

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 indented 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 provided open-source (<https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4>). The same applies for all presented PBPK models including *evaluation reports* on model building and evaluation of each model ([http s://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library](https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library)).

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

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

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

1.2 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 v1.2*): <https://github.com/Open-Systems-Pharmacology/Rifampicin-Model/releases/tag/v1.2>
- **Efavirenz** (moderate CYP3A4 inducer)
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Efavirenz-Model/releases/tag/v1.1>

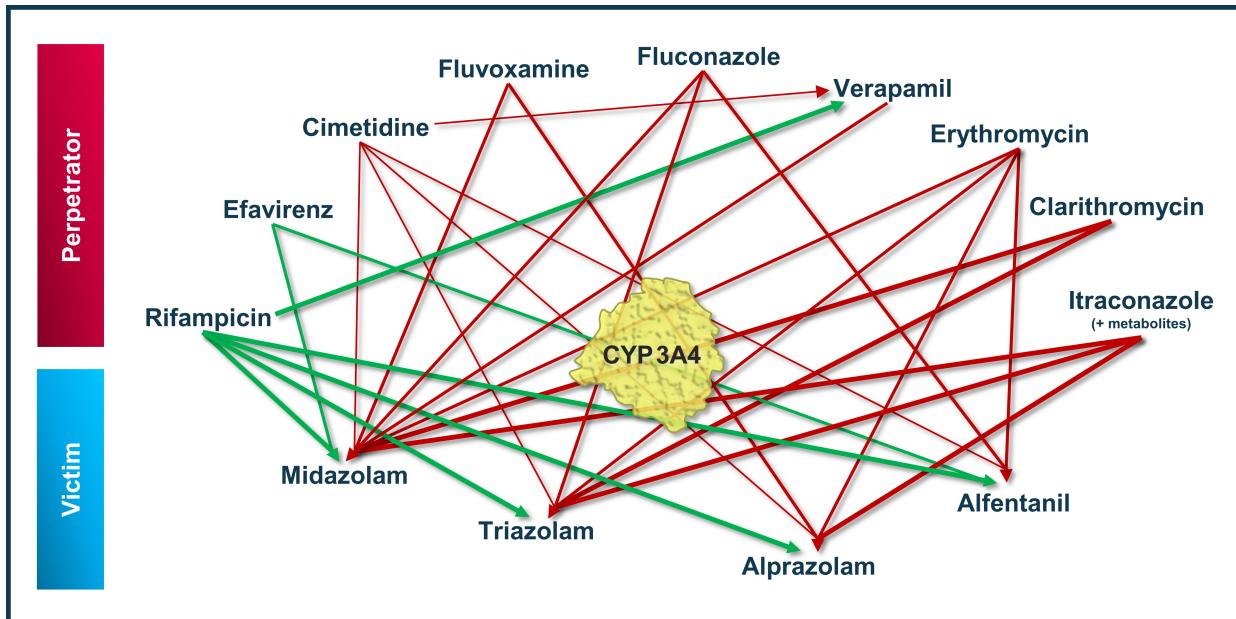
- **Cimetidine** (weak CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Cimetidine-Model/releases/tag/v1.1>
- **Fluvoxamine** (weak/moderate CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Fluvoxamine-Model/releases/tag/v1.1>
- **Verapamil** (moderate CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.2*): <https://github.com/Open-Systems-Pharmacology/Verapamil-Model/releases/tag/v1.2>
- **Fluconazole** (moderate CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Fluconazole-Model/releases/tag/v1.0>
- **Erythromycin** (moderate CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.2*): <https://github.com/Open-Systems-Pharmacology/Erythromycin-Model/releases/tag/v1.2>
- **Clarithromycin** (strong CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.2*): <https://github.com/Open-Systems-Pharmacology/Clarithromycin-Model/releases/tag/v1.2>
- **Itraconazole** including metabolites (strong CYP3A4 inhibitor)
Model snapshot and evaluation plan (*release v1.3*): <https://github.com/Open-Systems-Pharmacology/Itraconazole-Model/releases/tag/v1.3>

The following sensitive CYP3A4 substrates as victim drugs were selected:

- **Midazolam**
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Midazolam-Model/releases/tag/v1.1>
- **Triazolam**
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Triazolam-Model/releases/tag/v1.1>
- **Alprazolam**
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Alprazolam-Model/releases/tag/v1.1>
- **Alfentanil**
Model snapshot and evaluation plan (*release v2.2*): <https://github.com/Open-Systems-Pharmacology/Alfentanil-Model/releases/tag/v2.2>

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 arrows indicate where at least one clinical DDI study between the two connected substances was available and included in the model network. Red indicates inhibition and green indicates induction as the primary type of interaction. Thin arrows indicate weak, mid-thick arrows moderate and thick arrows strong CYP3A4 modulation by the perpetrator.

The published DDI studies between the respective perpetrators and victim drugs were simulated and compared to observed data. The following sections give an overview of the clinical studies being part of this qualification report. The respective data identifier (DataID) refers to the ID of the dataset in the [OSP PK database](#).

Cimetidine - Alfentanil DDI

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

<https://github.com/Open-Systems-Pharmacology/Cimetidine-Alfentanil-DDI/releases/tag/v1.1>.

The cimetidine-alfentanil interaction was evaluated using a single clinical DDI study quantifying the interaction following two different dosing regimens ([Kienlen 1993](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1344	CYP3A4	Cimetidine / alfentanil	Cimetidine: 1200 mg iv OD over 3 days Alfentanil: 125 µg/kg iv on day 3 concomitantly with the cimetidine dose	No cross-over study! Parallel group design -> the two groups may not really be comparable given the low number of subjects and considering alfentanil PK variability	Kienlen 1993

Cimetidine - Alprazolam DDI

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

<https://github.com/Open-Systems-Pharmacology/Cimetidine-Alprazolam-DDI/releases/tag/v1.1>.

The cimetidine-alprazolam interaction was evaluated using two clinical DDI studies quantifying the interaction following two different dosing regimens ([Pourbaix 1985](#), [Abernethy 1983](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1340	CYP3A4	Cimetidine / alprazolam	Cimetidine: 200 mg po TID and 400 mg at bedtime over two weeks Alprazolam: 0.5 mg po OD in the second week concomitantly with morning dose		Pourbaix 1985
1332	CYP3A4	Cimetidine / alprazolam	Cimetidine: 300 mg po QID (4 times) Alprazolam: 1 mg po single dose concomitantly with cimetidine dose at 12 h		Abernethy 1983

Cimetidine - Midazolam DDI

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

<https://github.com/Open-Systems-Pharmacology/Cimetidine-Midazolam-DDI/releases/tag/v1.1>.

The cimetidine-midazolam interaction was evaluated using five clinical DDI studies quantifying the interaction following six different dosing regimens ([Elliott 1984](#), [Fee 1987](#), [Greenblatt 1986](#), [Martinez 1999](#), [Salonen 1986](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1346	CYP3A4	Cimetidine / midazolam	Cimetidine: 200 mg po TID and 400 mg nocte on day before study and 200 mg on study day Midazolam: 7.5 mg po single dose, 2.5 hours after last cimetidine dose		Elliott 1984
1324	CYP3A4	Cimetidine / midazolam	Cimetidine: 400 mg po BID (3 times) Midazolam: 15 mg po single dose, 1 hour after the last cimetidine dose		Fee 1987
1319	CYP3A4	Cimetidine / midazolam	Cimetidine: 300 mg po QID (8 times) Midazolam: 5 mg iv single dose, concomitantly with the 5 th cimetidine dose		Greenblatt 1986
1321	CYP3A4	Cimetidine / midazolam	Cimetidine: 300 mg po QID (8 times) Midazolam: 15 mg po single dose concomitantly with the 5 th cimetidine dose		Greenblatt 1986
1322	CYP3A4	Cimetidine / midazolam	Cimetidine: 800 mg po single dose Midazolam: 7.5 mg po single dose concomitantly with cimetidine dose		Martinez 1999
1326	CYP3A4	Cimetidine / midazolam	Cimetidine: 400 mg po single dose Midazolam: 15 mg po single dose 2 hours after cimetidine dose		Salonen 1986

Cimetidine - Triazolam DDI

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

<https://github.com/Open-Systems-Pharmacology/Cimetidine-Triazolam-DDI/releases/tag/v1.1>.

The cimetidine-triazolam interaction was evaluated using four clinical DDI studies quantifying the interaction following four different dosing regimens ([Pourbaix 1985](#), [Abernethy 1983](#), [Cox 1986](#), [Friedman 1988](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1342	CYP3A4	Cimetidine / triazolam	Cimetidine: 200 mg po TID and 400 mg at bedtime over two weeks Triazolam: 0.5 mg po OD in the second week concomitantly with bedtime dose		Pourbaix 1985
1334	CYP3A4	Cimetidine / triazolam	Cimetidine: 300 mg po QID (4 times) Triazolam: 0.5 mg po single dose concomitantly with cimetidine dose at 12 h		Abernethy 1983
1338	CYP3A4	Cimetidine / triazolam	Cimetidine: 300 mg po QID (4 times) Triazolam: 0.5 mg intraduodenal single dose, 13 hours after study start		Cox 1986
1336	CYP3A4	Cimetidine / triazolam	Cimetidine: 300 mg po QID (8 times) Triazolam: 0.5 mg po single dose concomitantly with the 5 th cimetidine dose		Friedman 1988

Cimetidine - Verapamil DDI

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

<https://github.com/Open-Systems-Pharmacology/Cimetidine-Verapamil-DDI/releases/tag/v1.1>.

The cimetidine-verapamil interaction was evaluated using a single clinical DDI study quantifying the interaction following two different dosing regimens ([Smith 1984](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1328	CYP3A4	Cimetidine / verapamil	Cimetidine: 300 mg po QID over eight days Verapamil: 10 mg iv on day 8 concomitantly with the morning dose		Smith 1984
1330	CYP3A4	Cimetidine / verapamil	Cimetidine: 300 mg po QID over eight days Verapamil: 120 mg po on day 8 concomitantly with the morning dose		Smith 1984

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/v1.2>

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		Prueksaritanont 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/v1.2>

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/v1.2>

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/v1.2>

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/v1.2>

The erythromycin-midazolam interaction was evaluated using five clinical DDI studies quantifying the interaction following nine different dosing regimens ([Carls 2014](#), [Okudaira 2007](#), [Olkkola 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-Triazolam-DDI/releases/tag/v1.2>

The erythromycin-triazolam 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 3 rd 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/v1.1>

The fluvoxamine-alprazolam interaction was evaluated using one clinical DDI study quantifying the interaction following the first dose and in steady-state ([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/v1.2>

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/v1.2>

The itraconazole / alprazolam interaction was evaluated using one clinical DDI study ([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/v1.2>

The itraconazole / midazolam interaction was evaluated using seven clinical DDI studies including 12 different clinical settings ([Ahonen 1995](#), [Backman 1998](#), [Olkkola 1994](#), [Olkkola 1996](#), [Prueksaritanont 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

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
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
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/v1.2>

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/v1.2>

The verapamil / 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/v1.1>.

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/v1.2>

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/v1.2>

The rifampicin / alfentanil 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 6th 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/v1.2>

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/v1.2>

The rifampicin / midazolam interaction was evaluated using 24 clinical DDI studies including 43 different clinical settings ([Backman 1996](#), [Backman 1998](#), [Björkhem-Bergman 2013](#), [Chattopadhyay 2018](#), [Chung 2006](#), [Eap 2004](#), [Gorski 2003](#), [Gurley 2006](#), [Gurley 2008a](#), [Kharasch 1997](#), [Kharasch 2004](#), [Kharasch 2011](#), [Kim 2018](#), [Link 2008](#), [Lutz 2018](#), [Phimmasone 2001](#), [Pruksaritanont 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
1355	CYP3A4	Rifampicin / midazolam	Rifampicin: 10 mg po once daily (14 doses) Midazolam: 4 mg PO single dose, 1 day after 14th rifampicin dose		Björkhem-Bergman 2013
1356	CYP3A4	Rifampicin / midazolam	Rifampicin: 20 mg po once daily (14 doses) Midazolam: 4 mg PO single dose, 1 day after 14th rifampicin dose		Björkhem-Bergman 2013
1357	CYP3A4	Rifampicin / midazolam	Rifampicin: 100 mg po once daily (14 doses) Midazolam: 4 mg PO single dose, 1 day after 14th rifampicin dose		Björkhem-Bergman 2013
1362	CYP3A4	Rifampicin / midazolam	Rifampicin: 600 mg po once daily morning administrations (11 doses), 8th dose of rifampicin was taken in the evening (12 h after intake of midazolam) Midazolam: 1 mg PO single dose on day 8 (24 hours after the 7th rifampicin dose)	Subjects received a single dose of vilaprisan 4 mg simultaneously with midazolam (in both phases).	Chattopadhyay 2018
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

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
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
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

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
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
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
1350	CYP3A4	Rifampicin / midazolam	Rifampicin: 2 mg po once daily (18 doses) Midazolam: 2 mg PO single dose, 12 h after 10th rifampicin dose	Cohort2, Cocktail study	Lutz 2008
1351	CYP3A4	Rifampicin / midazolam	Rifampicin: 10 mg po once daily (18 doses) Midazolam: 2 mg PO single dose, 12 h after 10th rifampicin dose	Cohort 1, Cocktail study	Lutz 2008
1352	CYP3A4	Rifampicin / midazolam	Rifampicin: 10 mg po once daily (18 doses), then 75 mg po once daily (18 doses) Midazolam: 2 mg PO single dose, 12 h after 10th 75 mg rifampicin dose	Cohort 1, Cocktail study	Lutz 2008

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1353	CYP3A4	Rifampicin / midazolam	Rifampicin: 2 mg po once daily (18 doses), then 600 mg po once daily (18 doses) Midazolam: 2 mg PO single dose, 12 h after 10th 600mg rifampicin dose	Cohort 2, Cocktail study	Lutz 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		Pruksaranont 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 administered 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 administered 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 administered 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/v1.2>

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

Rifampicin - Verapamil DDI

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

<https://github.com/Open-Systems-Pharmacology/Rifampicin-Verapamil-DDI/releases/tag/v1.1>

The rifampicin / verapamil interaction was evaluated using 1 clinical DDI study including 2 different clinical settings ([Barbarash 1988](#)).

DataID	Enzyme, Transporter	Perpetrator / victim	Study design	Comments	Clinical study
2056	CYP3A4 (and CYP2C8)	Rifampicin / verapamil	Rifampicin: 600 mg QD for 15 days Verapamil: 10 mg iv single dose, 12 hours after the 13 th rifampicin dose		Barbarash 1988
2058	CYP3A4 (and CYP2C8), P-gp*	Rifampicin / verapamil	Rifampicin: 600 mg QD for 15 days Verapamil: 120 mg po single dose, 12 hours after the 15 th rifampicin dose		Barbarash 1988

* The substrate characteristics of verapamil towards P-gp are not considered in the verapamil PBPK model applied in this qualification (<https://github.com/Open-Systems-Pharmacology/Verapamil-Model/releases/tag/v1.0>).

Fluconazole - Alfentanil DDI

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

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

The fluconazole-alfentanil interaction was evaluated using a single clinical DDI study quantifying the interaction following two different dosing regimens ([Palkama 1998](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1398	CYP3A4	Fluconazole / alfentanil	Fluconazole: 400 mg iv infusion for 60 min single administration Alfentanil: 0.02 mg/kg iv infusion, 1 hour after start of fluconazole dosing		Palkama 1998
1399	CYP3A4	Fluconazole / alfentanil	Fluconazole: 400 mg po single administration Alfentanil: 0.02 mg/kg iv infusion, 1 hour after the fluconazole dose		Palkama 1998

Fluconazole - Midazolam DDI

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

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

The fluconazole-midazolam interaction was evaluated using two clinical DDI studies quantifying the interaction following 5 different dosing regimens ([Ahonen 1997](#), [Olkola 1996](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1392	CYP3A4	Fluconazole / midazolam	Fluconazole: 400 mg iv infusion for 60 min Midazolam: 7.5 mg po single dose, 1 hour after start of fluconazole dosing		Ahonen 1997
1393	CYP3A4	Fluconazole / midazolam	Fluconazole: 400 mg po Midazolam: 7.5 mg po single dose, 1 hour after the fluconazole dose		Ahonen 1997
380	CYP3A4	Fluconazole / midazolam	Fluconazole: 400 mg po QD (day 1) then 200 mg QD for 5 days Midazolam: 7.5 mg po, 2 hours after the day 1 fluconazole dose		Olkola 1996
381	CYP3A4	Fluconazole / midazolam	Fluconazole: 400 mg po QD (day 1) then 200 mg QD for 5 days Midazolam: 0.05 mg/kg iv infusion, 2 hours after the day 4 fluconazole dose		Olkola 1996
381	CYP3A4	Fluconazole / midazolam	Fluconazole: 400 mg po QD (day 1) then 200 mg QD for 5 days Midazolam: 7.5 mg po, 2 hours after the day 6 fluconazole dose		Olkola 1996

Fluconazole - Triazolam DDI

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

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

The fluconazole-triazolam interaction was evaluated using a single clinical DDI study quantifying the interaction following three different dosing regimens ([Varhe 1996](#)).

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
1394	CYP3A4	Fluconazole / triazolam	Fluconazole: 50 mg po QD for 4 days Triazolam: 0.25 mg po single dose, 1 hour after last fluconazole dose		Varhe 1996
1395	CYP3A4	Fluconazole / triazolam	Fluconazole: 100 mg po QD for 4 days Triazolam: 0.25 mg po single dose, 1 hour after last fluconazole dose		Varhe 1996
1396	CYP3A4	Fluconazole / triazolam	Fluconazole: 200 mg po QD for 4 days Triazolam: 0.25 mg po single dose, 1 hour after last fluconazole dose		Varhe 1996

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:

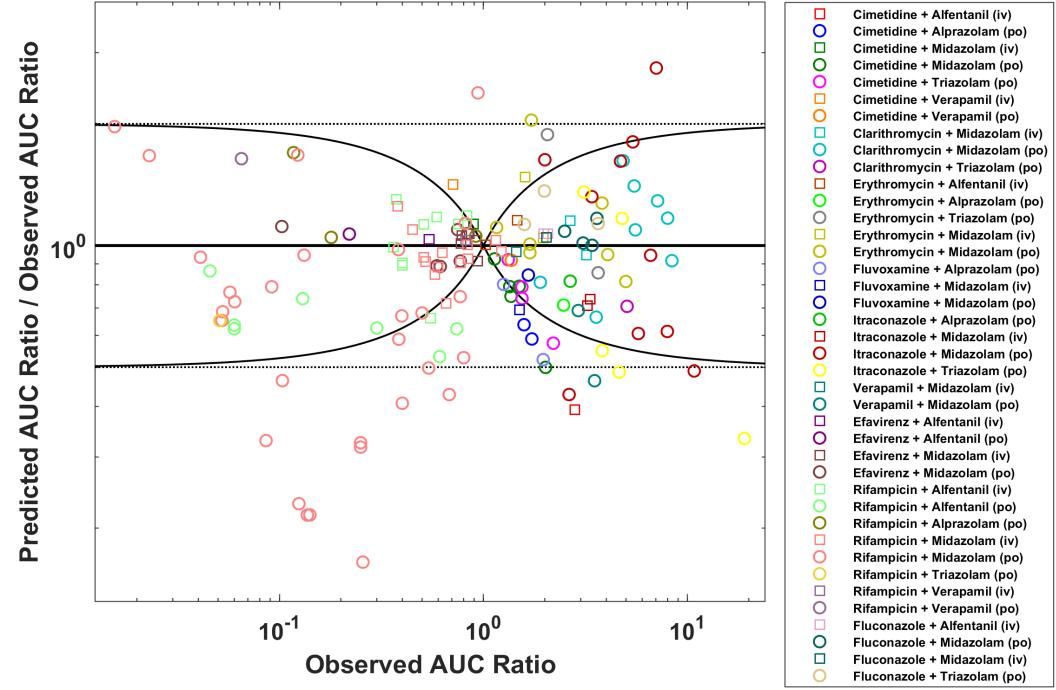
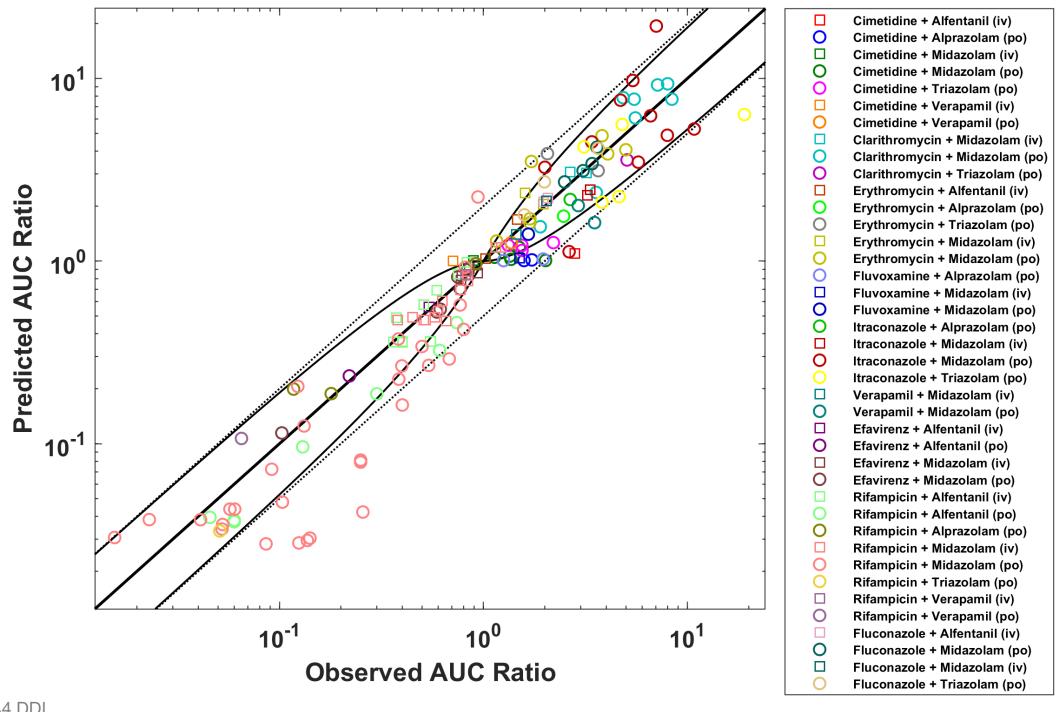
- predicted (*Pred*) vs. observed (*Obs*) plots
- $Pred/Obs$ vs. *Obs* plots
- geometric mean fold error (GMFE):

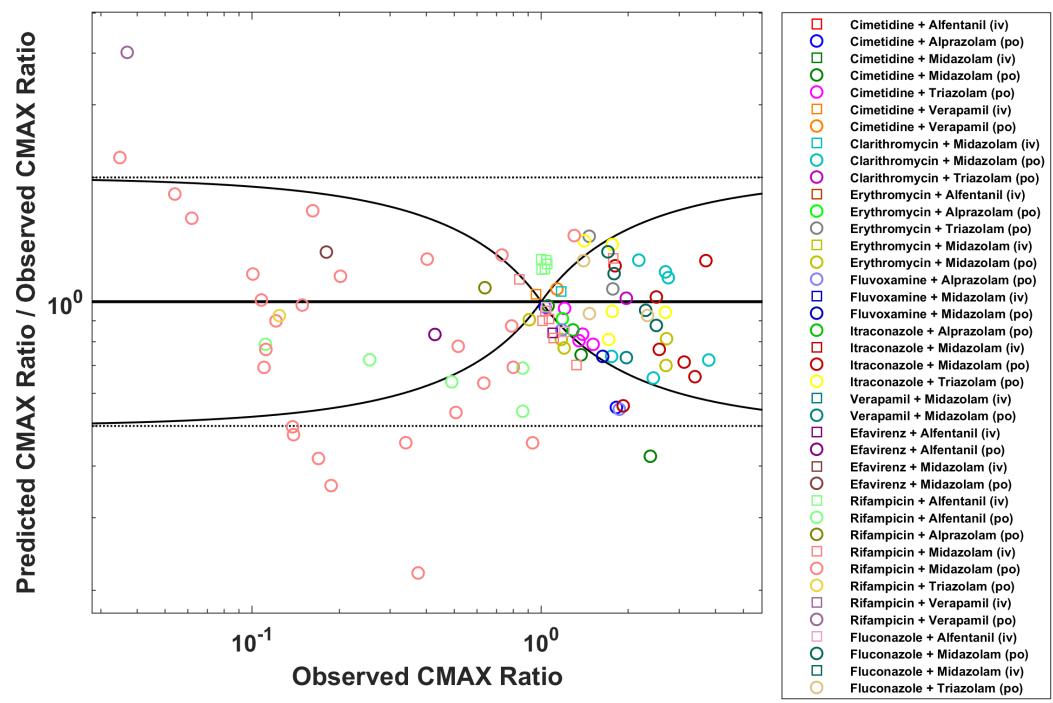
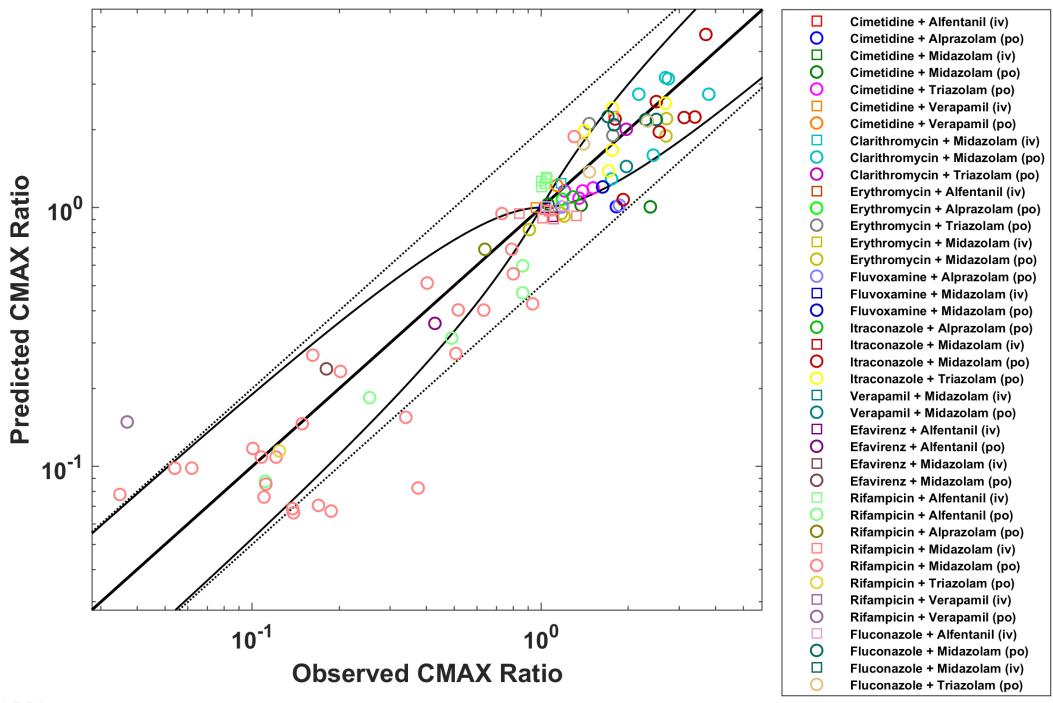
$$10^{\frac{\sum |\log(\frac{Pred}{Obs})|}{n}}$$

- 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) = 1.400949

GMFE (CMAX) = 1.350118

AUC	Number	Ratio [%]
Points total	153	-
Points within Guest et al.	109	71.2418
Points within 2-fold	132	86.2745

CMAX	Number	Ratio [%]
Points total	102	-
Points within Guest et al.	61	59.8039
Points within 2-fold	92	90.1961

DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
1344	Cimetidine, 1200 mg, IV, MD OD (2 days)	Alfentanil, IV	1.1005	2.8031	0.39259	1.0067	-	-	Kienlen 1993
1332	Cimetidine, 300 mg, PO, MD QID (1 day)	Alprazolam, PO	1.0071	1.581	0.63703	1.0024	1.0323	0.97108	Abernethy 1983
1340	Cimetidine, 200/400 mg, PO, (200mg): MD TID (17 days); (400mg): OD (17 days)	Alprazolam, PO	1.0148	1.7279	0.58732	1.0083	1.8187	0.55443	Pourbaix 1985
1319	Cimetidine, 300 mg, PO, MD QID (2 days)	Midazolam, IV	1.0091	0.89256	1.1305	1.0001	-	-	Greenblatt 1986
1321	Cimetidine, 300 mg, PO, MD QID (2 days)	Midazolam, PO	1.0497	1.1329	0.92657	1.0312	1.0556	0.97689	Greenblatt 1986
1322	Cimetidine, 800 mg, PO, SD	Midazolam, PO	1.1872	1.4973	0.7929	1.1184	-	-	Martinez 1999
1324	Cimetidine, 400 mg, PO, MD: BID (1 day), OD (1 day)	Midazolam, PO	1.0649	1.3456	0.79137	1.0292	-	-	Fee 1987
1326	Cimetidine, 400 mg, PO, SD	Midazolam, PO	1.0223	1.3649	0.74899	1.0209	1.3732	0.74344	Salonen 1986
1346	Cimetidine, 200/400 mg, PO, (200mg): MD TID (1 day), OD (1 day); (400mg): OD (1 day)	Midazolam, PO	1.0072	2.016	0.49959	1.0063	2.3833	0.42223	Elliott 1984
1334	Cimetidine, 300 mg, PO, MD QID (1 day)	Triazolam, PO	1.2187	1.5429	0.78992	1.1597	1.2041	0.96316	Abernethy 1983
1336	Cimetidine, 300 mg, PO, MD QID (2 days)	Triazolam, PO	1.2202	1.323	0.92231	1.1598	1.3902	0.83426	Friedman 1988
1342	Cimetidine, 200/400 mg, PO, (200mg): MD TID (17 days); (400mg): OD (17 days)	Triazolam, PO	1.2621	2.2013	0.57334	1.191	1.5109	0.78826	Pourbaix 1985
1338	Cimetidine, 300 mg, PO, MD QID (1 day)	Triazolam, intraduodenal	1.1431	1.5455	0.73968	1.087	1.3509	0.80463	Cox 1986
1328	Cimetidine, 300 mg, PO, MD QID (9 days)	Verapamil, IV	1.0025	0.70769	1.4166	1	0.95924	1.0425	Smith 1984
1330	Cimetidine, 300 mg, PO, MD QID (9 days)	Verapamil, PO	1.2595	1.3697	0.91958	1.2168	1.1333	1.0736	Smith 1984
175	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, IV	3.072	2.6667	1.152	1.2413	-	-	Gorski 1998
2027	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, IV	3.0345	3.2	0.94828	1.2413	1.1724	1.0587	Quinney 2008
173	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	9.2129	7.1429	1.2898	3.0765	-	-	Gorski 1998
217	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	7.6986	8.3929	0.91728	2.7413	3.7956	0.72224	Gurley 2006
223	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	7.6986	5.4834	1.404	2.7413	2.1743	1.2608	Gurley 2008a
354	Clarithromycin, 500 mg, PO, MD BID (4 days)	Midazolam, PO	6.0751	5.5556	1.0935	2.6201	-	-	Markert 2013
1099	Clarithromycin, 500 mg, PO, MD BID (5 days)	Midazolam, PO	7.8476	4.84	1.6214	3.1769	2.69	1.181	Pruksaritanont 2017
2030	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	9.3501	8	1.1688	3.1441	2.75	1.1433	Quinney 2008
2004	Clarithromycin, 250 mg, PO, MD BID (3 days)	Midazolam, PO	1.5409	1.9	0.81098	1.2897	1.75	0.73698	van Dyk 2018
469	Clarithromycin, 250 mg, PO, MD BID (5 days)	Midazolam, PO	2.3752	3.5716	0.66503	1.5939	2.44	0.65324	Yeates 1996
1102	Clarithromycin, 500 mg, PO, MD OD (2 days)	Triazolam, PO	3.5788	5.06	0.70727	2.0065	1.968	1.0195	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	1.6889	1.4611	1.1559	1.0269	-	-	Bartkowski 1989
777	Erythromycin, 400 mg, PO, MD TID (10 days)	Alprazolam, PO	1.7606	2.4716	0.71233	1.0761	1.1833	0.9094	Yasui 1996
781	Erythromycin, 500 mg, PO, MD OD (2 days)	Triazolam, PO	3.1252	3.65	0.85621	1.8989	1.768	1.074	Greenblatt 1998a
757	Erythromycin, 333 mg, PO, MD TID (3 days)	Triazolam, PO	3.8755	2.0597	1.8816	2.1096	1.4643	1.4407	Phillips 1986
420	Erythromycin, 500 mg, PO, MD QID (5 days)	Midazolam, IV	2.3598	1.5978	1.4769	1.027	-	-	Swart 2002
368	Erythromycin, 500 mg, PO, MD TID (7 days)	Midazolam, IV	2.0504	1.9619	1.0451	1.0191	-	-	Olkkola 1993
366	Erythromycin, 500 mg, PO, MD TID (7 days)	Midazolam, PO	3.8632	4.0674	0.9498	1.8913	2.7	0.70049	Olkkola 1993
471	Erythromycin, 500 mg, PO, MD TID (3 days)	Midazolam, PO	4.857	3.8137	1.2736	2.2058	2.7114	0.8135	Zimmermann 1996
362	Erythromycin, 200 mg, PO, MD QID (2 days)	Midazolam, PO	1.2862	1.16	1.1088	0.82235	0.90909	0.90459	Okudaira 2007
363	Erythromycin, 200 mg, PO, MD QID (4 days)	Midazolam, PO	1.6222	1.69	0.95989	0.92709	1.2	0.77257	Okudaira 2007

DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
364	Erythromycin, 200 mg, PO, MD QID (7 days)	Midazolam, PO	1.7038	1.69	1.0081	0.94997	1.1727	0.81005	Okudaira 2007
828	Erythromycin, 250 mg, PO, SD	Midazolam, PO	3.5089	1.7178	2.0427	3.2107	-	-	Carls 2014
829	Erythromycin, 1000 mg, PO, SD	Midazolam, PO	4.0666	4.9912	0.81476	3.6262	-	-	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	0.80148	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	0.52213	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	1.0403	1.5	0.69355	1.0018	-	-	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	1.4031	1.66	0.84523	1.2015	1.63	0.73709	Lam 2003
1026	Itraconazole, 200 mg, PO, MD OD (6 days)	Alprazolam, PO	2.1734	2.6627	0.81622	1.0994	1.2868	0.85432	Yasui 1998
378	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, IV	2.2908	3.2258	0.71015	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	3.4801	5.7451	0.60575	1.9612	2.5588	0.76645	Ahonen 1995
58	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	4.8856	7.97	0.613	2.2277	3.12	0.71401	Backman 1998
59	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	1.1255	2.63	0.42796	1.074	1.92	0.55939	Backman 1998
370	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	5.2865	10.8	0.48949	2.2375	3.4	0.65809	Olkkola 1994
377	Itraconazole, 200 mg, PO, SD	Midazolam, PO	4.491	3.4	1.3209	2.1994	1.8	1.2219	Olkkola 1996
379	Itraconazole, 200 mg, PO, MD OD (6 days)	Midazolam, PO	6.2435	6.6	0.94598	2.5663	2.5	1.0265	Olkkola 1996
1097	Itraconazole, 200 mg, PO, MD OD (5 days)	Midazolam, PO	19.3577	7.04	2.7497	4.6652	3.71	1.2575	Prueksaritanont 2017
424	Itraconazole, 50 mg, PO, SD	Midazolam, PO	3.2607	2	1.6304	2.2008	-	-	Templeton 2010
425	Itraconazole, 200 mg, PO, SD	Midazolam, PO	7.6015	4.7	1.6173	3.4395	-	-	Templeton 2010
426	Itraconazole, 400 mg, PO, SD	Midazolam, PO	9.7471	5.4	1.805	3.7303	-	-	Templeton 2010
1078	Itraconazole, 200 mg, PO, SD	Triazolam, PO	4.2175	3.11	1.3561	1.9807	1.41	1.4048	Neuvonen 1996
1079	Itraconazole, 200 mg, PO, SD	Triazolam, PO	5.5922	4.79	1.1675	2.4222	1.76	1.3763	Neuvonen 1996
1080	Itraconazole, 200 mg, PO, SD	Triazolam, PO	2.252	4.63	0.48638	1.668	1.76	0.94774	Neuvonen 1996
1081	Itraconazole, 200 mg, PO, SD	Triazolam, PO	2.0983	3.82	0.54929	1.3854	1.71	0.81018	Neuvonen 1996
1029	Itraconazole, 200 mg, PO, MD OD (4 days)	Triazolam, PO	6.3406	19.0287	0.33321	2.5313	2.6854	0.94259	Varhe 1994
1111	Verapamil, 240 mg, PO, MD OD (7 days)	Midazolam, IV	1.4027	1.4524	0.96581	1.1019	-	-	Wang 2005
1108	Verapamil, 80 mg, PO, MD TID (2 days)	Midazolam, PO	2.0137	2.9167	0.69042	1.4415	1.9692	0.73199	Backman 1994
1116	Verapamil, 240 mg, PO, MD OD (7 days)	Midazolam, PO	1.6228	3.5056	0.46291	1.3473	-	-	Wang 2005
803	Efavirenz, 600 mg, PO, MD OD (19 days)	Alfentanil, IV	0.55982	0.54	1.0367	0.92176	1.0978	0.83962	Kharasch 2012
801	Efavirenz, 600 mg, PO, MD OD (19 days)	Alfentanil, PO	0.23489	0.22	1.0677	0.35697	0.42857	0.83293	Kharasch 2012
2045	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.83032	0.78538	1.0572	0.932	-	-	Mikus 2017
2048	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.78652	0.77712	1.0121	0.91032	-	-	Mikus 2017
2050	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.85803	0.9375	0.91523	0.94251	-	-	Mikus 2017
2052	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.9126	0.85377	1.0689	0.96553	-	-	Mikus 2017
2054	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.94979	0.92217	1.03	0.98054	-	-	Mikus 2017
2041	Efavirenz, 400 mg, PO, MD OD (14 days)	Midazolam, PO	0.11446	0.1027	1.1145	0.23822	0.1806	1.319	Katzenmaier 2010

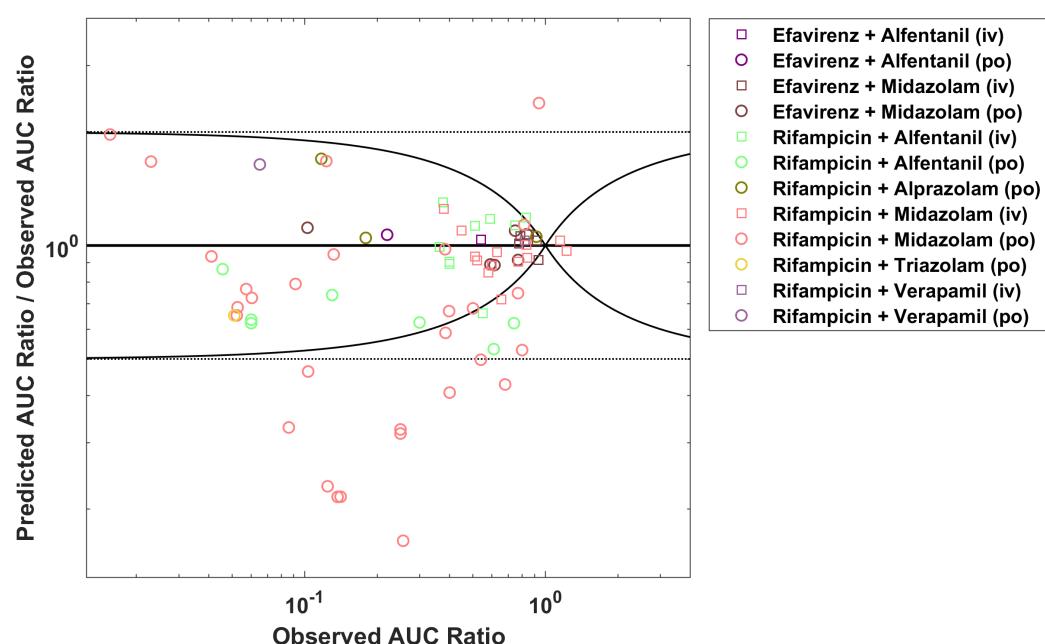
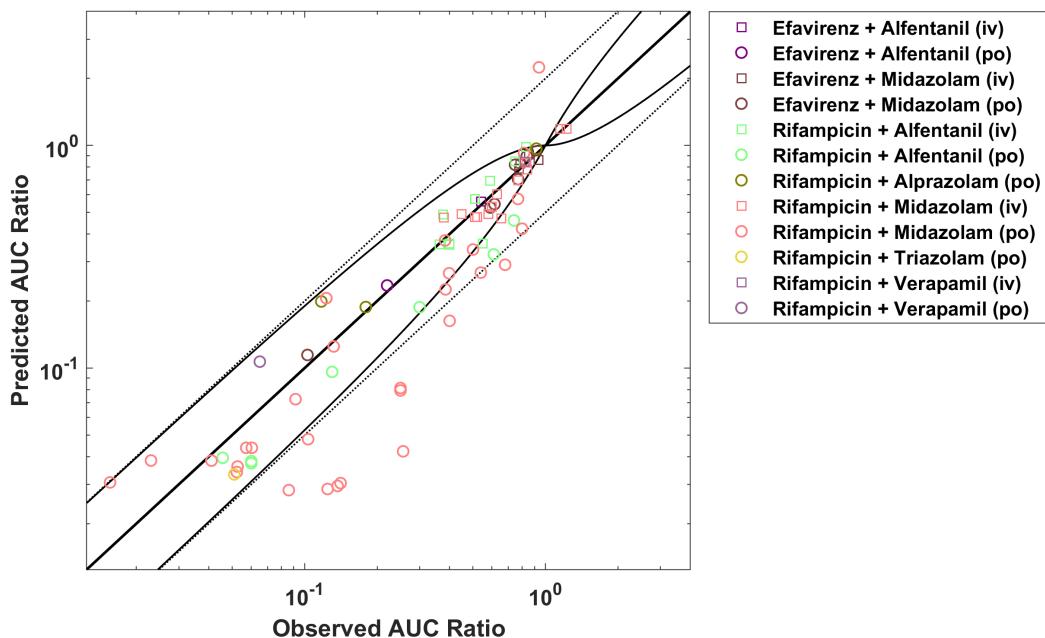
DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
2044	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.52606	0.59055	0.8908	0.64631	-	-	Mikus 2017
2047	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.54494	0.61417	0.88727	0.65525	-	-	Mikus 2017
2049	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.70464	0.76968	0.91549	0.78426	-	-	Mikus 2017
2051	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.81886	0.74803	1.0947	0.87153	-	-	Mikus 2017
2053	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.89582	0.83661	1.0708	0.92679	-	-	Mikus 2017
278	Rifampicin, 600 mg, PO, MD OD (5 days)	Alfentanil, IV	0.3601	0.36301	0.99197	0.89711	-	-	Kharasch 1997
283	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.48846	0.375	1.3026	1.2013	1.0033	1.1974	Kharasch 2004
299	Rifampicin, 5 mg, PO, MD OD (6 days)	Alfentanil, IV	0.98366	0.83	1.1851	1.309	1.0392	1.2596	Kharasch 2011
300	Rifampicin, 10 mg, PO, MD OD (6 days)	Alfentanil, IV	0.84761	0.75	1.1301	1.2933	1.049	1.2329	Kharasch 2011
301	Rifampicin, 25 mg, PO, MD OD (6 days)	Alfentanil, IV	0.69377	0.59	1.1759	1.2669	1	1.2669	Kharasch 2011
302	Rifampicin, 75 mg, PO, MD OD (6 days)	Alfentanil, IV	0.5757	0.51	1.1288	1.2353	1.0294	1.2	Kharasch 2011
763	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.36218	0.4	0.90545	0.8986	-	-	Kharasch 2011b
767	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.35793	0.4	0.89482	0.89649	-	-	Kharasch 2011b
391	Rifampicin, 600 mg, PO, MD OD (5 days)	Alfentanil, IV	0.36327	0.55	0.66049	0.89925	-	-	Phimmasone 2001
288	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.039489	0.045631	0.86539	0.087599	0.11111	0.78839	Kharasch 2004
309	Rifampicin, 5 mg, PO, MD OD (6 days)	Alfentanil, PO	0.46042	0.74	0.62219	0.59552	0.86275	0.69026	Kharasch 2011
310	Rifampicin, 10 mg, PO, MD OD (6 days)	Alfentanil, PO	0.32399	0.61	0.53113	0.46822	0.86275	0.54271	Kharasch 2011
311	Rifampicin, 25 mg, PO, MD OD (6 days)	Alfentanil, PO	0.18749	0.3	0.62496	0.31342	0.4902	0.63937	Kharasch 2011
312	Rifampicin, 75 mg, PO, MD OD (6 days)	Alfentanil, PO	0.096053	0.13	0.73887	0.18438	0.2549	0.72333	Kharasch 2011
771	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.038141	0.06	0.63568	0.084356	-	-	Kharasch 2011b
775	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.037329	0.06	0.62215	0.083078	-	-	Kharasch 2011b
2009	Rifampicin, 450 mg, PO, MD OD (5 days)	Alprazolam, PO	0.18786	0.17935	1.0475	0.67803	-	-	Gashaw 2003
2010	Rifampicin, 450 mg, PO, MD OD (5 days)	Alprazolam, PO	0.96731	0.91667	1.0552	0.99554	-	-	Gashaw 2003
1001	Rifampicin, 450 mg, PO, MD OD (4 days)	Alprazolam, PO	0.19908	0.11726	1.6978	0.68993	0.63816	1.0811	Schmider 1999
179	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, IV	0.49138	0.44898	1.0944	0.75231	-	-	Gorski 2003
276	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, IV	0.47391	0.37931	1.2494	0.90497	-	-	Kharasch 1997
280	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, IV	0.47603	0.52113	0.91347	0.90867	1.01	0.89971	Kharasch 2004
294	Rifampicin, 5 mg, PO, MD OD (6 days)	Midazolam, IV	0.77983	0.84	0.92837	0.98009	1.0323	0.94946	Kharasch 2011
295	Rifampicin, 10 mg, PO, MD OD (6 days)	Midazolam, IV	0.69792	0.77	0.90639	0.96805	1.0645	0.90938	Kharasch 2011
296	Rifampicin, 25 mg, PO, MD OD (6 days)	Midazolam, IV	0.60418	0.63	0.95902	0.94912	0.83871	1.1316	Kharasch 2011
297	Rifampicin, 75 mg, PO, MD OD (6 days)	Midazolam, IV	0.53121	0.6	0.88536	0.9285	1.3226	0.70204	Kharasch 2011
2036	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.1844	1.15	1.0299	2.257	-	-	Kim 2018
342	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, IV	0.47082	0.65501	0.71881	0.90385	1.106	0.81725	Link 2008
389	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, IV	0.47629	0.51	0.93391	0.9071	-	-	Phimmasone 2001
1092	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.1844	1.15	1.0299	2.257	-	-	Shin 2013
1095	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.1844	1.225	0.96686	2.257	1.775	1.2716	Shin 2016
422	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, IV	0.49138	0.57947	0.84799	0.75244	-	-	Szalat 2007
202	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	0.83601	0.83333	1.0032	1.892	-	-	Yu 2004
54	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.038355	0.041	0.9355	0.098471	0.061818	1.5929	Backman 1996
56	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.038393	0.023	1.6693	0.09847	0.054	1.8235	Backman 1998

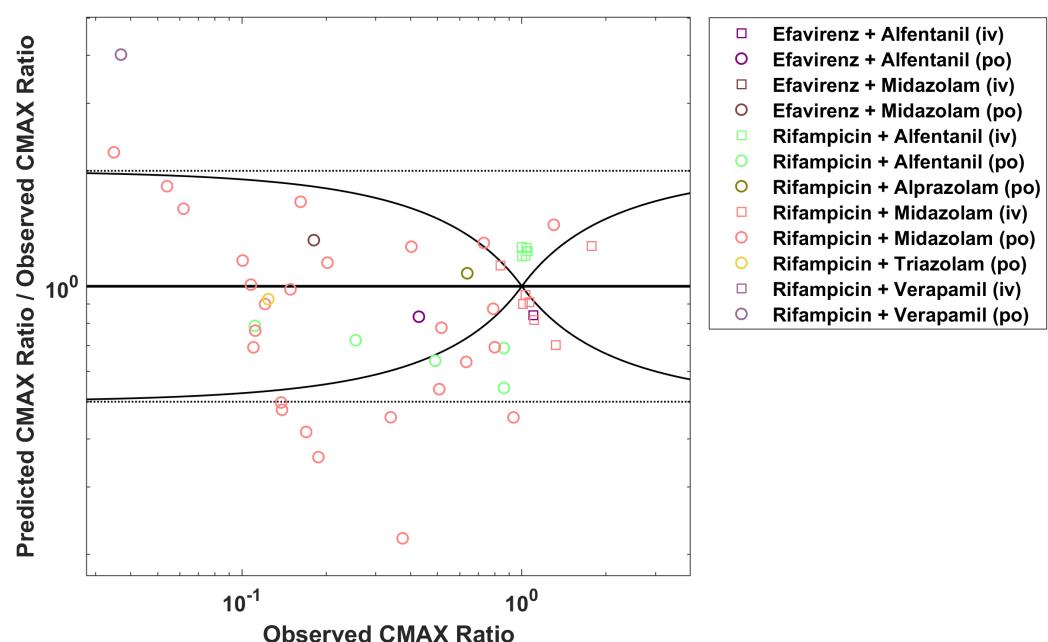
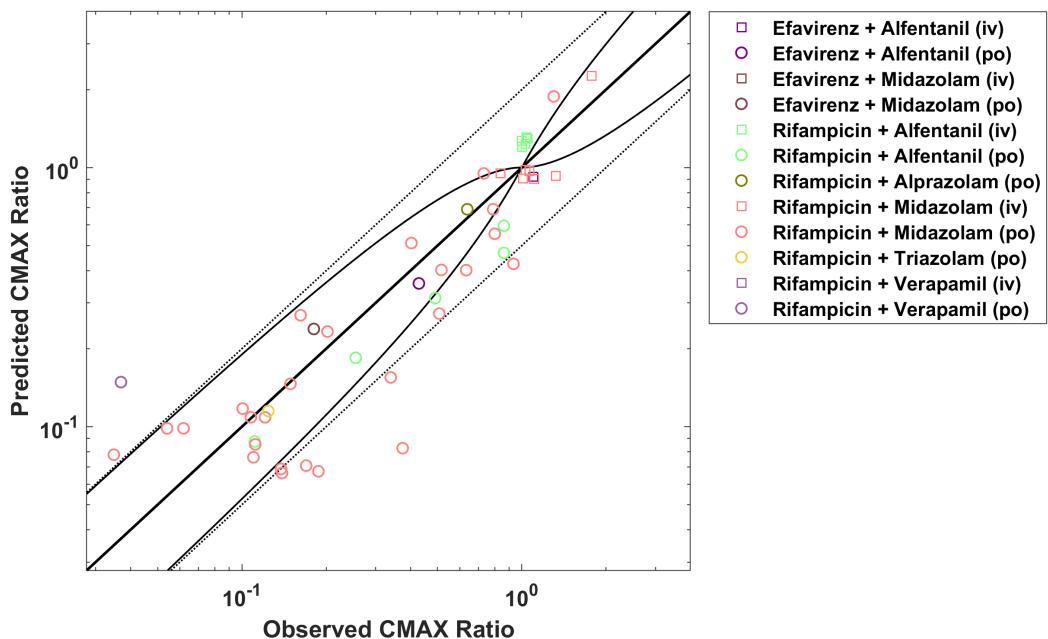
DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
57	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.12498	0.132	0.94684	0.23277	0.202	1.1523	Backman 1998
1355	Rifampicin, 10 mg, PO, MD OD (14 days)	Midazolam, PO	0.34051	0.5	0.68103	0.47531	-	-	Björkhem-Bergman 2013
1356	Rifampicin, 20 mg, PO, MD OD (14 days)	Midazolam, PO	0.22558	0.38462	0.5865	0.35016	-	-	Björkhem-Bergman 2013
1357	Rifampicin, 100 mg, PO, MD OD (14 days)	Midazolam, PO	0.079274	0.25	0.3171	0.15454	-	-	Björkhem-Bergman 2013
1362	Rifampicin, 600 mg, PO, MD OD (11 days)	Midazolam, PO	0.030393	0.141	0.21555	0.068682	0.138	0.4977	Chattopadhyay 2018
113	Rifampicin, 600 mg, PO, MD OD (9 days)	Midazolam, PO	0.028605	0.12449	0.22978	0.070705	0.16957	0.41698	Chung 2006
132	Rifampicin, 450 mg, PO, MD OD (5 days)	Midazolam, PO	0.034083	0.052239	0.65245	0.085451	0.11154	0.76611	Eap 2004
177	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, PO	0.047872	0.10335	0.46319	0.11734	0.10056	1.1669	Gorski 2003
215	Rifampicin, 300 mg, PO, MD BID (7 days)	Midazolam, PO	0.043798	0.057161	0.76622	0.10865	0.12092	0.89854	Gurley 2006
221	Rifampicin, 300 mg, PO, MD BID (7 days)	Midazolam, PO	0.043798	0.060317	0.72612	0.10865	0.10762	1.0095	Gurley 2008a
286	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, PO	0.036086	0.052632	0.68564	0.076159	0.10989	0.69305	Kharasch 2004
304	Rifampicin, 5 mg, PO, MD OD (6 days)	Midazolam, PO	0.42238	0.8	0.52798	0.55484	0.8	0.69355	Kharasch 2011
305	Rifampicin, 10 mg, PO, MD OD (6 days)	Midazolam, PO	0.29096	0.68	0.42788	0.42476	0.93333	0.4551	Kharasch 2011
306	Rifampicin, 25 mg, PO, MD OD (6 days)	Midazolam, PO	0.16288	0.4	0.40721	0.2731	0.50667	0.53901	Kharasch 2011
307	Rifampicin, 75 mg, PO, MD OD (6 days)	Midazolam, PO	0.081286	0.25	0.32514	0.15483	0.34	0.45539	Kharasch 2011
344	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, PO	0.030622	0.015549	1.9694	0.077909	0.034865	2.2346	Link 2008
1350	Rifampicin, 2 mg, PO, MD OD (18 days)	Midazolam, PO	0.57479	0.769	0.74746	0.68995	0.79	0.87336	Lutz 2018a
1351	Rifampicin, 10 mg, PO, MD OD (18 days)	Midazolam, PO	0.26655	0.398	0.66973	0.40237	0.516	0.77979	Lutz 2018a
1352	Rifampicin, first 10, then 75 mg, PO, MD OD (18 days 10 mg, then 18 days 75 mg)	Midazolam, PO	0.072422	0.0916	0.79063	0.14624	0.149	0.98145	Lutz 2018a
1353	Rifampicin, first 2, then 600 mg, PO, MD OD (18 days 2 mg, then 18 days 600 mg)	Midazolam, PO	0.028266	0.0859	0.32906	0.066198	0.139	0.47624	Lutz 2018a
1098	Rifampicin, 600 mg, PO, SD	Midazolam, PO	2.2431	0.94	2.3863	1.8802	1.3	1.4463	Prueksaritanont 2017
392	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.20598	0.123	1.6747	0.26909	0.162	1.661	Reitman 2011
393	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.37428	0.383	0.97724	0.51111	0.403	1.2683	Reitman 2011
394	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.92472	0.815	1.1346	0.94839	0.731	1.2974	Reitman 2011
2002	Rifampicin, 300 mg, PO, MD OD (7 days)	Midazolam, PO	0.042234	0.25641	0.16471	0.08256	0.375	0.22016	van Dyk 2018
204	Rifampicin, 10 mg, PO, MD OD (22 days)	Midazolam, PO	0.26829	0.539	0.49776	0.40169	0.63265	0.63493	Wiesinger 2020
205	Rifampicin, 600 mg, PO, MD OD (22 days)	Midazolam, PO	0.02951	0.137	0.2154	0.067236	0.18755	0.35849	Wiesinger 2020
1004	Rifampicin, 600 mg, PO, MD OD (5 days)	Triazolam, PO	0.033262	0.051	0.65219	0.11484	0.12414	0.9251	Vililika 1997
2056	Rifampicin, 600 mg, PO, MD OD (13 days)	Verapamil, IV	0.84443	0.81865	1.0315	0.97765	-	-	Barbarash 1988
2058	Rifampicin, 600 mg, PO, MD OD (15 days)	Verapamil, PO	0.1068	0.06511	1.6402	0.14856	0.036961	4.0193	Barbarash 1988
1398	Fluconazole, 400 mg, IV, SD	Alfentanil, IV	2.2141	2.07	1.0696	1.0123	1.2	0.84357	Palkama 1998
1399	Fluconazole, 400 mg, PO, SD	Alfentanil, IV	2.1087	1.97	1.0704	1.0079	1.04	0.96911	Palkama 1998
1392	Fluconazole, 400 mg, IV, SD	Midazolam, PO	3.1243	3.08	1.0144	2.0888	1.786	1.1696	Ahonen 1997
1393	Fluconazole, 400 mg, PO, SD	Midazolam, PO	3.4147	3.41	1.0014	2.1885	2.296	0.95317	Ahonen 1997
380	Fluconazole, 400 mg, PO, SD	Midazolam, PO	2.7119	2.5	1.0847	2.1899	2.5	0.87595	Olkkola 1996
382	Fluconazole, 400/200 mg, PO, MD OD (6 days)	Midazolam, PO	4.2031	3.6	1.1675	2.2455	1.7	1.3209	Olkkola 1996
381	Fluconazole, 400/200 mg, PO, MD OD (4 days)	Midazolam, IV	2.1349	2.0408	1.0461	0.31654	-	-	Olkkola 1996

DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
1394	Fluconazole, 50 mg, PO, MD for 4 days	Triazolam, PO	1.7898	1.587	1.1278	1.3731	1.467	0.936	Varhe 1996c
1395	Fluconazole, 100 mg, PO, MD for 4 days	Triazolam, PO	2.7152	1.99	1.3644	1.7603	1.4	1.2574	Varhe 1996c
1396	Fluconazole, 200 mg, PO, MD for 4 days	Triazolam, PO	4.1405	3.652	1.1338	2.1573	2.33	0.92588	Varhe 1996c

Mechanism

Induction





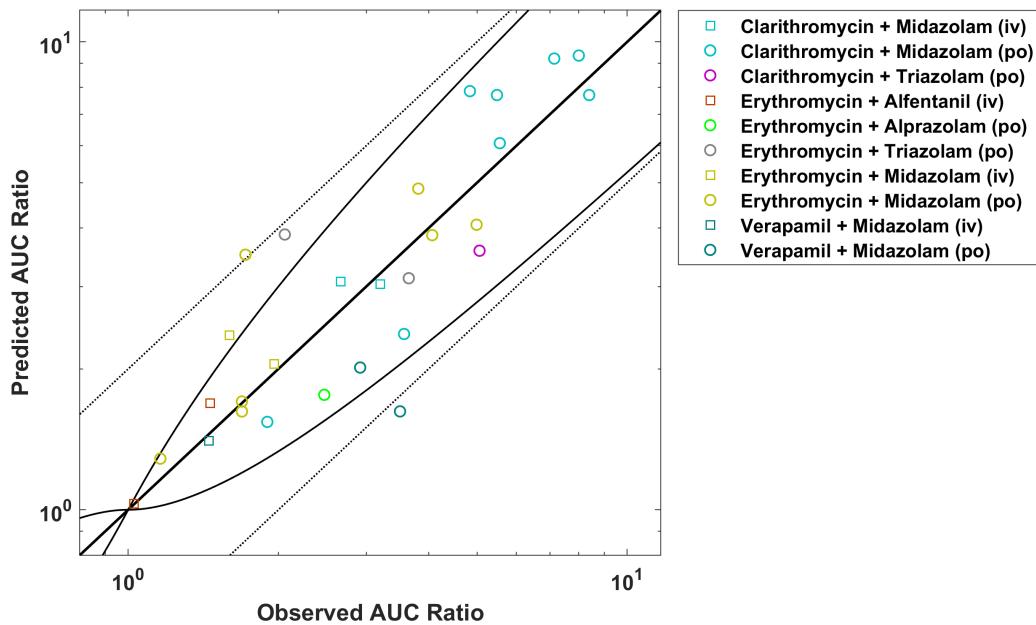
GMFE (AUC) = 1.432114

GMFE (CMAX) = 1.471937

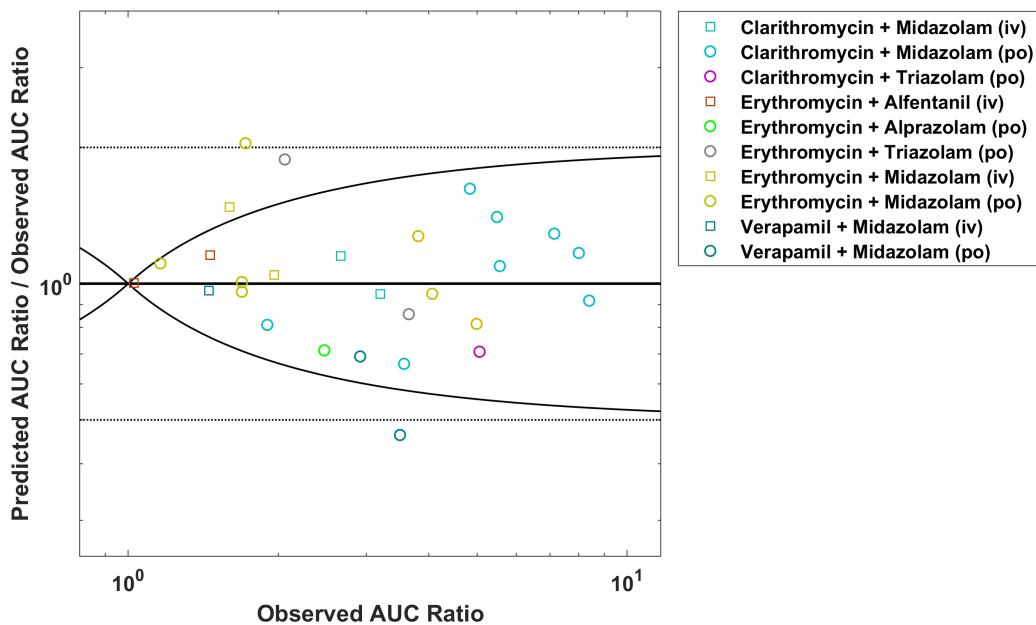
	AUC	Number	Ratio [%]
Points total		78	-
Points within Guest et al.		57	73.0769
Points within 2-fold		66	84.6154

CMAX	Number	Ratio [%]
Points total	49	-
Points within Guest et al.	21	42.8571
Points within 2-fold	40	81.6327

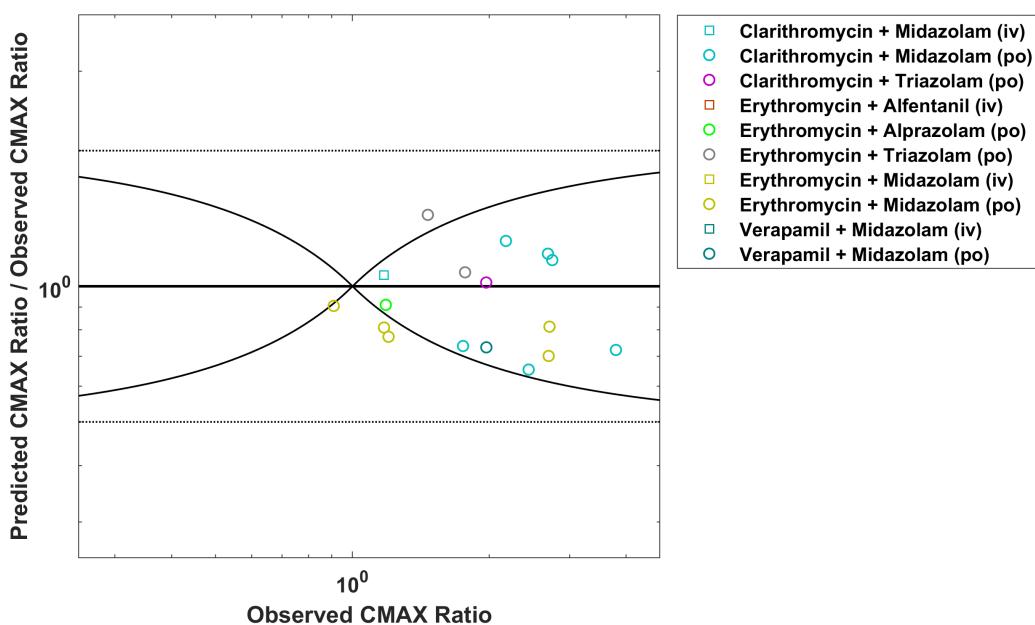
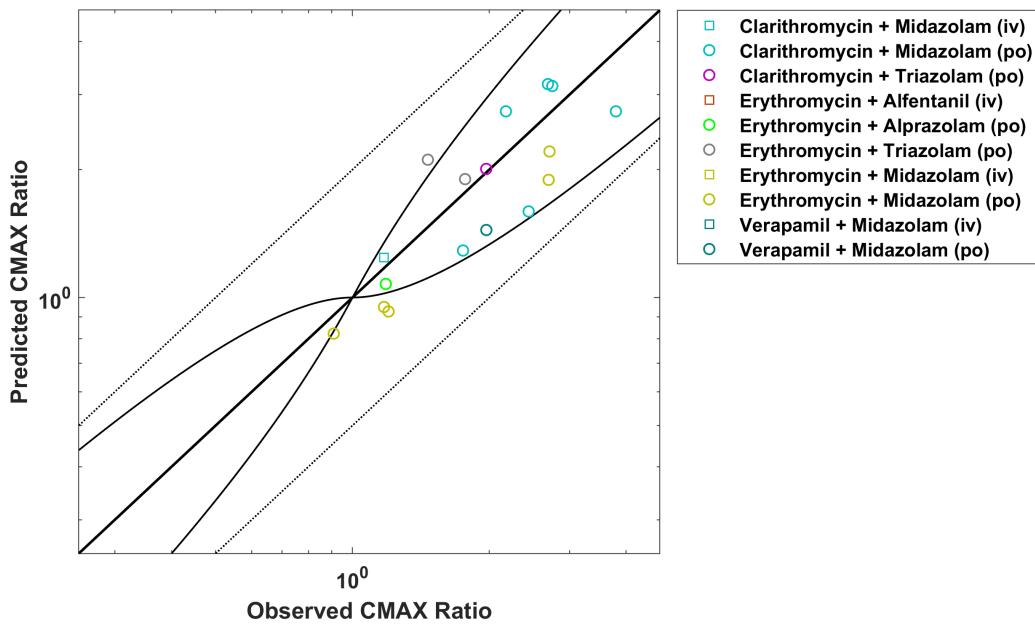
Mechanism based Inactivation



CYP3A4 DDI Mechanism based Inactivation



CYP3A4 DDI Mechanism based Inactivation



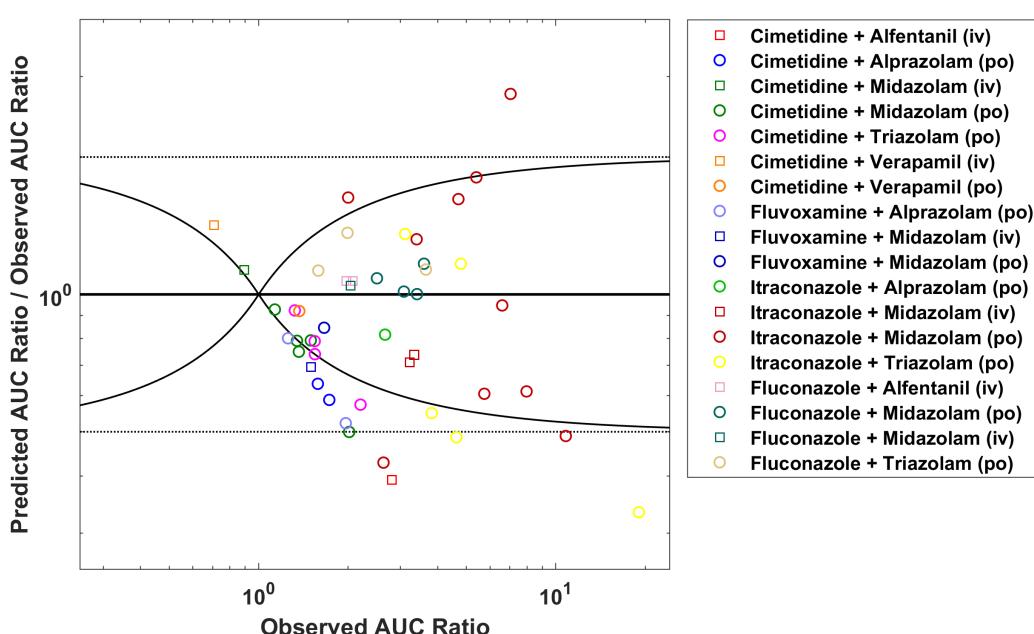
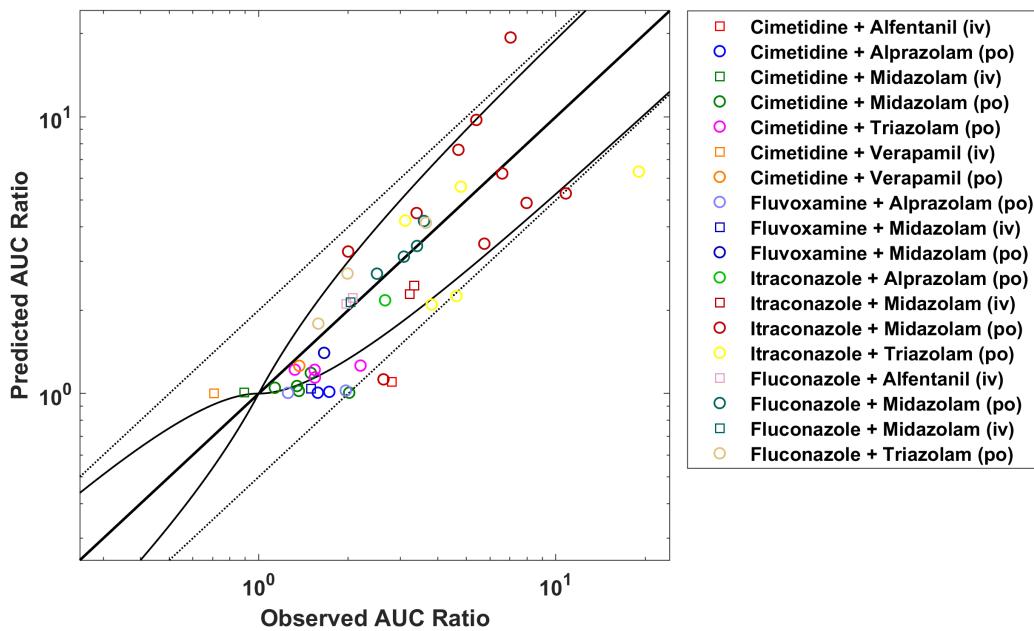
GMFE (AUC) = 1.275619

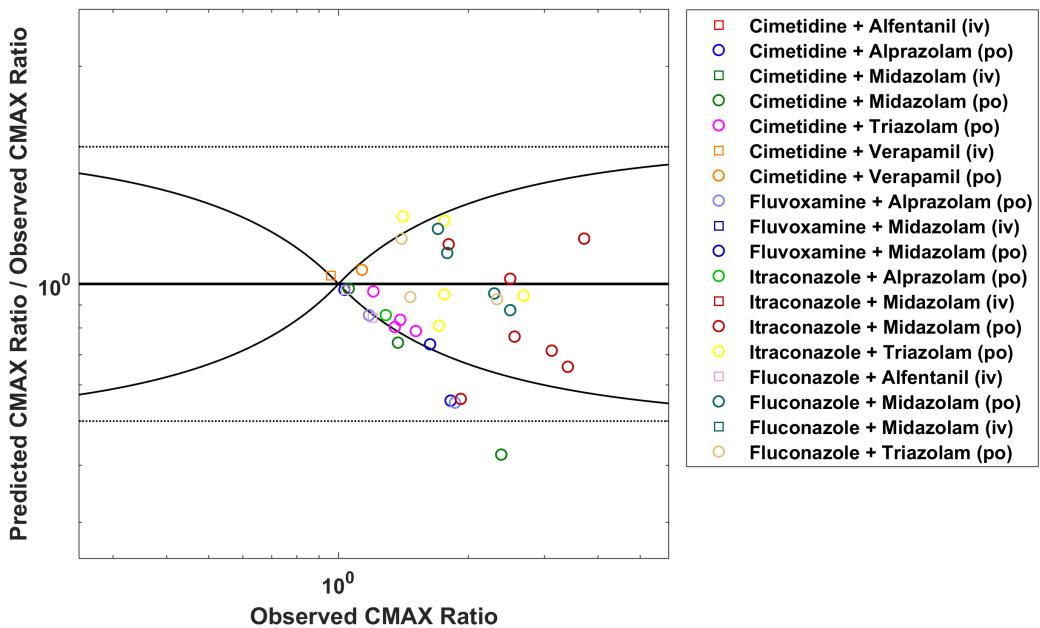
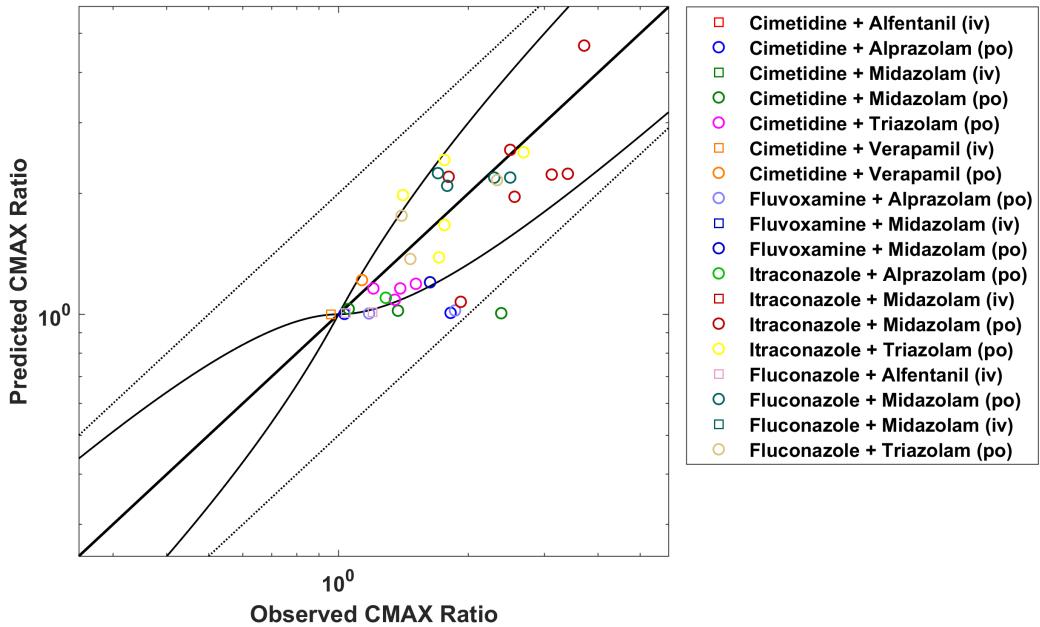
GMFE (CMAX) = 1.238745

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

Reversible Inhibition





GMFE (AUC) = 1.428276

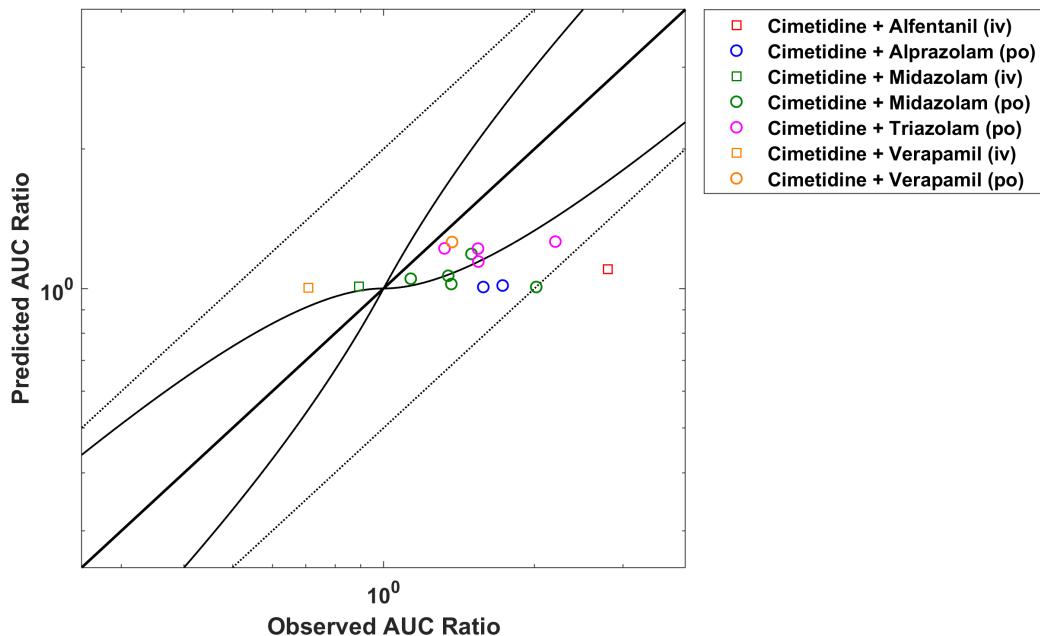
GMFE (CMAX) = 1.250150

	AUC	Number	Ratio [%]
Points total	47	-	
Points within Guest et al.	28	59.5745	
Points within 2-fold	40	85.1064	

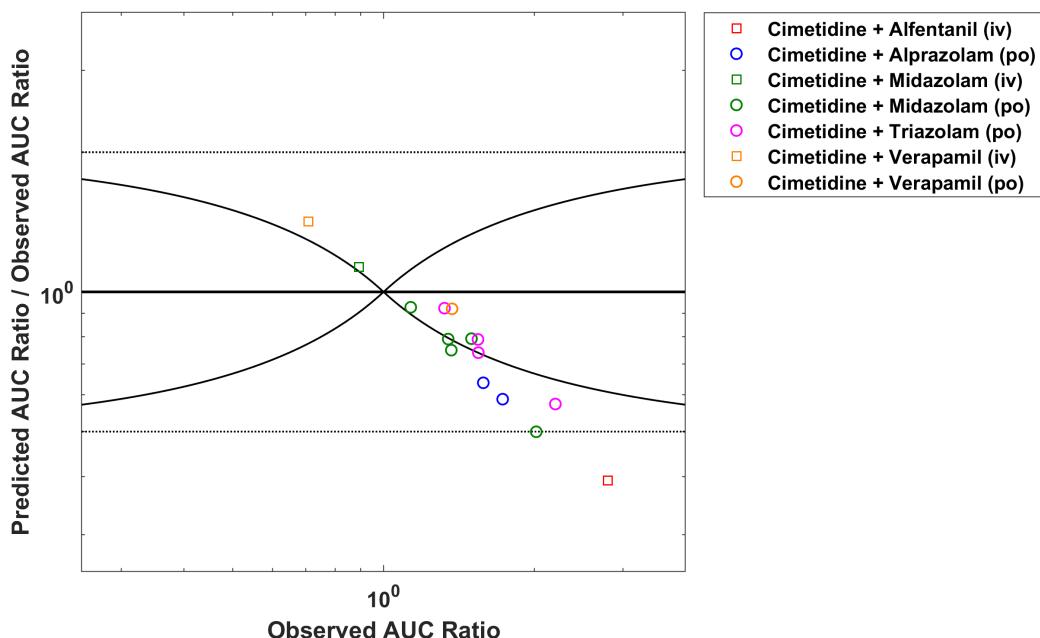
CMAX	Number	Ratio [%]
Points total	36	-
Points within Guest et al.	27	75
Points within 2-fold	35	97.2222

Perpetrator

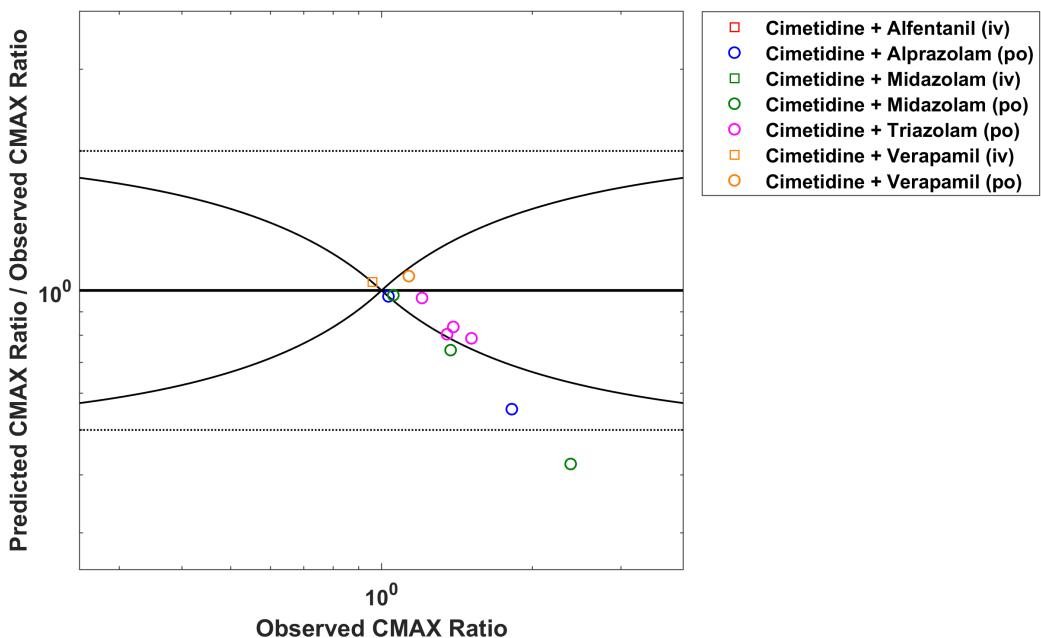
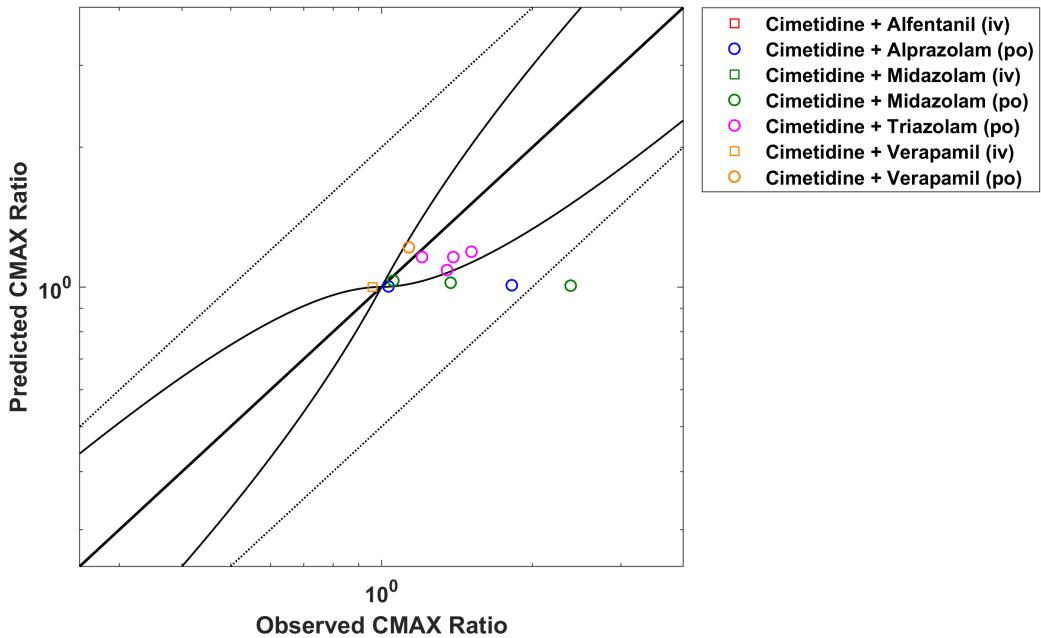
Cimetidine



CYP3A4 DDI Cimetidine



CYP3A4 DDI Cimetidine



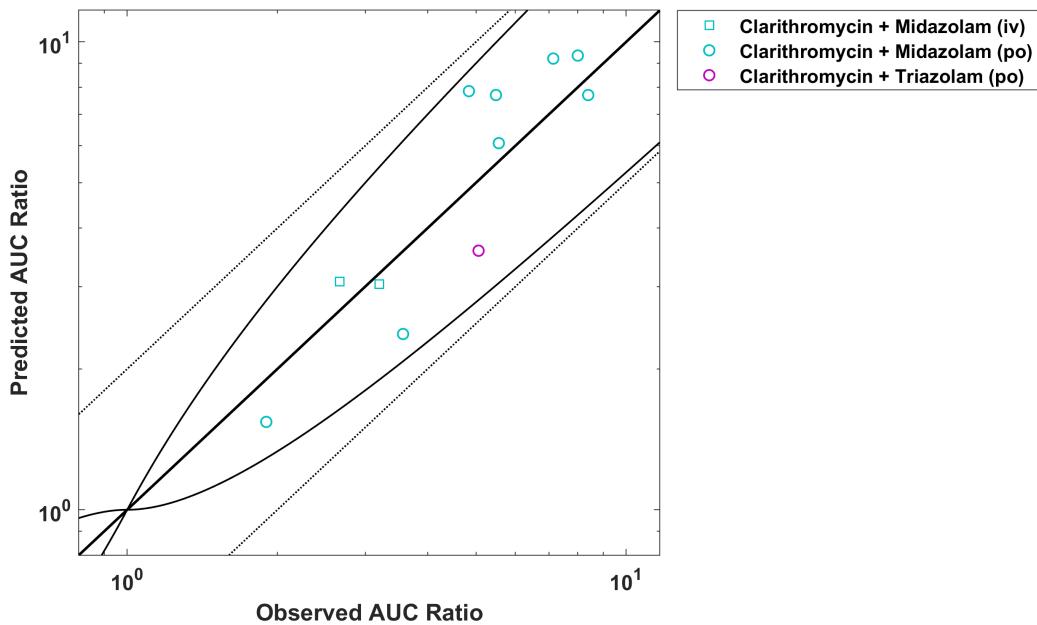
GMFE (AUC) = 1.411777

GMFE (CMAX) = 1.265247

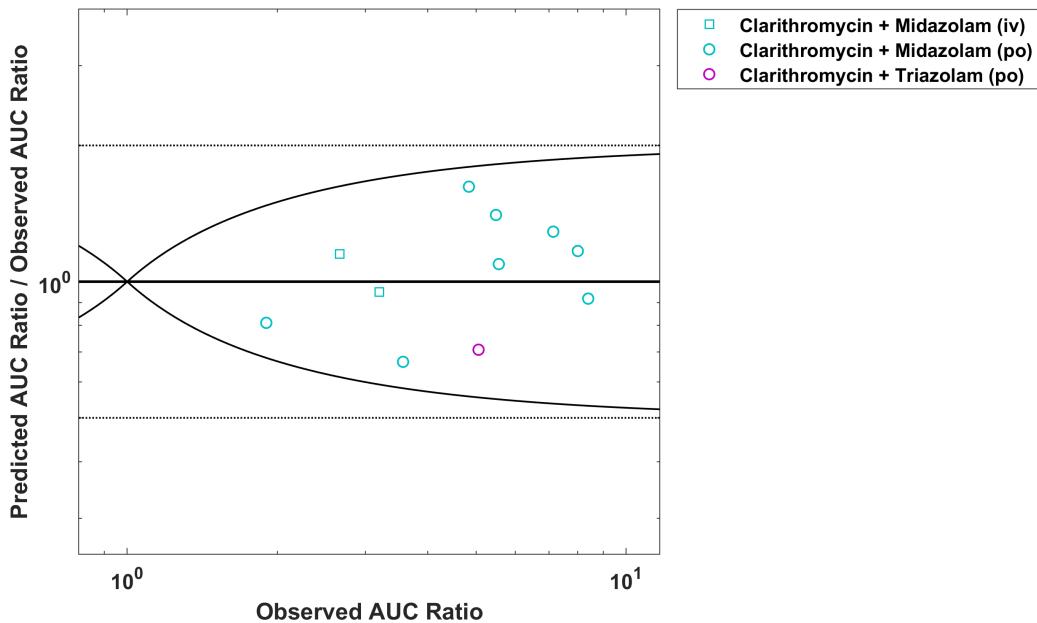
	AUC	Number	Ratio [%]
Points total		15	-
Points within Guest et al.		6	40
Points within 2-fold		13	86.6667

CMAX	Number	Ratio [%]
Points total	11	-
Points within Guest et al.	7	63.6364
Points within 2-fold	10	90.9091

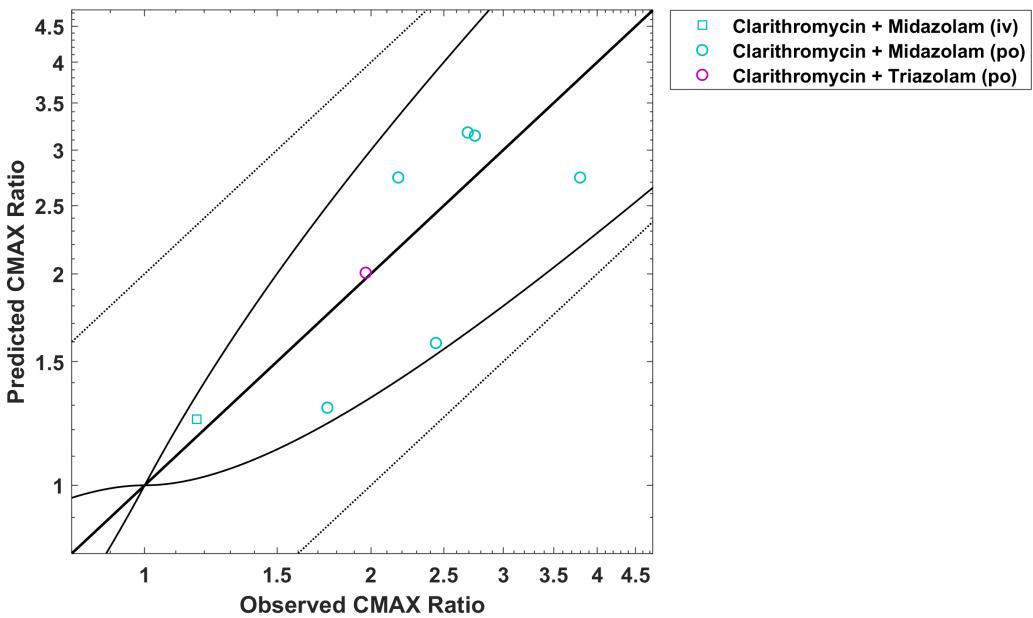
Clarithromycin



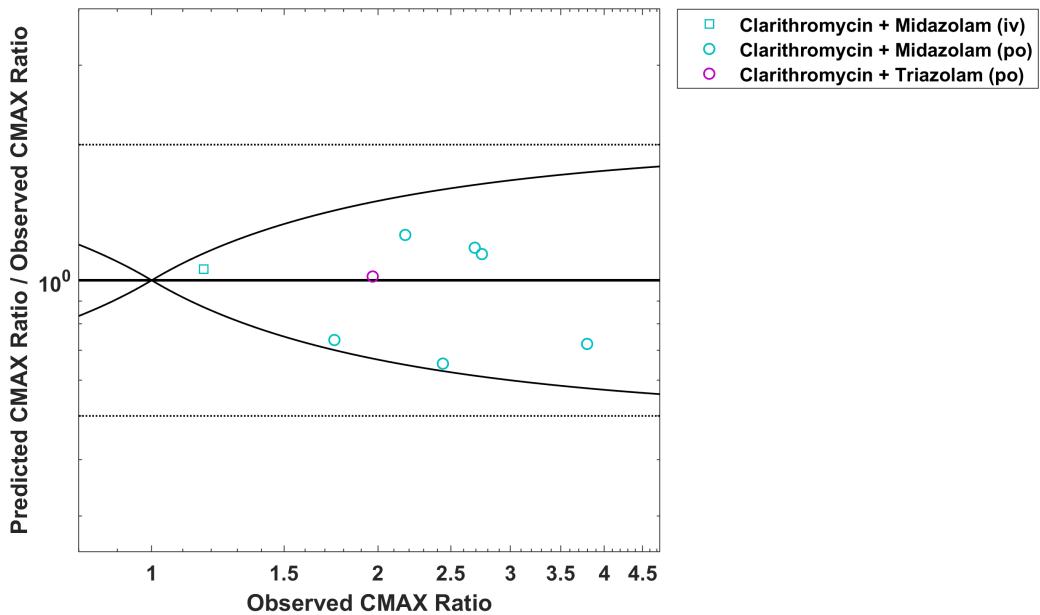
CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin

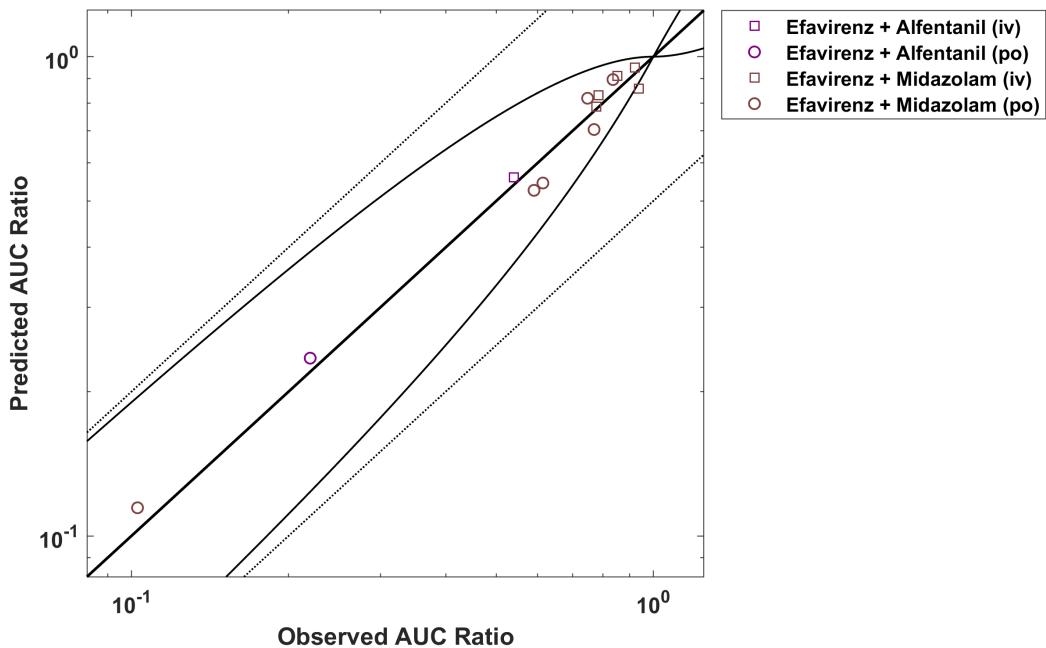
GMFE (AUC) = 1.262860

GMFE (CMAX) = 1.231344

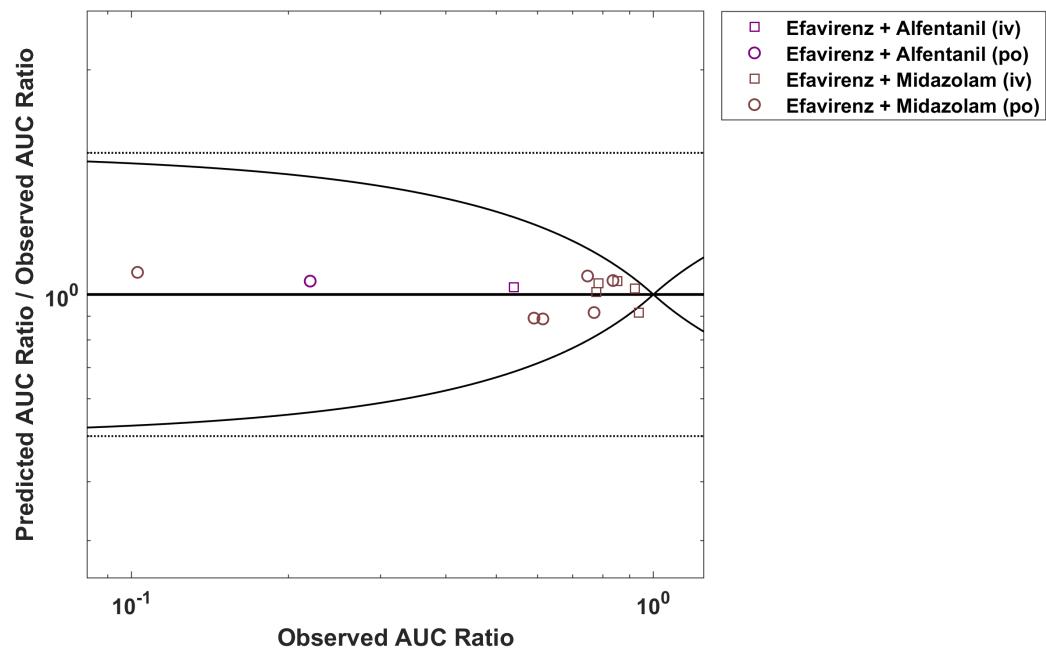
AUC	Number	Ratio [%]
Points total	11	-
Points within Guest et al.	11	100
Points within 2-fold	11	100

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

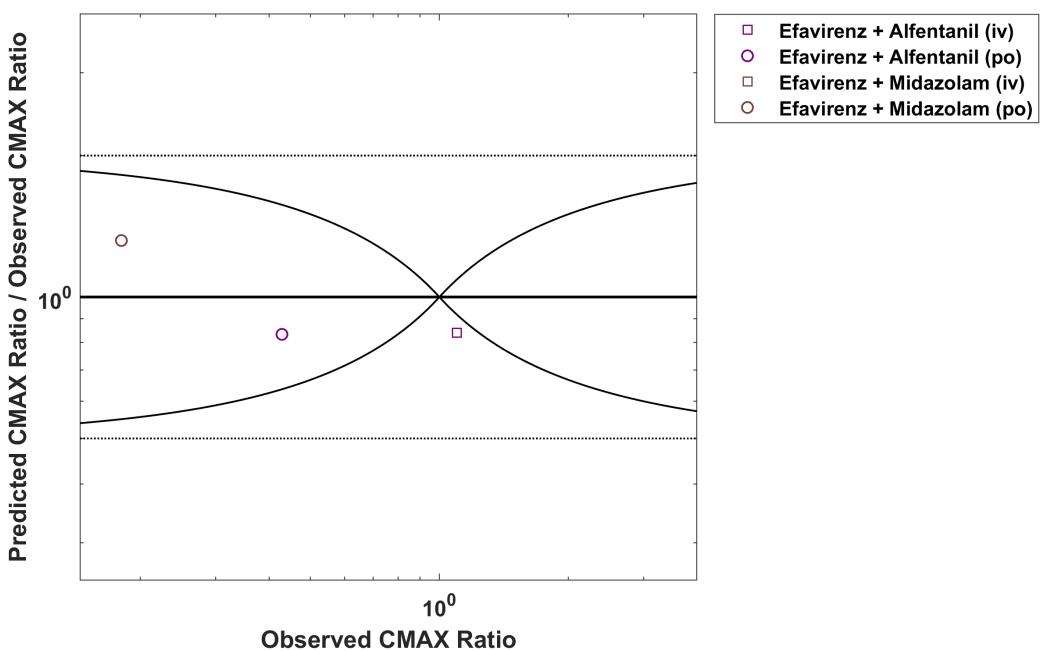
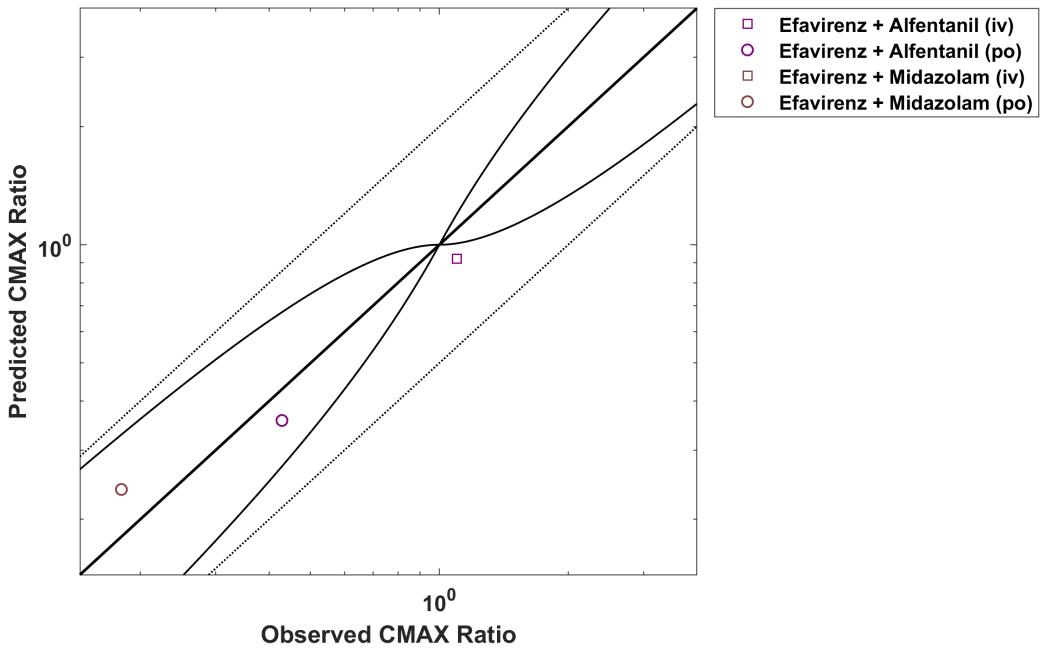
Efavirenz



CYP3A4 DDI Efavirenz



CYP3A4 DDI Efavirenz



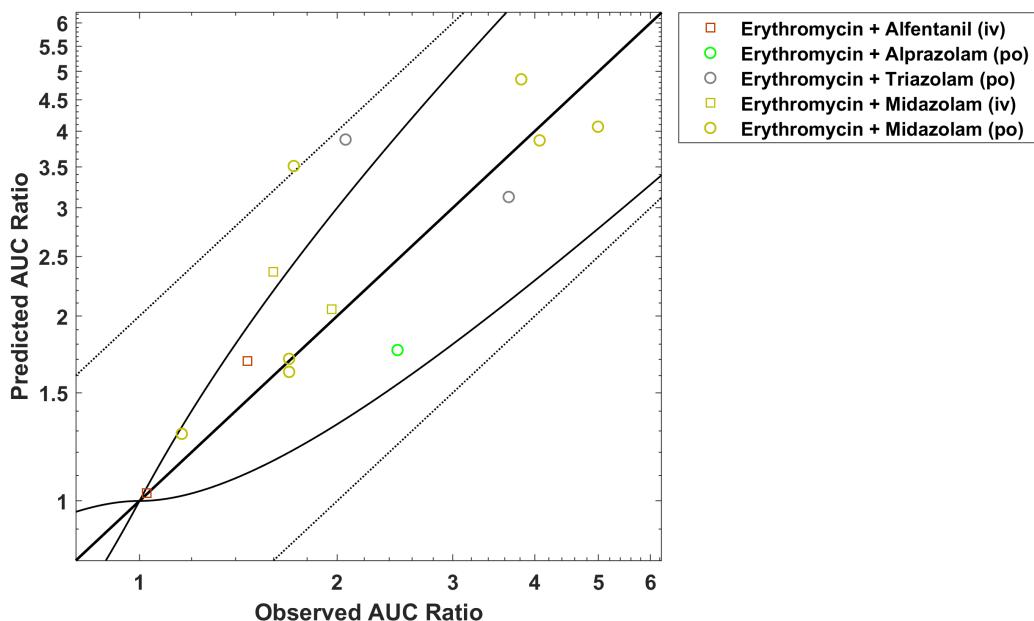
GMFE (AUC) = 1.075376

GMFE (CMAX) = 1.235531

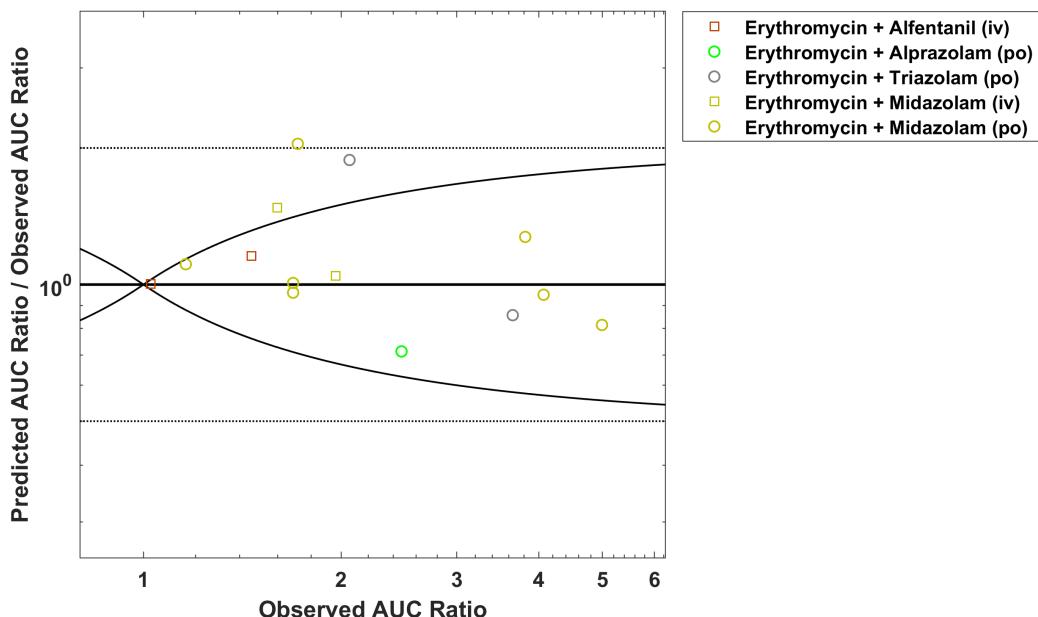
AUC	Number	Ratio [%]
Points total	13	-
Points within Guest et al.	12	92.3077
Points within 2-fold	13	100

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

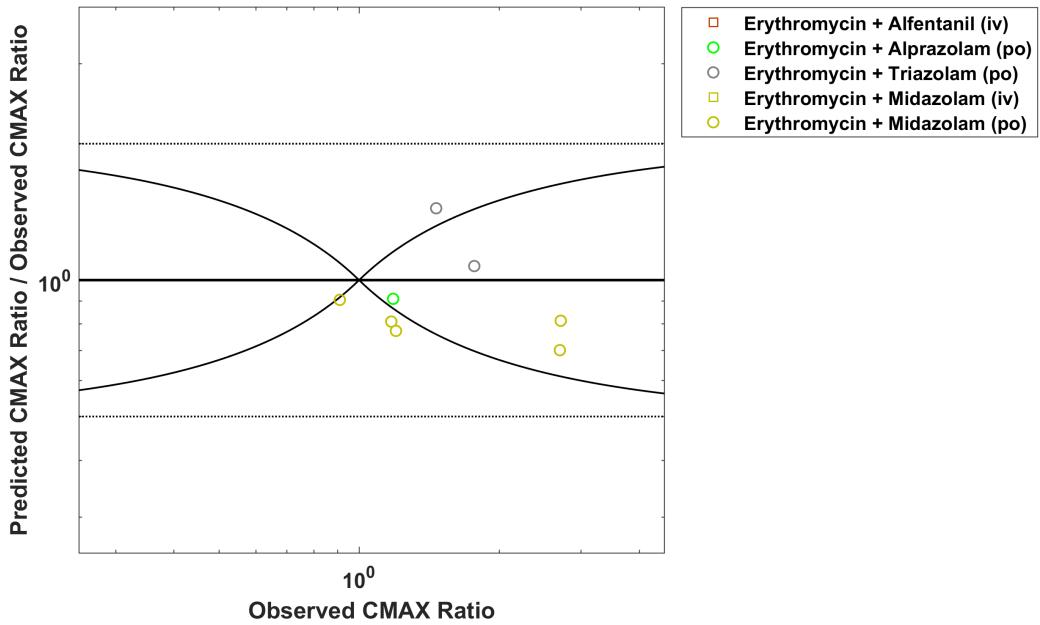
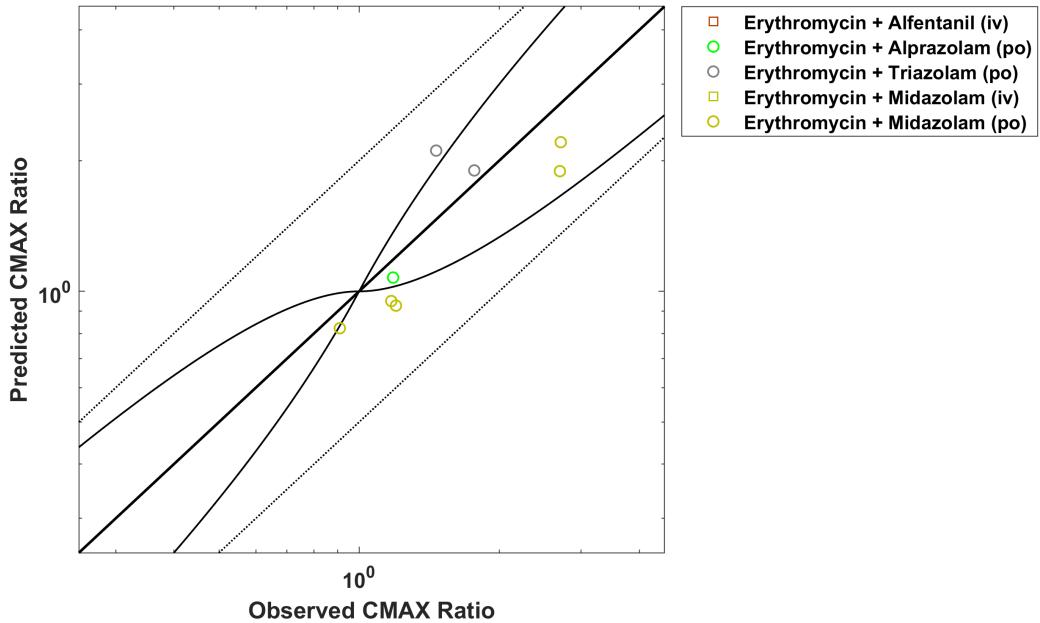
Erythromycin



CYP3A4 DDI Erythromycin



CYP3A4 DDI Erythromycin



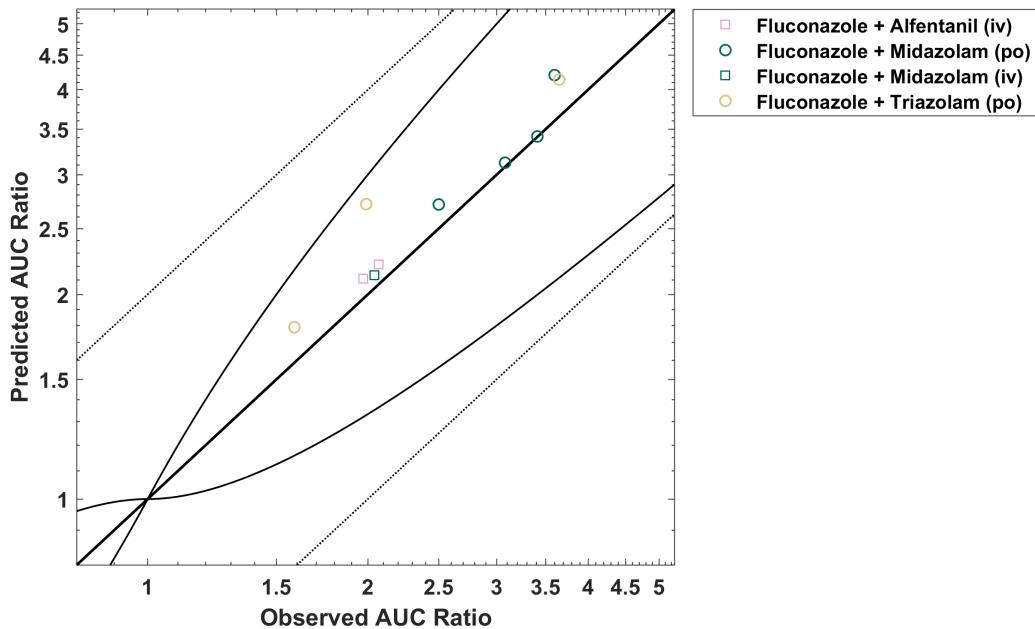
GMFE (AUC) = 1.245494

GMFE (CMAX) = 1.231033

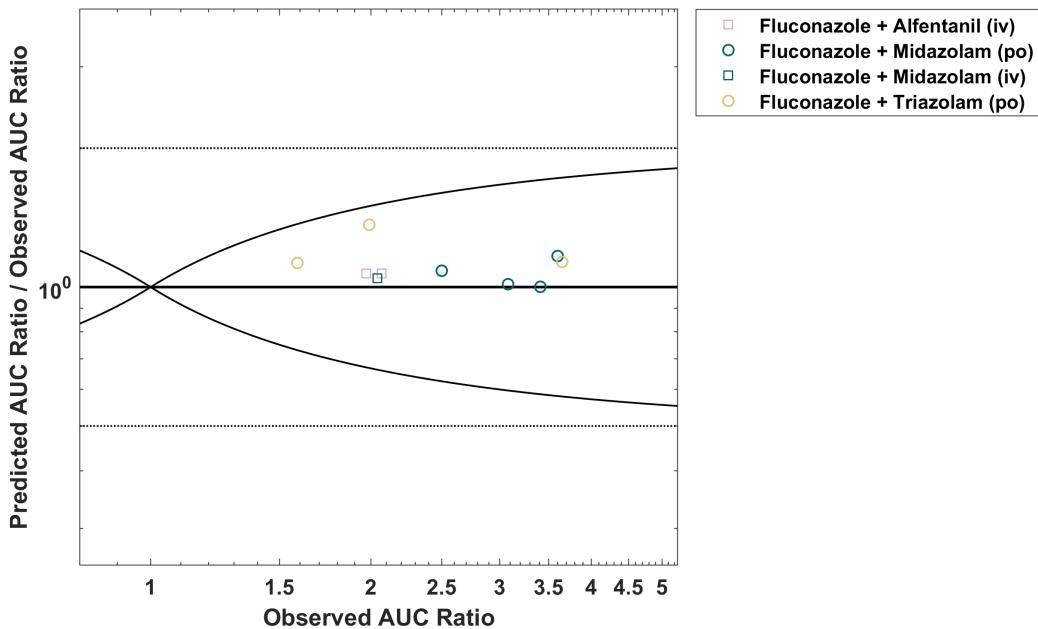
AUC	Number	Ratio [%]
Points total	14	-
Points within Guest et al.	11	78.5714
Points within 2-fold	13	92.8571

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

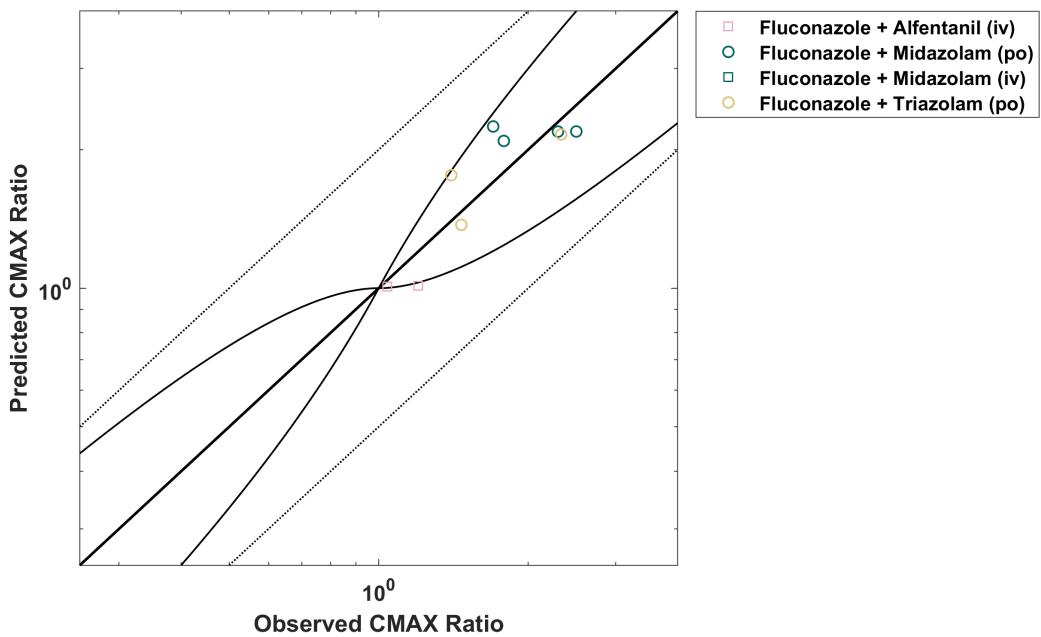
Fluconazole



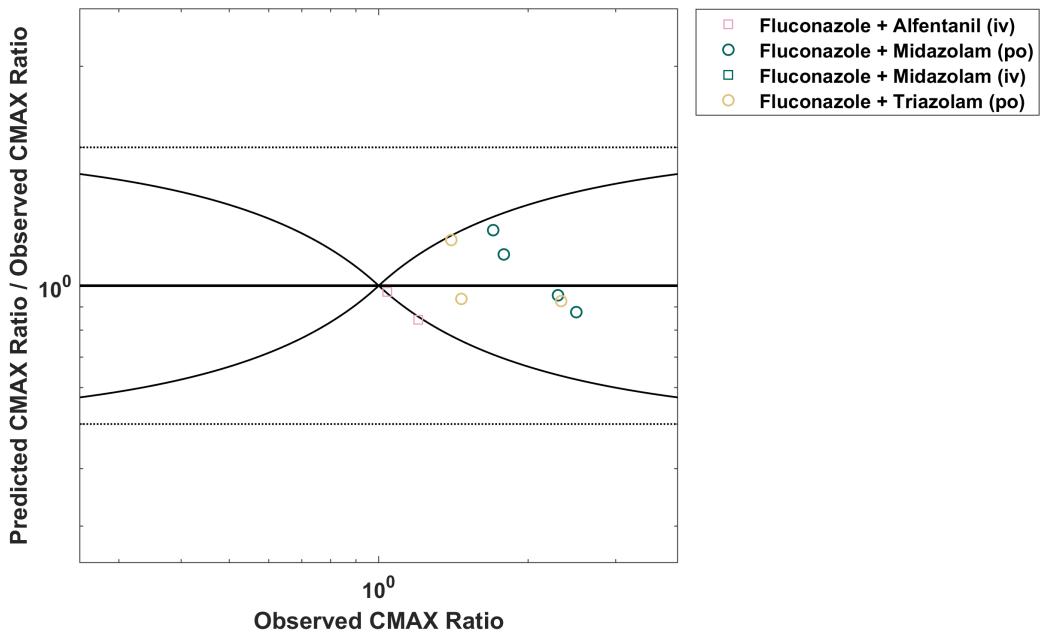
CYP3A4 DDI Fluconazole



CYP3A4 DDI Fluconazole



CYP3A4 DDI Fluconazole



CYP3A4 DDI Fluconazole

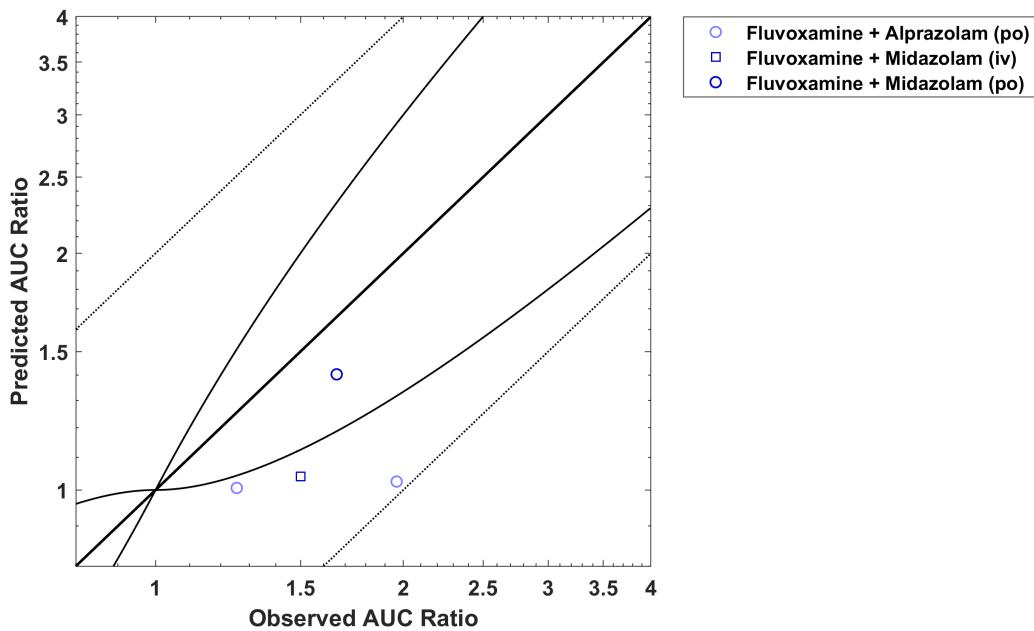
GMFE (AUC) = 1.103933

GMFE (CMAX) = 1.141236

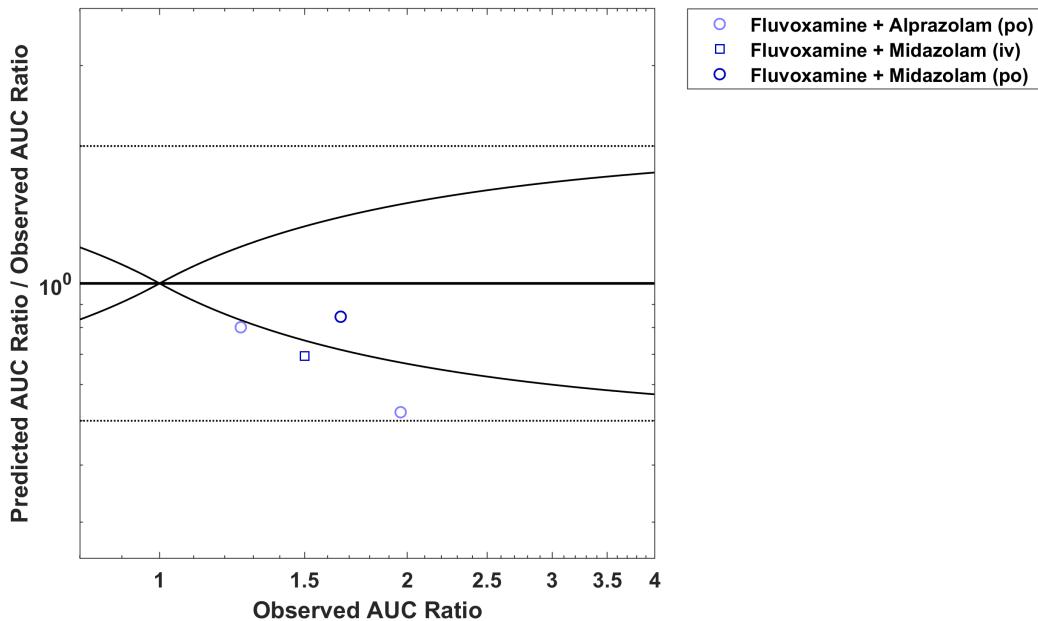
	AUC	Number	Ratio [%]
Points total		10	-
Points within Guest et al.		10	100
Points within 2-fold		10	100

CMAX	Number	Ratio [%]
Points total	9	-
Points within Guest et al.	8	88.8889
Points within 2-fold	9	100

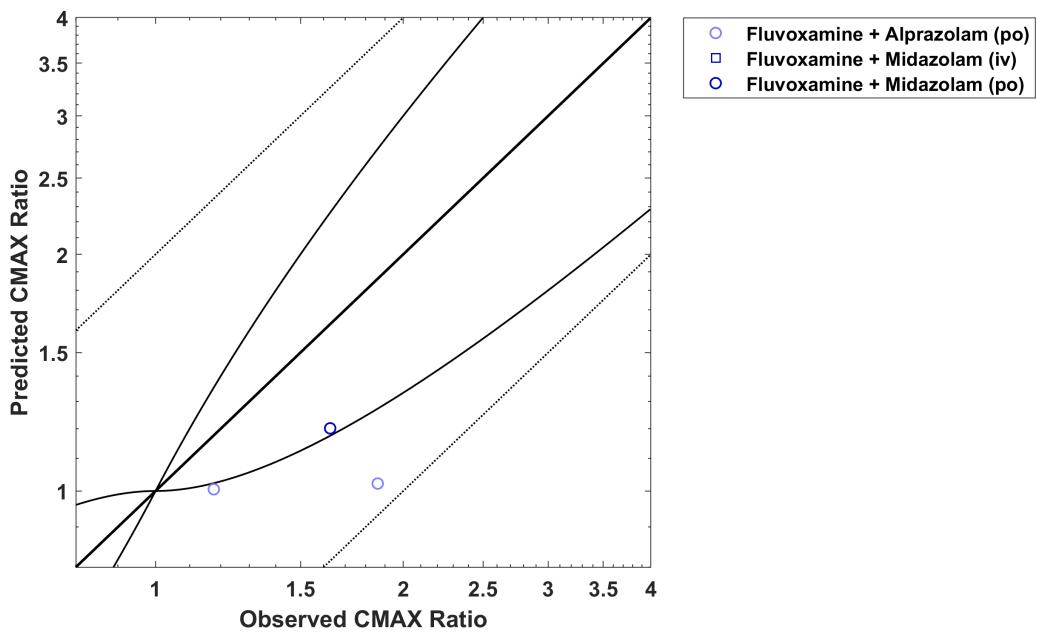
Fluvoxamine



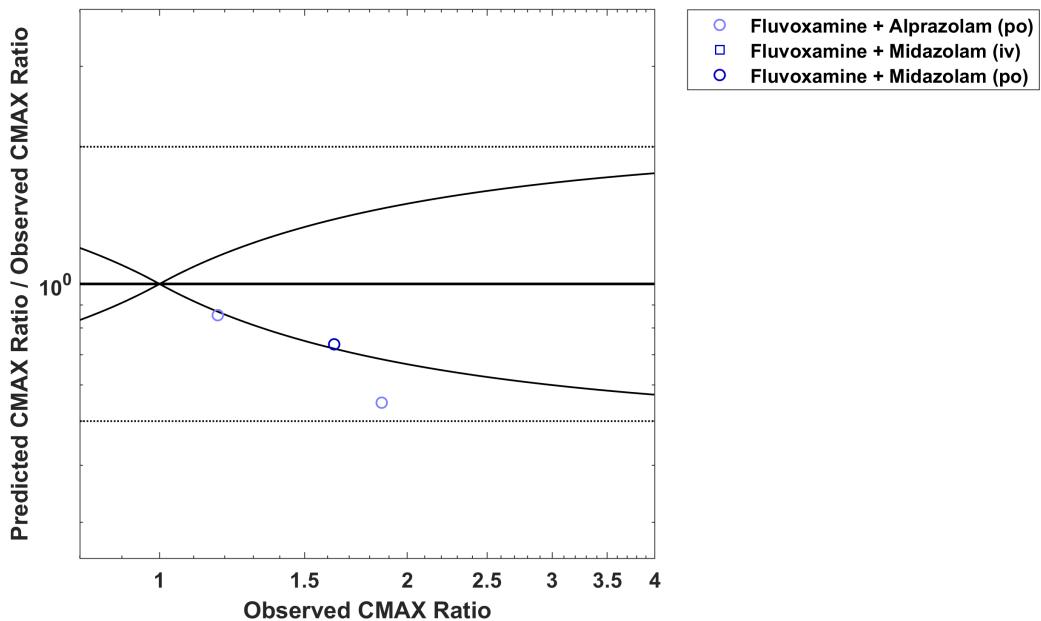
CYP3A4 DDI Fluvoxamine



CYP3A4 DDI Fluvoxamine



CYP3A4 DDI Fluvoxamine



CYP3A4 DDI Fluvoxamine

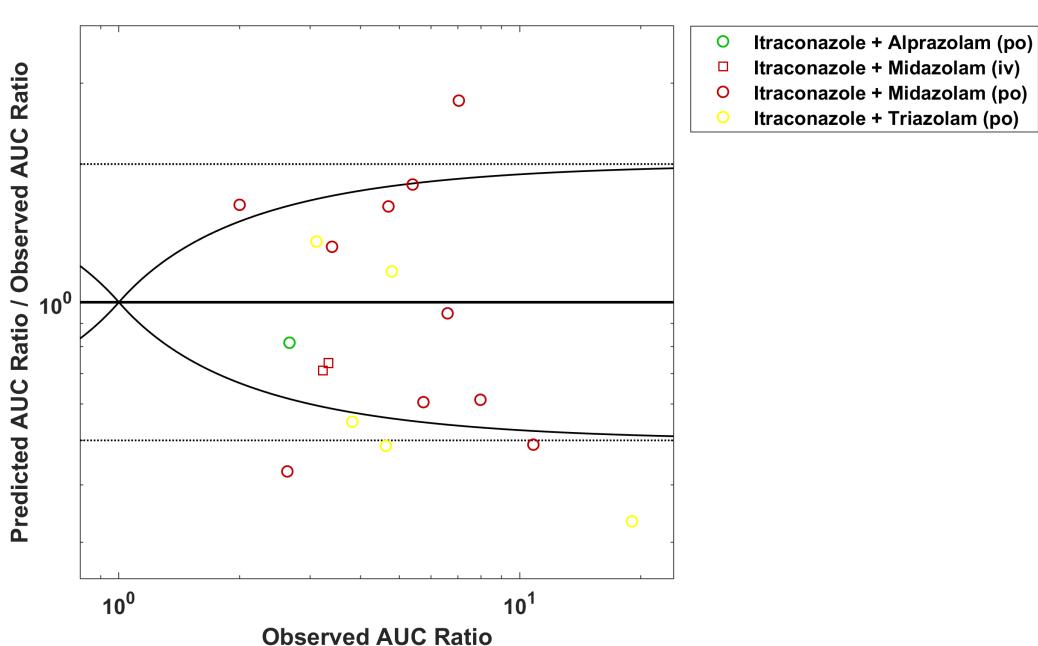
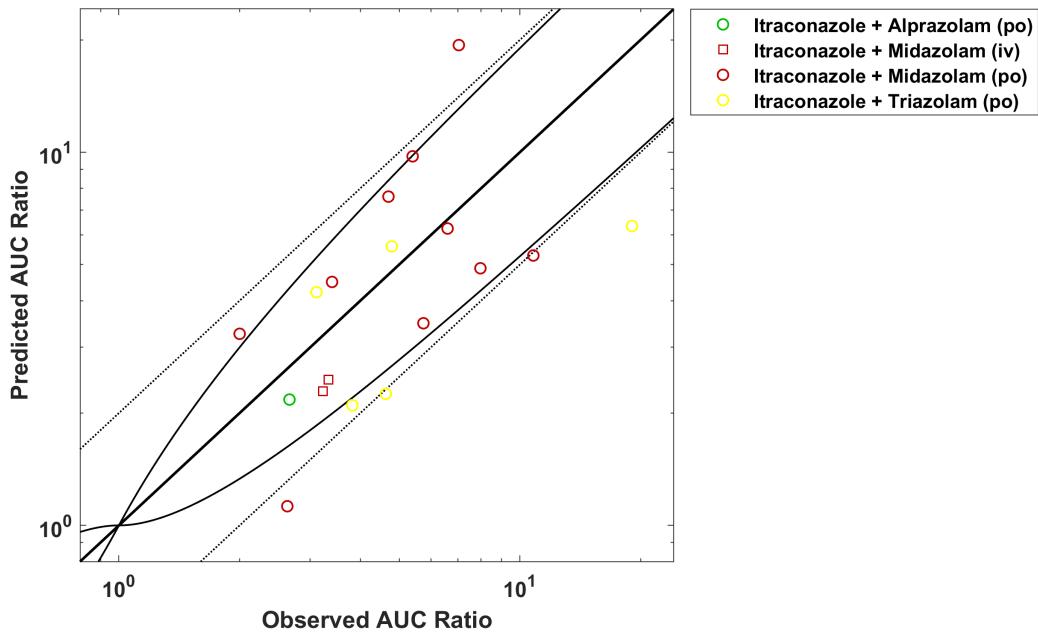
GMFE (AUC) = 1.420919

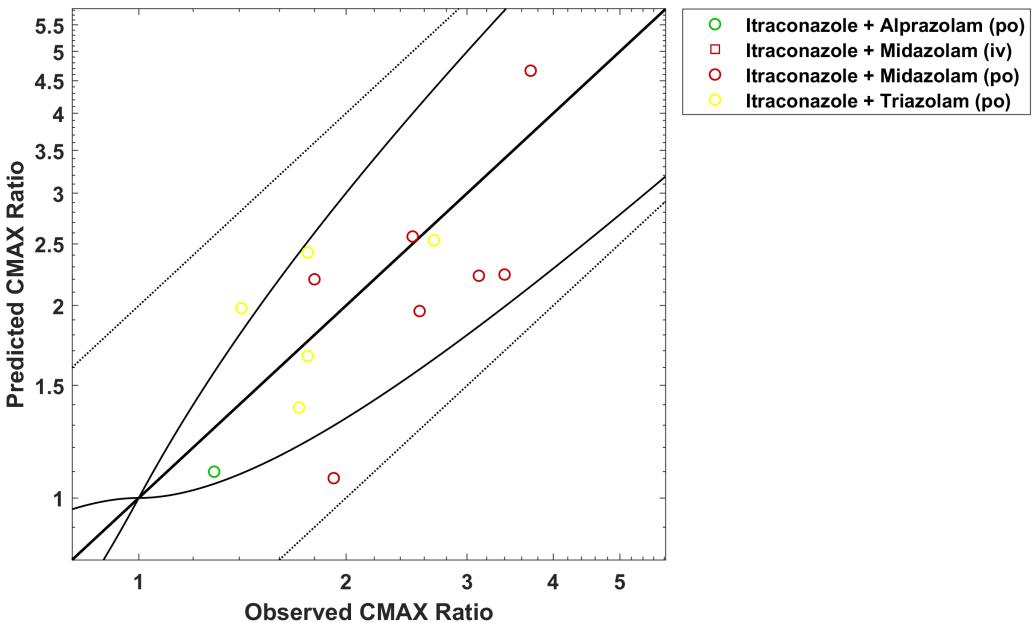
GMFE (CMAX) = 1.425106

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

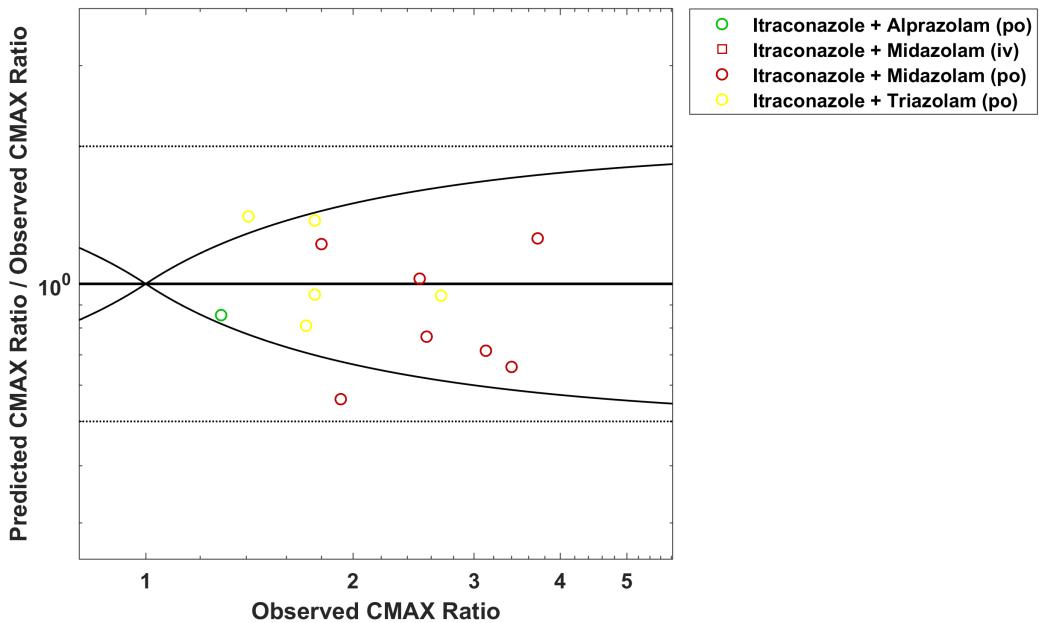
CMAX	Number	Ratio [%]
Points total	3	-
Points within Guest et al.	1	33.3333
Points within 2-fold	3	100

Itraconazole





CYP3A4 DDI Itraconazole



CYP3A4 DDI Itraconazole

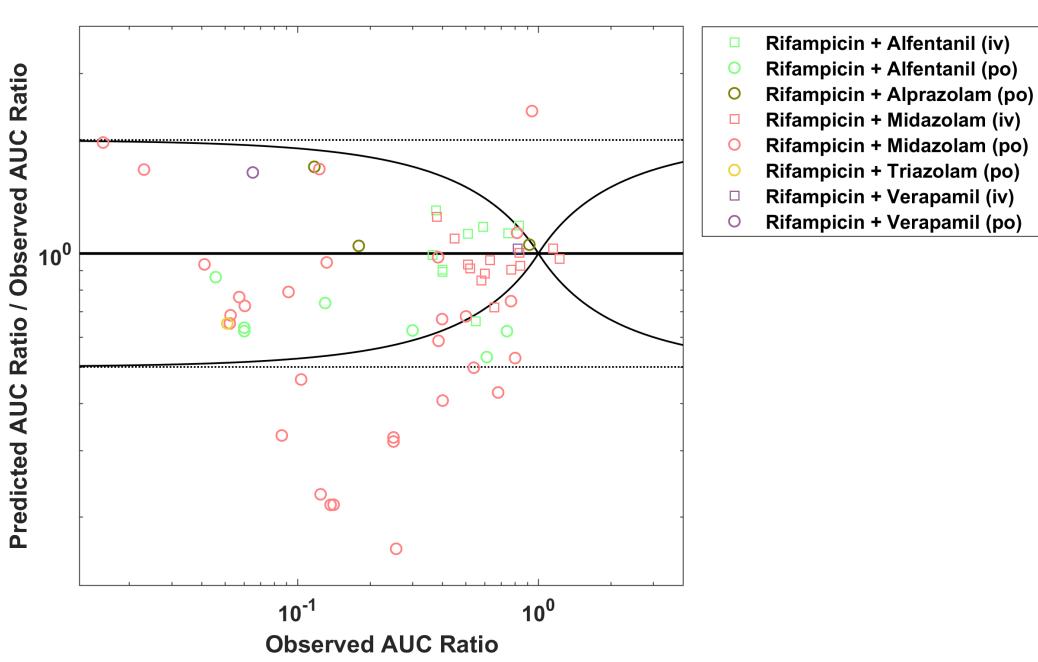
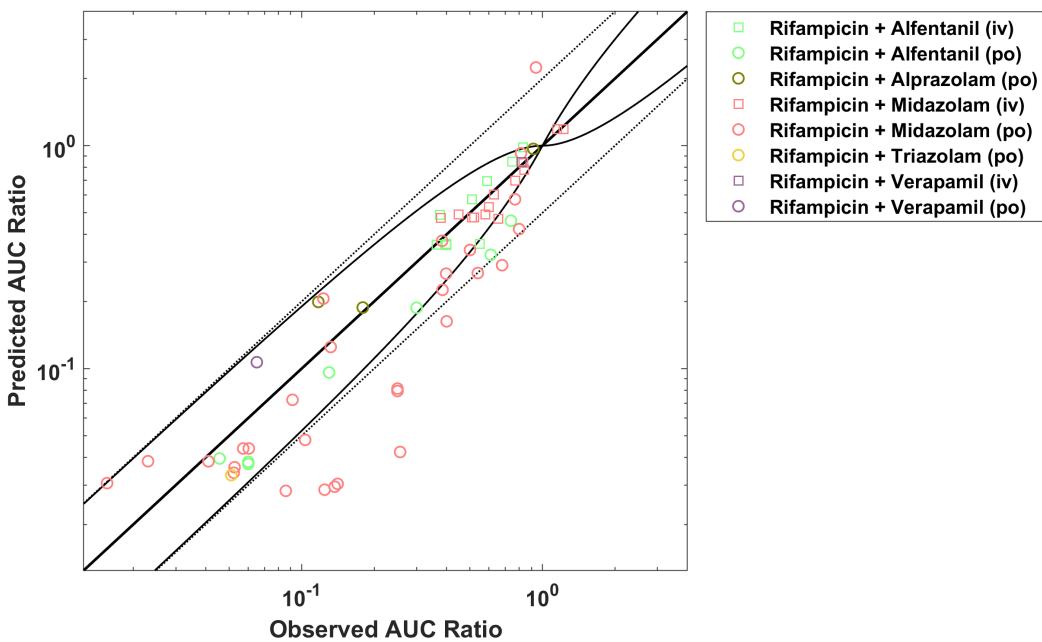
GMFE (AUC) = 1.665964

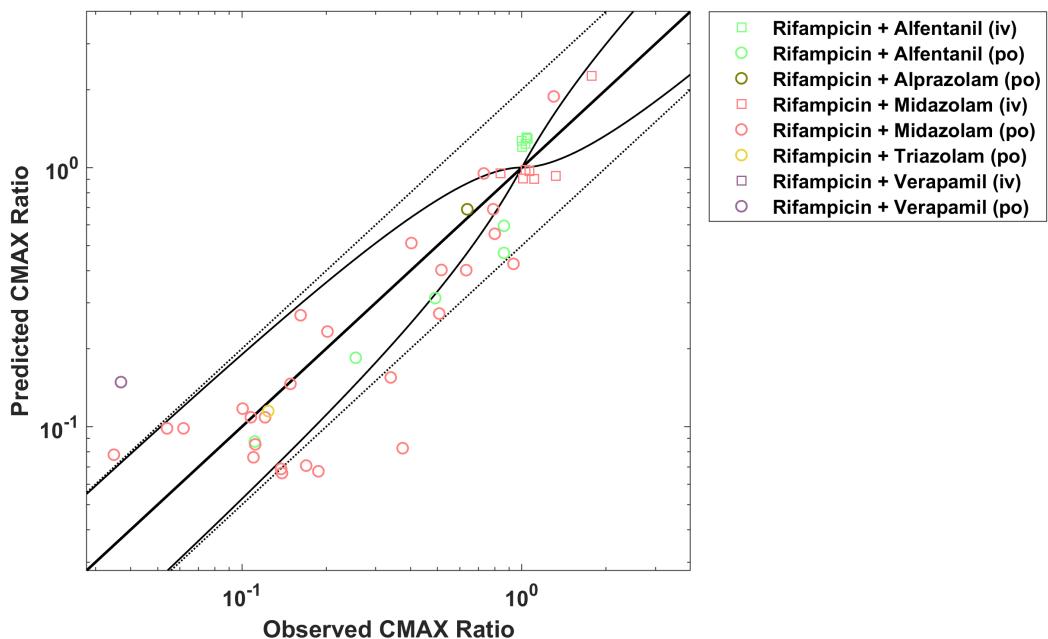
GMFE (CMAX) = 1.278880

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

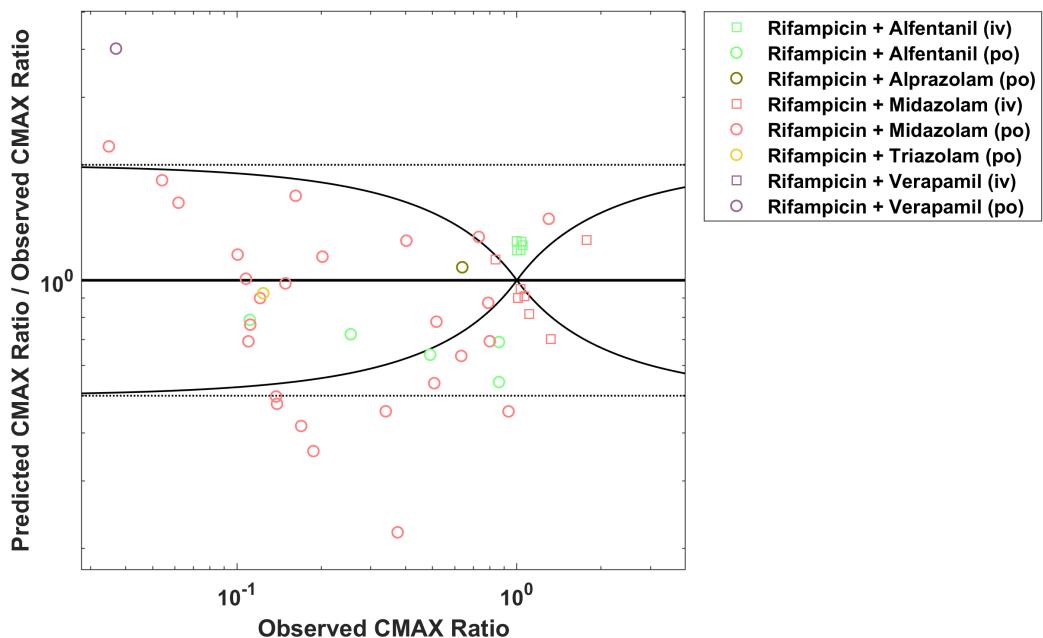
CMAX	Number	Ratio [%]
Points total	13	-
Points within Guest et al.	11	84.6154
Points within 2-fold	13	100

Rifampicin





CYP3A4 DDI Rifampicin



CYP3A4 DDI Rifampicin

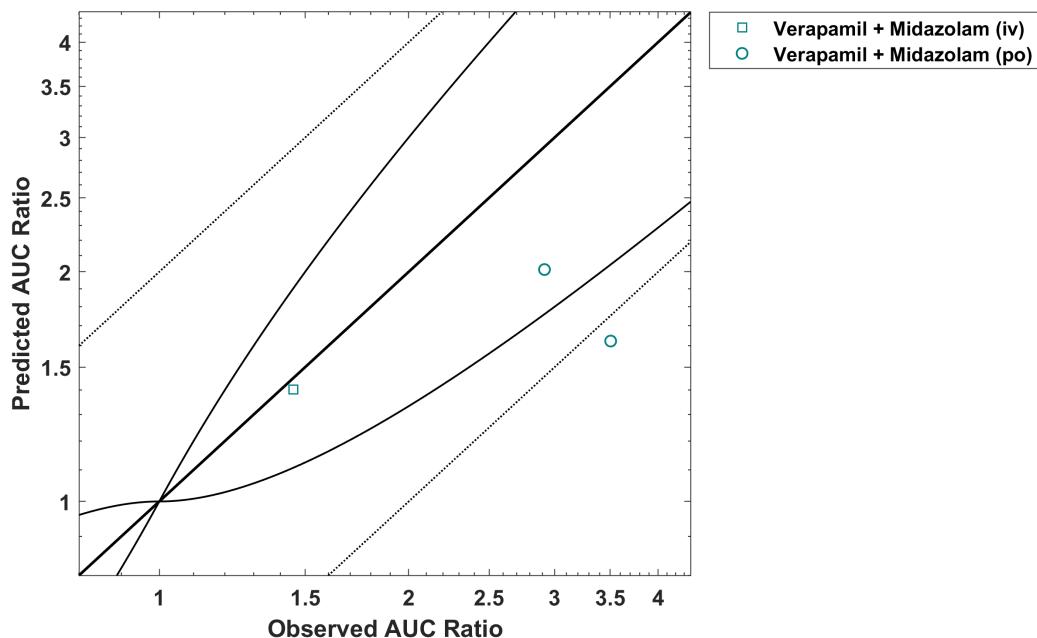
GMFE (AUC) = 1.516565

GMFE (CMAX) = 1.488840

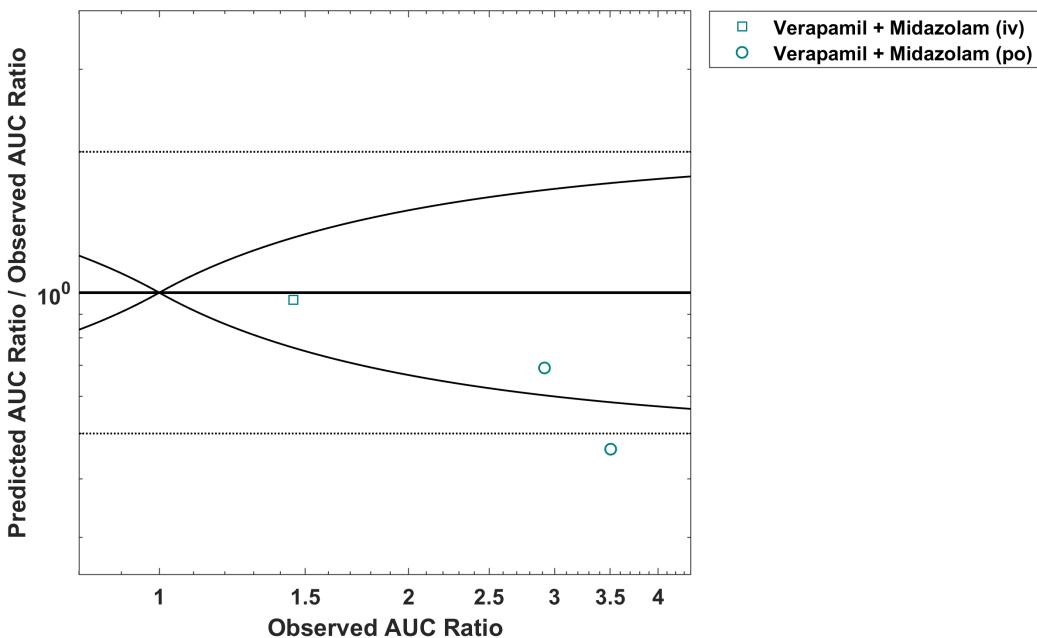
	AUC	Number	Ratio [%]
Points total		65	-
Points within Guest et al.		45	69.2308
Points within 2-fold		53	81.5385

CMAX	Number	Ratio [%]
Points total	46	-
Points within Guest et al.	19	41.3043
Points within 2-fold	37	80.4348

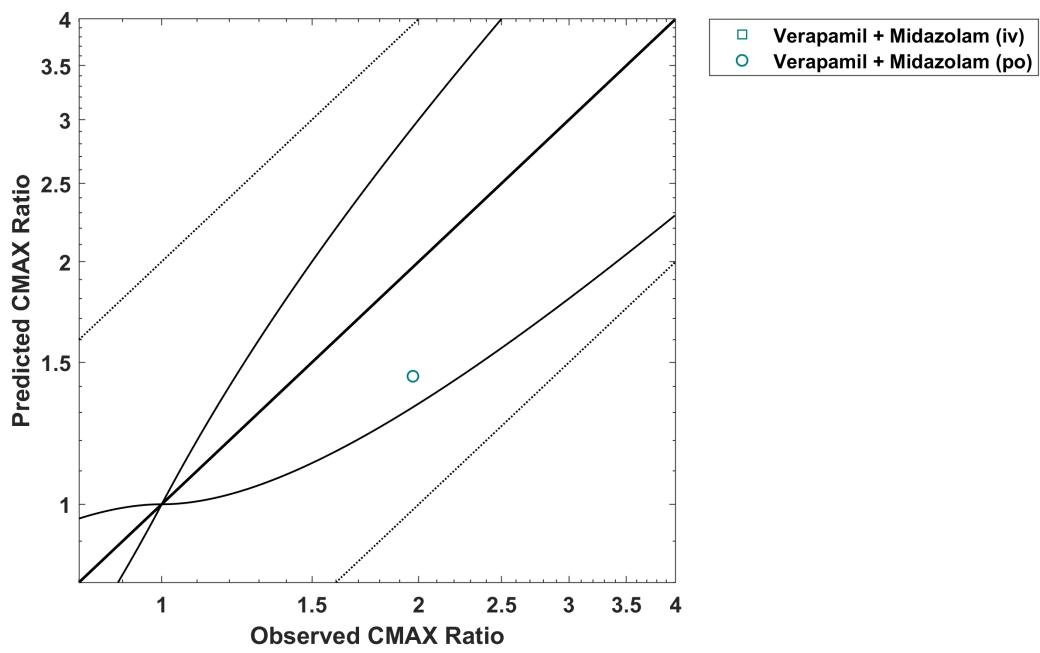
Verapamil



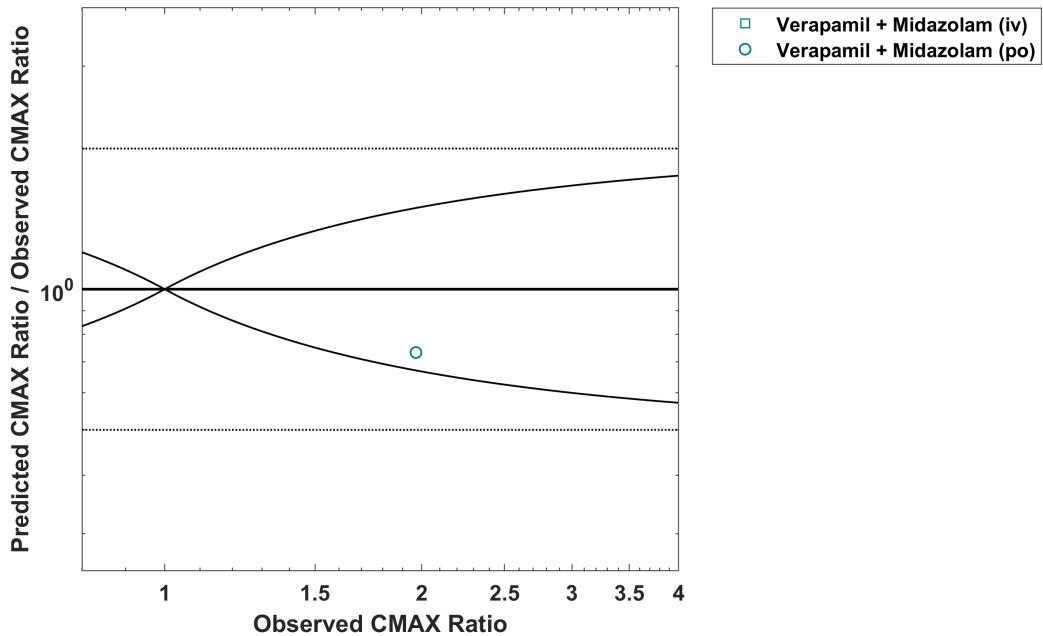
CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil

GMFE (AUC) = 1.479672

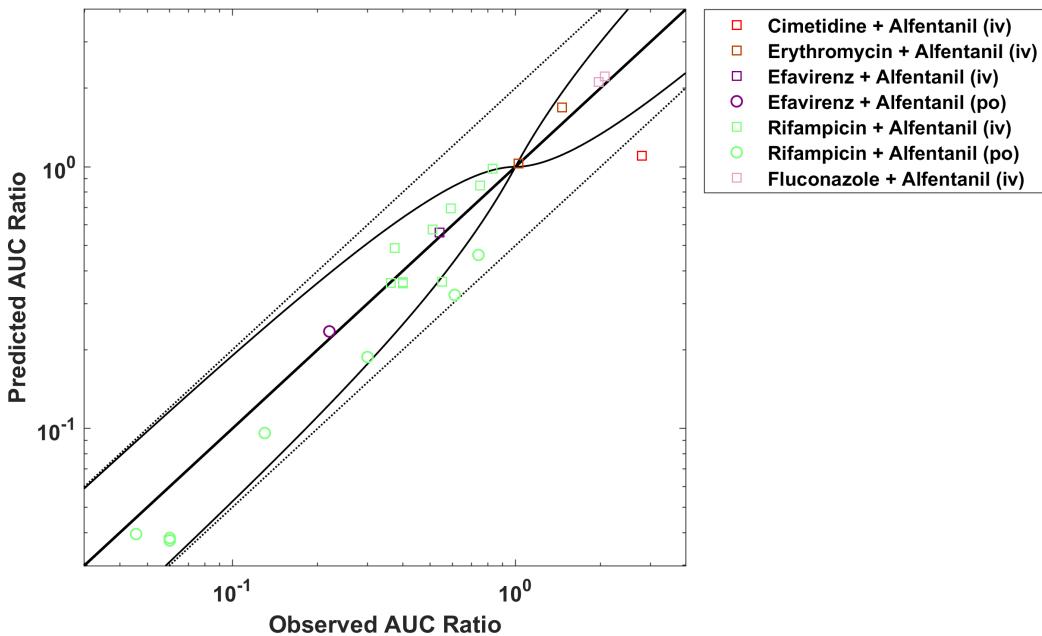
GMFE (CMAX) = 1.366144

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

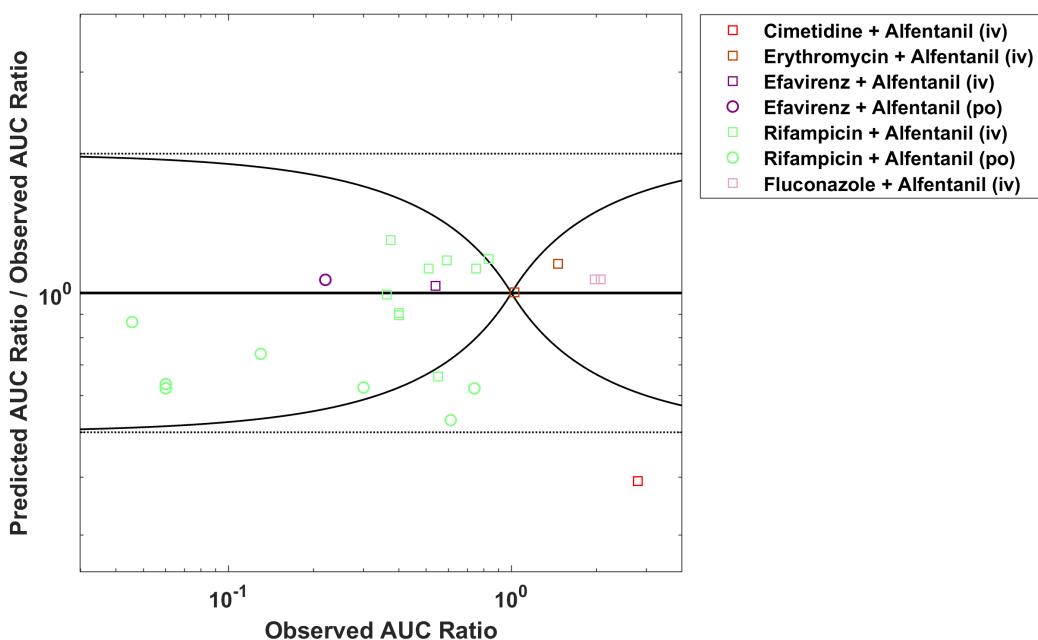
CMAX	Number	Ratio [%]
Points total	1	-
Points within Guest et al.	1	100
Points within 2-fold	1	100

Victim

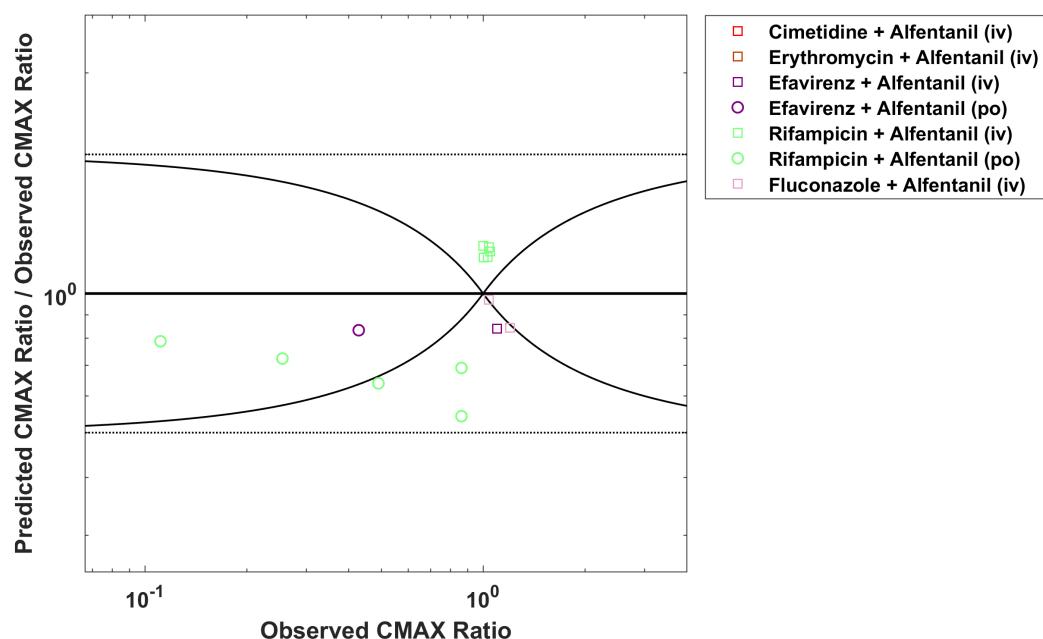
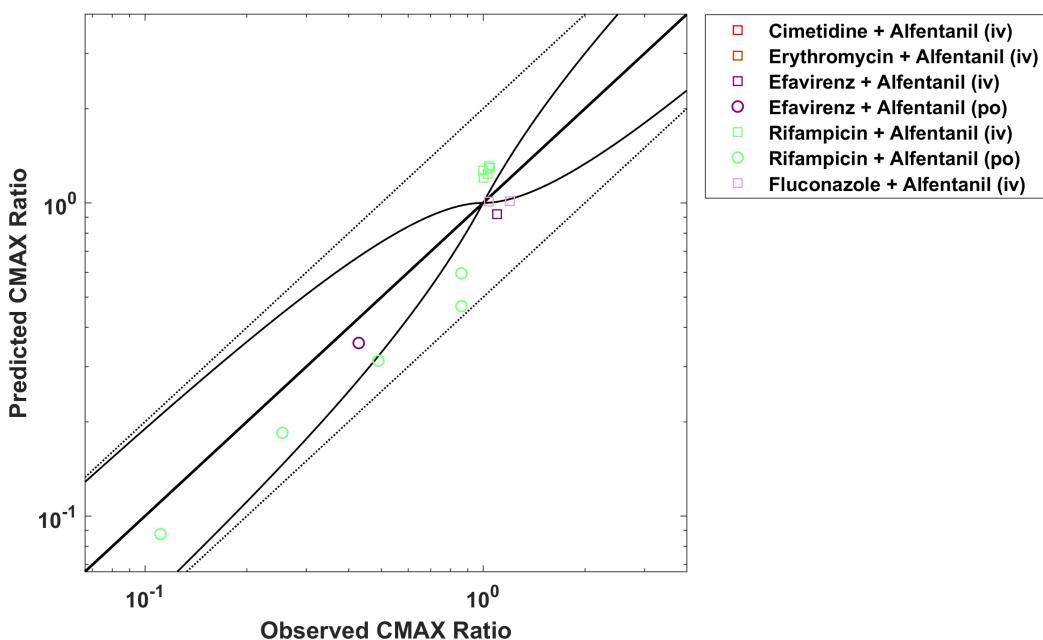
Alfentanil



CYP3A4 DDI Alfentanil



CYP3A4 DDI Alfentanil



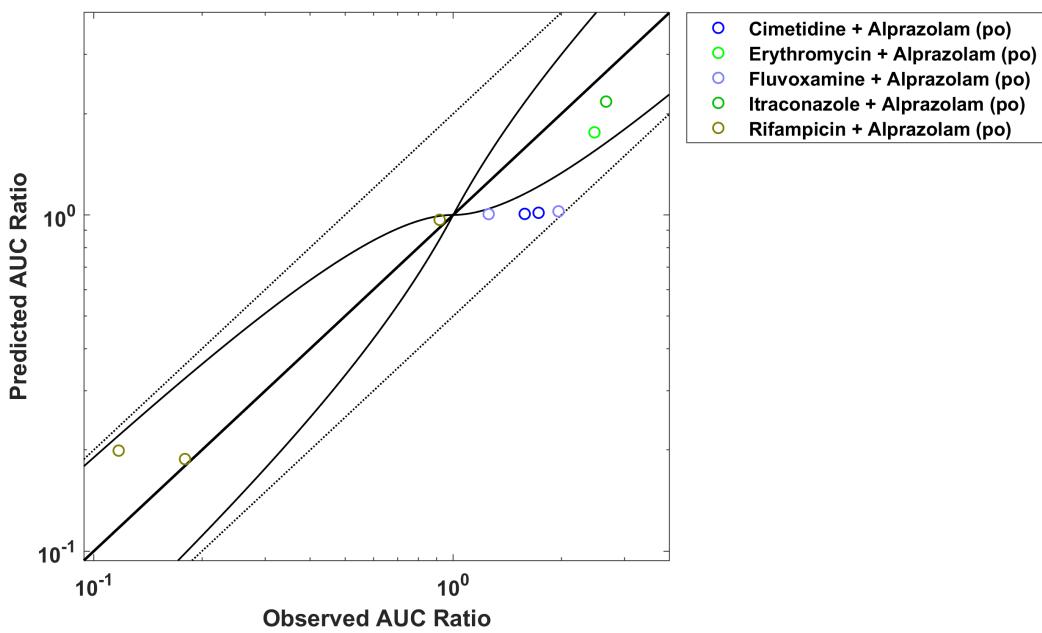
GMFE (AUC) = 1.283749

GMFE (CMAX) = 1.292222

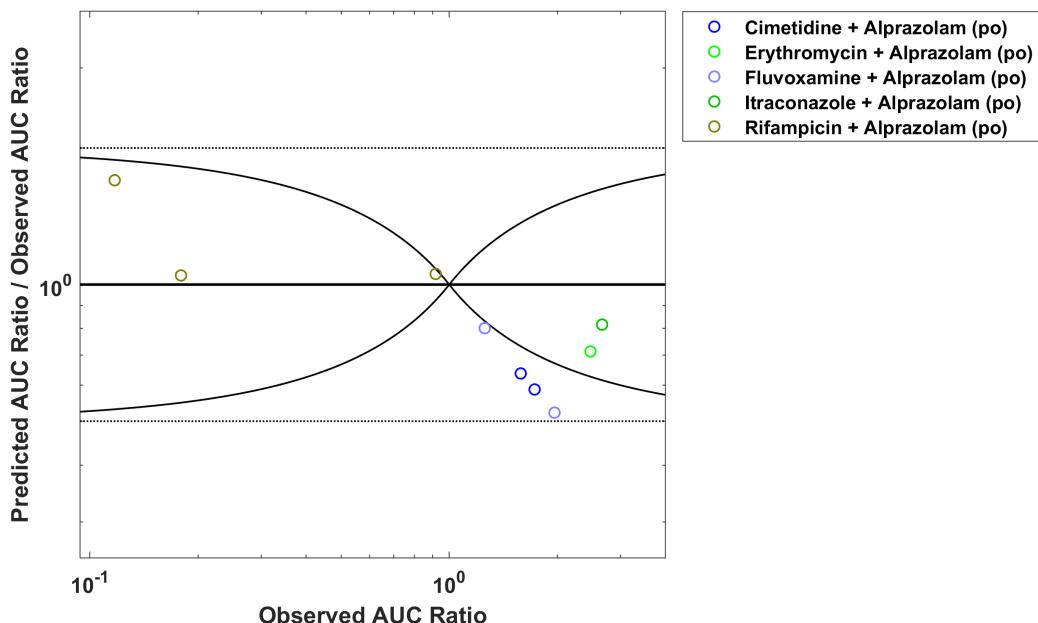
	AUC	Number	Ratio [%]
Points total		23	-
Points within Guest et al.		18	78.2609
Points within 2-fold		22	95.6522

CMAX	Number	Ratio [%]
Points total	14	-
Points within Guest et al.	4	28.5714
Points within 2-fold	14	100

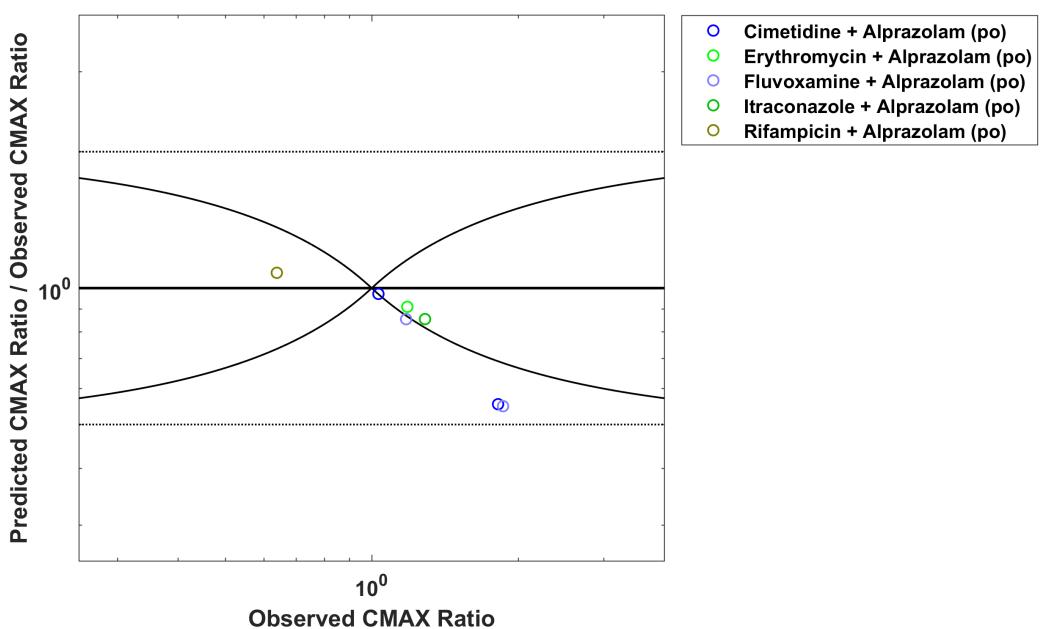
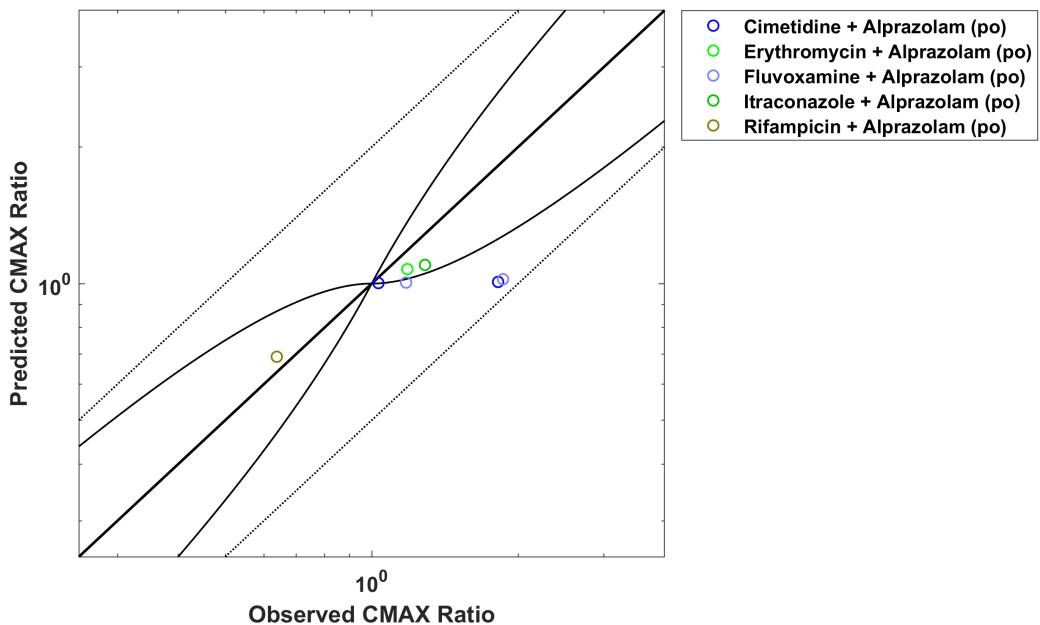
Alprazolam



CYP3A4 DDI Alprazolam



CYP3A4 DDI Alprazolam



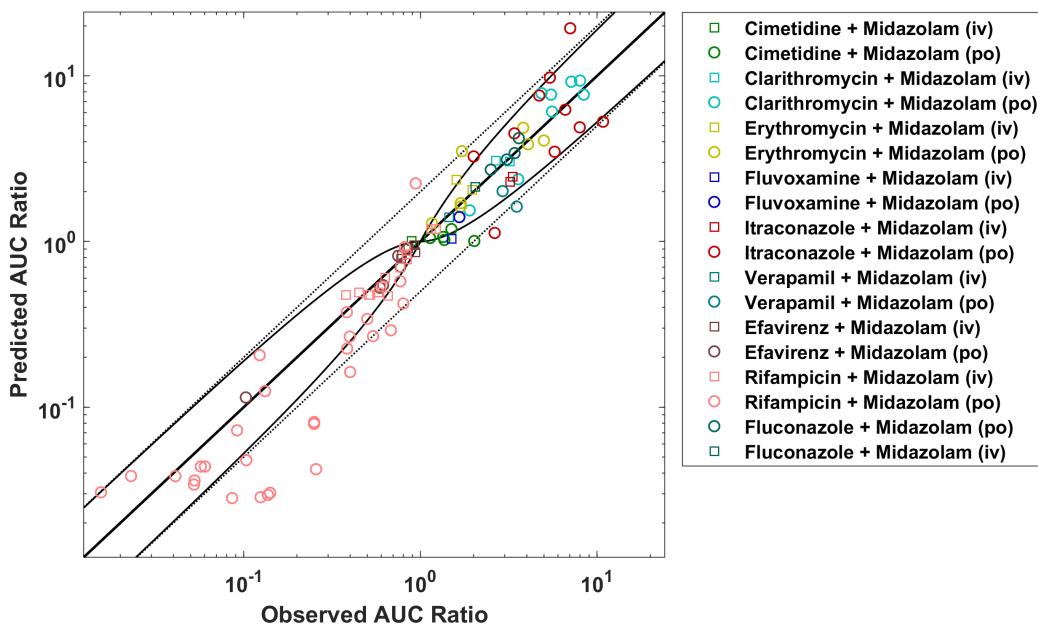
GMFE (AUC) = 1.399653

GMFE (CMAX) = 1.276214

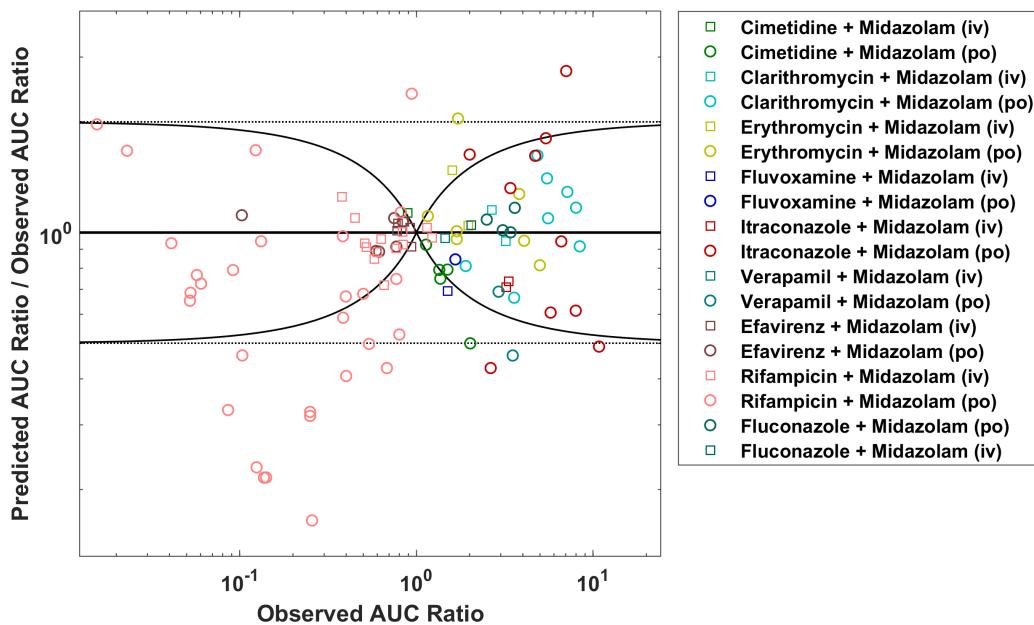
AUC	Number	Ratio [%]
Points total	9	-
Points within Guest et al.	5	55.5556
Points within 2-fold	9	100

CMAX	Number	Ratio [%]
Points total	7	-
Points within Guest et al.	4	57.1429
Points within 2-fold	7	100

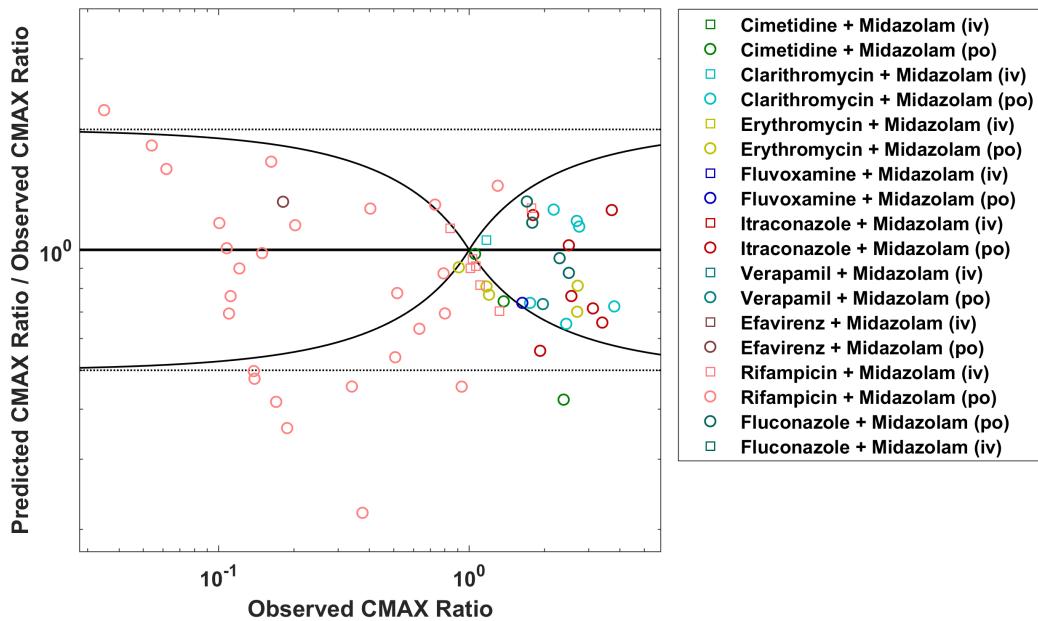
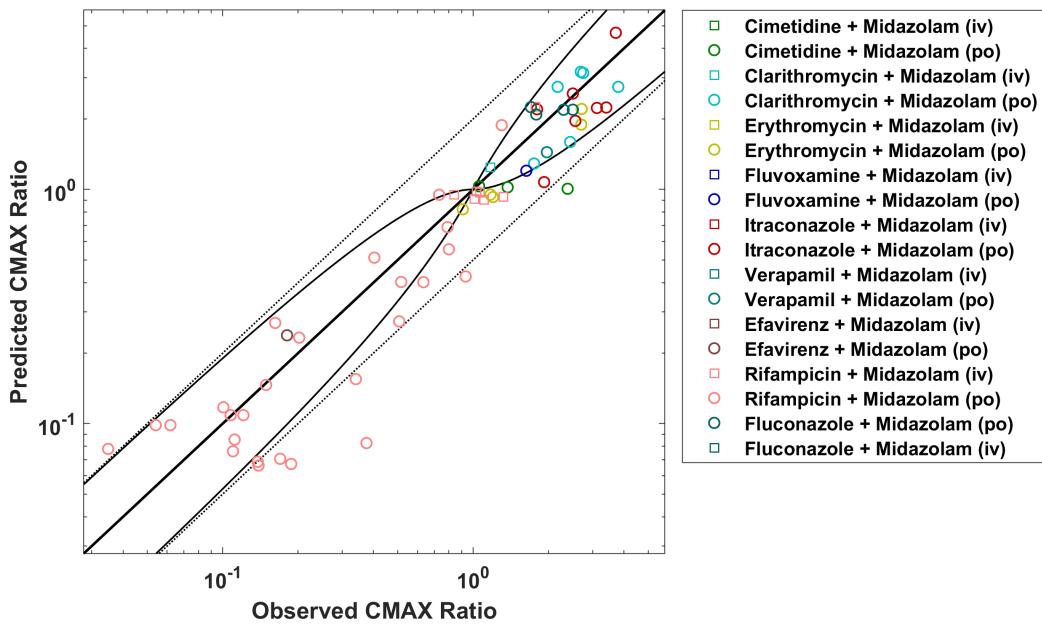
Midazolam



CYP3A4 DDI Midazolam



CYP3A4 DDI Midazolam



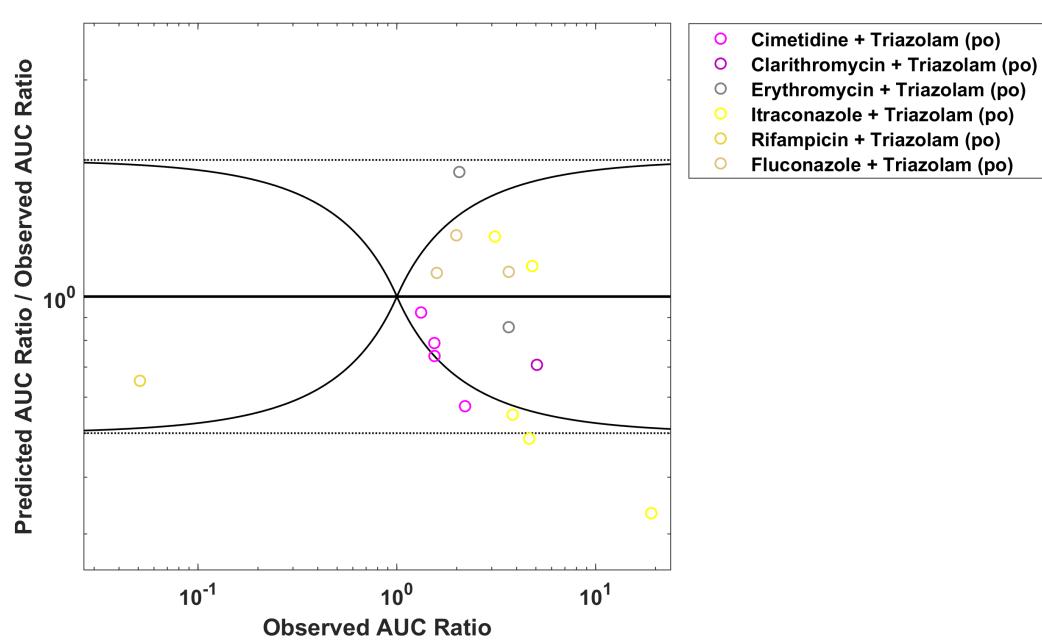
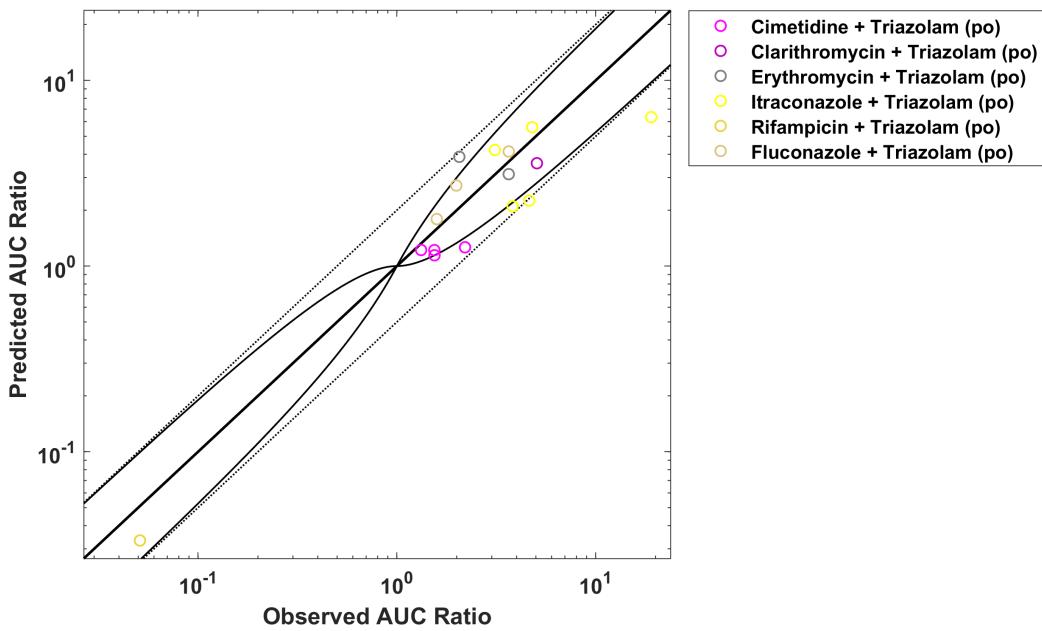
GMFE (AUC) = 1.423775

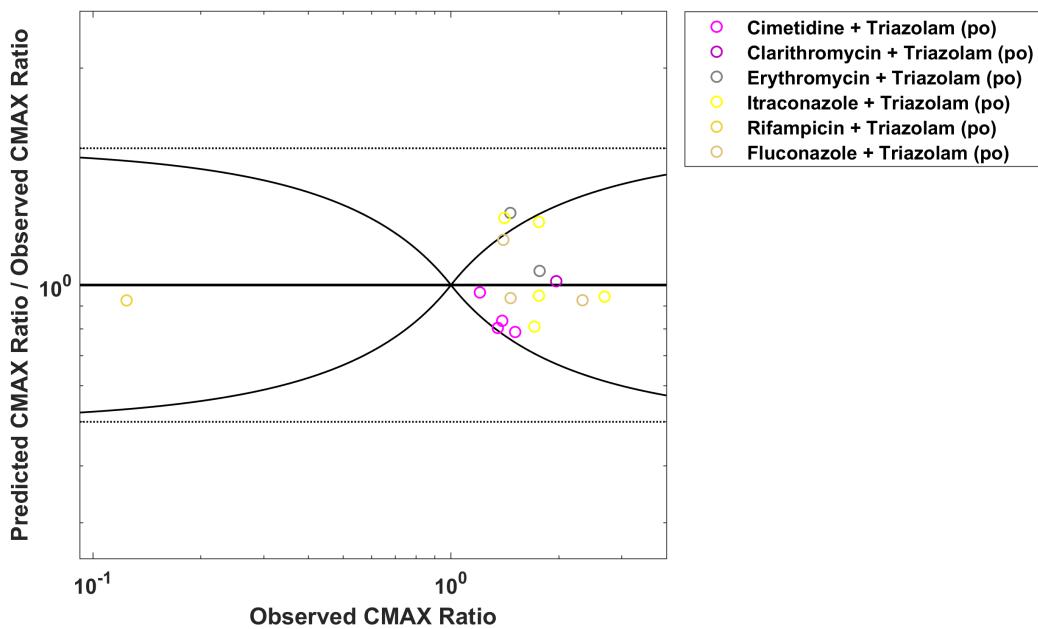
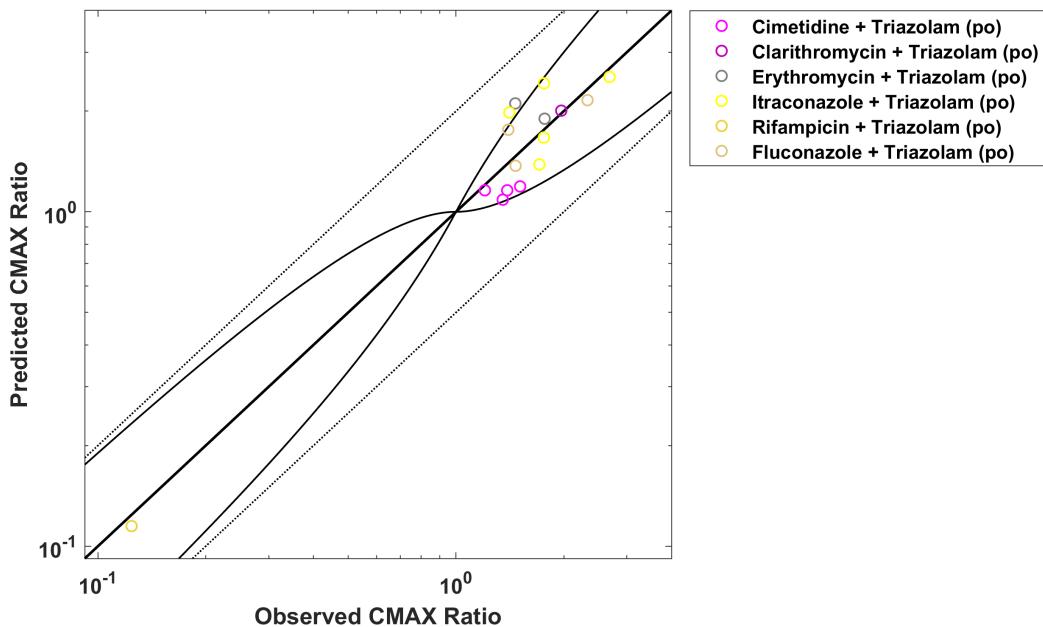
GMFE (CMAX) = 1.408962

	AUC	Number	Ratio [%]
Points total	101	-	
Points within Guest et al.	72	71.2871	
Points within 2-fold	83	82.1782	

CMAX	Number	Ratio [%]
Points total	62	-
Points within Guest et al.	38	61.2903
Points within 2-fold	53	85.4839

Triazolam





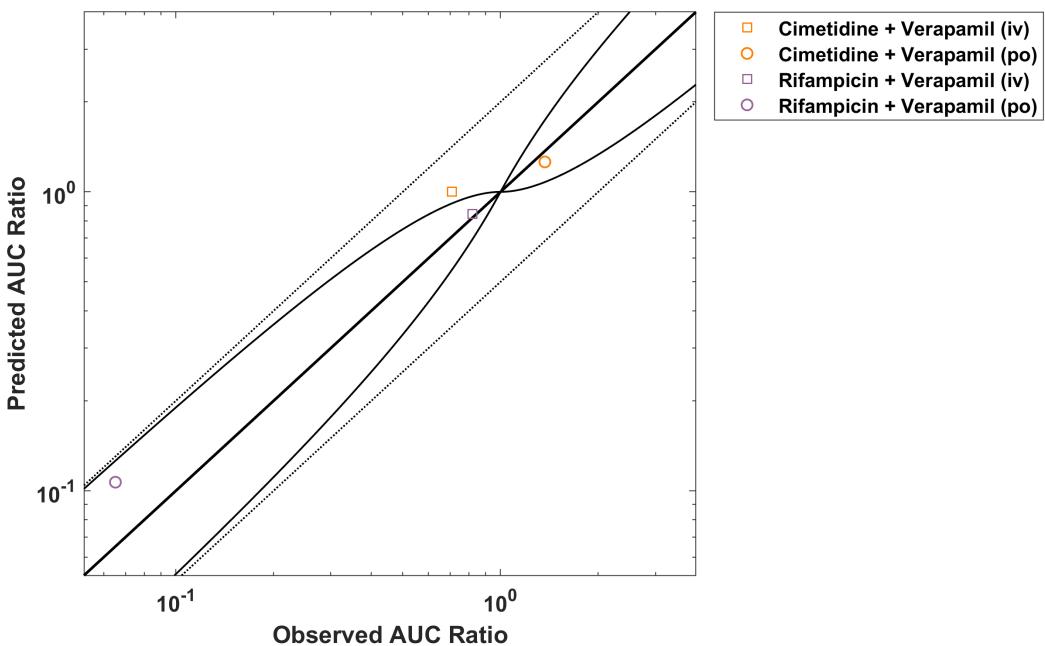
GMFE (AUC) = 1.470574

GMFE (CMAX) = 1.173696

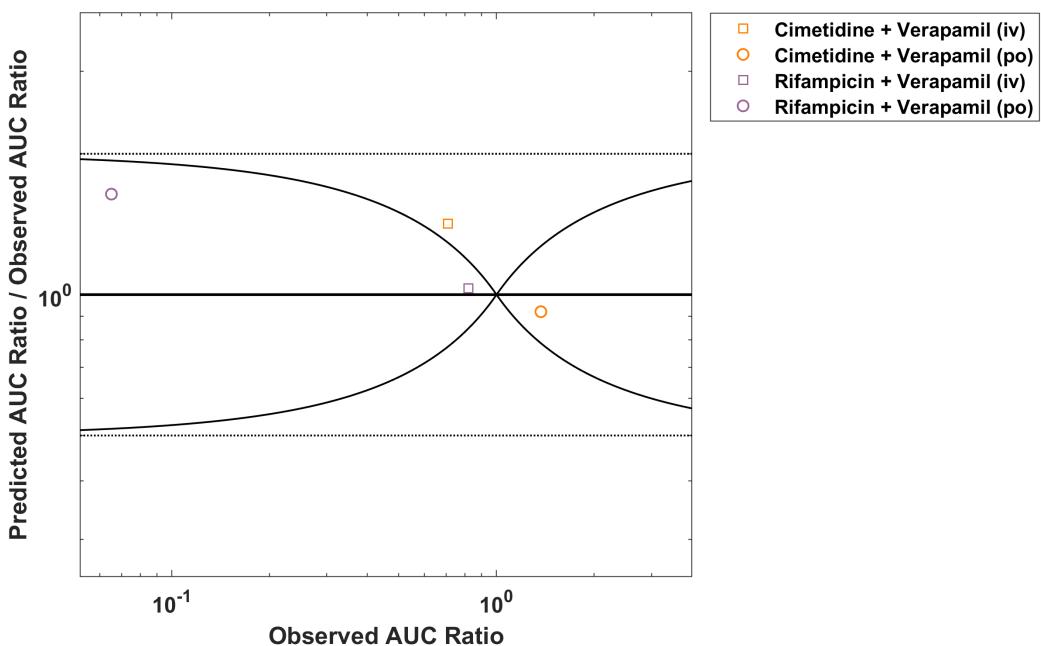
	AUC	Number	Ratio [%]
Points total		16	-
Points within Guest et al.		11	68.75
Points within 2-fold		14	87.5

CMAX	Number	Ratio [%]
Points total	16	-
Points within Guest et al.	14	87.5
Points within 2-fold	16	100

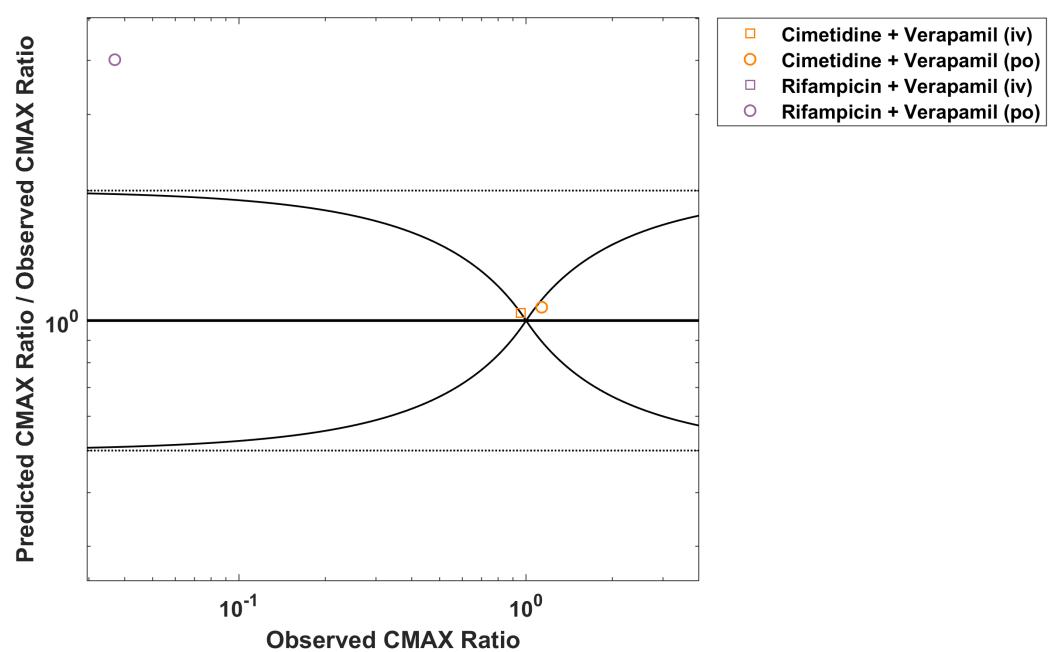
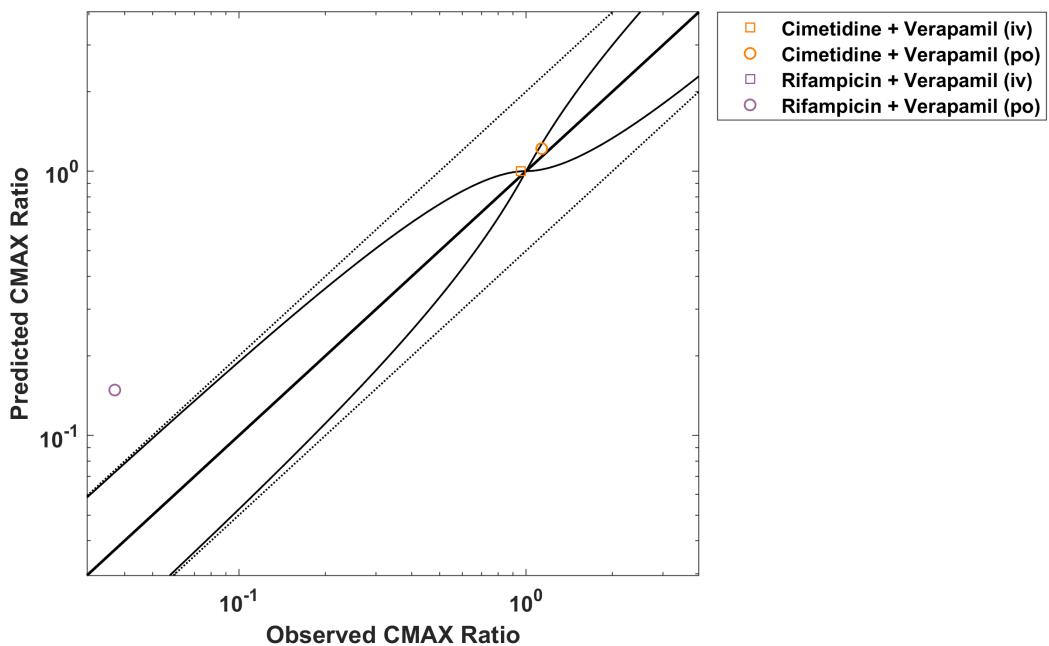
Verapamil



CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil



GMFE (AUC) = 1.270599

GMFE (CMAX) = 1.650804

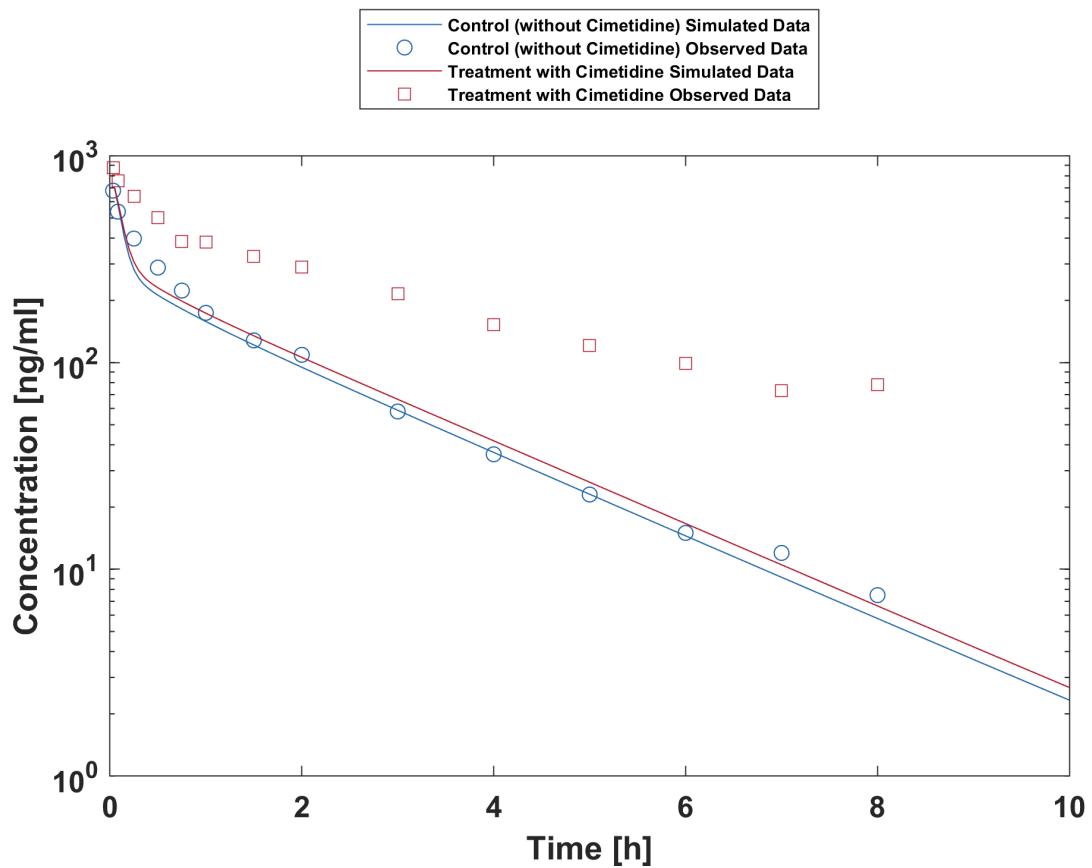
AUC	Number	Ratio [%]
Points total	4	-
Points within Guest et al.	3	75
Points within 2-fold	4	100

CMAX	Number	Ratio [%]
Points total	3	-
Points within Guest et al.	1	33.3333
Points within 2-fold	2	66.6667

3 Concentration-Time Profiles

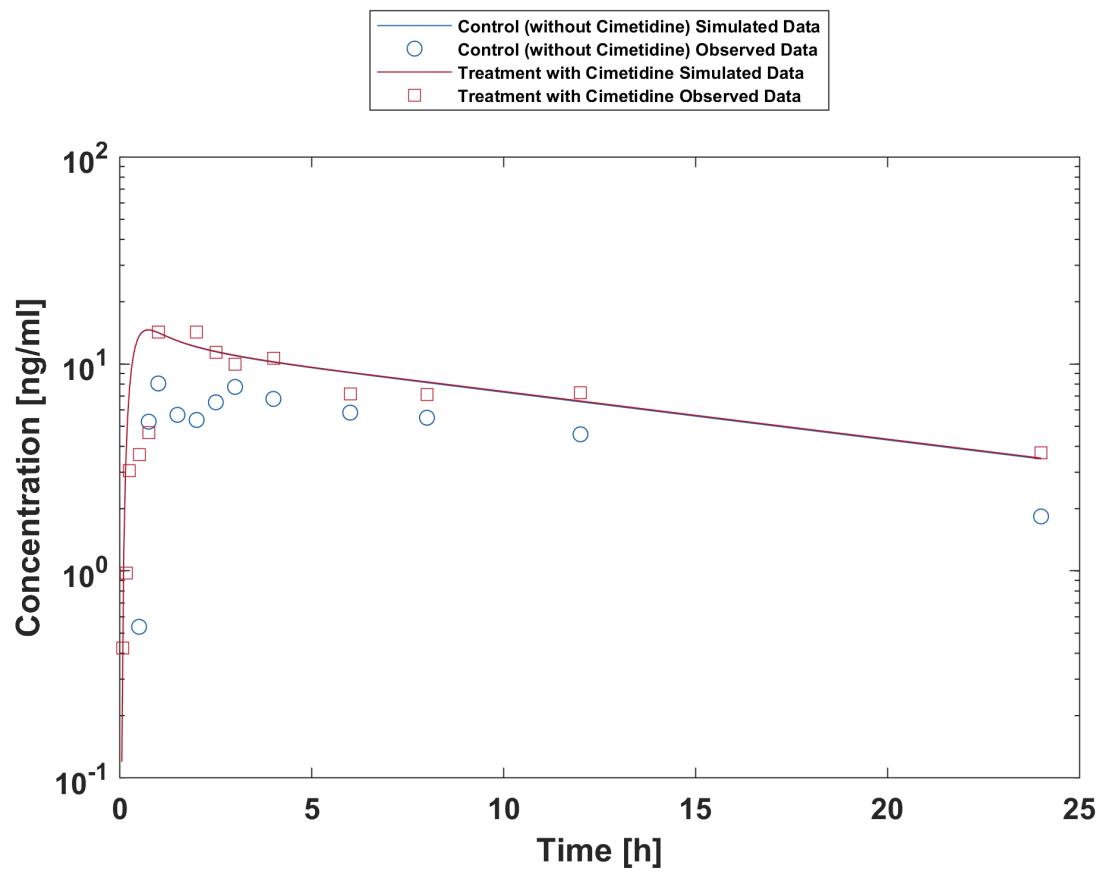
The following section shows concentration time profiles of the victim drugs of the simulated DDI studies in comparison to observed data (if available).

3.1 Cimetidine - Alfentanil DDI

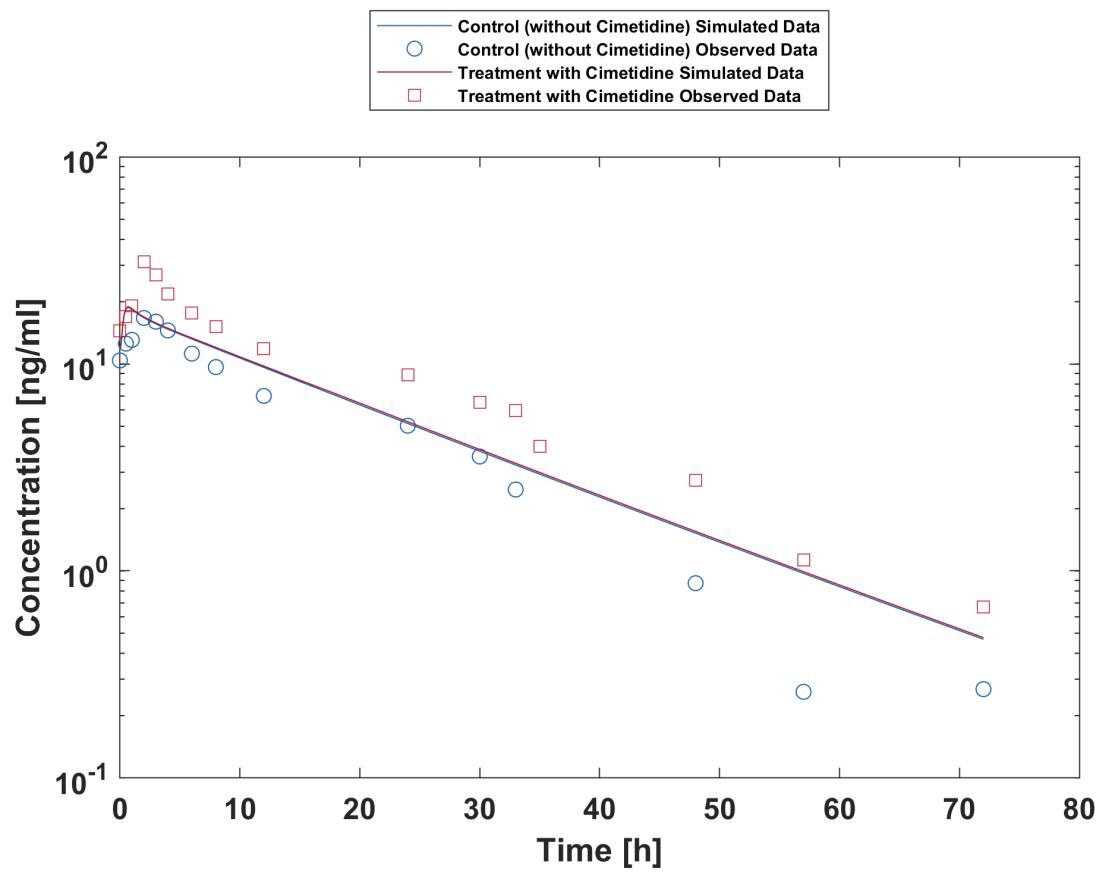


Kienlen 1993

3.2 Cimetidine - Alprazolam DDI

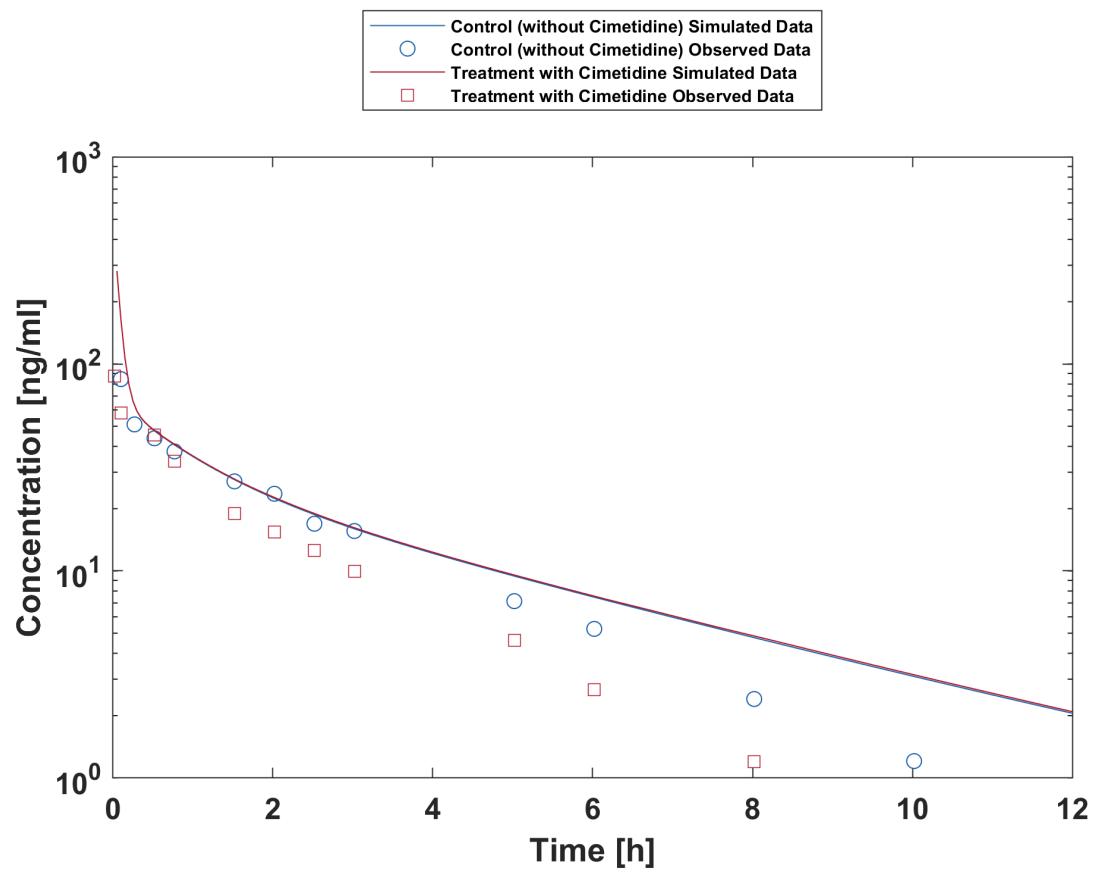


Abernethy 1983

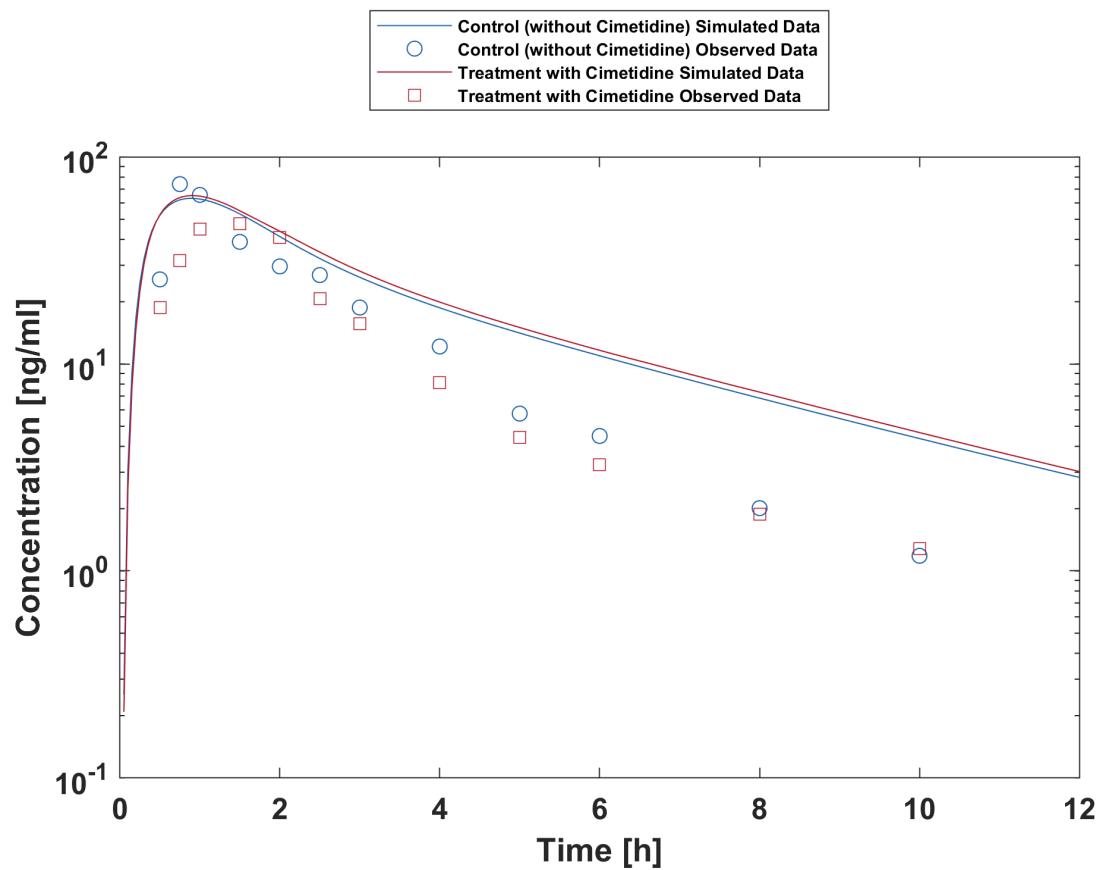


Pourbaix 1985

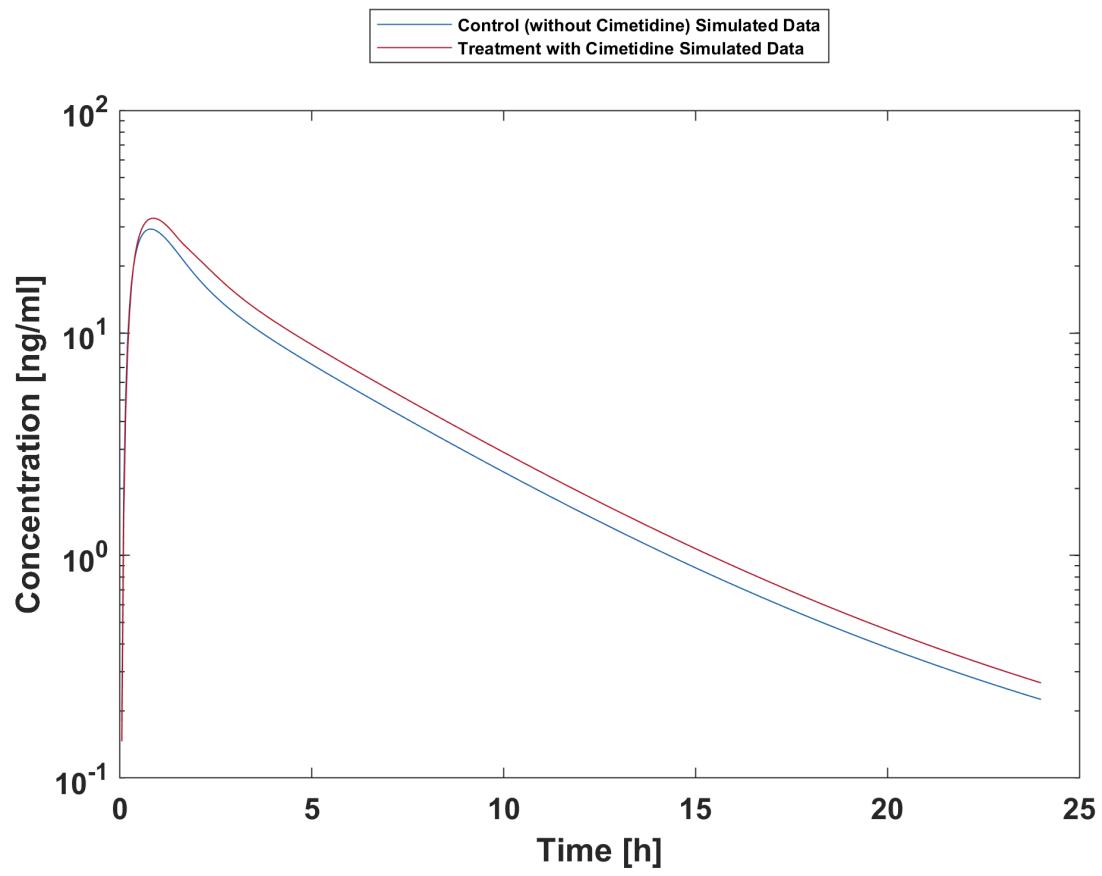
3.3 Cimetidine - Midazolam DDI



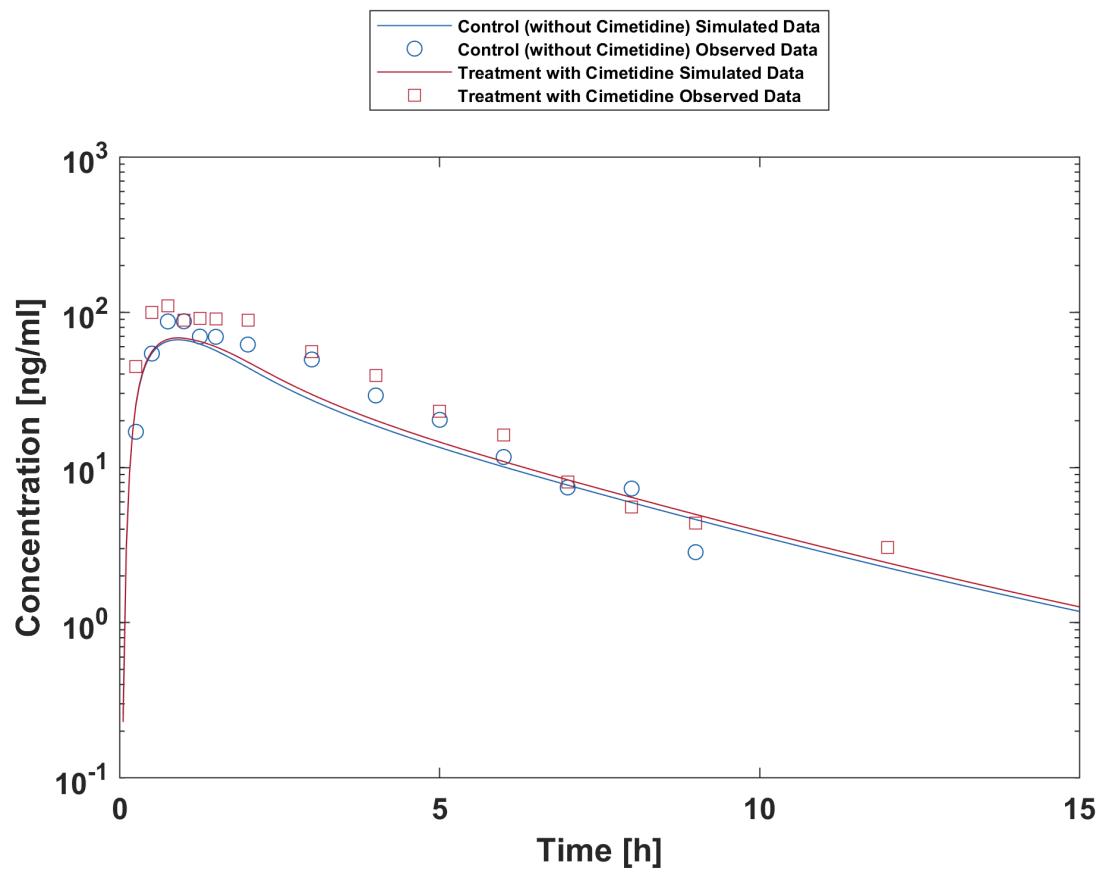
Greenblatt 1986 (midazolam IV)



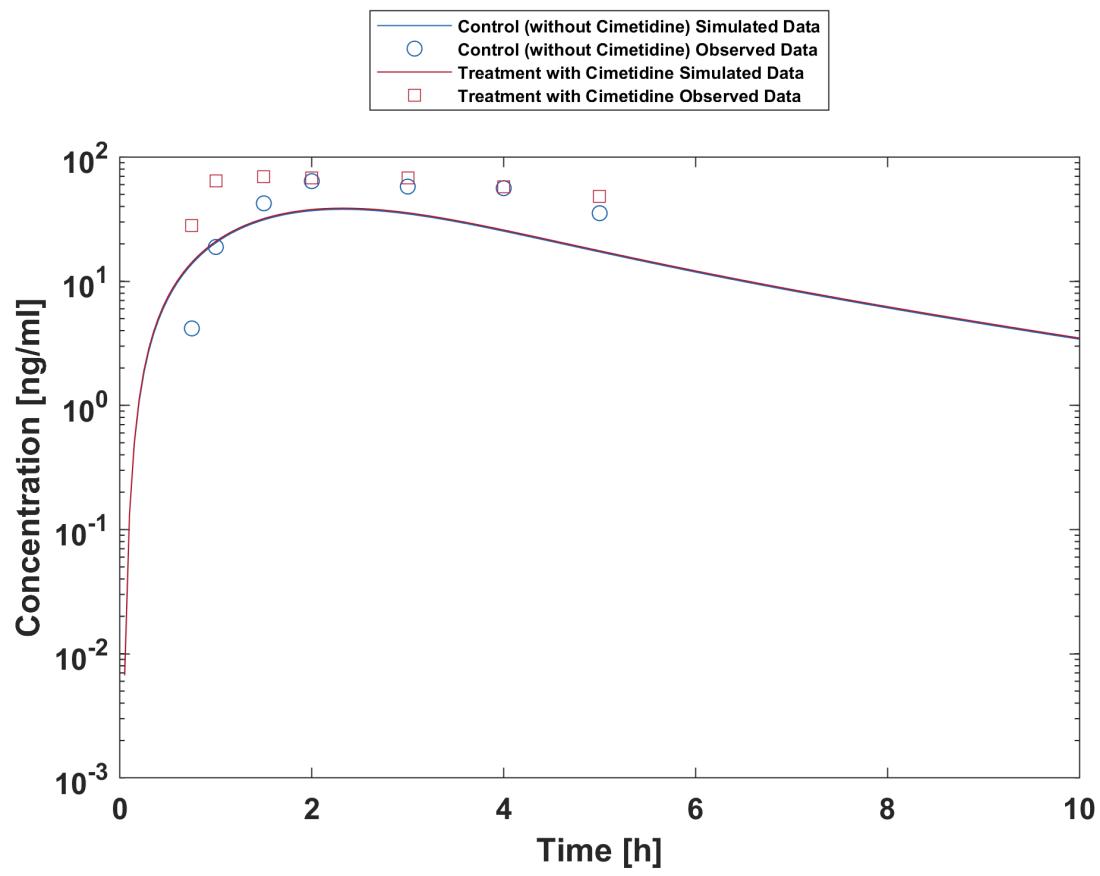
Greenblatt 1986 (midazolam PO)



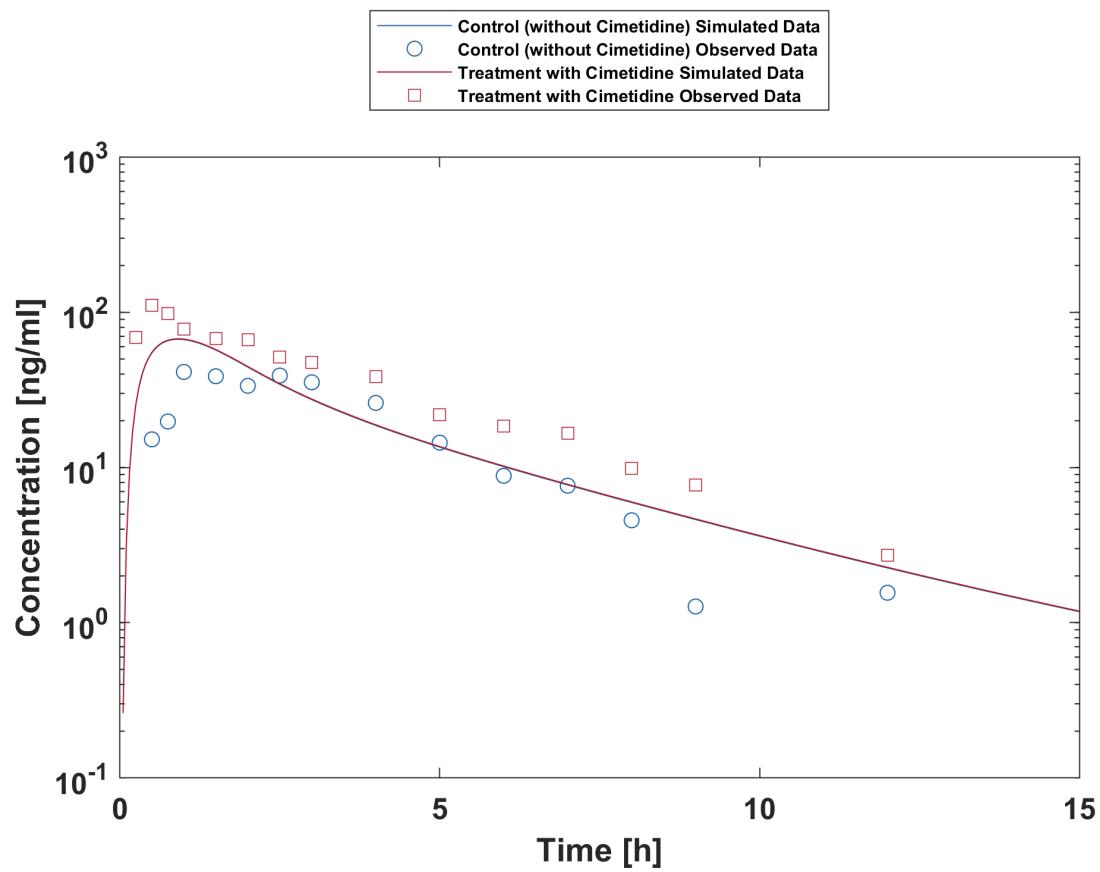
Martinez 1999



Fee 1987

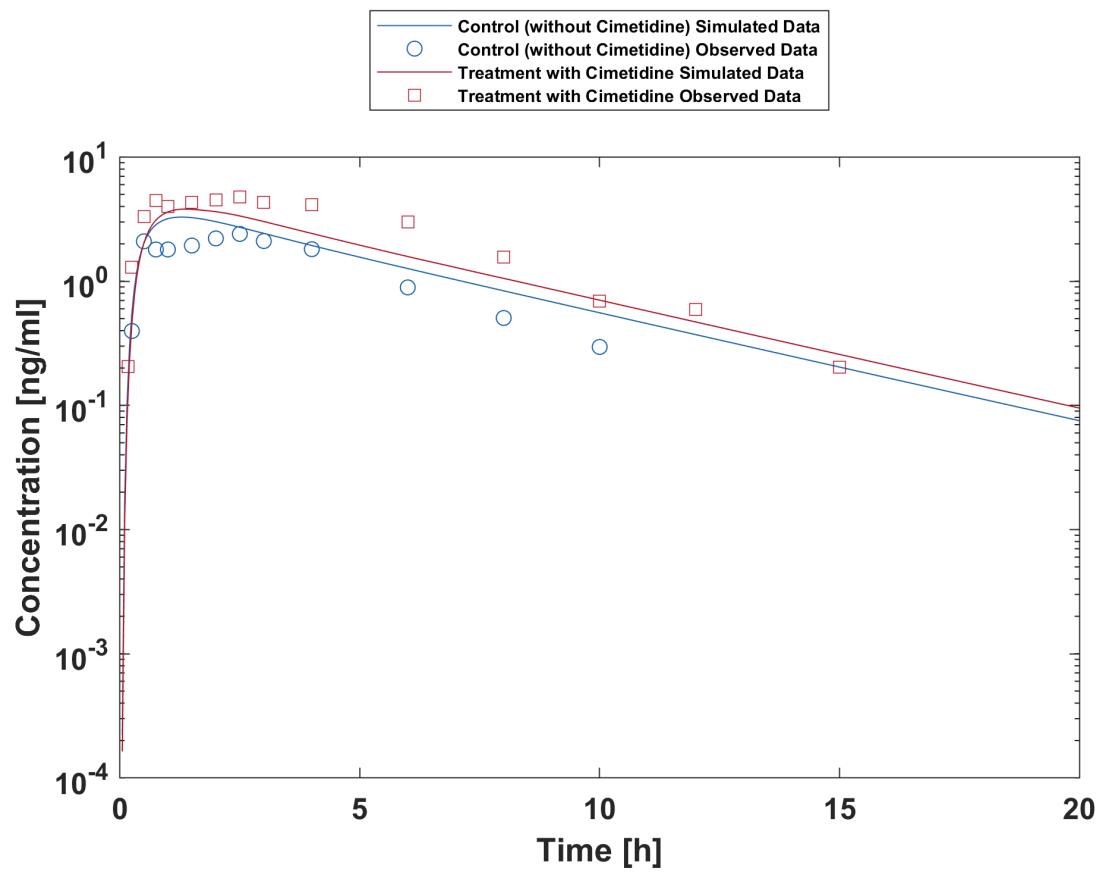


Salonen 1986

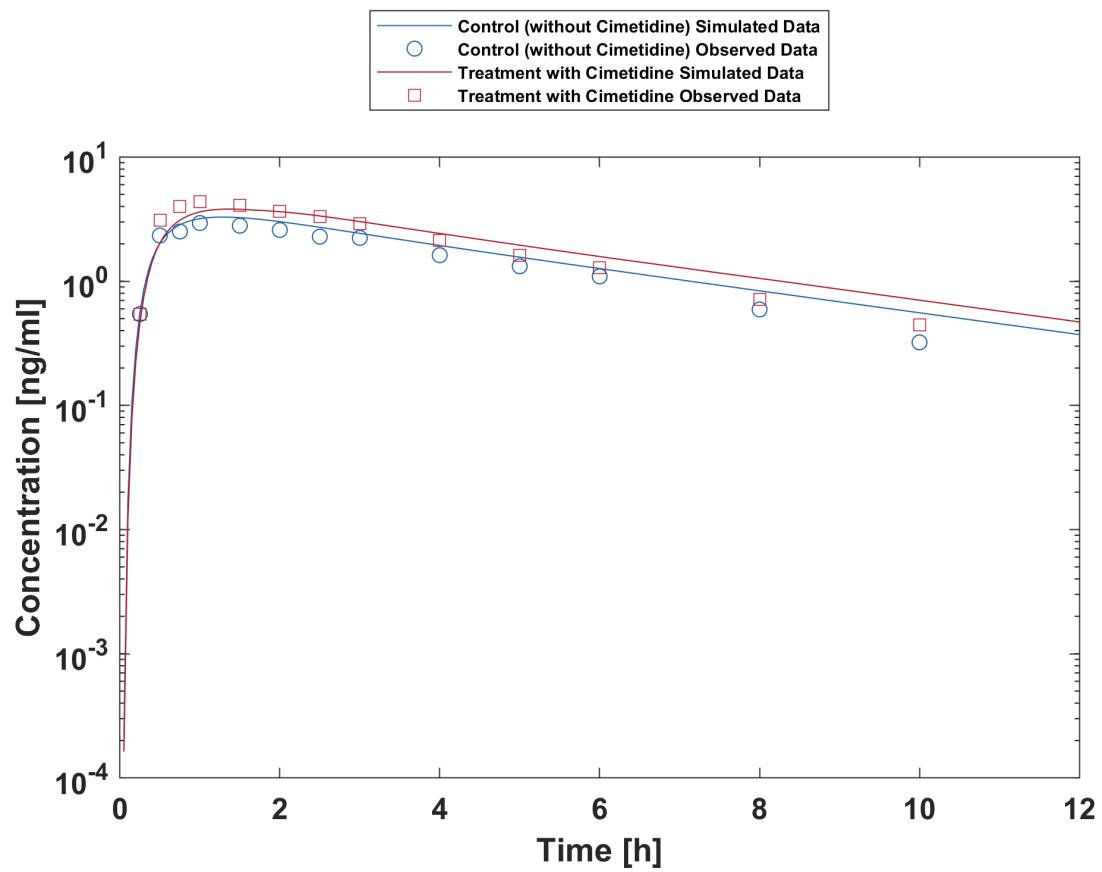


Elliott 1984

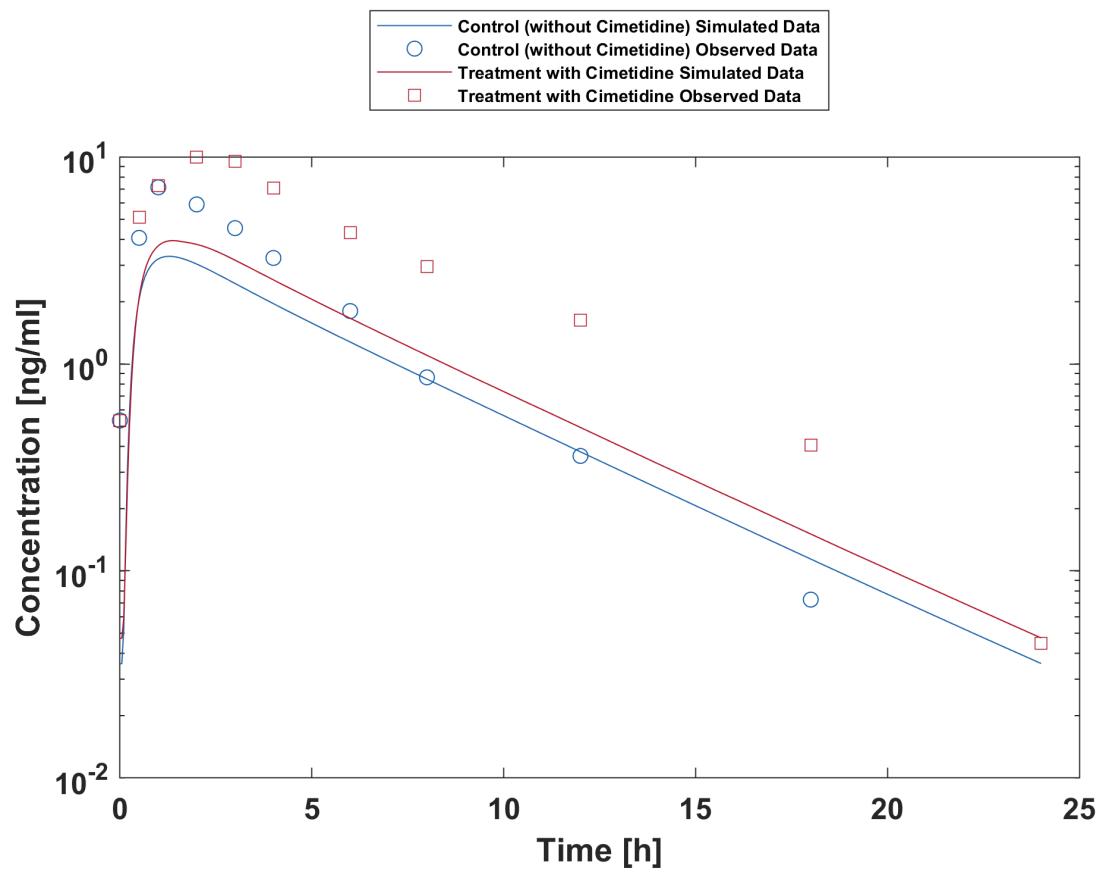
3.4 Cimetidine - Triazolam DDI



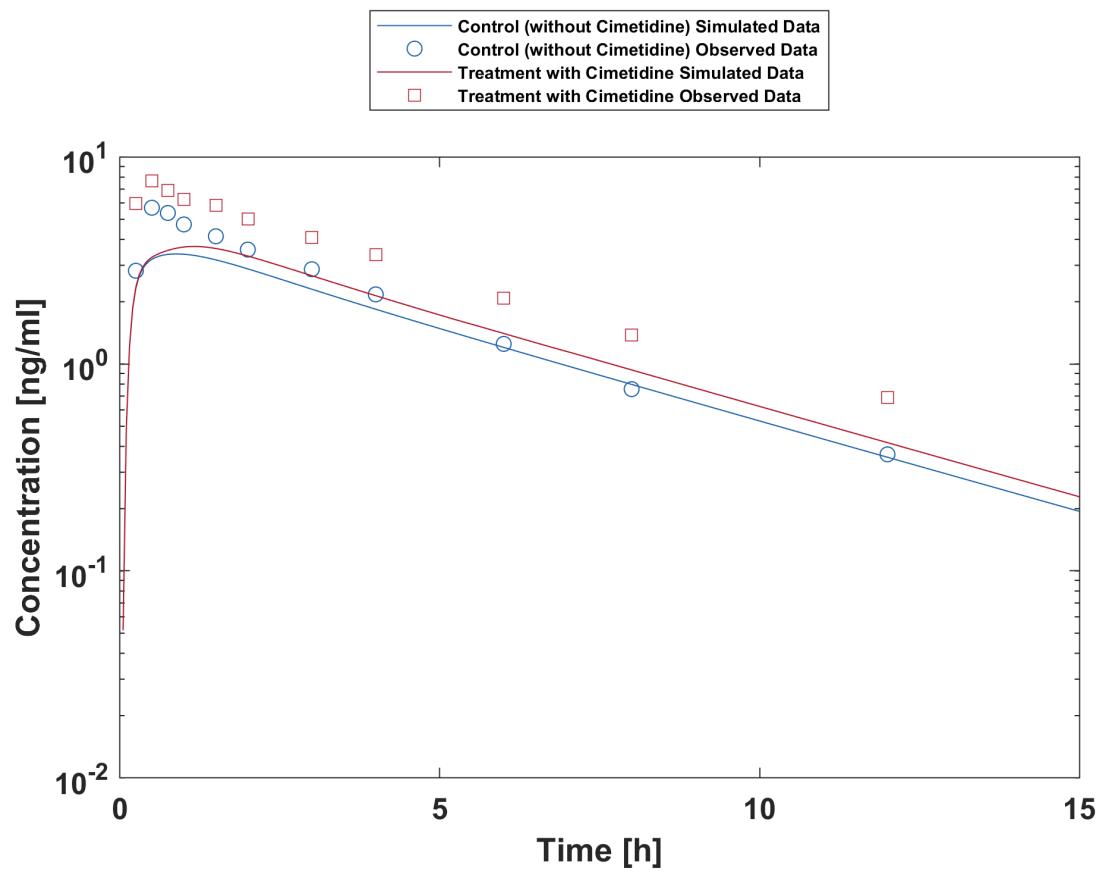
Abernethy 1983



Friedman 1988

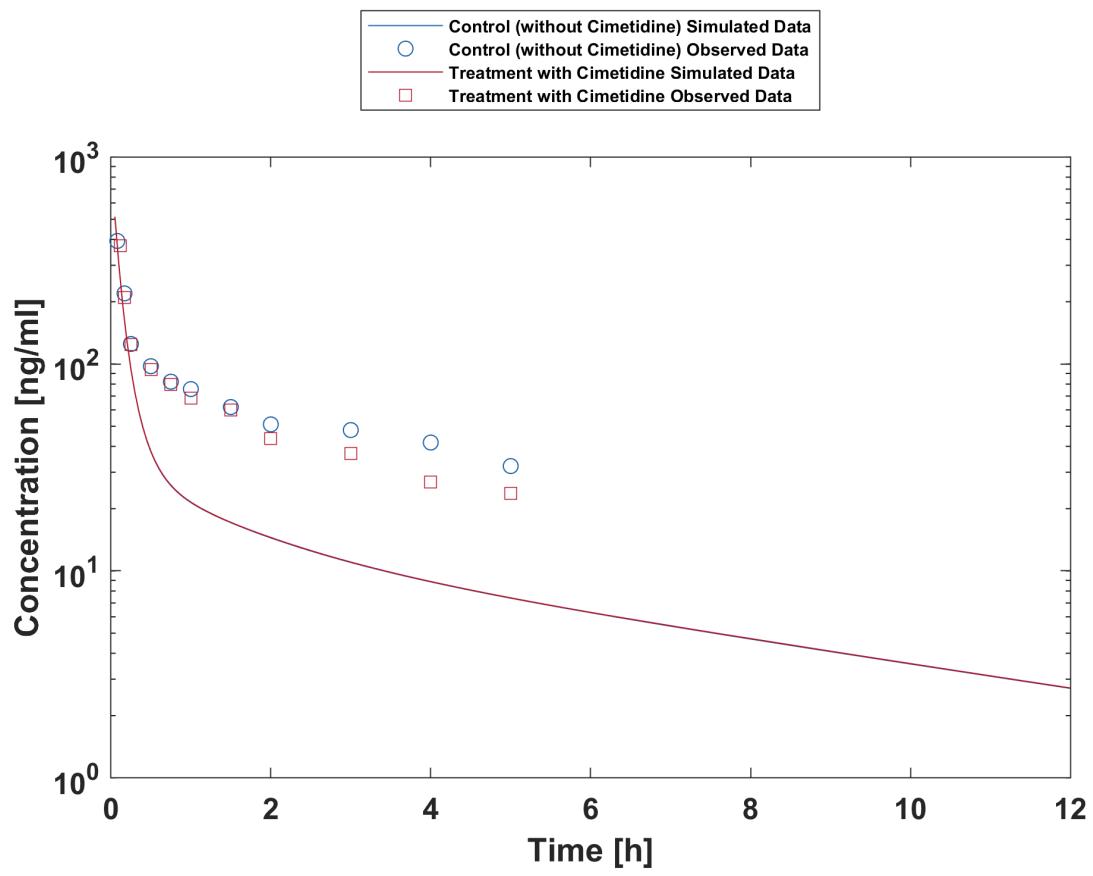


Pourbaix 1985

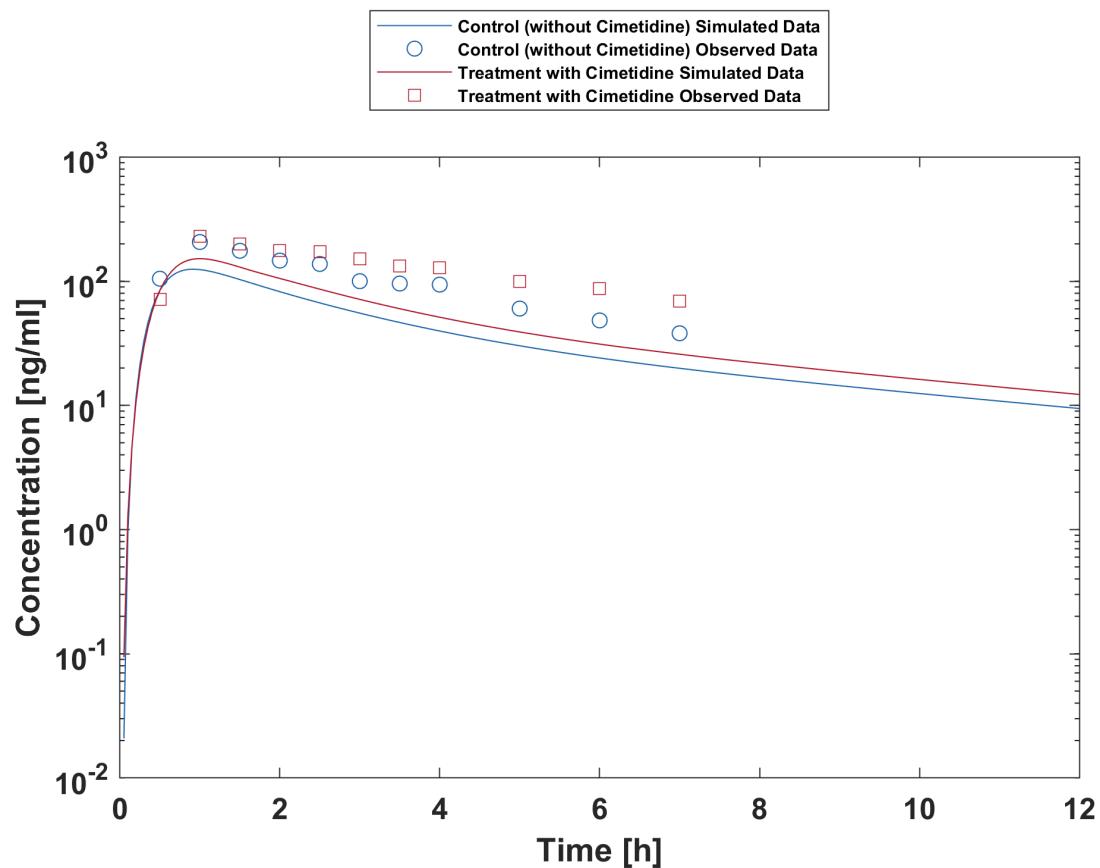


Cox 1986

3.5 Cimetidine - Verapamil DDI

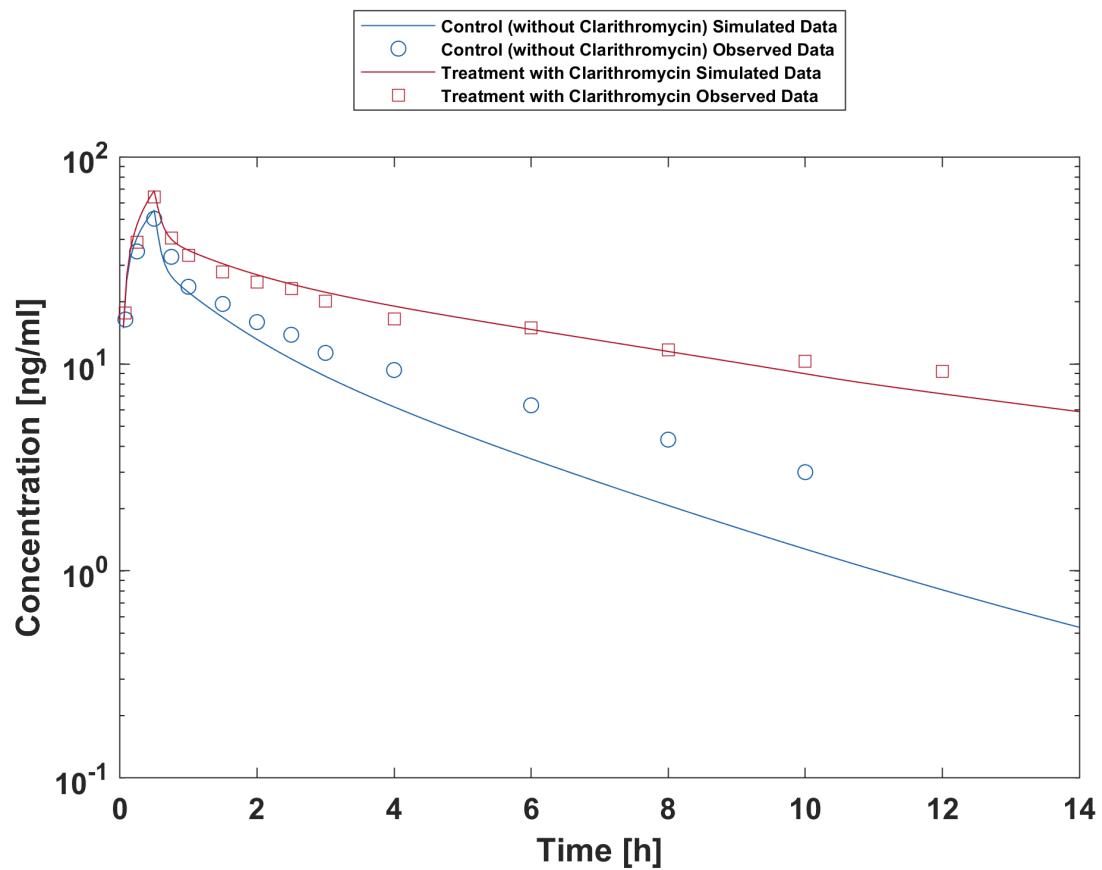


Smith 1984 (verapamil IV)

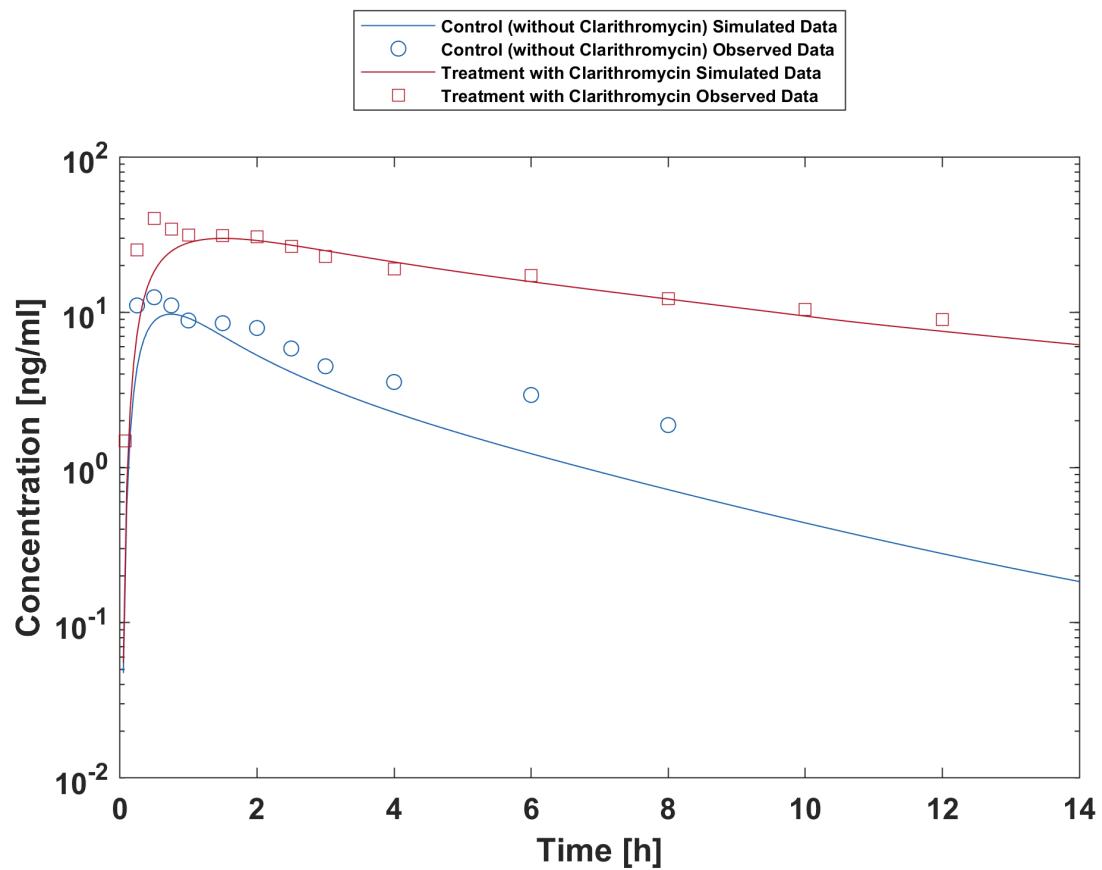


Smith 1984 (verapamil PO)

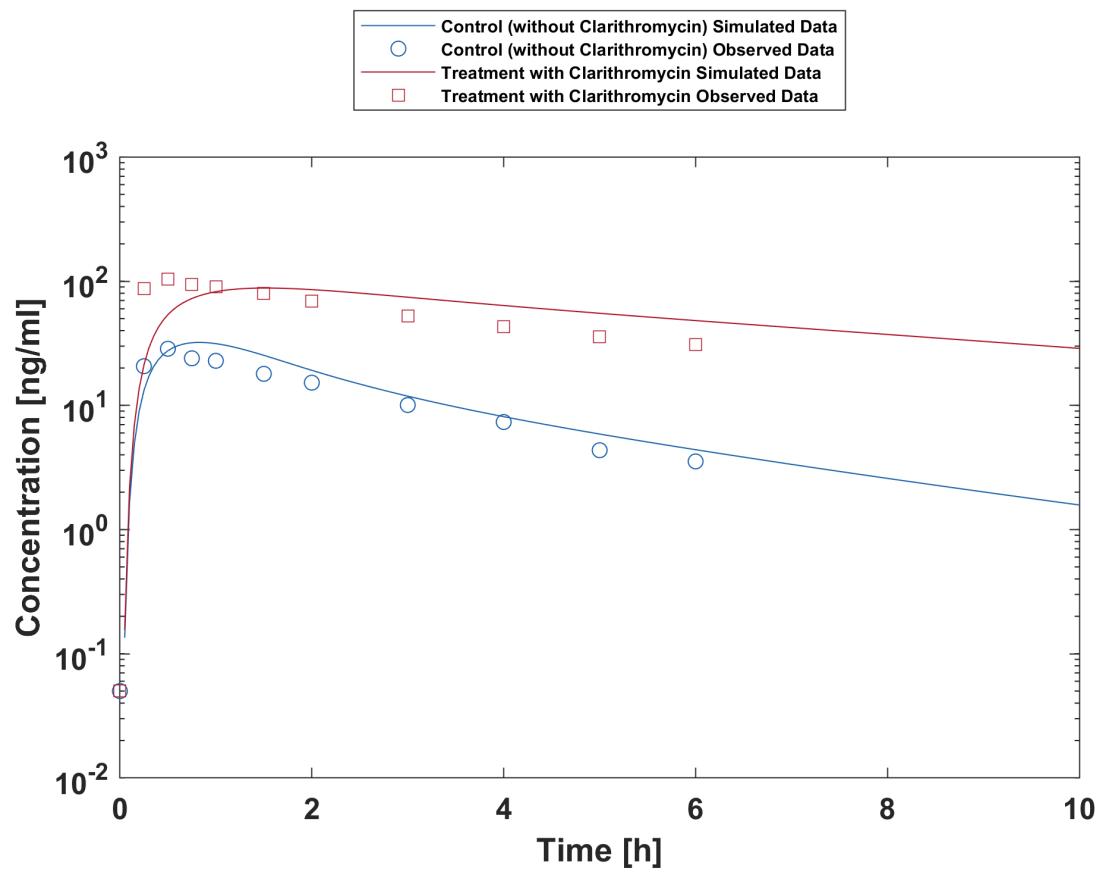
3.6 Clarithromycin - Midazolam DDI



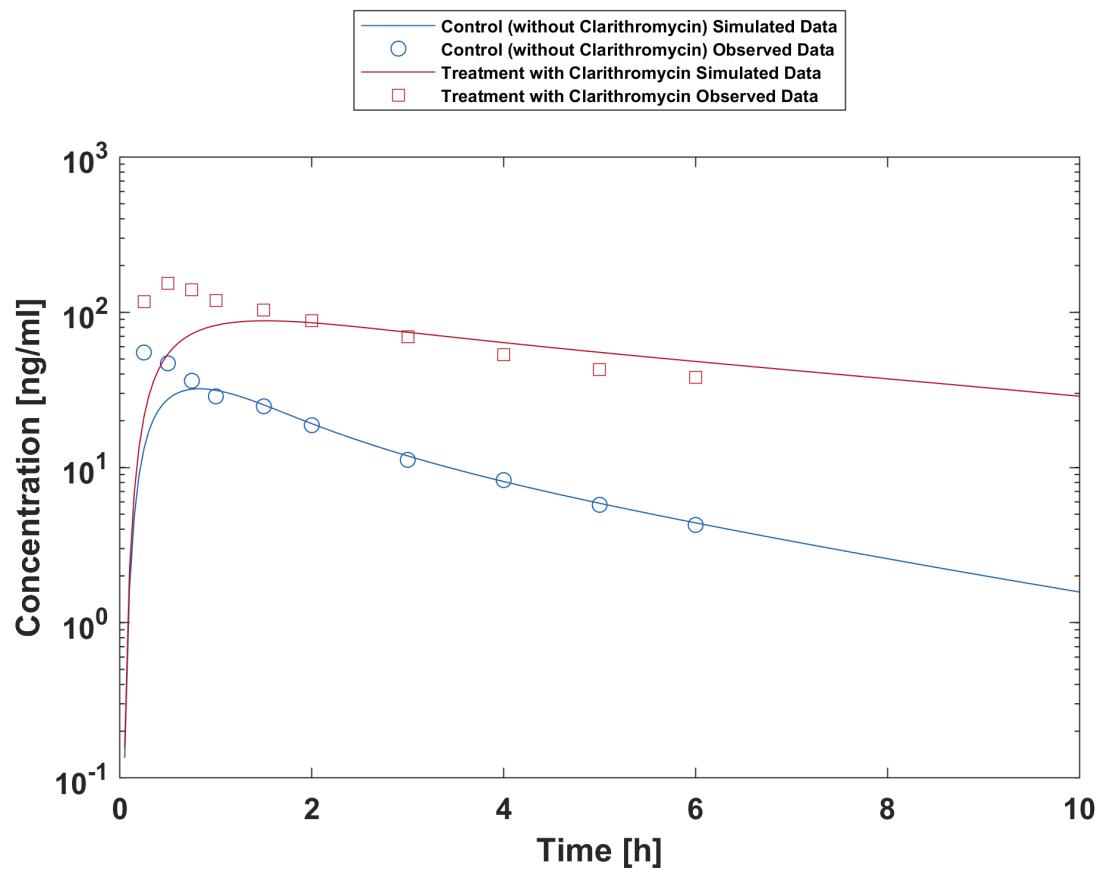
Gorski 1998 (midazolam IV)



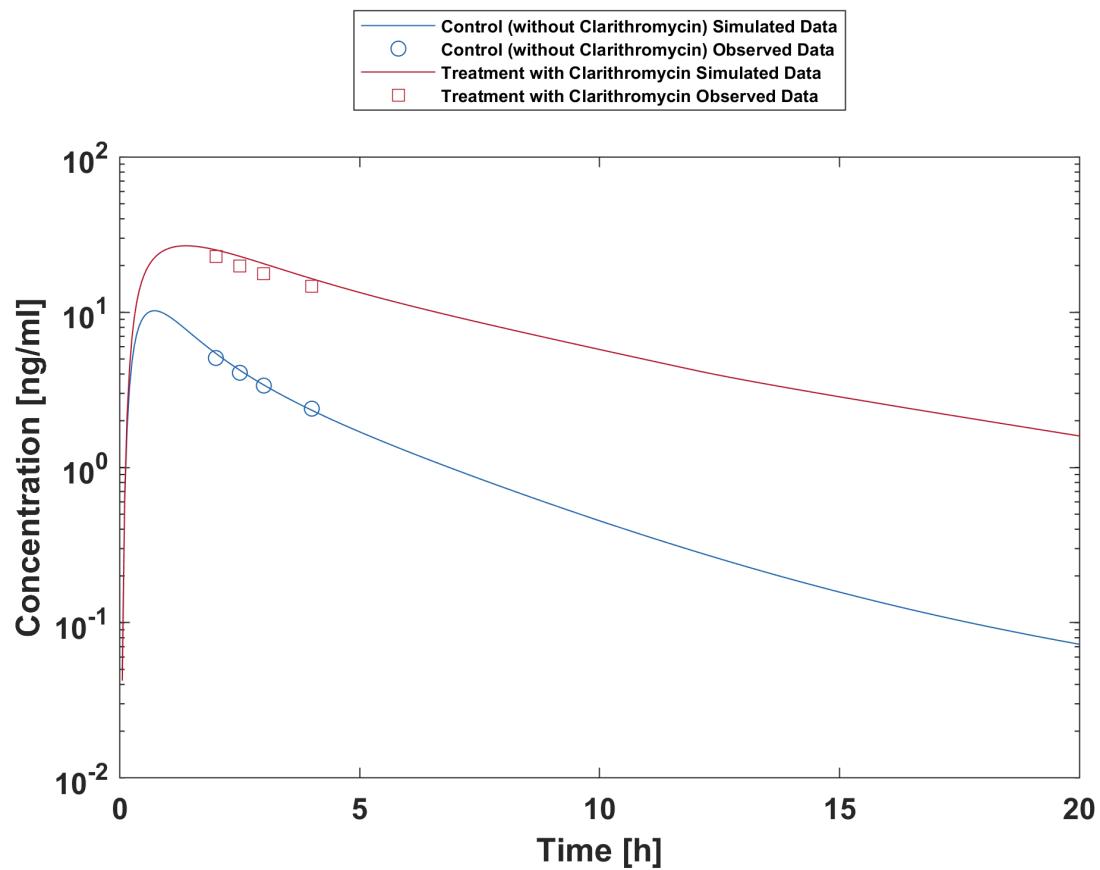
Gorski 1998 (midazolam po)



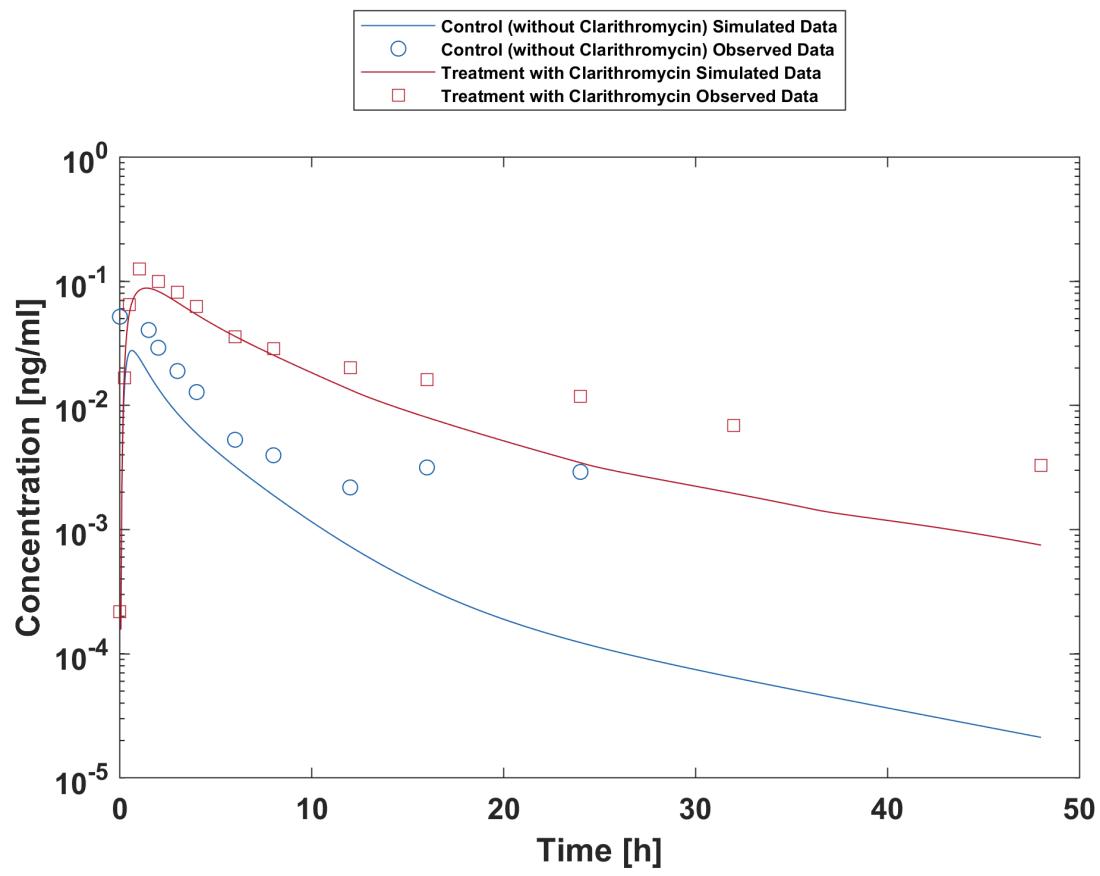
Gurley 2006



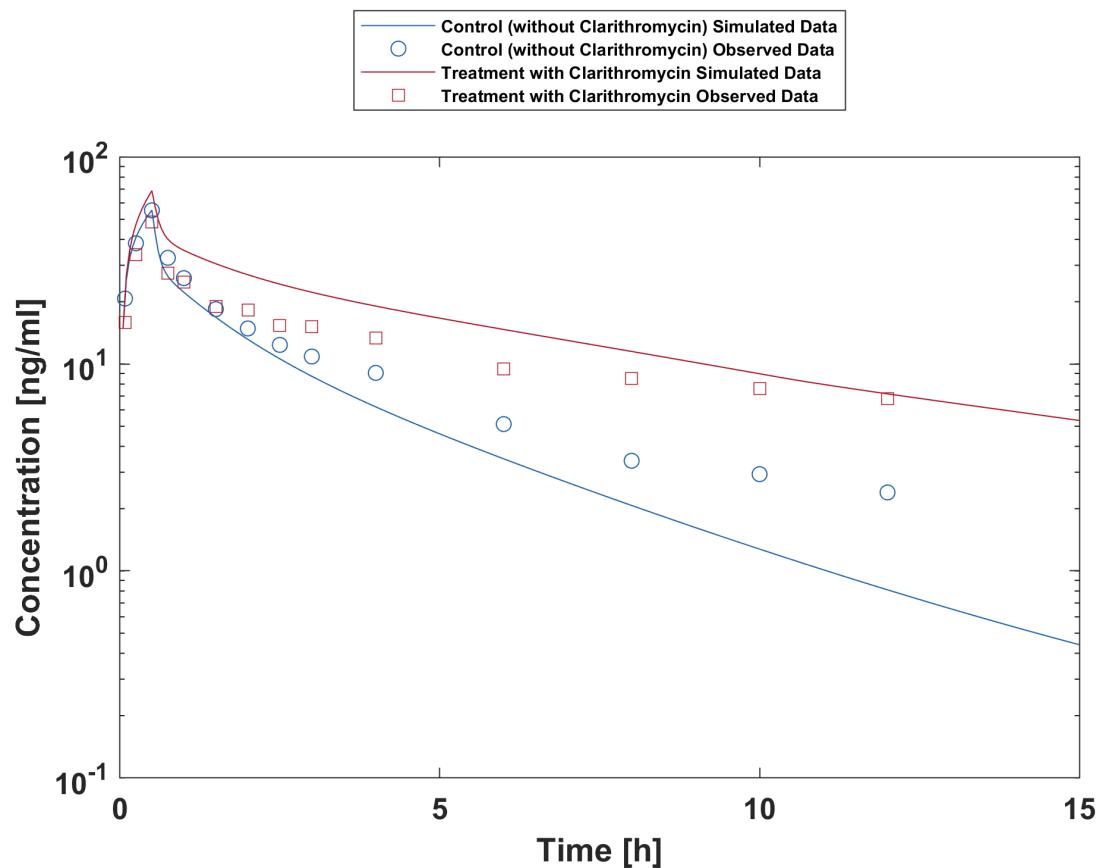
Gurley 2008a



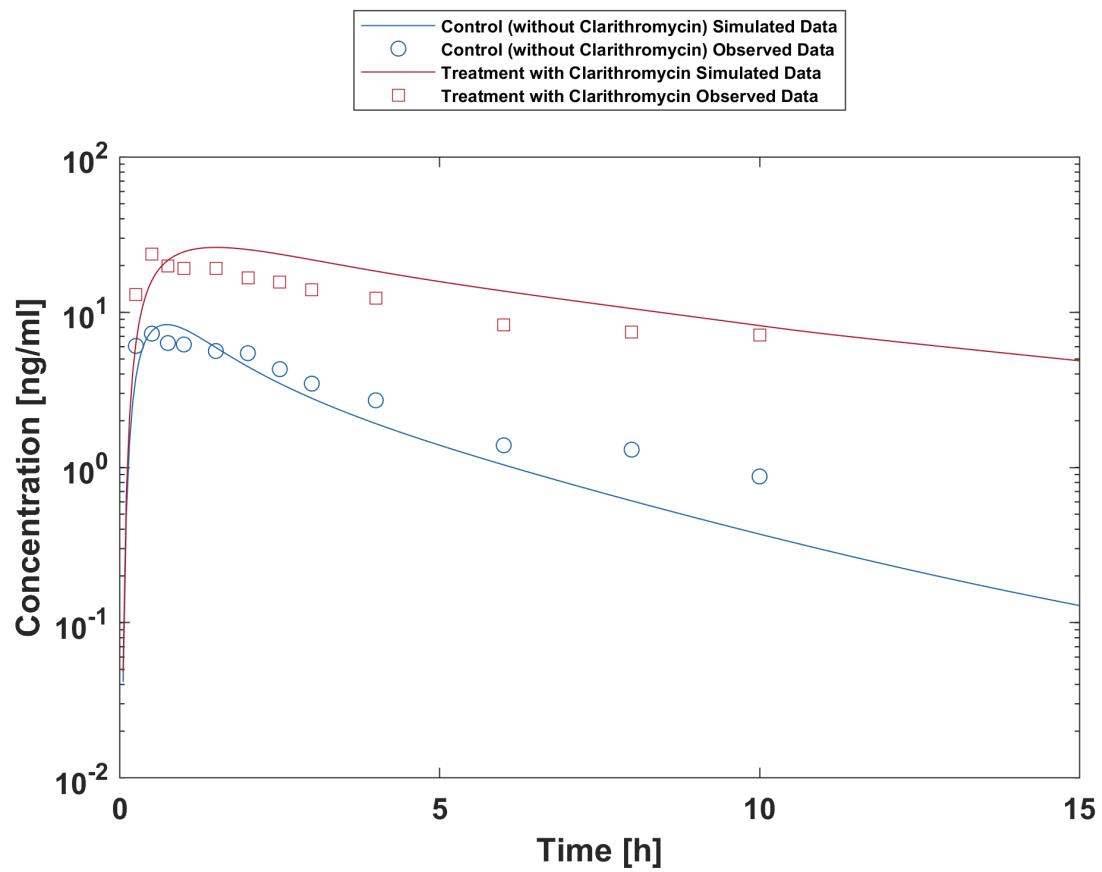
Markert 2013



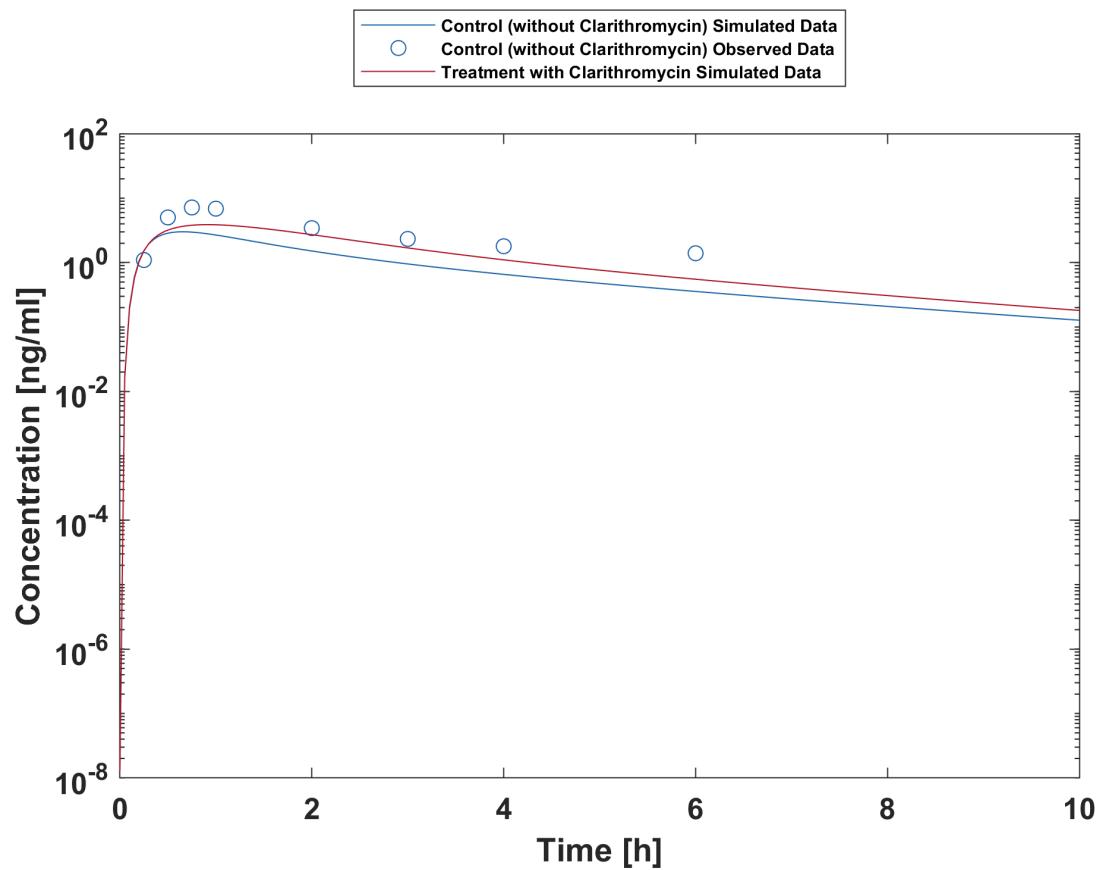
Pruksaritanont 2017



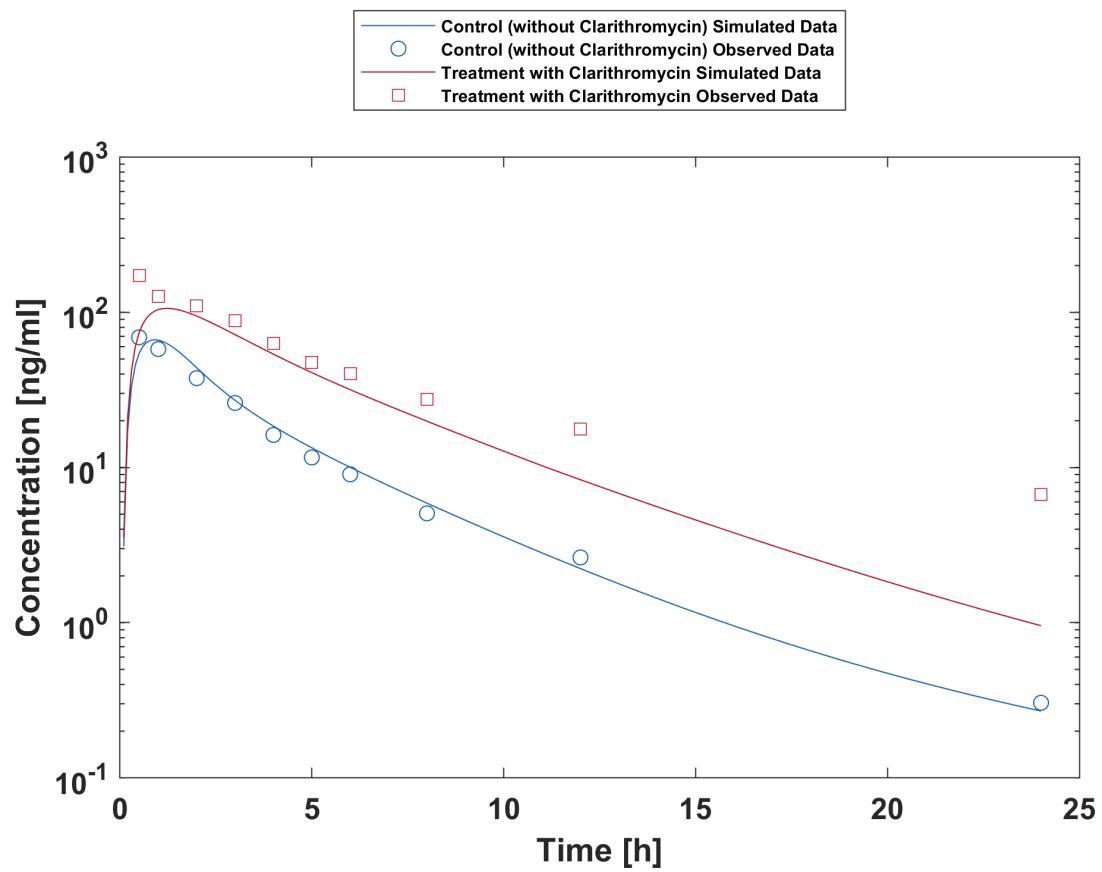
Quinney 2008 (midazolam IV)



Quinney 2008 (midazolam po)

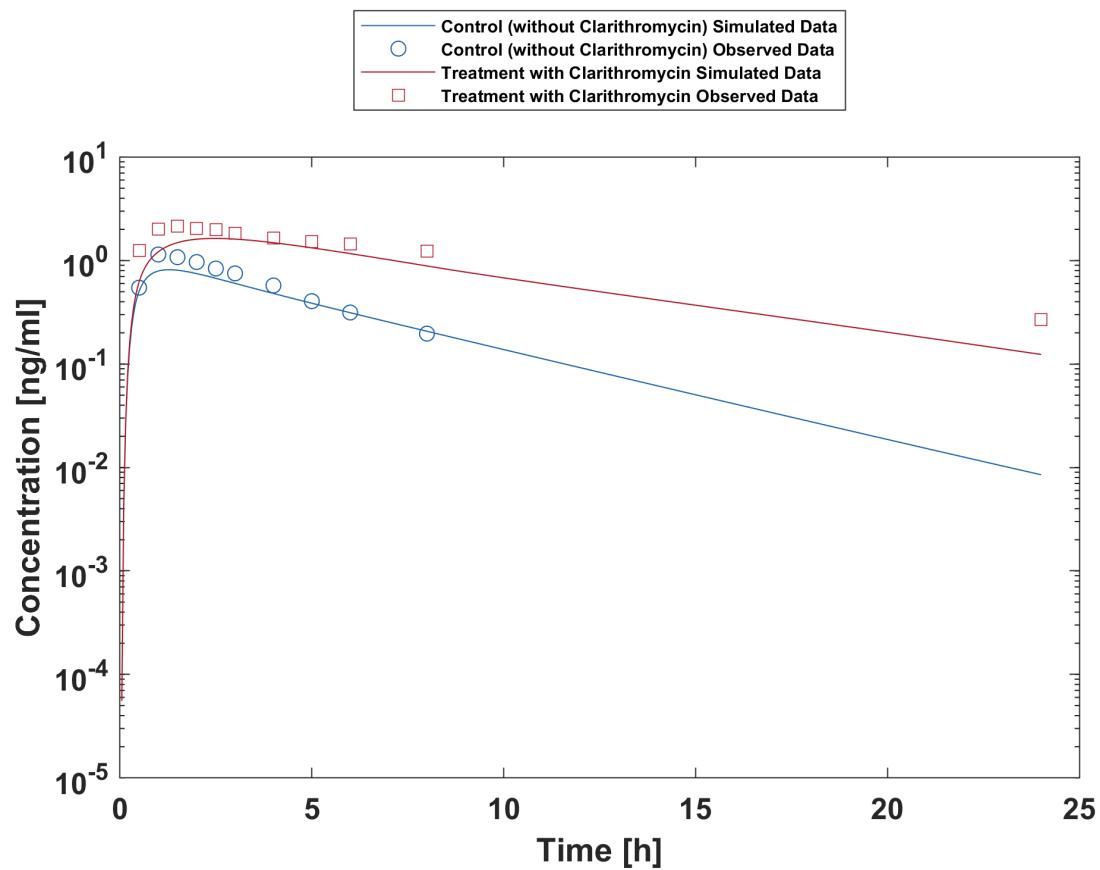


van Dyk 2018



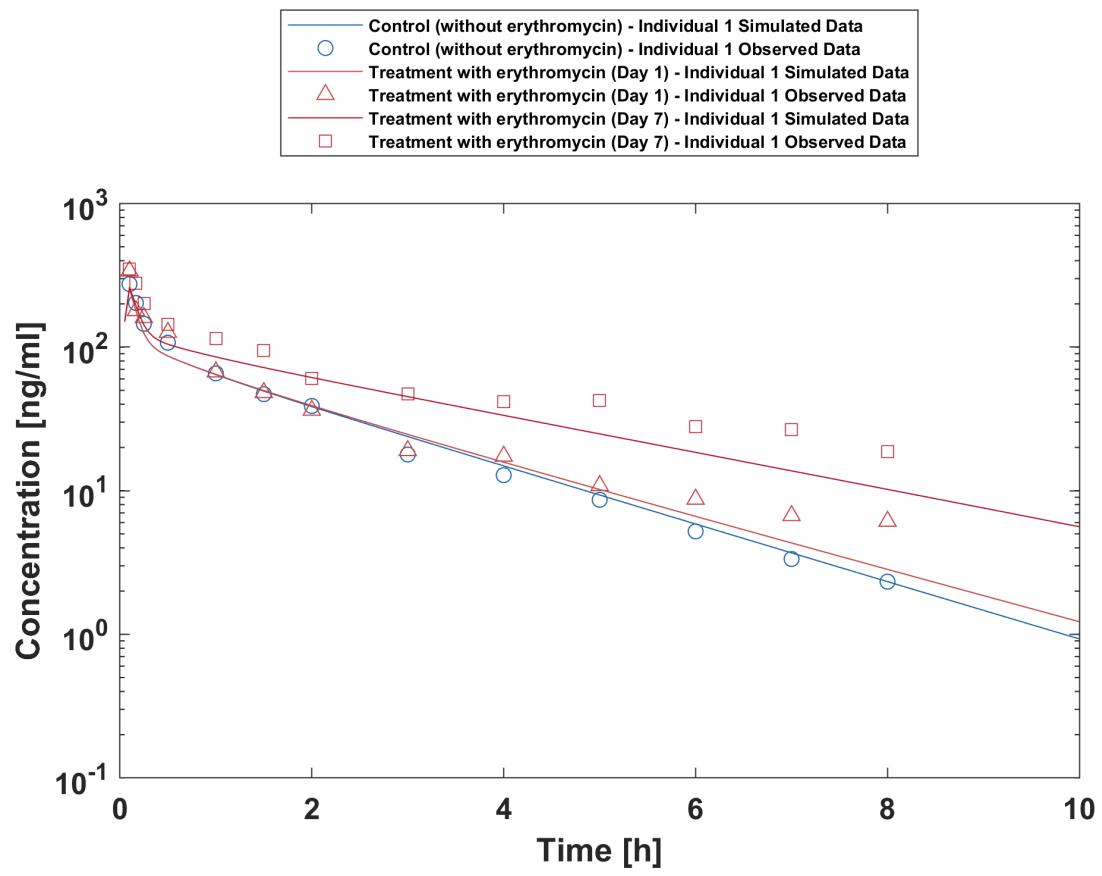
Yeates 1996

3.7 Clarithromycin - Triazolam DDI

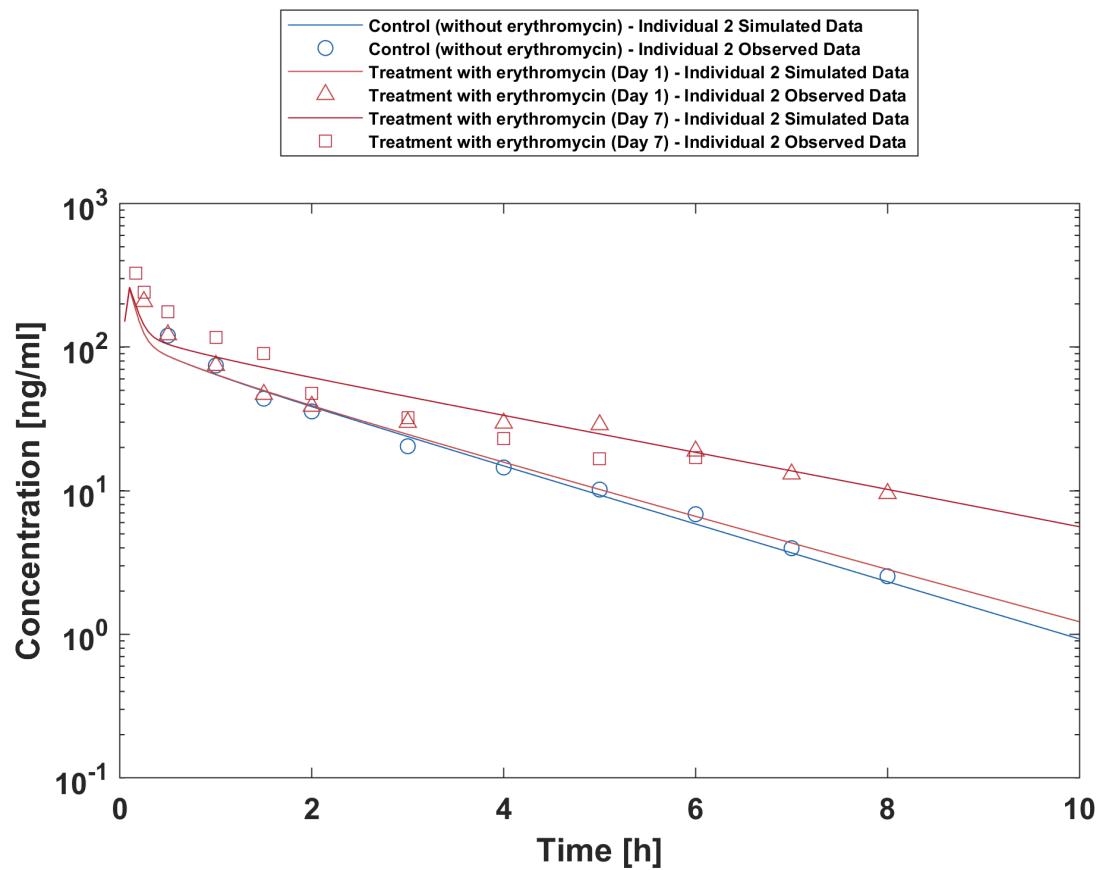


Greenblatt 1998a

3.8 Erythromycin - Alfentanil DDI

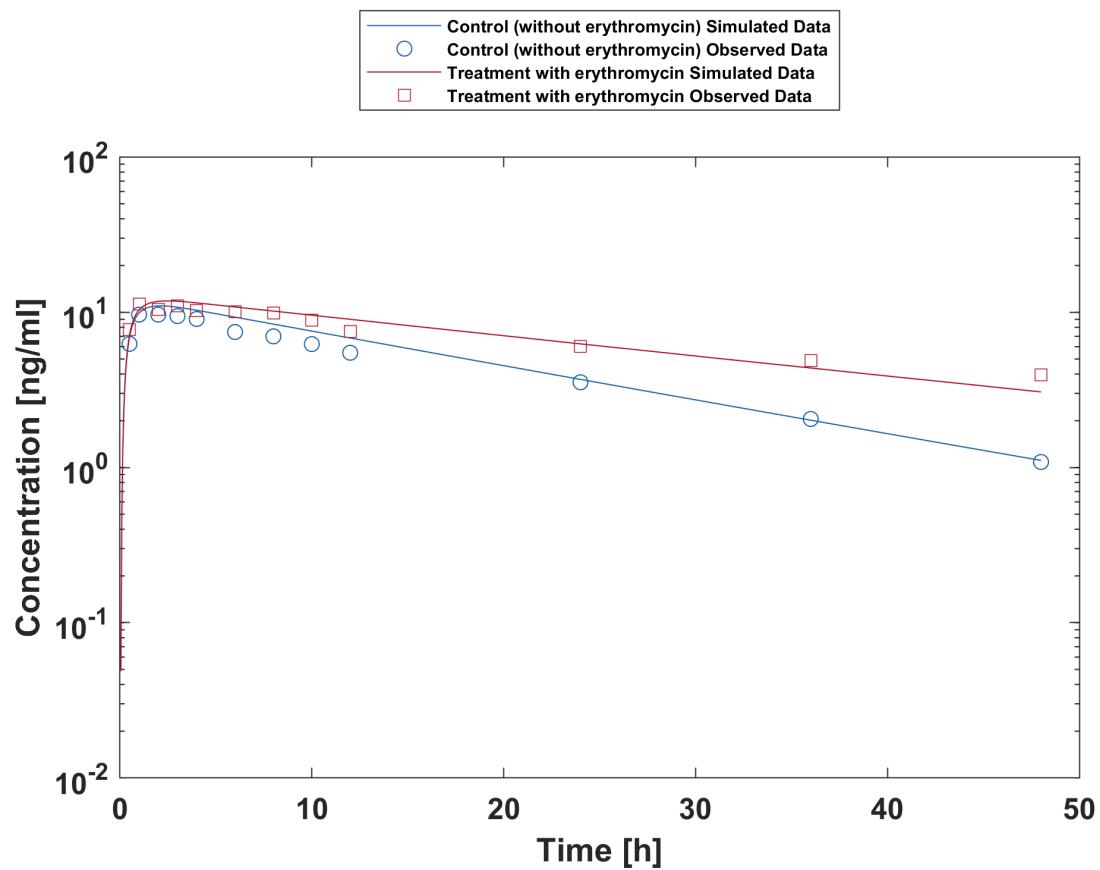


Bartkowski 1989



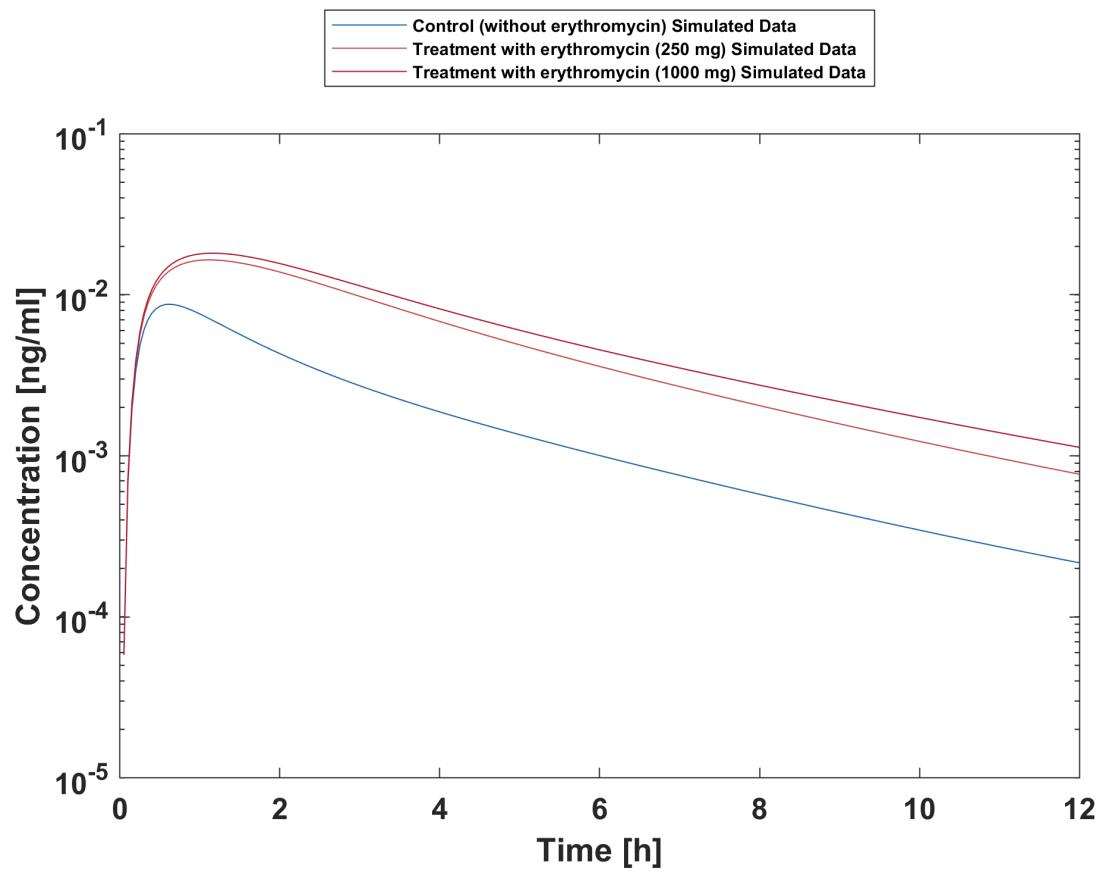
Bartkowski 1993

3.9 Erythromycin - Alprazolam DDI

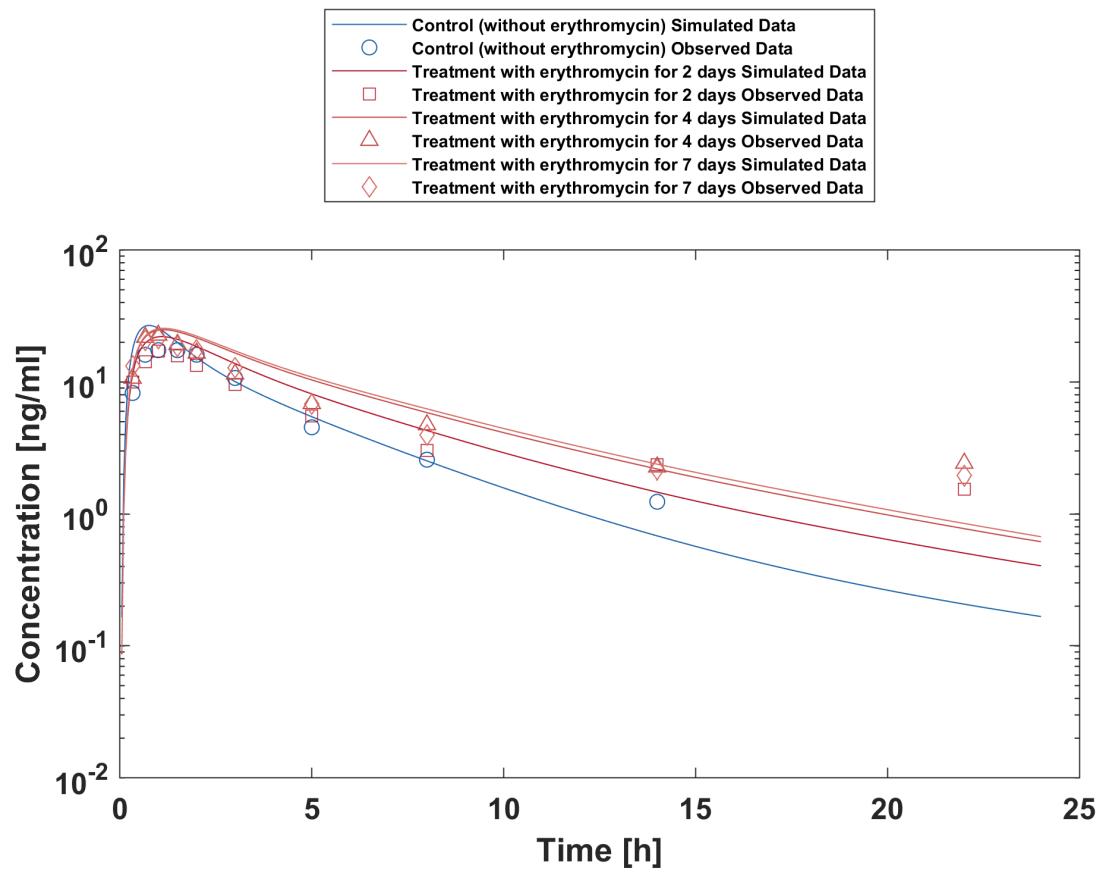


Yasui 1996

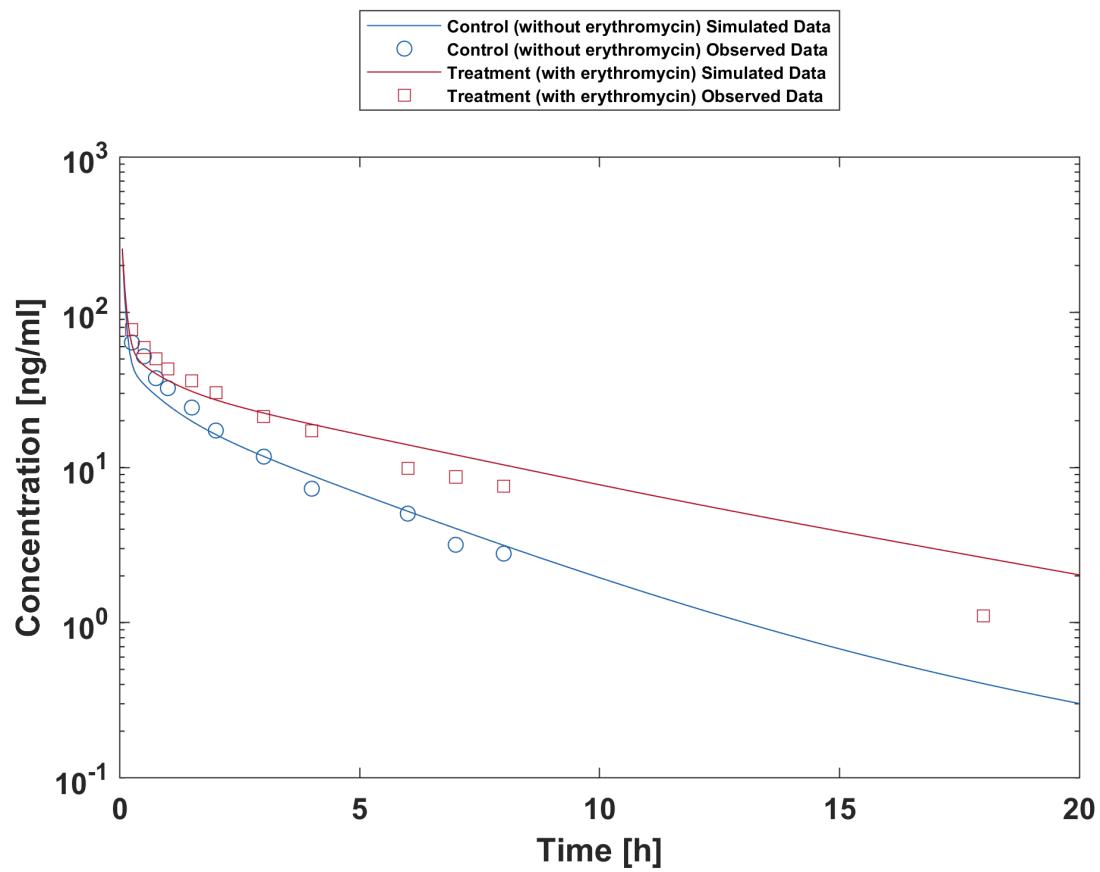
3.10 Erythromycin - Midazolam DDI



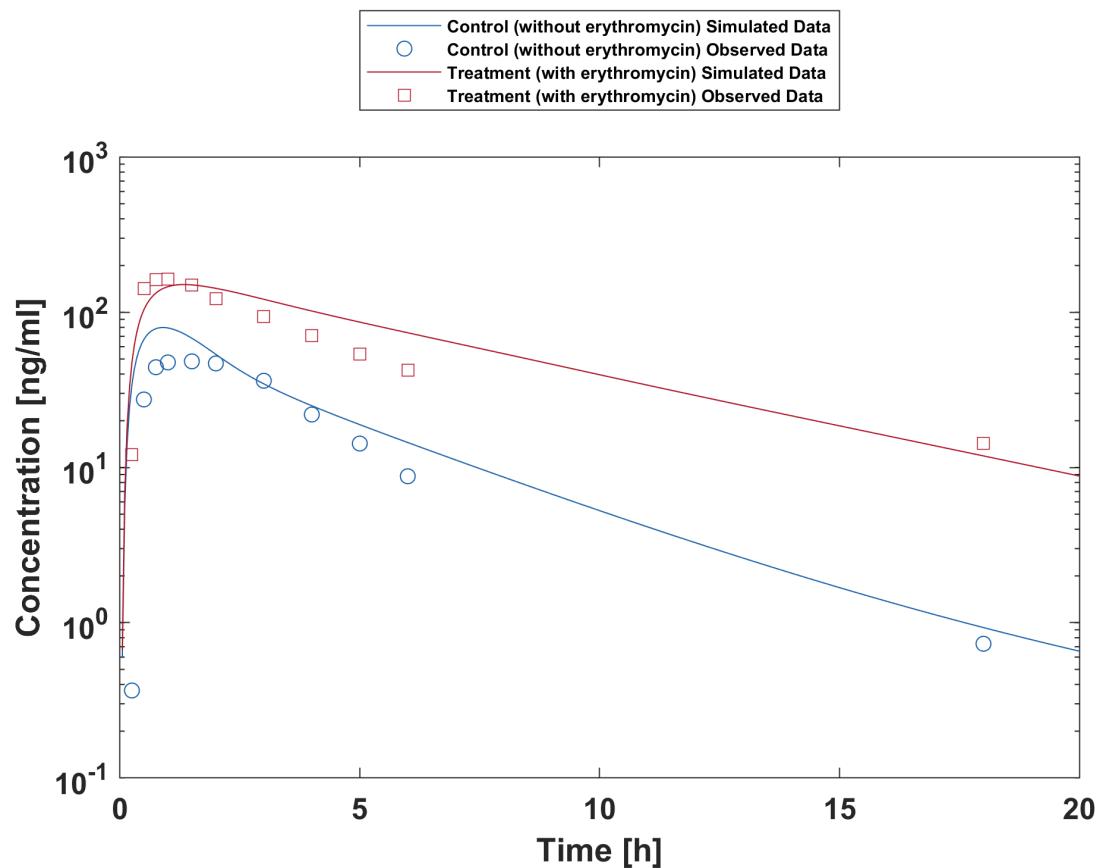
Carls 2014



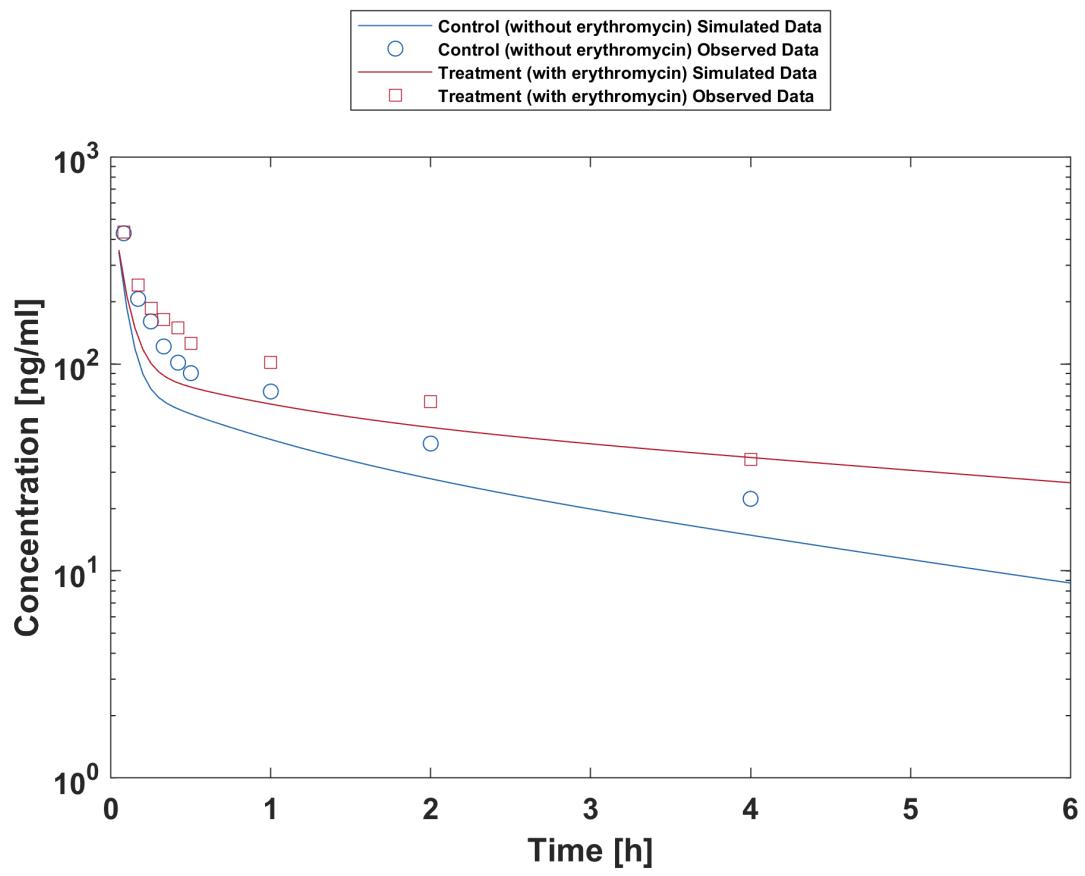
Okudaira 2007



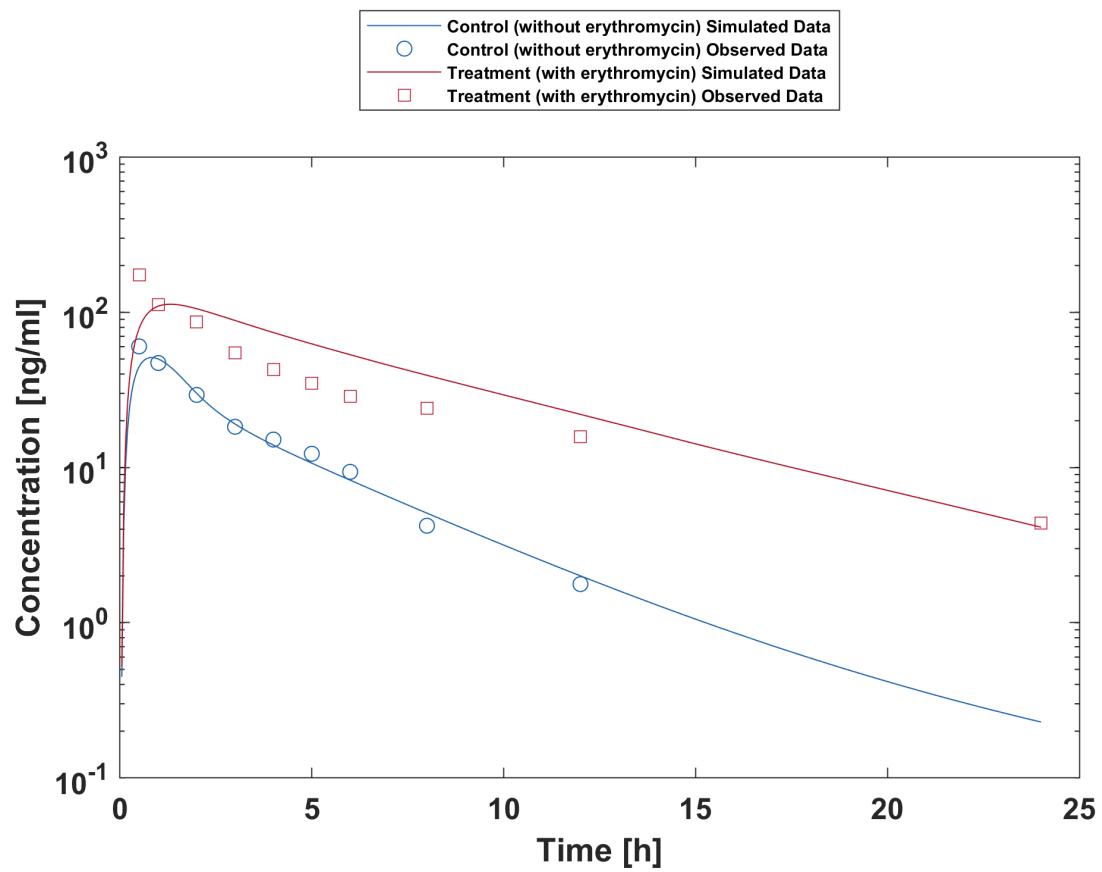
Olkola 1993 (midazolam IV)



Olkola 1993 (midazolam po)

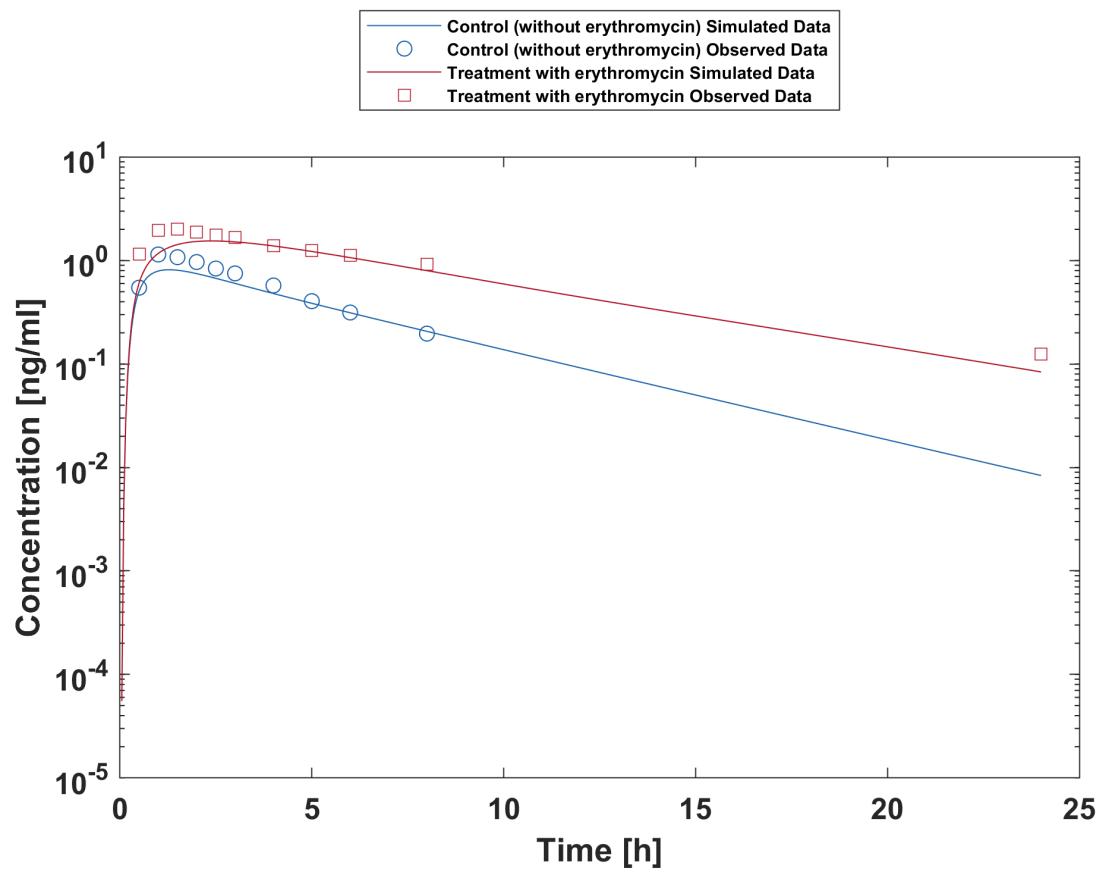


Swart 2002

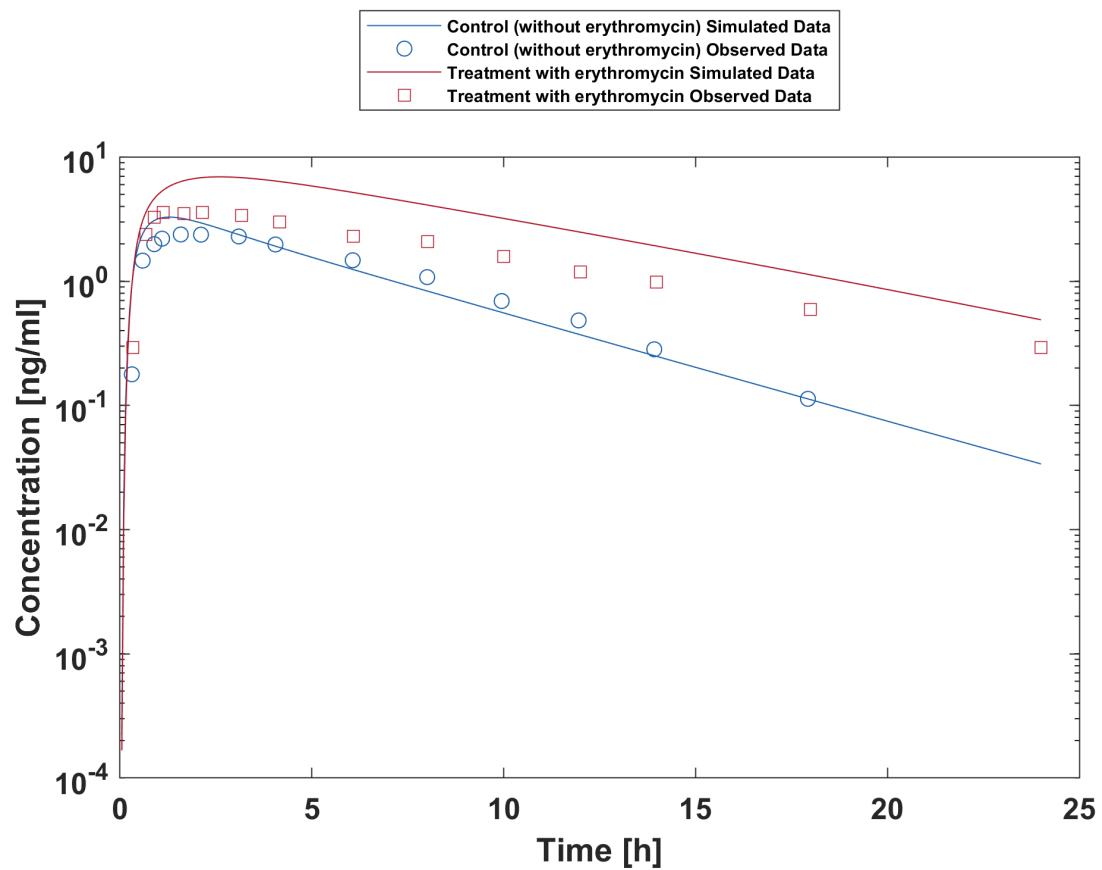


Zimmermann 1996

3.11 Erythromycin - Triazolam DDI

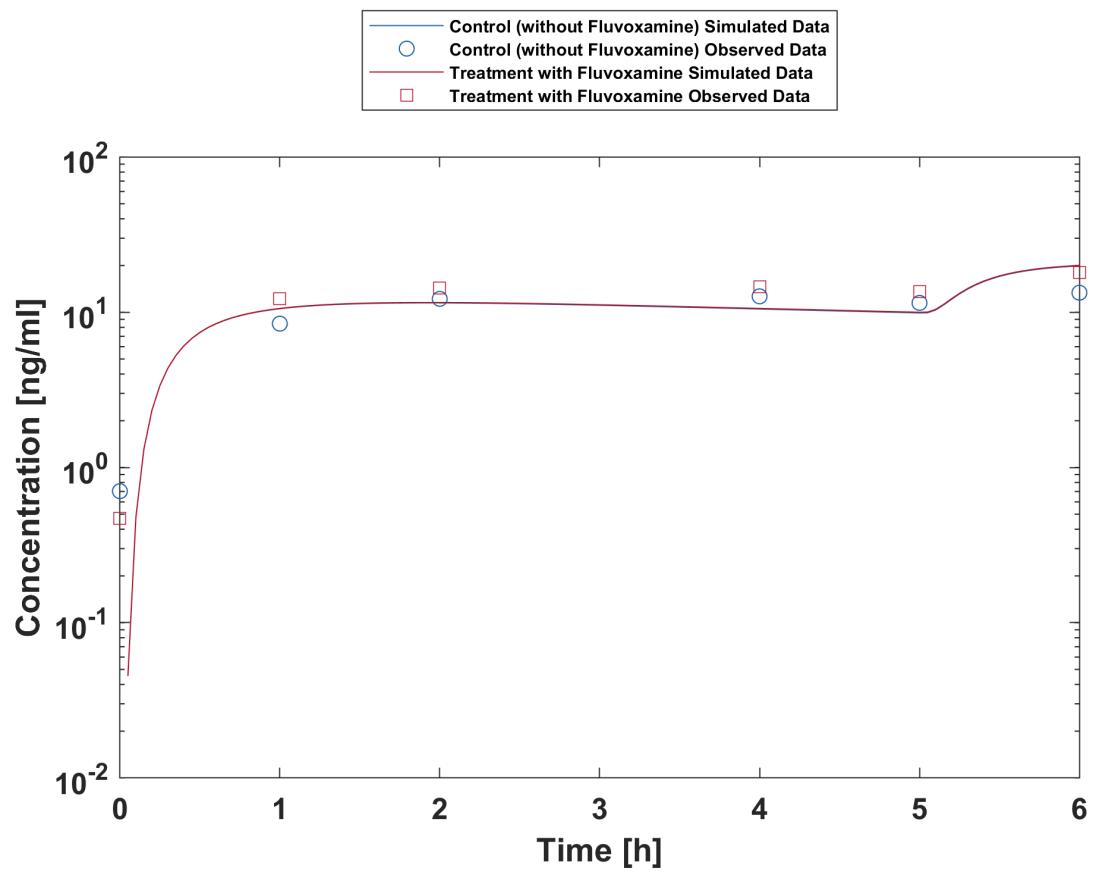


Greenblatt 1998

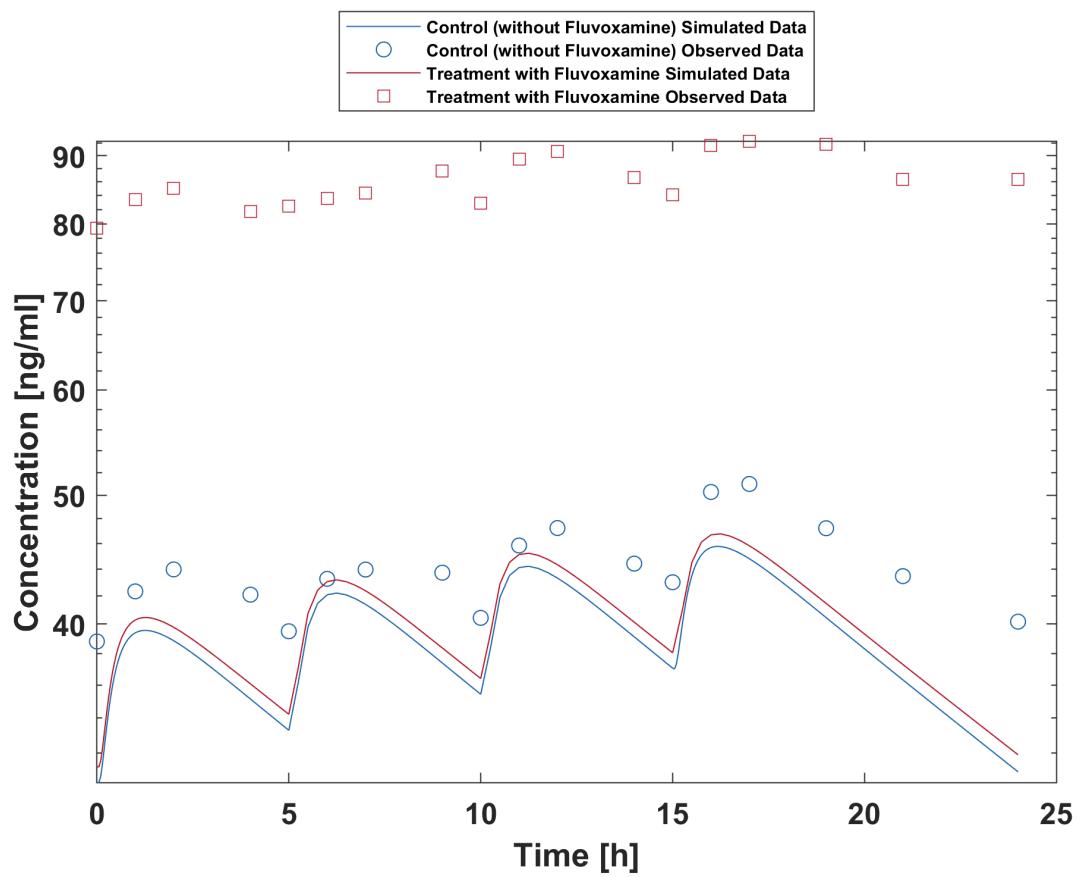


Phillips 1986

3.12 Fluvoxamine - Alprazolam DDI

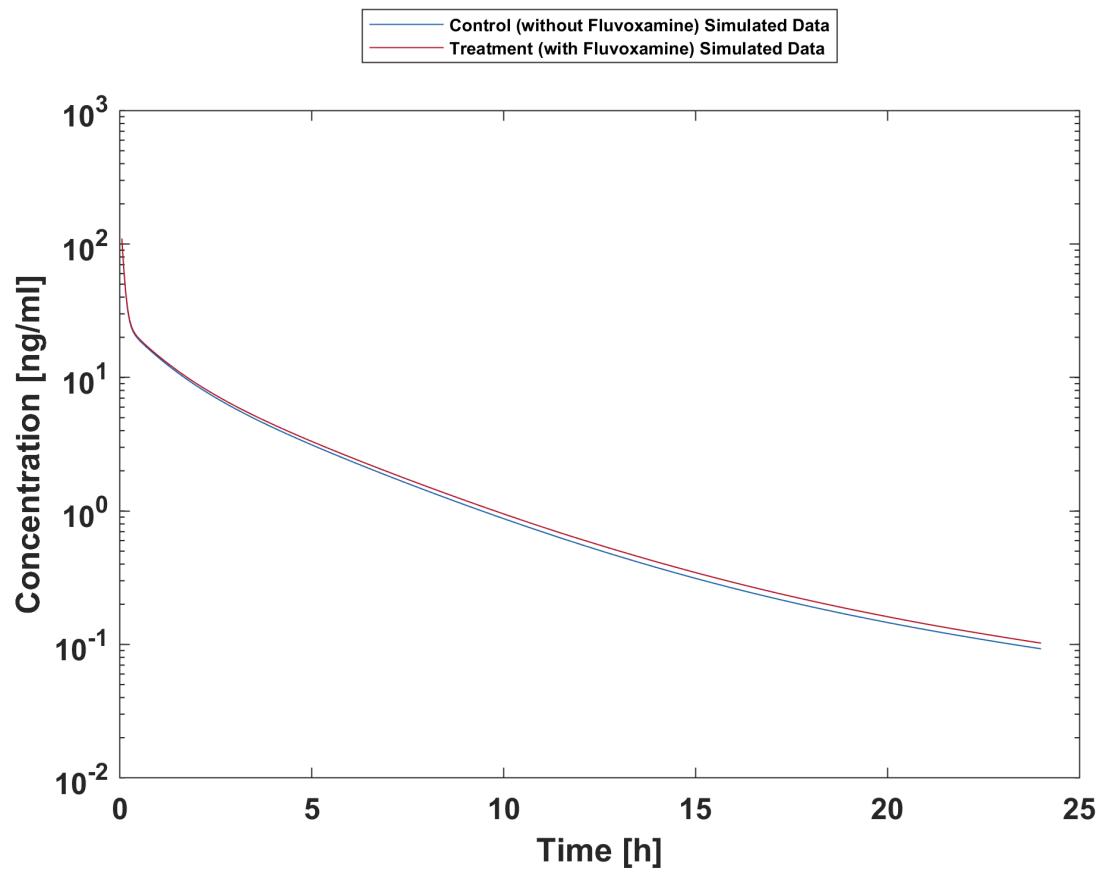


Fleishaker 1994 (Day 1, first dose)

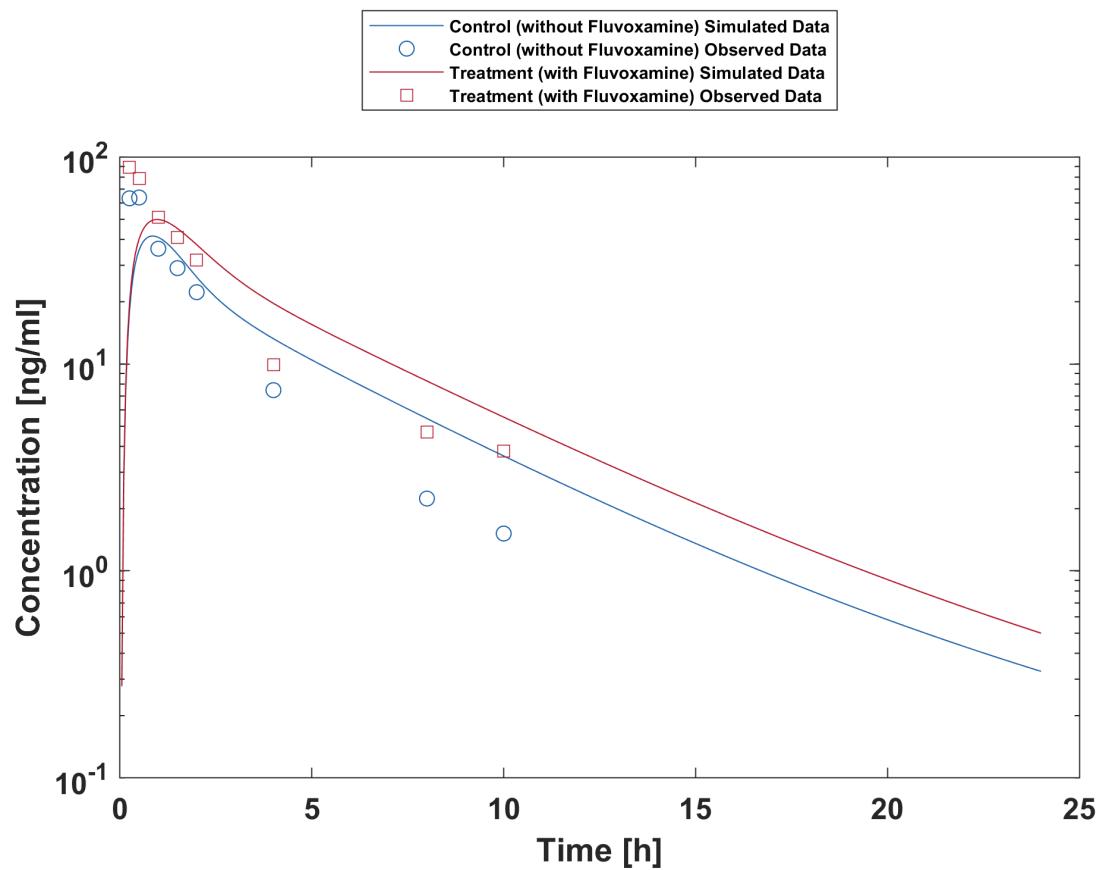


Fleishaker 1994 (Day 10)

3.13 Fluvoxamine - Midazolam DDI

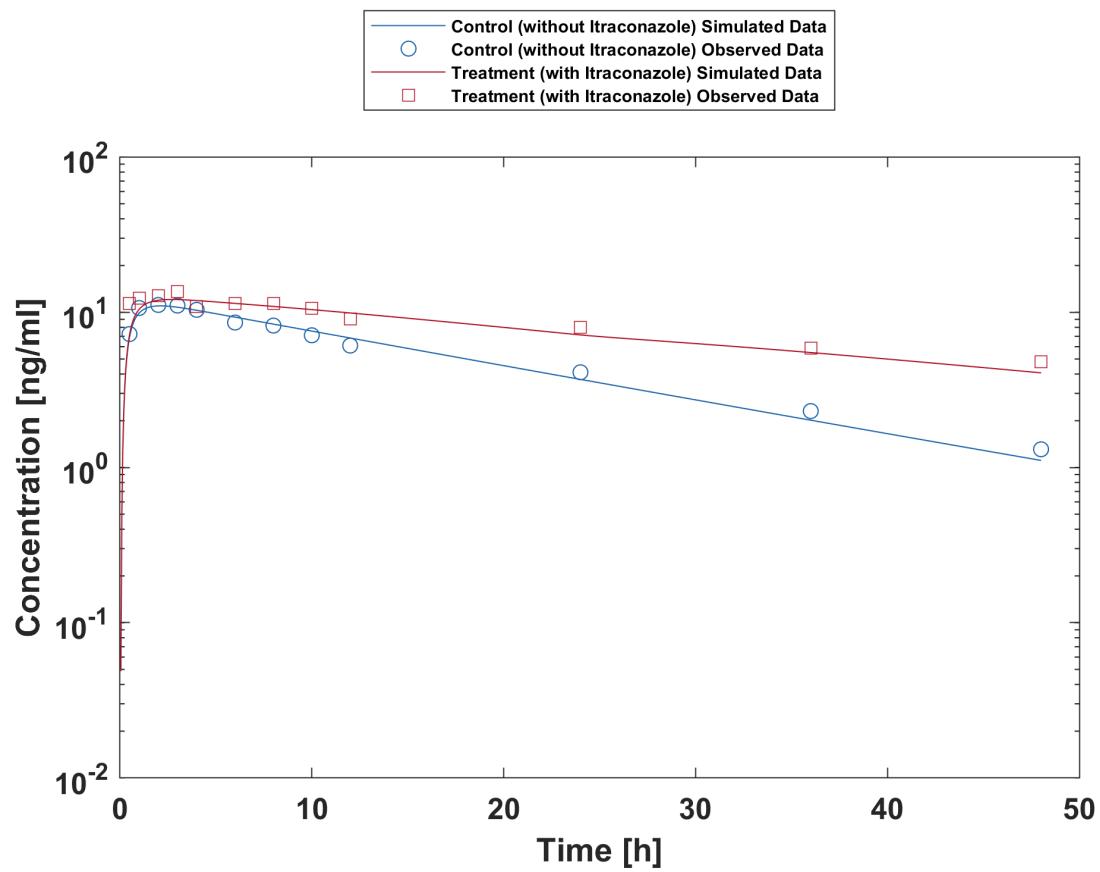


Kashuba 1998



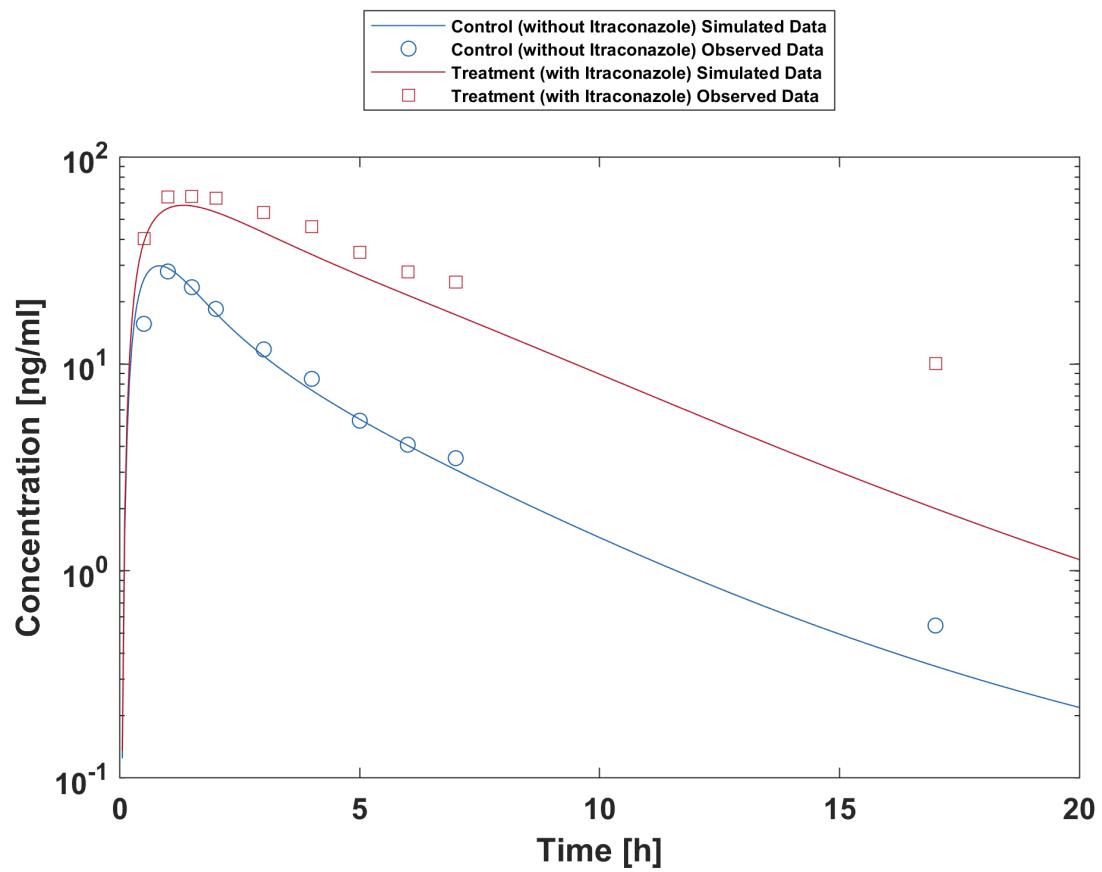
Lam 2003

3.14 Itraconazole - Alprazolam DDI

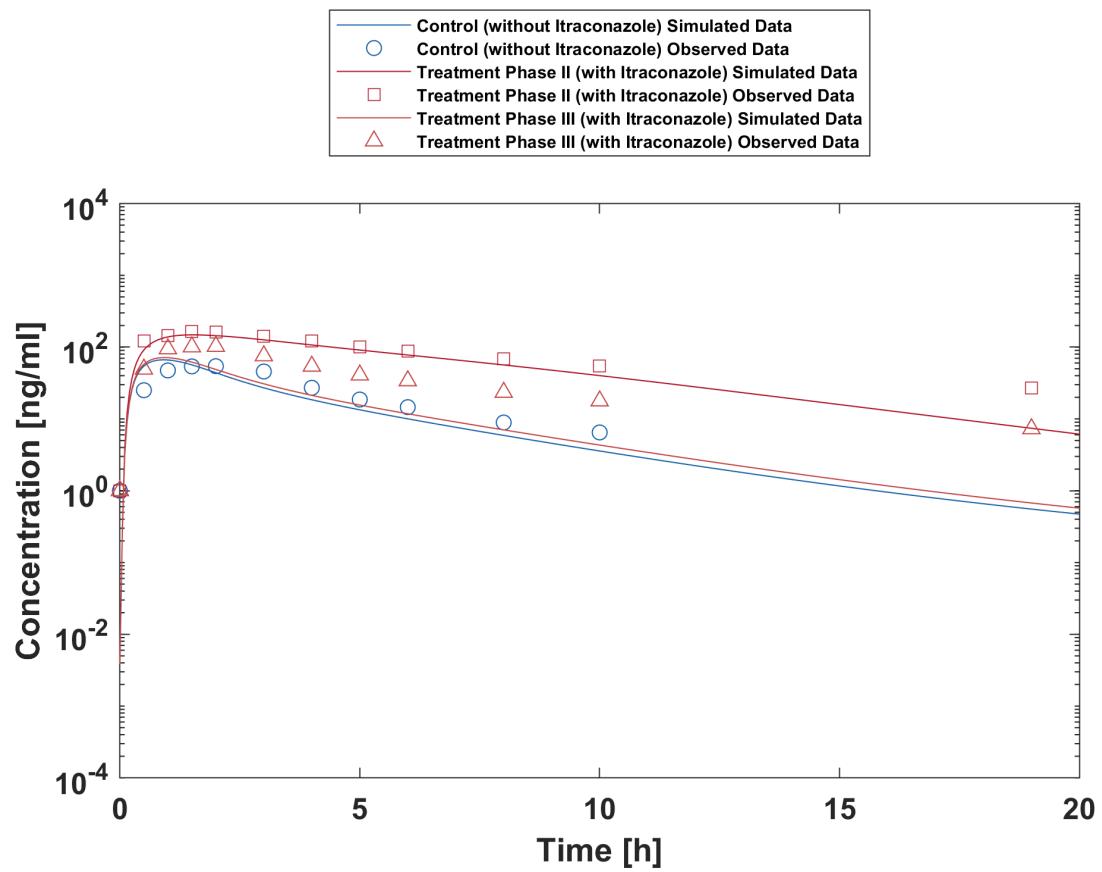


Yasui 1998

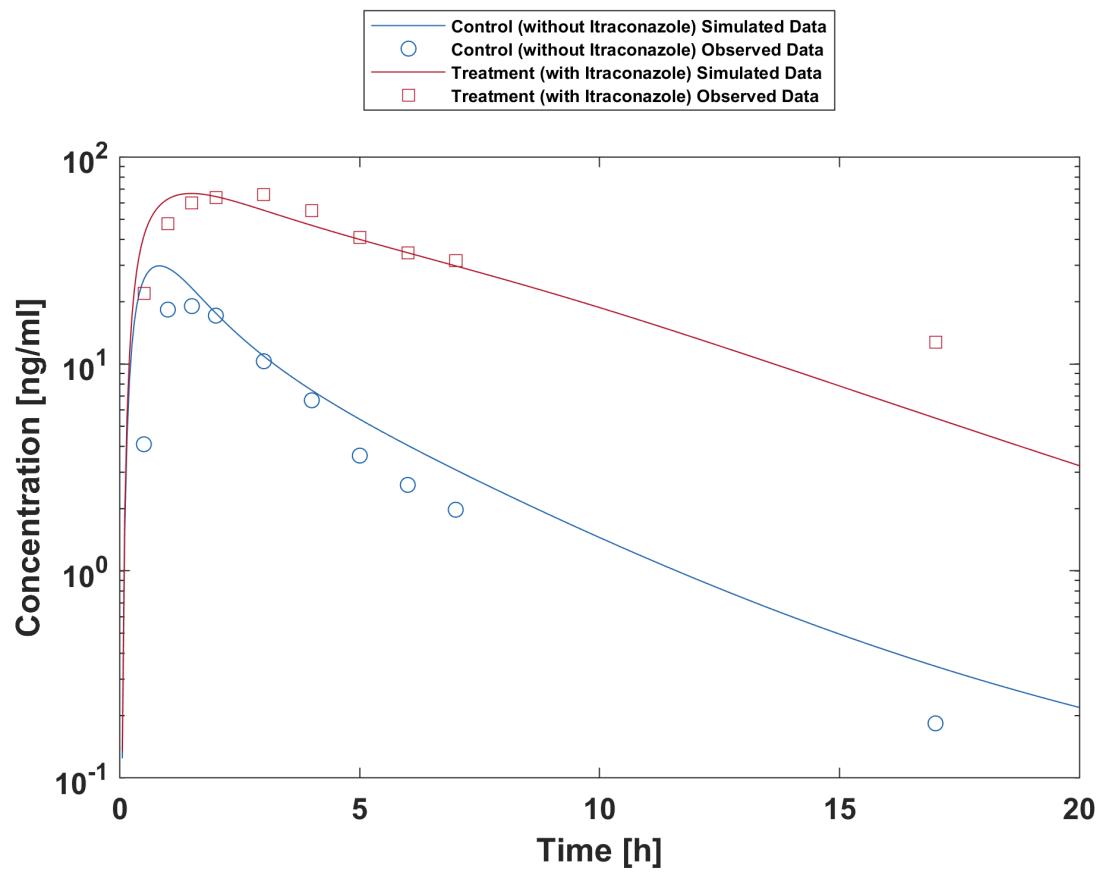
3.15 Itraconazole - Midazolam DDI



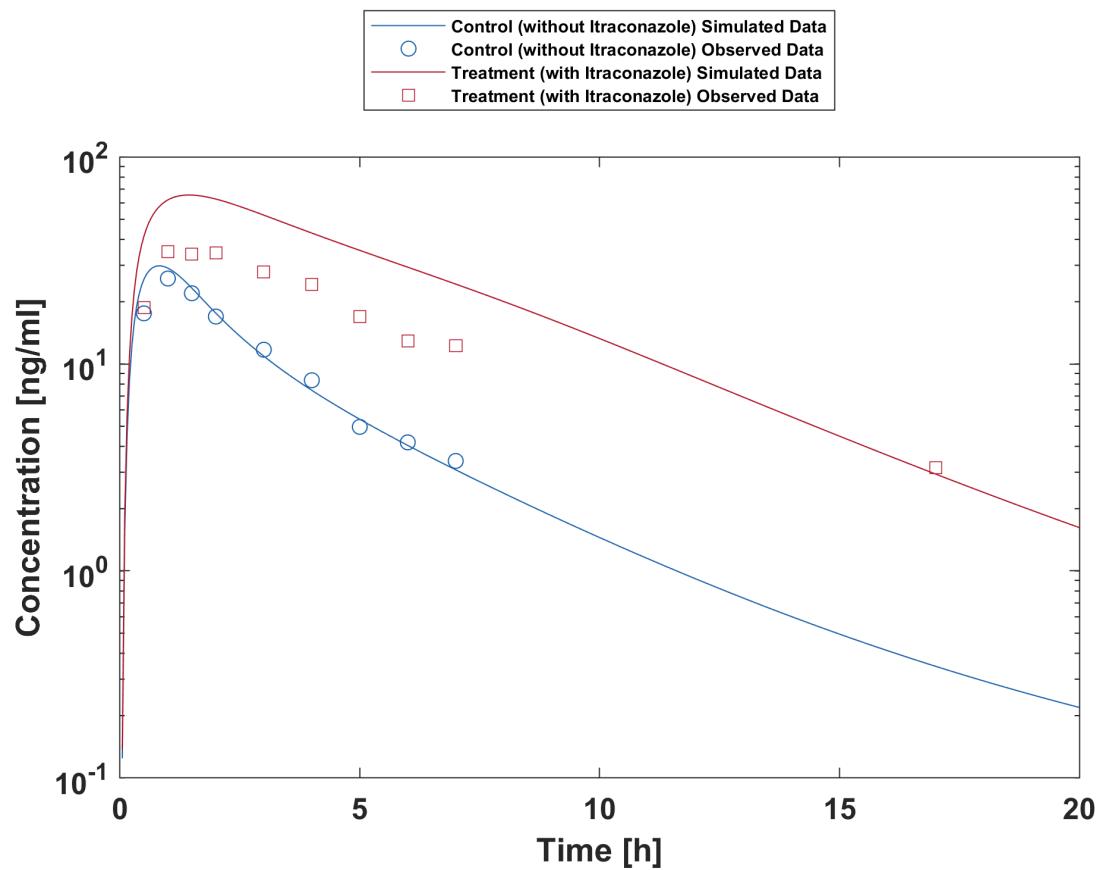
Ahonen 1995



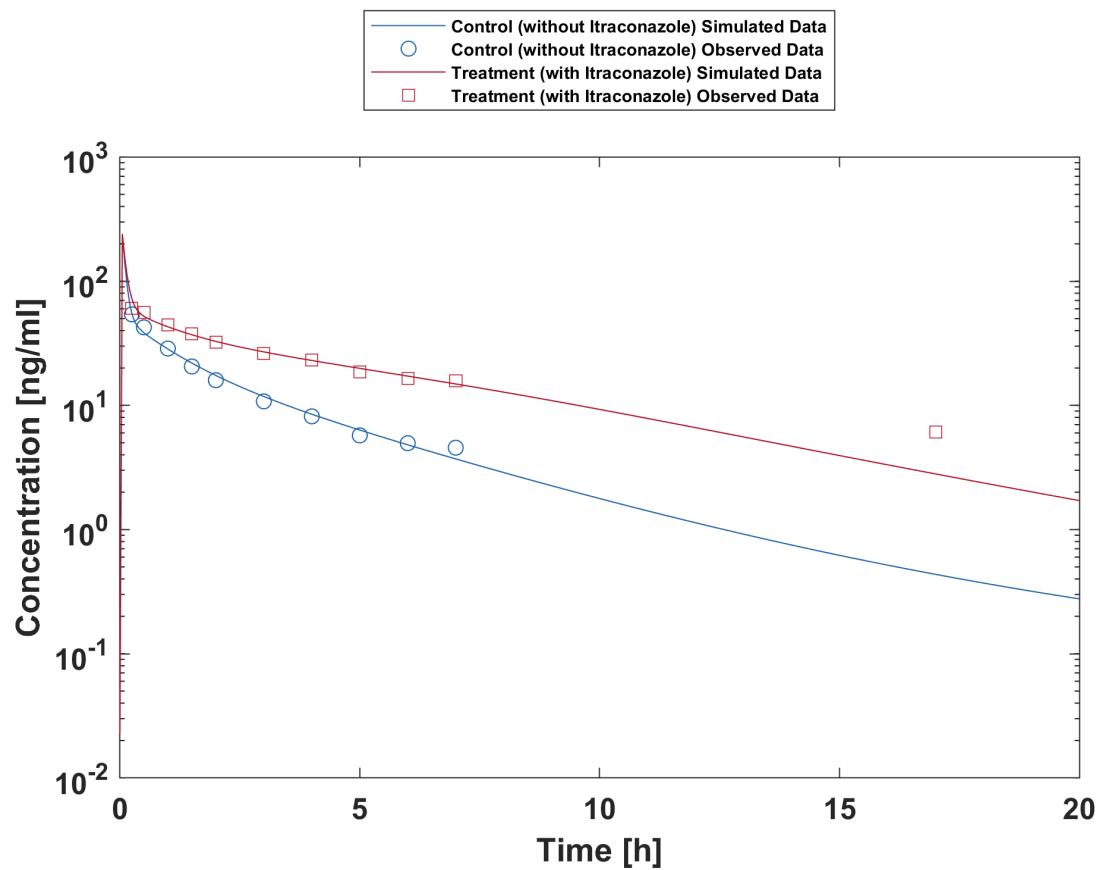
Backman 1998



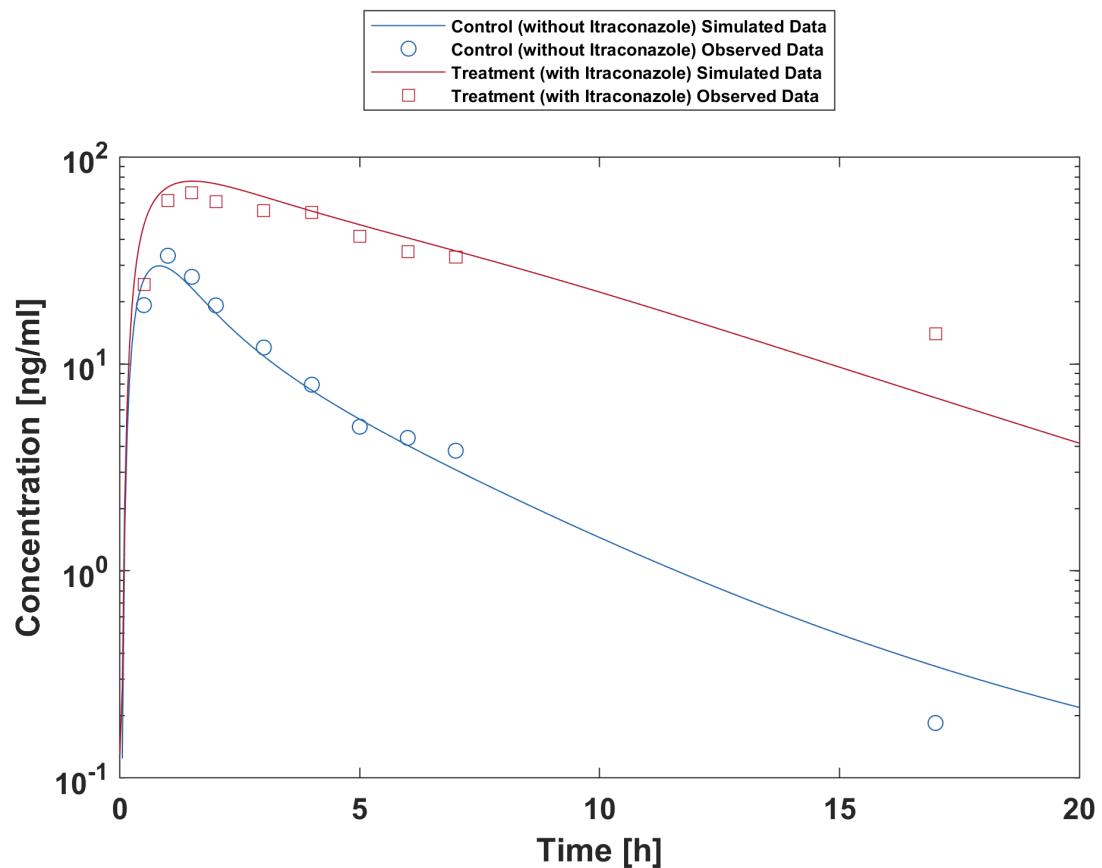
Olkola 1994



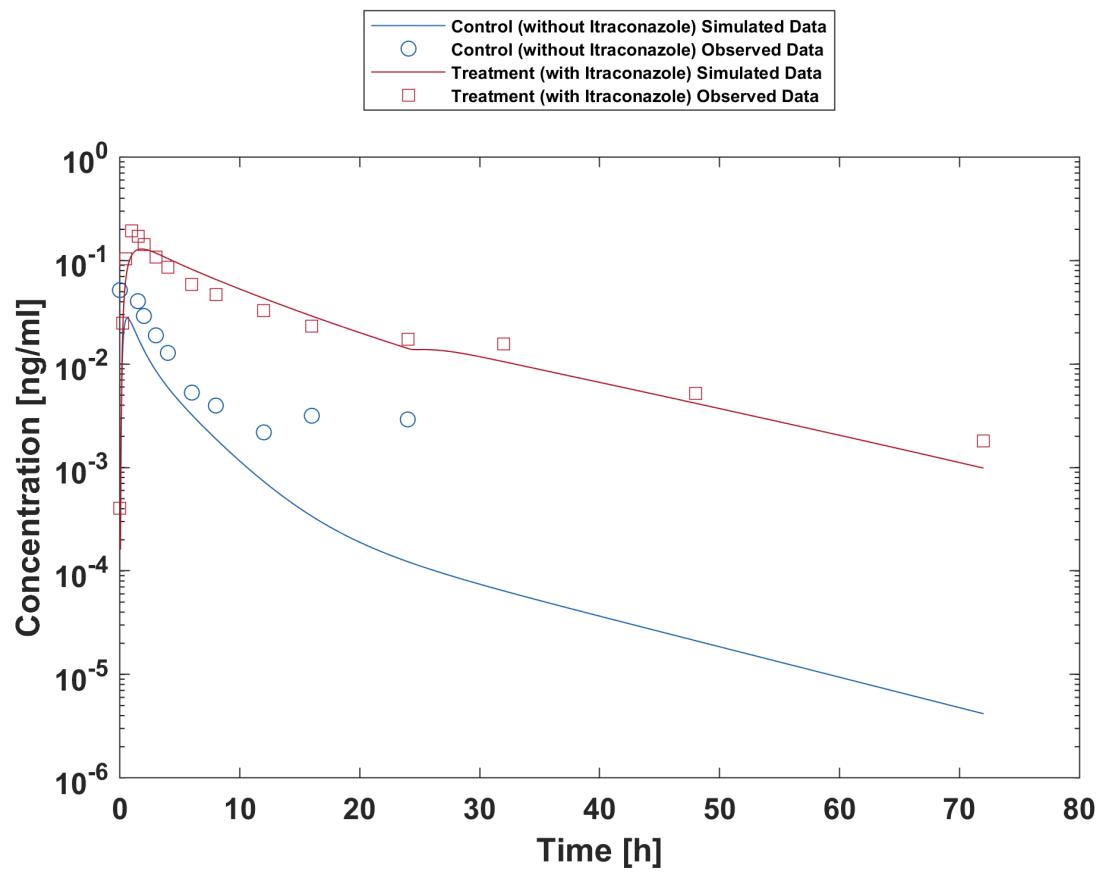
Olkola 1996 (day 1 po)



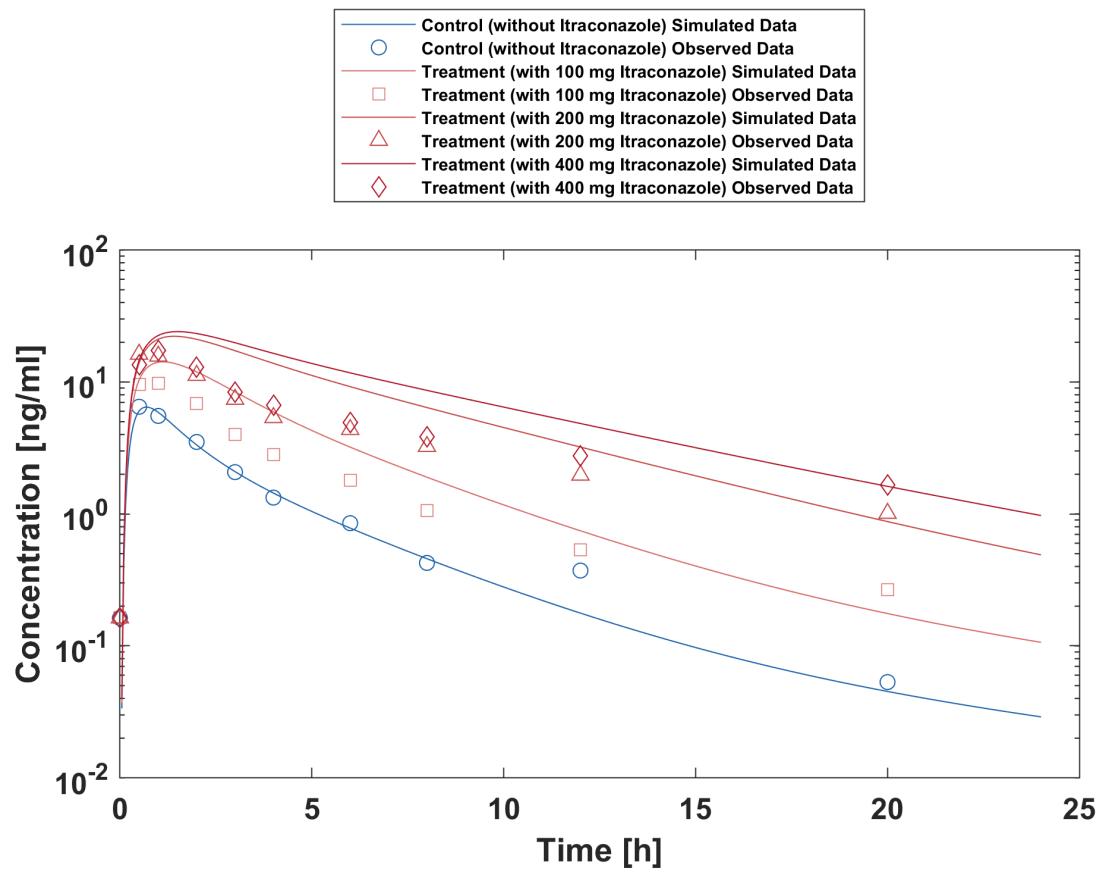
Olkola 1996 (day 4 iv)



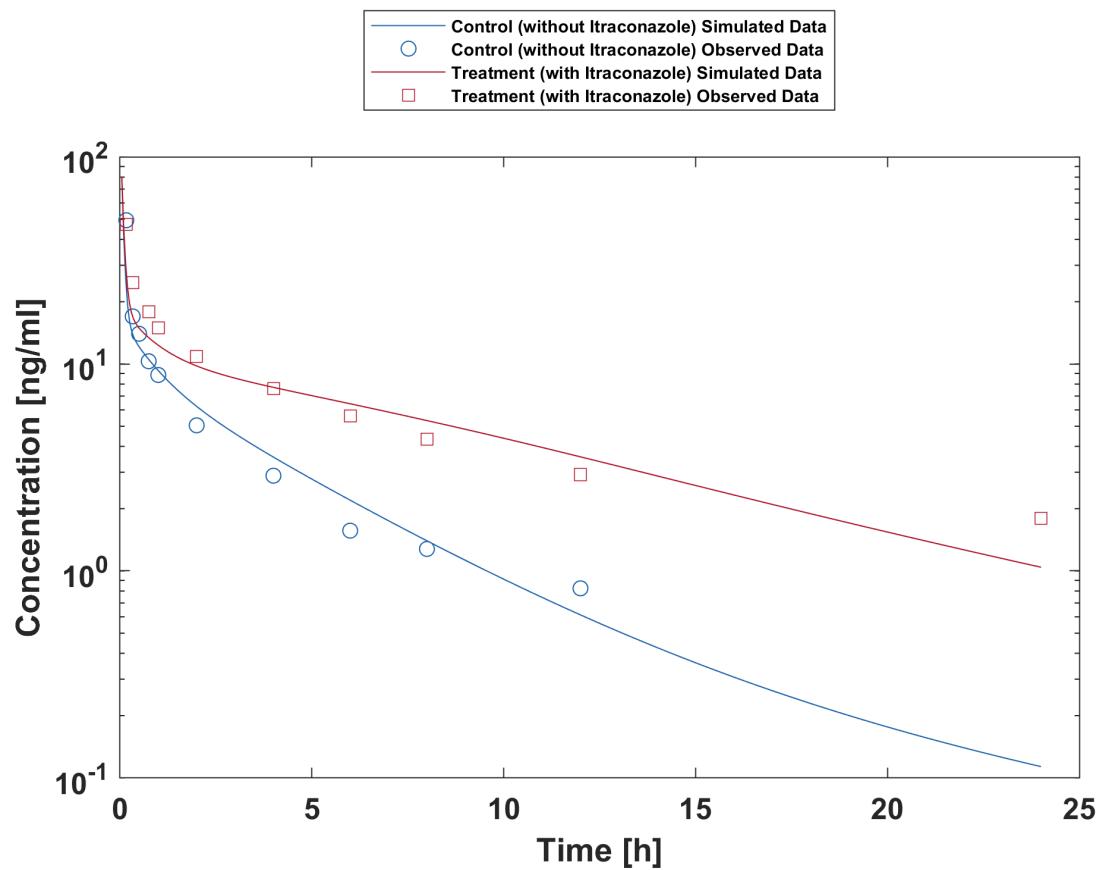
Olkola 1996 (day 6 po)



Pruksaritanont 2017

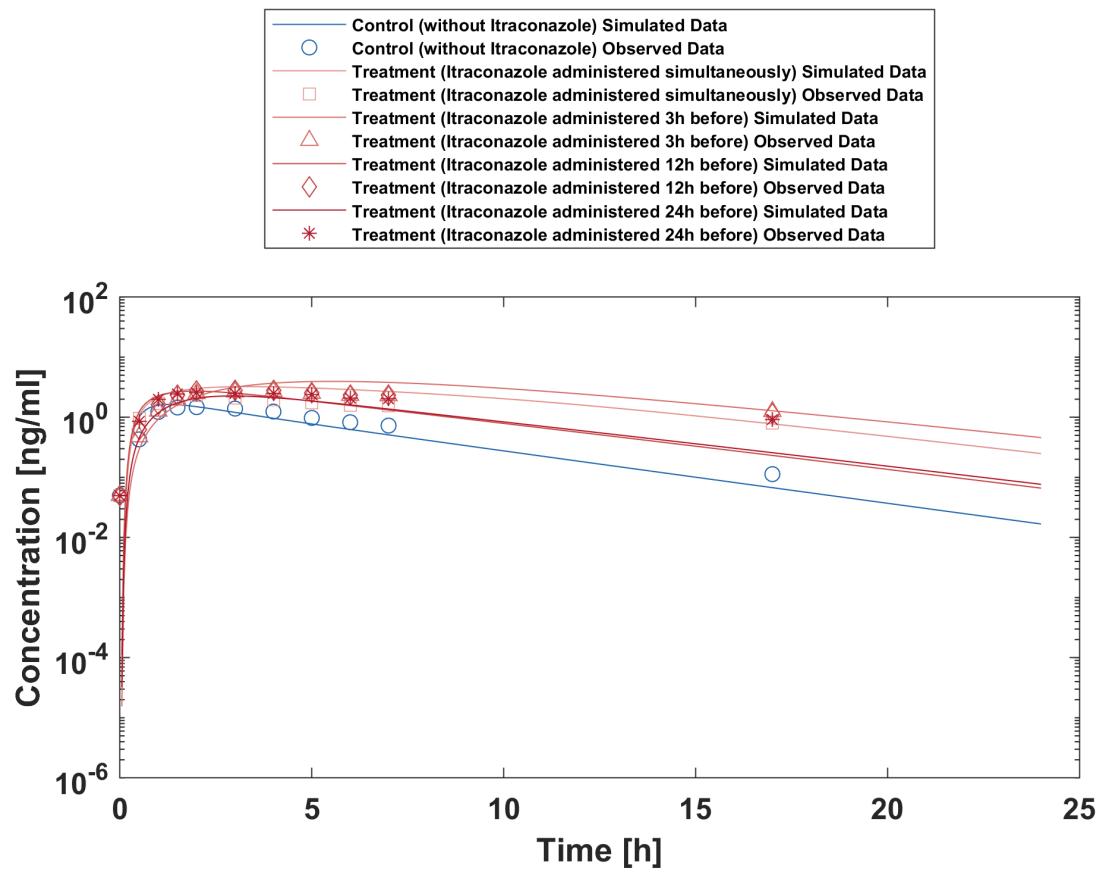


Templeton 2010

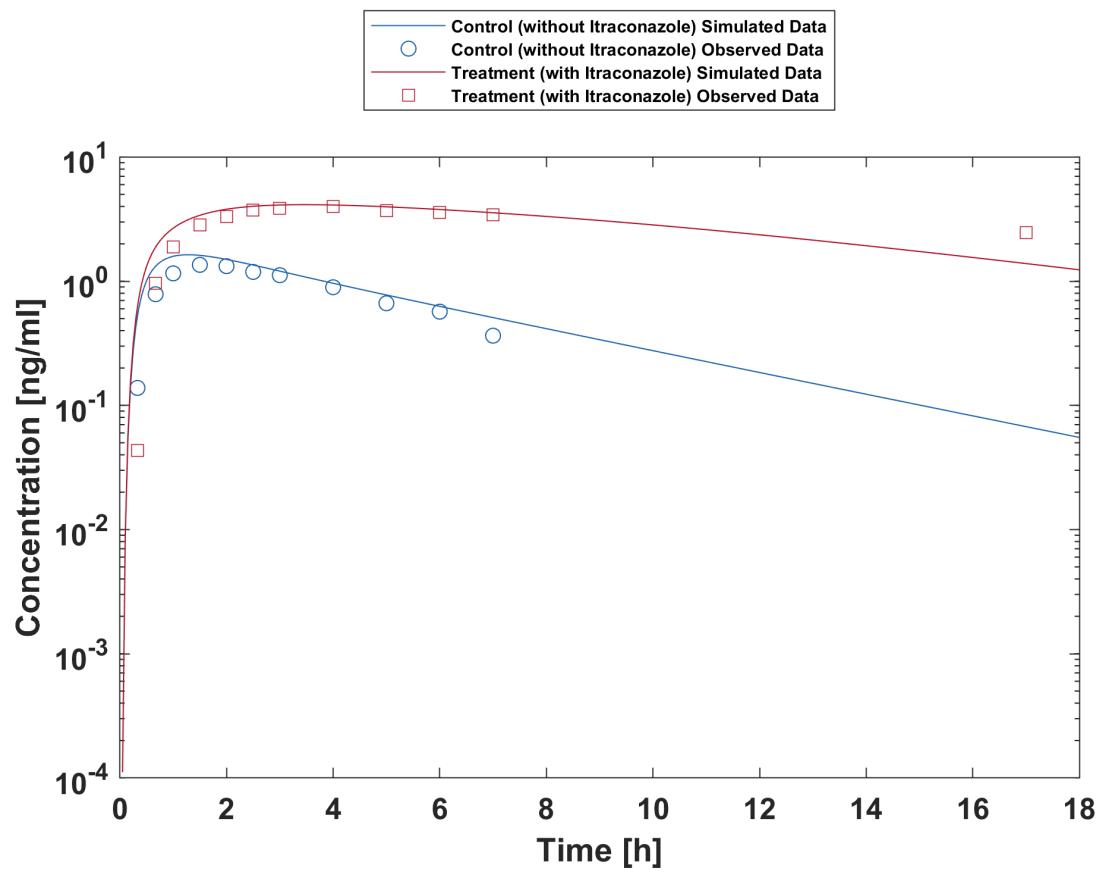


Yu 2004 (CYP3A5*3/*3)

3.16 Itraconazole - Triazolam DDI

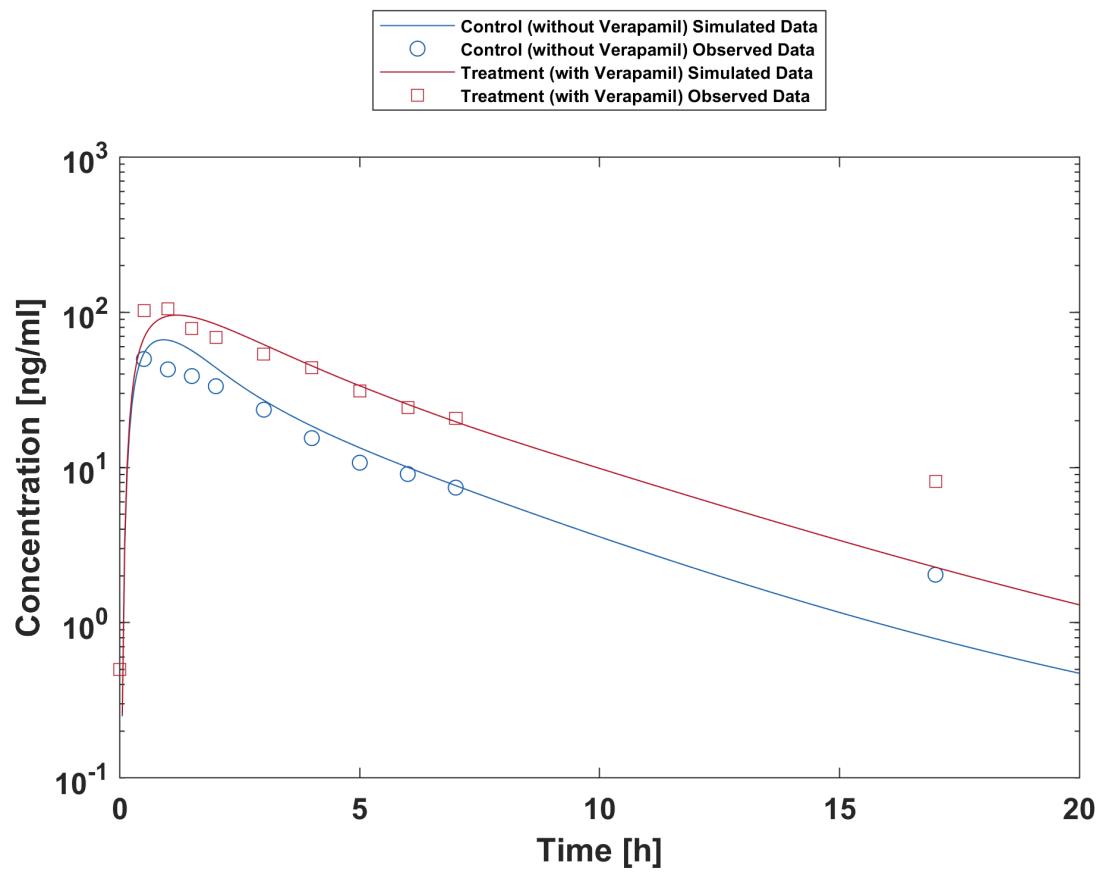


Neuvonen 1996

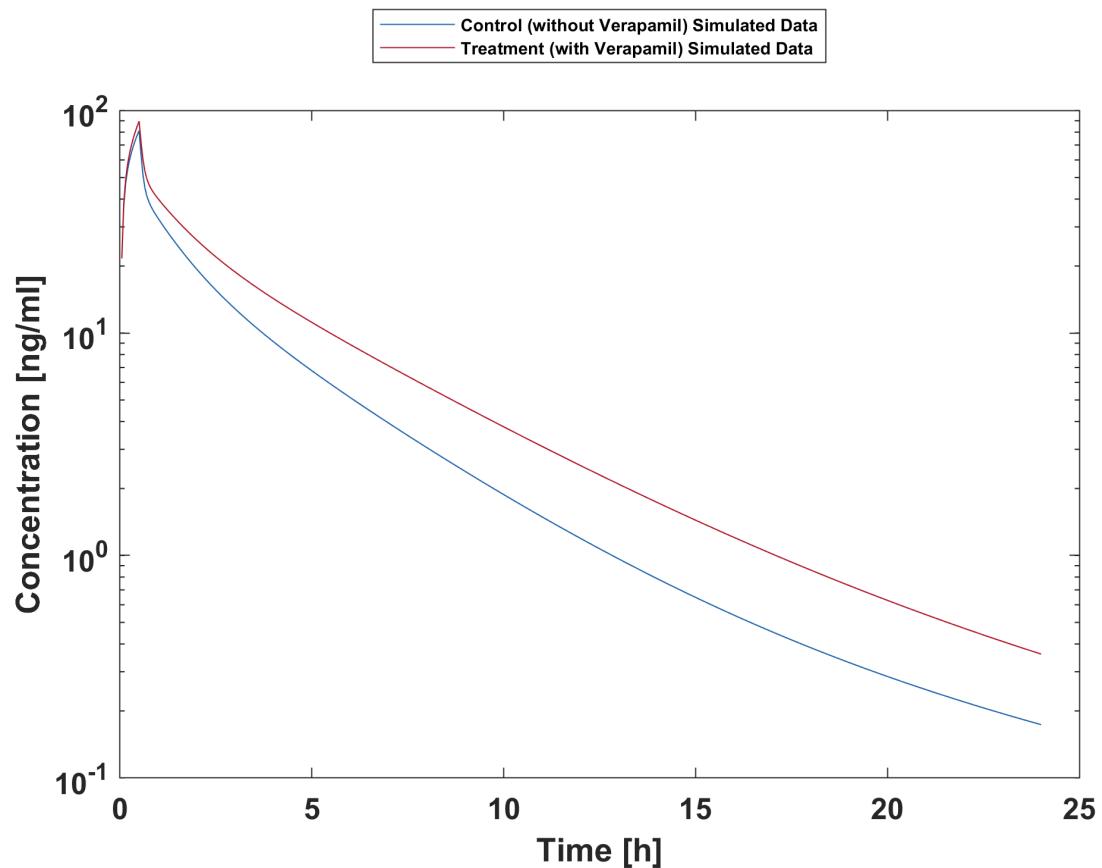


Varhe 1994

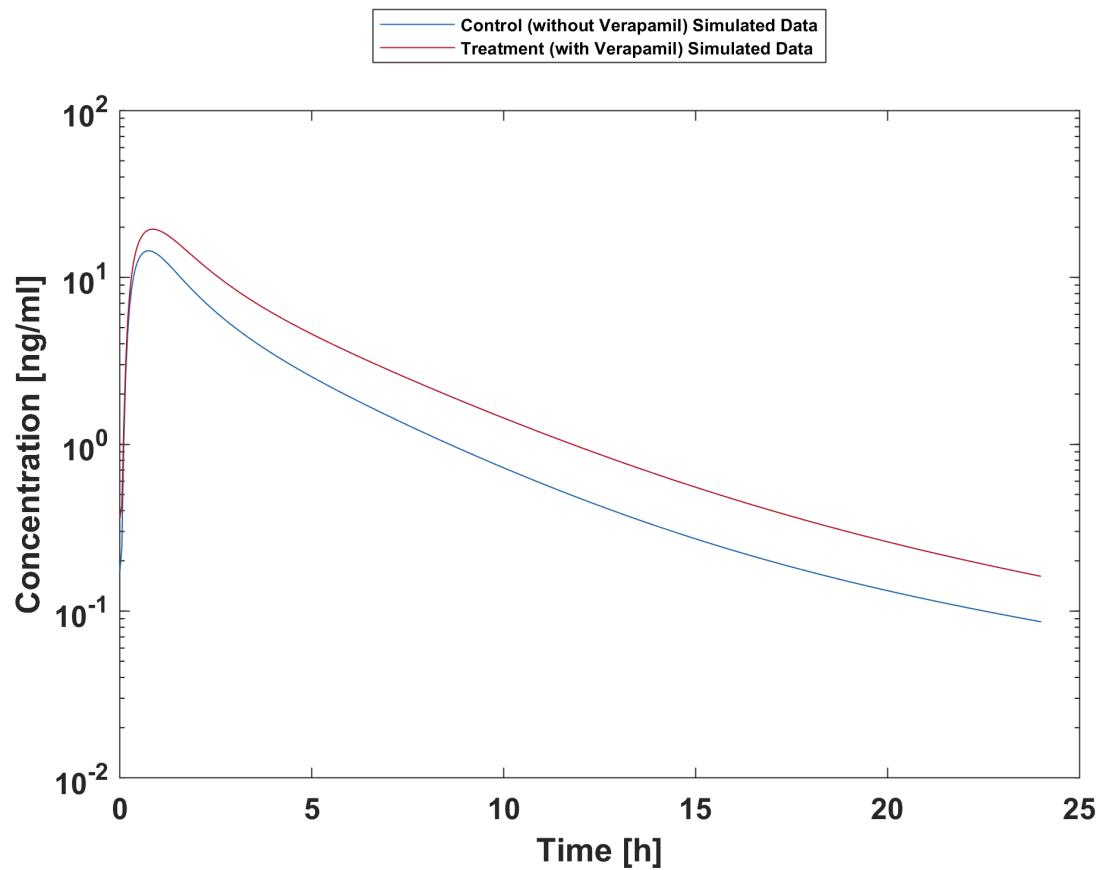
3.17 Verapamil - Midazolam DDI



Backman 1994

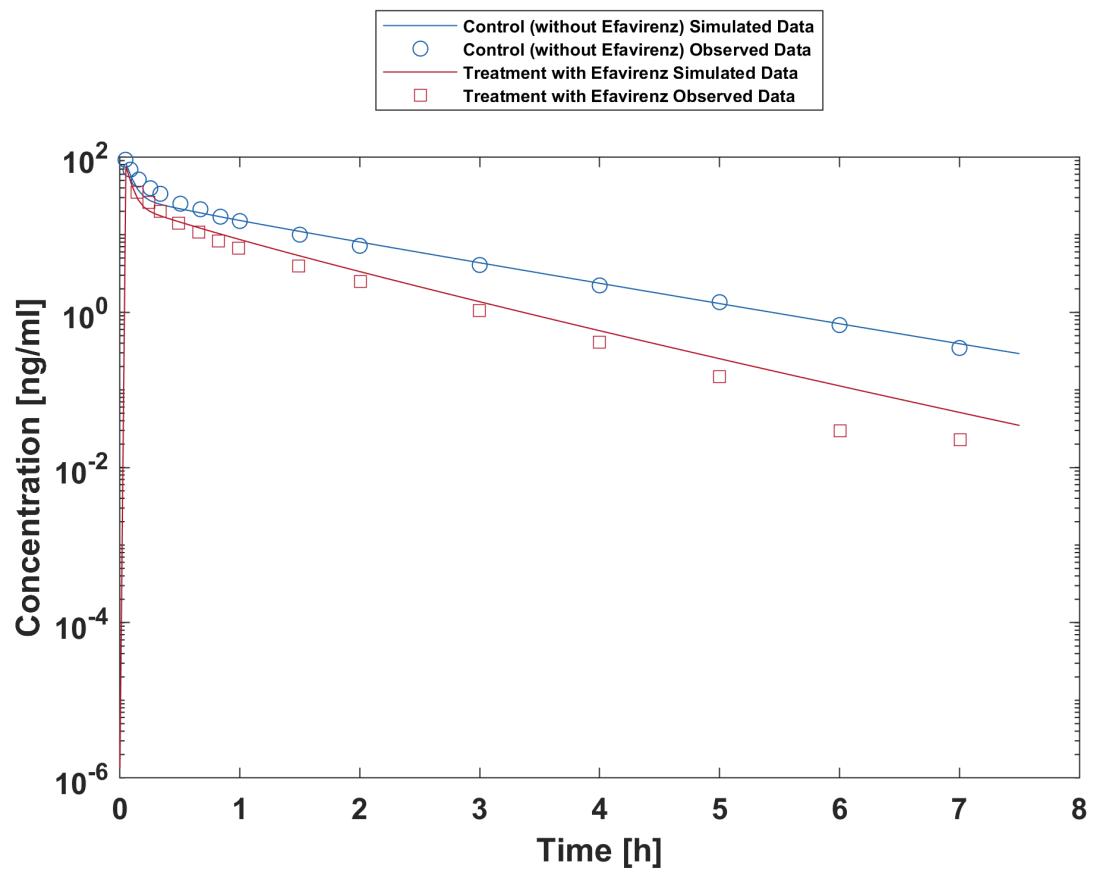


Wang 2005 (iv)

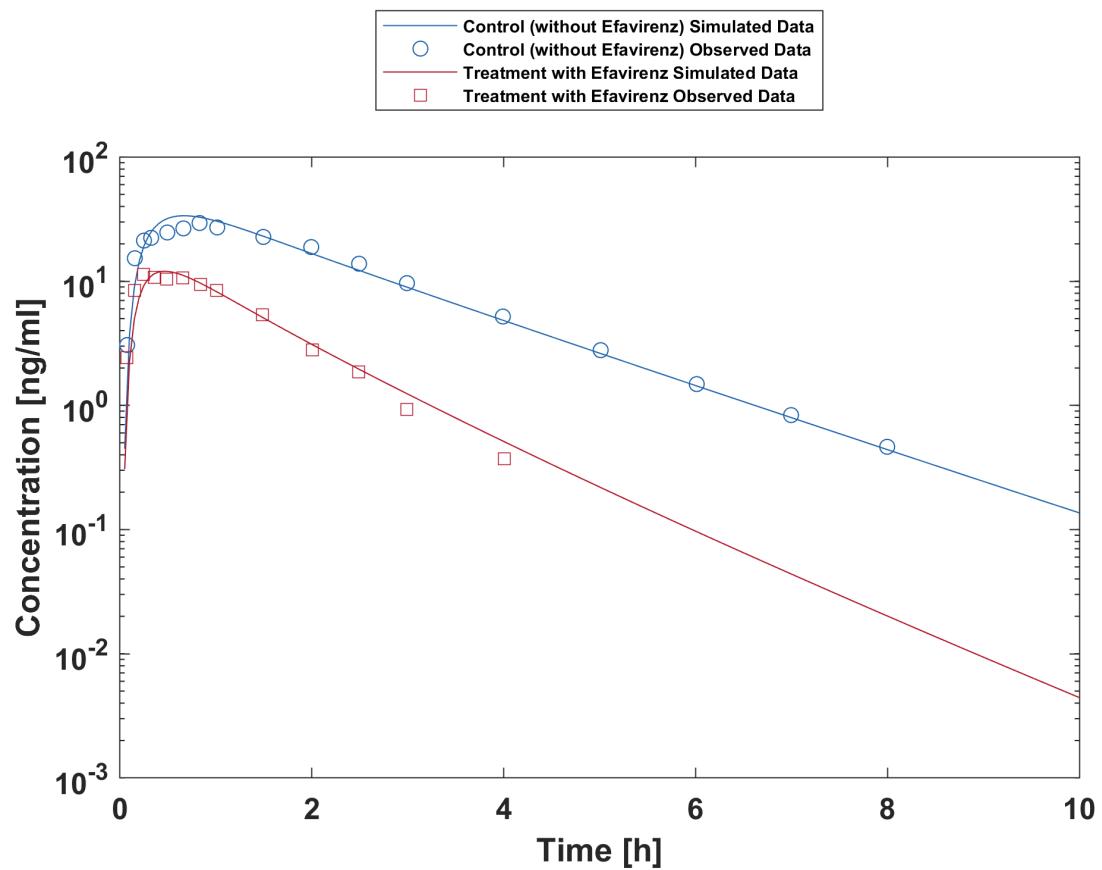


Wang 2005 (po)

3.18 Efavirenz - Alfentanil DDI

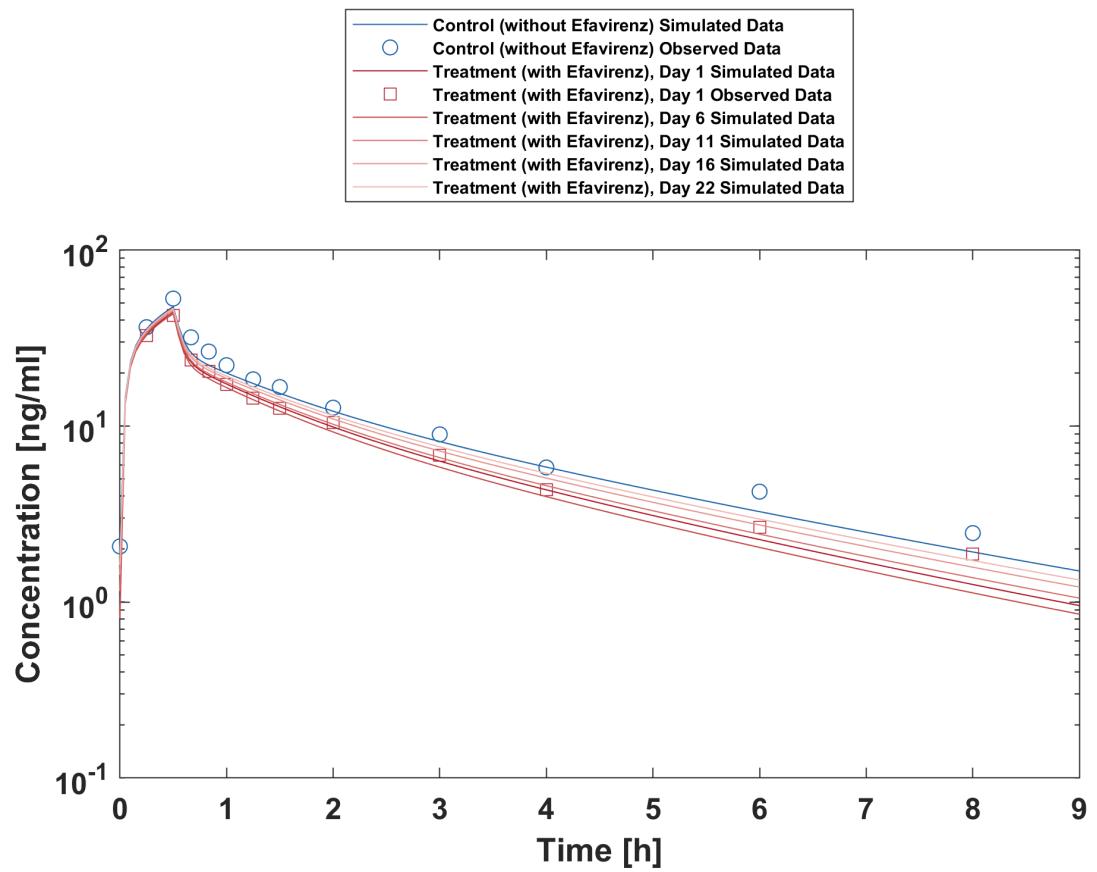


Kharasch 2012 IV

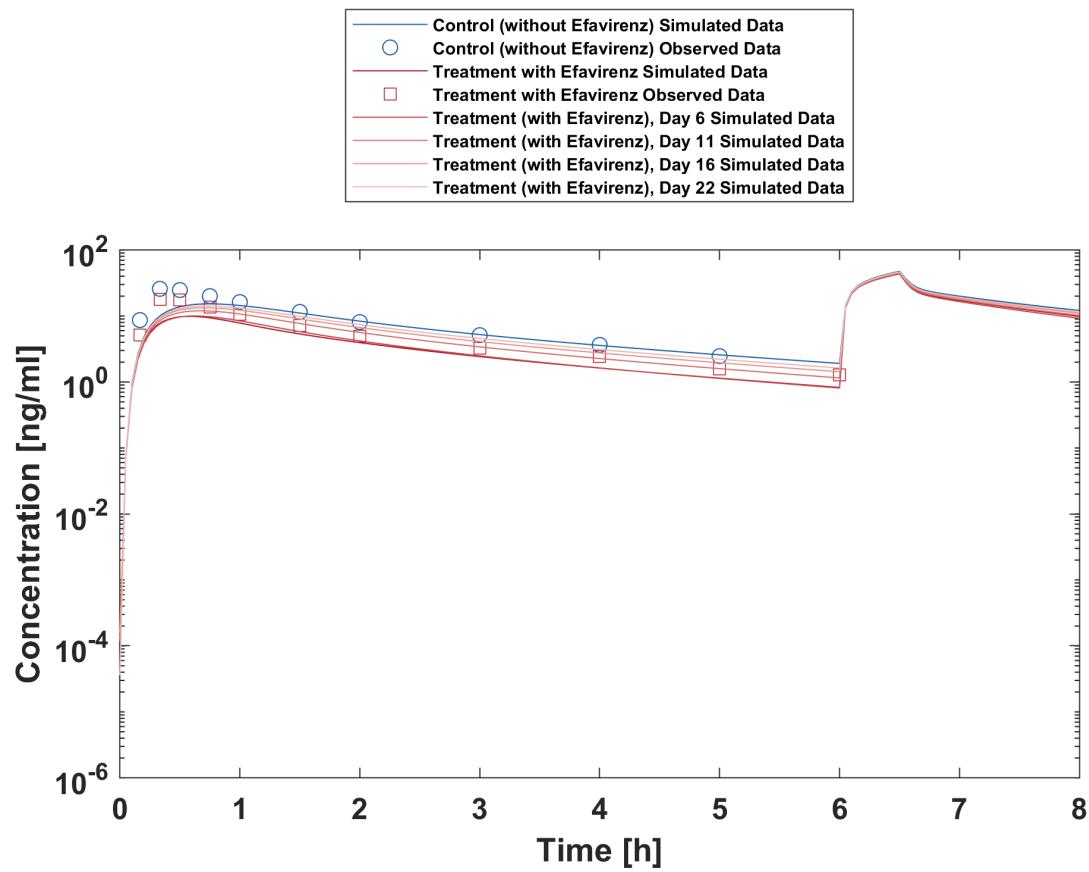


Kharasch 2012 PO

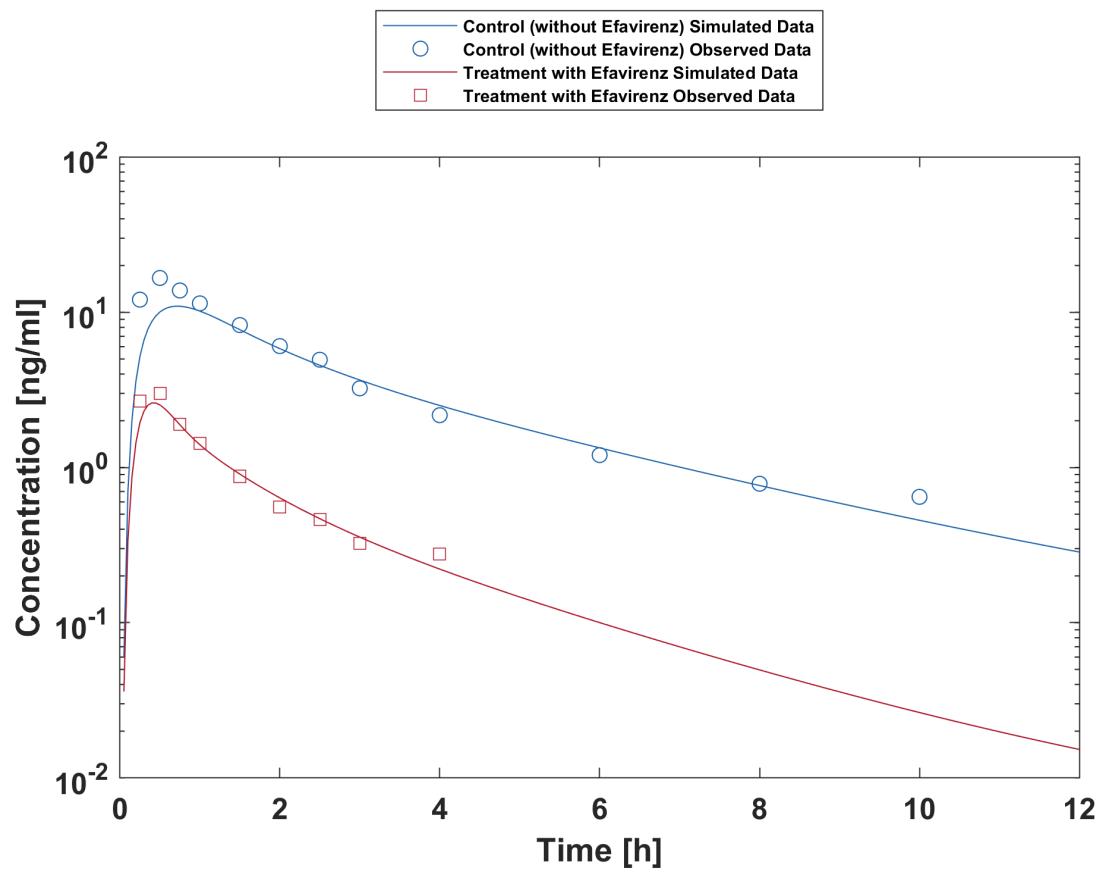
3.19 Efavirenz - Midazolam DDI



Mikus 2017 IV

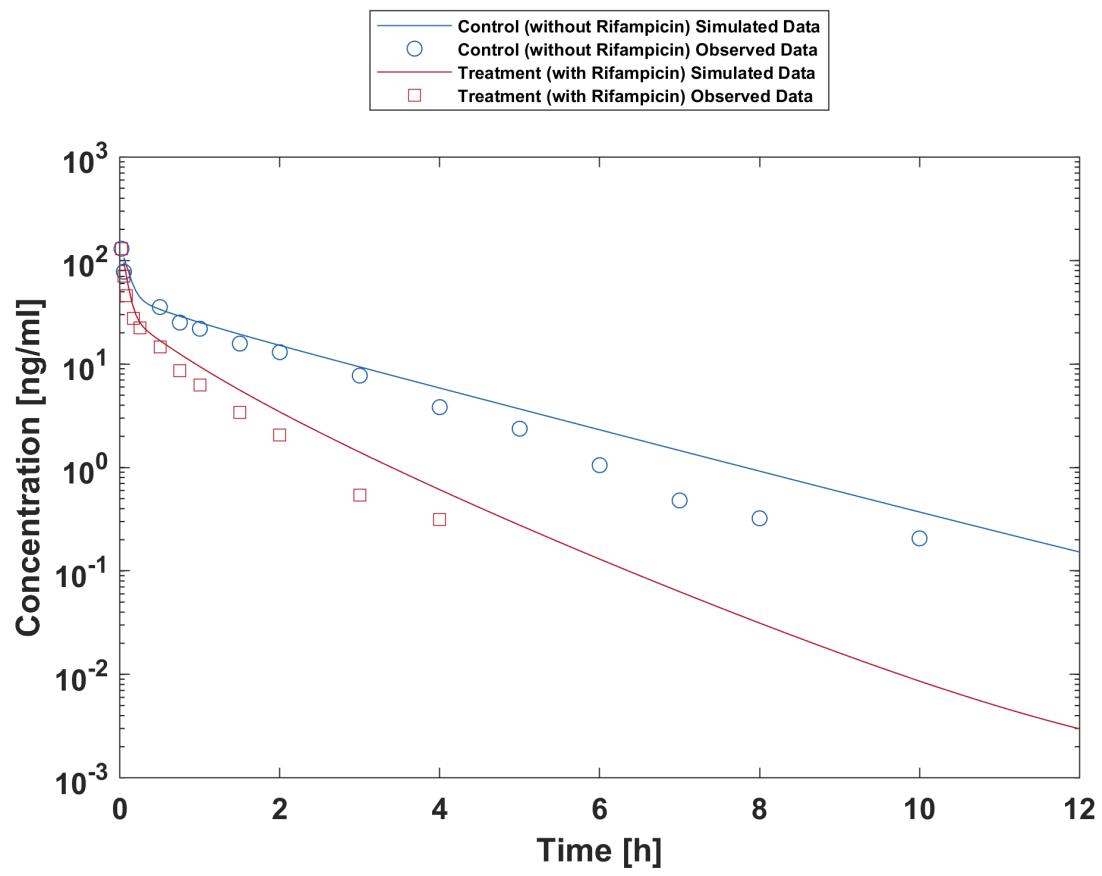


Mikus 2017 PO

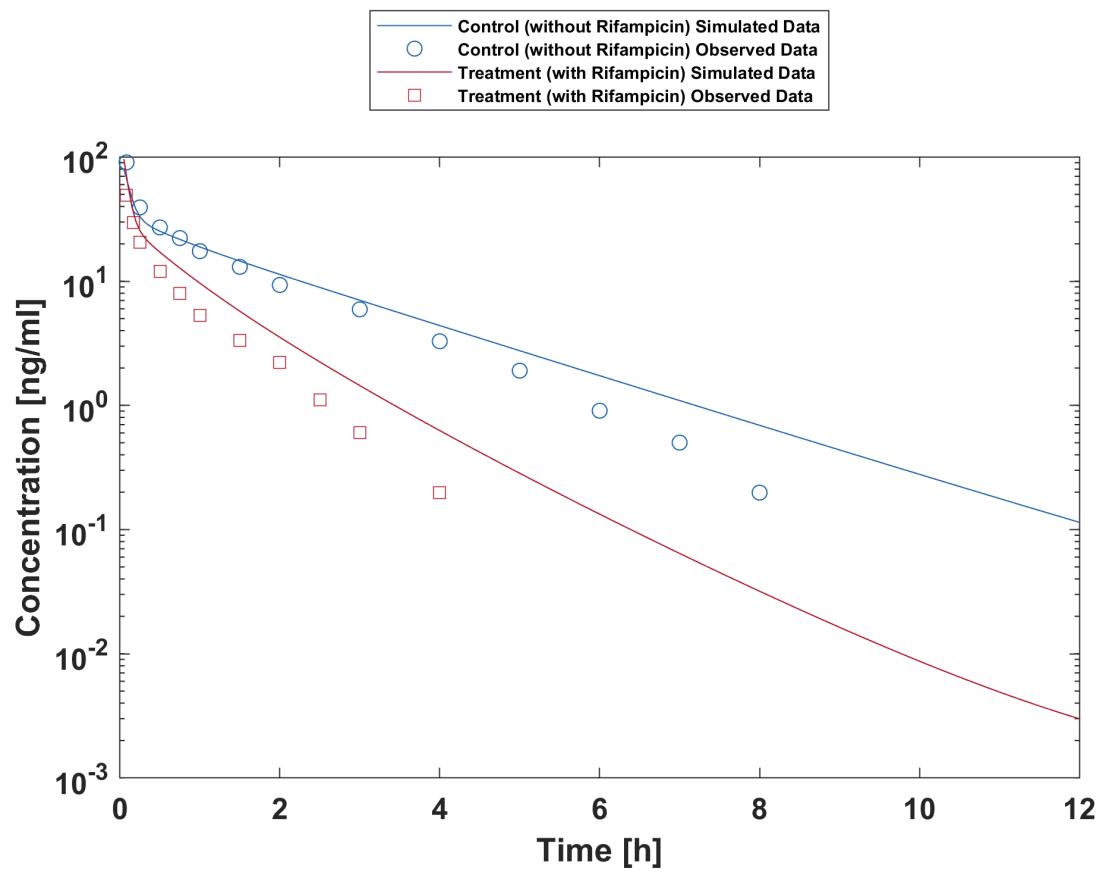


Katzenmaier 2010

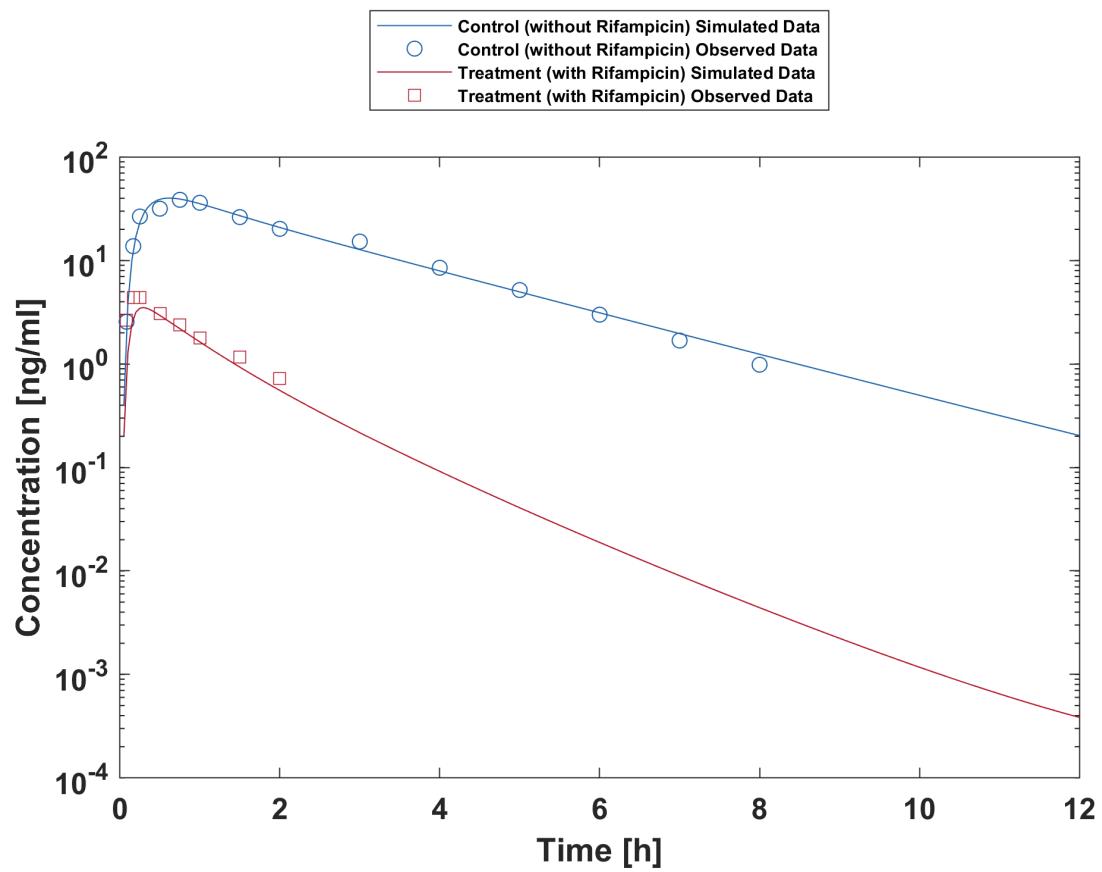
3.20 Rifampicin - Alfentanil DDI



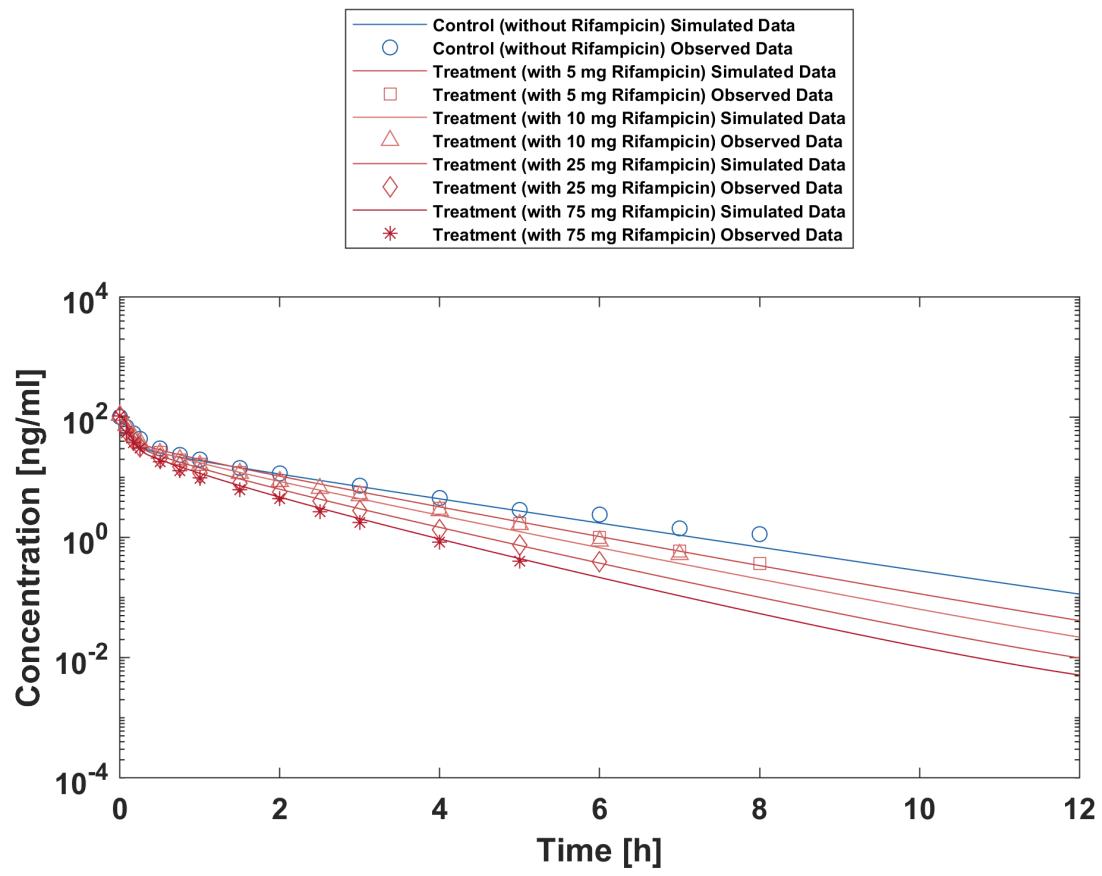
Kharasch 1997



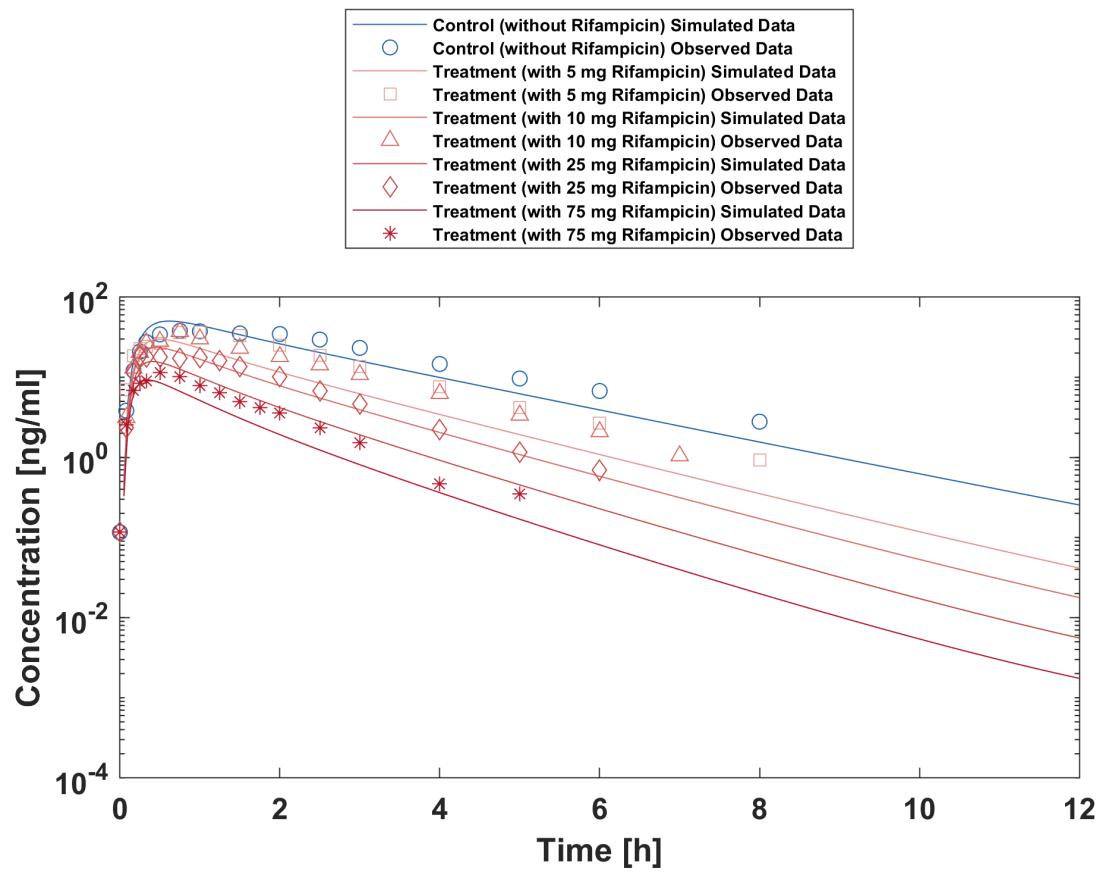
Kharasch 2004 (iv)



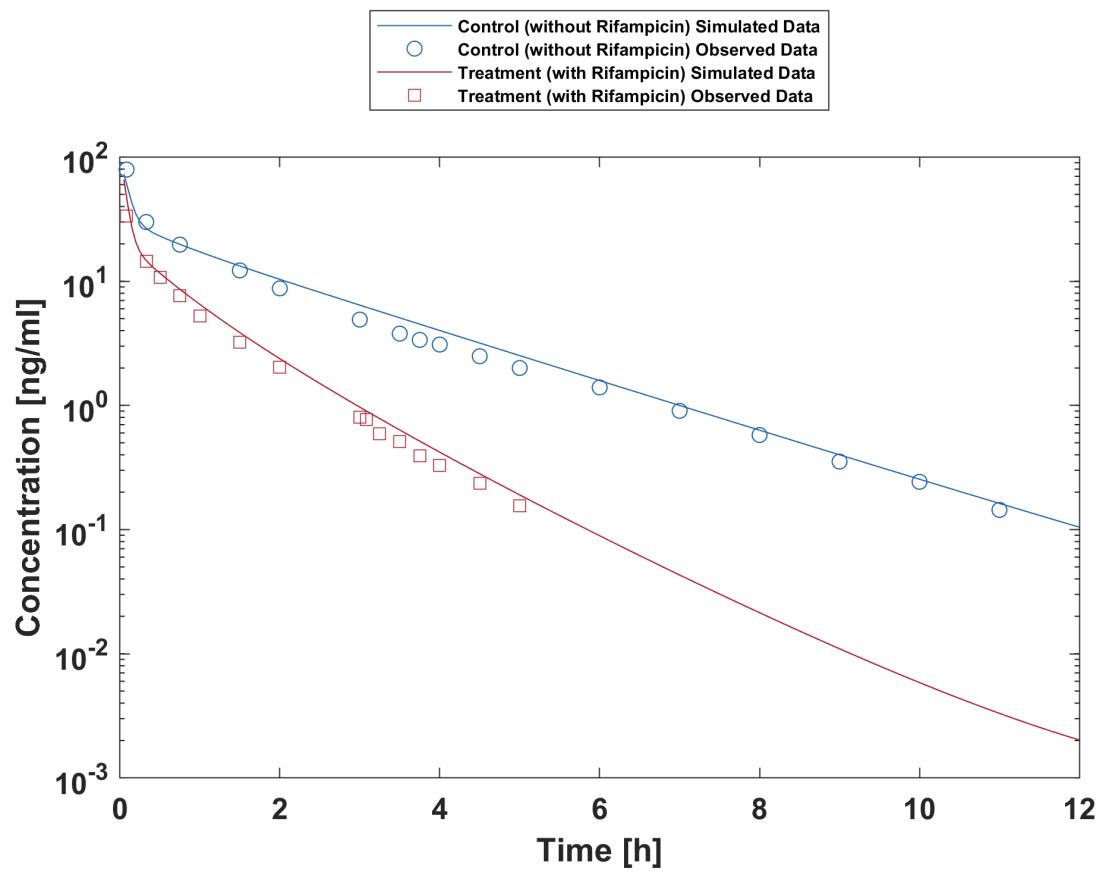
Kharasch 2004 (po)



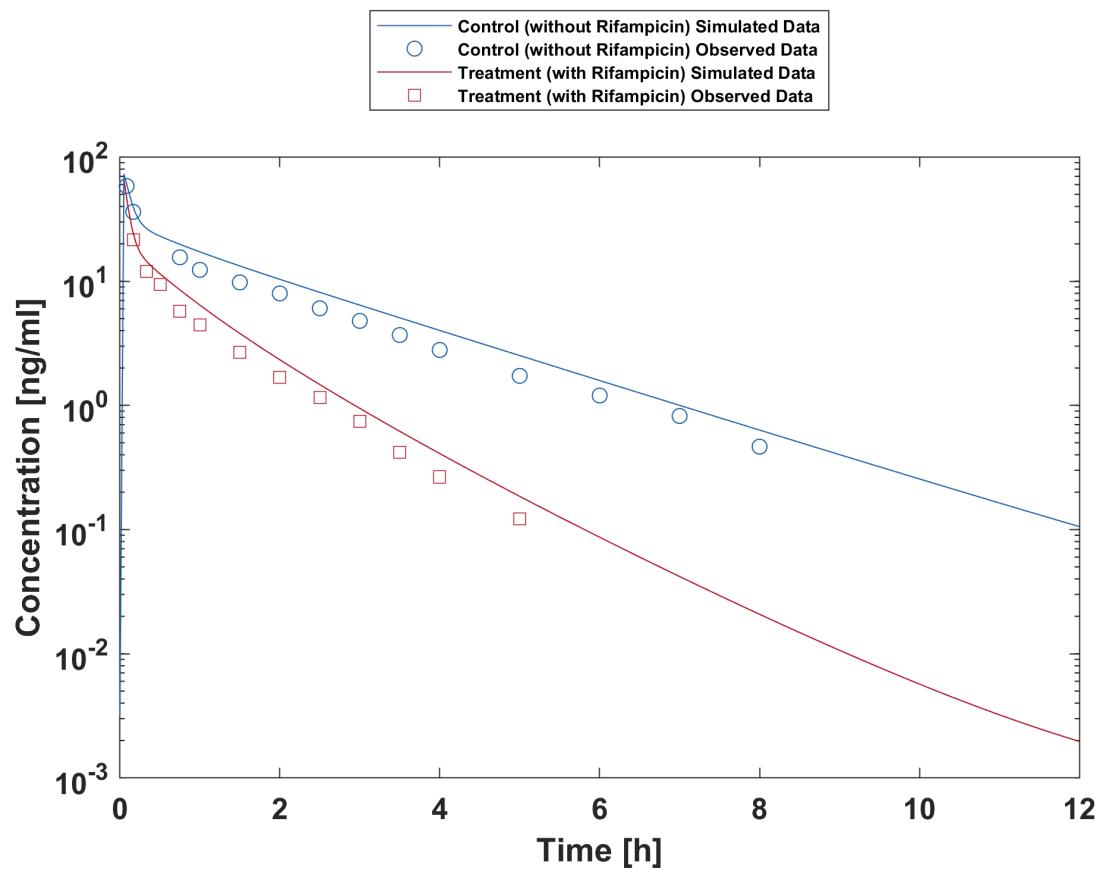
Kharasch 2011 (iv)



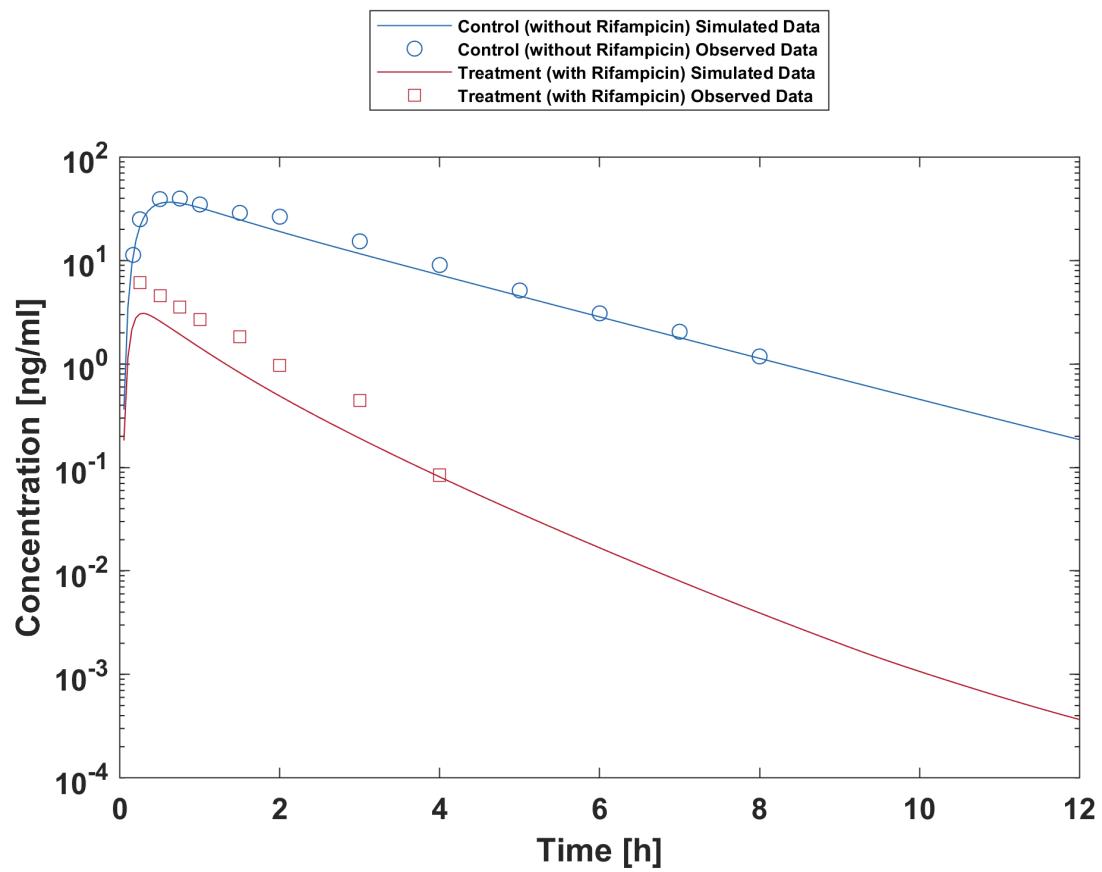
Kharasch 2011 (po)



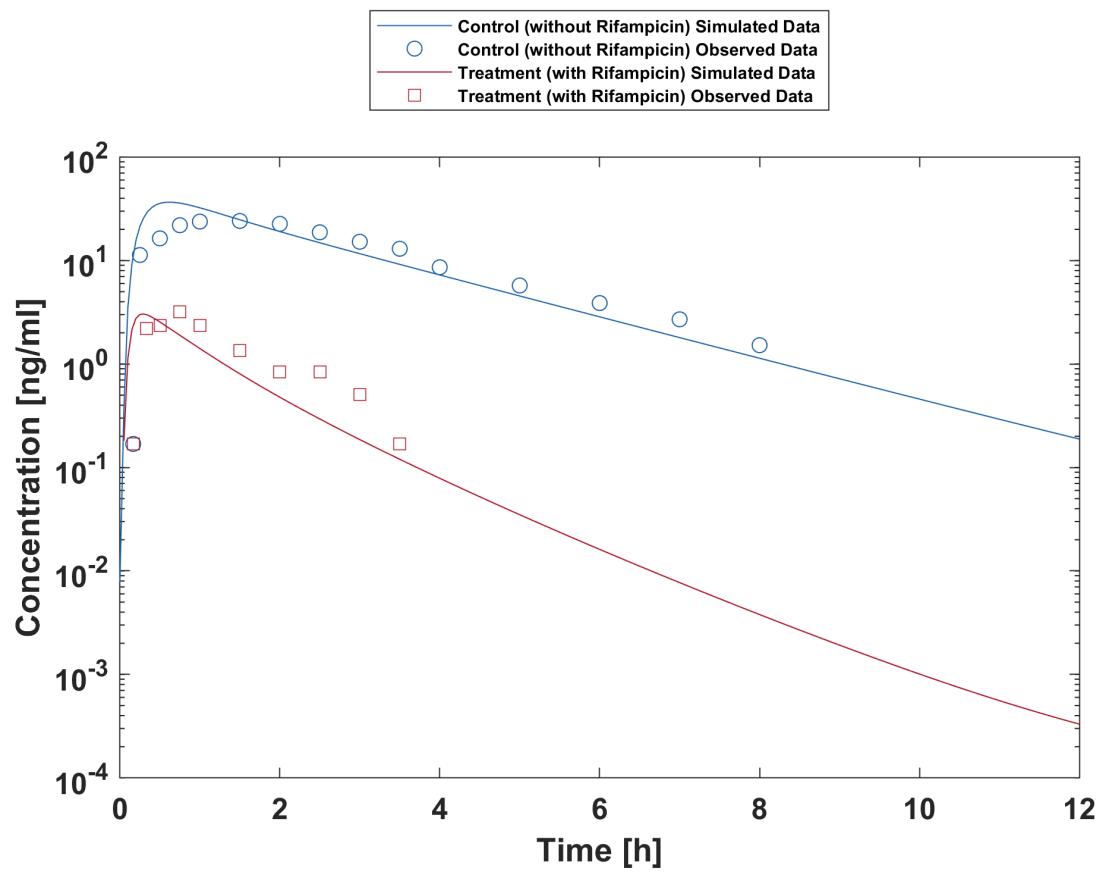
Kharasch 2011b (iv during sequential administration of iv unlabeled alfentanil and oral deuterated alfentanil)



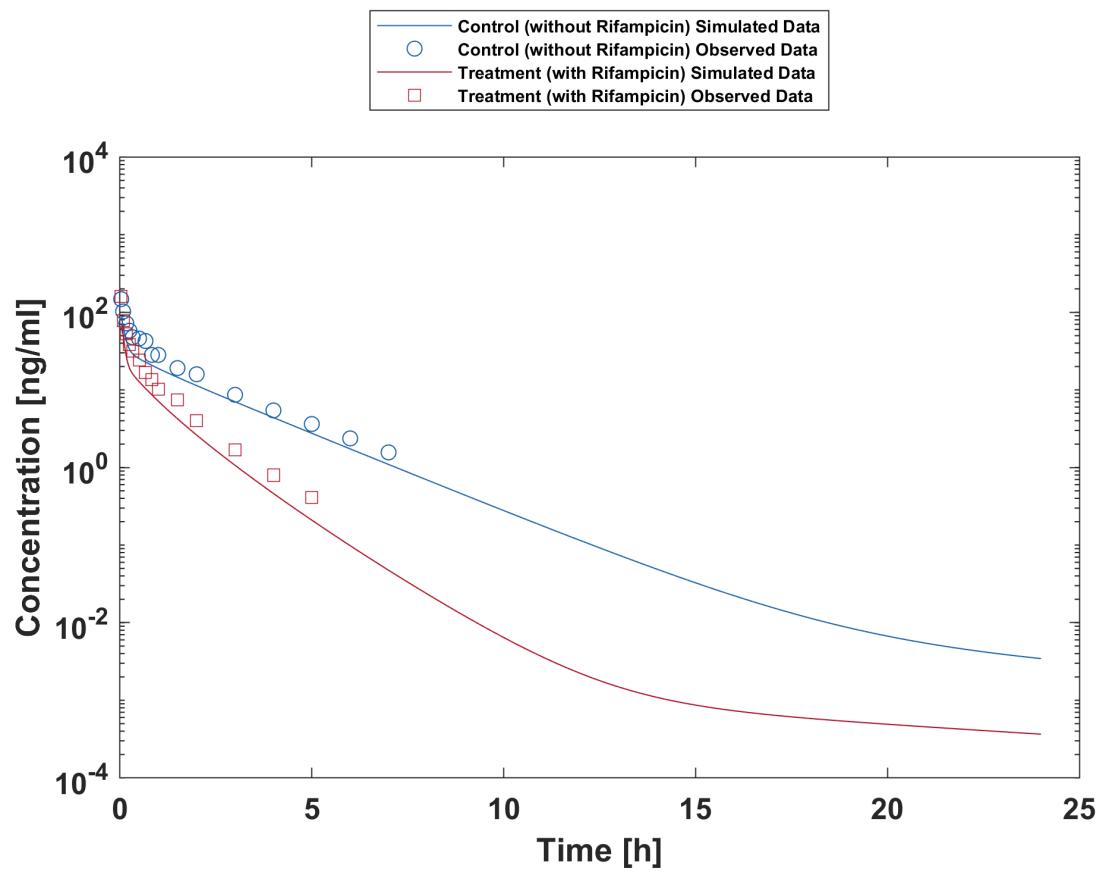
Kharasch 2011b (iv during simultaneous administration of iv unlabeled alfentanil and oral deuterated alfentanil)



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

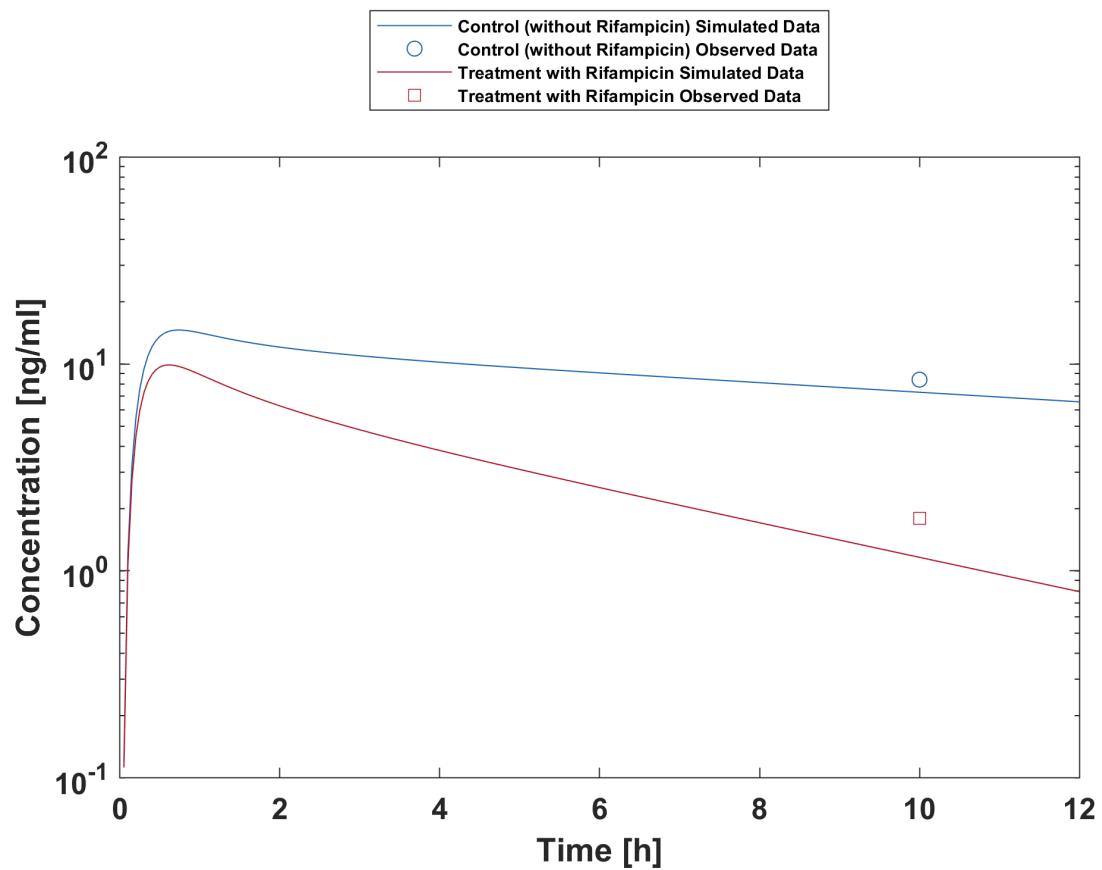


Kharasch 2011b (po during simultaneous administration of iv unlabeled alfentanil and oral deuterated alfentanil)

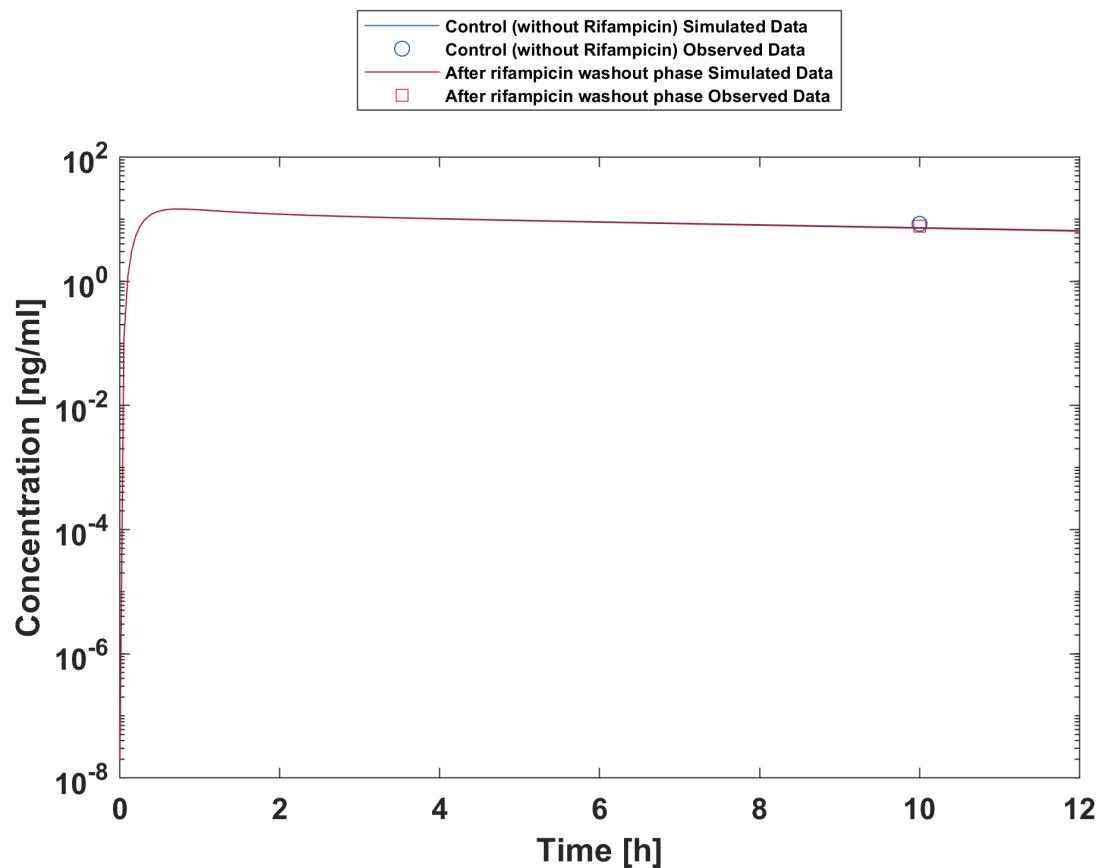


Phimmasone 2001

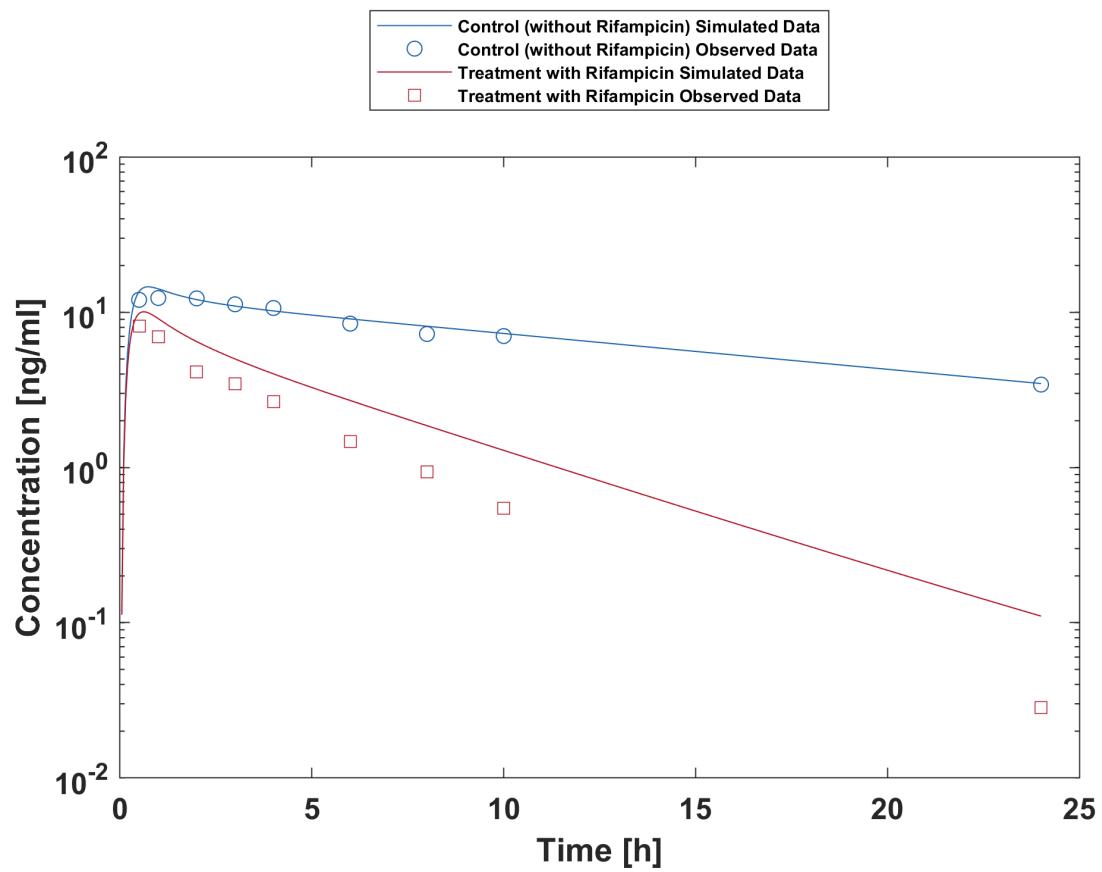
3.21 Rifampicin - Alprazolam DDI



Gashaw 2003 (Day 7)

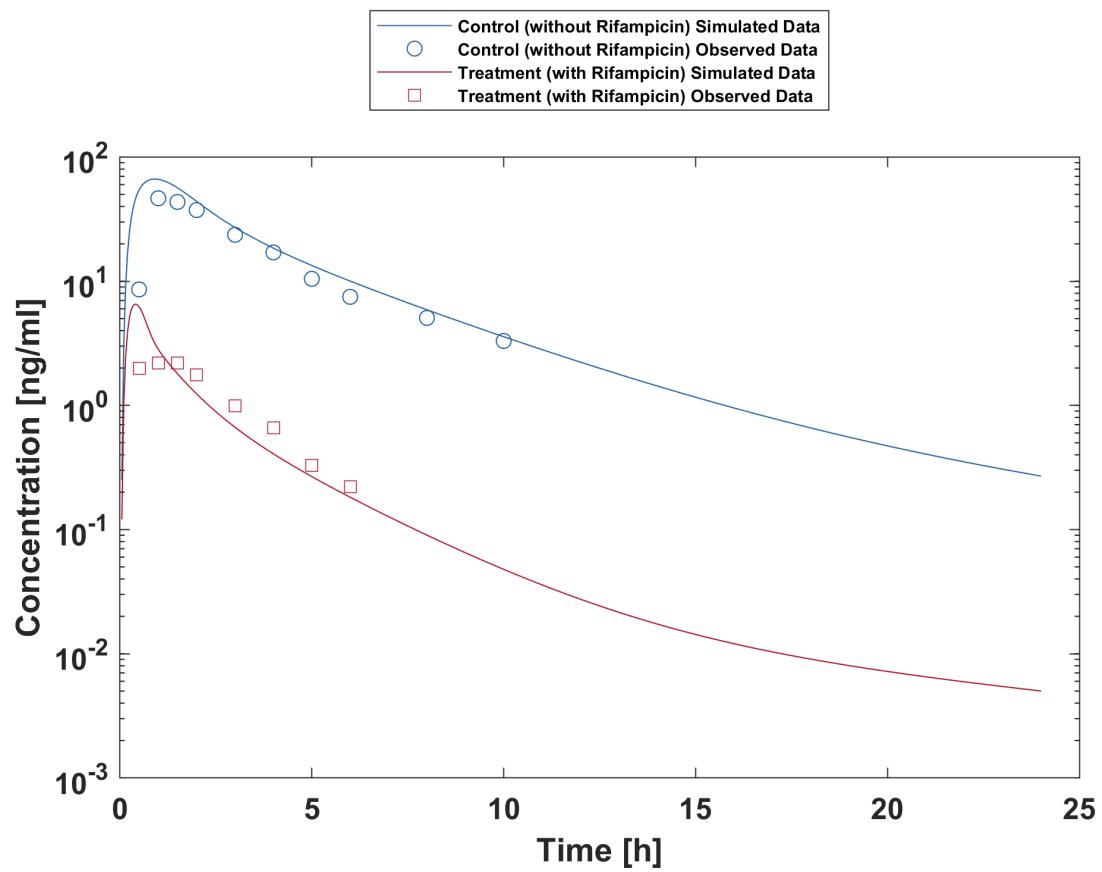


Gashaw 2003 (after washout phase)

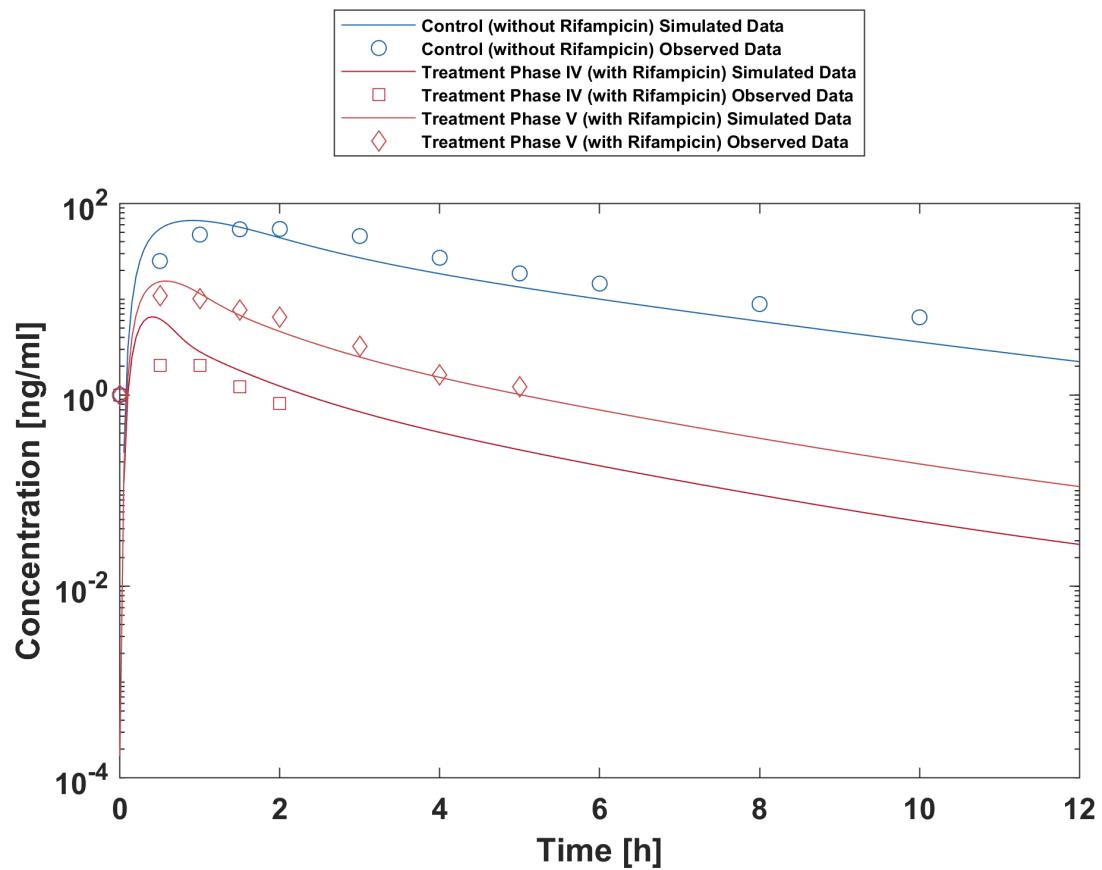


Schmider 1999

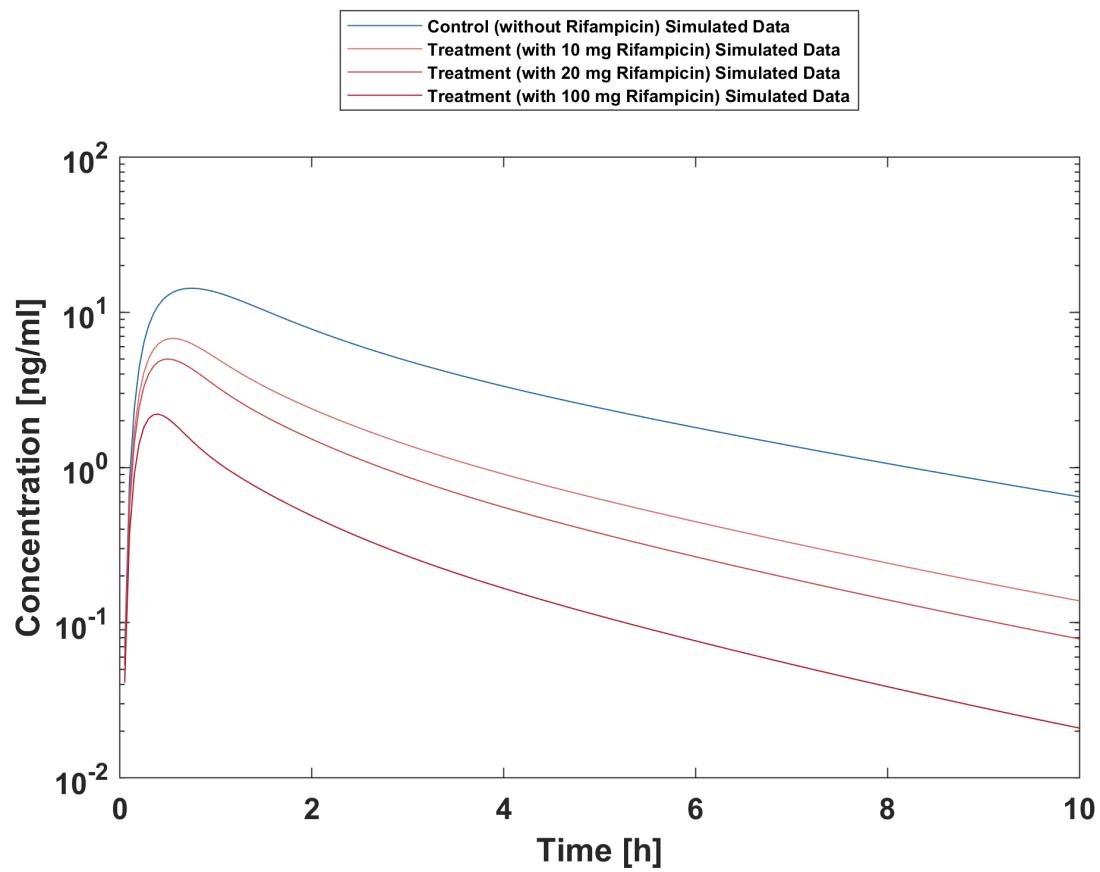
3.22 Rifampicin - Midazolam DDI



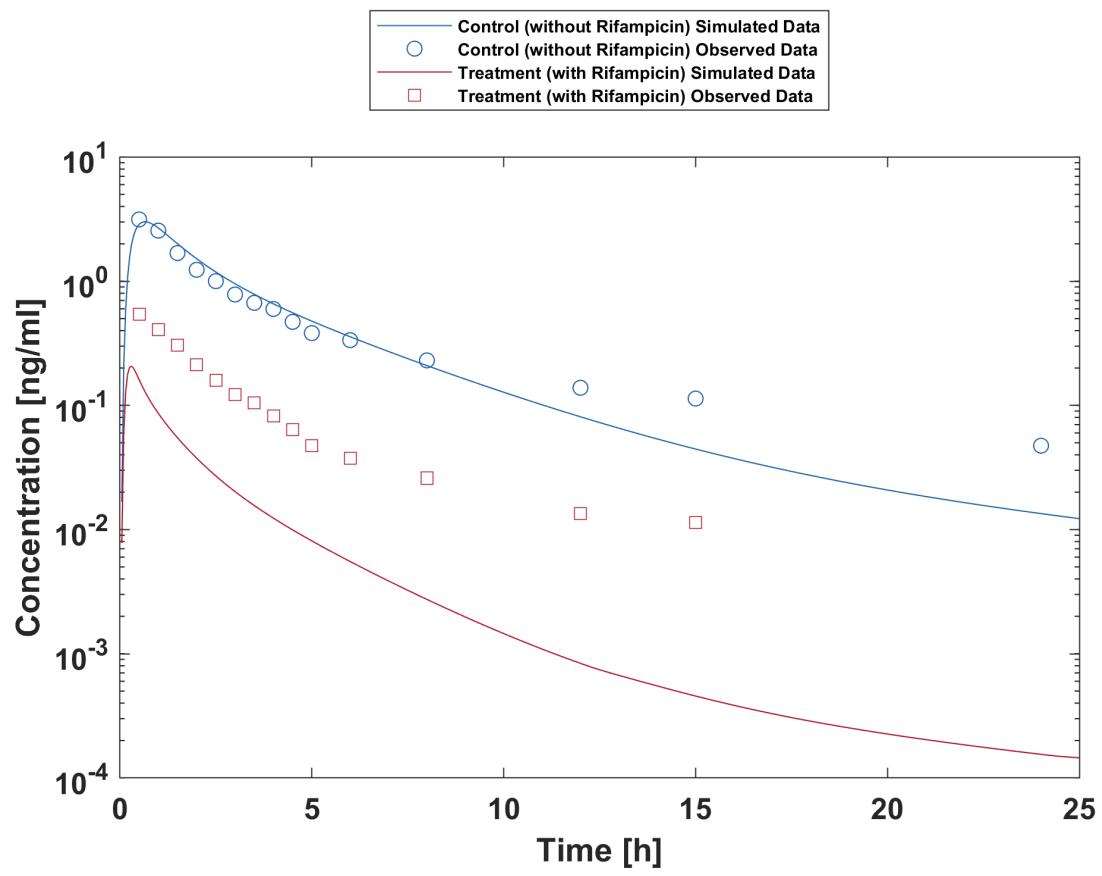
Backman 1996



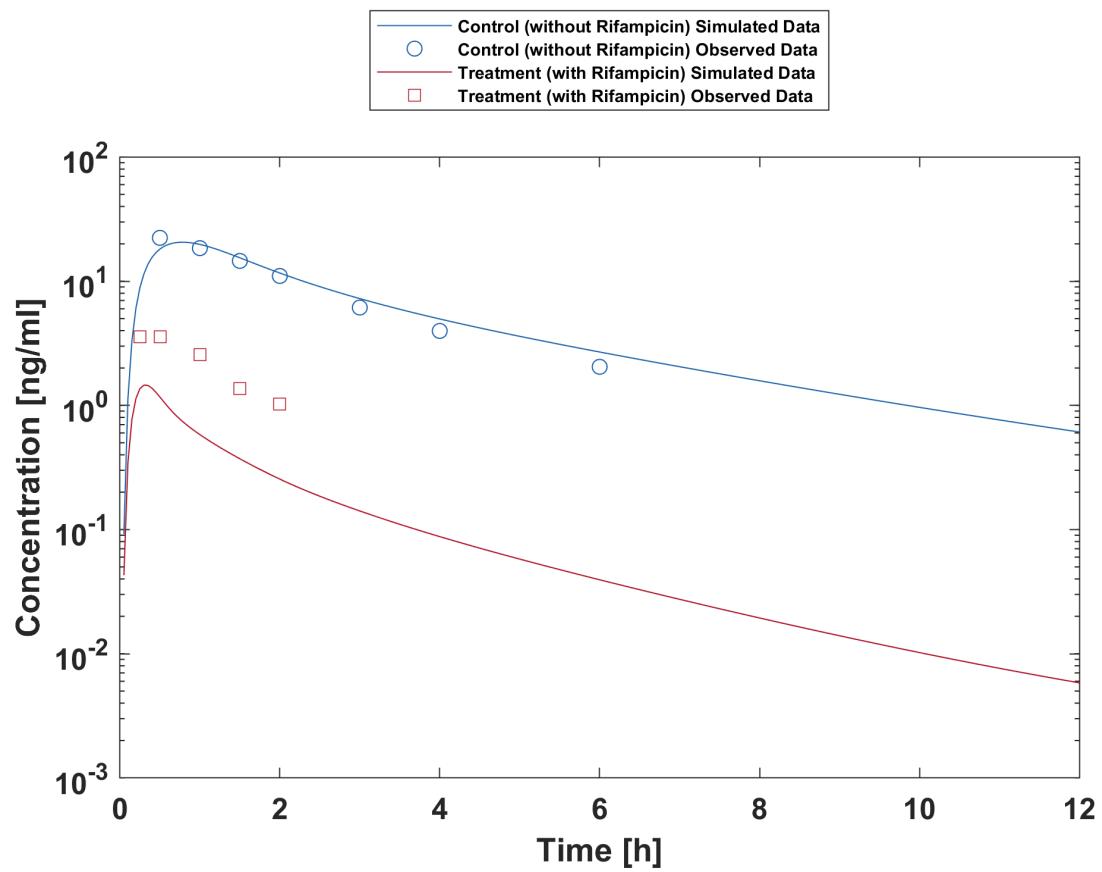
Backman 1998 (Phase IV and V vs. I)



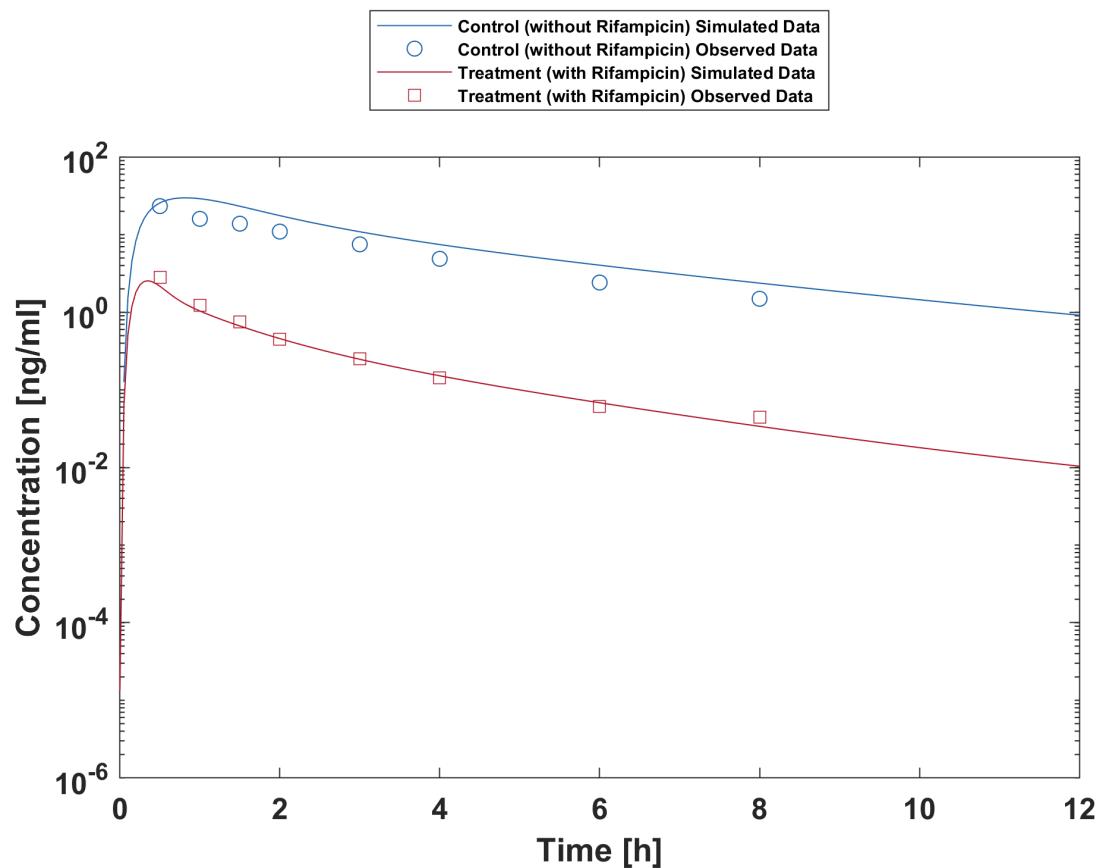
Björkhem-Bergman 2013



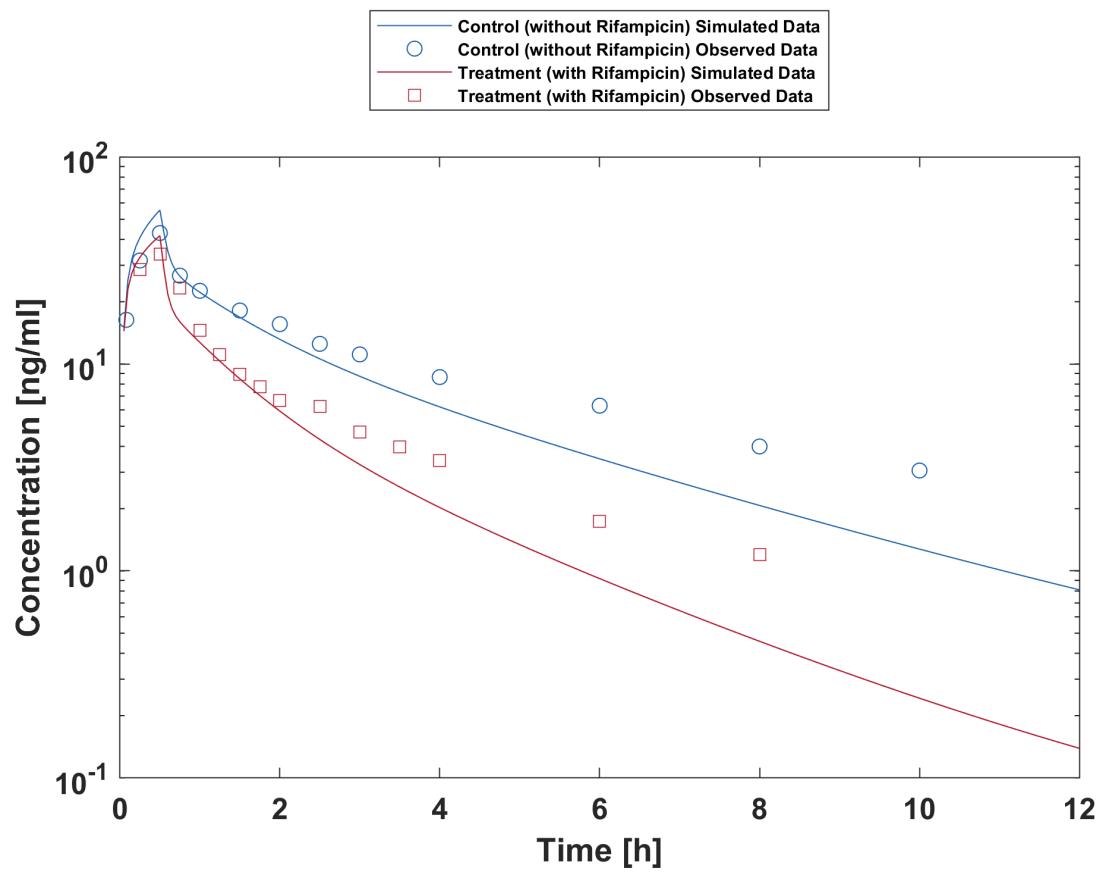
Chattopadhyay 2018



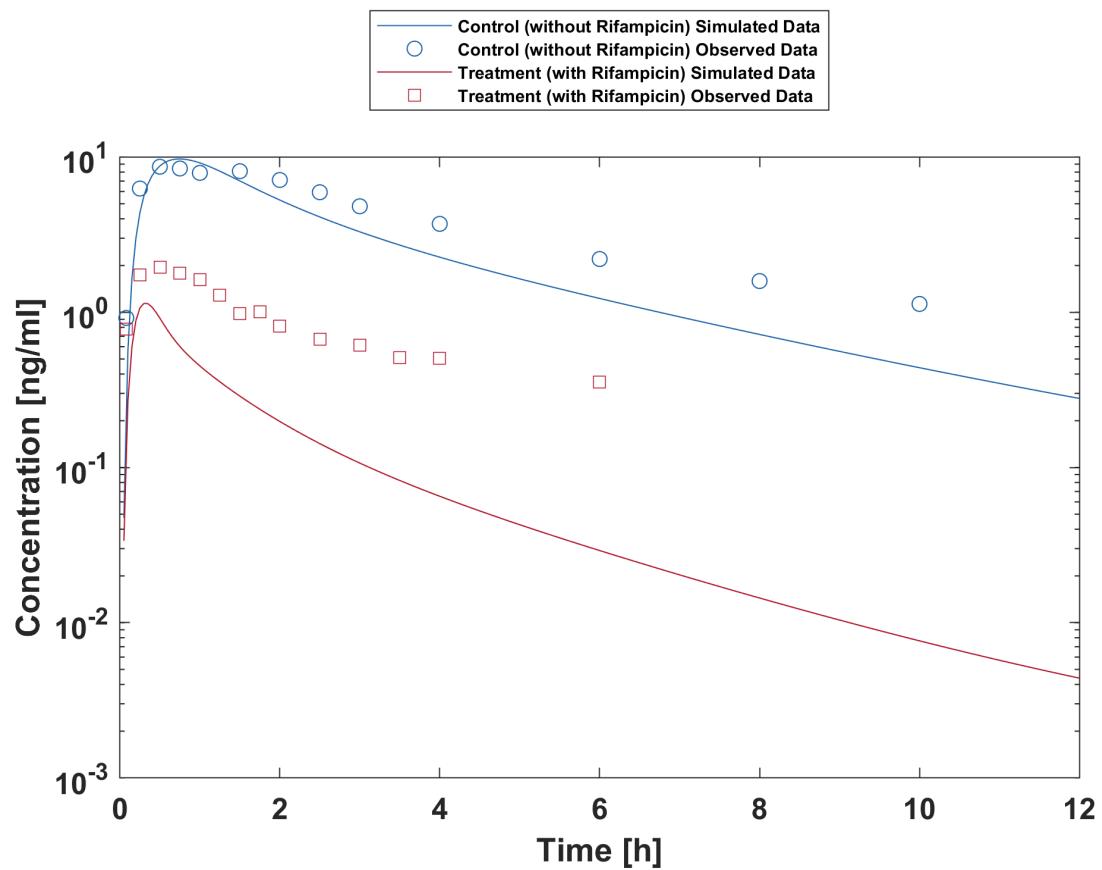
Chung 2006



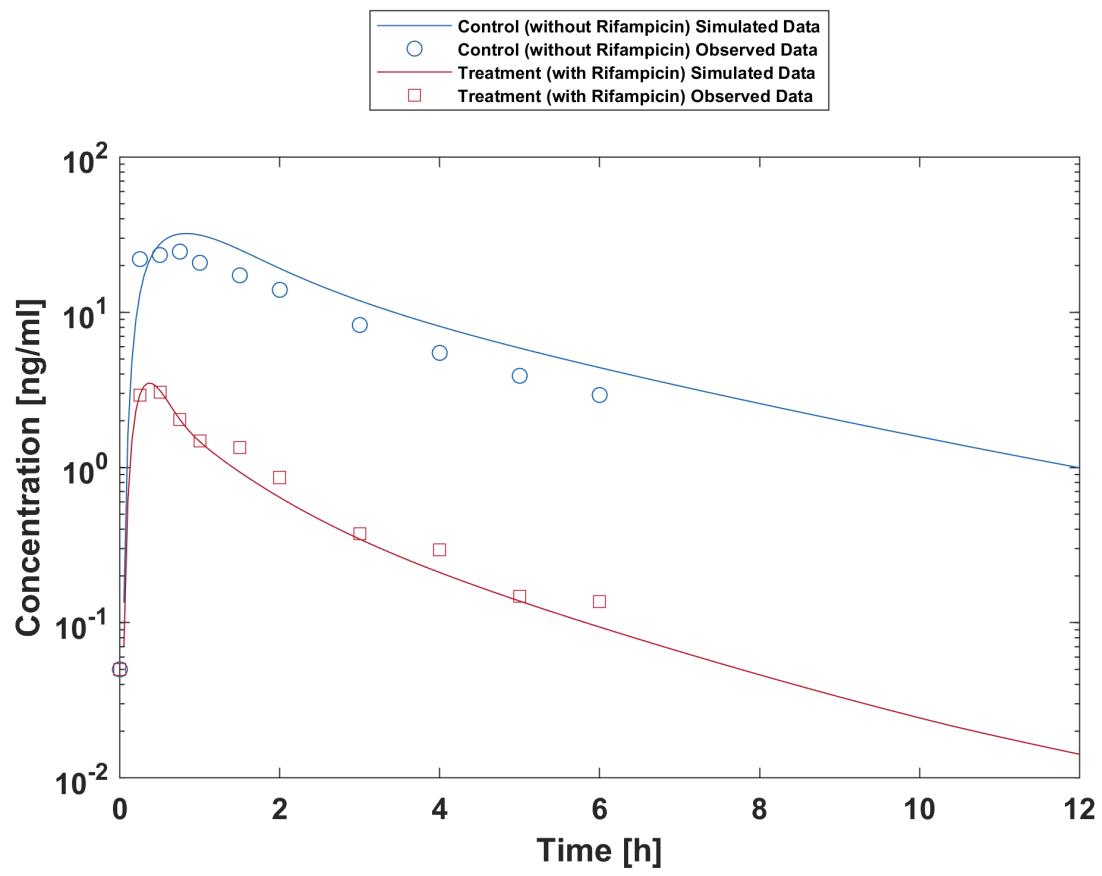
Eap 2004 (7.5 mg)



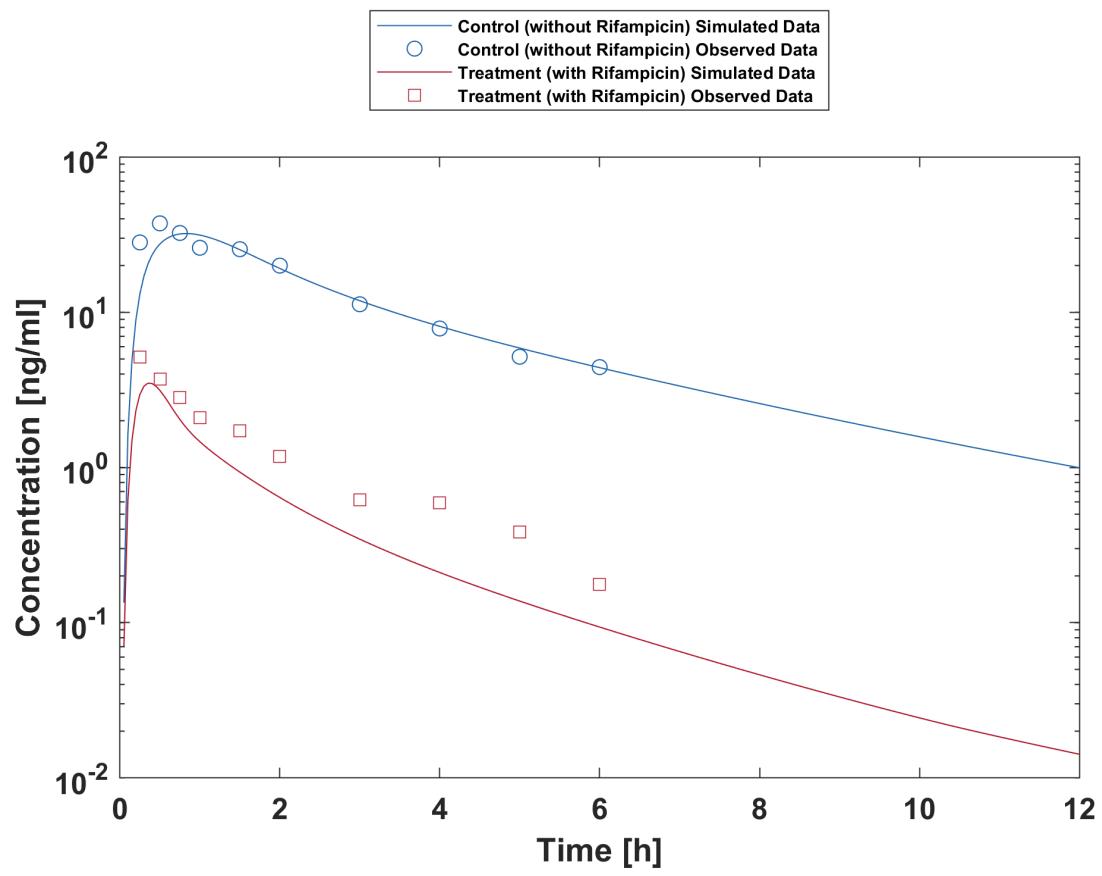
Gorski 2003 (iv)



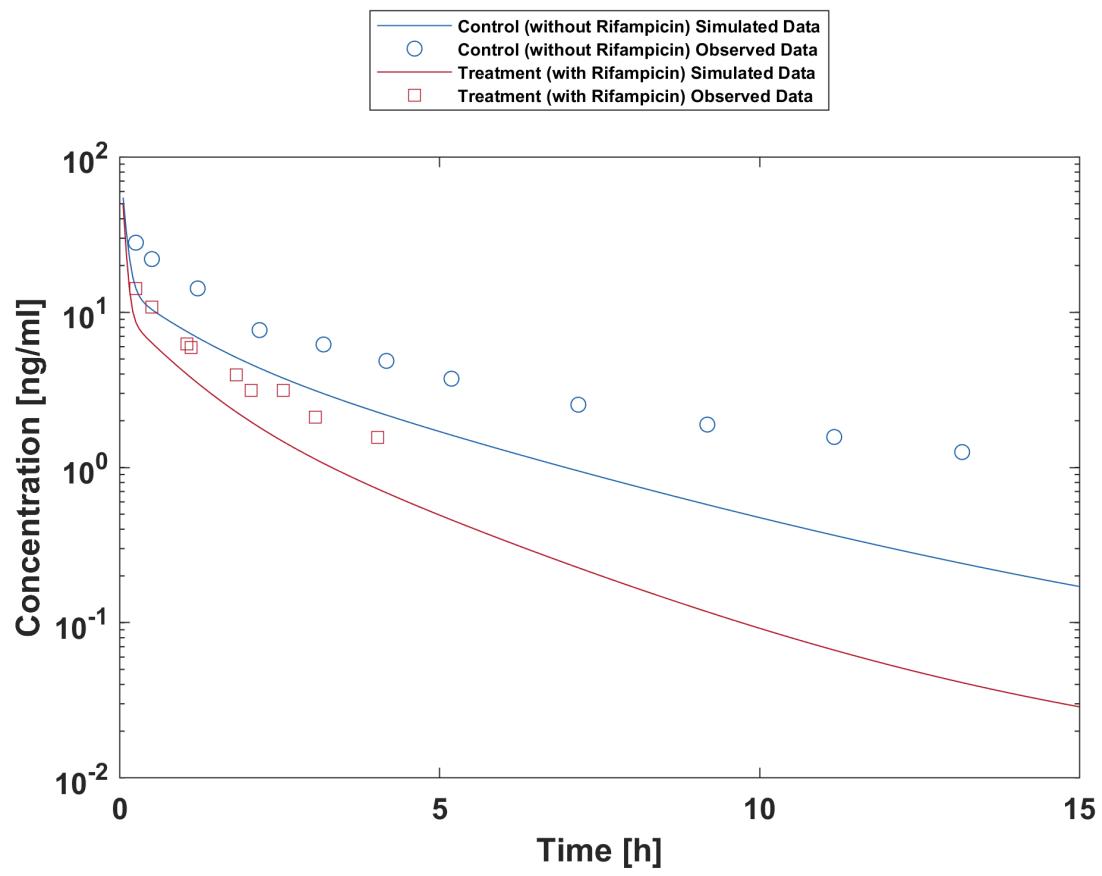
Gorski 2003 (po)



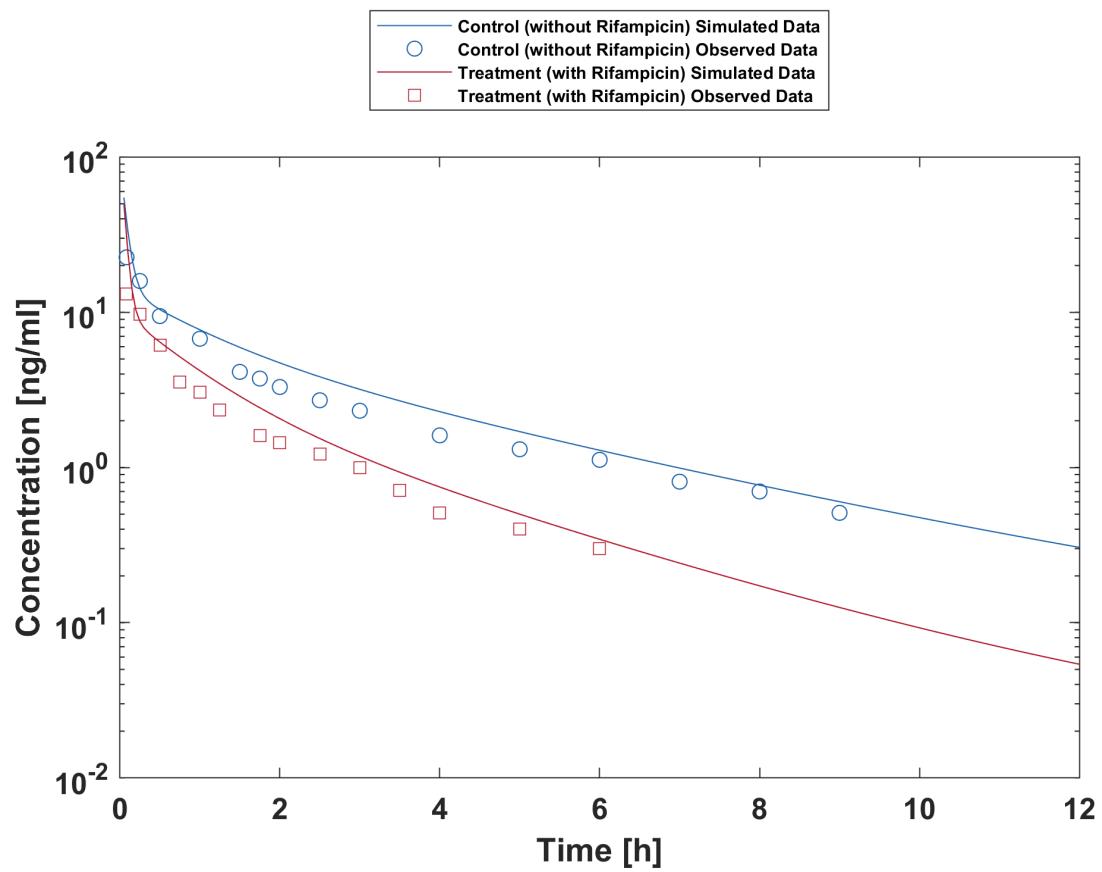
Gurley 2006



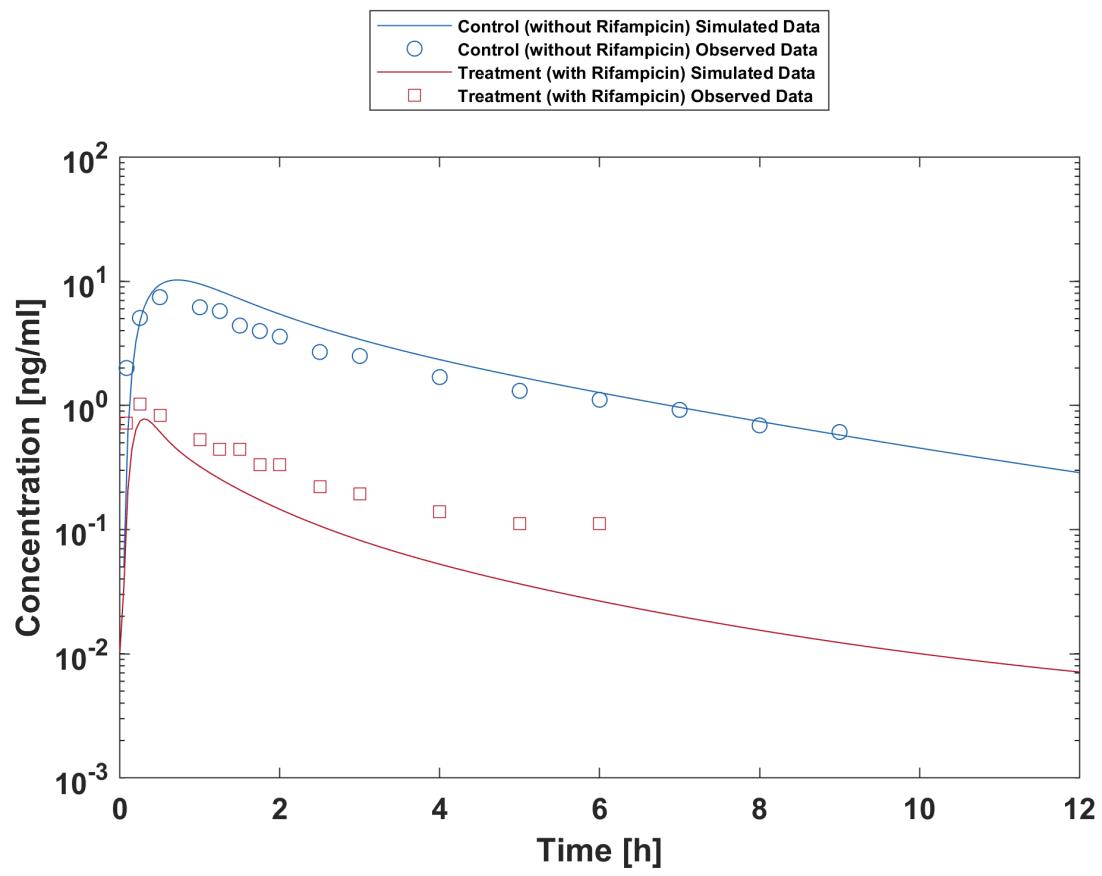
Gurley 2008a



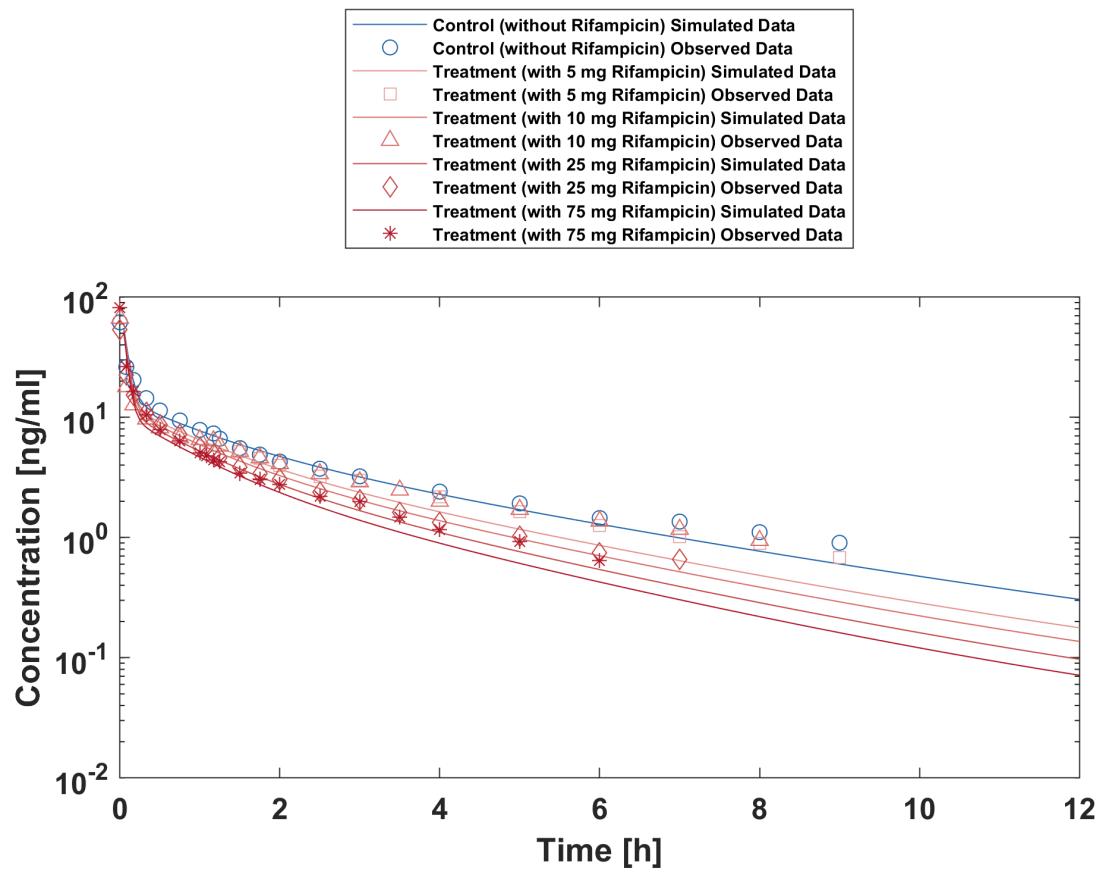
Kharasch 1997



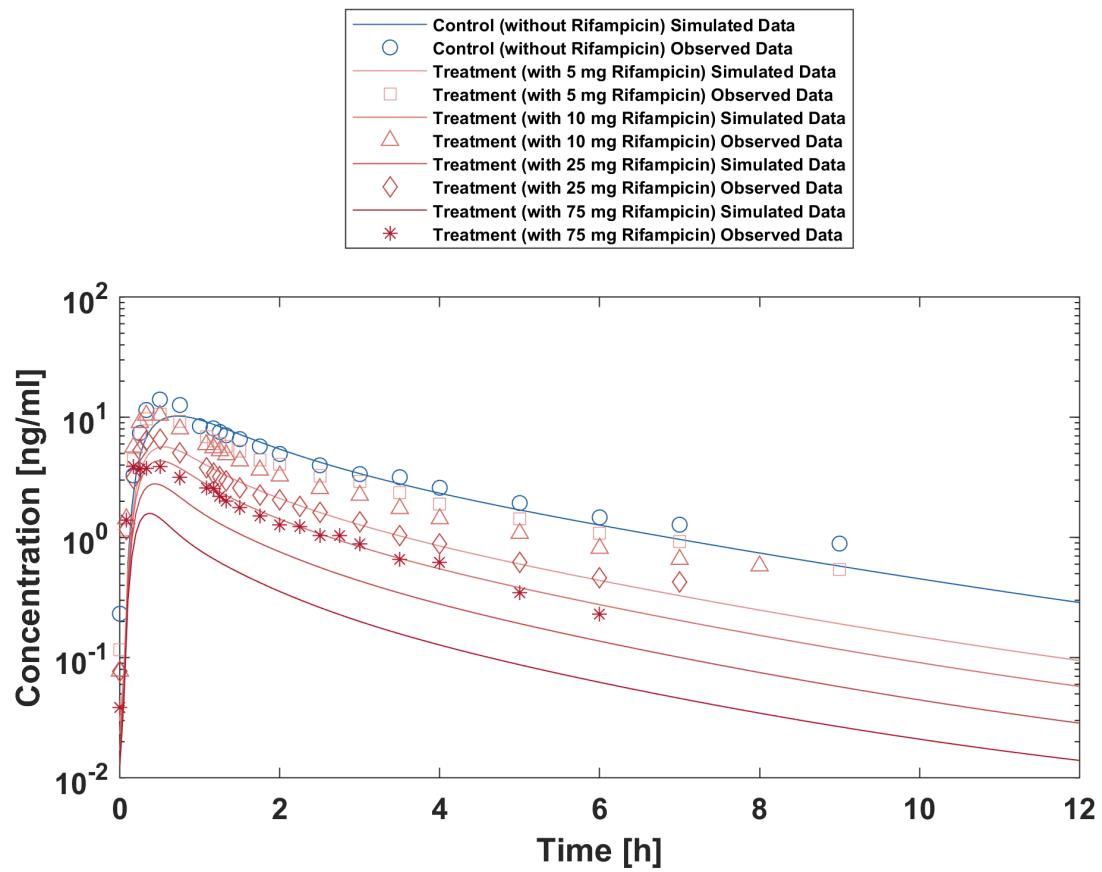
Kharasch 2004 (iv)



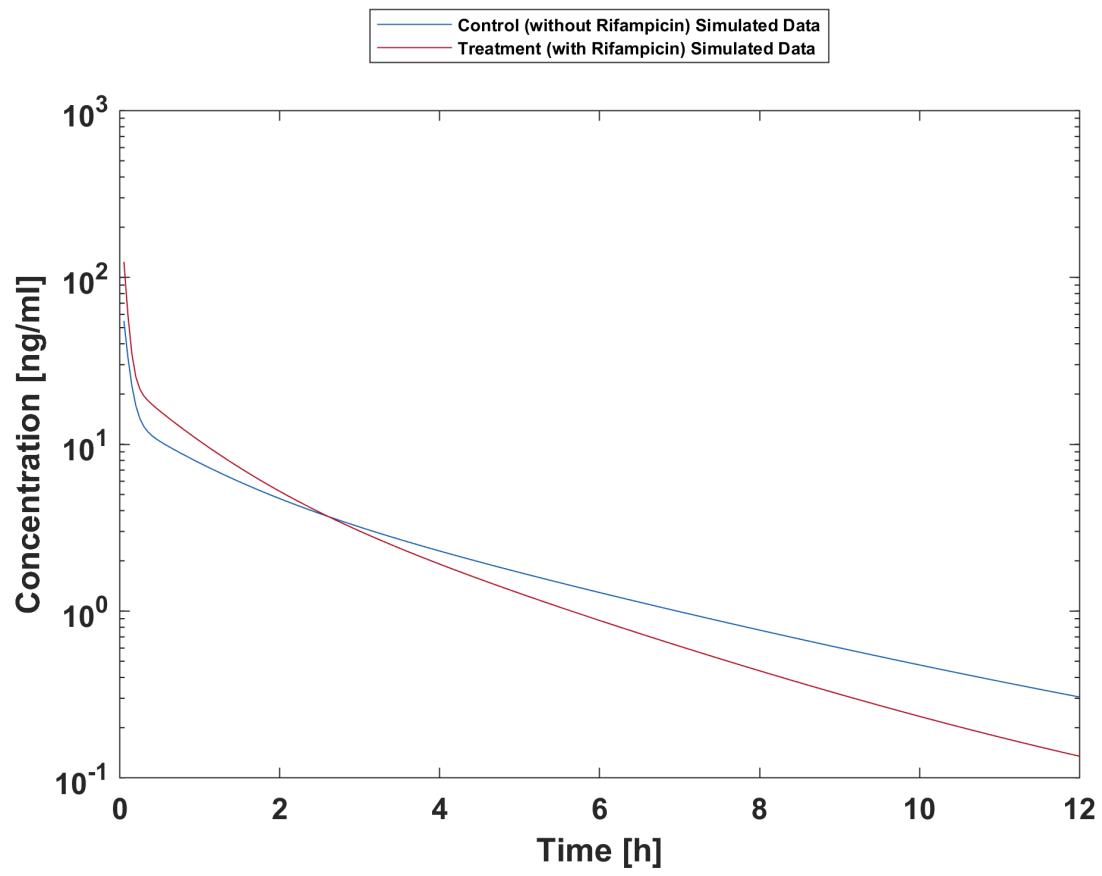
Kharasch 2004 (po)



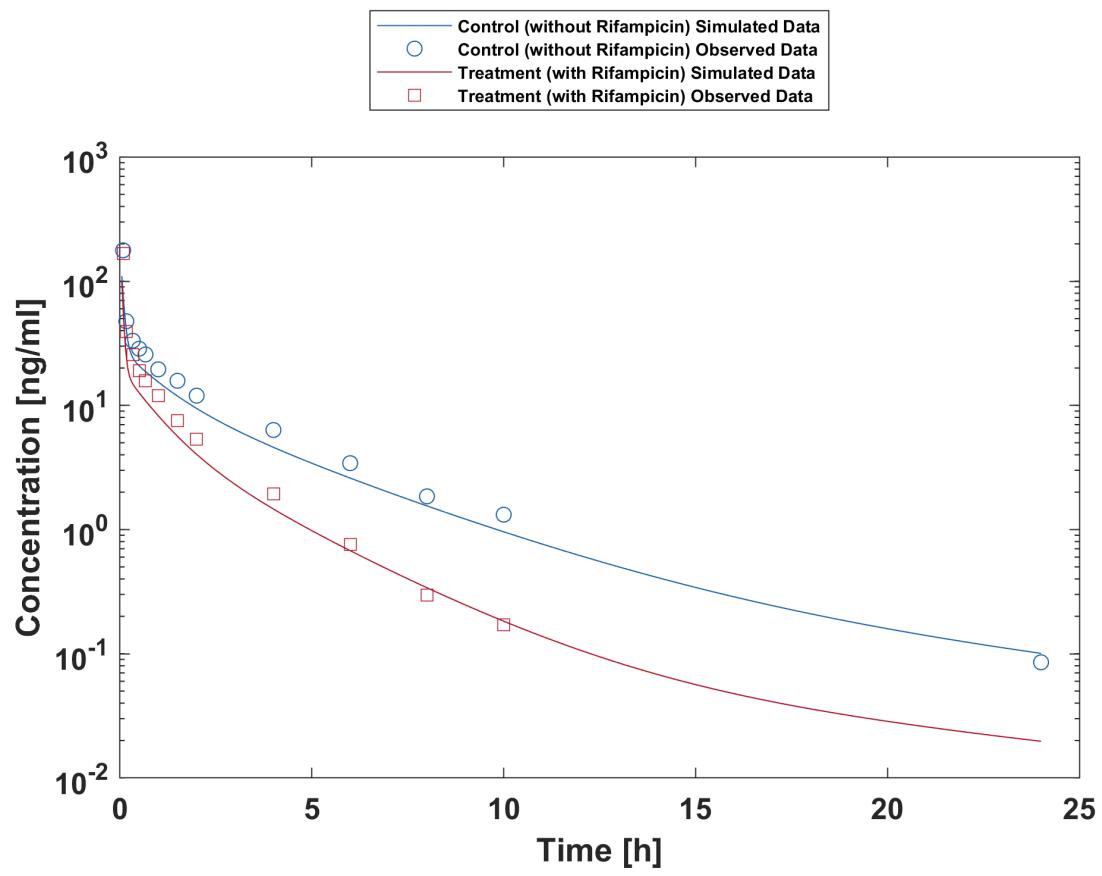
Kharasch 2011 (iv)



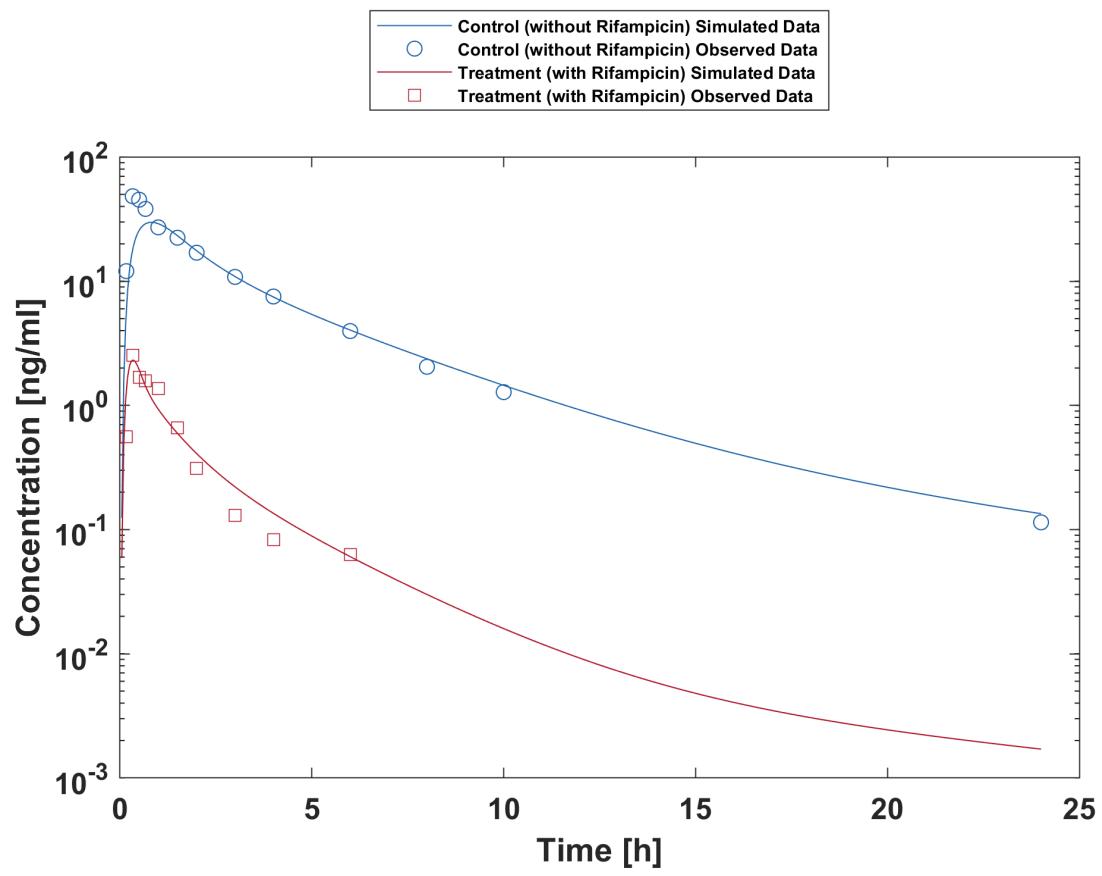
Kharasch 2011 (po)



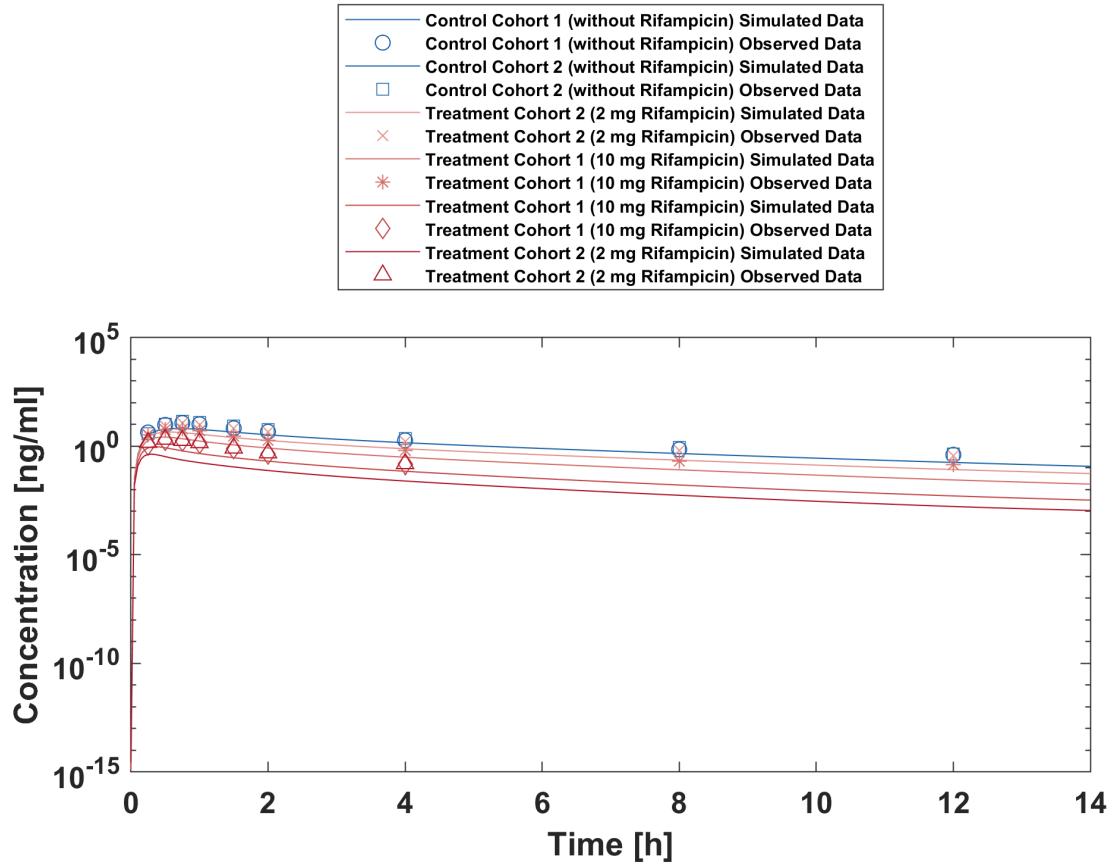
Kim 2018



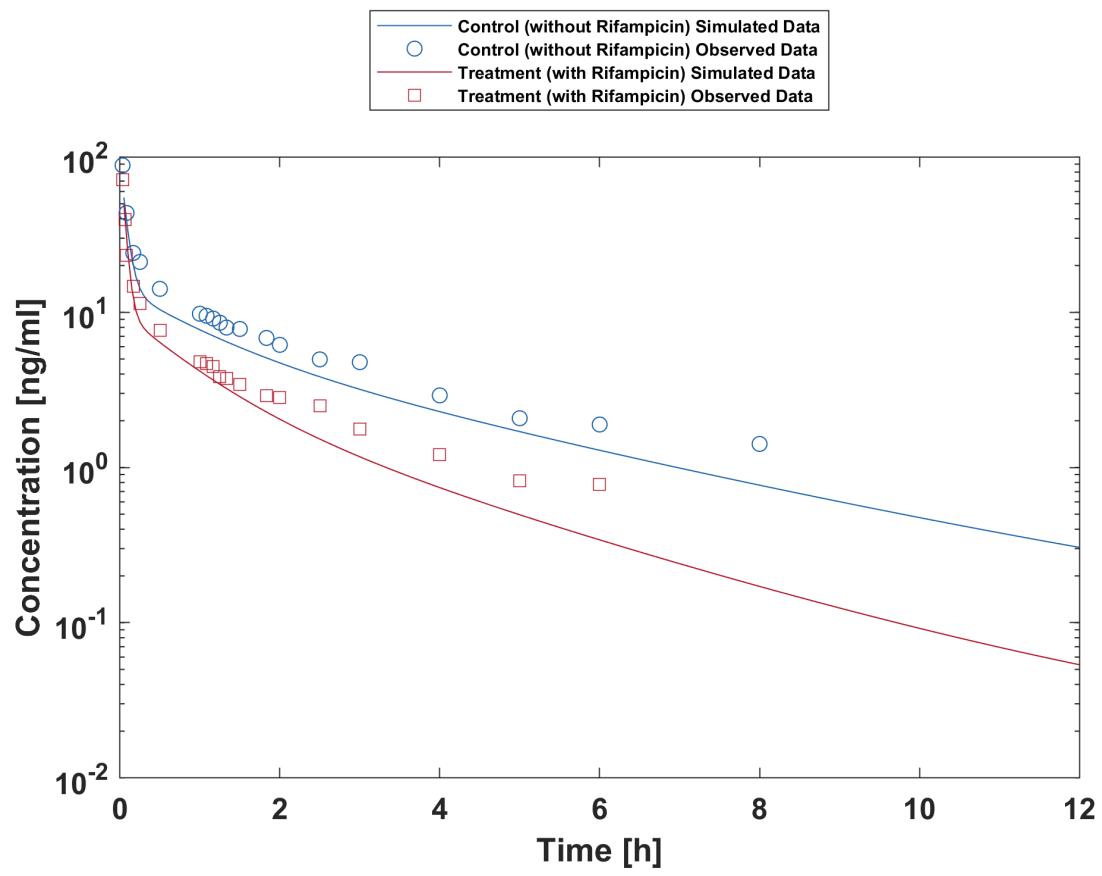
Link 2008 (iv)



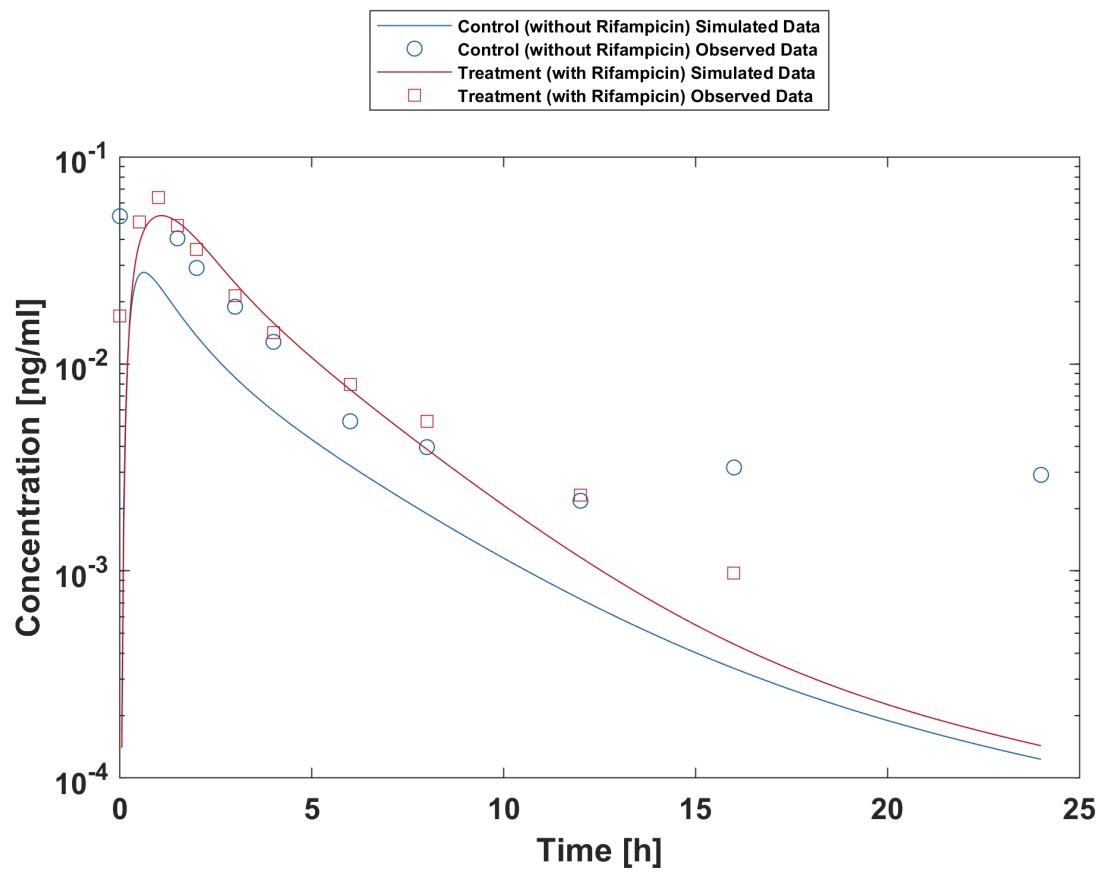
Link 2008 (po)



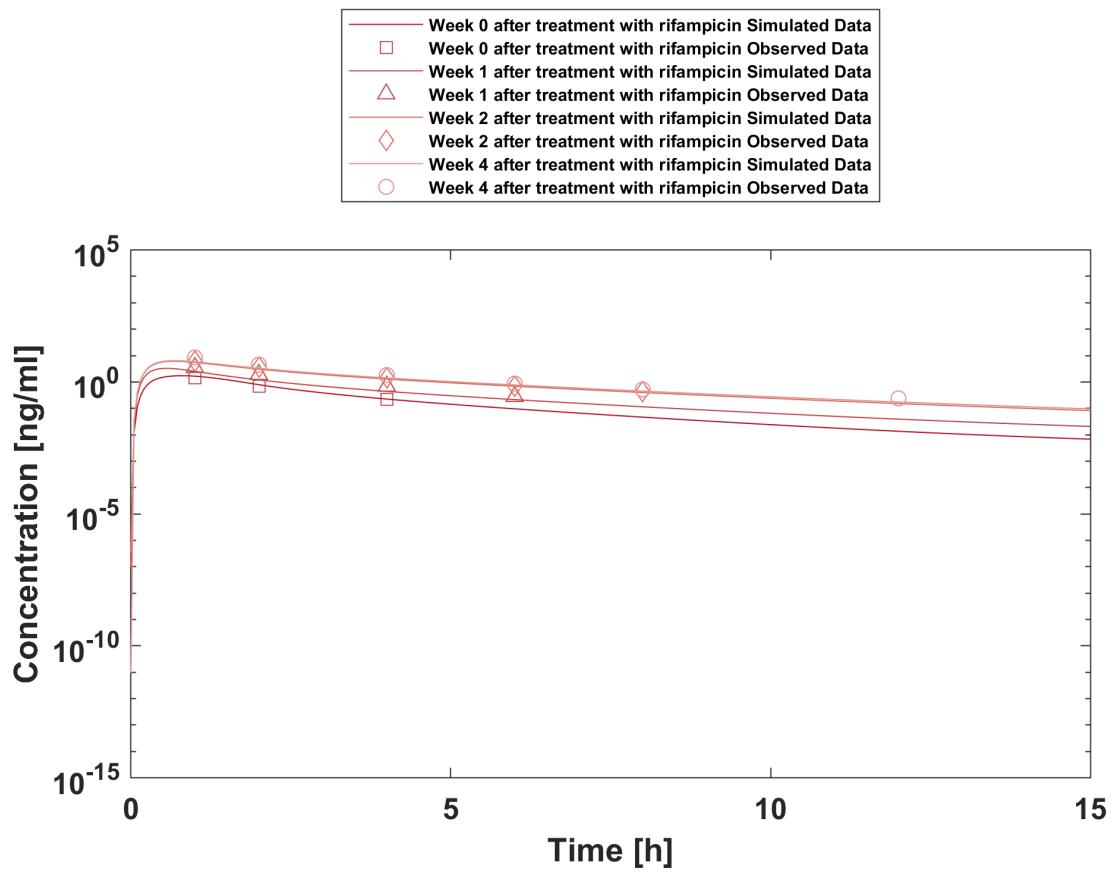
Lutz 2008



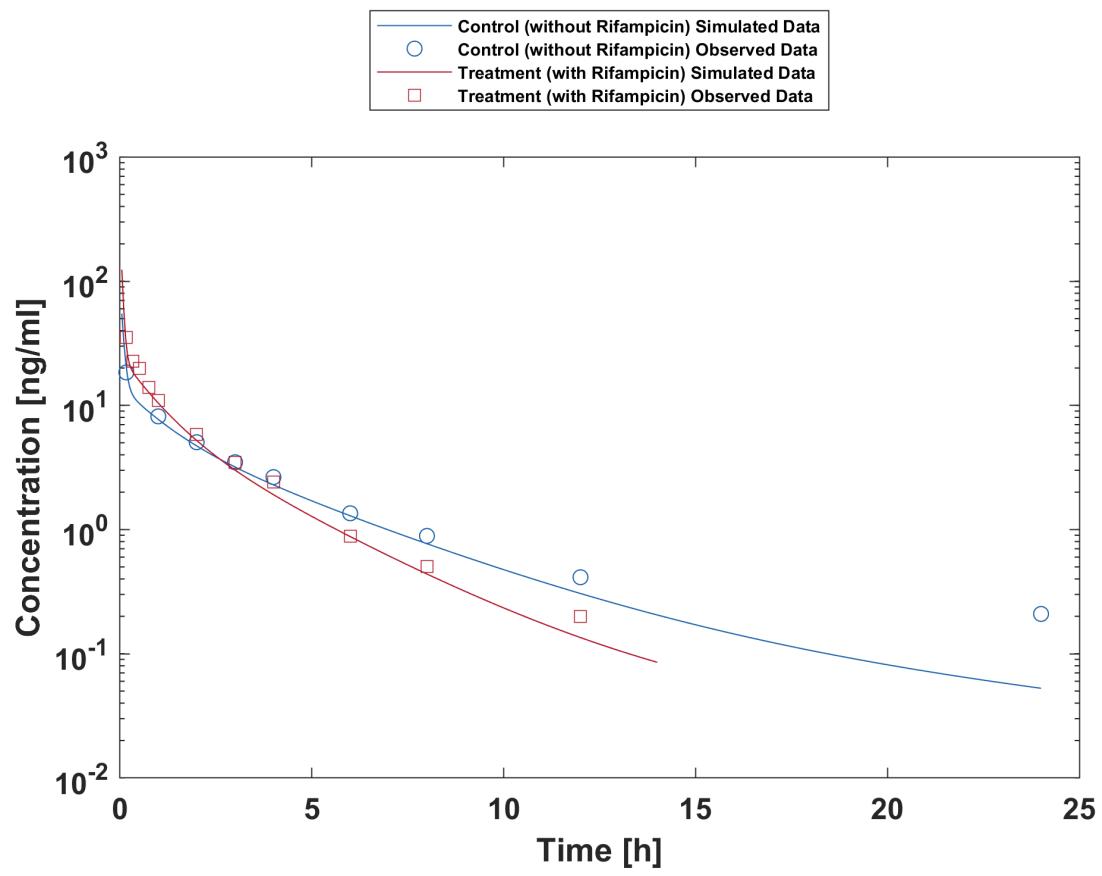
Phimmasone 2001



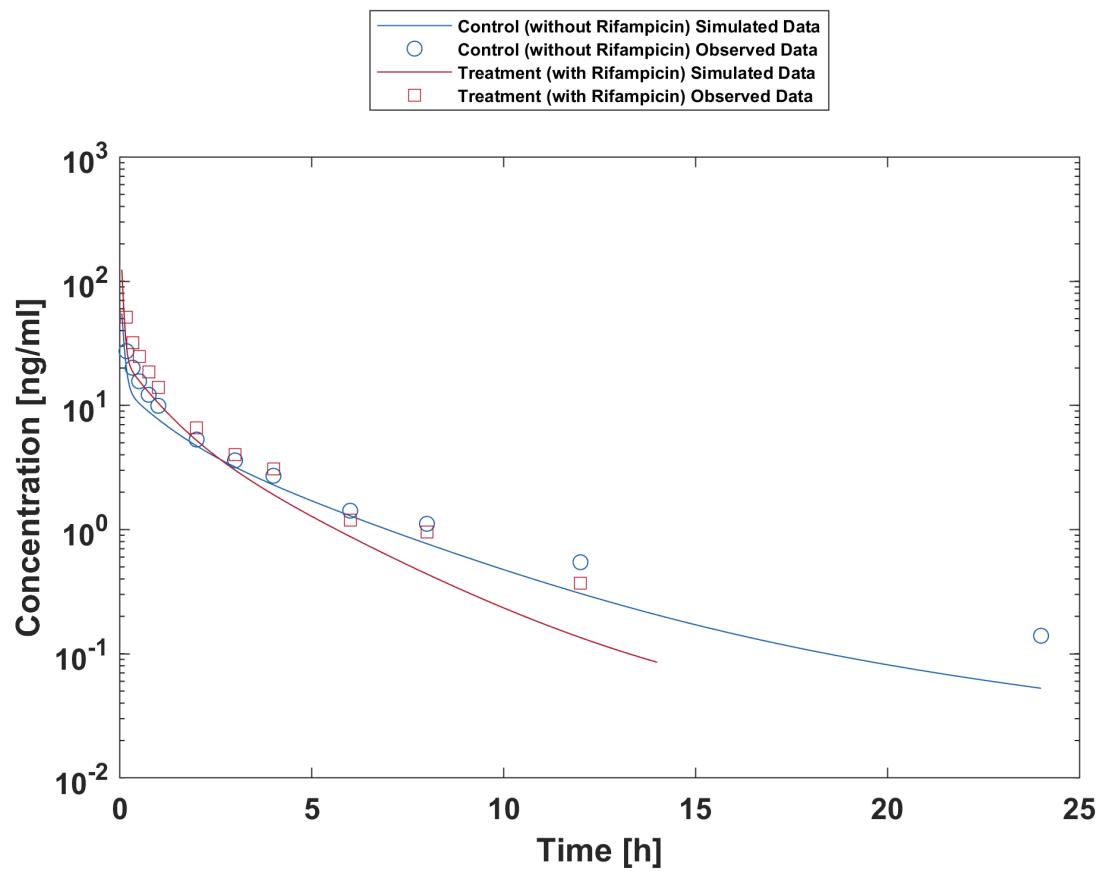
Prueksaritanont 2017



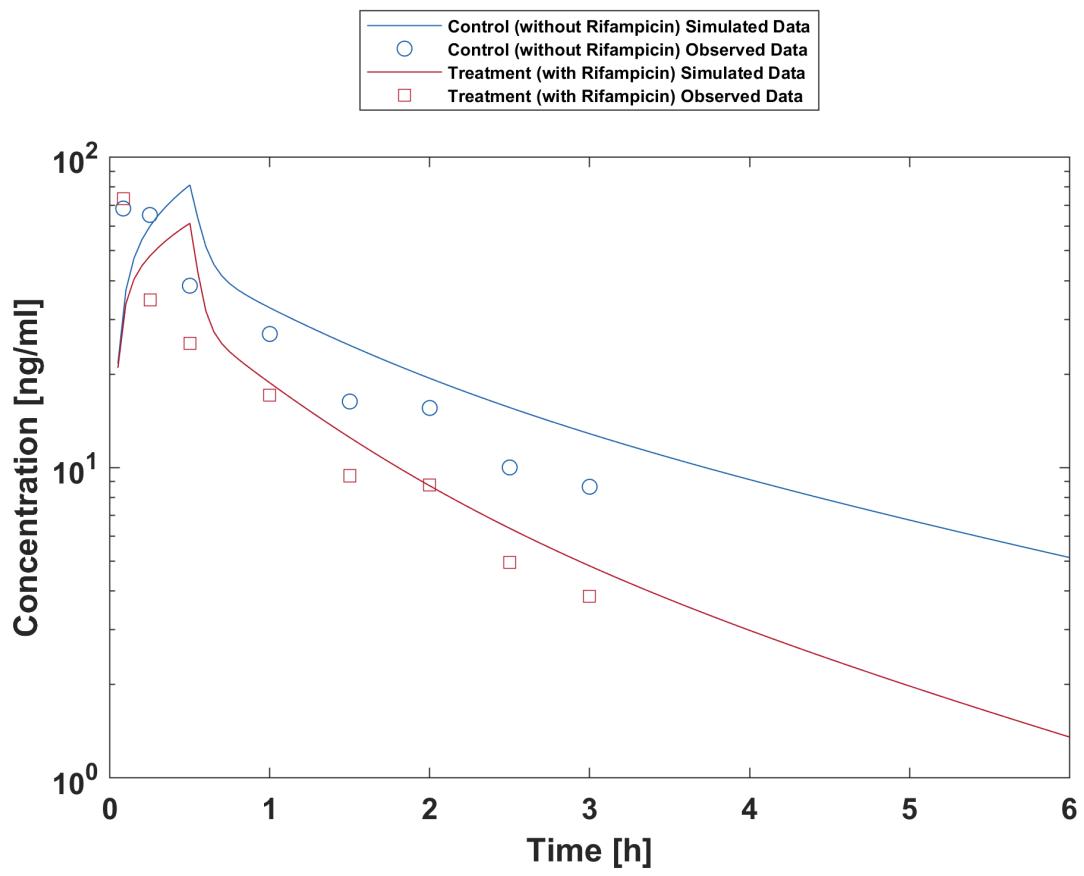
Reitman 2011



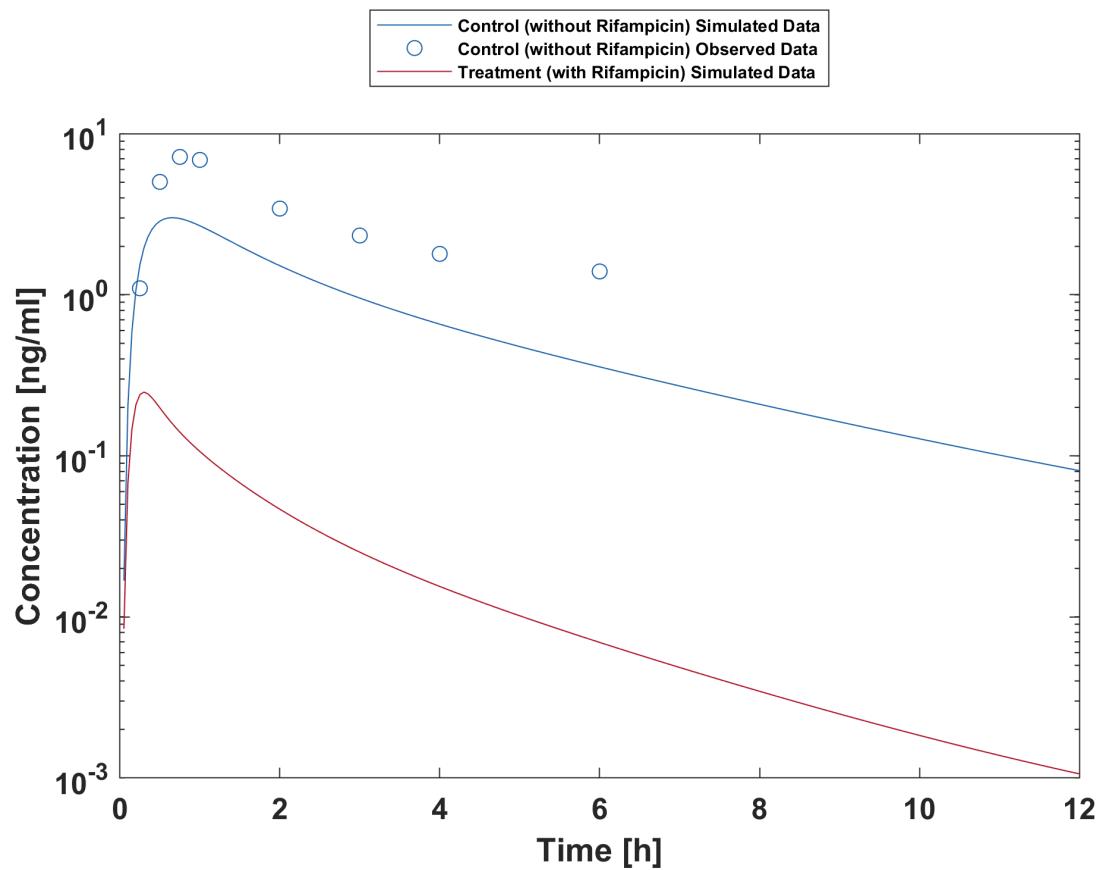
Shin 2013



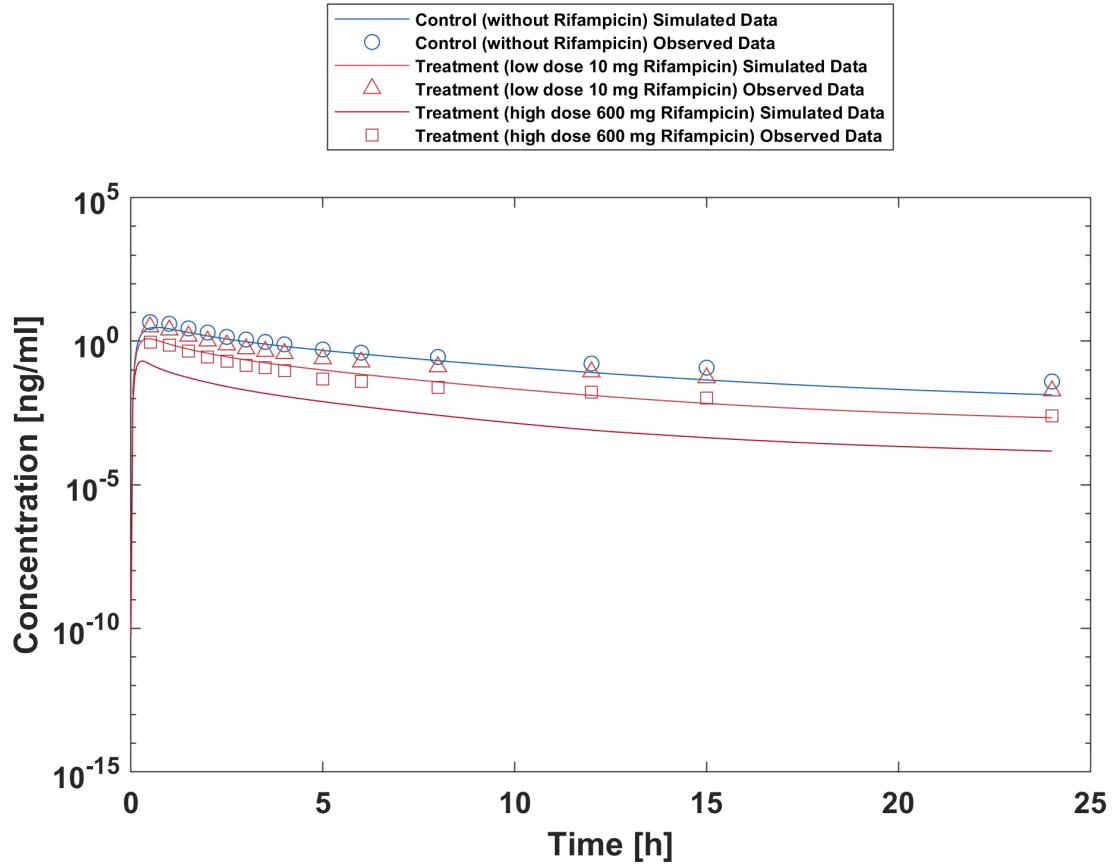
Shin 2016



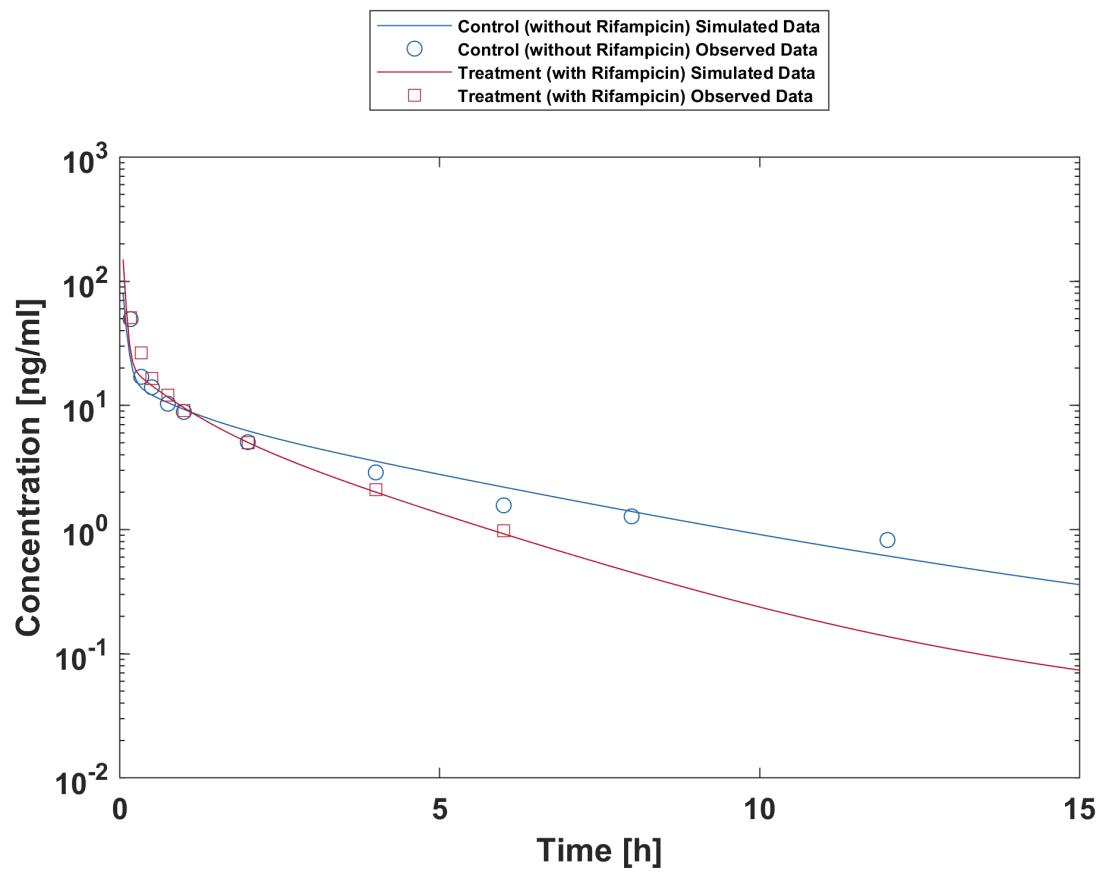
Szalat 2007



van Dyk 2018

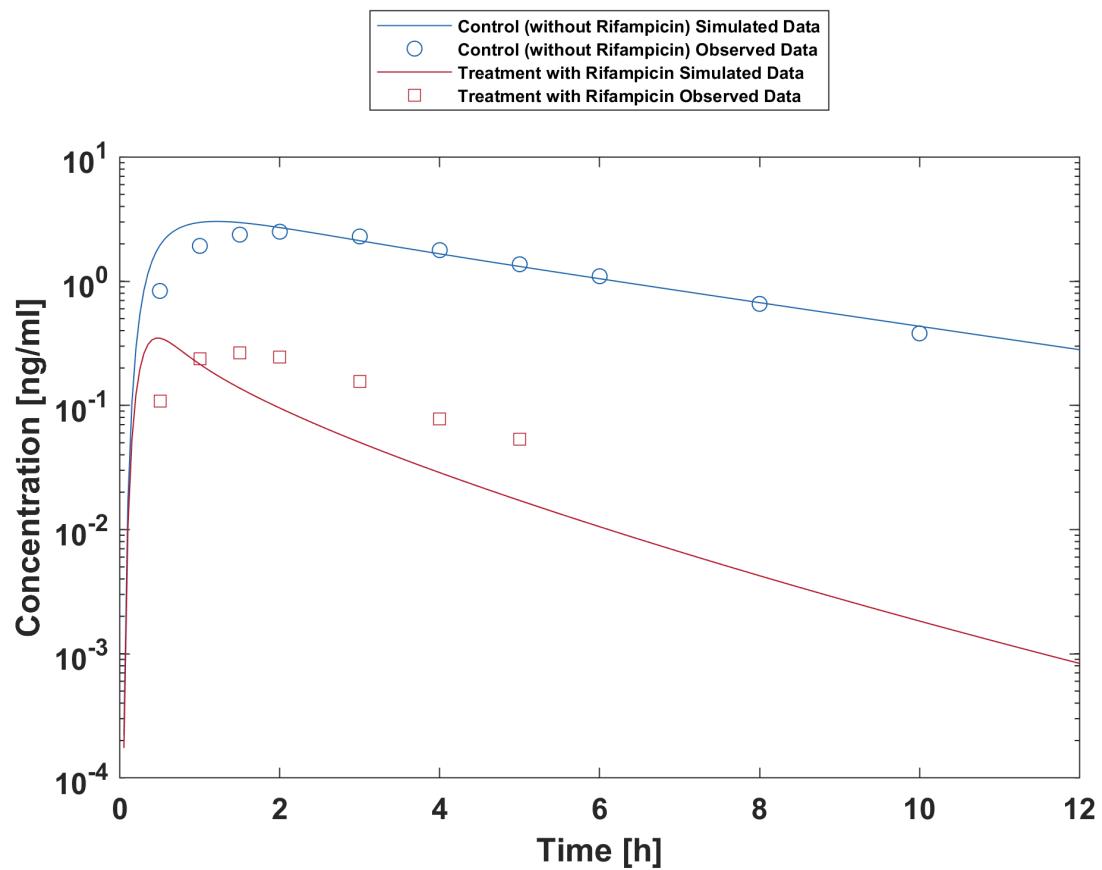


Wiesinger 2020



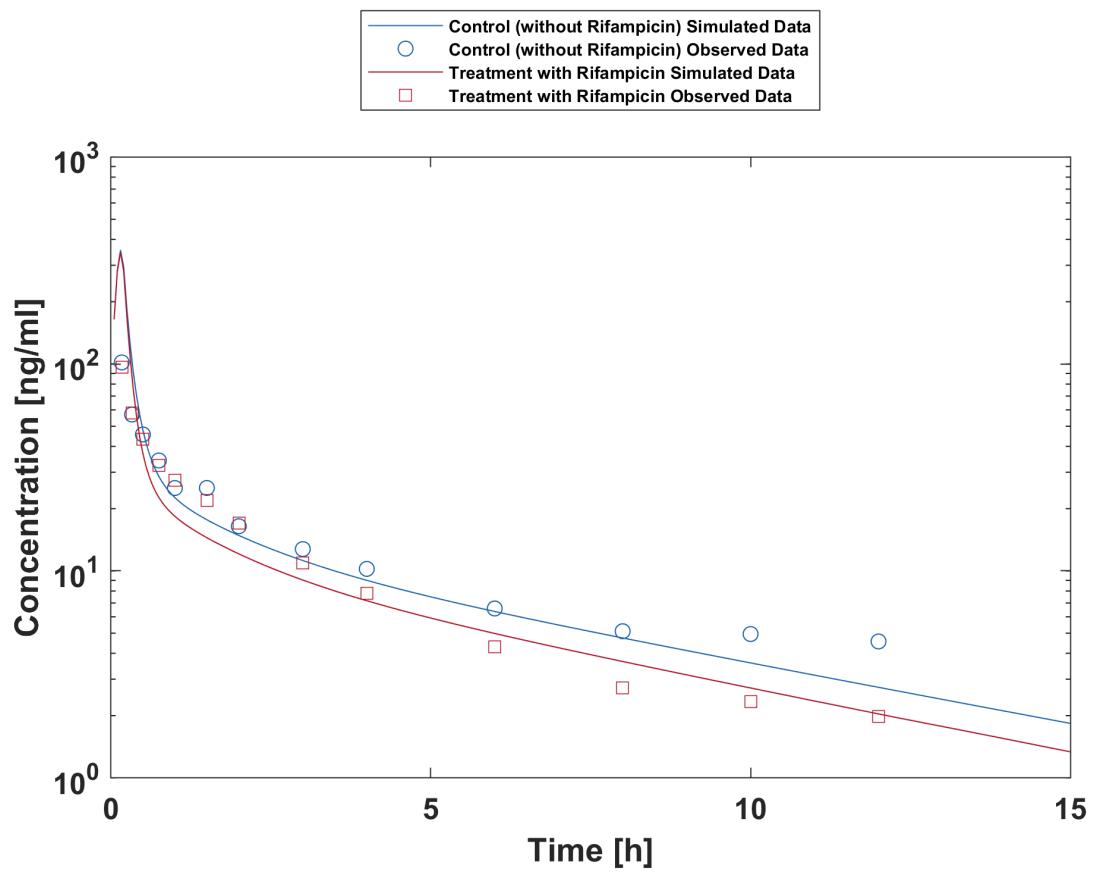
Yu 2004 (CYP3A5*3/*3)

3.23 Rifampicin - Triazolam DDI

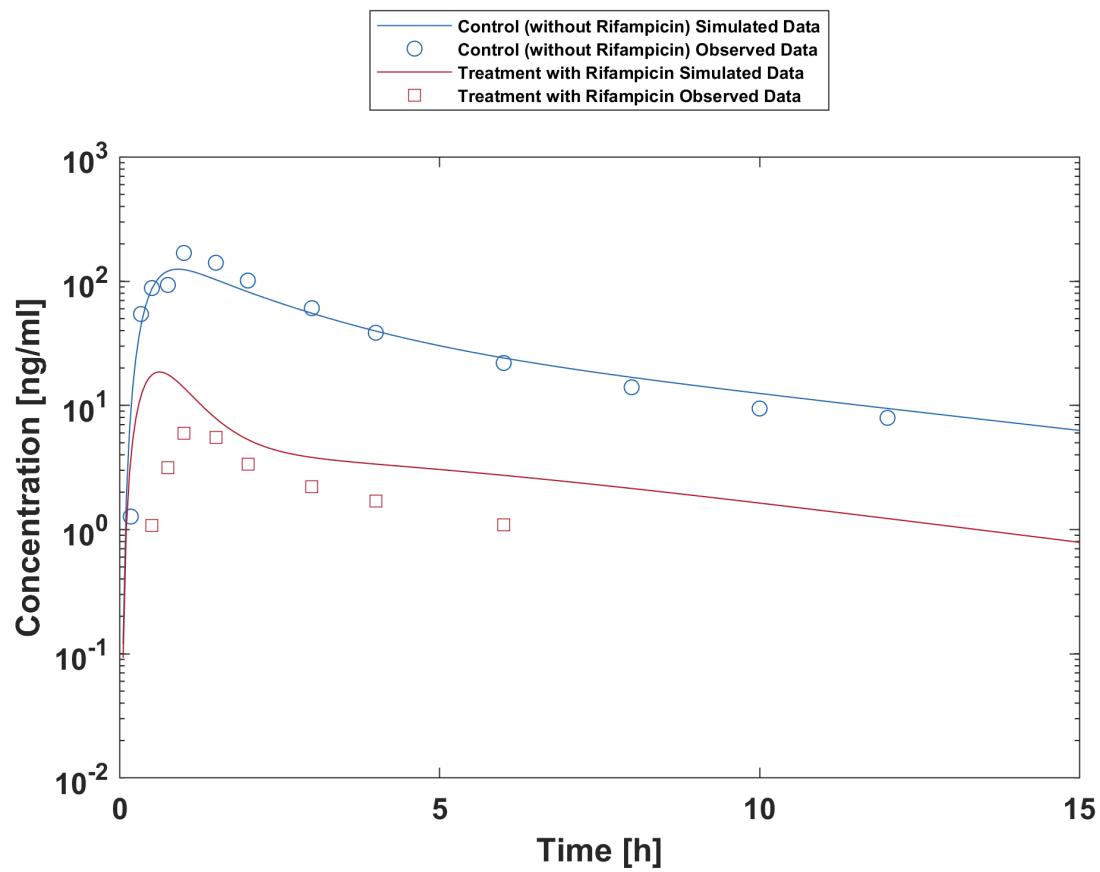


Villikka 1997

3.24 Rifampicin - Verapamil DDI

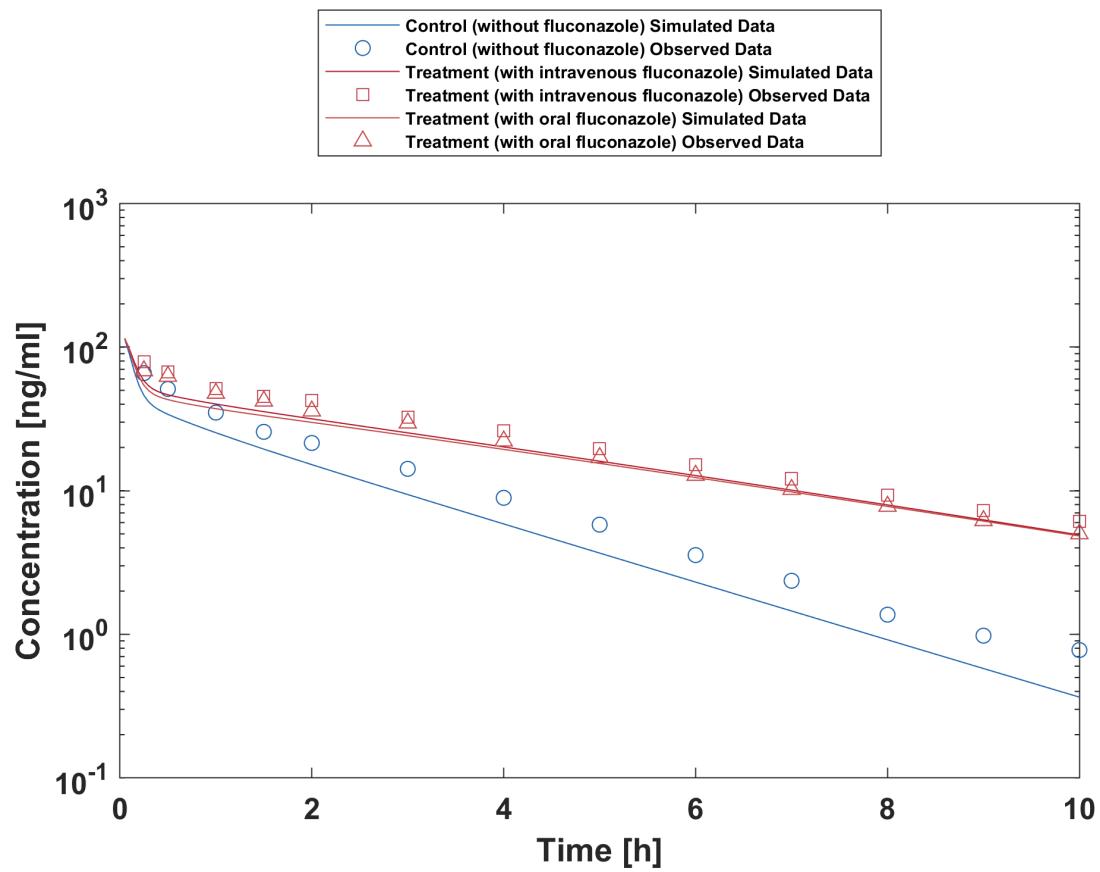


Barbarash 1988 (verapamil IV)



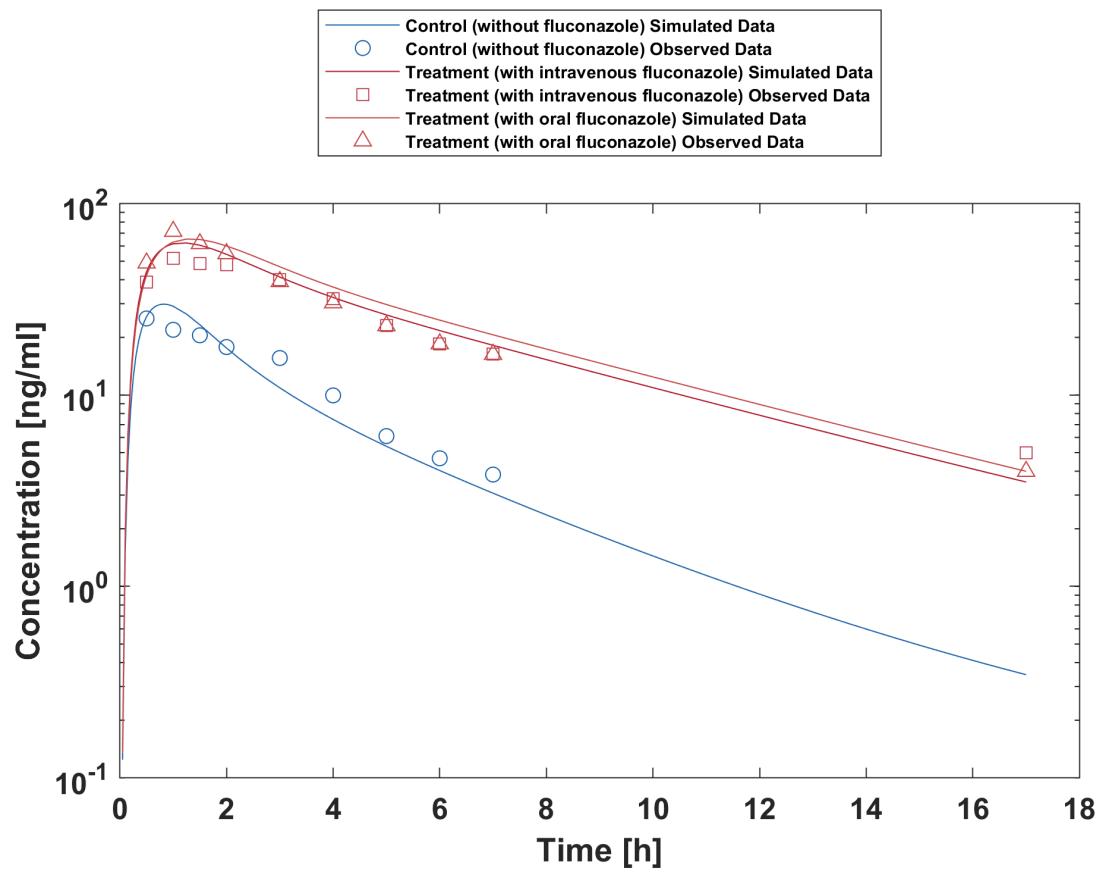
Barbarash 1988 (verapamil PO)

3.25 Fluconazole - Alfentanil DDI

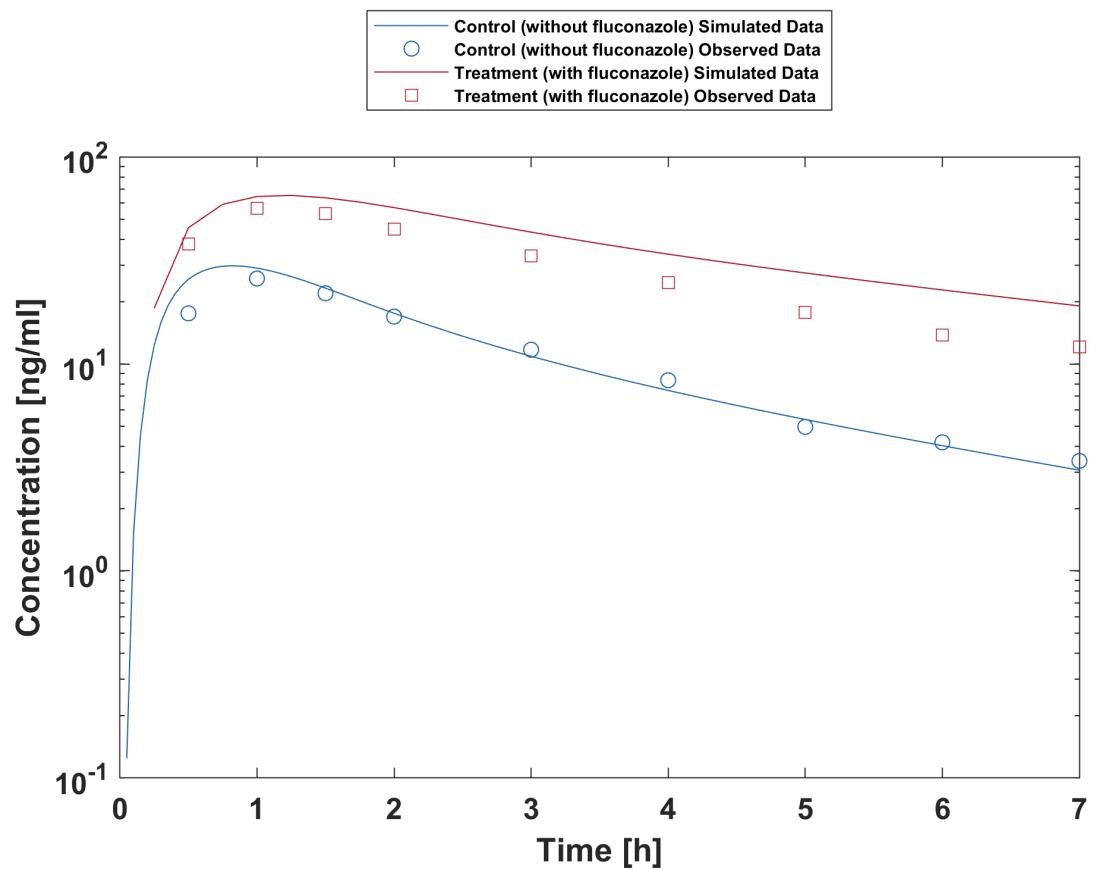


Palkama 1998

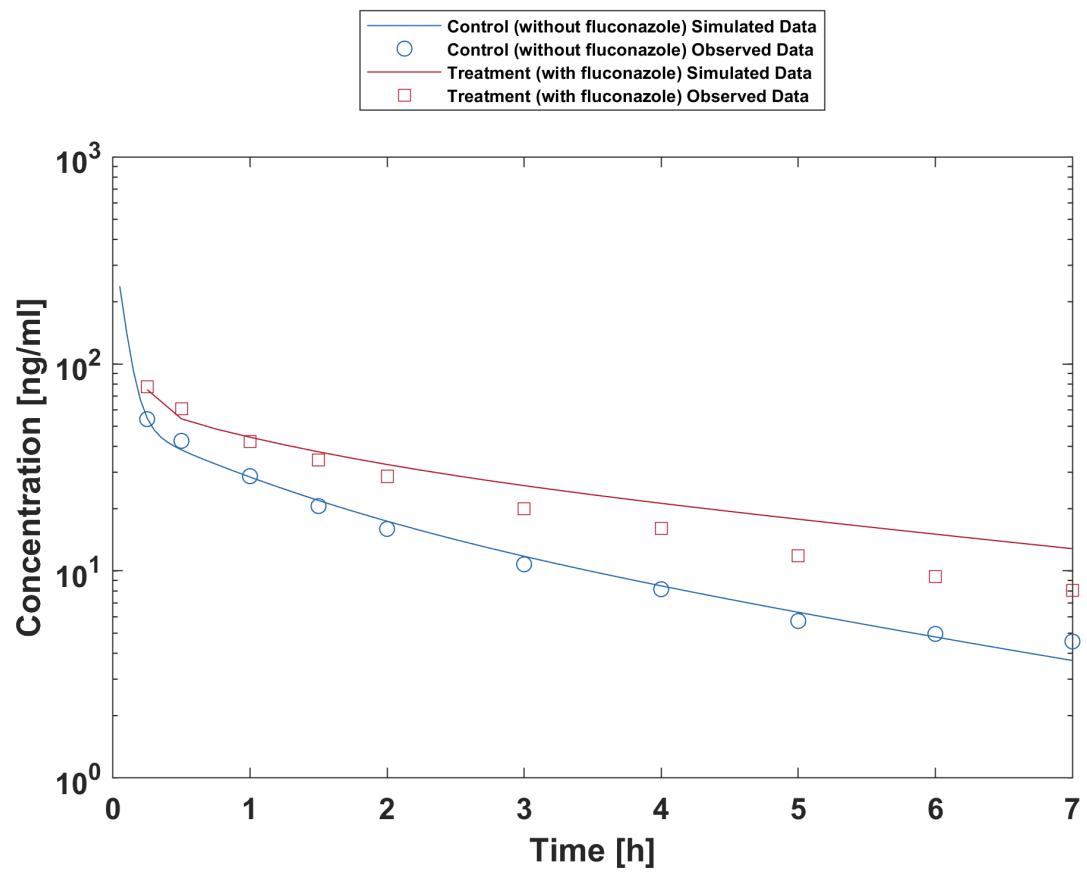
3.26 Fluconazole - Midazolam DDI



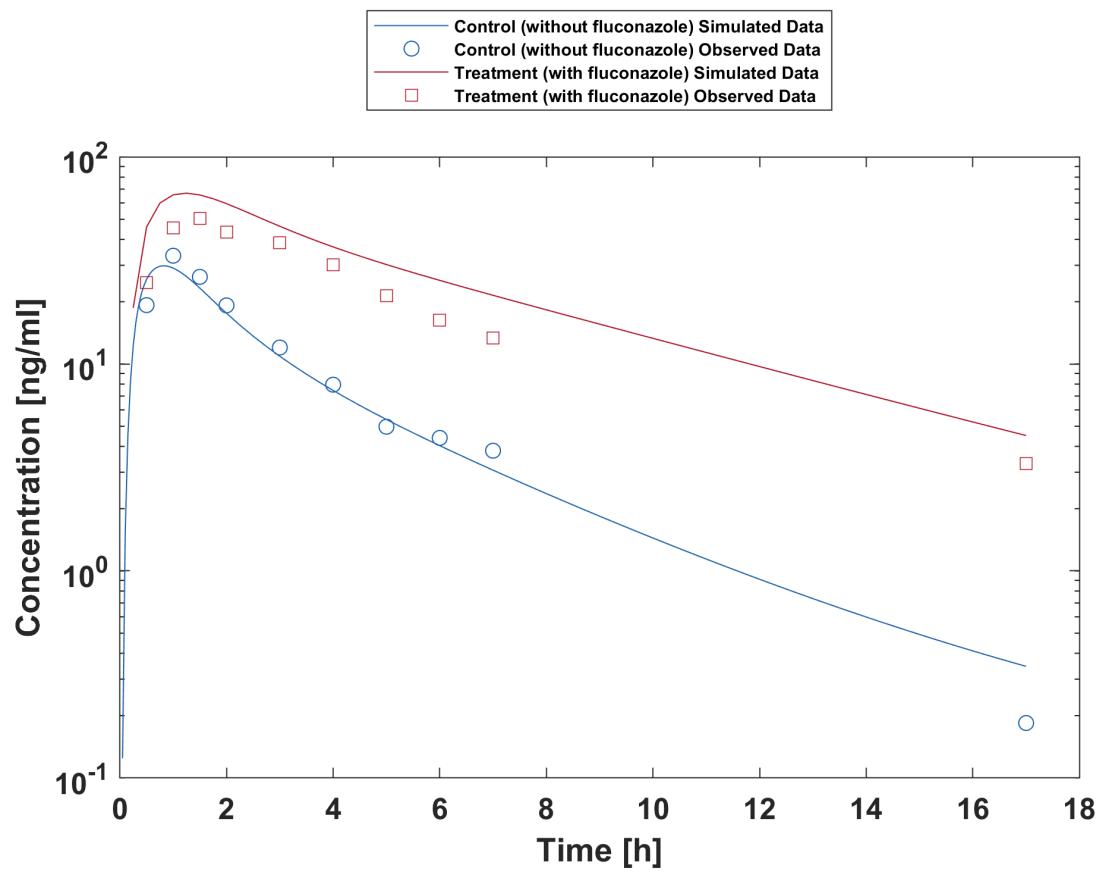
Ahonen 1997



Olkola 1996 Day 1

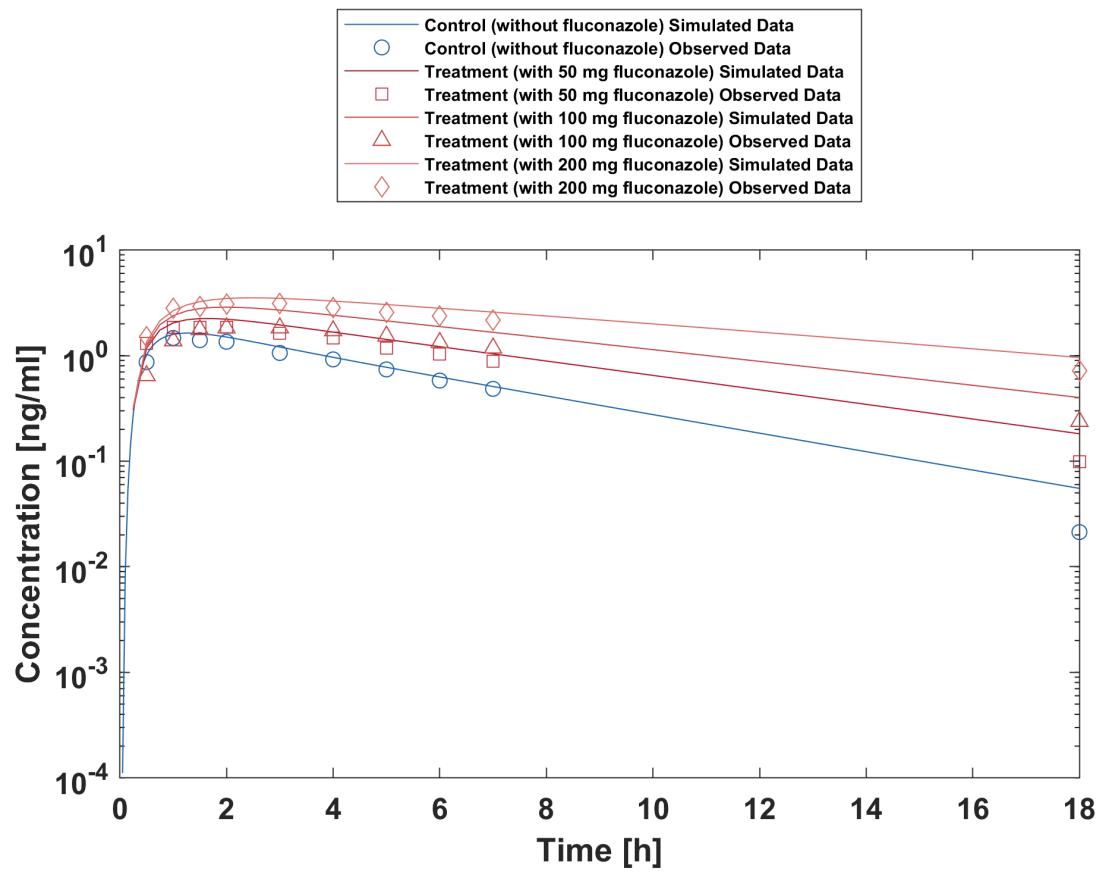


Olkola 1996 Day 4



Olkola 1996 Day 6

3.27 Fluconazole - Triazolam DDI



Varhe 1996c

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Rifampicin-Triazolam-DDI

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5 Appendix

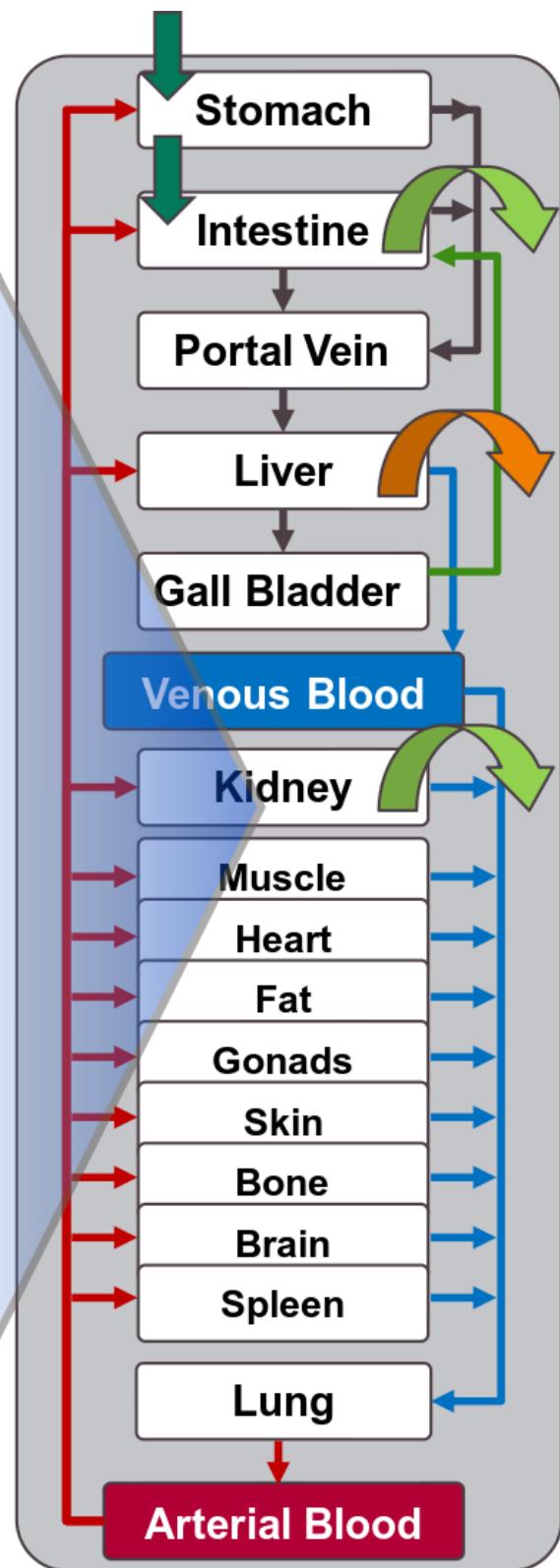
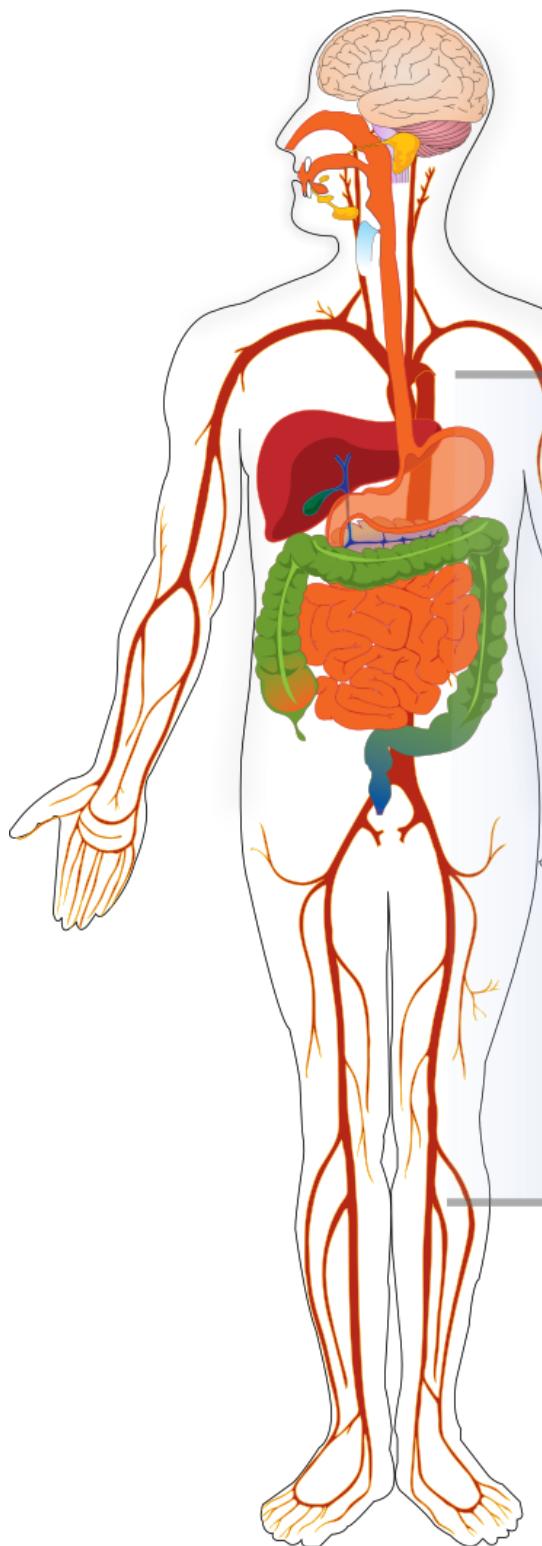
5.1 Open Systems Pharmacology Suite (OSPS) Introduction

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

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5.2 Mathematical Implementation of Drug-Drug Interactions

DDI modeling: Competitive inhibition

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

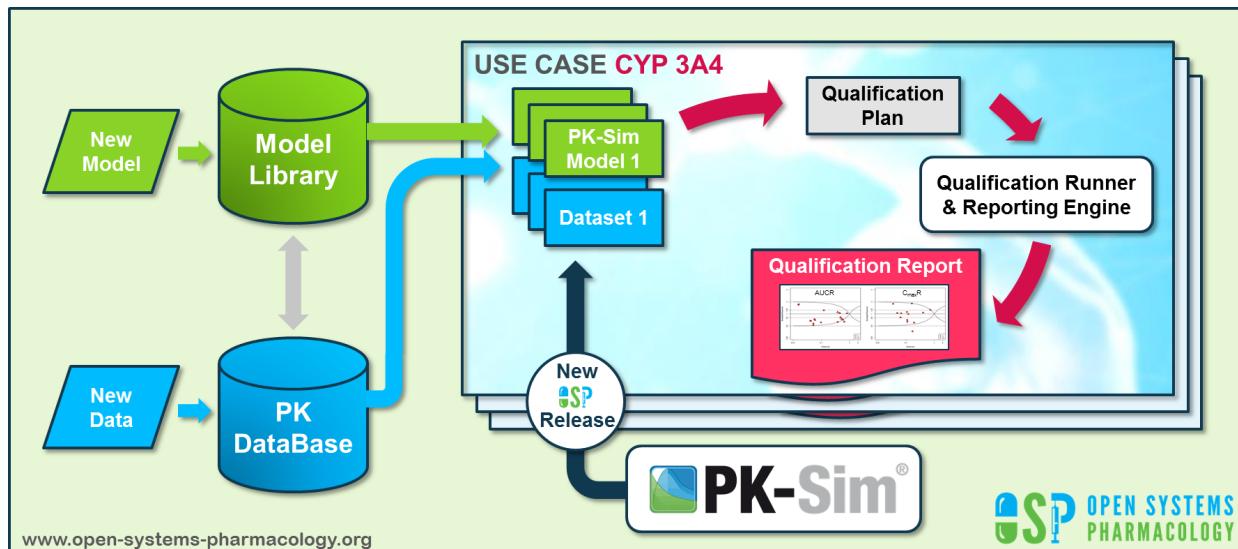
5.3 Automatic (re)-qualification workflow

[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

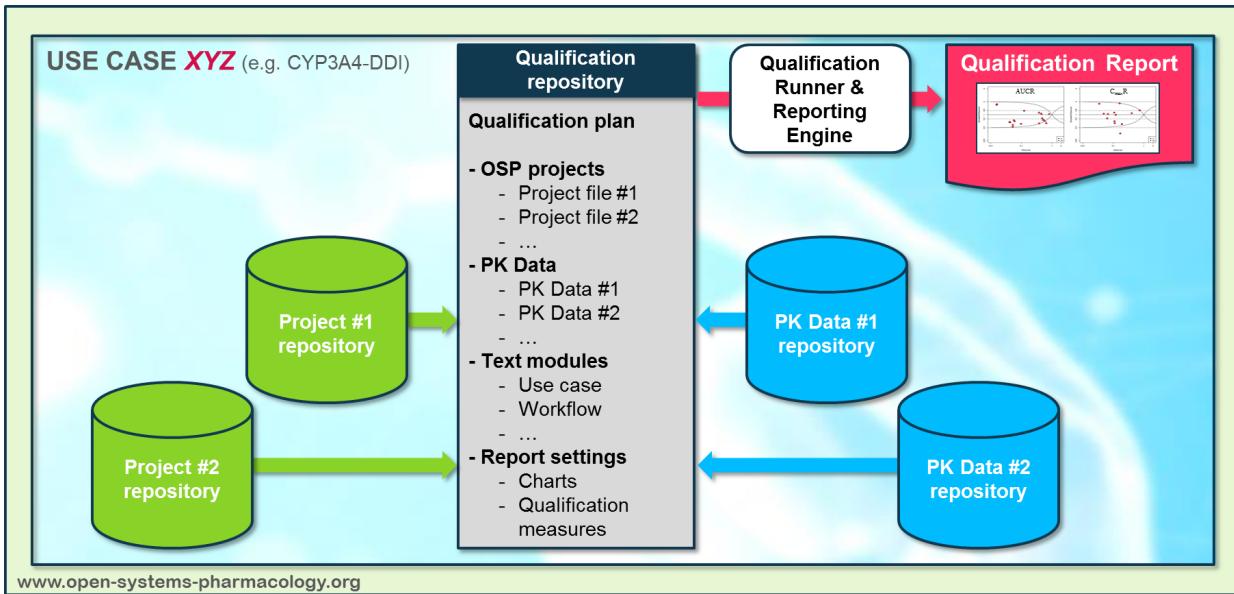


In a first step, the respective qualification scenario is saved in a special qualification repository on GitHub. This qualification scenario repository contains a detailed qualification plan that links and combines respective models and data to address the use case that shall be qualified. Therefore,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