

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

| | |
|---|---|
| Version | 2.0-OSP12.1 |
| Based on Model Snapshot and Evaluation Plan | https://github.com/Open-Systems-Pharmacology/Efavirenz-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 stored at:

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

Table of Contents

- 1 Introduction
- 2 Methods
 - 2.1 Modeling Strategy
 - 2.2 Data
 - 2.3 Model Parameters and Assumptions
- 3 Results and Discussion
 - 3.1 Final input parameters
 - 3.2 Diagnostics Plots
 - 3.3 Concentration-Time Profiles
 - 3.3.1 Model Building
 - 3.3.2 Fitted interaction with Midazolam
- 4 Conclusion
- 5 References

1 Introduction

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is an antiretroviral drug to treat HIV.

Its major metabolizing enzyme is CYP2B6, but CYP3A4, CYP3A5, CYP1A2 and CYP2A6 also play a role ([Ward 2003](#), [Ogburn 2010](#)). CYP2B6 polymorphism is a major determinant of clinical efavirenz disposition and dose adjustment.

Efavirenz activates the pregnane X receptor (PXR) and induces its target gene expression. As a consequence, some cytochrome P450 genes are upregulated, and, e.g. higher CYP3A4 ([Shou 2008](#)) and CYP2B6 ([Ke 2016](#)) activity levels can be measured.

It has a long half-life ranging from 52 to 76 hours following single oral doses and 40 to 55 hours following long term administration as a result of auto-induction of efavirenz metabolism. The long plasma half-life allows for once daily administration with long term administration of a single 600 mg daily dose ([Smith 2001](#)).

The presented efavirenz model was established using clinical PK data of 7 publications covering a dose range from 200 to 600 mg after single and multiple oral administration.

The herein presented model building and evaluation report evaluates the performance of the PBPK model for efavirenz in (healthy) adults.

The established efavirenz PBPK model is verified for the use as a perpetrator drug in drug-drug interaction simulations.

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by e.g. Kuepfer et al. ([Kuepfer 2016](#)). The relevant anthropometric (height, weight) and physiological information (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](#)). This information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

Variability of plasma proteins and CYP enzymes are integrated into PK-Sim® and 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 base mean model was built using clinical data including single and multiple dose studies with oral applications of efavirenz (Sustiva) to find an appropriate structure to describe the pharmacokinetics in plasma. The mean PBPK model was developed using a typical European individual adjusted to the demography of the respective study population. The relative tissue-specific expressions of enzymes predominantly being involved in the metabolism of efavirenz were derived from RT-PCR data from [Nishimura 2003](#) and are implemented in the model as described previously ([Meyer 2012](#)).

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.

CYP3A4 plays only a minor role in efavirenz metabolism, and, therefore, auto-induction of CYP3A4 plays a minor role for efavirenz pharmacokinetics. Hence, to parameterize CYP3A4 induction, midazolam was used as victim substance to identify the respective model parameter E_{max} and EC_{50} for induction. The respective parameter identification (please refer to [Section 2.3.4](#)) was performed using the midazolam model [version 1.0](#).

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 efavirenz. The obtained information from literature is summarized in the table below.

| Parameter | Unit | Value | Source | Description |
|------------------------------|--------|------------------------------|---|---|
| MW | g/mol | 315.675 | https://www.drugbank.ca/ | Molecular weight |
| pK _a | 10.1 | (base) | Rabel 1996 | Acid dissociation constant |
| Solubility (pH) | mg/L | 11.5 (6.4) | Cristofolletti 2013 | Water solubility |
| logP | | 2.07, 4.6 | Almond 2005, https://www.drugbank.ca/ | Partition coefficient between octanol and water |
| logD | | 5.1 | Janneh 2009 | Partition coefficient between octanol and buffer solution |
| f _u | | 0.006 [0.004 - 0.015] | Almond 2005 | Fraction unbound in plasma |
| E _{max} (CYP3A4) | | 7.27, 3.15 (average 5.21) | Shou 2008 | Maximum induction effect |
| E _{C50} (CYP3A4) | µmol/l | 12.5, 2.18 (average 7.34) | Shou 2008 | Concentration at half maximum induction |
| E _{max} (CYP2B6) | | 5.1 | Ke 2016 | Maximum induction effect |
| E _{C50} (CYP2B6) | µmol/l | 5.1 | Ke 2016 | Concentration at half maximum induction |

2.2.2 Clinical Data

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

2.2.2.1 Model Building

The following studies were used for model building:

| Publication | Arm / Treatment / Information used for model building |
|-------------|---|
| Mouly 2002 | Healthy subjects receiving a single oral dose of 200 and 400 mg |
| Ogburn 2013 | Healthy subjects receiving a single oral dose of 600 mg |
| Xu 2013 | Healthy subjects with different CYP2B6 genotypes receiving a single oral dose of 600 mg |
| Dooley 2012 | Healthy subjects with different CYP2B6 genotypes receiving multiple doses of 600 mg |
| Garg 2013 | Healthy subjects receiving multiple doses of 600 mg |
| Huang 2012 | Healthy subjects receiving multiple doses of 600 mg |

2.2.2.2 Midazolam interaction studies used to parameterize CYP3A4 interaction

The following studies were used for parameterization of CYP3A4 interaction:

| Publication | Arm / Treatment / Information used for model building |
|------------------|--|
| Mikus 2017 | Healthy subjects receiving a single oral dose of 400 mg Efavirenz at t=0h, 4 mg midazolam at t=12h and a single intravenous dose of 2 mg midazolam at t=18h. |
| Katzenmaier 2010 | Healthy subjects receiving multiple oral doses of 400 mg efavirenz QD. On day 14, subjects receive a single oral midazolam dose of 3 mg. |

2.3 Model Parameters and Assumptions

2.3.1 Absorption

Absorption observed in clinical studies can be fully explained by passive absorption.

2.3.2 Distribution

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 Schmitt and cellular permeability calculation by PK-Sim Standard.

2.3.3 Metabolism, Elimination and Induction

Efavirenz is metabolized by CYP2B6, CYP3A4, CYP3A5, CYP1A2 and CYP2A6.

Induction of CYP3A4 (Shou 2008) and CYP2B6 (Ke 2016) was taken into account.

2.3.4 Automated Parameter Identification

The parameter identification tool in PK-Sim has been used to estimate selected model parameters by adjusting to PK data of the clinical studies that were used in the model building process. For some of the parameters, factors were optimized to maintain their ratio, e.g. a factor for the kcat clearances values for CYP2B6, CYP3A4, CYP3A5, CYP1A2 and CYP2A6 was optimized to keep the ratio constant.

The result of the final parameter identification is shown in the table below:

| Model Parameter | Optimized Value | Unit |
|----------------------------------|---|--------|
| Lipophilicity | 3.437 | |
| Specific intestinal permeability | 2.972E-5 | cm/min |
| Solubility at reference pH | 39.922 | mg/l |
| fraction unbound | 5.955E-3 | |
| kcat CYP2B6 | 1.601 (factor: 0.31833 of literature reference) | 1/min |
| kcat CYP3A4 | 0.051 (factor: 0.31833 of literature reference) | 1/min |
| kcat CYP3A5 | 0.191 (factor: 0.31833 of literature reference) | 1/min |
| kcat CYP1A2 | 0.191 (factor: 0.31833 of literature reference) | 1/min |
| kcat CYP2A6 | 0.318 (factor: 0.31833 of literature reference) | 1/min |
| EC50 CYP3A4 | 0.071 (factor: 0.009711of literature reference) | µmol/l |
| EC50 CYP2B6 | 0.012 (factor: 0.009711of literature reference) | µmol/l |
| Dissolution time (50% dissolved) | 60 | min |
| Dissolution shape | 0.272 | |

3 Results and Discussion

The PBPK model for efavirenz was developed and evaluated using publicly available clinical pharmacokinetic data from studies listed in [Section 2.2.2](#).

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: Efavirenz

Parameters

| Name | Value | Value Origin | Alternative | Default |
|--|-------------------------|--|-------------|---------|
| Solubility at reference pH | 39.9217804729 mg/l | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 | Measurement | True |
| Reference pH | 0 | | Measurement | True |
| Lipophilicity | 3.4369753585 Log Units | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 | Optimized | True |
| Fraction unbound (plasma, reference value) | 0.0059553692487 | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 | Measurement | True |
| Specific intestinal permeability (transcellular) | 2.9720579005E-05 cm/min | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 | Optimized | True |
| Cl | 1 | | | |
| F | 3 | | | |
| Is small molecule | Yes | | | |
| Molecular weight | 315.675 g/mol | | | |
| Plasma protein binding partner | Albumin | | | |

Calculation methods

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

Processes

Metabolizing Enzyme: CYP2B6-Ward2003

Molecule: CYP2B6

Metabolite: 8-OH efavirenz

Parameters

| Name | Value | Value Origin |
|----------------------------------|-------------------------------|--|
| In vitro Vmax/recombinant enzyme | 3.5 pmol/min/pmol rec. enzyme | |
| Km | 6.4 μmol/l | |
| kcat | 1.601451904 1/min | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |

Metabolizing Enzyme: CYP1A2-Ward2003

Molecule: CYP1A2

Metabolite: 8-OH efavirenz

Parameters

| Name | Value | Value Origin |
|----------------------------------|-------------------------------|--|
| In vitro Vmax/recombinant enzyme | 0.6 pmol/min/pmol rec. enzyme | |
| Km | 8.3 μmol/l | |
| kcat | 0.1910198104 1/min | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |

Metabolizing Enzyme: CYP3A4-Ward2003

Molecule: CYP3A4

Metabolite: 8-OH efavirenz

Parameters

| Name | Value | Value Origin |
|----------------------------------|--------------------------------|--|
| In vitro Vmax/recombinant enzyme | 0.16 pmol/min/pmol rec. enzyme | |
| Km | 23.5 μmol/l | |
| kcat | 0.0509386161 1/min | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |

Metabolizing Enzyme: CYP3A5-Ward2003

Molecule: CYP3A5

Metabolite: 8-OH efavirenz

Parameters

| Name | Value | Value Origin |
|----------------------------------|-------------------------------|--|
| In vitro Vmax/recombinant enzyme | 0.6 pmol/min/pmol rec. enzyme | |
| Km | 19.1 μmol/l | |
| kcat | 0.1910198104 1/min | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |

Metabolizing Enzyme: CYP2A6-Ogburn2010

Molecule: CYP2A6

Metabolite: 8-OH efavirenz

Parameters

| Name | Value | Value Origin |
|----------------------------------|-----------------------------|--|
| In vitro Vmax/recombinant enzyme | 1 pmol/min/pmol rec. enzyme | |
| Km | 7.7 μmol/l | |
| kcat | 0.3183663507 1/min | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |

Metabolizing Enzyme: CYP2B6-CYP2B6*1/*6

Molecule: CYP2B6

Metabolite: 8-OH efavirenz

Parameters

| Name | Value | Value Origin |
|----------------------------------|------------------------------------|--------------|
| In vitro Vmax/recombinant enzyme | 2.268966 pmol/min/pmol rec. enzyme | |
| Km | 6.4 µmol/l | |

Metabolizing Enzyme: CYP2B6-CYP2B6*6/*6

Molecule: CYP2B6

Metabolite: 8-OH efavirenz

Parameters

| Name | Value | Value Origin |
|----------------------------------|------------------------------------|--------------|
| In vitro Vmax/recombinant enzyme | 1.448276 pmol/min/pmol rec. enzyme | |
| Km | 6.4 µmol/l | |

Induction: CYP3A4-Shou2008

Molecule: CYP3A4

Parameters

| Name | Value | Value Origin |
|------|--------------------|--|
| EC50 | 0.071279975 µmol/l | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |
| Emax | 5.21 | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |

Induction: CYP2B6-Ke2016

Molecule: CYP2B6

Parameters

| Name | Value | Value Origin |
|------|---------------------|--|
| EC50 | 0.0116534019 µmol/l | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |
| Emax | 5.2 | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

| Name | Value | Value Origin |
|--------------|-------|--------------|
| GFR fraction | 1 | |

Formulation: Sustiva

Type: Weibull

Parameters

| Name | Value | Value Origin |
|----------------------------------|--------------|--|
| Dissolution time (50% dissolved) | 60 min | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |
| Lag time | 0 min | |
| Dissolution shape | 0.2720936819 | Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02 |
| 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 first plot shows simulated versus observed plasma concentration, the second weighted residuals versus time.

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

| Group | GMFE |
|------------------------------|------|
| First dose administration | 1.47 |
| Multiple dose administration | 1.40 |
| All | 1.45 |

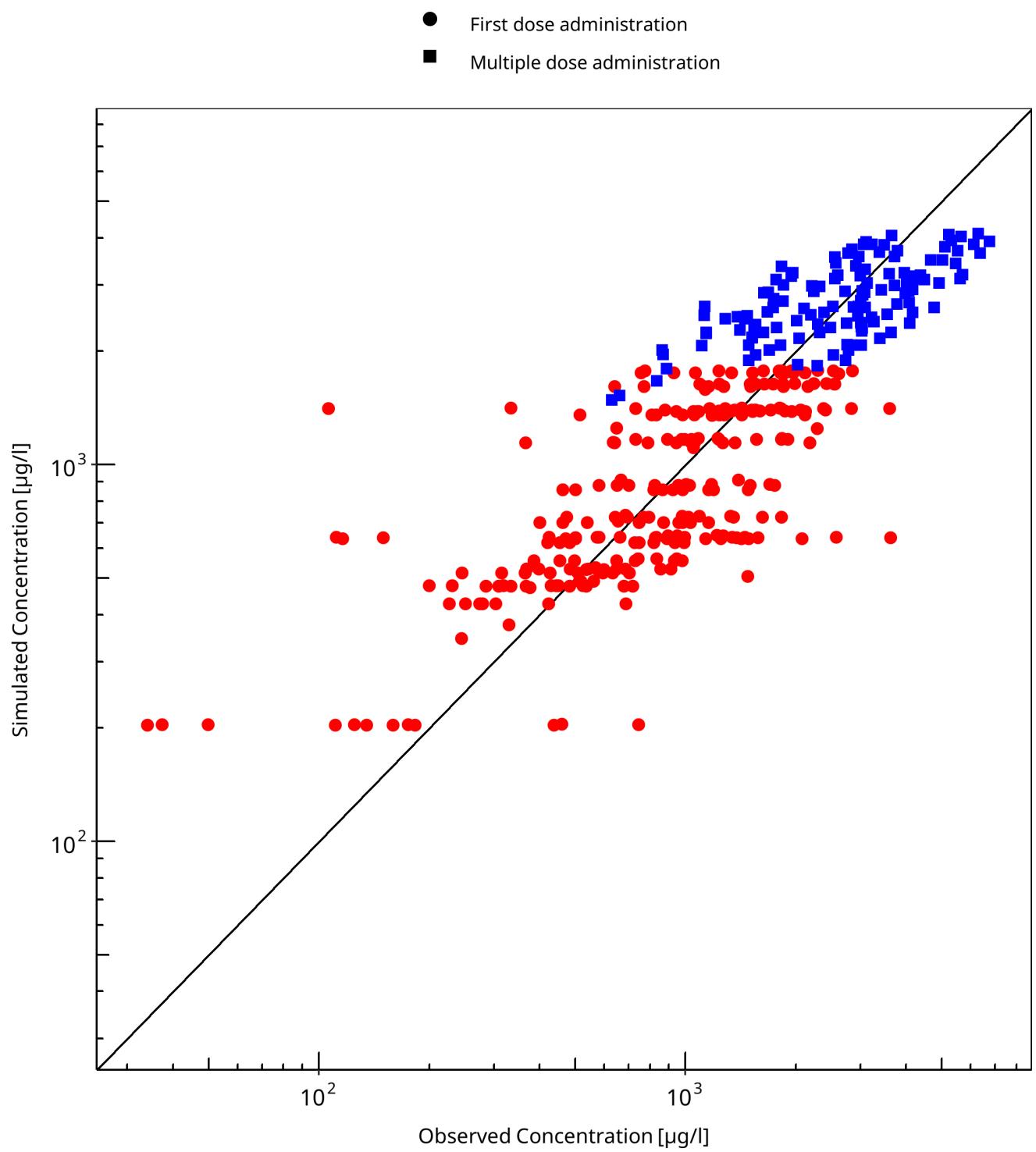


Figure 3-1: Goodness of fit plot for concentration in plasma

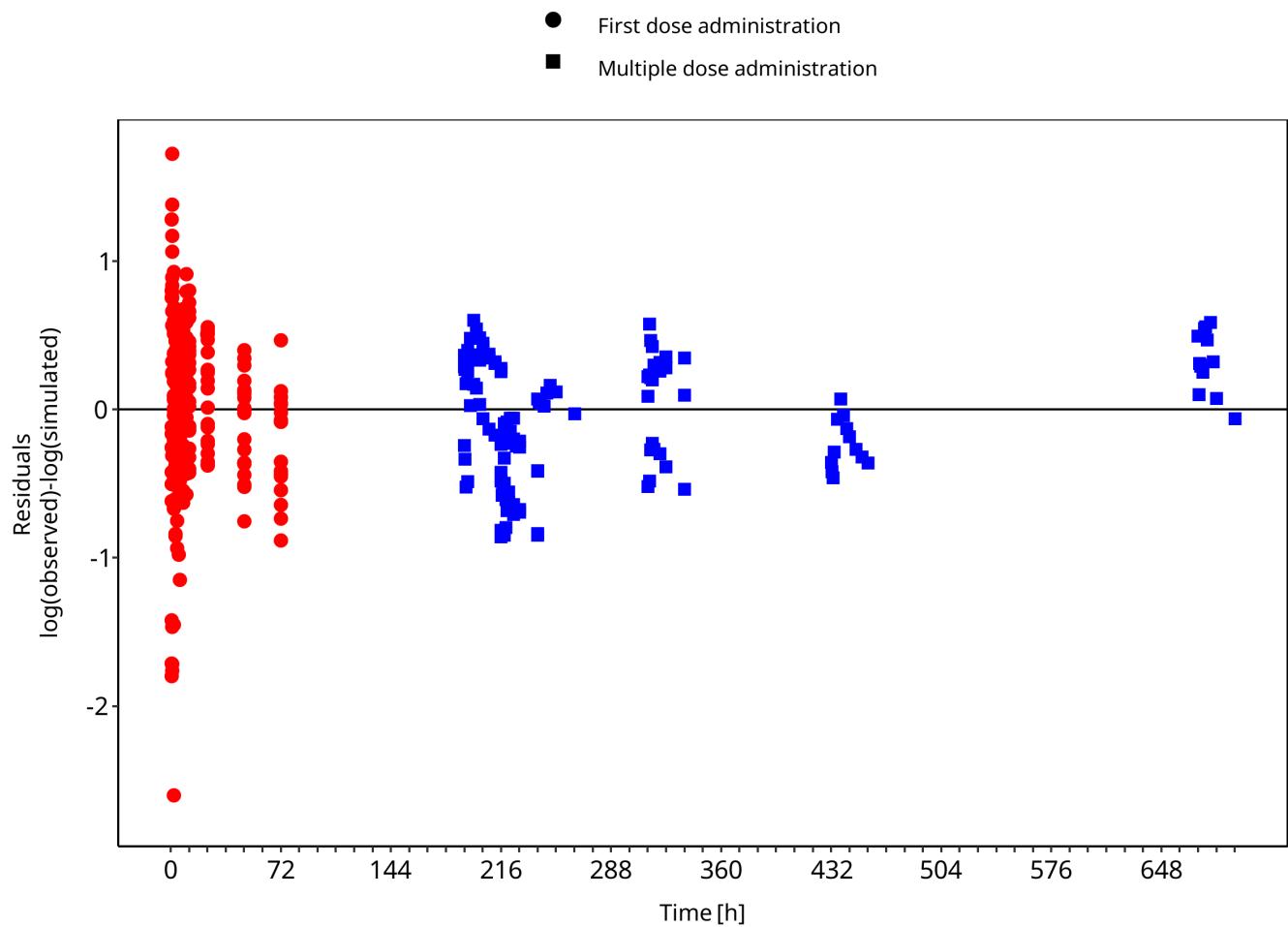


Figure 3-2: Goodness of fit plot for concentration in plasma

3.3 Concentration-Time Profiles

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

3.3.1 Model Building

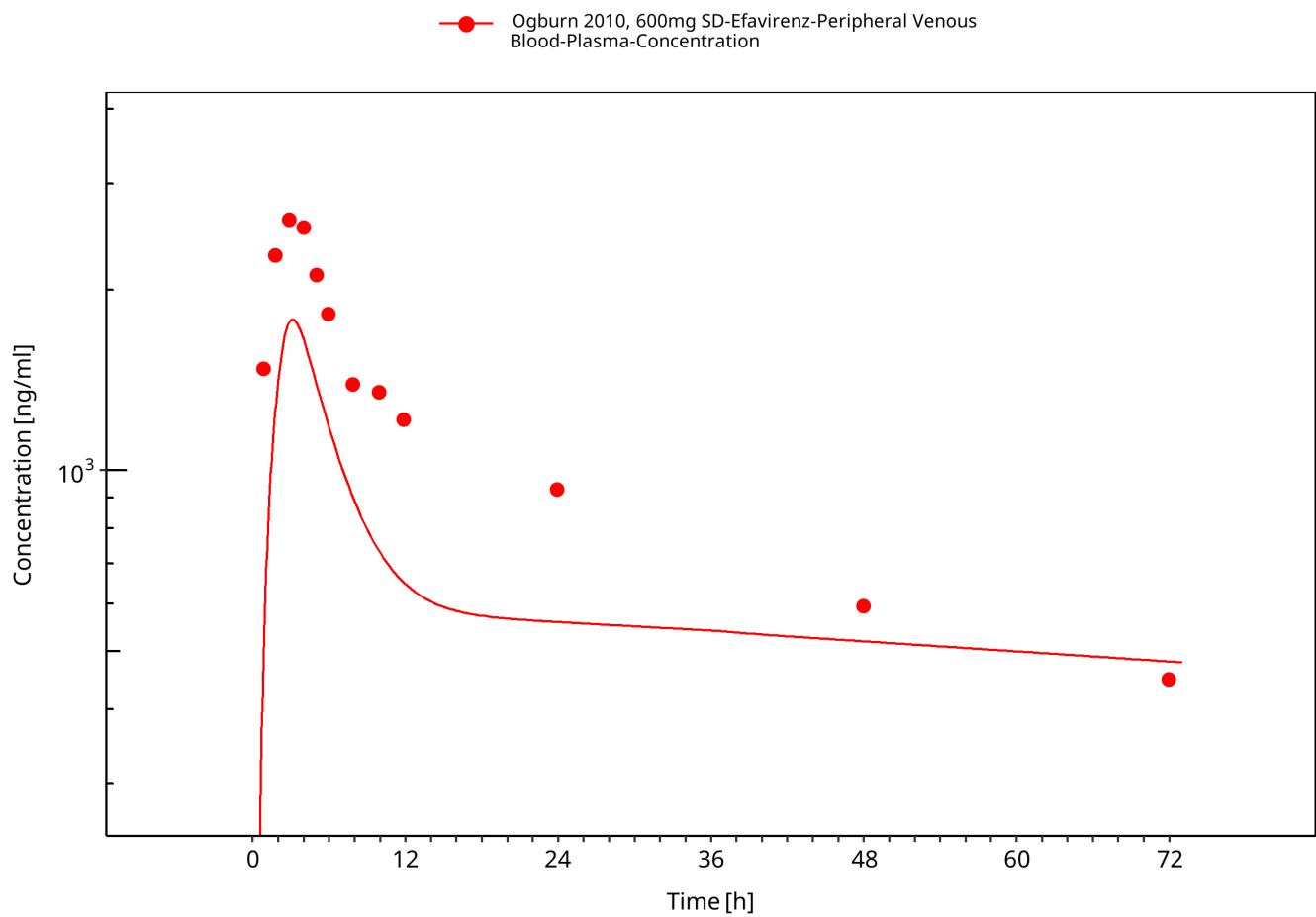


Figure 3-3: Ogburn 2010, 600mg SD

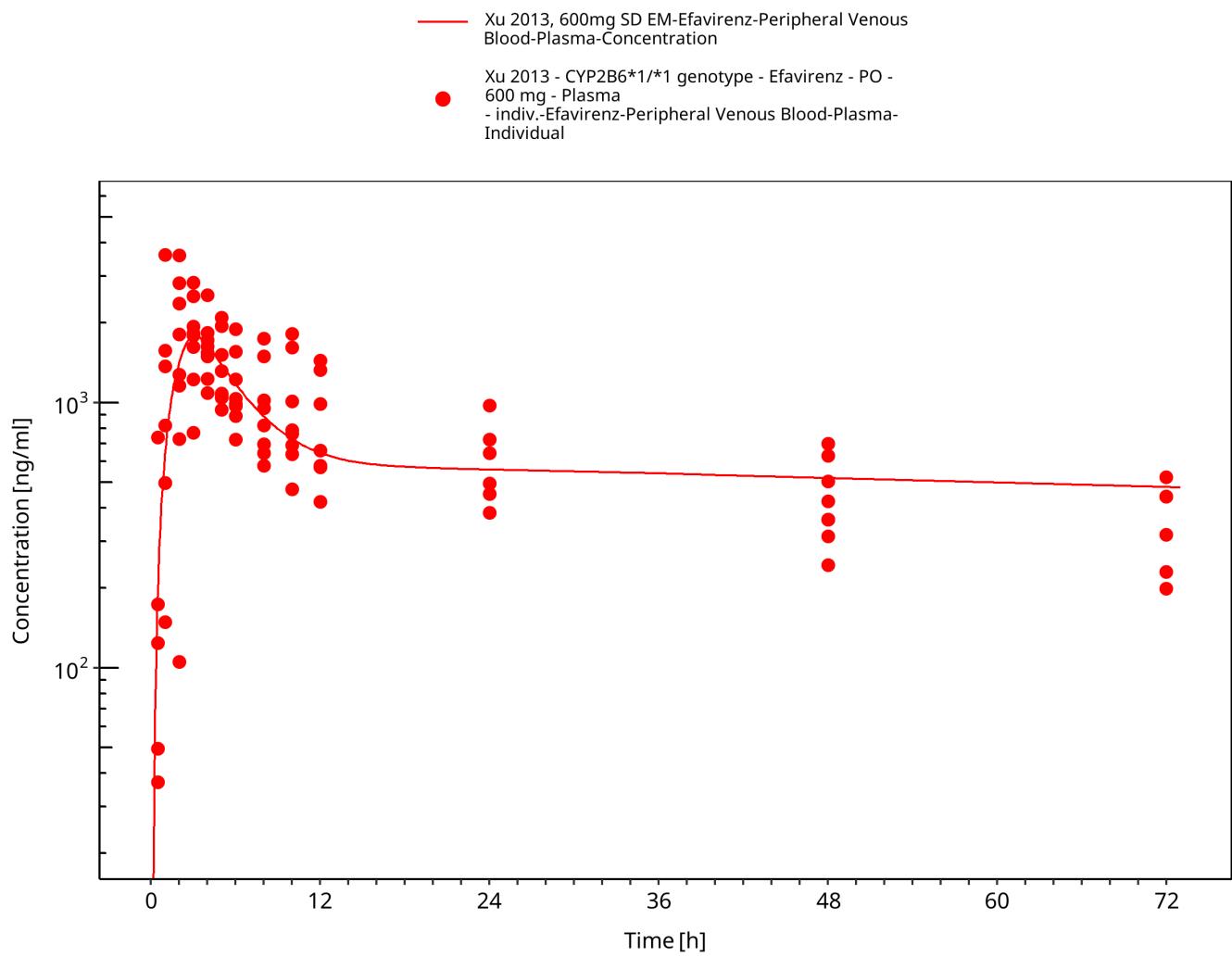


Figure 3-4: Xu 2013, 600mg SD EM

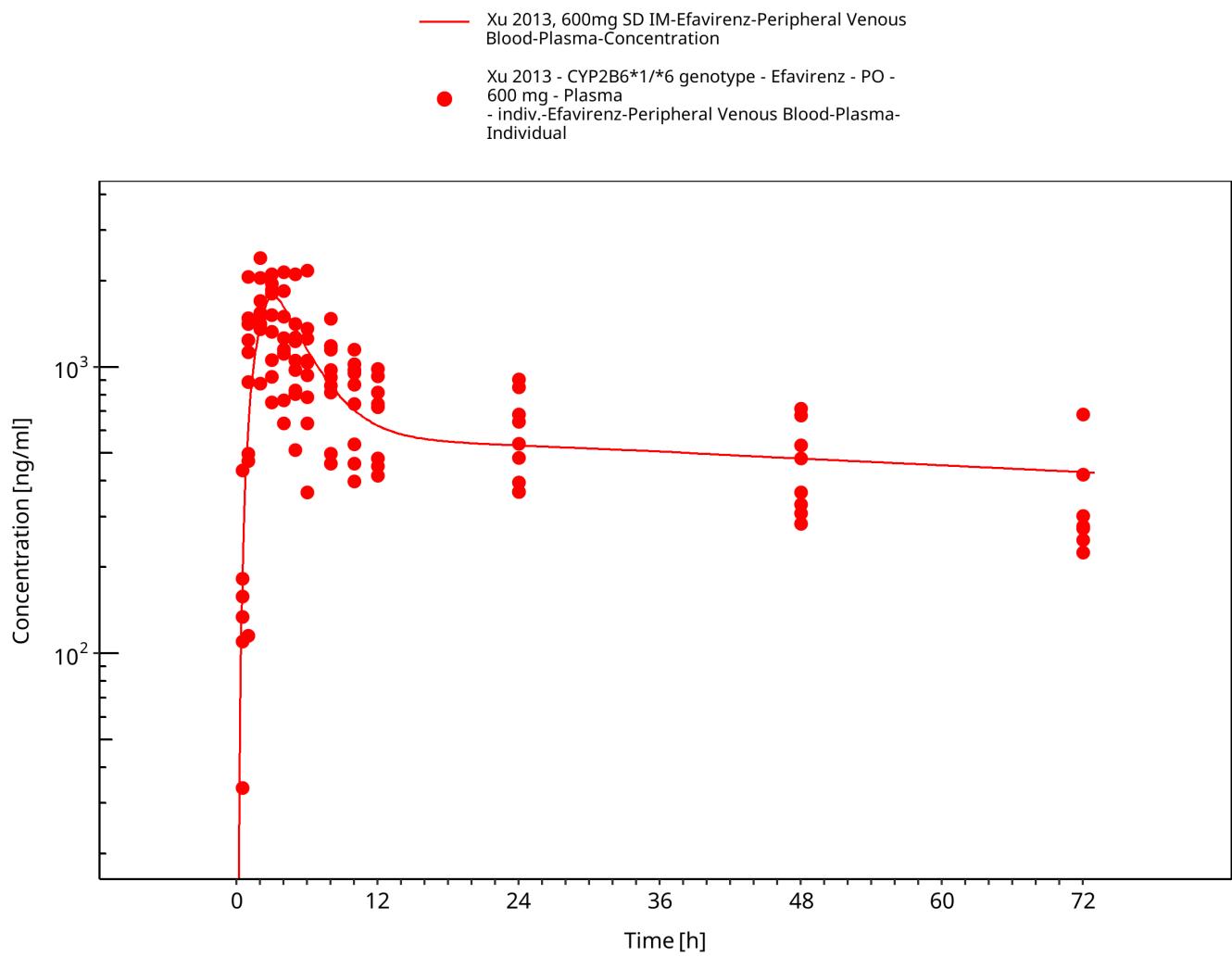


Figure 3-5: Xu 2013, 600mg SD IM

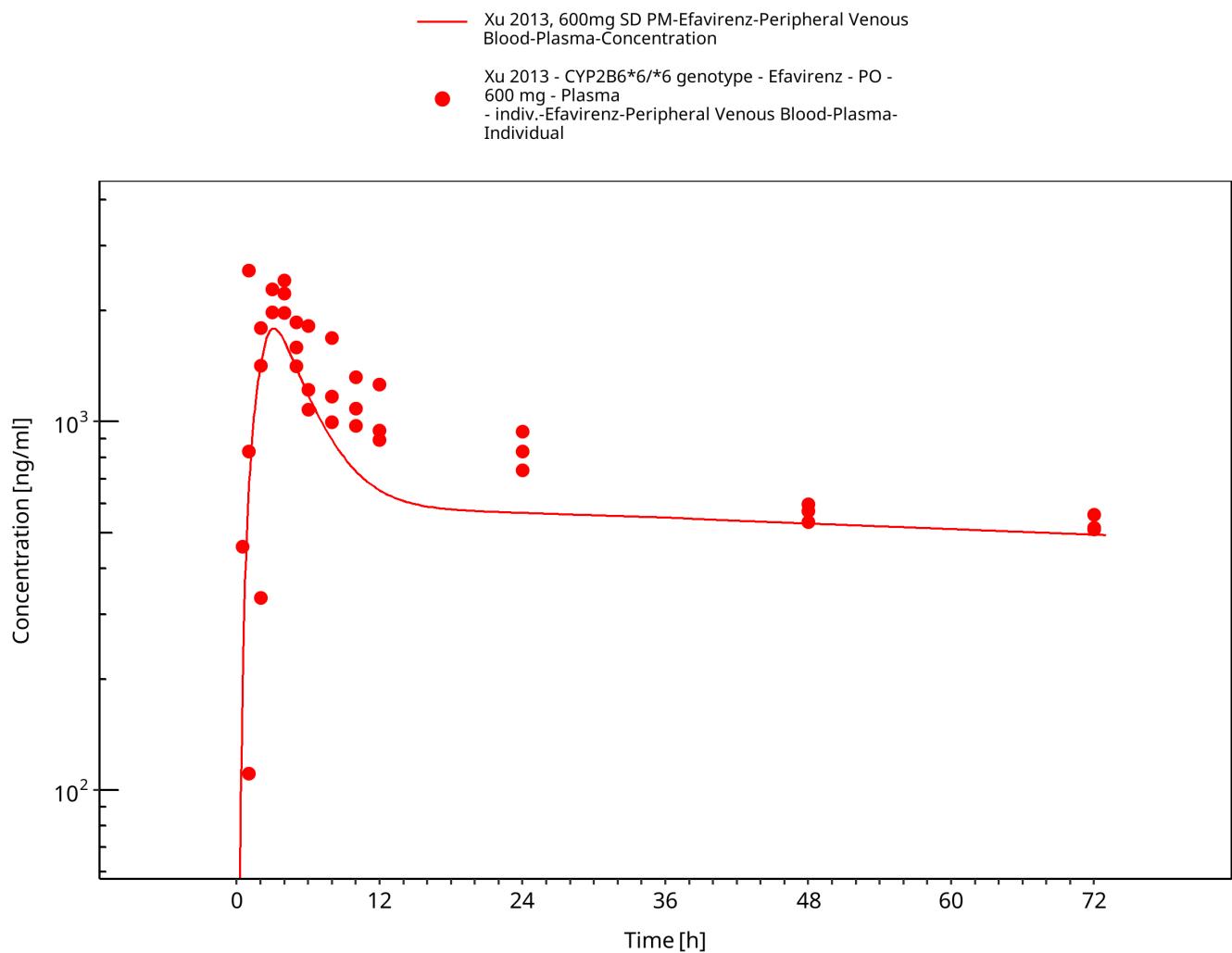


Figure 3-6: Xu 2013, 600mg SD PM

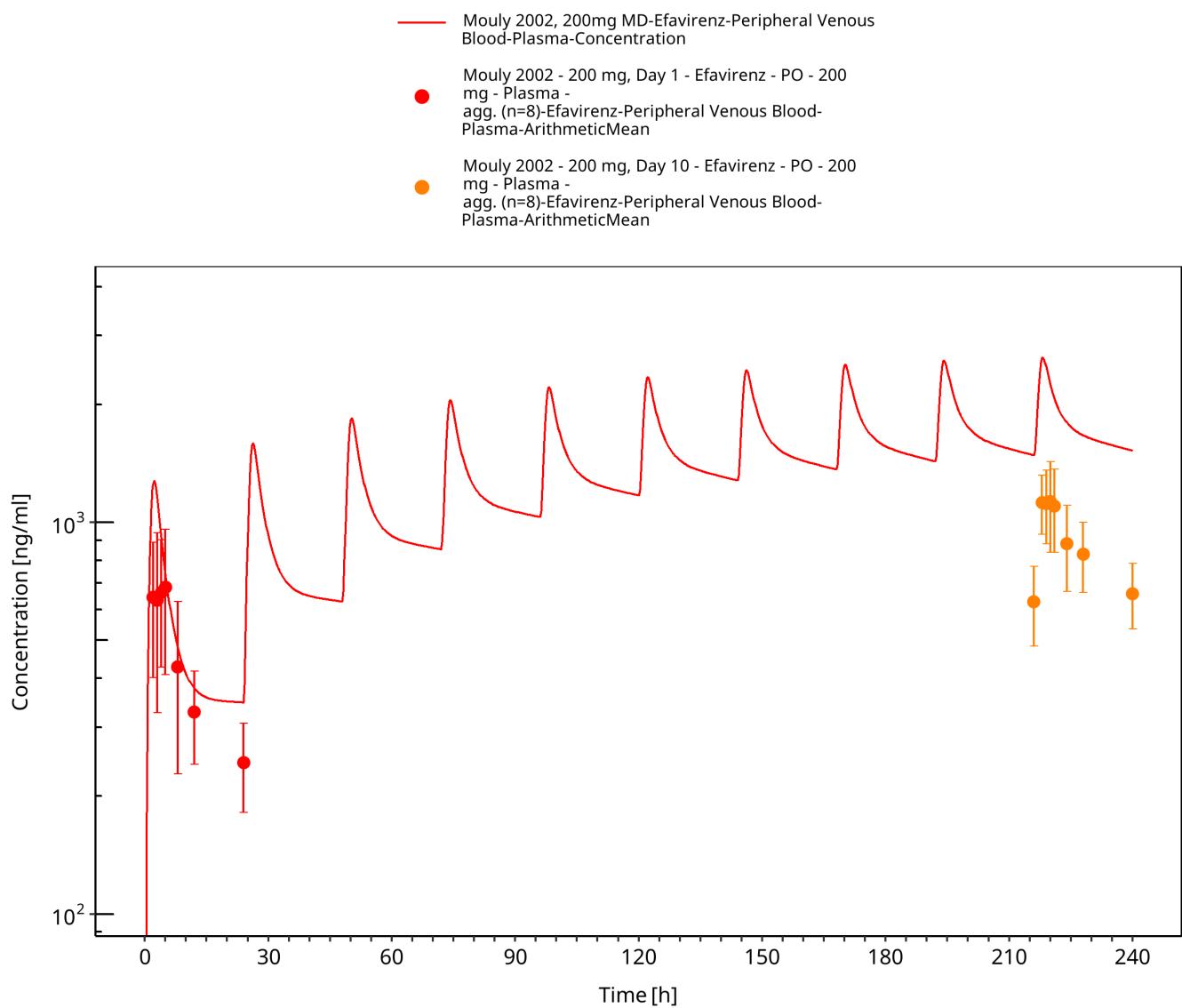


Figure 3-7: Mouly 2002, 200mg MD

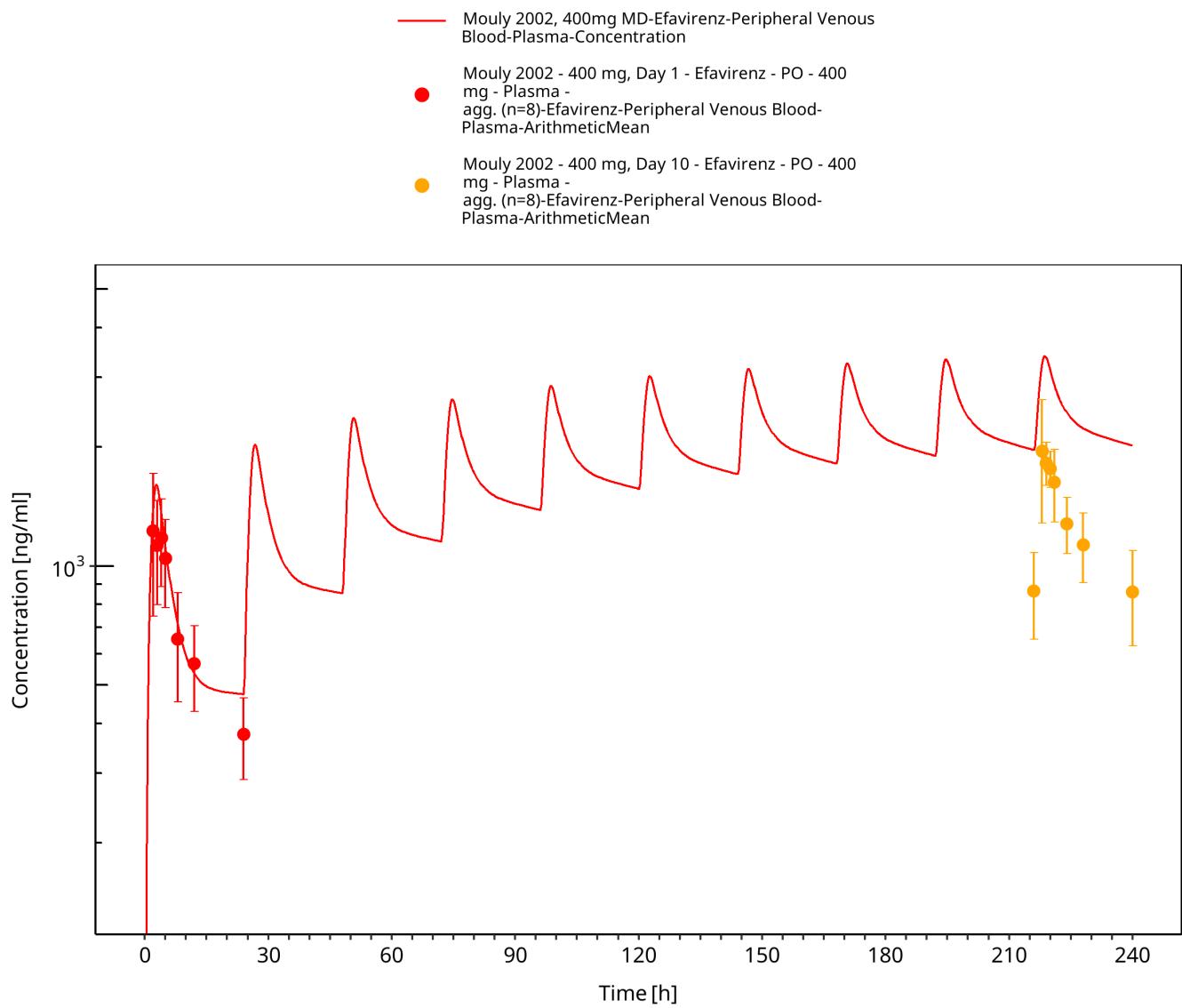


Figure 3-8: Mouly 2002, 400mg MD

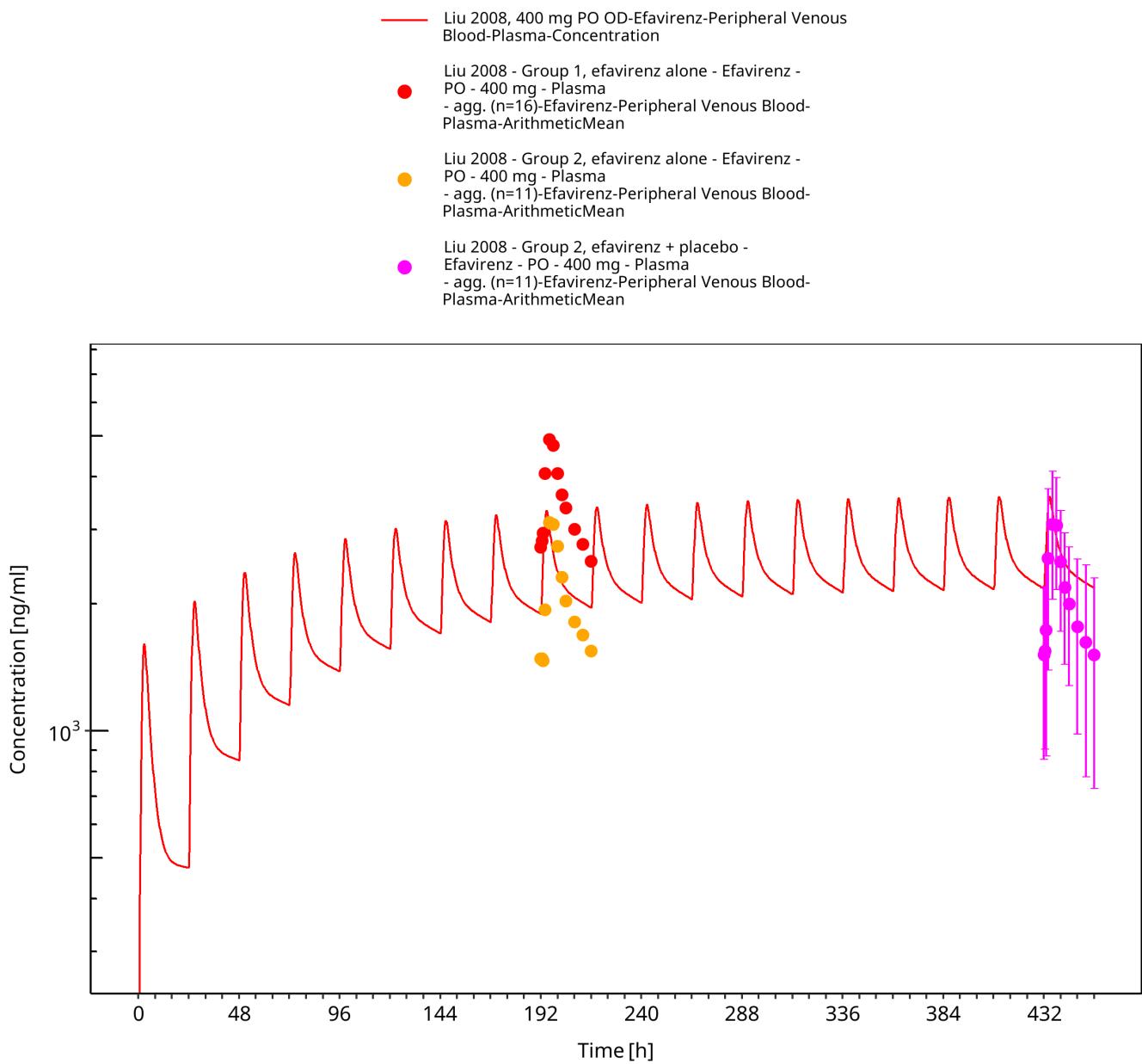


Figure 3-9: Liu 2008, 400 mg PO OD

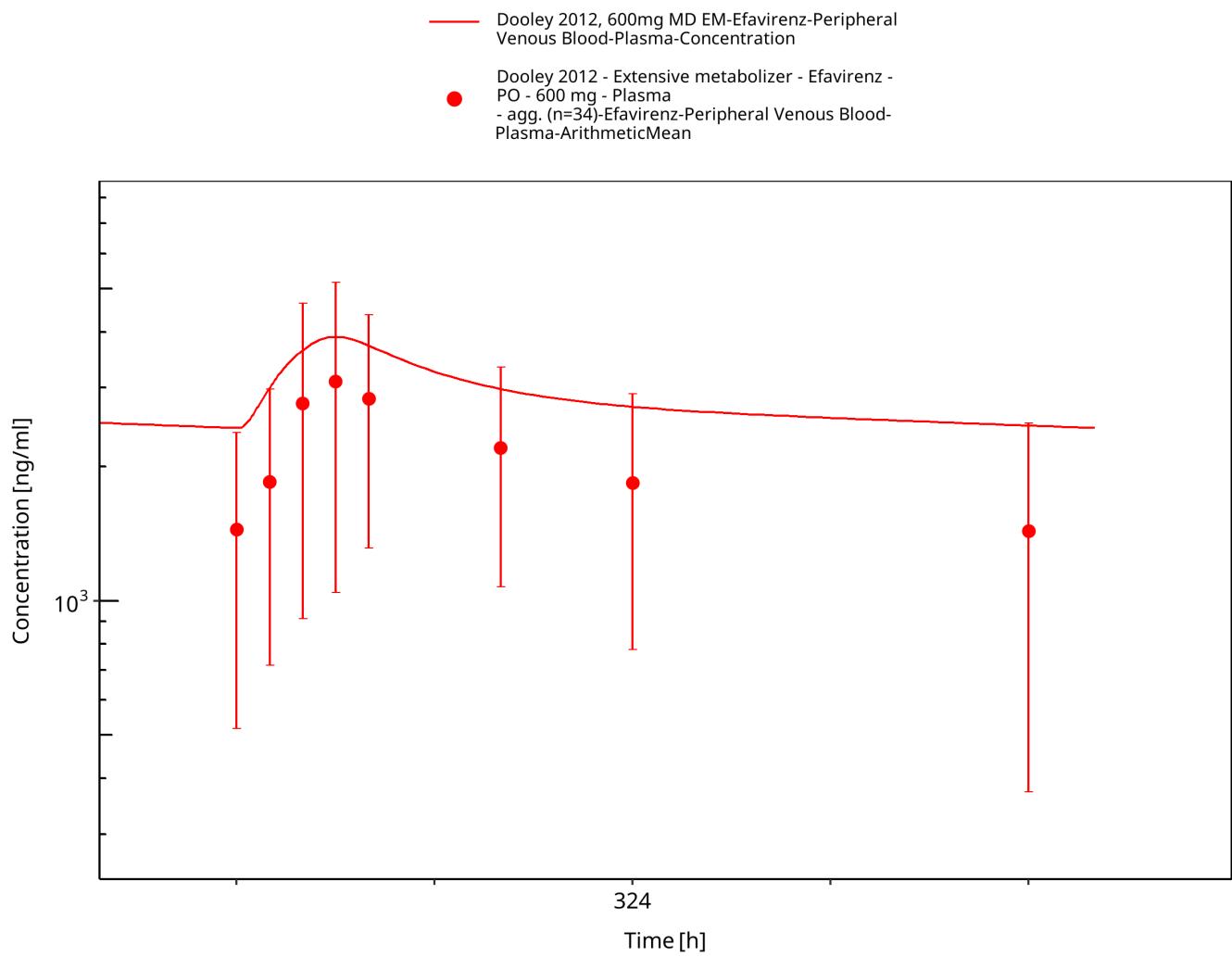


Figure 3-10: Dooley 2012, 600mg MD EM

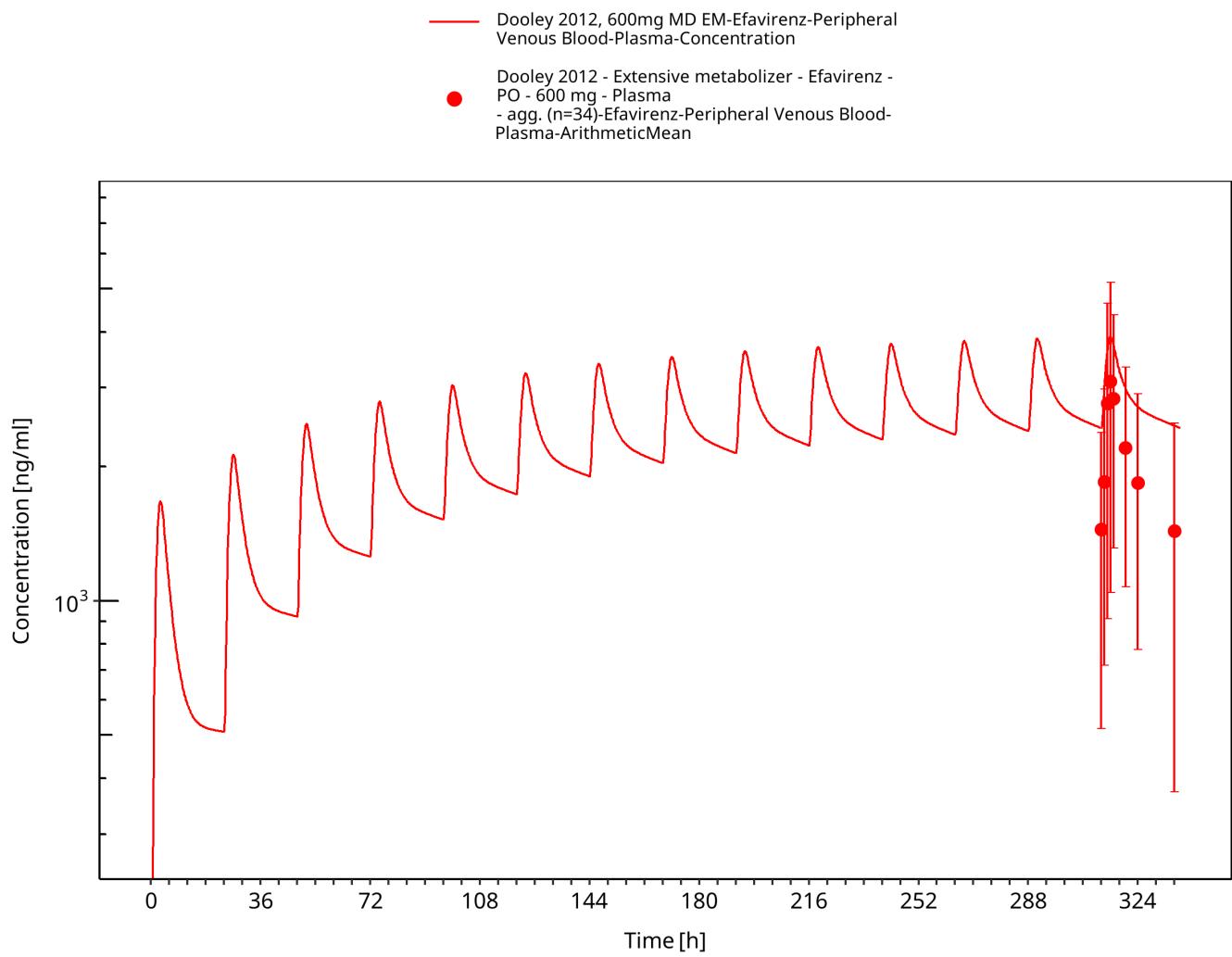


Figure 3-11: Dooley 2012, 600mg MD EM

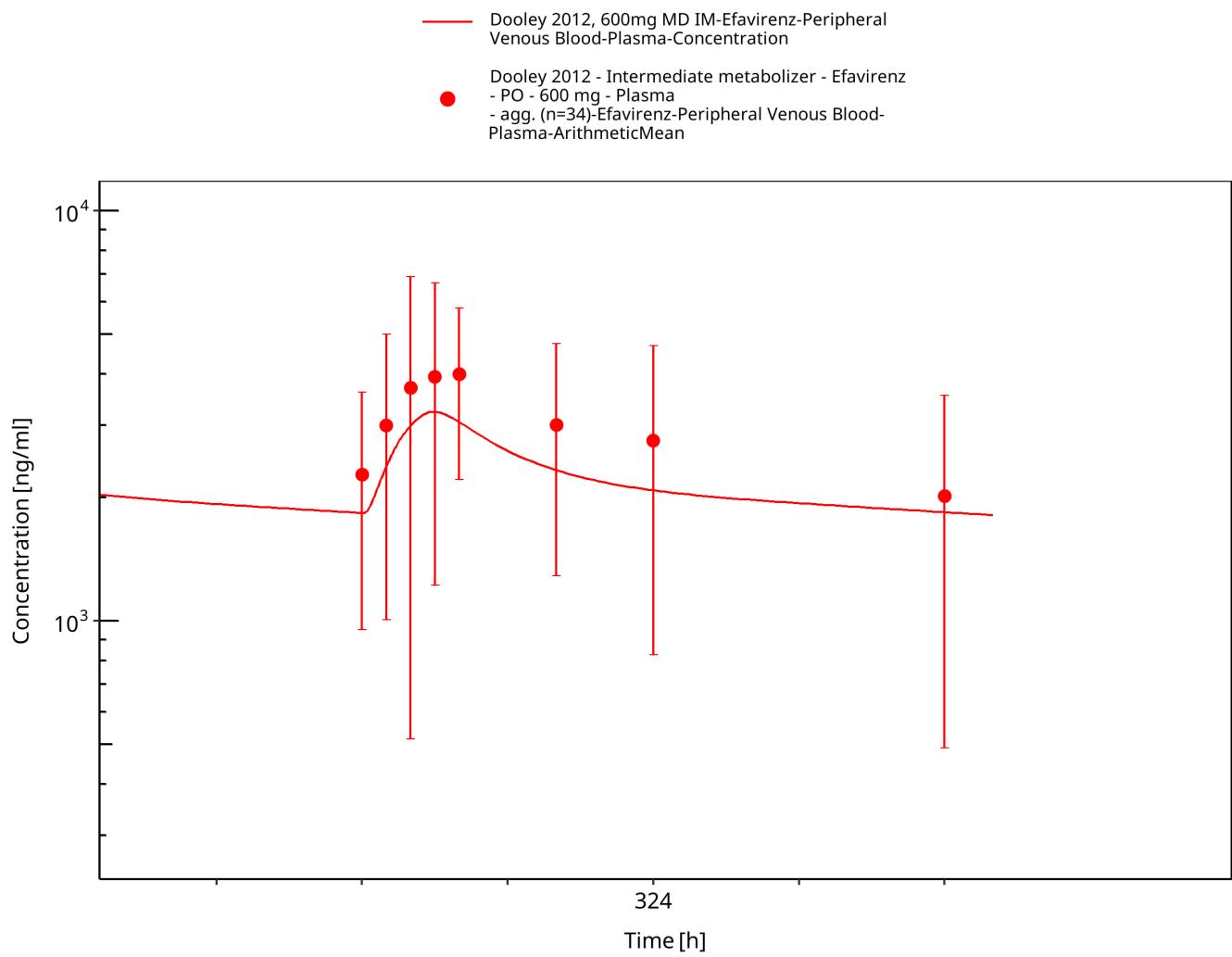


Figure 3-12: Dooley 2012, 600mg MD IM

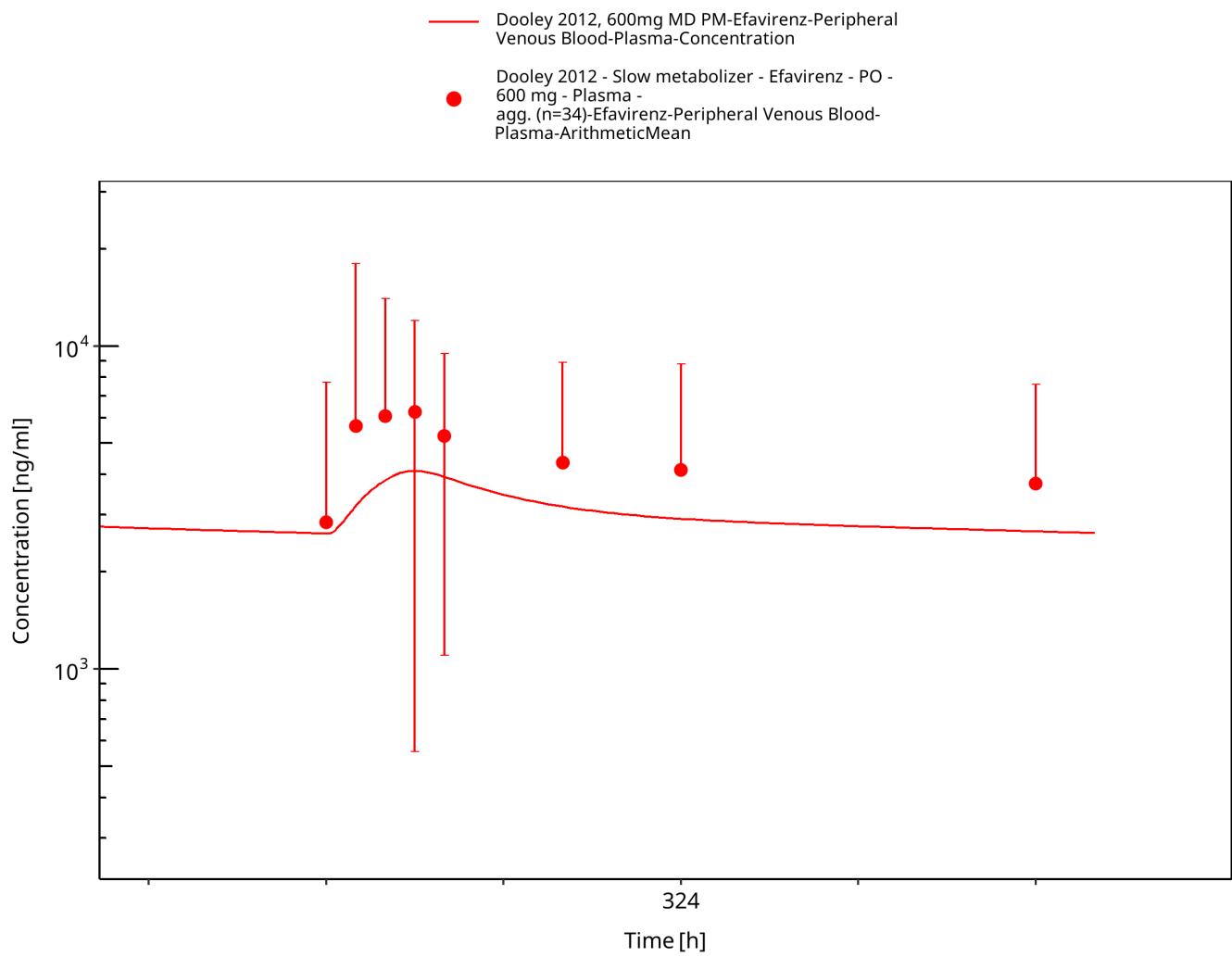


Figure 3-13: Dooley 2012, 600mg MD PM

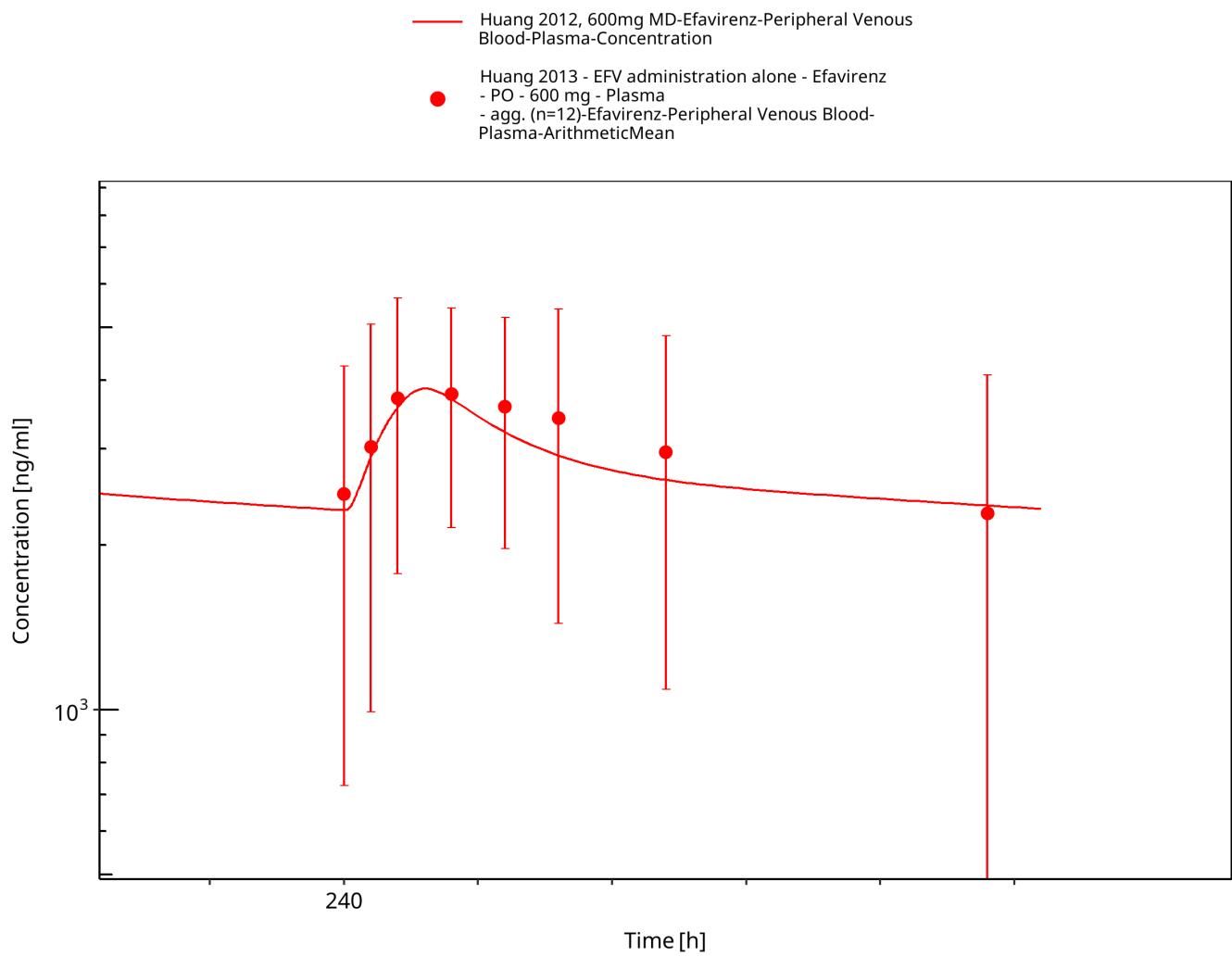


Figure 3-14: Huang 2012, 600mg MD

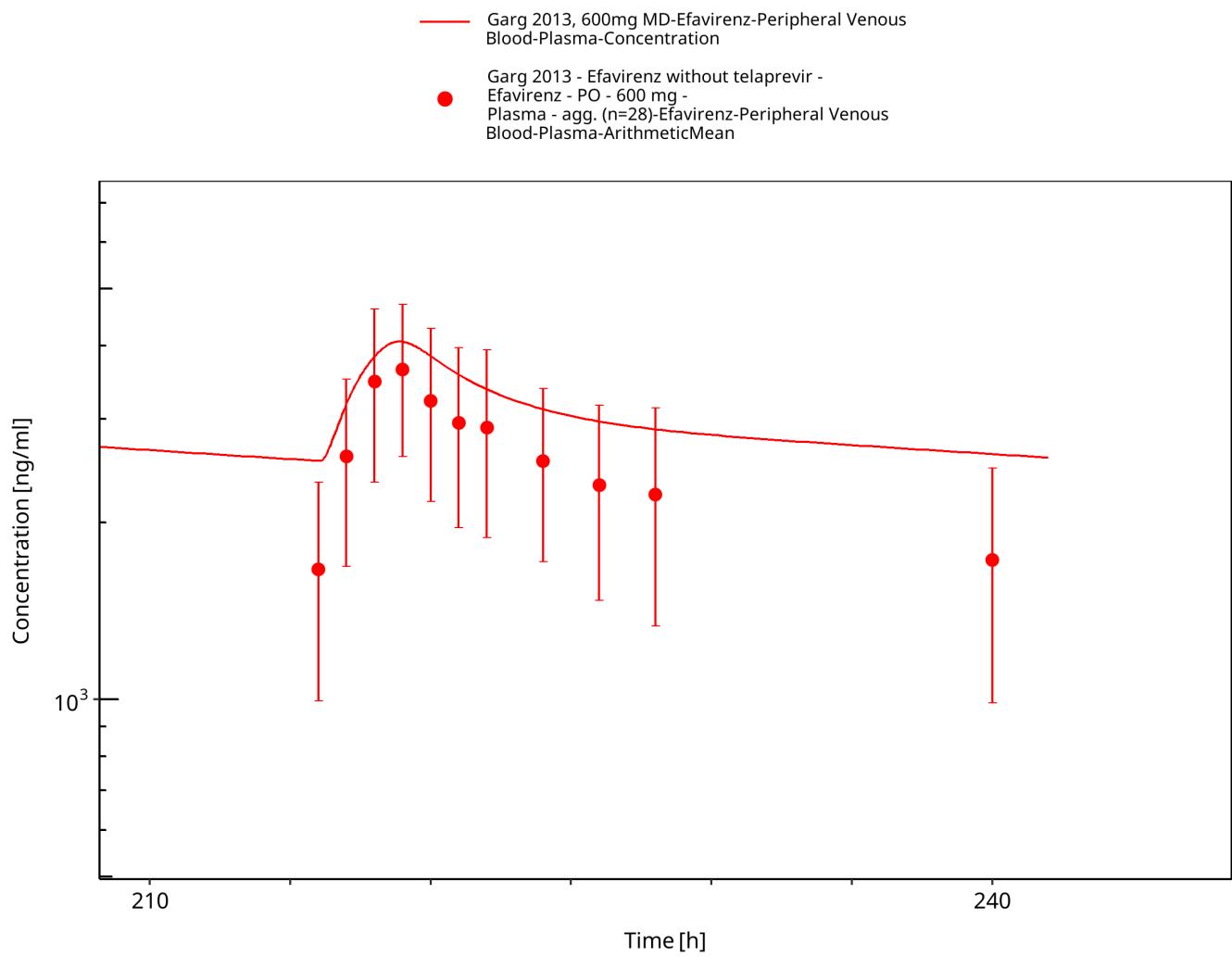


Figure 3-15: Garg 2013, 600mg MD

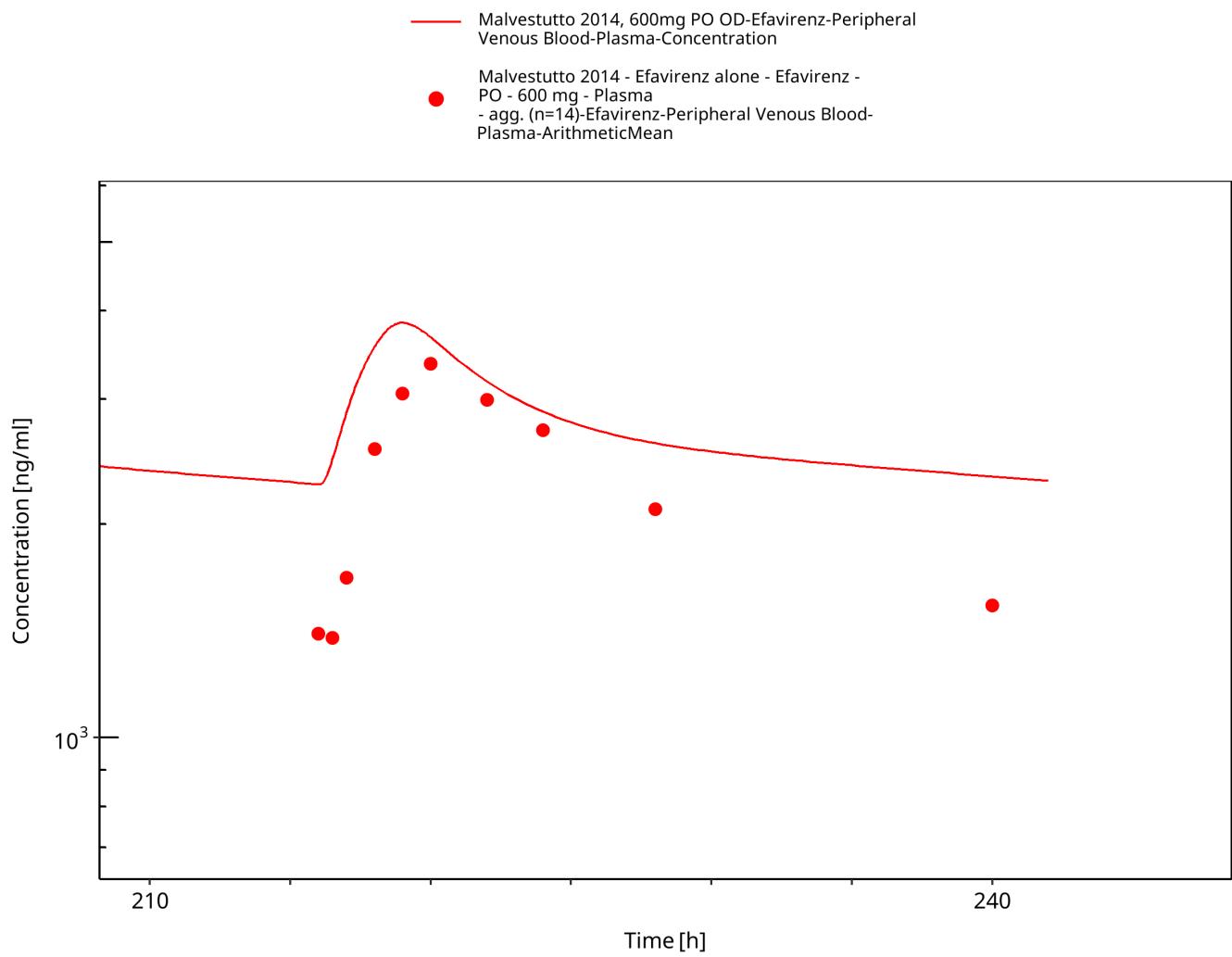


Figure 3-16: Malvestutto 2014, 600mg PO OD

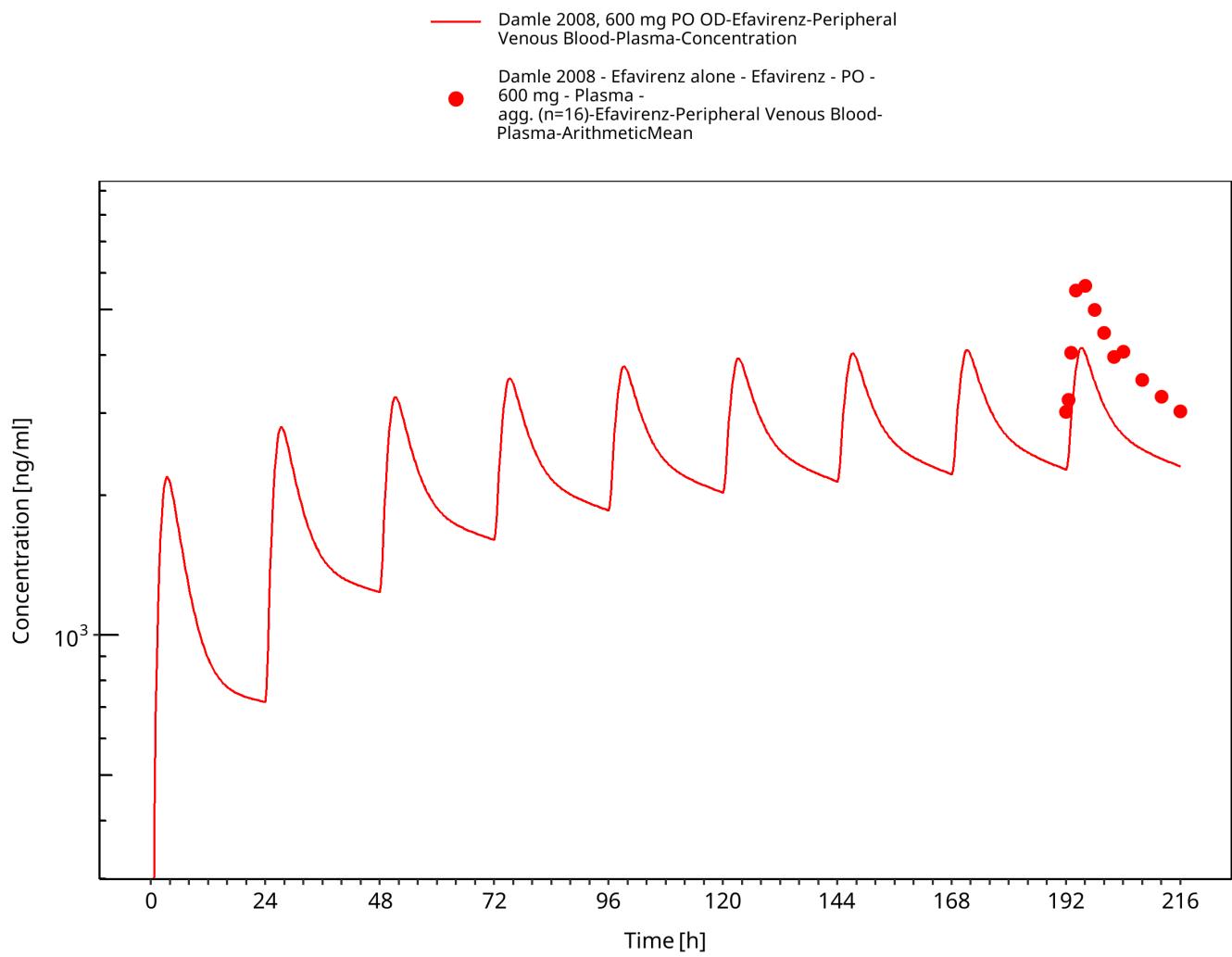


Figure 3-17: Damle 2008, 600 mg PO OD

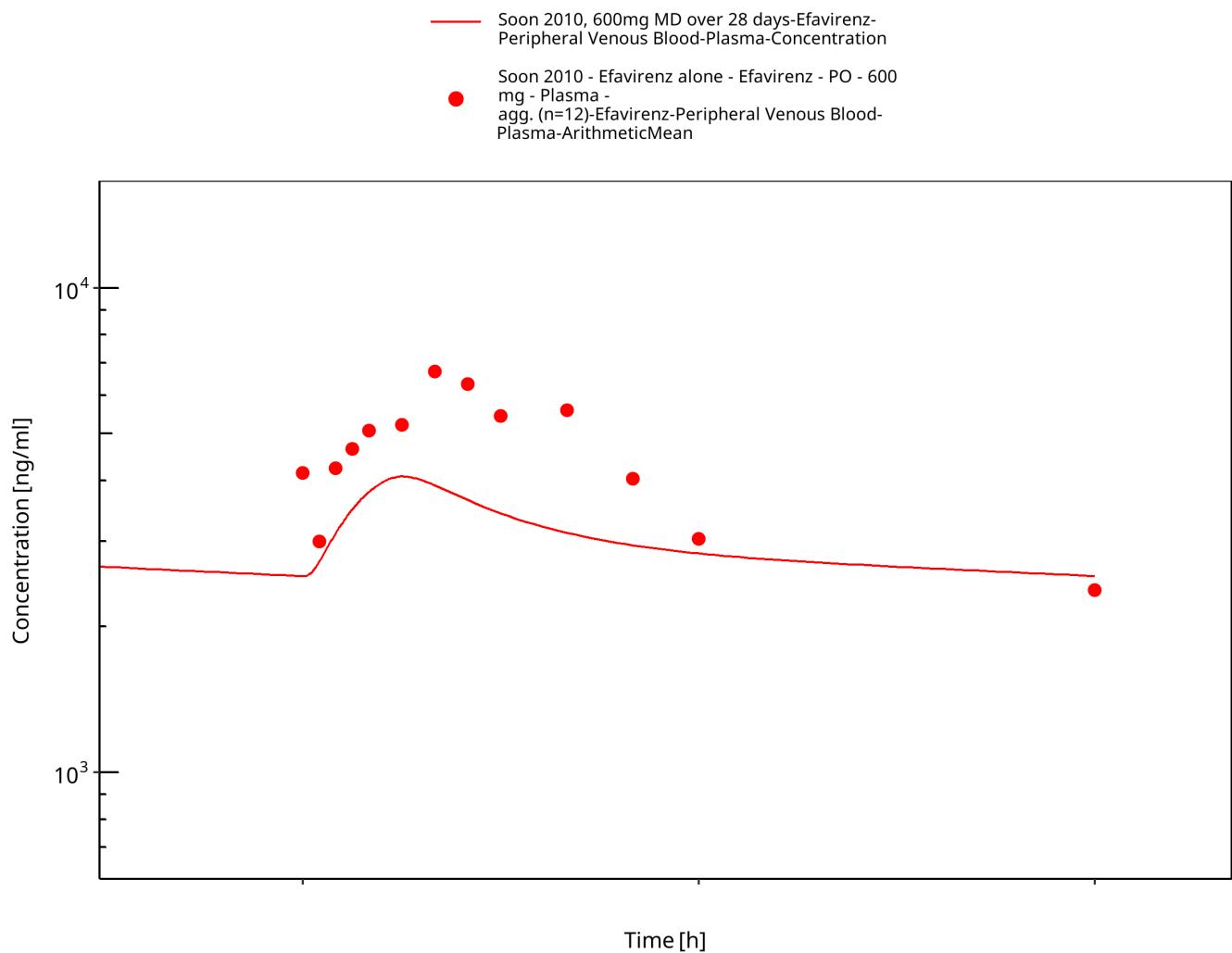


Figure 3-18: Soon 2010, 600mg MD over 28 days

3.3.2 Fitted interaction with Midazolam

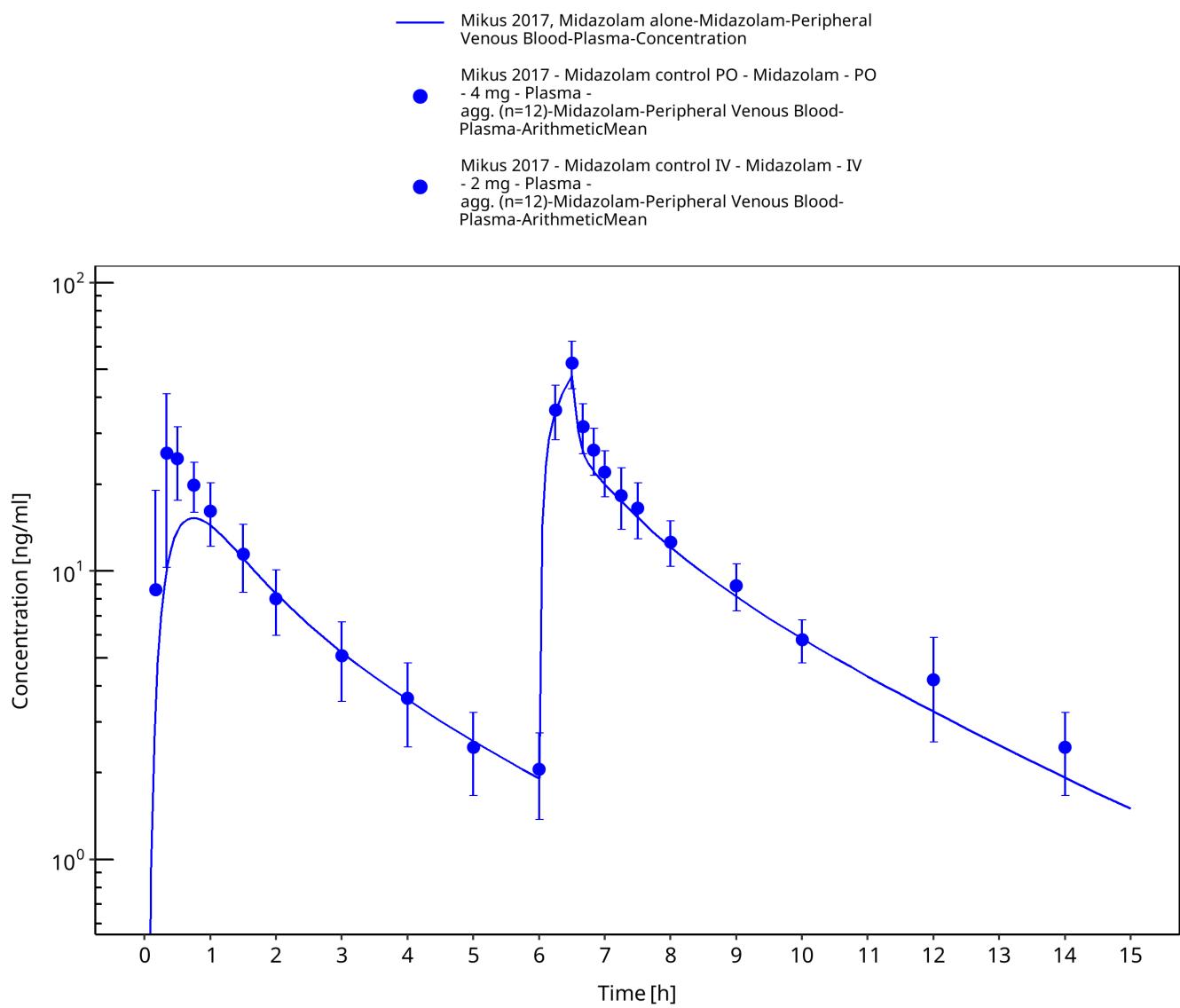


Figure 3-19: Mikus 2017, Midazolam alone

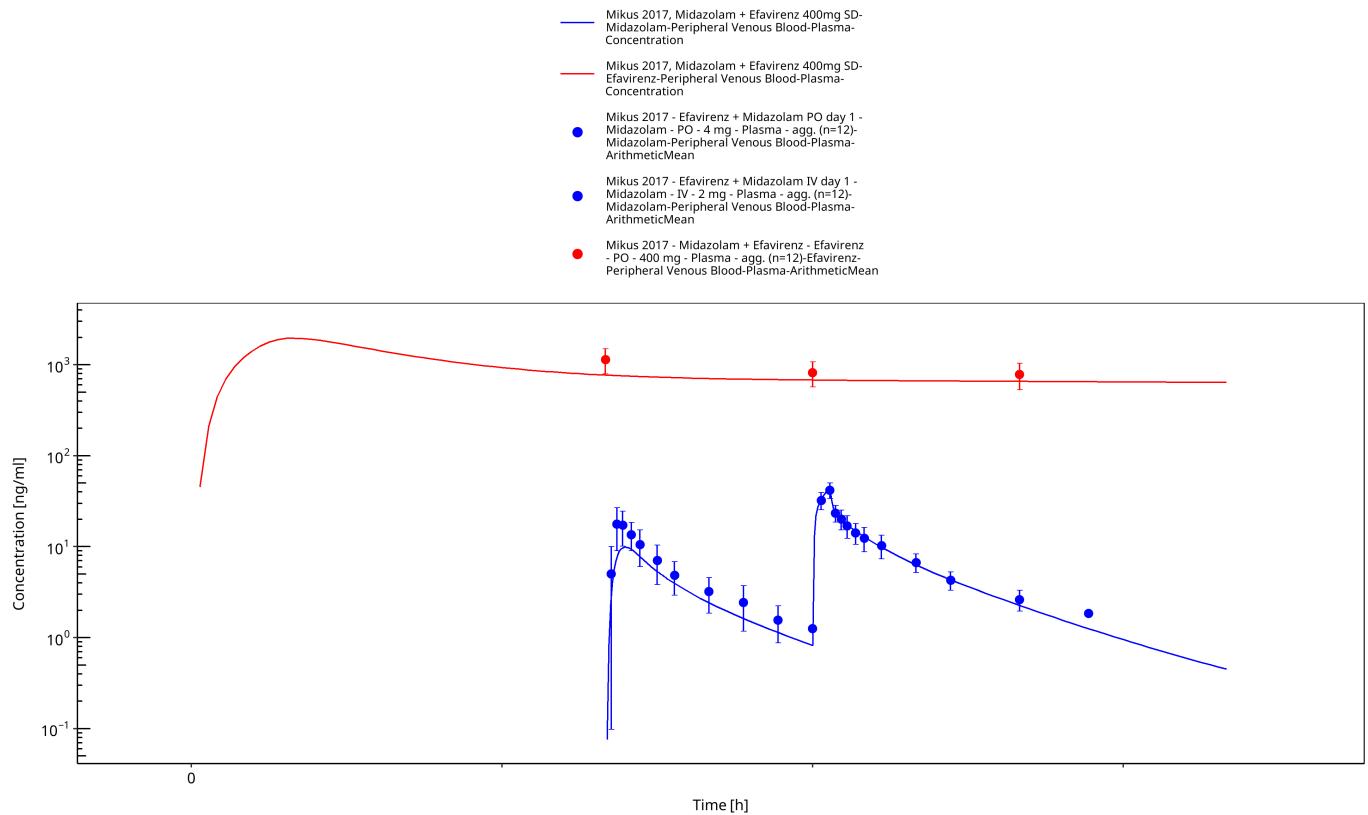


Figure 3-20: Mikus 2017, Midazolam + Efavirenz 400mg SD

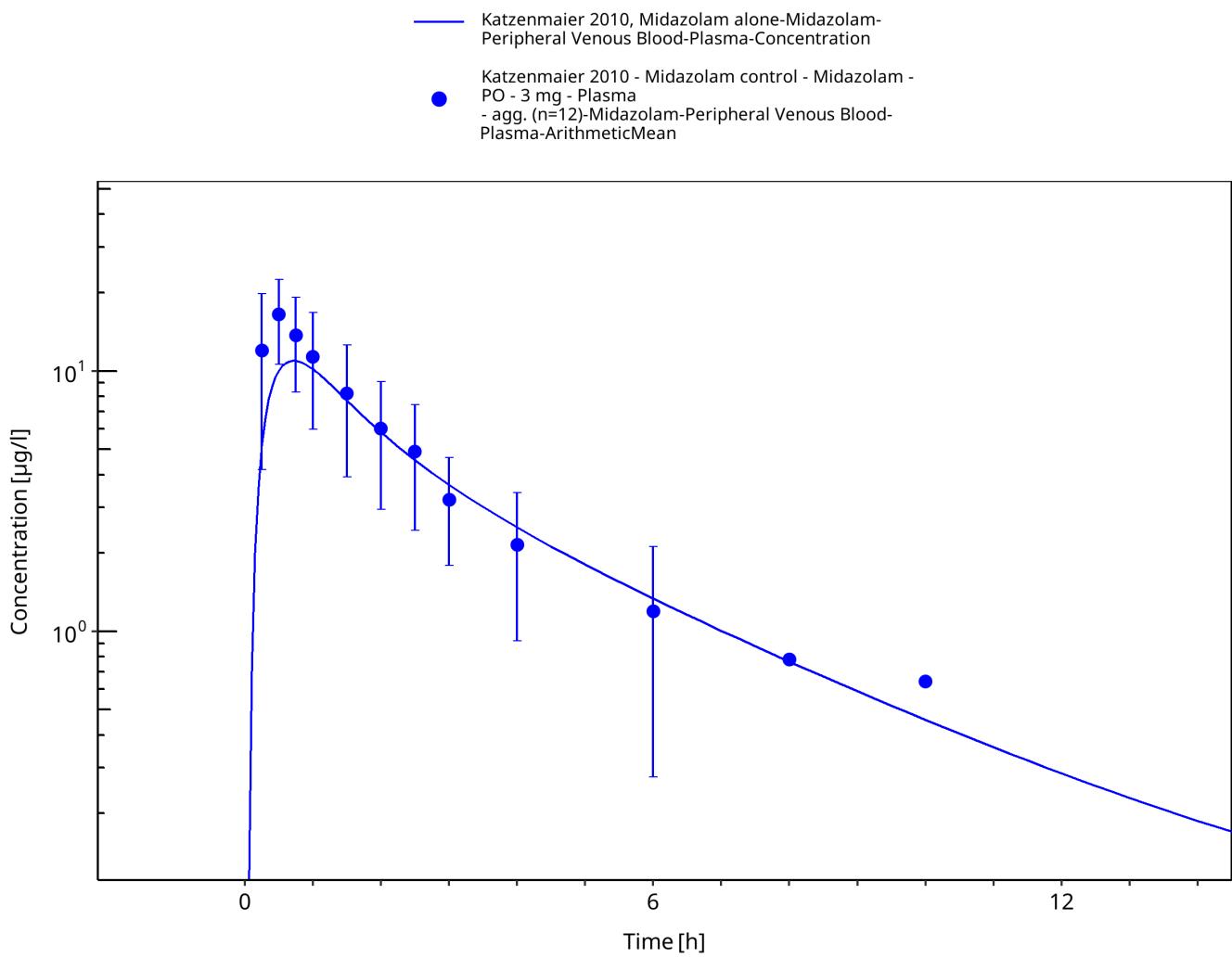


Figure 3-21: Katzenmaier 2010, Midazolam alone

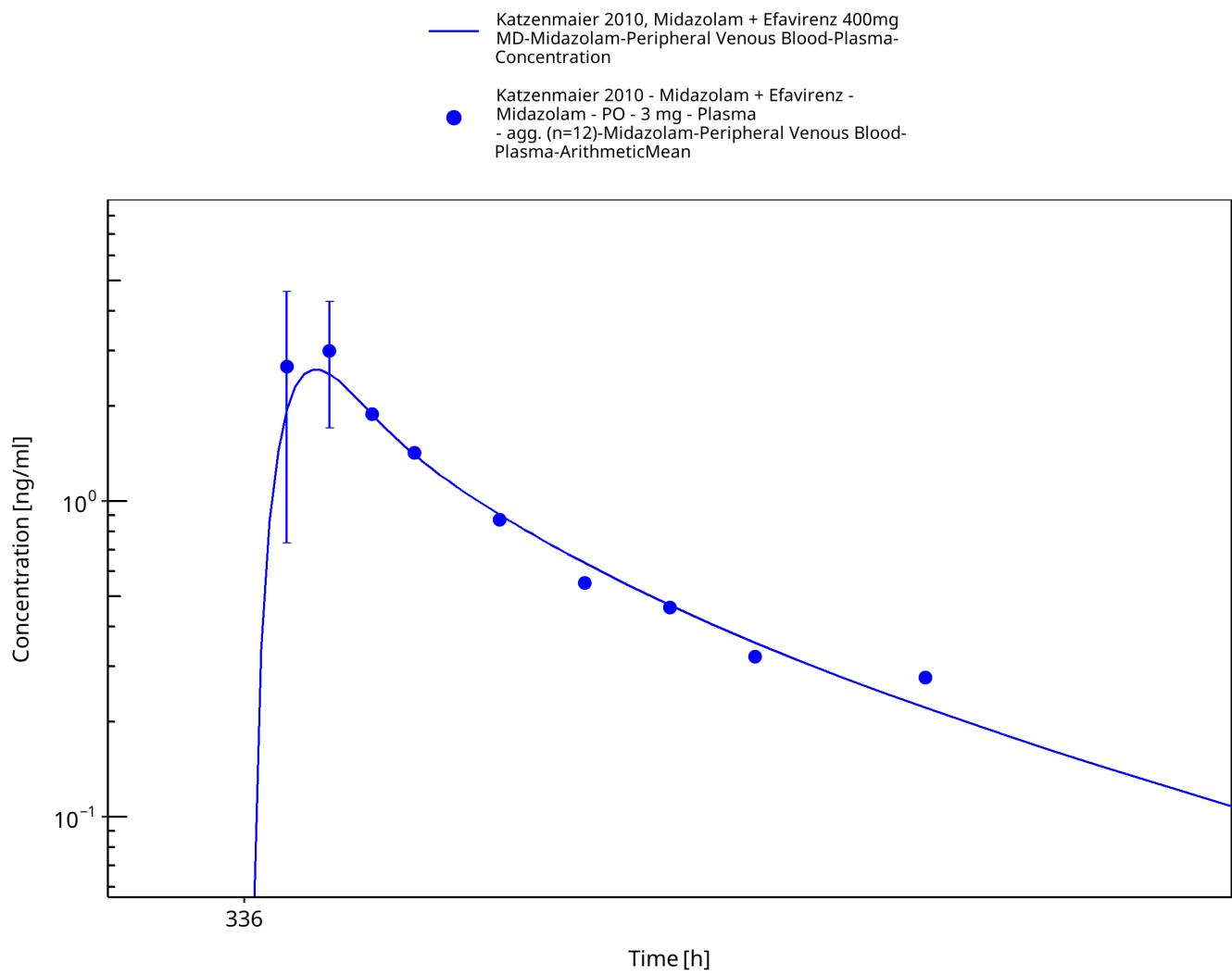


Figure 3-22: Katzenmaier 2010, Midazolam + Efavirenz 400mg MD

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of efavirenz after single and multiple oral administration of various doses to healthy adults.

Apart from drug-drug interaction parameters, all optimized parameters are in a close range to the measured or calculated values. EC₅₀ values for CYP3A4 and CYP2B6 were reduced approximately 100-fold in order to reach a relevant induction.

In conclusion, the presented efavirenz PBPK model is well-suited to be applied in drug-drug-interaction scenarios.

5 References

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