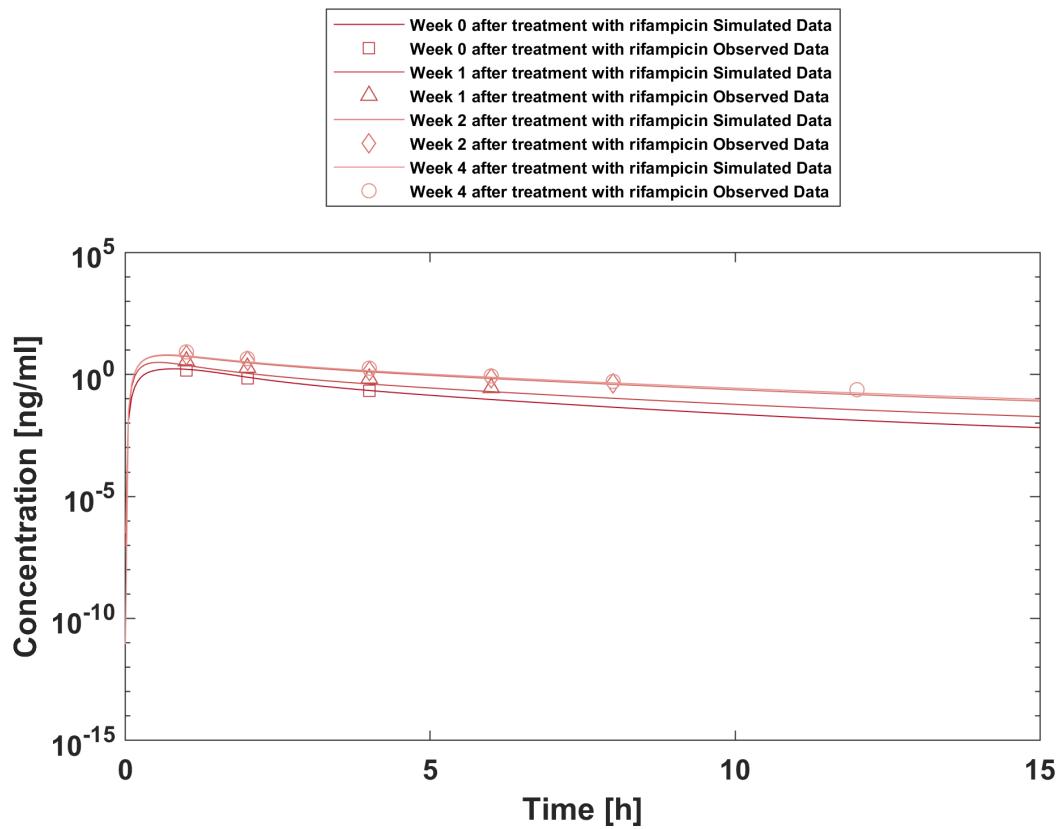
Link 2008 (po)



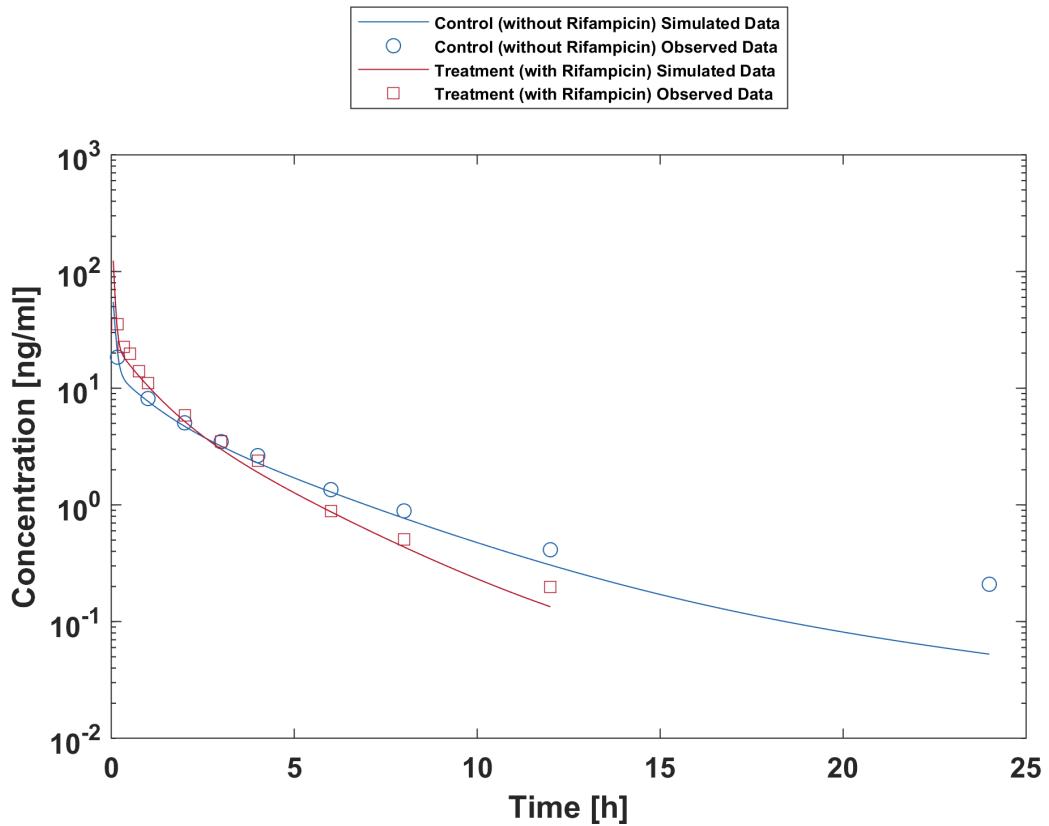
Phimmasone 2001



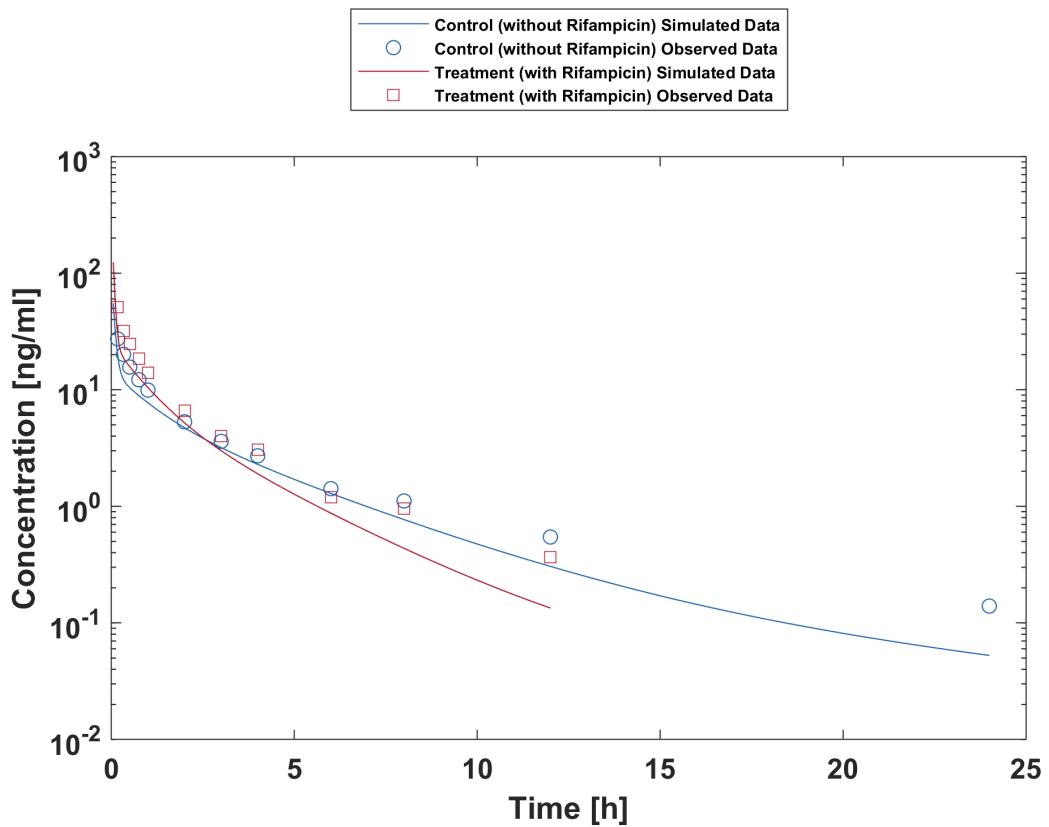
Prueksaritanont 2017



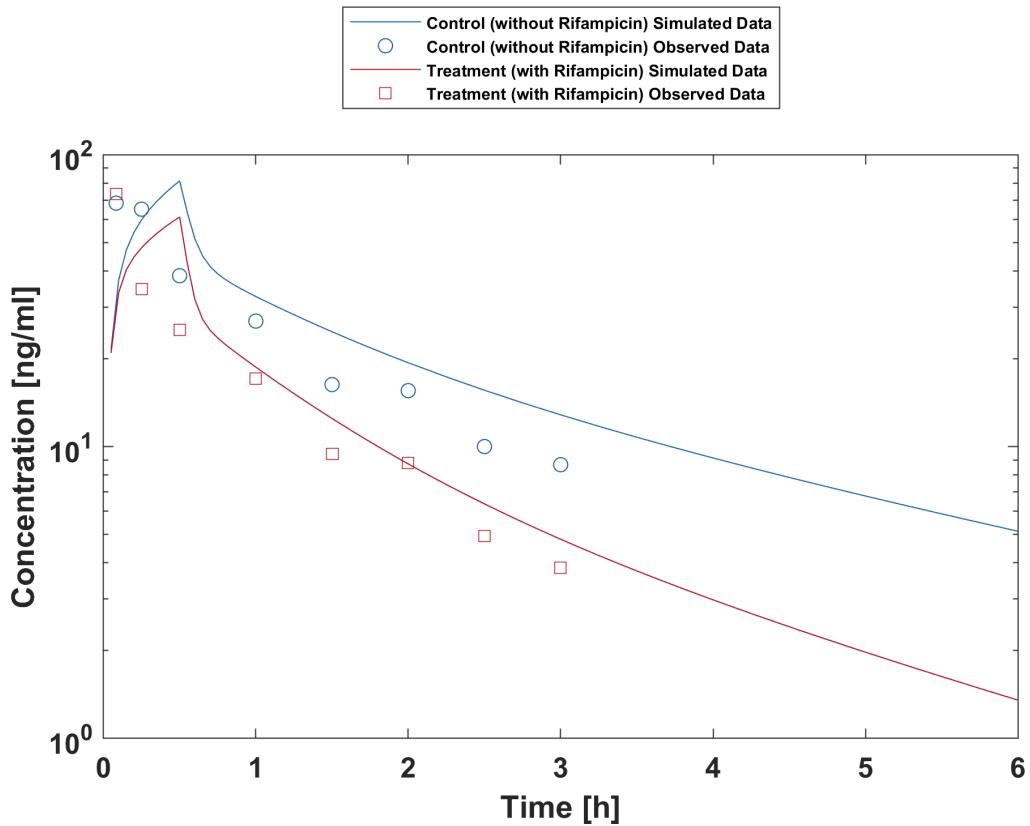
Reitman 2011



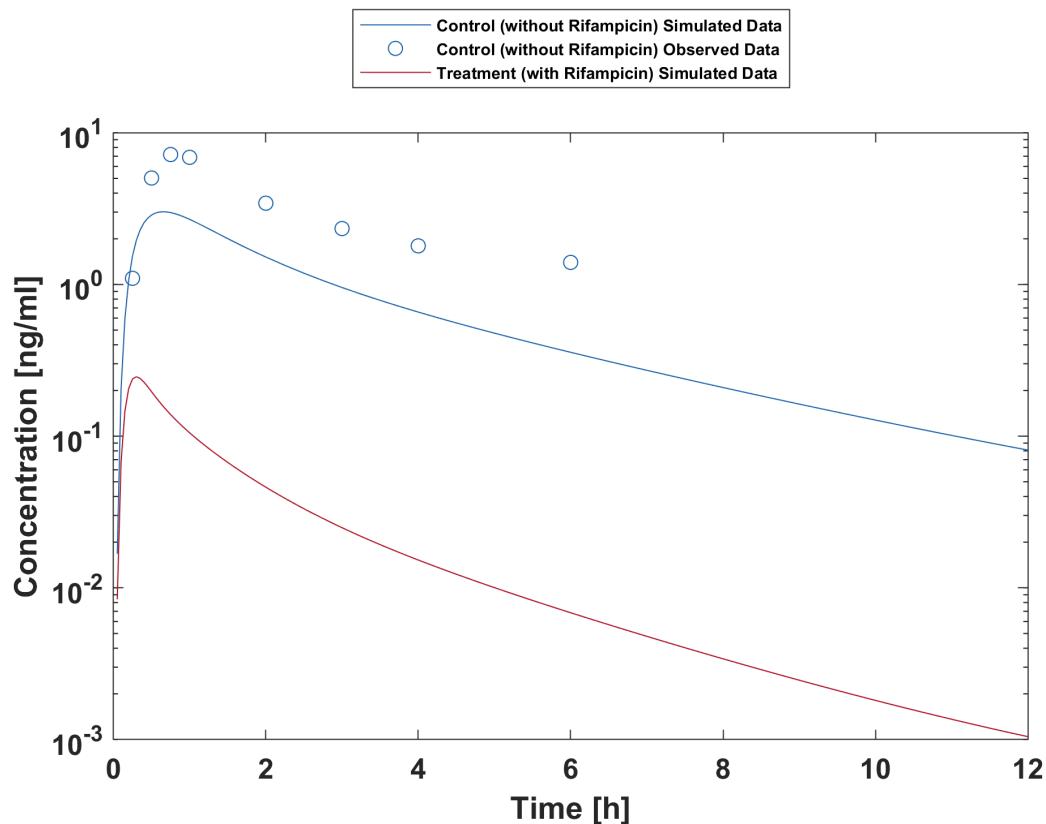
Shin 2013



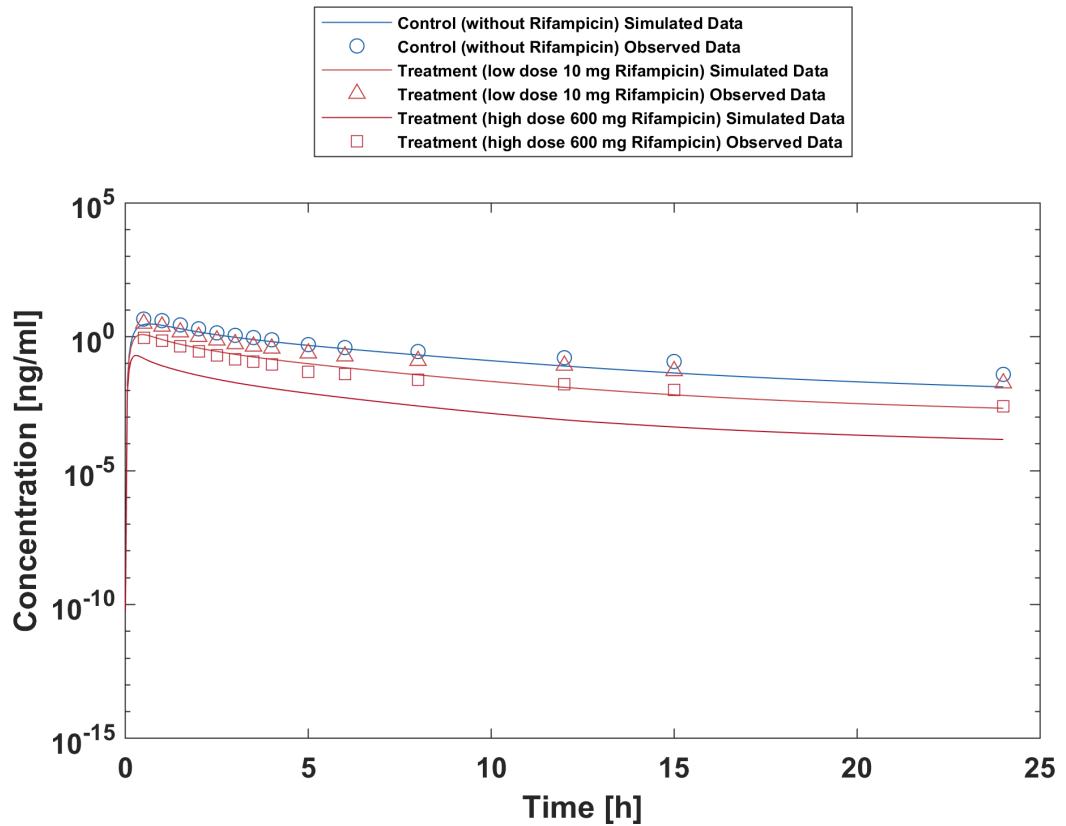
Shin 2016



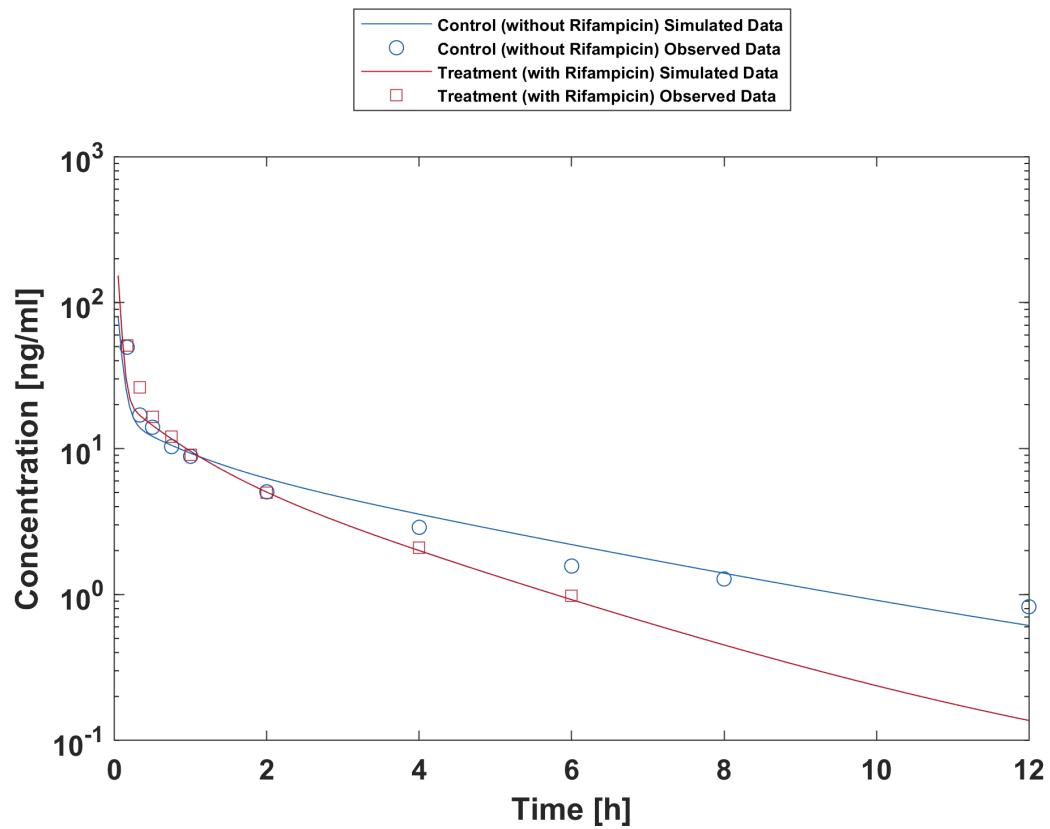
Szalat 2007



van Dyk 2018

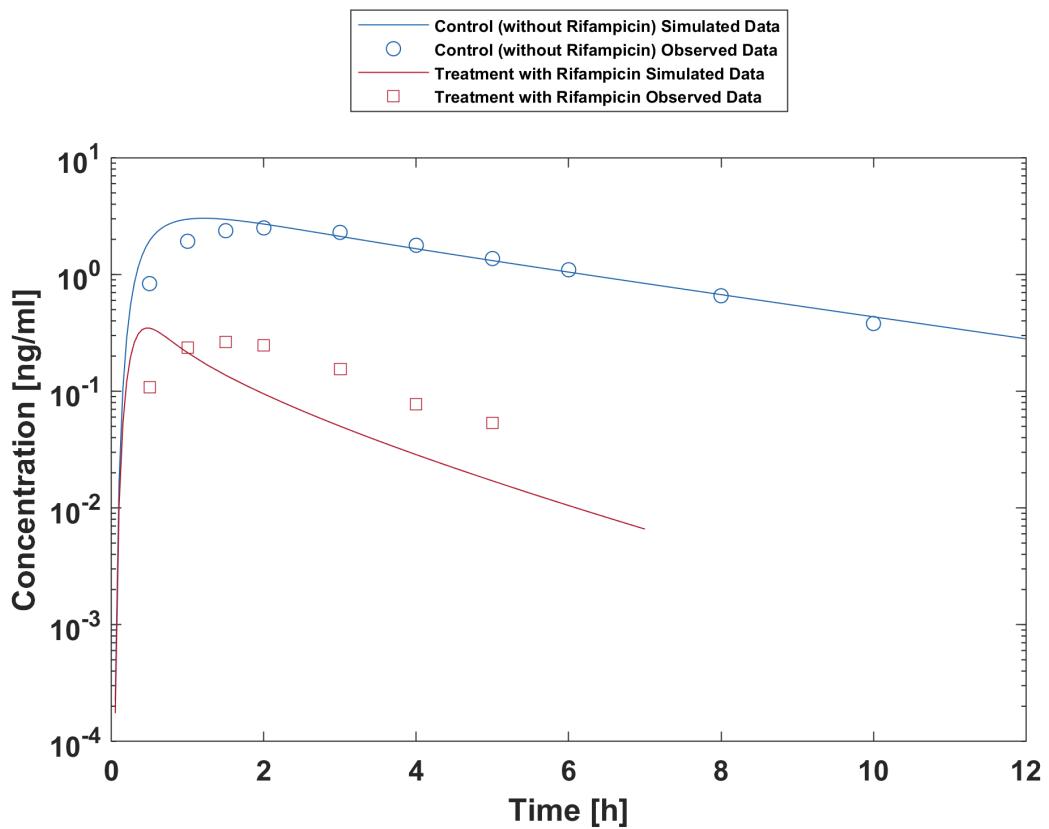


Wiesinger 2020



Yu 2004 (CYP3A5*3/*3)

3.18 Rifampicin - Triazolam DDI



Villikka 1997

4 References

Almond 2016 Almond LM, Mukadam S, Gardner I, Okialda K, Wong S, Hatley O, Tay S, Rowland-Yeo K, Jamei M, Rostami-Hodjegan A, Kenny JR. Prediction of Drug-Drug Interactions Arising from CYP3A induction Using a Physiologically Based Dynamic Model. *Drug Metab Dispos.* 2016 Jun;44(6):821-32.

Guest 2011 Guest EJ, Aarons L, Houston JB, Rostami-Hodjegan A, Galetin A. Critique of the two-fold measure of prediction success for ratios: application for the assessment of drug-drug interactions. *Drug Metab Dispos.* 2011 Feb;39(2):170-3.

OSP PK Database (<https://github.com/Open-Systems-Pharmacology/Database-for-observed-data>)

Clarithromycin-Midazolam-DDI

Gorski 1998 Gorski, J. C., Jones, D. R., Haehner-Daniels, B. D., Hamman, M. A., O'Mara Jr, E. M., & Hall, S. D. (1998). The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clinical Pharmacology & Therapeutics*, 64(2), 133-143.

Gurley 2006 Gurley, B., Hubbard, M. A., Williams, D. K., Thaden, J., Tong, Y., Gentry, W. B., ... & Cheboyina, S. (2006). Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. *The Journal of Clinical Pharmacology*, 46(2), 201-213.

Gurley 2008a Gurley, B. J., Swain, A., Hubbard, M. A., Hartsfield, F., Thaden, J., Williams, D. K., ... & Tong, Y. (2008). Supplementation with goldenseal (*Hydrastis canadensis*), but not kava kava (*Piper methysticum*), inhibits human CYP3A activity in vivo. *Clinical Pharmacology & Therapeutics*, 83(1), 61-69.

Markert 2013 Markert, C., Hellwig, R., Burhenne, J., Hoffmann, M. M., Weiss, J., Mikus, G., & Haefeli, W. E. (2013). Interaction of ambrisentan with clarithromycin and its modulation by polymorphic SLCO1B1. *European journal of clinical pharmacology*, 69(10), 1785-1793.

Prueksaritanont 2017 Prueksaritanont, T., Tatosian, D. A., Chu, X., Railkar, R., Evers, R., Chavez-Eng, C., ... & Cai, X. (2017). Validation of a microdose probe drug cocktail for clinical drug interaction assessments for drug transporters and CYP3A. *Clinical Pharmacology & Therapeutics*, 101(4), 519-530.

Quinney 2008 Quinney, S. K., Haehner, B. D., Rhoades, M. B., Lin, Z., Gorski, J. C., & Hall, S. D. (2008). Interaction between midazolam and clarithromycin in the elderly. *British journal of clinical pharmacology*, 65(1), 98-109.

van Dyk 2018 van Dyk, M., Marshall, J. C., Sorich, M. J., Wood, L. S., & Rowland, A. (2018). Assessment of inter-racial variability in CYP3A4 activity and inducibility among healthy adult males of Caucasian and South Asian ancestries. *European journal of clinical pharmacology*, 74(7), 913-920.

Yeates 1996 Yeates, R. A., Laufen, H., & Zimmermann, T. (1996). Interaction between midazolam and clarithromycin: comparison with azithromycin. *International journal of clinical pharmacology and therapeutics*, 34(9), 400-405.

Clarithromycin-Triazolam-DDI

Greenblatt 1998a Greenblatt DJ, von Moltke LL, Harmatz JS, Counihan M, Graf JA, Durol AL, Mertzanis P, Duan SX, Wright CE, Shader RI. Inhibition of triazolam clearance by macrolide antimicrobial agents: in vitro correlates and dynamic consequences. *Clin Pharmacol Ther.* 1998 Sep;64(3):278-85.

Erythromycin-Alfentanil-DDI

Bartkowski 1989 Bartkowski, R. R., Goldberg, M. E., Larijani, G. E., & Boerner, T. (1989). Inhibition of alfentanil metabolism by erythromycin. *Clinical Pharmacology & Therapeutics*, 46(1), 99-102.

Bartkowski 1993 Bartkowski, R. R., Goldberg, M. E., Huffnagle, S., & Epstein, R. H. (1993). Sufentanil disposition. Is it affected by erythromycin administration?. *Anesthesiology*, 78(2), 260-265.

Erythromycin-Alprazolam-DDI

Yasui 1996 Yasui, N., Otani, K., Kaneko, S., Ohkubo, T., Osanai, T., Sugawara, K., ... & Ishizaki, T. (1996). A kinetic and dynamic study of oral alprazolam with and without erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in alprazolam metabolism. *Clinical Pharmacology & Therapeutics*, 59(5), 514-519.

Erythromycin-Midazolam-DDI

Carls 2014 Carls, A., Jedamzik, J., Witt, L., Hohmann, N., Burhenne, J., & Mikus, G. (2014). Systemic exposure of topical erythromycin in comparison to oral administration and the effect on cytochrome P450 3A4 activity. *British journal of clinical pharmacology*, 78(6), 1433-1440.

Okudaira 2007 Okudaira, T., Kotegawa, T., Imai, H., Tsutsumi, K., Nakano, S., & Ohashi, K. (2007). Effect of the treatment period with erythromycin on cytochrome P450 3A activity in humans. *The Journal of Clinical Pharmacology*, 47(7), 871-876.

Olkkola 1993 Olkkola, K. T., Aranko, K., Luurila, H., Hiller, A., Saarnivaara, L., Himberg, J. J., & Neuvonen, P. J. (1993). A potentially hazardous interaction between erythromycin and midazolam. *Clinical Pharmacology & Therapeutics*, 53(3), 298-305.

Swart 2002 Swart, E. L., van der Hoven, B., Johan Groeneveld, A. B., Touw, D. J., & Danhof, M. (2002). Correlation between midazolam and lignocaine pharmacokinetics and MEGX formation in healthy volunteers. *British journal of clinical pharmacology*, 53(2), 133-139.

Zimmermann 1996 Zimmermann, T., Yeates, R. A., Laufen, H., Scharpf, F., Leitold, M., & Wildfeuer, A. (1996). Influence of the antibiotics erythromycin and azithromycin on the pharmacokinetics and pharmacodynamics of midazolam. *Arzneimittel-Forschung*, 46(2), 213-217.

Erythromycin-Triazolam-DDI

Greenblatt 1998 Greenblatt, D. J., von Moltke, L. L., Harmatz, J. S., Counihan, M., Graf, J. A., Durol, A. L. B., ... & Shader, R. I. (1998). Inhibition of triazolam clearance by macrolide antimicrobial agents: in vitro correlates and dynamic consequences. *Clinical Pharmacology & Therapeutics*, 64(3), 278-285.

Phillips 1986 Phillips, J. P., Antal, E. J., & Smith, R. B. (1986). A pharmacokinetic drug interaction between erythromycin and triazolam. *Journal of clinical psychopharmacology*, 6(5), 297-299.

Fluvoxamine-Midazolam-DDI

Kashuba 1998 Kashuba AD1, Nafziger AN, Kearns GL, Leeder JS, Gotschall R, Rocci ML Jr, Kulawy RW, Beck DJ, Bertino JS Jr. Effect of fluvoxamine therapy on the activities of CYP1A2, CYP2D6, and CYP3A as determined by phenotyping. *Clin Pharmacol Ther*. 1998 Sep;64(3):257-68.

Lam 2003 Lam YW1, Alfaro CL, Ereshefsky L, Miller M. Pharmacokinetic and pharmacodynamic interactions of oral midazolam with ketoconazole, fluoxetine, fluvoxamine, and nefazodone. *J Clin Pharmacol*. 2003 Nov;43(11):1274-82.

Fluvoxamine-Alprazolam-DDI

Fleishaker 1994 Fleishaker, J. C., & Hulst, L. K. (1994). A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *European journal of clinical pharmacology*, 46(1), 35-39.

Itraconazole-Alprazolam-DDI

Yasui 1998 Yasui N, Kondo T, Otani K, Furukori H, Kaneko S, Ohkubo T, Nagasaki T, Sugawara K. Effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of alprazolam. *Psychopharmacology (Berl)*. 1998 Oct;139(3):269-73.

Itraconazole-Midazolam-DDI

Ahonen 1995 Ahonen J, Olkkola KT, Neuvonen PJ. Effect of itraconazole and terbinafine on the pharmacokinetics and pharmacodynamics of midazolam in healthy volunteers. *Br J Clin Pharmacol*. 1995 Sep;40(3):270-2.

Backman 1998 Backman JT, Kivistö KT, Olkkola KT, Neuvonen PJ. The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. *Eur J Clin Pharmacol*. 1998 Mar;54(1):53-8.

Olkkola 1994 Olkkola KT, Backman JT, Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther*. 1994 May;55(5):481-5.

Olkkola 1996 Olkkola KT, Ahonen J, Neuvonen PJ. The effects of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Anesth Analg*. 1996 Mar;82(3):511-6.

Pruksaritanont 2017 Prueksaritanont T, Tatosian DA, Chu X, Railkar R, Evers R, Chavez-Eng C, Lutz R, Zeng W, Yabut J, Chan GH, Cai X, Latham AH, Hehman J, Stypinski D, Brejda J, Zhou C, Thornton B, Bateman KP, Fraser I, Stoch SA. Validation of a microdose probe drug cocktail for clinical drug interaction assessments for drug transporters and CYP3A. *Clin Pharmacol Ther.* 2017 Apr;101(4):519-530.

Templeton 2010 Templeton I, Peng CC, Thummel KE, Davis C, Kunze KL, Isoherranen N. Accurate prediction of dose-dependent CYP3A4 inhibition by itraconazole and its metabolites from in vitro inhibition data. *Clin Pharmacol Ther.* 2010 Oct;88(4):499-505.

Yu 2004 Yu KS, Cho JY, Jang IJ, Hong KS, Chung JY, Kim JR, Lim HS, Oh DS, Yi SY, Liu KH, Shin JG, Shin SG. Effect of the CYP3A5 genotype on the pharmacokinetics of intravenous midazolam during inhibited and induced metabolic states. *Clin Pharmacol Ther.* 2004 Aug;76(2):104-12.

Itraconazole-Triazolam-DDI

Neuvonen 1996 Neuvonen PJ, Varhe A, Olkkola KT. The effect of ingestion time interval on the interaction between itraconazole and triazolam. *Clin Pharmacol Ther.* 1996 Sep;60(3):326-31.

Varhe 1994 Varhe A, Olkkola KT, Neuvonen PJ. Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther.* 1994 Dec;56(6 Pt 1):601-7.

Verapamil-Midazolam-DDI

Backman 1994 Backman JT, Olkkola KT, Aranko K, Himberg JJ, Neuvonen PJ. Dose of midazolam should be reduced during diltiazem and verapamil treatments. *Br J Clin Pharmacol.* 1994 Mar;37(3):221-5.

Wang 2005 Wang Y, Jin Y, Hilligoss JK, Ho H, Hamman MA, Hu Z, Gorski JD, Hall SD. Effect of CYP3A5 genotype on the extent of CYP3A inhibition by verapamil. *Clin Pharmacol Ther.* 2005; 77(2):P3.

Efavirenz-Alfentanil-DDI

Kharasch 2012 Kharasch ED, Whittington D, Ensign D, Hoffer C, Bedynek PS, Campbell S, Stubbert K, Crafford A, London A, Kim T. Mechanism of efavirenz influence on methadone pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther.* 2012 Apr;91(4):673-84.

Efavirenz-Midazolam-DDI

Katzenmaier 2010 Katzenmaier S, Markert C, Mikus G. Proposal of a new limited sampling strategy to predict CYP3A activity using a partial AUC of midazolam. *Eur J Clin Pharmacol.* 2010 Nov;66(11):1137-41.

Mikus 2017 Mikus G, Heinrich T, Bödigheimer J, Röder C, Matthee AK, Weiss J, Burhenne J, Haefeli WE. Semisimultaneous Midazolam Administration to Evaluate the Time Course of CYP3A Activation by a Single Oral Dose of Efavirenz. *J Clin Pharmacol.* 2017 Jul;57(7):899-905.

Rifampicin-Alfentanil-DDI

Kharasch 1997 Kharasch ED, Russell M, Mautz D, Thummel KE, Kunze KL, Bowdle A, Cox K. The role of cytochrome P450 3A4 in alfentanil clearance. Implications for interindividual variability in disposition and perioperative drug interactions. *Anesthesiology*. 1997 Jul;87(1):36-50.

Kharasch 2004 Kharasch ED, Walker A, Hoffer C, Sheffels P. Intravenous and oral alfentanil as in vivo probes for hepatic and first-pass cytochrome P450 3A activity: noninvasive assessment by use of pupillary miosis. *Clin Pharmacol Ther*. 2004 Nov;76(5):452-66.

Kharasch 2011 Kharasch ED, Francis A, London A, Frey K, Kim T, Blood J. Sensitivity of intravenous and oral alfentanil and pupillary miosis as minimal and noninvasive probes for hepatic and first-pass CYP3A induction. *Clin Pharmacol Ther*. 2011 Jul;90(1):100-8.

Kharasch 2011b Kharasch ED, Vangveravong S, Buck N, London A, Kim T, Blood J, Mach RH. Concurrent assessment of hepatic and intestinal cytochrome P450 3A activities using deuterated alfentanil. *Clin Pharmacol Ther*. 2011 Apr;89(4):562-70.

Phimmasone 2001 Phimmasone S, Kharasch ED. A pilot evaluation of alfentanil-induced miosis as a noninvasive probe for hepatic cytochrome P450 3A4 (CYP3A4) activity in humans. *Clin Pharmacol Ther*. 2001 Dec;70(6):505-17.

Rifampicin-Alprazolam-DDI

Gashaw 2003 Gashaw, I., Kirchheimer, J., Goldammer, M., Bauer, S., Seidemann, J., Zoller, K., ... & Brockmöller, J. (2003). Cytochrome p450 3A4 messenger ribonucleic acid induction by rifampin in human peripheral blood mononuclear cells: correlation with alprazolam pharmacokinetics. *Clinical Pharmacology & Therapeutics*, 74(5), 448-457.

Schmider 1999 Schmider, J., Brockmöller, J., Aruld, G., Bauer, S., & Roots, I. (1999). Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics*, 9(6), 725-734.

Rifampicin-Midazolam-DDI

Backman 1996 Backman JT, Olkkola KT, Neuvonen PJ. Rifampin drastically reduces plasma concentrations and effects of oral midazolam. *Clin Pharmacol Ther*. 1996 Jan;59(1):7-13.

Backman 1998 Backman JT, Kivistö KT, Olkkola KT, Neuvonen PJ. The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. *Eur J Clin Pharmacol*. 1998 Mar;54(1):53-8.

Chung 2006 Chung E, Nafziger AN, Kazierad DJ, Bertino JS Jr. Comparison of midazolam and simvastatin as cytochrome P450 3A probes. *Clin Pharmacol Ther*. 2006 Apr;79(4):350-61.

Eap 2004 Eap CB, Buclin T, Cucchia G, Zullino D, Hustert E, Bleiber G, Golay KP, Aubert AC, Baumann P, Telenti A, Kerb R. Oral administration of a low dose of midazolam (75 microg) as an in vivo probe for CYP3A activity. *Eur J Clin Pharmacol*. 2004 Jun;60(4):237-46.

Gorski 2003 Gorski JC, Vannaprasaht S, Hamman MA, Ambrosius WT, Bruce MA, Haehner-Daniels B, Hall SD. The effect of age, sex, and rifampin administration on intestinal and hepatic cytochrome P450 3A activity. *Clin Pharmacol Ther.* 2003 Sep;74(3):275-87.

Gurley 2006 Gurley B, Hubbard MA, Williams DK, Thaden J, Tong Y, Gentry WB, Breen P, Carrier DJ, Cheboyina S. Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. *J Clin Pharmacol.* 2006 Feb;46(2):201-13.

Gurley 2008a Gurley BJ, Swain A, Hubbard MA, Hartsfield F, Thaden J, Williams DK, Gentry WB, Tong Y. Supplementation with goldenseal (*Hydrastis canadensis*), but not kava kava (*Piper methysticum*), inhibits human CYP3A activity in vivo. *Clin Pharmacol Ther.* 2008 Jan;83(1):61-9.

Kharasch 1997 Kharasch ED, Russell M, Mautz D, Thummel KE, Kunze KL, Bowdle A, Cox K. The role of cytochrome P450 3A4 in alfentanil clearance. Implications for interindividual variability in disposition and perioperative drug interactions. *Anesthesiology.* 1997 Jul;87(1):36-50.

Kharasch 2004 Kharasch ED, Walker A, Hoffer C, Sheffels P. Intravenous and oral alfentanil as in vivo probes for hepatic and first-pass cytochrome P450 3A activity: noninvasive assessment by use of pupillary miosis. *Clin Pharmacol Ther.* 2004 Nov;76(5):452-66.

Kharasch 2011 Kharasch ED, Francis A, London A, Frey K, Kim T, Blood J. Sensitivity of intravenous and oral alfentanil and pupillary miosis as minimal and noninvasive probes for hepatic and first-pass CYP3A induction. *Clin Pharmacol Ther.* 2011 Jul;90(1):100-8.

Kim 2018 Kim B, Lee J, Shin KH, Lee S, Yu KS, Jang IJ, Cho JY. Identification of ω - or (ω -1)-Hydroxylated Medium-Chain Acylcarnitines as Novel Urinary Biomarkers for CYP3A Activity. *Clin Pharmacol Ther.* 2018 May;103(5):879-887.

Link 2008 Link B, Haschke M, Grignaschi N, Bodmer M, Aschmann YZ, Wenk M, Krähenbühl S. Pharmacokinetics of intravenous and oral midazolam in plasma and saliva in humans: usefulness of saliva as matrix for CYP3A phenotyping. *Br J Clin Pharmacol.* 2008 Oct;66(4):473-84.

Phimmaseone 2001 Phimmaseone S, Kharasch ED. A pilot evaluation of alfentanil-induced miosis as a noninvasive probe for hepatic cytochrome P450 3A4 (CYP3A4) activity in humans. *Clin Pharmacol Ther.* 2001 Dec;70(6):505-17.

Prueksaritanont 2017 Prueksaritanont T, Tatosian DA, Chu X, Railkar R, Evers R, Chavez-Eng C, Lutz R, Zeng W, Yabut J, Chan GH, Cai X, Latham AH, Hehman J, Stypinski D, Brejda J, Zhou C, Thornton B, Bateman KP, Fraser I, Stoch SA. Validation of a microdose probe drug cocktail for clinical drug interaction assessments for drug transporters and CYP3A. *Clin Pharmacol Ther.* 2017 Apr;101(4):519-530.

Reitman 2011 Reitman ML, Chu X, Cai X, Yabut J, Venkatasubramanian R, Zajic S, Stone JA, Ding Y, Witter R, Gibson C, Roupe K, Evers R, Wagner JA, Stoch A. Rifampin's acute inhibitory and chronic inductive drug interactions: experimental and model-based approaches to drug-drug interaction trial design. *Clin Pharmacol Ther.* 2011 Feb;89(2):234-42.

Shin 2013 Shin KH, Choi MH, Lim KS, Yu KS, Jang IJ, Cho JY. Evaluation of endogenous metabolic markers of hepatic CYP3A activity using metabolic profiling and midazolam clearance. *Clin Pharmacol Ther.* 2013 Nov;94(5):601-9.

Shin 2016 Shin KH, Ahn LY, Choi MH, Moon JY, Lee J, Jang IJ, Yu KS, Cho JY. Urinary 6 β -Hydroxcortisol/Cortisol Ratio Most Highly Correlates With Midazolam Clearance Under Hepatic CYP3A Inhibition and Induction in Females: A Pharmacometabolomics Approach. *AAPS J.* 2016 Sep;18(5):1254-1261.

Szalat 2007 Szalat A, Gershkovich P, Ben-Ari A, Shaish A, Liberman Y, Boutboul E, Gotkine M, Hoffman A, Harats D, Leitersdorf E, Meiner V. Rifampicin-induced CYP3A4 activation in CTX patients cannot replace chenodeoxycholic acid treatment. *Biochim Biophys Acta*. 2007 Jul;1771(7):839-44.

van Dyk 2018 van Dyk M, Marshall JC, Sorich MJ, Wood LS, Rowland A. Assessment of inter-racial variability in CYP3A4 activity and inducibility among healthy adult males of Caucasian and South Asian ancestries. *Eur J Clin Pharmacol*. 2018 Jul;74(7):913-920.

Wiesinger 2020 Wiesinger H, Klein S, Rottmann A, Nowotn B, Riecke K, Gashaw I, Brudny-Klöppel M, Fricke R, Höchel J, Friedrich C. The effects of weak and strong CYP3A induction by rifampicin on the pharmacokinetics of five progestins and ethinylestradiol compared to midazolam. *Clin Pharmacol Ther*. 2020 Apr 10.

Yu 2004 Yu KS, Cho JY, Jang IJ, Hong KS, Chung JY, Kim JR, Lim HS, Oh DS, Yi SY, Liu KH, Shin JG, Shin SG. Effect of the CYP3A5 genotype on the pharmacokinetics of intravenous midazolam during inhibited and induced metabolic states. *Clin Pharmacol Ther*. 2004 Aug;76(2):104-12.

Rifampicin-Triazolam-DDI

Villikka 1997 Villikka, K., Kivistö, K. T., Backman, J. T., Olkkola, K. T., & Neuvonen, P. J. (1997). Triazolam is ineffective in patients taking rifampin. *Clinical Pharmacology & Therapeutics*, 61(1), 8-14.

5 Appendix

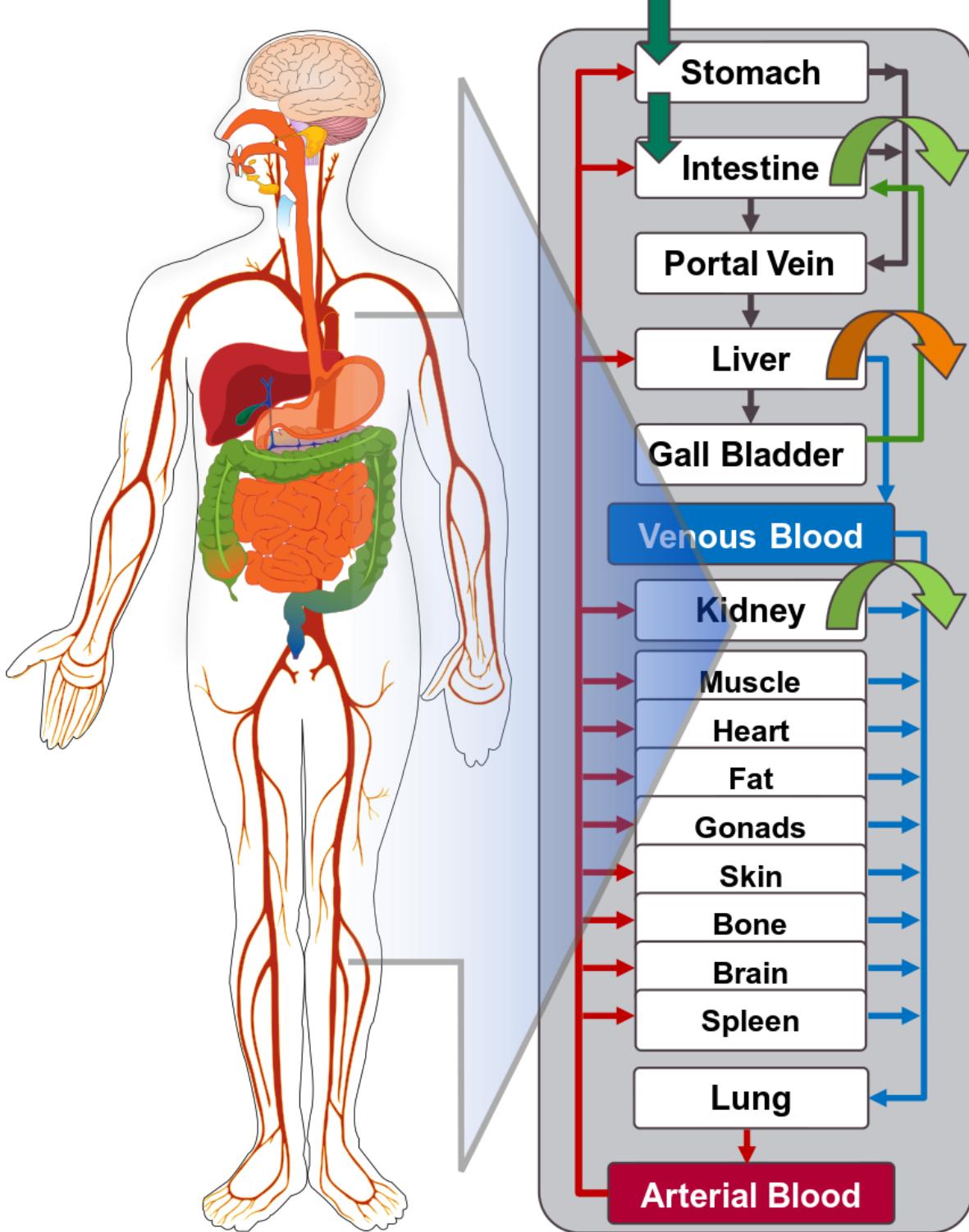
5.1 Open Systems Pharmacology Suite (OSPS) Introduction

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



References for OSPS introduction

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

[2] Willmann S, Schmitt W, Keldenich J, Lippert J, Dressman JB. A physiological model for the estimation of the fraction dose absorbed in humans. *J Med Chem*. 2004 Jul;47(16):4022-31.

[3] Haerter MW, K.J., Schmitt W, *Estimation of physicochemical and ADME parameters*, in *Handbook of Combinatorial Chemistry: Drugs, Catalysts, Materials*, H.W. Nicolaou KC HR, Editor. 2002, Wiley-VCH Verlag GmbH: Weinheim, Germany. p. 743-60.

- [4] Willmann S, Lippert J, Schmitt W. From physicochemistry to absorption and distribution: predictive mechanistic modelling and computational tools. *Expert Opin Drug Metab Toxicol.* 2005 Jun;1(1):159-68.
- [5] Rodgers T, D. Leahy, and M. Rowland. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J Pharm Sci.* 2005 Jun;94(6):1259-76.
- [6] Rodgers T, Rowland M. Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *J Pharm Sci.* 2006 Jun;95(6):1238-57.
- [7] Rodgers T, Rowland M. Mechanistic approaches to volume of distribution predictions: understanding the processes. *Pharm Res.* 2007 May;24(5):918-33.
- [8] Willmann S, Höhn K, Edginton A, Sevestre M, Solodenko J, Weiss W, Lippert J, Schmitt W. Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. *J Pharmacokinet Pharmacodyn.* 2007 Jun;34(3):401-31.
- [9] Willmann S, Lippert J, Sevestre M, Solodenko J, Fois F, Schmitt W. PK-Sim®: a physiologically based pharmacokinetic 'whole-body' model. *Biosilico* 2003.1(4):121-24.

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 [here](#).

DDI modeling: Mechanism-based inhibition

A detailed representation of the mathematical implementation of mechanism-based enzyme inhibition can be found in the OSP manual [here](#).

DDI modeling: Induction

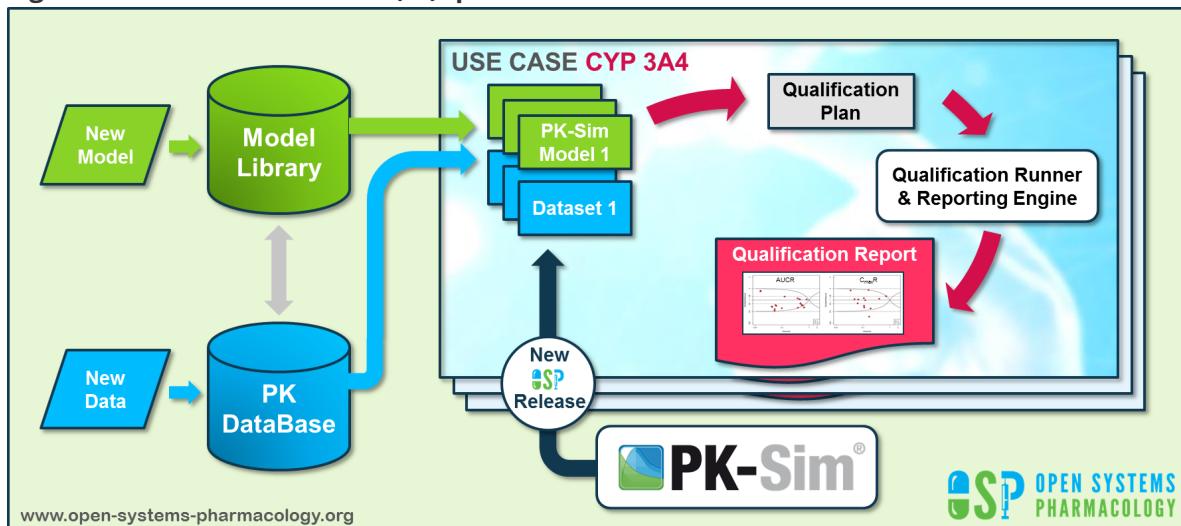
A detailed representation of the mathematical implementation of enzyme induction can be found in the OSP manual [here](#).

5.3 Automatic (re)-qualification workflow

[Open Systems Pharmacology](#) 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 1**):

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

Figure 1: OSP suite automatic (re)-qualification workflow

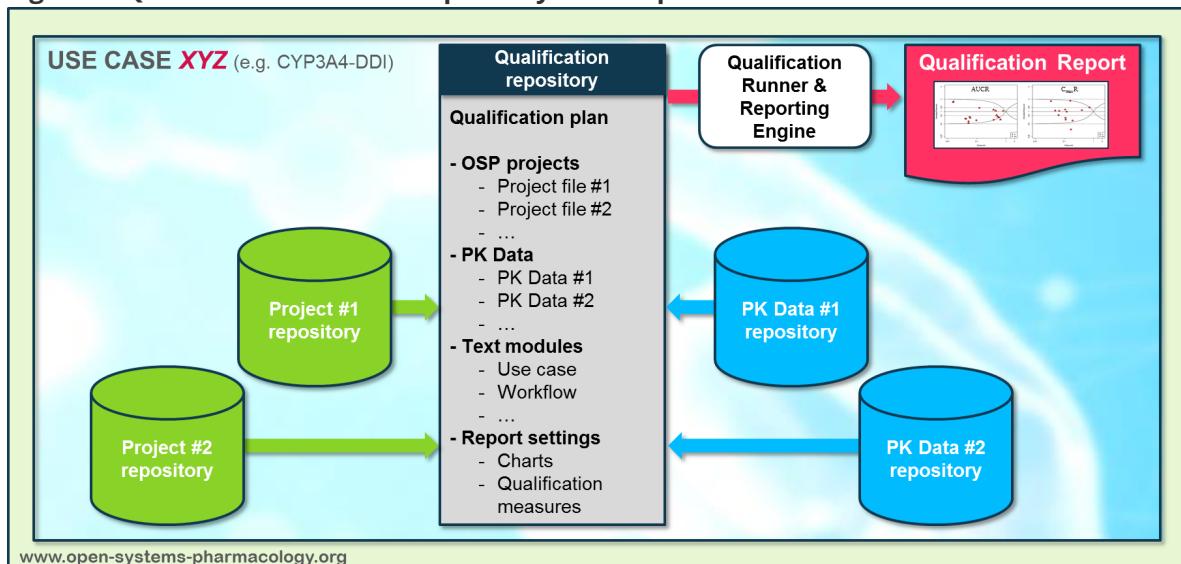


In a first step, the respective qualification scenario is saved in a special qualification repository on [GitHub](#). This qualification scenario repository contains a detailed qualification plan that links and combines respective models and data to address the use case that shall be qualified. Therefore, 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 2**).

Figure 2: Qualification scenario repository landscape on GitHub



In a second step the [qualification runner](#) processes the qualification plan, i.e. all project parts are exported and prepared for the [reporting engine](#). The reporting engine provides a validated environment (currently implemented in MATLAB®, a transfer to R is in development) 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.