

# Building and evaluation of a PBPK model for Itraconazole in healthy adults

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Version	1.1-OSP9.1
based on <i>Model Snapshot</i> and <i>Evaluation Plan</i>	<a href="https://github.com/Open-Systems-Pharmacology/Itraconazole-Model/releases/tag/v1.1">https://github.com/Open-Systems-Pharmacology/Itraconazole-Model/releases/tag/v1.1</a>
OSP Version	9.1
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This evaluation report and the corresponding PK-Sim project file are filed at:

<https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/>

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# 1 Introduction

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Itraconazole is a triazole agent prescribed for the treatment of fungal infections. It is predominantly metabolized by CYP3A4, resulting in the sequential formation of several metabolites, starting with the major metabolite hydroxy-itraconazole, followed by keto-itraconazole and N-desalkyl-itraconazole. All three metabolites are further metabolized by CYP3A4 and parent and metabolites are reported to competitively inhibit CYP3A4 ([Isoherranen 2004](#)). Therefore, the metabolites inhibit their own formation and itraconazole inhibits further conversion of its metabolites by CYP3A4. Itraconazole has been proposed as one of the most appropriate CYP3A4 inhibitors for clinical DDI studies, to replace the currently no longer recommended CYP3A4 inhibitor drug ketoconazole.

The herein presented model represents an update of the itraconazole model published by Hanke *et al.* ([Hanke 2018](#)). The model was originally established using various clinical studies, covering a dosing range from 100 to 200 mg in different formulations (solution and capsules), administered under fasted conditions or together with food. Although the plasma concentrations of keto-itraconazole and N-desalkyl-itraconazole are lower than those of itraconazole and hydroxy-itraconazole, N-desalkyl-itraconazole is reported to be a very potent inhibitor *in vitro*, and integration of the two further metabolites into the model with their inhibitory effects enabled the description the strong non-linearity and plasma accumulation of itraconazole. The model applies sequential metabolism of itraconazole to hydroxy-itraconazole to keto-itraconazole to N-desalkyl-itraconazole by CYP3A4, including competitive inhibition of CYP3A4 by the parent drug and all three metabolites, and glomerular filtration. Competitive inhibition of P-gp was included for itraconazole.

In comparison to the published version by Hanke *et al.* 2018 ([Hanke 2018](#)), the dissolution and solubility has been optimized and updated for the administration of itraconazole capsules in fasted state (by integrating additional data ([Jalava 1997](#)) into the optimization routine).

## 2 Methods

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### 2.1 Modeling Strategy

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The general concept of building a PBPK model has previously been described by Kuepfer et al. ([Kuepfer 2016](#)). Relevant information on anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in adults was gathered from the literature and has been previously published ([Willmann 2007](#)). The information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available PK-Sim® Ontogeny Database Version 7.3 ([PK-Sim Ontogeny Database Version 7.3](#)) or otherwise referenced for the specific process.

First, a mean model including sequential metabolism of itraconazole to hydroxy-itraconazole to keto-itraconazole to N-desalkyl-itraconazole by CYP3A4 was built using clinical data from single dose and multiple dose studies with intravenous and oral administration (solution, fasted state) of itraconazole. Hereby, competitive inhibition of CYP3A4 was considered for all four compounds. The mean PBPK model was developed using a typical European individual. The relative tissue-specific expressions of enzymes predominantly being involved in the metabolism of midazolam (CYP3A4) were considered.

A specific set of parameters (see below) was optimized using the Parameter Identification module provided in PK-Sim®. Structural model selection was mainly guided by visual inspection of the resulting description of data and biological plausibility.

Once the appropriate structural model was identified, additional parameters for different administration states (*solution fed*, *capsule fasted* and *capsule fed* versus the reference state *solution fasted*) were empirically optimized. Clinical data suggest that the bioavailability of itraconazole is enhanced when an oral solution is given in the fasted state compared to fed state ([Van de Welde 1996](#), [Barone 1998a](#)). In contrast, a meal significantly enhances the amount of itraconazole absorbed after administrations of capsules (in comparison to fasted state administrations of capsules) ([Barone 1993a](#)). To reflect these observations, relevant parameters, in particular solubility and those describing dissolution kinetics (of capsules), were assumed to be variable between these four scenarios and were independently identified using the Parameter Identification module provided in PK-Sim®.

Details about compound properties (physicochemical, *in vitro* and clinical) can be found in [Section 2.2](#).

Details about the structural model and its parameters can be found in [Section 2.3](#).

## 2.2 Data

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### 2.2.1 In vitro and physicochemical data

A literature search was performed to collect available information on physicochemical properties of itraconazole and metabolites. The obtained information from literature is summarized in the table below and was used for model building. Note that not all parameters were used in the final model. A list of final model parameters is provided below in later sections.

## Itraconazole

Parameter	Unit	Value	Source	Description
MW	g/mol	705.633	<a href="#">DrugBank DB01167</a>	Molecular weight
pK <sub>a,base</sub>		3.7	<a href="#">Heykants 1989</a>	acid dissociation constant of conjugate acid; compound type: base
Solubility (pH)	mg/L	8.0 (6.5)	<a href="#">Taupitz 2013</a>	Solubility in FaSSIF (fasted state simulated intestinal fluid)
logP		5.66	<a href="#">Heykants 1989</a>	Partition coefficient between octanol and water
f <sub>u</sub>	%	0.2	<a href="#">Heykants 1989</a>	Fraction unbound in plasma
	%	0.2	<a href="#">Riccardi 2015</a>	Fraction unbound in plasma
	%	1.58	<a href="#">Ishigam 2001</a>	Fraction unbound in plasma
	%	3.6	<a href="#">Templeton 2008</a>	Fraction unbound in plasma
V <sub>max</sub> , K <sub>m</sub> CYP3A4	pmol/min/nmol, nmol/L	270 3.9	<a href="#">Isoherranen 2004</a>	CYP3A4 supersomes Michaelis-Menten kinetics
K <sub>i</sub> CYP3A4	nmol/L	1.3	<a href="#">Isoherranen 2004</a>	CYP3A4 inhibition constant
K <sub>i</sub> P-gp	nmol/L	8.0	<a href="#">Shityakov 2014</a>	P-gp inhibition constant

## Hydroxy-itraconazole

Parameter	Unit	Value	Source	Description
MW	g/mol	721.633	<a href="#">DrugBank DBMET00374</a>	Molecular weight
logP		4.5	<a href="#">PubChem CID 108222</a>	Partition coefficient between octanol and water, computed by XLogP3 3.0
f <sub>u</sub>	%	0.5	<a href="#">Templeton 2008</a>	Fraction unbound in plasma
	%	1.7	<a href="#">Riccardi 2015</a>	Fraction unbound in plasma
	%	2.12	<a href="#">Chen 2016</a>	Fraction unbound in plasma
V <sub>max</sub> , K <sub>m</sub> CYP3A4	pmol/min/nmol, nmol/L	543 27	<a href="#">Isoherranen 2004</a>	CYP3A4 supersomes Michaelis-Menten kinetics
K <sub>i</sub> CYP3A4	nmol/L	14.4	<a href="#">Isoherranen 2004</a>	CYP3A4 inhibition constant

## Keto-itraconazole

Parameter	Unit	Value	Source	Description
MW	g/mol	719.617	<a href="#">PubChem CID 53865186</a>	Molecular weight
logP		4.5	<a href="#">PubChem CID 53865186</a>	Partition coefficient between octanol and water, computed by XLogP3 3.0
fu	%	1.0	<a href="#">Riccardi 2015</a>	Fraction unbound in plasma
	%	5.3	<a href="#">Templeton 2008</a>	Fraction unbound in plasma
V <sub>max</sub> , K <sub>m</sub> CYP3A4	pmol/min/nmol, nmol/L	86.9 1.4	<a href="#">Isoherranen 2004</a>	CYP3A4 supersomes Michaelis-Menten kinetics
IC <sub>50</sub> CYP3A4 <sup>†</sup>	nmol/L	7.0	<a href="#">Isoherranen 2004</a>	CYP3A4 inhibition constant for half maximal inhibitory concentration at constant substrate concentration

<sup>†</sup> The IC<sub>50</sub> values was converted to a K<sub>i</sub> value via Cheng-Prusoff equation ([Chen 1973](#)) with a substrate (*midazolam*) concentration of 1 µmol/L and an assumed substrate (*midazolam*) K<sub>m</sub> value of 2.73 µmol/L: **5.12 nmol/L**

## N-Desalkyl-itraconazole

Parameter	Unit	Value	Source	Description
MW	g/mol	649.527	<a href="#">PubChem CID 53789808</a>	Molecular weight
logP		4.2	<a href="#">PubChem CID 53789808</a>	Partition coefficient between octanol and water, computed by XLogP3 3.0
fu	%	1.1	<a href="#">Riccardi 2015</a>	Fraction unbound in plasma
	%	1.2	<a href="#">Templeton 2008</a>	Fraction unbound in plasma
IC <sub>50</sub> CYP3A4 <sup>†</sup>	nmol/L	0.44	<a href="#">Isoherranen 2004</a>	CYP3A4 inhibition constant for half maximal inhibitory concentration at constant substrate concentration

<sup>†</sup> The IC<sub>50</sub> values was converted to a K<sub>i</sub> value via Cheng-Prusoff equation ([Chen 1973](#)) with a substrate (*midazolam*) concentration of 1 µmol/L and an assumed substrate (*midazolam*) K<sub>m</sub> value of 2.73 µmol/L: **0.32 nmol/L**

## 2.2.2 Clinical data

A literature search was performed to collect available clinical data on itraconazole and its metabolites in adults. The itraconazole model was built and verified using various clinical studies, covering a dosing range of 100 to 200 mg with different formulations (solution vs. capsule), administered under fasting conditions or together with food.

The following dosing scenarios were simulated and compared to respective data:

Route	Formulation	Food state	Dose [mg]	Dosing	PK Data	Used for <sup>†</sup>	Reference
iv	-	-	100	SD	Itraconazole	mv	<a href="#">Heykants 1989</a>
			200	OD	Itraconazole Hydroxy-ltr.	mbb	<a href="#">Mouton 2006</a>
po	solution	fasted	100	SD	Itraconazole	mbb	<a href="#">Van de Velde 1996</a>
					Itraconazole Hydroxy-ltr.	mbb	<a href="#">Van Peer 1989</a>
				OD	Itraconazole Hydroxy-ltr. Keto-ltr. N-Desalkyl-ltr.	mbb	<a href="#">Templeton 2008</a>
			200	OD	Itraconazole Hydroxy-ltr.	mbb	<a href="#">Barone 1998a</a>
		fed	100	SD	Itraconazole Hydroxy-ltr.	mbe	<a href="#">Van de Velde 1996</a>
					Itraconazole	mbe	<a href="#">Heykants 1989</a>
			200	SD	Itraconazole Hydroxy-ltr.	mbe	<a href="#">Barone 1998b</a>
				OD	Itraconazole Hydroxy-ltr.	mbe	<a href="#">Barone 1998a</a>
	capsule	fasted	100	SD	Itraconazole	mbe	<a href="#">Van Peer 1989</a>
				BID	Itraconazole	mv	<a href="#">Kivistö 1997</a>
			200	SD	Itraconazole Hydroxy-ltr.	mbe	<a href="#">Barone 1993</a>
					Itraconazole	mv	<a href="#">Neuvonen 1996</a>
				OD	Itraconazole	mbe	<a href="#">Jalava 1997</a>
					Itraconazole	mbe	<a href="#">Olkola 1994</a>
					Itraconazole	mv	<a href="#">Varhe 1994</a>
		fed	100	SD	Itraconazole	mbe	<a href="#">Van Peer 1989</a>
				OD	Itraconazole	mbe	<a href="#">Van Peer 1989</a>
					Itraconazole	mv	<a href="#">Hardin 1988</a>
			200	SD	Itraconazole Hydroxy-ltr.	mbe	<a href="#">Barone 1993</a>
					Itraconazole Hydroxy-ltr.	mbe	<a href="#">Barone 1998b</a>
					Itraconazole	mv	<a href="#">Neuvonen 1996</a>
			200	OD	Itraconazole	mv	<a href="#">Hardin 1988</a>
				BID	Itraconazole	mbe	<a href="#">Barone 1993</a>
					Itraconazole Hydroxy-ltr.	mv	<a href="#">Hardin 1988</a>

<sup>†</sup> *mbb* model building basic: used to inform the basic model parameters (see [Section 2.3.5](#)); *mbe* model building extended: used to inform solubility and, if applicable, formulation-dependent parameters only (see [Section 2.3.5](#)); *mv* model verification only

## 2.3 Model Parameters and Assumptions

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### 2.3.1 Absorption

Clinical data suggest that the bioavailability of itraconazole is enhanced when an oral solution is given in the fasted state compared to fed state ([Van de Welde 1996](#), [Barone 1998a](#)). In contrast, a meal significantly enhances the amount of itraconazole absorbed after administrations of capsules (in comparison to fasted state administrations of capsules) ([Barone 1993a](#)). Thus, four different scenarios can be identified: *solution fasted*, *solution fed*, *capsule fasted* and *capsule fed*. The *solution fasted* scenario was considered to be the reference scenario.

Herein, the model parameter `specific intestinal permeability` was optimized to best match clinical data (see [Section 2.3.5](#)). The default solubility was assumed to be the measured value in FaSSIF (fasted state simulated intestinal fluid; see [Section 2.2.1](#)).

In a next step, the solubility was optimized for the *solution fed* scenario (in comparison to *solution fasted*).

Then, for the scenarios *capsule fasted* and *capsule fed*, solubility and the dissolution rate of the capsules (implemented via an empirical Weibull dissolution) were optimized.

The results of the optimization can be found in [Section 2.3.5](#).

### 2.3.2 Distribution

Various values for the fraction unbound of itraconazole have been reported in literature, ranging from 0.2 to 3.6% (see [Section 2.2.1](#)). For this model, the final value was optimized within this range to best match observed clinical data (see [Section 2.3.5](#)). For the metabolites, the measured values reported by Riccardi *et al.* ([Riccardi 2015](#)) were incorporated into the model. It was assumed that the major binding partner is albumin.

No  $pK_a$  values were reported for the three metabolites. Here, it was assumed that the metabolites are similar to the parent drug and the reported basic  $pK_a$  value of 3.7 was applied (see also [Section 2.2.1](#)).

An important parameter influencing the resulting volume of distribution is lipophilicity. The reported experimental or predicted  $\log P$  values served as starting values for the four compounds. Finally, the model parameters `Lipophilicity` were optimized to match best clinical data (see also [Section 2.3.5](#)).

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built in PK-Sim®, observed clinical data was best described by choosing the partition coefficient calculation by `Rodgers` and `Rowland` and cellular permeability calculation by `PK-Sim Standard` for itraconazole and its metabolites.

### 2.3.3 Metabolism and Elimination



Metabolic pathways via CYP3A4 were implemented in the model via Michaelis-Menten kinetics for all four compounds. If available, *in vitro* determined unbound  $K_m$  values ([Isoherranen 2004](#)) served as starting values. Respective  $k_{cat}$  values were optimized to best match clinical data (see also [Section 2.3.5](#)).

The CYP3A4 expression profile is based on high-sensitivity real-time RT-PCR ([Nishimura 2013](#)). Absolute tissue-specific concentrations were obtained by considering the respective absolute concentration in the liver. The PK-Sim® Ontogeny Database Version 7.3 provides a default value for CYP3A4 reference concentration in the liver (compare [Rodrigues 1999](#) and assume 40 mg protein per gram liver).

Additionally, for all four compounds a renal clearance (assumed to be driven by glomerular filtration) was implemented.

## 2.3.4 DDI Parameters

The following subsections describe the model input for DDI-related parameters, i.e. inhibition of certain enzymes and transporters, for which itraconazole may act in a perpetrator role. Verification of these model parameters and linked processes in combination with sensitive CYP3A4 / P-gp substrates is not evaluated in this report. Applications are assessed in specific use cases and reported elsewhere. Note, however, that the competitive CYP3A4 inhibition of the four compounds results in inhibition of metabolite formation (of hydroxy-itraconazole, keto-itraconazole, N-desalkyl-itraconazole) and the metabolism of N-desalkyl-itraconazole. This effectively contributes to the PK non-linearity of itraconazole and its metabolites, especially after multiple doses.

### CYP3A4 inhibition

*In vitro* determined unbound  $K_i$  values for itraconazole and hydroxy-itraconazole ([Isoherranen 2004](#)) served directly as model input (see [Section 2.2.1](#)).

*In vitro* determined unbound  $IC_{50}$  values for keto-itraconazole and N-desalkyl-itraconazole ([Isoherranen 2004](#)) were converted to  $K_i$  values via the Cheng-Prusoff equation ([Chen 1973](#)) with a substrate (*midazolam*) concentration of 1  $\mu\text{mol/L}$  and an assumed substrate (*midazolam*)  $K_m$  value of 2.73  $\mu\text{mol/L}$  (see [Section 2.2.1](#)).

### P-gp inhibition

An *in vitro* determined  $K_i$  values for itraconazole ([Shityakov 2014](#)) served directly as model input (see [Section 2.2.1](#)).

## 2.3.5 Automated Parameter Identification

This is the result of the final parameter identification for the basic model:

Compound	Model Parameter	Optimized Value	Unit
Itraconazole	Lipophilicity	4.62	Log Units
	Specific intestinal permeability	5.33E-05	dm/min
	Fraction unbound (plasma, reference value)	0.6	%
	K <sub>m</sub> (CYP3A4)	2.07	nmol/L
	k <sub>cat</sub> (CYP3A4)	0.040	1/min
Hydroxy-Itr.	Lipophilicity	3.72	Log Units
	Fraction unbound (plasma, reference value)	1.7 FIXED (see <a href="#">Section 2.2.1</a> )	%
	K <sub>m</sub> (CYP3A4)	4.17	nmol/L
	k <sub>cat</sub> (CYP3A4)	0.020	1/min
Keto-Itr.	Lipophilicity	4.21	Log Units
	Fraction unbound (plasma, reference value)	1.0 FIXED (see <a href="#">Section 2.2.1</a> )	%
	K <sub>m</sub> (CYP3A4)	2.22	nmol/L
	k <sub>cat</sub> (CYP3A4)	0.393	1/min
N-Desalkyl-Itr.	Lipophilicity	5.18	Log Units
	Fraction unbound (plasma, reference value)	1.1 FIXED (see <a href="#">Section 2.2.1</a> )	%
	K <sub>m</sub> (CYP3A4)	0.63	nmol/L
	k <sub>cat</sub> (CYP3A4)	0.061	1/min

This is the result of the final parameter identification for the solubility and, in case of capsule administrations, the dissolution parameters of an empirical Weibull function according to the different administration scenarios of itraconazole:

Scenario	Model Parameter	Optimized Value	Unit
Solution fasted	Solubility at reference pH	8.0 FIXED (see <a href="#">Section 2.2.1</a> )	mg/L
Solution fed	Solubility at reference pH	1.58	mg/L
Capsule fasted	Solubility at reference pH	0.97	mg/L
	Dissolution time (50% dissolved)	406	min
	Dissolution shape	1.43	
Capsule fed	Solubility at reference pH	0.70	mg/L
	Dissolution time (50% dissolved)	139	min
	Dissolution shape	0.82	

## 3 Results and Discussion

The PBPK model for itraconazole was developed and verified with clinical pharmacokinetic data.

The model was built and evaluated covering data from various clinical studies, covering a dosing range of 100 to 200 mg in different formulations (solution vs. capsule), administered under fasting conditions or together with food.

The model quantifies metabolism via CYP3A4 and inhibition of CYP3A4.

The next sections show:

1. the final model input parameters for the building blocks: [Section 3.1](#).
2. the overall goodness of fit: [Section 3.2](#).
3. simulated vs. observed concentration-time profiles for the clinical studies used for model building and for model verification: [Section 3.3](#).

### 3.1 Final input parameters

The compound parameter values of the final PBPK model are illustrated below.

#### Formulation: Capsule fasted

Type: Weibull

##### Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	406.3001802552 min	Parameter Identification-Parameter Identification-Value updated from 'Capsule fasted' on 2019-05-15 12:25
Lag time	0 min	
Dissolution shape	1.4297720052	Parameter Identification-Parameter Identification-Value updated from 'Capsule fasted' on 2019-05-15 12:25
Use as suspension	Yes	

#### Formulation: Capsule fed

Type: Weibull

##### Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	138.95 min	
Lag time	0 min	
Dissolution shape	0.82	
Use as suspension	Yes	

#### Compound: Hydroxy-Itraconazole

## Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	1 mg/l		No value available	True
Reference pH	7		No value available	True
Lipophilicity	3.718 Log Units		Fit	True
Fraction unbound (plasma, reference value)	1.7 %	Publication-Templeton, 2008	Templeton, 2008	True
Cl	2			
Is small molecule	Yes			
Molecular weight	721.633 g/mol			
Plasma protein binding partner	Albumin			

## Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	PK-Sim Standard

## Processes

### Metabolizing Enzyme: CYP3A4-Isoherranen 2004

Molecule: CYP3A4

Metabolite: Keto-Itraconazole

#### Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.543 nmol/min/pmol rec. enzyme	Publication-Isoherranen 2004
Km	4.1716224833 nmol/l	Publication-Isoherranen 2004
kcat	0.0203370845 1/min	Unknown

### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Isoherranen, 2004

### Inhibition: CYP3A4-Isoherranen, 2004

Molecule: CYP3A4

## Parameters

Name	Value	Value Origin
Ki	14.4 nmol/l	Publication-Isoherranen, 2004

## Compound: Itraconazole

### Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	8 mg/l	Publication-Taupitz et al. 2013	Solution fasted (Taupitz et al. 2013)	True
Reference pH	6.5	Publication-Taupitz et al. 2013	Solution fasted (Taupitz et al. 2013)	True
Solubility at reference pH	1.58 mg/l		Solution fed	False
Reference pH	6.5		Solution fed	False
Solubility at reference pH	0.9728307177 mg/l	Parameter Identification-Parameter Identification-Value updated from 'Capsule fasted' on 2019-05-15 12:25	Capsule fasted	False
Reference pH	6.5		Capsule fasted	False
Solubility at reference pH	0.7 mg/l		Capsule fed	False
Reference pH	6.5		Capsule fed	False
Lipophilicity	4.624 Log Units	Parameter Identification-Fit	Fit	True
Fraction unbound (plasma, reference value)	0.6016197247 %		Templeton, 2008	True
Permeability	0.1111202419 cm/min	Parameter Identification-Fit	Fit	False
Specific intestinal permeability (transcellular)	5.3261558344E-05 dm/min	Parameter Identification-Fit	Fit	True
Cl	2			
Is small molecule	Yes			
Molecular weight	705.633 g/mol			
Plasma protein binding partner	Albumin			

### Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	PK-Sim Standard

## Processes

### Metabolizing Enzyme: CYP3A4-Isoherranen 2004

Molecule: CYP3A4

Metabolite: Hydroxy-Itraconazole

#### Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.27 pmol/min/pmol rec. enzyme	Publication-Isoherranen 2004
Km	2.0688492598 nmol/l	Publication-Isoherranen 2004
kcat	0.0402937875 1/min	Unknown

### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Isoherranen 2004

### Inhibition: CYP3A4-Isoherranen, 2004

Molecule: CYP3A4

#### Parameters

Name	Value	Value Origin
Ki	1.3 nmol/l	Parameter Identification-Isoherranen, 2004

### Inhibition: ABCB1-Shityakov 2014

Molecule: ABCB1

#### Parameters

Name	Value	Value Origin
Ki	0.008 µmol/l	Publication-Shityakov 2014

## Compound: Keto-Itraconazole

#### Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	1 mg/l		No value available	True
Reference pH	7		No value available	True
Lipophilicity	4.2109086248 Log Units		Fit	True
Fraction unbound (plasma, reference value)	1 %	Publication-Templeton, 2008	Templeton, 2008	True
Cl	2			
Is small molecule	Yes			
Molecular weight	719.617 g/mol			
Plasma protein binding partner	Albumin			

## Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	PK-Sim Standard

## Processes

### Metabolizing Enzyme: CYP3A4-Isoherranen 2004

Molecule: CYP3A4

Metabolite: N-desalkyl-litraconazole

#### Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.0869 pmol/min/pmol rec. enzyme	Publication-Isoherranen 2004
Km	2.2214874285 nmol/l	Publication-Isoherranen 2004
kcat	0.3933927416 1/min	Unknown

### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Isoherranen 2004

### Inhibition: CYP3A4-Isoherranen, 2004

Molecule: CYP3A4

#### Parameters

Name	Value	Value Origin
Ki	5.12 nmol/l	Publication-Isoherranen 2004

## Compound: N-desalkyl-Itraconazole

### Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	1 mg/l		No value available	True
Reference pH	7		No value available	True
Lipophilicity	5.1837535822 Log Units		Fit	True
Fraction unbound (plasma, reference value)	1.1 %	Publication-Templeton, 2008	Templeton, 2008	True
Cl	2			
Is small molecule	Yes			
Molecular weight	649.527 g/mol			
Plasma protein binding partner	Albumin			

### Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	PK-Sim Standard

### Processes

#### Metabolizing Enzyme: CYP3A4-Isoherranen 2004

Molecule: CYP3A4

#### Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0 nmol/min/pmol rec. enzyme	
Km	0.6284266369 nmol/l	Publication-Isoherranen 2004
kcat	0.0605873508 1/min	Unknown

#### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters



Name	Value	Value Origin
GFR fraction	1	Publication-Isoherranen 2004

**Inhibition: CYP3A4-Isoherranen, 2004**

Molecule: CYP3A4

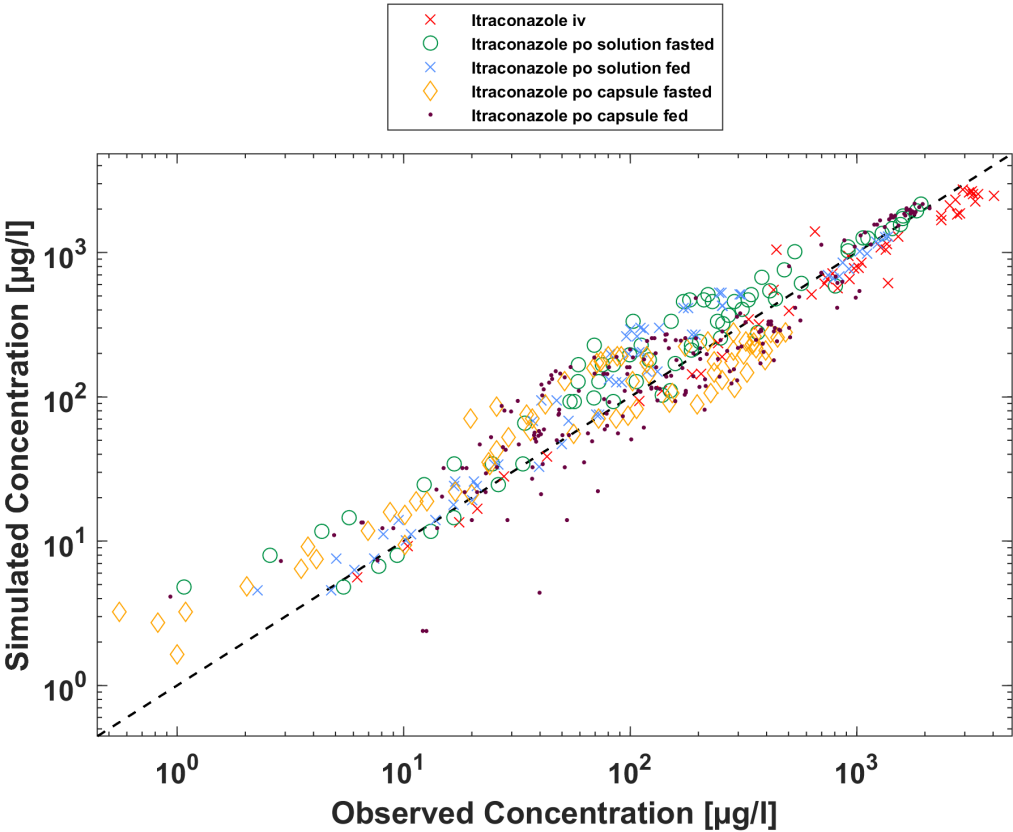
**Parameters**

Name	Value	Value Origin
Ki	0.32 nmol/l	Publication-Isoherranen, 2004

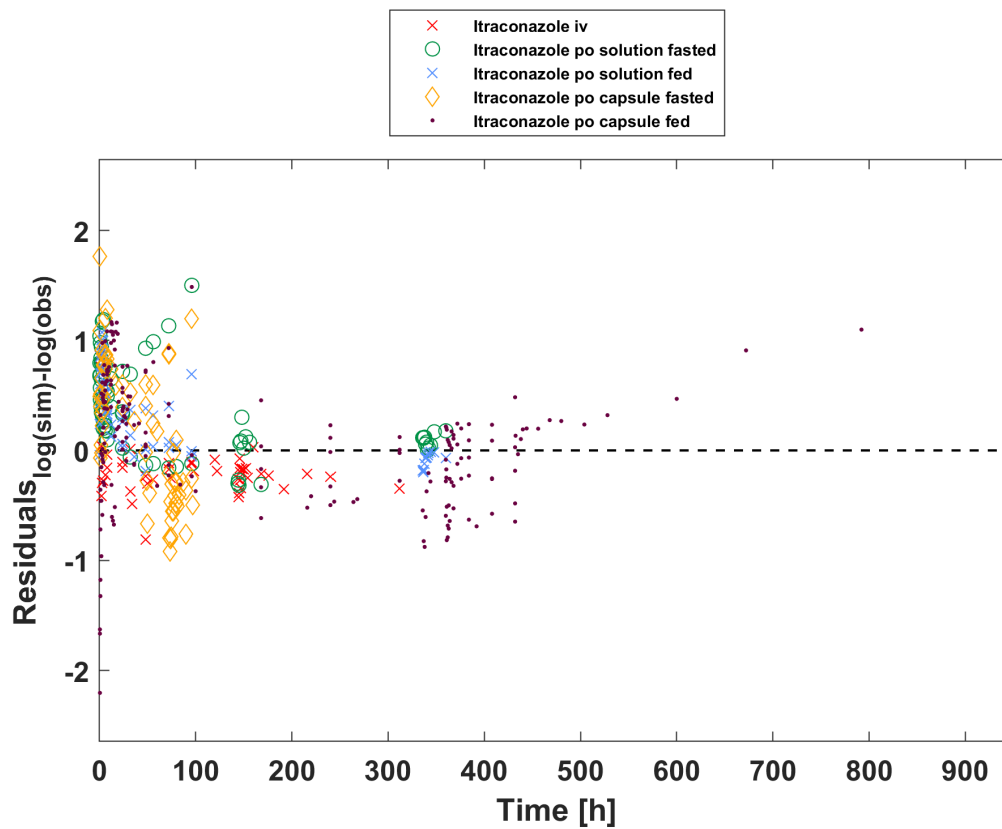
**3.2 Diagnostics Plots**

Below you find the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data used presented in [Section 2.2.2](#).

The plot show observed versus simulated plasma concentration and second weighted residuals versus time for itraconazole, hydroxy-itraconazole, keto-itraconazole and N-desalkyl-itraconazole.

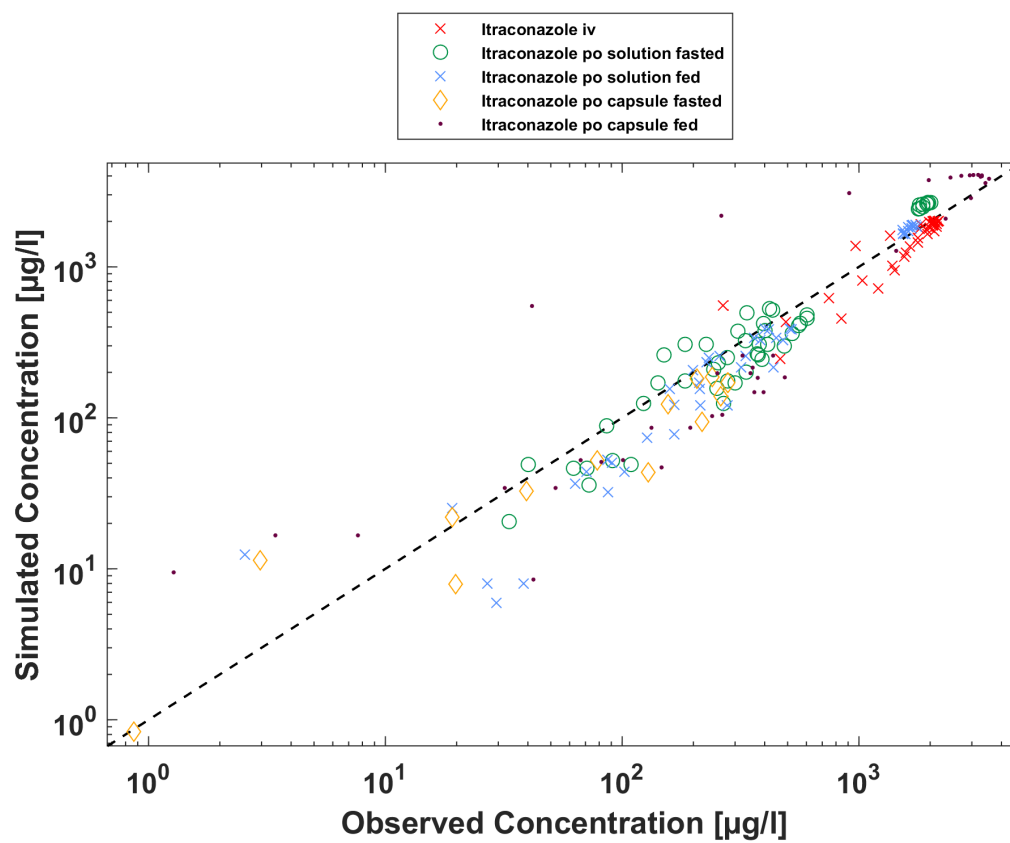


Itraconazole concentration in plasma

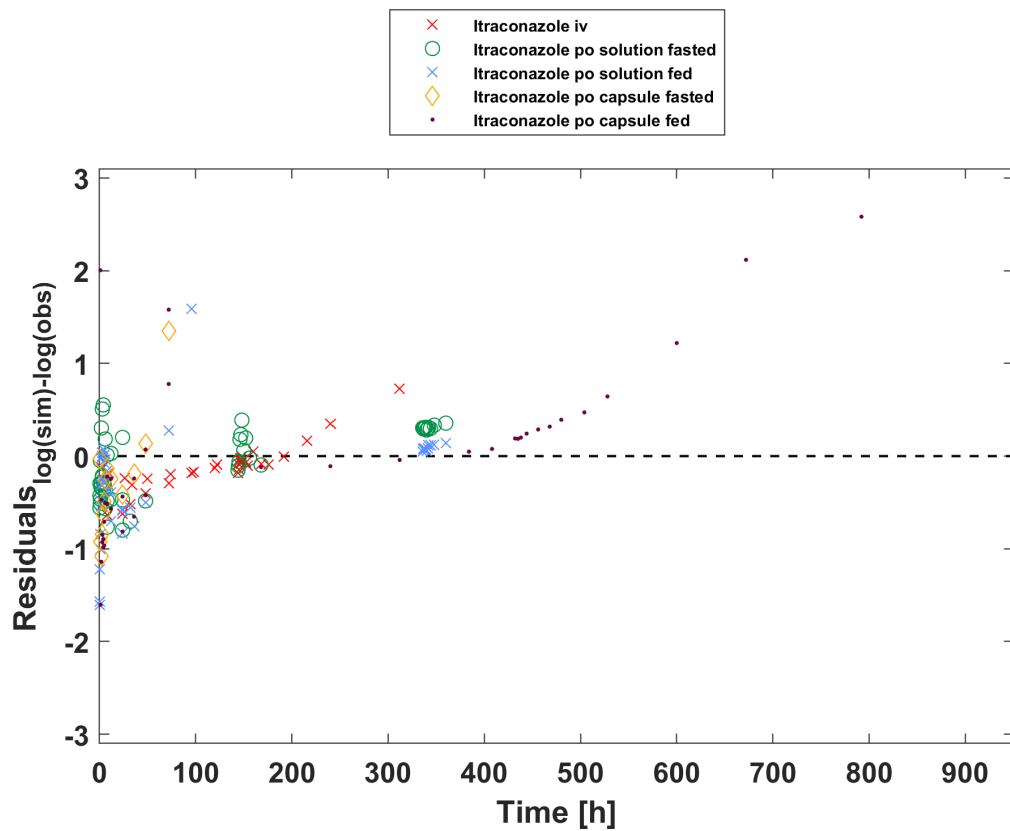


Itraconazole concentration in plasma

GMFE = 1.540898

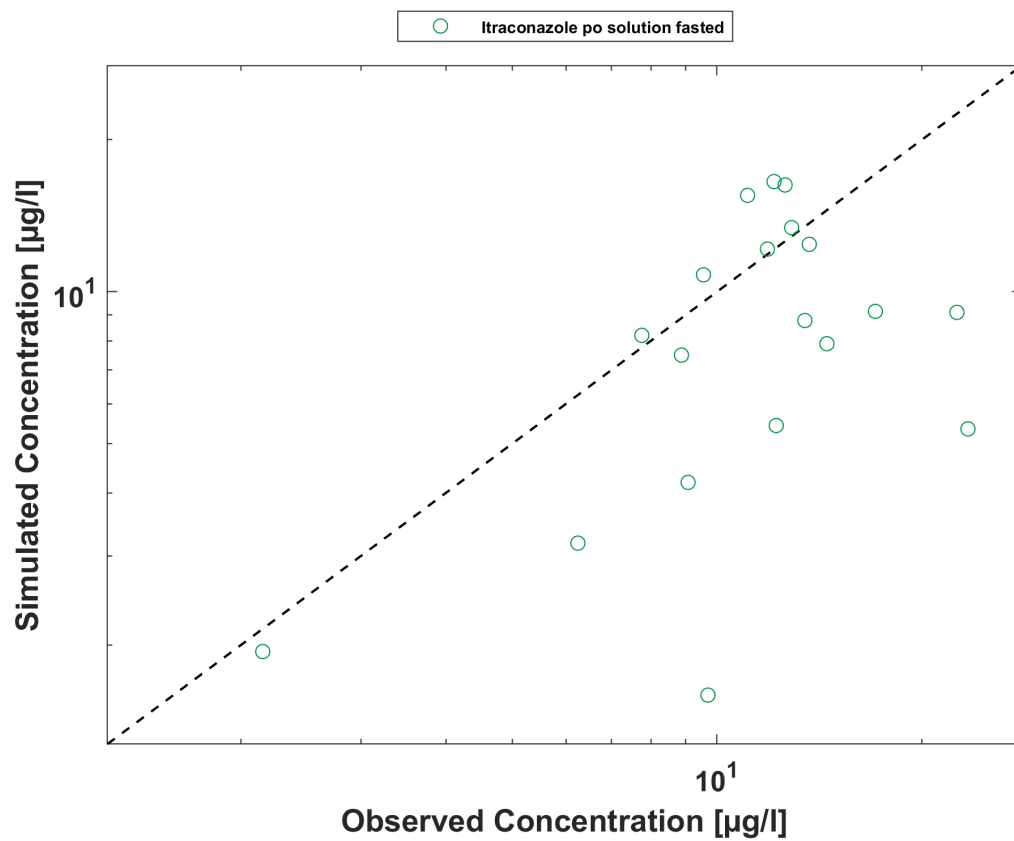


Hydroxy-Itraconazole concentration in plasma

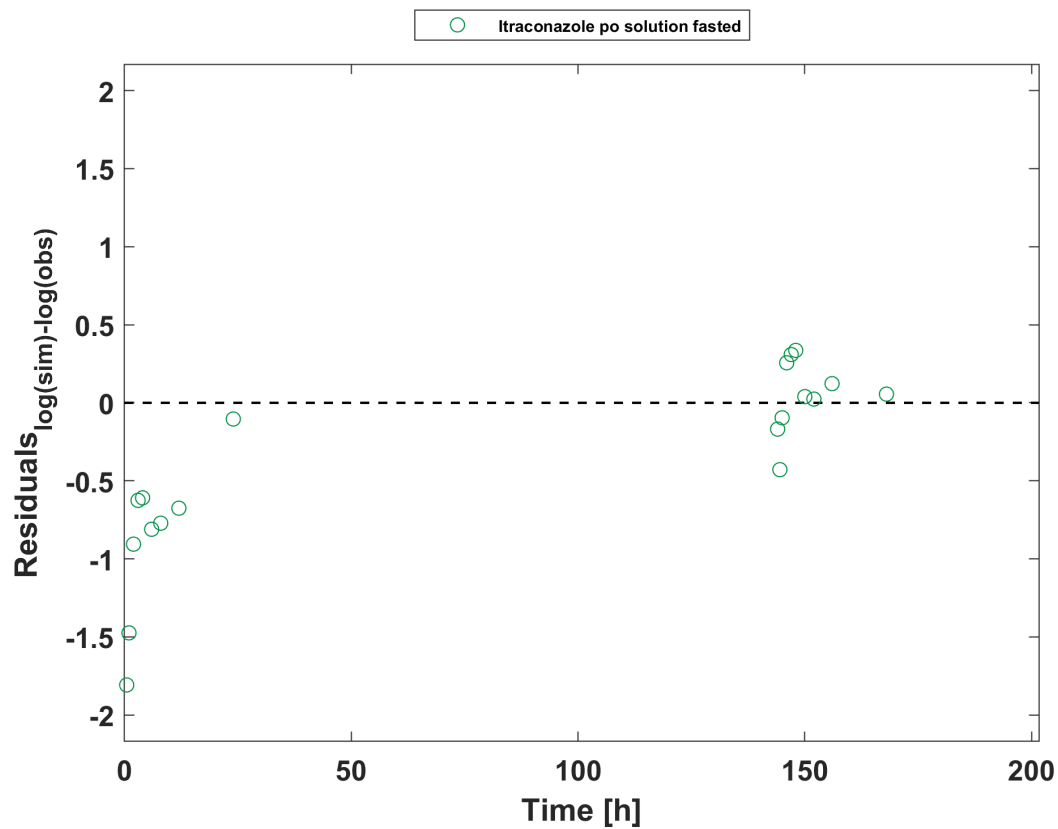


Hydroxy-Itraconazole concentration in plasma

GMFE = 1.498618

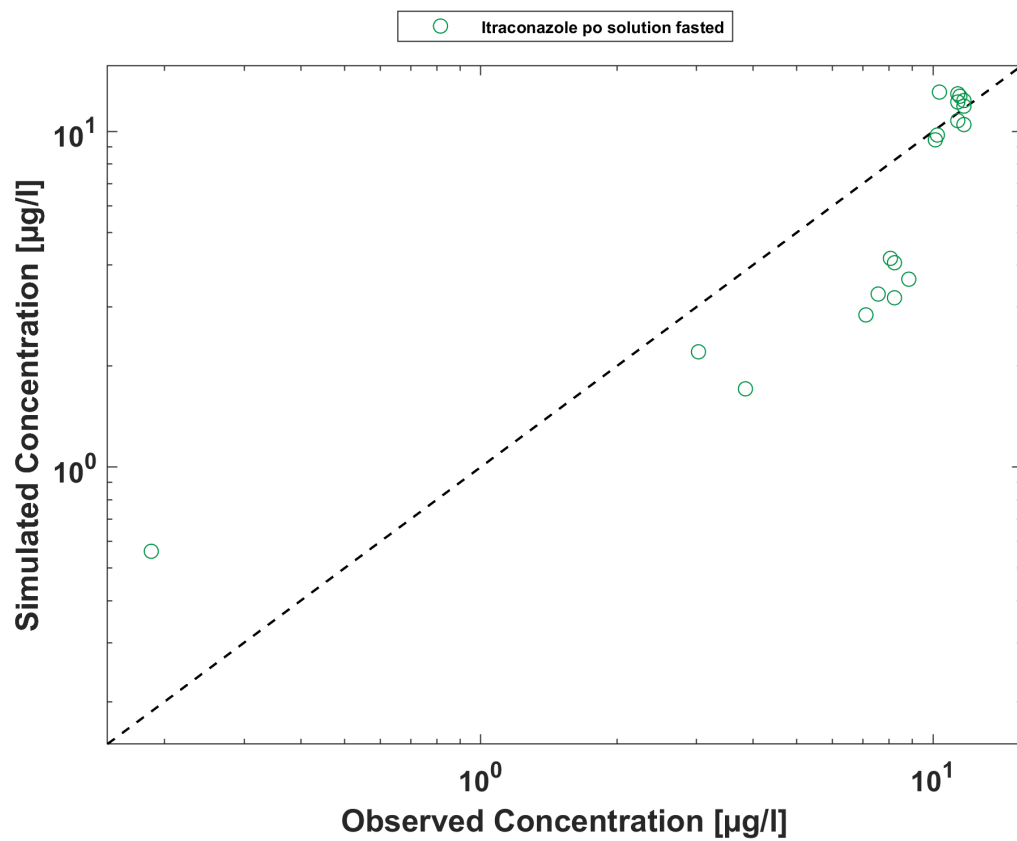


Keto-Itraconazole concentration in plasma

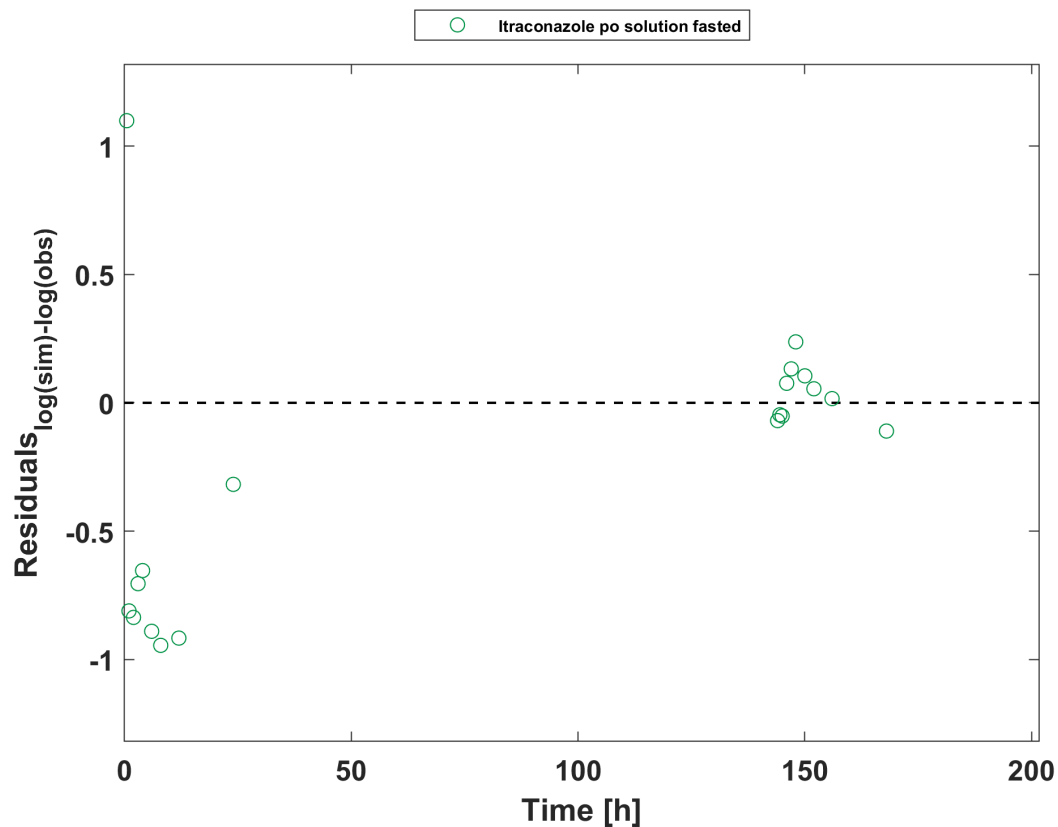


Keto-Itraconazole concentration in plasma

GMFE = 1.658855



N-desalkyl-Itraconazole concentration in plasma

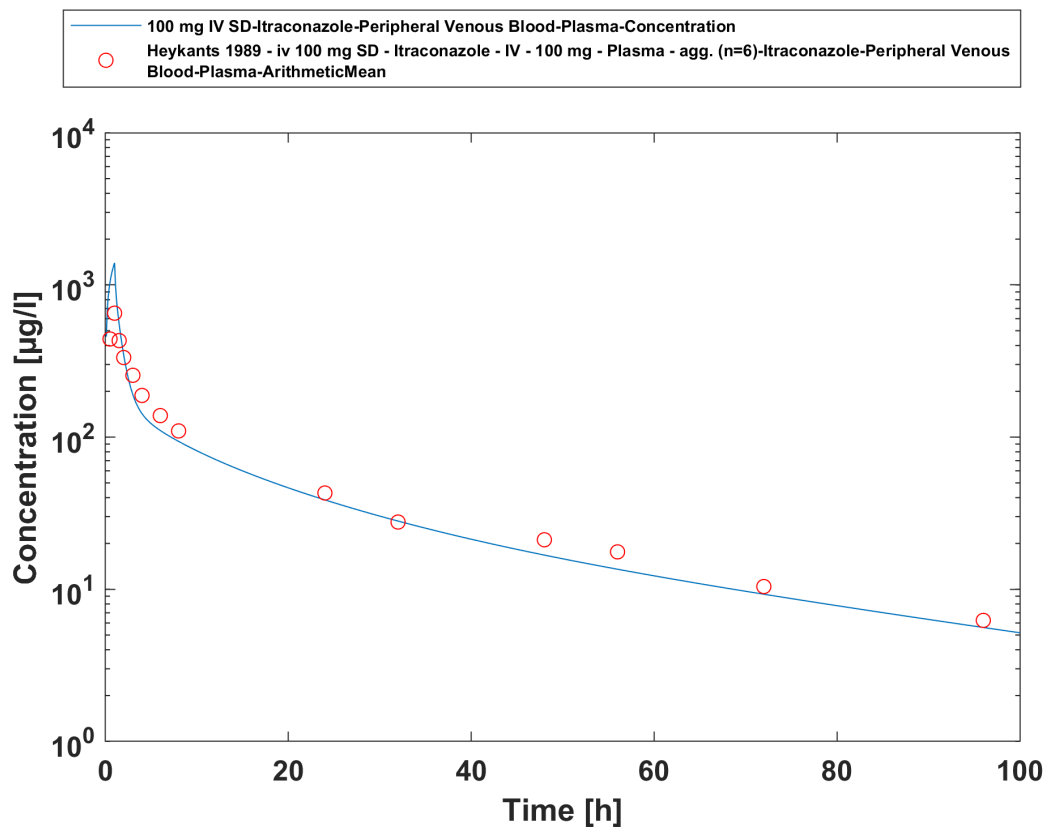


N-desalkyl-Itraconazole concentration in plasma

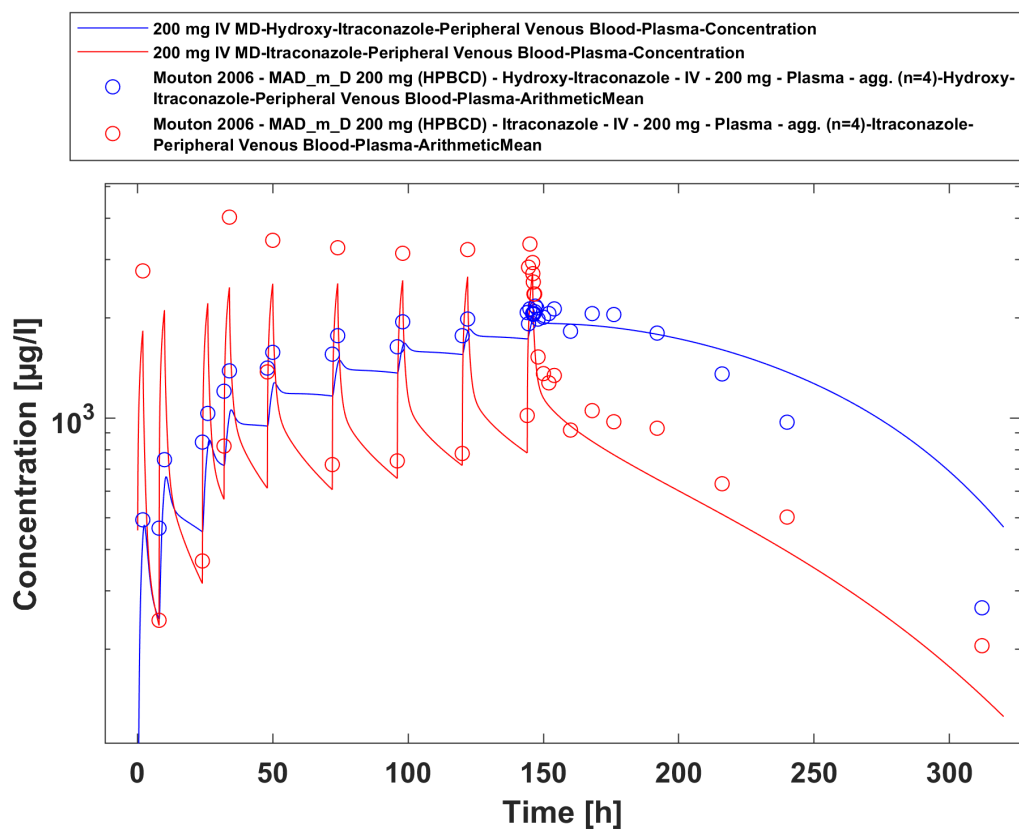
GMFE = 1.529602

### 3.3 Concentration-Time Profiles

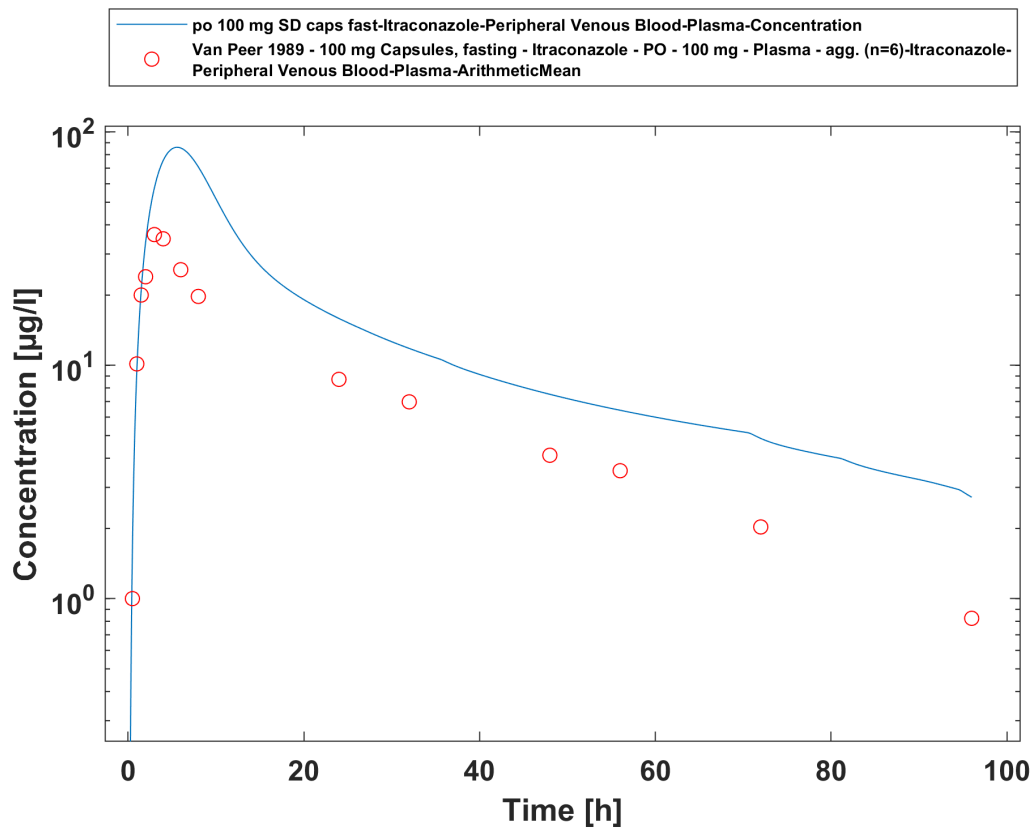
Simulated versus observed concentration-time profiles of all data listed in [Section 2.2.2](#) are presented below.



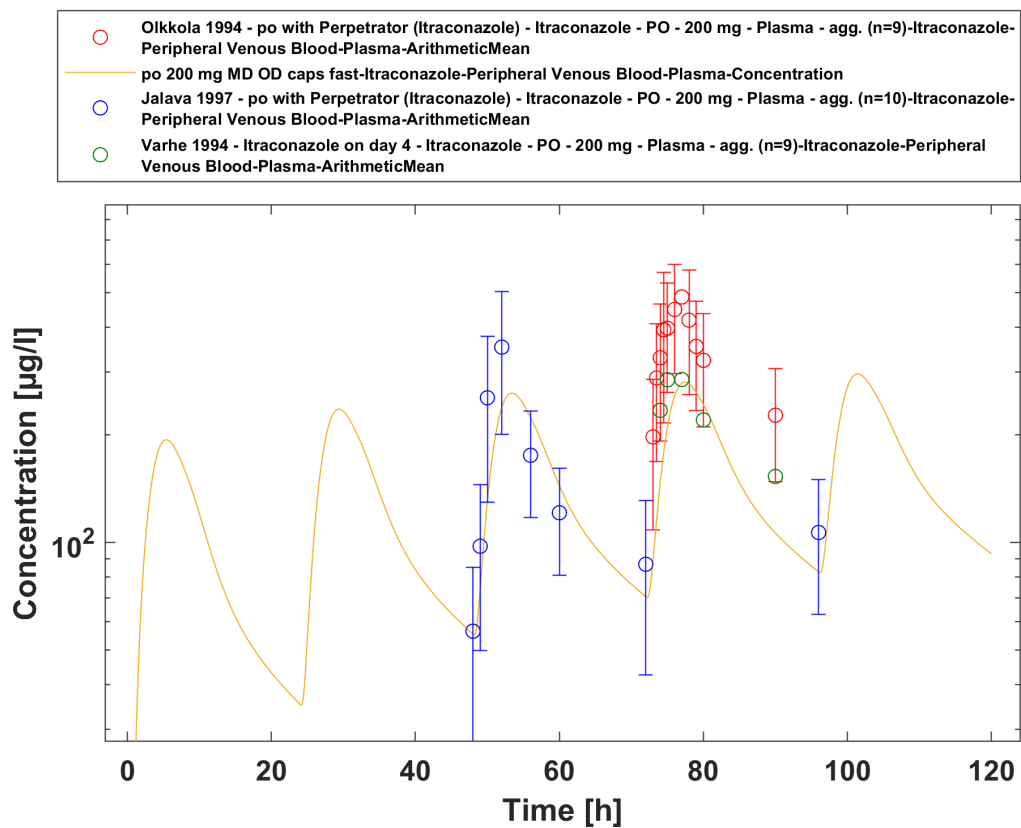
100 mg IV SD - Plasma



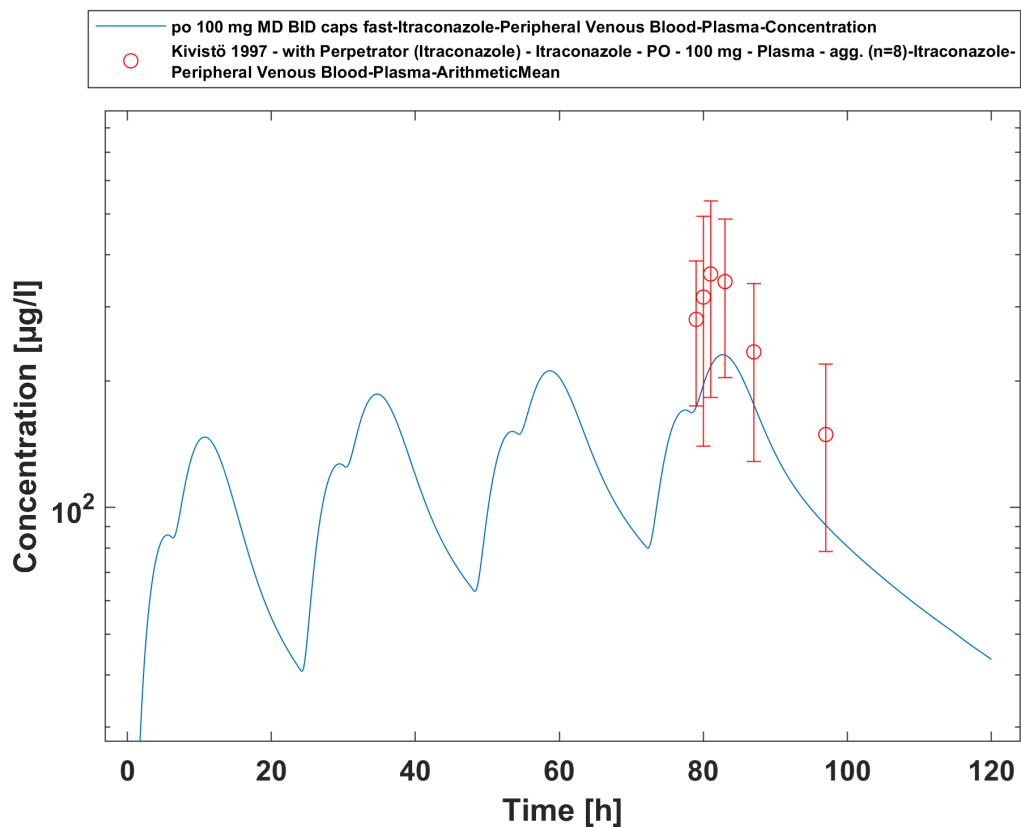
200 mg IV MD - Plasma



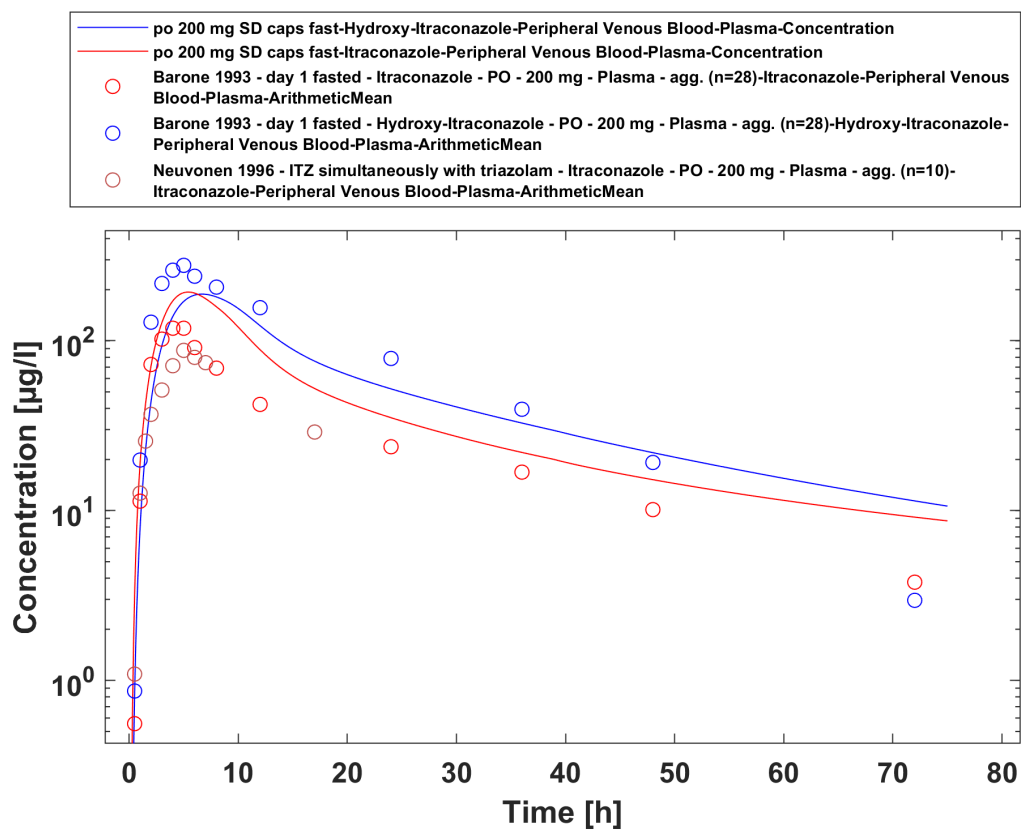
po 100 mg SD caps fast - Plasma



po 200 mg MD OD caps fast - Plasma

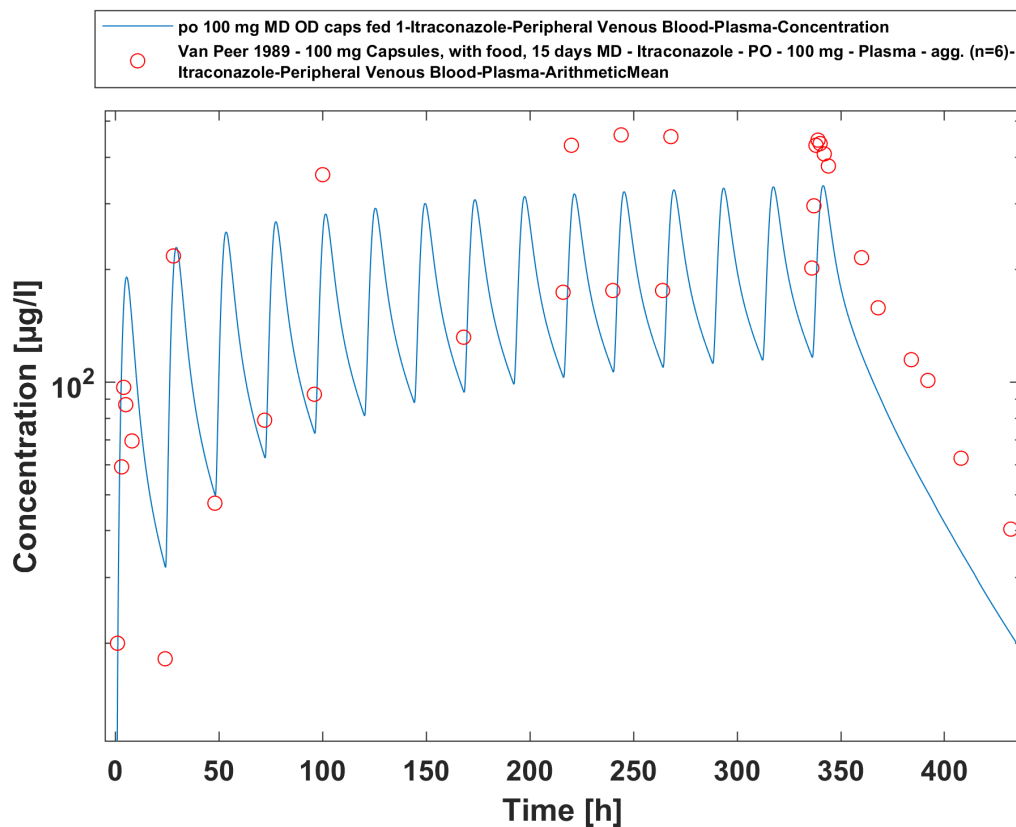


po 100 mg MD BID caps fast - Plasma

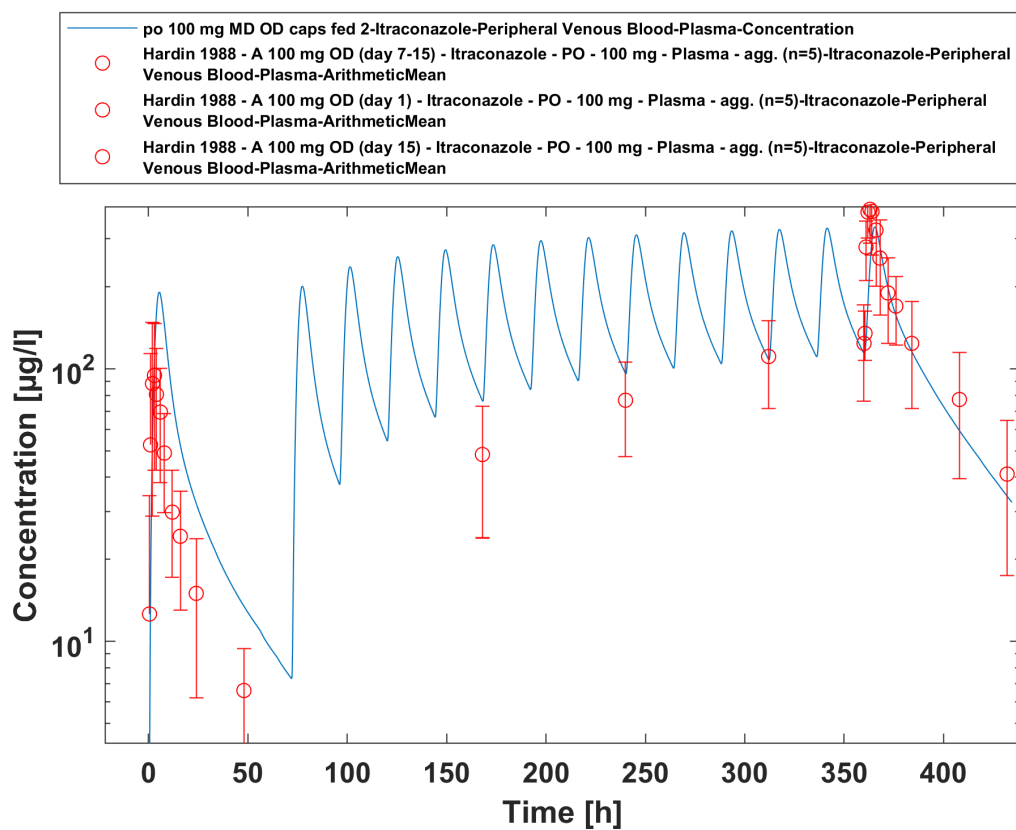


po 200 mg SD caps fast - Plasma

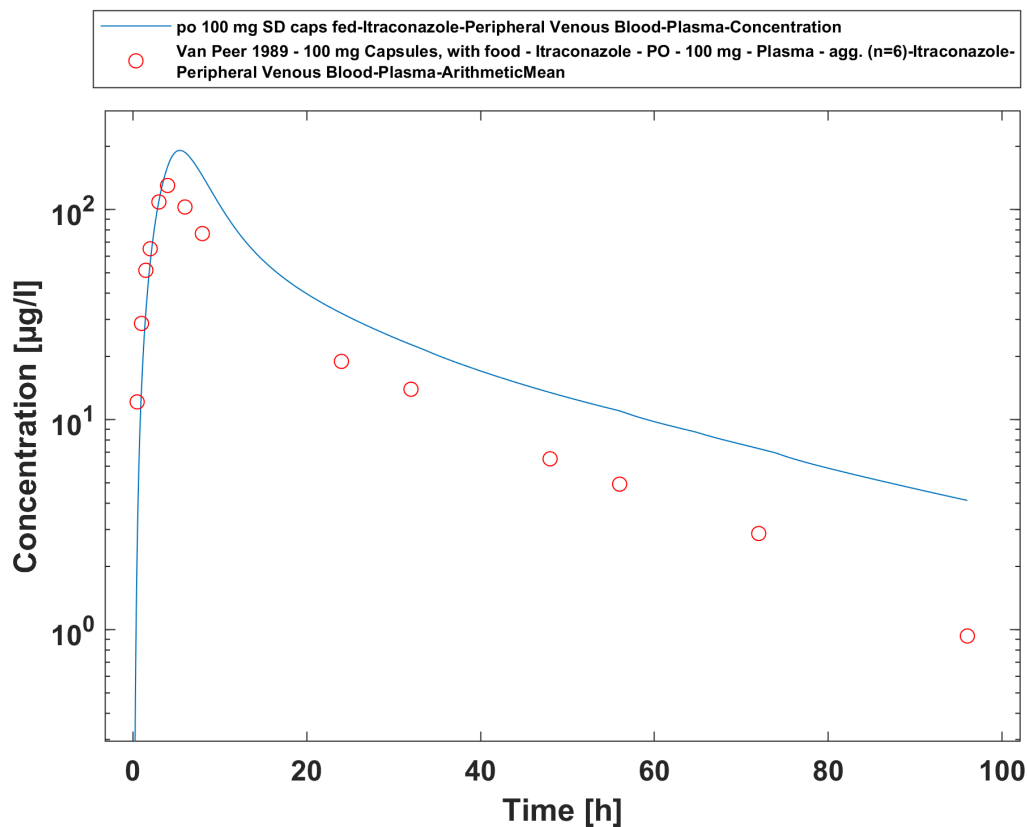




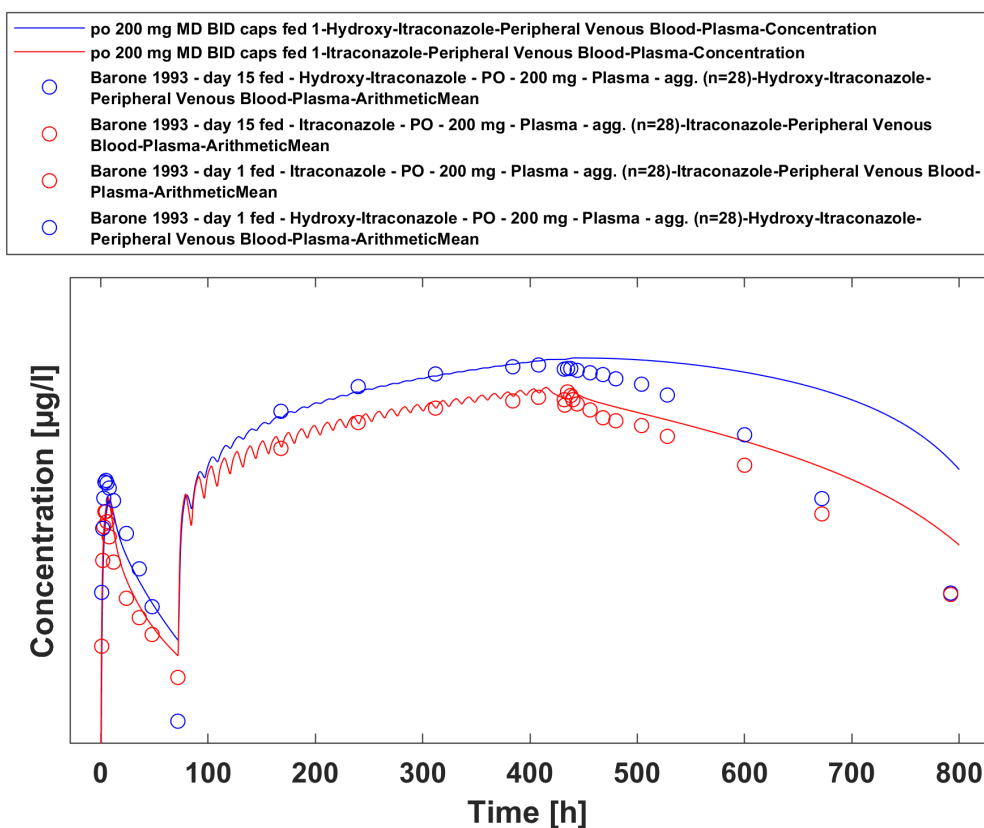
po 100 mg MD OD caps fed 1 - Plasma



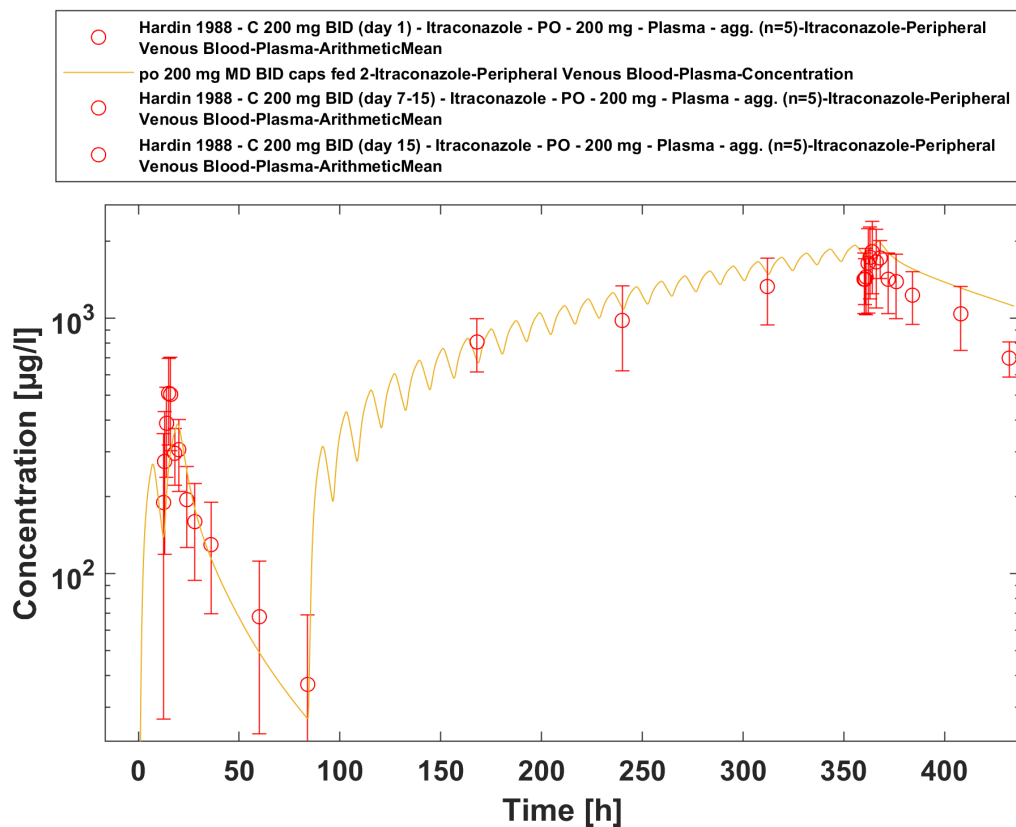
po 100 mg MD OD caps fed 2 - Plasma



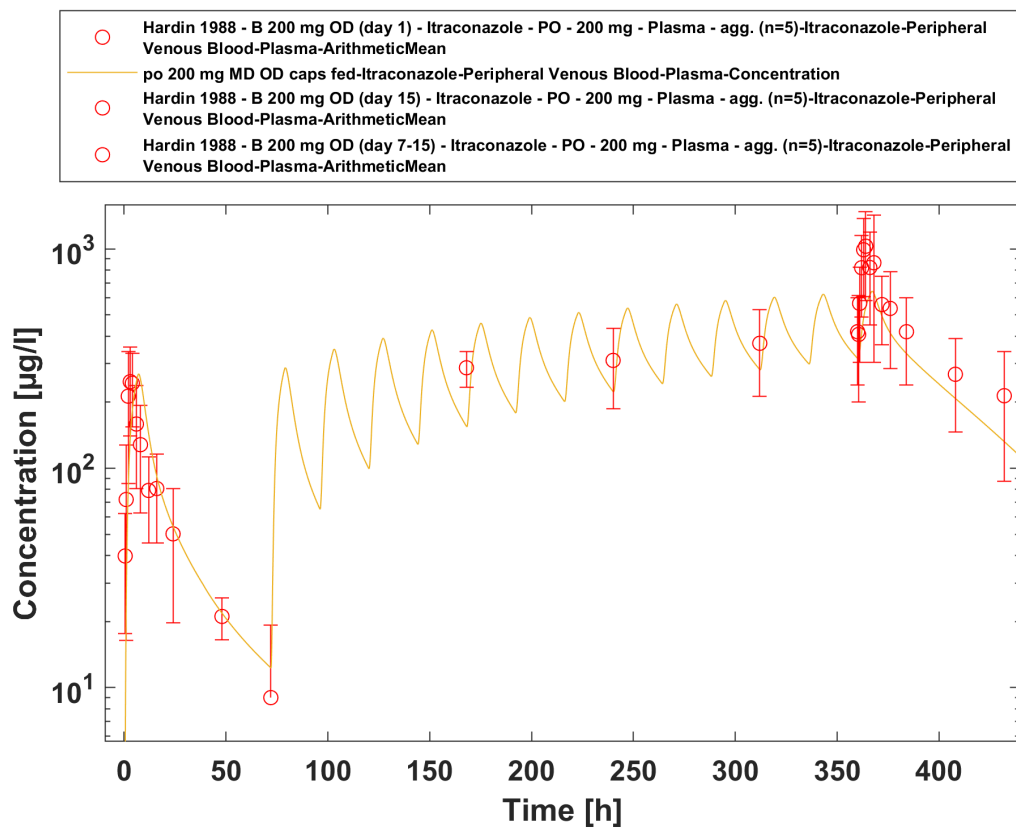
po 100 mg SD caps fed - Plasma



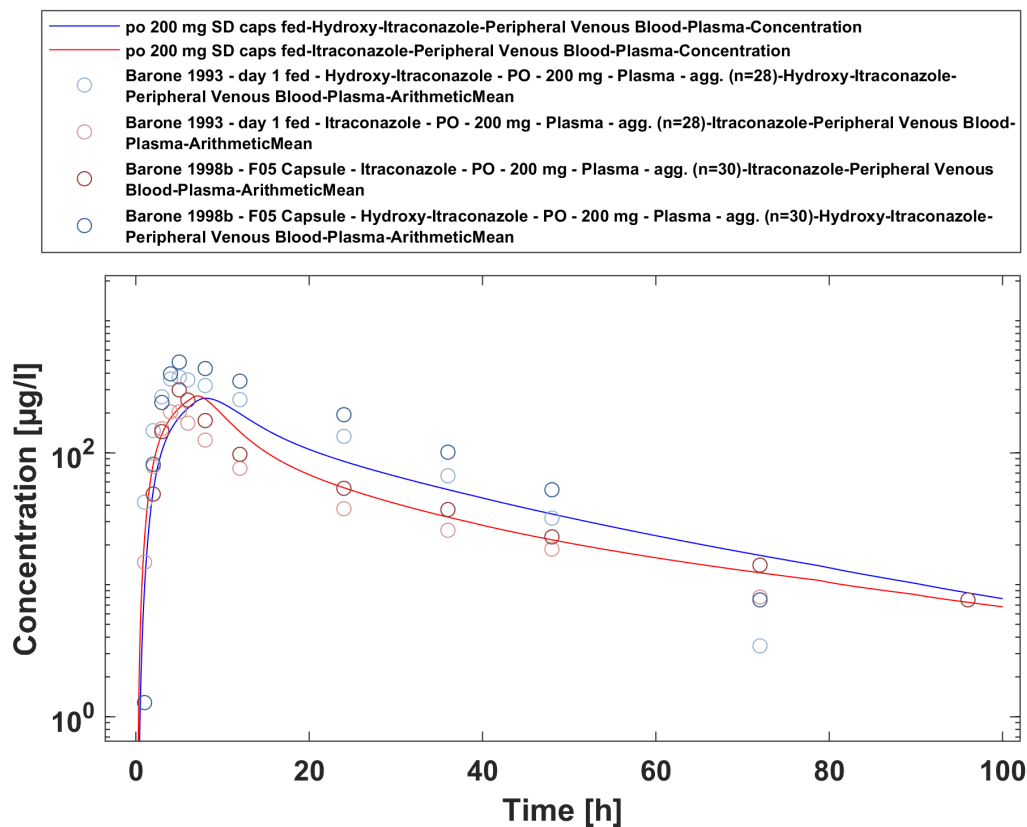
po 200 mg MD BID caps fed 1 - Plasma



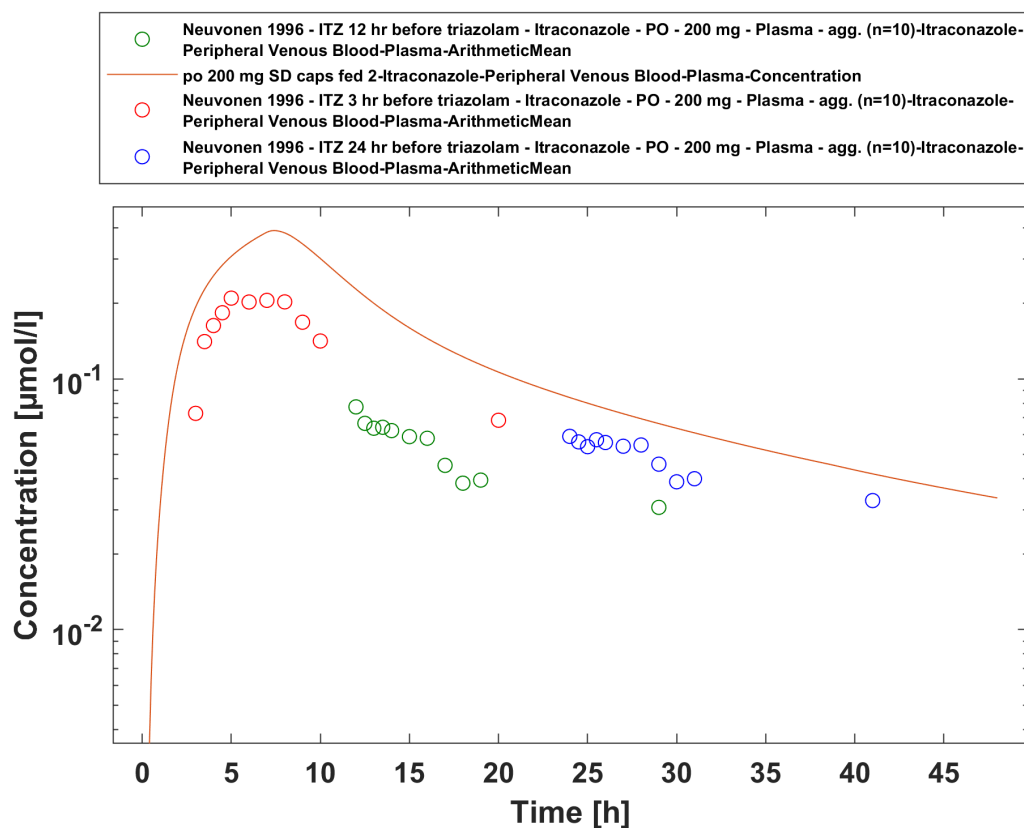
po 200 mg MD BID caps fed 2 - Plasma



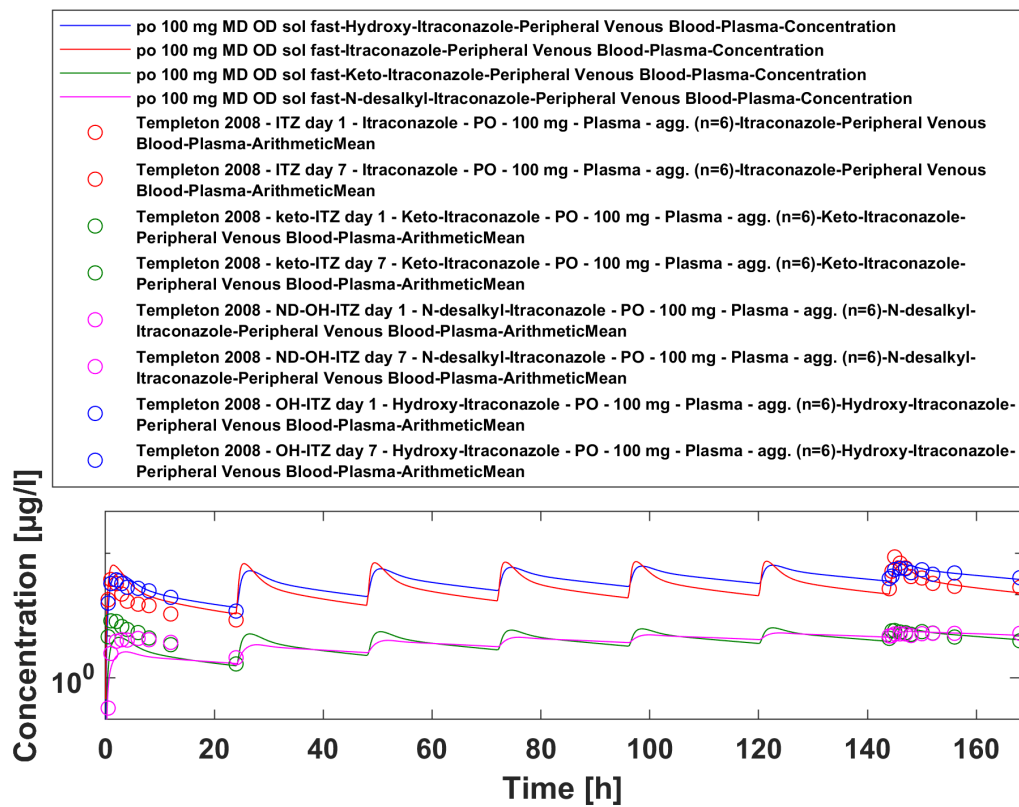
po 200 mg MD OD caps fed - Plasma



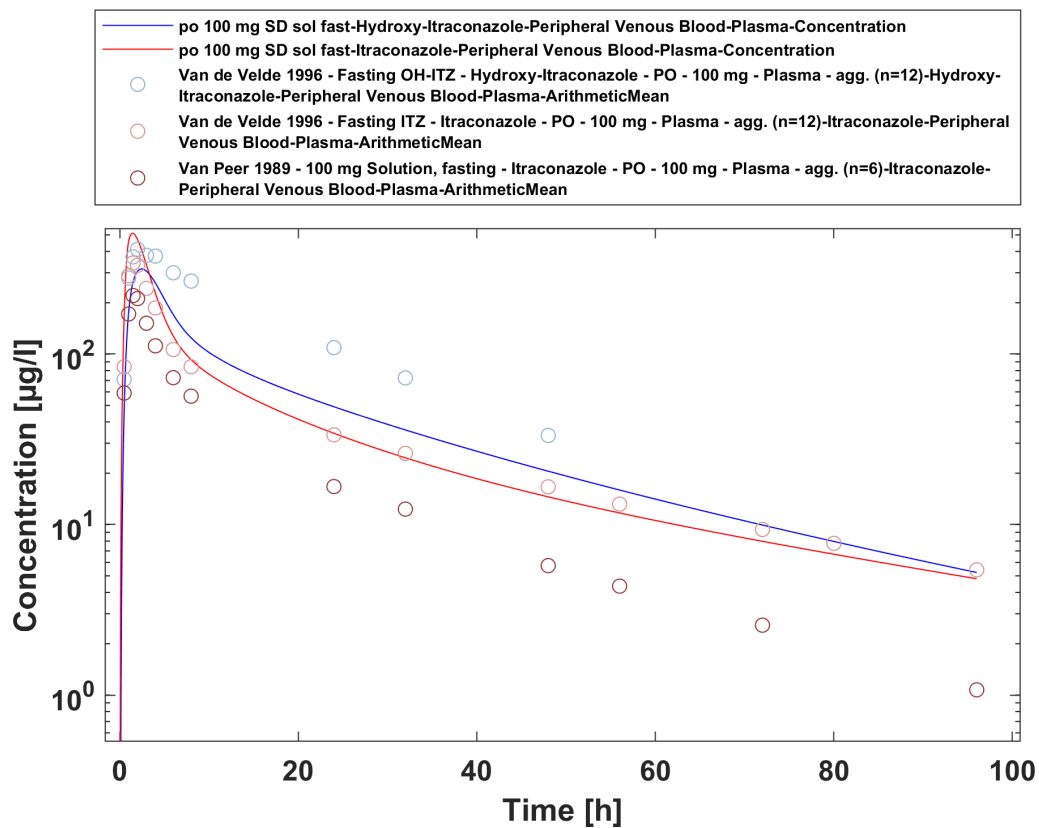
po 200 mg SD caps fed - Plasma



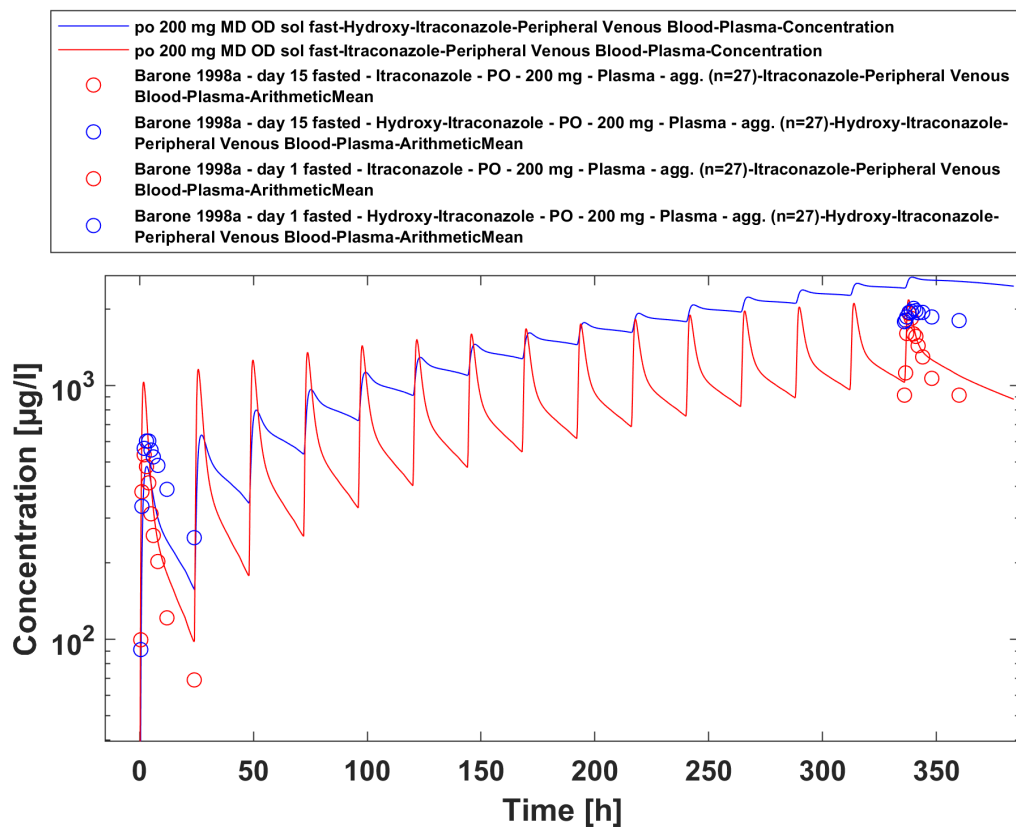
po 200 mg SD caps fed 2 - Plasma



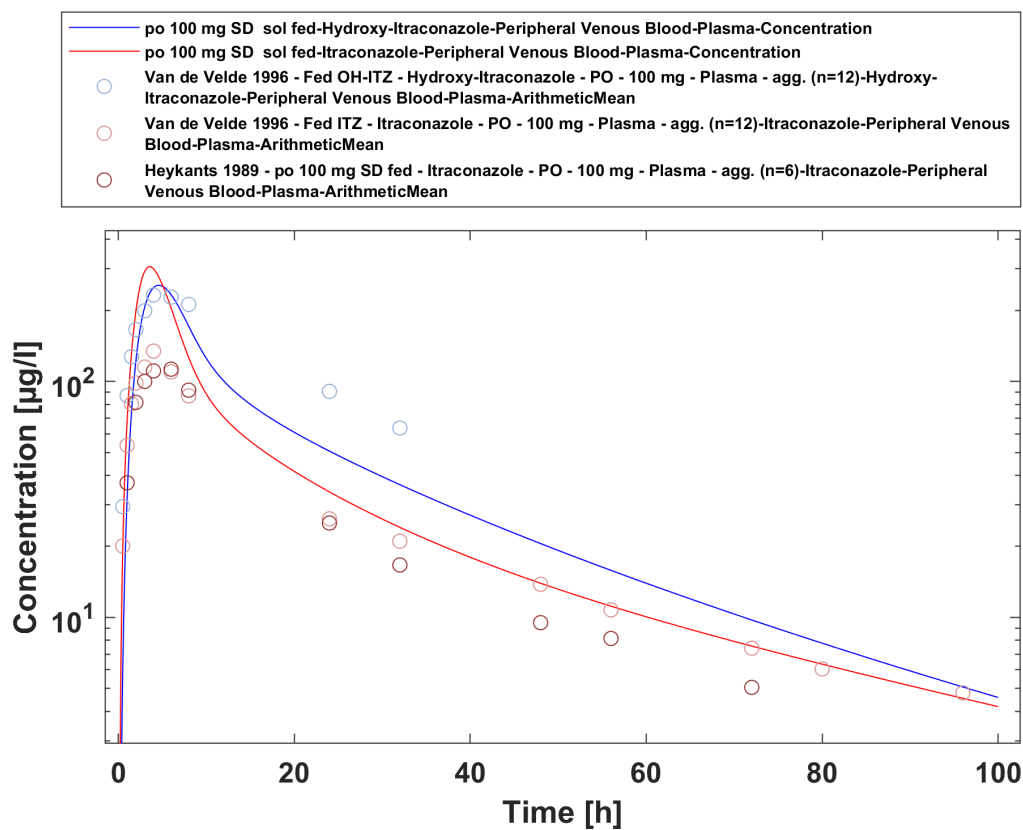
po 100 mg MD OD sol fast - Plasma



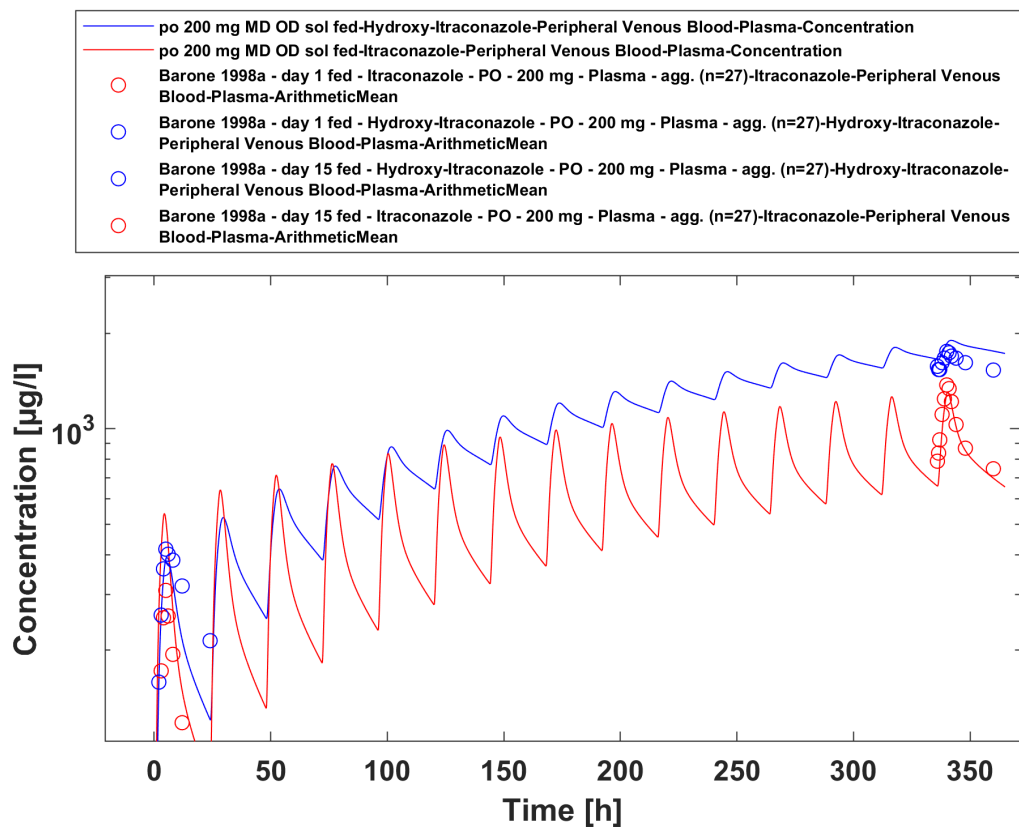
po 100 mg SD sol fast - Plasma



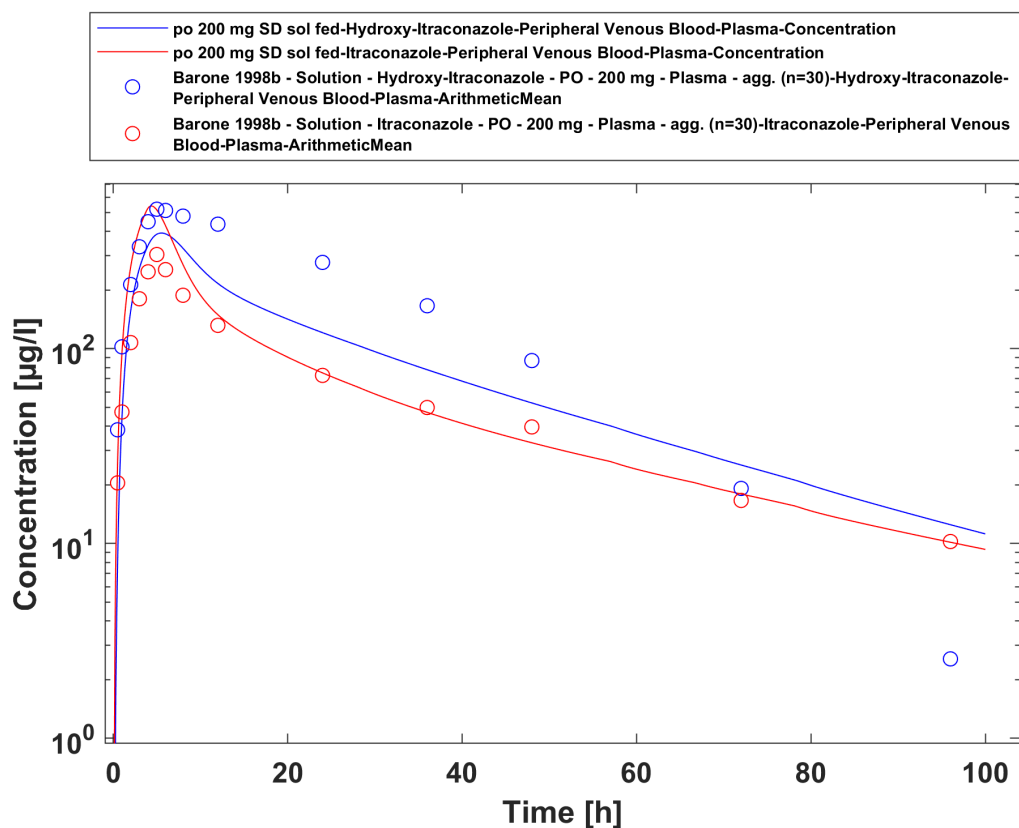
po 200 mg MD OD sol fast - Plasma



po 100 mg SD sol fed - Plasma



po 200 mg MD OD sol fed - Plasma



po 200 mg SD sol fed - Plasma

## 4 Conclusion

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The herein presented PBPK model adequately describes the pharmacokinetics of itraconazole in adults.

In particular, the model includes the sequential metabolites hydroxy-itraconazole, keto-itraconazole and N-desalkyl-itraconazole - all of them formed by CYP3A4. The model applies competitive inhibition of CYP3A4 by itraconazole and the three metabolites. Thus, the model is fit for purpose to be applied for the investigation of drug-drug interactions with regard to strong CYP3A4 inhibition.



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