Building and evaluation of a PBPK model for montelukast in adults

Version	2.0-OSP12.1
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Montelukast-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

The presented model building and evaluation report evaluates the performance of a physiology-based pharmacokinetic (PBPK) model for montelukast in adults.

Montelukast is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene (CysLT) receptor 1, used in the maintenance treatment of asthma. Montelukast is mainly metabolized by CYP2C8 (72%) (Marzolini 2017). Montelukast is a strongly lipophilic drug. The final lipophilicity was estimated to be lower than the reported values, as with lipophilicity values above 3-4 log units the drug already reached maximal permeability levels. The final montelukast model applies metabolism by CYP2C8, and to a minor extend involved clearance by the enzymes CYP3A4/5 (16%), CYP2C9 (12%) and glomerular filtration (Marzolini 2017, Filppula 2011, Zhou 2017) and adequately described the pharmacokinetics of montelukast in adults.

The montelukast model is a whole-body PBPK model, allowing for dynamic translation between individuals. The montelukast report demonstrates the level of confidence in the montelukast PBPK model built with the OSP suite with regard to reliable predictions of montelukast pharmacokinetics (PK) in adults during model-informed drug development.

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 (Schlender 2016). 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 base mean model was built using data from the single dose escalation study to find an appropriate structure describing the PK of montelukast. The mean PK model was developed using a typical European individual. Unknown parameters 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.

Once the appropriate structural model was identified, additional parameters for different formulations were identified, if available.

A final PBPK model was established and simulations were compared to the reported data to evaluate model appropriateness and to assess model verification, by means of diagnostics plots and predicted versus observed concentration-time profiles, of which the results support an adequate prediction of the PK in adults.

During model building, uncertainties in data quality, as well as study differences may cause not being able to adequately describe the PK of all reported clinical studies.

2.2 Data used

2.2.1 In vitro / physicochemical data

A literature search was performed to collect available information on physicochemical properties of montelukast. The obtained information from literature is summarized in the table below and is used for model building.

Parameter	Unit	Value (reference)	Description
MW	g/mol	586.2 (Marzolini 2017)	Molecular weight
pKa		4.4 (Marzolini 2017)	Acid dissociation constant
Solubility (pH)	mg/mL	8.2E-06 (7) (Drugbank)	Solubility
logP		7.90 (Marzolini 2017)	Partition coefficient between octanol and water
fu		0.0018 (Marzolini 2017)	Fraction unbound
fe**		<0.002 (Marzolini 2017)	fraction of dose excreted unchanged in urine
CYP3A4-CLint	µl/min/pmol	1.8 (Marzolini 2017)	Cytochrome-P450 3A4 mediated intrinsic clearance
CYP3A5-CLint	µl/min/pmol	1.8 (Marzolini 2017)	Cytochrome-P450 3A5 mediated intrinsic clearance
CYP2C8-CLint	µl/min/pmol	3.6 (Marzolini 2017)	Cytochrome-P450 2C8 mediated intrinsic clearance
CYP2C9-CLint	µl/min/pmol	0.48 (Marzolini 2017)	Cytochrome-P450 2C9 mediated intrinsic clearance

** fe was matched by modeling unchanged renal excretion in PK-Sim as glomerular filtration (GF)

2.2.2 Clinical data

A literature search was performed to collect available clinical data on montelukast PK in adults.

The following publications were found in adults for model building and evaluation:

Publication	Study description
Cheng 1996	Pharmacokinetics, bioavailability, and safety of montelukast sodium (MK-0476) in healthy males and females
Fey 2014	Bioequivalence of two formulations of montelukast sodium 4 mg oral granules in healthy adults
Knorr 2000	Montelukast adult (10-mg film-coated tablet) and pediatric (5-mg chewable tablet) dose selections
Zhao 1997	Pharmacokinetics and bioavailability of montelukast sodium (MK-0476) in healthy young and elderly volunteers

2.3 Model parameters and assumptions

2.3.1 Absorption

Montelukast is a selective and orally active leukotriene receptor antagonist. For oral administration the following parameters play, amongst others, a role with regard to the absorption kinetics of a compound, which can be estimated with PBPK: solubility, lipophilicity and intestinal permeability. Montelukast is a strongly lipophilic drug. The final lipophilicity was estimated to be lower than the reported values, as with lipophilicity values above 3-4 log units the drug already reached maximal permeability levels.

2.3.2 Distribution

It has been determined that the protein binding of montelukast to plasma proteins exceeds 99% (FDA drug label). The fraction unbound (fu) of montelukast is built-in as 0.0018 as also reported by Marzolini et al. (Marzolini 2017).

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built-in in PK-Sim, observed clinical data was best described by choosing the partition coefficient calculation method by Rodgers and Rowland, and PK-Sim standard cell permeability calculation method. Specific organ permeability normalized to surface area was automatically calculated by PK-Sim.

2.3.3 Metabolism and Elimination

Montelukast is mainly metabolized by CYP2C8 (72%) (Marzolini 2017). The final montelukast model applies metabolism by CYP2C8, and to a minor involved clearance by the enzymes CYP3A4/5 (16%), CYP2C9 (12%) and glomerular filtration (Marzolini 2017, Filppula 2011, Zhou 2017) and adequately described the pharmacokinetics of montelukast in adults.

3 Results and Discussion

The PBPK model for montelukast was developed with clinical pharmacokinetic data covering intravenous as well as oral administration with a dose range of 2-10mg including single dose and multiple dose clinical data, for different types of tablet formulations.

During the model fitting, the following parameters were estimated (all other parameters were fixed to reported values):

- Lipophilicity
- Specific intestinal permeability (transcellular)
- Formulation kinetics : Weibull function parameters (Dissolution shape and Dissolution time) for
  - Singular tablet
  - Sandoz tablet
  - Film-coated tablet
  - Chewable tablet

The fit resulted in an adequate description of the clinical data. Overall the model results show that the PBPK model of montelukast adequately described the data for intravenous administration for single dose. The estimated clearance values as a fraction of the reported clearance using only intravenous data resulted in a value close to 1, which allowed to fix the clearance parameters to the reported values. This was done to prevent the otherwise high correlation with the estimated absorption related parameters (dissolution kinetics for the different tablet formulations, lipophilicity and intestinal permeability during model building).

3.1 Montelukast final input parameters

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

Compound: Montelukast

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	8.2E-06 mg/ml	Internet-source: Drugbank (ALOGPS)	Water Solubility (ALOGPS)	True
Reference pH	7	Internet-source: Drugbank (ALOGPS)	Water Solubility (ALOGPS)	True
Lipophilicity	3.3153408097 Log Units	Parameter Identification-Parameter Identification	Fit	True
Fraction unbound (plasma, reference value)	0.0018	Publication-Marzolini 2017	Marzolini 2017	True
Specific intestinal permeability (transcellular)	0.0819181318 cm/min	Parameter Identification-Parameter Identification	Fit	True
Cl	1	Publication-Marzolini 2017		
Is small molecule	Yes			
Molecular weight	586.2 g/mol	Publication-Marzolini 2017		
Plasma protein binding partner	Albumin			

Calculation methods

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

Processes

Metabolizing Enzyme: CYP2C8-Marzolini 2017

Molecule: CYP2C8

Parameters

Name	Value	Value Origin
In vitro CL/recombinant enzyme	3.6 µl/min/pmol rec. enzyme	Publication-Marzolini 2017

Metabolizing Enzyme: CYP3A4-Marzolini 2017

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
In vitro CL/recombinant enzyme	1.8 µl/min/pmol rec. enzyme	Publication-Marzolini 2017

Metabolizing Enzyme: CYP2C9-Marzolini 2017

Molecule: CYP2C9

Parameters

Name	Value	Value Origin
In vitro CL/recombinant enzyme	0.48 µl/min/pmol rec. enzyme	Publication-Marzolini 2017

Metabolizing Enzyme: CYP3A5-Filppula 2011

Molecule: CYP3A5

Parameters

Name	Value	Value Origin
In vitro CL/recombinant enzyme	0.16 µl/min/pmol rec. enzyme	Publication-Marzolini 2017

Systemic Process: Glomerular Filtration-Marzolini 2017

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Marzolini 2017

Formulation: Filmcoated tablet

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	130.7856594083 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 15' on 2019-03-21 11:13
Lag time	0 min	
Dissolution shape	1.309742335	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 15' on 2019-03-21 11:13
Use as suspension	Yes	

Formulation: Chewable tablet

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	70.3249031902 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 15' on 2019-03-21 11:13
Lag time	0 min	
Dissolution shape	1.2919957494	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 15' on 2019-03-21 11:13
Use as suspension	Yes	

Formulation: Sandoz Oral granules

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	96.1730639663 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 15' on 2019-03-21 11:13
Lag time	0 min	
Dissolution shape	1.9271553023	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 15' on 2019-03-21 11:13
Use as suspension	Yes	

Formulation: Singulair mini Oral granules

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	133.9238802749 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 15' on 2019-03-21 11:13
Lag time	0 min	
Dissolution shape	1.6357552071	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 15' on 2019-03-21 11:13
Use as suspension	Yes	

3.2 Montelukast Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for montelukast PBPK model performance (Individually simulated versus observed plasma concentration and weighted residuals versus time, including the geometric mean fold error (GMFE)) of all data used for model building.

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

Group	GMFE
Montelukast Chewable Tablet	1.17
Montelukast Filmcoated Tablet	1.38
Montelukast iv	1.32
Montelukast Oral Granules	1.31
All	1.31
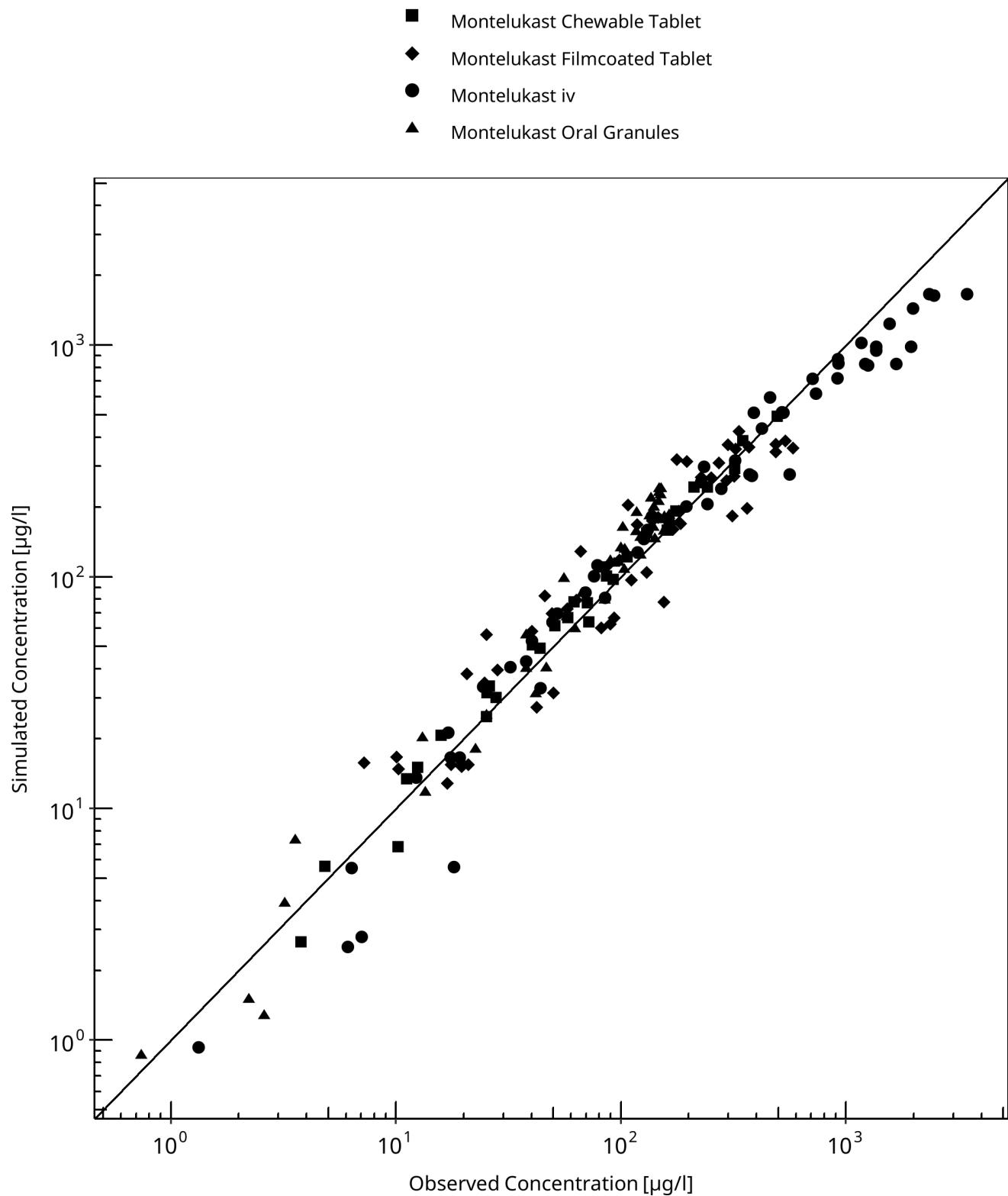
Figure 3-1: Goodness of fit plot for concentration in plasma.
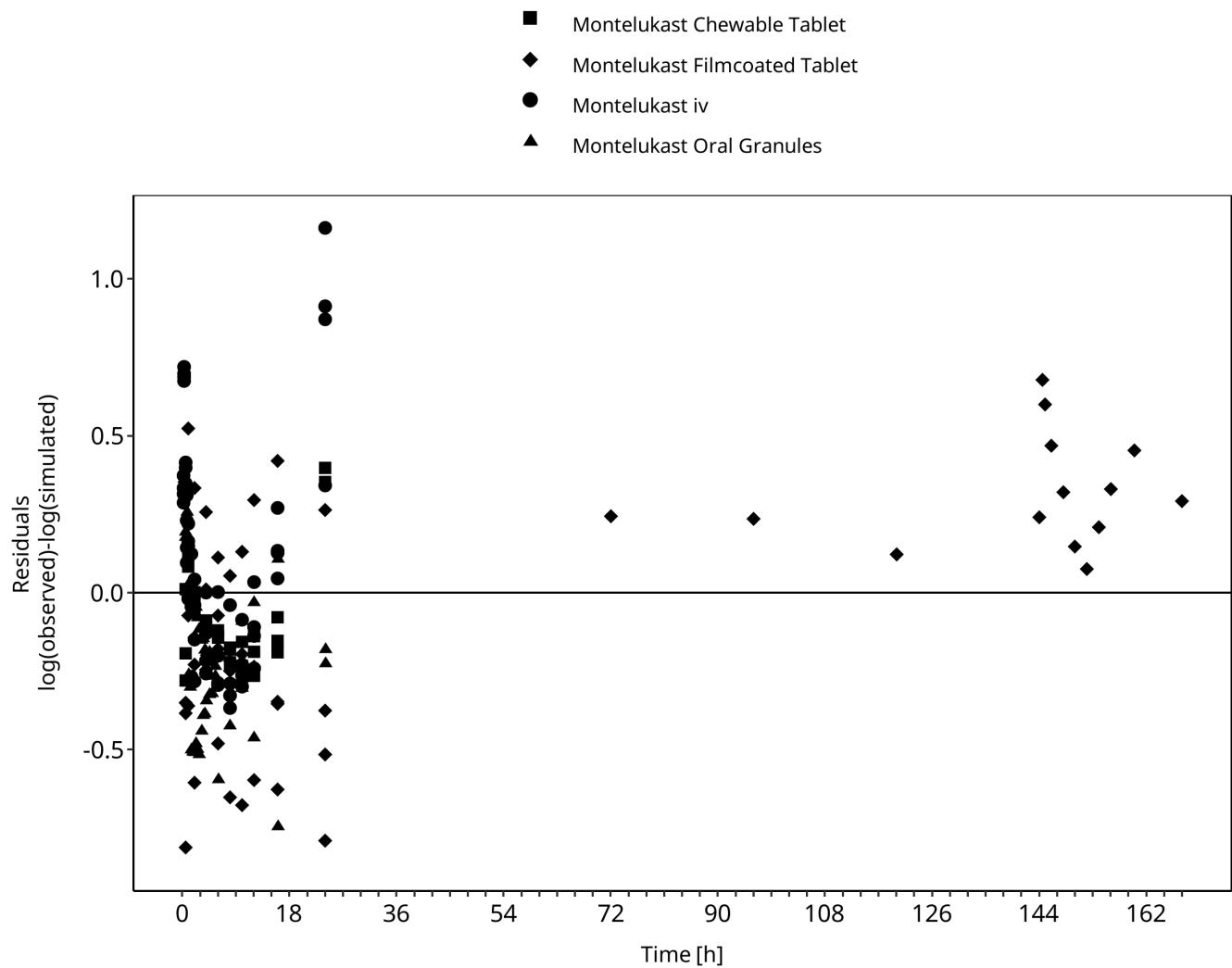
Figure 3-2: Goodness of fit plot for concentration in plasma.

3.3 Montelukast Concentration-Time profiles

Simulated versus observed plasma concentration-time profiles of all data are listed below.
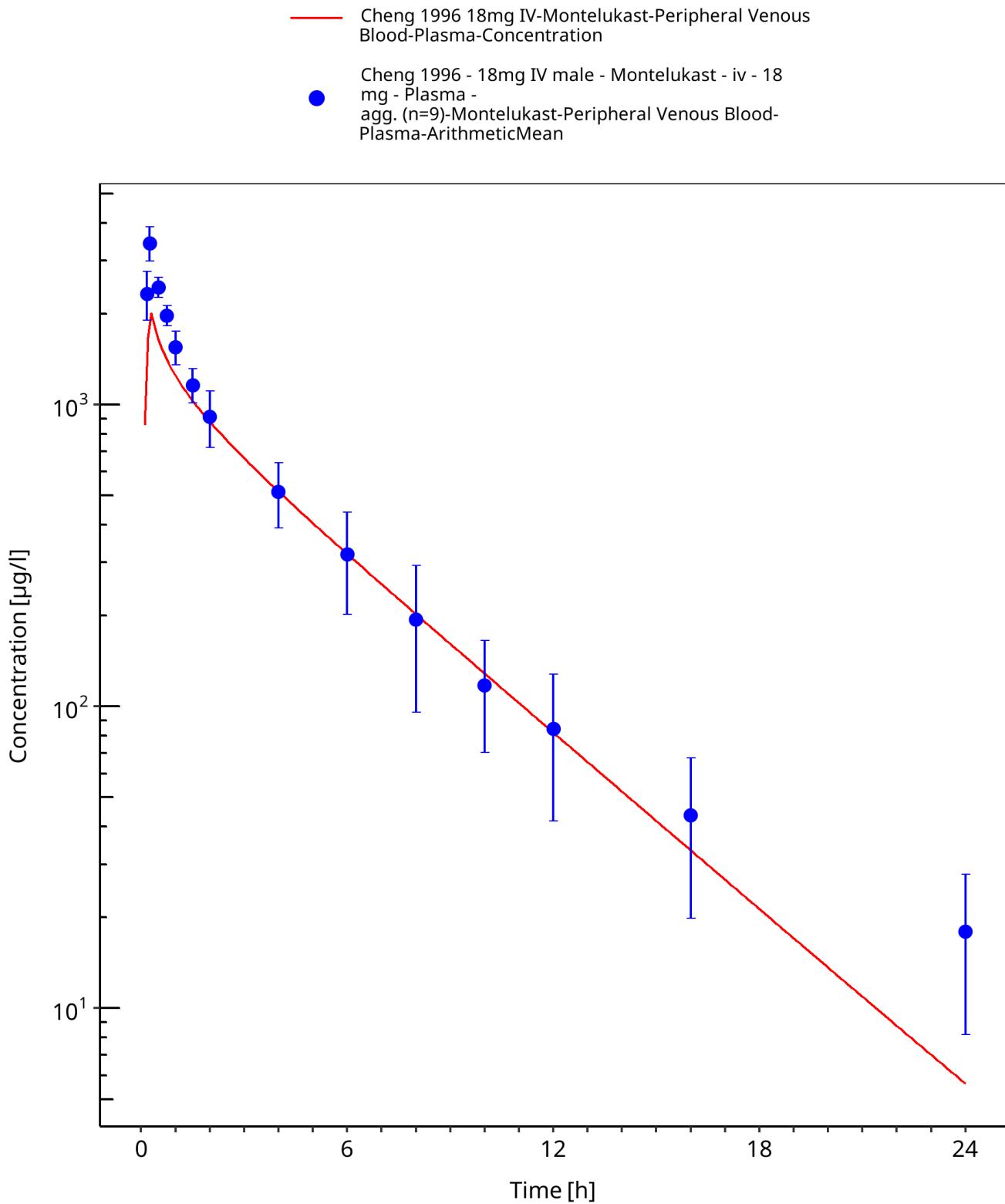
Figure 3-3: Time Profile Analysis
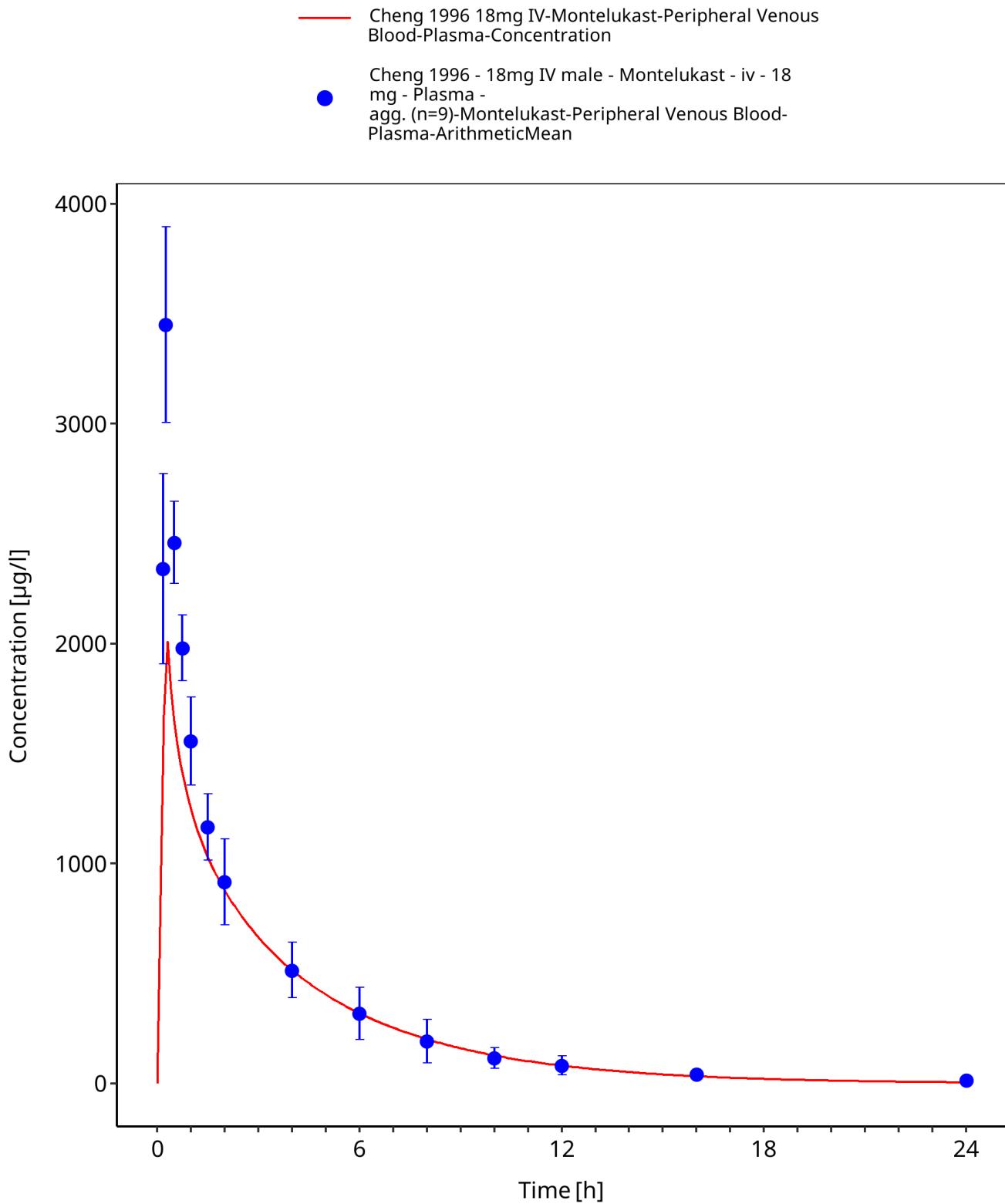
**Figure 3-4: Time Profile Analysis 1**
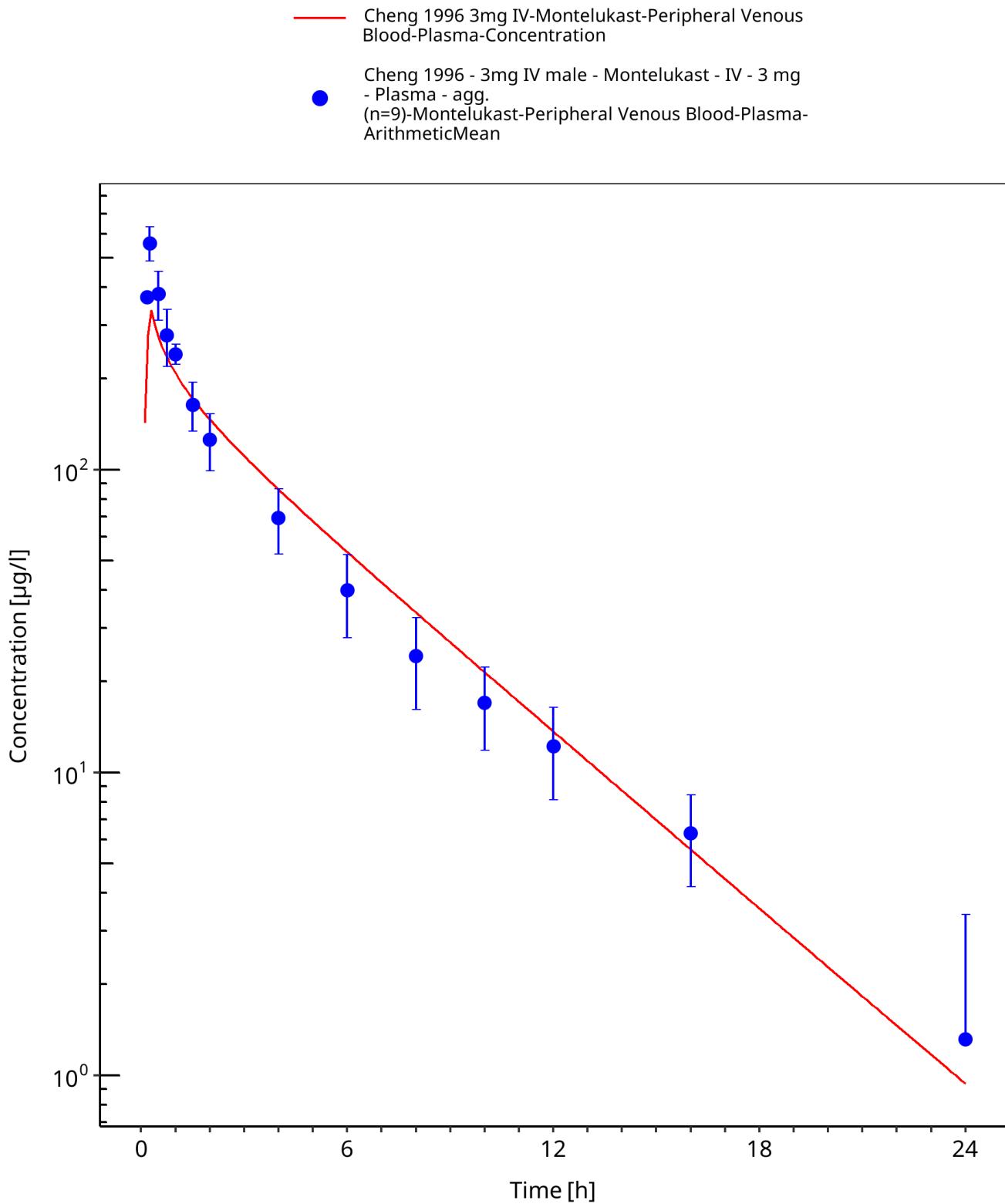
**Figure 3-5: Time Profile Analysis**
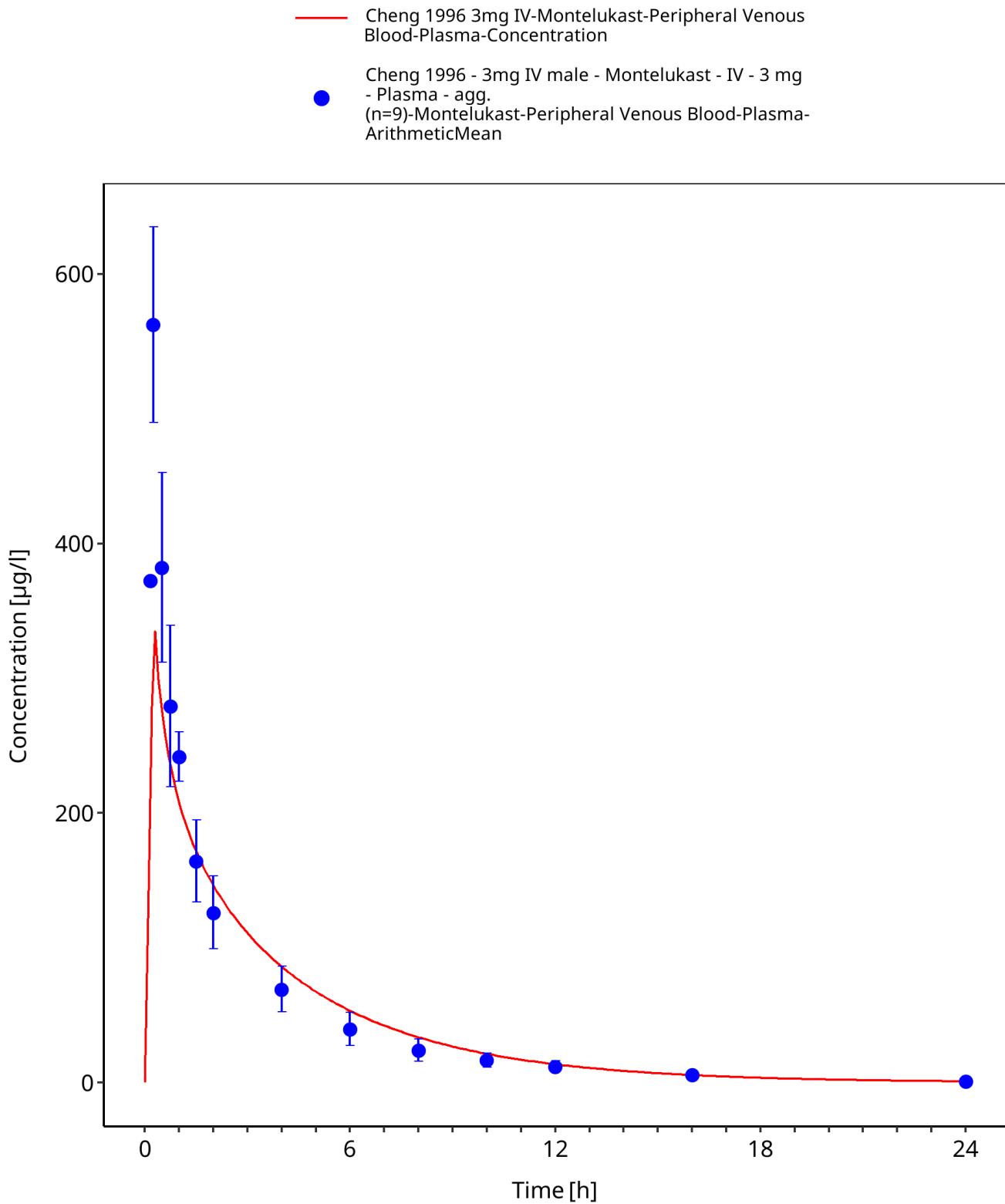
Figure 3-6: Time Profile Analysis 1
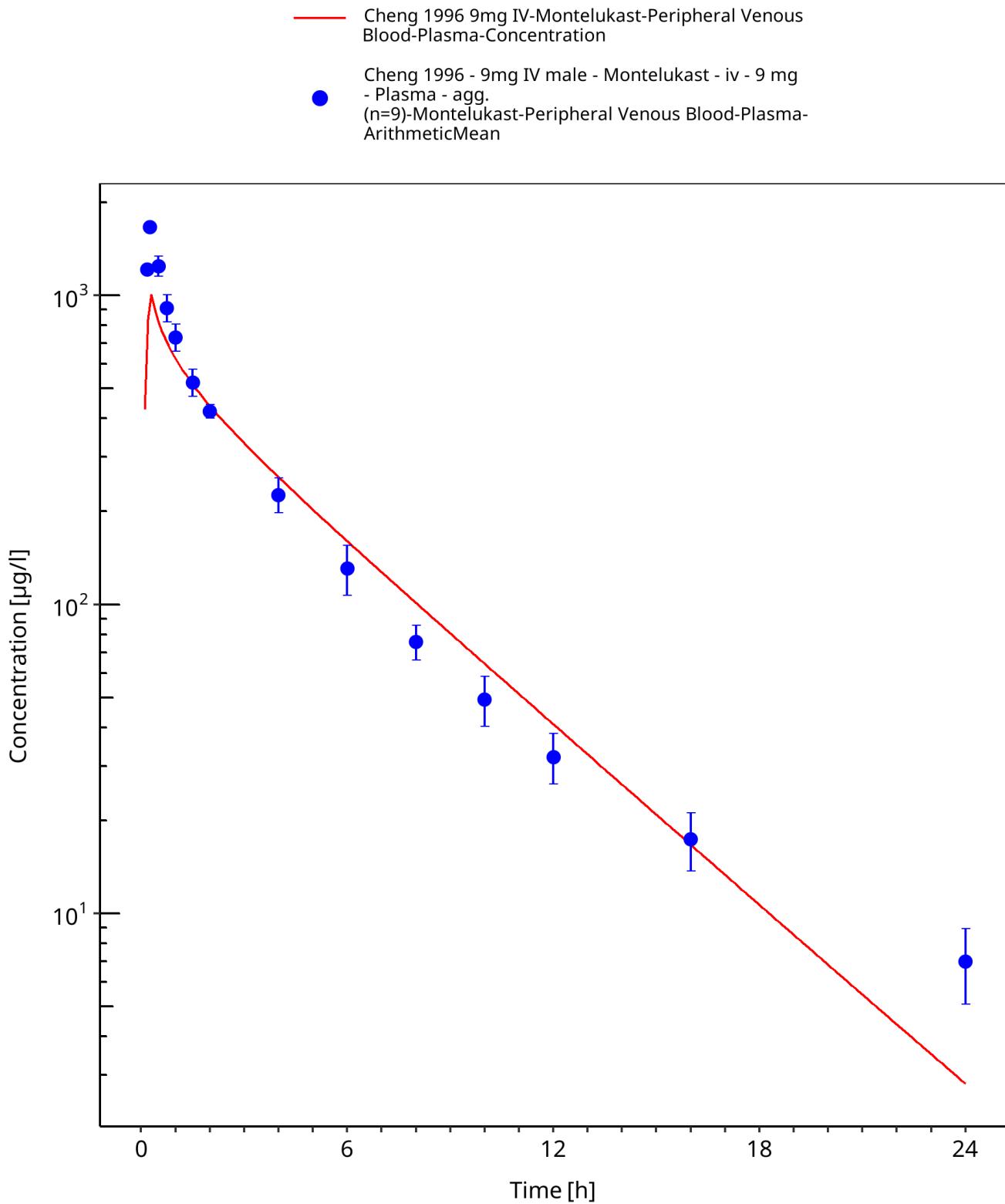
Figure 3-7: Time Profile Analysis
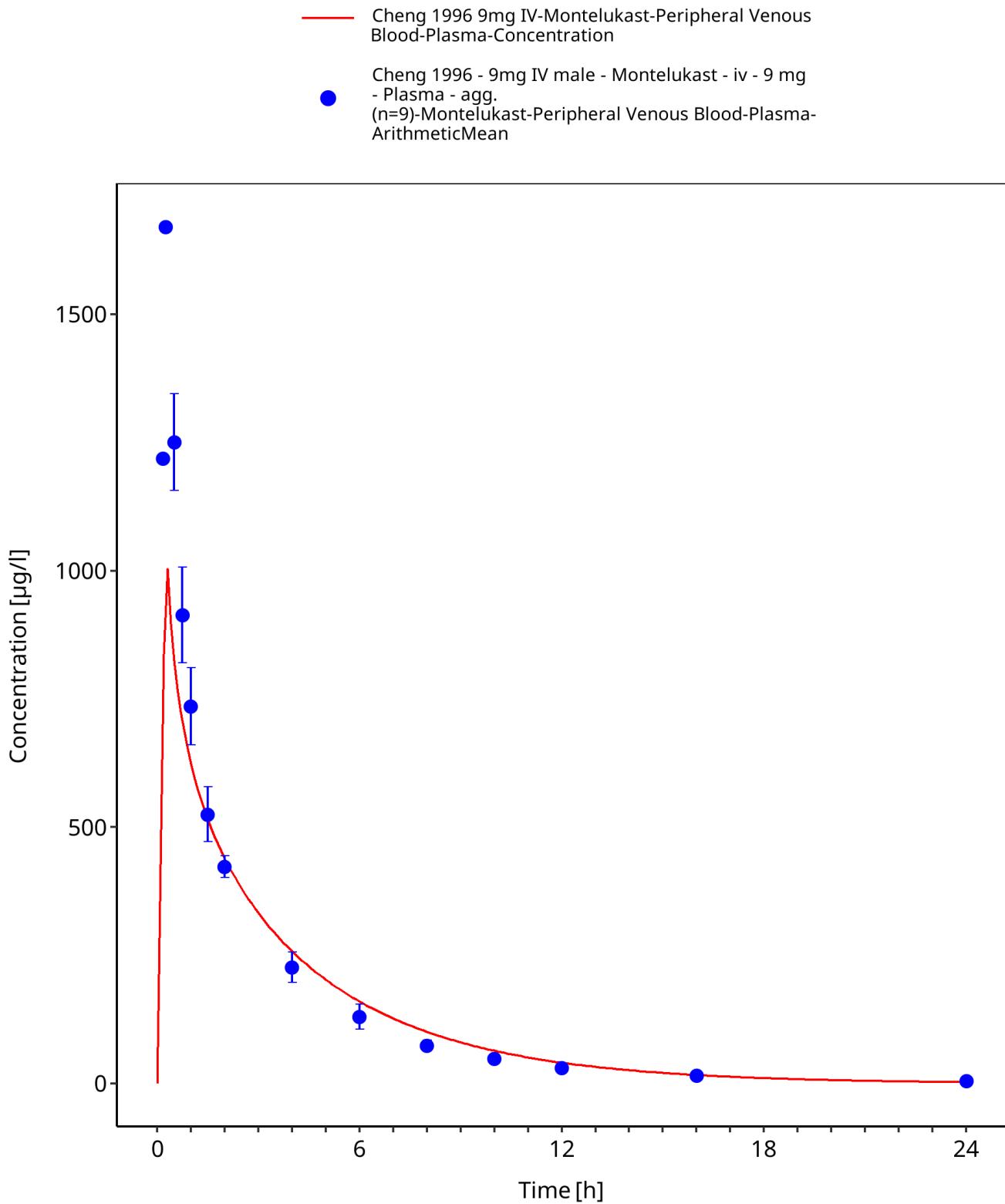
Figure 3-8: Time Profile Analysis 1
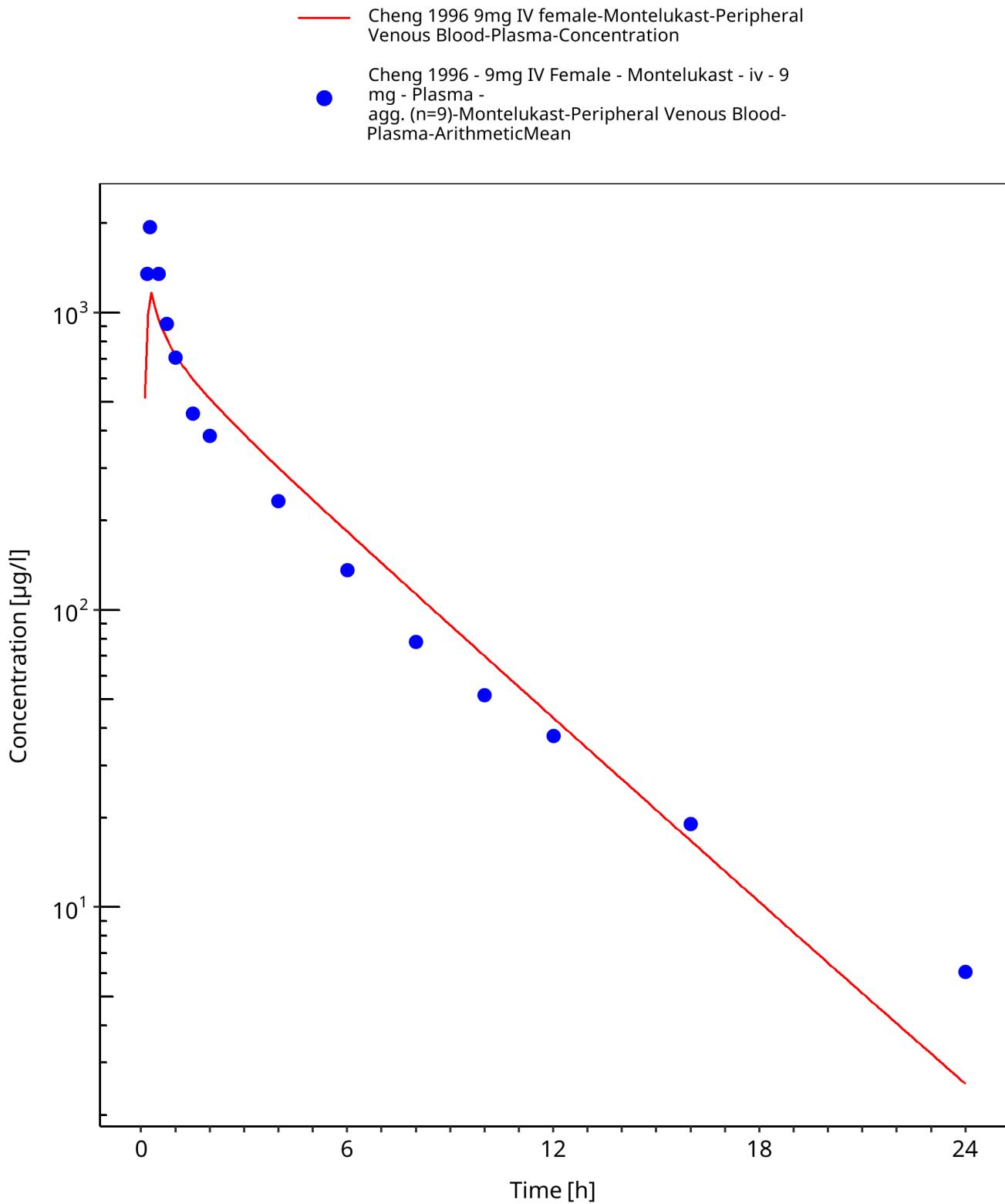
Figure 3-9: Time Profile Analysis
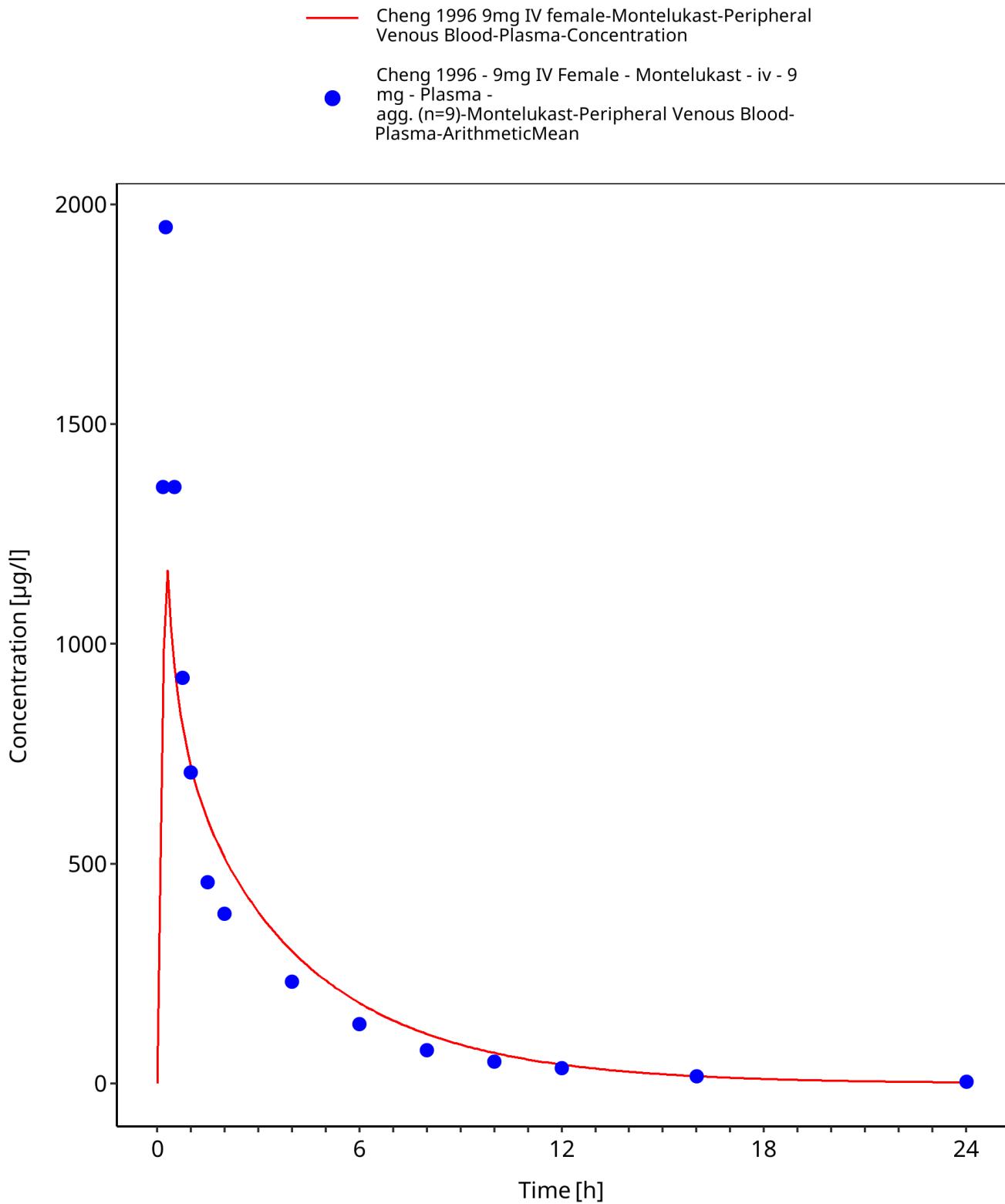
Figure 3-10: Time Profile Analysis 1
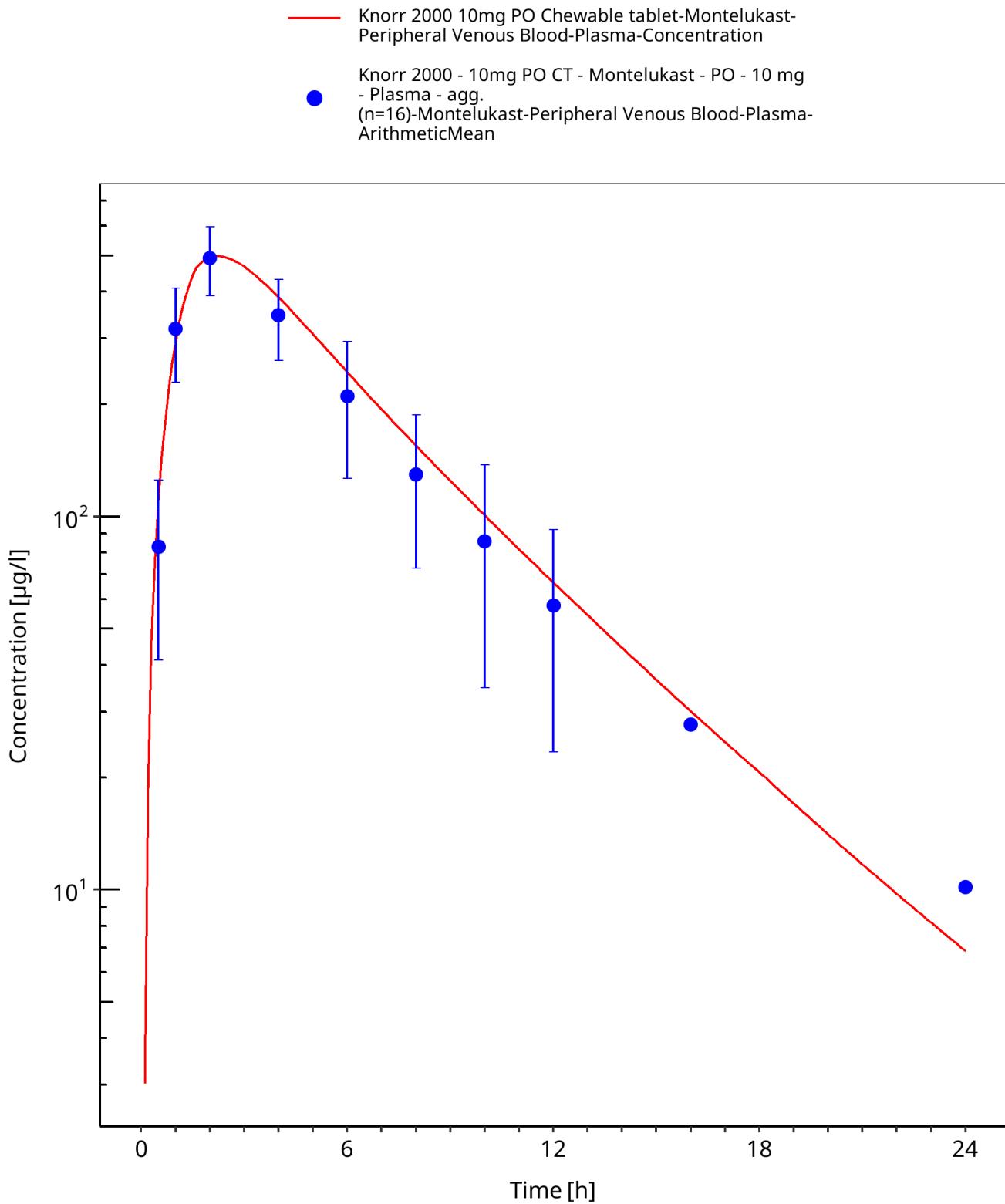
Figure 3-11: Time Profile Analysis
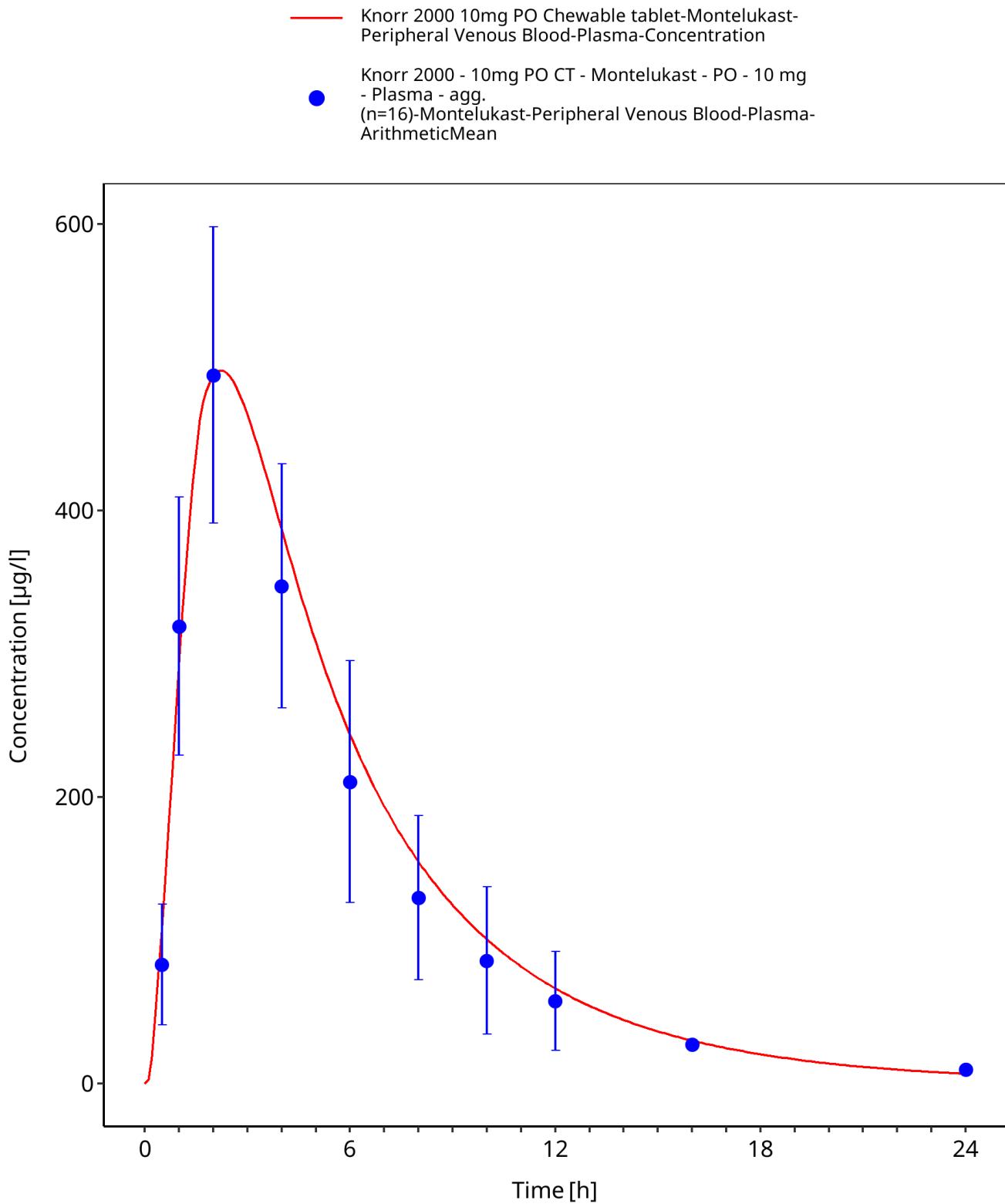
Figure 3-12: Time Profile Analysis 1
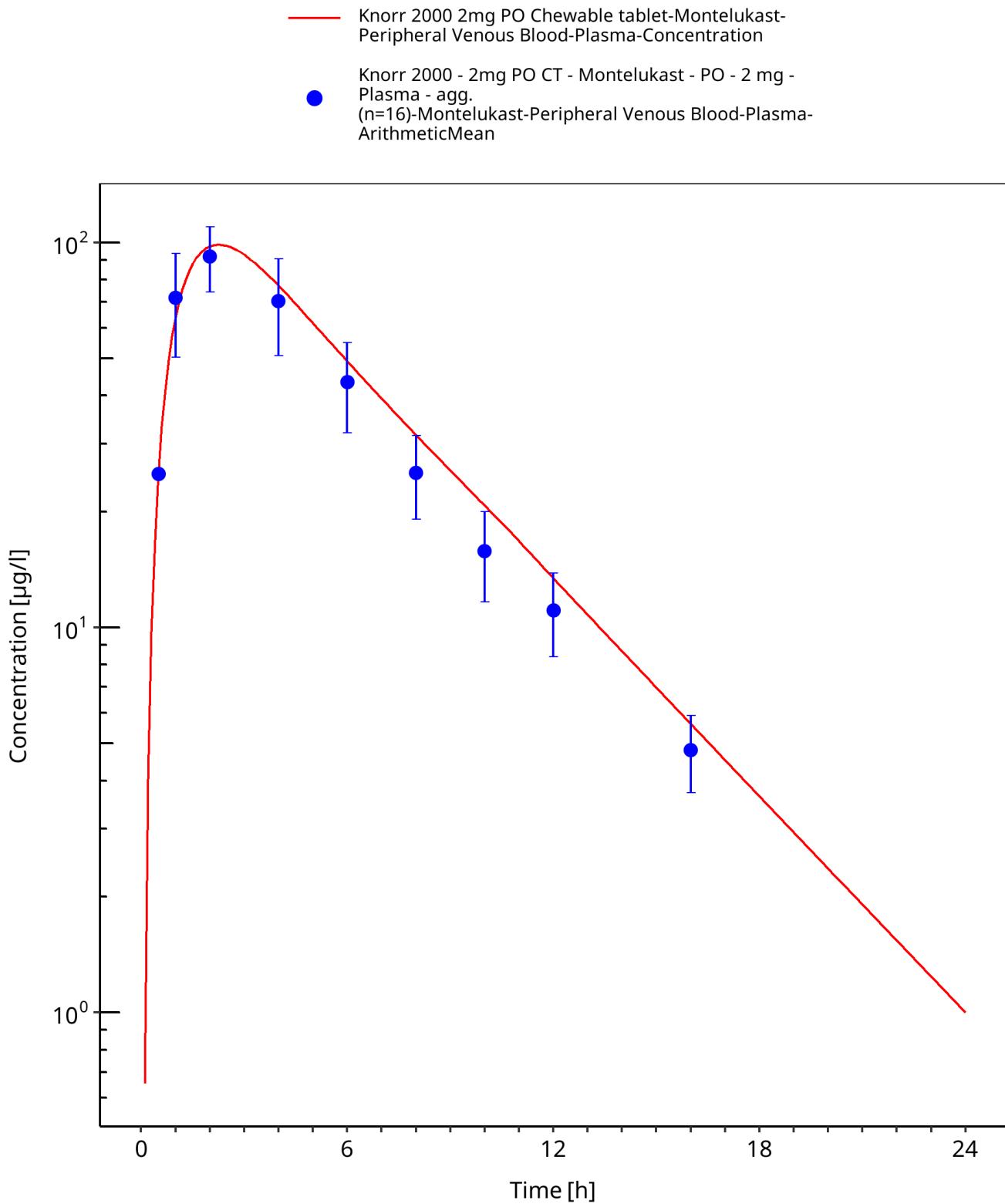
Figure 3-13: Time Profile Analysis
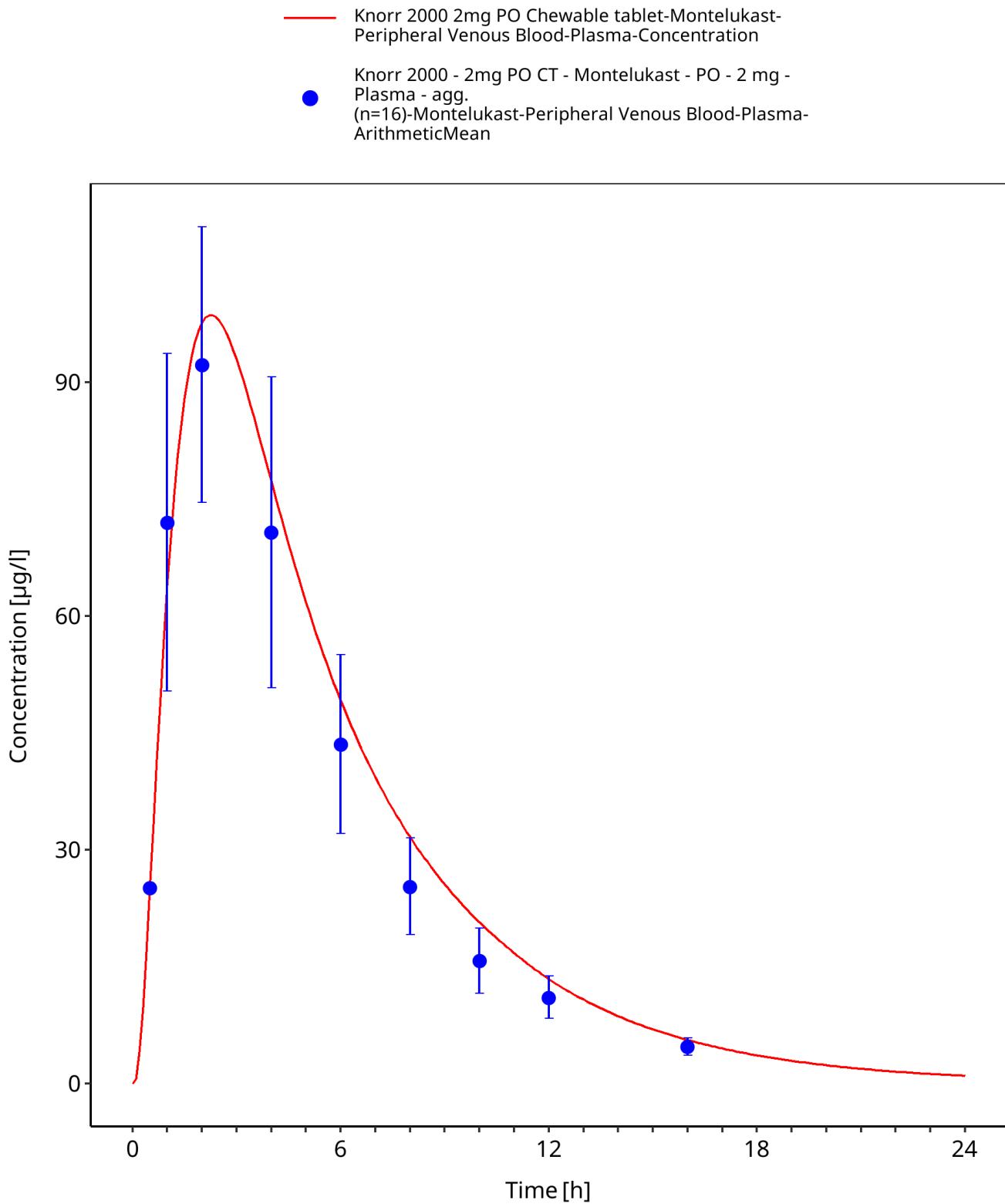
Figure 3-14: Time Profile Analysis 1

Knorr 2000 5mg PO Chewable tablet-Montelukast-
Peripheral Venous Blood-Plasma-Concentration

Knorr 2000 - 5mg PO CT - Montelukast - PO - 5 mg -
Plasma - agg.
(n=16)-Montelukast-Peripheral Venous Blood-Plasma-
ArithmeticMean
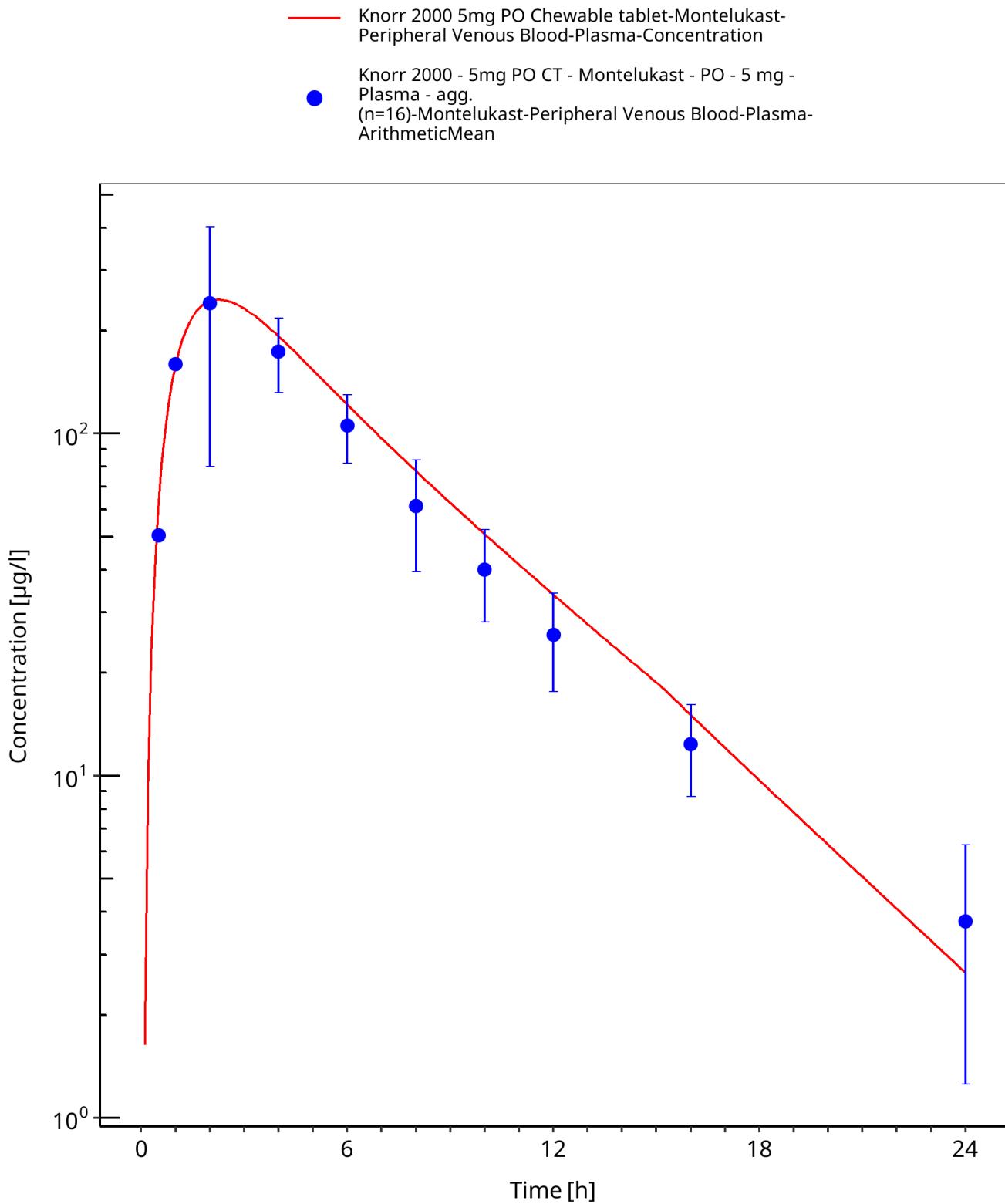
Figure 3-15: Time Profile Analysis
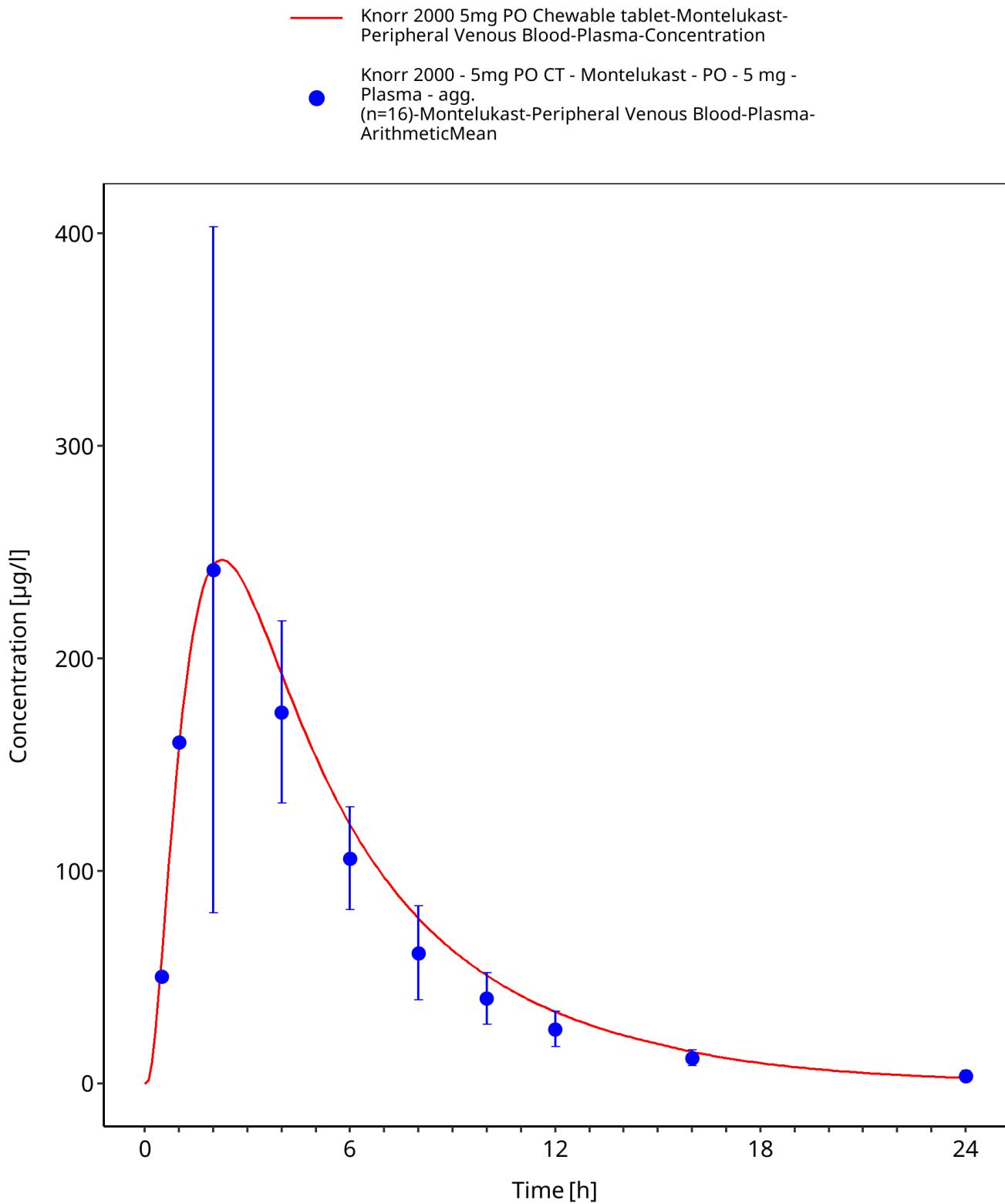
Figure 3-16: Time Profile Analysis 1
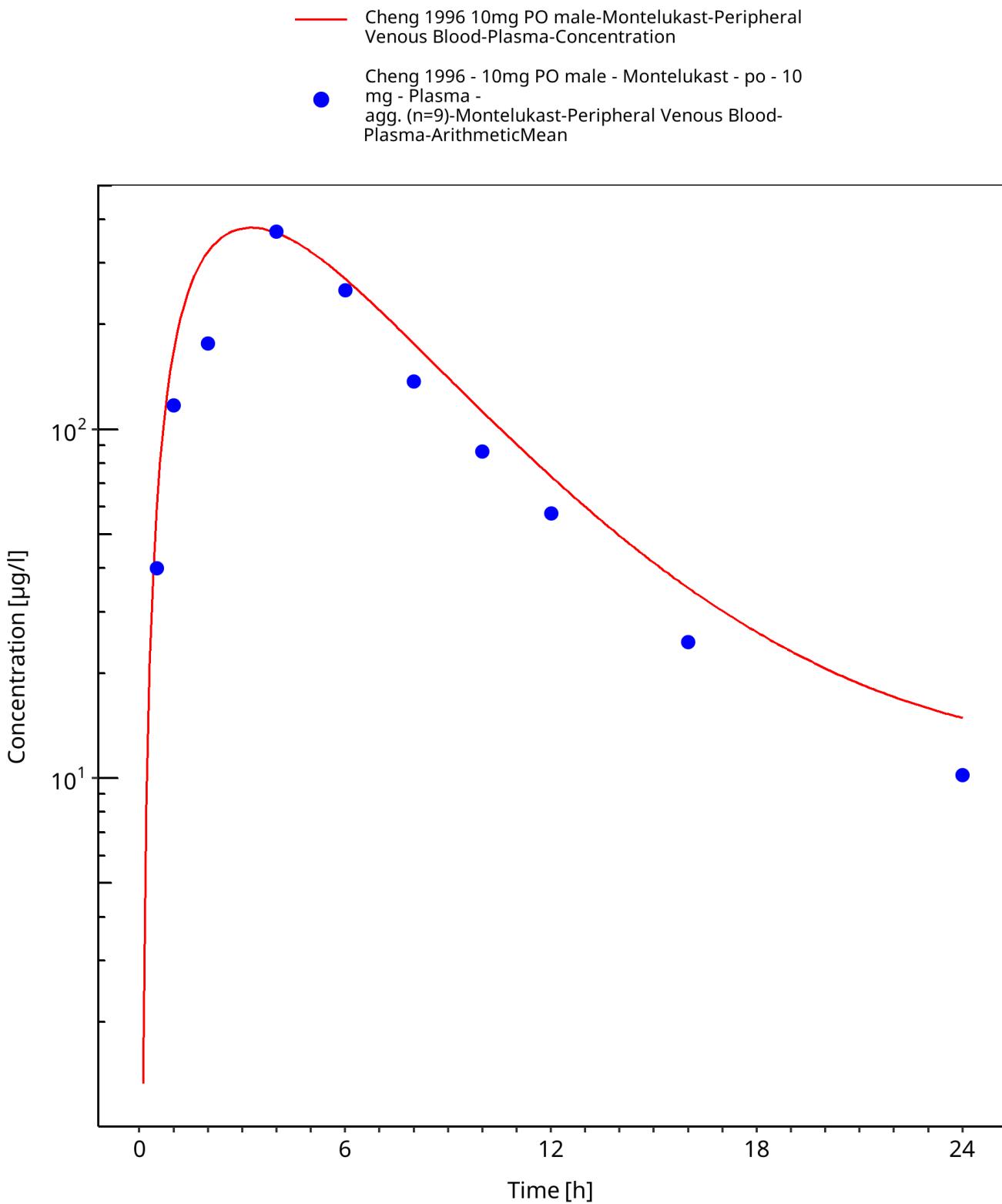
Figure 3-17: Time Profile Analysis
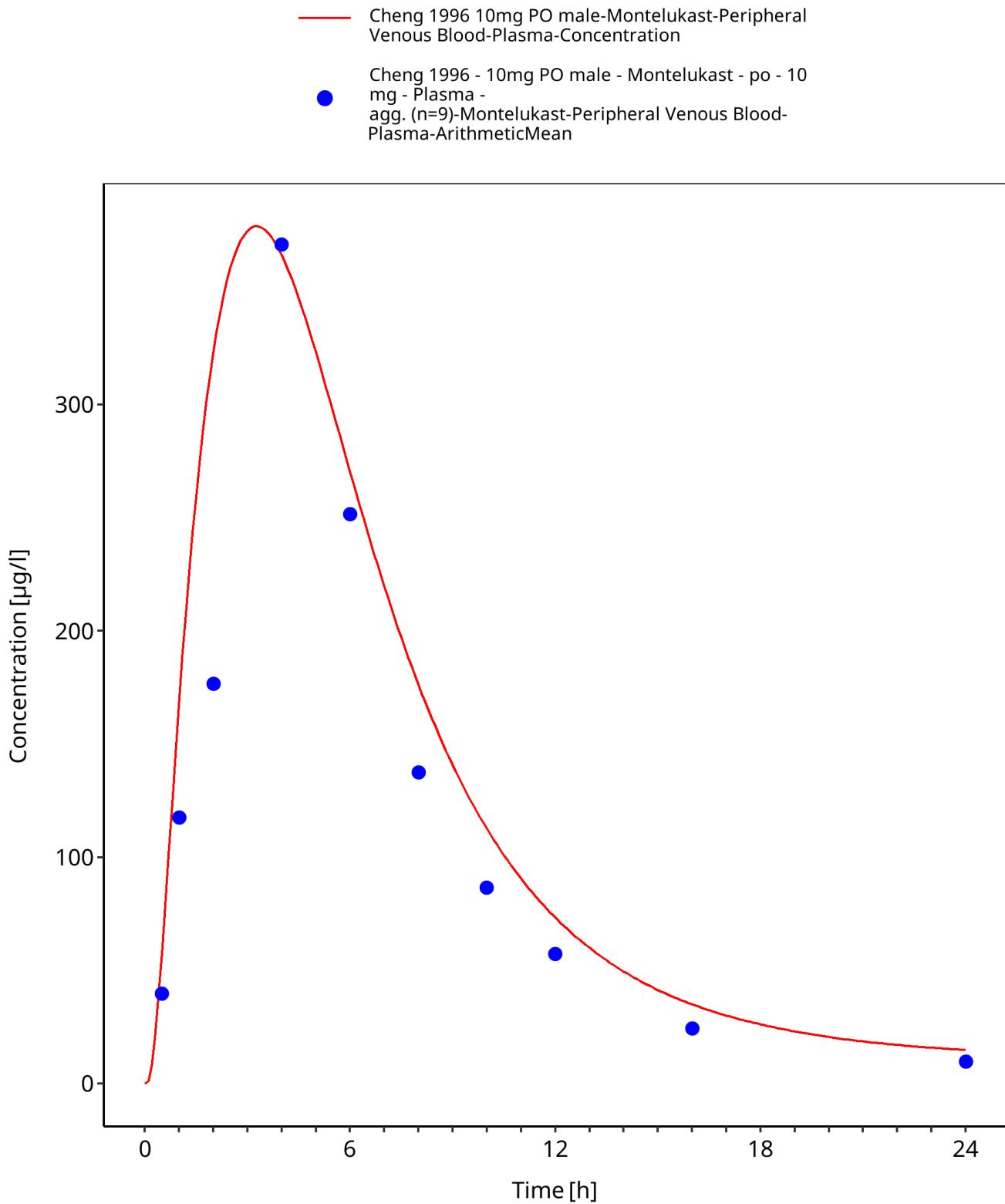
Figure 3-18: Time Profile Analysis 1
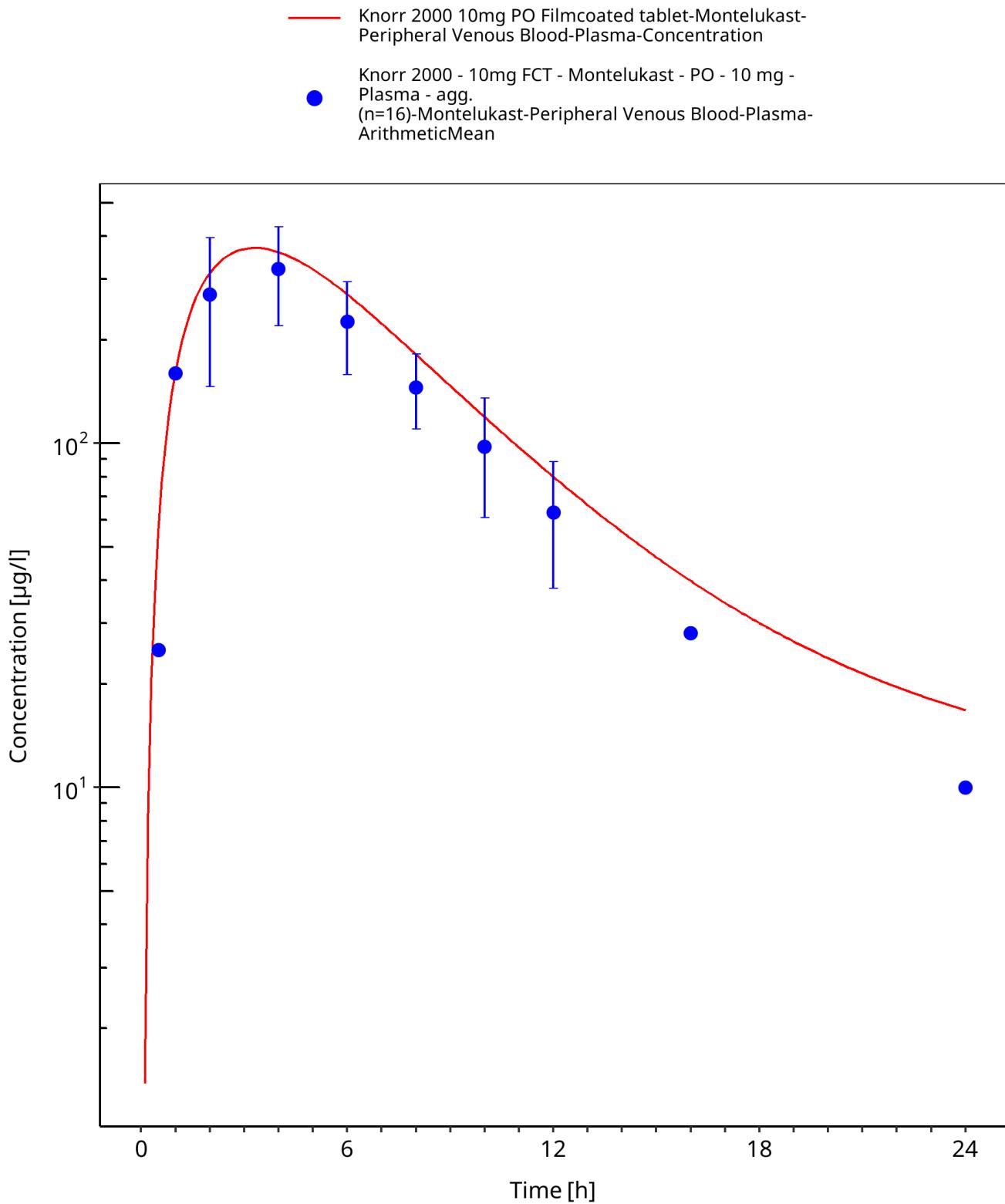
Figure 3-19: Time Profile Analysis
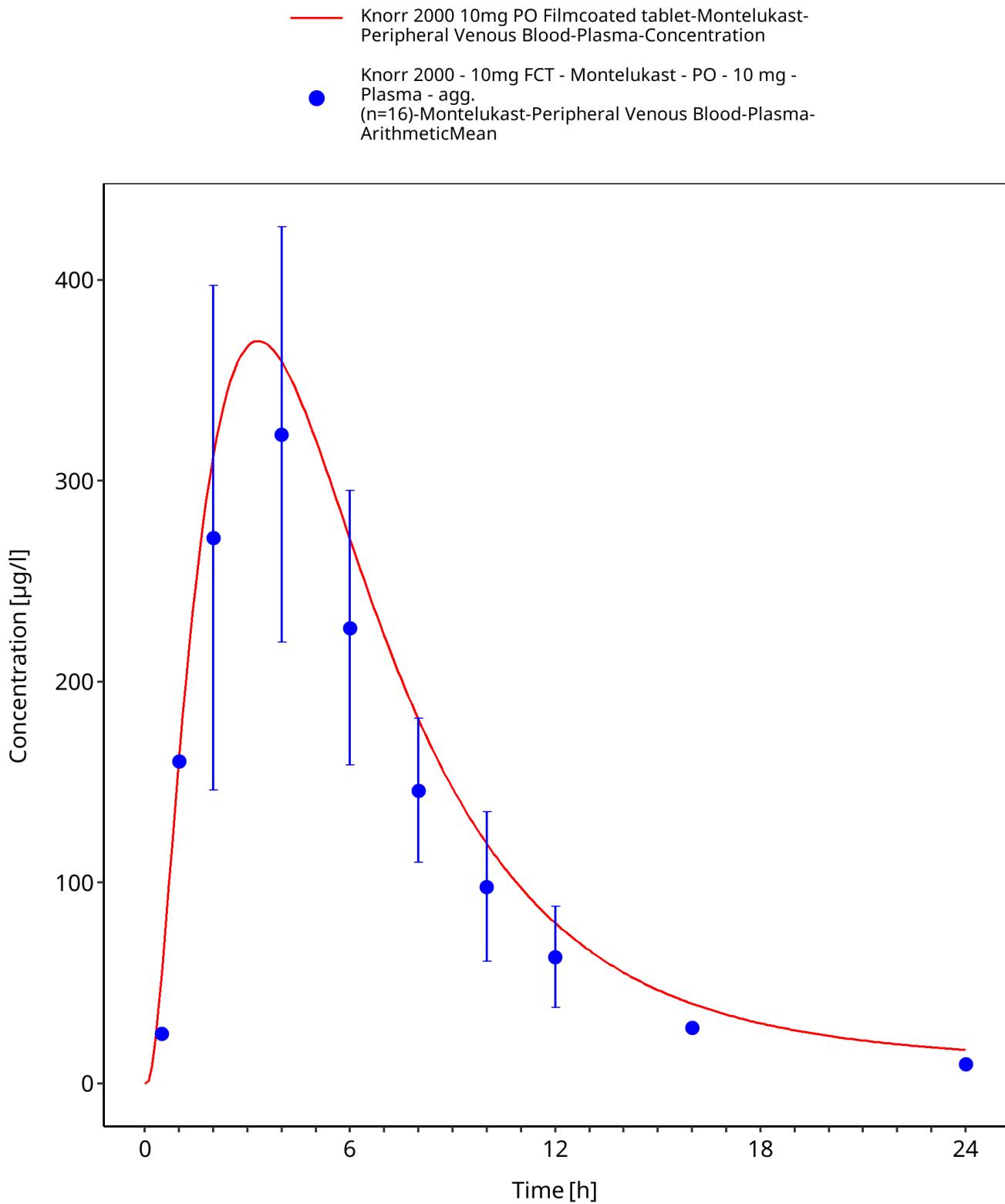
Figure 3-20: Time Profile Analysis 1
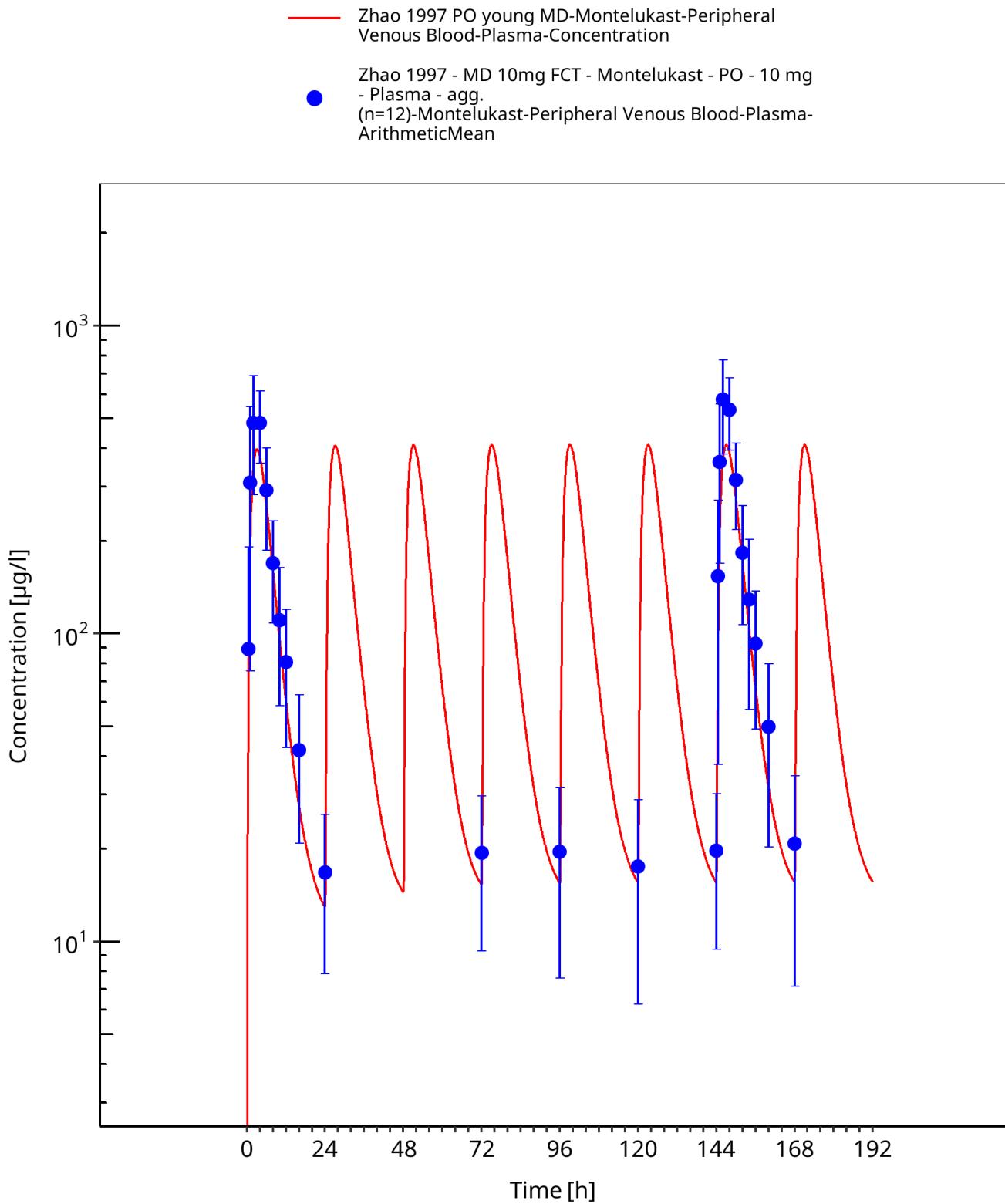
**Figure 3-21: Time Profile Analysis**
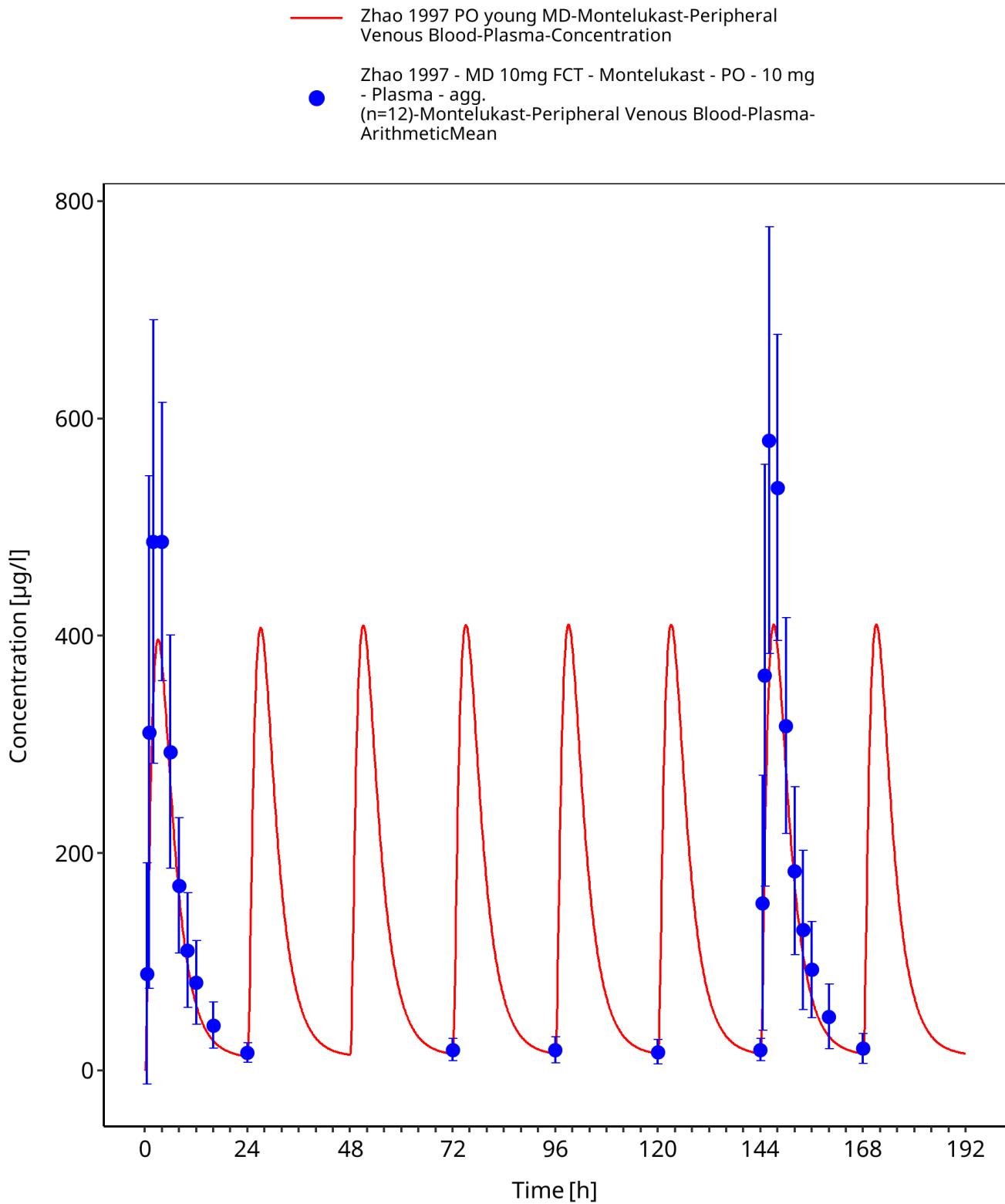
Figure 3-22: Time Profile Analysis 1
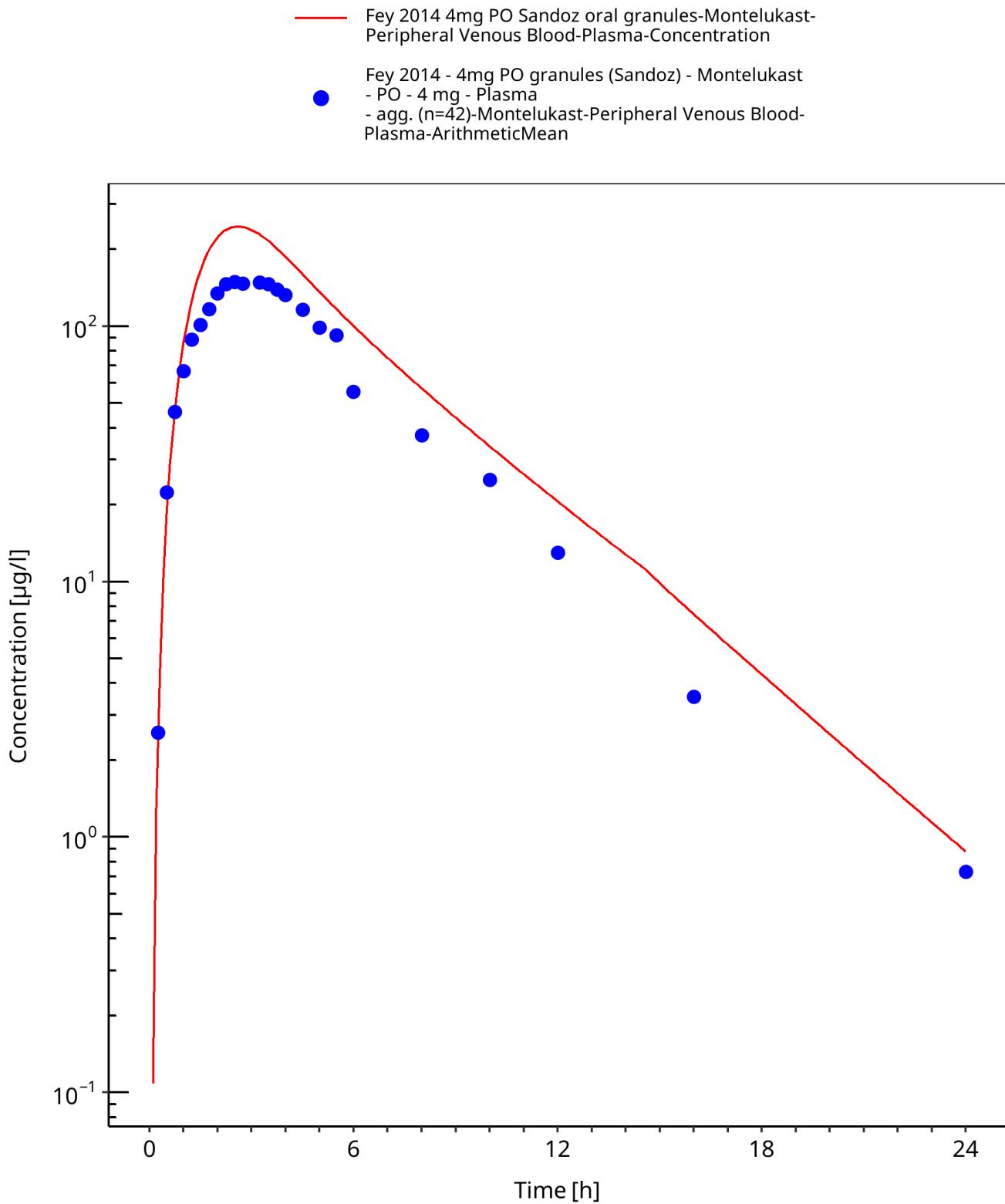
Figure 3-23: Time Profile Analysis
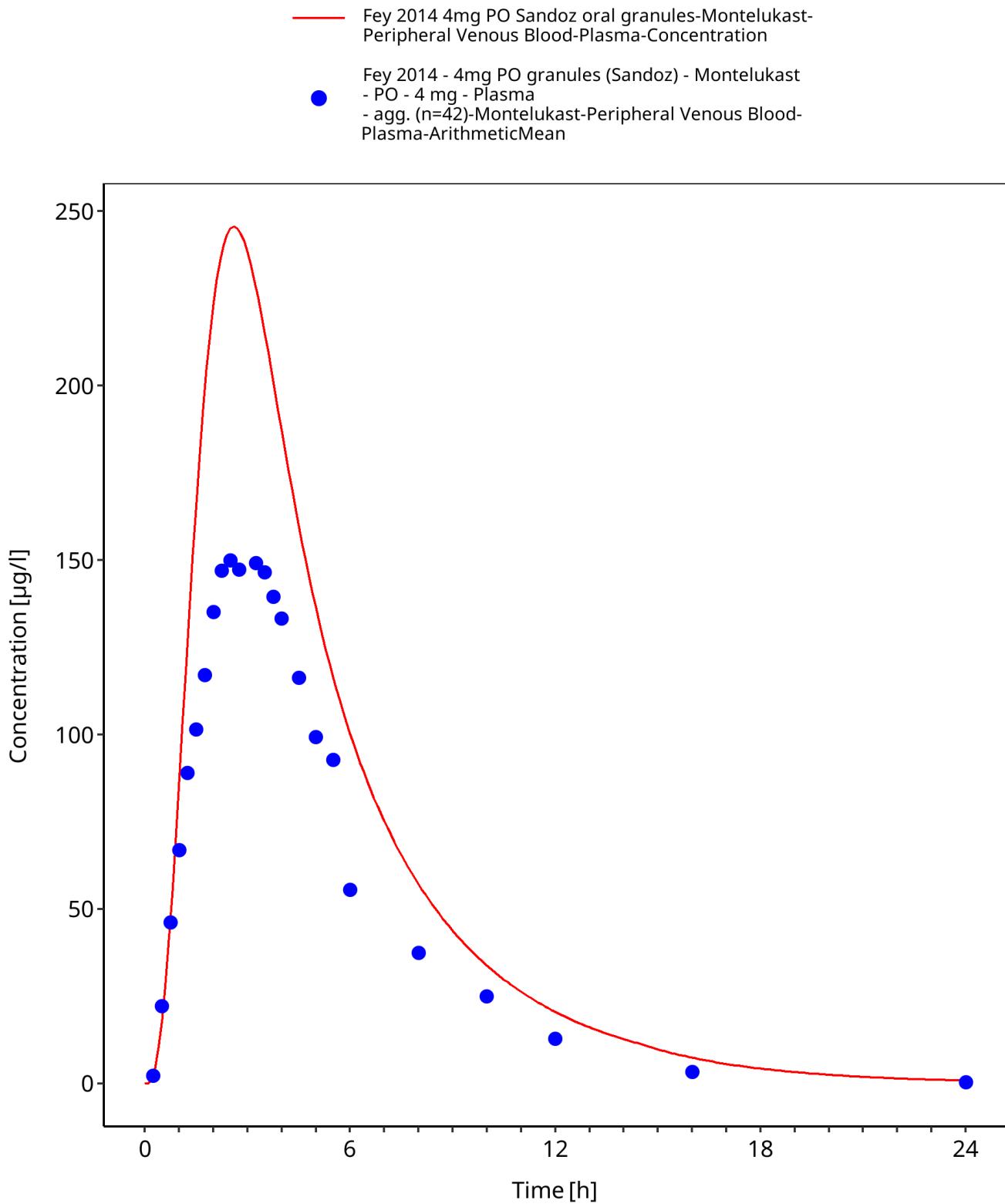
Figure 3-24: Time Profile Analysis 1
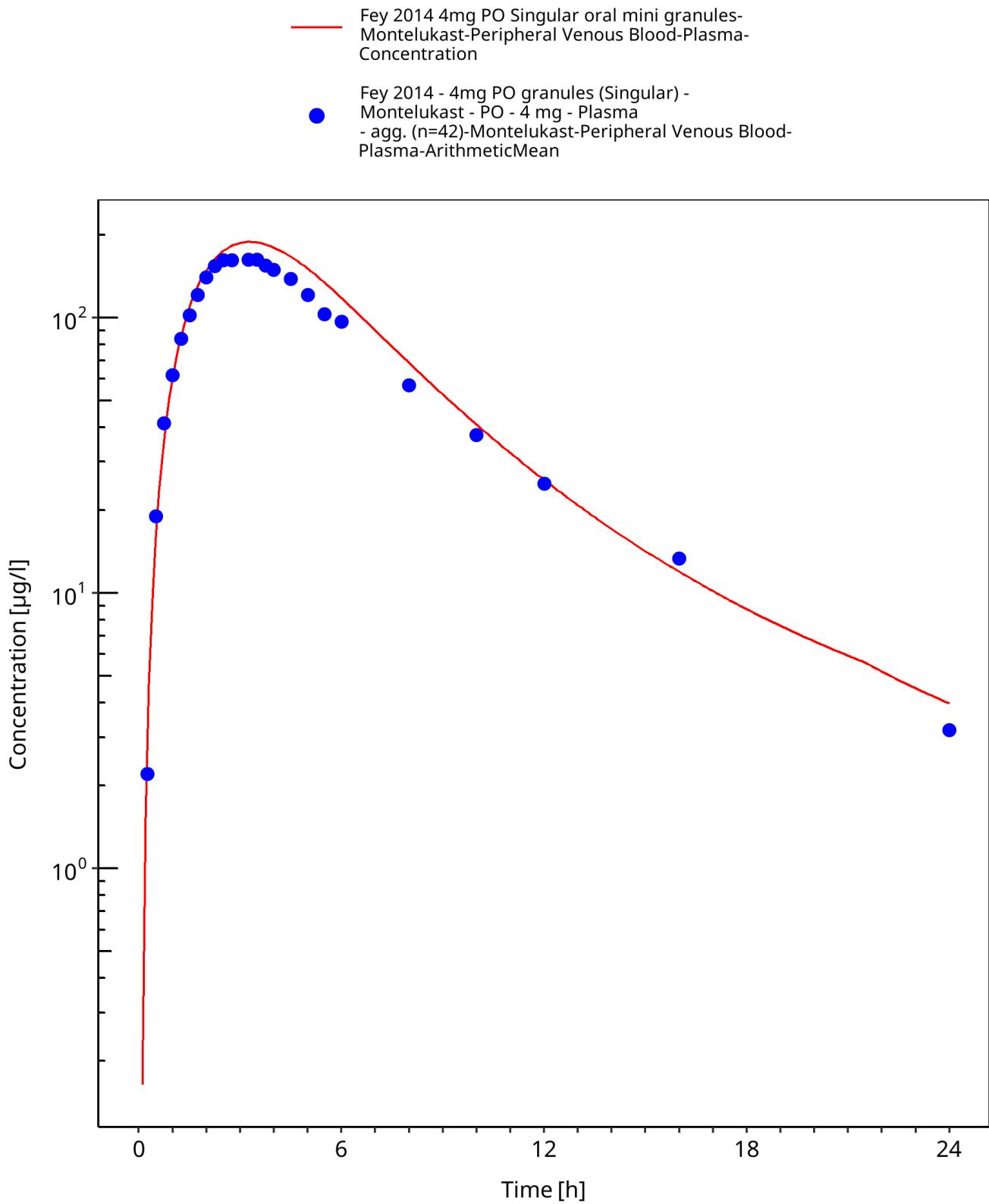
**Figure 3-25: Time Profile Analysis**

Figure 3-26: Time Profile Analysis 1

4 Conclusion

The final montelukast PBPK model applies elimination mainly by CYP2C8 and adequately describes the pharmacokinetics of montelukast in adults receiving intravenous and oral SD and MD of montelukast ranging from 2-10mg, for different types of tablet formulations.

This model could be applied for the investigation of drug-drug interactions (DDI), and translation to special populations such as pediatrics with regard to CYP2C8 based elimination.

5 References

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