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

Version	**master-OSP12.1**
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Moxidectin-Model/releases/tag/vmaster
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/

Table of Contents

1 Introduction

Moxidectin is a potent, broad-spectrum endectocide (antiparasitic active against endo- and ectoparasites) (Cotreau 2003, Tan 2022). It is used to in the treatment of river blindness (onchocerciasis). It selectively binds to parasite GABA-A and glutamate-gated chloride ion channels, causing paralysis of the parasite. Moxidectin shows potential for the treatment of tuberculosis, but is currently not used in clinical practice for this indication.

Moxidectin absorption reaches Tmax after 3-4h and shows a long half-life in humans (Drugbank). Oral bioavailability is enhanced by lipids, but does not result in a clinically relevant food-drug interaction. The volume of distribution is 1.2 L/kg. Moxidectin is lipophilic and highly protein bound. Metabolism is mediated via CYP3A and CYP2B. Moxidectin is eliminated mainly in feces, with negligible renal elimination.

The herein presented model building and evaluation report evaluates the performance of the PBPK model for moxidectin in (healthy) adults. The aim of this work was to establish a model that can be used to evaluate moxidectin use in tuberculosis.

The presented moxidectin PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (https://github.com/Open-Systems-Pharmacology/Moxidectin-Model).

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. (Kuepfer 2016). Information regarding the relevant 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 (PK-Sim Ontogeny Database Version 7.3). 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 (Schlender 2016) or otherwise referenced for the specific process.

First, a base mean model was built using clinical Phase I data including single dose oral administration of moxidectin solution in fasted and fed state, as well as single dose oral administration as solution or tablet was used to find an appropriate structure to describe the pharmacokinetics in plasma (Korth-Bradley 2012b). The mean PBPK model was developed using individuals matching the study demographics. The relative tissue specific expressions of CYP3A4 was considered. The aim of the current work was to establish a PBPK model of moxidectin for its use in tuberculosis. Although moxidectin is not approved yet for this indication, a daily dosing regimen is generally the standard for tuberculosis. Therefore, the model development prioritized prediction of the first day(s) compared to the terminal phase.

Unknown parameters (see below) were identified 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.

Moxidectin is absorbed relatively quickly (Tmax after 3-4h) (Drugbank). For simplicity, a dissolved formulation was applied for both solution and tablet formulations.

The model was then verified by simulating (Cotreau 2003, Kinrade 2018):

- a dose range between 3 mg and 36 mg
- fed and fasted state

Details about input data (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 / physico-chemical Data

A literature search was performed to collect available information on physicochemical properties of moxidectin. The obtained information from literature is summarized in the table below.

Parameter	Unit	Value	Source	Description
MW	g/mol	639.83	Drugbank	Molecular weight
pK_a	- (neutral)		Wood 2024	Acid dissociation constant
Solubility (pH 7)	mg/mL	5.20E-3	Drugbank	Aqueous Solubility, FaSSIF, ...
logP		6	Drugbank (experimental)	Partition coefficient between octanol and water
logP		5.3	Drugbank (predicted)	Partition coefficient between octanol and water
logP		5.67	Wood 2024 (predicted)	Partition coefficient between octanol and water
logP		4.3	Pubchem (predicted)	Partition coefficient between octanol and water
fu		0.00078	Wood 2024	Fraction unbound in plasma
CLint CYP3A4	µL/min/mg protein	36	Wood 2024 (predicted)	Intrinsic clearance mediated by CYP3A4

2.2.2 Clinical Data

A literature search was performed to collect available clinical data on moxidectin in healthy adults.

2.2.2.1 Model Building

The following studies were used for model building (training data):

Publication	Arm / Treatment / Information used for model building
Korth-Bradley 2012a	Healthy Subjects with a single oral dose of 10 mg solution in fasted or fed conditions
Korth-Bradley 2012b	Healthy Subjects with a single oral dose of 10 mg solution or tablet

Data for Korth-Bradley 2012a and Korth-Bradley 2012b was extracted from the study reports S101 and S1005, respectively.

2.2.2.2 Model Verification

The following studies were used for model verification:

Publication	Arm / Treatment / Information used for model building
Cotreau 2003	Healthy Subjects with a single oral dose of 3 mg, 9 mg, 18 mg or 36 mg in fasted or fed conditions
Kinrade 2018	Healthy Subjects with a single oral dose of 4 mg, 8 mg, 16 mg, 24 mg, 36 mg in fasted conditions

Data for Kinrade 2018 was extracted from the study report S1008.

2.3 Model Parameters and Assumptions

2.3.1 Absorption

The model parameter `Specific intestinal permeability` was calculated by default based on the lipophilicity. Predicted aqueous solubility (Drugbank, see Section 2.2.1) was set as default solubility. For simplicity, all oral administrations were modelled as solution. Food effects were not specifically evaluated, as they did not result in clinically significant effect. Nevertheless, data for fasted and fed conditions were used to develop and verify the PBPK model. For fed conditions, a standard high-fat breakfast event was implemented according to the study information.

2.3.2 Distribution

Fraction unbound was reported approximately 0.00078 (Wood 2024, see Section 2.2.1). `Lipophilicity` was optimized within the range of measured values (4.30-6.00) to find a best match of simulated to observed moxidectin PK profile data (Korth-Bradley 2012a, Korth-Bradley 2012b). 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 `PK-Sim Standard` and cellular permeability calculation by `PK-Sim Standard` for moxidectin.

2.3.3 Metabolism and Elimination

Data regarding metabolism and elimination of moxidectin is limited. Retrograde calculation of clearance, assuming 7% of clearance is CYP3A4-mediated, resulted in an intrinsic clearance of 36 µL/min/mg protein (Wood 2024). The majority of clearance (93%) was assumed to be biliary clearance. Retrograde calculation based on an apparent total clearance of 2760-3506 mL/h for healthy volunteers results in an estimated biliary clearance of 40 mL/h/kg (FDA 2018).

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
`Lipophilicity`	4.60	Log units

3 Results and Discussion

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

The model was evaluated covering data from studies including in particular (Korth-Bradley 2012a, Korth-Bradley 2012b, Cotreau 2003, Kinrade 2018)

- oral administration (solution or tablet)
- a dose range between 3 mg and 36 mg
- fed and fasted state

The model quantifies metabolism via biliary clearance and CYP3A4.

The PBPK model was able to capture the PK of moxidectin over the first days, but not the late phase as indicated by the GMFE. As the standard dosing regimen for tuberculosis is once daily (i.e., based on dosing regimens of other tuberculosis medicines, since moxidectin is not approved for tuberculosis yet), the model is fit for purpose to evaluate moxidectin in treatment of tuberculosis. Nevertheless, further model refinement is required to describe the late phase.

The next sections show:

1. the final model 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: Moxidectin

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	0.0052 mg/ml	Unknown-Drugbank ALOGPS	Measurement	True
Reference pH	7	Unknown-Drugbank ALOGPS	Measurement	True
Lipophilicity	4.5953885122 Log Units	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 1' on 2025-05-16 16:40	Measurement	True
Fraction unbound (plasma, reference value)	0.00078	Unknown-Woods 2024	Measurement	True
Is small molecule	Yes			
Molecular weight	639.83 g/mol			
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Processes

Metabolizing Enzyme: CYP3A4-Wood 2024

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
In vitro CL for liver microsomes	36 µl/min/mg mic. protein	Unknown-Wood 2024

Systemic Process: Biliary Clearance-Assumption

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.00078	
Lipophilicity (experiment)	6 Log Units	
Plasma clearance	40 ml/h/kg	Unknown-Assumption

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 first plot shows observed versus simulated plasma concentration, the second weighted residuals versus time.

Table 3-1: GMFE for Goodness of fit plot for concentration in plasma

Group	GMFE
Moxidectin (model building)	3.69
Moxidectin (model building) 24h only	1.20
Moxidectin (model verification)	2.87
Moxidectin (model verification) 24h only	1.32
All	2.36

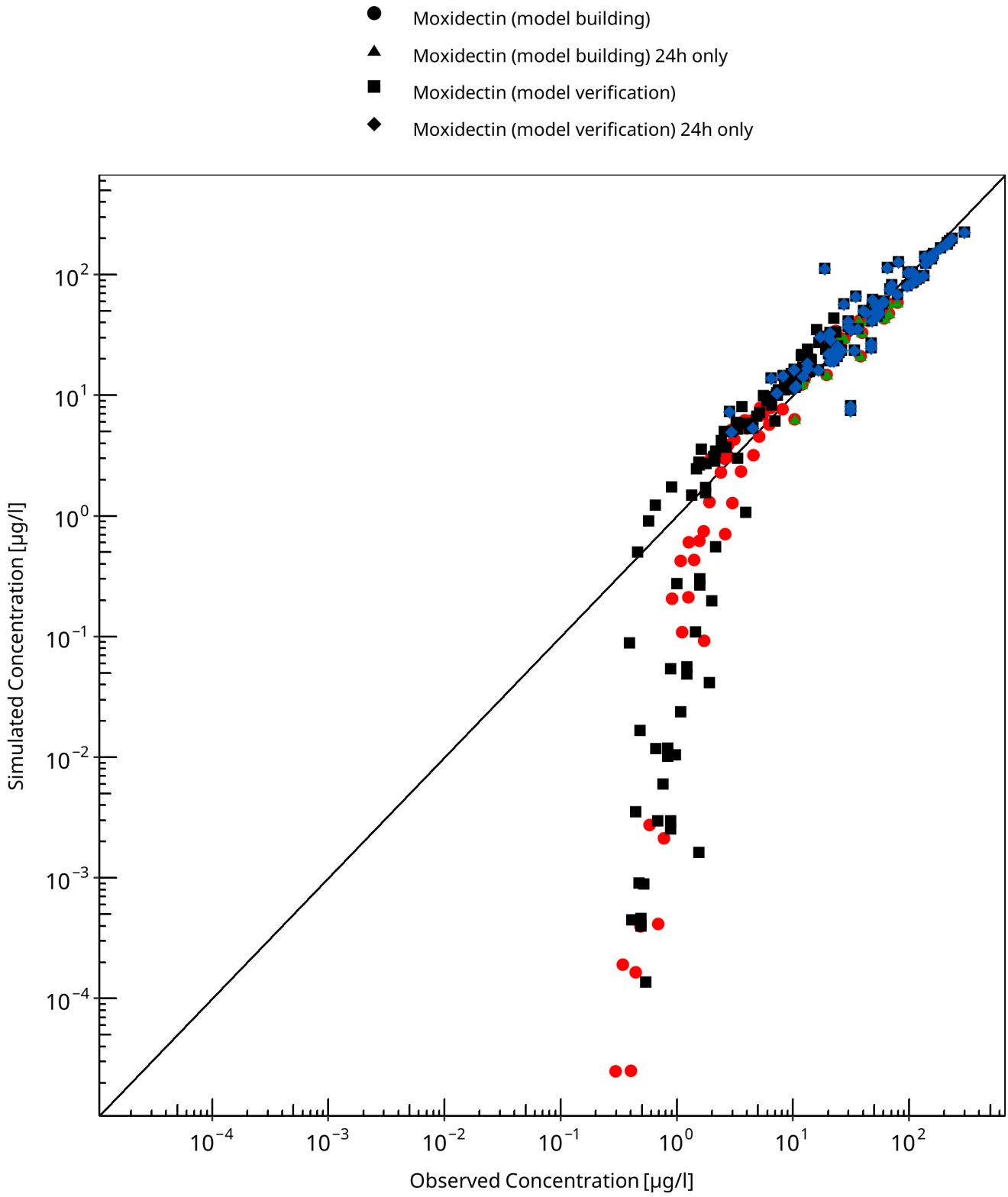

Figure 3-1: Goodness of fit plot for concentration in plasma

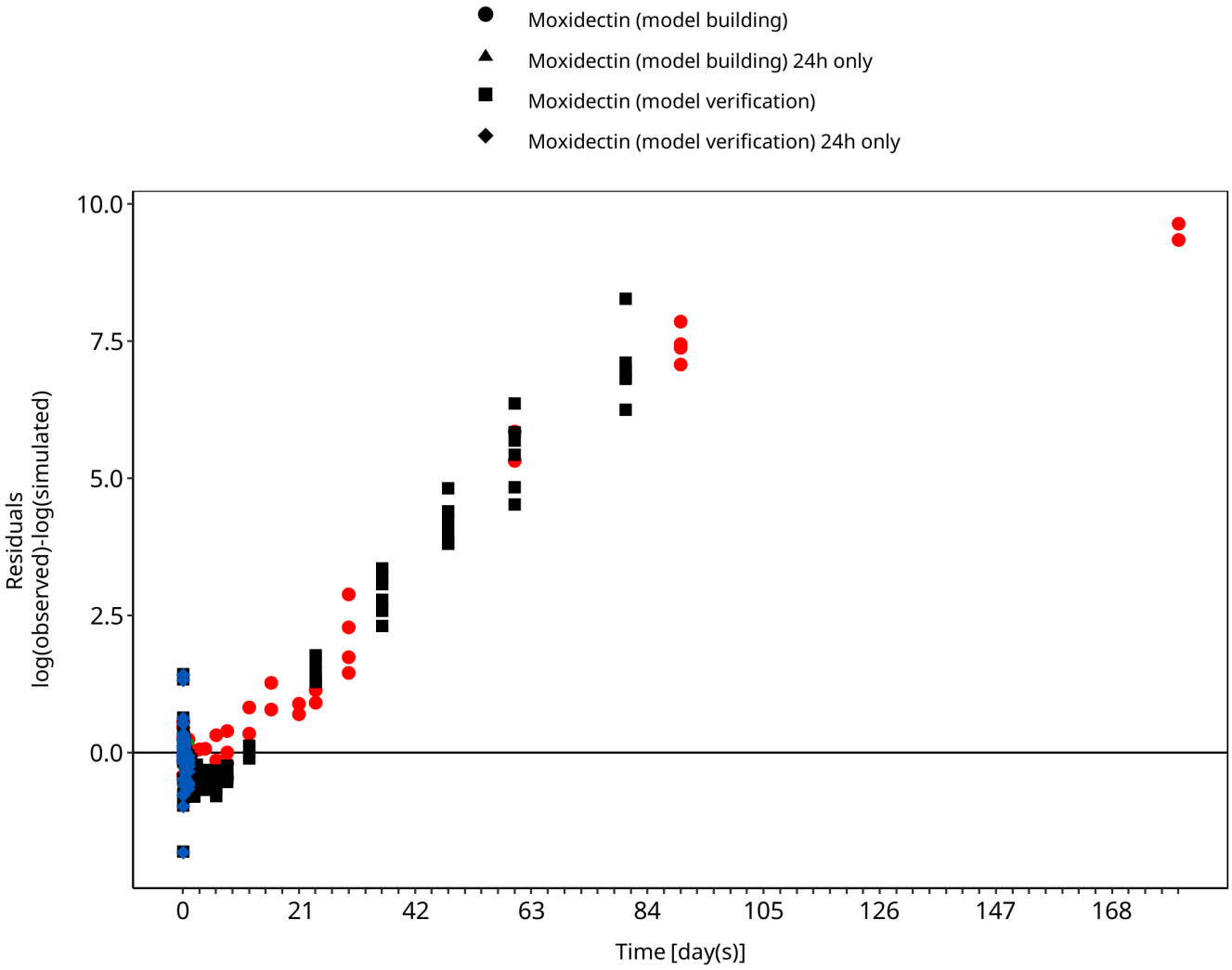

Figure 3-2: Goodness of fit plot for concentration in plasma

3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in Section 2.2.2 are presented below.

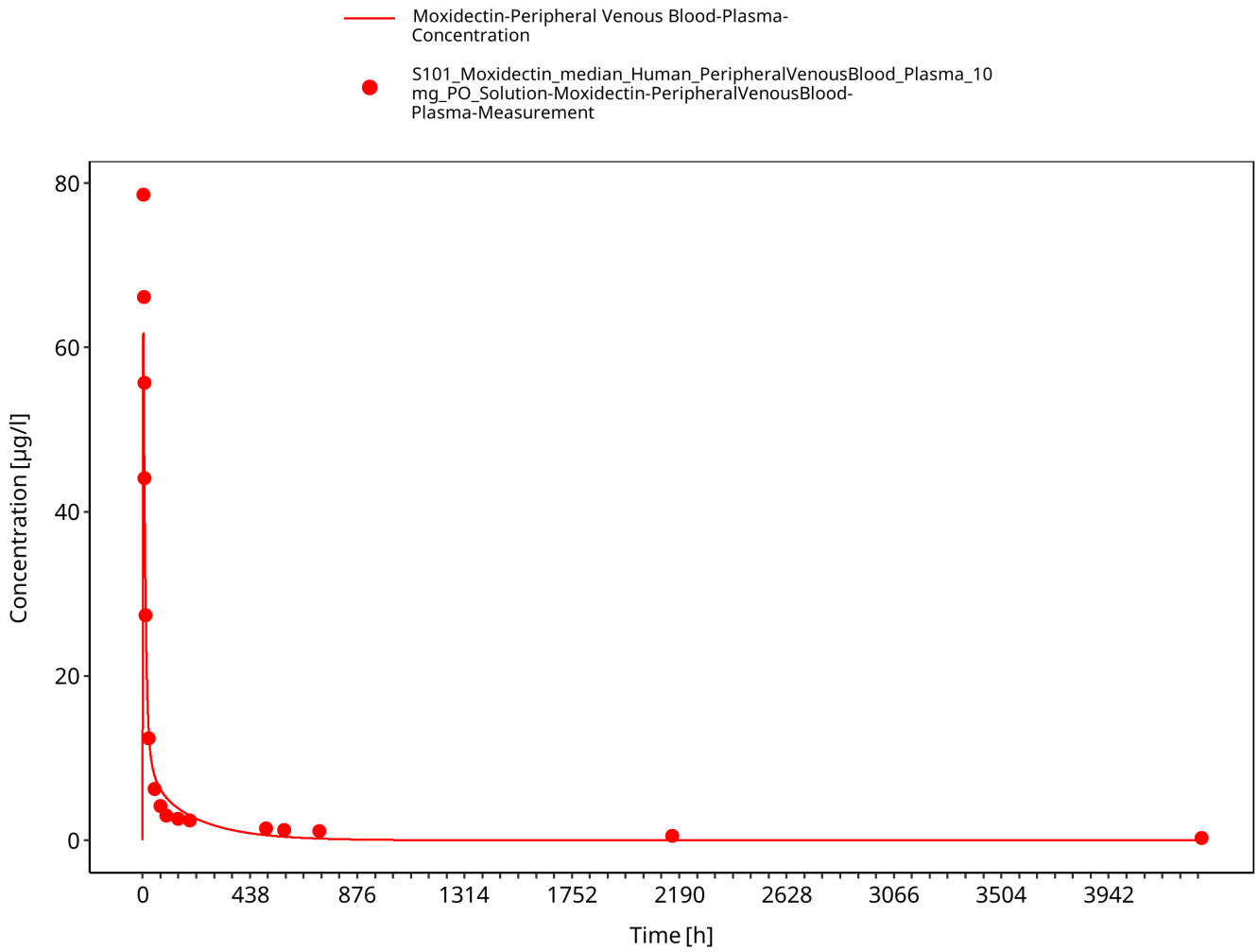

Figure 3-3: Korth-Bradley 2012_PO_10mg_solution

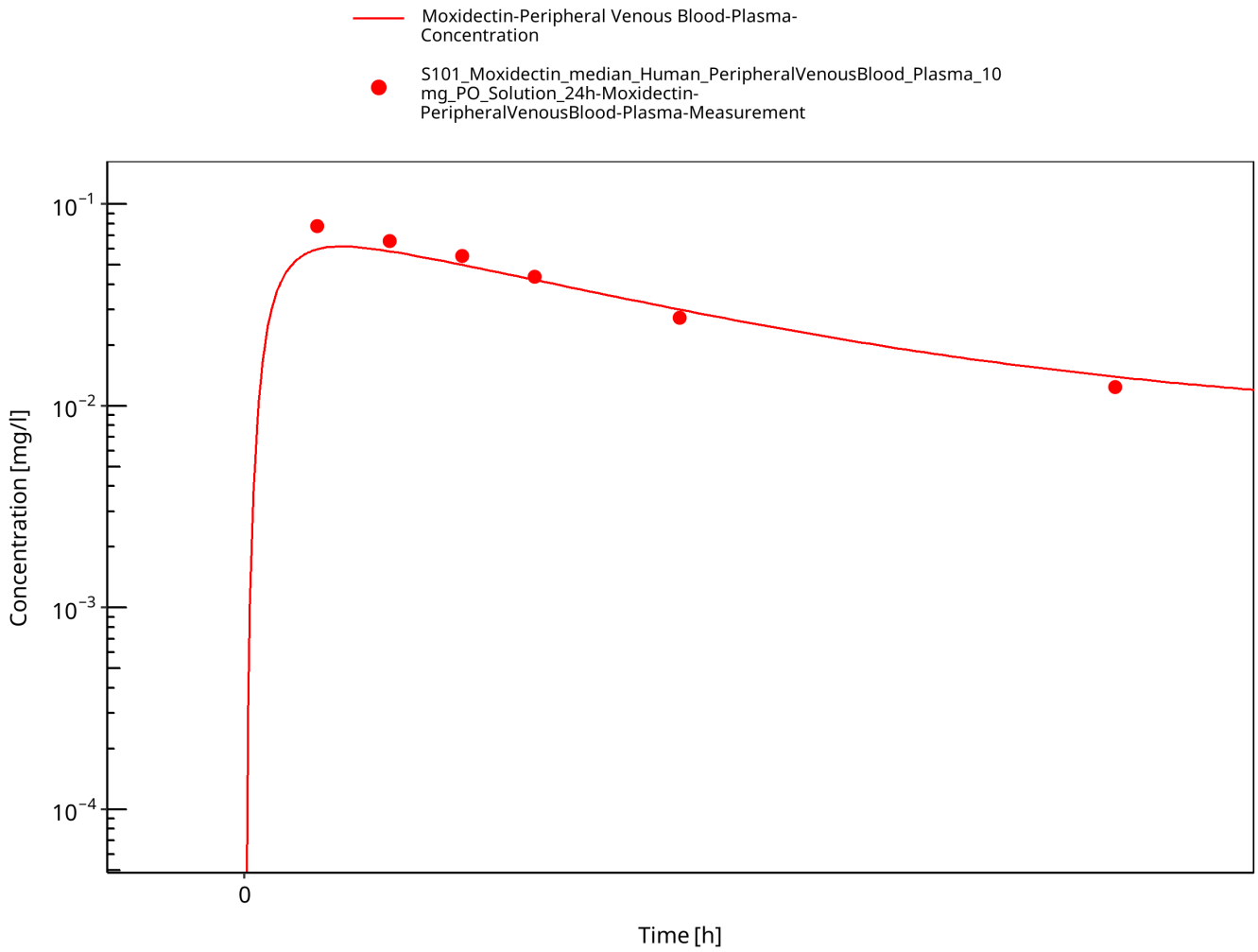

Figure 3-4: Korth-Bradley 2012_PO_10mg_solution 24h

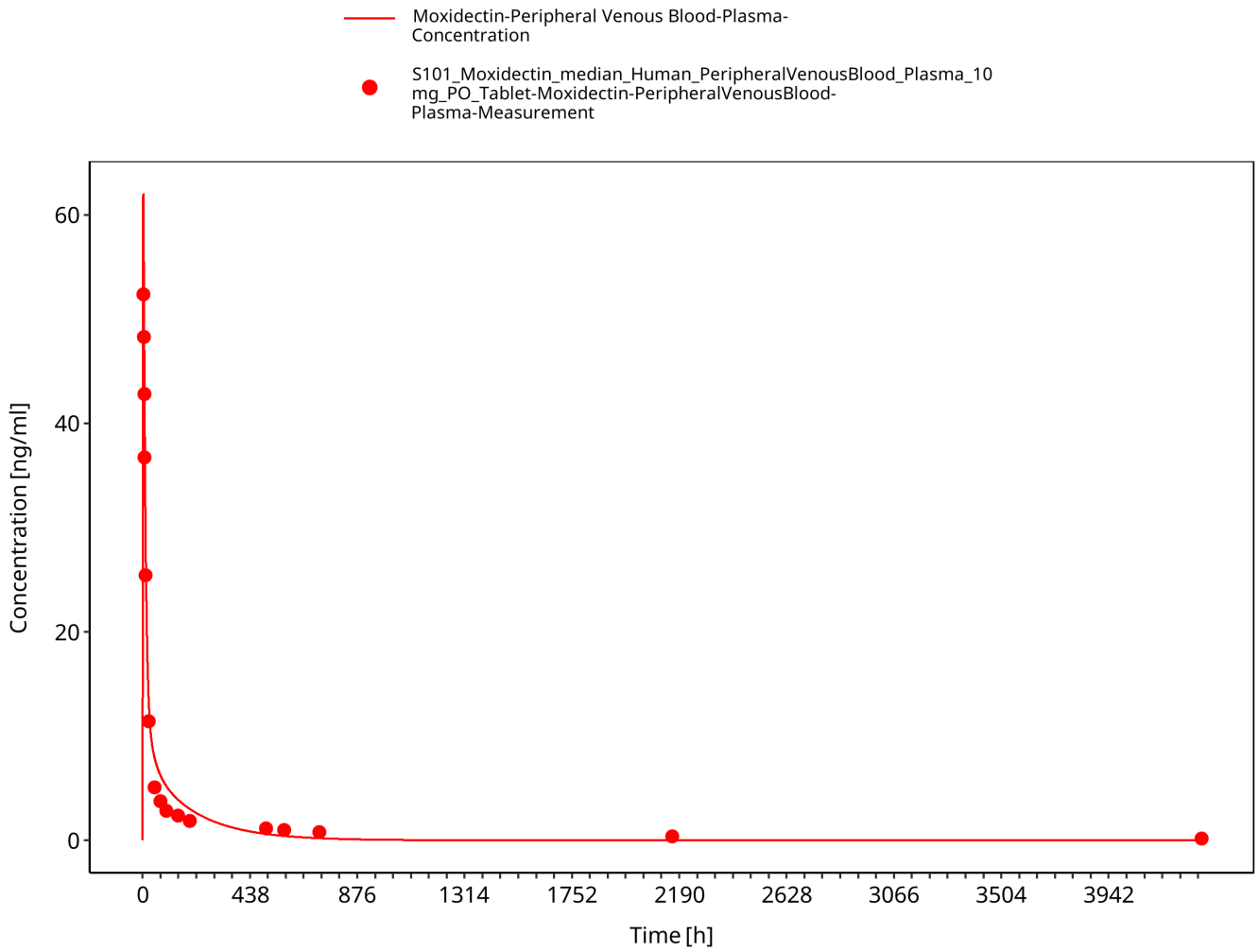

Figure 3-5: Korth-Bradley 2012_PO_10mg_tablet

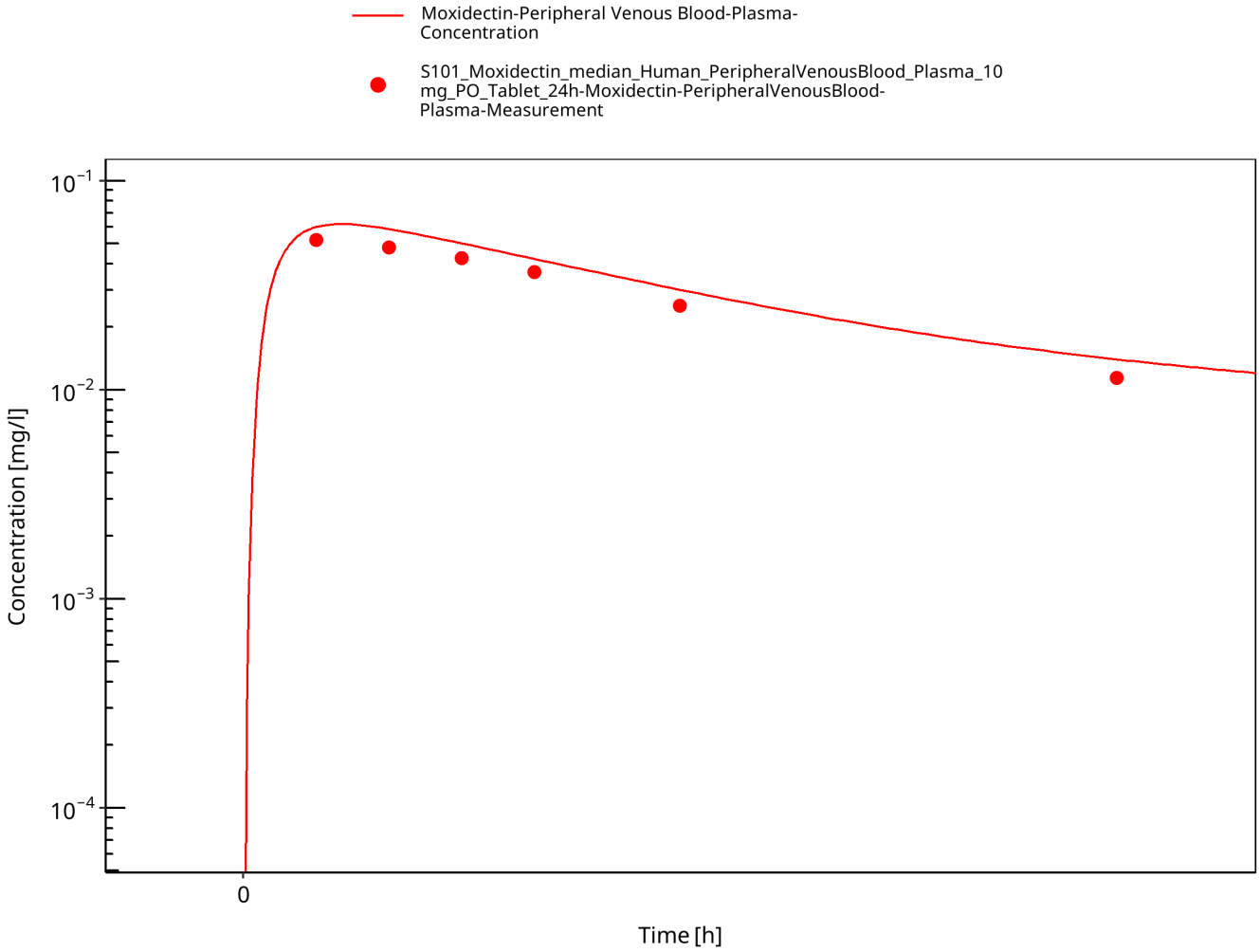

Figure 3-6: Korth-Bradley 2012_PO_10mg_tablet 24h

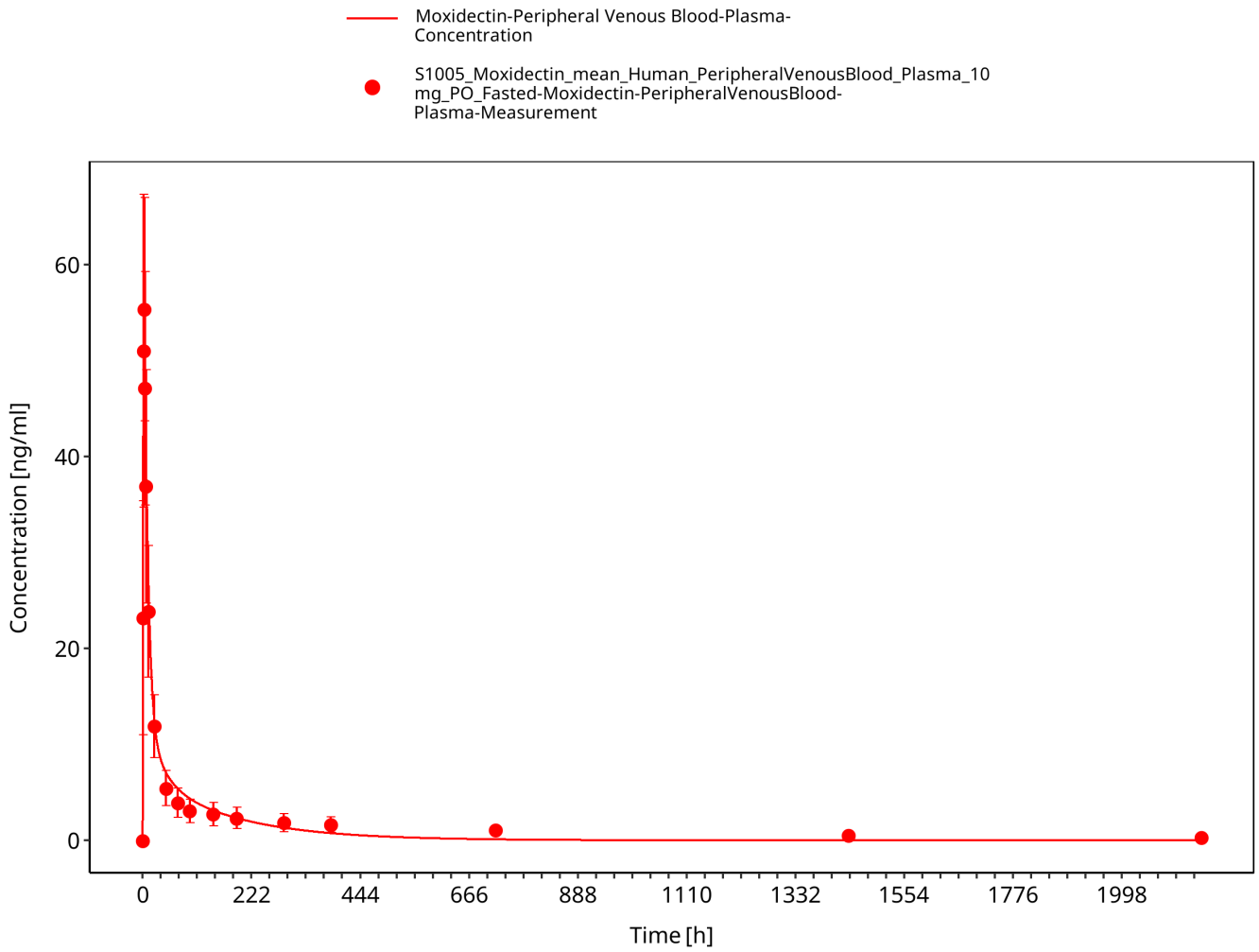

Figure 3-7: Korth-Bradley 2012_PO_8mg_fasted

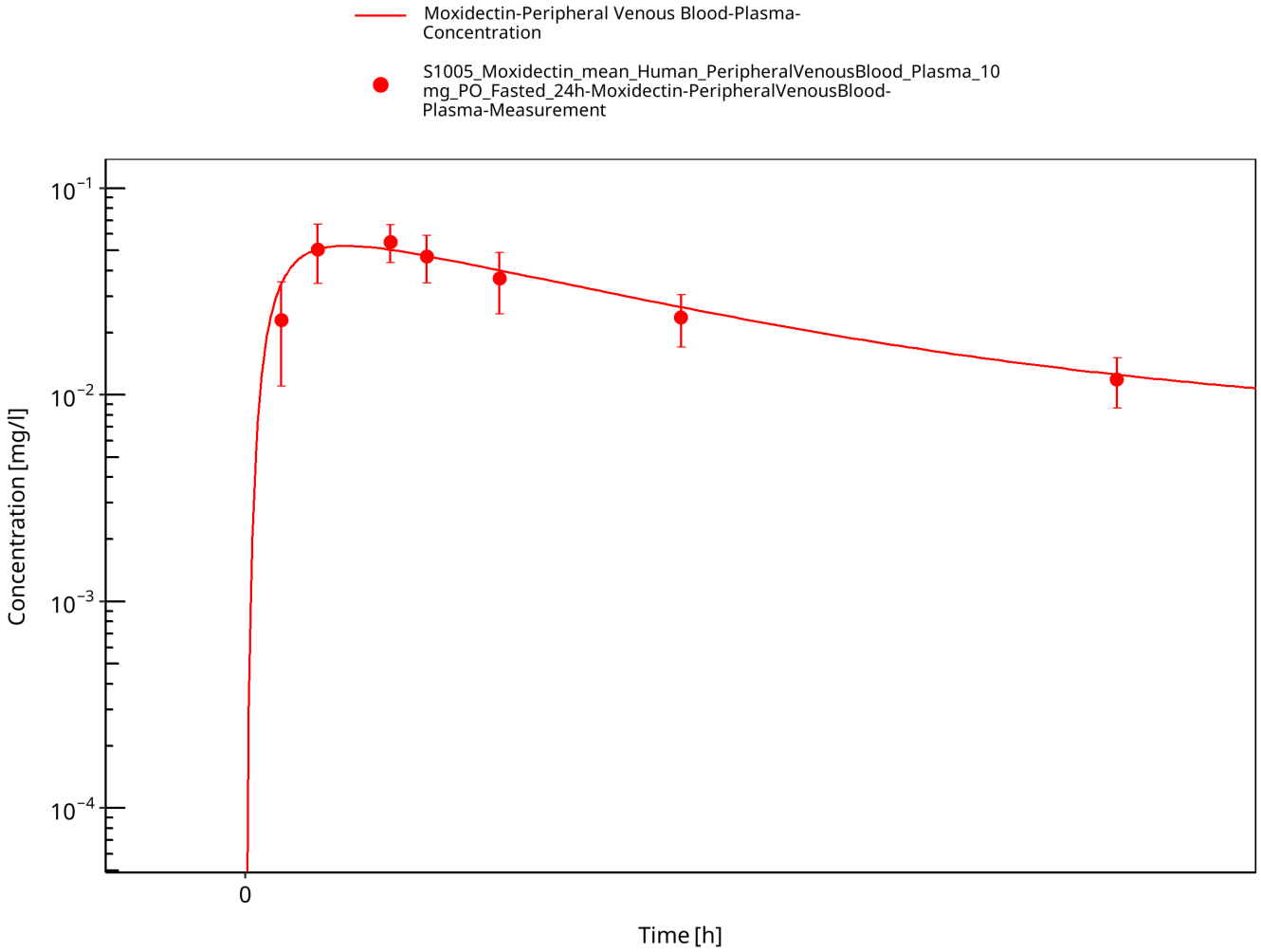

Figure 3-8: Korth-Bradley 2012_PO_8mg_fasted 24h

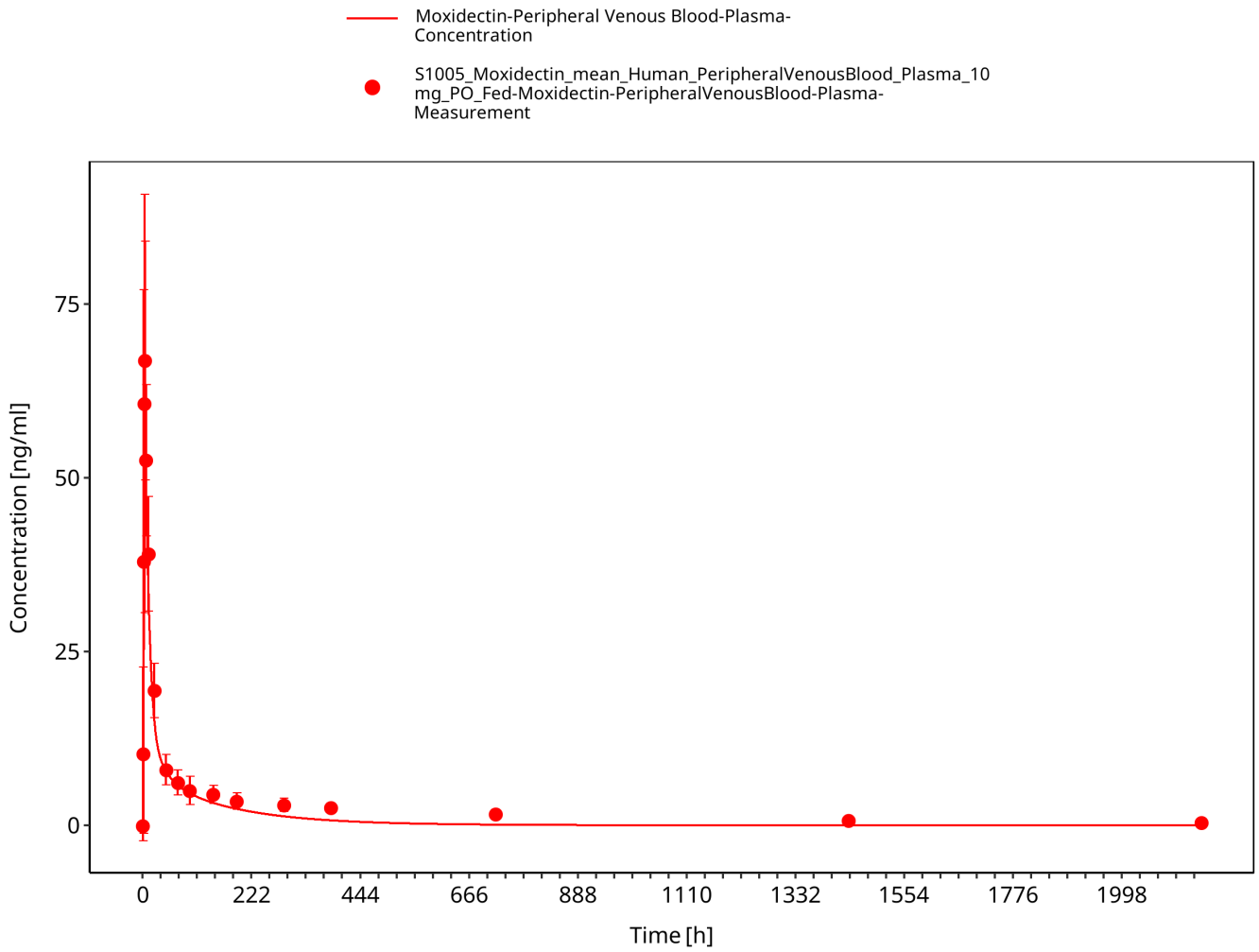

Figure 3-9: Korth-Bradley 2012_PO_8mg_fed

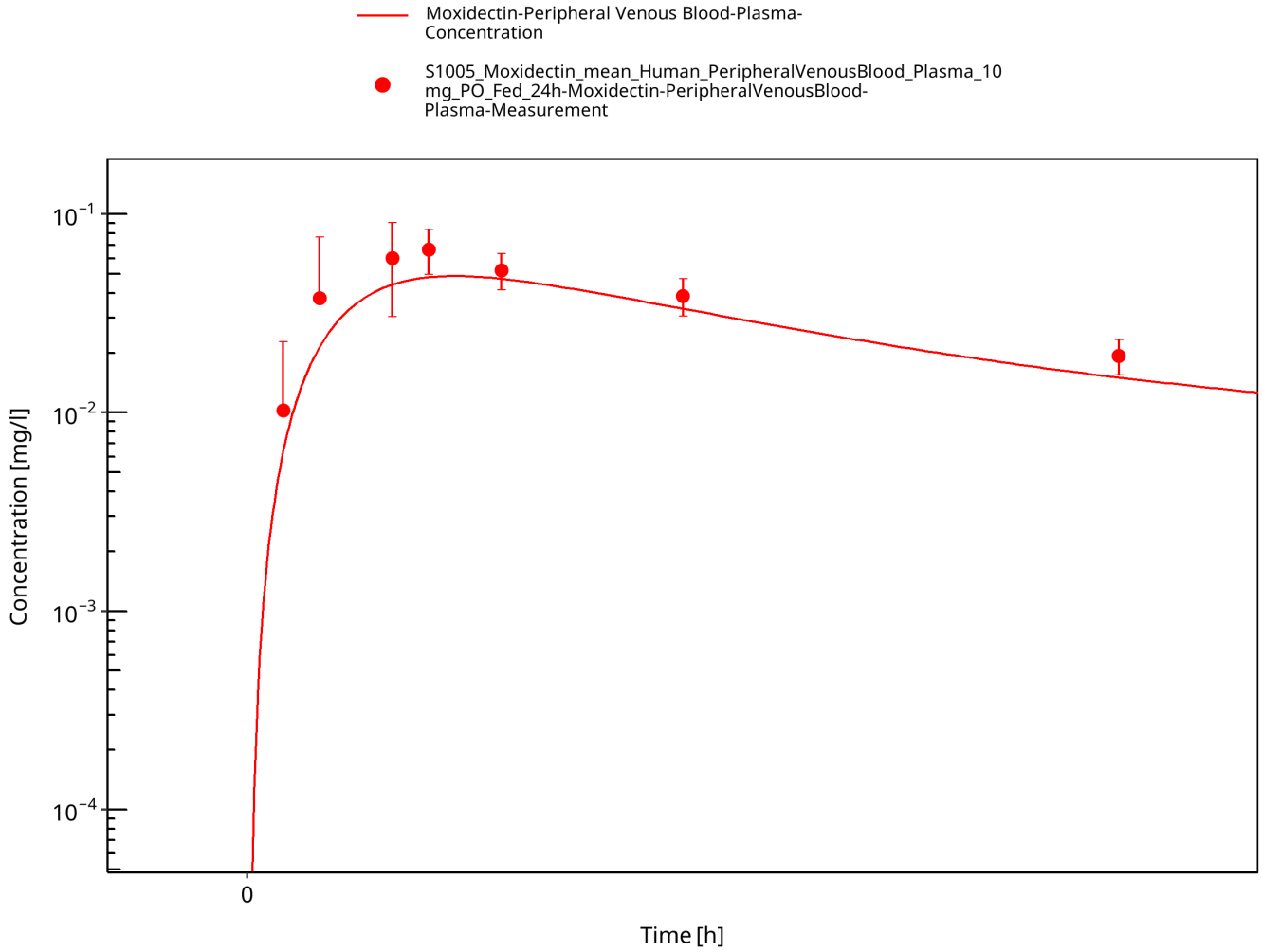

Figure 3-10: Korth-Bradley 2012_PO_8mg_fed 24h

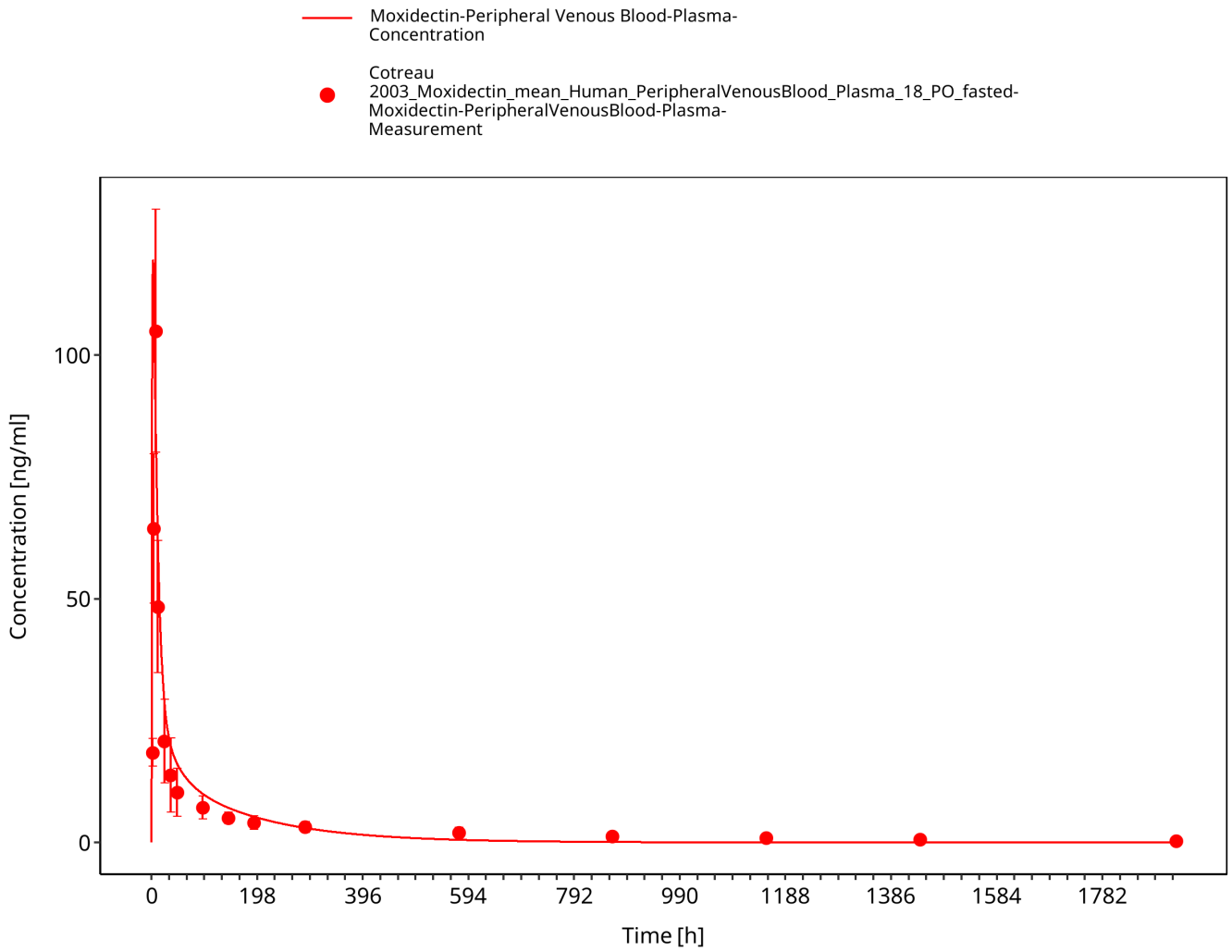

Figure 3-11: Cotreau 2003_PO_18mg_solution_fasted

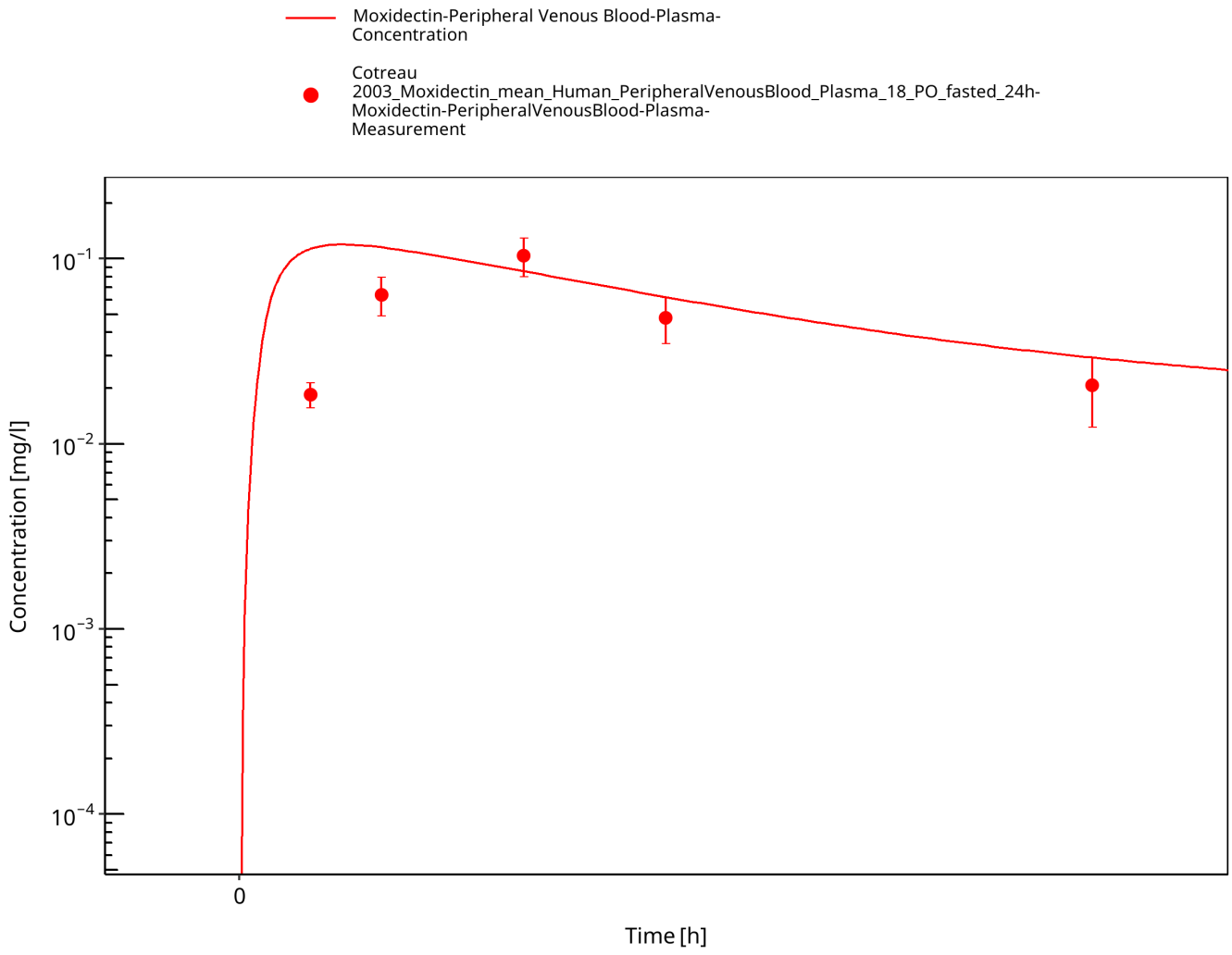

Figure 3-12: Cotreau 2003_PO_18mg_solution_fasted 24h

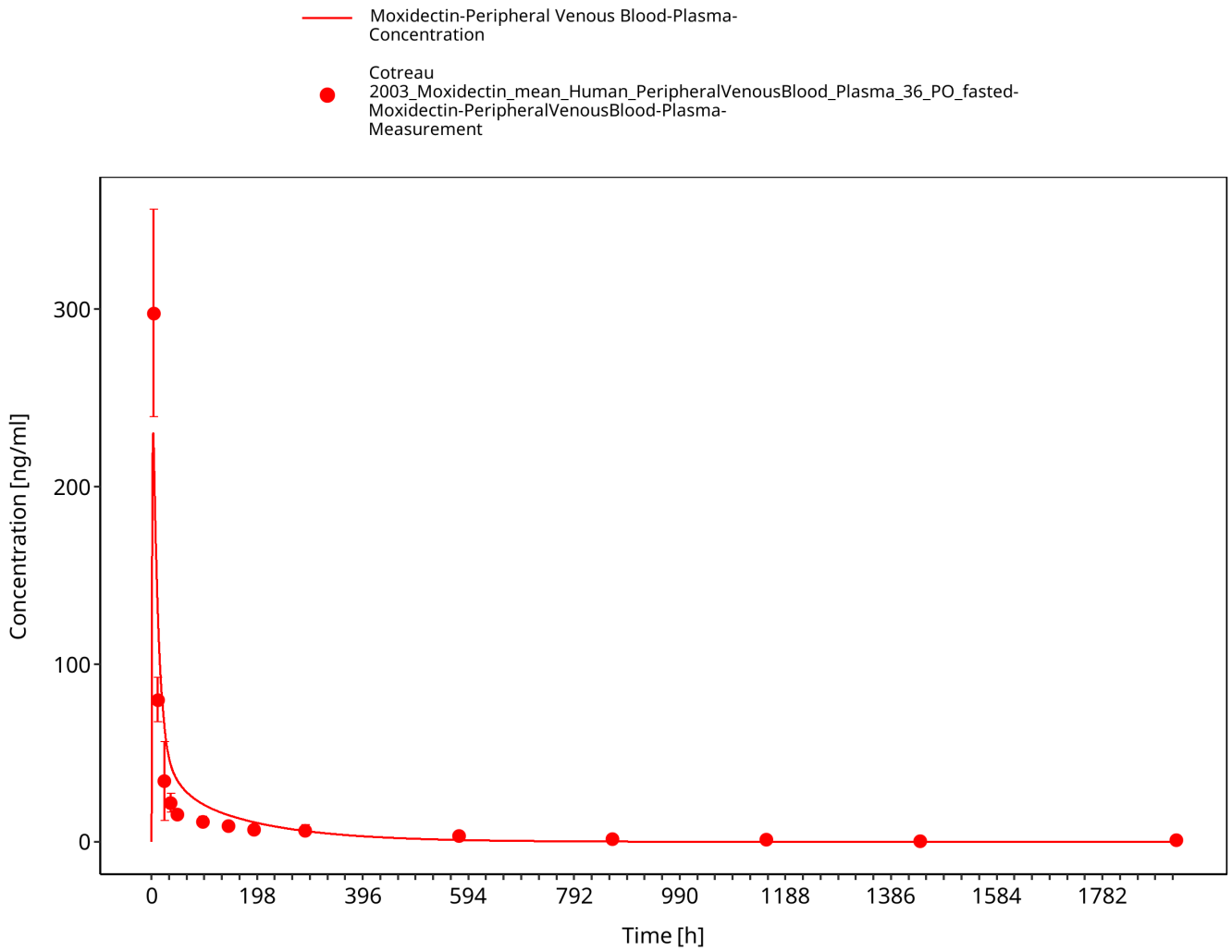

Figure 3-13: Cotreau 2003_PO_36mg_solution_fasted

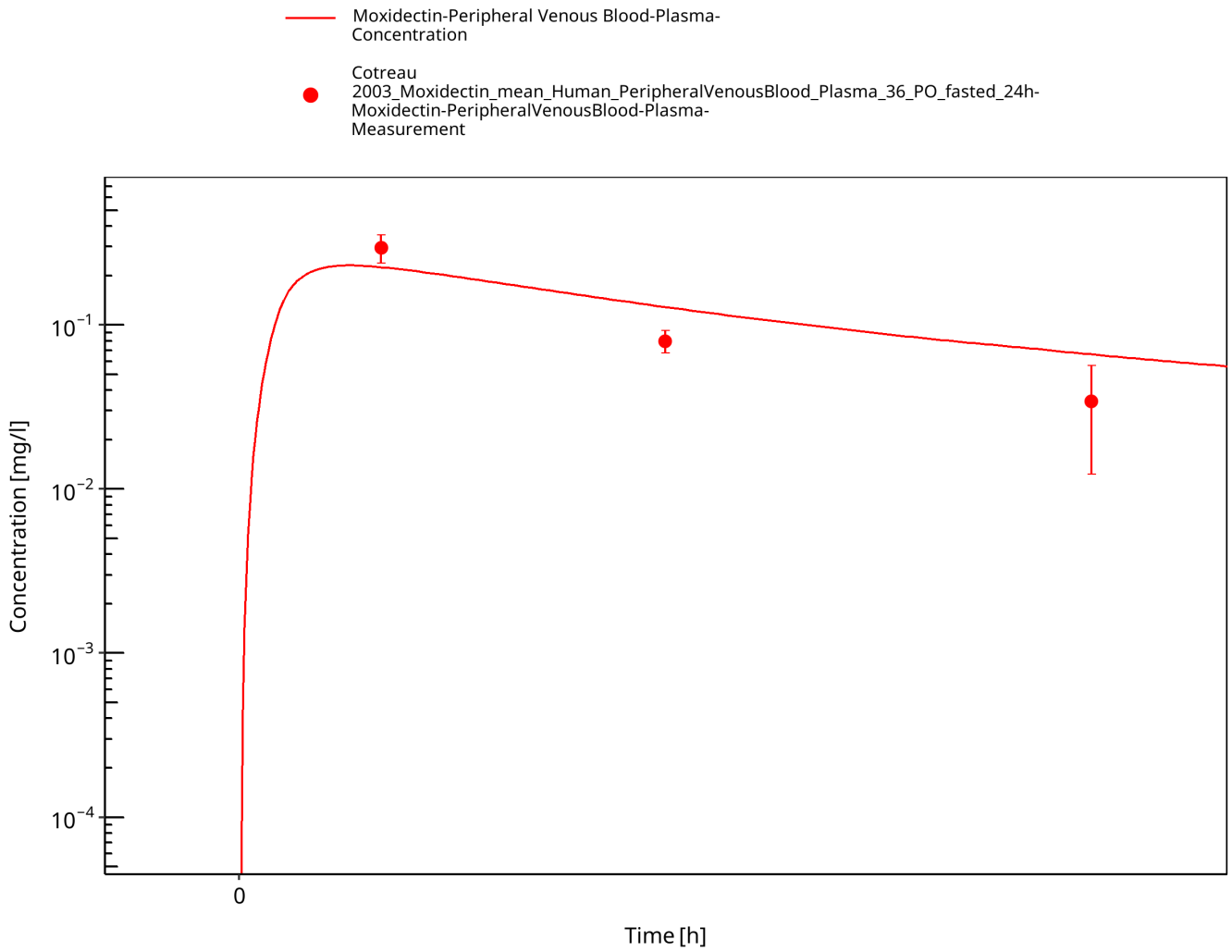

Figure 3-14: Cotreau 2003_PO_36mg_solution_fasted 24h

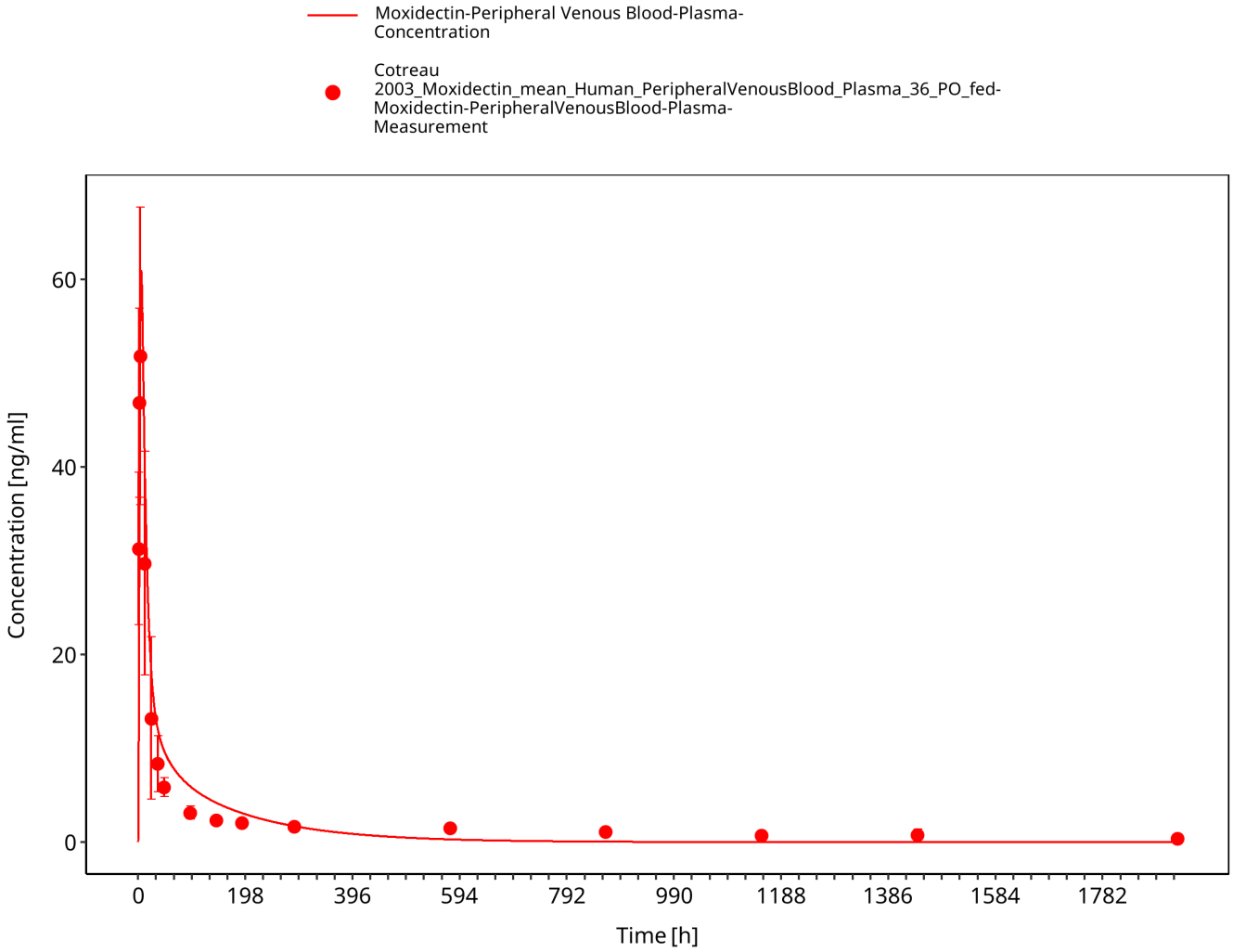

Figure 3-15: Cotreau 2003_PO_36mg_solution_fed

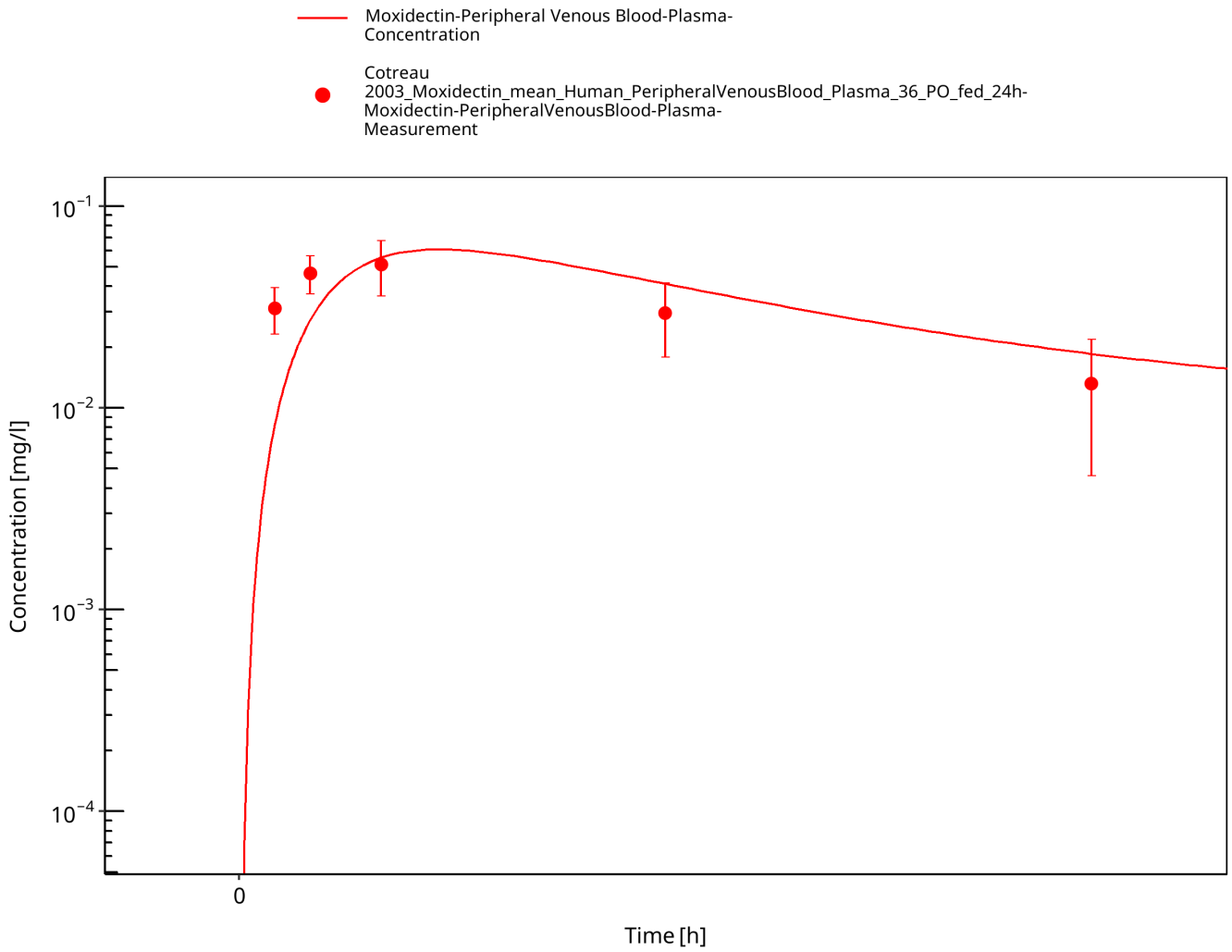

Figure 3-16: Cotreau 2003_PO_36mg_solution_fed 24h

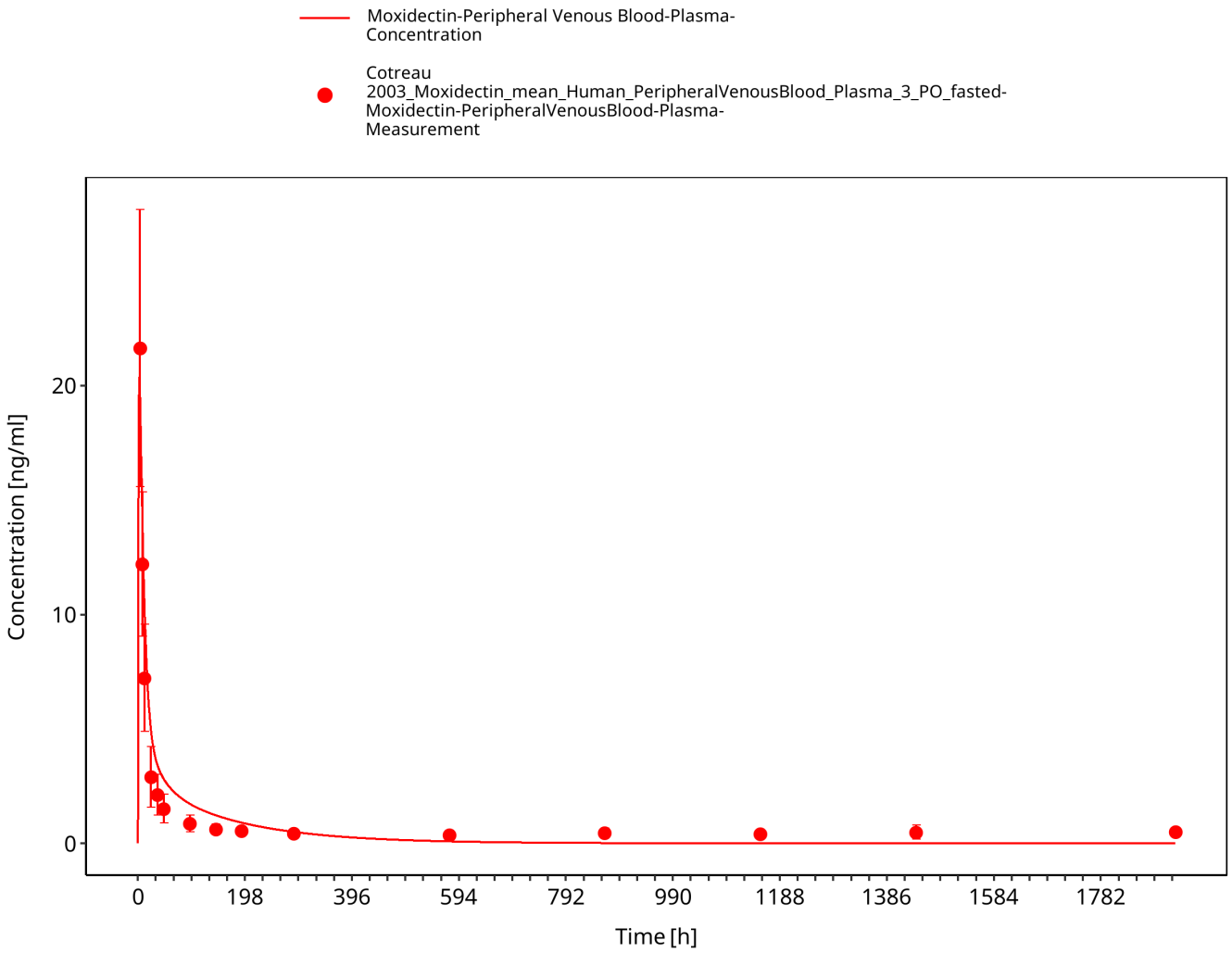

Figure 3-17: Cotreau 2003_PO_3mg_solution_fasted

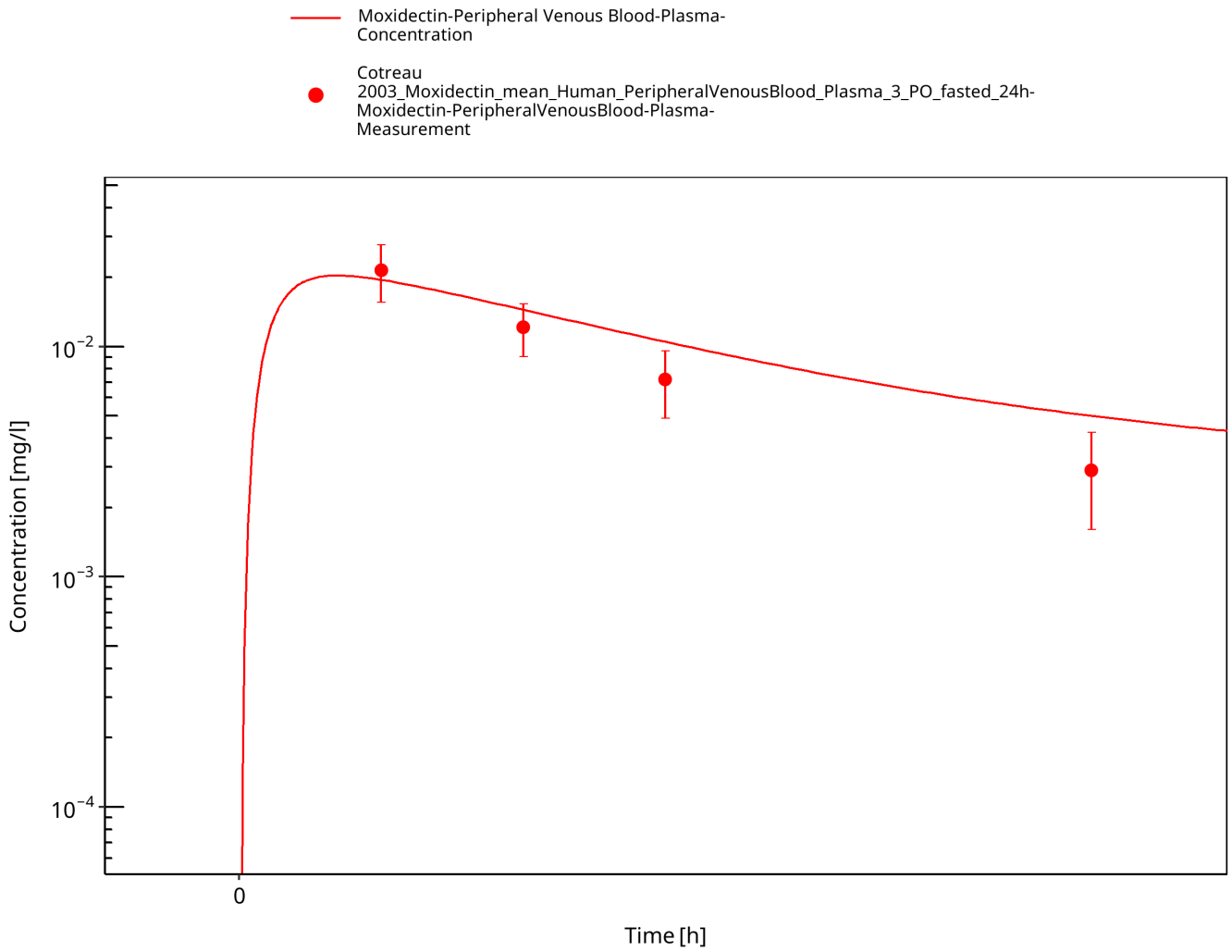

Figure 3-18: Cotreau 2003_PO_3mg_solution_fasted 24h

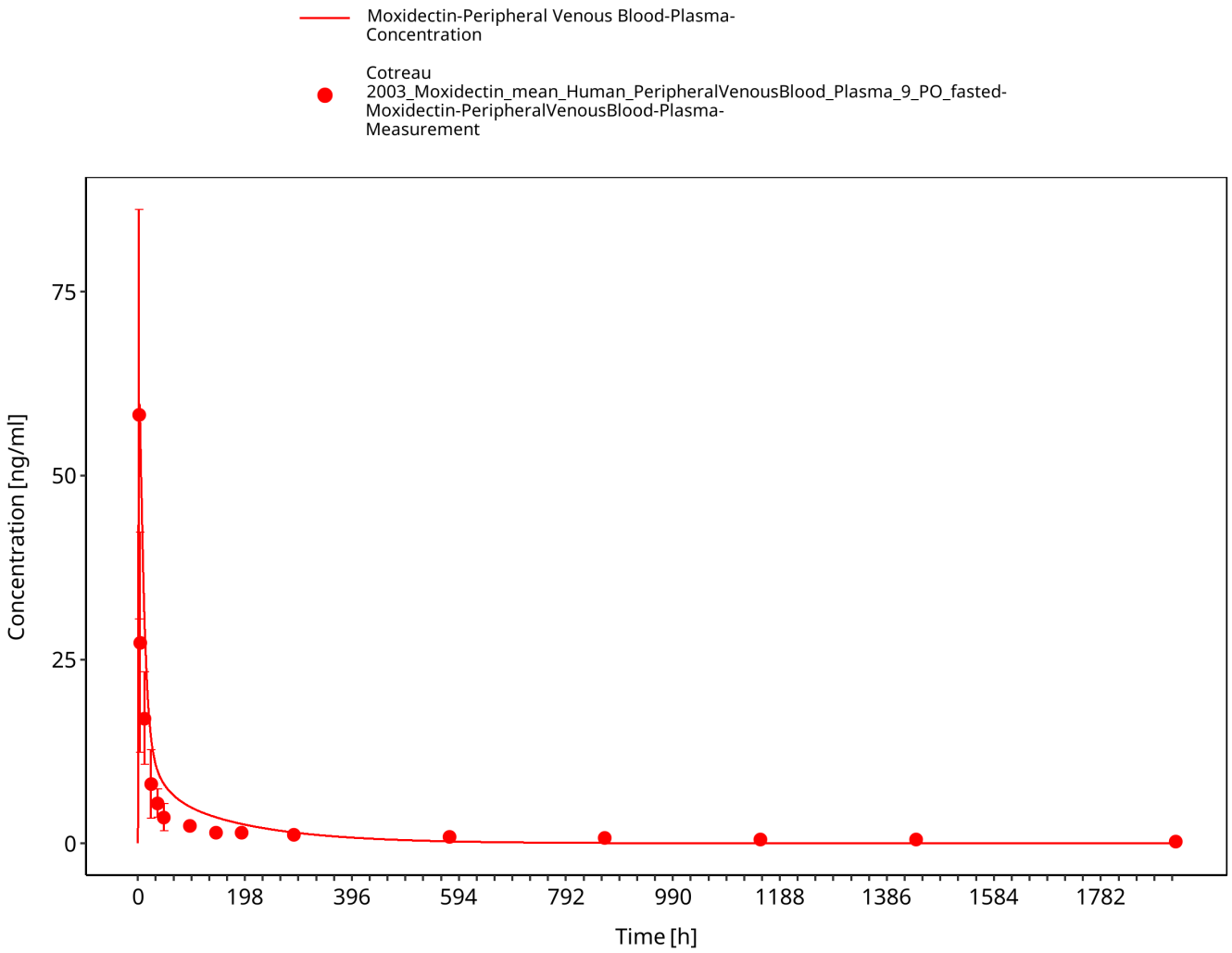

Figure 3-19: Cotreau 2003_PO_9mg_solution_fasted

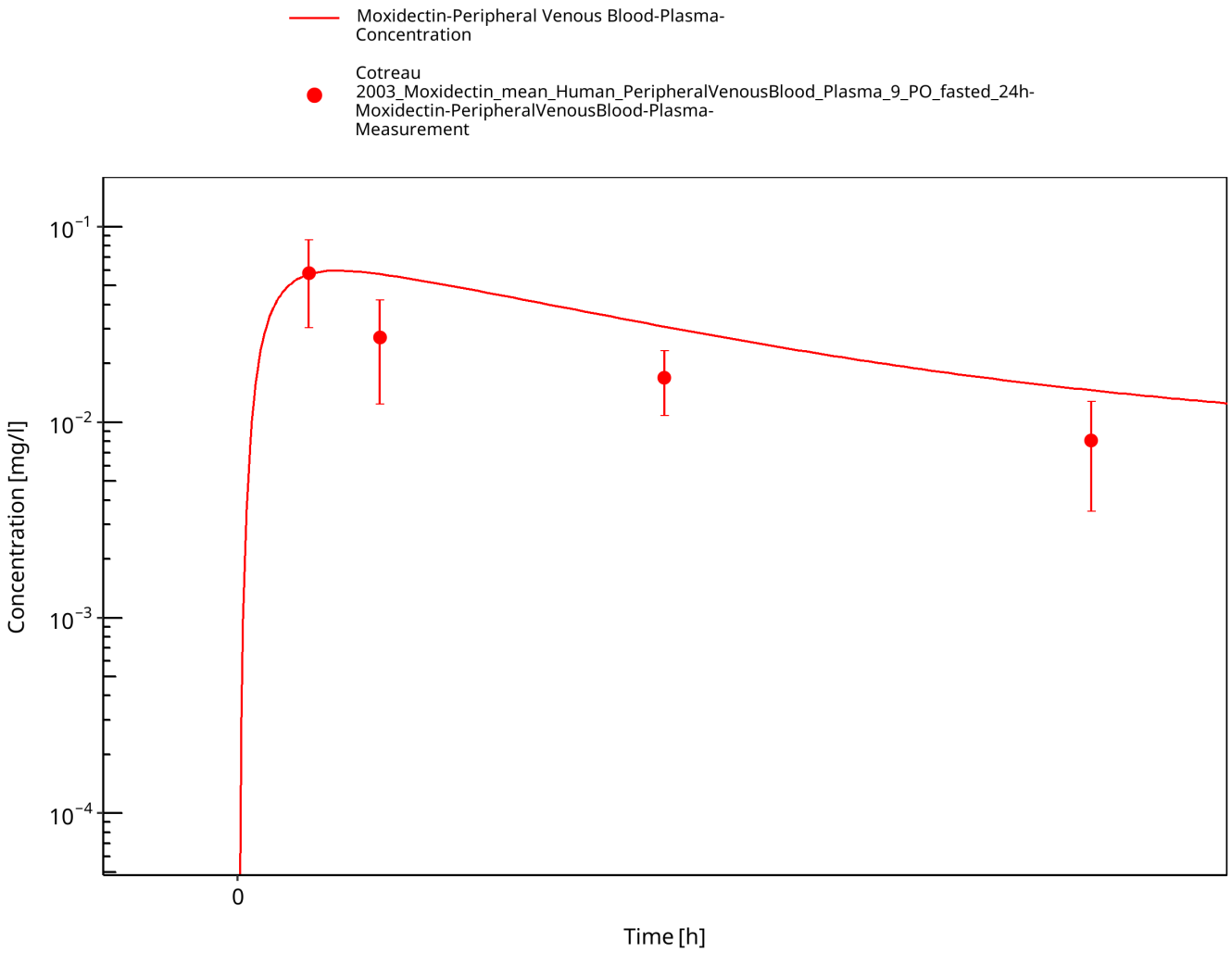

Figure 3-20: Cotreau 2003_PO_9mg_solution_fasted 24h

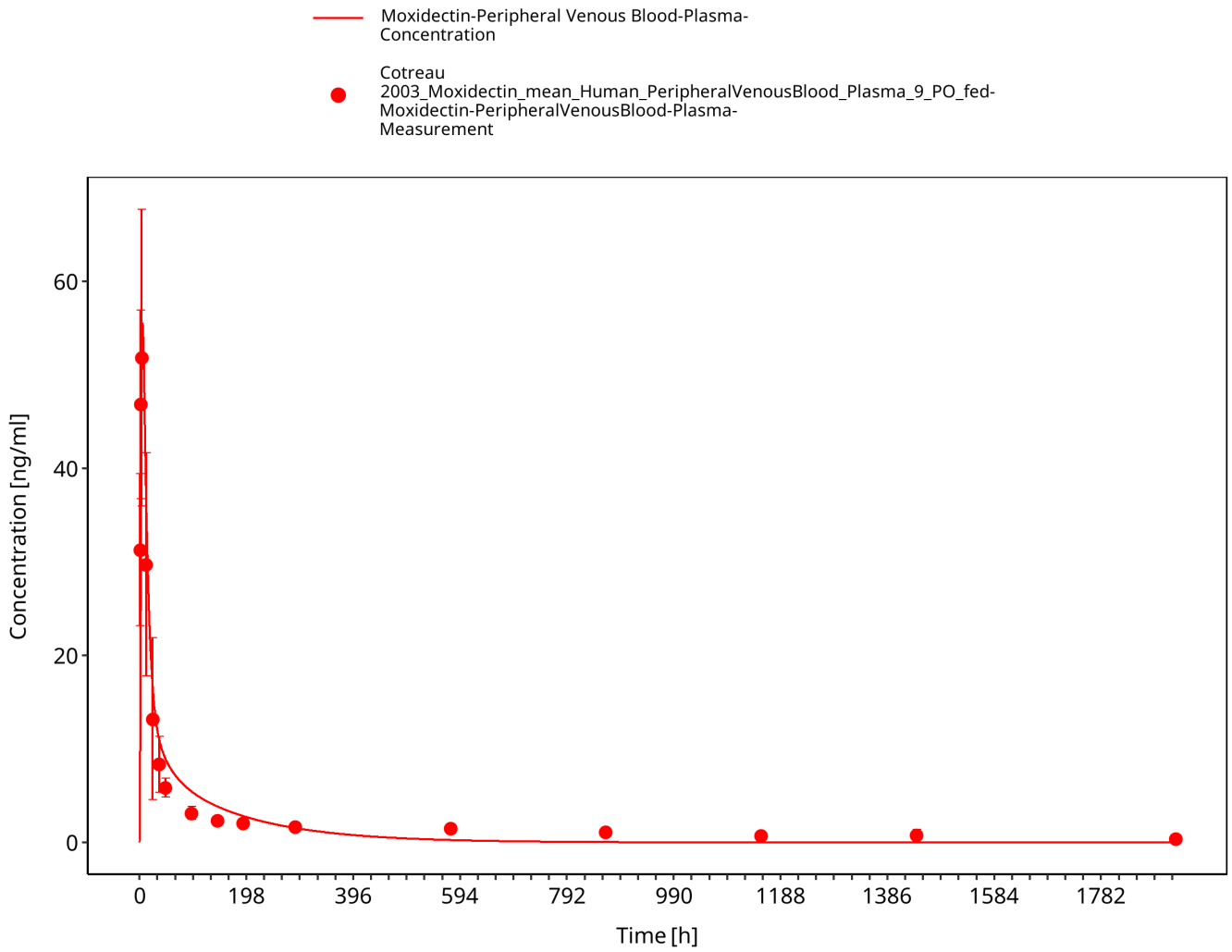

Figure 3-21: Cotreau 2003_PO_9mg_solution_fed

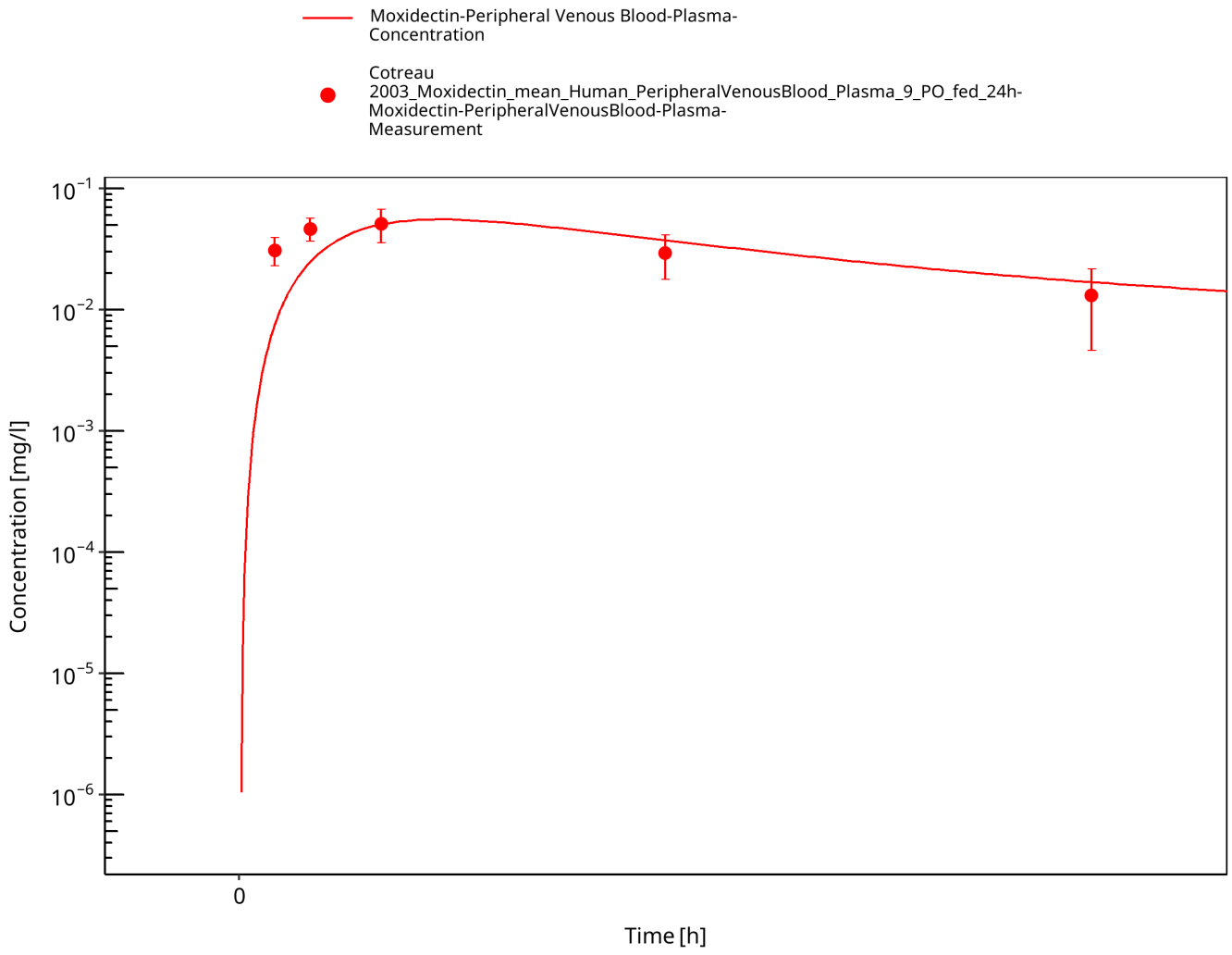

Figure 3-22: Cotreau 2003_PO_9mg_solution_fed 24h

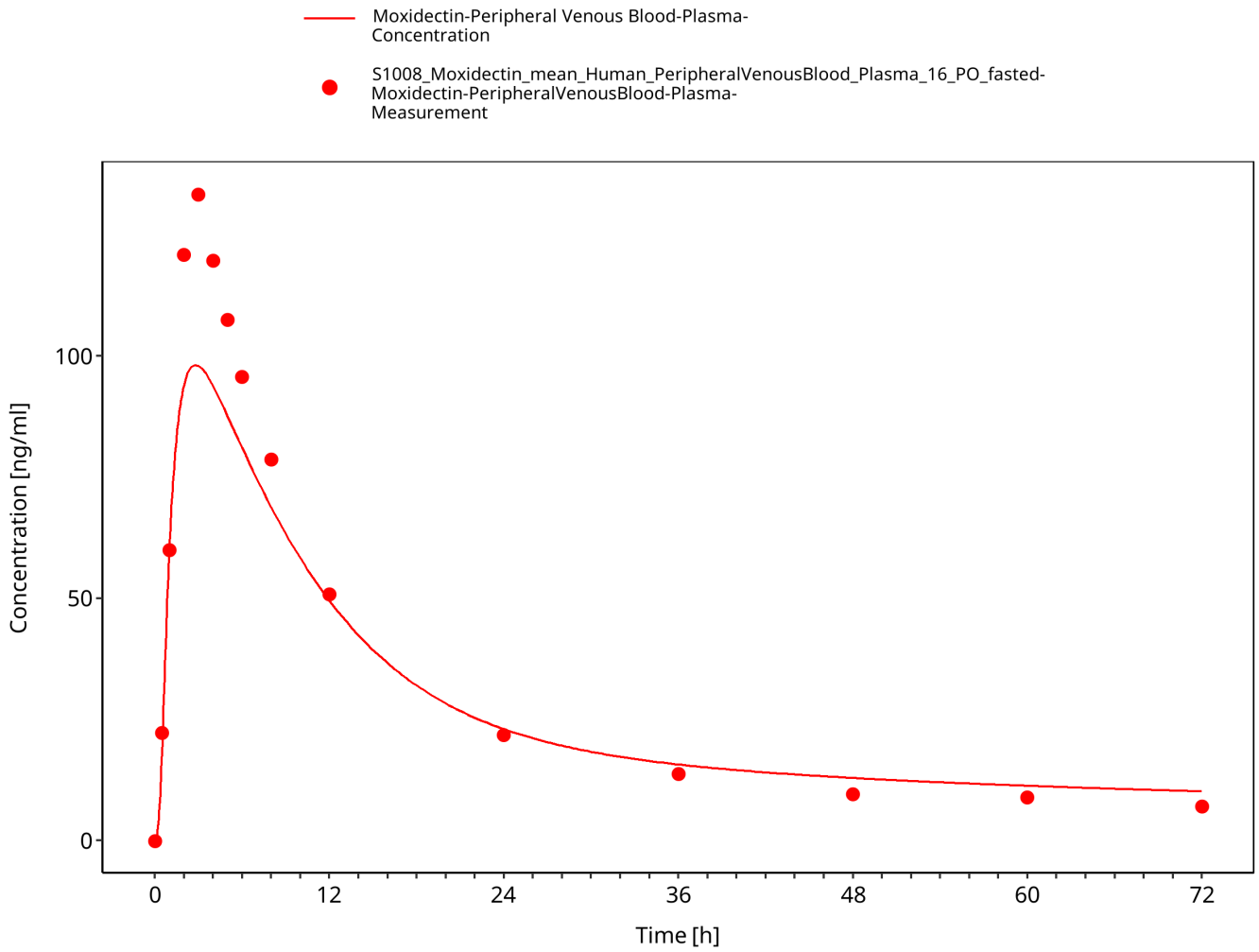

Figure 3-23: Kinrade 2018_PO_16 mg

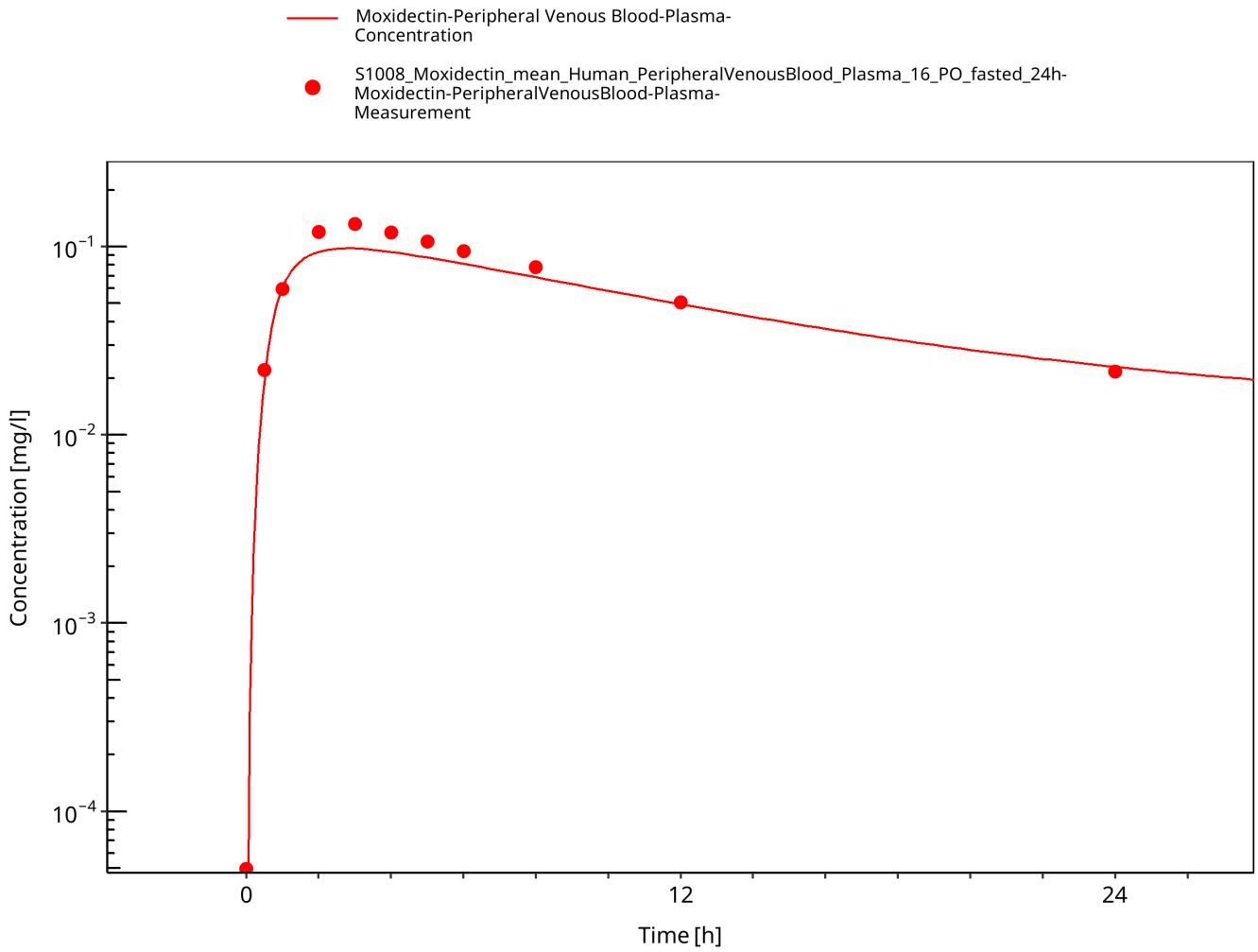

Figure 3-24: Kinrade 2018_PO_16 mg 24h

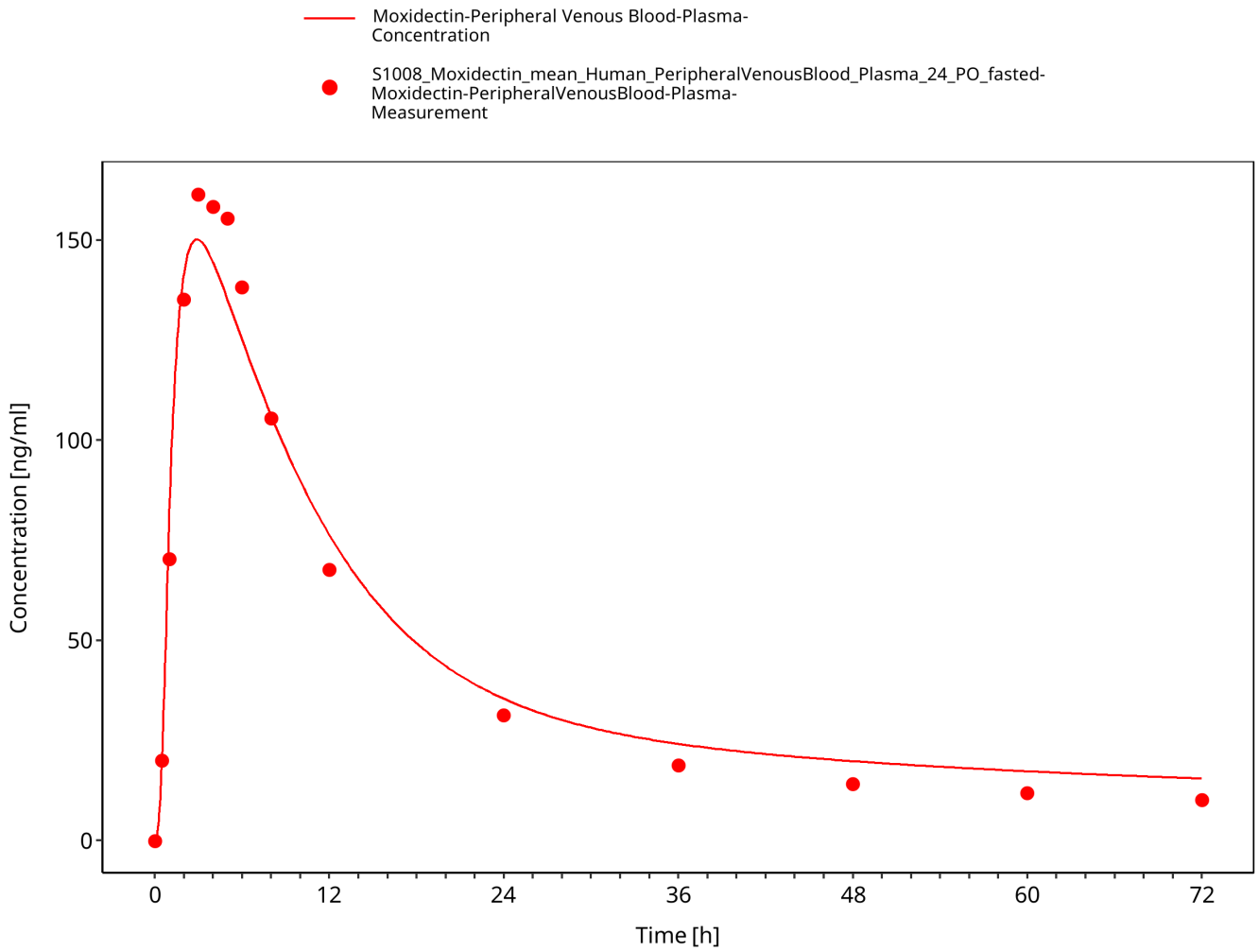

Figure 3-25: Kinrade 2018_PO_24 mg

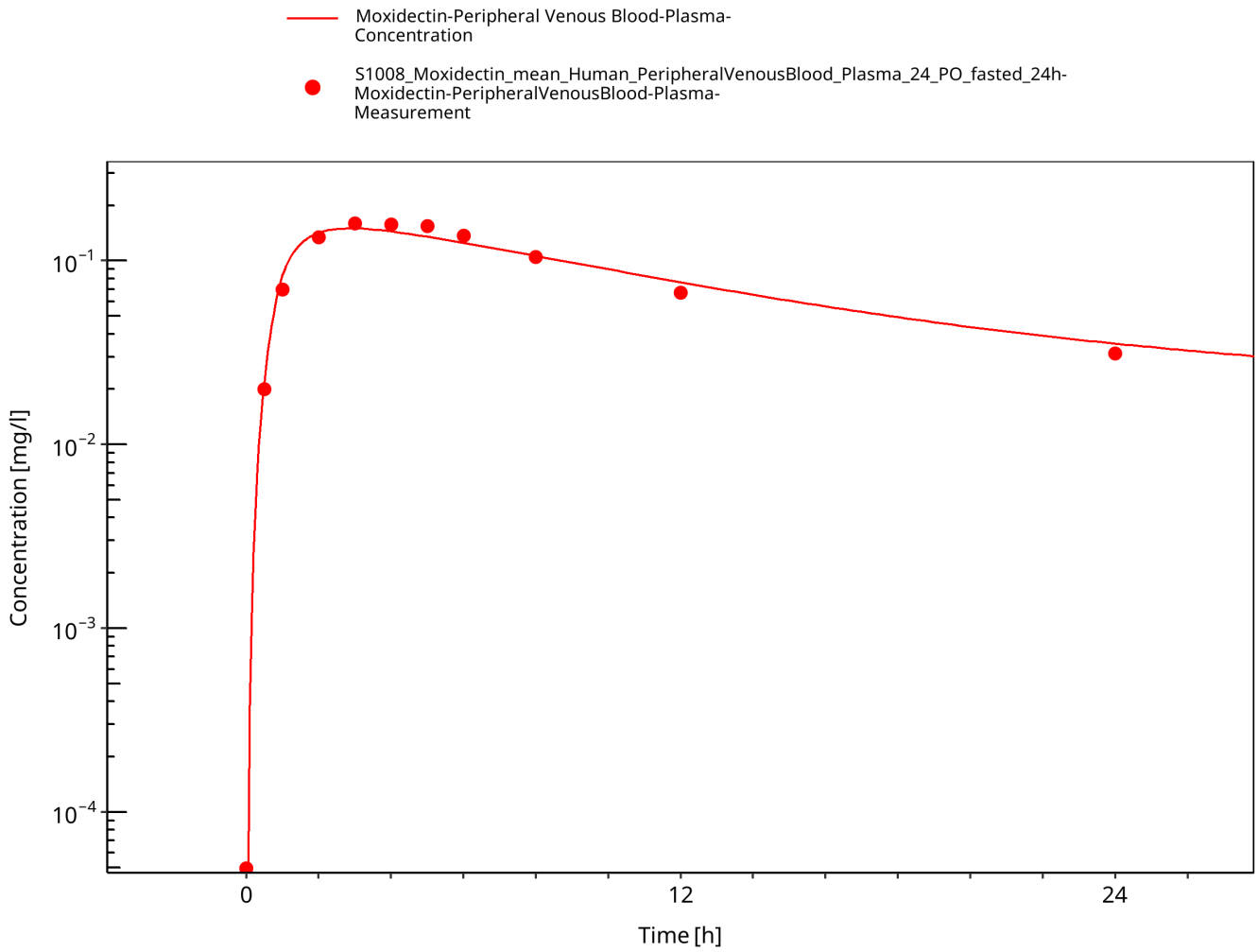

Figure 3-26: Kinrade 2018_PO_24 mg 24h

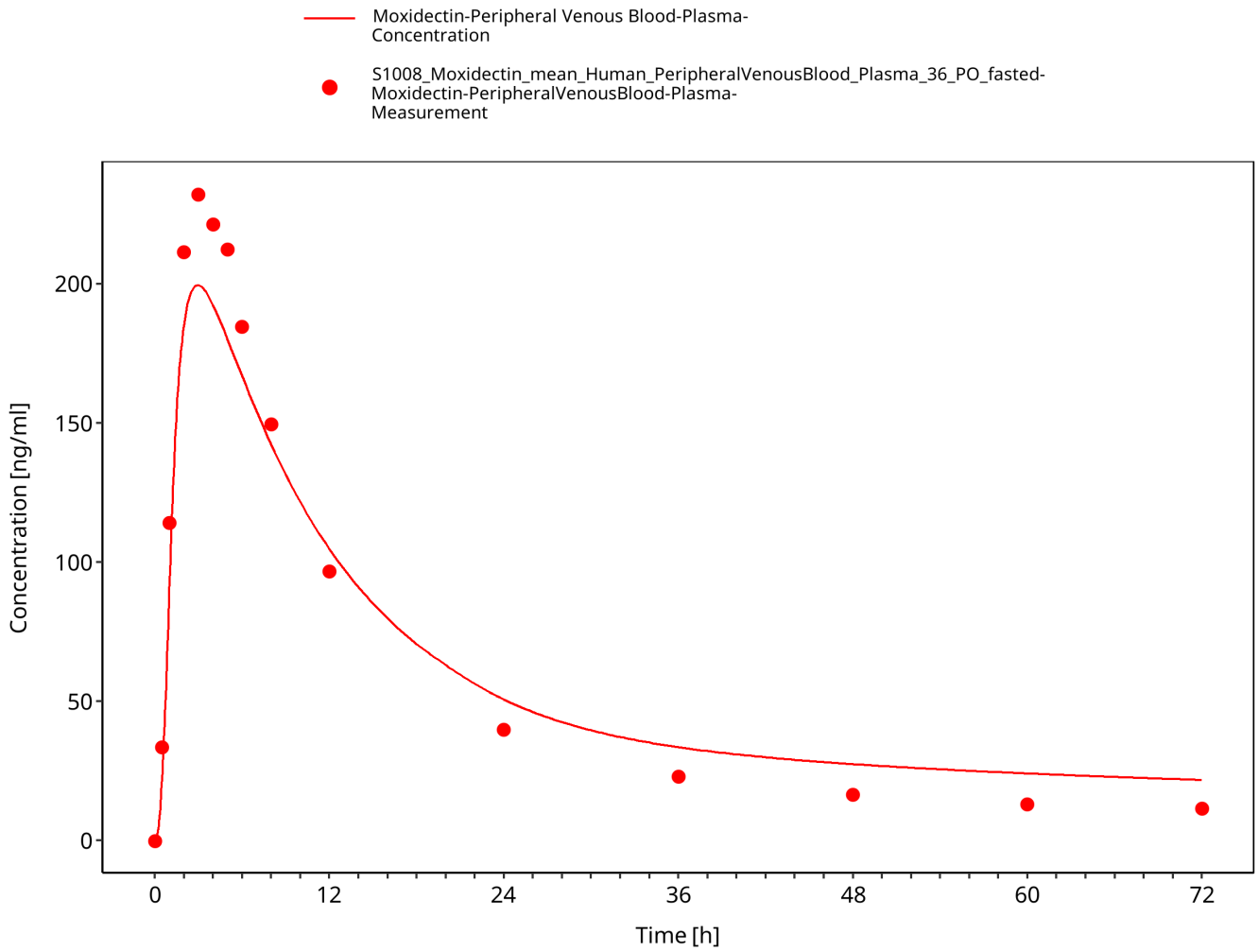

Figure 3-27: Kinrade 2018_PO_36 mg

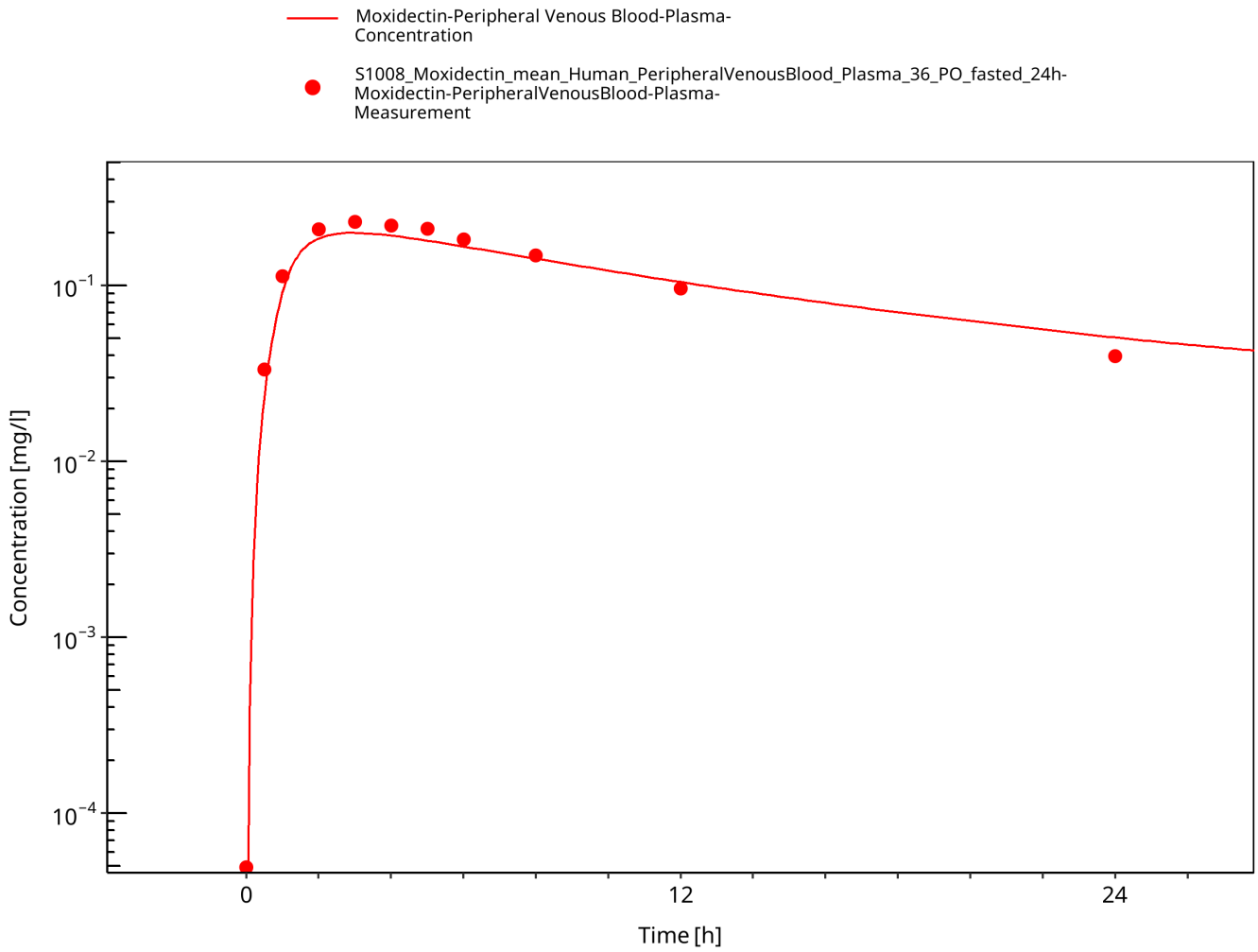

Figure 3-28: Kinrade 2018_PO_36 mg 24h

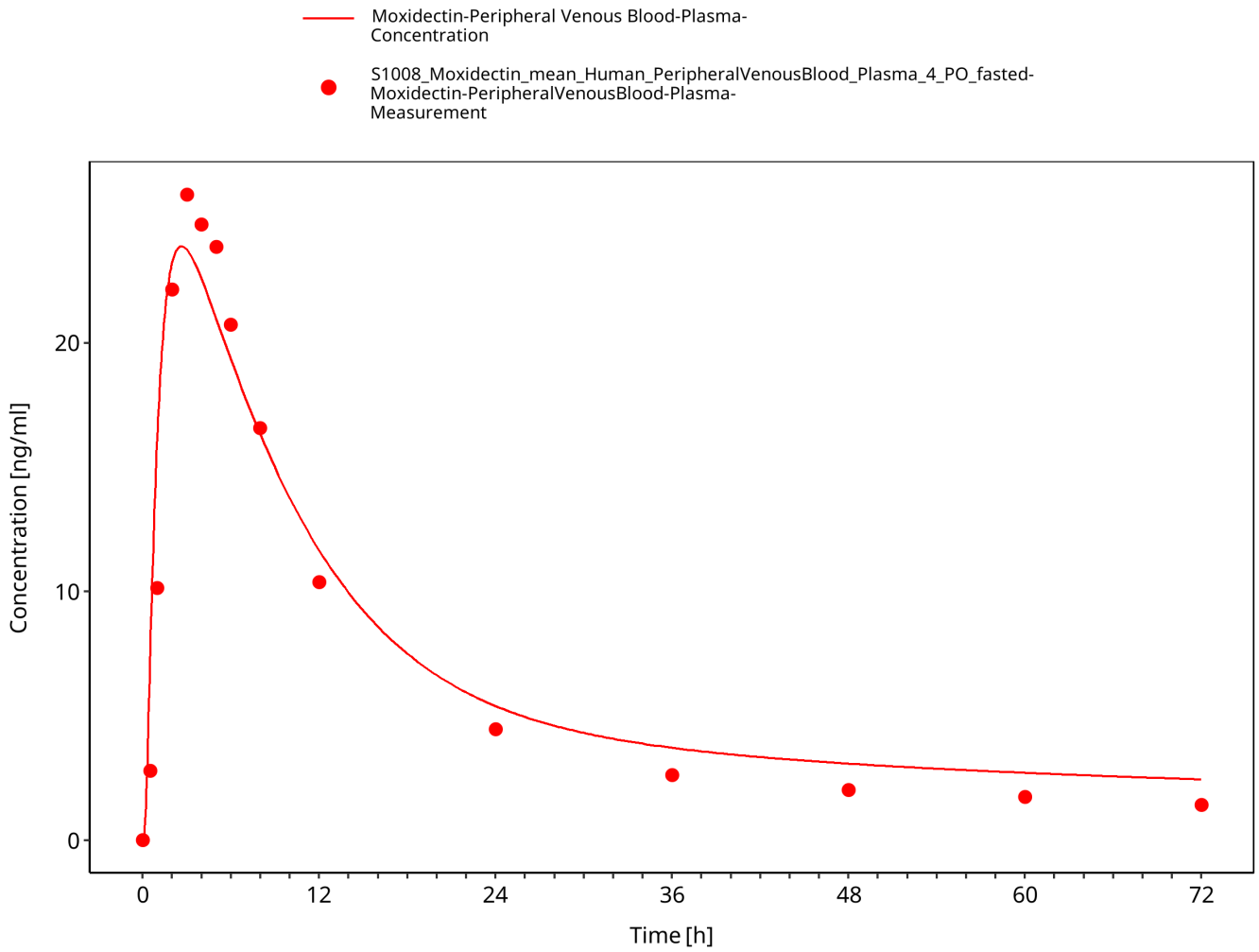

Figure 3-29: Kinrade 2018_PO_4 mg

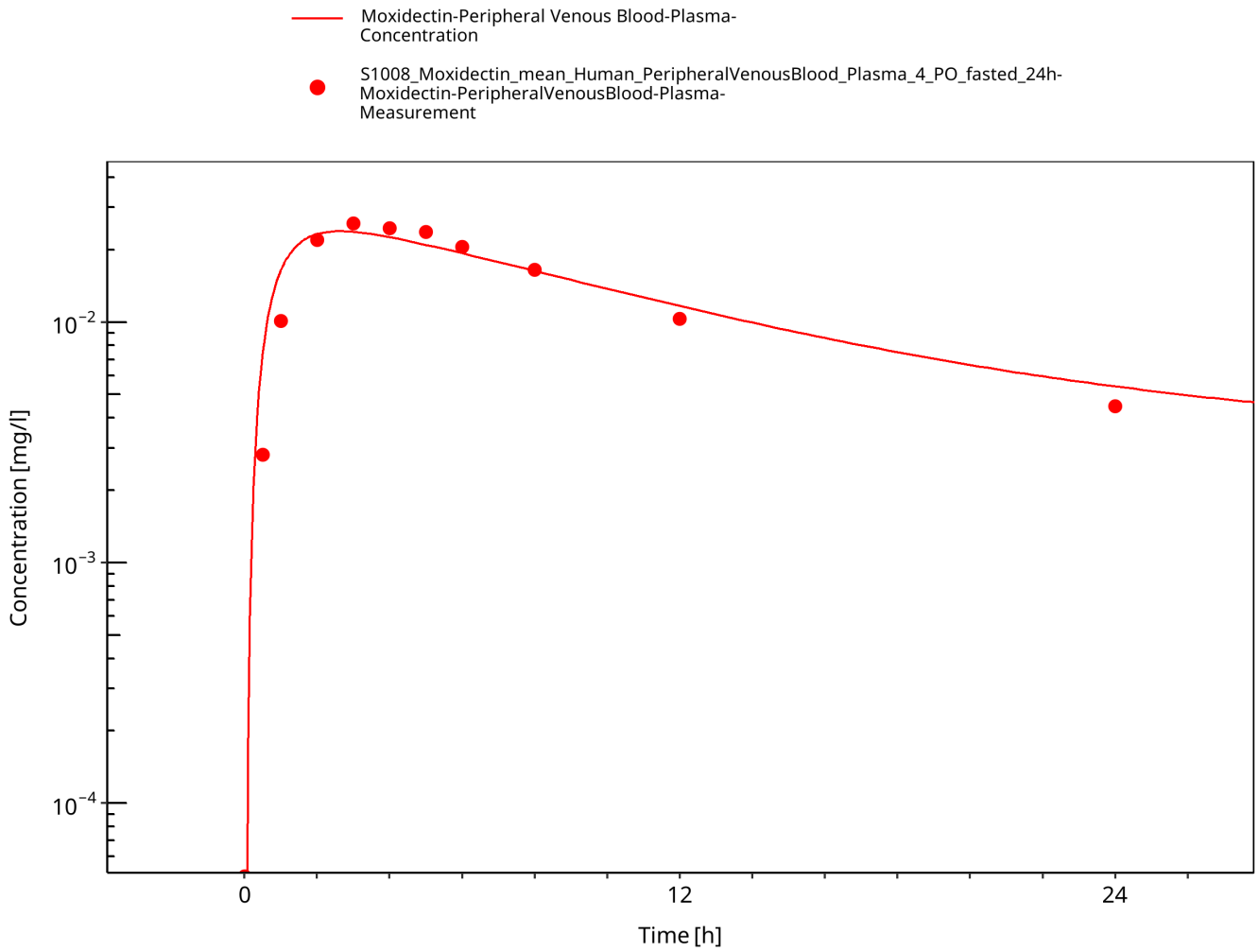

Figure 3-30: Kinrade 2018_PO_4 mg 24h

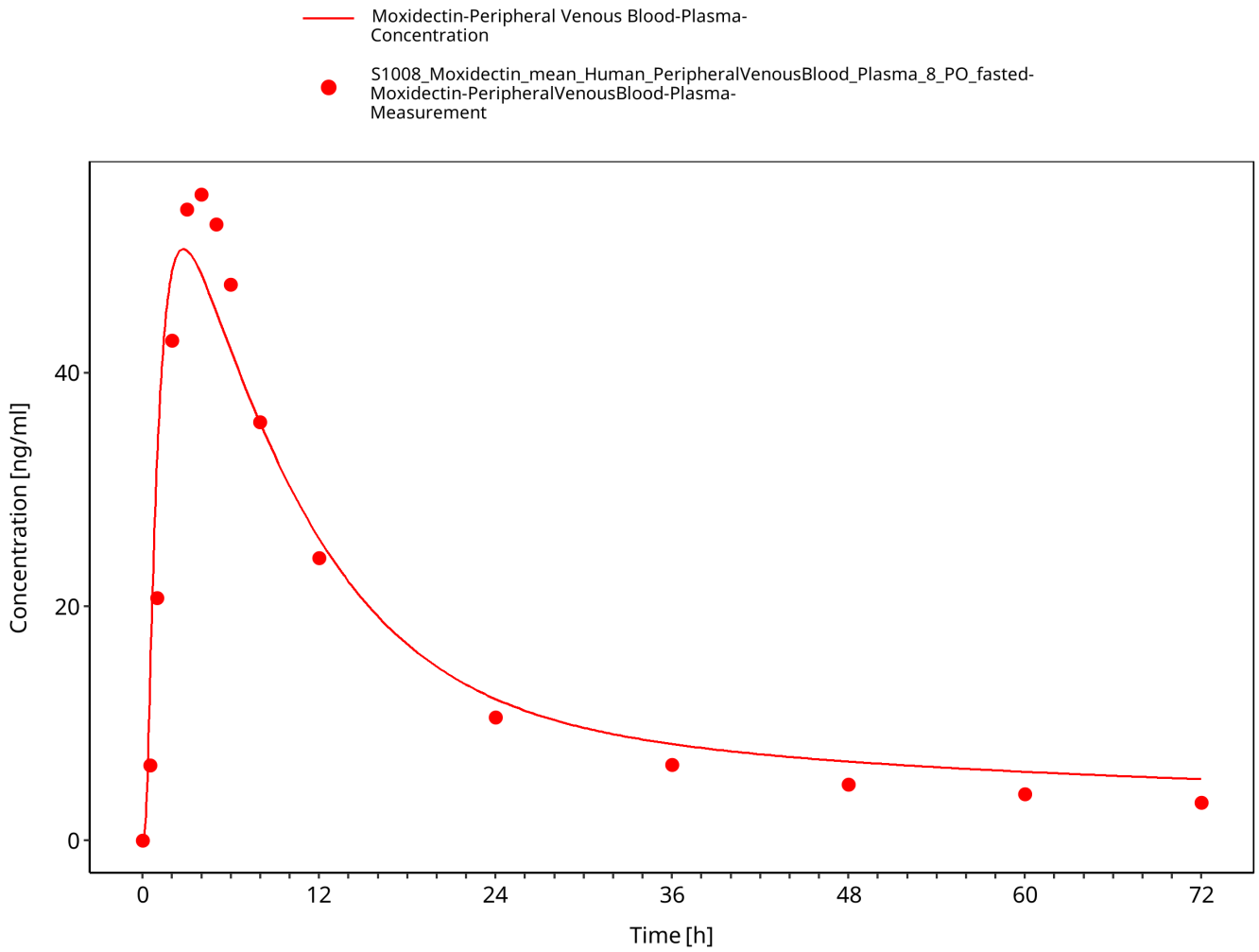

Figure 3-31: Kinrade 2018_PO_8 mg

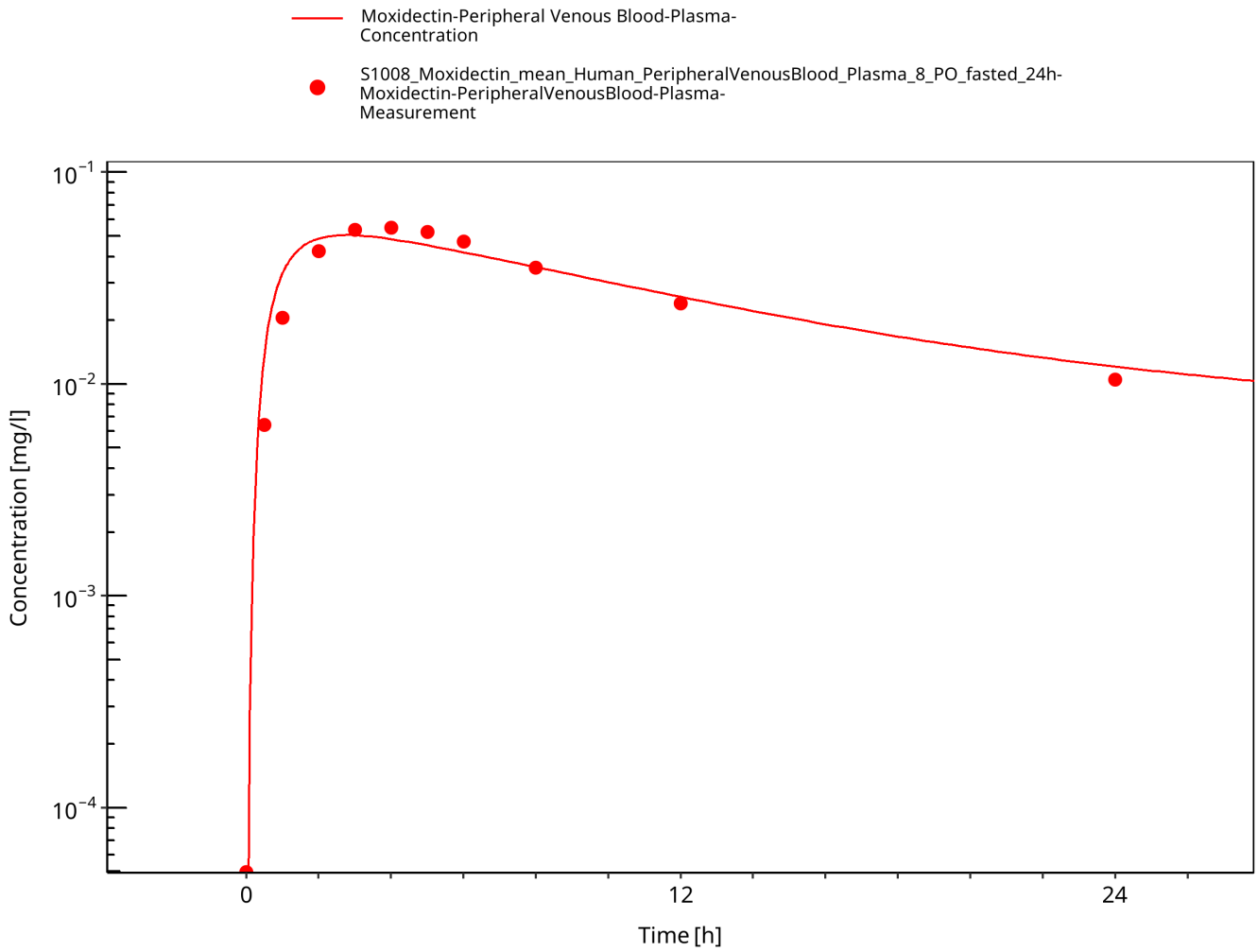

Figure 3-32: Kinrade 2018_PO_8 mg 24h

4 Conclusion

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

In particular, it applies metabolism and elimination via biliary clearance and CYP3A4-mediated metabolism. The PBPK model is verified for the first day(s) after administration. Thus, the model is fit for purpose to be applied for predictions of AUC and Cmax in the first days (e.g. in application such as tuberculosis), but further refinement is suggested for evaluation of the terminal half-life.

5 References

Cotreau 2003 Cotreau MM, Warren S, Ryan JL, Fleckenstein L, Vanapalli SR, Brown KR, Rock D, Chen CY, Schwertschlag US. The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. J Clin Pharmacol. 2003 Oct;43(10):1108-15. doi: 10.1177/0091270003257456.

FDA 2018 U.S. Food and Drug Administration. (2018). Clinical pharmacology and biopharmaceutics review(s): NDA 210867 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210867Orig1s000ClinPharmR.pdf)

Drugbank DrugBank DB11431 https://go.drugbank.com/drugs/DB11431, accessed 27-06-2025.

Kinrade 2018 Kinrade SA, Mason JW, Sanabria CR, Rayner CR, Bullock JM, Stanworth SH, Sullivan MT. Evaluation of the Cardiac Safety of Long-Acting Endectocide Moxidectin in a Randomized Concentration-QT Study. Clin Transl Sci. 2018 Nov;11(6):582-589. doi: 10.1111/cts.12583.

Korth-Bradley 2012a Korth-Bradley JM, Parks V, Chalon S, Gourley I, Matschke K, Cailleux K, Fitoussi S, Fleckenstein L. The effect of a high-fat breakfast on the pharmacokinetics of moxidectin in healthy male subjects: a randomized phase I trial. Am J Trop Med Hyg. 2012 Jan;86(1):122-125. doi: 10.4269/ajtmh.2012.11-0415.

Korth-Bradley 2012b Korth-Bradley JM, Parks V, Patat A, Matschke K, Mayer P, Fleckenstein L. Relative Bioavailability of Liquid and Tablet Formulations of the Antiparasitic Moxidectin. Clin Pharmacol Drug Dev. 2012 Jan;1(1):32-7. doi: 10.1177/2160763X11432508.

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. doi: 10.1002/psp4.12134. Epub 2016 Oct 19.

PK-Sim Ontogeny Database Version 7.3 (https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/38cf71b384cfc25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf)

Pubchem Pubchem 9832912 https://pubchem.ncbi.nlm.nih.gov/compound/Moxidectin, accessed 27-06-2025.

Schlender 2016 Schlender JF, Meyer M, Thelen K, Krauss M, Willmann S, Eissing T, Jaehde U. Development of a Whole-Body Physiologically Based Pharmacokinetic Approach to Assess the Pharmacokinetics of Drugs in Elderly Individuals. Clin Pharmacokinet. 2016 Dec;55(12):1573-1589.

Tan 2022 Tan B, Opoku N, Attah SK, Awadzi K, Kuesel AC, Lazdins-Helds J, Rayner C, Ryg-Cornejo V, Sullivan M, Fleckenstein L. Pharmacokinetics of oral moxidectin in individuals with Onchocerca volvulus infection. PLoS Negl Trop Dis. 2022 Mar 25;16(3):e0010005. doi: 10.1371/journal.pntd.0010005.

Wood 2024 Wood ND, Smith D, Kinrade SA, Sullivan MT, Rayner CR, Wesche D, Patel K, Rowland-Yeo K. The use of quantitative clinical pharmacology approaches to support moxidectin dosing recommendations in lactation. PLoS Negl Trop Dis. 2024 Aug 5;18(8):e0012351. doi: 10.1371/journal.pntd.0012351.