

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

Version	2.0-OSP12.1
based on <i>Model Snapshot</i> and <i>Evaluation Plan</i>	https://github.com/Open-Systems-Pharmacology/Itraconazole-Model/releases/tag/v2.0
OSP Version	12.1
Qualification Framework Version	3.4

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

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

2.1 Modeling Strategy

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

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	DrugBank DB01167	Molecular weight
pK _{a,base}		3.7	Heykants 1989	acid dissociation constant of conjugate acid; compound type: base
Solubility (pH)	mg/L	8.0 (6.5)	Taupitz 2013	Solubility in FaSSIF (fasted state simulated intestinal fluid)
logP		5.66	Heykants 1989	Partition coefficient between octanol and water
fu	%	0.2	Heykants 1989	Fraction unbound in plasma
	%	0.2	Riccardi 2015	Fraction unbound in plasma
	%	1.58	Ishigami 2001	Fraction unbound in plasma
	%	3.6	Templeton 2008	Fraction unbound in plasma
V _{max} , K _m CYP3A4	pmol/min/nmol, nmol/L	270 3.9	Isoherranen 2004	CYP3A4 supersomes Michaelis-Menten kinetics
K _i CYP3A4	nmol/L	1.3	Isoherranen 2004	CYP3A4 inhibition constant
K _i P-gp	nmol/L	8.0	Shityakov 2014	P-gp inhibition constant

Hydroxy-itraconazole

Parameter	Unit	Value	Source	Description
MW	g/mol	721.633	DrugBank DBMET00374	Molecular weight
logP		4.5	PubChem CID 108222	Partition coefficient between octanol and water, computed by XLogP3 3.0
fu	%	0.5	Templeton 2008	Fraction unbound in plasma
	%	1.7	Riccardi 2015	Fraction unbound in plasma
	%	2.12	Chen 2016	Fraction unbound in plasma
V _{max} , K _m CYP3A4	pmol/min/nmol, nmol/L	543 27	Isoherranen 2004	CYP3A4 supersomes Michaelis-Menten kinetics
K _i CYP3A4	nmol/L	14.4	Isoherranen 2004	CYP3A4 inhibition constant

Keto-itraconazole

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

† The IC₅₀ values was converted to a K_i value via Cheng-Prusoff equation (Chen 1973) with a substrate (*midazolam*) concentration of 1 μmol/L and an assumed substrate (*midazolam*) K_m value of 2.73 μmol/L: **5.12 nmol/L**

N-Desalkyl-itraconazole

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

† The IC₅₀ values was converted to a K_i value via Cheng-Prusoff equation (Chen 1973) with a substrate (*midazolam*) concentration of 1 μmol/L and an assumed substrate (*midazolam*) K_m 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 [†]	Reference
iv	-	-	100	SD	Itraconazole	mv	Heykants 1989
			200	OD	Itraconazole Hydroxy-Itr.	mbb	Mouton 2006
po	solution	fasted	100	SD	Itraconazole	mbb	Van de Velde 1996
					Itraconazole Hydroxy-Itr.	mbb	Van Peer 1989
				OD	Itraconazole Hydroxy-Itr. Keto-Itr. N-Desalkyl-Itr.	mbb	Templeton 2008
			200	OD	Itraconazole Hydroxy-Itr.	mbb	Barone 1998a
		fed	100	SD	Itraconazole Hydroxy-Itr.	mbe	Van de Velde 1996
					Itraconazole	mbe	Heykants 1989
			200	SD	Itraconazole Hydroxy-Itr.	mbe	Barone 1998b
				OD	Itraconazole Hydroxy-Itr.	mbe	Barone 1998a
capsule	fasted	100	SD	Itraconazole	mbe		Van Peer 1989
				BID	Itraconazole	mv	Kivistö 1997
			200	SD	Itraconazole Hydroxy-Itr.	mbe	Barone 1993
					Itraconazole	mv	Neuvonen 1996
				OD	Itraconazole	mbe	Jalava 1997
					Itraconazole	mbe	Olkola 1994
					Itraconazole	mv	Varhe 1994
	fed	100	SD	Itraconazole	mbe		Van Peer 1989
				OD	Itraconazole	mbe	Van Peer 1989
					Itraconazole	mv	Hardin 1988
			200	SD	Itraconazole Hydroxy-Itr.	mbe	Barone 1993

Route	Formulation	Food state	Dose [mg]	Dosing	PK Data	Used for [†]	Reference
					Itraconazole Hydroxy-Itr.	mbe	Barone 1998b
					Itraconazole	mv	Neuvonen 1996
		200	OD		Itraconazole	mv	Hardin 1988
			BID		Itraconazole	mbe	Barone 1993
					Itraconazole Hydroxy-Itr.	mv	Hardin 1988

[†] *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

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 logP 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 _m (CYP3A4)	2.07	nmol/L
	k _{cat} (CYP3A4)	0.040	1/min
Hydroxy-Itr.	Lipophilicity	3.72	Log Units
	Fraction unbound (plasma, reference value)	1.7 FIXED (see Section 2.2.1)	%
	K _m (CYP3A4)	4.17	nmol/L
	k _{cat} (CYP3A4)	0.020	1/min
	Lipophilicity	4.21	Log Units
Keto-Itr.	Fraction unbound (plasma, reference value)	1.0 FIXED (see Section 2.2.1)	%
	K _m (CYP3A4)	2.22	nmol/L
	k _{cat} (CYP3A4)	0.393	1/min
	Lipophilicity	5.18	Log Units
	Fraction unbound (plasma, reference value)	1.1 FIXED (see Section 2.2.1)	%
N-Desalkyl-Itr.	K _m (CYP3A4)	0.63	nmol/L
	k _{cat} (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 Section 2.2.1)	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.

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
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: 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

Inhibition: OATP1B1-Tuerk 2019

Molecule: OATP1B1

Parameters

Name	Value	Value Origin
Ki	0.0177818488 μmol/l	Parameter Identification-Parameter Identification

Inhibition: OATP1B3-Tuerk 2019

Molecule: OATP1B3

Parameters

Name	Value	Value Origin
Ki	0.0111606334 μmol/l	Parameter Identification-Parameter Identification

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-Itraconazole

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

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	

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.

Table 3-1: GMFE for Itraconazole concentration in plasma

Group	GMFE
Itraconazole iv	1.29
Itraconazole po capsule fasted	1.74
Itraconazole po capsule fed	1.57
Itraconazole po solution fasted	1.54
Itraconazole po solution fed	1.46
All	1.54

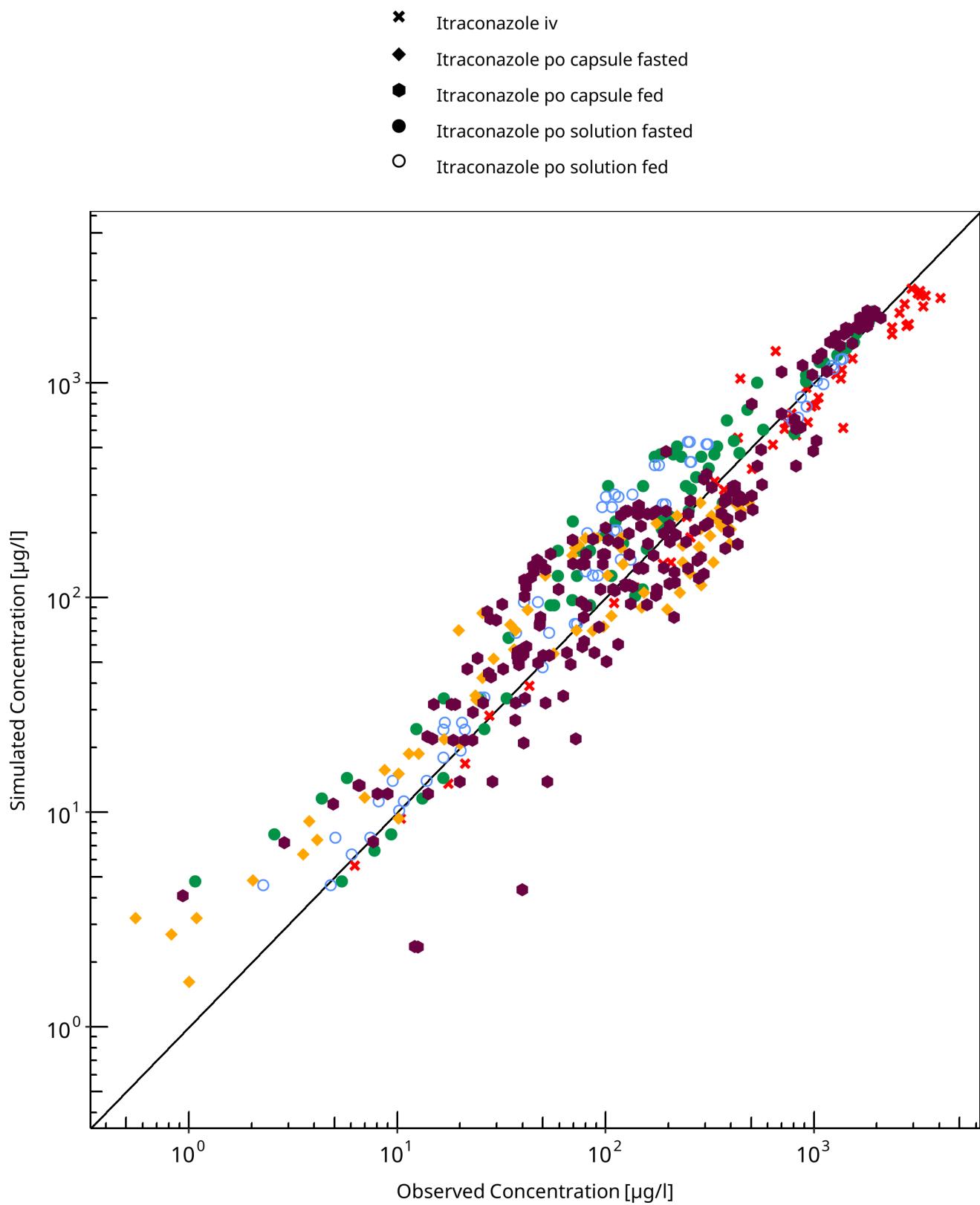


Figure 3-1: Itraconazole concentration in plasma

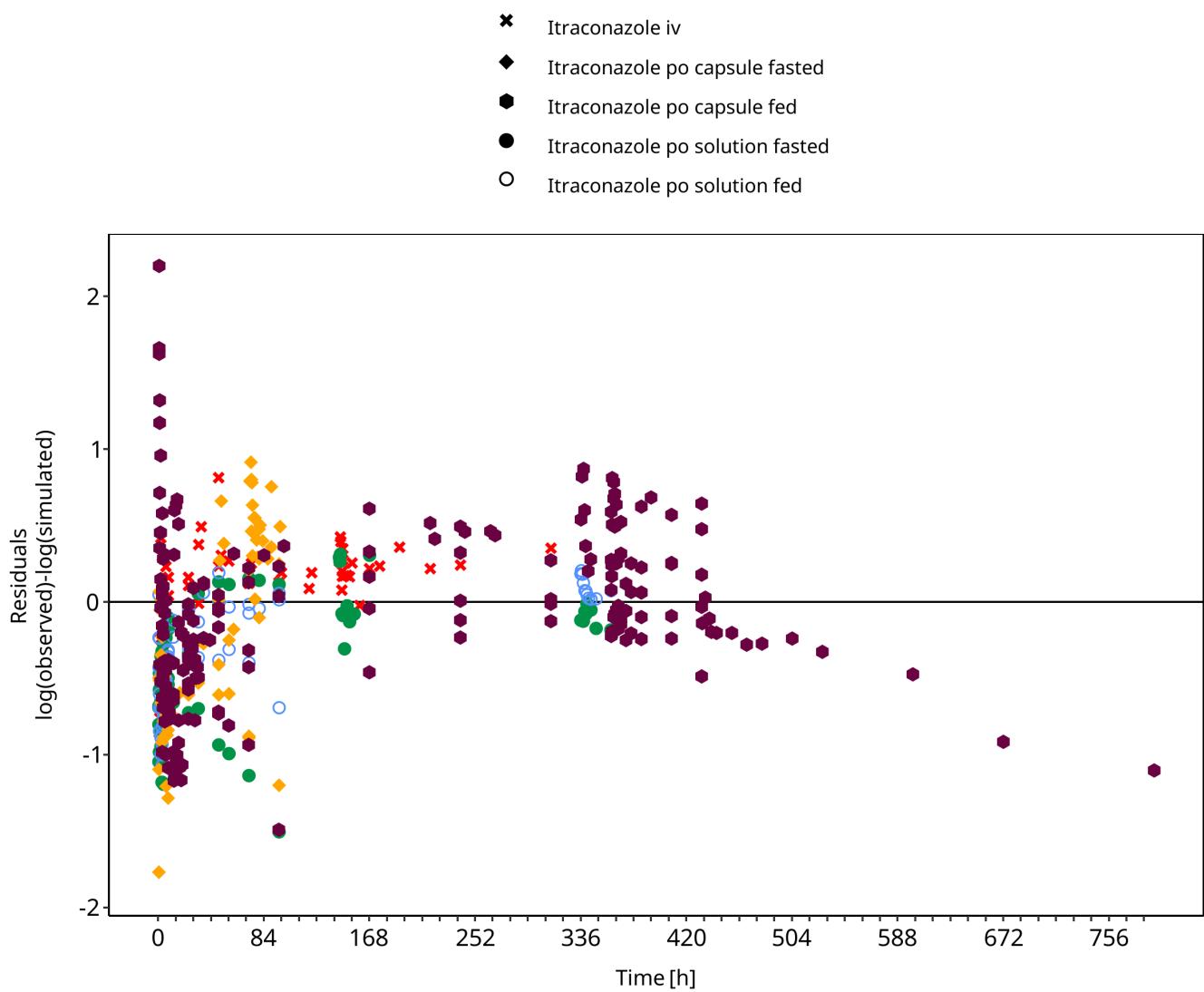


Figure 3-2: Itraconazole concentration in plasma

Table 3-2: GMFE for Hydroxy-Itraconazole concentration in plasma

Group	GMFE
Itraconazole iv	1.21
Itraconazole po capsule fasted	1.68
Itraconazole po capsule fed	1.95
Itraconazole po solution fasted	1.38
Itraconazole po solution fed	1.48
All	1.50

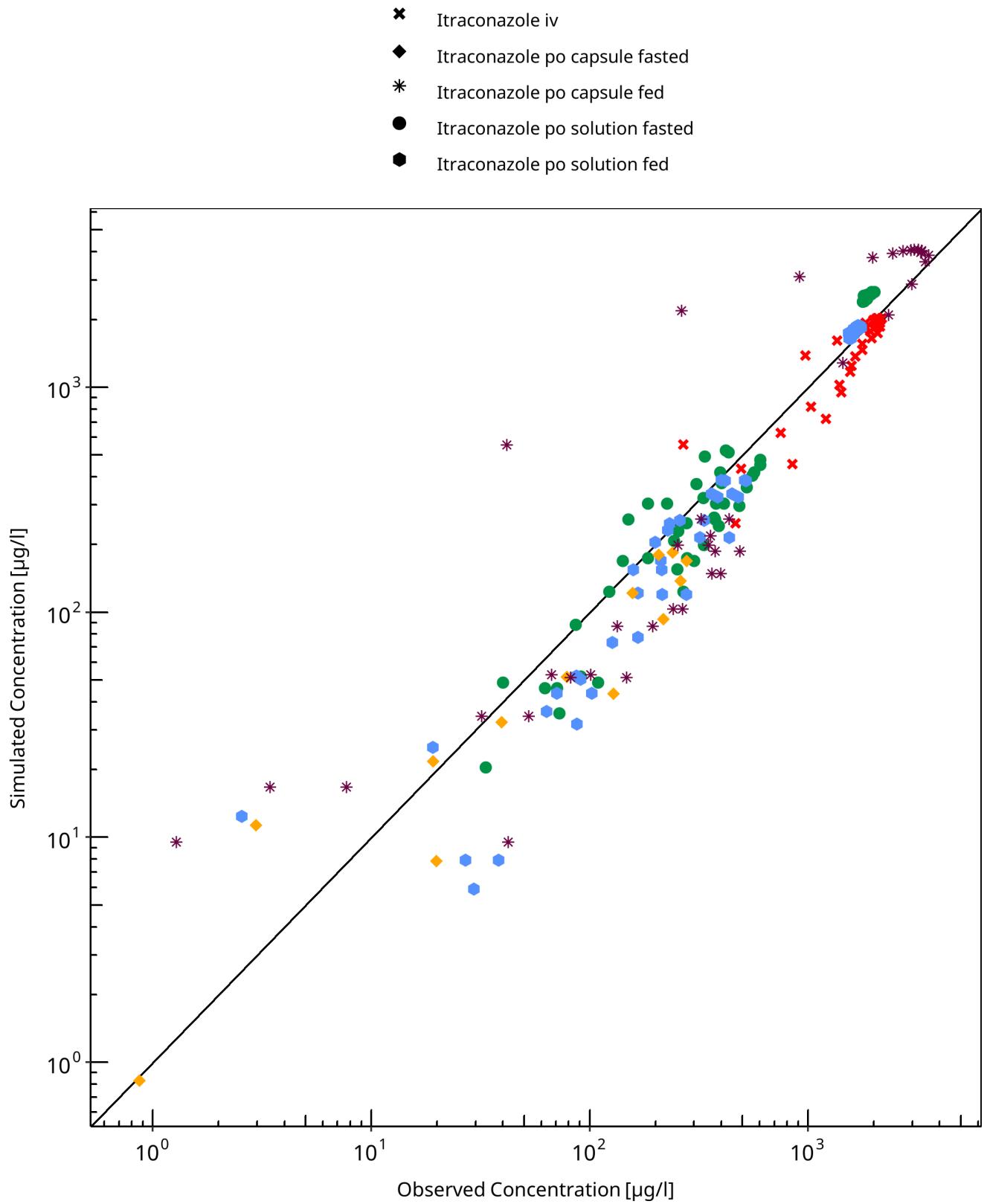


Figure 3-3: Hydroxy-Itraconazole concentration in plasma

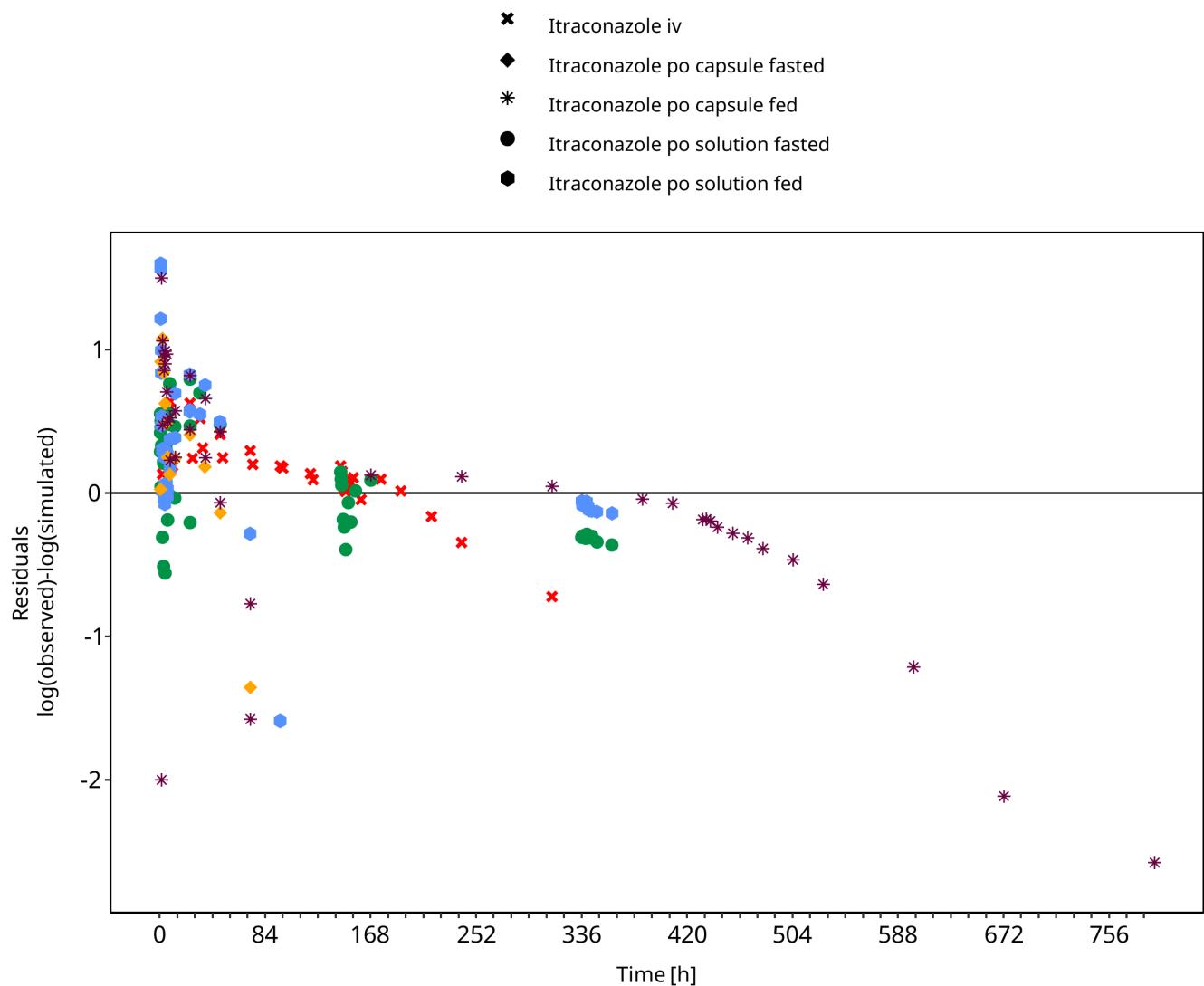


Figure 3-4: Hydroxy-Itraconazole concentration in plasma

Table 3-3: GMFE for Keto-Itraconazole concentration in plasma

Group	GMFE
Itraconazole po solution fasted	1.66

● Itraconazole po solution fasted

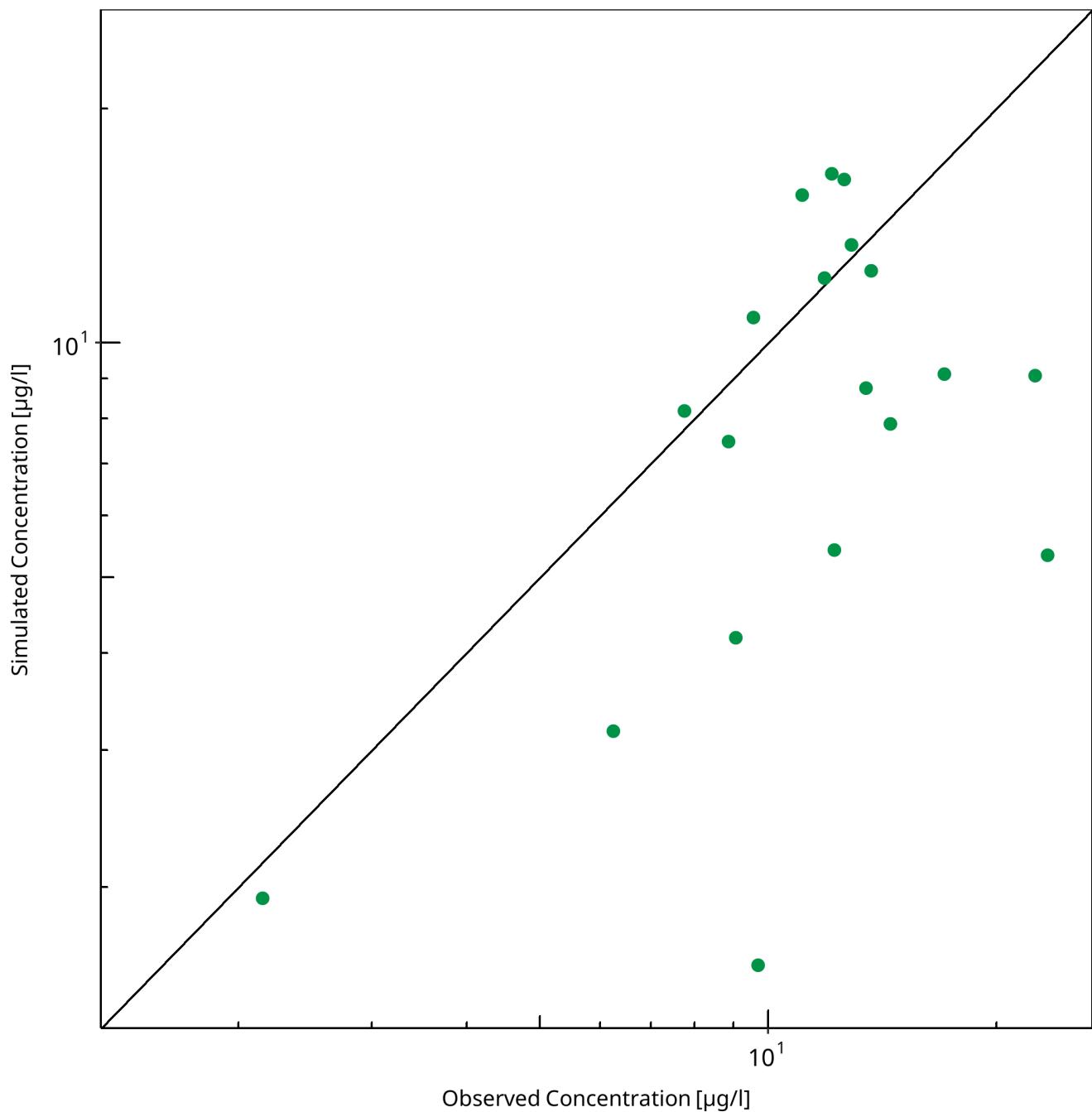


Figure 3-5: Keto-Itraconazole concentration in plasma

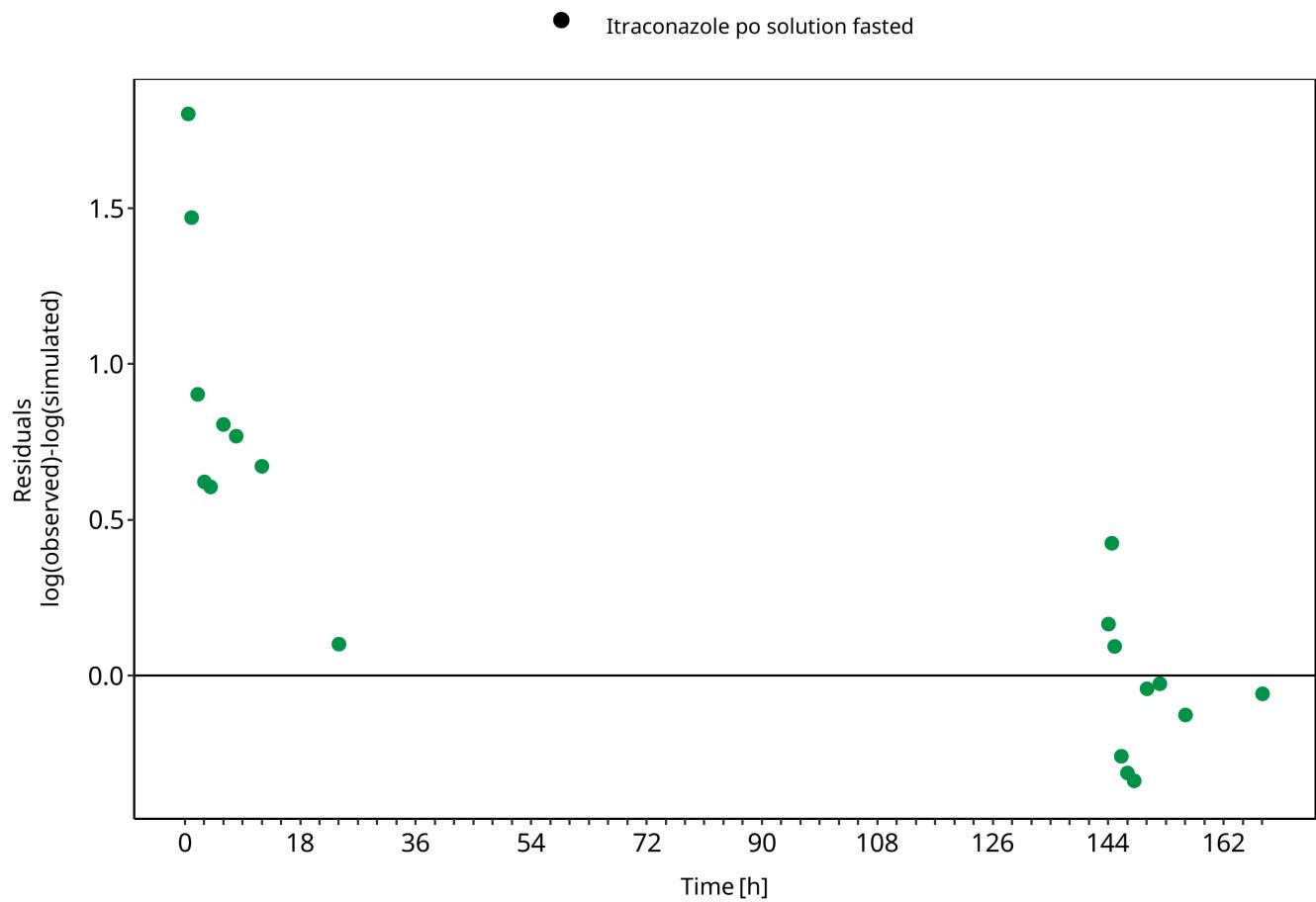


Figure 3-6: Keto-Itraconazole concentration in plasma

Table 3-4: GMFE for N-desalkyl-Itraconazole concentration in plasma

Group	GMFE
Itraconazole po solution fasted	1.53

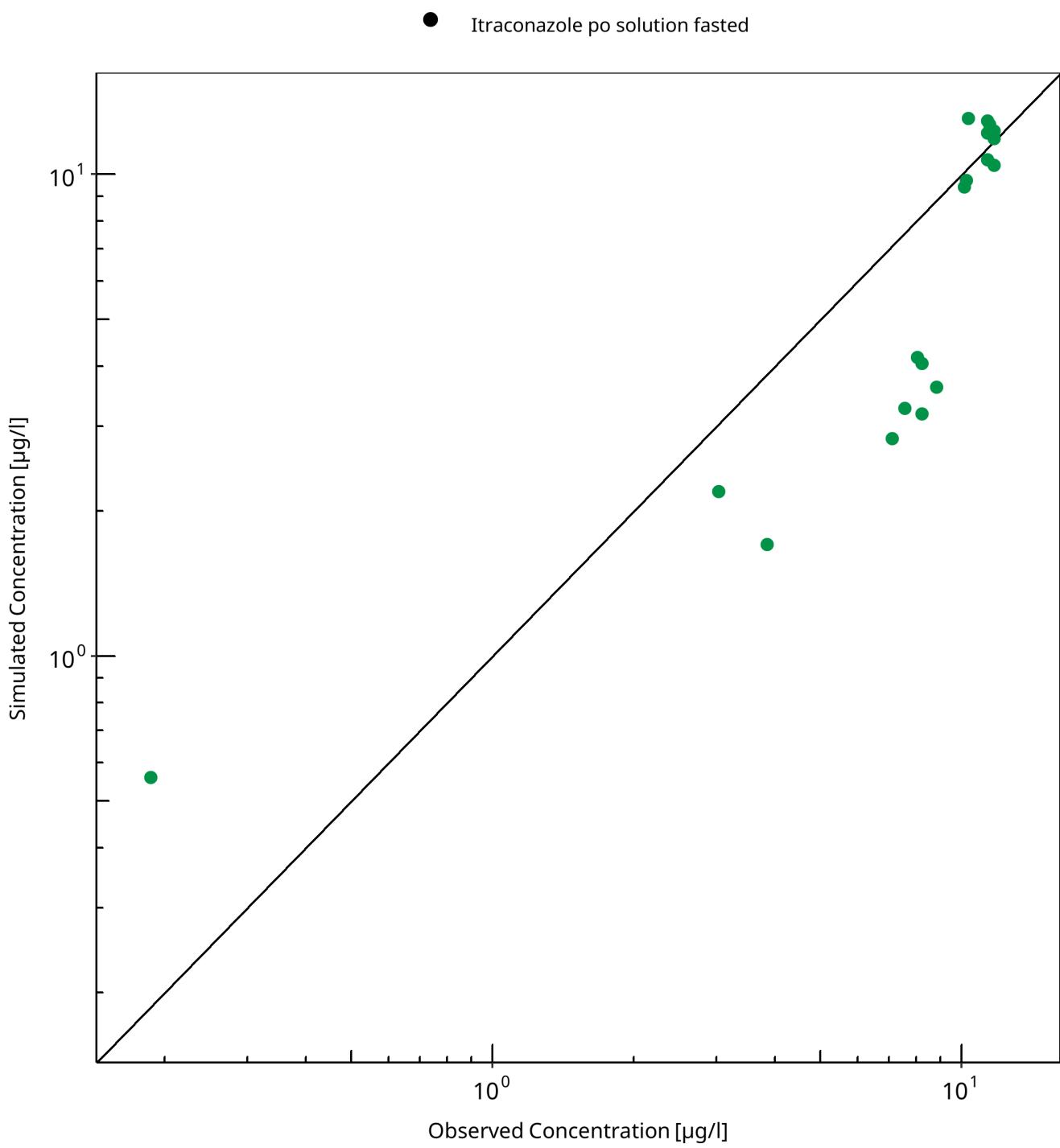


Figure 3-7: N-desalkyl-Itraconazole concentration in plasma

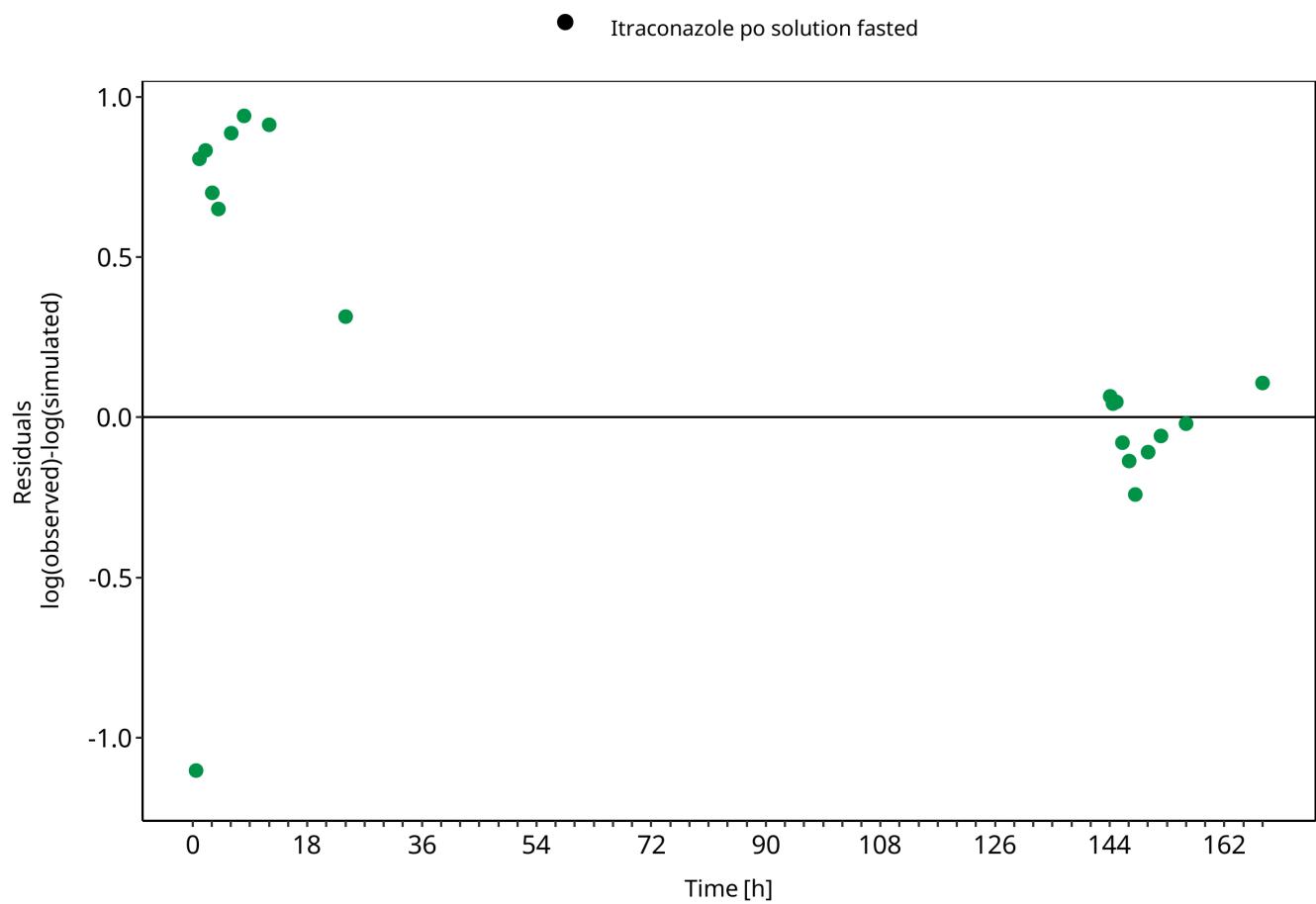


Figure 3-8: N-desalkyl-Itraconazole concentration in plasma

3.3 Concentration-Time Profiles

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

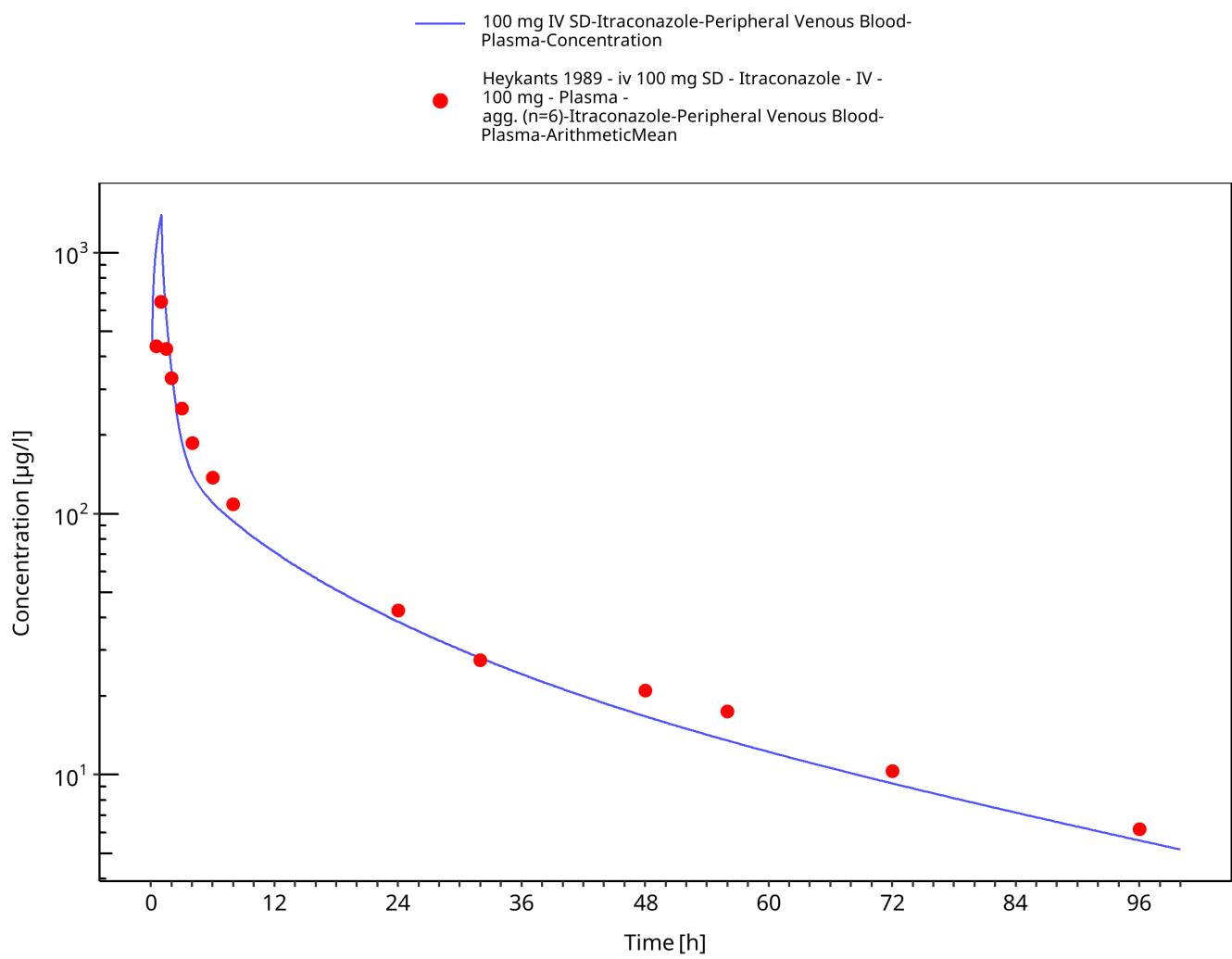


Figure 3-9: 100 mg IV SD - Plasma

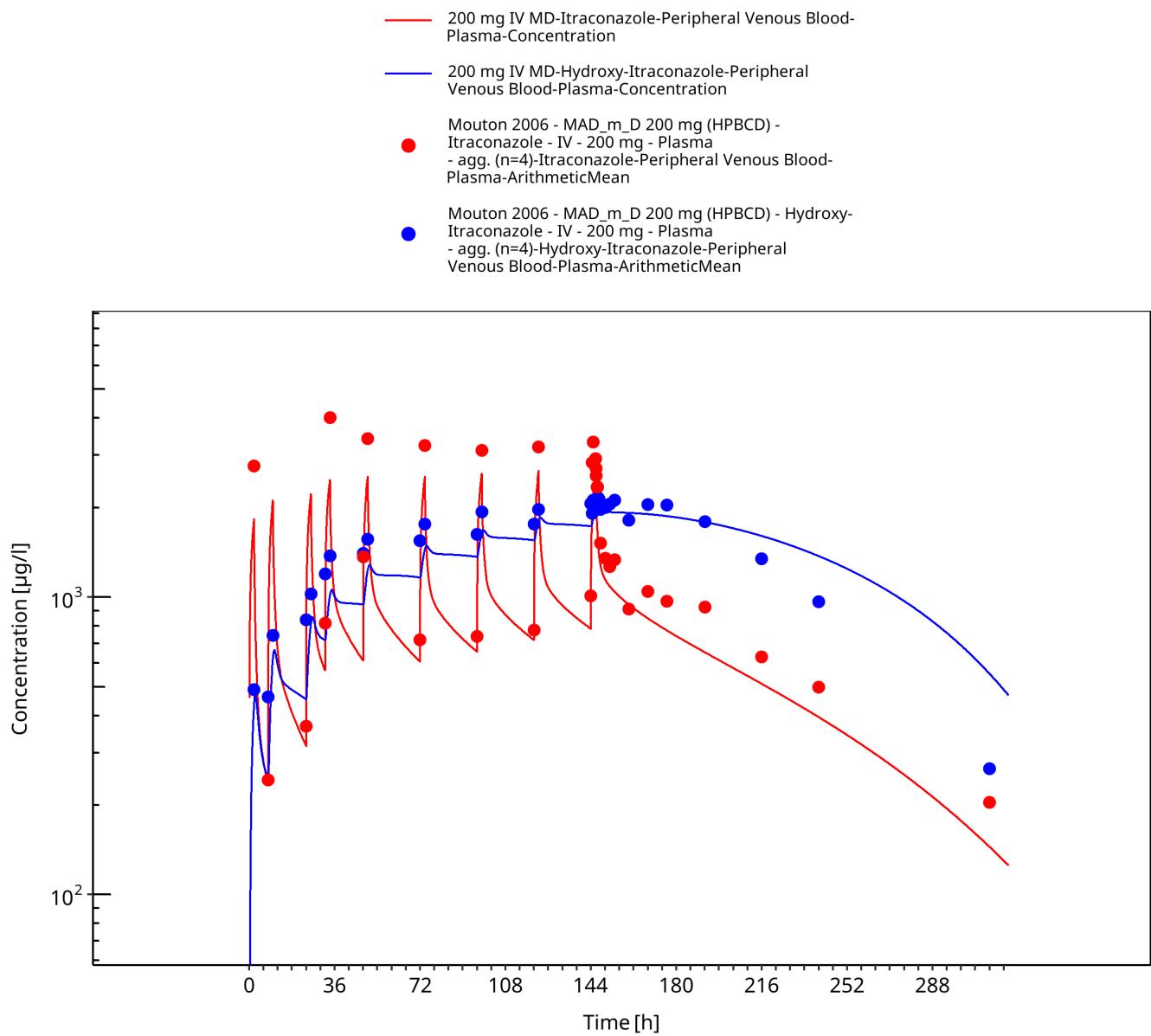


Figure 3-10: 200 mg IV MD - Plasma

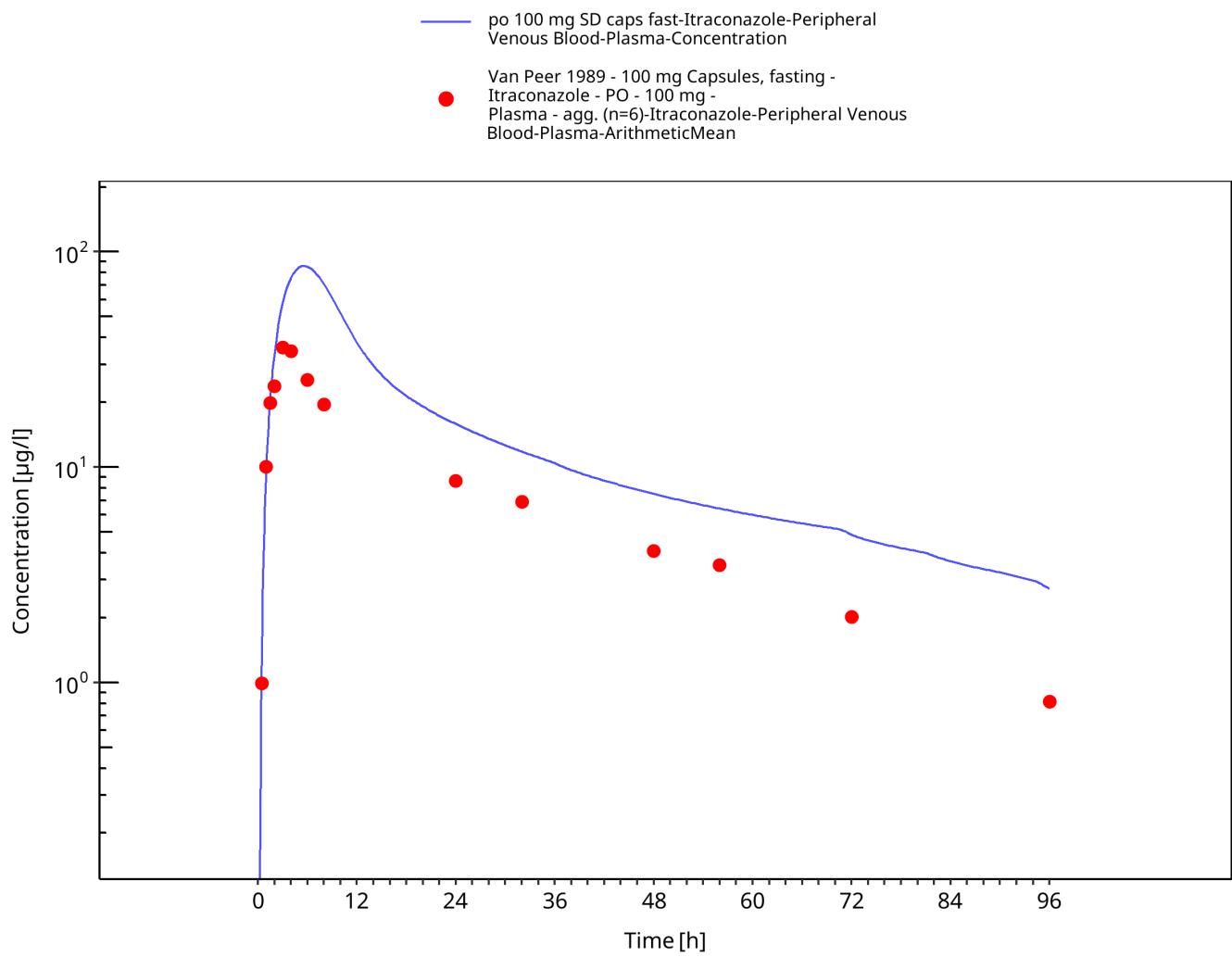


Figure 3-11: po 100 mg SD caps fast - Plasma

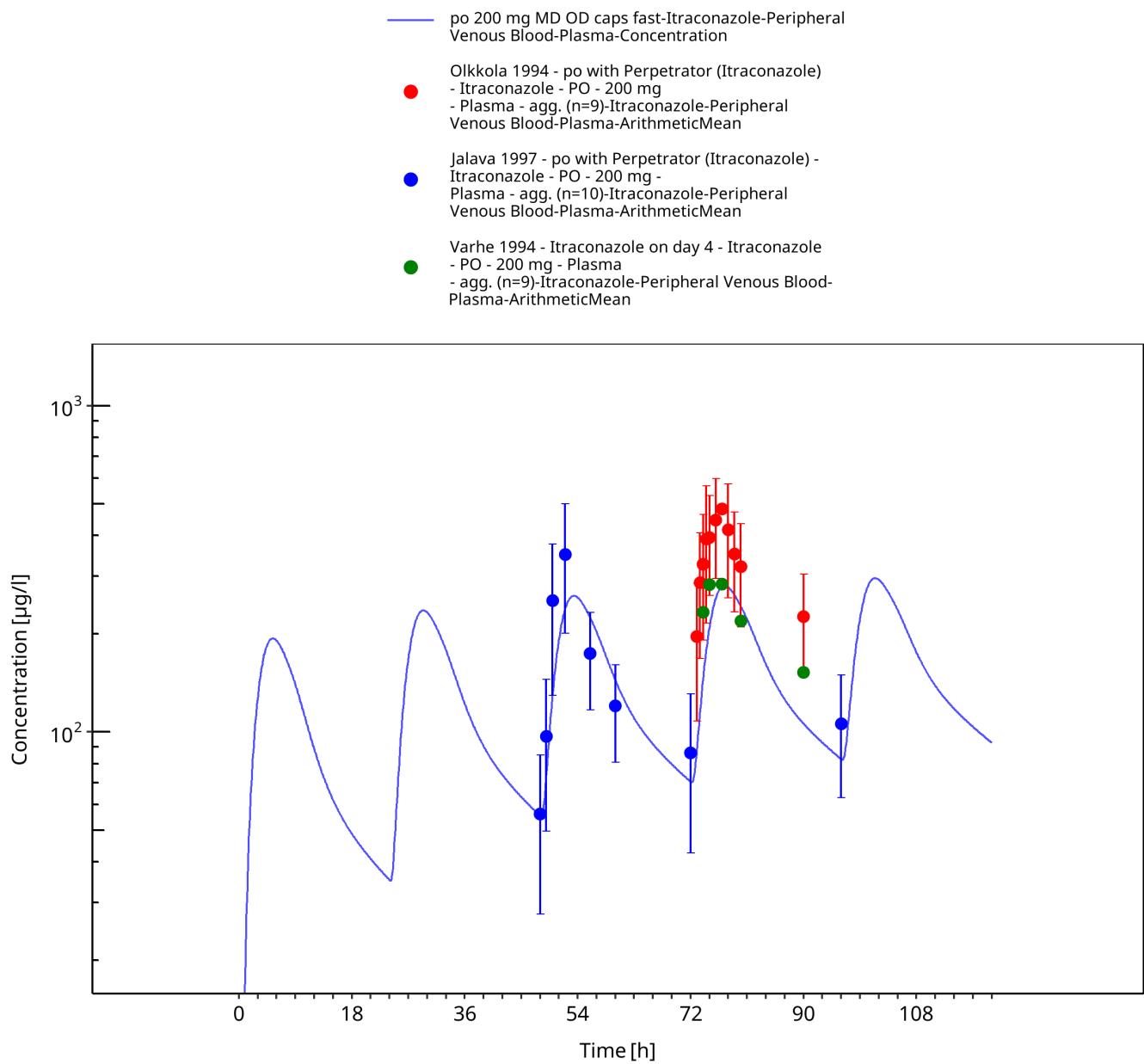


Figure 3-12: po 200 mg MD OD caps fast - Plasma

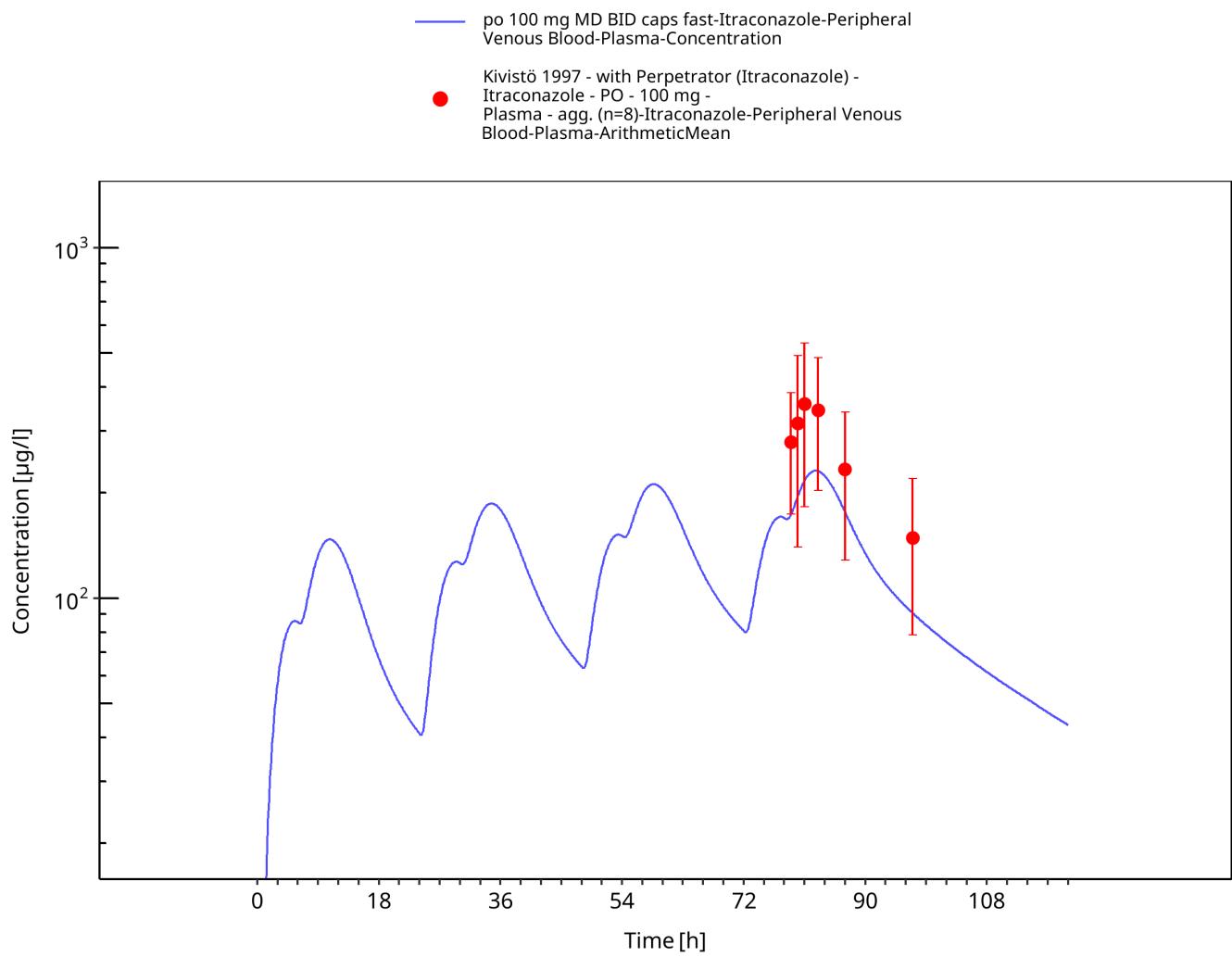


Figure 3-13: po 100 mg MD BID caps fast - Plasma

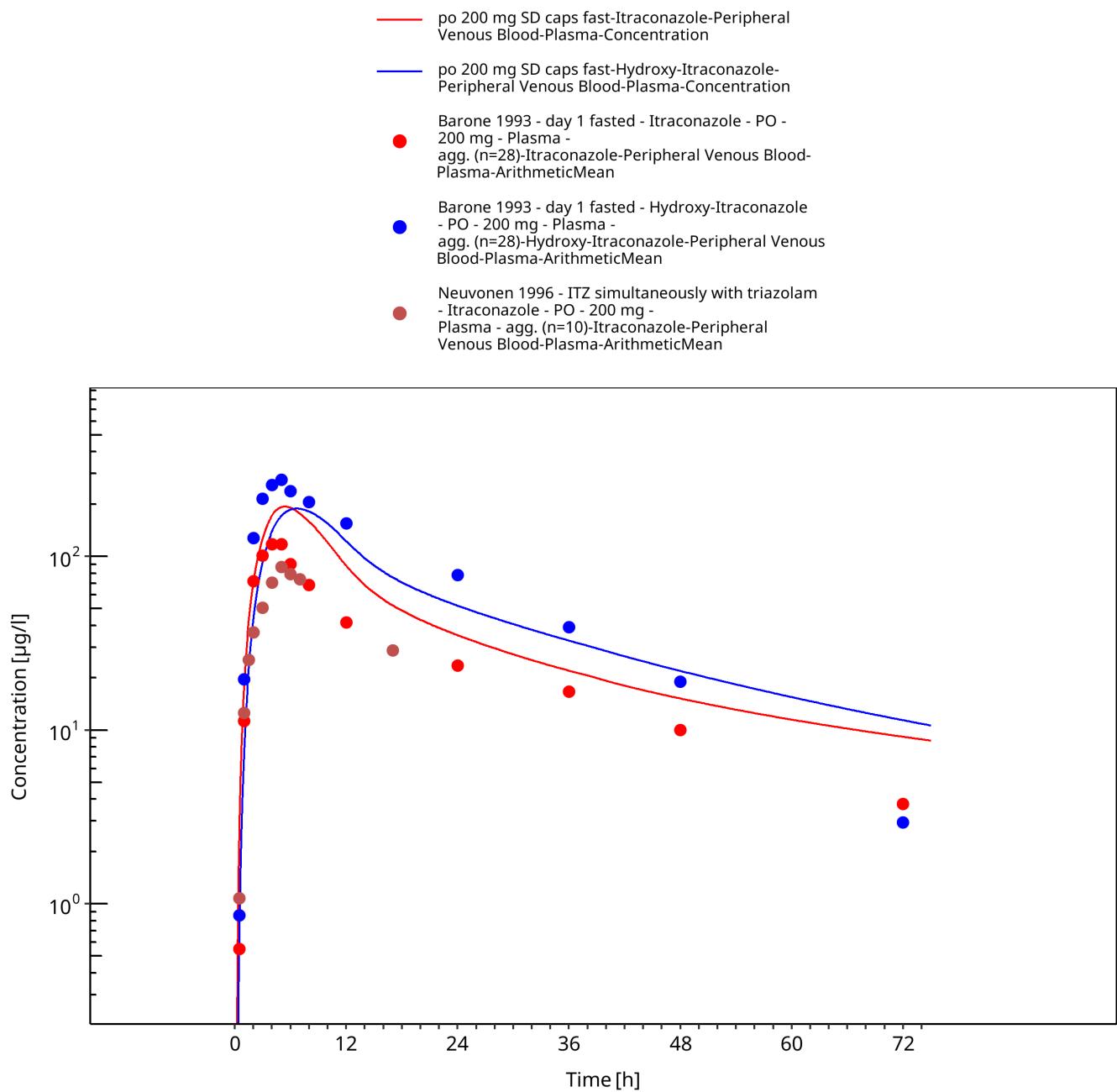


Figure 3-14: po 200 mg SD caps fast - Plasma

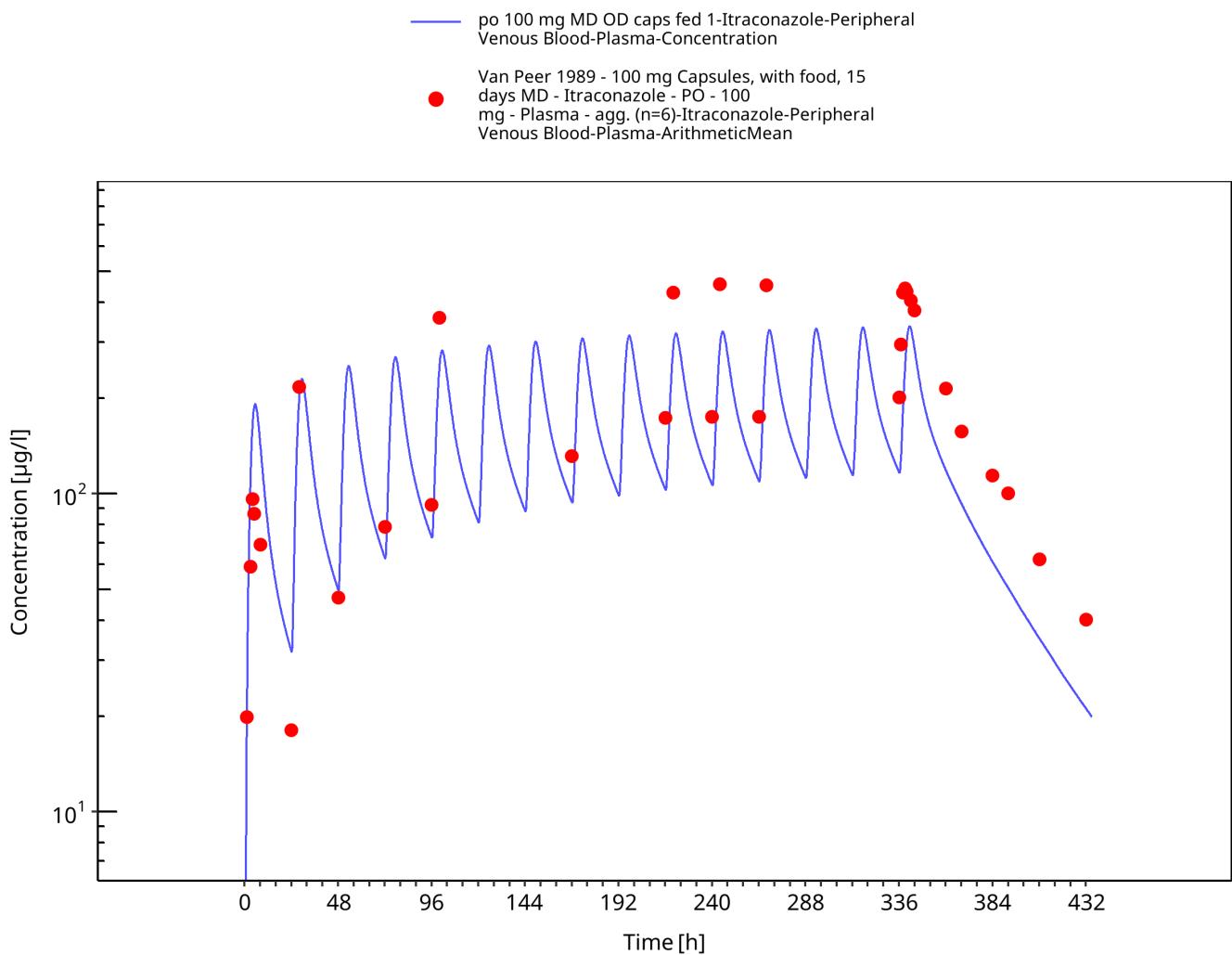


Figure 3-15: po 100 mg MD OD caps fed 1 - Plasma

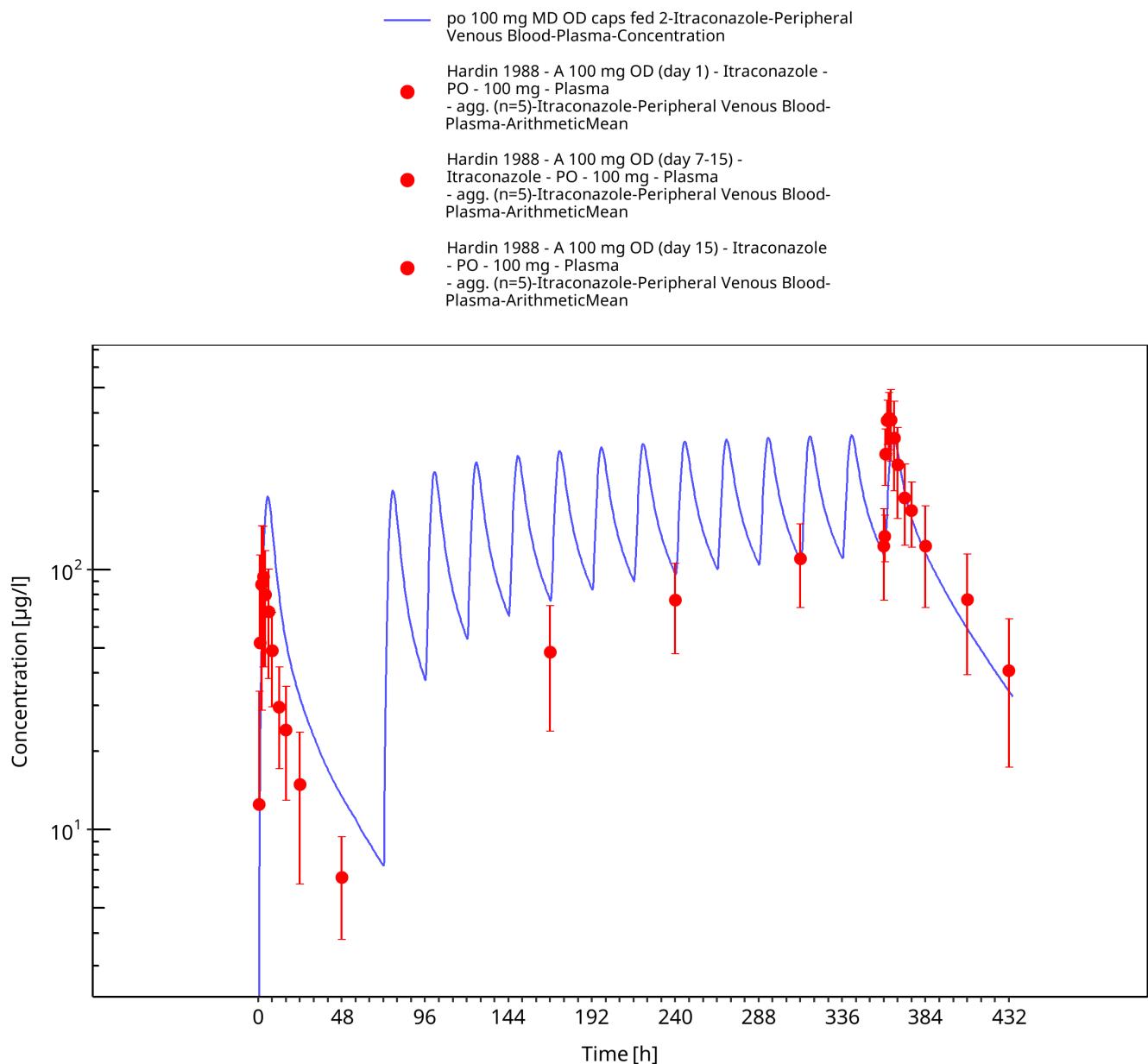


Figure 3-16: po 100 mg MD OD caps fed 2 - Plasma

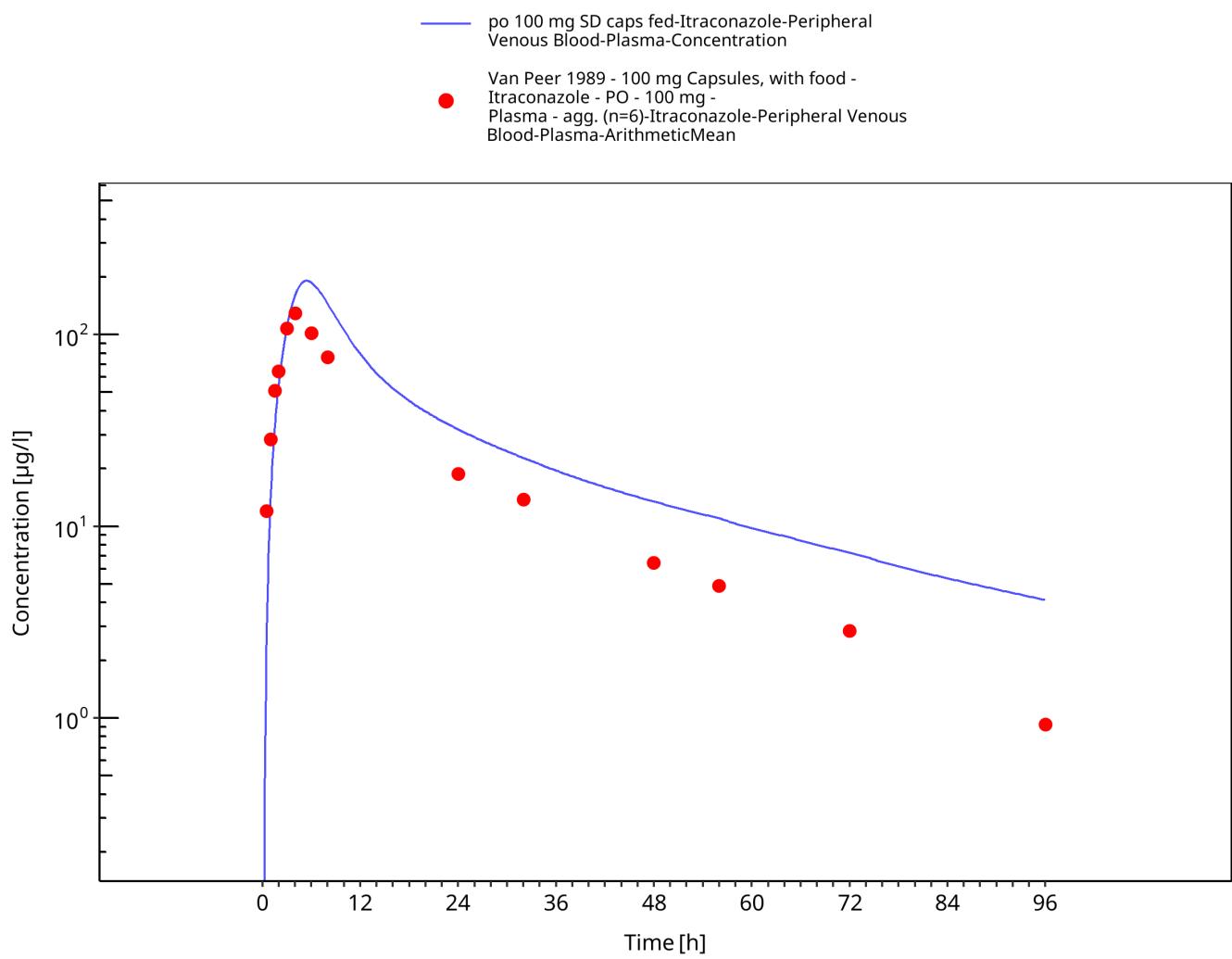


Figure 3-17: po 100 mg SD caps fed - Plasma

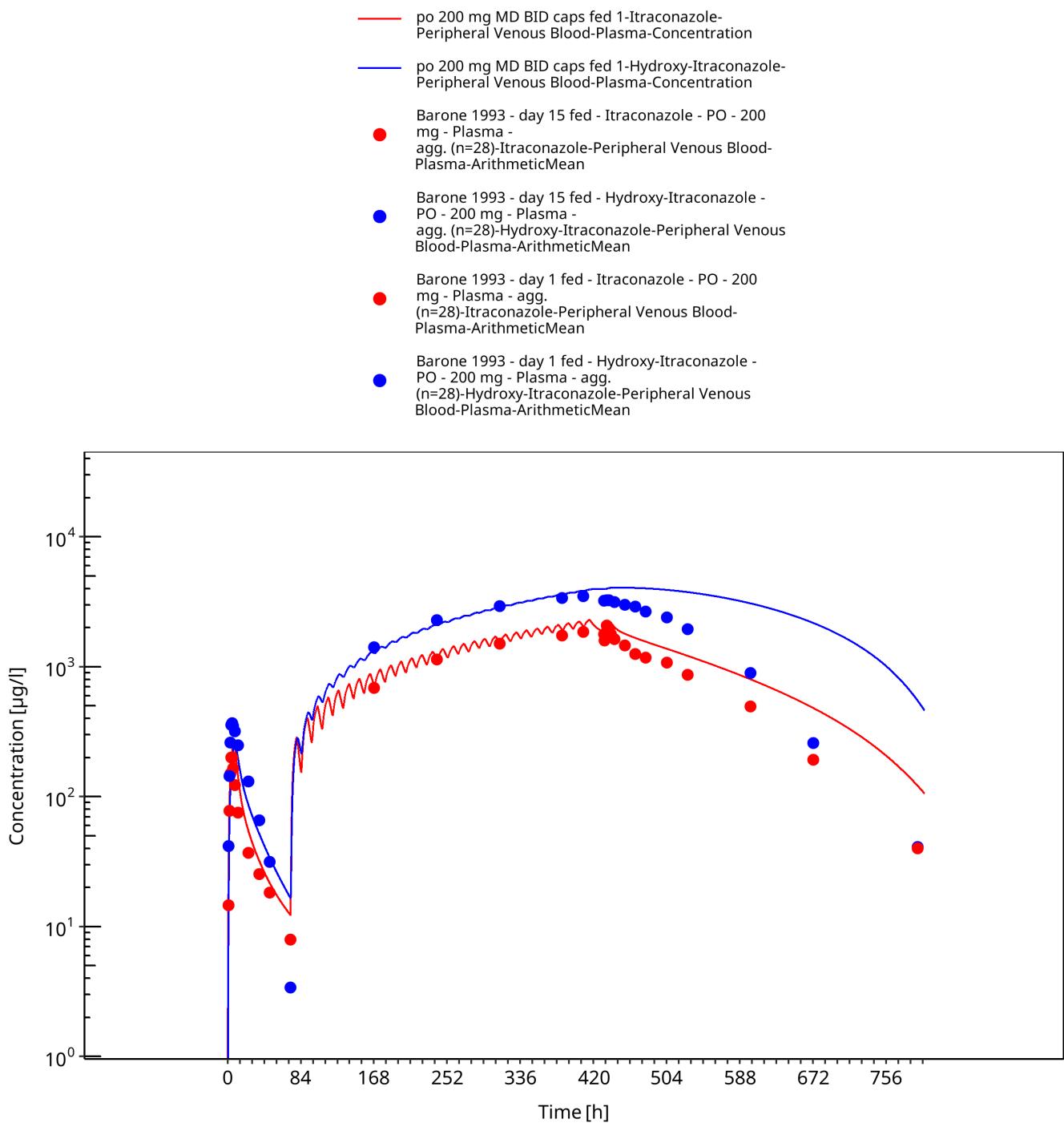


Figure 3-18: po 200 mg MD BID caps fed 1 - Plasma

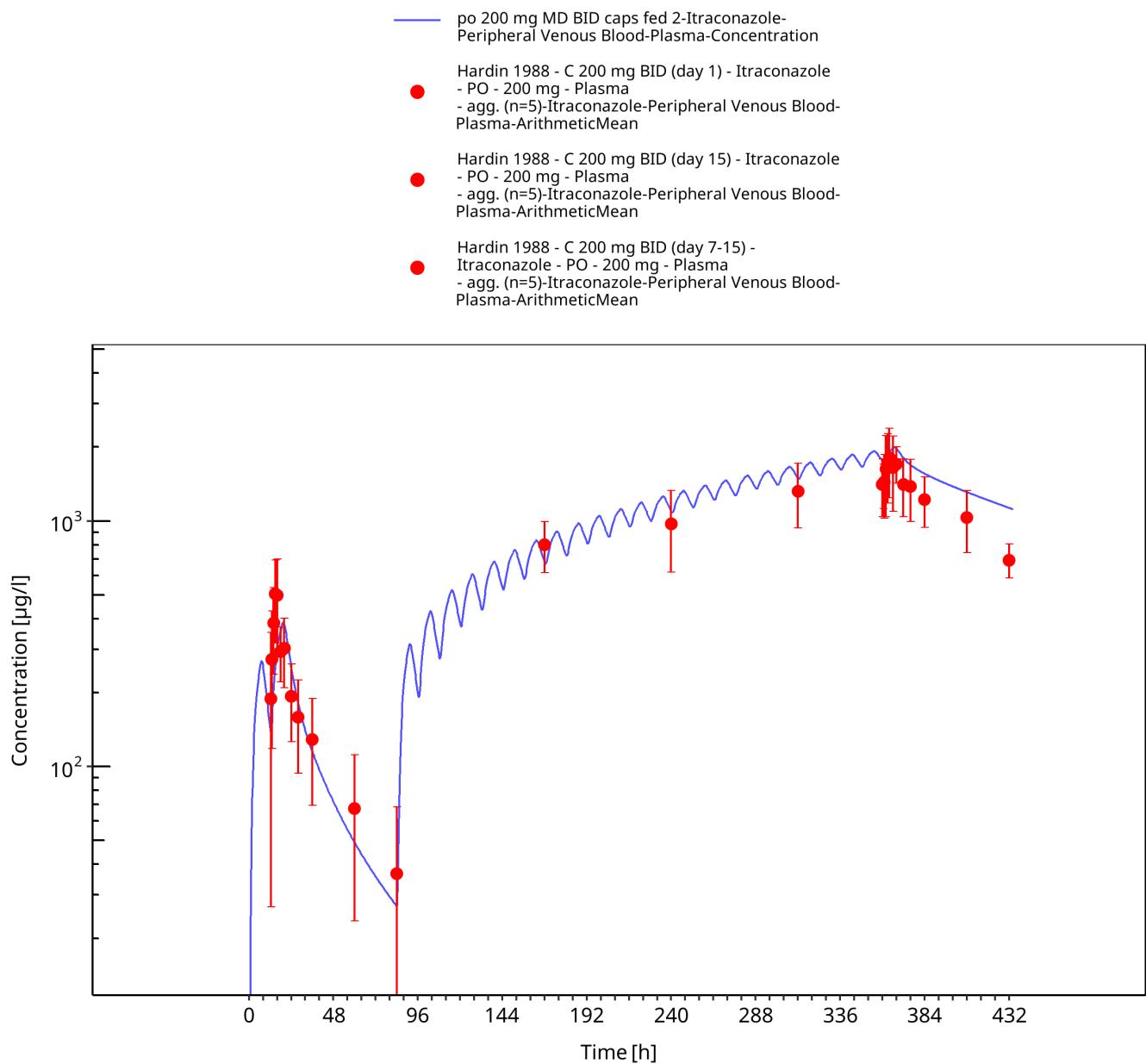


Figure 3-19: po 200 mg MD BID caps fed 2 - Plasma

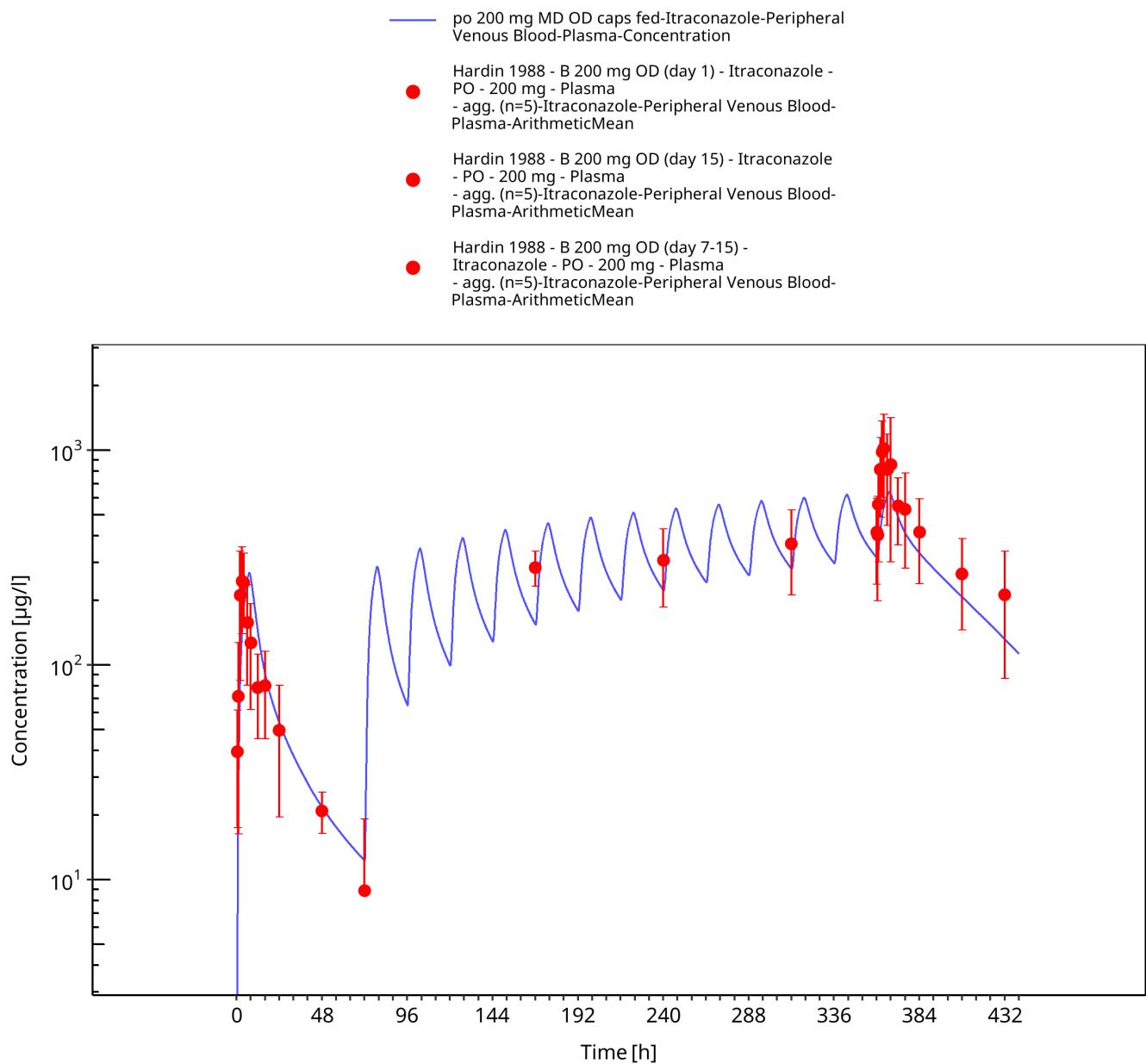


Figure 3-20: po 200 mg MD OD caps fed - Plasma

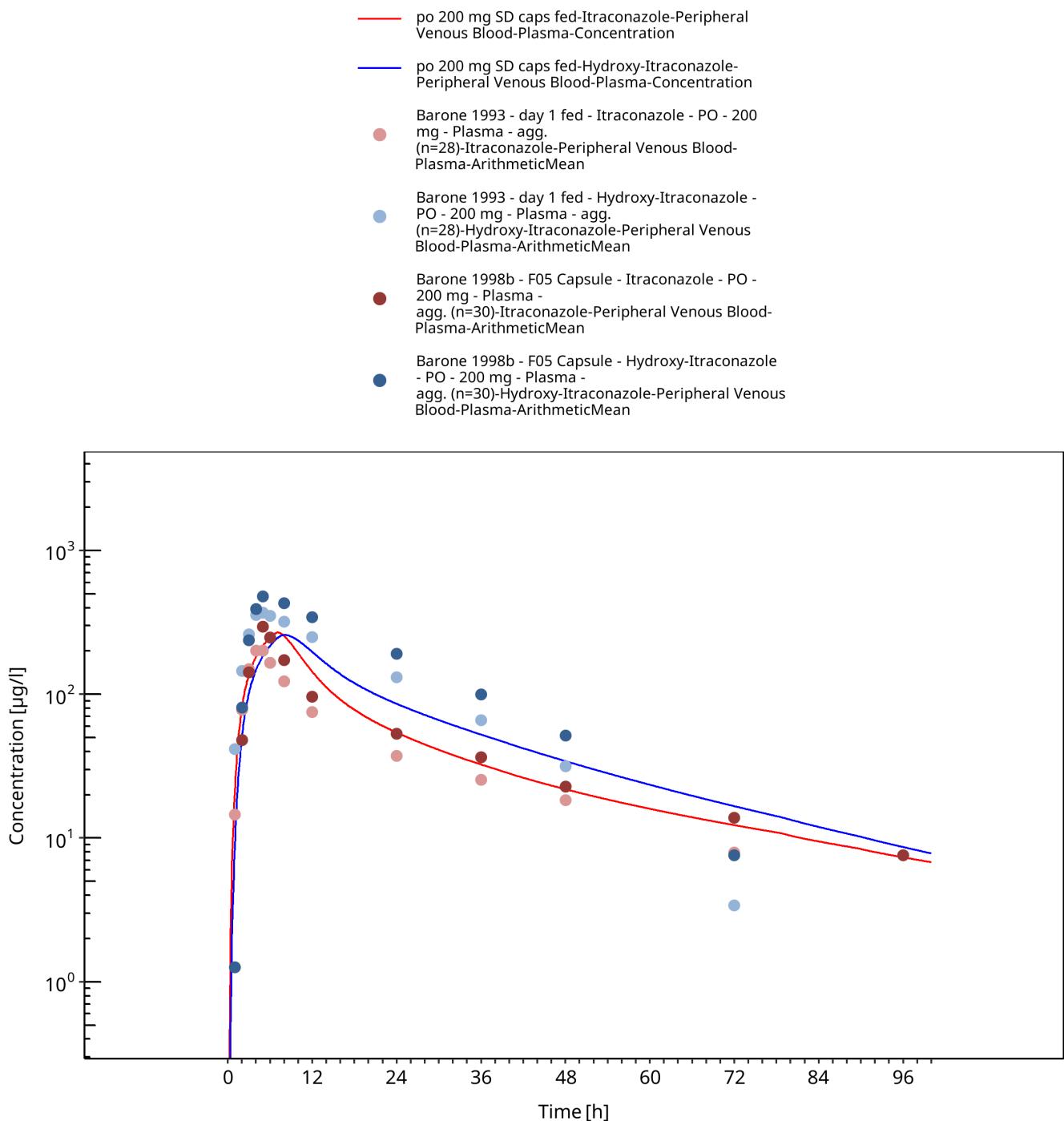


Figure 3-21: po 200 mg SD caps fed - Plasma

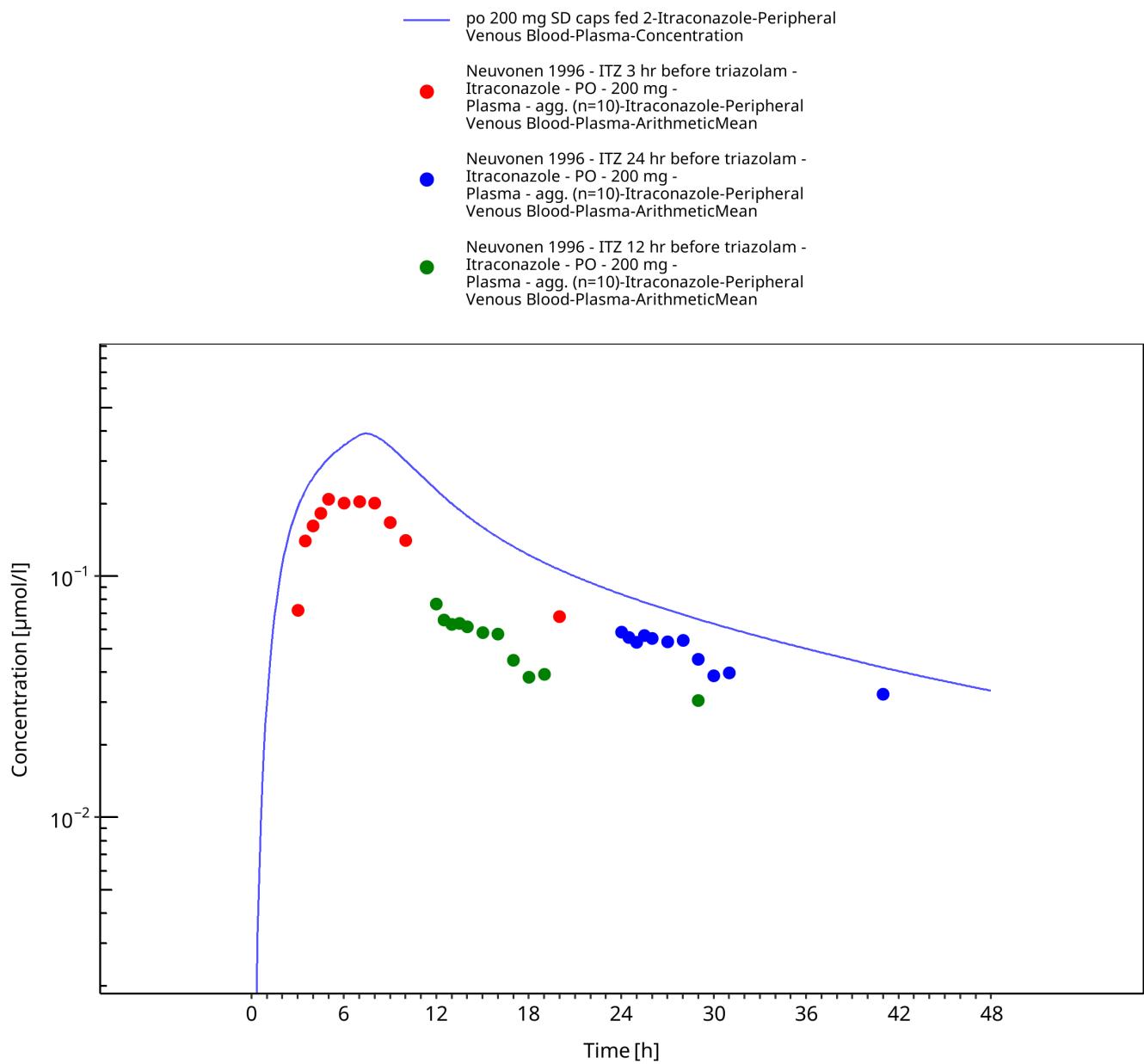


Figure 3-22: po 200 mg SD caps fed 2 - Plasma

- po 100 mg MD OD sol fast-Itraconazole-Peripheral Venous Blood-Plasma-Concentration
- po 100 mg MD OD sol fast-Hydroxy-Itraconazole-Peripheral Venous Blood-Plasma-Concentration
- po 100 mg MD OD sol fast-Keto-Itraconazole-Peripheral Venous Blood-Plasma-Concentration
- po 100 mg MD OD sol fast-N-desalkyl-Itraconazole-Peripheral Venous Blood-Plasma-Concentration
- Templeton 2008 - ITZ day 1 - Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Templeton 2008 - ITZ day 7 - Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Templeton 2008 - keto-ITZ day 1 - Keto-Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-Keto-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Templeton 2008 - keto-ITZ day 7 - Keto-Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-Keto-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Templeton 2008 - ND-OH-ITZ day 1 - N-desalkyl-Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-N-desalkyl-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Templeton 2008 - ND-OH-ITZ day 7 - N-desalkyl-Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-N-desalkyl-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Templeton 2008 - OH-ITZ day 1 - Hydroxy-Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-Hydroxy-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Templeton 2008 - OH-ITZ day 7 - Hydroxy-Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-Hydroxy-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean

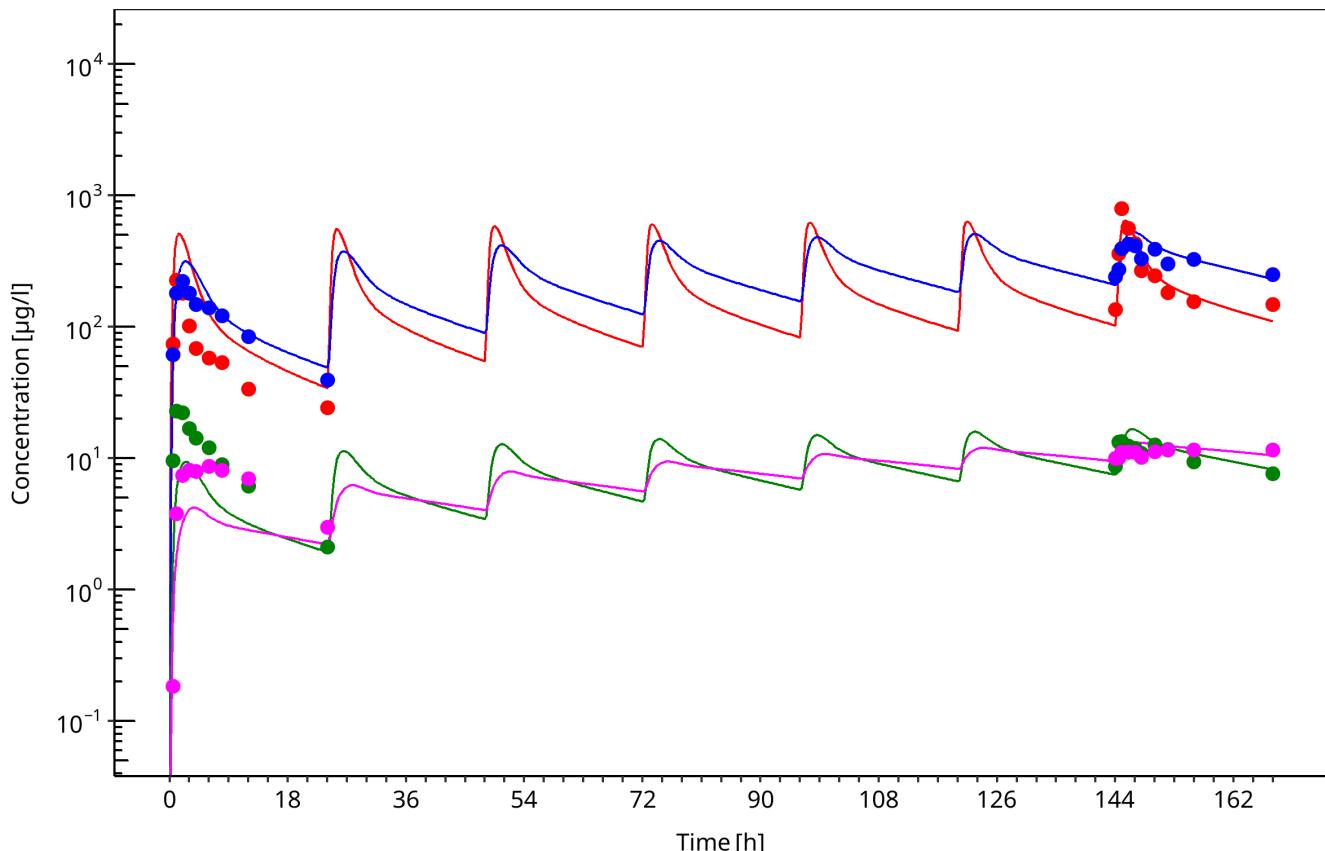


Figure 3-23: po 100 mg MD OD sol fast - Plasma

— po 100 mg SD sol fast-Itraconazole-Peripheral Venous Blood-Plasma-Concentration
— po 100 mg SD sol fast-Hydroxy-Itraconazole-Peripheral Venous Blood-Plasma-Concentration

- Van de Velde 1996 - Fasting ITZ - Itraconazole - PO - 100 mg - Plasma - agg. (n=12)-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Van de Velde 1996 - Fasting OH-ITZ - Hydroxy-Itraconazole - PO - 100 mg - Plasma - agg. (n=12)-Hydroxy-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean
- Van Peer 1989 - 100 mg Solution, fasting - Itraconazole - PO - 100 mg - Plasma - agg. (n=6)-Itraconazole-Peripheral Venous Blood-Plasma-ArithmeticMean

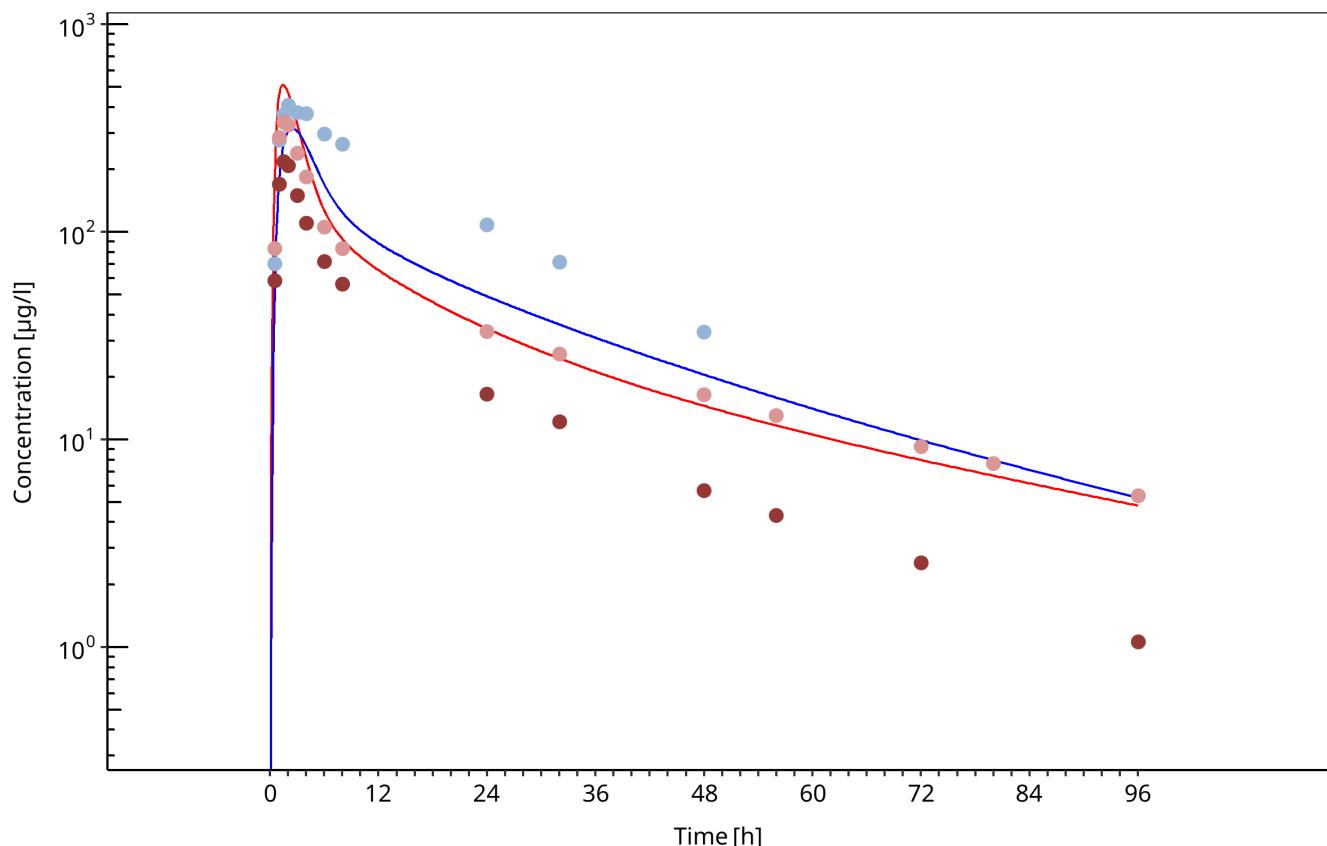


Figure 3-24: po 100 mg SD sol fast - Plasma

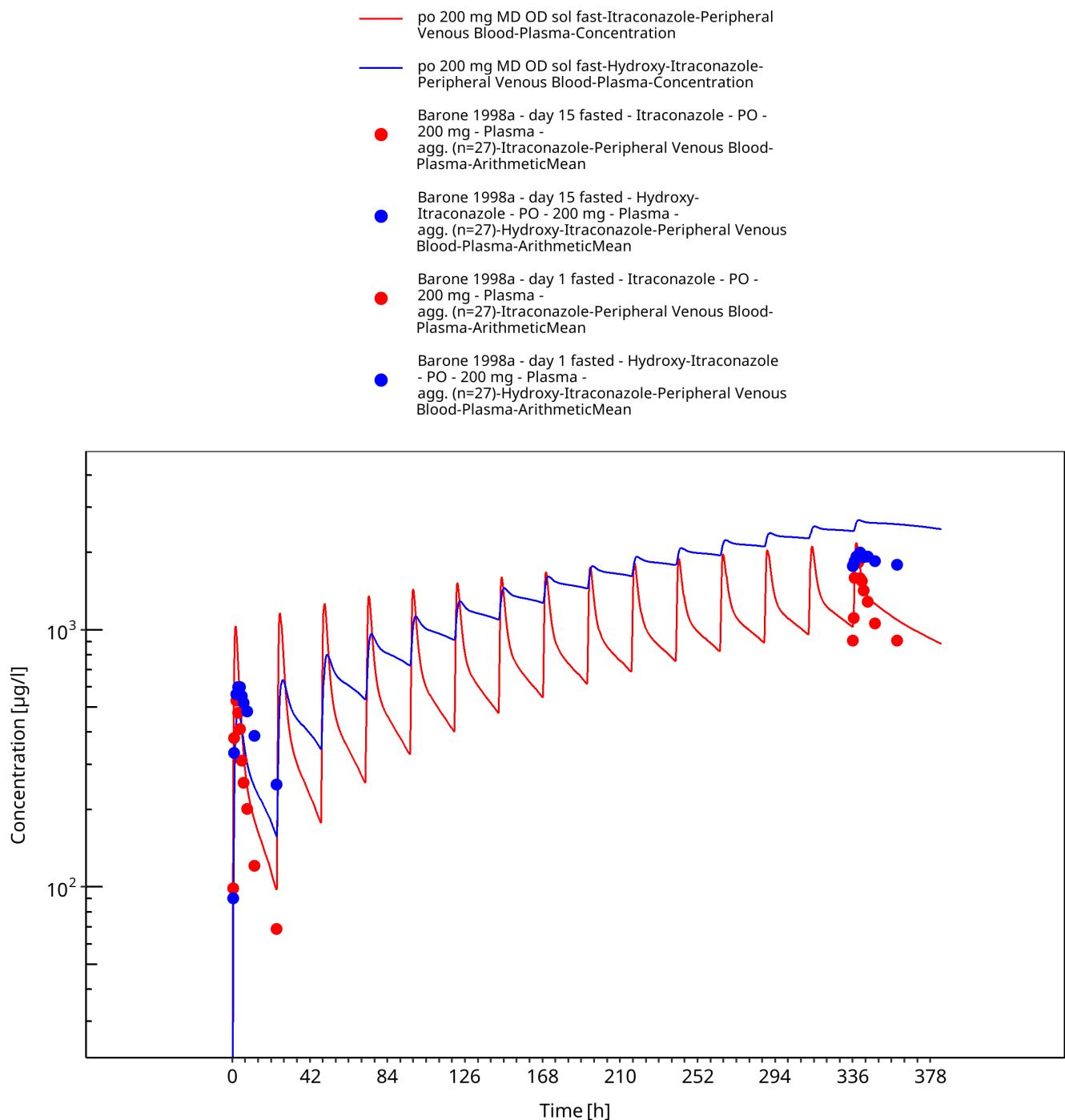


Figure 3-25: po 200 mg MD OD sol fast - Plasma

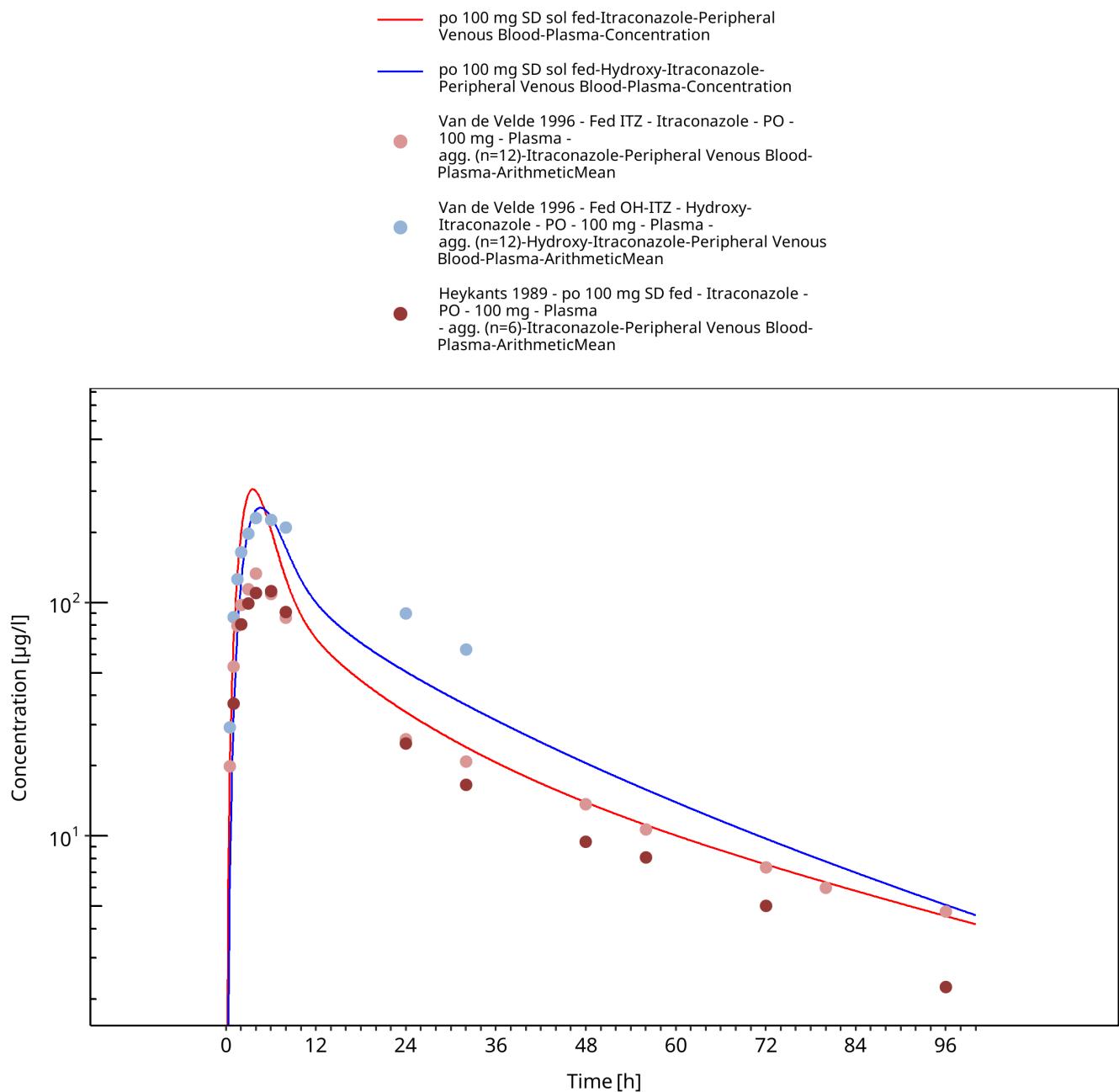


Figure 3-26: po 100 mg SD sol fed - Plasma

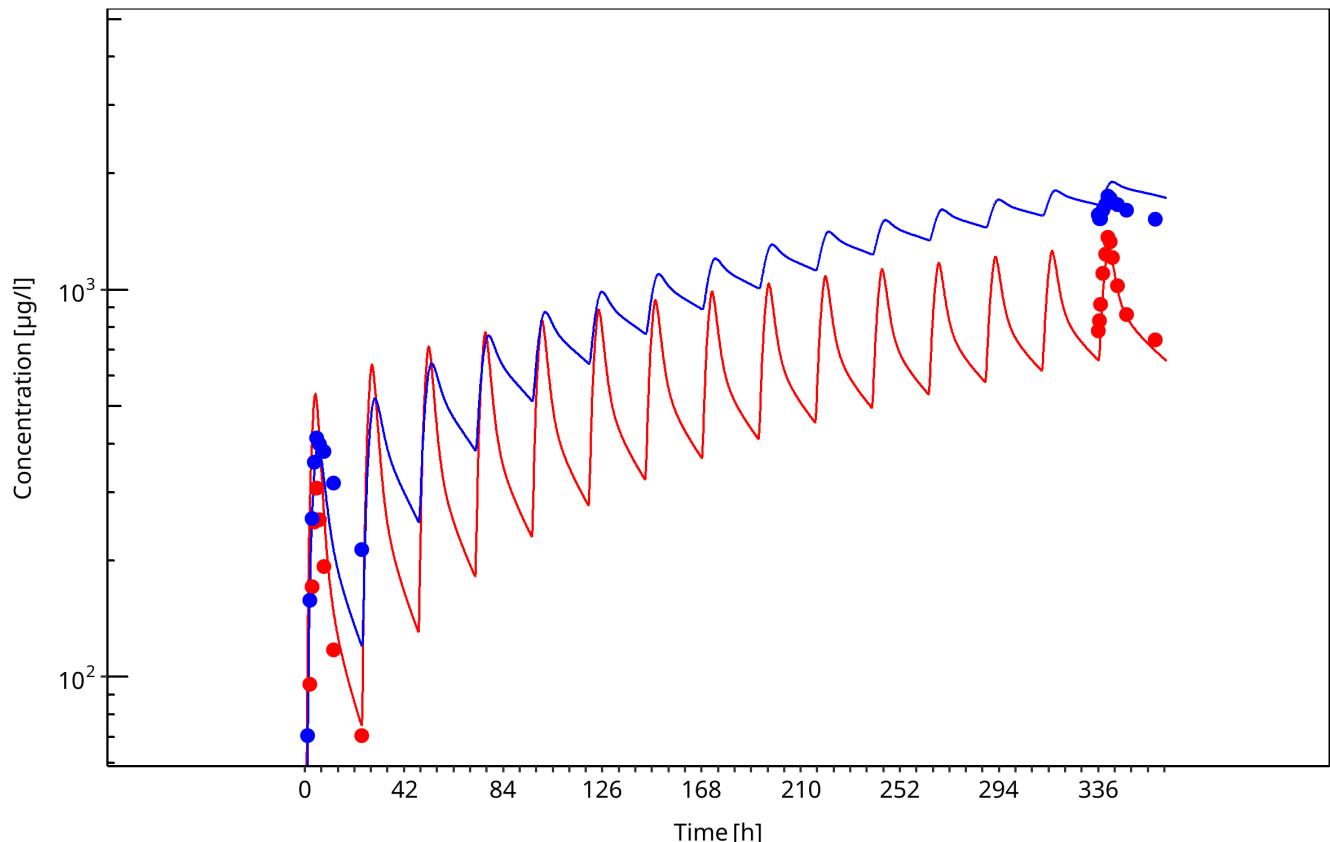
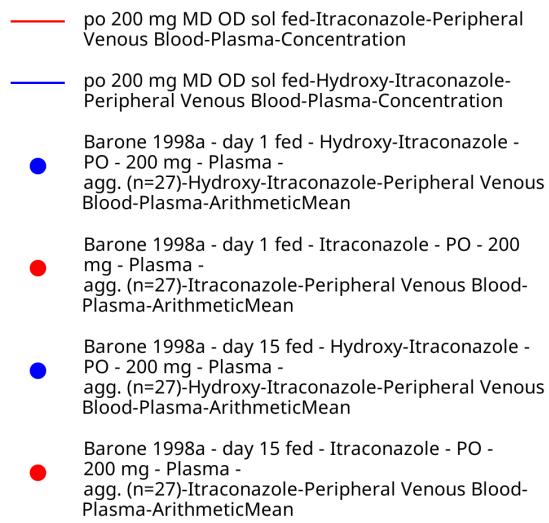


Figure 3-27: po 200 mg MD OD sol fed - Plasma

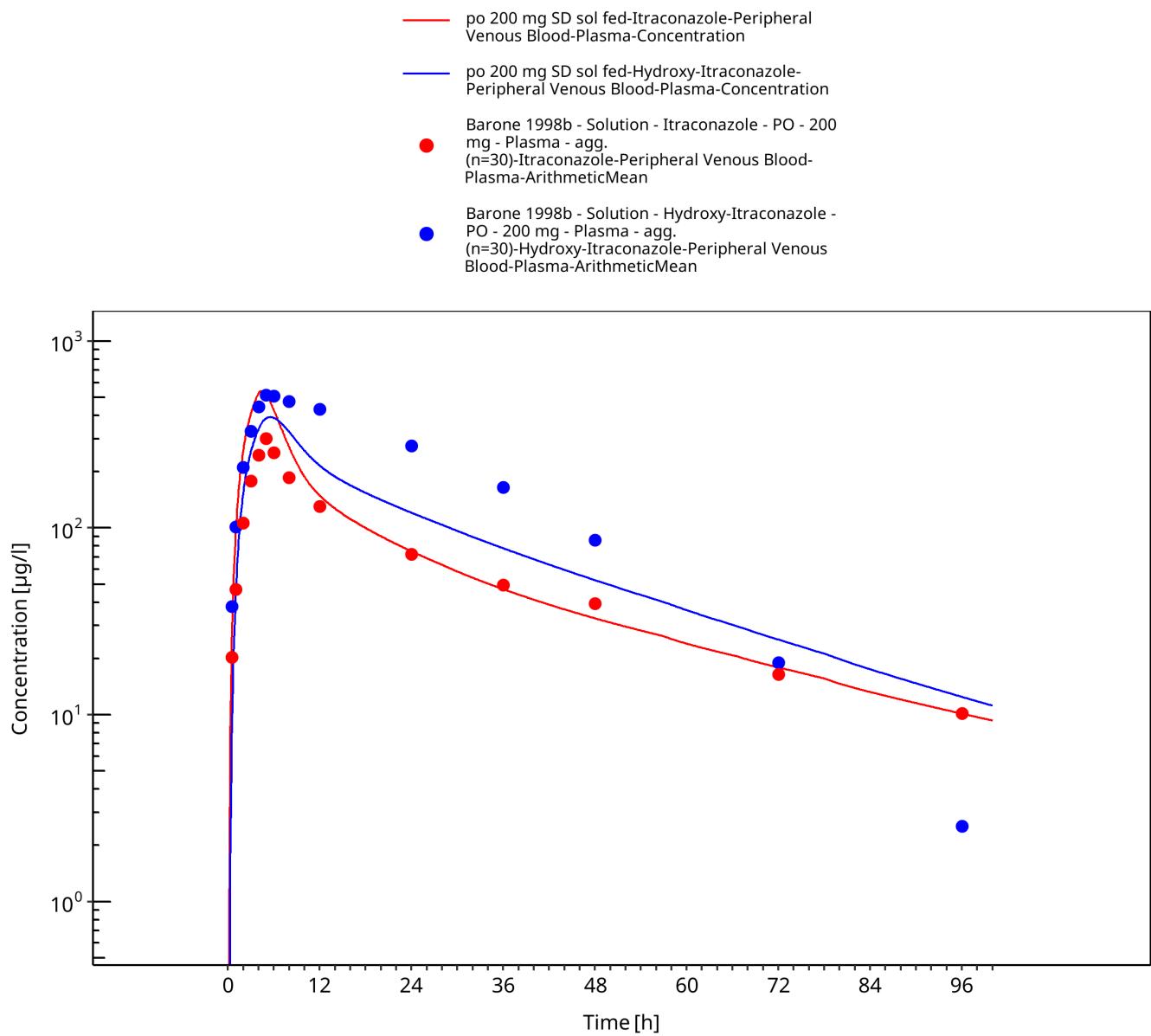


Figure 3-28: po 200 mg SD sol fed - Plasma

4 Conclusion

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.

5 References

- Barone 1993** Barone JA, Koh JG, Bierman RH, Colaizzi JL, Swanson KA, Gaffar MC, Moskovitz BL, Mechlinski W, Van de Velde V. Food interaction and steady-state pharmacokinetics of itraconazole capsules in healthy male volunteers. *Antimicrob Agents Chemother.* 1993 Apr;37(4):778-84.
- Barone 1998a** Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH, Jessen L. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. *Pharmacotherapy.* 1998 Mar-Apr;18(2):295-301.
- Barone 1998b** Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH, Jessen L. Enhanced bioavailability of itraconazole in hydroxypropyl-beta-cyclodextrin solution versus capsules in healthy volunteers. *Antimicrob Agents Chemother.* 1998 Jul;42(7):1862-5.
- Chen 2016** Chen Y, Ma F, Lu T, Budha N, Jin JY, Kenny JR, Wong H, Hop CE, Mao J. Development of a Physiologically Based Pharmacokinetic Model for Itraconazole Pharmacokinetics and Drug-Drug Interaction Prediction. *Clin Pharmacokinet.* 2016 Jun;55(6):735-49.
- Cheng 1973** Cheng Y, Prusoff WH. Relationship between the inhibition constant (K₁) and the concentration of inhibitor which causes 50 per cent inhibition (I₅₀) of an enzymatic reaction. *Biochem Pharmacol.* 1973 Dec 1;22(23):3099-108.
- DrugBank DB01167** (<https://www.drugbank.ca/drugs/DB01167>)
- DrugBank DBMET00374** (<https://www.drugbank.ca/metabolites/DBMET00374>)
- Hanke 2018** Hanke N, Frechen S, Moj D, Britz H, Eissing T, Wendl T, Lehr T. PBPK Models for CYP3A4 and P-gp DDI Prediction: A Modeling Network of Rifampicin, Itraconazole, Clarithromycin, Midazolam, Alfentanil, and Digoxin. *CPT Pharmacometrics Syst Pharmacol.* 2018 Oct;7(10):647-659.
- Hardin 1988** Hardin TC, Graybill JR, Fetchick R, Woestenborghs R, Rinaldi MG, Kuhn JG. Pharmacokinetics of itraconazole following oral administration to normal volunteers. *Antimicrob Agents Chemother.* 1988 Sep;32(9):1310-3.
- Heykants 1989** Heykants J, Van Peer A, Van de Velde V, Van Rooy P, Meuldermans W, Lavrijsen K, Woestenborghs R, Van Cutsem J, Cauwenbergh G. The clinical pharmacokinetics of itraconazole: an overview. *Mycoses.* 1989;32 Suppl 1:67-87.
- Ishigam 2001** Ishigam M, Uchiyama M, Kondo T, Iwabuchi H, Inoue S, Takasaki W, Ikeda T, Komai T, Ito K, Sugiyama Y. Inhibition of in vitro metabolism of simvastatin by itraconazole in humans and prediction of in vivo drug-drug interactions. *Pharm Res.* 2001 May;18(5):622-31.
- Isoherranen 2004** Isoherranen N, Kunze KL, Allen KE, Nelson WL, Thummel KE. Role of itraconazole metabolites in CYP3A4 inhibition. *Drug Metab Dispos.* 2004 Oct;32(10):1121-31.
- Jalava 1997** Jalava KM, Partanen J, Neuvonen PJ. Itraconazole decreases renal clearance of digoxin. *Ther Drug Monit.* 1997 Dec;19(6):609-13.
- Kivistö 1997** Kivistö KT, Lamberg TS, Kantola T, Neuvonen PJ. Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther.* 1997 Sep;62(3):348-54.
- Kuepfer 2016** Kuepfer L, Niederalt C, Wendl T, Schlender JF, Willmann S, Lippert J, Block M, Eissing T, Teutonico D. Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model. *CPT Pharmacometrics Syst Pharmacol.* 2016 Oct;5(10):516-531.
- Mouton 2006** Mouton JW, van Peer A, de Beule K, Van Vliet A, Donnelly JP, Soons PA. Pharmacokinetics of itraconazole and hydroxyitraconazole in healthy subjects after single and multiple doses of a novel formulation. *Antimicrob Agents Chemother.* 2006 Dec;50(12):4096-102.

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

Nishimura 2013 Nishimura M, Yaguti H, Yoshitsugu H, Naito S, Satoh T. Tissue distribution of mRNA expression of human cytochrome P450 isoforms assessed by high-sensitivity real-time reverse transcription PCR. Yakugaku Zasshi. 2003 May;123(5):369-75.

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

PK-Sim Ontogeny Database Version 7.3 (<https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/38cf71b384fcf25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf>)

PubChem CID 108222 (<https://pubchem.ncbi.nlm.nih.gov/compound/Hydroxy-Itraconazole>)

PubChem CID 53865186 (<https://pubchem.ncbi.nlm.nih.gov/compound/Keto-Itraconazole>)

PubChem CID 53789808 (<https://pubchem.ncbi.nlm.nih.gov/compound/169437521#section=Computed-Properties>)

Riccardi 2015 Riccardi K, Cawley S, Yates PD, Chang C, Funk C, Niosi M, Lin J, Di L. Plasma Protein Binding of Challenging Compounds. J Pharm Sci. 2015 Aug;104(8):2627-36.

Rodrigues 1999 Rodrigues AD. Integrated cytochrome P450 reaction phenotyping: attempting to bridge the gap between cDNA-expressed cytochromes P450 and native human liver microsomes. Biochem Pharmacol. 1999 Mar 1;57(5):465-80.

Shityakov 2014 Shityakov S, Förster C. In silico structure-based screening of versatile P-glycoprotein inhibitors using polynomial empirical scoring functions. Adv Appl Bioinform Chem. 2014 Mar 24;7:1-9.

Taupitz 2013 Taupitz T, Dressman JB, Buchanan CM, Klein S. Cyclodextrin-water soluble polymer ternary complexes enhance the solubility and dissolution behaviour of poorly soluble drugs. Case example: itraconazole. Eur J Pharm Biopharm. 2013 Apr;83(3):378-87.

Templeton 2008 Templeton IE, Thummel KE, Kharasch ED, Kunze KL, Hoffer C, Nelson WL, Isoherranen N. Contribution of itraconazole metabolites to inhibition of CYP3A4 in vivo. Clin Pharmacol Ther. 2008 Jan;83(1):77-85.

Van de Velde 1996 Van de Velde VJ, Van Peer AP, Heykants JJ, Woestenborghs RJ, Van Rooy P, De Beule KL, Cauwenbergh GF. Effect of food on the pharmacokinetics of a new hydroxypropyl-beta-cyclodextrin formulation of itraconazole. Pharmacotherapy. 1996 May-Jun;16(3):424-8.

Van Peer 1989 Van Peer A, Woestenborghs R, Heykants J, Gasparini R, Gauwenbergh G. The effects of food and dose on the oral systemic availability of itraconazole in healthy subjects. Eur J Clin Pharmacol. 1989;36(4):423-6.

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

Willmann 2007 Willmann S, Höhn K, Edginton A, Sevestre M, Solodenko J, Weiss W, Lippert J, Schmitt W. Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. J Pharmacokinet Pharmacodyn. 2007, 34(3):401-31.