

# CYP3A4 DDI Qualification

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<b>Version</b>	<b>1.1-OSP9.1</b>
Qualification Plan Release	<a href="https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4/releases/tag/v1.1">https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4/releases/tag/v1.1</a>
OSP Version	9.1
Qualification Framework Version	2.2

This qualification report is filed at:

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

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# 1 Introduction

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## 1.1 Objective

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This **qualification report** evaluates for the PBPK platform **PK-Sim** (as part of the open systems pharmacology (OSP) suite) the ability to perform simulations with the intended purpose to predict cytochrome P450 3A4 (**CYP3A4**)-mediated drug-drug interactions (**DDI**).

To demonstrate the level of confidence, the predictive performance of the platform for this intended purpose is assessed via a network of PBPK models of selected index CYP3A4 DDI perpetrators (covering the range from strong induction to strong inhibition), and respective sensitive index CYP3A4 victim drugs and a comprehensive dataset from published clinical DDI studies. All PBPK models represent whole-body PBPK models, which allow dynamic DDI simulations in organs expressing CYP3A4.

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

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

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

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

## 1.2 CYP3A4 DDI Network

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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 v1.1*): <https://github.com/Open-Systems-Pharmacology/Rifampicin-Model/releases/tag/v1.1>
- **Efavirenz** (moderate CYP3A4 inducer)  
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Efavirenz-Model/releases/tag/v1.0>
- **Cimetidine** (weak CYP3A4 inhibitor)  
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Cimetidine-Model/releases/tag/v1.0>

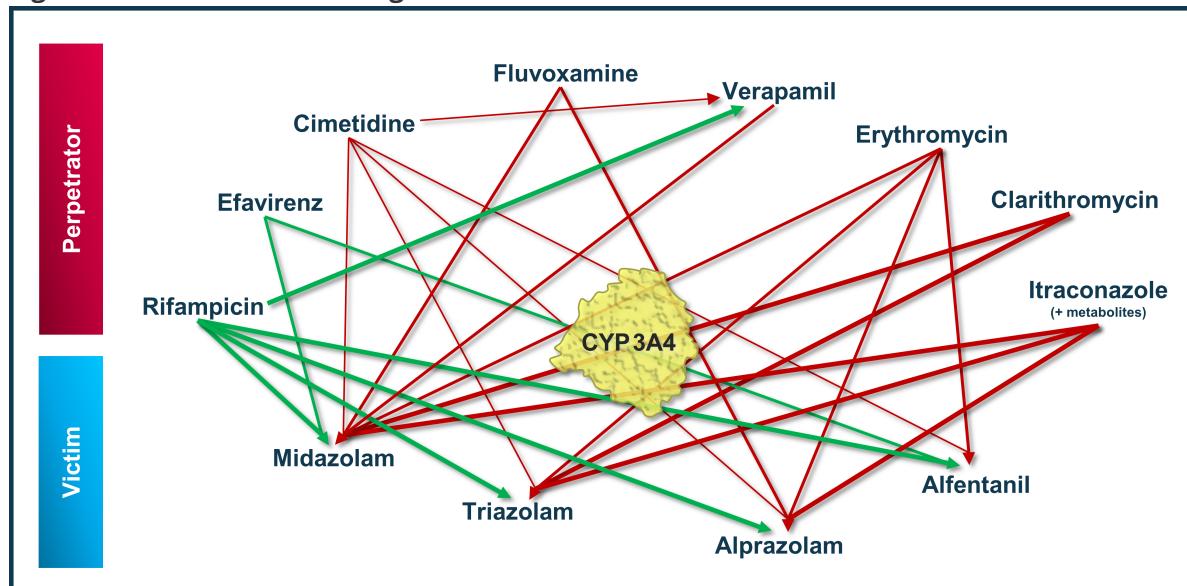
- **Fluvoxamine** (weak/moderate CYP3A4 inhibitor)  
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Fluvoxamine-Model/releases/tag/v1.1>
- **Verapamil** (moderate CYP3A4 inhibitor)  
Model snapshot and evaluation plan (*release v1.1*): <https://github.com/Open-Systems-Pharmacology/Verapamil-Model/releases/tag/v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

The following sensitive CYP3A4 substrates as victim drugs were selected:

- **Midazolam**  
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Midazolam-Model/releases/tag/v1.0>
- **Triazolam**  
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Triazolam-Model/releases/tag/v1.0>
- **Alprazolam**  
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Alprazolam-Model/releases/tag/v1.0>
- **Alfentanil**  
Model snapshot and evaluation plan (*release v2.1*): <https://github.com/Open-Systems-Pharmacology/Alfentanil-Model/releases/tag/v2.1>

**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/v1.0>.

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	<a href="#">Kienlen 1993</a>

## 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/v1.0>.

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		<a href="#">Pourbaix 1985</a>
1332	CYP3A4	Cimetidine / alprazolam	Cimetidine: 300 mg po QID (4 times) Alprazolam: 1 mg po single dose concomitantly with cimetidine dose at 12 h		<a href="#">Abernethy 1983</a>

## 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/v1.0>.

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		<a href="#">Elliott 1984</a>
1324	CYP3A4	Cimetidine / midazolam	Cimetidine: 400 mg po BID (3 times) Midazolam: 15 mg po single dose, 1 hour after the last cimetidine dose		<a href="#">Fee 1987</a>
1319	CYP3A4	Cimetidine / midazolam	Cimetidine: 300 mg po QID (8 times) Midazolam: 5 mg iv single dose, concomitantly with the 5 <sup>th</sup> cimetidine dose		<a href="#">Greenblatt 1986</a>
1321	CYP3A4	Cimetidine / midazolam	Cimetidine: 300 mg po QID (8 times) Midazolam: 15 mg po single dose concomitantly with the 5 <sup>th</sup> cimetidine dose		<a href="#">Greenblatt 1986</a>
1322	CYP3A4	Cimetidine / midazolam	Cimetidine: 800 mg po single dose Midazolam: 7.5 mg po single dose concomitantly with cimetidine dose		<a href="#">Martinez 1999</a>
1326	CYP3A4	Cimetidine / midazolam	Cimetidine: 400 mg po single dose Midazolam: 15 mg po single dose 2 hours after cimetidine dose		<a href="#">Salonen 1986</a>

## 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/v1.0>.

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 <sup>th</sup> 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/v1.0>.

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/v1.1>

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 <sup>th</sup> 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 <sup>th</sup> 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 <sup>th</sup> 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 <sup>th</sup> 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 <sup>th</sup> 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 <sup>th</sup> clarithromycin dose		Pruksaritanont 2017
2027	CYP3A4	Clarithromycin / midazolam	Clarithromycin: 500 mg po BID for 7 days Midazolam: 0.05 mg/kg iv single dose, 2 hours after the 13 <sup>th</sup> 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 <sup>th</sup> 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 <sub>0-6h</sub> 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 <sup>th</sup> 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/v1.1>

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 <sup>rd</sup> 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/v1.1>

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	<a href="#">Bartkowski 1989</a>
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 <sup>th</sup> erythromycin dose	<a href="#">Bartkowski 1989</a>

## 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/v1.1>

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 <sup>nd</sup> erythromycin dose	<a href="#">Yasui 1996</a>

## 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/v1.1>

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 <sub>2-4h</sub> ratio reported and simulated for comparison.	<a href="#">Carls 2014</a>
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 <sub>2-4h</sub> ratio reported and simulated for comparison.	<a href="#">Carls 2014</a>
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 <sup>th</sup> erythromycin dose	Subjects received 5 mg midazolam po in control phase	<a href="#">Okudaira 2007</a>
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 <sup>th</sup> erythromycin dose	Subjects received 5 mg midazolam po in control phase	<a href="#">Okudaira 2007</a>
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 <sup>th</sup> erythromycin dose	Subjects received 5 mg midazolam po in control phase	<a href="#">Okudaira 2007</a>
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 <sup>th</sup> erythromycin dose		<a href="#">Olkola 1993</a>
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 <sup>th</sup> erythromycin dose		<a href="#">Olkola 1993</a>
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 <sup>th</sup> erythromycin dose		<a href="#">Swart 2002</a>
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 <sup>th</sup> erythromycin dose		<a href="#">Zimmermann 1996</a>

## 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/v1.1>

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 <sup>rd</sup> erythromycin dose	<a href="#">Greenblatt 1998</a>
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	<a href="#">Phillips 1986</a>

## 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 <sup>th</sup> fluvoxamine dose	<a href="#">Fleishaker 1994</a>
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 <sup>th</sup> fluvoxamine dose	<a href="#">Fleishaker 1994</a>

## 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/v1.1>

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 <b>150</b> mg (50 mg in the morning (6 a.m.), 50 mg in the evening (8 p.m.)) Midazolam: 0.025 mg/kg <b>iv</b> single dose, 3 hours after a morning fluvoxamine dose	<b>Observed data:</b> 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. <b>Simulated:</b> 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 <b>200</b> mg (100 mg BID) Midazolam: 10 mg <b>po</b> 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/v1.1>

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: <b>200</b> mg <b>po</b> once daily (6 doses, capsule fasted) Alprazolam: 0.8 mg <b>po</b> single dose, 1 hour after <b>4<sup>th</sup></b> 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/v1.1>

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

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
50	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>100</b> mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg <b>po</b> single dose, simultaneous with <b>4<sup>th</sup></b> itraconazole dose		Ahonen 1995
58	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>200</b> mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg <b>po</b> single dose, 2 hours after <b>4<sup>th</sup></b> 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: <b>200</b> mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg <b>po</b> single dose, <b>4 days</b> after <b>4<sup>th</sup></b> 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: <b>200</b> mg po once daily (4 doses, capsule fasted) Midazolam: 7.5 mg <b>po</b> single dose, 1 hours after <b>4<sup>th</sup></b> itraconazole dose		Olkola 1994
377	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>200</b> mg po once daily (6 doses, capsule fasted) Midazolam: 7.5 mg <b>po</b> single dose, 2 hours after <b>1<sup>st</sup></b> itraconazole dose		Olkola 1996
378	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>200</b> mg po once daily (6 doses, capsule fasted) Midazolam: 0.05 mg/kg <b>iv</b> single dose, 2 hours after <b>4<sup>th</sup></b> itraconazole dose		Olkola 1996
379	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>200</b> mg po once daily (6 doses, capsule fasted) Midazolam: 7.5 mg <b>po</b> single dose, 2 hours after <b>6<sup>th</sup></b> itraconazole dose		Olkola 1996
1097	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>200</b> mg po once daily (5 doses) (solution fasted) Midazolam: 10 µg <b>po</b> single dose, simultaneous with <b>4<sup>th</sup></b> itraconazole dose		Pruksaritanont 2017
424	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>50</b> mg po <b>single dose</b> (solution fasted) Midazolam: 2 mg po single dose, 4 hours after itraconazole dose		Templeton 2010

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
425	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>100</b> mg po <b>single dose</b> (solution fasted) Midazolam: 2 mg po <b>single dose</b> , 4 hours after itraconazole dose		Templeton 2010
426	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>400</b> mg po <b>single dose</b> (solution fasted) Midazolam: 2 mg po single dose, 4 hours after itraconazole dose		Templeton 2010
199	CYP3A4	Itraconazole / midazolam	Itraconazole: <b>200</b> mg po once daily (4 doses, capsule fasted) Midazolam: 1 mg <b>iv</b> single dose, simultaneous with <b>4<sup>th</sup></b> 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/v1.1>

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: <b>200</b> mg po single dose (capsule fasted) triazolam: 0.25 mg <b>po</b> single dose, <b>simultaneous</b> with itraconazole dose	3 hours fasting before triazolam/itraconazole administration	<a href="#">Neuvonen 1996</a>
1079	CYP3A4	Itraconazole / triazolam	Itraconazole: <b>200</b> mg po single dose (capsule fed) triazolam: 0.25 mg <b>po</b> single dose, <b>3 hours</b> after itraconazole dose	itraconazole dose was taken after lunch	<a href="#">Neuvonen 1996</a>
1080	CYP3A4	Itraconazole / triazolam	Itraconazole: <b>200</b> mg po single dose (capsule fed) triazolam: 0.25 mg <b>po</b> single dose, <b>12 hours</b> after itraconazole dose	itraconazole dose was taken with a snack, 3 hours fasting before triazolam administration	<a href="#">Neuvonen 1996</a>
1081	CYP3A4	Itraconazole / triazolam	Itraconazole: <b>200</b> mg po single dose (capsule fed) triazolam: 0.25 mg <b>po</b> single dose, <b>24 hours</b> after itraconazole dose	itraconazole dose was taken with a snack, 3 hours fasting before triazolam administration	<a href="#">Neuvonen 1996</a>
1029	CYP3A4	Itraconazole / triazolam	Itraconazole: <b>200</b> mg po once daily (4 doses, capsule fasted) triazolam: 0.25 mg <b>po</b> single dose, 1 hour after <b>4<sup>th</sup></b> itraconazole dose		<a href="#">Varhe 1994</a>

## 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/v1.1>

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: <b>80</b> mg po three times a day (5 doses) Midazolam: 15 mg <b>po</b> single dose, 1 hours after <b>4<sup>th</sup></b> verapamil dose		<a href="#">Backman 1994</a>
1111	CYP3A4	Verapamil / midazolam	Verapamil: <b>240</b> mg po once daily (7 doses, sustained release) Midazolam: 0.05 mg/kg <b>iv</b> single dose, 24 hours after the <b>7<sup>th</sup></b> verapamil dose		<a href="#">Wang 2005</a>
1116	CYP3A4	Verapamil / midazolam	Verapamil: <b>240</b> mg po once daily (7 doses, sustained release) Midazolam: 4 mg/kg <b>po</b> single dose, 48 hours after the <b>7<sup>th</sup></b> verapamil dose		<a href="#">Wang 2005</a>

## 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 <sup>th</sup> efavirenz dose		<a href="#">Kharasch 2012</a>
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 <sup>th</sup> efavirenz dose		<a href="#">Kharasch 2012</a>

## 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/v1.1>

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 ( <b>day 1</b> ) 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 ( <b>day 1</b> ) 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 ( <b>day 6</b> ) 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 ( <b>day 6</b> ) 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 ( <b>day 11</b> ) 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 ( <b>day 11</b> ) 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 ( <b>day 16</b> ) 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 ( <b>day 16</b> ) 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 ( <b>*day 22</b> ) 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 ( <b>day 22</b> ) 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/v1.1>

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: <b>600</b> mg po once daily (5 doses) Alfentanil: 20 µg/kg <b>IV</b> single dose, <b>24.5</b> h after <b>5<sup>th</sup></b> rifampicin dose		Kharasch 1997
283	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>600</b> mg po once daily (6 doses) Alfentanil: 15 µg/kg <b>IV</b> single dose, <b>9</b> h after <b>5<sup>th</sup></b> rifampicin dose		Kharasch 2004
288	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>600</b> mg po once daily (6 doses) Alfentanil: 60 µg/kg <b>PO</b> single dose, <b>9</b> h after <b>6<sup>th</sup></b> rifampicin dose		Kharasch 2004
299	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>5</b> mg po once daily (6 doses) Alfentanil: 15 µg/kg <b>IV</b> single dose, <b>13</b> h after <b>5<sup>th</sup></b> rifampicin dose		Kharasch 2011
300	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>10</b> mg po once daily (6 doses) Alfentanil: 15 µg/kg <b>IV</b> single dose, <b>13</b> h after <b>5<sup>th</sup></b> rifampicin dose		Kharasch 2011
301	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>25</b> mg po once daily (6 doses) Alfentanil: 15 µg/kg <b>IV</b> single dose, <b>13</b> h after <b>5<sup>th</sup></b> rifampicin dose		Kharasch 2011
302	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>75</b> mg po once daily (6 doses) Alfentanil: 15 µg/kg <b>IV</b> single dose, <b>13</b> h after <b>5<sup>th</sup></b> rifampicin dose		Kharasch 2011
309	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>5</b> mg po once daily (6 doses) Alfentanil: 75 µg/kg <b>PO</b> single dose, <b>13</b> h after <b>6<sup>th</sup></b> rifampicin dose		Kharasch 2011
310	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>10</b> mg po once daily (6 doses) Alfentanil: 75 µg/kg <b>PO</b> single dose, <b>13</b> h after <b>6<sup>th</sup></b> rifampicin dose		Kharasch 2011

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
311	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>25</b> mg po once daily (6 doses) Alfentanil: 75 µg/kg <b>PO</b> single dose, <b>13</b> h after <b>6<sup>th</sup></b> rifampicin dose		Kharasch 2011
312	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>75</b> mg po once daily (6 doses) Alfentanil: 75 µg/kg <b>PO</b> single dose, <b>13</b> h after <b>6<sup>th</sup></b> rifampicin dose		Kharasch 2011
763	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>600</b> mg po once daily (6 doses) Alfentanil: 1 mg <b>IV</b> single dose, <b>12</b> h after <b>5<sup>th</sup></b> rifampicin dose	sequential administration of intravenous unlabeled alfentanil and oral deuterated alfentanil	Kharasch 2011b
771	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>600</b> mg po once daily (6 doses) Alfentanil: 4 mg <b>PO</b> single dose, <b>15</b> h after <b>5<sup>th</sup></b> rifampicin dose	sequential administration of intravenous unlabeled alfentanil and oral deuterated alfentanil	Kharasch 2011b
767	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>600</b> mg po once daily (6 doses) Alfentanil: 1 mg <b>IV</b> single dose, <b>12</b> h after <b>6<sup>th</sup></b> rifampicin dose	simultaneous administration of intravenous unlabeled alfentanil and oral deuterated alfentanil	Kharasch 2011b
775	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>600</b> mg po once daily (6 doses) Alfentanil: 4 mg <b>PO</b> single dose, <b>12</b> h after <b>6<sup>th</sup></b> rifampicin dose	simultaneous administration of intravenous unlabeled alfentanil and oral deuterated alfentanil	Kharasch 2011b
391	CYP3A4	Rifampicin / alfentanil	Rifampicin: <b>600</b> mg po once daily (5 doses) Alfentanil: 15 µg/kg <b>IV</b> single dose, <b>11</b> h after <b>5<sup>th</sup></b> 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/v1.1>

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 rifampicin 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/v1.1>

The rifampicin / midazolam interaction was evaluated using 21 clinical DDI studies including 35 different clinical settings ([Backman 1996](#), [Backman 1998](#), [Chung 2006](#), [Eap 2004](#), [Gorski 2003](#), [Gurley 2006](#), [Gurley 2008a](#), [Kharasch 1997](#), [Kharasch 2004](#), [Kharasch 2011](#), [Kim 2018](#), [Link 2008](#), [Phimmasone 2001](#), [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: <b>600</b> mg po once daily (5 doses) Midazolam: 15 mg <b>PO</b> single dose, <b>17</b> h after <b>5<sup>th</sup></b> rifampicin dose		<a href="#">Backman 1996</a>
56	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>600</b> mg po once daily (5 doses) Midazolam: 15 mg <b>PO</b> single dose, <b>17</b> h after <b>5<sup>th</sup></b> rifampicin dose (Phase IV)		<a href="#">Backman 1998</a>
57	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>600</b> mg po once daily (5 doses) Midazolam: 15 mg <b>PO</b> single dose, <b>7 days</b> after <b>5<sup>th</sup></b> rifampicin dose (Phase V)		<a href="#">Backman 1998</a>
113	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>600</b> mg po once daily (9 doses) Midazolam: 0.075 mg/kg <b>PO</b> single dose, <b>22</b> h after <b>7<sup>th</sup></b> rifampicin dose		<a href="#">Chung 2006</a>
129	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>450</b> mg po once daily (5 doses) Midazolam: 0.075 mg <b>PO</b> single dose, <b>18</b> h after <b>4<sup>th</sup></b> rifampicin dose	Dataset excluded (see comment above)	<a href="#">Eap 2004</a>
132	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>450</b> mg po once daily (5 doses) Midazolam: 7.5 mg <b>PO</b> single dose, <b>18</b> h after <b>5<sup>th</sup></b> rifampicin dose		<a href="#">Eap 2004</a>
179	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>600</b> mg po once daily (7 doses) Midazolam: 0.05 mg/kg <b>IV</b> single dose, <b>12</b> h after <b>6<sup>th</sup></b> rifampicin dose		<a href="#">Gorski 2003</a>
177	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>600</b> mg po once daily (7 doses) Midazolam: 6 mg <b>PO</b> single dose, <b>12</b> h after <b>6<sup>th</sup></b> rifampicin dose	Subjects received a 4 mg midazolam dose in control phase.	<a href="#">Gorski 2003</a>
215	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>300</b> mg po twice daily (14 doses, 7 days) Midazolam: 8 mg <b>PO</b> single dose, <b>2</b> h after <b>13<sup>th</sup></b> rifampicin dose		<a href="#">Gurley 2006</a>
221	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>300</b> mg po twice daily (14 doses, 7 days) Midazolam: 8 mg <b>PO</b> single dose, <b>2</b> h after <b>13<sup>th</sup></b> rifampicin dose		<a href="#">Gurley 2008a</a>
276	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>600</b> mg po once daily (5 doses) Midazolam: 1 mg <b>IV</b> single dose, <b>24</b> h after <b>5<sup>th</sup></b> rifampicin dose		<a href="#">Kharasch 1997</a>

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

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

DataID	Enzyme	Perpetrator / victim	Study design	Comment	Clinical study
204	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>10</b> mg po once daily (11 doses) Midazolam: 1 mg <b>PO</b> single dose, <b>12</b> h after <b>8<sup>th</sup></b> rifampicin dose	In the study midazolam was coadministered with either etonogestrel, dienogest, drospirenone, levonorgestrel or norethindrone.	<a href="#">Wiesinger 2020</a>
205	CYP3A4	Rifampicin / midazolam	Rifampicin: 11 doses of <b>10</b> mg po once daily, followed by 11 doses of <b>600</b> mg po once daily Midazolam: 1 mg <b>PO</b> single dose, <b>12</b> h after <b>8<sup>th</sup></b> 600 mg rifampicin dose (after the 19 <sup>th</sup> overall rifampicin dose)	In the study midazolam was coadministered with either etonogestrel, dienogest, drospirenone, levonorgestrel or norethindrone.	<a href="#">Wiesinger 2020</a>
202	CYP3A4	Rifampicin / midazolam	Rifampicin: <b>600</b> mg po once daily (10 doses) Midazolam: 2 mg <b>IV</b> single dose, <b>24</b> h after <b>10<sup>th</sup></b> 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.	<a href="#">Yu 2004</a>

## 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/v1.1>

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		<a href="#">Villikka 1997</a>

## 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/v1.0>

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 <sup>th</sup> rifampicin dose		<a href="#">Barbarash 1988</a>
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 <sup>th</sup> rifampicin dose		<a href="#">Barbarash 1988</a>

\* 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>).

## 2 Qualification of Use Case CYP3A4-mediated DDI

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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:

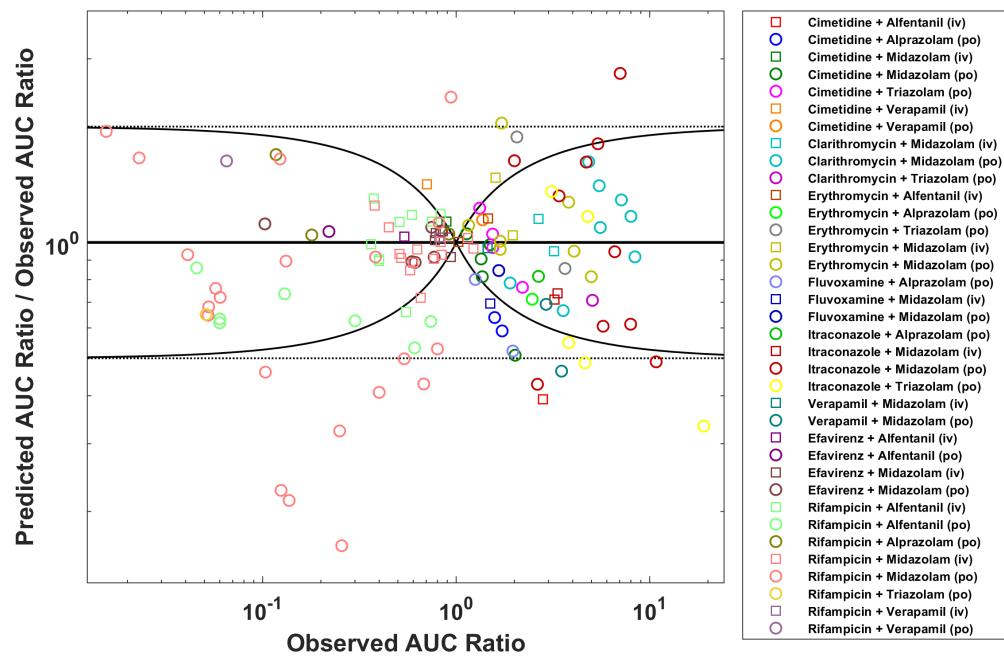
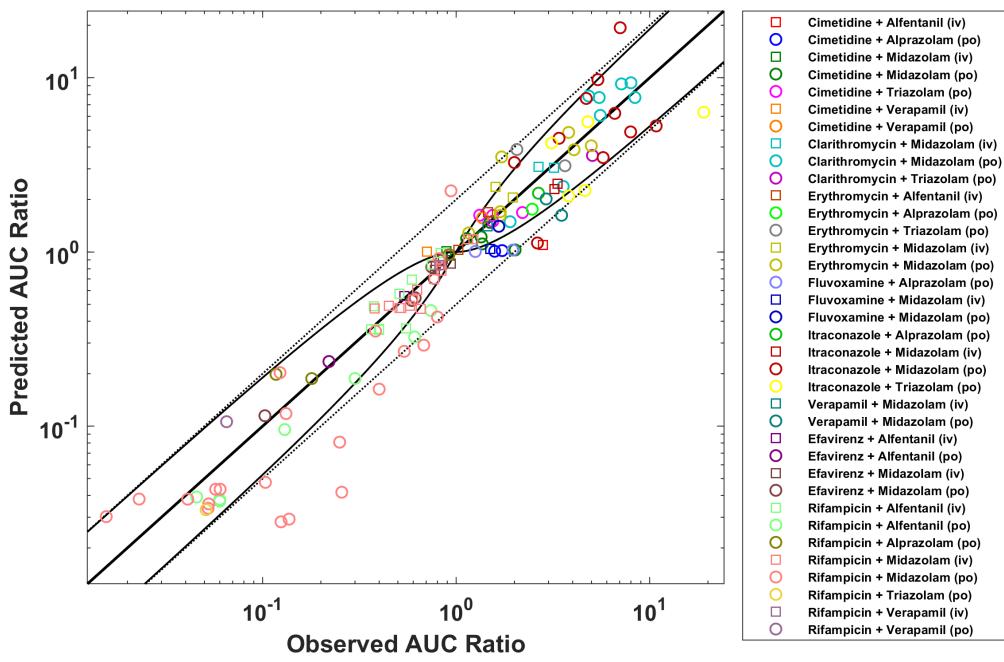
- predicted (*Pred*) vs. observed (*Obs*) plots
- $Pred/Obs$  vs. *Obs* plots
- geometric mean fold error (GMFE):

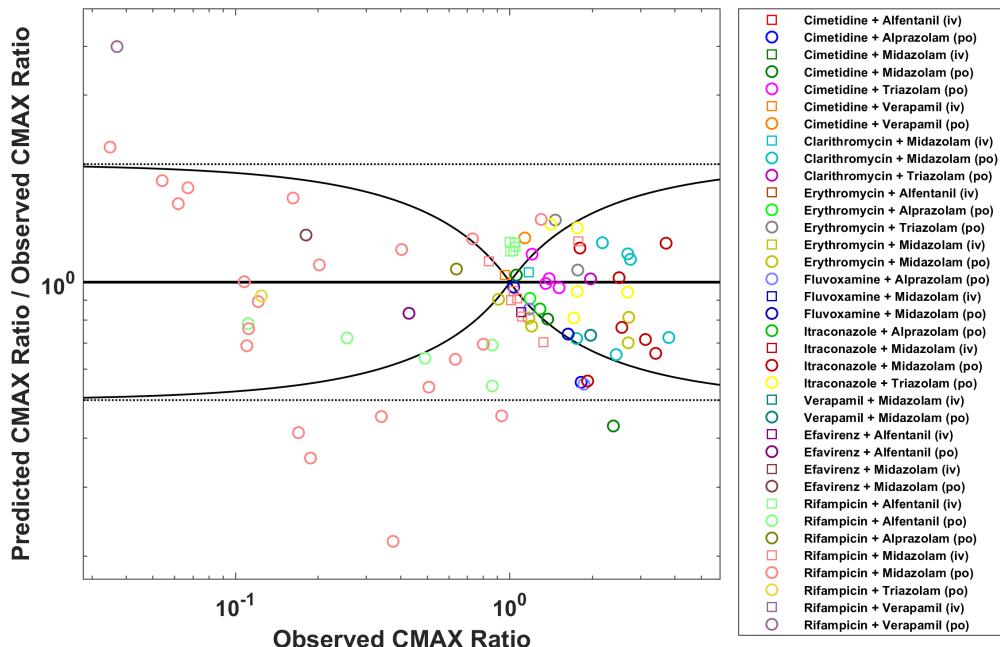
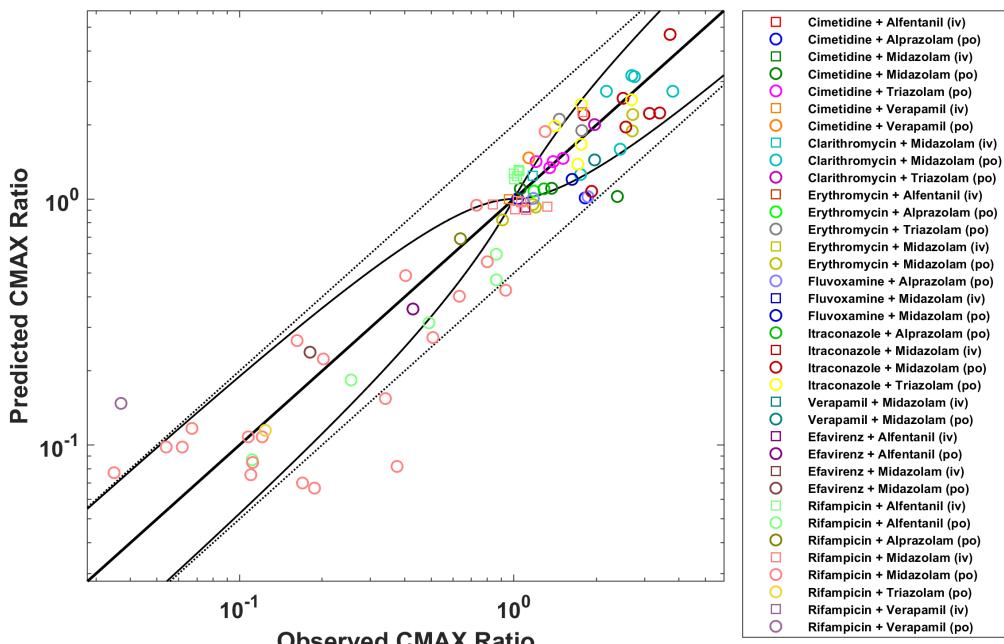
$$10^{\frac{\sum |\log(\frac{Pred}{Obs})|}{n}}$$

- 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) = 1.386372

GMFE (CMAX) = 1.368272

AUC	Number	Ratio [%]
Points total	135	-
Points within Guest et al.	99	73.3333
Points within 2-fold	118	87.4074

	<b>CMAX</b>	<b>Number</b>	<b>Ratio [%]</b>
Points total		88	-
Points within Guest et al.		49	55.6818
Points within 2-fold		80	90.9091

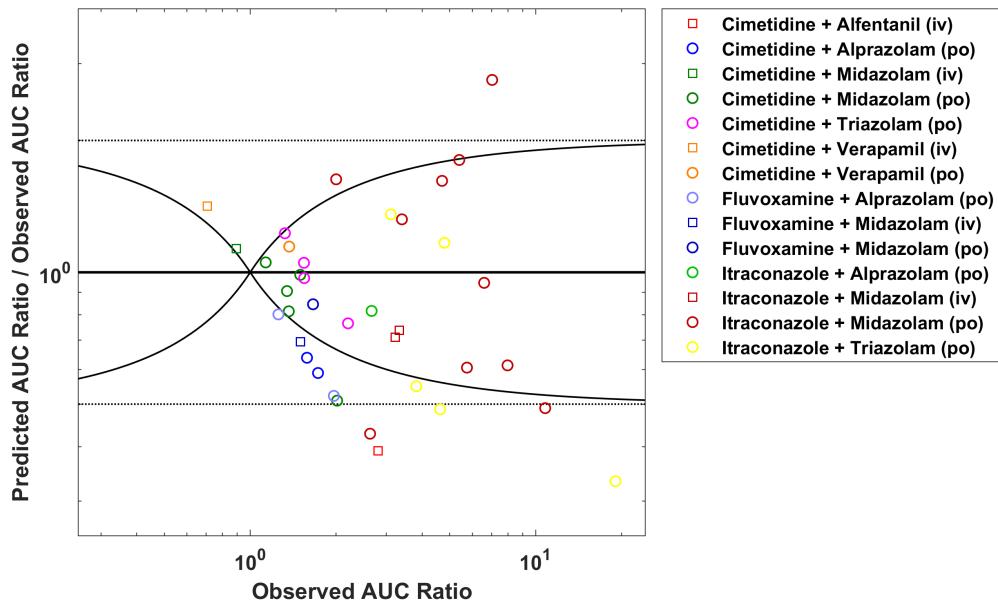
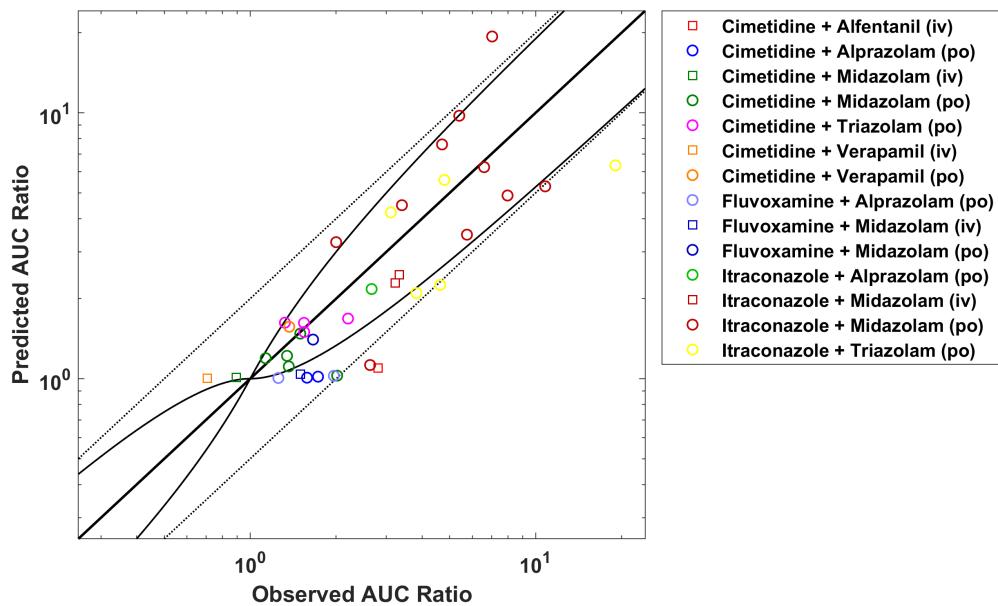
DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
1344	Cimetidine, 1200 mg, IV, MD OD (2 days)	Alfentanil, IV	1.0973	2.8031	0.39144	1.0066	-	-	Kienlen 1993
1332	Cimetidine, 300 mg, PO, MD QID (1 day)	Alprazolam, PO	1.0087	1.581	0.63806	1.0031	1.0323	0.97175	Abernethy 1983
1340	Cimetidine, 200/400 mg, PO, (200mg): MD TID (17 days); (400mg): OD (17 days)	Alprazolam, PO	1.0176	1.7279	0.58892	1.0101	1.8187	0.55539	Pourbaix 1985
1319	Cimetidine, 300 mg, PO, MD QID (2 days)	Midazolam, IV	1.0103	0.89256	1.1319	1.0001	-	-	Greenblatt 1986
1321	Cimetidine, 300 mg, PO, MD QID (2 days)	Midazolam, PO	1.1933	1.1329	1.0533	1.1005	1.0556	1.0426	Greenblatt 1986
1322	Cimetidine, 800 mg, PO, SD	Midazolam, PO	1.4776	1.4973	0.9868	1.2463	-	-	Martinez 1999
1324	Cimetidine, 400 mg, PO, MD: BID (1 day), OD (1 day)	Midazolam, PO	1.219	1.3456	0.9059	1.1013	-	-	Fee 1987
1326	Cimetidine, 400 mg, PO, SD	Midazolam, PO	1.1117	1.3649	0.8145	1.1054	1.3732	0.80497	Salonen 1986
1346	Cimetidine, 200/400 mg, PO, (200mg): MD TID (1 day), OD (1 day); (400mg): OD (1 day)	Midazolam, PO	1.0266	2.016	0.5092	1.0235	2.3833	0.42945	Elliott 1984
1334	Cimetidine, 300 mg, PO, MD QID (1 day)	Triazolam, PO	1.6217	1.5429	1.0511	1.419	1.2041	1.1785	Abernethy 1983
1336	Cimetidine, 300 mg, PO, MD QID (2 days)	Triazolam, PO	1.6243	1.323	1.2278	1.4192	1.3902	1.0209	Friedman 1988
1342	Cimetidine, 200/400 mg, PO, (200mg): MD TID (17 days); (400mg): OD (17 days)	Triazolam, PO	1.6829	2.2013	0.76453	1.4623	1.5109	0.96785	Pourbaix 1985
1338	Cimetidine, 300 mg, PO, MD QID (1 day)	Triazolam, intraduodenal	1.4987	1.5455	0.96973	1.3403	1.3509	0.99219	Cox 1986
1328	Cimetidine, 300 mg, PO, MD QID (9 days)	Verapamil, IV	1.0029	0.70769	1.4172	1	0.95924	1.0425	Smith 1984
1330	Cimetidine, 300 mg, PO, MD QID (9 days)	Verapamil, PO	1.5679	1.3697	1.1447	1.47	1.1333	1.297	Smith 1984
175	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, IV	3.0722	2.6667	1.1521	1.2413	-	-	Gorski 1998
2027	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, IV	3.0346	3.2	0.94832	1.2413	1.1724	1.0587	Quinney 2008
173	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	9.2134	7.1429	1.2899	3.0765	-	-	Gorski 1998
217	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	7.699	8.3929	0.91733	2.7414	3.7956	0.72225	Gurley 2006
223	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	7.699	5.4834	1.4041	2.7414	2.1743	1.2608	Gurley 2008a
354	Clarithromycin, 500 mg, PO, MD BID (4 days)	Midazolam, PO	6.0752	5.5556	1.0935	2.6201	-	-	Markert 2013
1099	Clarithromycin, 500 mg, PO, MD BID (5 days)	Midazolam, PO	7.8478	4.84	1.6215	3.177	2.69	1.181	Prueksaritanont 2017
2030	Clarithromycin, 500 mg, PO, MD BID (7 days)	Midazolam, PO	9.3506	8	1.1688	3.1442	2.75	1.1433	Quinney 2008
2004	Clarithromycin, 250 mg, PO, MD BID (3 days)	Midazolam, PO	1.4904	1.9	0.7844	1.2571	1.75	0.71833	van Dyk 2018
469	Clarithromycin, 250 mg, PO, MD BID (5 days)	Midazolam, PO	2.3752	3.5716	0.66504	1.5939	2.44	0.65325	Yeates 1996
1102	Clarithromycin, 500 mg, PO, MD OD (2 days)	Triazolam, PO	3.5783	5.06	0.70718	2.0063	1.968	1.0195	Greenblatt 1998a
779	Erythromycin, 500 mg, PO, SD	Alfentanil, IV	1.0293	1.0262	1.0031	1	-	-	Bartkowski 1989
780	Erythromycin, 500 mg, PO, MD BID (6 days)	Alfentanil, IV	1.6878	1.4611	1.1551	1.0269	-	-	Bartkowski 1989
777	Erythromycin, 400 mg, PO, MD TID (10 days)	Alprazolam, PO	1.7597	2.4716	0.71195	1.0761	1.1833	0.90935	Yasui 1996
781	Erythromycin, 500 mg, PO, MD OD (2 days)	Triazolam, PO	3.1233	3.65	0.85569	1.8985	1.768	1.0738	Greenblatt 1998a
757	Erythromycin, 333 mg, PO, MD TID (3 days)	Triazolam, PO	3.8725	2.0597	1.8802	2.109	1.4643	1.4403	Phillips 1986
420	Erythromycin, 500 mg, PO, MD QID (5 days)	Midazolam, IV	2.3576	1.5978	1.4755	1.027	-	-	Swart 2002
368	Erythromycin, 500 mg, PO, MD TID (7 days)	Midazolam, IV	2.0491	1.9619	1.0444	1.0191	-	-	Olkkola 1993
366	Erythromycin, 500 mg, PO, MD TID (7 days)	Midazolam, PO	3.8603	4.0674	0.94909	1.8908	2.7	0.70029	Olkkola 1993
471	Erythromycin, 500 mg, PO, MD TID (3 days)	Midazolam, PO	4.8526	3.8137	1.2724	2.205	2.7114	0.81322	Zimmermann 1996
362	Erythromycin, 200 mg, PO, MD QID (2 days)	Midazolam, PO	1.2854	1.16	1.1081	0.82212	0.90909	0.90434	Okudaira 2007
363	Erythromycin, 200 mg, PO, MD QID (4 days)	Midazolam, PO	1.6208	1.69	0.95908	0.92675	1.2	0.77229	Okudaira 2007
364	Erythromycin, 200 mg, PO, MD QID (7 days)	Midazolam, PO	1.7024	1.69	1.0073	0.94964	1.1727	0.80977	Okudaira 2007
828	Erythromycin, 250 mg, PO, SD	Midazolam, PO	3.5088	1.7178	2.0426	3.2106	-	-	Carls 2014
829	Erythromycin, 1000 mg, PO, SD	Midazolam, PO	4.066	4.9912	0.81463	3.6258	-	-	Carls 2014
1104	Fluvoxamine, 50/100 mg, PO, MD OD (10 days), 50 mg day 1-3, then 100 mg	Alprazolam, PO	1.006	1.2551	0.80147	1.005	1.1769	0.85396	Fleishaker 1994
1113	Fluvoxamine, 50/100 mg, PO, MD OD (10 days), 50 mg day 1-3, then 100 mg	Alprazolam, PO	1.025	1.9631	0.52213	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	1.0017	-	-	Kashuba 1998

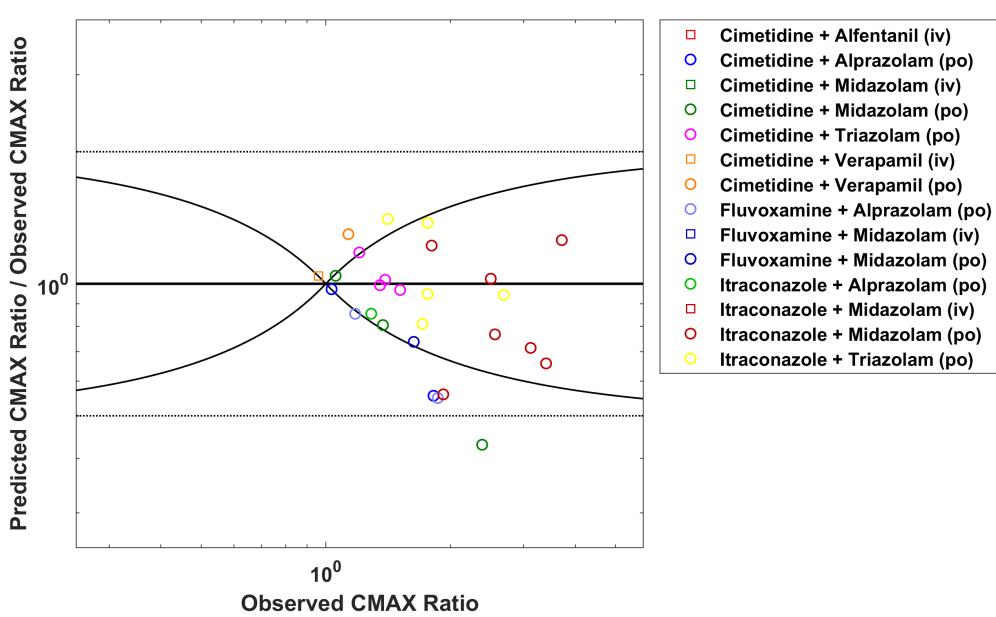
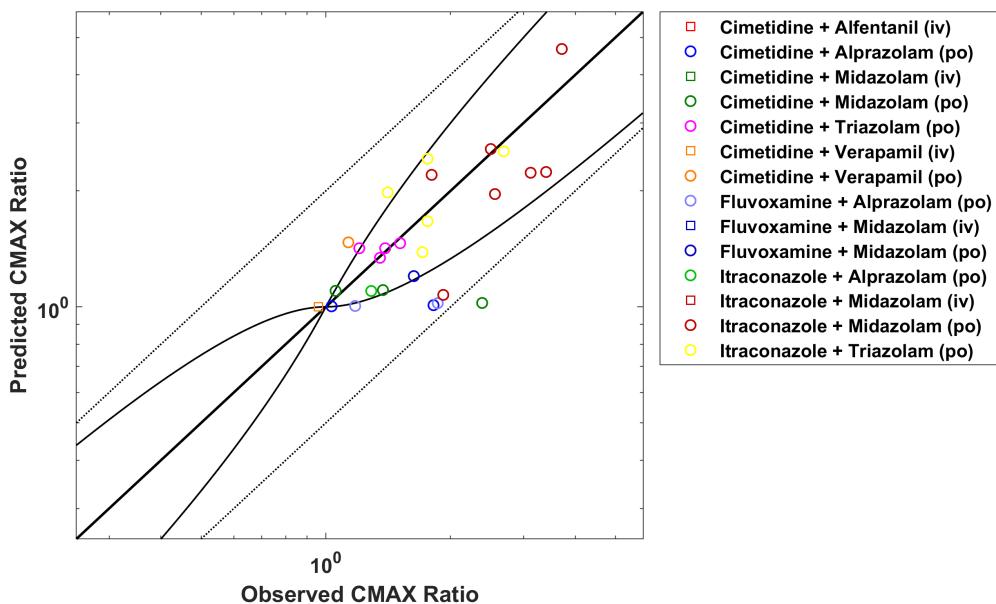
DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
1089	Fluvoxamine, 50/100 mg, PO, MD OD (12 days), titrated from 50 mg BID to 100 mg BID administered for 6 days	Midazolam, PO	1.4031	1.66	0.84522	1.2015	1.63	0.73709	Lam 2003
1026	Itraconazole, 200 mg, PO, MD OD (6 days)	Alprazolam, PO	2.1733	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	0.71016	1.0117	-	-	Olkkola 1996
199	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, IV	2.4587	3.3333	0.73761	1.0112	-	-	Yu 2004
50	Itraconazole, 100 mg, PO, MD OD (4 days)	Midazolam, PO	3.4803	5.7451	0.60579	1.9613	2.5588	0.7665	Ahonen 1995
58	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	4.8857	7.97	0.61301	2.2277	3.12	0.71402	Backman 1998
59	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	1.1256	2.63	0.42797	1.074	1.92	0.55939	Backman 1998
370	Itraconazole, 200 mg, PO, MD OD (4 days)	Midazolam, PO	5.2868	10.8	0.48952	2.2377	3.4	0.65813	Olkkola 1994
377	Itraconazole, 200 mg, PO, SD	Midazolam, PO	4.4916	3.4	1.3211	2.1997	1.8	1.222	Olkkola 1996
379	Itraconazole, 200 mg, PO, MD OD (6 days)	Midazolam, PO	6.244	6.6	0.94606	2.5665	2.5	1.0266	Olkkola 1996
1097	Itraconazole, 200 mg, PO, MD OD (5 days)	Midazolam, PO	19.3578	7.04	2.7497	4.6651	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	5.5923	4.79	1.1675	2.4222	1.76	1.3763	Neuvonen 1996
1080	Itraconazole, 200 mg, PO, SD	Triazolam, PO	2.252	4.63	0.48639	1.6681	1.76	0.94776	Neuvonen 1996
1081	Itraconazole, 200 mg, PO, SD	Triazolam, PO	2.0983	3.82	0.54928	1.3854	1.71	0.81017	Neuvonen 1996
1029	Itraconazole, 200 mg, PO, MD OD (4 days)	Triazolam, PO	6.3408	19.0287	0.33322	2.5313	2.6854	0.94261	Varhe 1994
1111	Verapamil, 240 mg, PO, MD OD (7 days)	Midazolam, IV	1.4027	1.4524	0.96579	1.1019	-	-	Wang 2005
1108	Verapamil, 80 mg, PO, MD TID (2 days)	Midazolam, PO	2.0138	2.9167	0.69043	1.4415	1.9692	0.732	Backman 1994
1116	Verapamil, 240 mg, PO, MD OD (7 days)	Midazolam, PO	1.6229	3.5056	0.46295	1.3474	-	-	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	0.23488	0.22	1.0676	0.35697	0.42857	0.83293	Kharasch 2012
2045	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.83136	0.78538	1.0586	0.93223	-	-	Mikus 2017
2048	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.78761	0.77712	1.0135	0.91054	-	-	Mikus 2017
2050	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.85881	0.9375	0.91607	0.94266	-	-	Mikus 2017
2052	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.91313	0.85377	1.0695	0.96565	-	-	Mikus 2017
2054	Efavirenz, 400 mg, PO, SD	Midazolam, IV	0.9501	0.92217	1.0303	0.9806	-	-	Mikus 2017
2041	Efavirenz, 400 mg, PO, MD OD (14 days)	Midazolam, PO	0.11474	0.1027	1.1172	0.23823	0.1806	1.3191	Katzenmaier 2010
2044	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.52617	0.59055	0.89098	0.64634	-	-	Mikus 2017
2047	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.54513	0.61417	0.88758	0.6553	-	-	Mikus 2017
2049	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.70481	0.76968	0.91571	0.7843	-	-	Mikus 2017
2051	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.819	0.74803	1.0949	0.87157	-	-	Mikus 2017
2053	Efavirenz, 400 mg, PO, SD	Midazolam, PO	0.8959	0.83661	1.0709	0.92682	-	-	Mikus 2017
278	Rifampicin, 600 mg, PO, MD OD (5 days)	Alfentanil, IV	0.35971	0.36301	0.9909	0.89694	-	-	Kharasch 1997
283	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.48813	0.375	1.3017	1.2012	1.0033	1.1972	Kharasch 2004
299	Rifampicin, 5 mg, PO, MD OD (6 days)	Alfentanil, IV	0.98482	0.83	1.1865	1.3091	1.0392	1.2597	Kharasch 2011
300	Rifampicin, 10 mg, PO, MD OD (6 days)	Alfentanil, IV	0.84898	0.75	1.132	1.2935	1.049	1.233	Kharasch 2011
301	Rifampicin, 25 mg, PO, MD OD (6 days)	Alfentanil, IV	0.69486	0.59	1.1777	1.2671	1	1.2671	Kharasch 2011
302	Rifampicin, 75 mg, PO, MD OD (6 days)	Alfentanil, IV	0.57588	0.51	1.1292	1.2354	1.0294	1.2001	Kharasch 2011
763	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.36202	0.4	0.90506	0.89854	-	-	Kharasch 2011b
767	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, IV	0.35767	0.4	0.89416	0.89637	-	-	Kharasch 2011b
391	Rifampicin, 600 mg, PO, MD OD (5 days)	Alfentanil, IV	0.3631	0.55	0.66018	0.89919	-	-	Phimmasone 2001
288	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.039185	0.045631	0.85873	0.087	0.11111	0.783	Kharasch 2004
309	Rifampicin, 5 mg, PO, MD OD (6 days)	Alfentanil, PO	0.46114	0.74	0.62316	0.59606	0.86275	0.69088	Kharasch 2011
310	Rifampicin, 10 mg, PO, MD OD (6 days)	Alfentanil, PO	0.32464	0.61	0.5322	0.46881	0.86275	0.5434	Kharasch 2011
311	Rifampicin, 25 mg, PO, MD OD (6 days)	Alfentanil, PO	0.18765	0.3	0.62552	0.31358	0.4902	0.63971	Kharasch 2011
312	Rifampicin, 75 mg, PO, MD OD (6 days)	Alfentanil, PO	0.095594	0.13	0.73534	0.18365	0.2549	0.72046	Kharasch 2011
771	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.037949	0.06	0.63248	0.083994	-	-	Kharasch 2011b
775	Rifampicin, 600 mg, PO, MD OD (6 days)	Alfentanil, PO	0.037079	0.06	0.61798	0.082592	-	-	Kharasch 2011b

DataID	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
2009	Rifampicin, 450 mg, PO, MD, q.d. for 5 days	Alprazolam, PO	0.1875	0.17935	1.0455	0.67772	-	-	Gashaw 2003
2010	Rifampicin, 450 mg, PO, MD, q.d. for 5 days	Alprazolam, PO	0.96407	0.91667	1.0517	0.9951	-	-	Gashaw 2003
1001	Rifampicin, 450 mg, PO, MD OD (4 days)	Alprazolam, PO	0.19835	0.11726	1.6915	0.68932	0.63816	1.0802	Schmider 1999
179	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, IV	0.49105	0.44898	1.0937	0.75209	-	-	Gorski 2003
276	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, IV	0.47345	0.37931	1.2482	0.90482	-	-	Kharasch 1997
280	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, IV	0.47571	0.52113	0.91284	0.90853	1.01	0.89957	Kharasch 2004
294	Rifampicin, 5 mg, PO, MD OD (6 days)	Midazolam, IV	0.78053	0.84	0.9292	0.98019	1.0323	0.94956	Kharasch 2011
295	Rifampicin, 10 mg, PO, MD OD (6 days)	Midazolam, IV	0.69874	0.77	0.90746	0.9682	1.0645	0.90952	Kharasch 2011
296	Rifampicin, 25 mg, PO, MD OD (6 days)	Midazolam, IV	0.60481	0.63	0.96002	0.9493	0.83871	1.1319	Kharasch 2011
297	Rifampicin, 75 mg, PO, MD OD (6 days)	Midazolam, IV	0.53127	0.6	0.88544	0.92855	1.3226	0.70208	Kharasch 2011
2036	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.1815	1.15	1.0274	2.2563	-	-	Kim 2018
342	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, IV	0.47026	0.65501	0.71794	0.90365	1.106	0.81708	Link 2008
389	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, IV	0.47603	0.51	0.93339	0.907	-	-	Phimmasone 2001
1092	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.1815	1.15	1.0274	2.2563	-	-	Shin 2013
1095	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	1.1815	1.225	0.96453	2.2563	1.775	1.2712	Shin 2016
422	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, IV	0.49105	0.57947	0.84742	0.75222	-	-	Szalat 2007
202	Rifampicin, 600 mg, PO, MD OD (10 days)	Midazolam, IV	0.83493	0.83333	1.0019	1.8917	-	-	Yu 2004
54	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.038106	0.041	0.92941	0.098048	0.061818	1.5861	Backman 1996
56	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.038143	0.023	1.6584	0.098049	0.054	1.8157	Backman 1998
57	Rifampicin, 600 mg, PO, MD OD (5 days)	Midazolam, PO	0.11806	0.132	0.89436	0.22359	0.202	1.1069	Backman 1998
113	Rifampicin, 600 mg, PO, MD OD (9 days)	Midazolam, PO	0.028237	0.12449	0.22682	0.070021	0.16957	0.41294	Chung 2006
132	Rifampicin, 450 mg, PO, MD OD (5 days)	Midazolam, PO	0.033781	0.052239	0.64666	0.08487	0.11154	0.7609	Eap 2004
177	Rifampicin, 600 mg, PO, MD OD (7 days)	Midazolam, PO	0.047557	0.10335	0.46015	0.11675	0.067039	1.7415	Gorski 2003
215	Rifampicin, 300 mg, PO, MD BID (7 days)	Midazolam, PO	0.043421	0.057161	0.75962	0.10788	0.12092	0.89216	Gurley 2006
221	Rifampicin, 300 mg, PO, MD BID (7 days)	Midazolam, PO	0.043421	0.060317	0.71987	0.10788	0.10762	1.0023	Gurley 2008a
286	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, PO	0.035796	0.052632	0.68013	0.075637	0.10989	0.6883	Kharasch 2004
304	Rifampicin, 5 mg, PO, MD OD (6 days)	Midazolam, PO	0.42307	0.8	0.52884	0.55551	0.8	0.69438	Kharasch 2011
305	Rifampicin, 10 mg, PO, MD OD (6 days)	Midazolam, PO	0.2916	0.68	0.42882	0.42549	0.93333	0.45588	Kharasch 2011
306	Rifampicin, 25 mg, PO, MD OD (6 days)	Midazolam, PO	0.16308	0.4	0.40769	0.27343	0.50667	0.53966	Kharasch 2011
307	Rifampicin, 75 mg, PO, MD OD (6 days)	Midazolam, PO	0.080927	0.25	0.32371	0.15436	0.34	0.45399	Kharasch 2011
344	Rifampicin, 600 mg, PO, MD OD (6 days)	Midazolam, PO	0.03022	0.015549	1.9435	0.07709	0.034865	2.2111	Link 2008
1098	Rifampicin, 600 mg, PO, SD	Midazolam, PO	2.2424	0.94	2.3856	1.88	1.3	1.4461	Prueksaritanont 2017
392	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.20272	0.123	1.6481	0.26564	0.162	1.6397	Reitman 2011
393	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.35111	0.383	0.91673	0.48815	0.403	1.2113	Reitman 2011
394	Rifampicin, 600 mg, PO, MD OD (28 days)	Midazolam, PO	0.91636	0.815	1.1244	0.94285	0.731	1.2898	Reitman 2011
2002	Rifampicin, 300 mg, PO, MD OD (7 days)	Midazolam, PO	0.041765	0.25641	0.16288	0.08178	0.375	0.21808	van Dyk 2018
204	Rifampicin, 10 mg, PO, MD OD (22 days)	Midazolam, PO	0.26865	0.539	0.49842	0.40212	0.63265	0.6356	Wiesinger 2020
205	Rifampicin, 600 mg, PO, MD OD (22 days)	Midazolam, PO	0.029255	0.137	0.21354	0.06674	0.18755	0.35585	Wiesinger 2020
1004	Rifampicin, 600 mg, PO, MD OD (5 days)	Triazolam, PO	0.033137	0.051	0.64975	0.11455	0.12414	0.92277	Villikka 1997
2056	Rifampicin, 600 mg, PO, MD OD (13 days)	Verapamil, IV	0.84349	0.81865	1.0303	0.97751	-	-	Barbarash 1988
2058	Rifampicin, 600 mg, PO, MD OD (15 days)	Verapamil, PO	0.10604	0.06511	1.6286	0.14753	0.036961	3.9915	Barbarash 1988

## Mechanism

# Competitive Inhibition





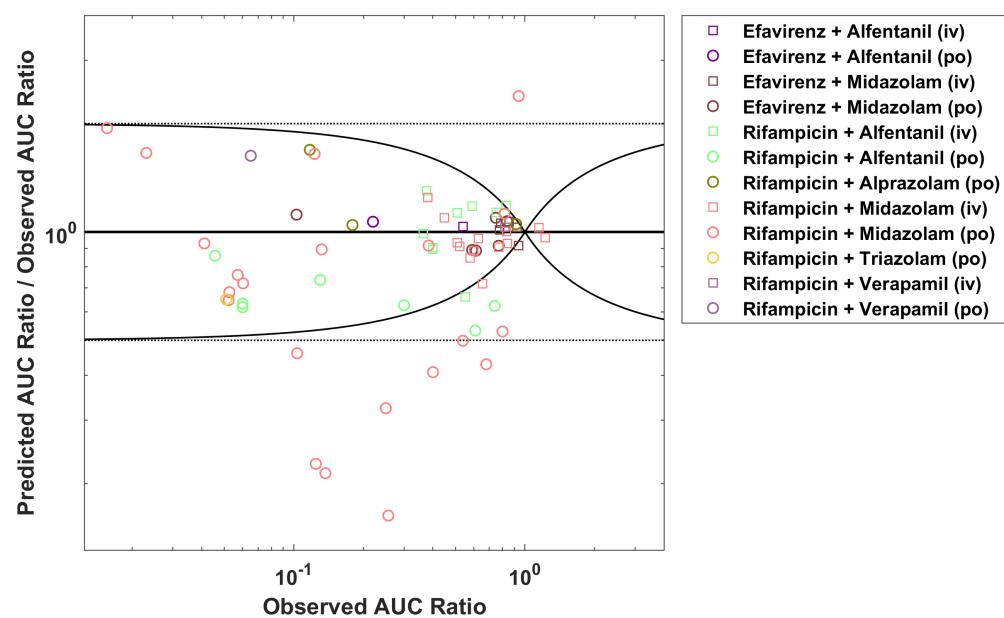
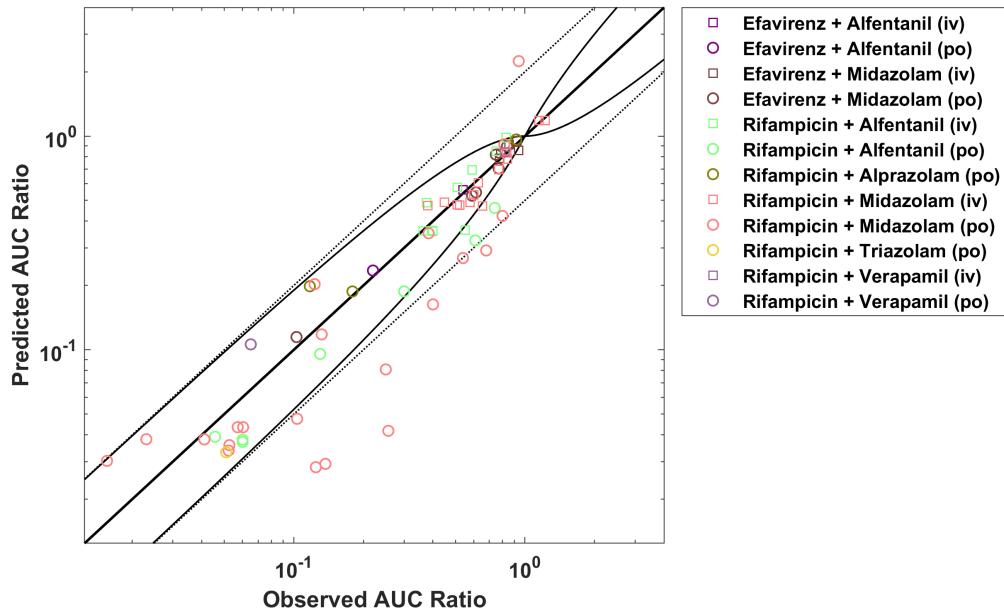
GMFE (AUC) = 1.488414

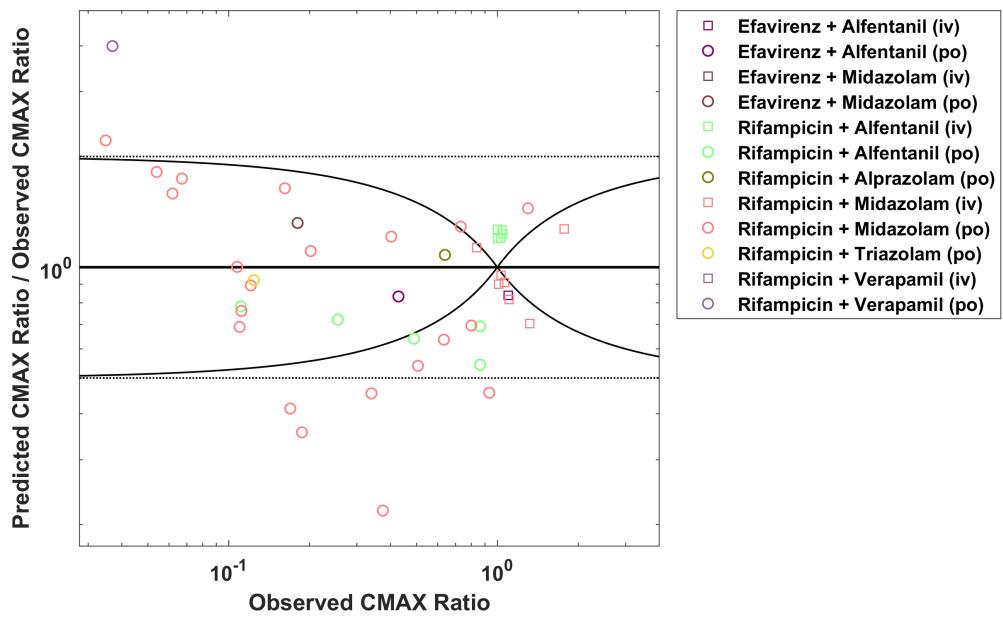
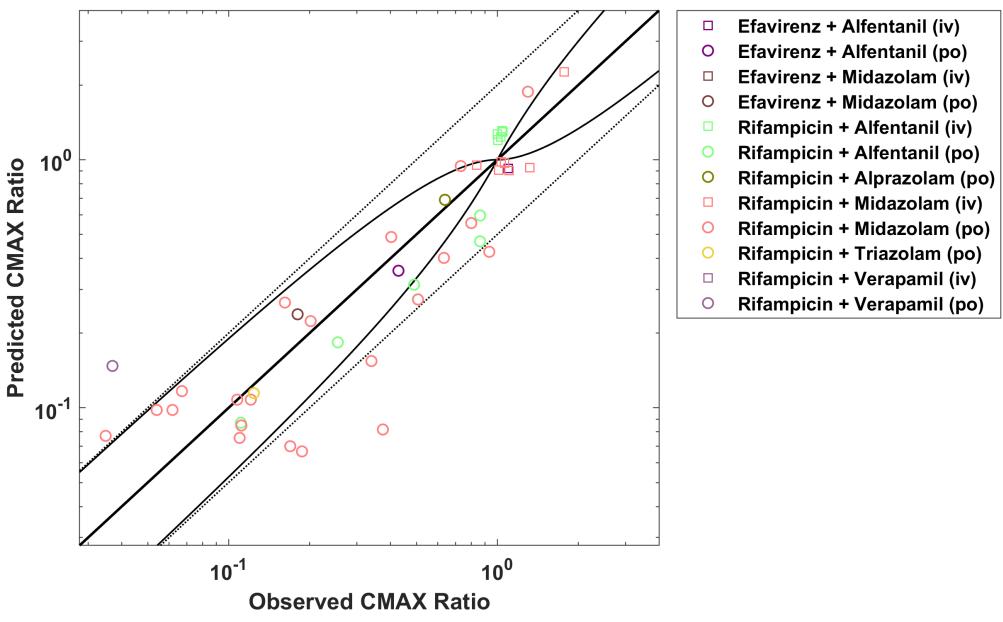
GMFE (CMAX) = 1.272584

AUC	Number	Ratio [%]
Points total	37	-
Points within Guest et al.	21	56.7568
Points within 2-fold	31	83.7838

CMAX	Number	Ratio [%]
Points total	27	-
Points within Guest et al.	18	66.6667
Points within 2-fold	26	96.2963

# Induction





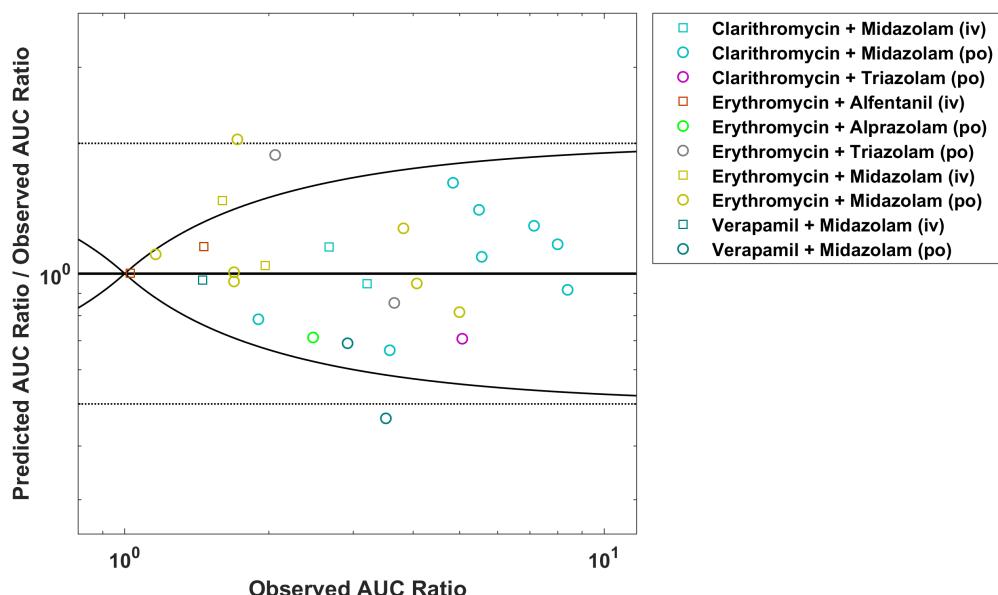
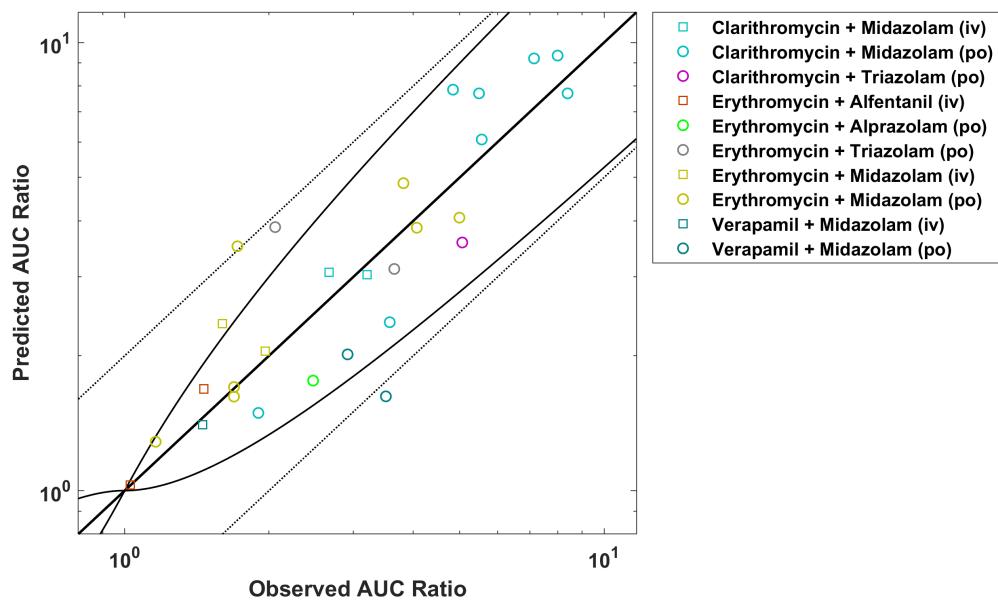
GMFE (AUC) = 1.379900

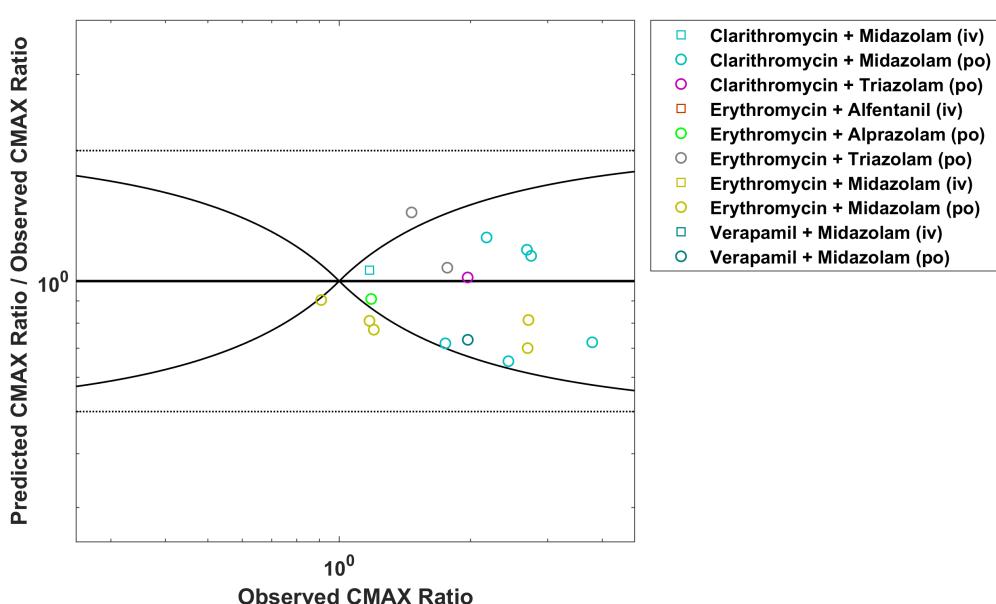
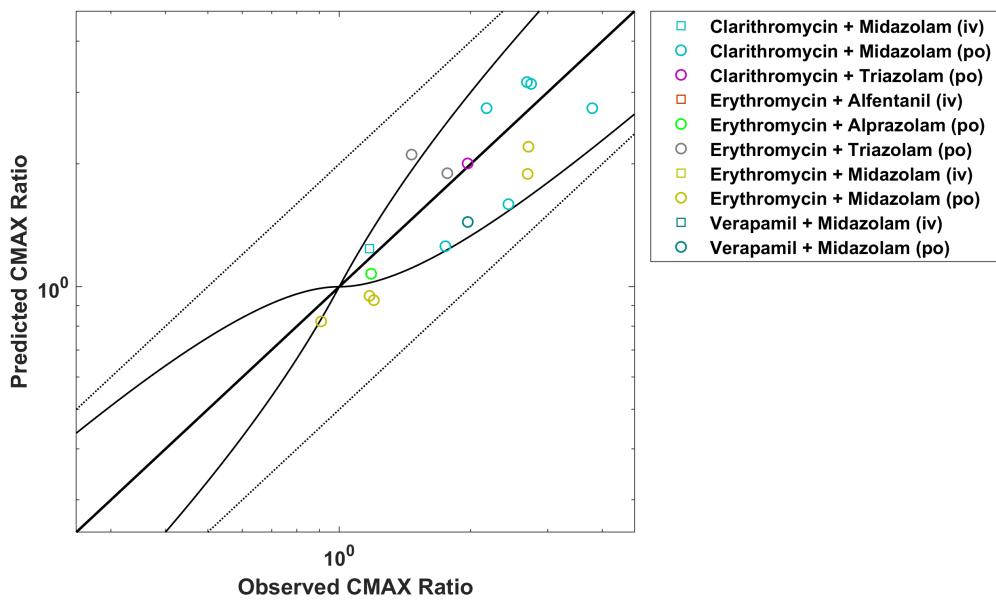
GMFE (CMAX) = 1.485651

	AUC	Number	Ratio [%]
Points total		70	-
Points within Guest et al.		54	77.1429
Points within 2-fold		61	87.1429

	CMAX	Number	Ratio [%]
Points total		44	-
Points within Guest et al.		18	40.9091
Points within 2-fold		37	84.0909

# Mechanism based Inactivation





GMFE (AUC) = 1.277032

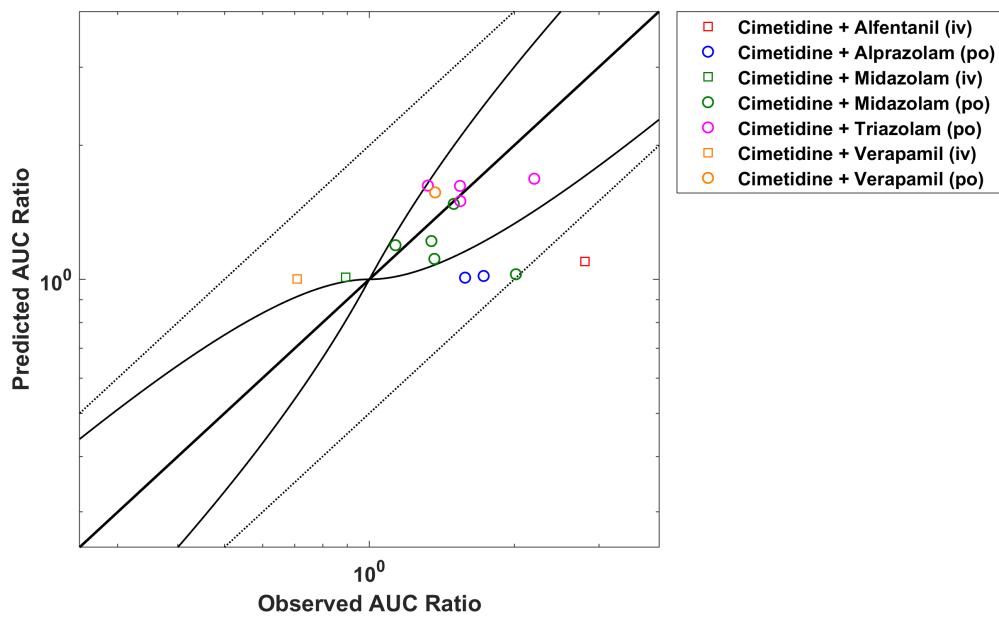
GMFE (CMAX) = 1.240697

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

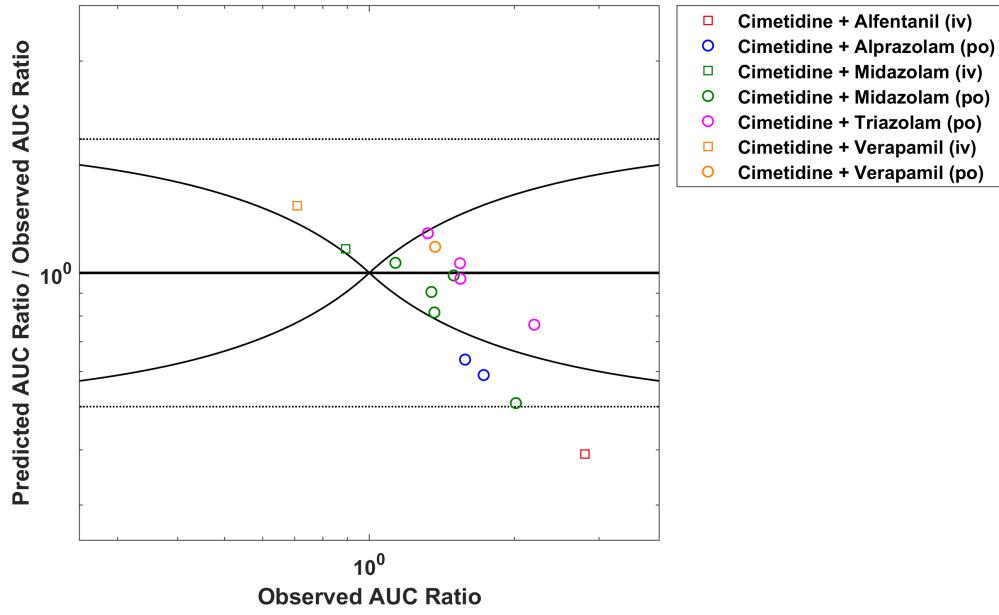
	CMAX	Number	Ratio [%]
Points total		17	-
Points within Guest et al.		13	76.4706
Points within 2-fold		17	100

# Perpetrator

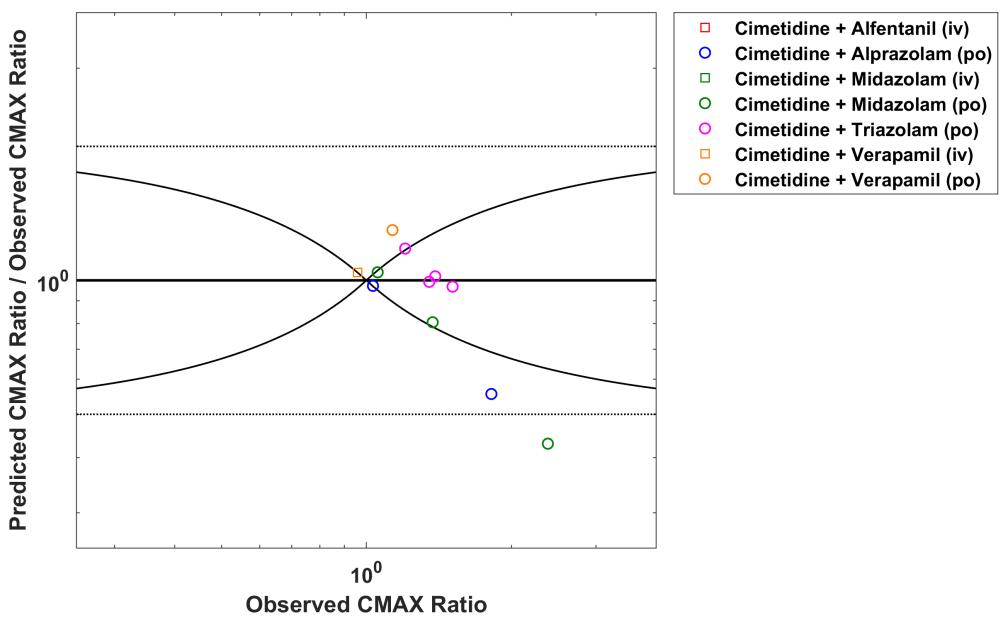
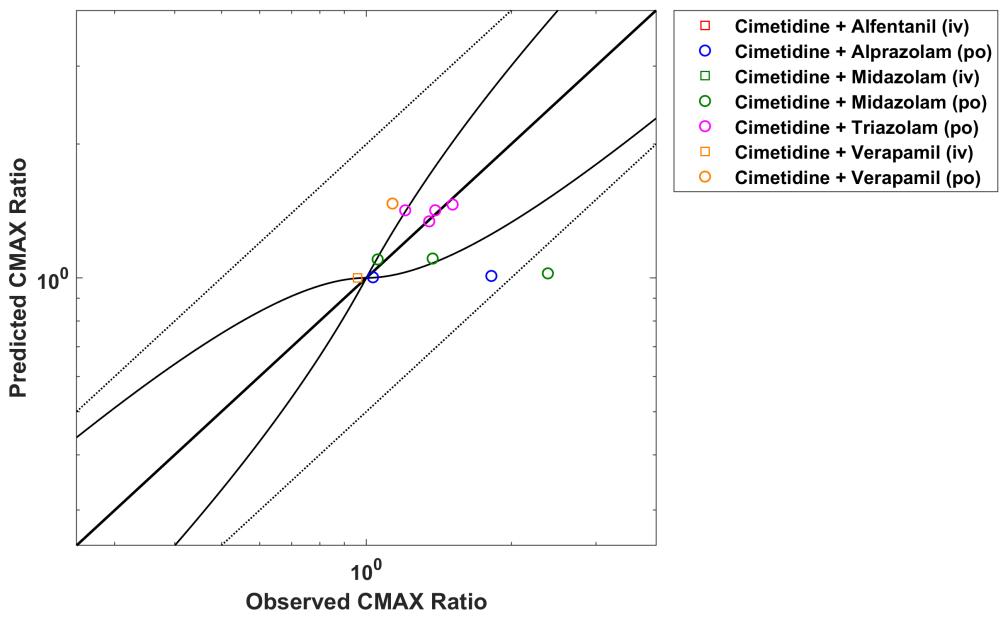
## Cimetidine



CYP3A4 DDI Cimetidine



CYP3A4 DDI Cimetidine



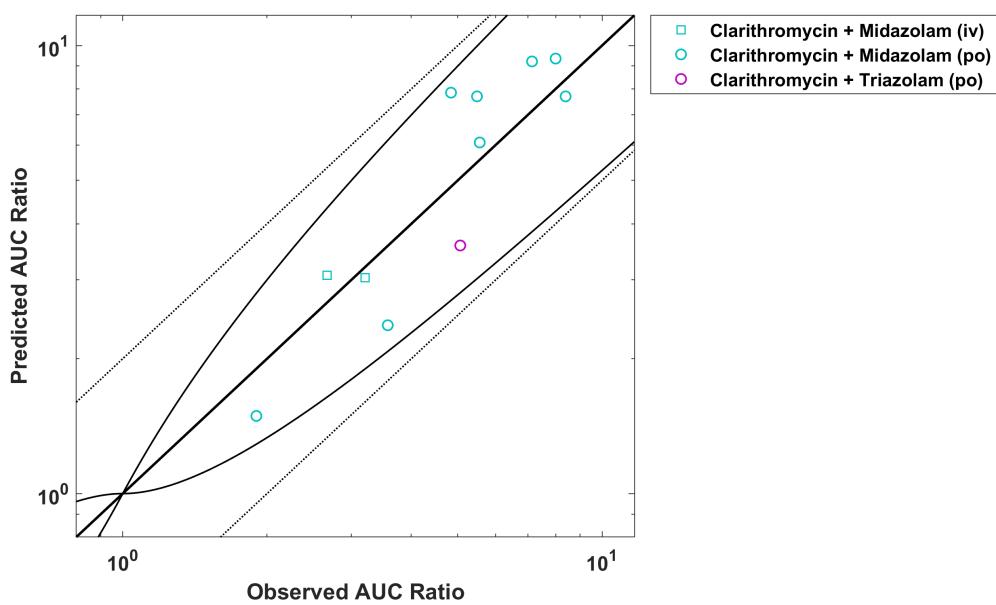
GMFE (AUC) = 1.316350

GMFE (CMAX) = 1.226719

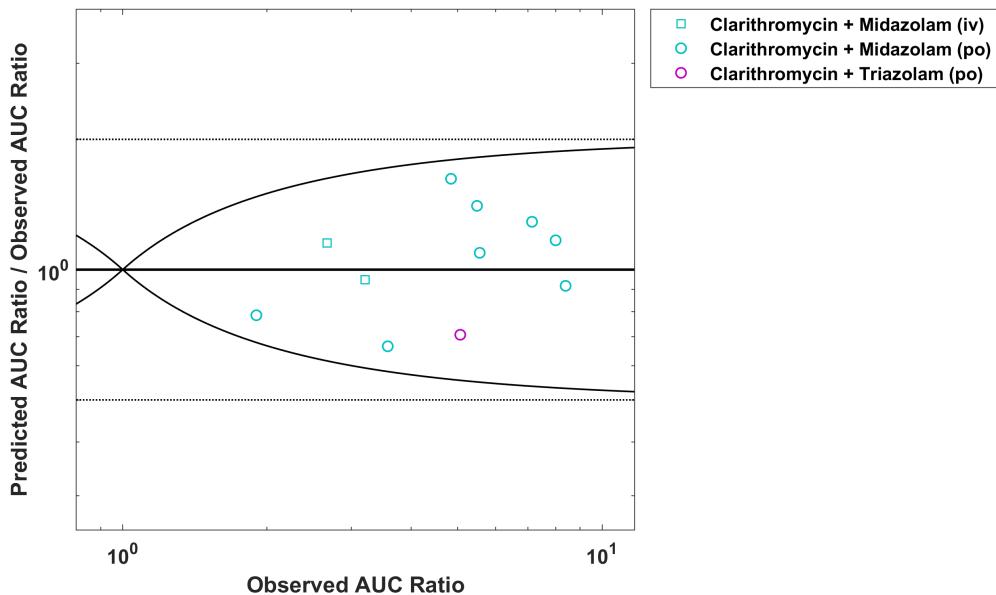
	AUC	Number	Ratio [%]
Points total		15	-
Points within Guest et al.		9	60
Points within 2-fold		14	93.3333

	CMAX	Number	Ratio [%]
Points total		11	-
Points within Guest et al.		6	54.5455
Points within 2-fold		10	90.9091

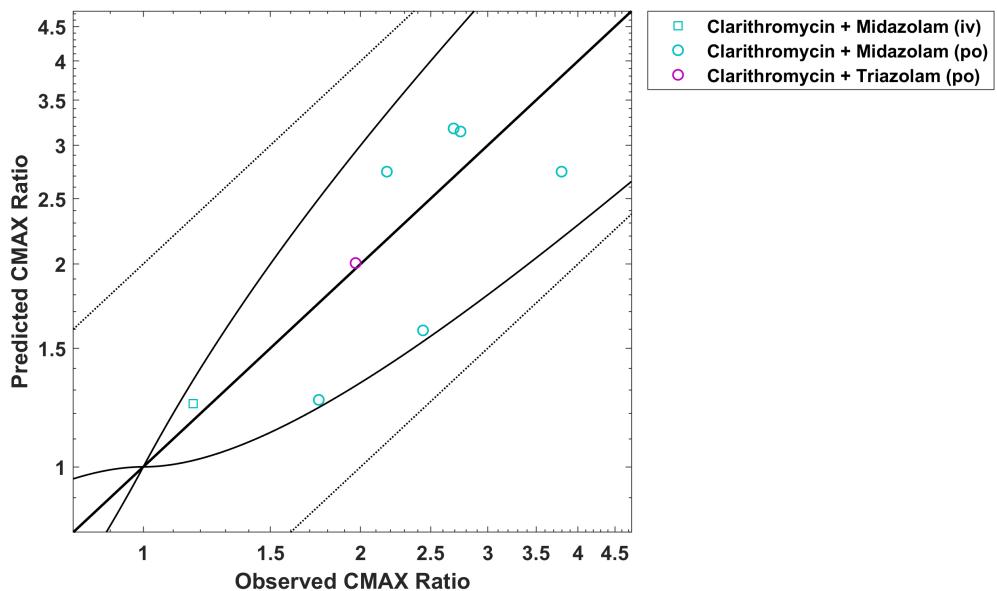
# Clarithromycin



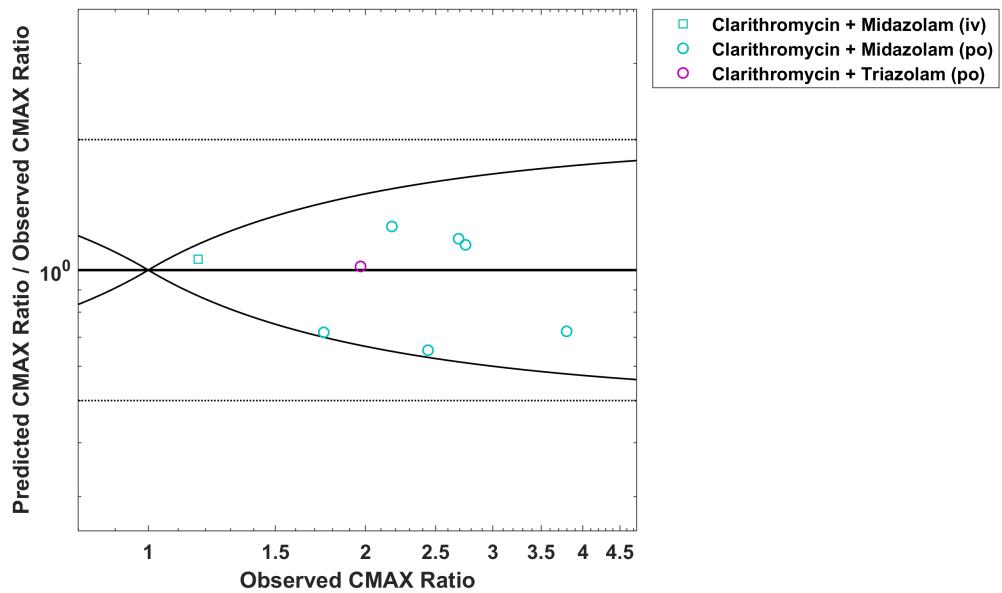
CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin



CYP3A4 DDI Clarithromycin

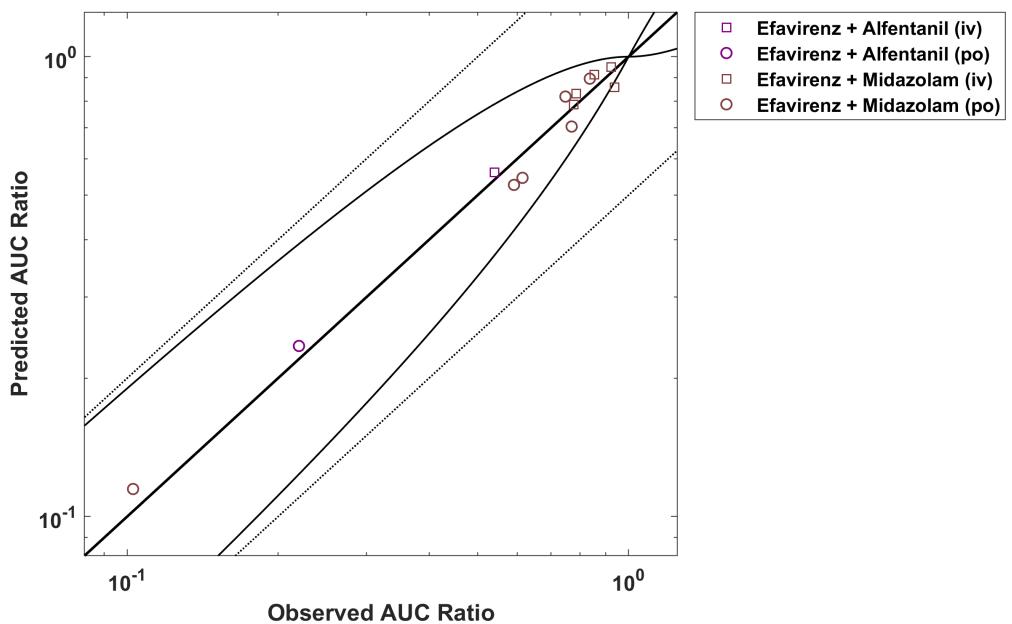
GMFE (AUC) = 1.266724

GMFE (CMAX) = 1.235285

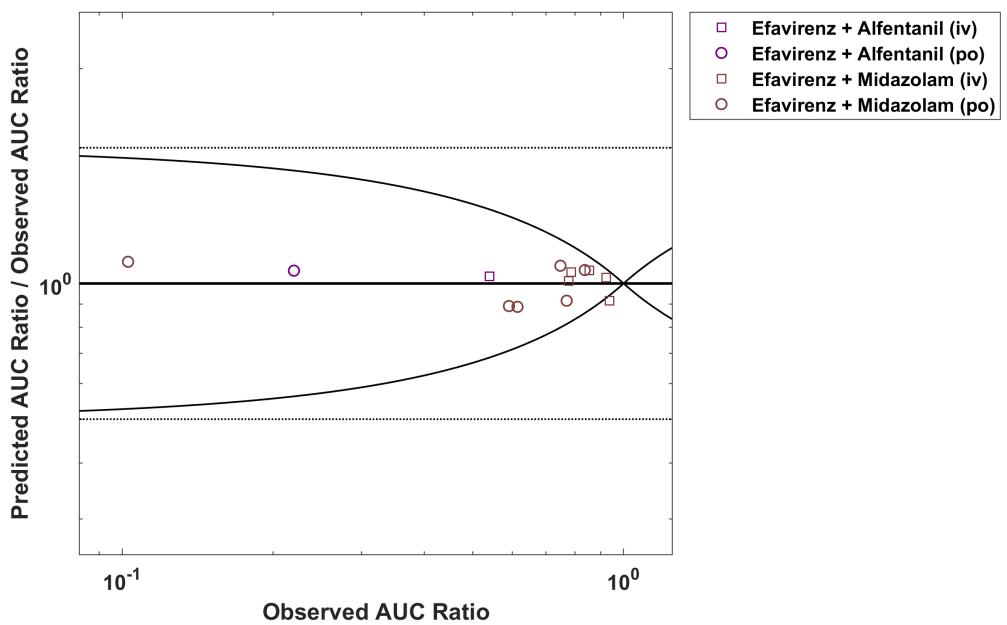
	AUC	Number	Ratio [%]
Points total		11	-
Points within Guest et al.		11	100
Points within 2-fold		11	100

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

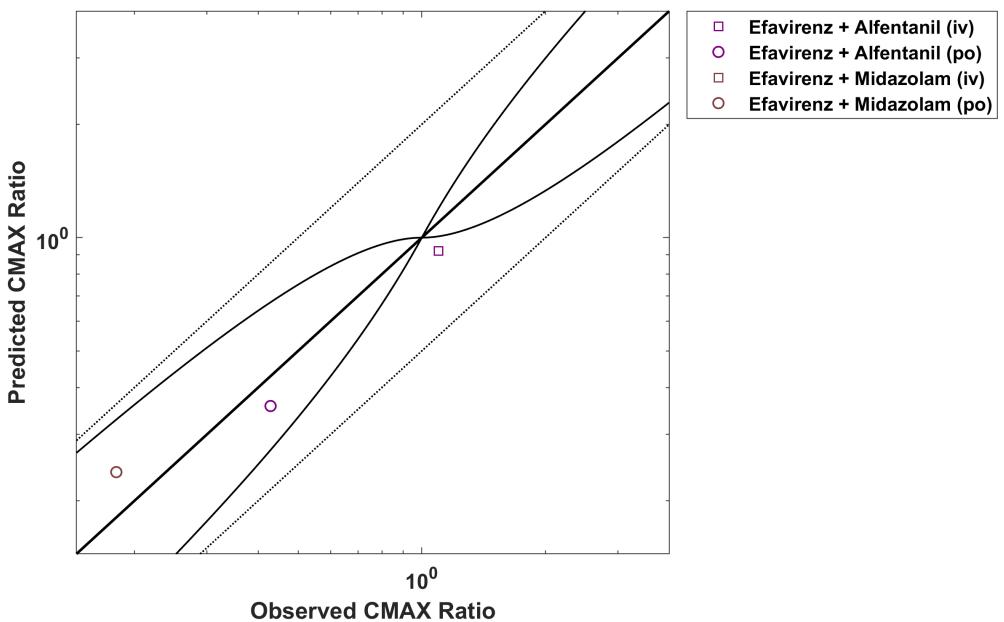
# Efavirenz



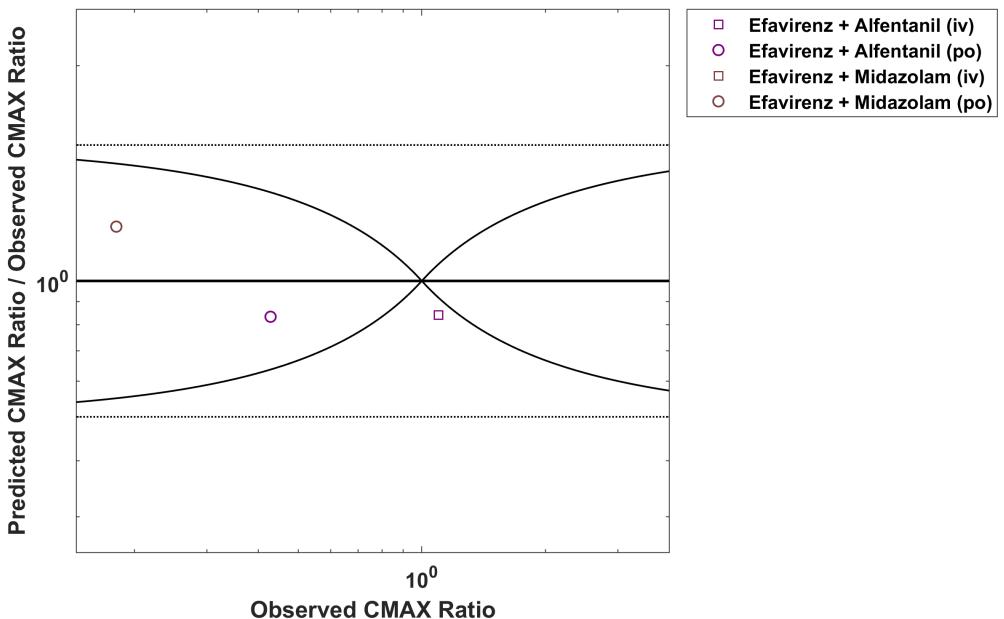
CYP3A4 DDI Efavirenz



CYP3A4 DDI Efavirenz



CYP3A4 DDI Efavirenz



CYP3A4 DDI Efavirenz

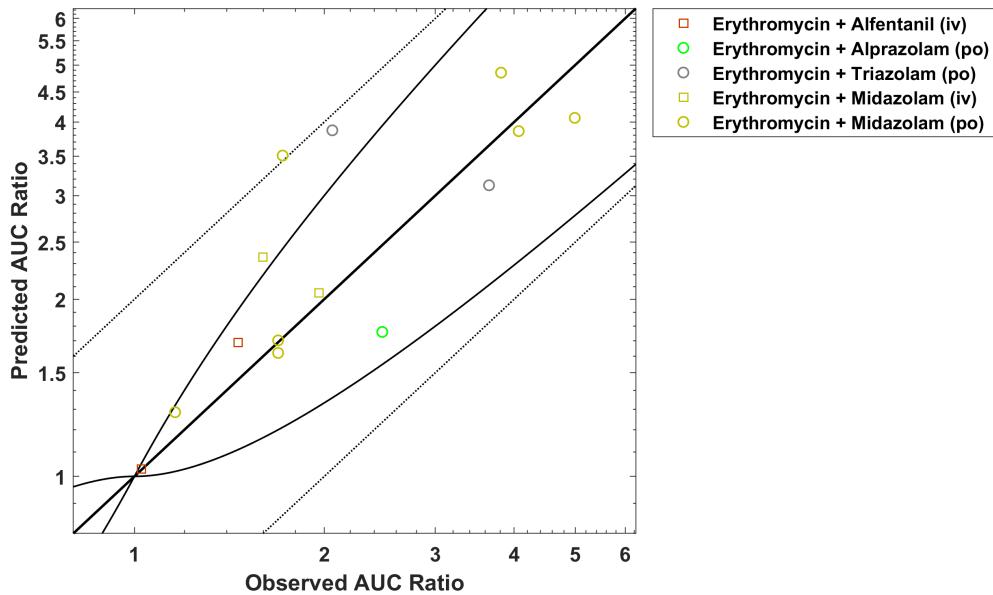
GMFE (AUC) = 1.075747

GMFE (CMAX) = 1.235565

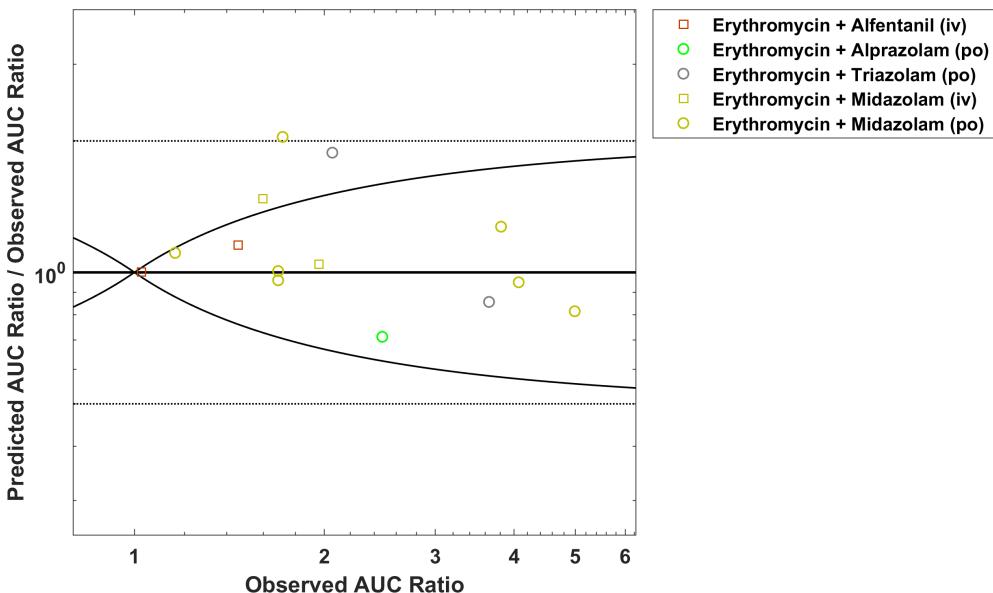
AUC	Number	Ratio [%]
Points total	13	-
Points within Guest et al.	12	92.3077
Points within 2-fold	13	100

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

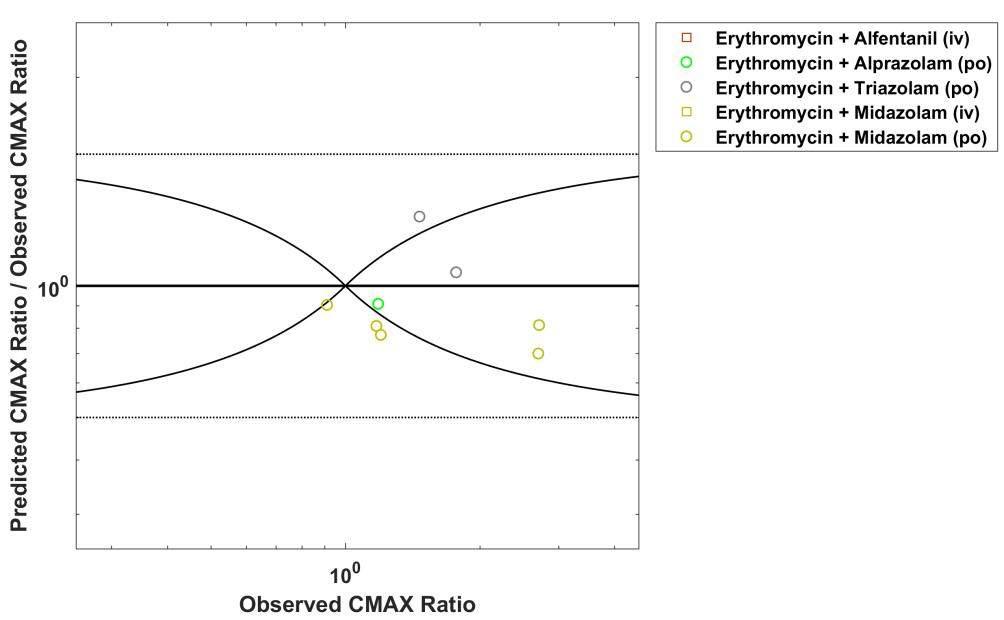
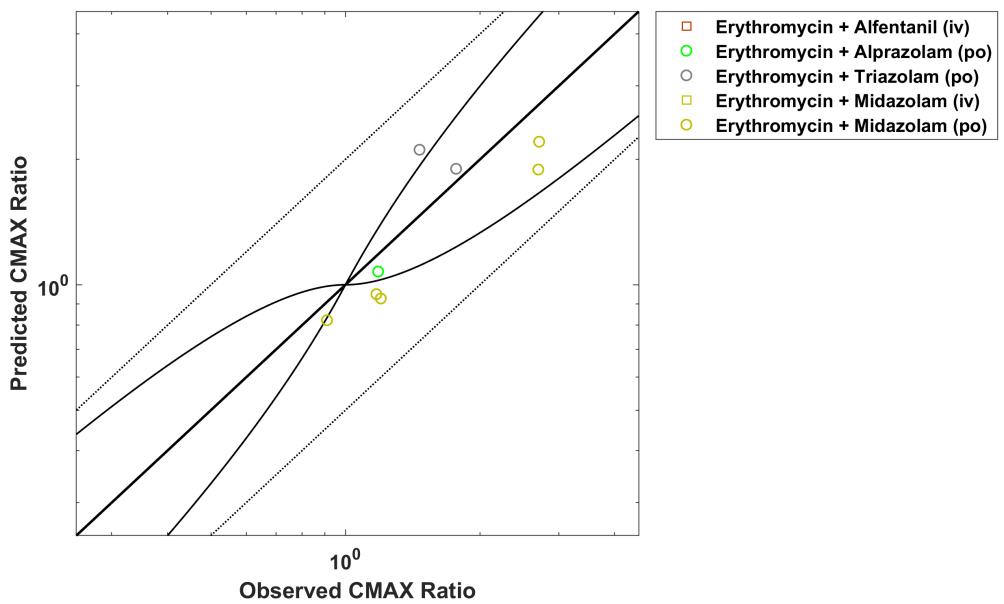
# Erythromycin



CYP3A4 DDI Erythromycin



CYP3A4 DDI Erythromycin



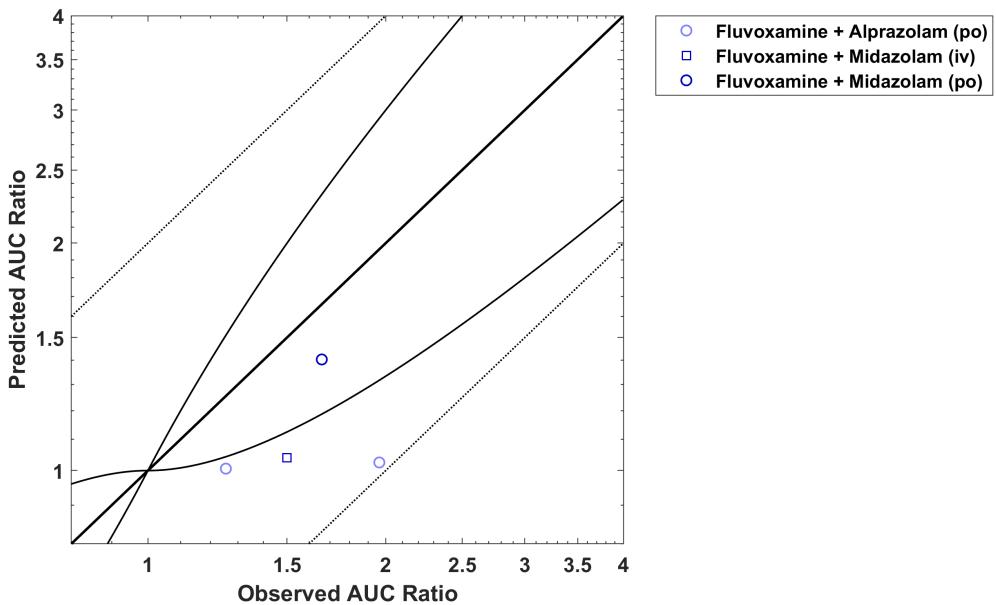
GMFE (AUC) = 1.245268

GMFE (CMAX) = 1.231222

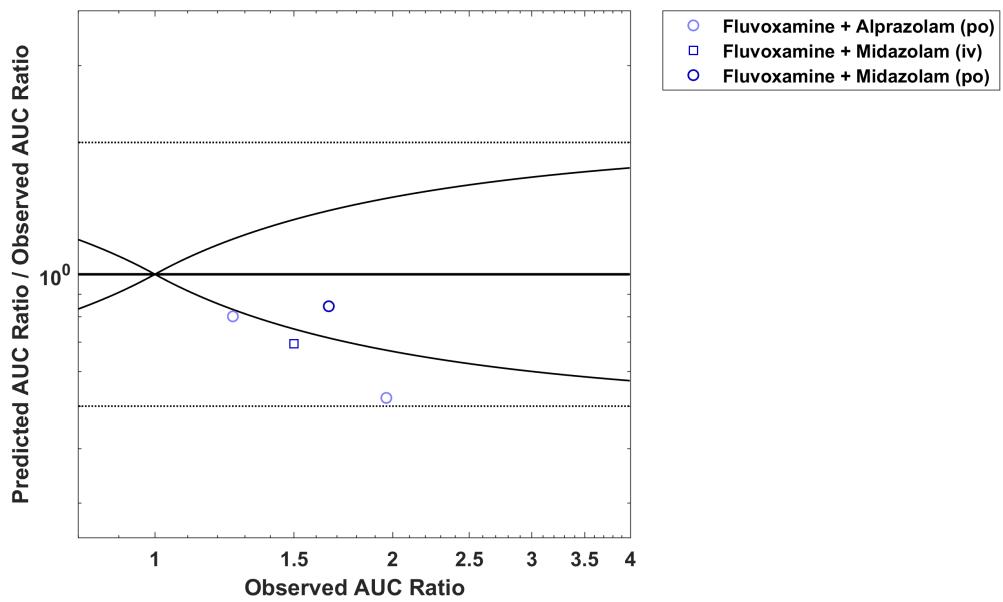
	AUC	Number	Ratio [%]
Points total		14	-
Points within Guest et al.		11	78.5714
Points within 2-fold		13	92.8571

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

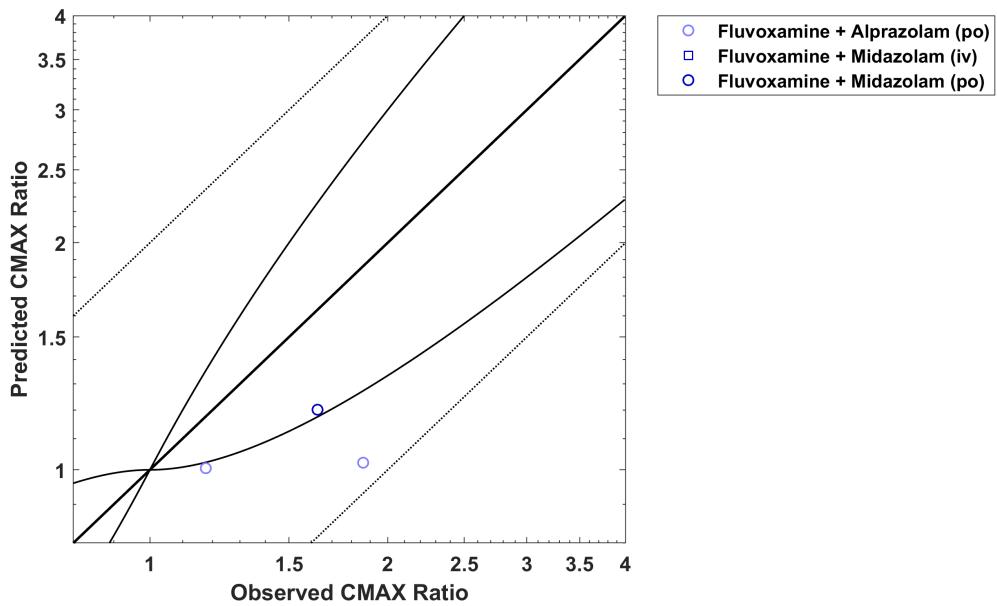
# Fluvoxamine



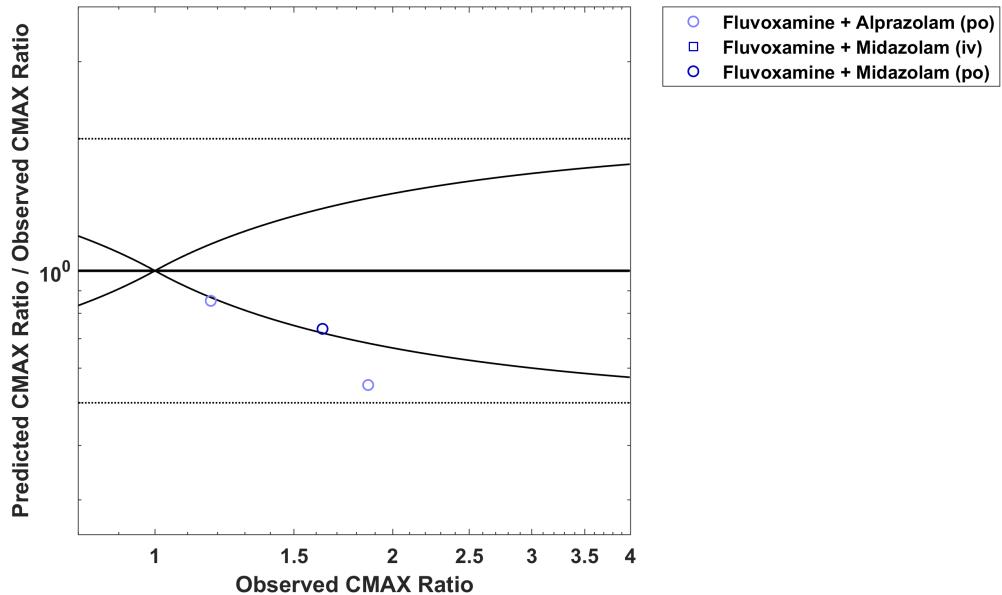
CYP3A4 DDI Fluvoxamine



CYP3A4 DDI Fluvoxamine



CYP3A4 DDI Fluvoxamine



CYP3A4 DDI Fluvoxamine

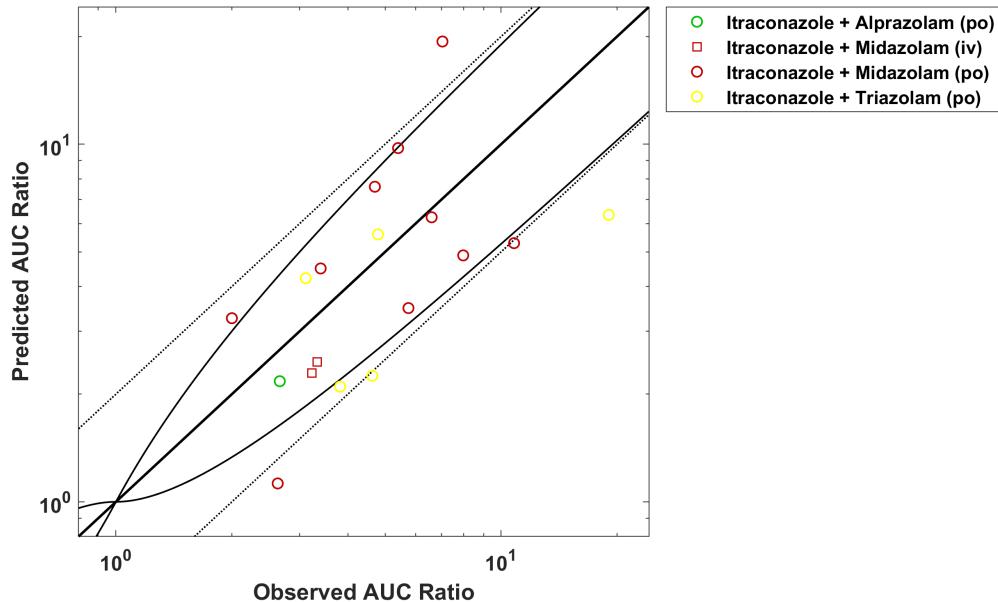
GMFE (AUC) = 1.420923

GMFE (CMAX) = 1.425108

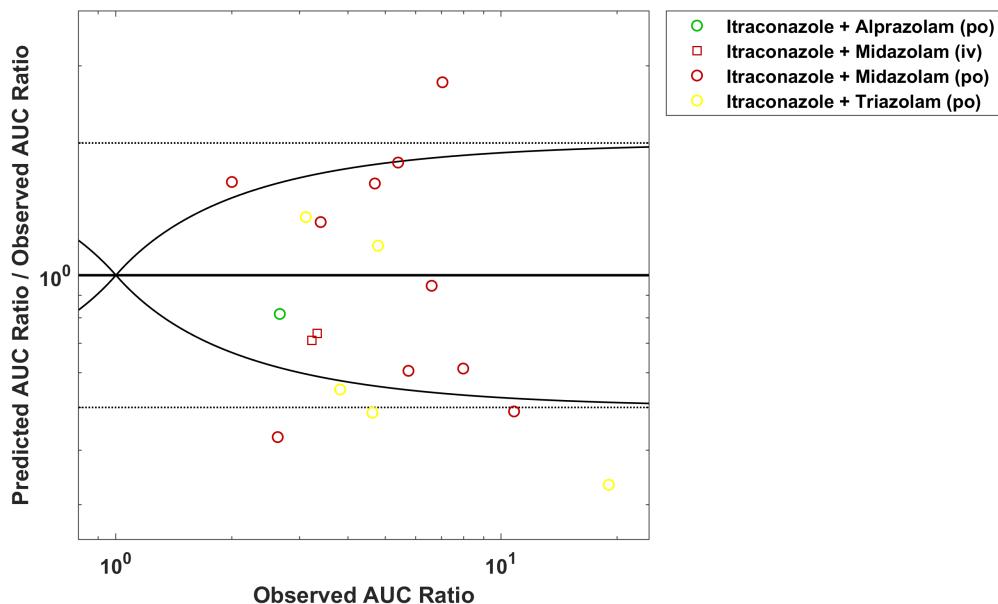
AUC	Number	Ratio [%]
Points total	4	-
Points within Guest et al.	1	25
Points within 2-fold	4	100

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

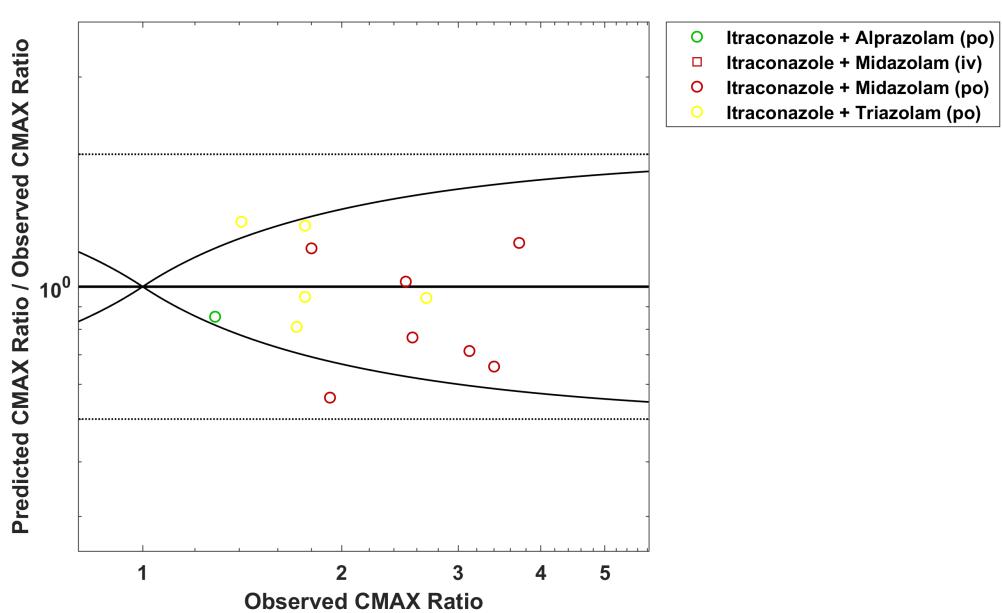
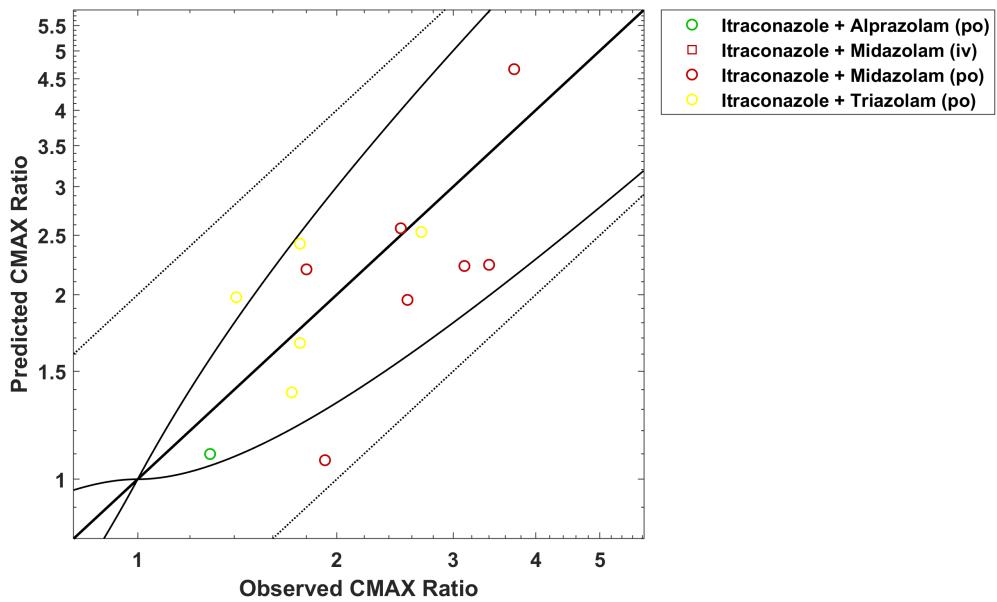
## Itraconazole



CYP3A4 DDI Itraconazole



CYP3A4 DDI Itraconazole



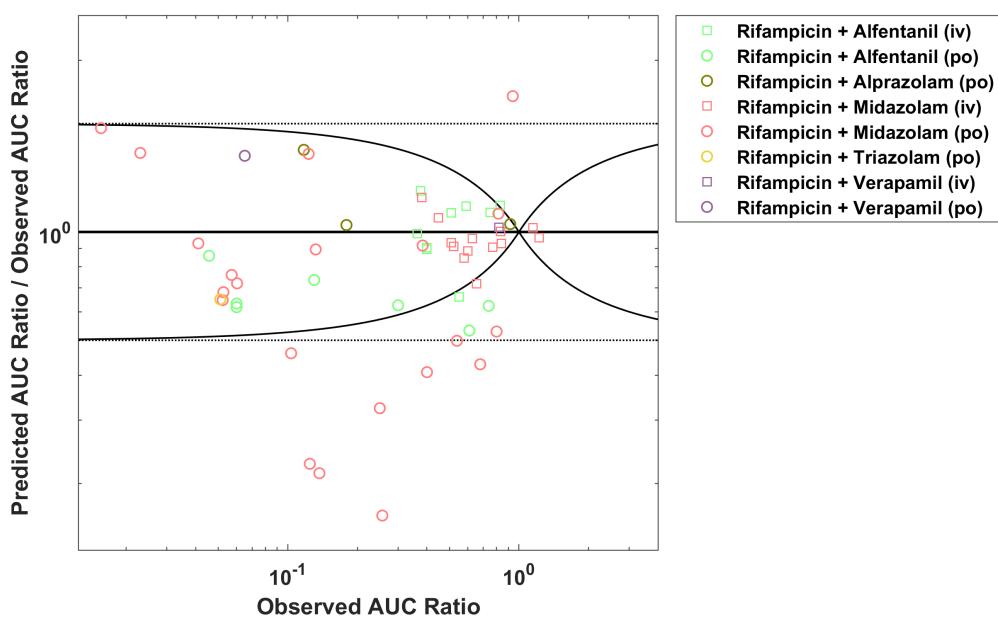
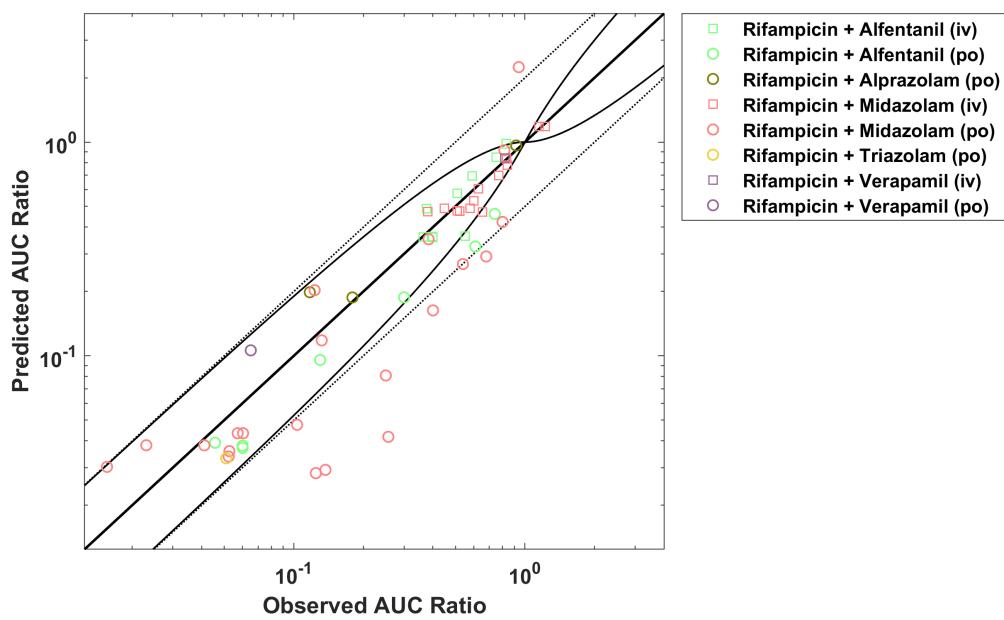
GMFE (AUC) = 1.665952

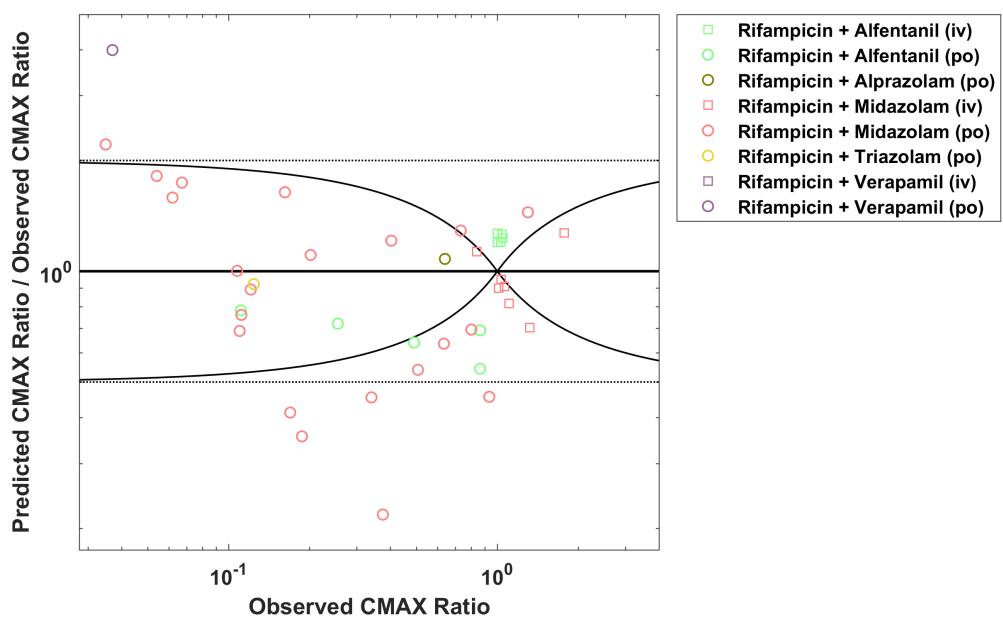
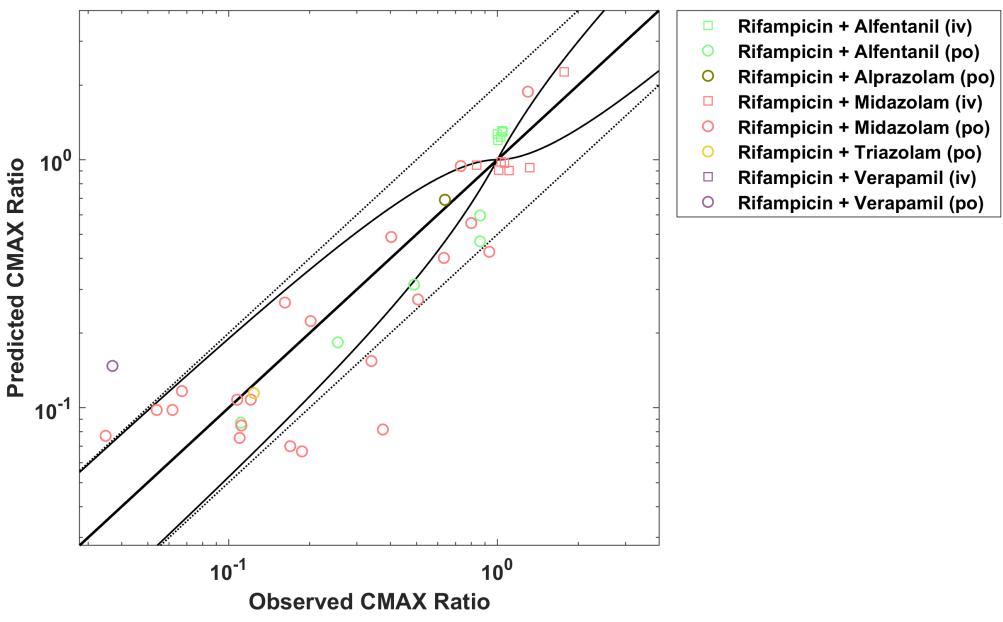
GMFE (CMAX) = 1.278882

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





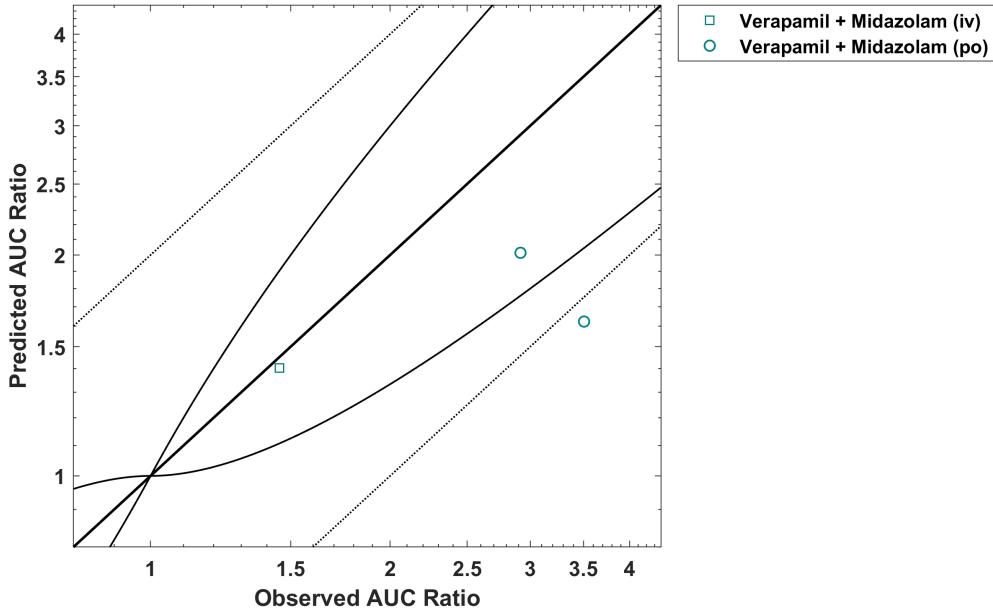
GMFE (AUC) = 1.460530

GMFE (CMAX) = 1.505824

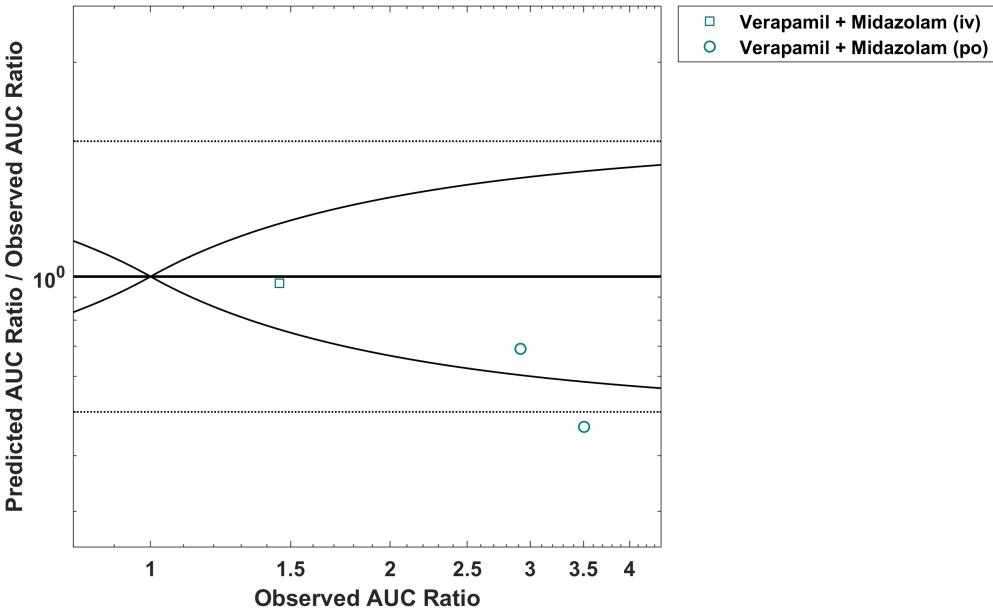
	AUC	Number	Ratio [%]
Points total		57	-
Points within Guest et al.		42	73.6842
Points within 2-fold		48	84.2105

	CMAX	Number	Ratio [%]
Points total		41	-
Points within Guest et al.		16	39.0244
Points within 2-fold		34	82.9268

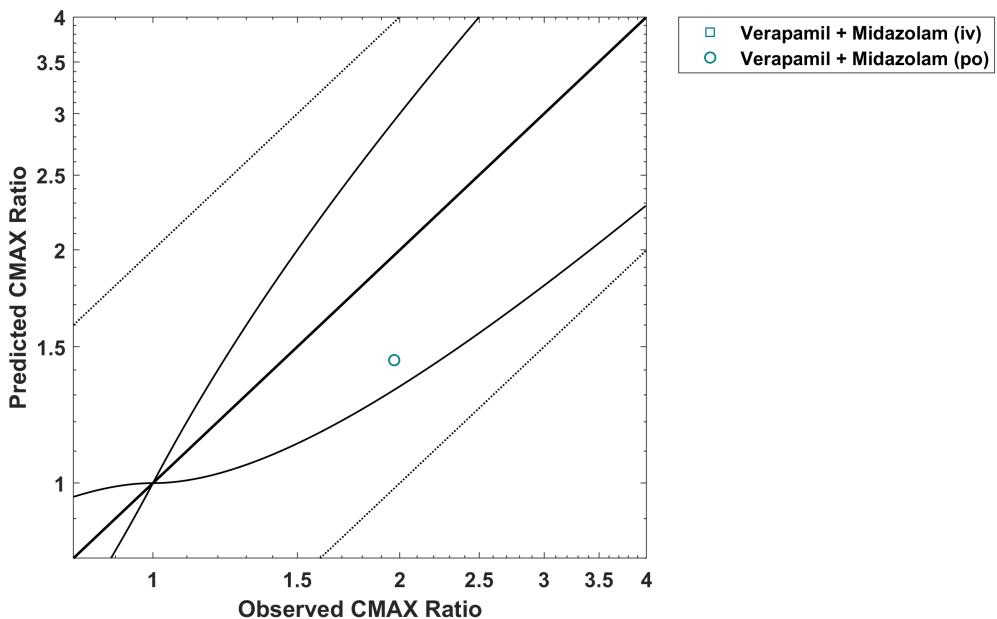
# Verapamil



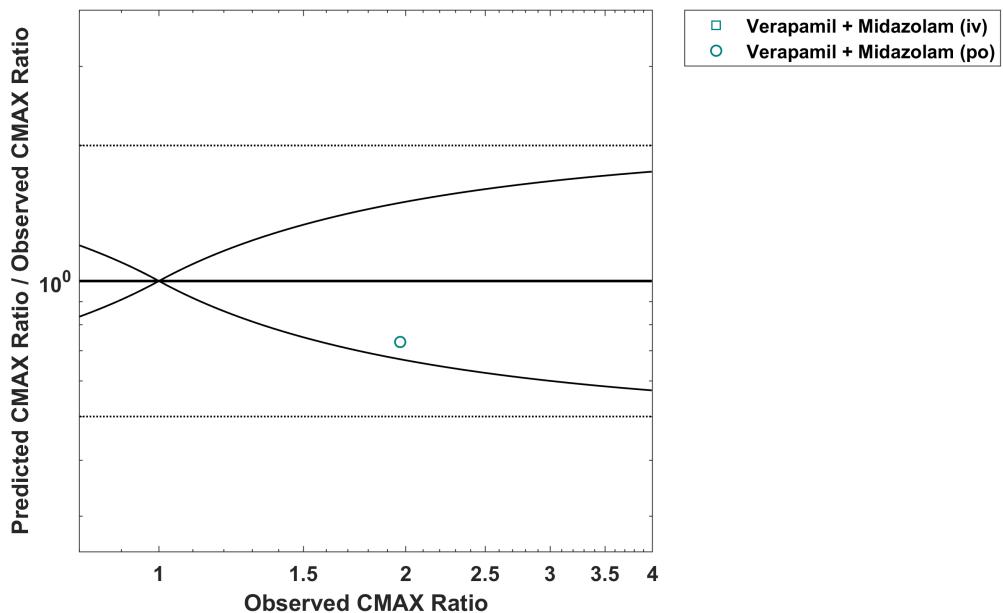
CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil

GMFE (AUC) = 1.479636

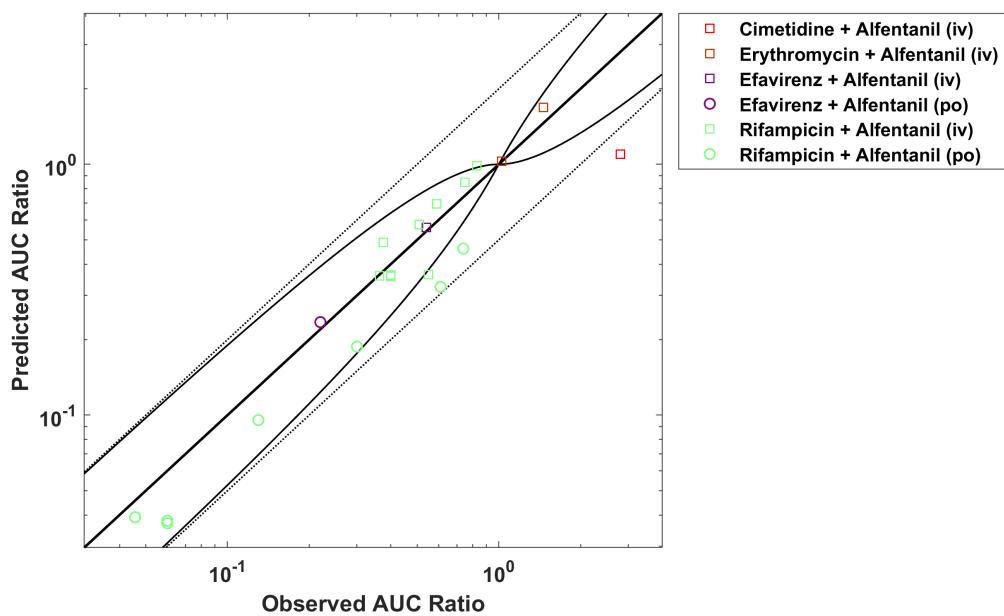
GMFE (CMAX) = 1.366122

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

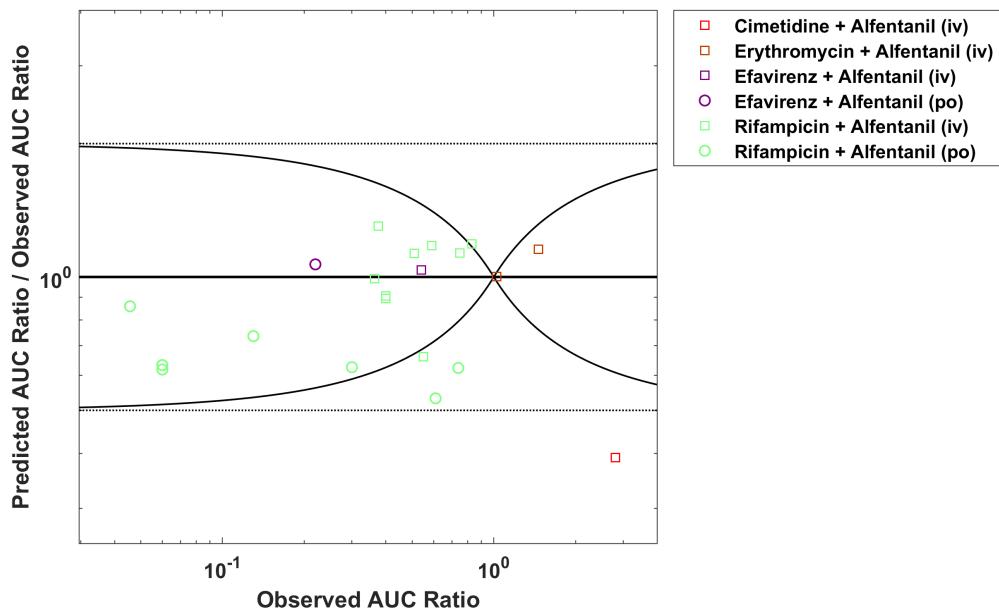
	CMAX	Number	Ratio [%]
Points total		1	-
Points within Guest et al.		1	100
Points within 2-fold		1	100

# Victim

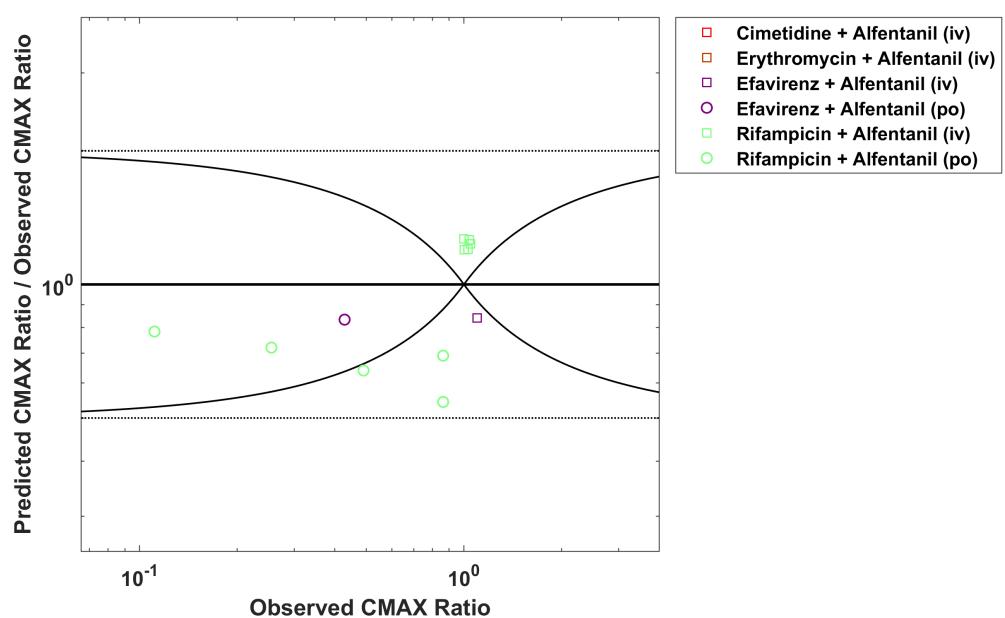
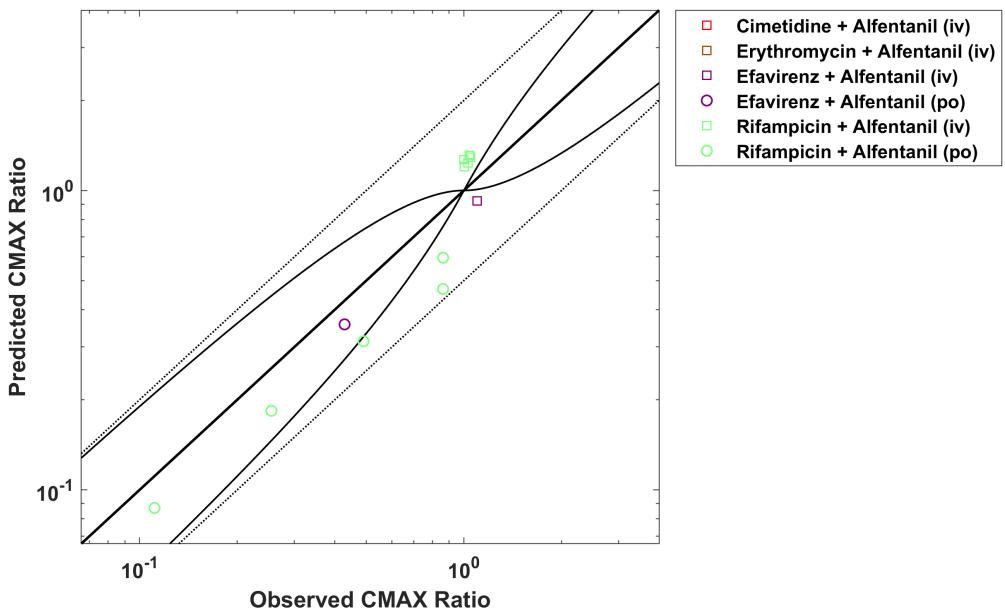
## Alfentanil



CYP3A4 DDI Alfentanil



CYP3A4 DDI Alfentanil



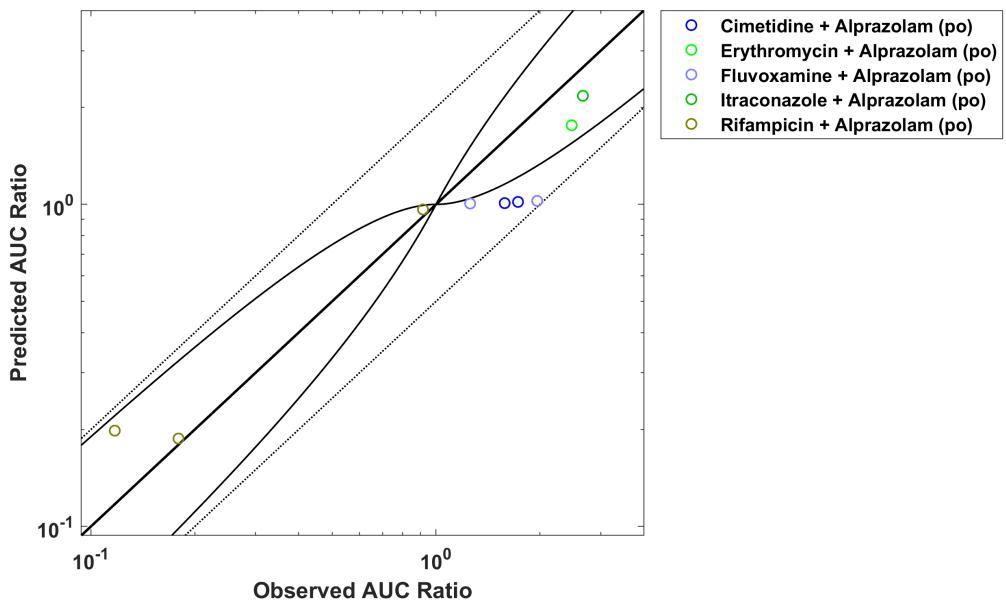
GMFE (AUC) = 1.307997

GMFE (CMAX) = 1.327112

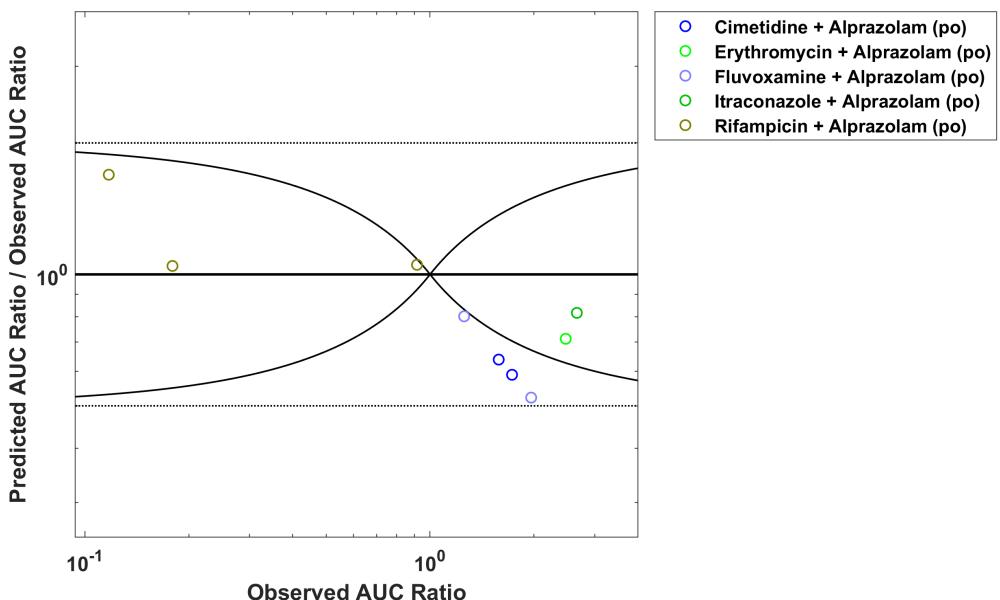
	AUC	Number	Ratio [%]
Points total		21	-
Points within Guest et al.		16	76.1905
Points within 2-fold		20	95.2381

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

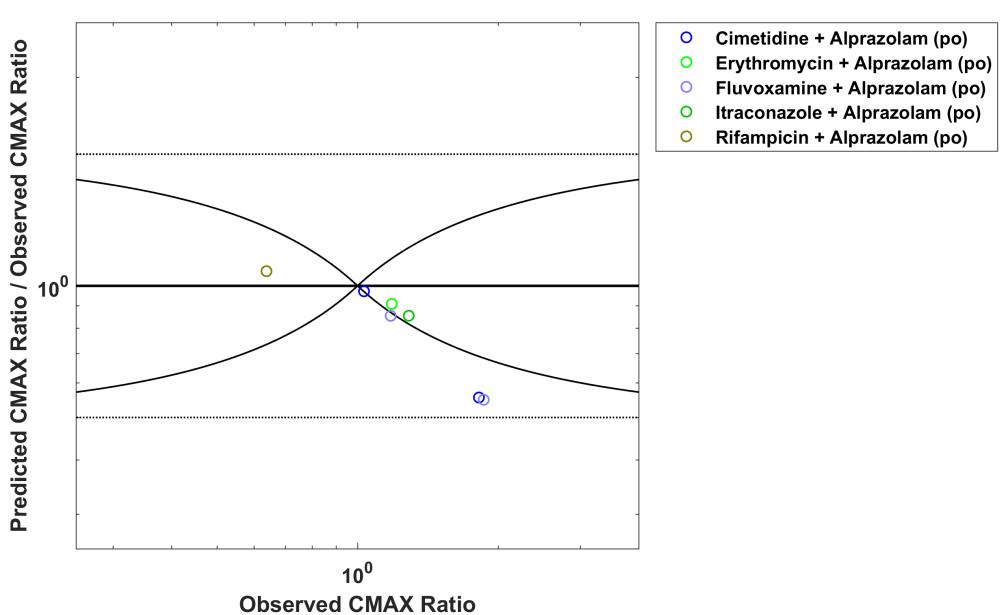
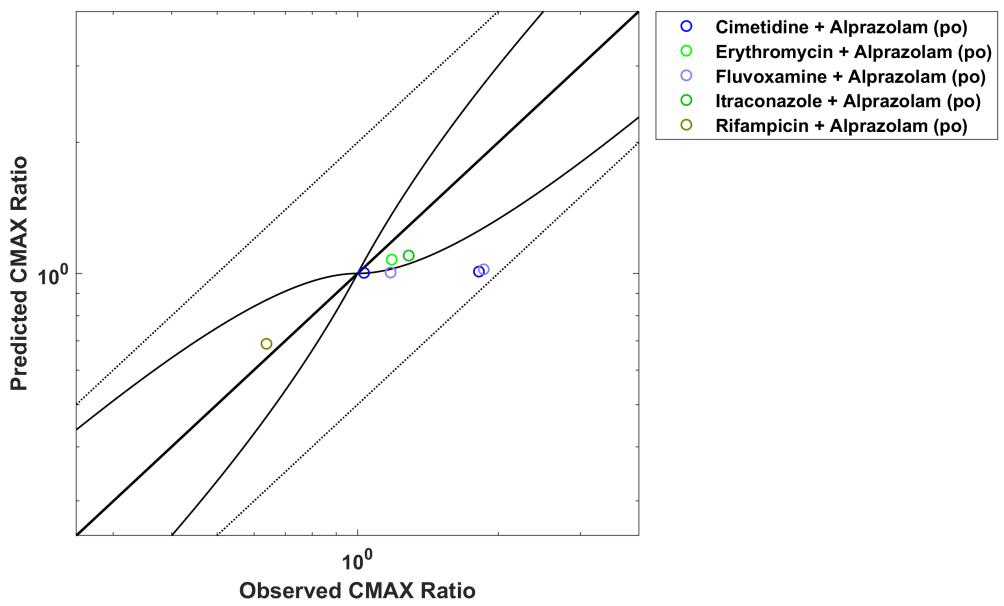
# Alprazolam



CYP3A4 DDI Alprazolam



CYP3A4 DDI Alprazolam



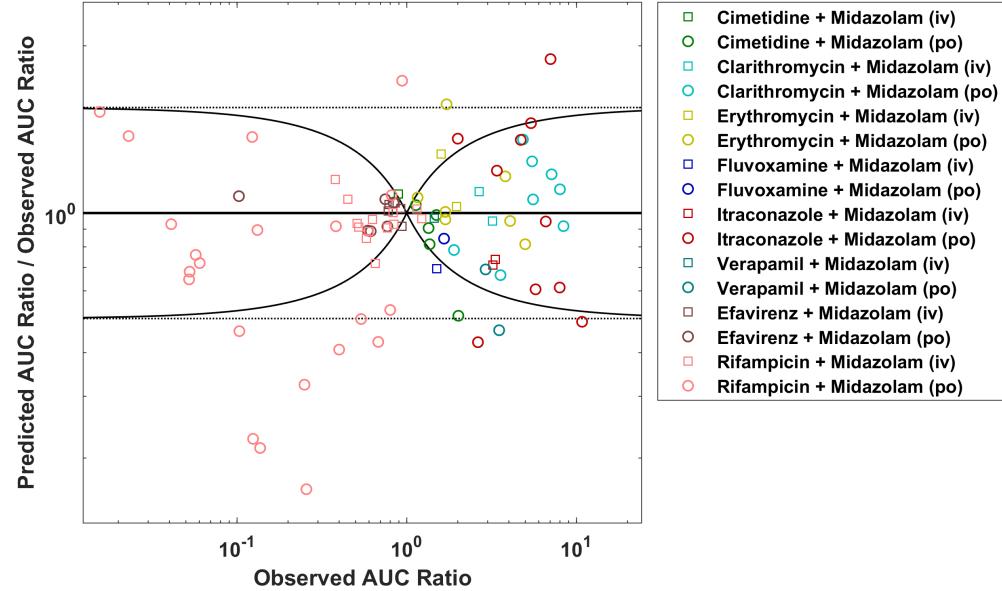
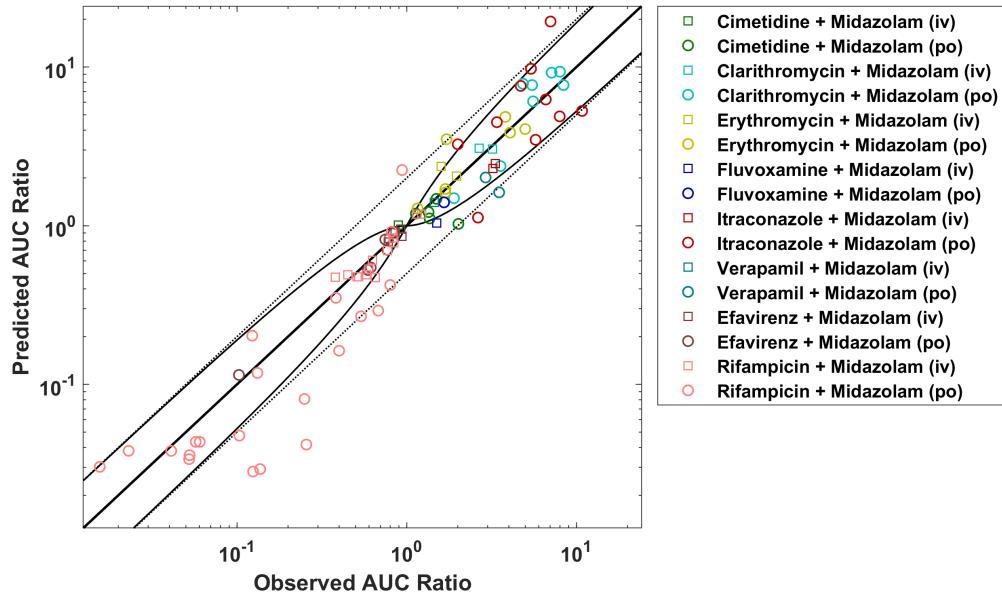
GMFE (AUC) = 1.397670

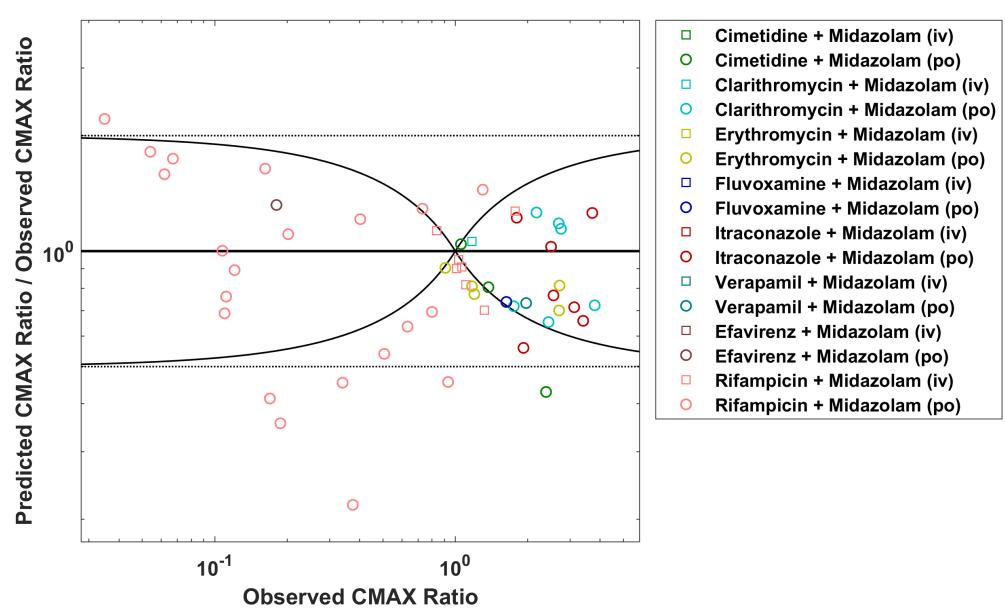
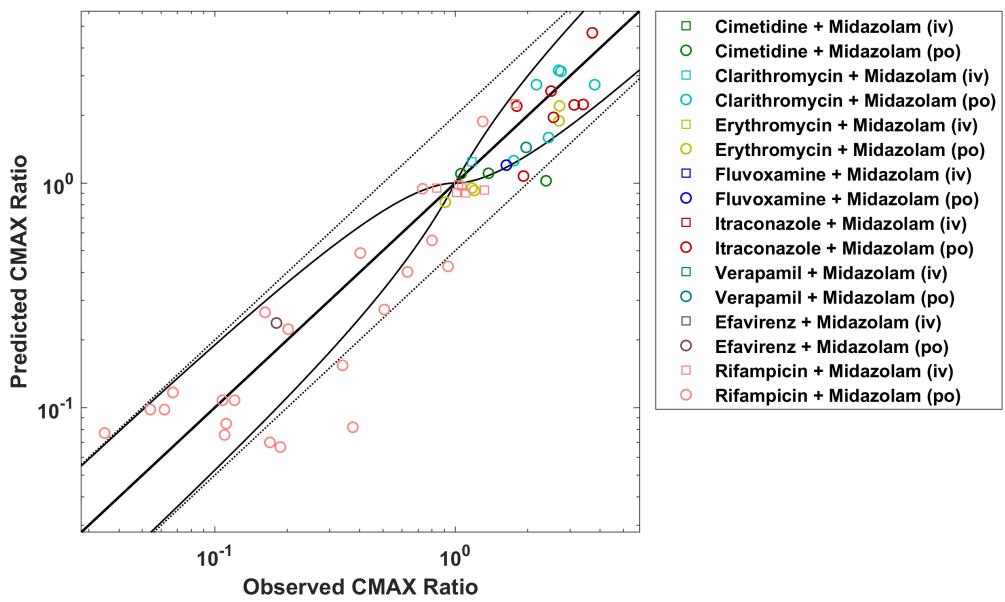
GMFE (CMAX) = 1.275623

	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





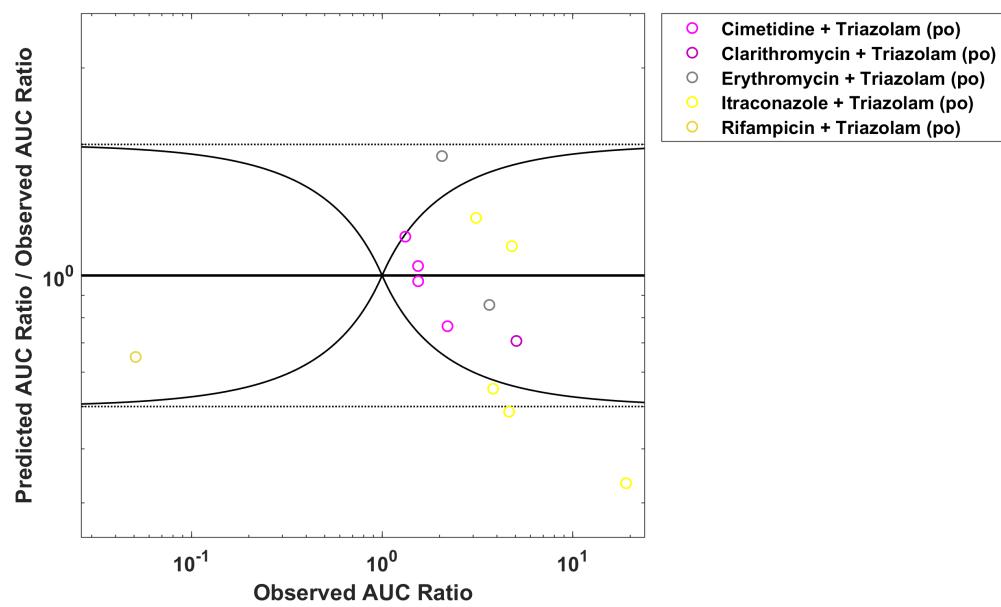
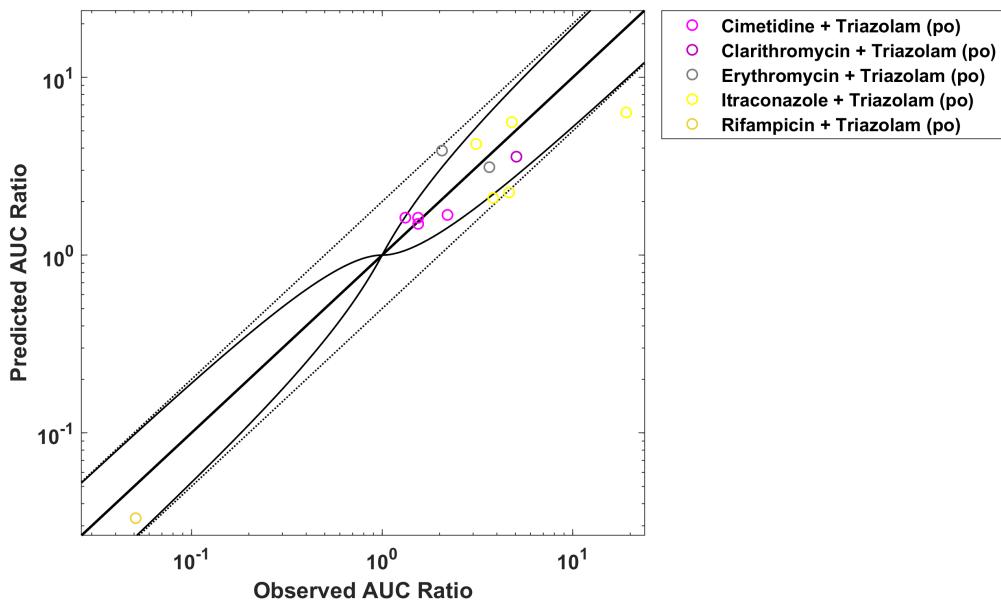
GMFE (AUC) = 1.397505

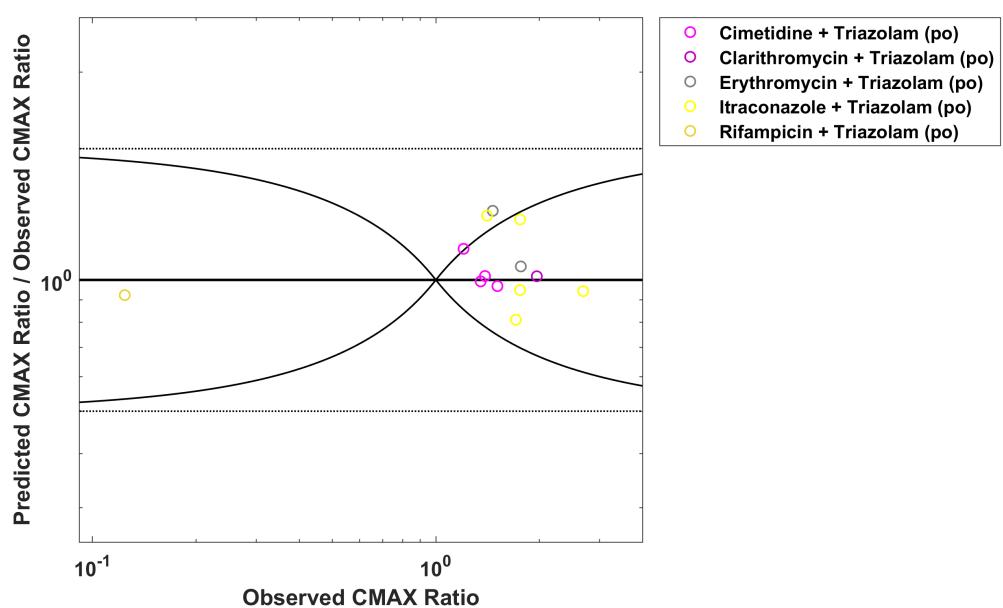
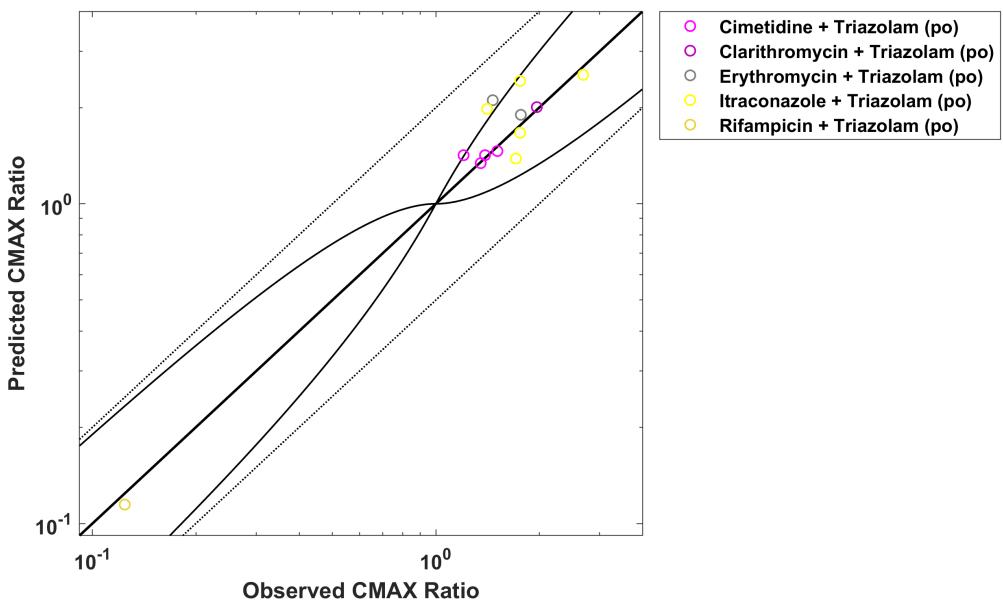
GMFE (CMAX) = 1.432862

	AUC	Number	Ratio [%]
Points total		88	-
Points within Guest et al.		66	75
Points within 2-fold		74	84.0909

	CMAX	Number	Ratio [%]
Points total		53	-
Points within Guest et al.		32	60.3774
Points within 2-fold		46	86.7925

# Triazolam





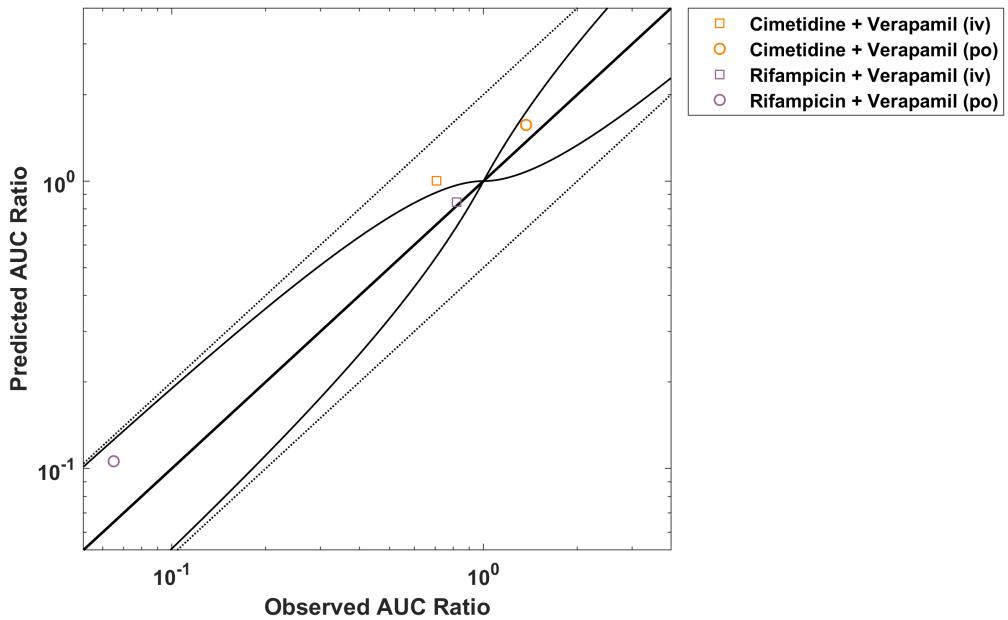
GMFE (AUC) = 1.468759

GMFE (CMAX) = 1.143534

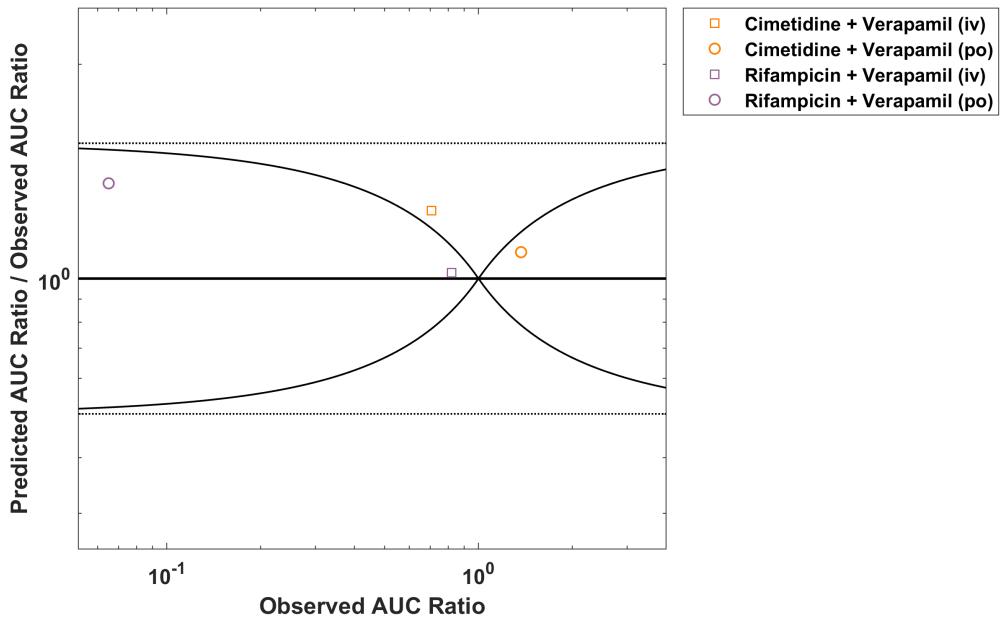
	AUC	Number	Ratio [%]
Points total		13	-
Points within Guest et al.		9	69.2308
Points within 2-fold		11	84.6154

	CMAX	Number	Ratio [%]
Points total		13	-
Points within Guest et al.		10	76.9231
Points within 2-fold		13	100

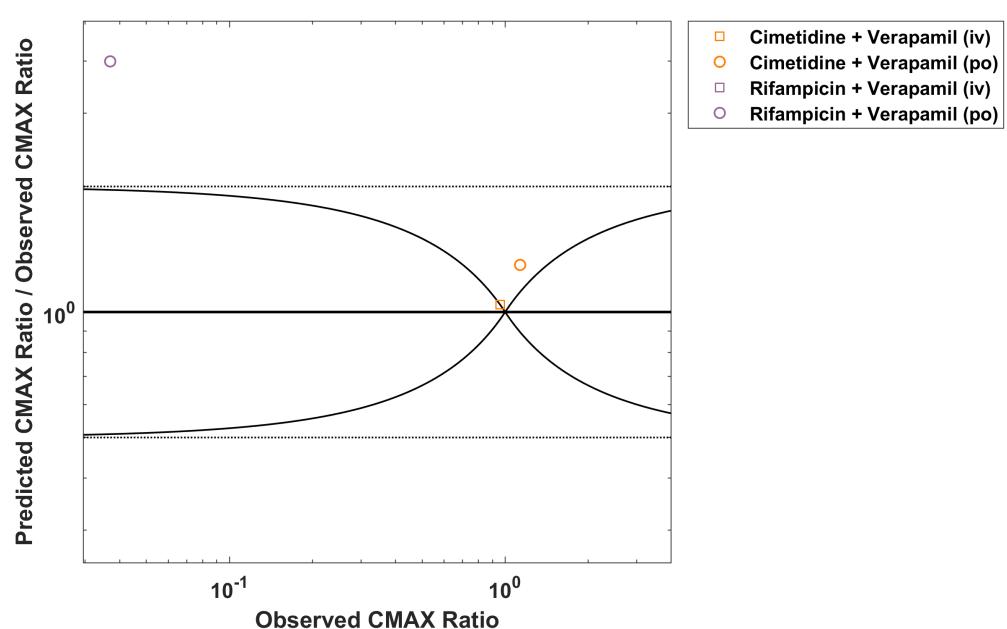
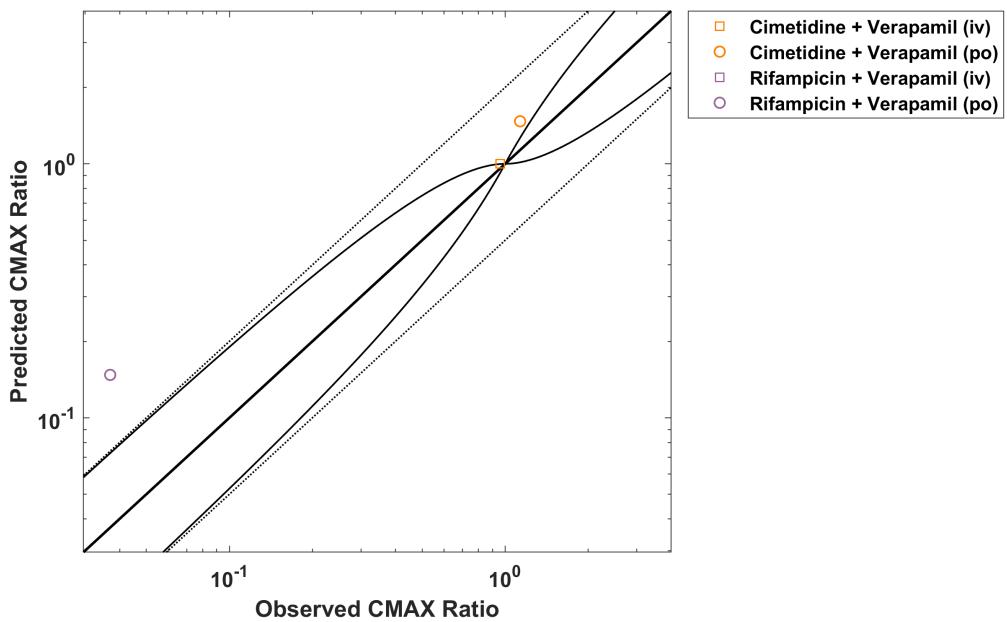
# Verapamil



CYP3A4 DDI Verapamil



CYP3A4 DDI Verapamil



GMFE (AUC) = 1.284476

GMFE (CMAX) = 1.754106

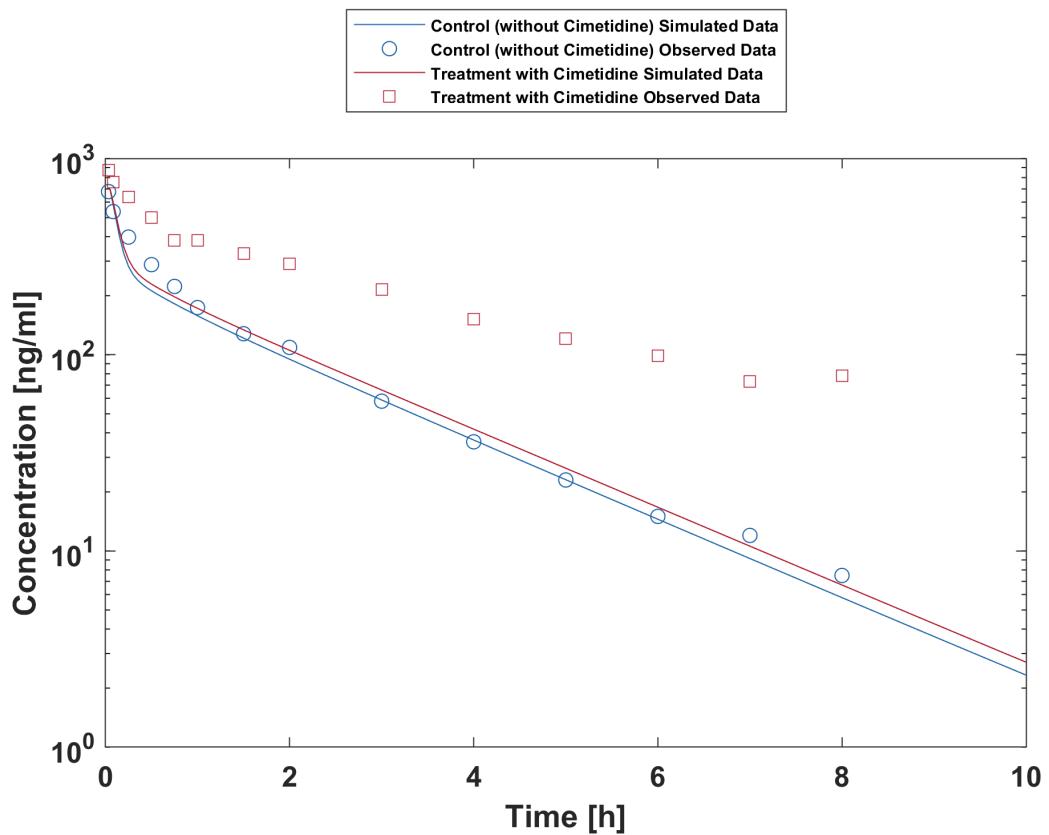
	AUC	Number	Ratio [%]
Points total	4	-	
Points within Guest et al.	3	75	
Points within 2-fold	4	100	

	CMAX	Number	Ratio [%]
Points total	3	-	
Points within Guest et al.	0	0	
Points within 2-fold	2	66.6667	

# 3 Concentration-Time Profiles

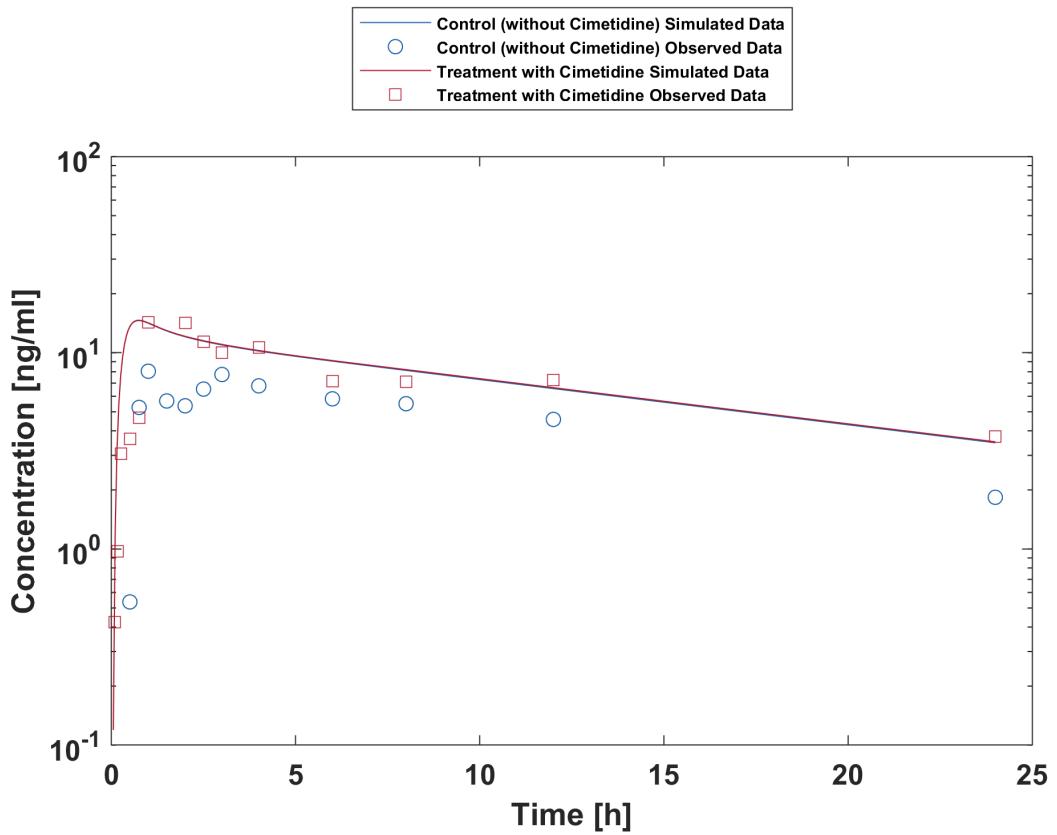
The following section shows concentration time profiles of the victim drugs of the simulated DDI studies in comparison to observed data (if available).

## 3.1 Cimetidine - Alfentanil DDI

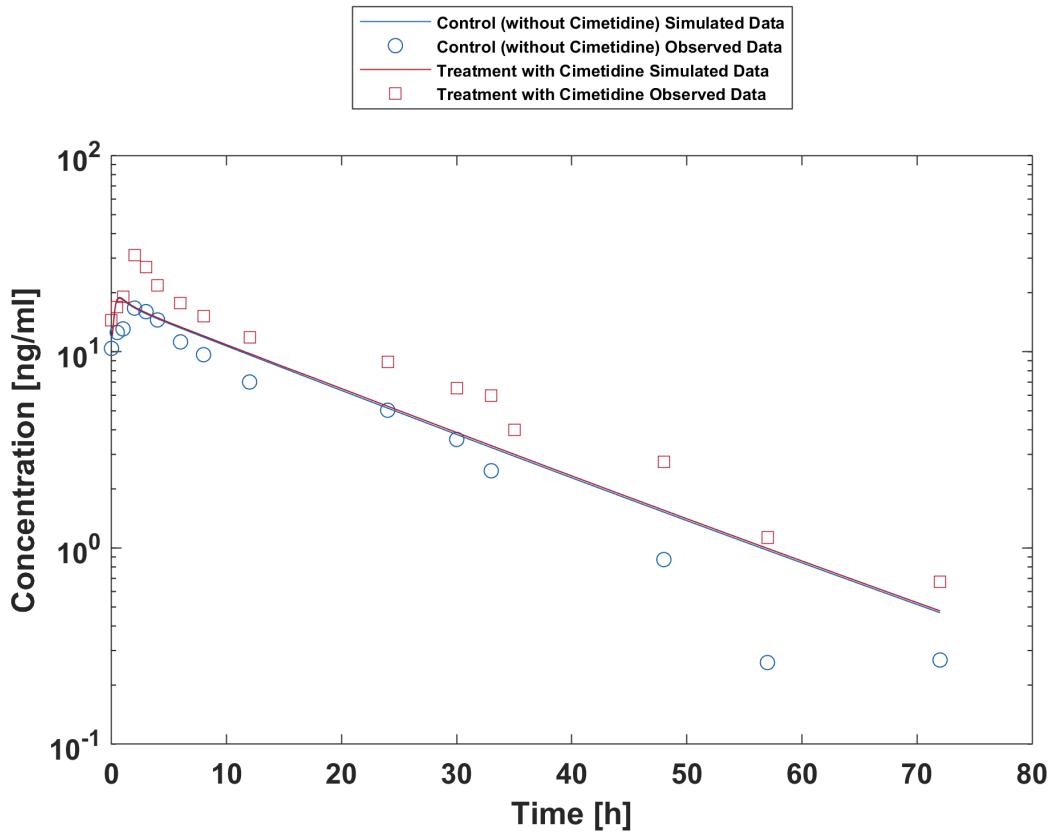


Kienlen 1993

## 3.2 Cimetidine - Alprazolam DDI

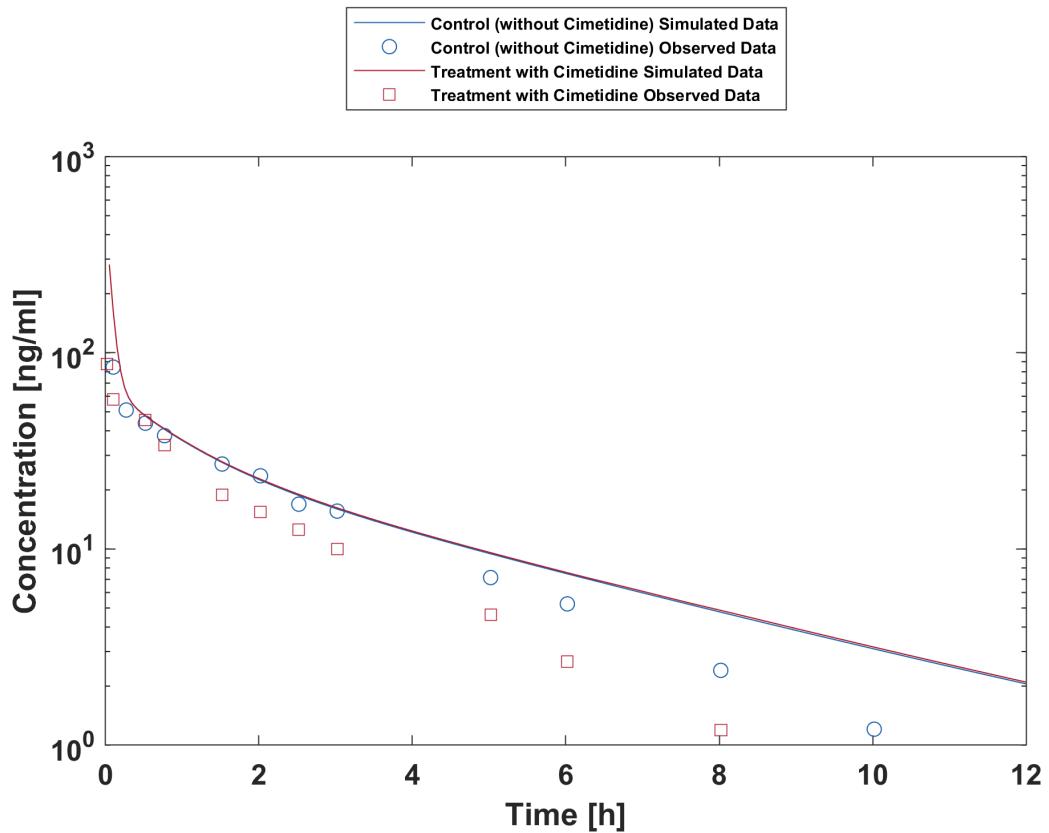


Abernethy 1983

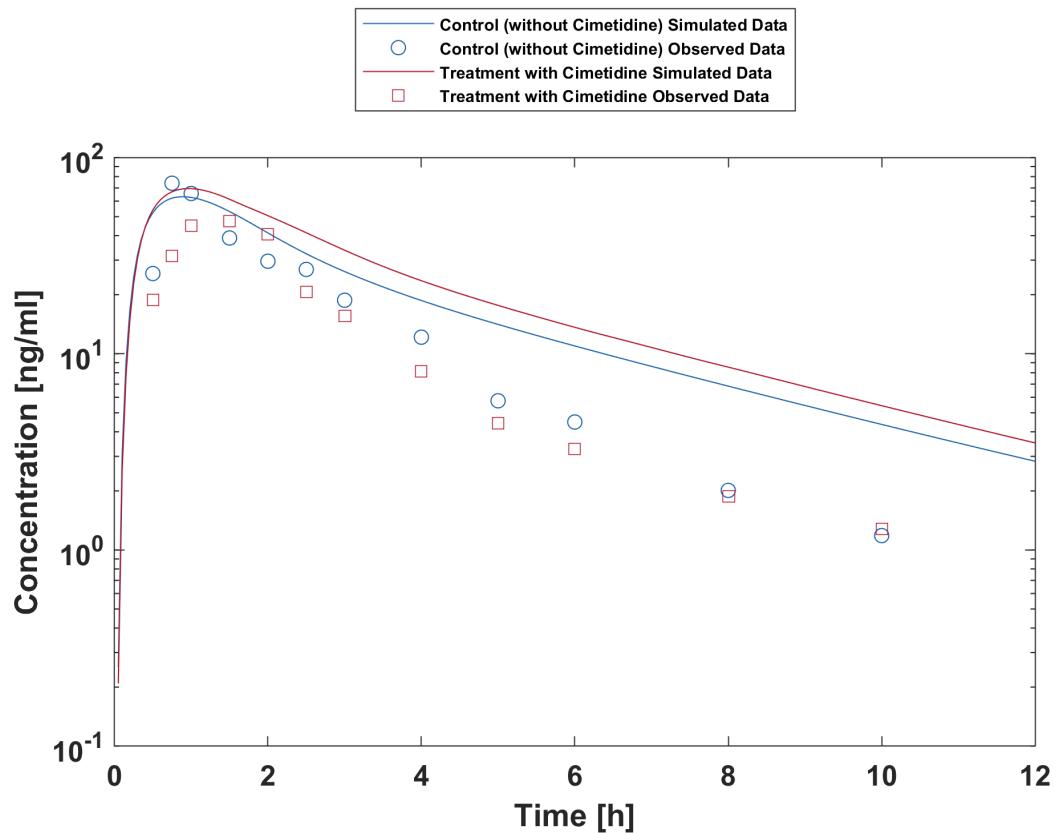


Pourbaix 1985

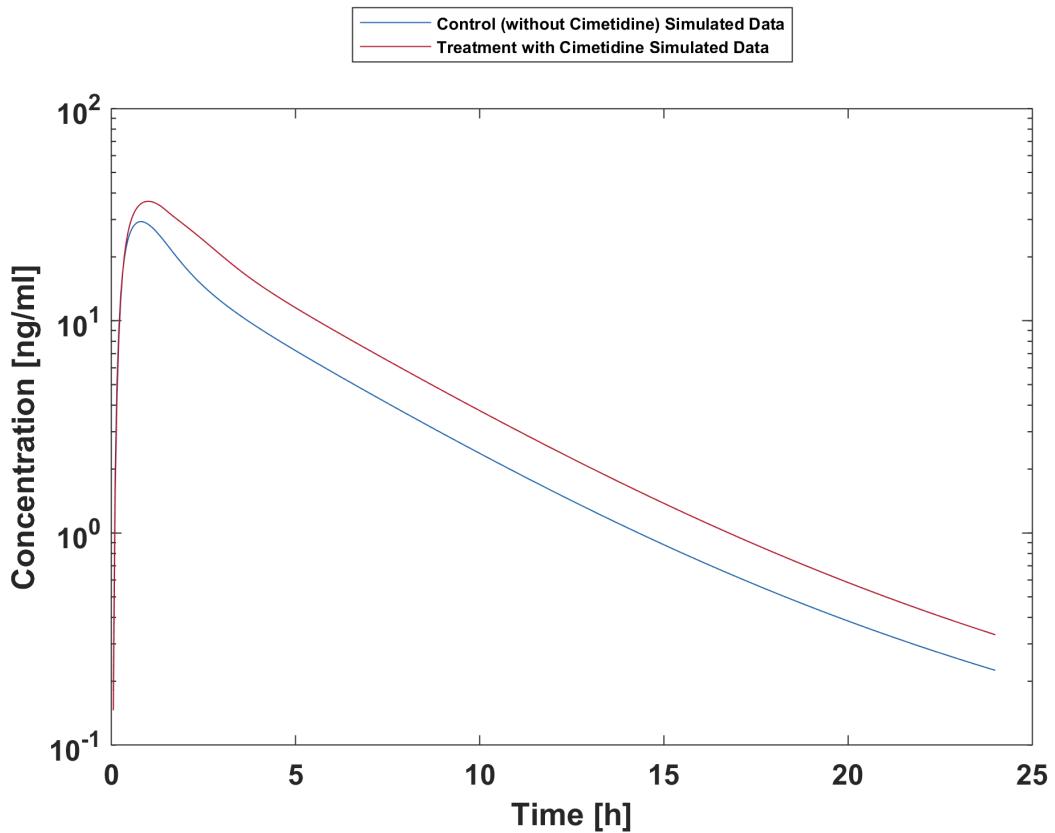
### 3.3 Cimetidine - Midazolam DDI



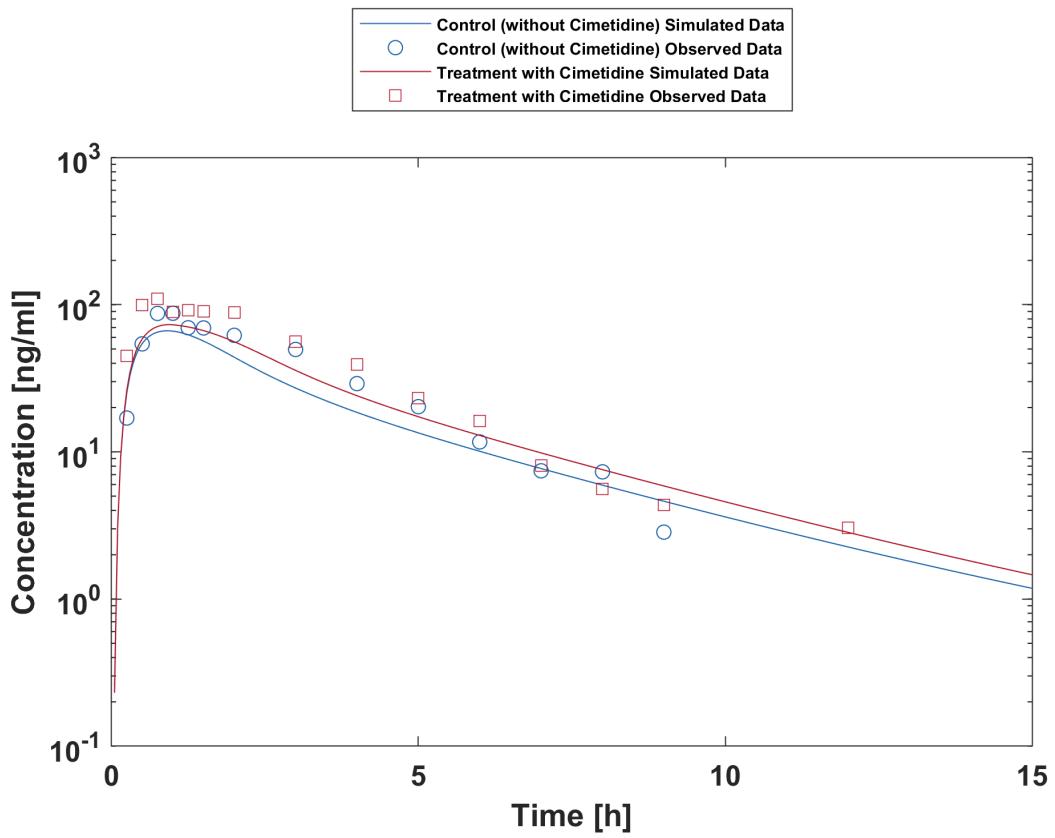
Greenblatt 1986 (midazolam IV)



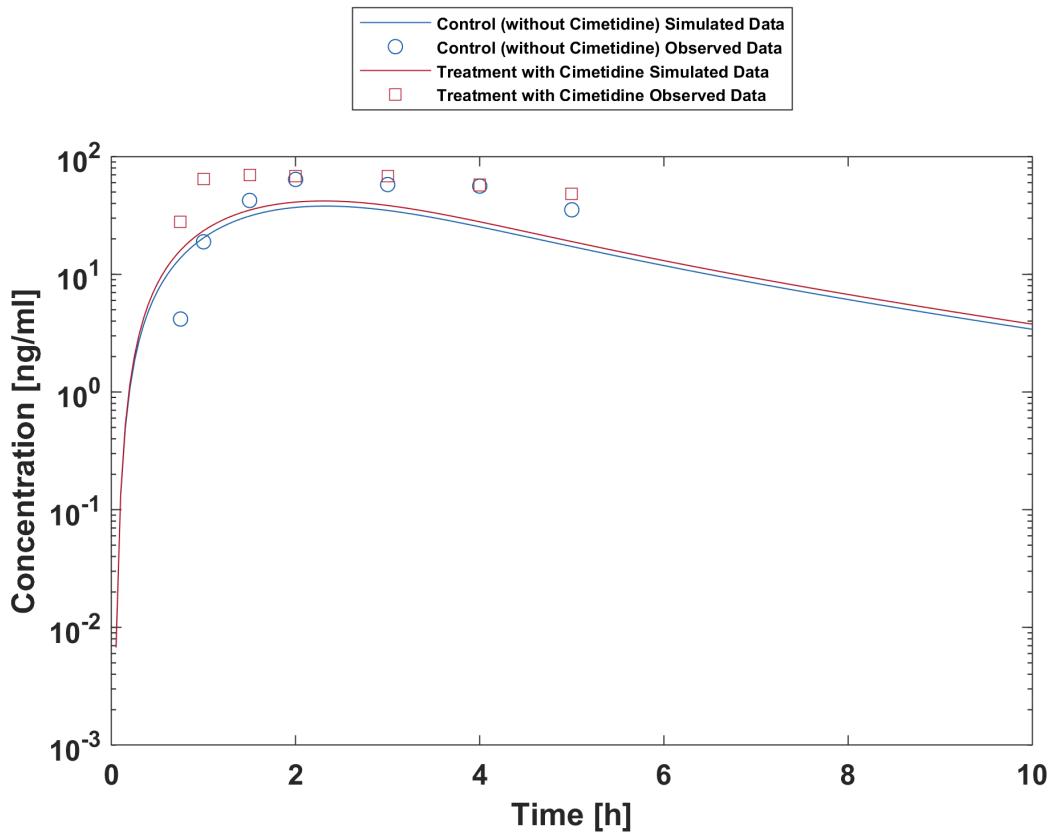
Greenblatt 1986 (midazolam PO)



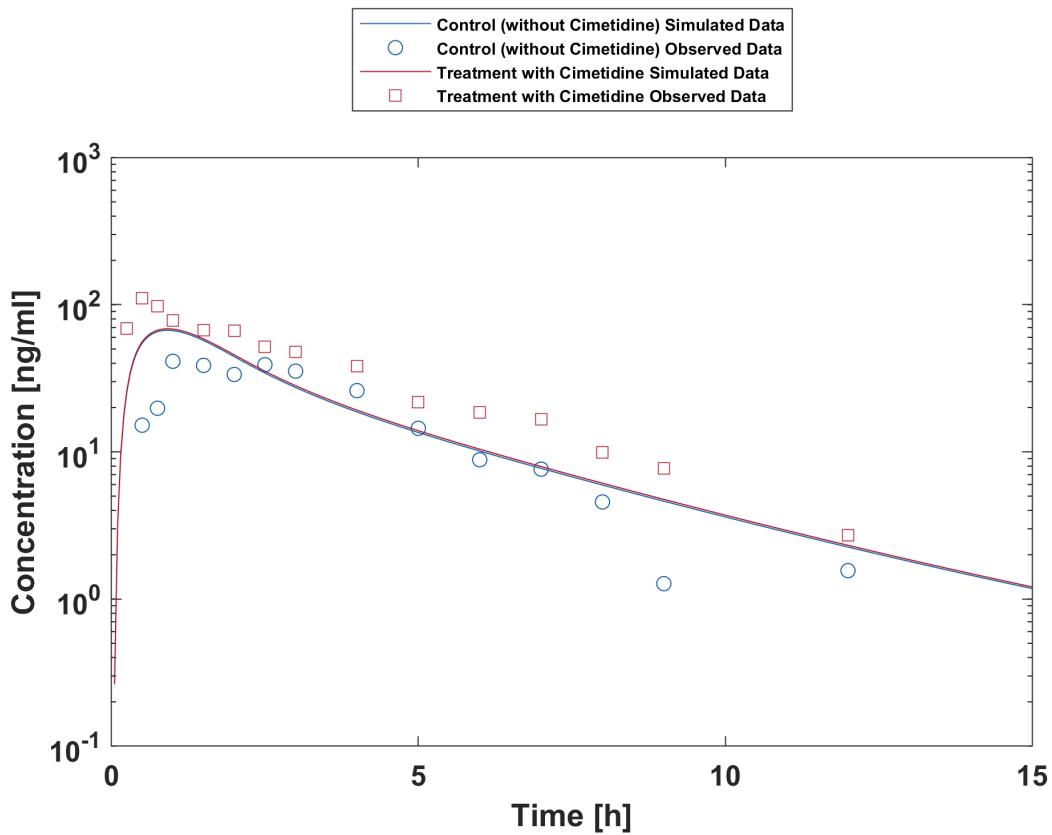
Martinez 1999



Fee 1987

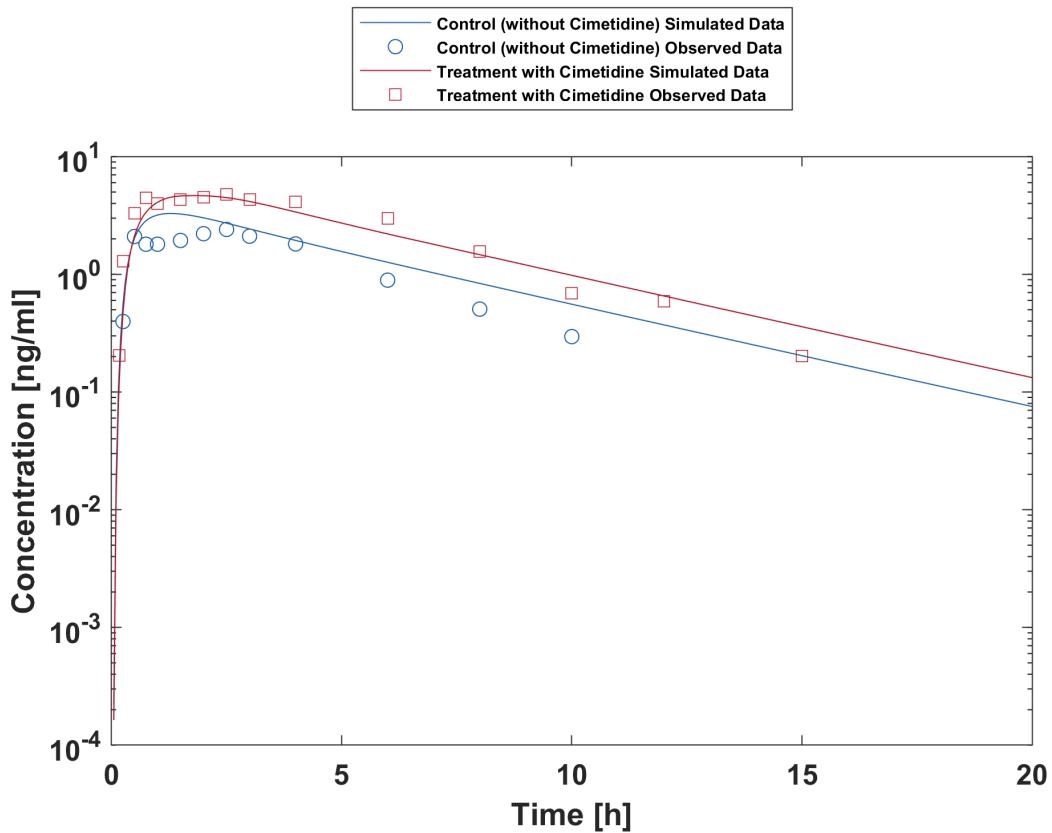


Salonen 1986

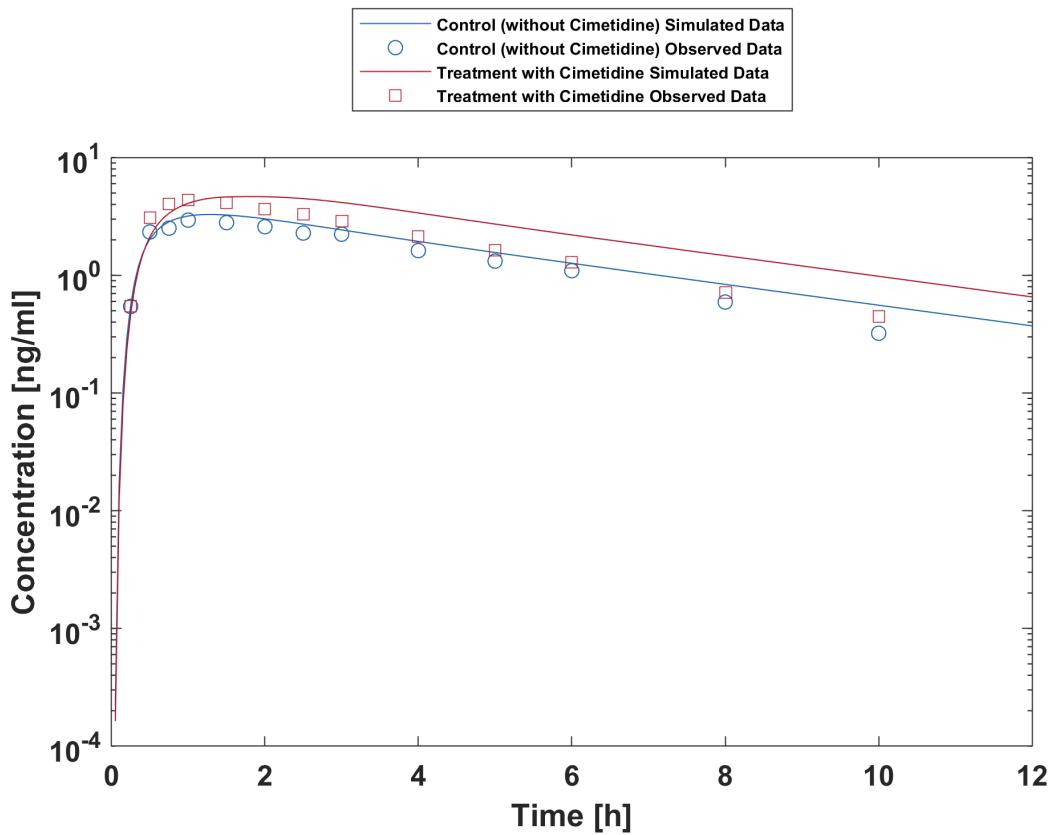


Elliott 1984

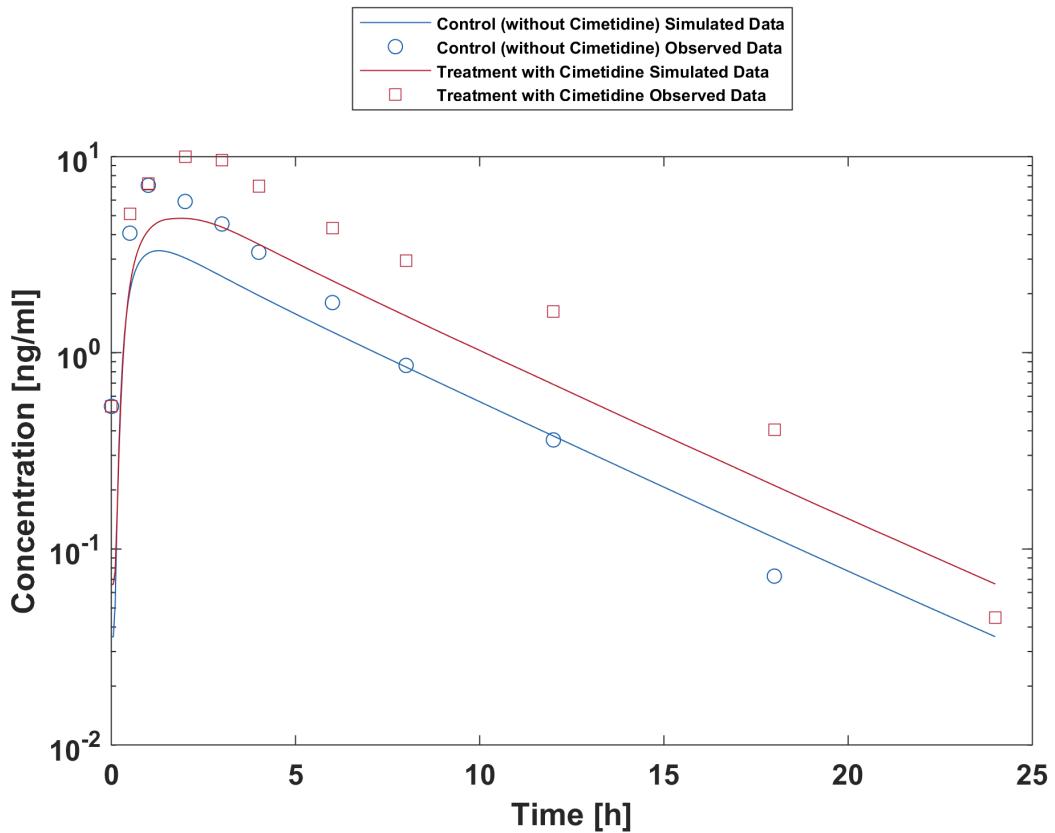
### 3.4 Cimetidine - Triazolam DDI



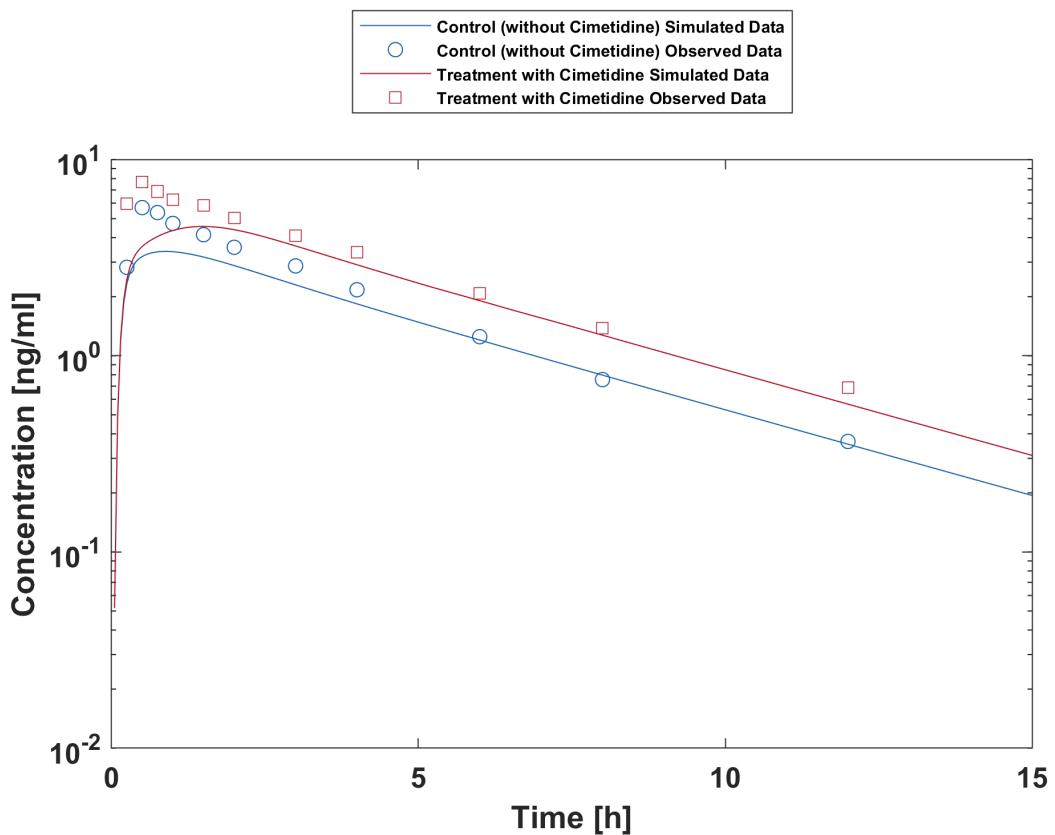
Abernethy 1983



Friedman 1988

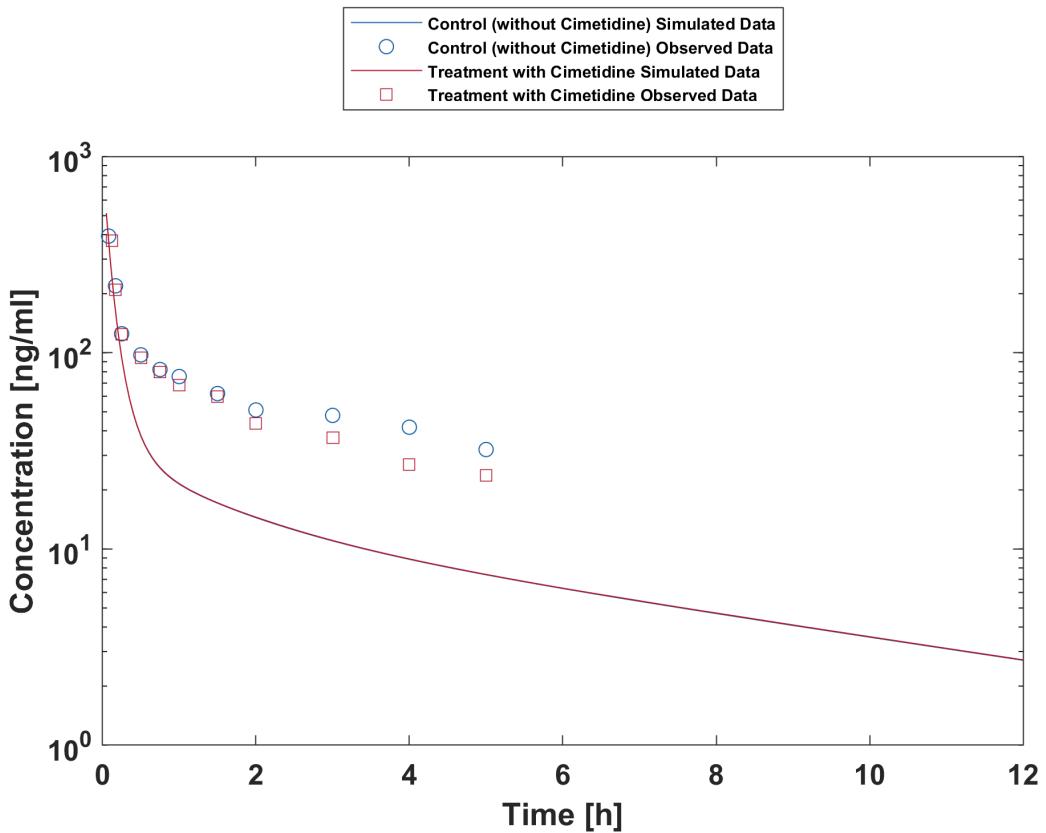


Pourbaix 1985

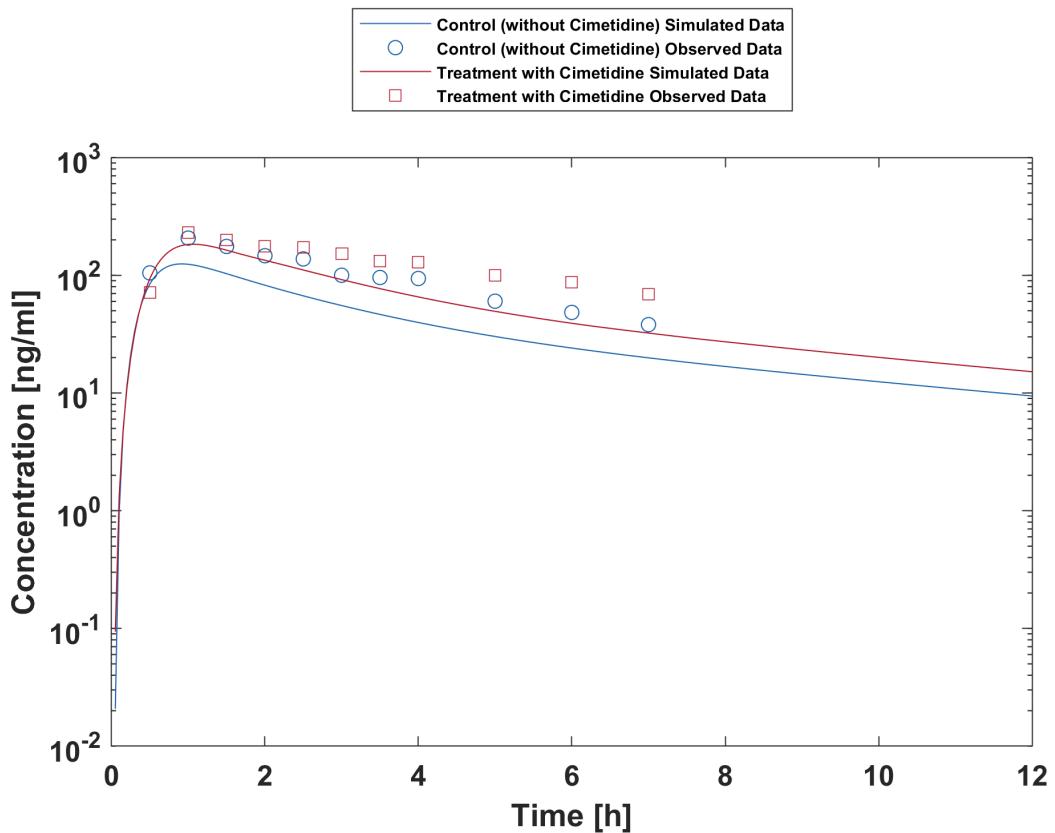


Cox 1986

### 3.5 Cimetidine - Verapamil DDI

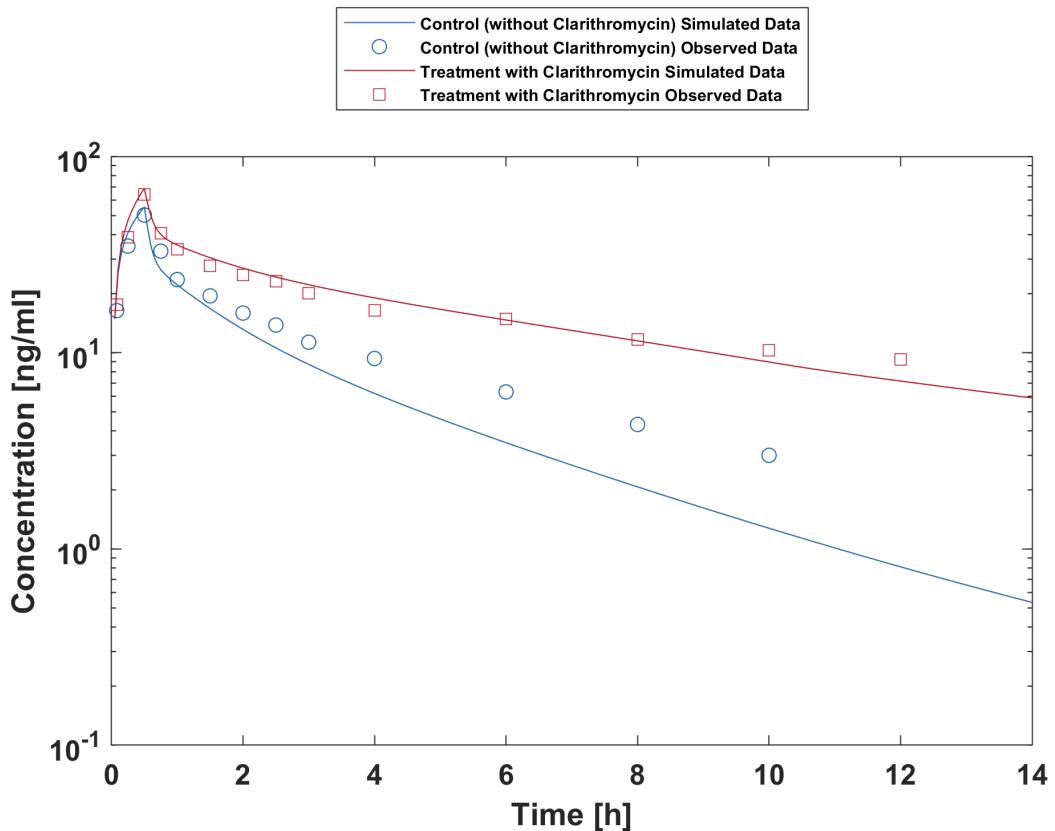


Smith 1984 (verapamil IV)

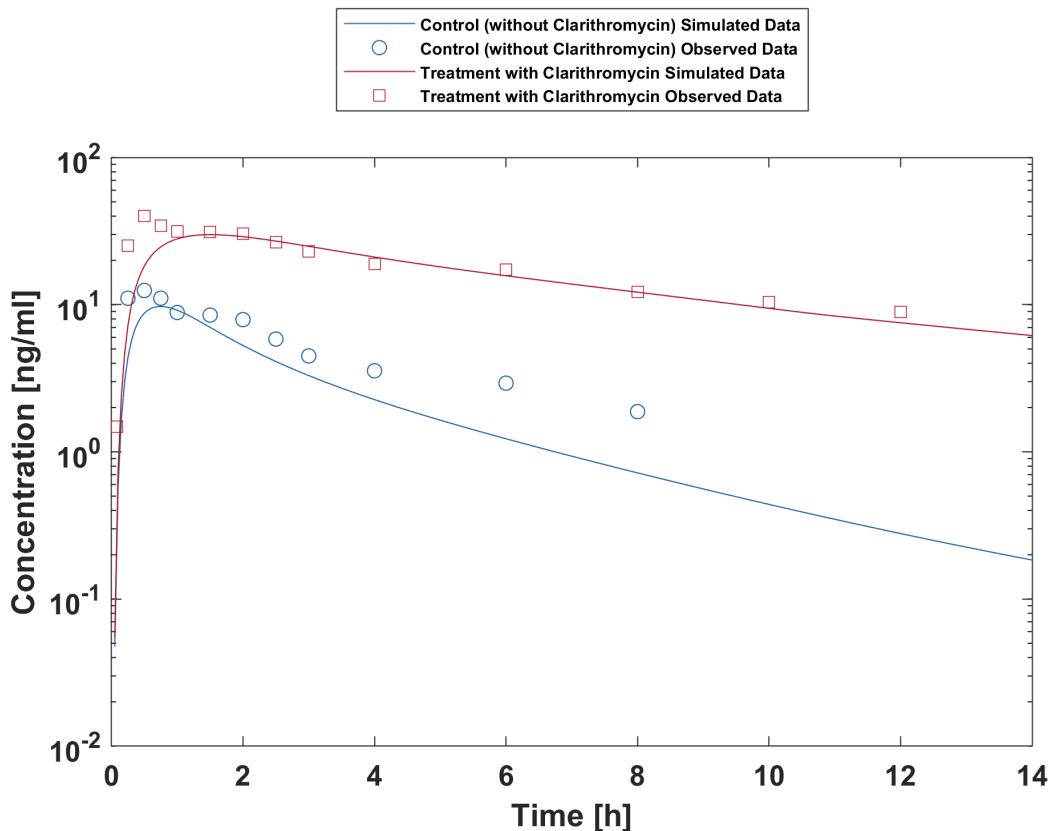


Smith 1984 (verapamil PO)

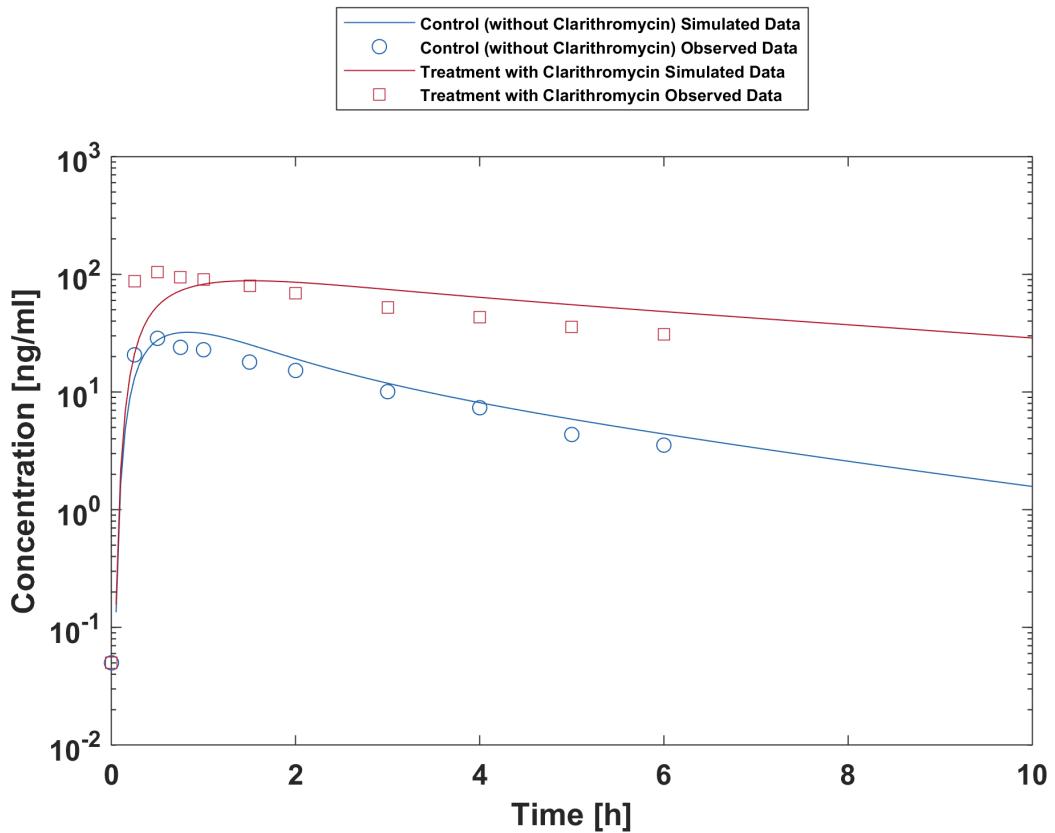
### 3.6 Clarithromycin - Midazolam DDI



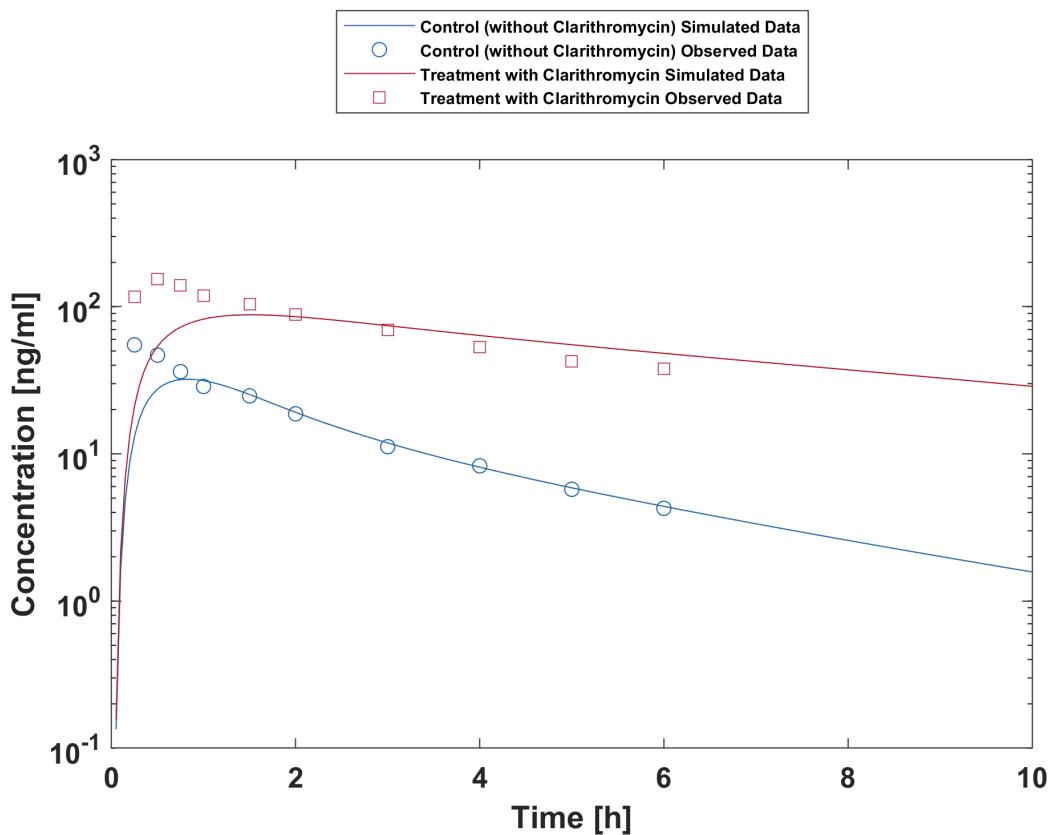
Gorski 1998 (midazolam IV)



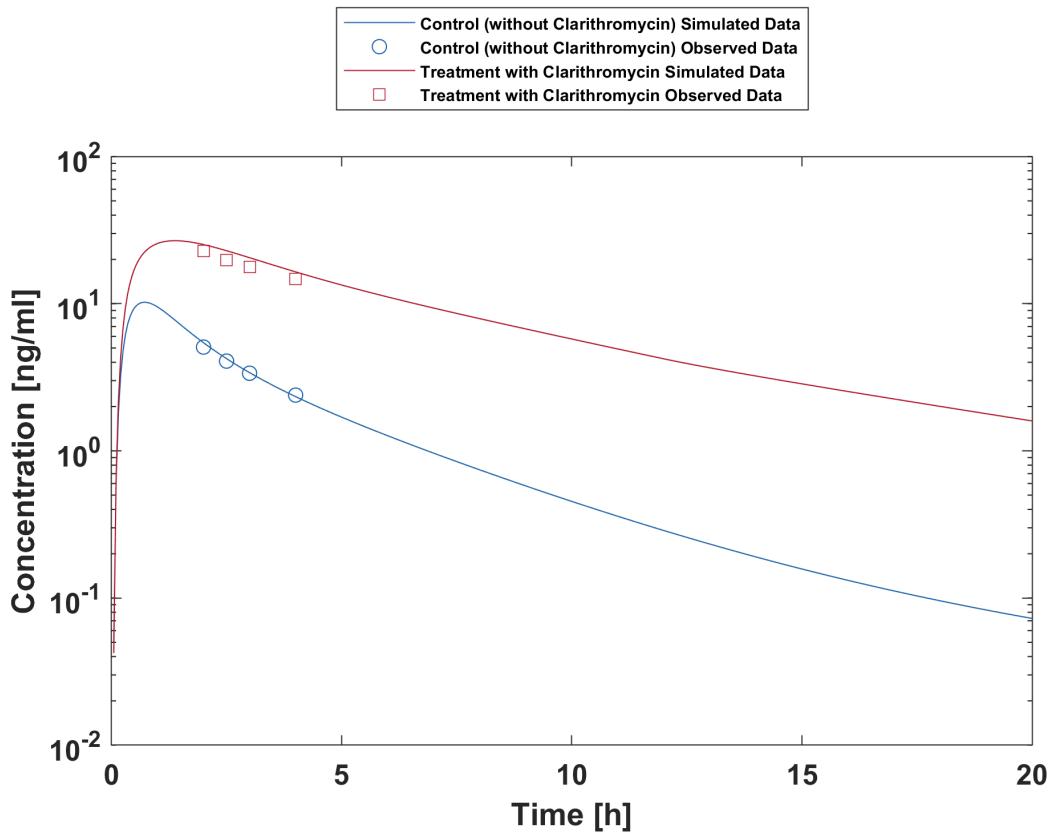
Gorski 1998 (midazolam po)



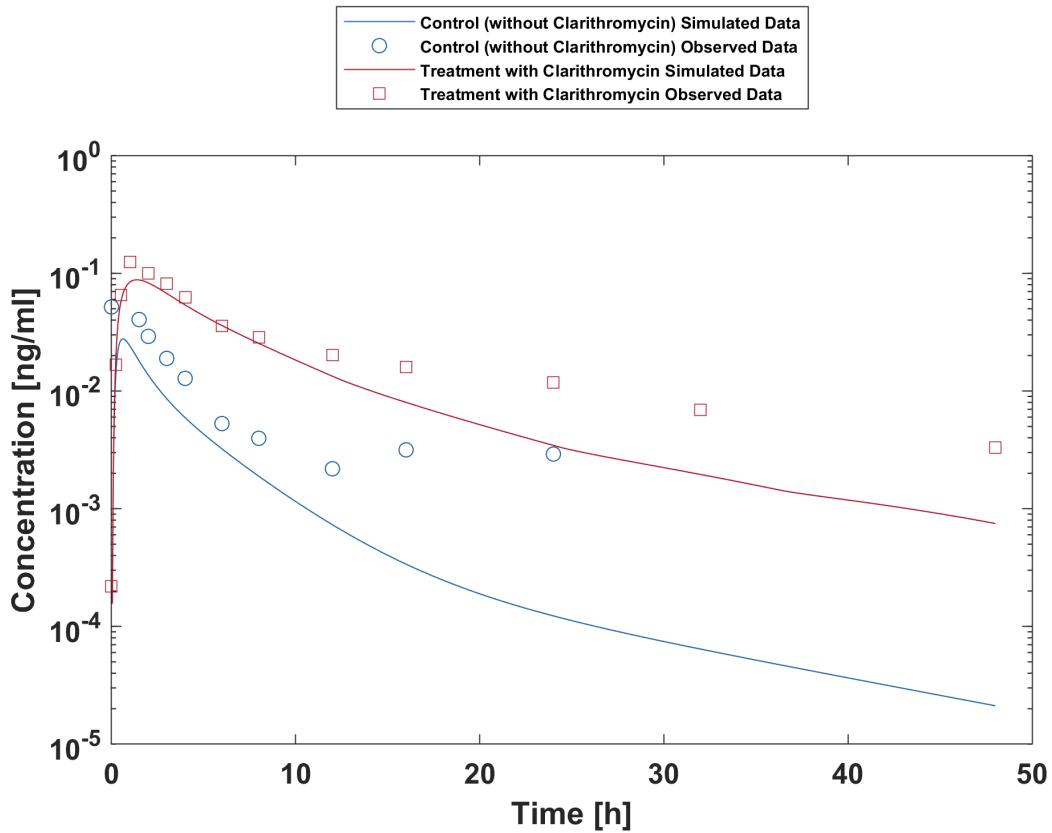
Gurley 2006



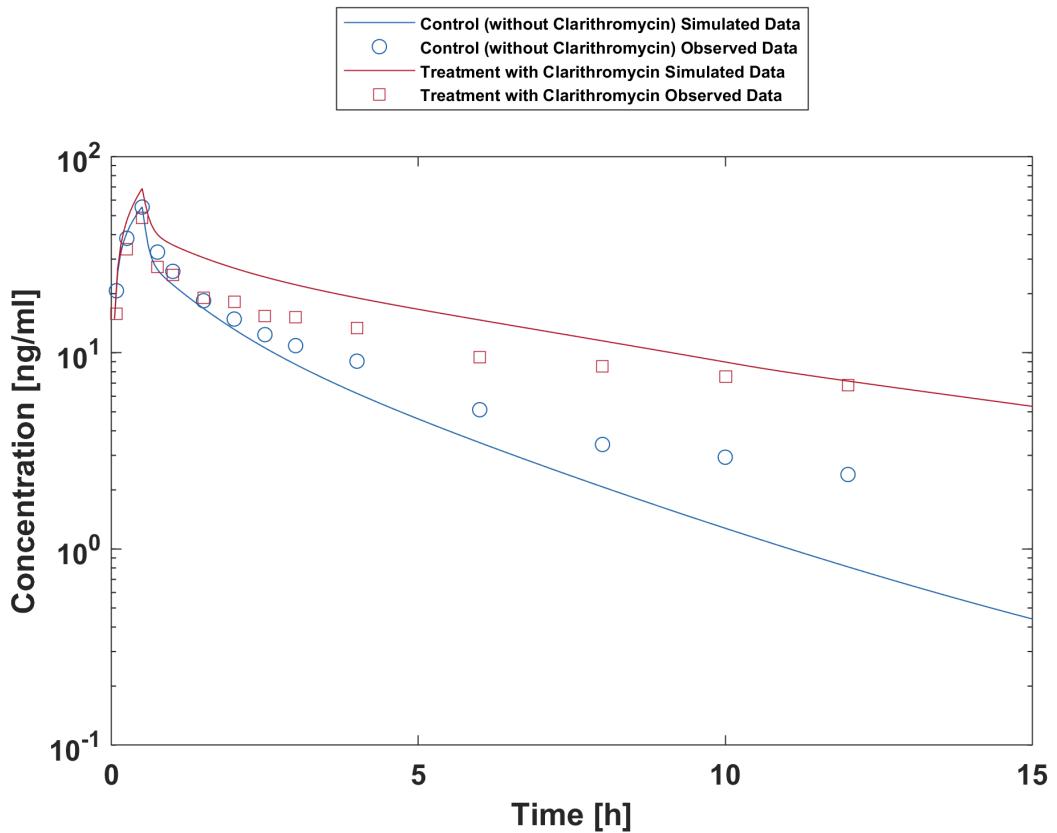
Gurley 2008a



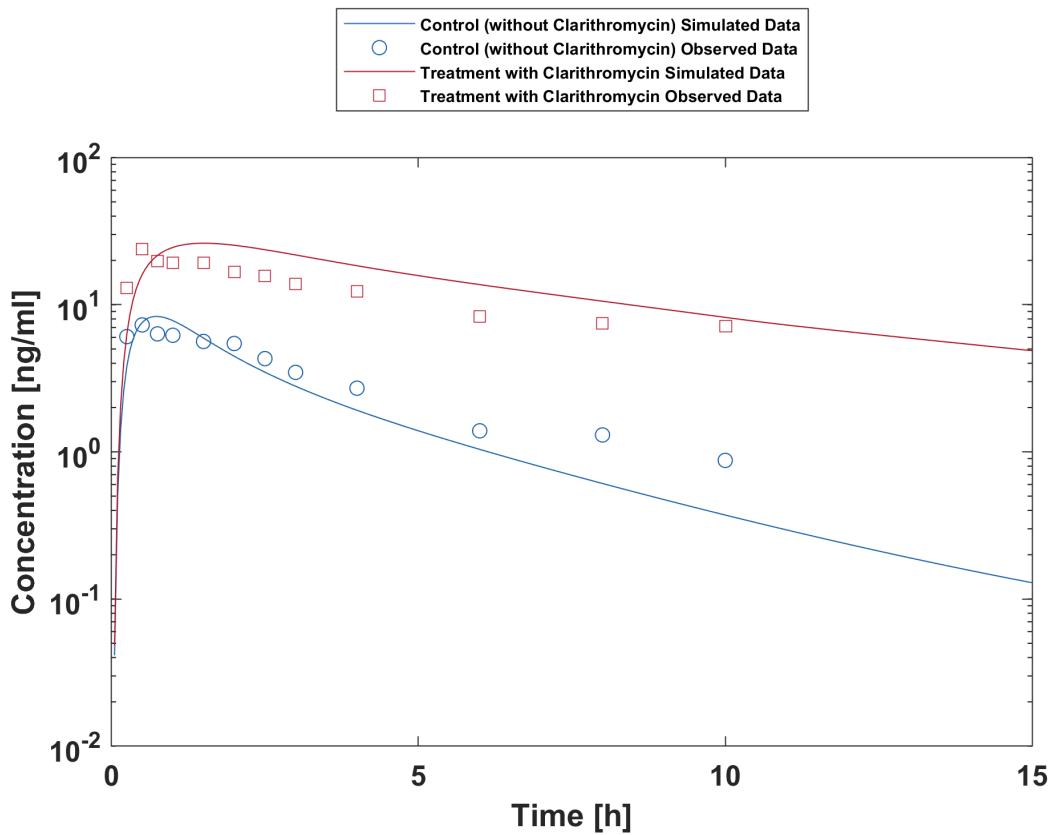
Markert 2013



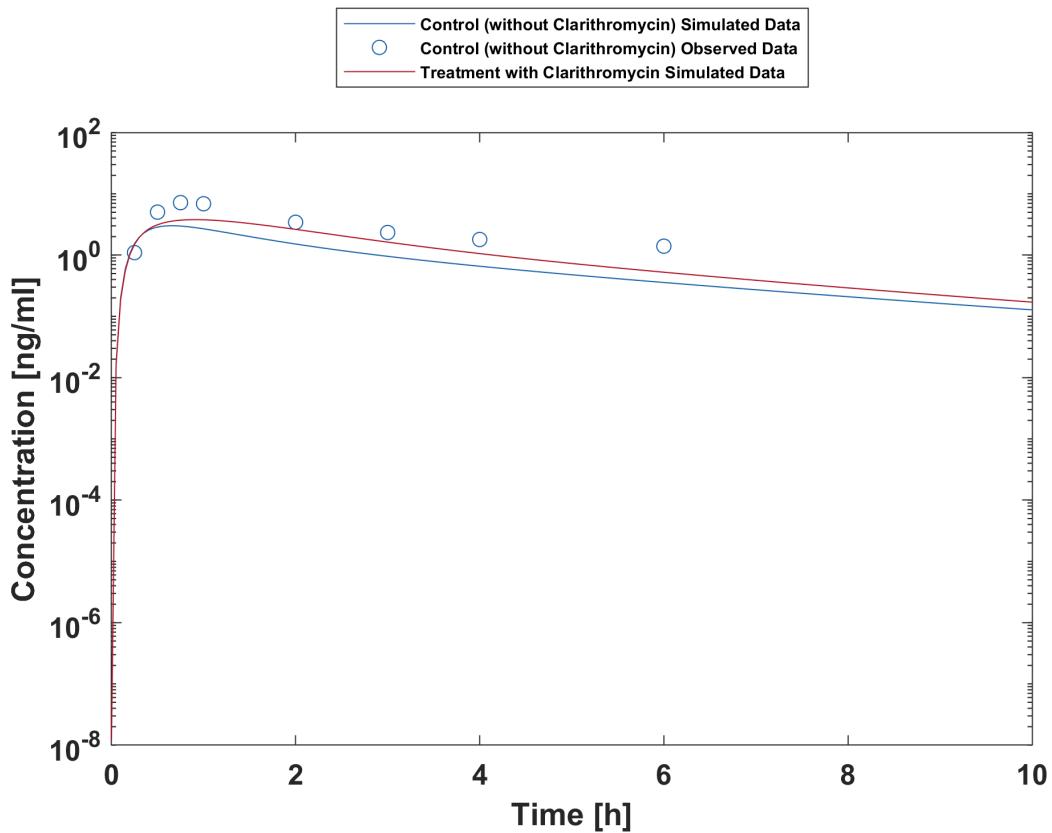
Pruksaritanont 2017



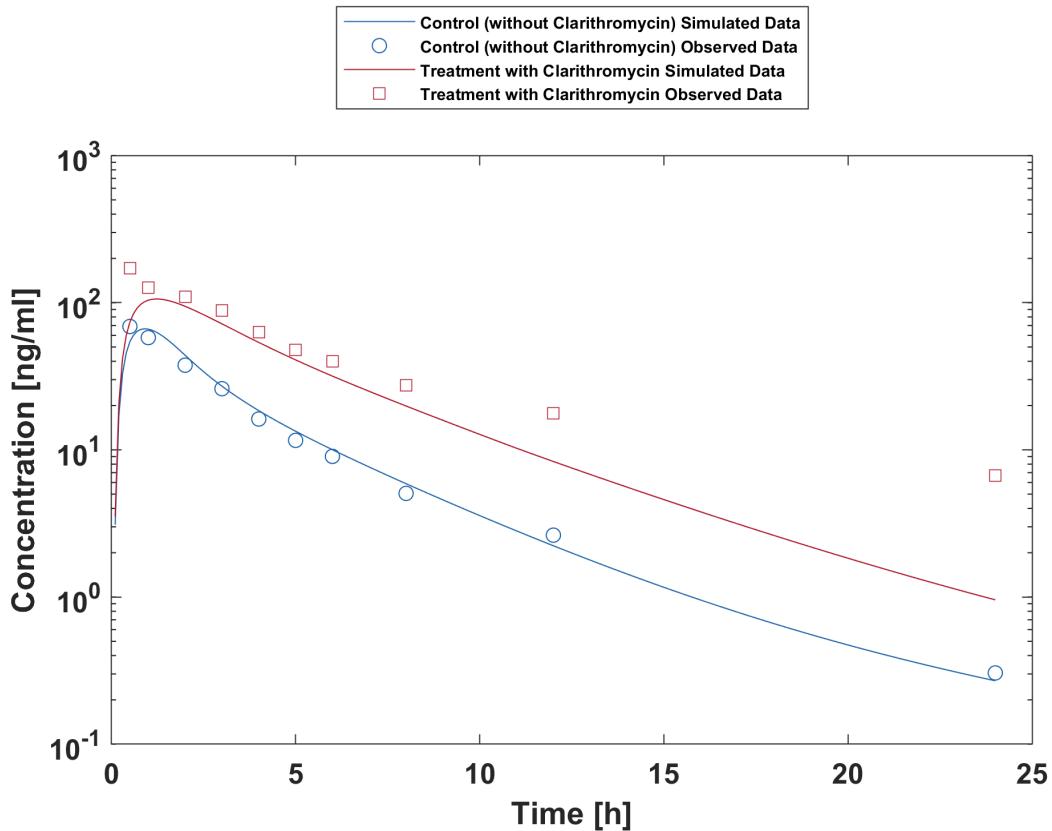
Quinney 2008 (midazolam IV)



Quinney 2008 (midazolam po)

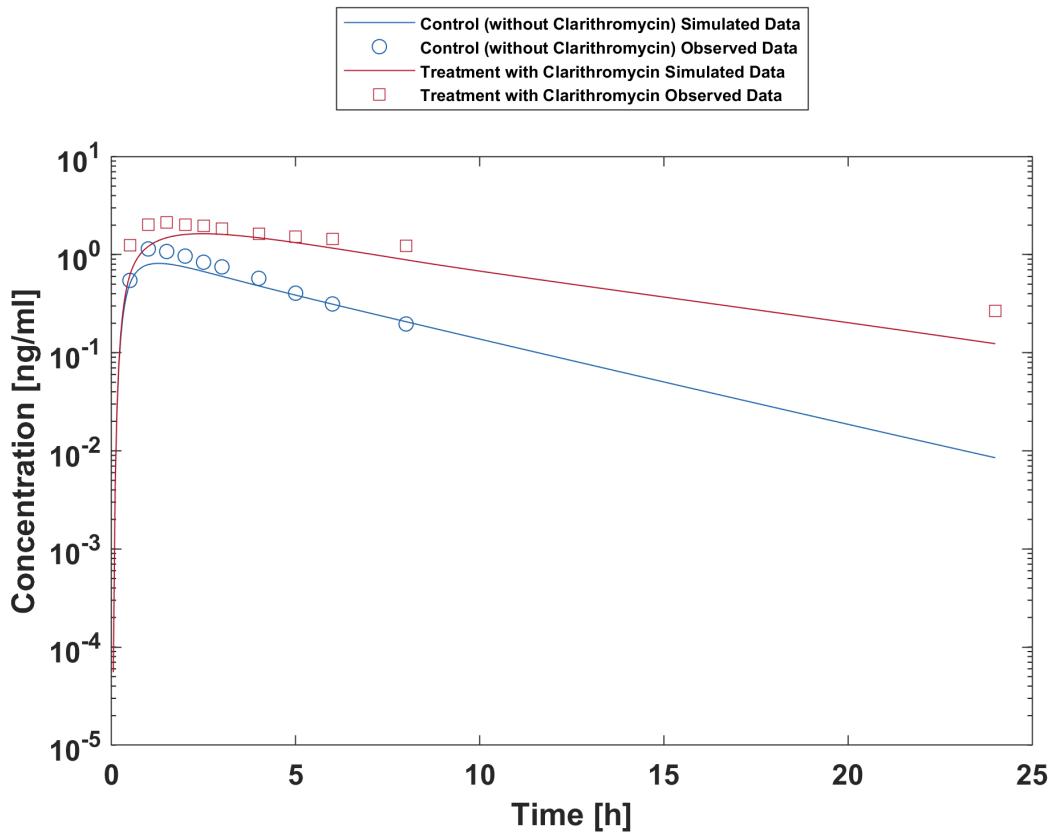


van Dyk 2018



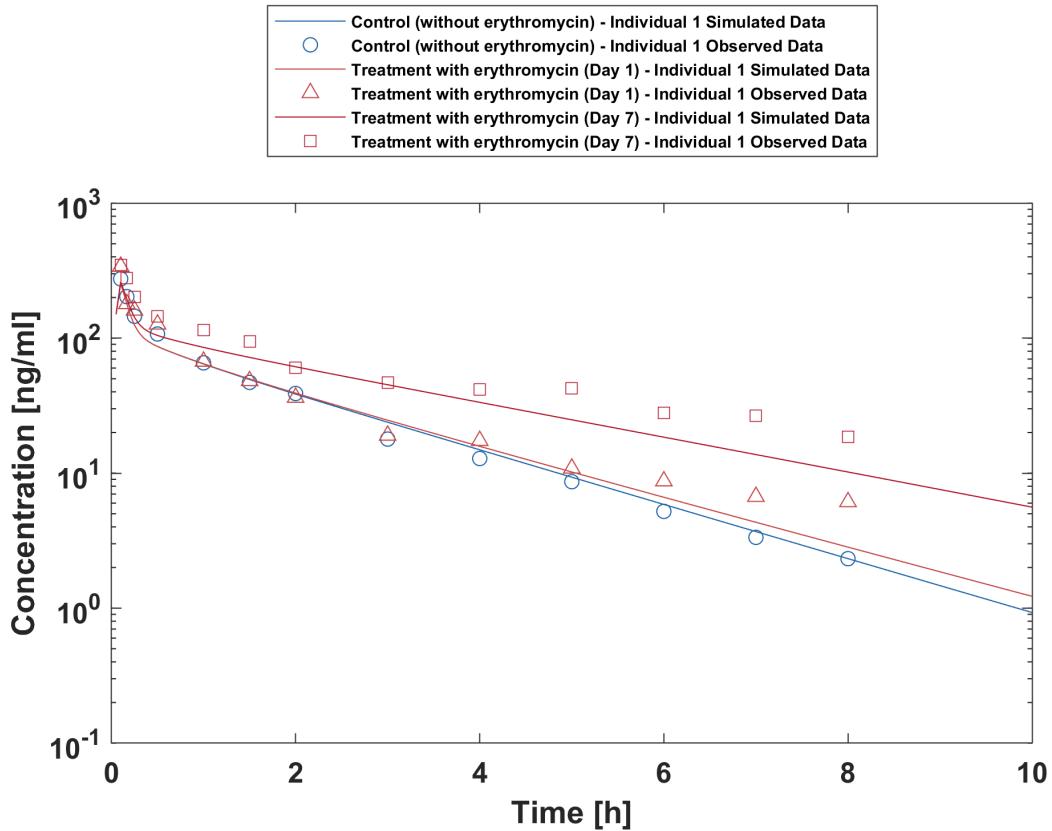
Yeates 1996

### 3.7 Clarithromycin - Triazolam DDI

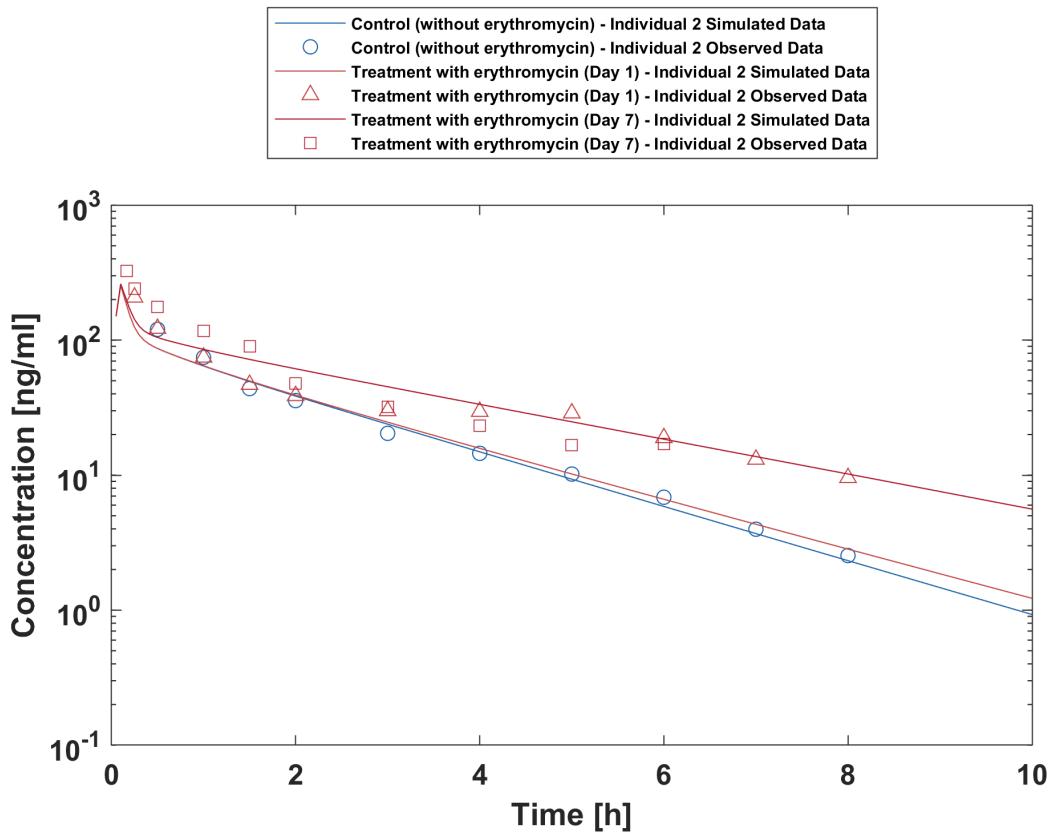


Greenblatt 1998a

### 3.8 Erythromycin - Alfentanil DDI

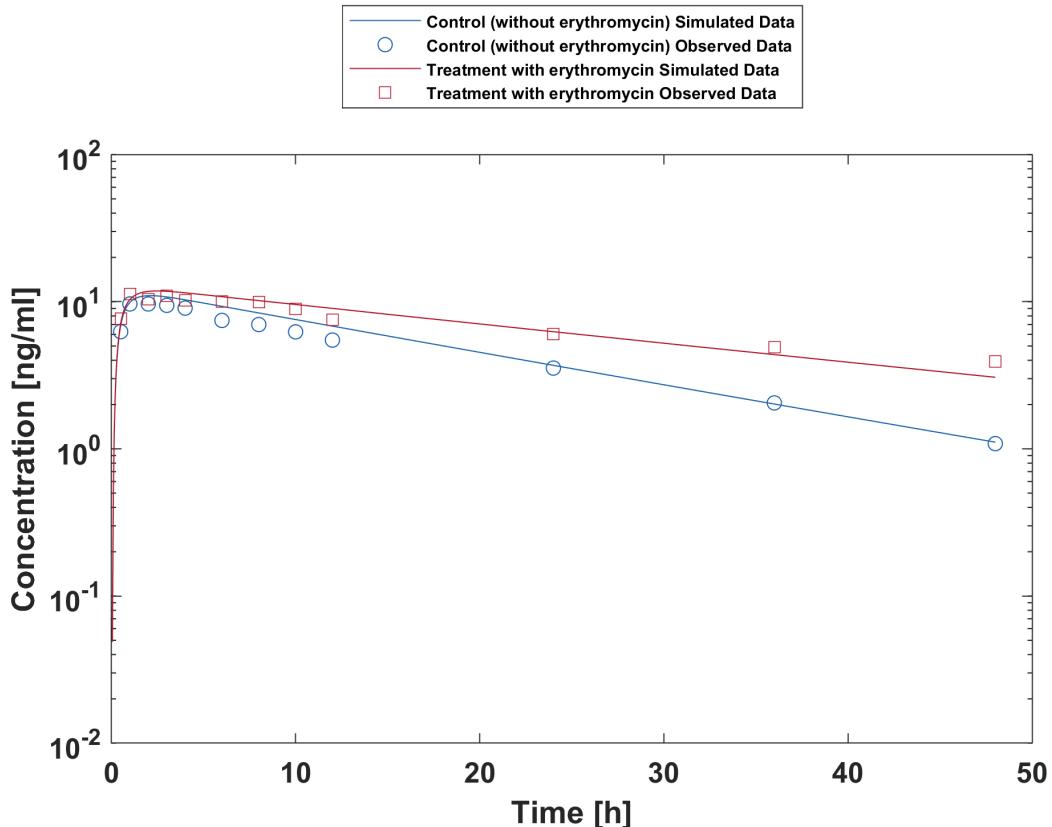


Bartkowski 1989



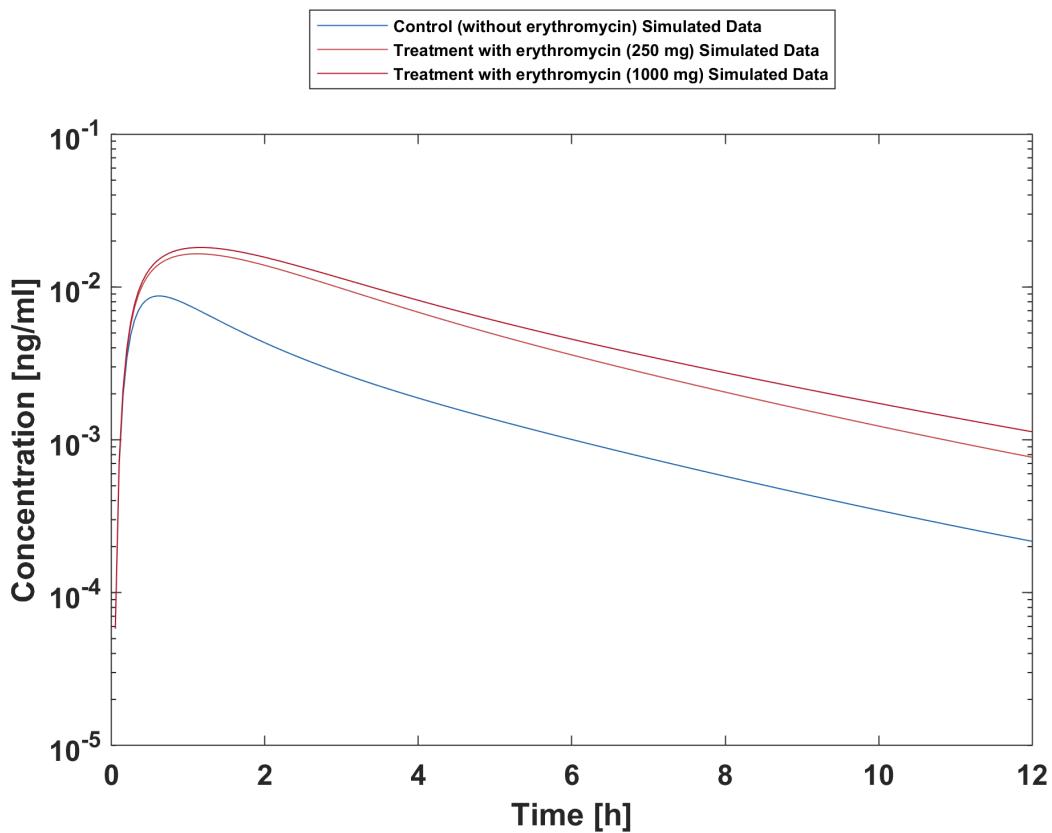
Bartkowski 1993

### 3.9 Erythromycin - Alprazolam DDI

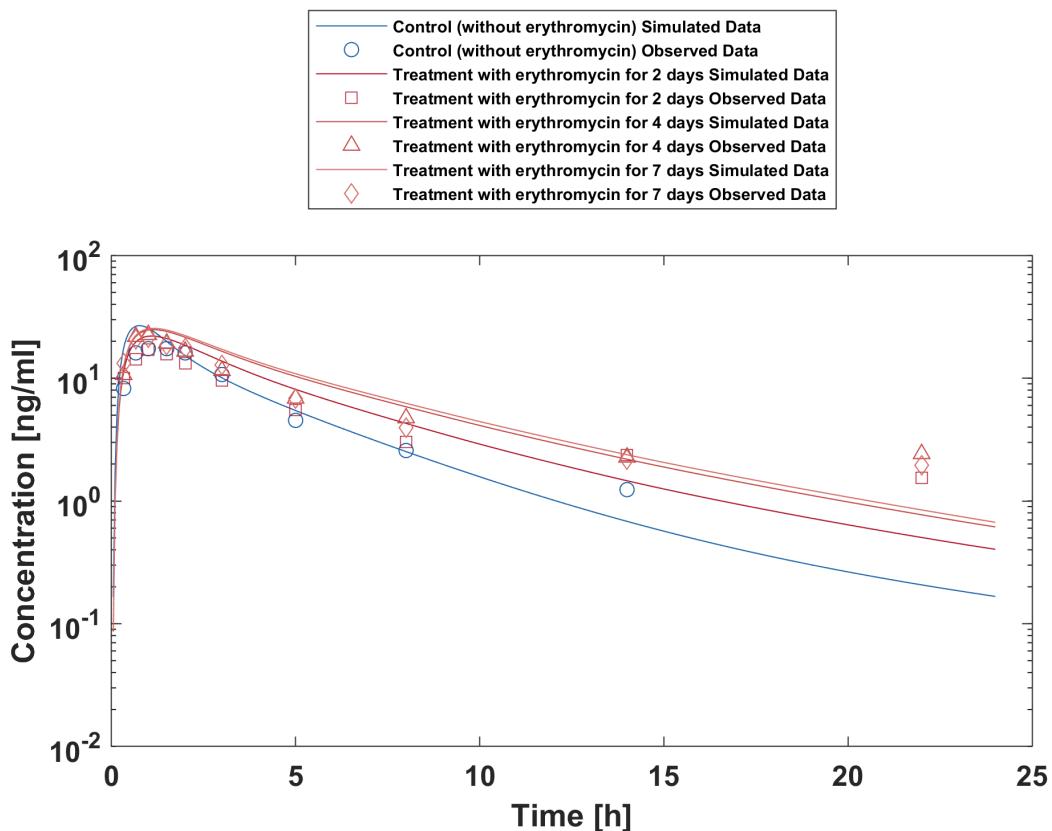


Yasui 1996

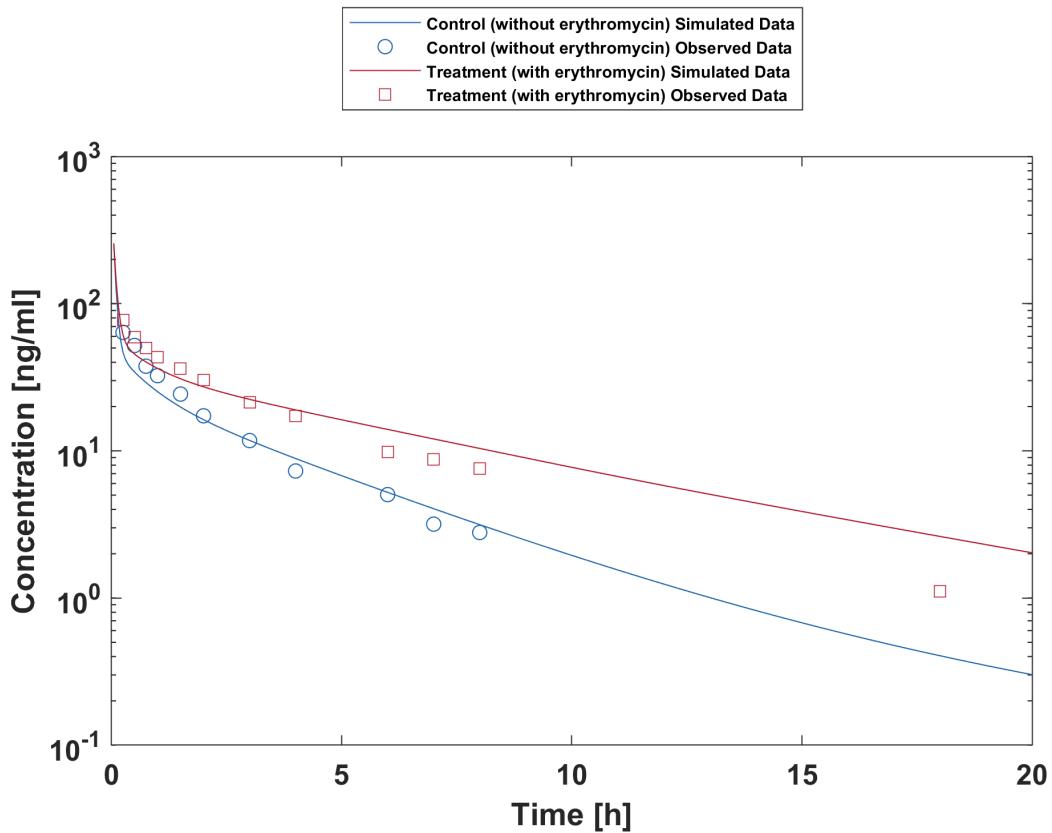
### 3.10 Erythromycin - Midazolam DDI



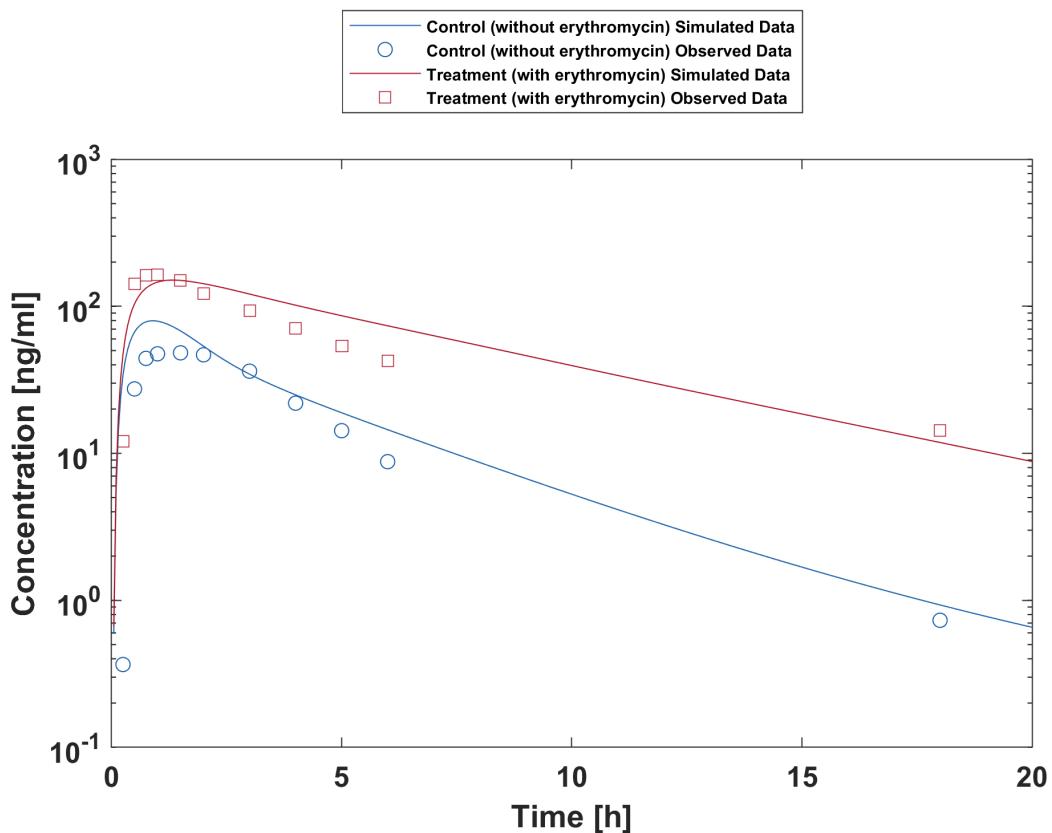
Carls 2014



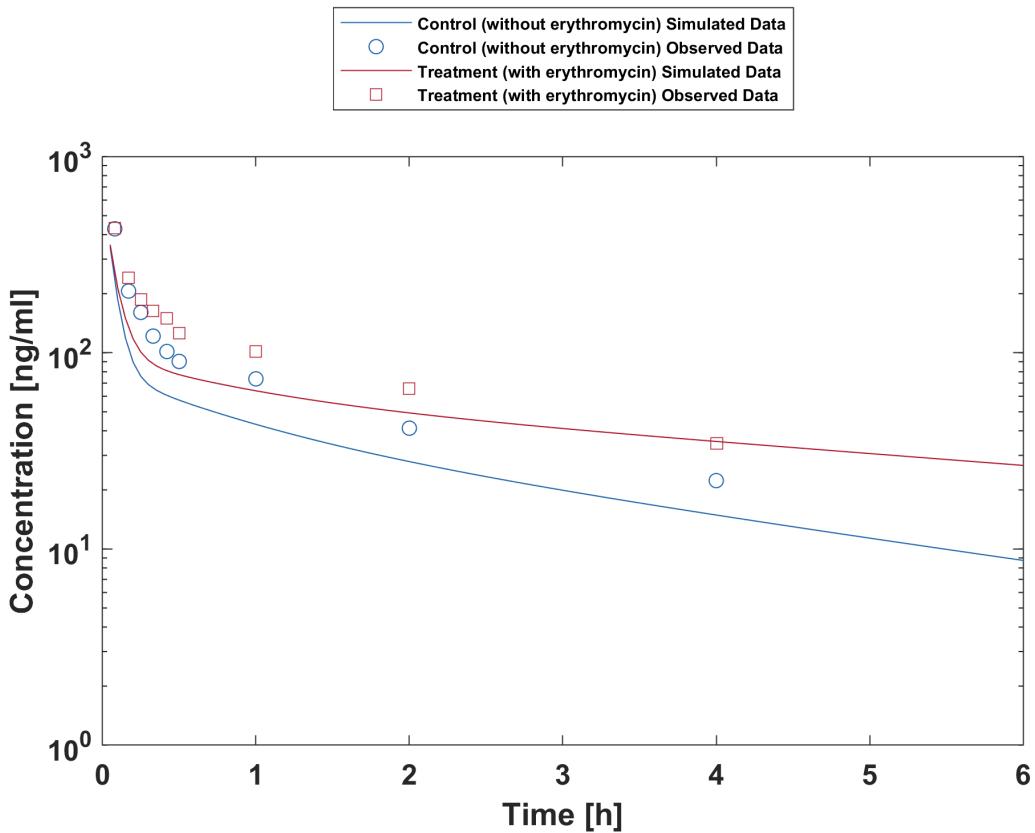
Okudaira 2007



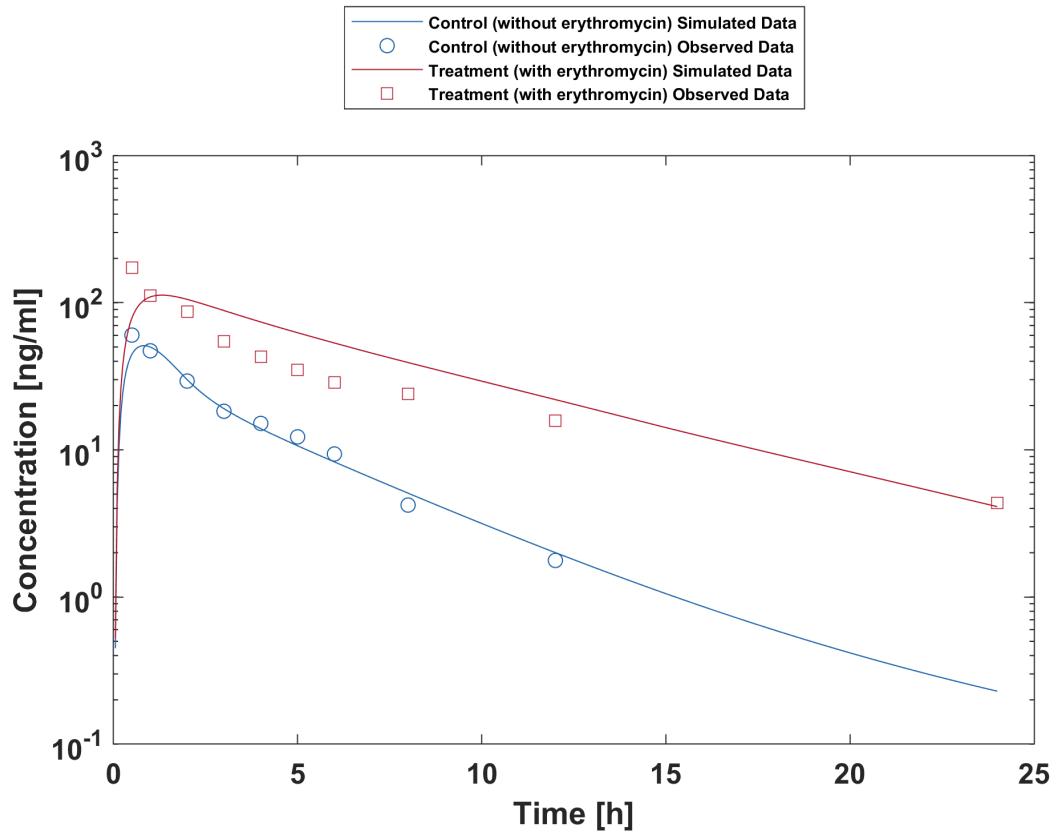
Olkola 1993 (midazolam IV)



Olkola 1993 (midazolam po)

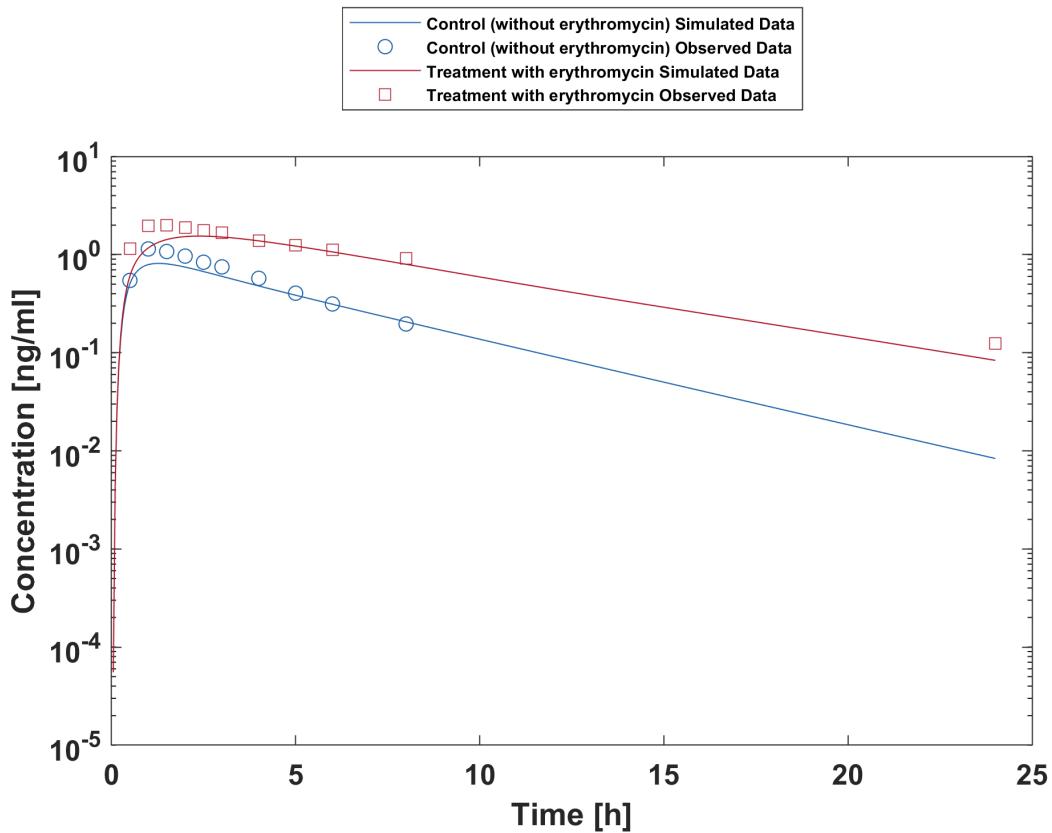


Swart 2002

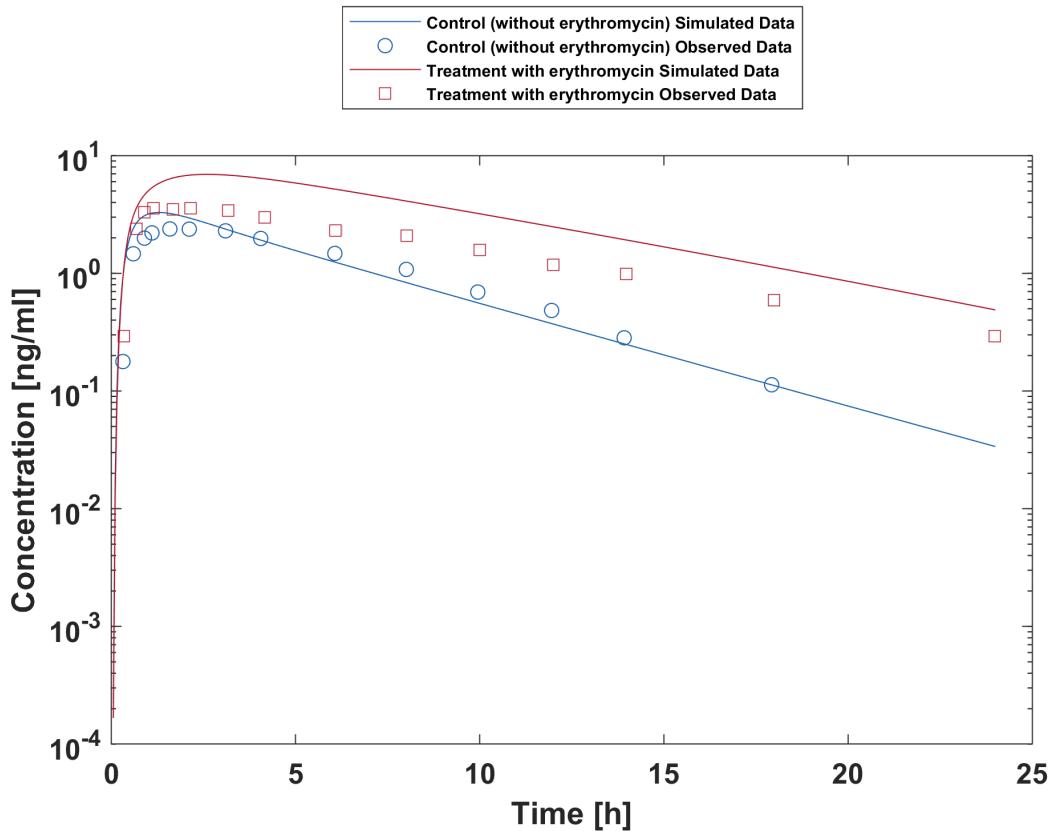


Zimmermann 1996

### 3.11 Erythromycin - Triazolam DDI

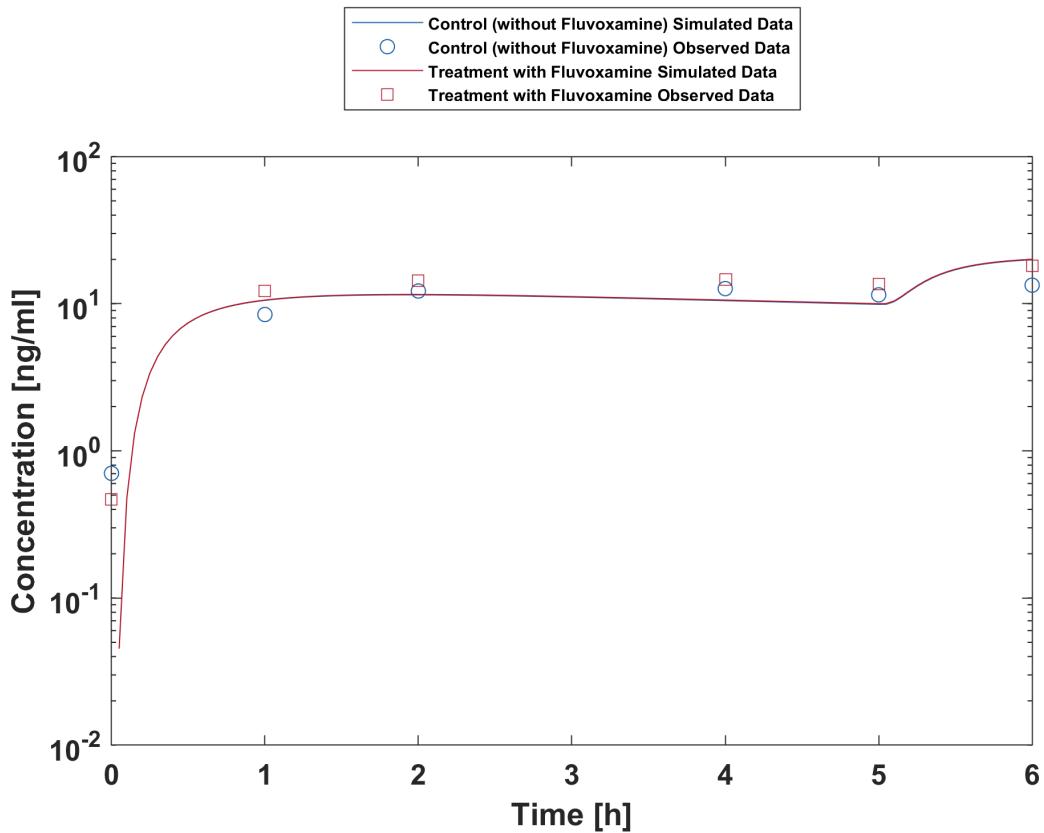


Greenblatt 1998

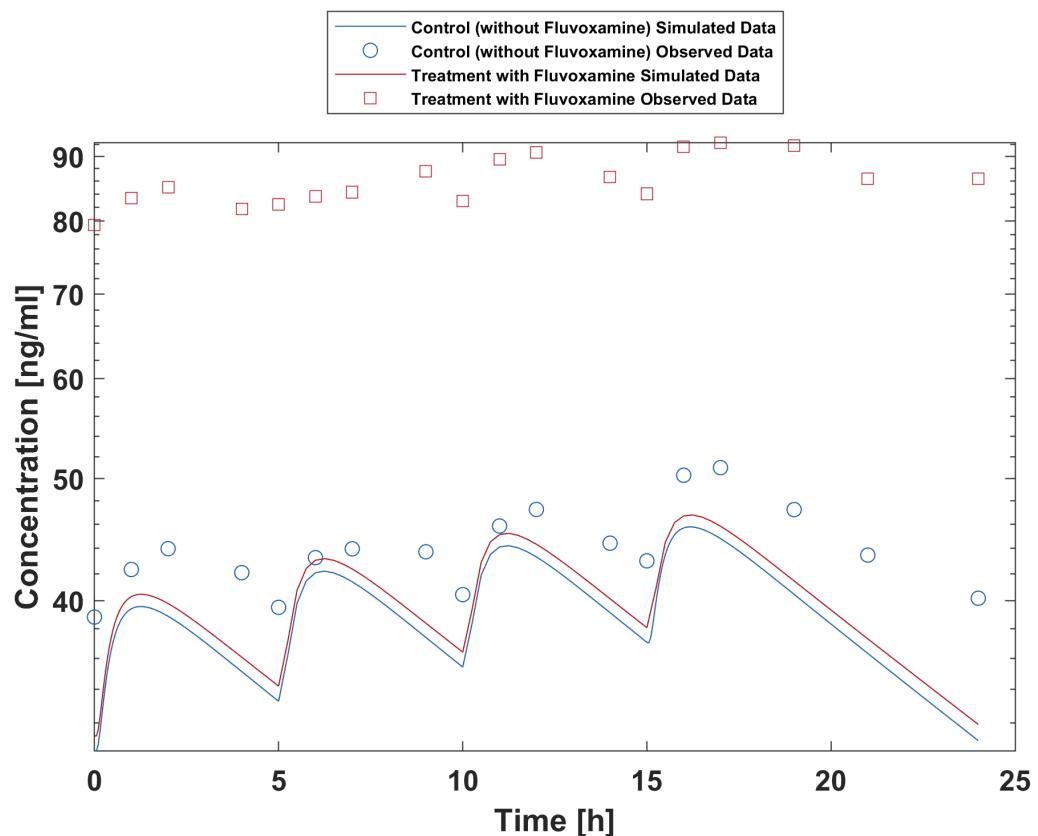


Phillips 1986

### 3.12 Fluvoxamine - Alprazolam DDI

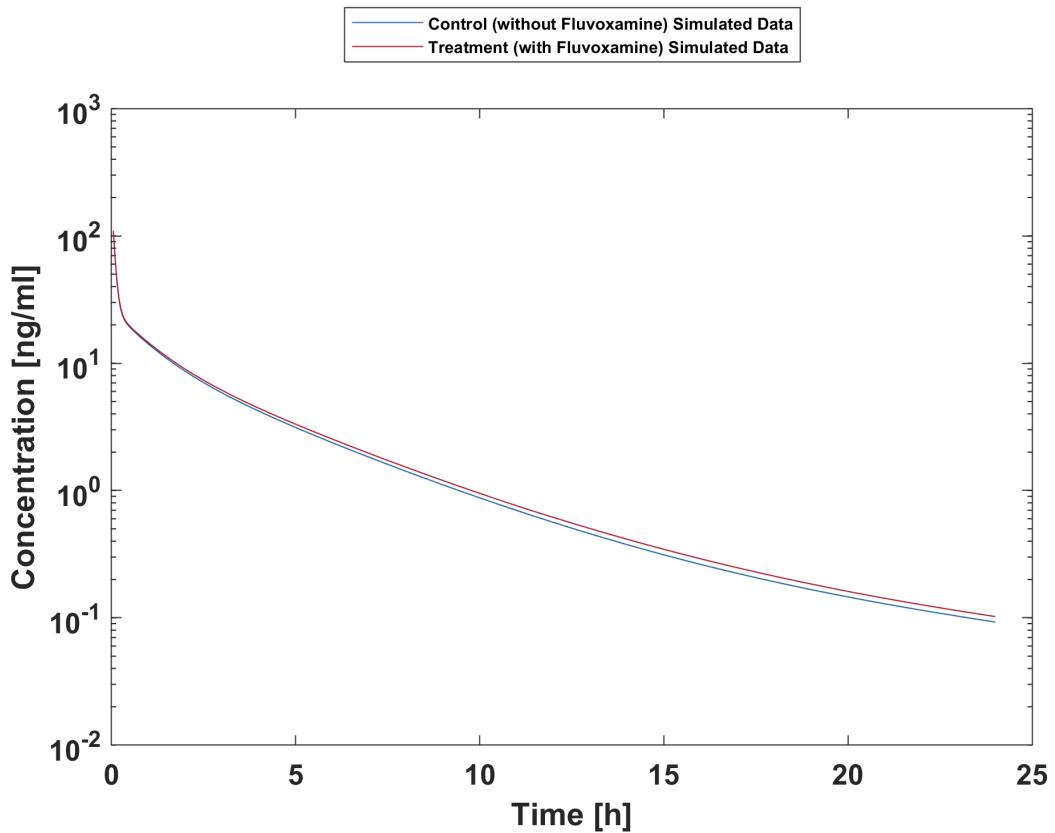


Fleishaker 1994 (Day 1, first dose)

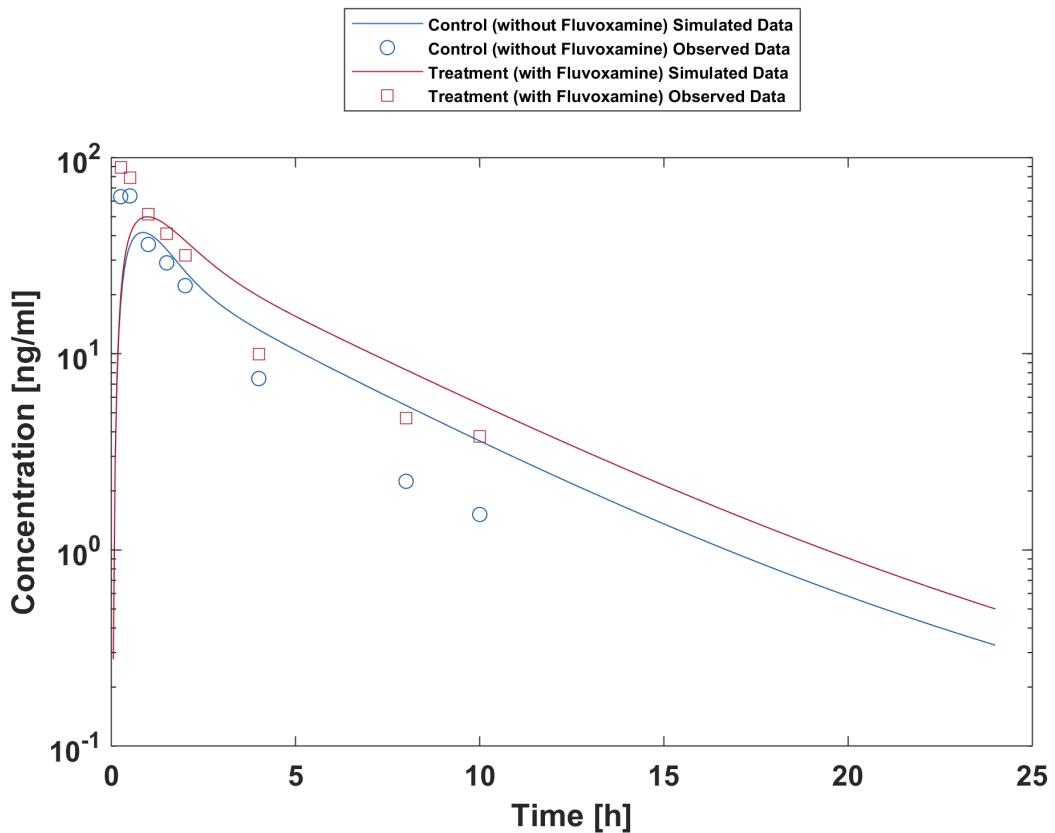


Fleishaker 1994 (Day 10)

### 3.13 Fluvoxamine - Midazolam DDI

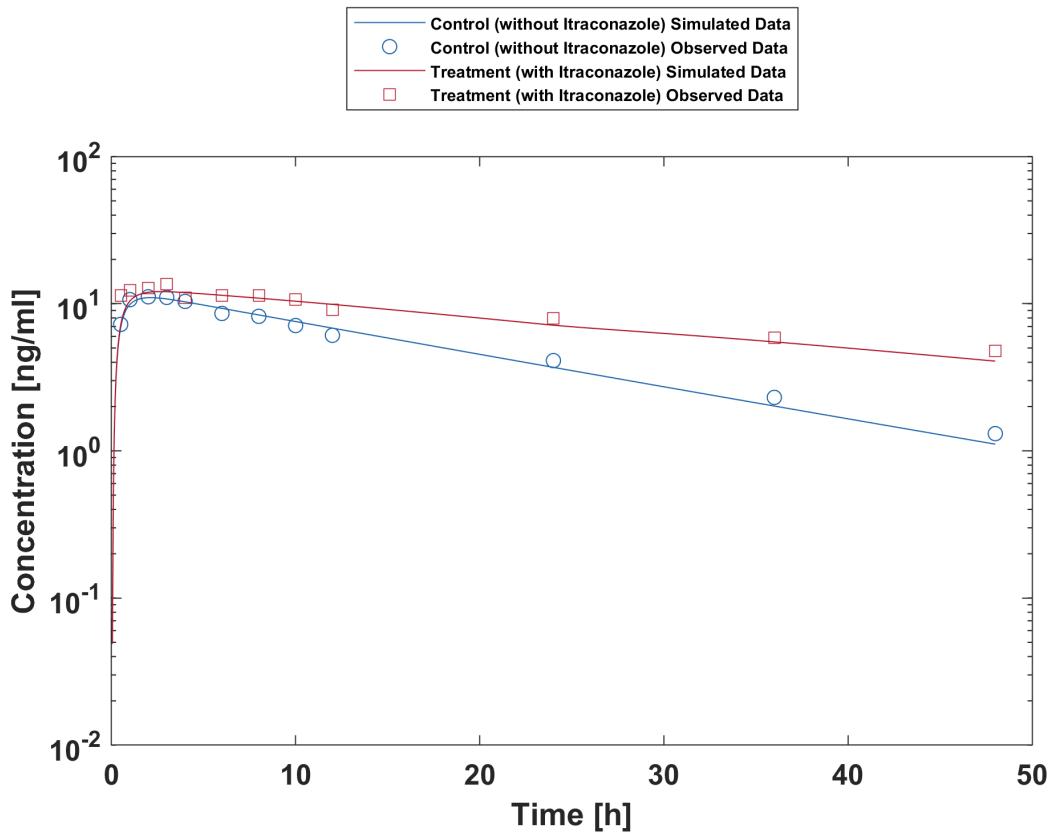


Kashuba 1998



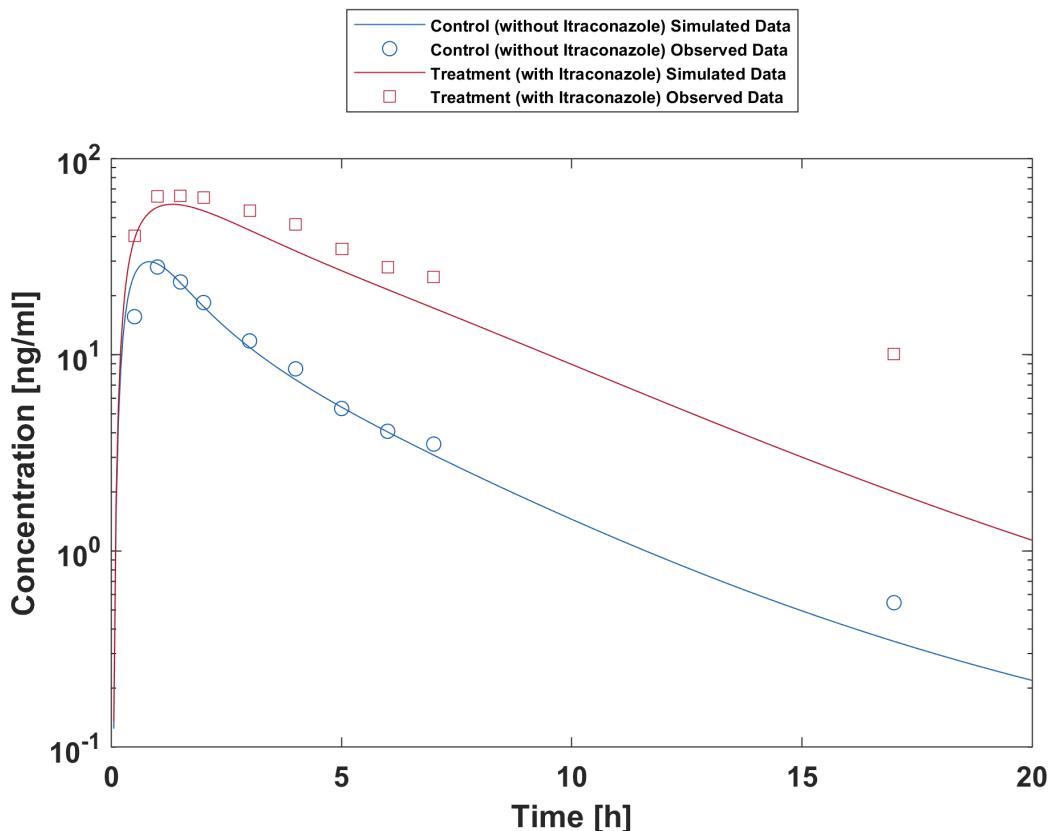
Lam 2003

### 3.14 Itraconazole - Alprazolam DDI

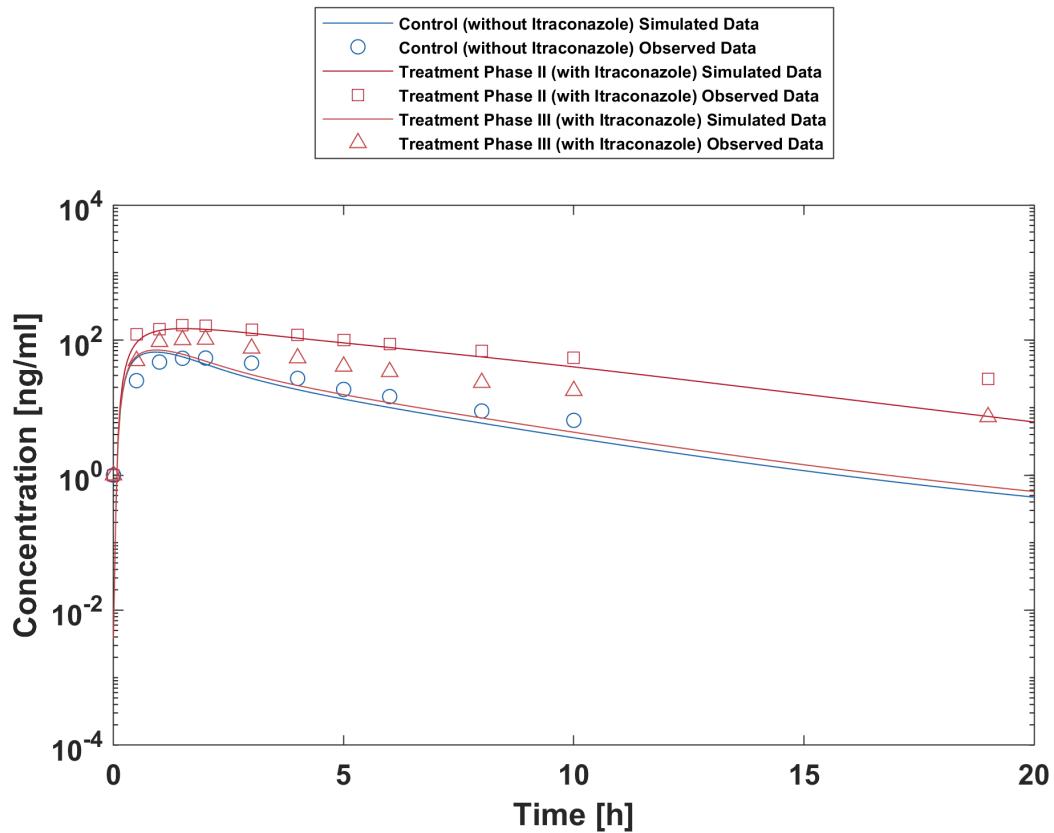


Yasui 1998

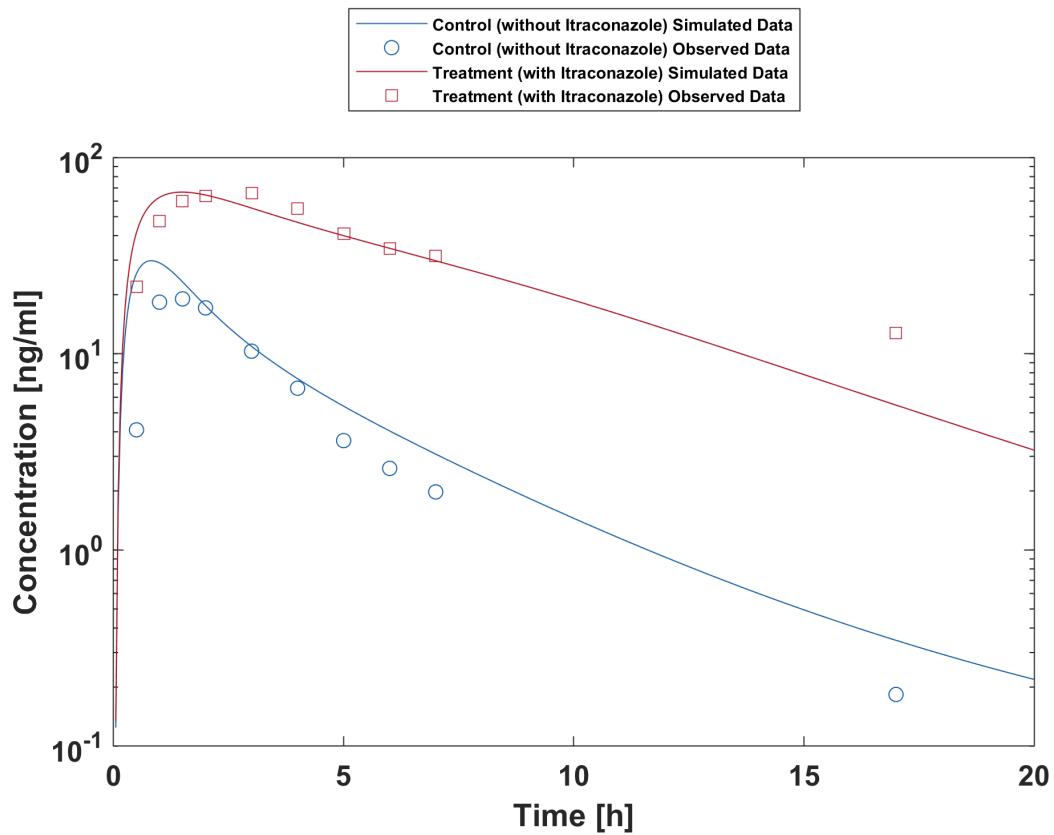
### 3.15 Itraconazole - Midazolam DDI



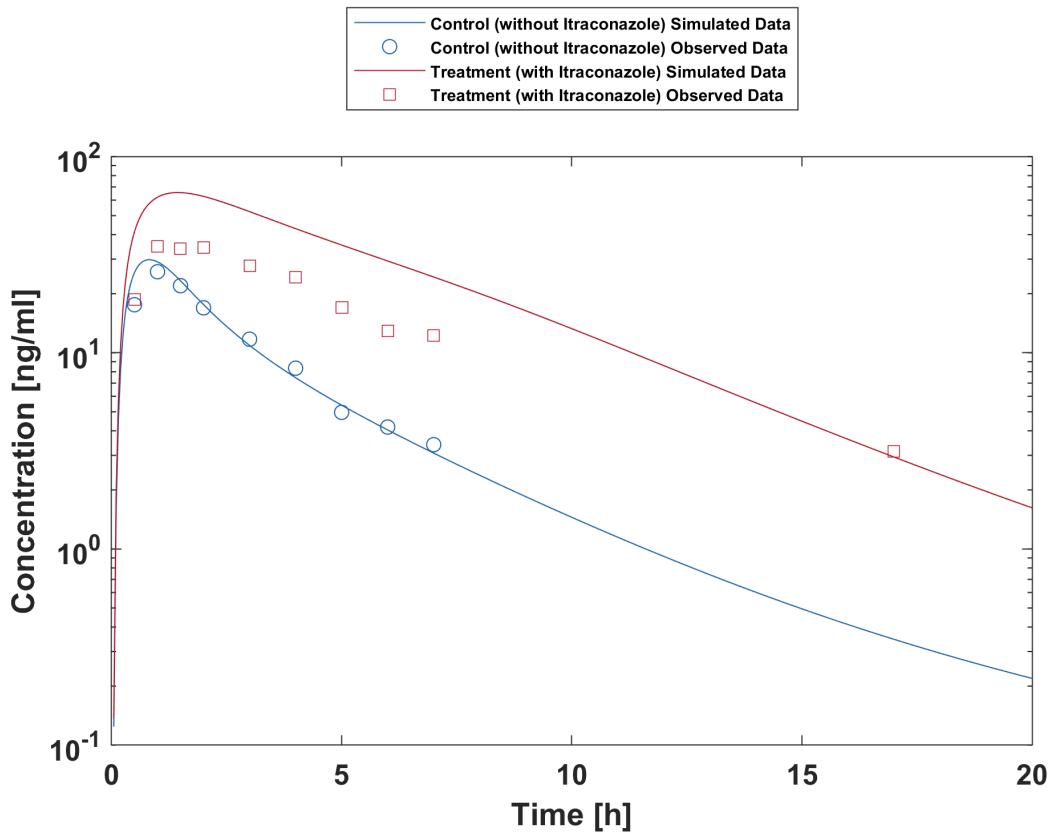
Ahonen 1995



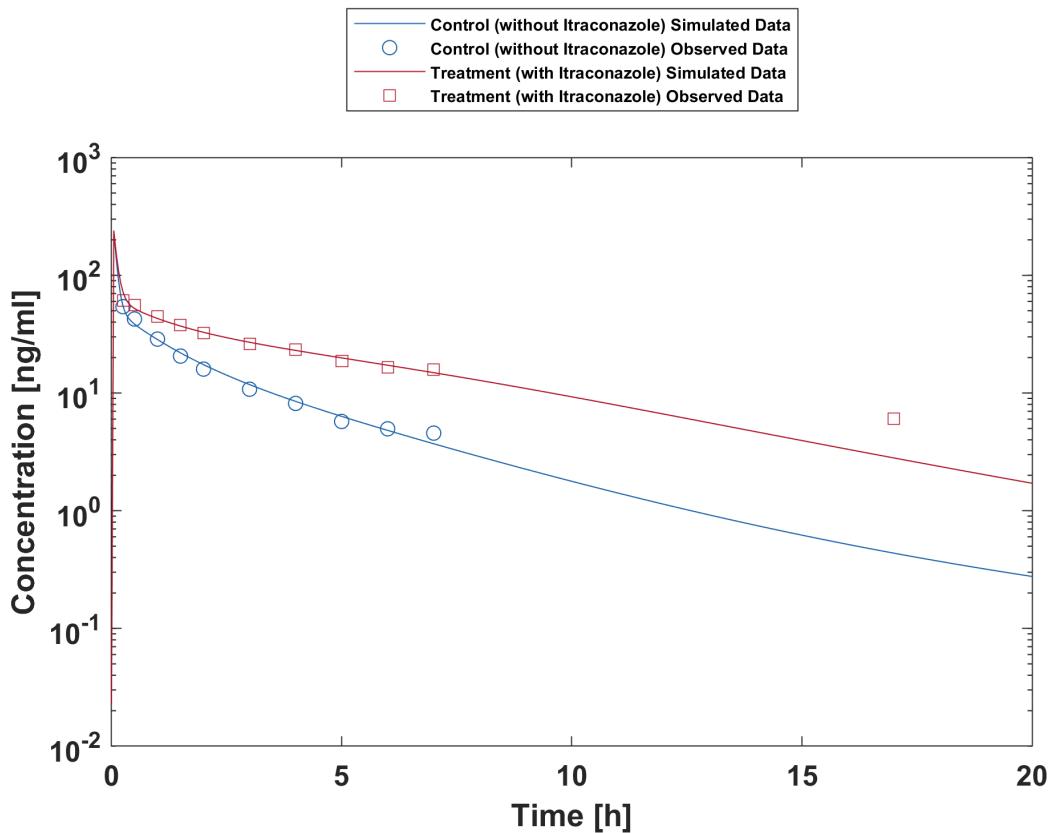
Backman 1998



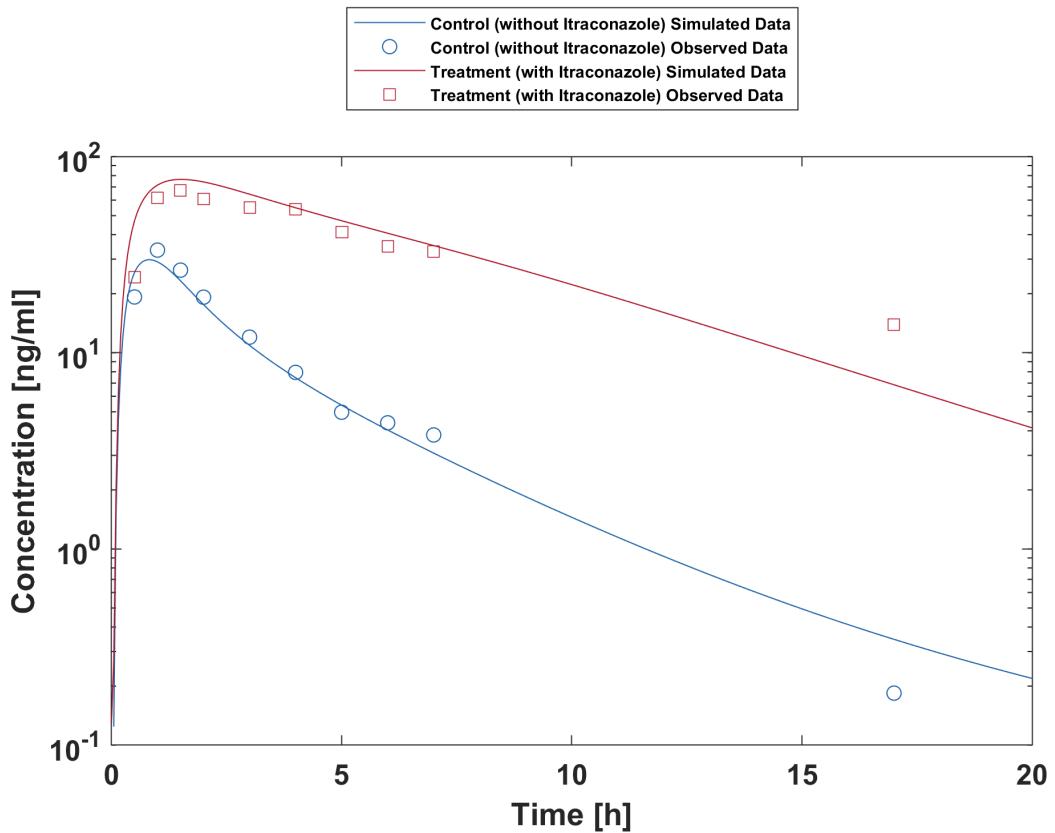
Olkola 1994



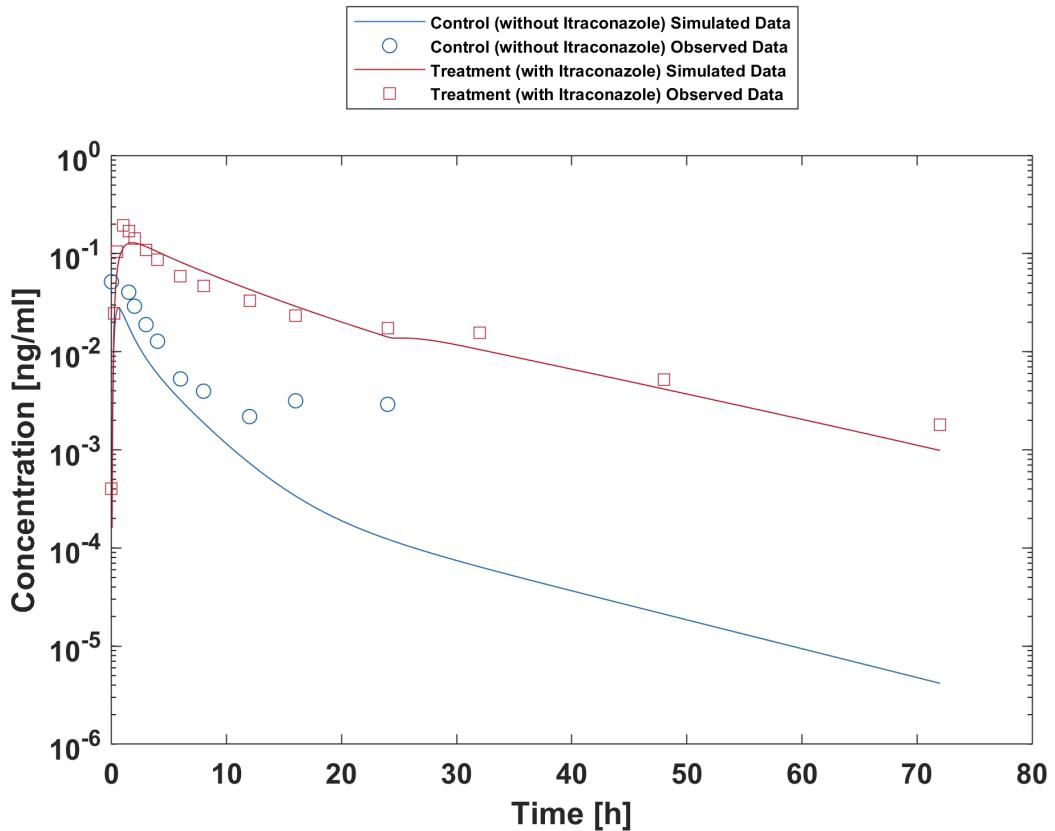
Olkola 1996 (day 1 po)



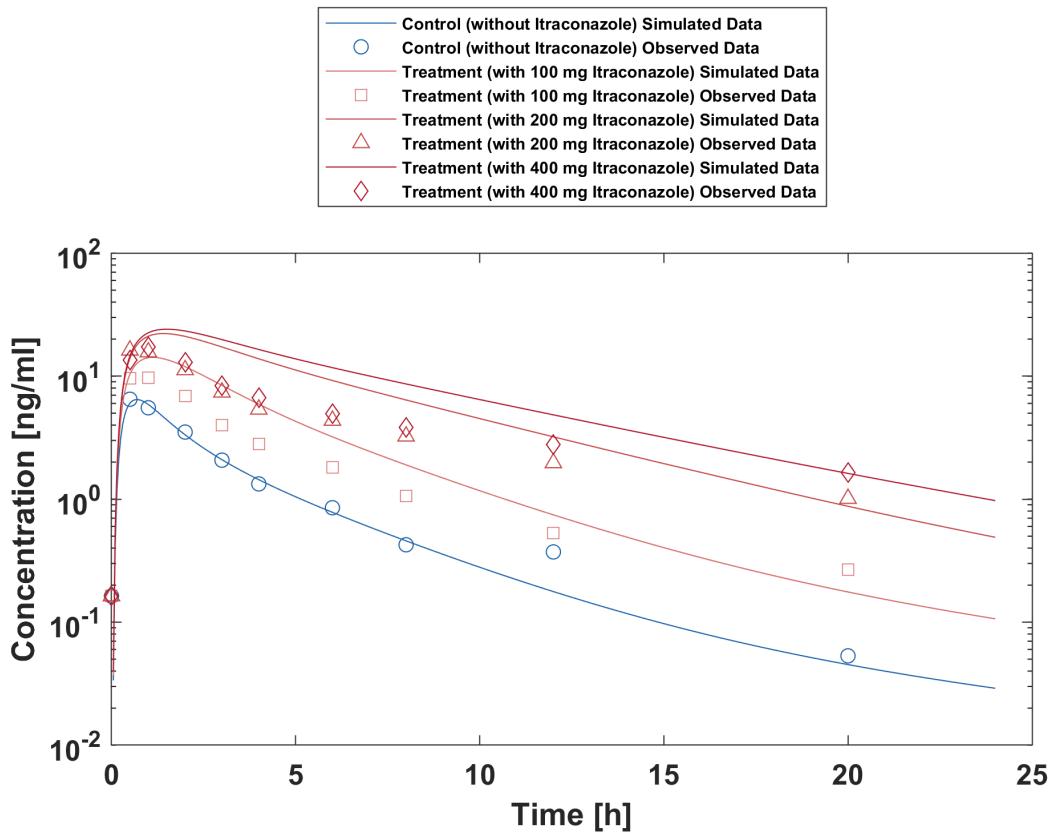
Olkola 1996 (day 4 iv)



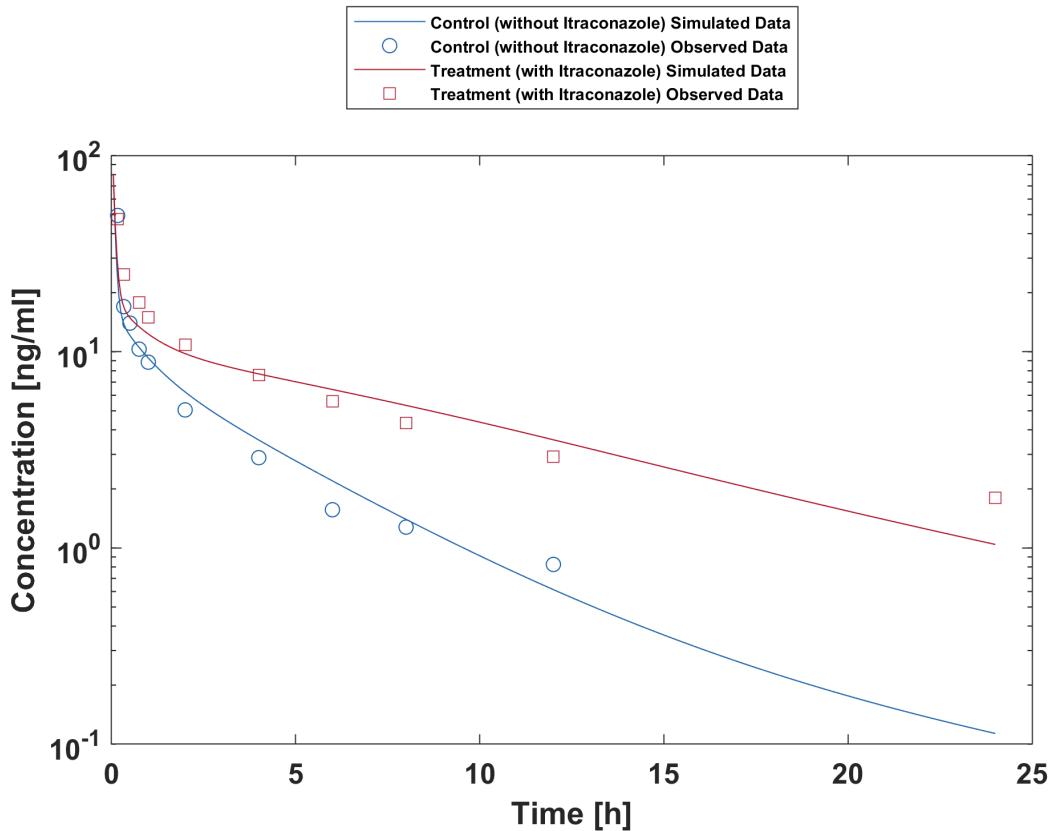
Olkola 1996 (day 6 po)



Pruksaritanont 2017

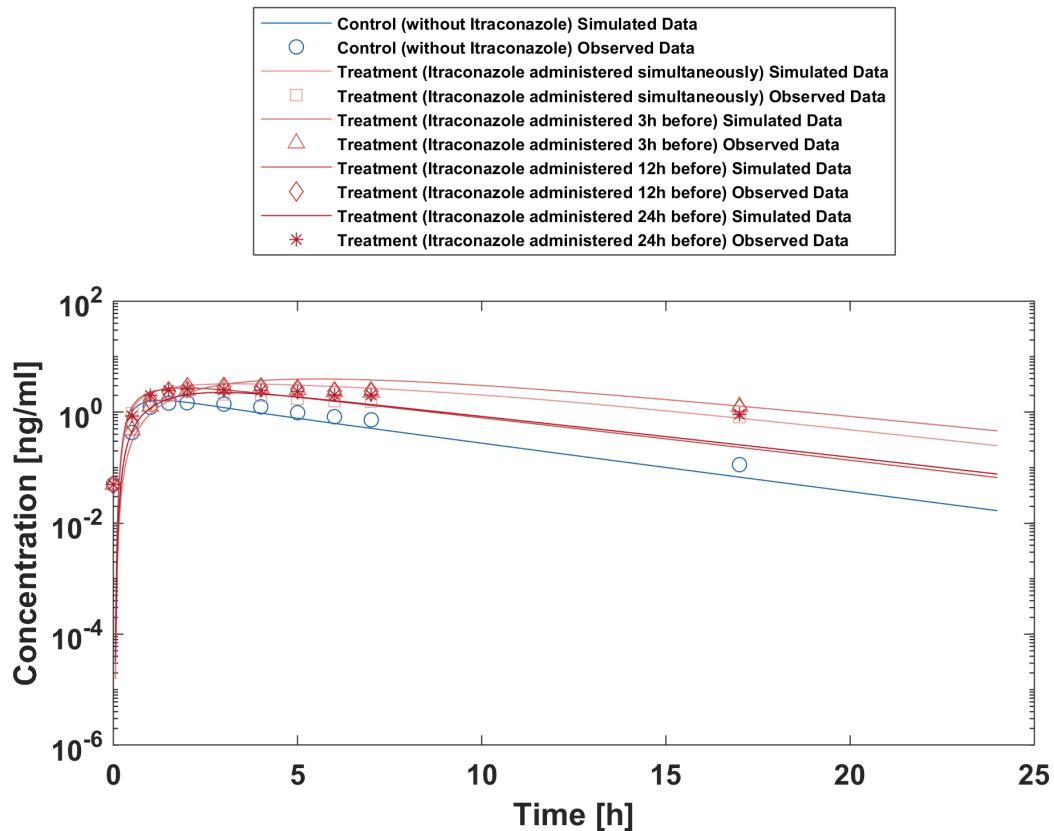


Templeton 2010

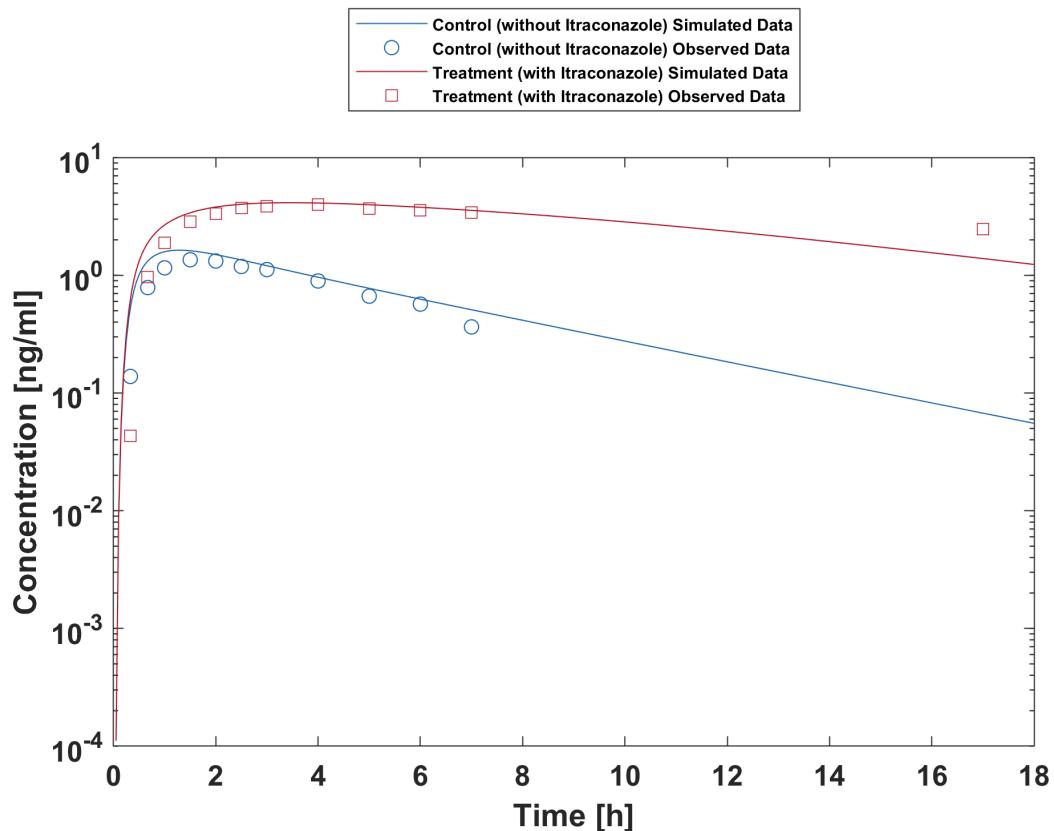


Yu 2004 (CYP3A5\*3/\*3)

### 3.16 Itraconazole - Triazolam DDI

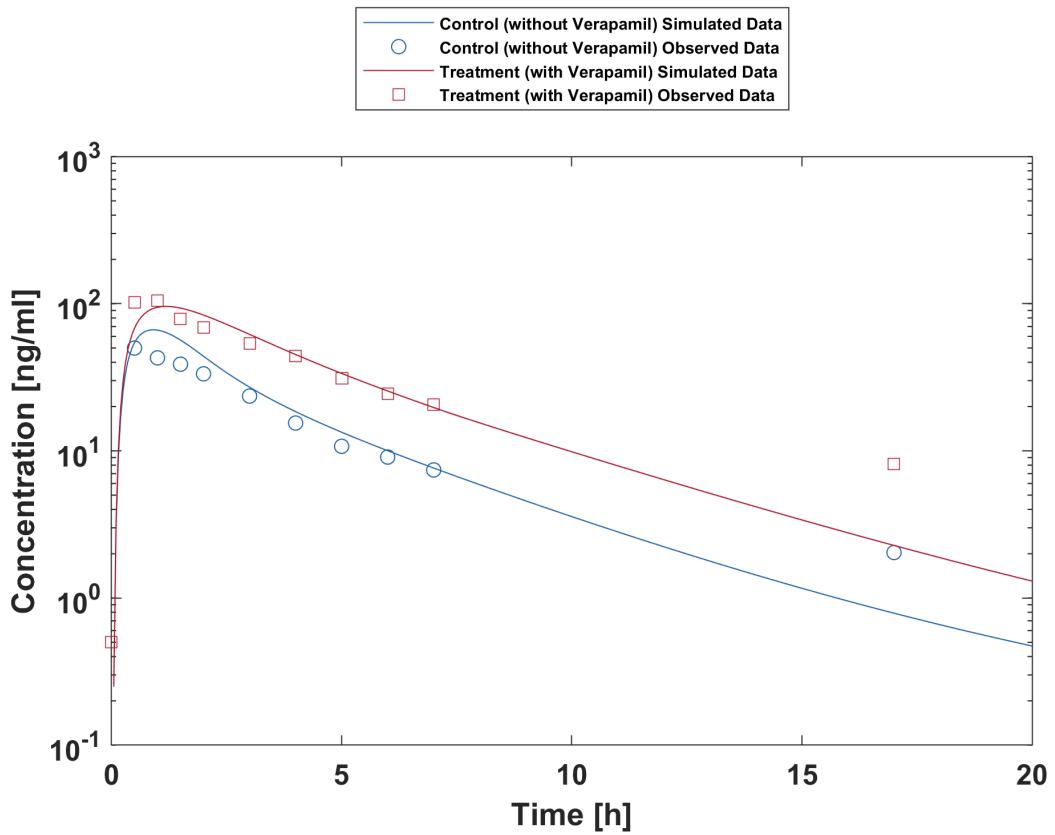


Neuvonen 1996

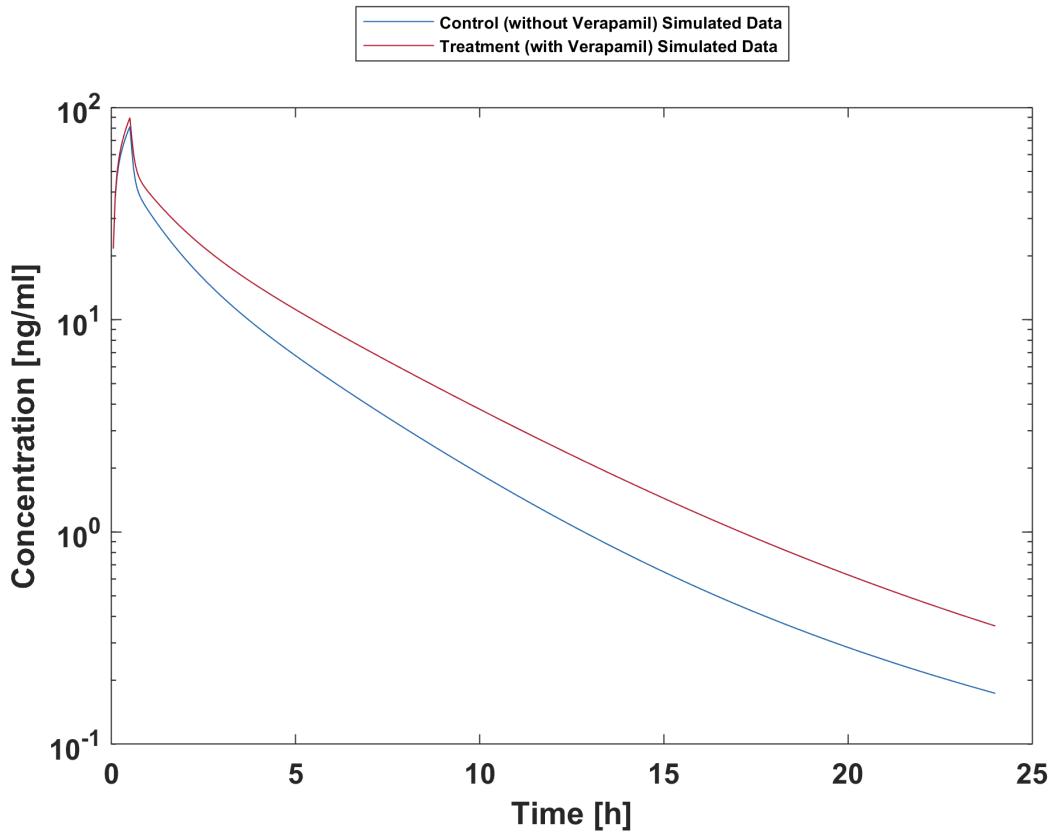


Varhe 1994

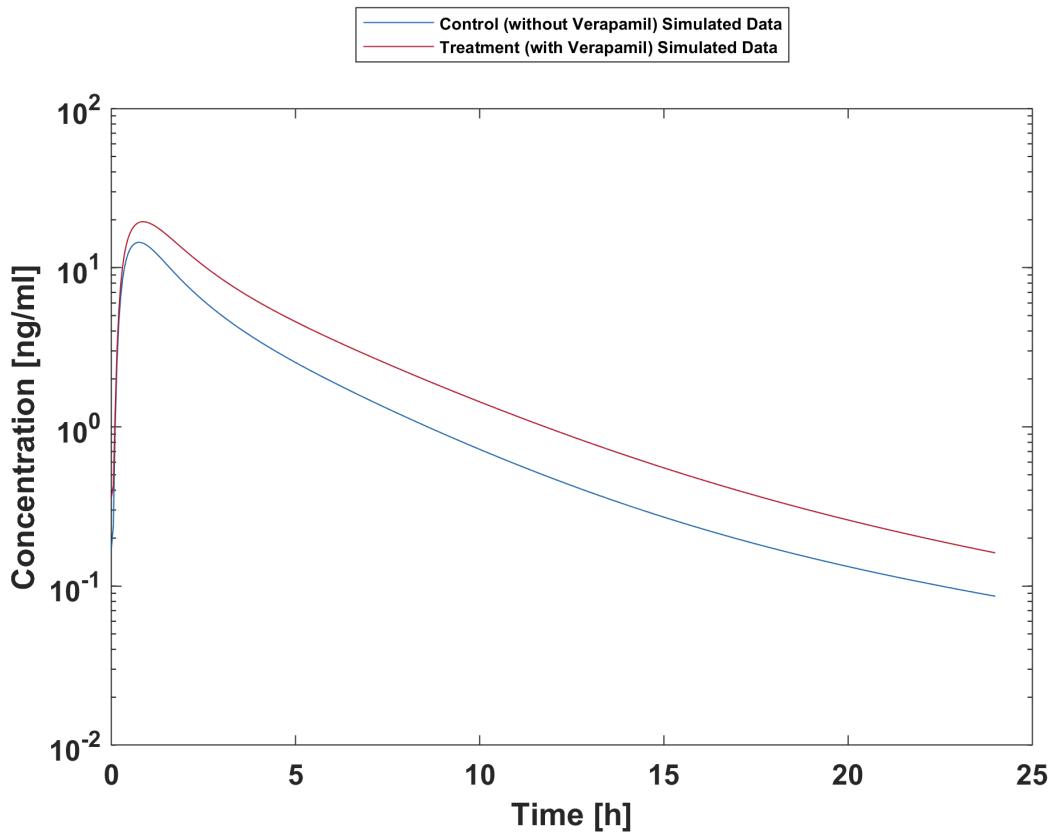
### 3.17 Verapamil - Midazolam DDI



Backman 1994

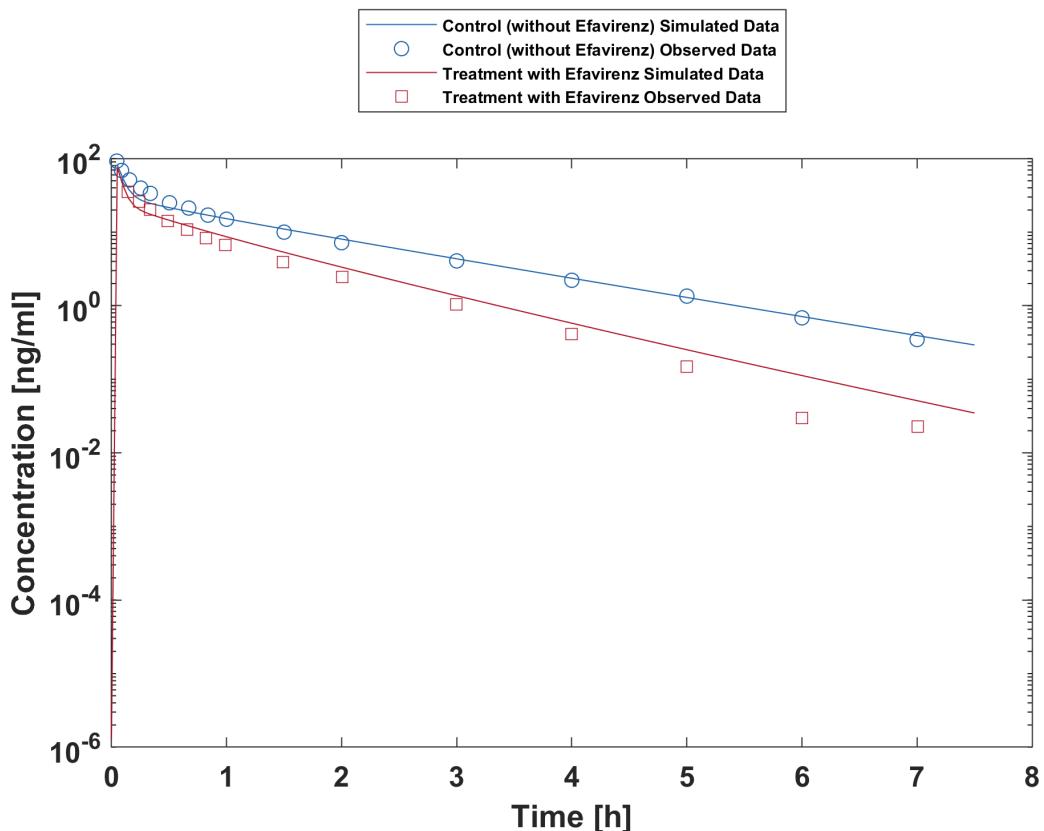


Wang 2005 (iv)

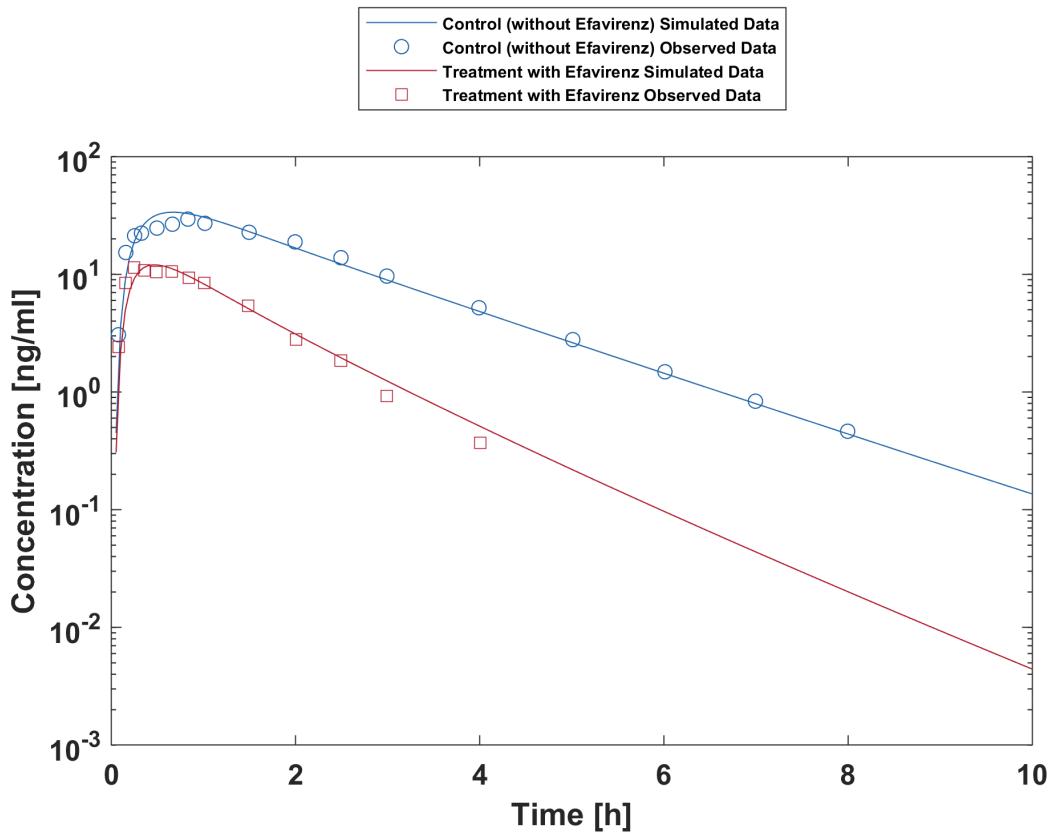


Wang 2005 (po)

### 3.18 Efavirenz - Alfentanil DDI

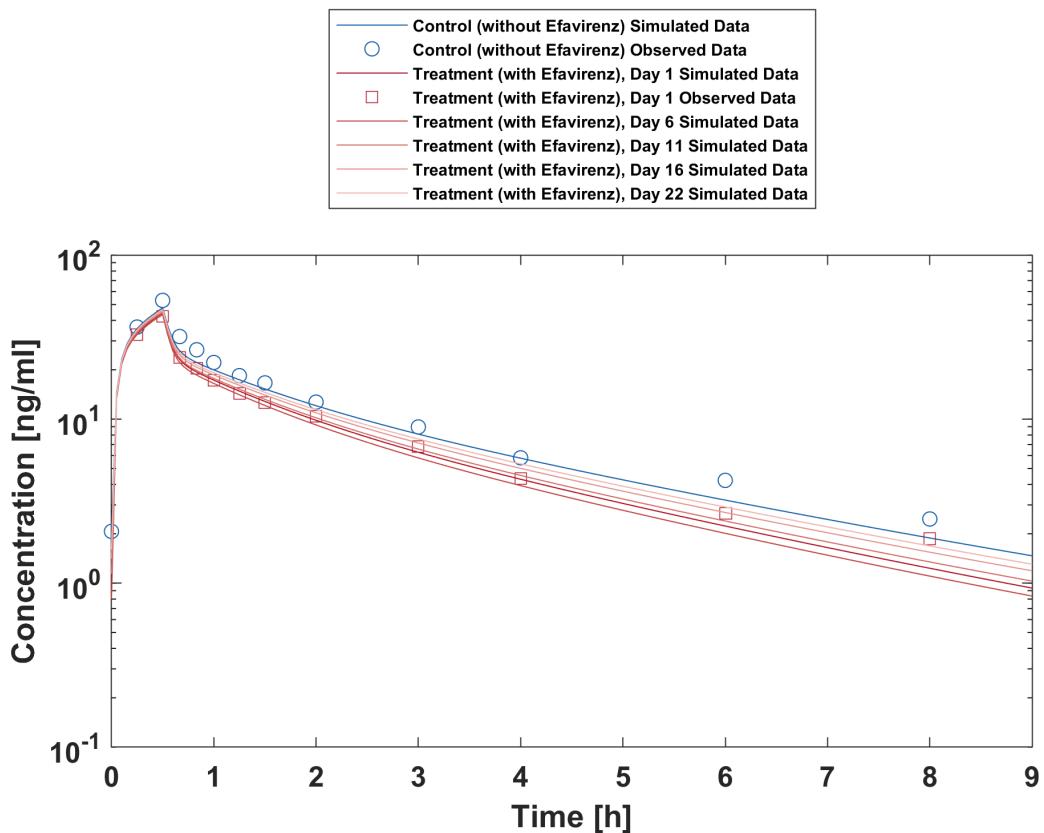


Kharasch 2012 IV

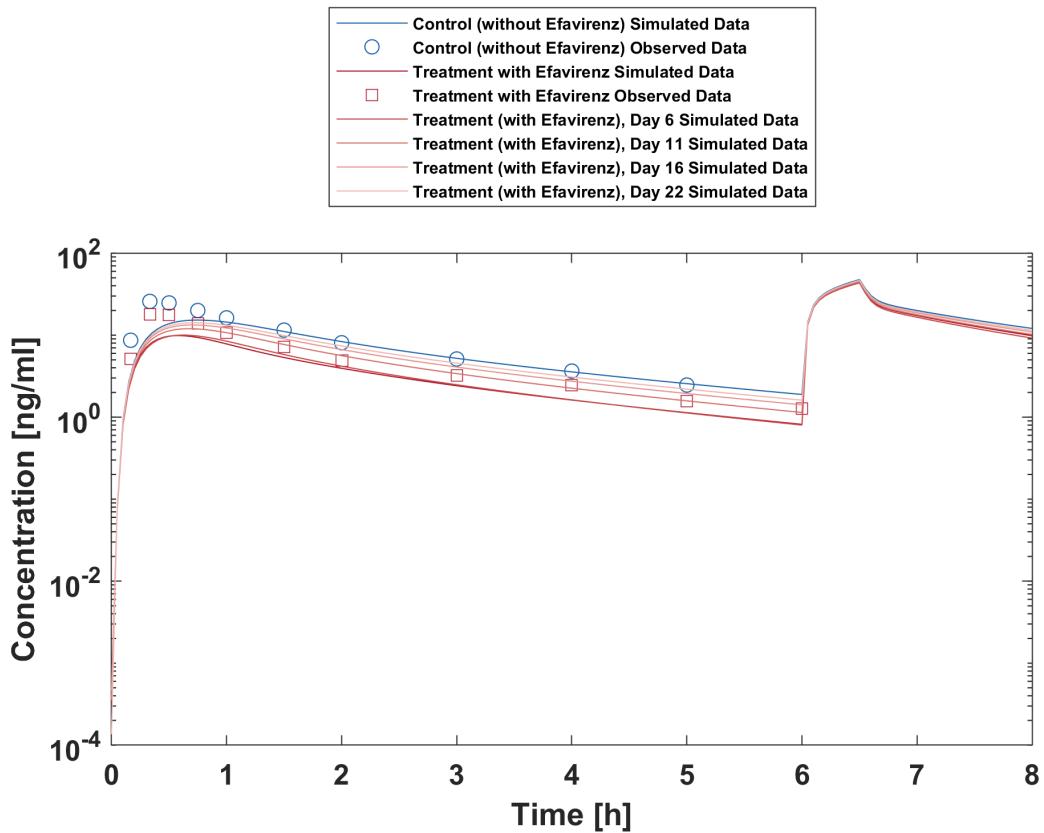


Kharasch 2012 PO

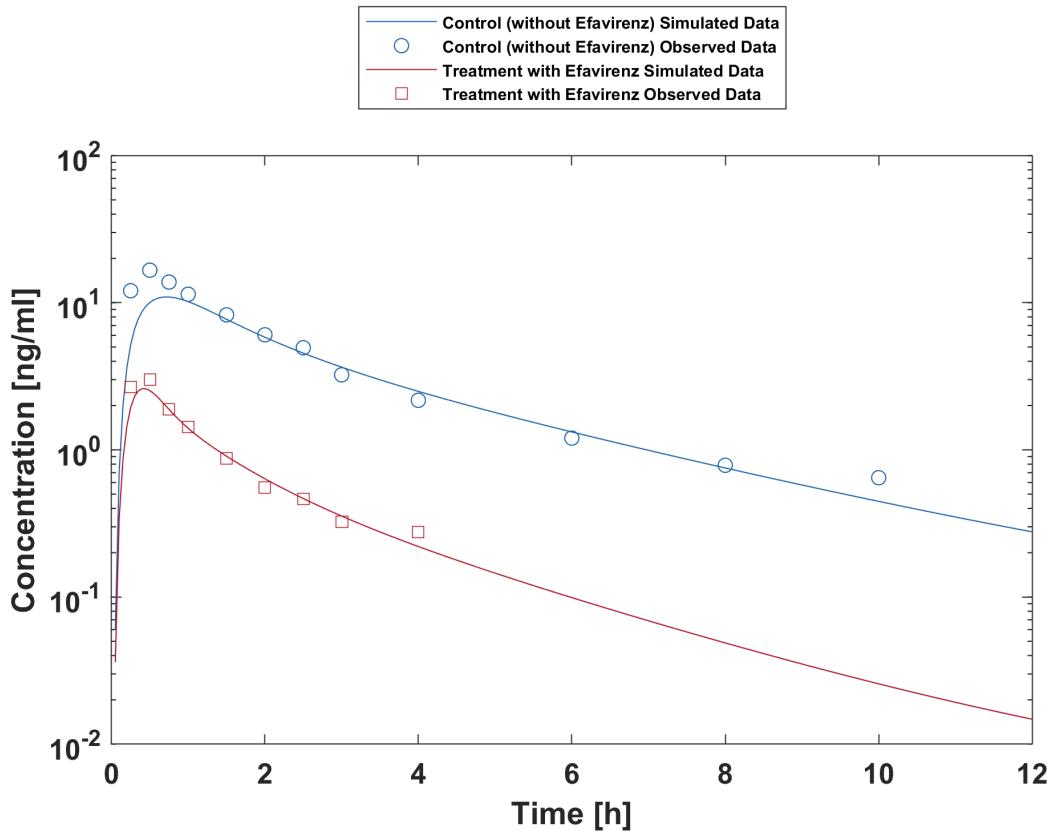
### 3.19 Efavirenz - Midazolam DDI



Mikus 2017 IV

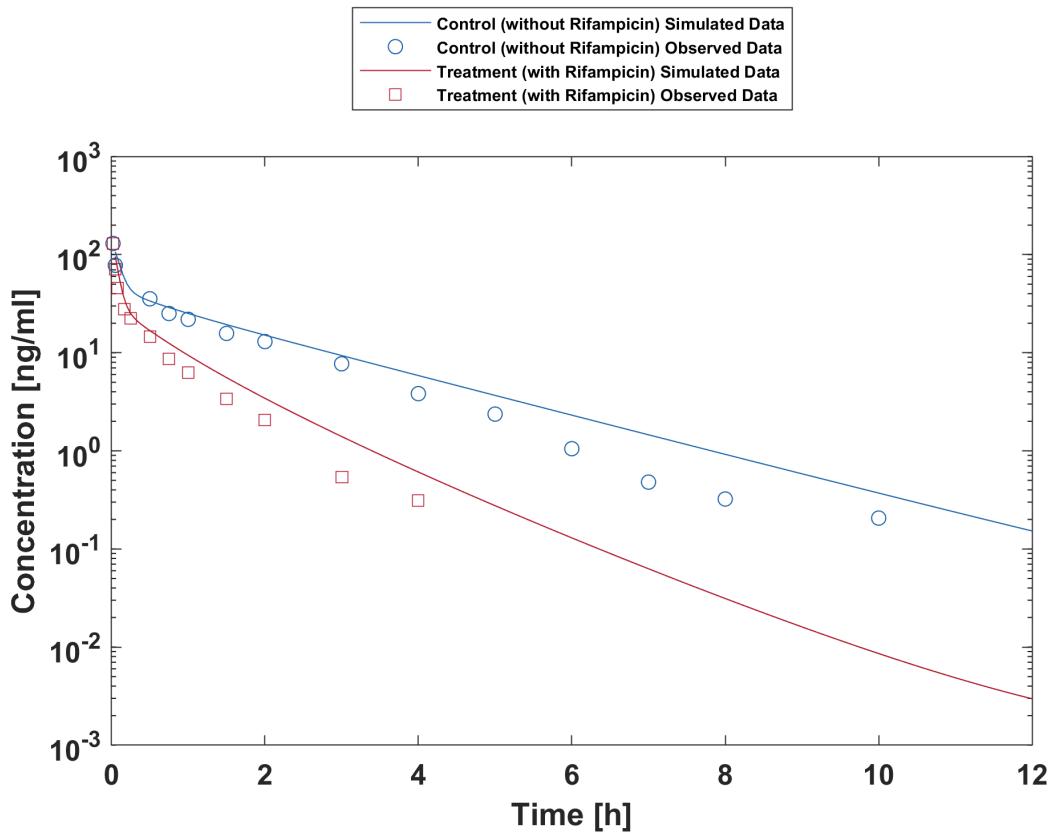


Mikus 2017 PO

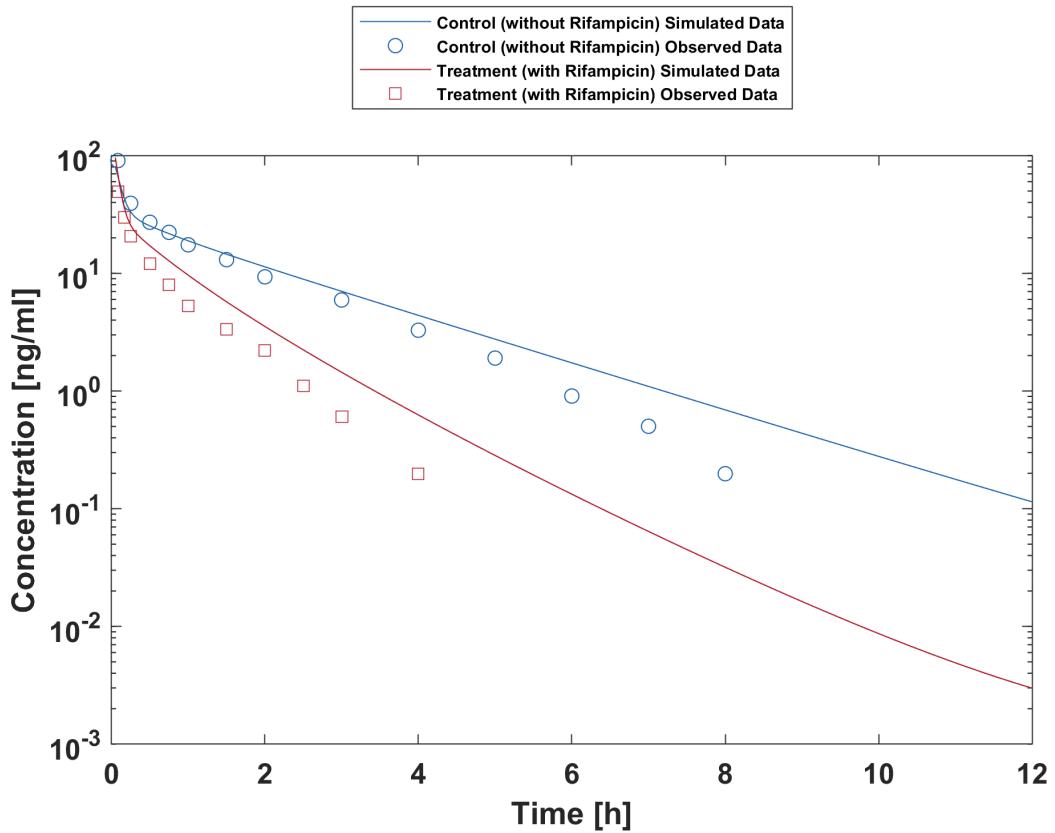


Katzenmaier 2010

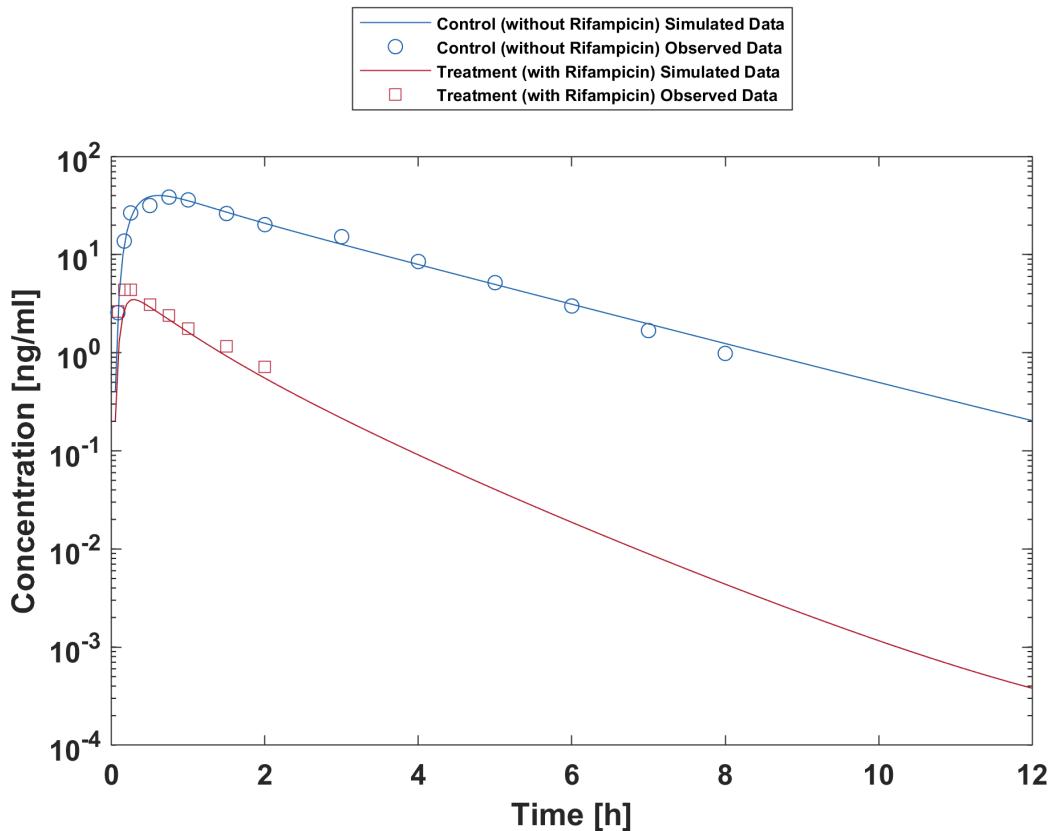
### 3.20 Rifampicin - Alfentanil DDI



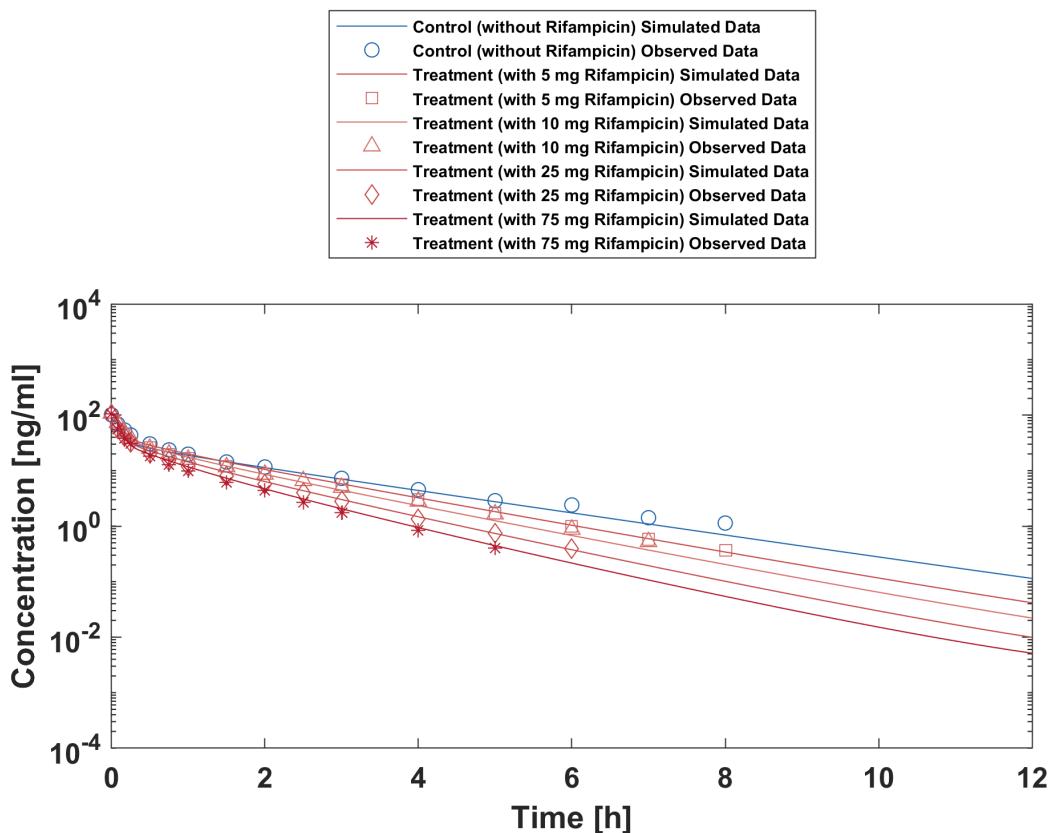
Kharasch 1997



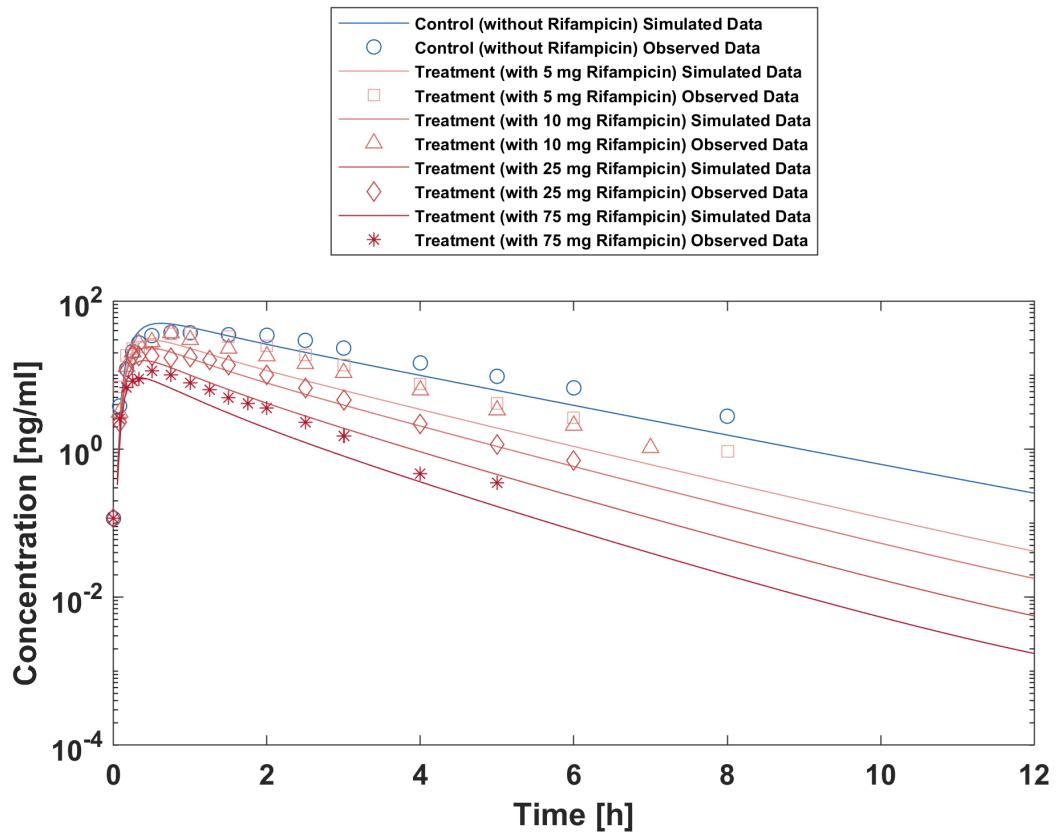
Kharasch 2004 (iv)



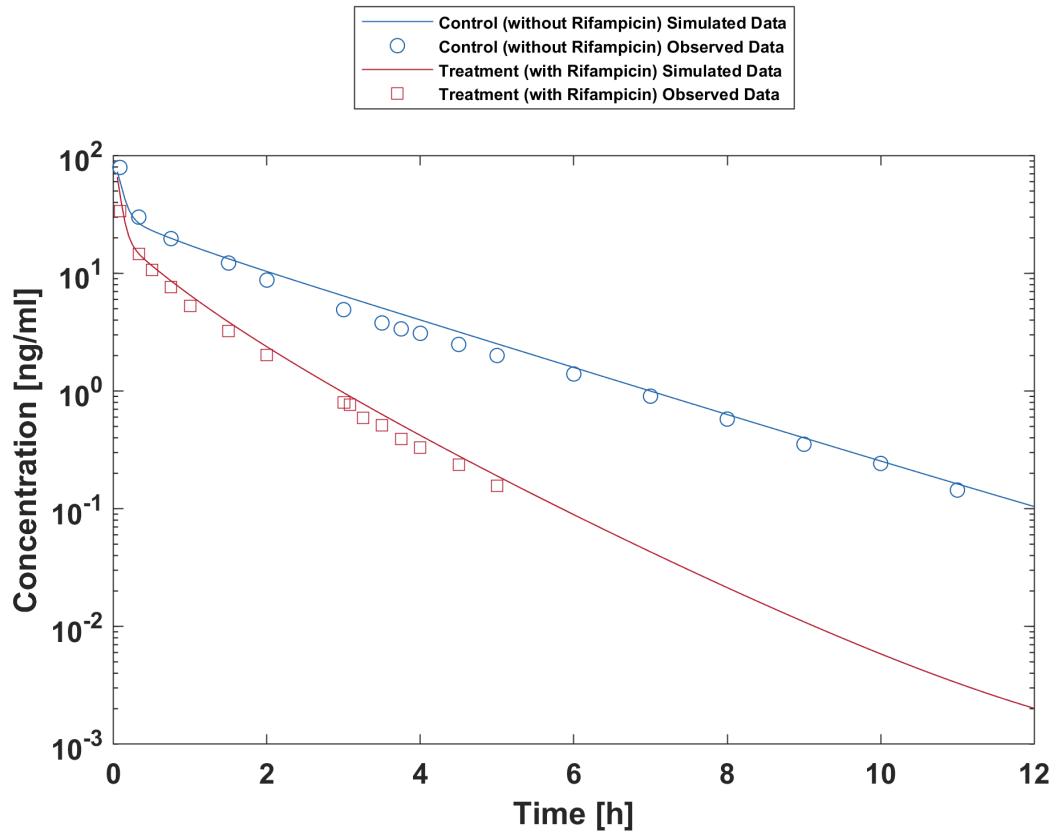
Kharasch 2004 (po)



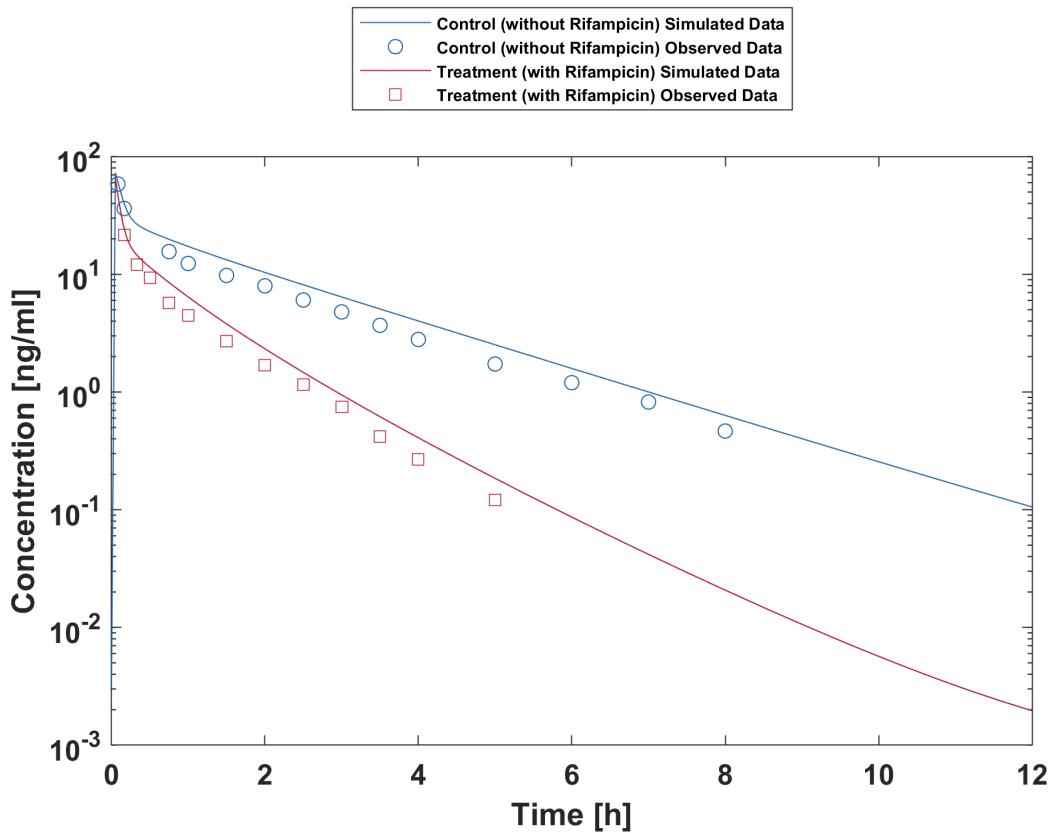
Kharasch 2011 (iv)



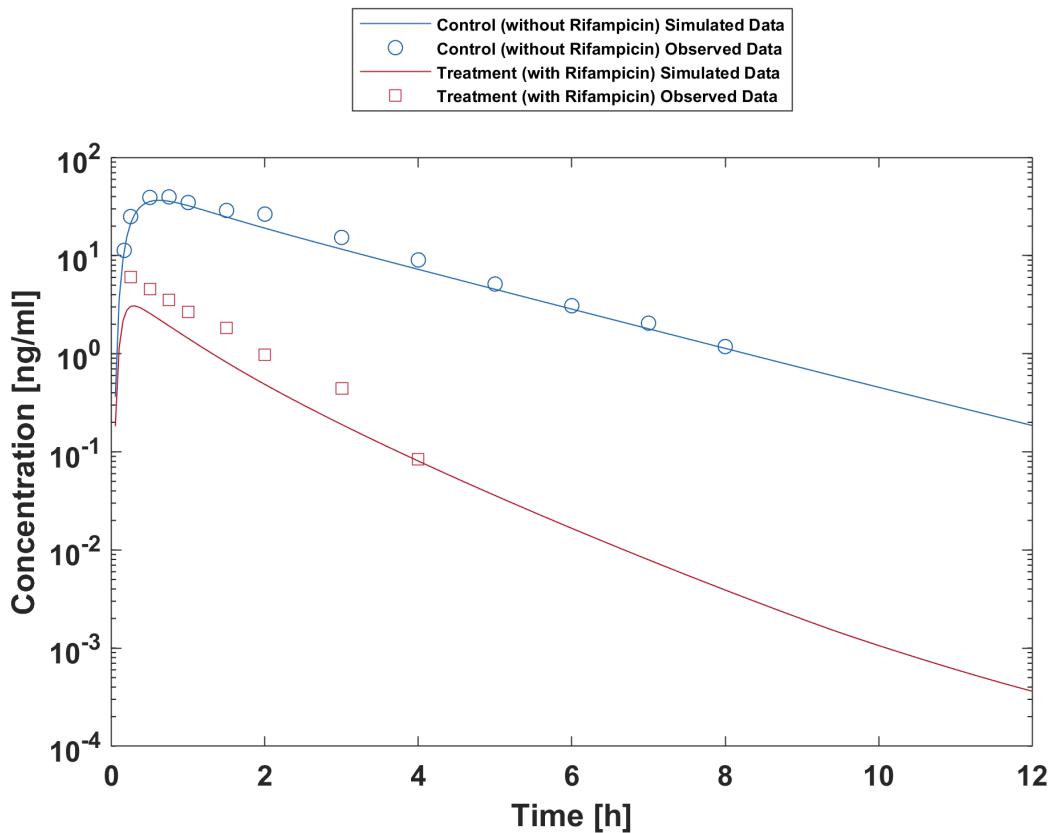
Kharasch 2011 (po)



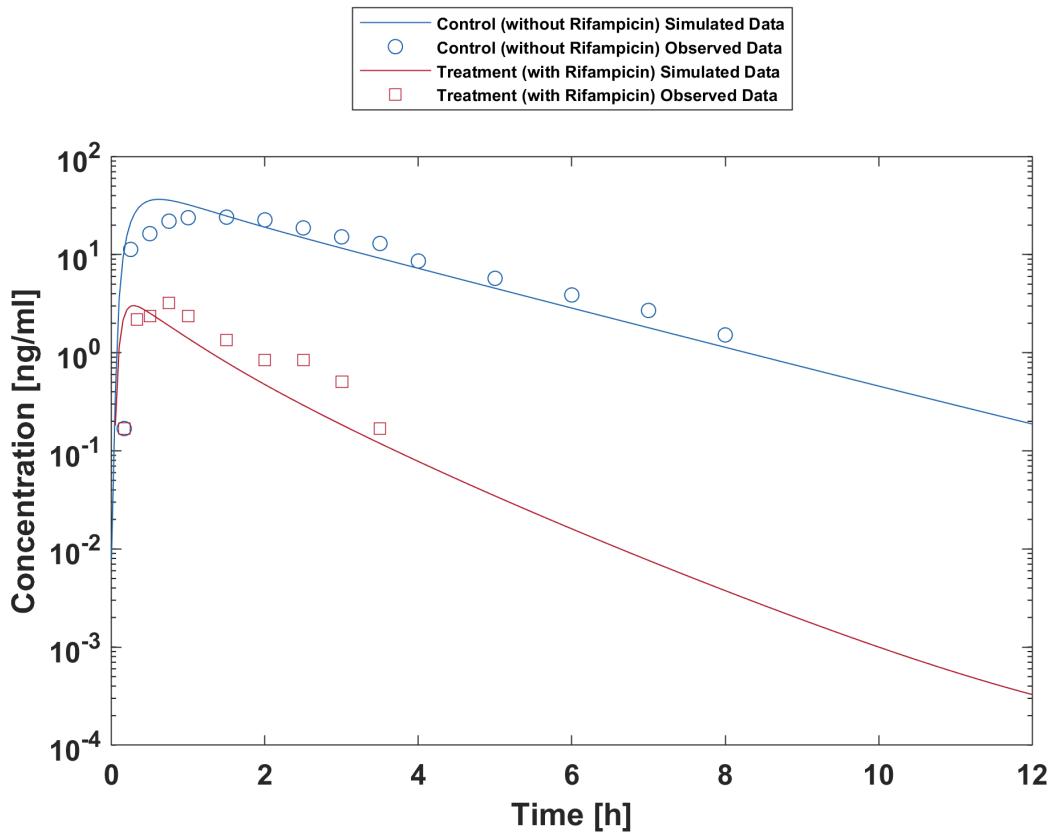
Kharasch 2011b (iv during sequential administration of iv unlabeled alfentanil and oral deuterated alfentanil)



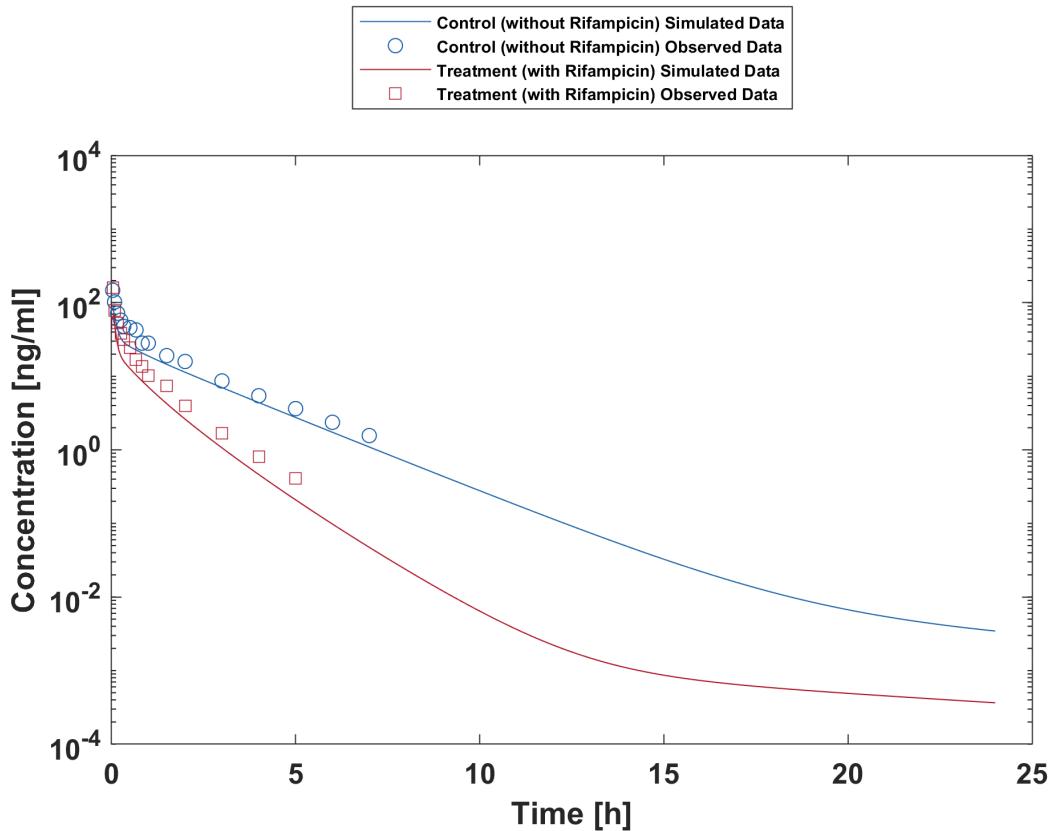
Kharasch 2011b (iv during simultaneous administration of iv unlabeled alfentanyl and oral deuterated alfentanyl)



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

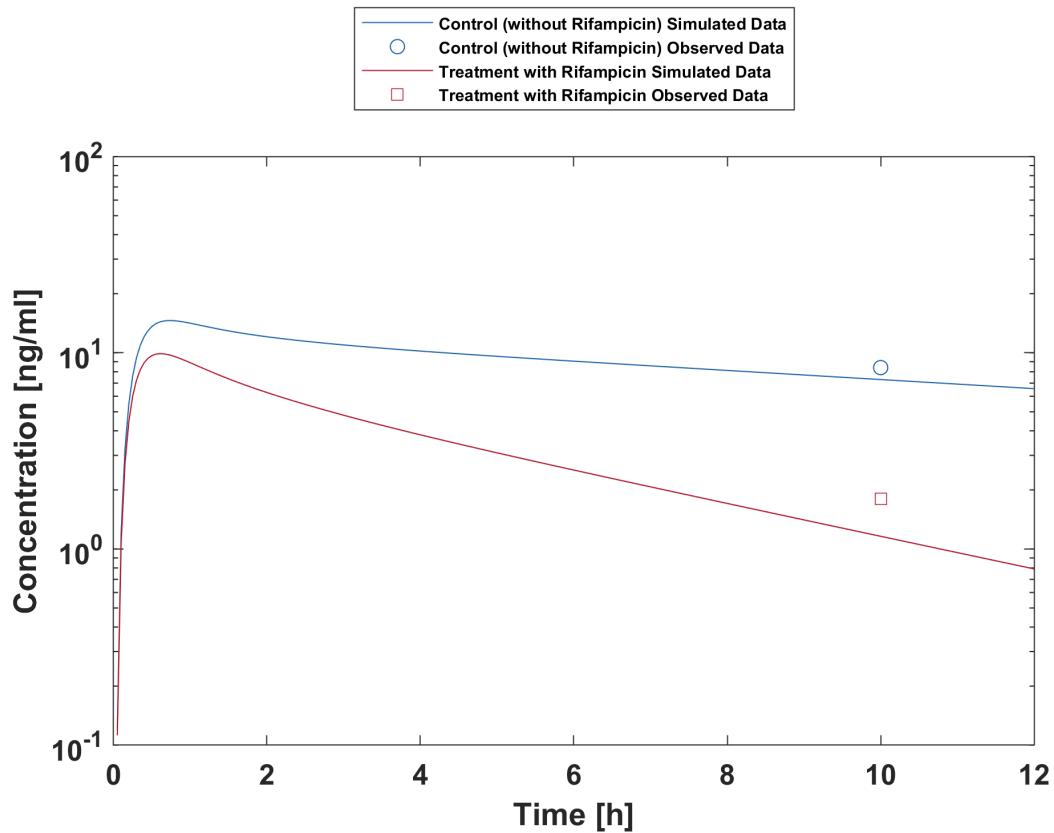


Kharasch 2011b (po during simultaneous administration of iv unlabeled alfentanil and oral deuterated alfentanil)

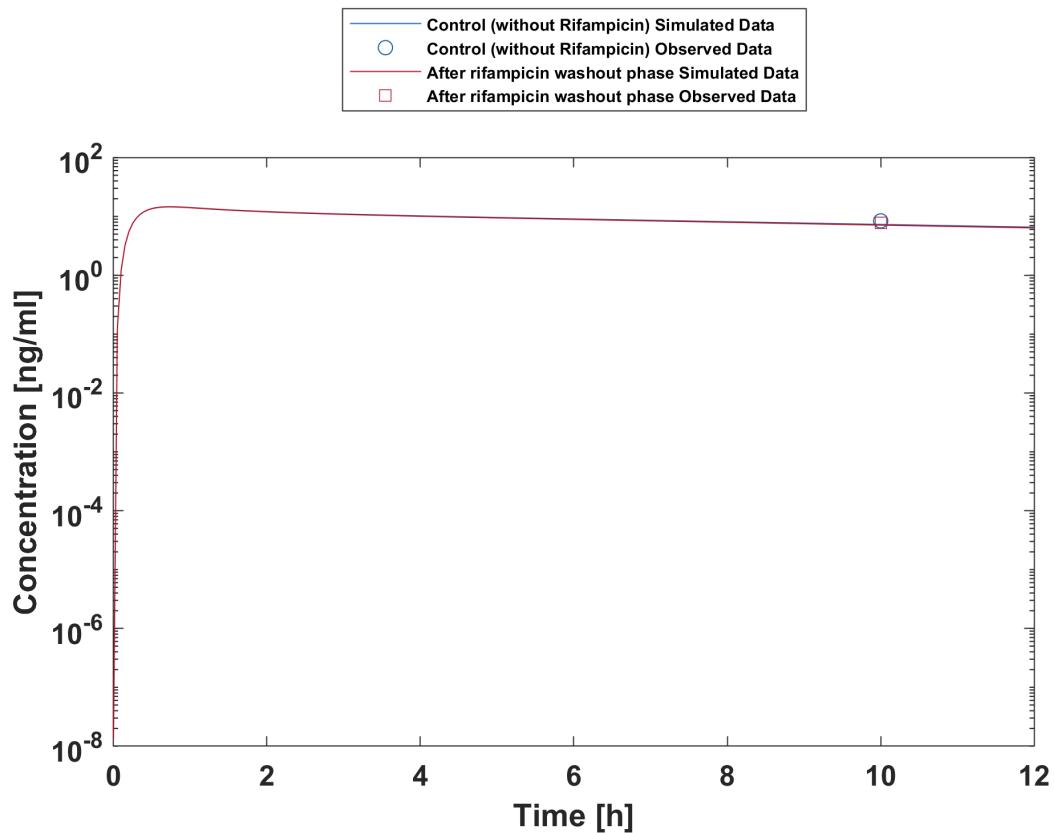


Phimmasone 2001

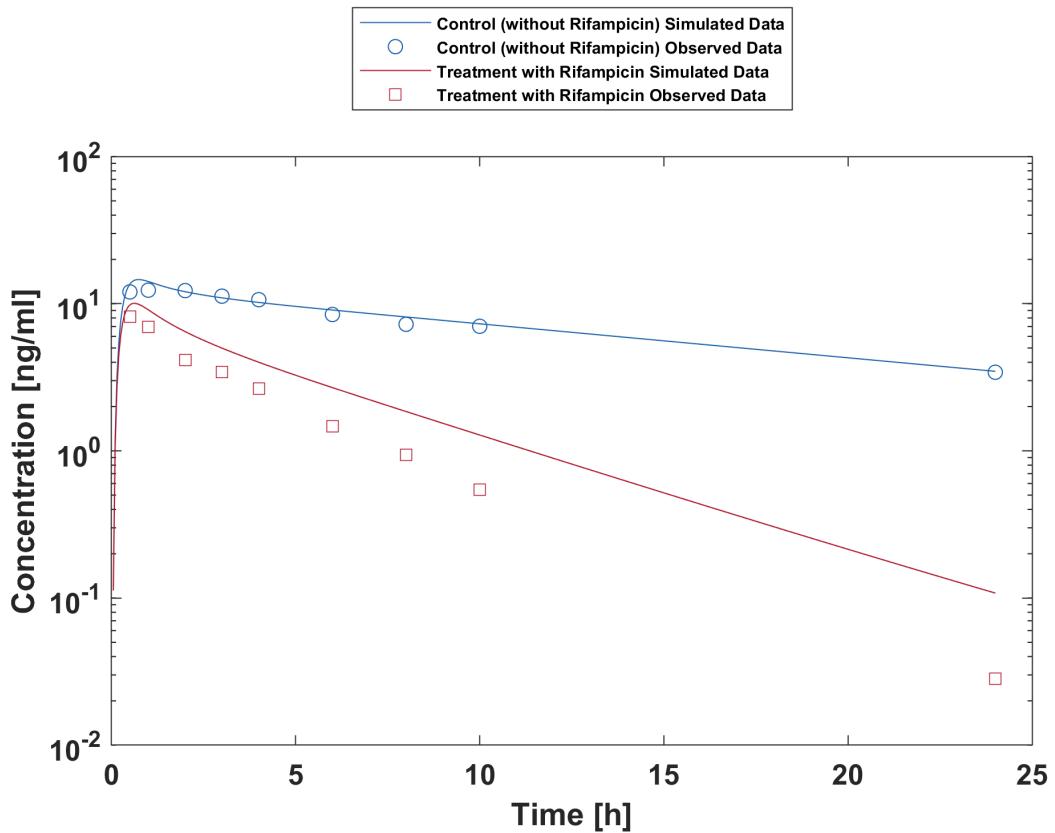
### 3.21 Rifampicin - Alprazolam DDI



Gashaw 2003 (Day 7)

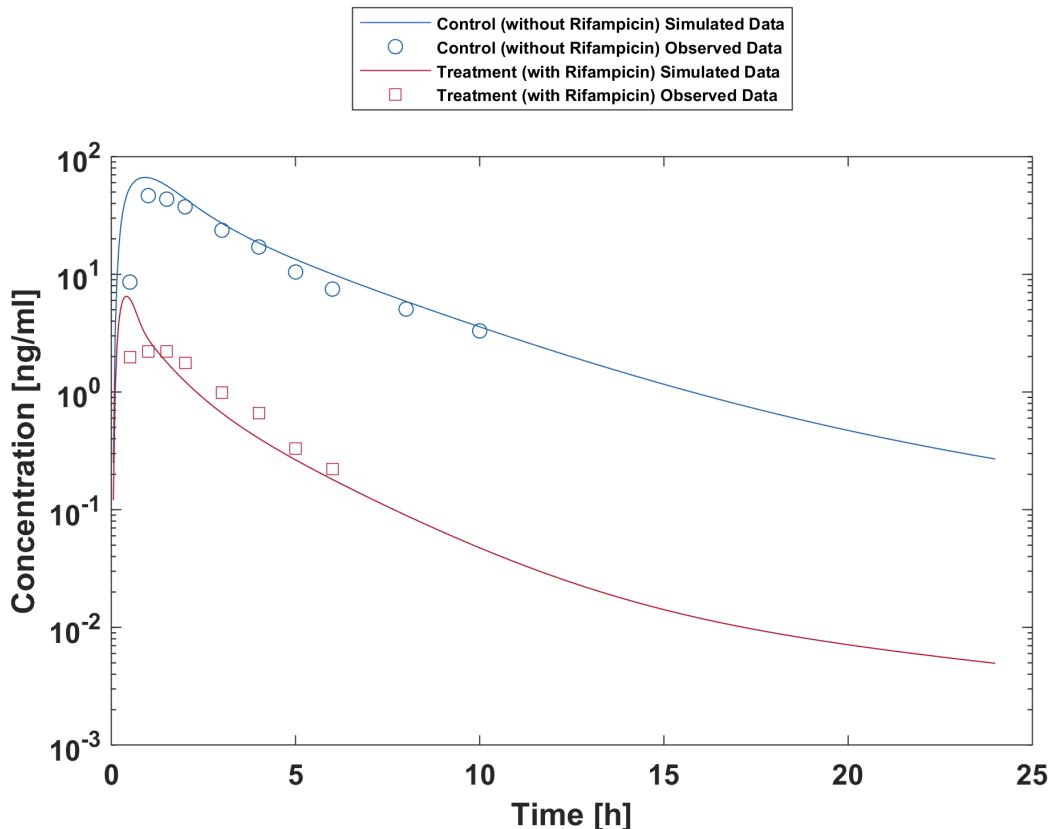


Gashaw 2003 (after washout phase)

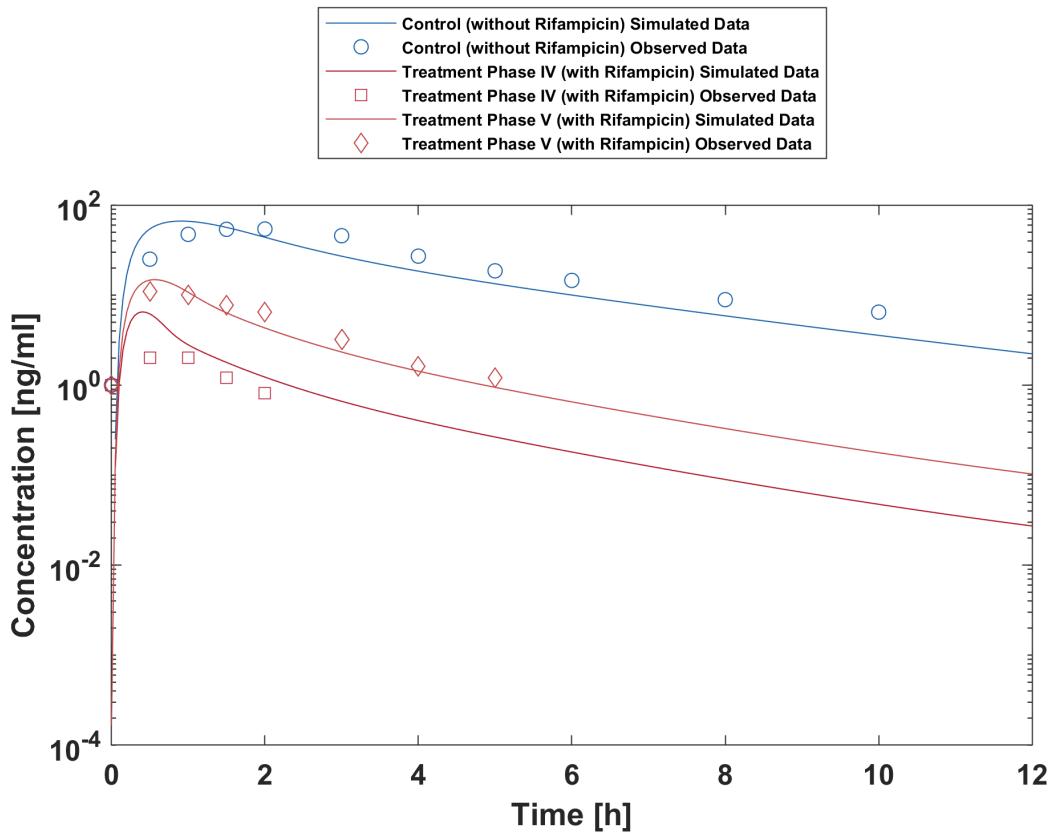


Schmider 1999

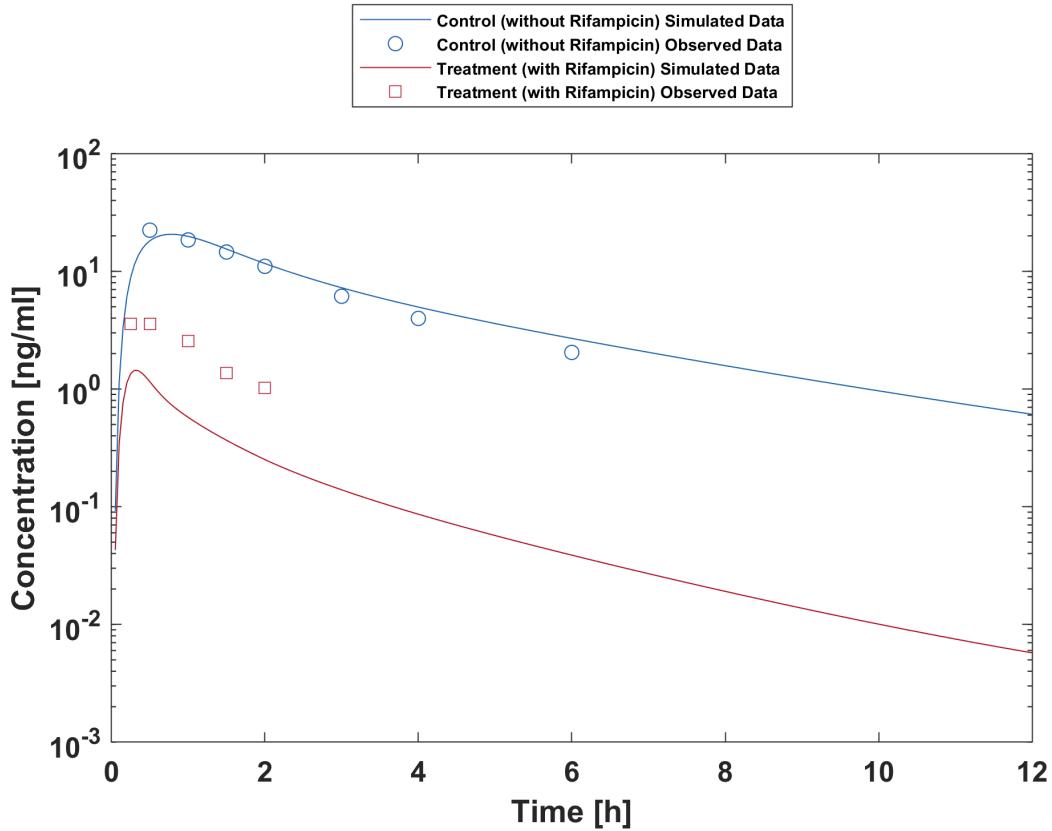
### 3.22 Rifampicin - Midazolam DDI



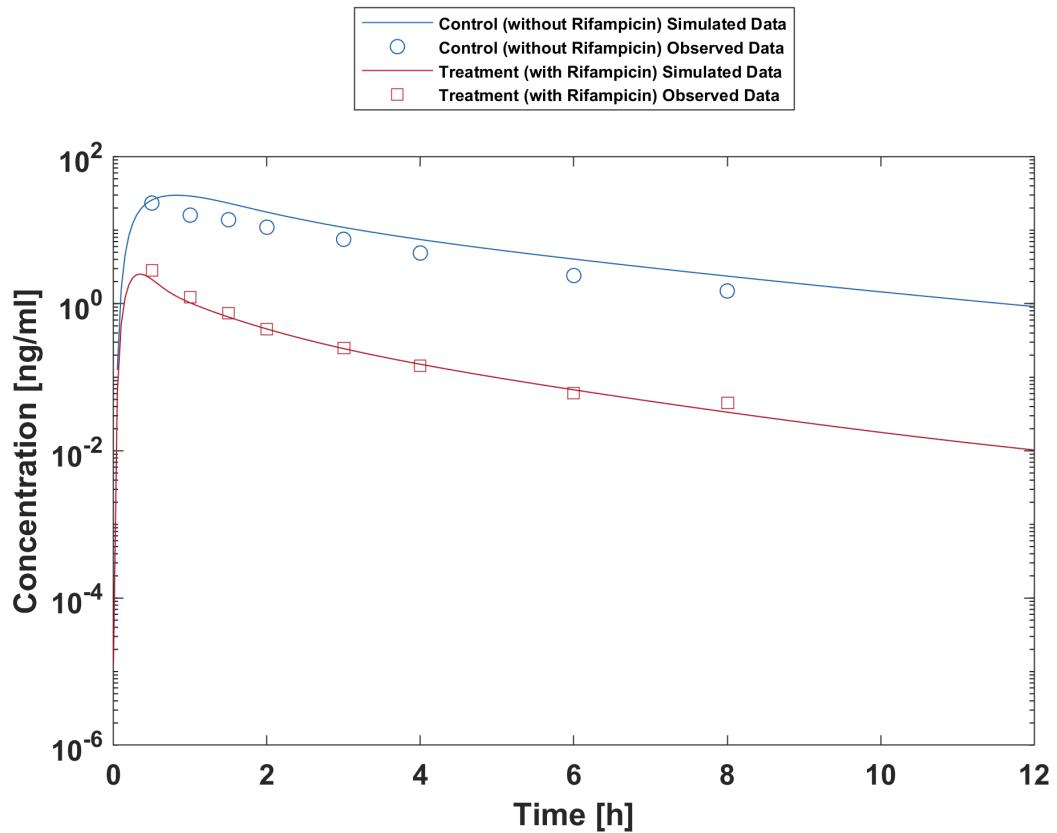
Backman 1996



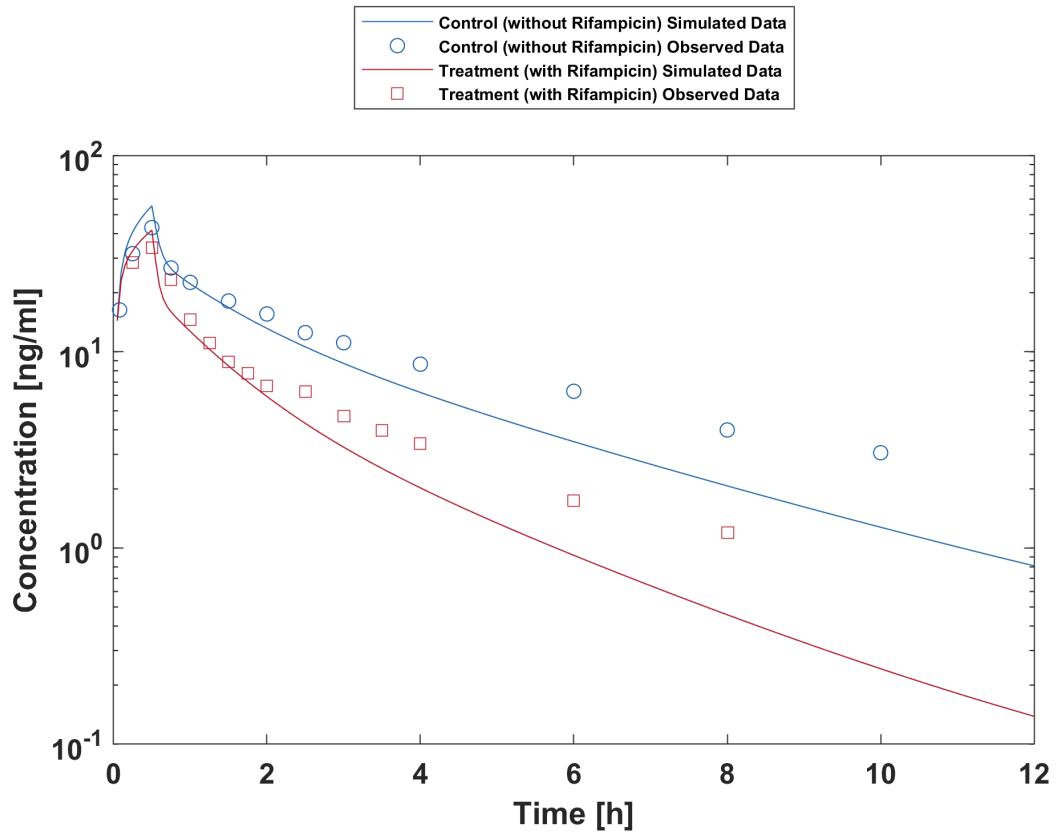
Backman 1998 (Phase IV and V vs. I)



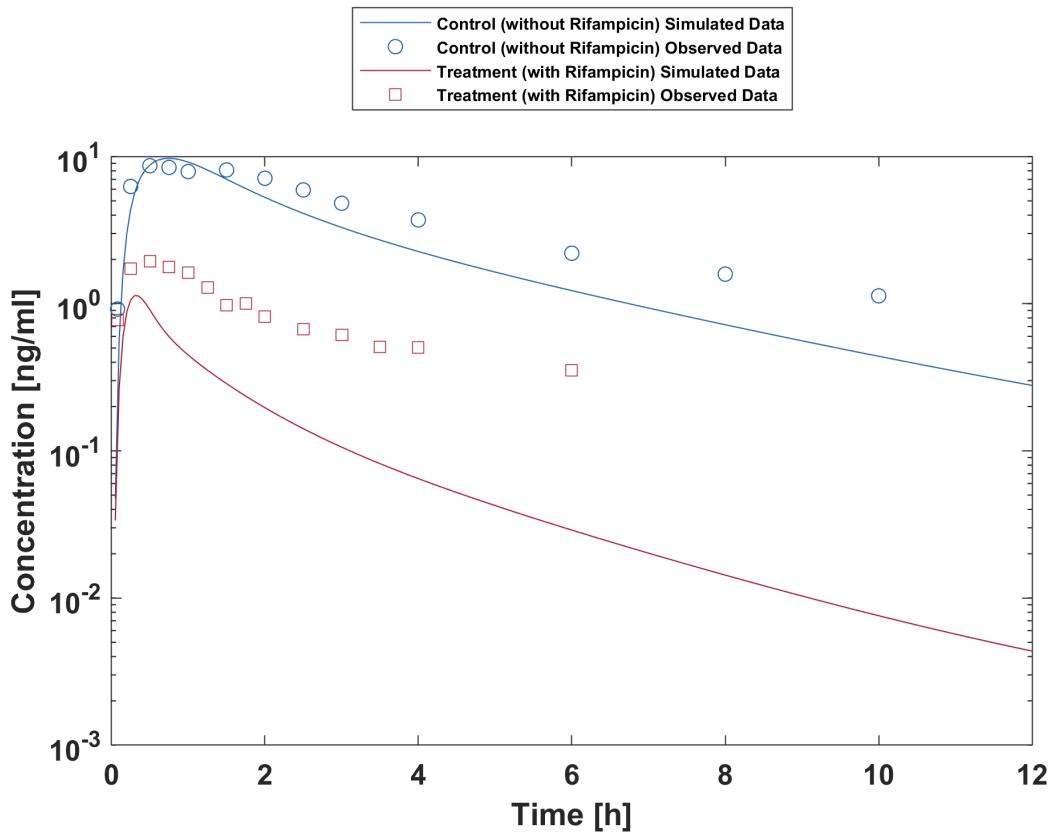
Chung 2006



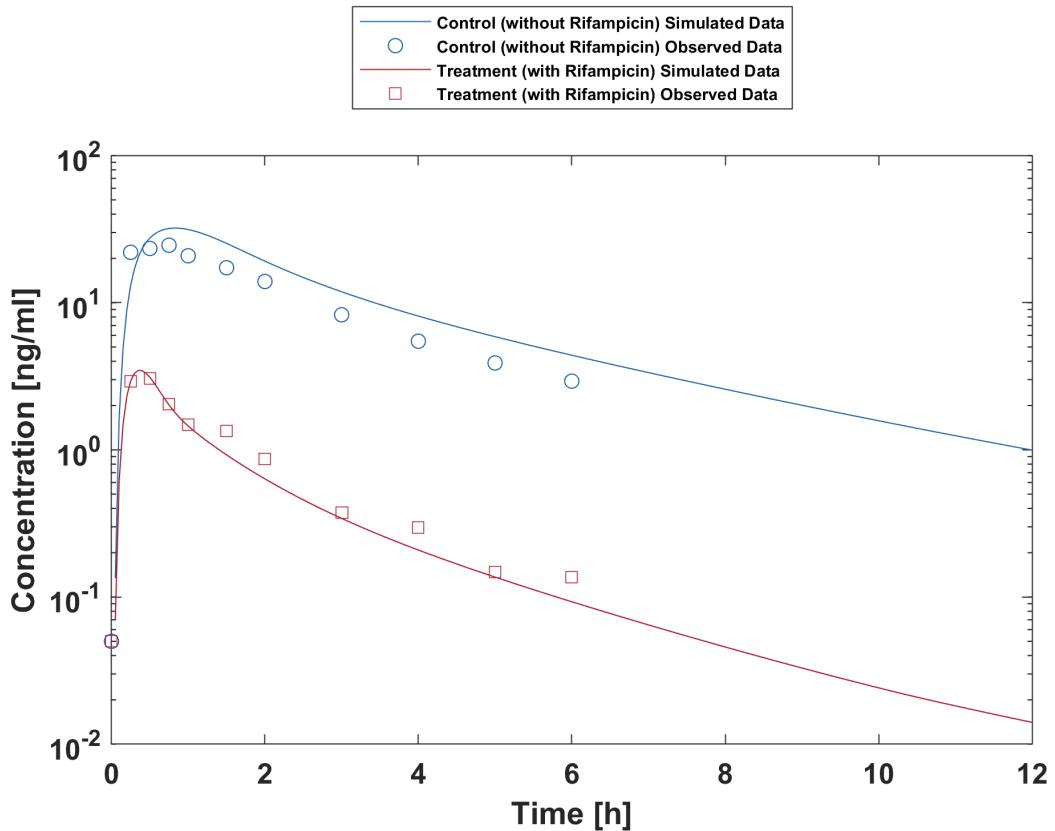
Eap 2004 (7.5 mg)



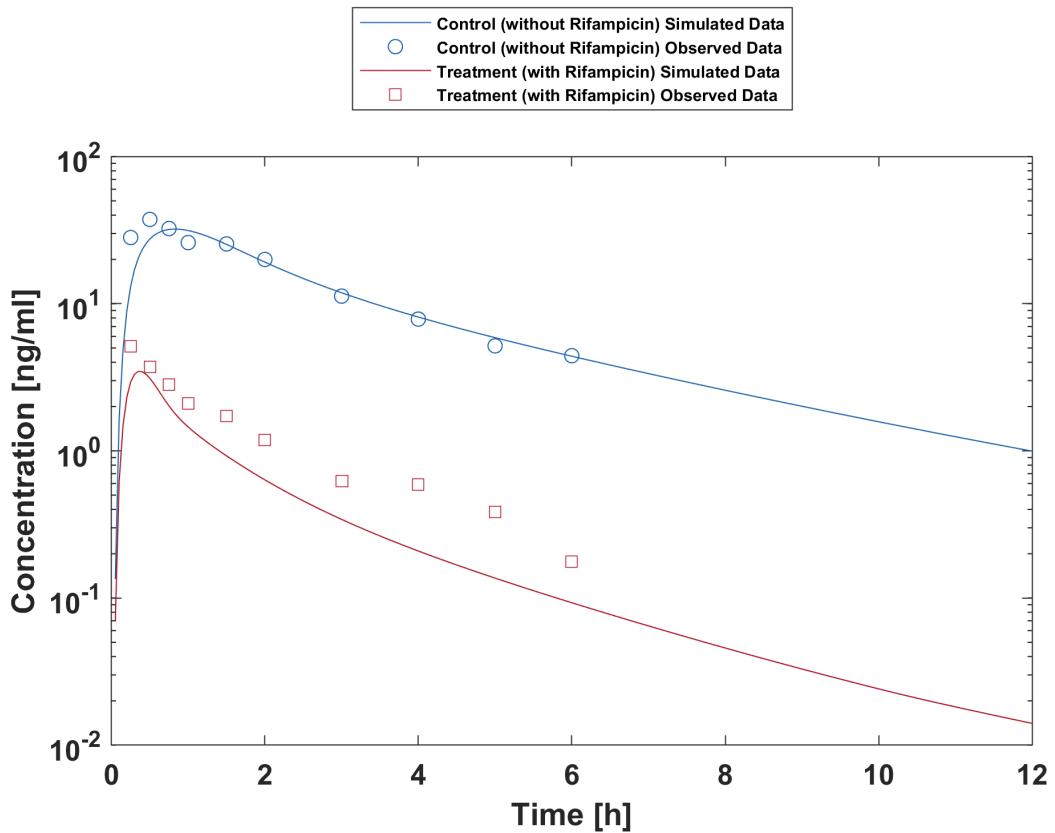
Gorski 2003 (iv)



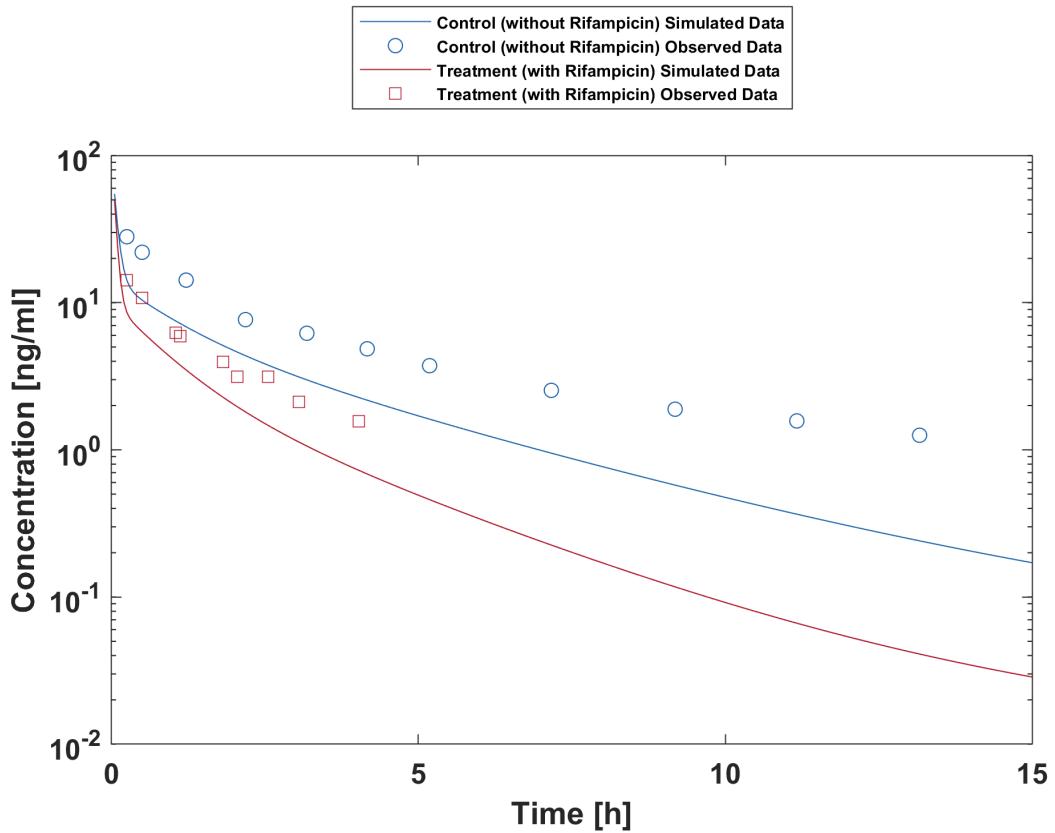
Gorski 2003 (po)



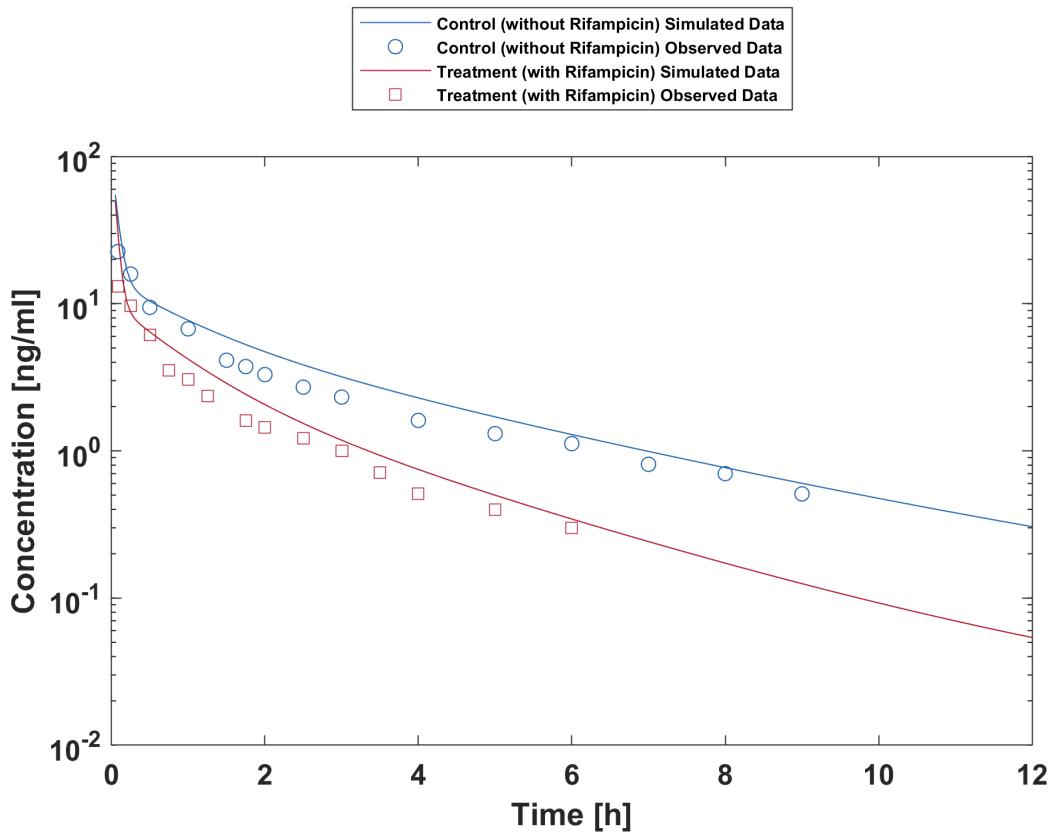
Gurley 2006



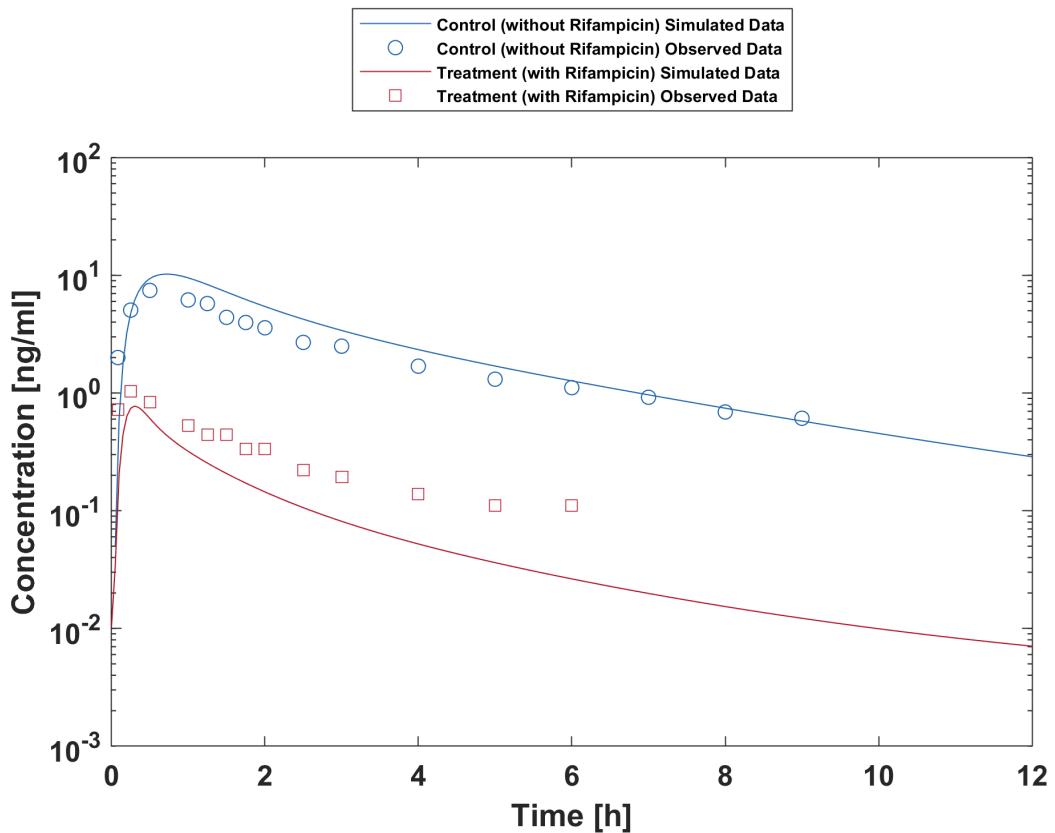
Gurley 2008a



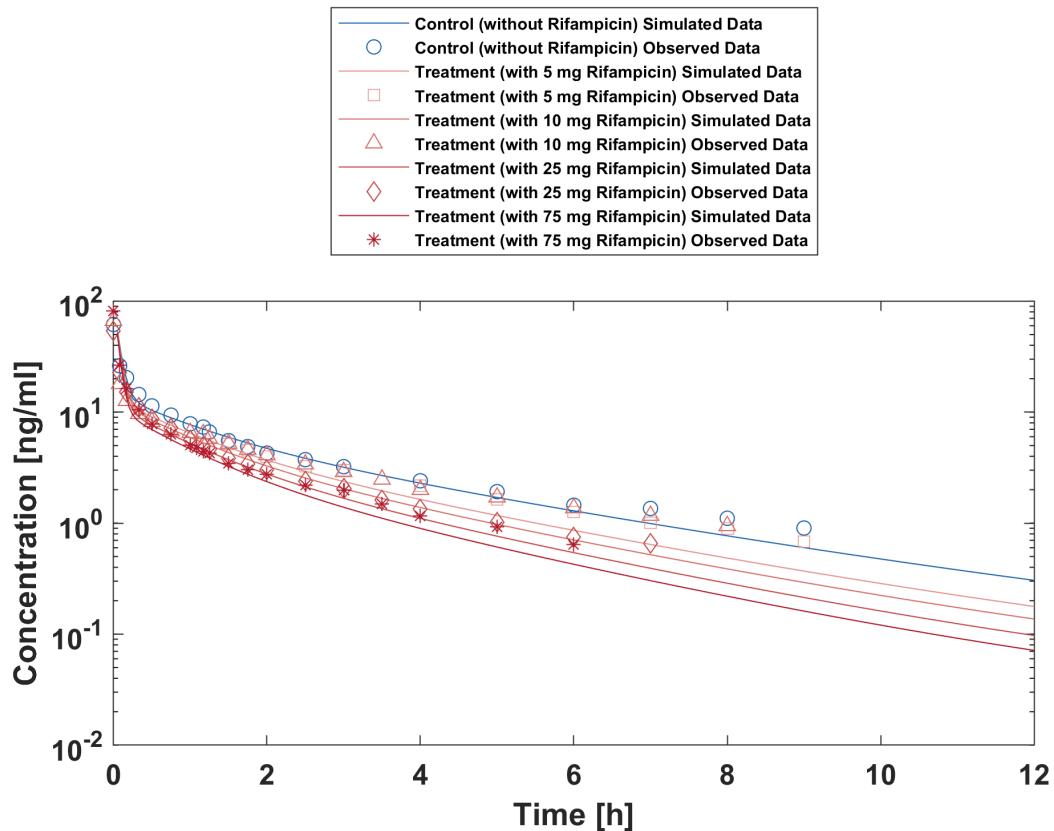
Kharasch 1997



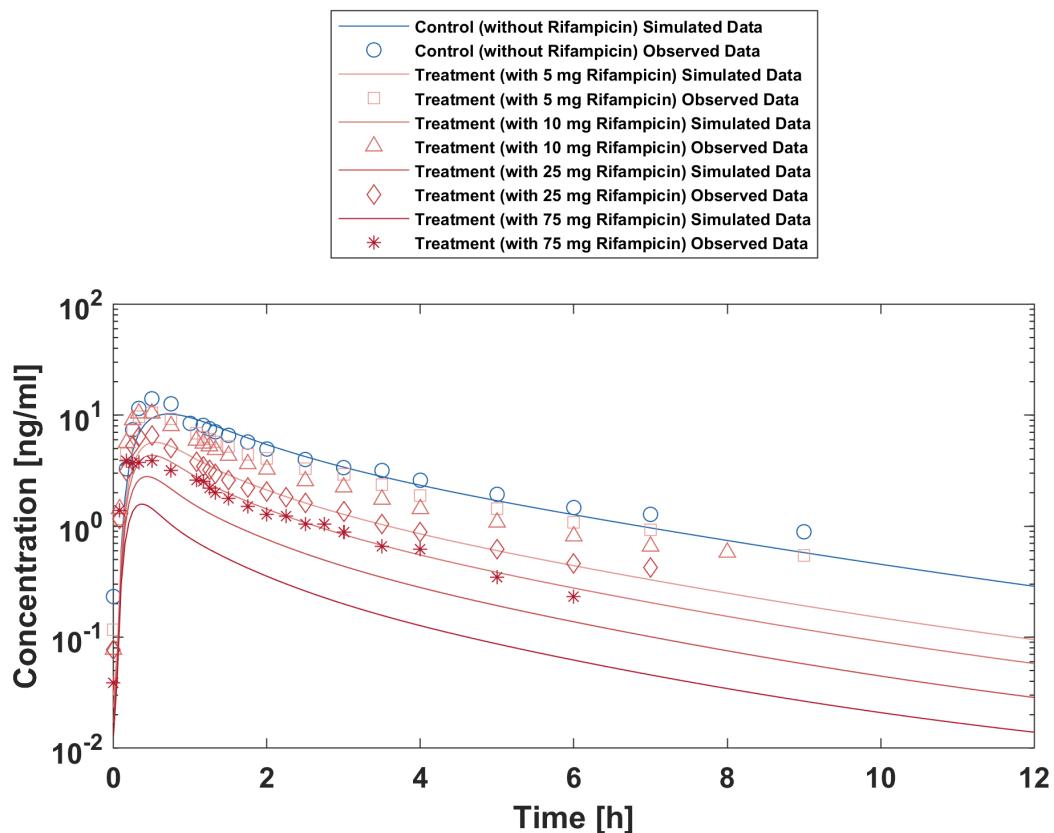
Kharasch 2004 (iv)



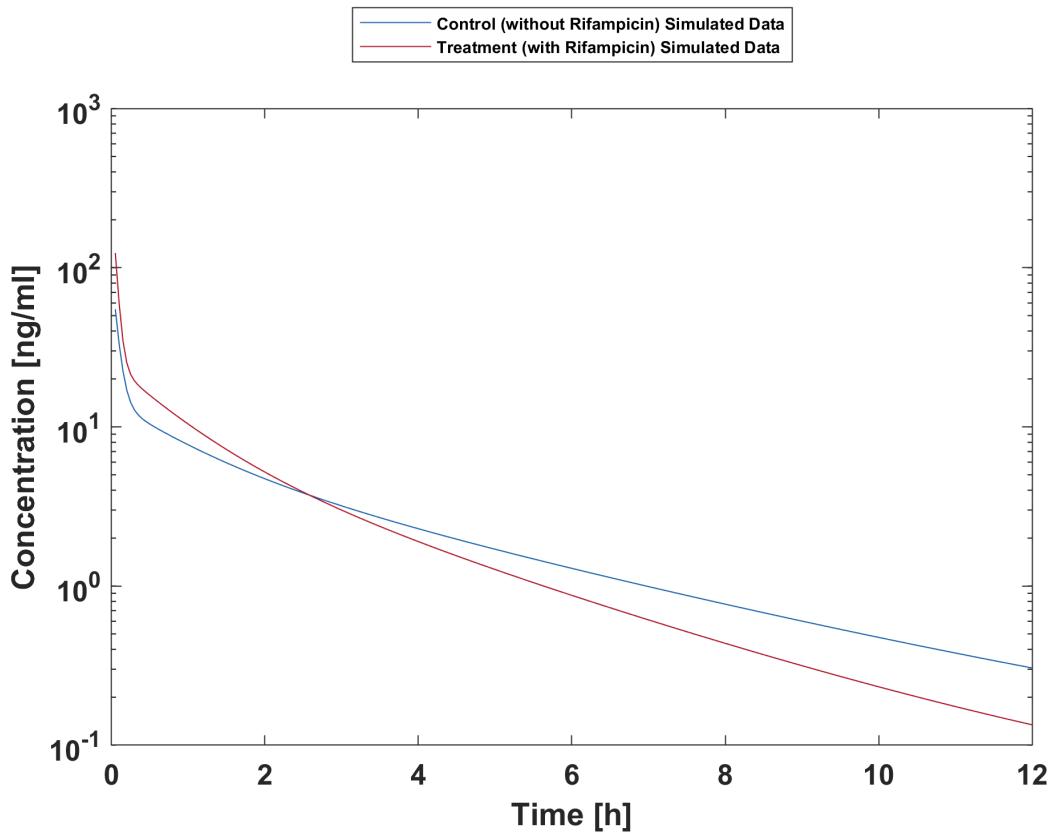
Kharasch 2004 (po)



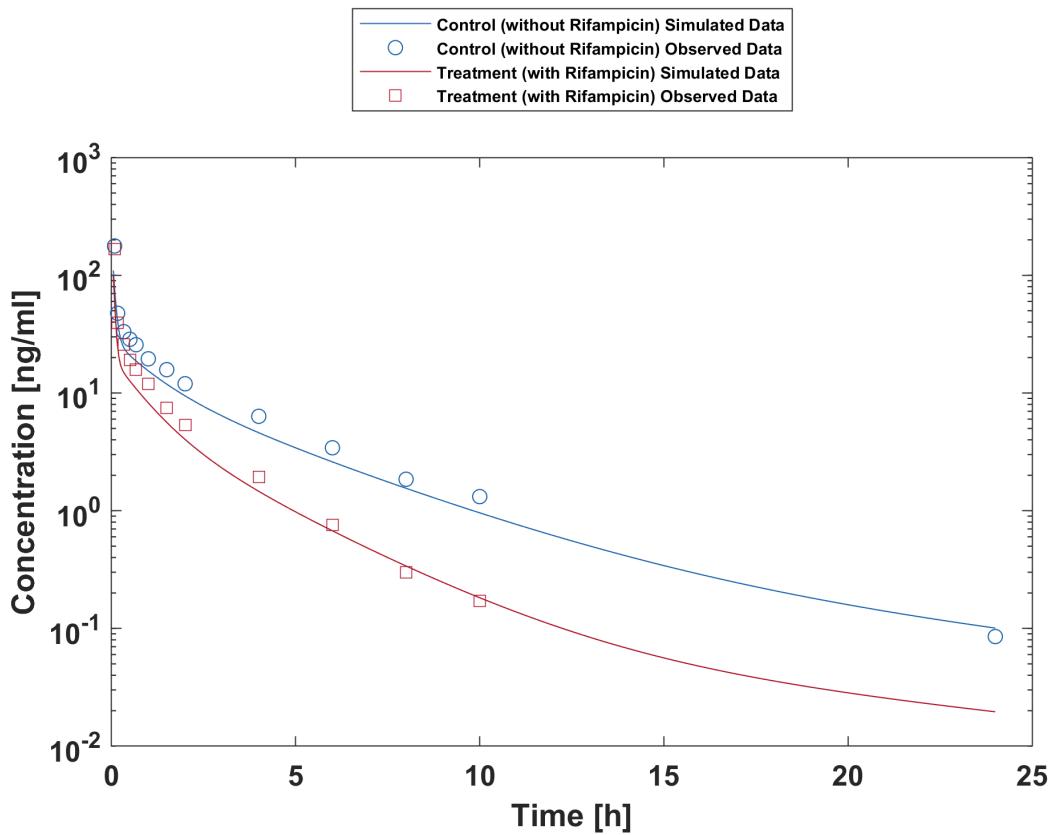
Kharasch 2011 (iv)



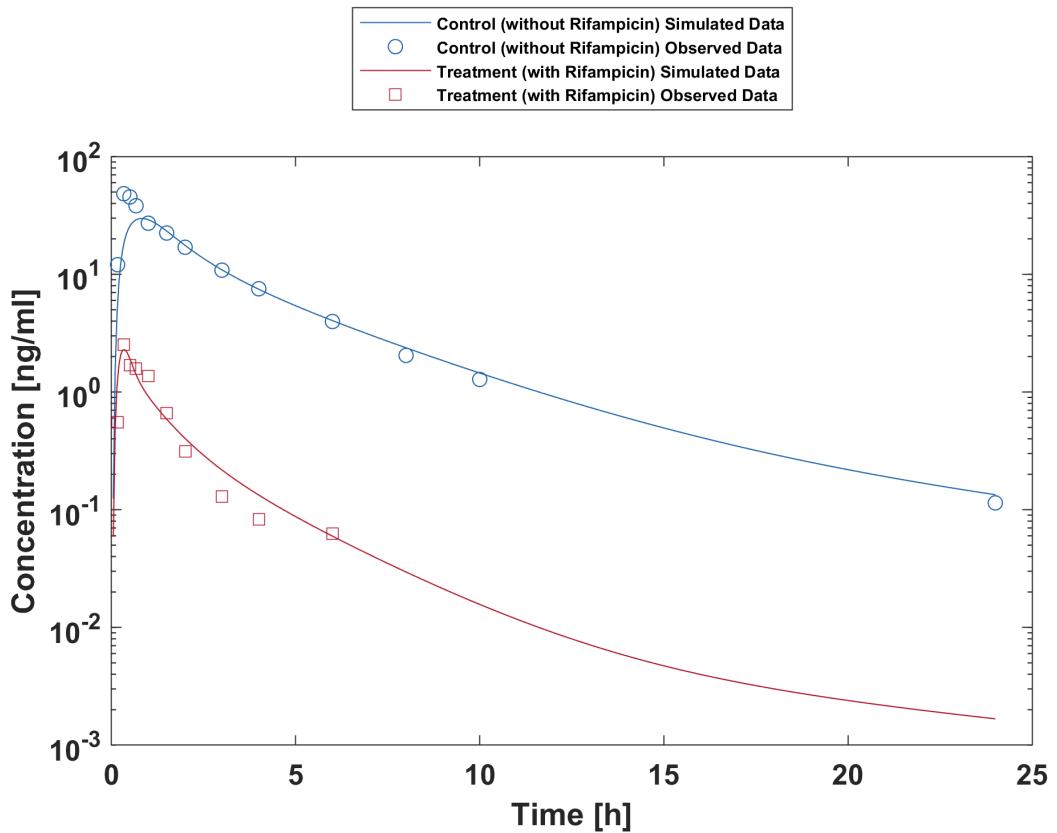
Kharasch 2011 (po)



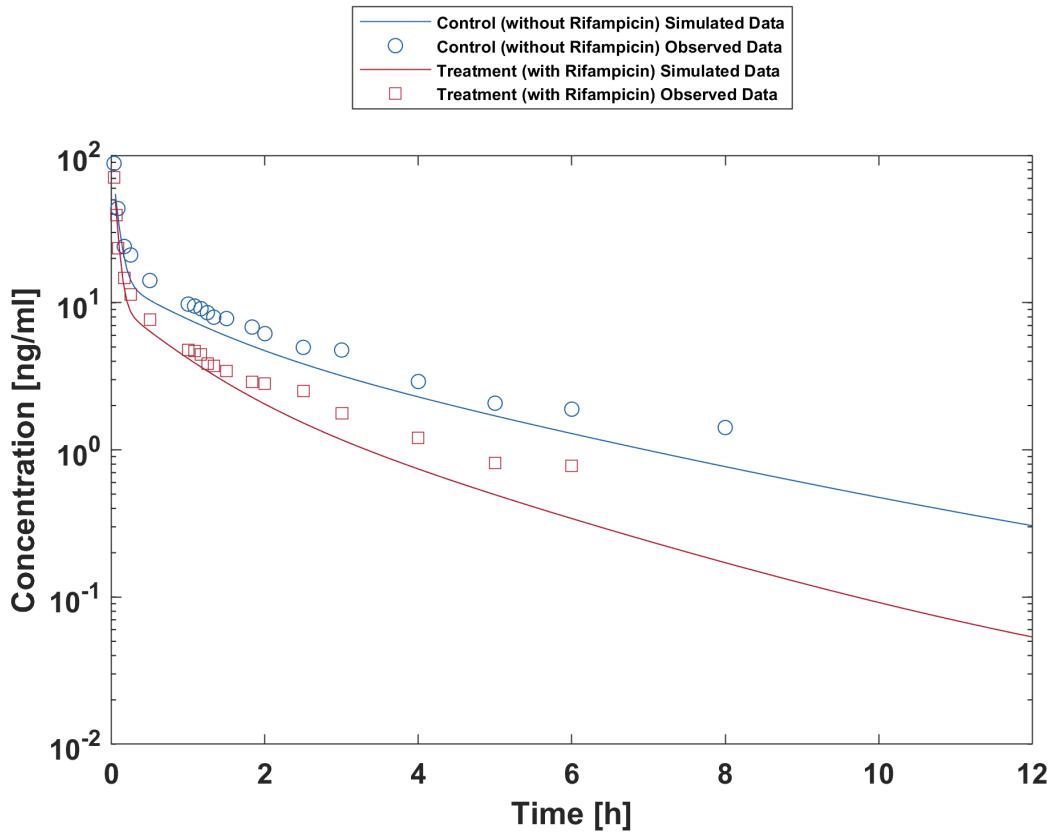
Kim 2018



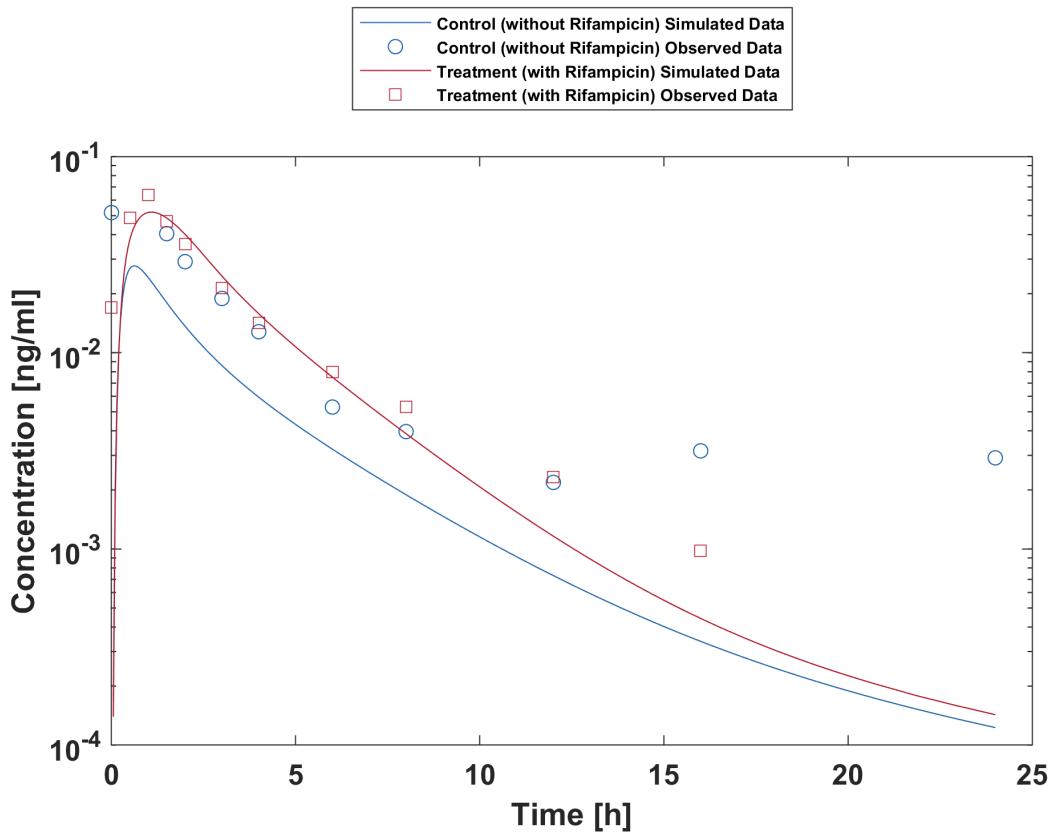
Link 2008 (iv)



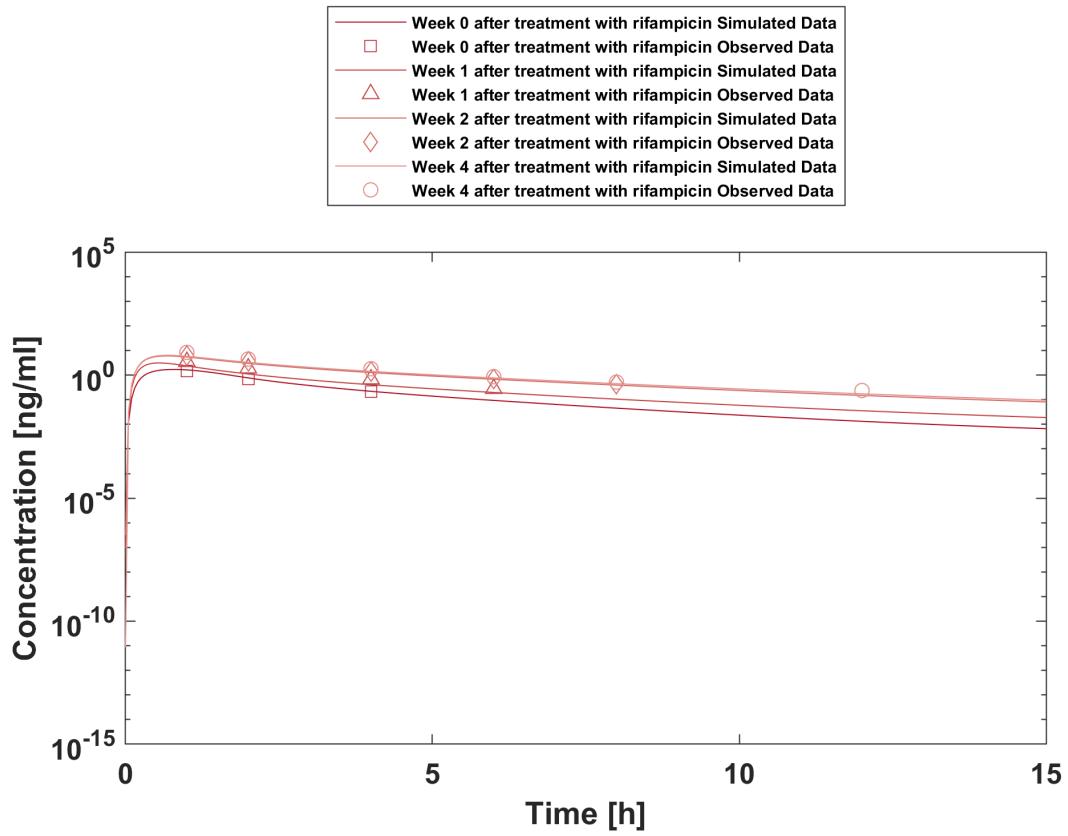
Link 2008 (po)



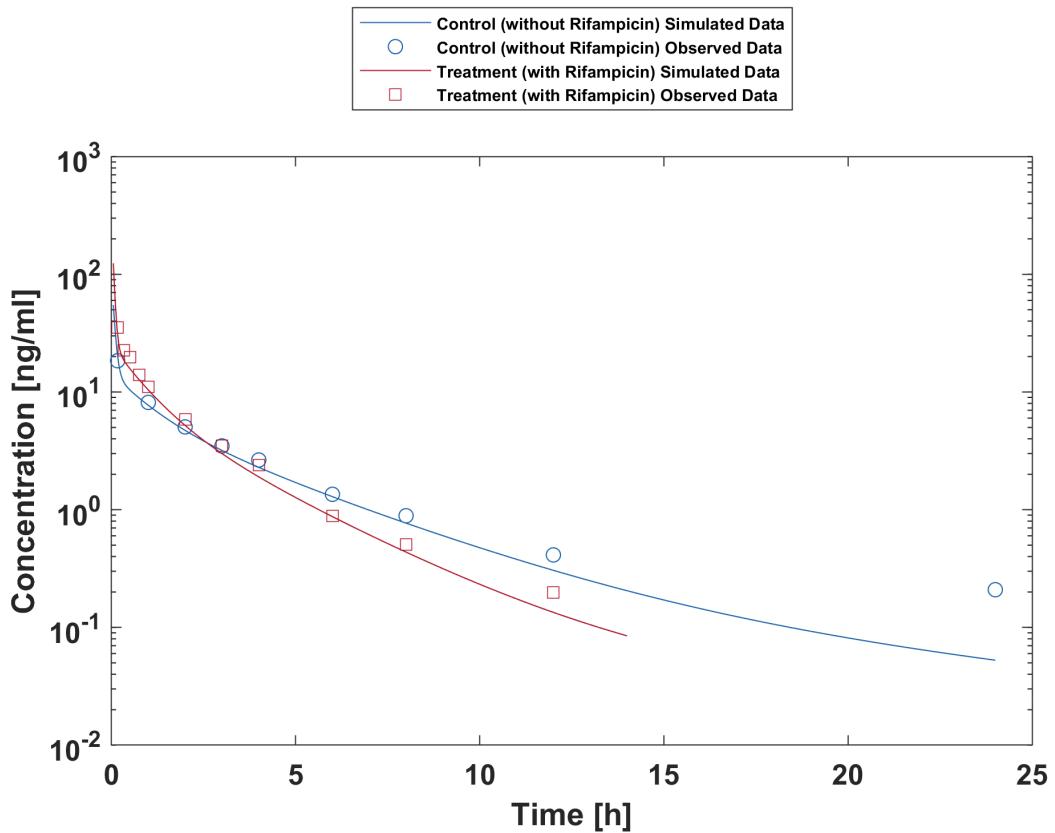
Phimmasone 2001



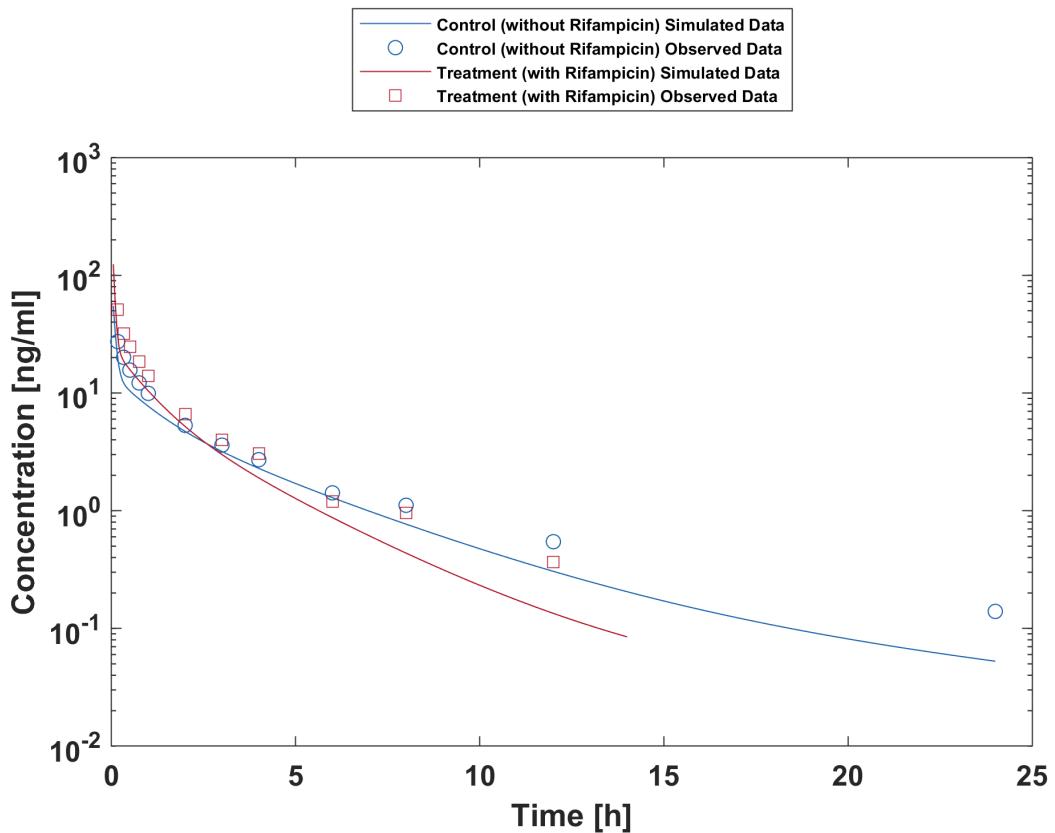
Pruksaritanont 2017



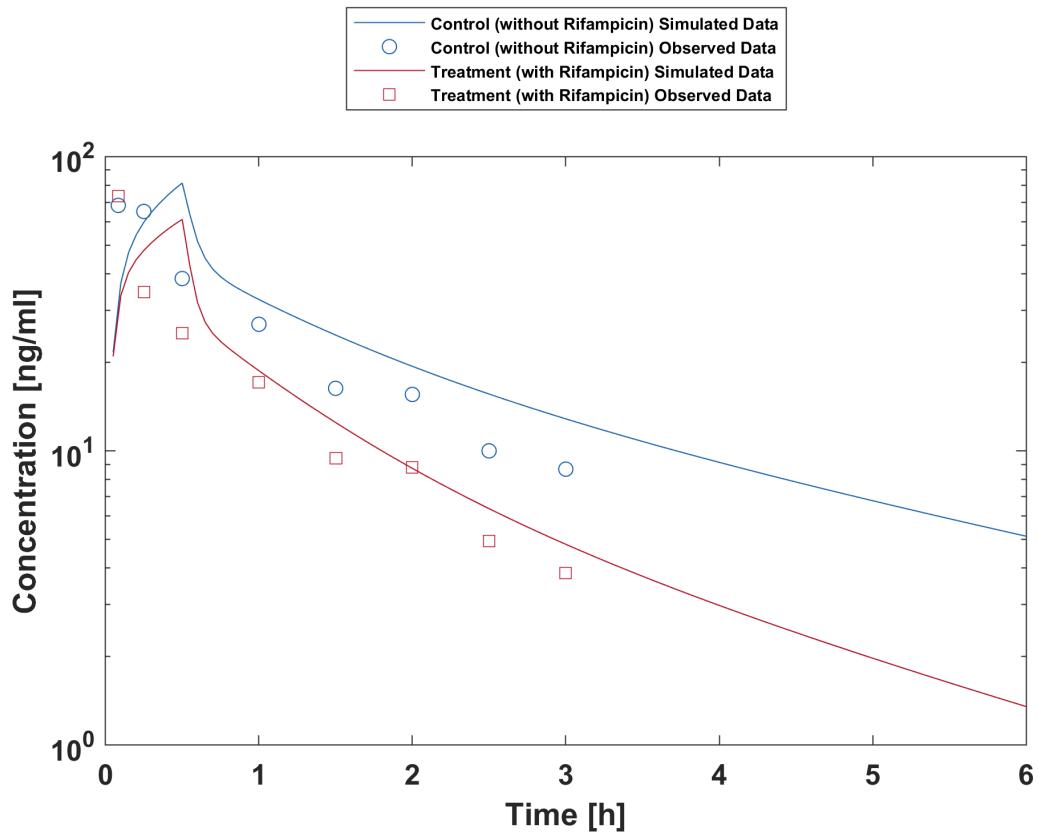
Reitman 2011



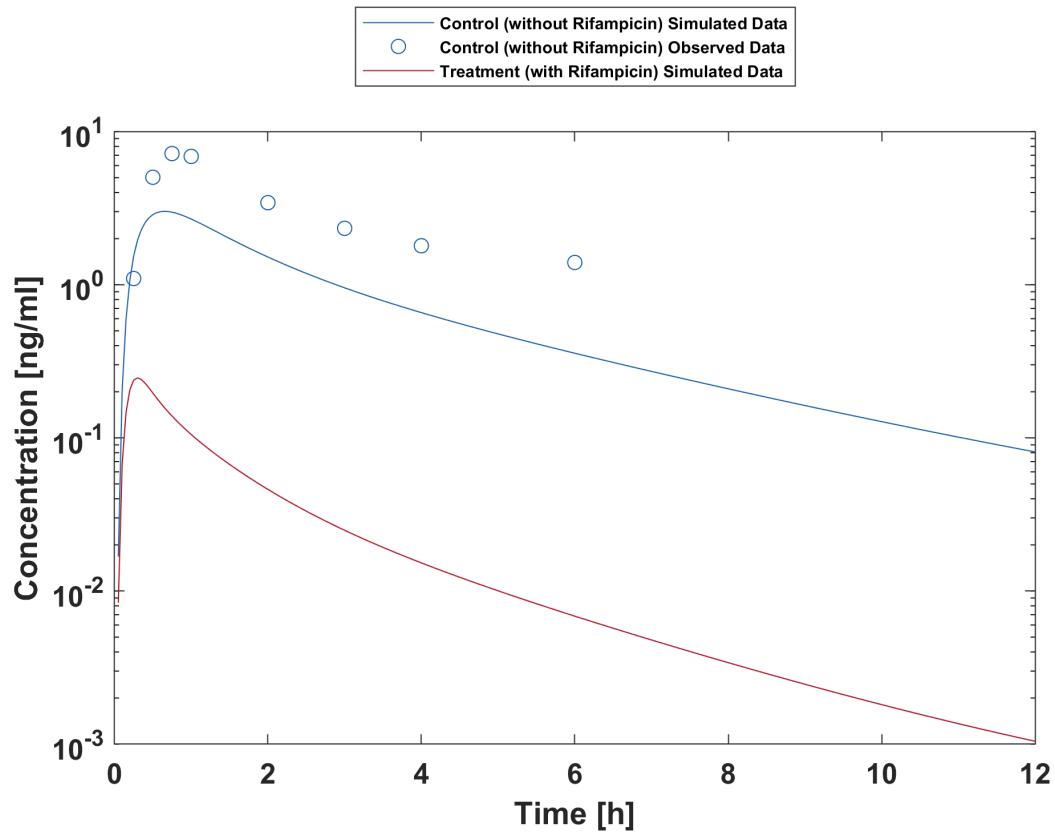
Shin 2013



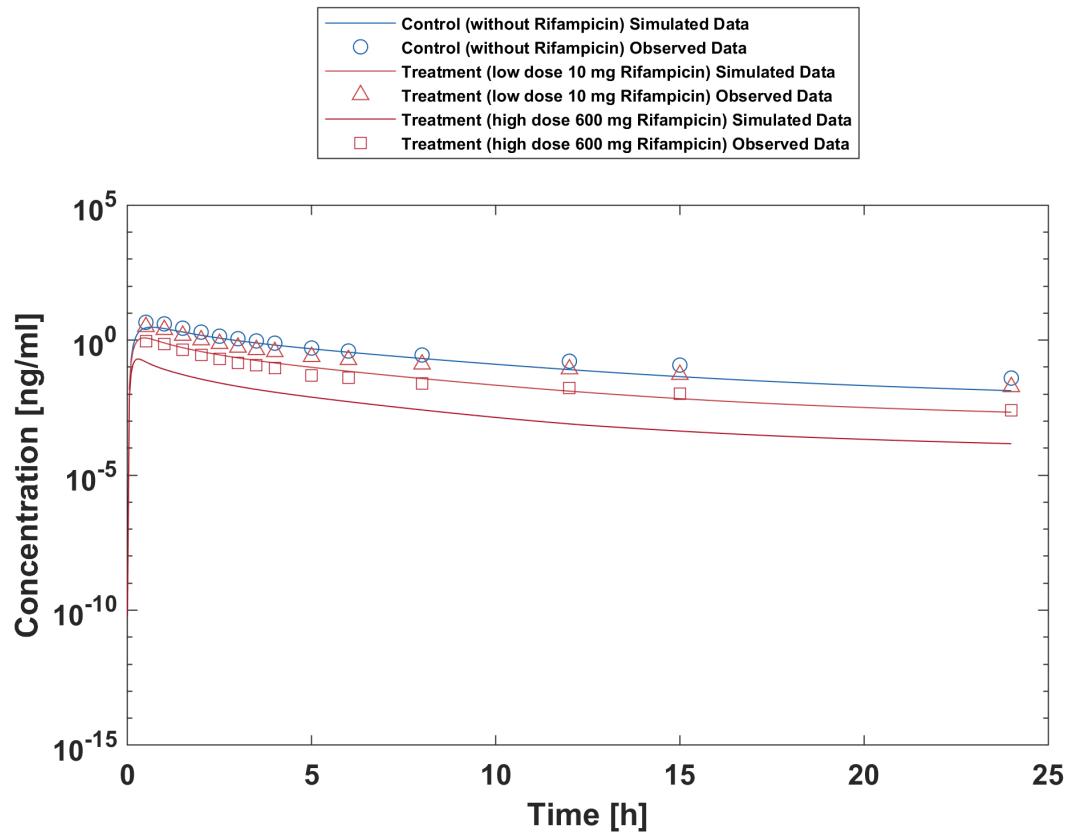
Shin 2016



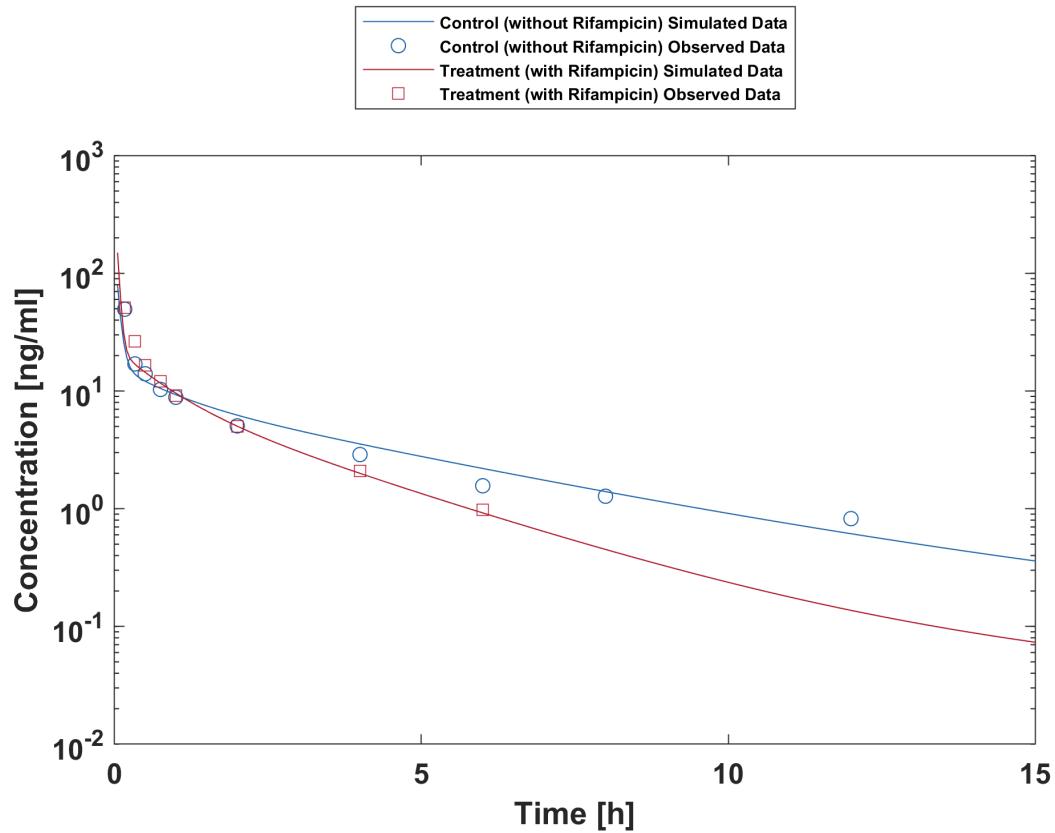
Szalat 2007



van Dyk 2018

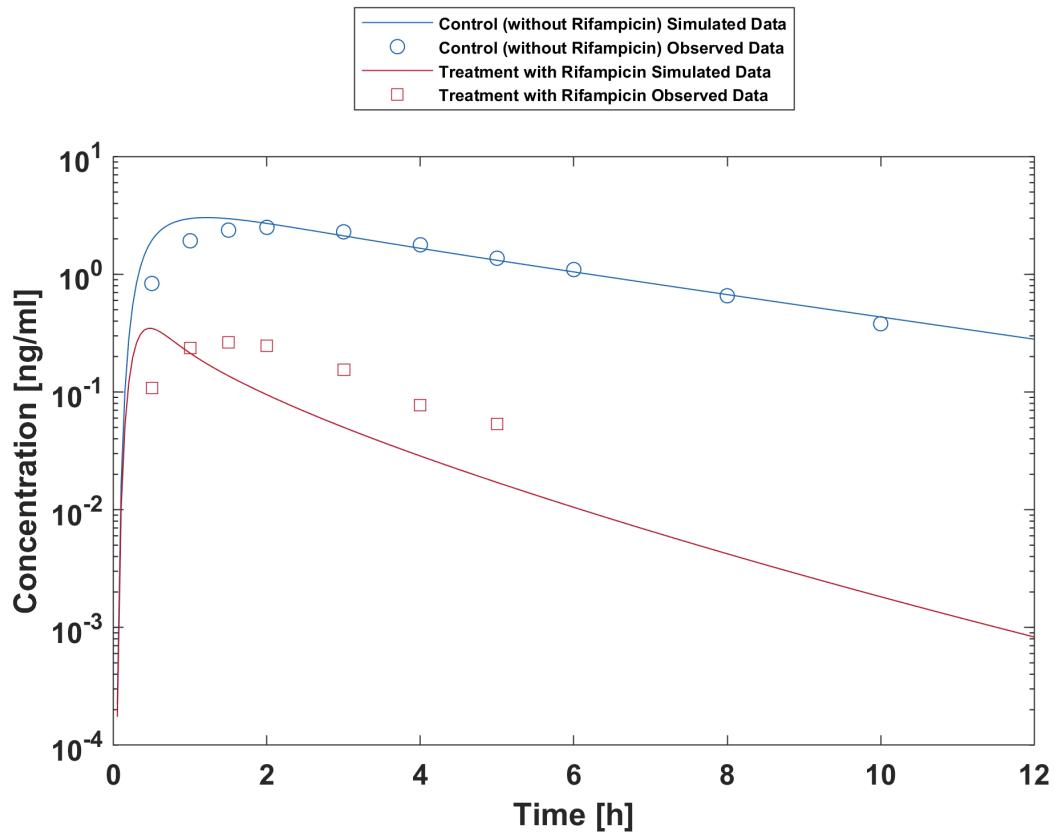


Wiesinger 2020



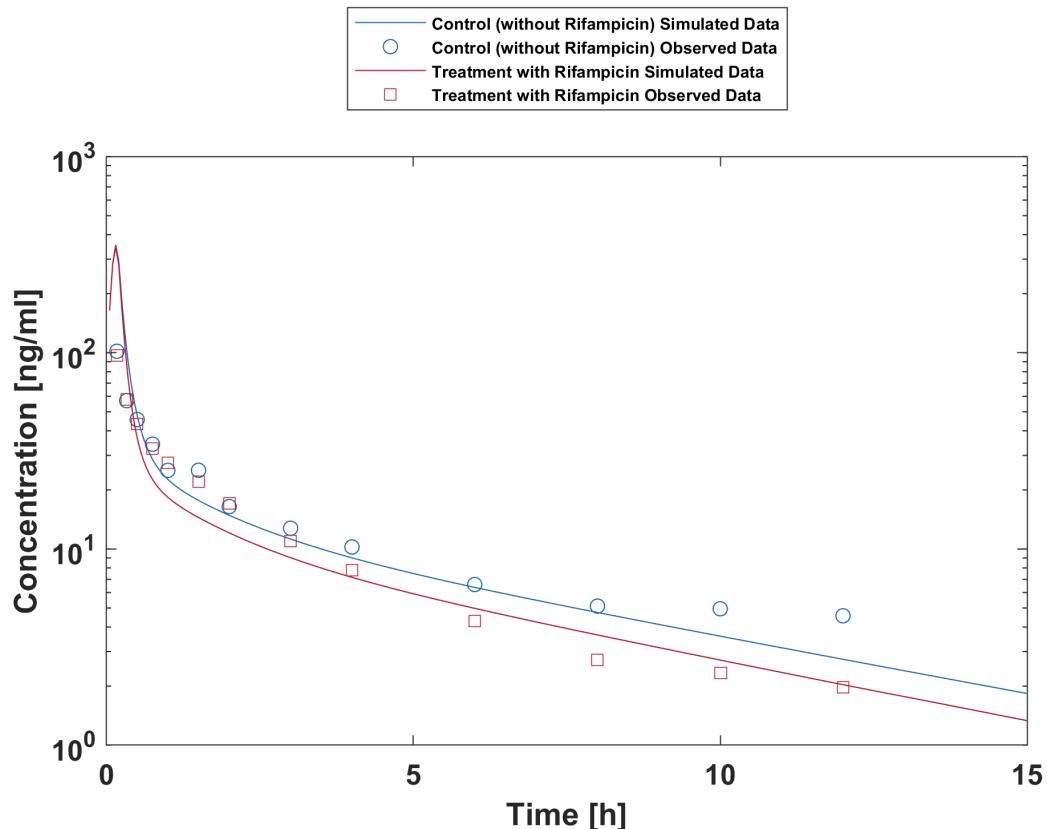
Yu 2004 (CYP3A5\*3/\*3)

### 3.23 Rifampicin - Triazolam DDI

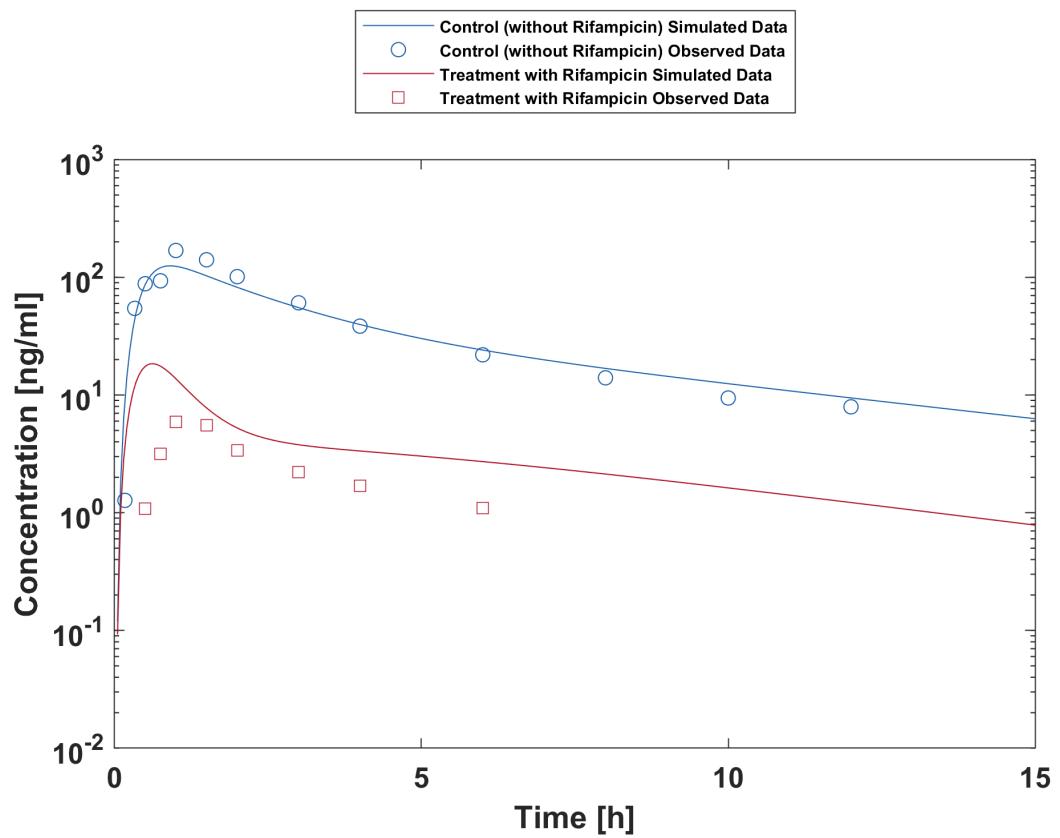


Villikka 1997

### 3.23 Rifampicin - Verapamil DDI



Barbarash 1988 (verapamil IV)



Barbarash 1988 (verapamil PO)

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## Cimetidine-Alfentanil-DDI

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## Cimetidine-Midazolam-DDI

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## Cimetidine-Triazolam-DDI

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## Clarithromycin-Triazolam-DDI

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## Erythromycin-Triazolam-DDI

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## Fluvoxamine-Alprazolam-DDI

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# 5 Appendix

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## 5.1 Open Systems Pharmacology Suite (OSPS) Introduction

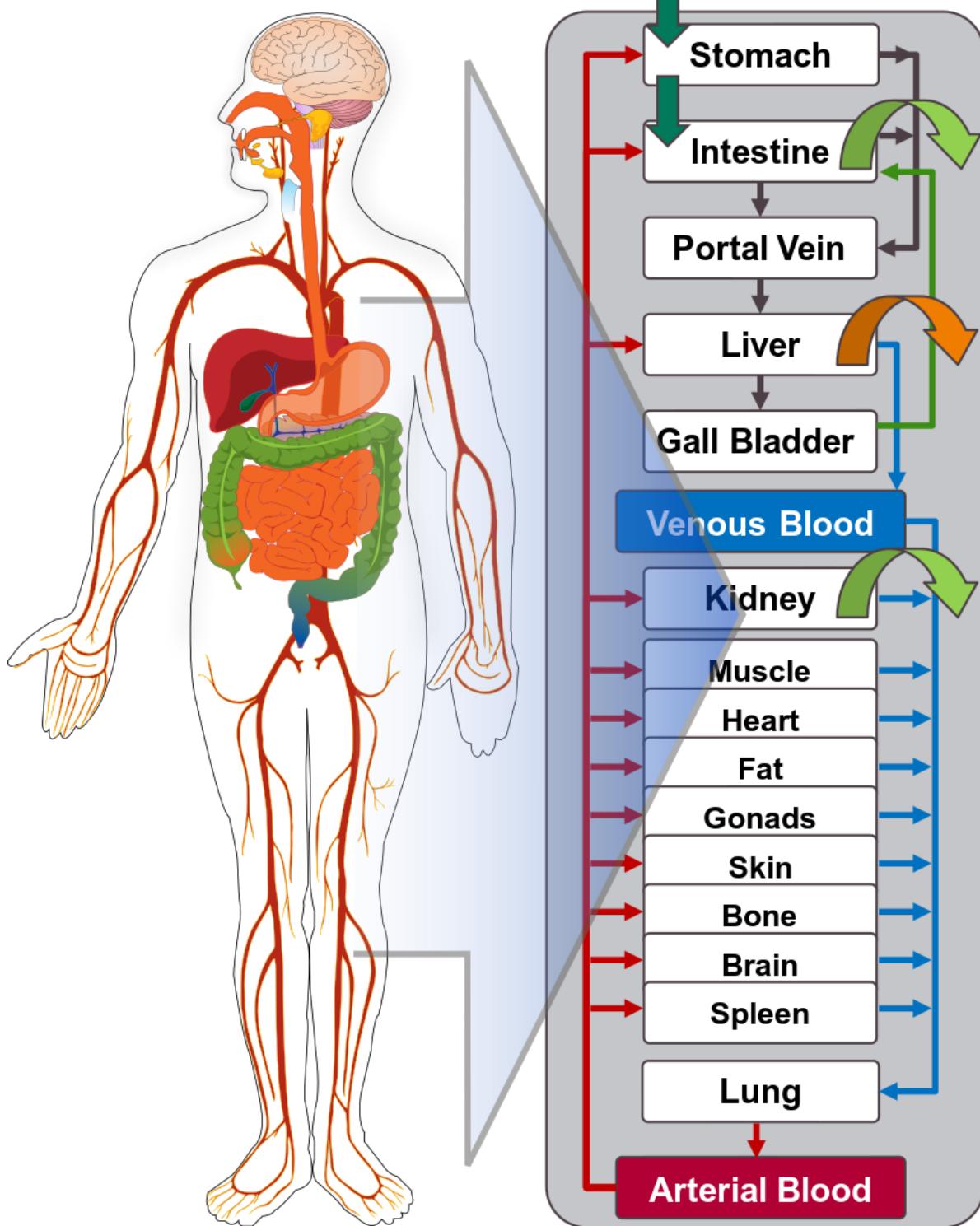
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Open Systems Pharmacology Suite (OSP suite) is a tool for PBPK modeling and simulation of drugs in laboratory animals and humans. PK-Sim® and MoBi® are part of the OSP suite [1]. PK-Sim® is based on a generic PBPK-model with 18 organs and tissues. 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

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## 5.2 Mathematical Implementation of Drug-Drug Interactions

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### 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](#).

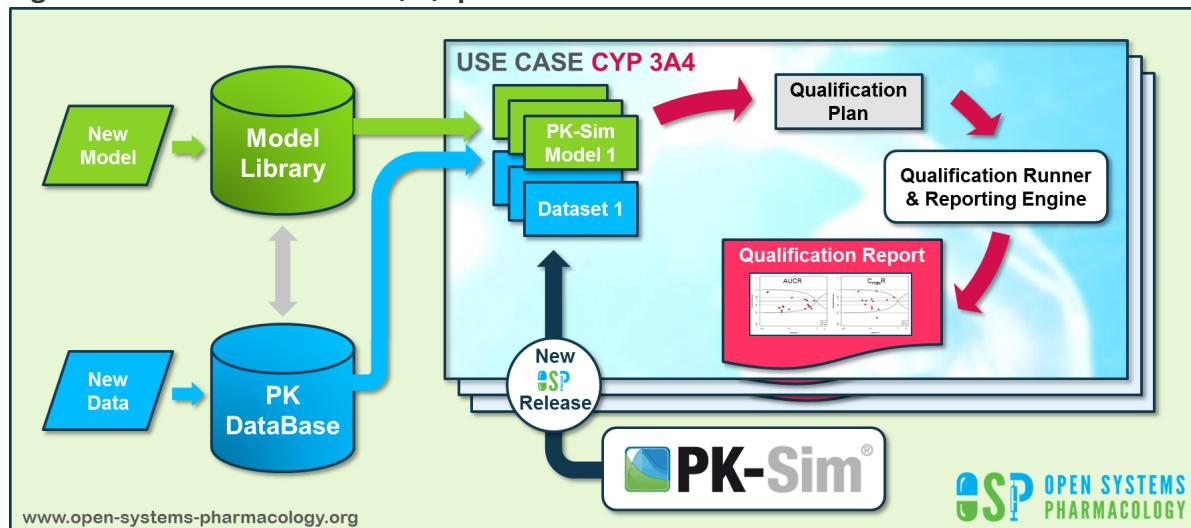
## 5.3 Automatic (re)-qualification workflow

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[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**

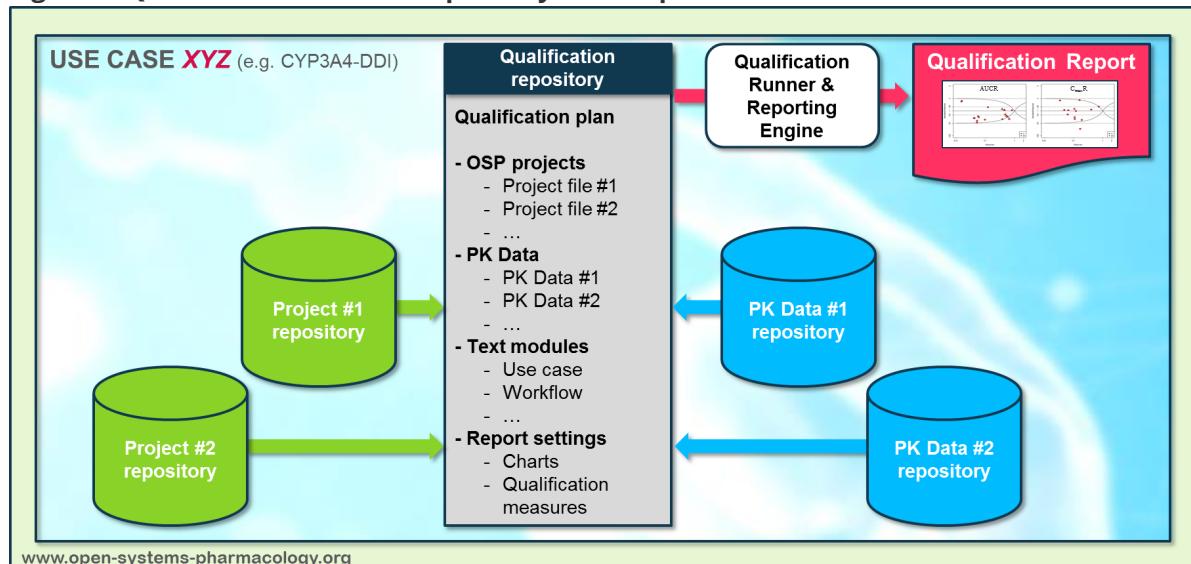


In a first step, the respective qualification scenario is saved in a special qualification repository on [GitHub](#). This qualification scenario repository contains a detailed qualification plan that links and combines respective models and data to address the use case that shall be qualified. Therefore,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