

# Building and Evaluation of a PBPK Model for Verapamil in Adults

|                                                    |                                                                                                                                                                             |
|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Version                                            | 2.2-OSP12.3                                                                                                                                                                 |
| based on <i>Model Snapshot and Evaluation Plan</i> | <a href="https://github.com/Open-Systems-Pharmacology/Verapamil-Model/releases/tag/v2.2">https://github.com/Open-Systems-Pharmacology/Verapamil-Model/releases/tag/v2.2</a> |
| OSP Version                                        | 12.3                                                                                                                                                                        |
| Qualification Framework Version                    | 3.7                                                                                                                                                                         |

This evaluation report and the corresponding PK-Sim project file are filed at:

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

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# 1 Introduction

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Verapamil is used for the treatment of high blood pressure, angina (chest pain from not enough blood flow to the heart), and supraventricular tachycardia.

Verapamil is administered as a 1:1 racemat of R- and S-verapamil which are metabolized mainly by CYP3A4 to S- and R-norverapamil. All four entities are mechanism-based inactivators of CYP3A4 and non-competitive inhibitors of P-gp.

The presented verapamil model was established using observed concentration-time profiles of more than 45 clinical studies with doses from 0.1 mg to 250 mg in different verapamil dosing schedules including multiple doses and different routes of administration (intravenous, single and multiple oral administration). It includes enantioselective plasma protein binding, enantioselective metabolism by CYP3A4, non-stereospecific P-gp transport, and passive glomerular filtration. The model building and application has been published by Hanke *et al.* 2020 ([Hanke 2020](#)).

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

## 2 Methods

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### 2.1 Modeling Strategy

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The general concept of building a PBPK model has previously been described by 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 ([Schlender 2016](#)). 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](#), [Schlender 2016](#)) or otherwise referenced for the specific process.

First, a base mean model was built and adjusted to clinical data including single and multiple dose studies with intravenous (only single dose) and oral applications of verapamil 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.

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.

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

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### In vitro / physico-chemical Data

A literature search was performed to collect available information on physiochemical properties of R- and S-verapamil and R- and S-norverapamil. The obtained information from literature is summarized in the tables below.

#### R-verapamil

| Parameter              | Unit   | Value   | Source                             | Description                                                 |
|------------------------|--------|---------|------------------------------------|-------------------------------------------------------------|
| MW                     | g/mol  | 454.611 | <a href="#">Wishart 2006</a>       | Molecular weight                                            |
| pK <sub>a</sub> (base) | -      | 8.75    | <a href="#">Hasegawa 1984</a>      | Acid dissociation constant                                  |
| Solubility (pH 6.54)   | g/L    | 46.0    | <a href="#">Vogelpoel 2004</a>     | Water solubility                                            |
| logP                   |        | 3.79    | <a href="#">Hansch 1995</a>        | Partition coefficient between octanol and water             |
| fu                     | %      | 5.1     | <a href="#">Sanaee 2011</a>        | Fraction unbound in plasma                                  |
| CYP3A4 Km -> Norvera   | μmol/L | 19.59   | <a href="#">Wang 2013</a>          | CYP3A4 Michaelis-Menten constant for norverapamil formation |
| CYP3A4 Km -> D617      | μmol/L | 35.34   | <a href="#">Wang 2013</a>          | CYP3A4 Michaelis-Menten constant for D617 formation         |
| P-gp Km                | μmol/L | 1.01    | <a href="#">Shirasaka 2008</a>     | Pgp Michaelis-Menten constant                               |
| CYP3A4 MBI KI          | μmol/L | 27.63   | <a href="#">Wang 2013</a>          | Conc. for half-maximal inactivation                         |
| CYP3A4 MBI kinact      | 1/min  | 0.038   | <a href="#">Wang 2013</a>          | Maximum inactivation rate                                   |
| Pgp non-competitive Ki | μmol/L | 0.31    | <a href="#">Döppenschmitt 1999</a> | Conc. for half-maximal inactivation                         |

## S-verapamil

| Parameter              | Unit   | Value   | Source                             | Description                                                 |
|------------------------|--------|---------|------------------------------------|-------------------------------------------------------------|
| MW                     | g/mol  | 454.611 | <a href="#">Wishart 2006</a>       | Molecular weight                                            |
| pK <sub>a</sub> (base) | -      | 8.75    | <a href="#">Hasegawa 1984</a>      | Acid dissociation constant                                  |
| Solubility (pH 6.54)   | g/L    | 46.0    | <a href="#">Vogelpoel 2004</a>     | Water solubility                                            |
| logP                   |        | 3.79    | <a href="#">Hansch 1995</a>        | Partition coefficient between octanol and water             |
| fu                     | %      | 11      | <a href="#">Sanaee 2011</a>        | Fraction unbound in plasma                                  |
| CYP3A4 Km -> Norvera   | μmol/L | 9.72    | <a href="#">Wang 2013</a>          | CYP3A4 Michaelis-Menten constant for norverapamil formation |
| CYP3A4 Km -> D617      | μmol/L | 23.64   | <a href="#">Wang 2013</a>          | CYP3A4 Michaelis-Menten constant for D617 formation         |
| P-gp Km                | μmol/L | 1.01    | <a href="#">Shirasaka 2008</a>     | Pgp Michaelis-Menten constant                               |
| CYP3A4 MBI KI          | μmol/L | 3.85    | <a href="#">Wang 2013</a>          | Conc. for half-maximal inactivation                         |
| CYP3A4 MBI kinact      | 1/min  | 0.034   | <a href="#">Wang 2013</a>          | Maximum inactivation rate                                   |
| Pgp non-competitive Ki | μmol/L | 0.31    | Döppenschmitt 1999 (#5-references) | Conc. for half-maximal inactivation                         |

## R-norverapamil

| Parameter              | Unit   | Value     | Source                             | Description                                                   |
|------------------------|--------|-----------|------------------------------------|---------------------------------------------------------------|
| MW                     | g/mol  | 440.584   | <a href="#">Wishart 2006</a>       | Molecular weight                                              |
| pK <sub>a</sub> (base) | -      | 8.6 - 8.9 | <a href="#">Sigma-Aldrich 2013</a> | Acid dissociation constant                                    |
| fu                     | %      | 5.1       | assumed (from parent)              | Fraction unbound in plasma                                    |
| CYP3A4 Km -> D620      | μmol/L | 144       | <a href="#">Tracy 1999</a>         | CYP3A4 Michaelis-Menten constant for norverapamil degradation |
| P-gp Km                | μmol/L | 1.01      | assumed (from parent)              | Pgp Michaelis-Menten constant                                 |
| CYP3A4 MBI KI          | μmol/L | 6.1       | <a href="#">Wang 2013</a>          | Conc. for half-maximal inactivation                           |
| CYP3A4 MBI kinact      | 1/min  | 0.048     | <a href="#">Wang 2013</a>          | Maximum inactivation rate                                     |
| Pgp non-competitive Ki | μmol/L | 0.30      | <a href="#">Pauli-Magnus 2000</a>  | Conc. for half-maximal inactivation                           |

## S-norverapamil

| Parameter              | Unit   | Value     | Source                             | Description                                                   |
|------------------------|--------|-----------|------------------------------------|---------------------------------------------------------------|
| MW                     | g/mol  | 440.584   | <a href="#">Wishart 2006</a>       | Molecular weight                                              |
| pK <sub>a</sub> (base) | -      | 8.6 - 8.9 | <a href="#">Sigma-Aldrich 2013</a> | Acid dissociation constant                                    |
| fu                     | %      | 11        | assumed (from parent)              | Fraction unbound in plasma                                    |
| CYP3A4 Km -> D620      | μmol/L | 36        | <a href="#">Tracy 1999</a>         | CYP3A4 Michaelis-Menten constant for norverapamil degradation |
| P-gp Km                | μmol/L | 1.01      | assumed (from parent)              | Pgp Michaelis-Menten constant                                 |
| CYP3A4 MBI KI          | μmol/L | 2.90      | <a href="#">Wang 2013</a>          | Conc. for half-maximal inactivation                           |
| CYP3A4 MBI kinact      | 1/min  | 0.080     | <a href="#">Wang 2013</a>          | Maximum inactivation rate                                     |
| Pgp non-competitive Ki | μmol/L | 0.30      | <a href="#">Pauli-Magnus 2000</a>  | Conc. for half-maximal inactivation                           |

## Individual

| Parameter               | Unit | Value | Source     | Description             |
|-------------------------|------|-------|------------|-------------------------|
| EHC continuous fraction |      | 1     | Assumption | EHC continuous fraction |

## Clinical Data

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

### Model Building and parameterizing of CYP3A4 interaction

The following studies were used for model building and parameterization of CYP3A4 interaction: If not stated otherwise, the drug was given as a 1:1 racemat of S- and R-verapamil.

| Publication                     | Arm / Treatment / Information used for model building                                                                     |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Eichelbaum 1984</a> | Healthy subjects receiving single intravenous doses of 5, 25 and 50 mg of R-verapamil and 5, 7.5 and 10 mg of S-verapamil |
| <a href="#">Streit 2005</a>     | Healthy subjects receiving single intravenous doses of 5 mg                                                               |
| <a href="#">Barbarash 1988</a>  | Healthy subjects receiving single intravenous doses of 10 mg                                                              |
| <a href="#">Abernethy 1993</a>  | Healthy subjects receiving single intravenous doses of 20 mg                                                              |
| <a href="#">Maeda 2011</a>      | Healthy subjects receiving single oral doses of 0.1, 3 and 16 mg                                                          |
| <a href="#">Blume 1989</a>      | Healthy subjects receiving single oral doses of 80 mg                                                                     |
| <a href="#">Ratiopharm 1988</a> | Healthy subjects receiving single oral doses of 80 mg                                                                     |
| <a href="#">Johnson 2001</a>    | Healthy subjects receiving multiple oral doses of 80 mg TID.                                                              |
| <a href="#">Härtter 2012</a>    | Healthy subjects receiving single oral doses of 120 mg and multiple oral doses of 120 mg BID                              |
| <a href="#">Hla 1987</a>        | Healthy subjects receiving multiple oral doses of 120 mg BID                                                              |

### Model verification

The following studies were used for model verification:

| Publication                     | Arm / Treatment / Information used for model building                                            |
|---------------------------------|--------------------------------------------------------------------------------------------------|
| <a href="#">Mooy 1985</a>       | Healthy subjects receiving single intravenous doses of 3 mg and single oral doses of 80 mg       |
| <a href="#">Johnston 1981</a>   | Healthy subjects receiving single intravenous doses of 0.1 mg/kg and single oral doses of 120 mg |
| <a href="#">Abernethy 1985</a>  | Healthy subjects receiving single intravenous doses of 10 mg and single oral doses of 120 mg     |
| <a href="#">Barbarash 1988</a>  | Healthy subjects receiving single oral doses of 120 mg                                           |
| <a href="#">Wing 1985</a>       | Healthy subjects receiving single intravenous doses 10mg and single oral doses of 80 mg          |
| <a href="#">McAllister 1982</a> | Healthy subjects receiving single intravenous doses of 10 mg                                     |
| <a href="#">Smith 1984</a>      | Healthy subjects receiving single intravenous doses of 10 mg and single oral doses of 120 mg     |
| <a href="#">Freedman 1981</a>   | Healthy subjects receiving single intravenous doses of 13.1 mg                                   |
| <a href="#">Vogelsang 1984</a>  | Healthy subjects receiving single oral doses of 250mg R-verapamil                                |
| <a href="#">Blume 1983</a>      | Healthy subjects receiving single oral doses of 40 mg                                            |
| <a href="#">Blume 1990</a>      | Healthy subjects receiving single oral doses of 40 mg                                            |
| <a href="#">John 1992</a>       | Healthy subjects receiving single oral doses of 40 mg                                            |
| <a href="#">Sawicki 2002</a>    | Healthy subjects receiving single oral doses of 40 mg                                            |
| <a href="#">Choi 2008</a>       | Healthy subjects receiving single oral doses of 60 mg                                            |
| <a href="#">Wing 1985</a>       | Healthy subjects receiving single oral doses of 80 mg                                            |
| <a href="#">Maeda 2011</a>      | Healthy subjects receiving single oral doses of 80 mg                                            |
| <a href="#">Ratiopharm 1989</a> | Healthy subjects receiving single oral doses of 80 mg                                            |
| <a href="#">Boehringer 2018</a> | Healthy subjects receiving single oral doses of 120 mg                                           |
| <a href="#">Blume 1987</a>      | Healthy subjects receiving single oral doses of 120 mg                                           |
| <a href="#">Johnston 1981</a>   | Healthy subjects receiving single oral doses of 120 mg                                           |
| <a href="#">Mikus 1990</a>      | Healthy subjects receiving single oral doses of 160 mg                                           |
| <a href="#">van Haarst 2009</a> | Healthy subjects receiving multiple oral doses of 180 mg BID                                     |
| <a href="#">Blume 1994</a>      | Healthy subjects receiving single oral doses of 240 mg QD                                        |
| <a href="#">Joergenson 1988</a> | Healthy subjects receiving multiple oral doses of 120 mg BID                                     |

| Publication                | Arm / Treatment / Information used for model building        |
|----------------------------|--------------------------------------------------------------|
| <a href="#">Shand 1981</a> | Healthy subjects receiving multiple oral doses of 120 mg TID |
| <a href="#">Karim 1995</a> | Healthy subjects receiving single oral doses of 240 mg       |

## 2.3 Model Parameters and Assumptions

### Absorption

Verapamil is transported by P-gp. The model includes non-stereospecific P-gp transport.

### 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 [Rodgers and Rowland](#) and cellular permeability calculation by [PK-Sim Standard](#).

### Metabolism, Elimination and Inhibition

Verapamil is metabolized by CYP3A4 and transported by P-gp. The model includes enantioselective metabolism by CYP3A4, non-stereospecific P-gp transport. Additionally passive glomerular filtration was integrated. For biliary excretion, an EHC continuous fraction of 1 was assumed.

Mechanism-based inactivation of CYP3A4 and non-competitive inhibition of P-gp by all four entities (S-verapamil, R-verapamil, S-norverapamil and R-norverapamil) was taken into account. The CYP3A4 MBI KI and kinact values were taken from literature, the KI values for P-gp inhibition were optimized.

### 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.

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

### R-verapamil

| Model Parameter         | Optimized Value | Unit   |
|-------------------------|-----------------|--------|
| logP                    | 2.84            |        |
| CYP3A4 kcat -> Norvera  | 34.94           | 1/min  |
| CYP3A4 kcat -> D617     | 43.98           | 1/min  |
| P-gp kcat               | 12.60           | 1/min  |
| Pgp non-competitive Ki  | 0.038           | μmol/L |
| Cellular permeability   | 9.94E-02        | cm/min |
| Intestinal permeability | 3.54E-06        | cm/min |
| SR tablet Weibull time  | 155.24          | min    |
| SR tablet Weibull shape | 2.37            |        |

## S-verapamil

| Model Parameter         | Optimized Value | Unit   |
|-------------------------|-----------------|--------|
| logP                    | 2.84            |        |
| CYP3A4 kcat -> Norvera  | 26.17           | 1/min  |
| CYP3A4 kcat -> D617     | 56.42           | 1/min  |
| P-gp kcat               | 12.60           | 1/min  |
| Pgp non-competitive Ki  | 0.038           | μmol/L |
| Cellular permeability   | 9.94E-02        | cm/min |
| Intestinal permeability | 3.54E-06        | cm/min |
| SR tablet Weibull time  | 155.24          | min    |
| SR tablet Weibull shape | 2.37            |        |

## R-norverapamil

| Model Parameter         | Optimized Value | Unit   |
|-------------------------|-----------------|--------|
| logP                    | 2.84            |        |
| CYP3A4 kcat -> D620     | 145.64          | 1/min  |
| P-gp kcat               | 3.39            | 1/min  |
| Pgp non-competitive Ki  | 0.038           | μmol/L |
| Cellular permeability   | 9.94E-02        | cm/min |
| Intestinal permeability | 3.54E-06        | cm/min |

## S-norverapamil

| Model Parameter         | Optimized Value | Unit   |
|-------------------------|-----------------|--------|
| logP                    | 2.84            |        |
| CYP3A4 kcat -> D620     | 41.10           | 1/min  |
| P-gp kcat               | 3.39            | 1/min  |
| Pgp non-competitive Ki  | 0.038           | μmol/L |
| Cellular permeability   | 9.94E-02        | cm/min |
| Intestinal permeability | 3.54E-06        | cm/min |

## Individual

| Model Parameter         | Optimized Value | Unit |
|-------------------------|-----------------|------|
| EHC continuous fraction | 1               |      |

## 3 Results and Discussion

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The PBPK model for verapamil was developed and evaluated using publically available, clinical pharmacokinetic data from studies listed in [Section 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

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

#### **Compound: R-Verapamil**

##### **Parameters**

| Name                                             | Value                   | Value Origin                                                                                           | Alternative | Default |
|--------------------------------------------------|-------------------------|--------------------------------------------------------------------------------------------------------|-------------|---------|
| Solubility at reference pH                       | 46 mg/ml                |                                                                                                        | Measurement | True    |
| Reference pH                                     | 6.54                    |                                                                                                        | Measurement | True    |
| Lipophilicity                                    | 2.8407448658 Log Units  | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | logP        | True    |
| Fraction unbound (plasma, reference value)       | 5.1 %                   | Publication-In Vivo                                                                                    | Measurement | True    |
| Permeability                                     | 0.0994098912 cm/min     | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | Fitted      | True    |
| Specific intestinal permeability (transcellular) | 3.5447164381E-06 cm/min | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | Fitted      | True    |
| Is small molecule                                | Yes                     |                                                                                                        |             |         |
| Molecular weight                                 | 454.611 g/mol           |                                                                                                        |             |         |
| Plasma protein binding partner                   | Unknown                 |                                                                                                        |             |         |

## Calculation methods

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

## Processes

### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters

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

### Transport Protein: P-gp-Paper

Molecule: P-gp

#### Parameters

| Name                         | Value                                   | Value Origin                                                                                           |
|------------------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro<br>Vmax/transporter | 0.00057724 pmol/min/pmol<br>transporter |                                                                                                        |
| Km                           | 1.01 $\mu\text{mol/l}$                  |                                                                                                        |
| kcat                         | 12.5970868779 1/min                     | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Inhibition: P-gp-Non-competitive

Molecule: P-gp

#### Parameters

| Name | Value                             | Value Origin                                                                                           |
|------|-----------------------------------|--------------------------------------------------------------------------------------------------------|
| Ki   | 0.0383697779<br>$\mu\text{mol/l}$ | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Inhibition: CYP3A4-MBI

Molecule: CYP3A4

#### Parameters

| Name          | Value                   | Value Origin |
|---------------|-------------------------|--------------|
| kinact        | 0.038 1/min             |              |
| K_kinact_half | 27.63 $\mu\text{mol/l}$ |              |

### Metabolizing Enzyme: CYP3A4-Norverapamil

Molecule: CYP3A4

Metabolite: R-Norverapamil

#### Parameters

| Name                               | Value                         | Value Origin                                                                                           |
|------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro Vmax for liver microsomes | 1.27 nmol/min/mg mic. protein |                                                                                                        |
| Km                                 | 19.59 $\mu$ mol/l             |                                                                                                        |
| kcat                               | 34.9352466212 1/min           | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Metabolizing Enzyme: CYP3A4-D617

Molecule: CYP3A4

#### Parameters

| Name                               | Value                         | Value Origin                                                                                           |
|------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro Vmax for liver microsomes | 1.17 nmol/min/mg mic. protein |                                                                                                        |
| Km                                 | 35.34 $\mu$ mol/l             |                                                                                                        |
| kcat                               | 43.9812289146 1/min           | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Compound: S-Verapamil

#### Parameters

| Name                                             | Value                   | Value Origin                                                                                           | Alternative | Default |
|--------------------------------------------------|-------------------------|--------------------------------------------------------------------------------------------------------|-------------|---------|
| Solubility at reference pH                       | 46 mg/ml                |                                                                                                        | Measurement | True    |
| Reference pH                                     | 6.54                    |                                                                                                        | Measurement | True    |
| Lipophilicity                                    | 2.8407448658 Log Units  | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | logP        | True    |
| Fraction unbound (plasma, reference value)       | 11 %                    | Publication-In Vivo                                                                                    | Measurement | True    |
| Permeability                                     | 0.0994098912 cm/min     | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | Fitted      | True    |
| Specific intestinal permeability (transcellular) | 3.5447164381E-06 cm/min | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | Fitted      | True    |
| Is small molecule                                | Yes                     |                                                                                                        |             |         |
| Molecular weight                                 | 454.611 g/mol           |                                                                                                        |             |         |
| Plasma protein binding partner                   | Unknown                 |                                                                                                        |             |         |

## Calculation methods

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

## Processes

### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters

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

### Transport Protein: P-gp-Paper

Molecule: P-gp

#### Parameters

| Name                         | Value                                   | Value Origin                                                                                           |
|------------------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro<br>Vmax/transporter | 0.00057724 pmol/min/pmol<br>transporter |                                                                                                        |
| Km                           | 1.01 $\mu\text{mol/l}$                  |                                                                                                        |
| kcat                         | 12.5970868779 1/min                     | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Inhibition: P-gp-Non-competitive

Molecule: P-gp

#### Parameters

| Name | Value                             | Value Origin                                                                                           |
|------|-----------------------------------|--------------------------------------------------------------------------------------------------------|
| Ki   | 0.0383697779<br>$\mu\text{mol/l}$ | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Inhibition: CYP3A4-MBI

Molecule: CYP3A4

#### Parameters

| Name          | Value                  | Value Origin |
|---------------|------------------------|--------------|
| kinact        | 0.034 1/min            |              |
| K_kinact_half | 3.85 $\mu\text{mol/l}$ |              |

### Metabolizing Enzyme: CYP3A4-Norverapamil

Molecule: CYP3A4

Metabolite: S-Norverapamil

#### Parameters

| Name                               | Value                            | Value Origin                                                                                           |
|------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro Vmax for liver microsomes | 1.02 nmol/min/mg<br>mic. protein |                                                                                                        |
| Km                                 | 9.72 $\mu$ mol/l                 |                                                                                                        |
| kcat                               | 26.1743386639<br>1/min           | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Metabolizing Enzyme: CYP3A4-D617

Molecule: CYP3A4

#### Parameters

| Name                               | Value                            | Value Origin                                                                                           |
|------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro Vmax for liver microsomes | 0.86 nmol/min/mg<br>mic. protein |                                                                                                        |
| Km                                 | 23.64 $\mu$ mol/l                |                                                                                                        |
| kcat                               | 56.4245798193<br>1/min           | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Compound: R-Norverapamil

#### Parameters

| Name                                             | Value                   | Value Origin                                                                                           | Alternative | Default |
|--------------------------------------------------|-------------------------|--------------------------------------------------------------------------------------------------------|-------------|---------|
| Solubility at reference pH                       | 46 mg/ml                |                                                                                                        | Measurement | True    |
| Reference pH                                     | 6.54                    |                                                                                                        | Measurement | True    |
| Lipophilicity                                    | 2.8407448658 Log Units  | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | logP        | True    |
| Fraction unbound (plasma, reference value)       | 5.1 %                   | Other-Assumption                                                                                       | Measurement | True    |
| Permeability                                     | 0.0994098912 cm/min     | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | Fitted      | True    |
| Specific intestinal permeability (transcellular) | 3.5447164381E-06 cm/min | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | Fitted      | True    |
| Is small molecule                                | Yes                     |                                                                                                        |             |         |
| Molecular weight                                 | 440.584 g/mol           |                                                                                                        |             |         |
| Plasma protein binding partner                   | Unknown                 |                                                                                                        |             |         |

## Calculation methods

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

## Processes

**Metabolizing Enzyme: CYP3A4-D620**

Molecule: CYP3A4

## Parameters

| Name                                   | Value                          | Value Origin                                                                                           |
|----------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro<br>Vmax/recombinant<br>enzyme | 9 pmol/min/pmol<br>rec. enzyme |                                                                                                        |
| Km                                     | 144 µmol/l                     |                                                                                                        |
| kcat                                   | 145.6385399671<br>1/min        | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters

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

### Transport Protein: P-gp-Paper

Molecule: P-gp

#### Parameters

| Name                         | Value                                   | Value Origin                                                                                           |
|------------------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro<br>Vmax/transporter | 0.00057724 pmol/min/pmol<br>transporter |                                                                                                        |
| Km                           | 1.01 µmol/l                             |                                                                                                        |
| kcat                         | 3.3916609583 1/min                      | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Inhibition: P-gp-Non-competitive

Molecule: P-gp

#### Parameters

| Name | Value                  | Value Origin                                                                                           |
|------|------------------------|--------------------------------------------------------------------------------------------------------|
| Ki   | 0.0383697779<br>µmol/l | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

## Inhibition: CYP3A4-MBI

Molecule: CYP3A4

### Parameters

| Name          | Value       | Value Origin |
|---------------|-------------|--------------|
| kinact        | 0.048 1/min |              |
| K_kinact_half | 6.1 µmol/l  |              |

## Compound: S-Norverapamil

### Parameters

| Name                                             | Value                   | Value Origin                                                                                           | Alternative | Default |
|--------------------------------------------------|-------------------------|--------------------------------------------------------------------------------------------------------|-------------|---------|
| Solubility at reference pH                       | 46 mg/ml                |                                                                                                        | Measurement | True    |
| Reference pH                                     | 6.54                    |                                                                                                        | Measurement | True    |
| Lipophilicity                                    | 2.8407448658 Log Units  | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | logP        | True    |
| Fraction unbound (plasma, reference value)       | 11 %                    | Other-Assumption                                                                                       | Measurement | True    |
| Permeability                                     | 0.0994098912 cm/min     | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | Fitted      | True    |
| Specific intestinal permeability (transcellular) | 3.5447164381E-06 cm/min | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 | Fitted      | True    |
| Is small molecule                                | Yes                     |                                                                                                        |             |         |
| Molecular weight                                 | 440.584 g/mol           |                                                                                                        |             |         |
| Plasma protein binding partner                   | Unknown                 |                                                                                                        |             |         |

### Calculation methods

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

## Processes

### Metabolizing Enzyme: CYP3A4-D620

Molecule: CYP3A4

#### Parameters

| Name                                   | Value                            | Value Origin                                                                                           |
|----------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro<br>Vmax/recombinant<br>enzyme | 6.5 pmol/min/pmol<br>rec. enzyme |                                                                                                        |
| Km                                     | 36 µmol/l                        |                                                                                                        |
| kcat                                   | 41.0994047535 1/min              | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters

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

### Transport Protein: P-gp-Paper

Molecule: P-gp

#### Parameters

| Name                         | Value                                   | Value Origin                                                                                           |
|------------------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------|
| In vitro<br>Vmax/transporter | 0.00057724 pmol/min/pmol<br>transporter |                                                                                                        |
| Km                           | 1.01 µmol/l                             |                                                                                                        |
| kcat                         | 3.3916609583 1/min                      | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Inhibition: P-gp-Non-competitive

Molecule: P-gp

#### Parameters

| Name | Value                  | Value Origin                                                                                           |
|------|------------------------|--------------------------------------------------------------------------------------------------------|
| Ki   | 0.0383697779<br>µmol/l | Parameter Identification-Parameter Identification-Value updated from '30b - final' on 2019-12-30 13:23 |

### Inhibition: CYP3A4-MBI

Molecule: CYP3A4

#### Parameters

| Name          | Value      | Value Origin |
|---------------|------------|--------------|
| kinact        | 0.08 1/min |              |
| K_kinact_half | 2.9 µmol/l |              |

### Formulation: Solution

Type: Dissolved

### Formulation: Retard Tablet Verapamil (Knoll)

Type: Weibull

#### Parameters

| Name                                | Value                 | Value Origin                                                                                                                                |
|-------------------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Dissolution time<br>(50% dissolved) | 155.2445399403<br>min | Parameter Identification-Parameter Identification-Value updated from '240 mg retard (Isoptin RR) QD vs Verabeta 240 RR' on 2019-12-31 11:13 |
| Lag time                            | 0 min                 |                                                                                                                                             |
| Dissolution shape                   | 2.3662989419          | Parameter Identification-Parameter Identification-Value updated from '240 mg retard (Isoptin RR) QD vs Verabeta 240 RR' on 2019-12-31 11:13 |
| Use as<br>suspension                | Yes                   |                                                                                                                                             |

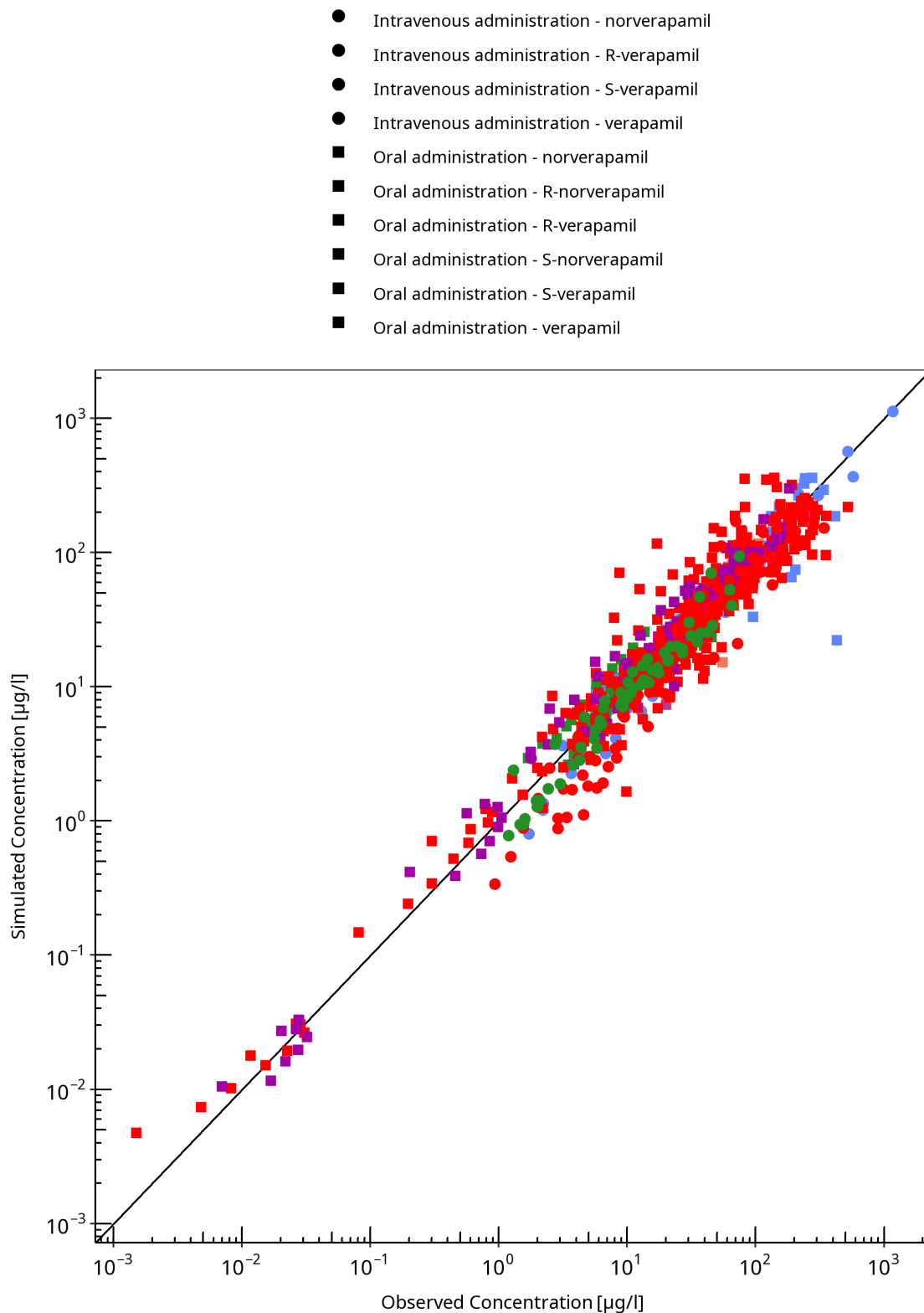
## 3.2 Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data used presented in [Section 2.2](#).

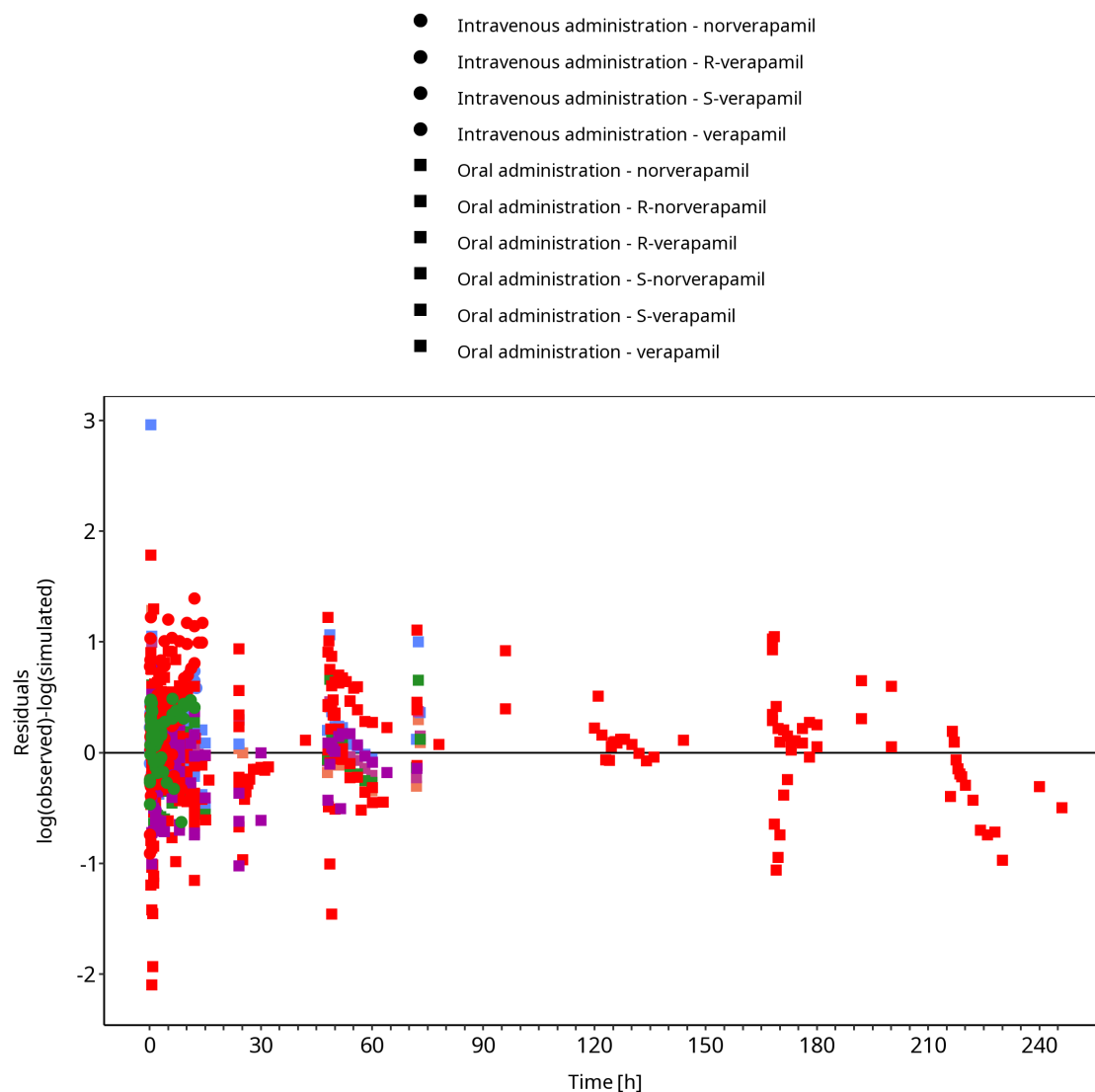
The first plot shows observed versus simulated plasma concentration, the second weighted residuals versus time.

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

| Group                                     | GMFE |
|-------------------------------------------|------|
| Intravenous administration - norverapamil | 1.66 |
| Intravenous administration - R-verapamil  | 1.25 |
| Intravenous administration - S-verapamil  | 1.31 |
| Intravenous administration - verapamil    | 1.44 |
| Oral administration - norverapamil        | 1.29 |
| Oral administration - R-norverapamil      | 1.14 |
| Oral administration - R-verapamil         | 1.33 |
| Oral administration - S-norverapamil      | 1.16 |
| Oral administration - S-verapamil         | 1.31 |
| Oral administration - verapamil           | 1.42 |
| All                                       | 1.35 |



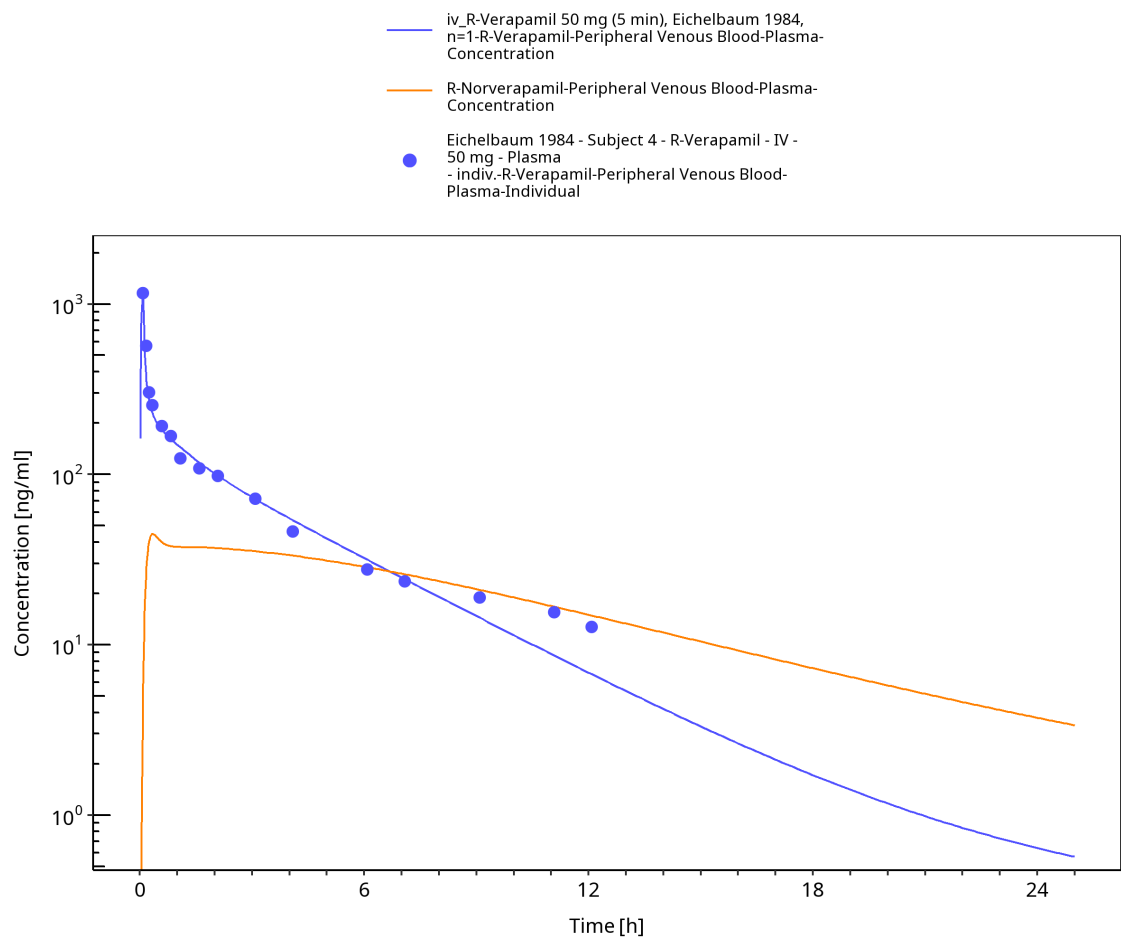
**Figure 3-1: Goodness of fit plot for concentration in plasma**



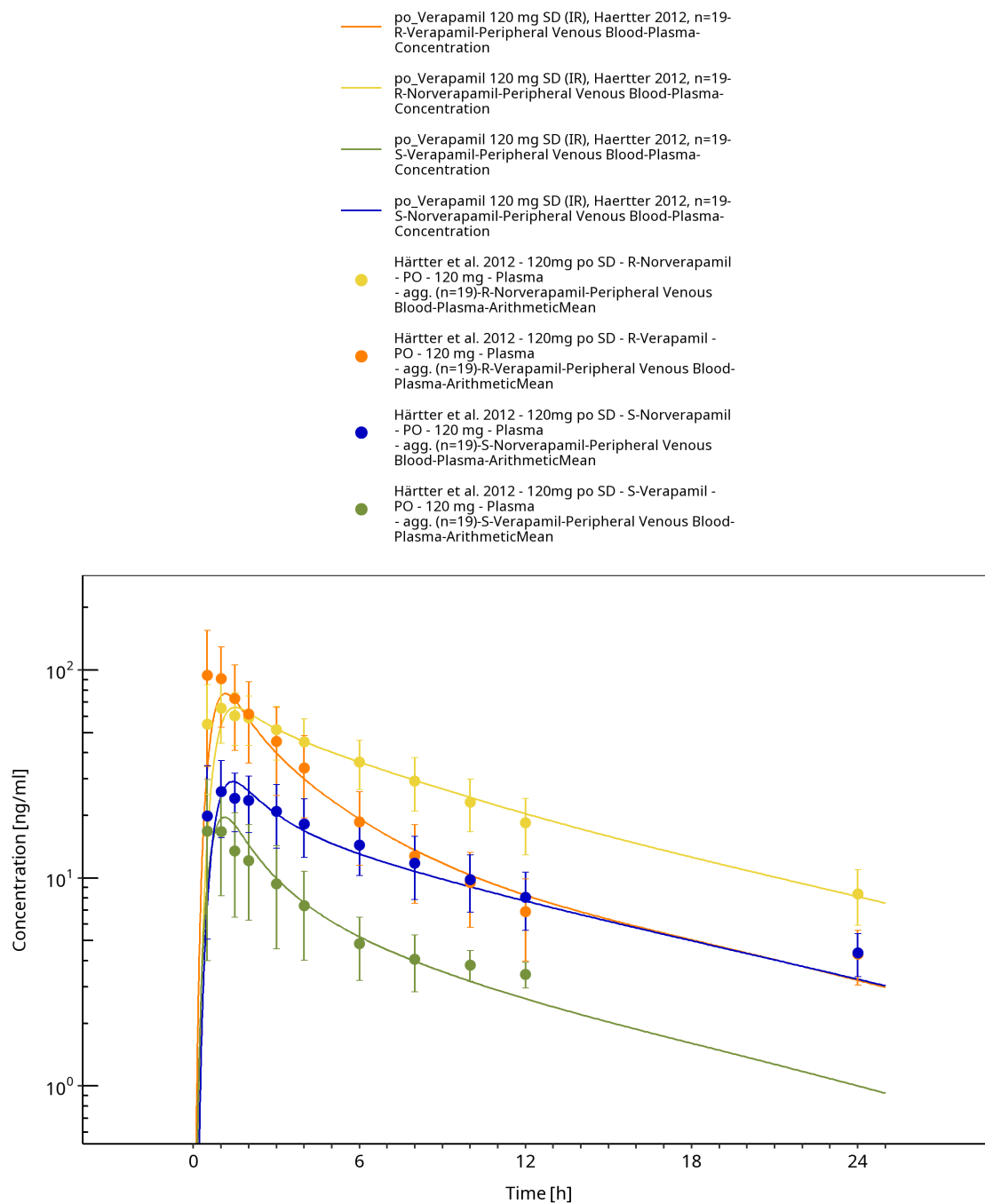
**Figure 3-2: Goodness of fit plot for concentration in plasma**

### 3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in [Section 2.2](#) are presented below.



**Figure 3-3: Time Profile Analysis**



**Figure 3-4: Time Profile Analysis**

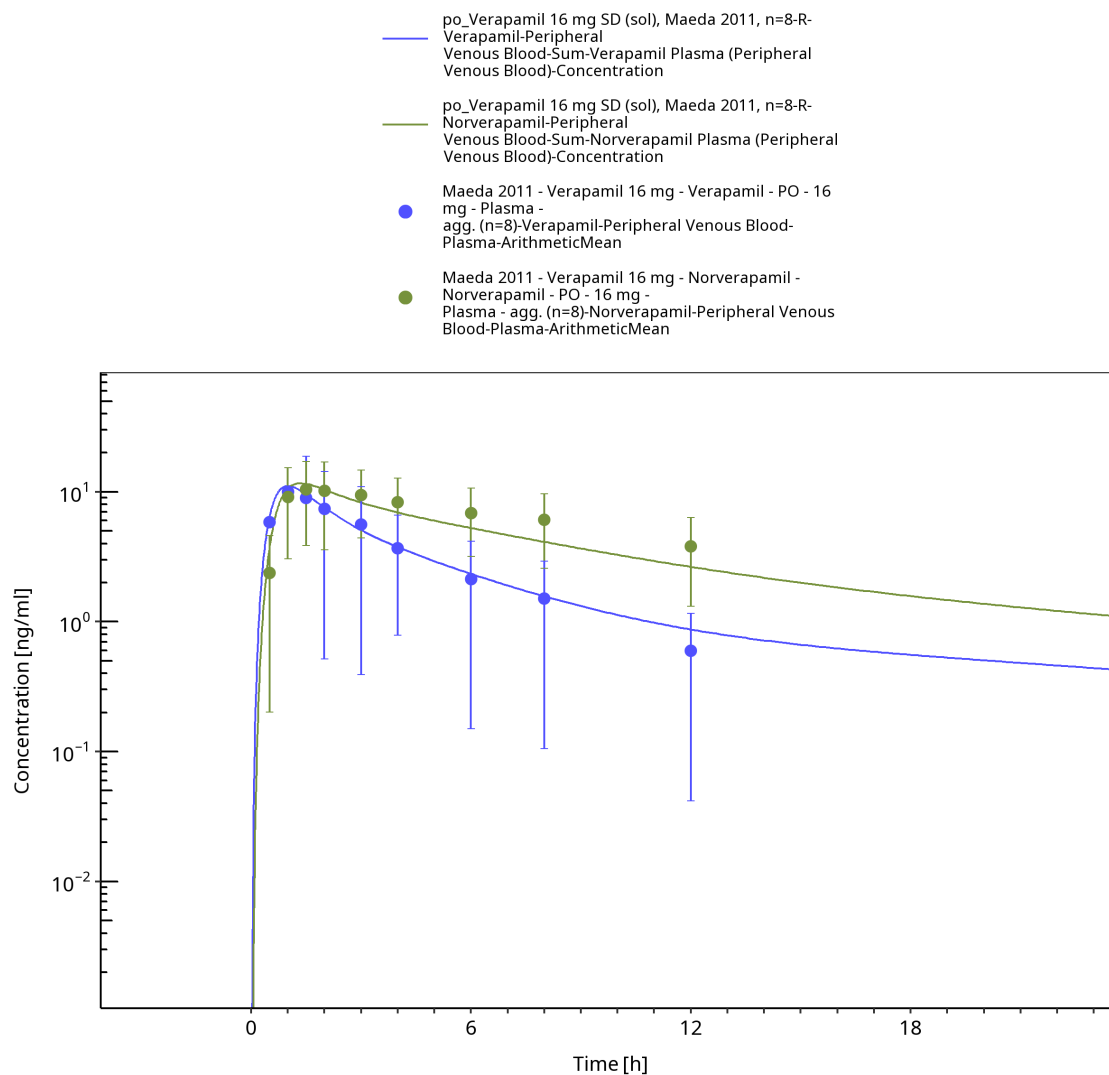
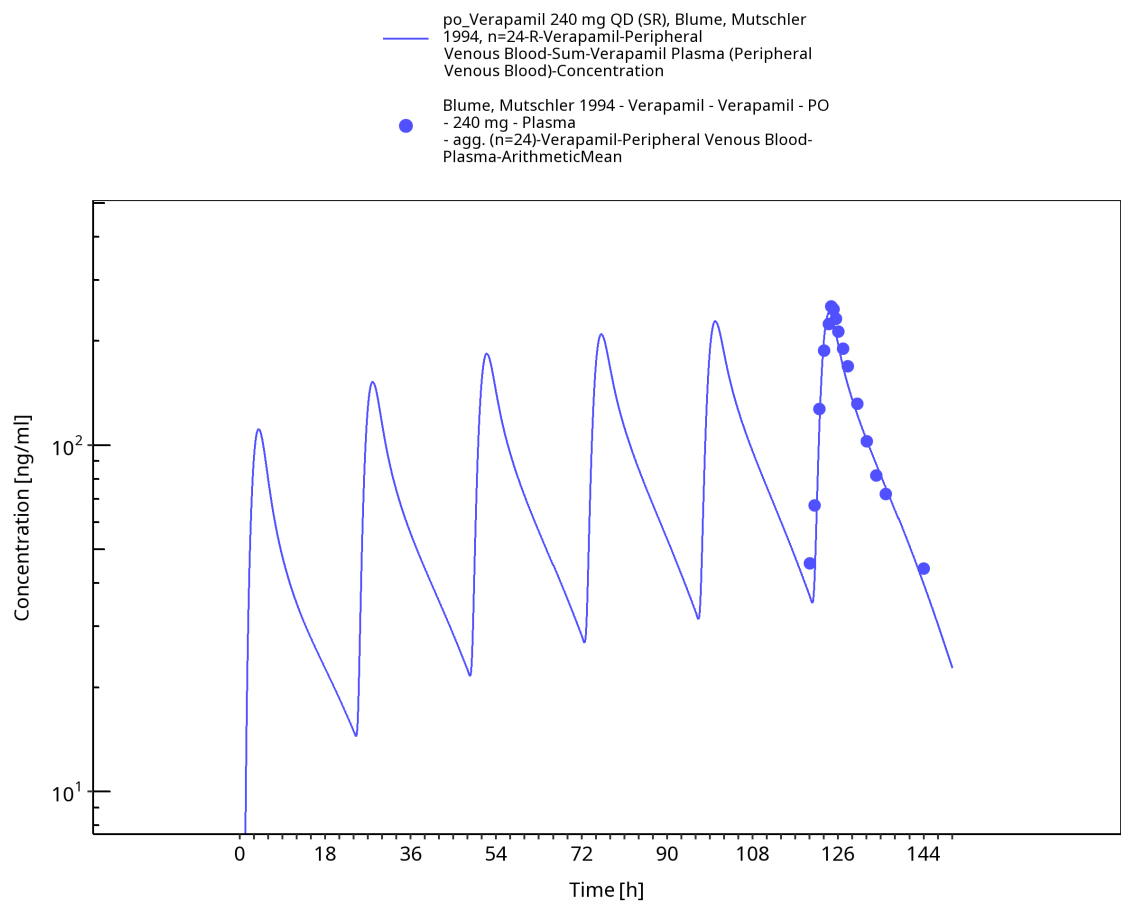
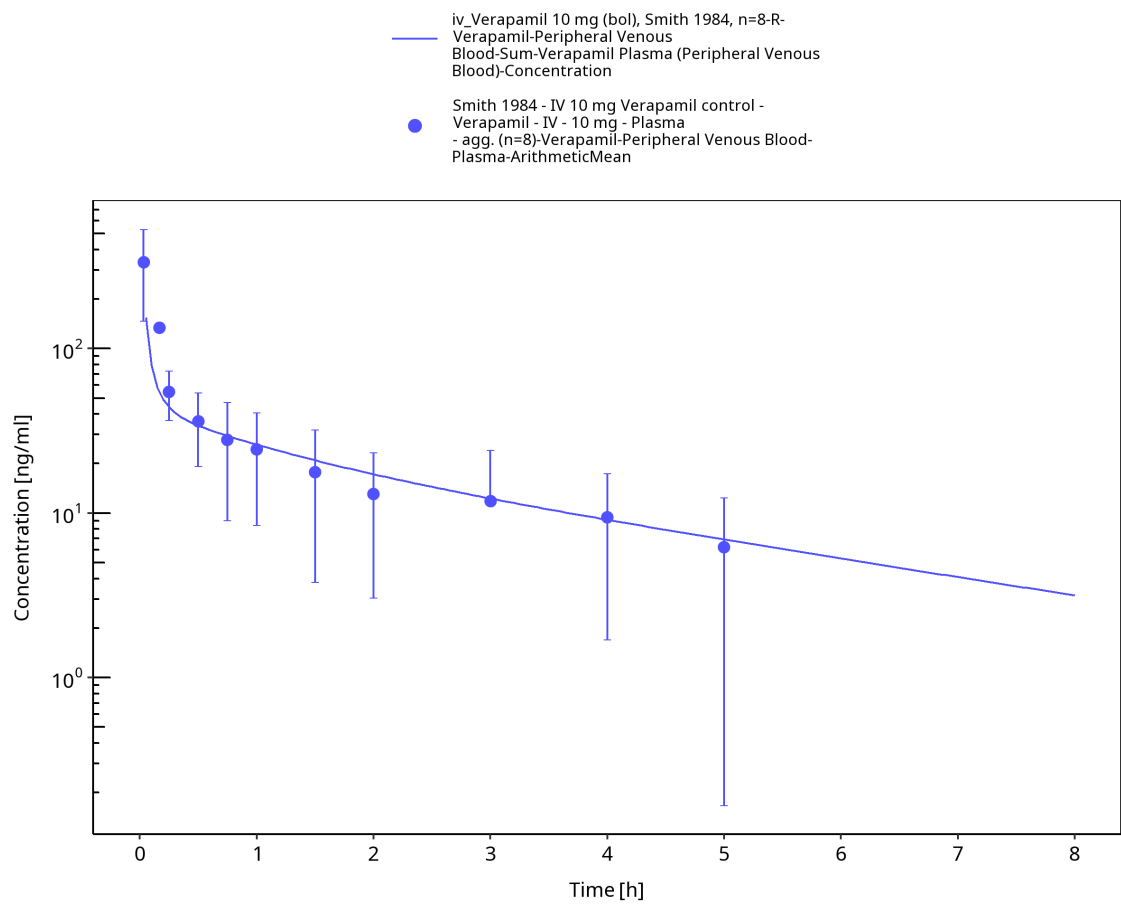


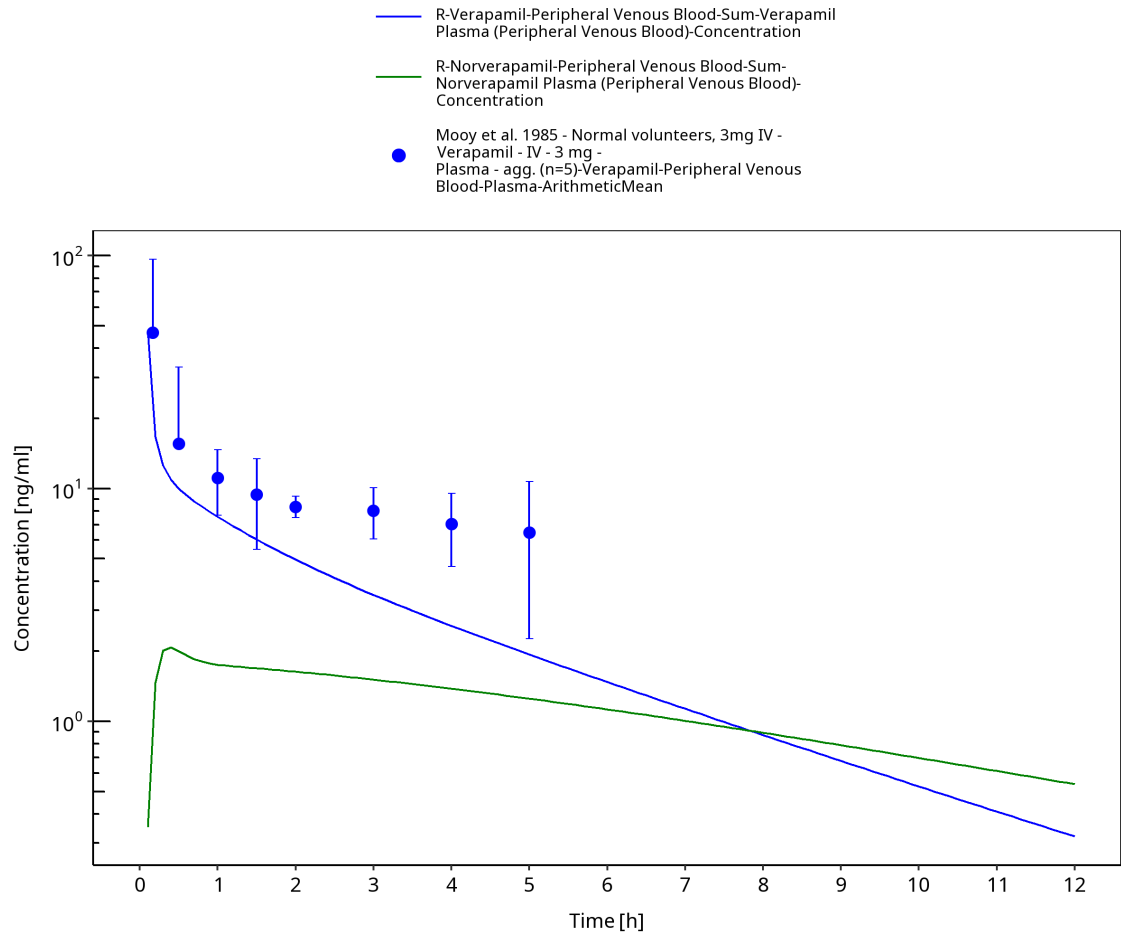
Figure 3-5: Time Profile Analysis



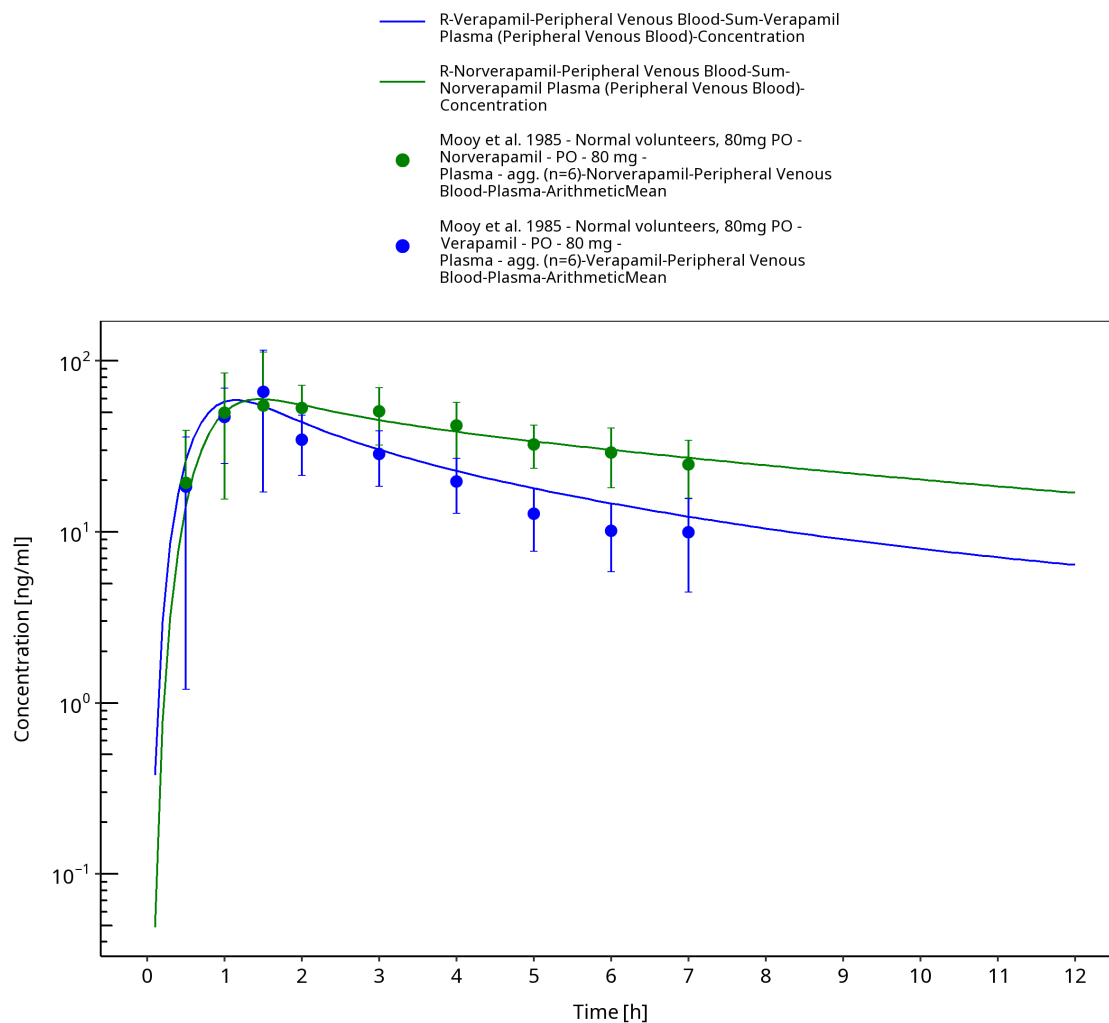
**Figure 3-6: Time Profile Analysis**



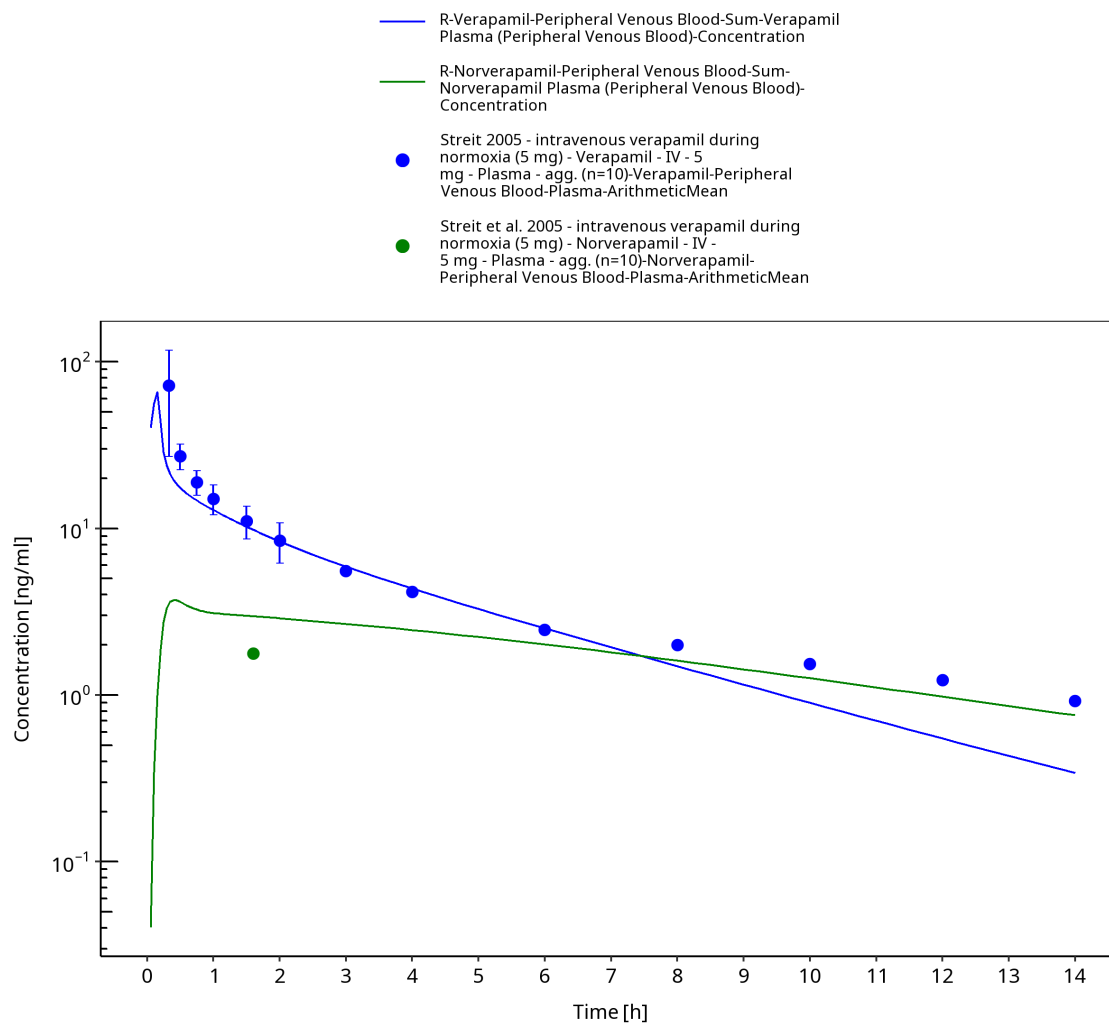
**Figure 3-7: Time Profile Analysis**



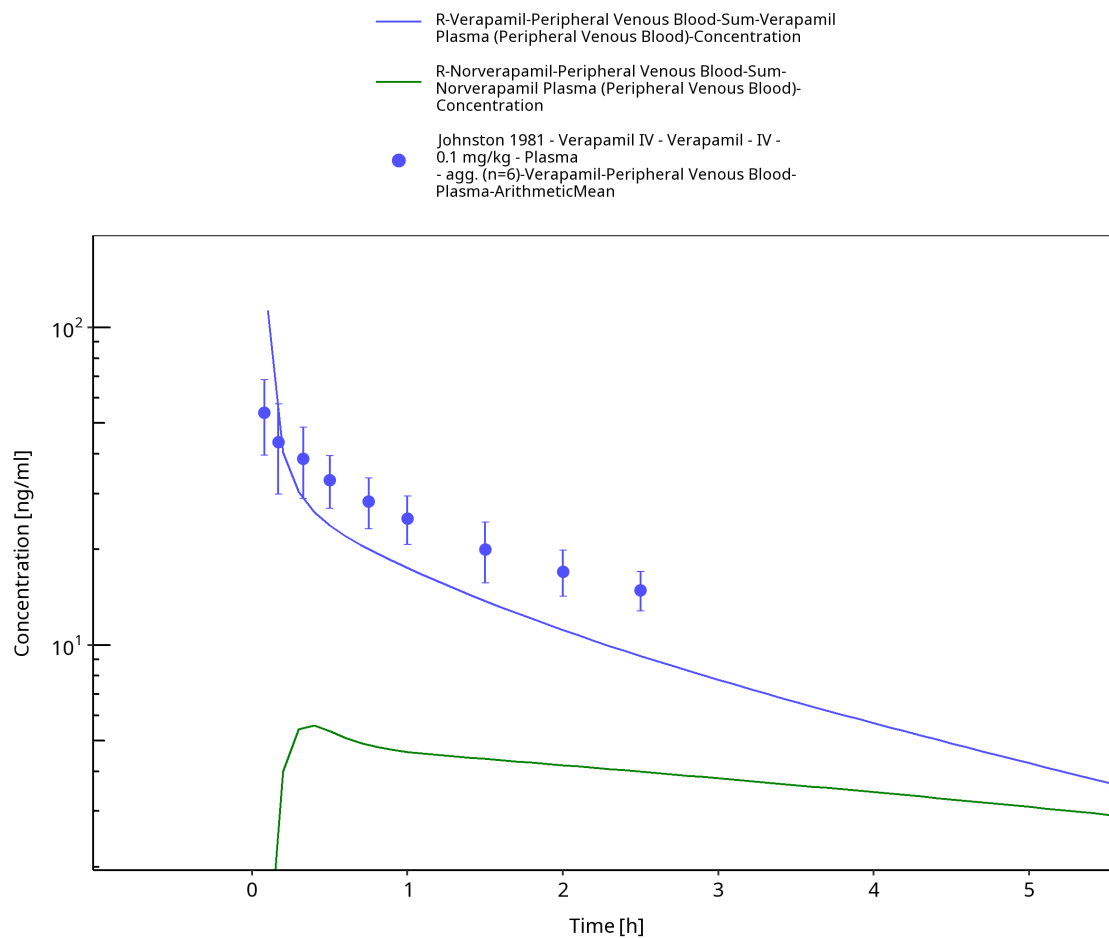
**Figure 3-8: Time Profile Analysis**



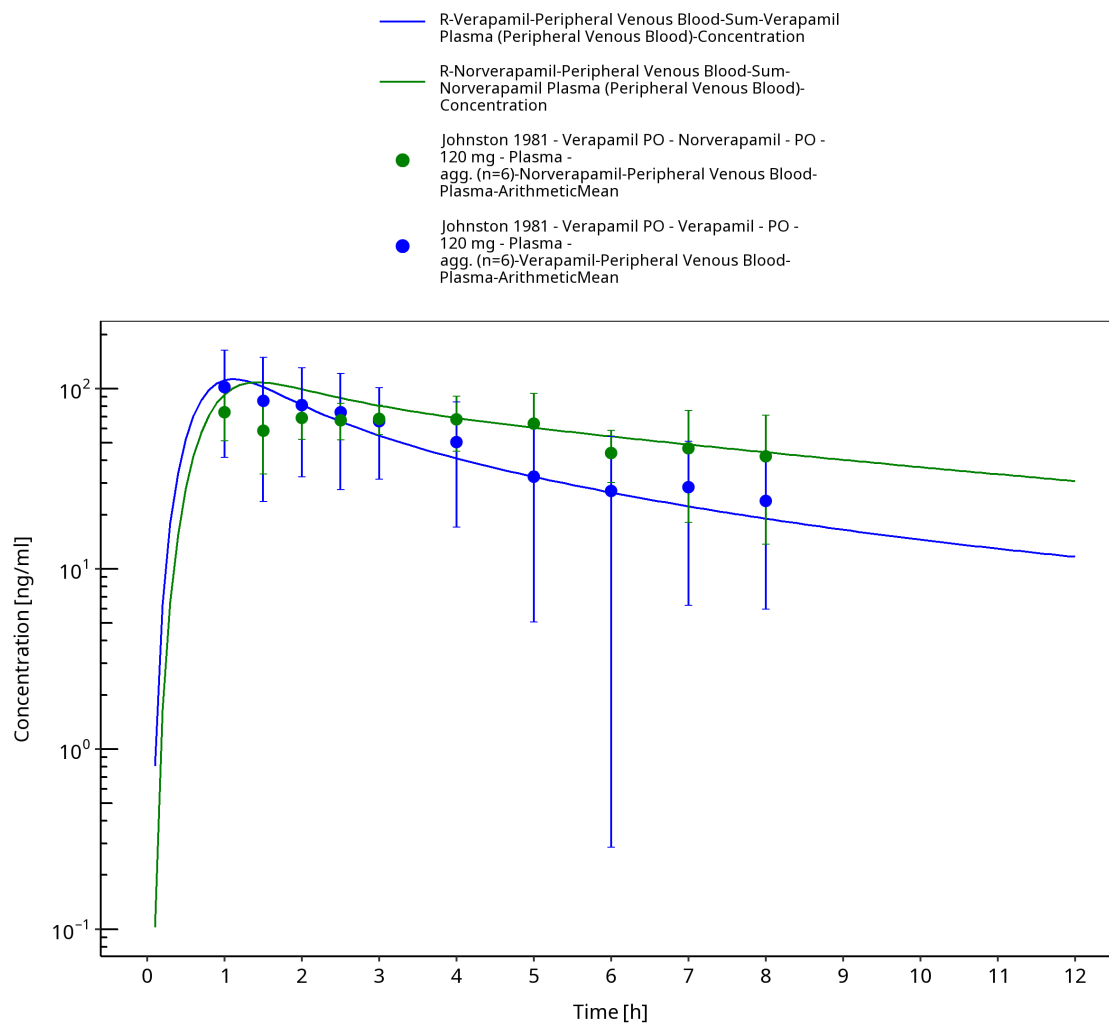
**Figure 3-9: Time Profile Analysis**



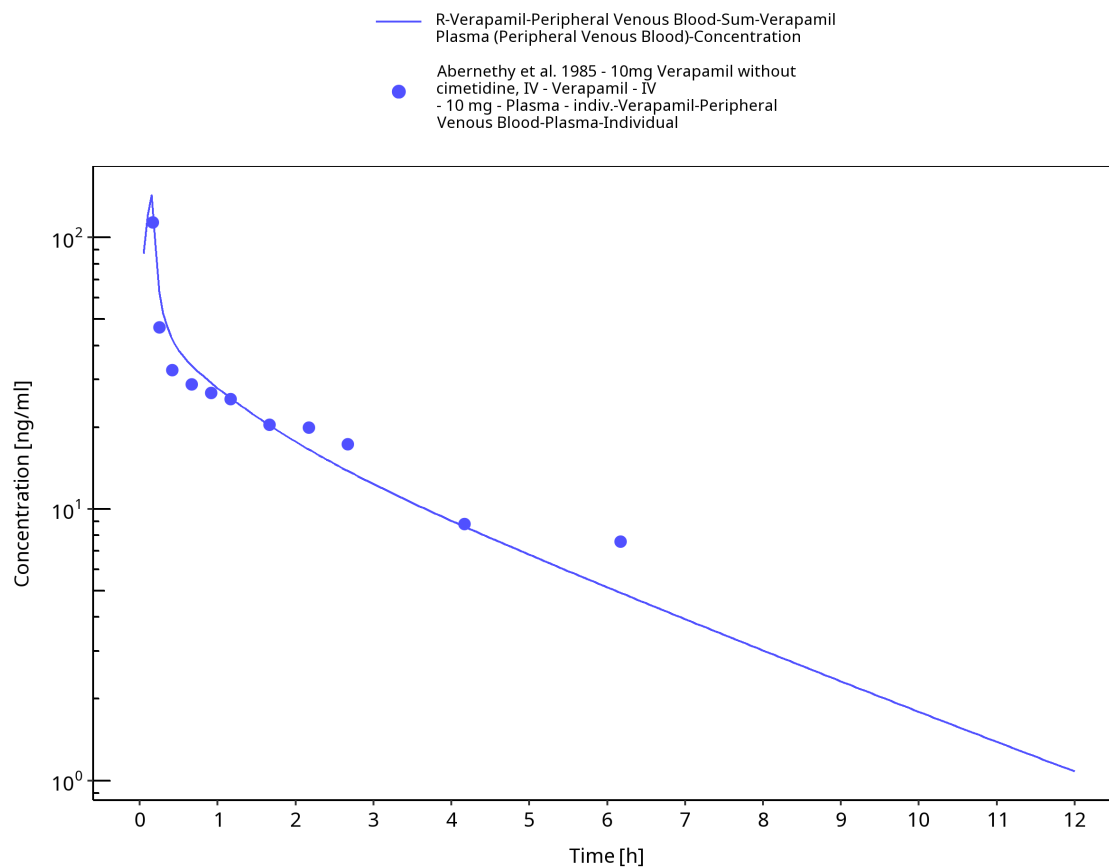
**Figure 3-10: Time Profile Analysis**



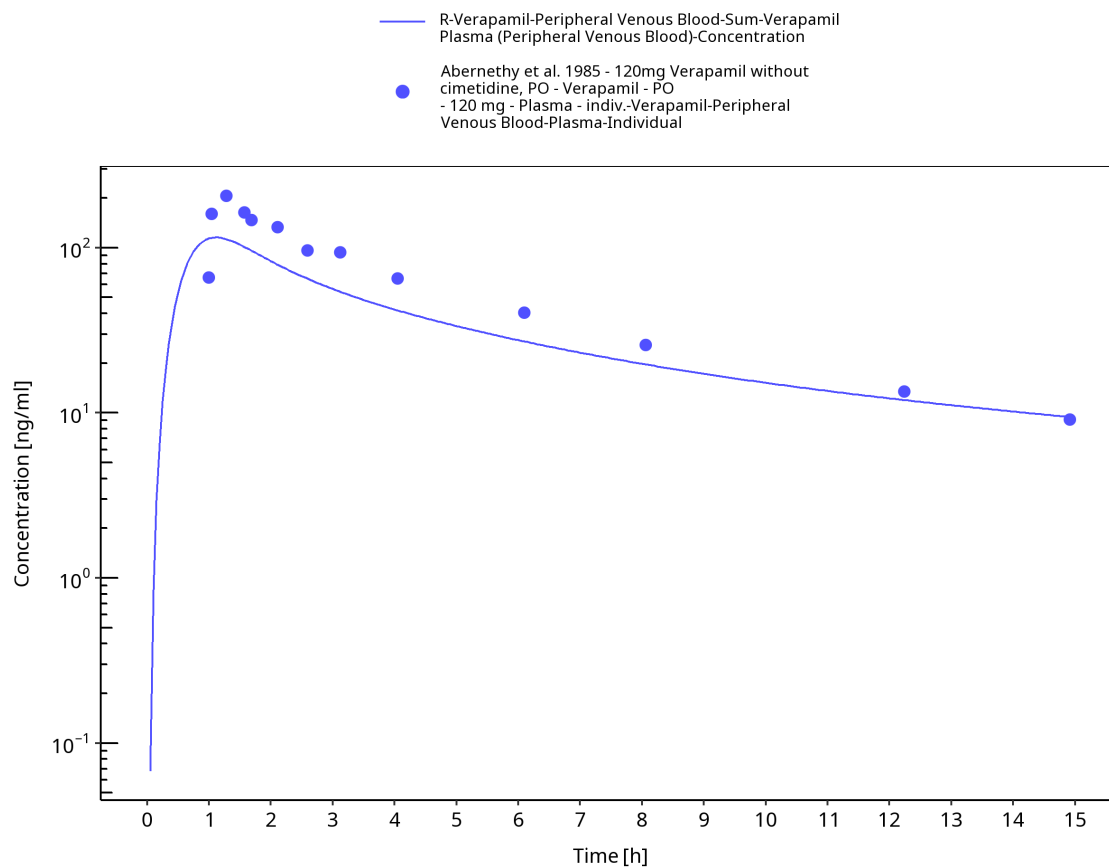
**Figure 3-11: Time Profile Analysis**



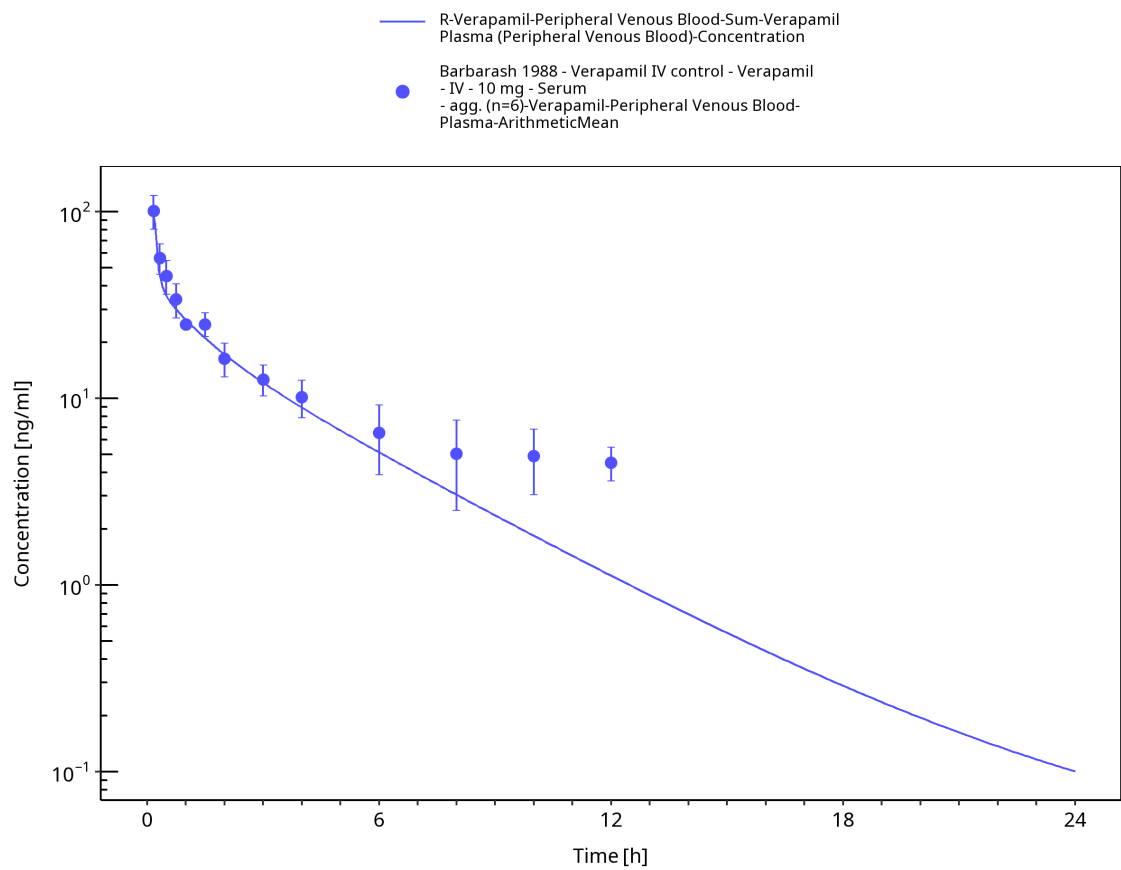
**Figure 3-12: Time Profile Analysis**



**Figure 3-13: Time Profile Analysis**



**Figure 3-14: Time Profile Analysis**



**Figure 3-15: Time Profile Analysis**

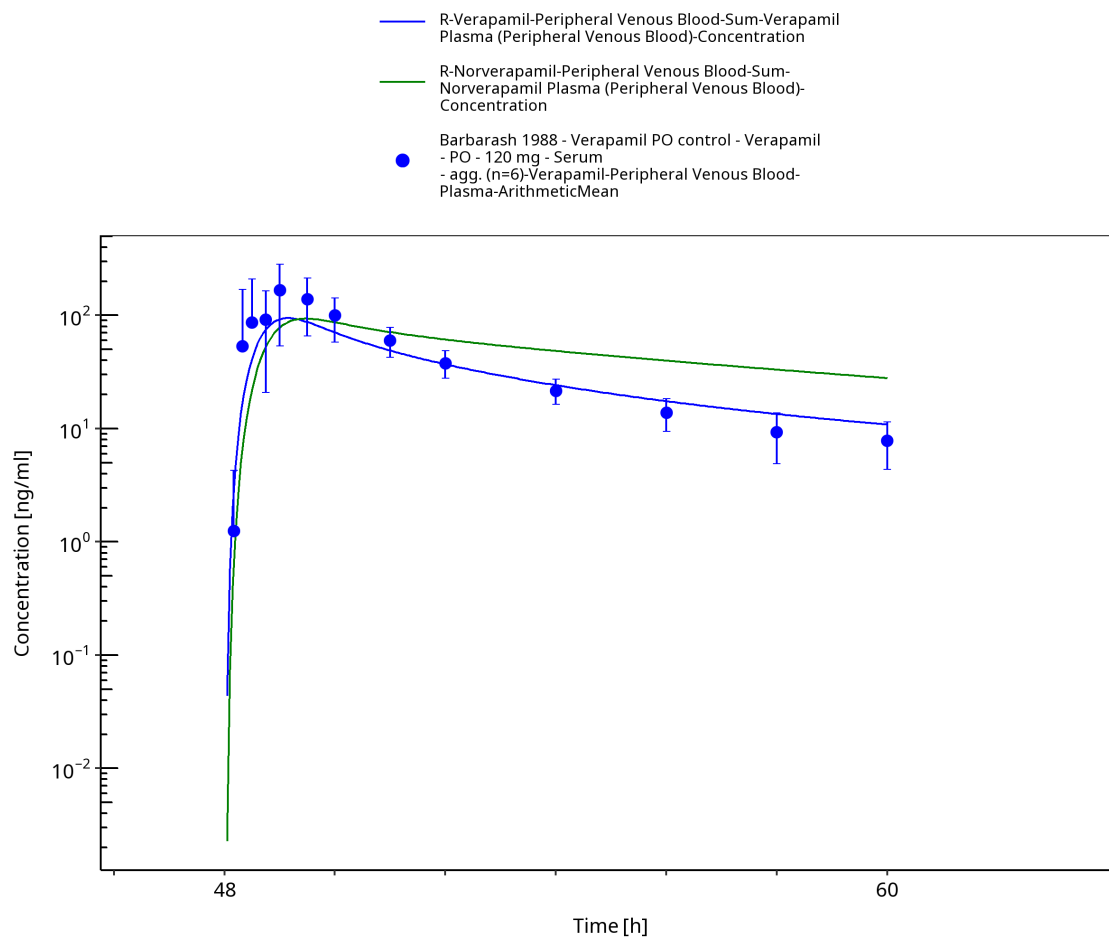
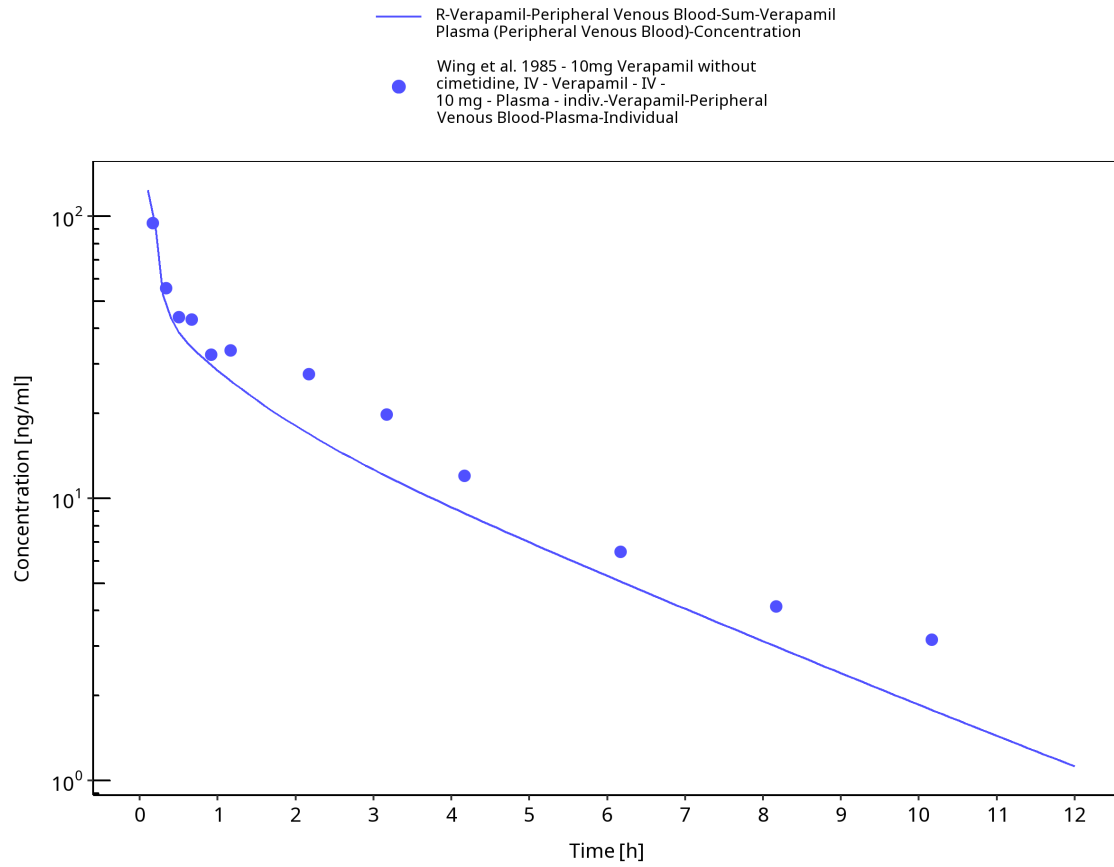
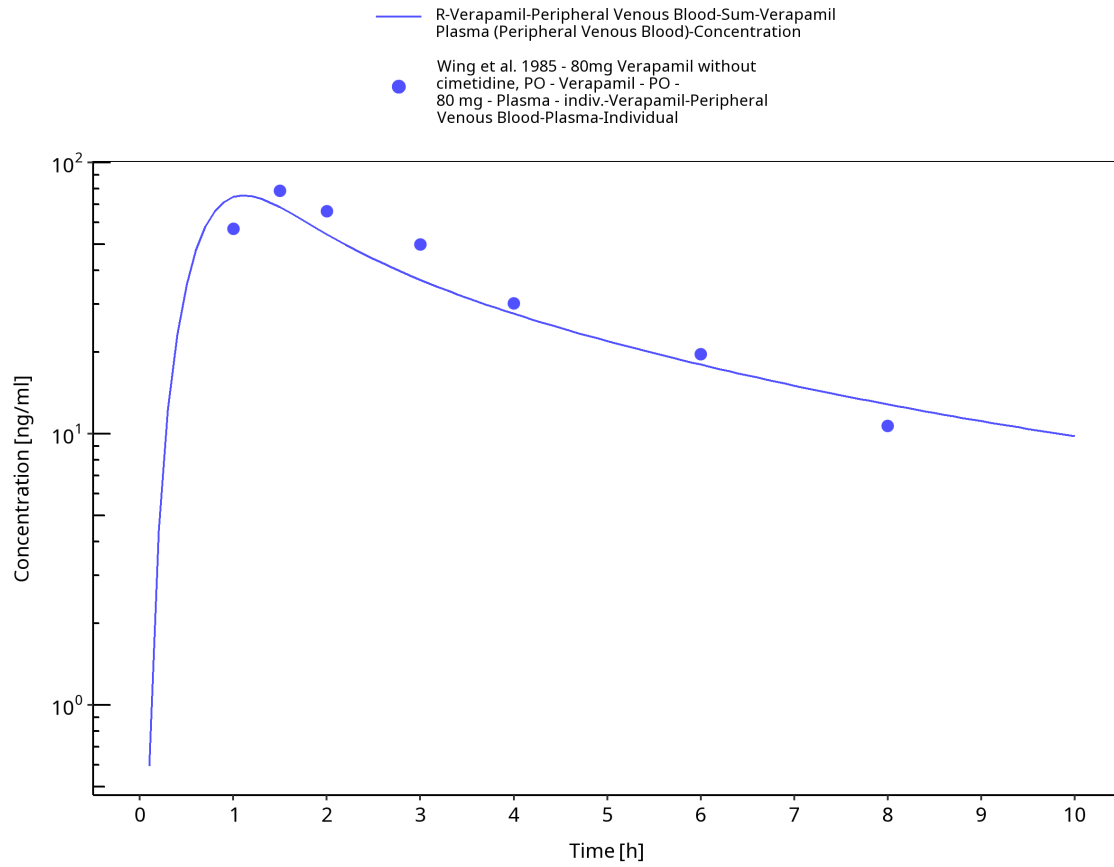


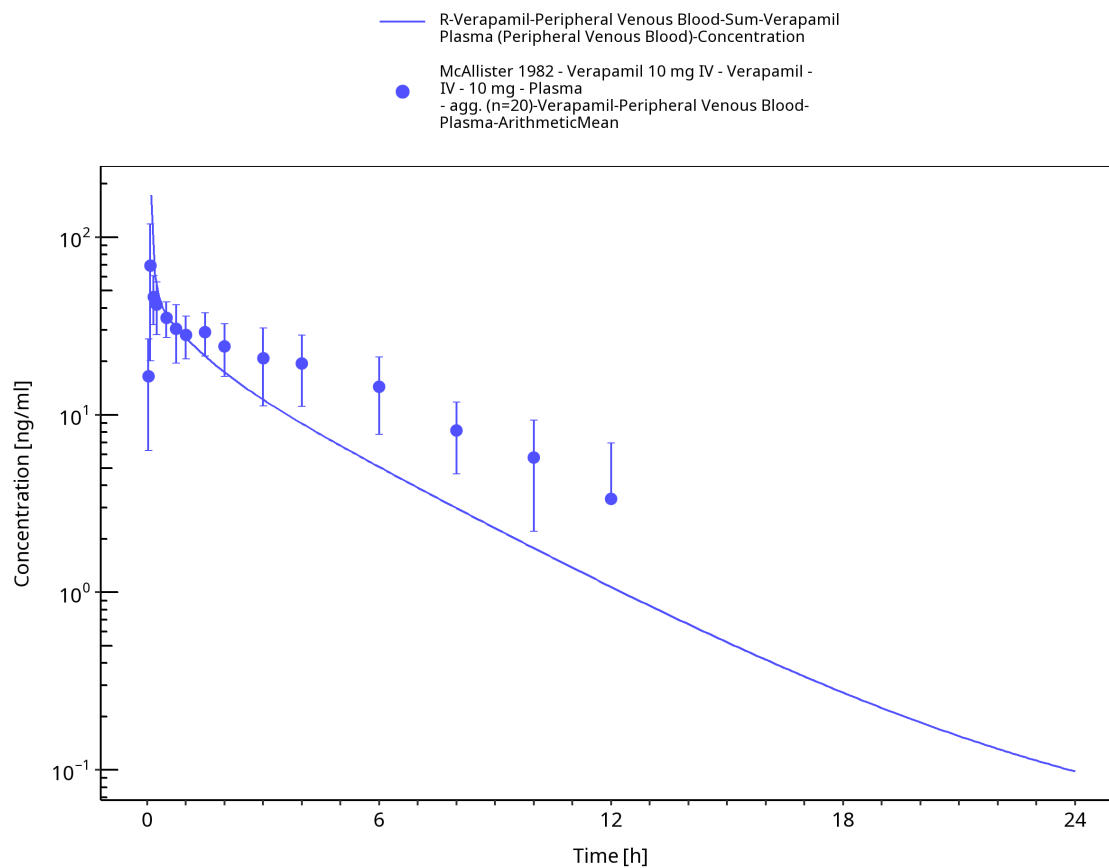
Figure 3-16: Time Profile Analysis



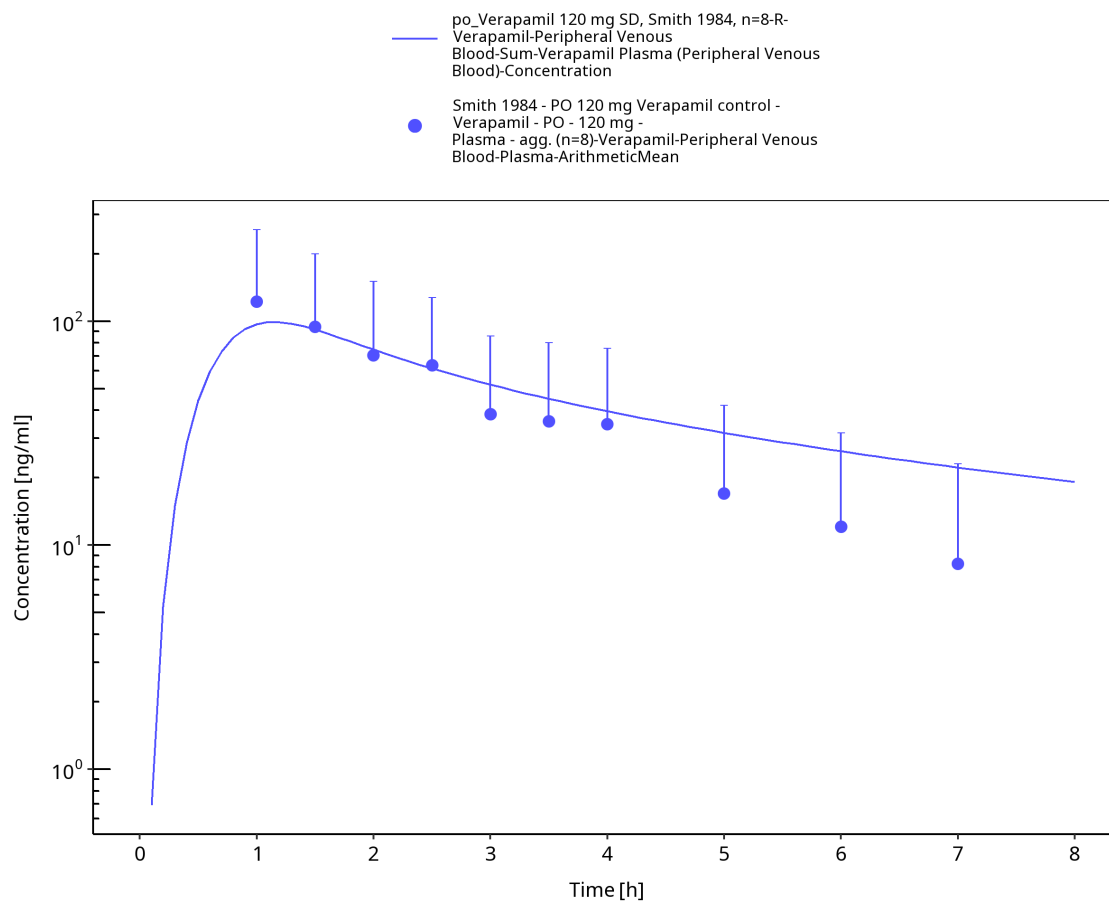
**Figure 3-17: Time Profile Analysis**



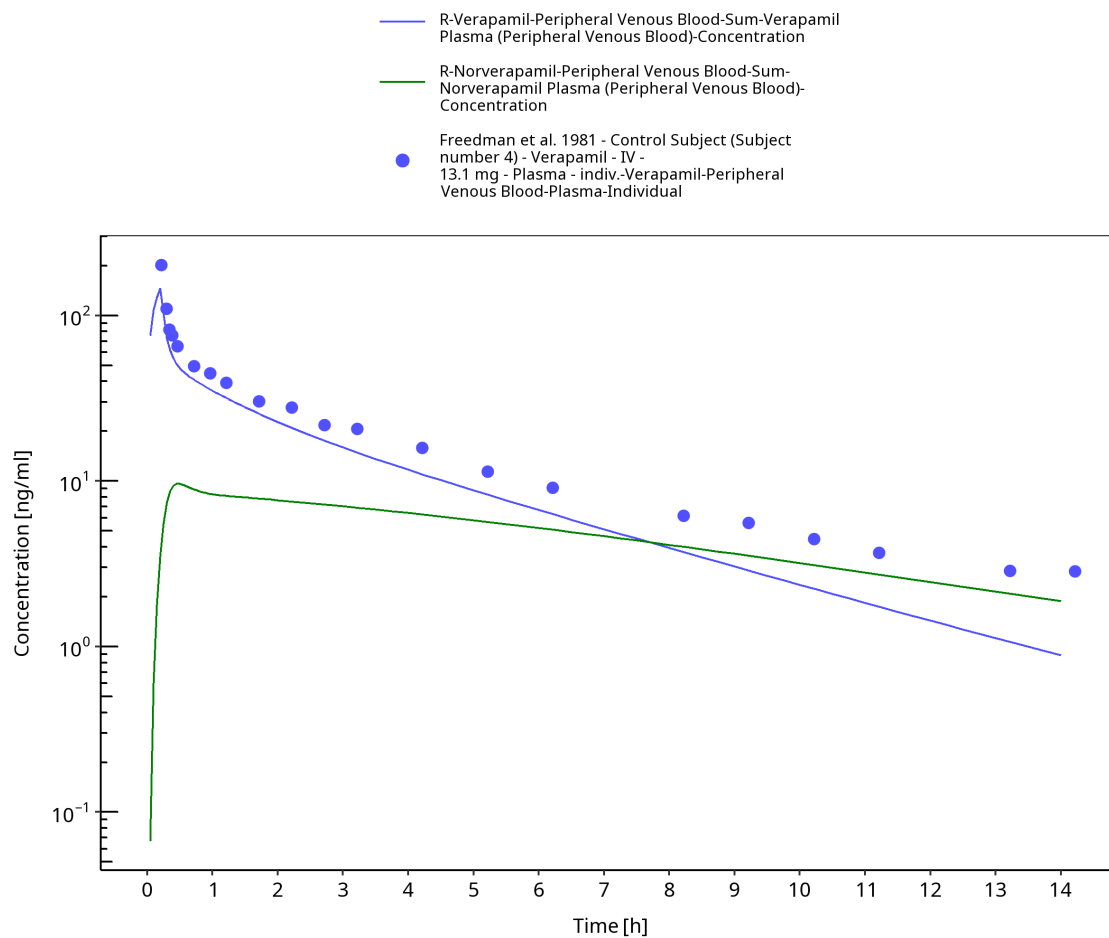
**Figure 3-18: Time Profile Analysis**



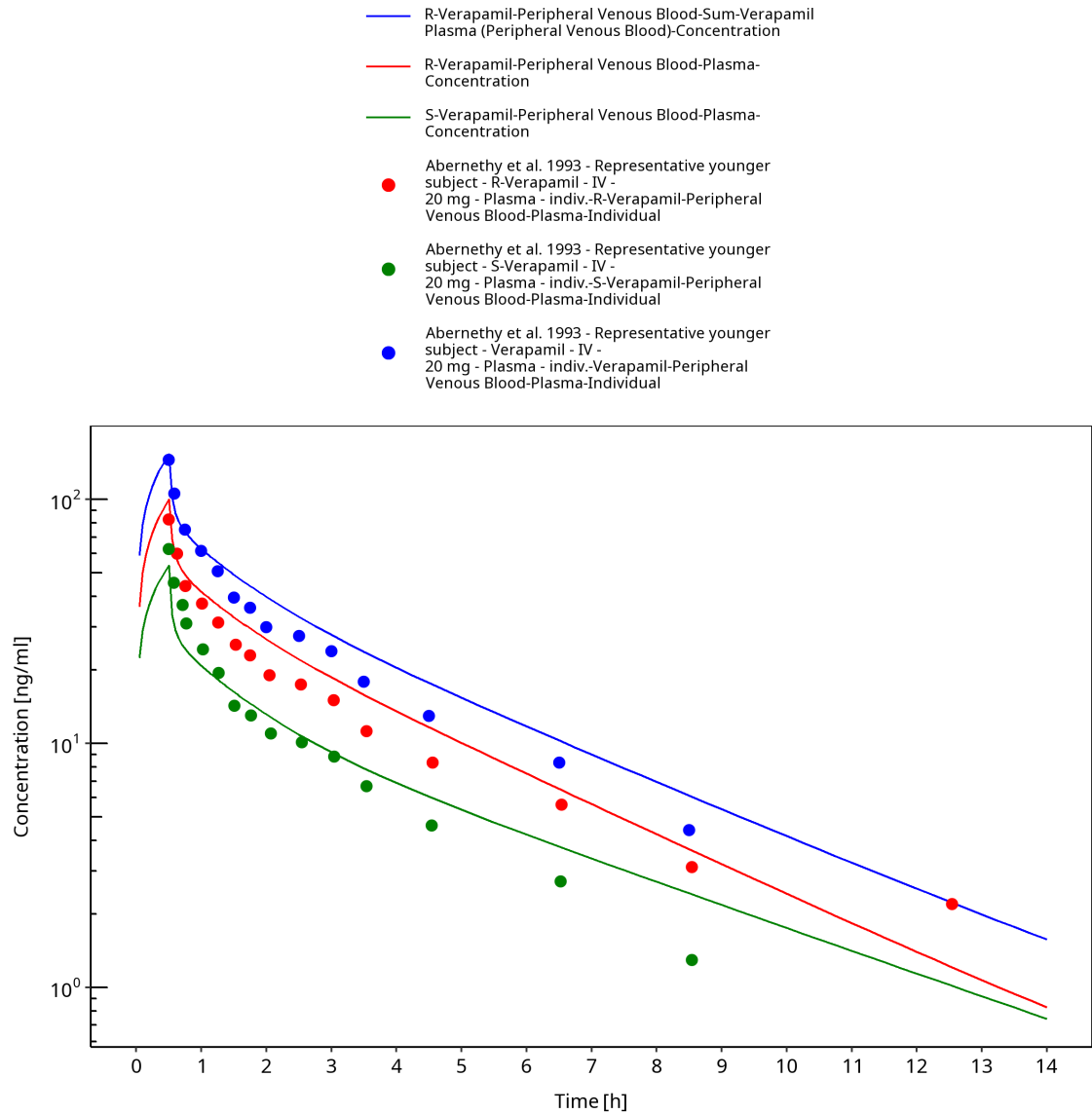
**Figure 3-19: Time Profile Analysis**



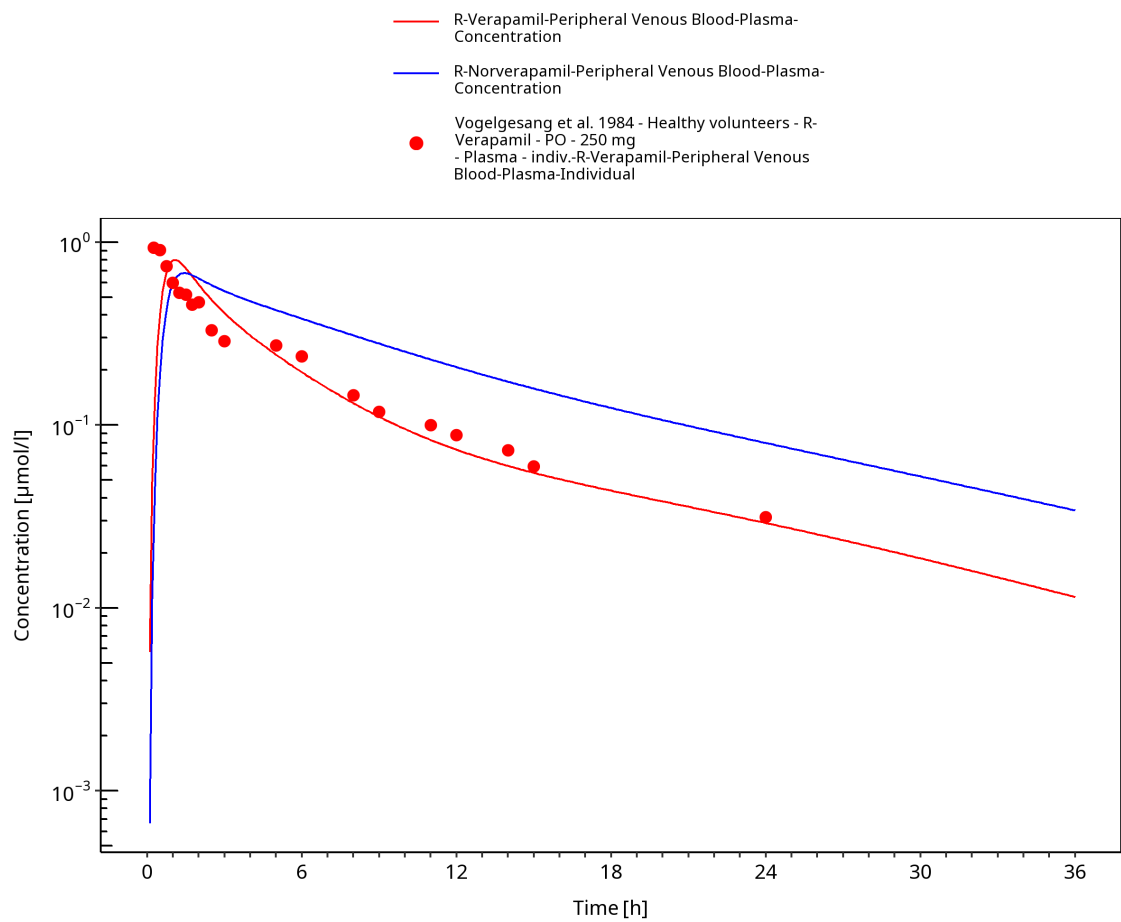
**Figure 3-20: Time Profile Analysis**



**Figure 3-21: Time Profile Analysis**



**Figure 3-22: Time Profile Analysis**



**Figure 3-23: Time Profile Analysis**

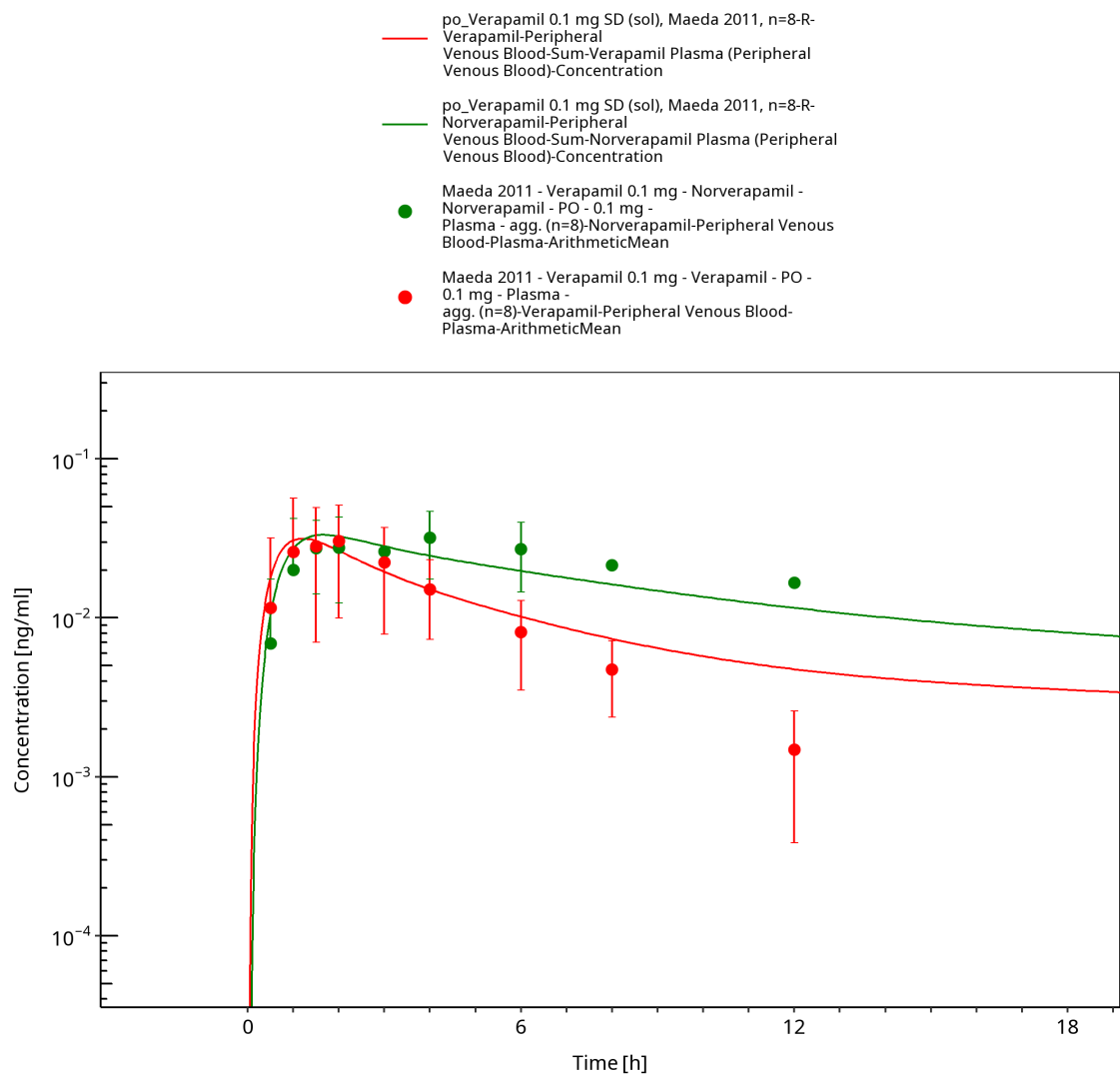


Figure 3-24: Time Profile Analysis

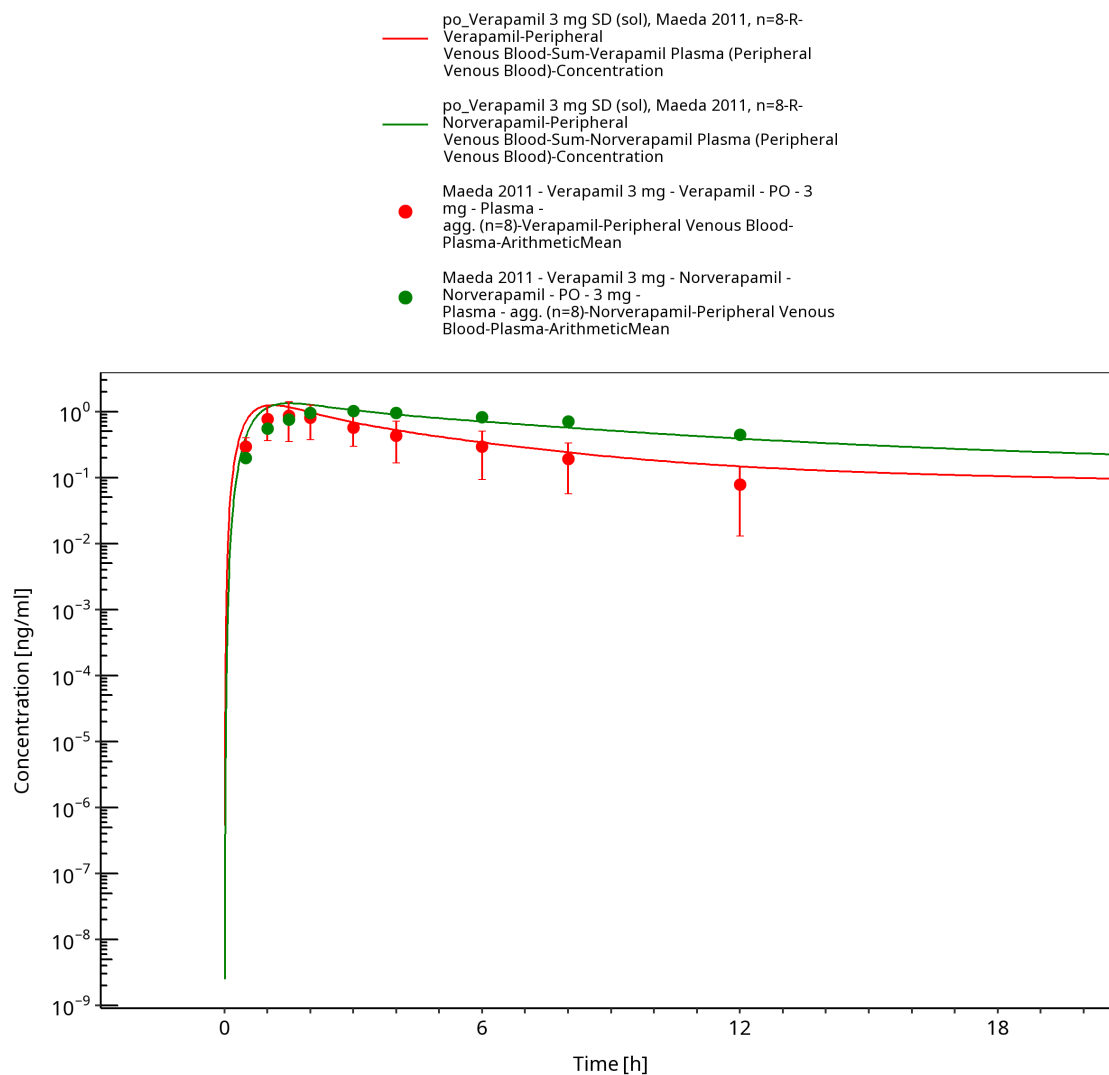


Figure 3-25: Time Profile Analysis

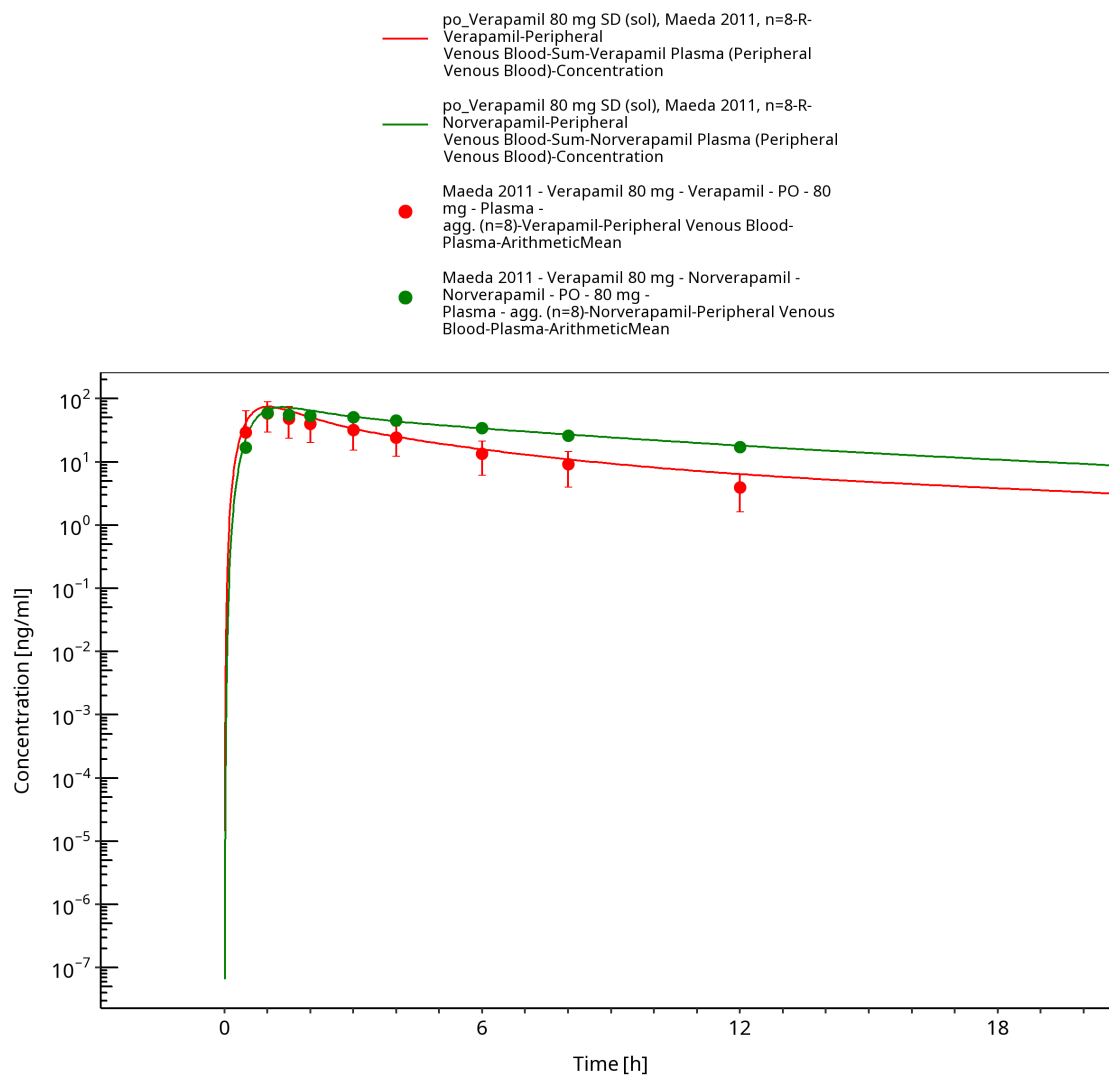
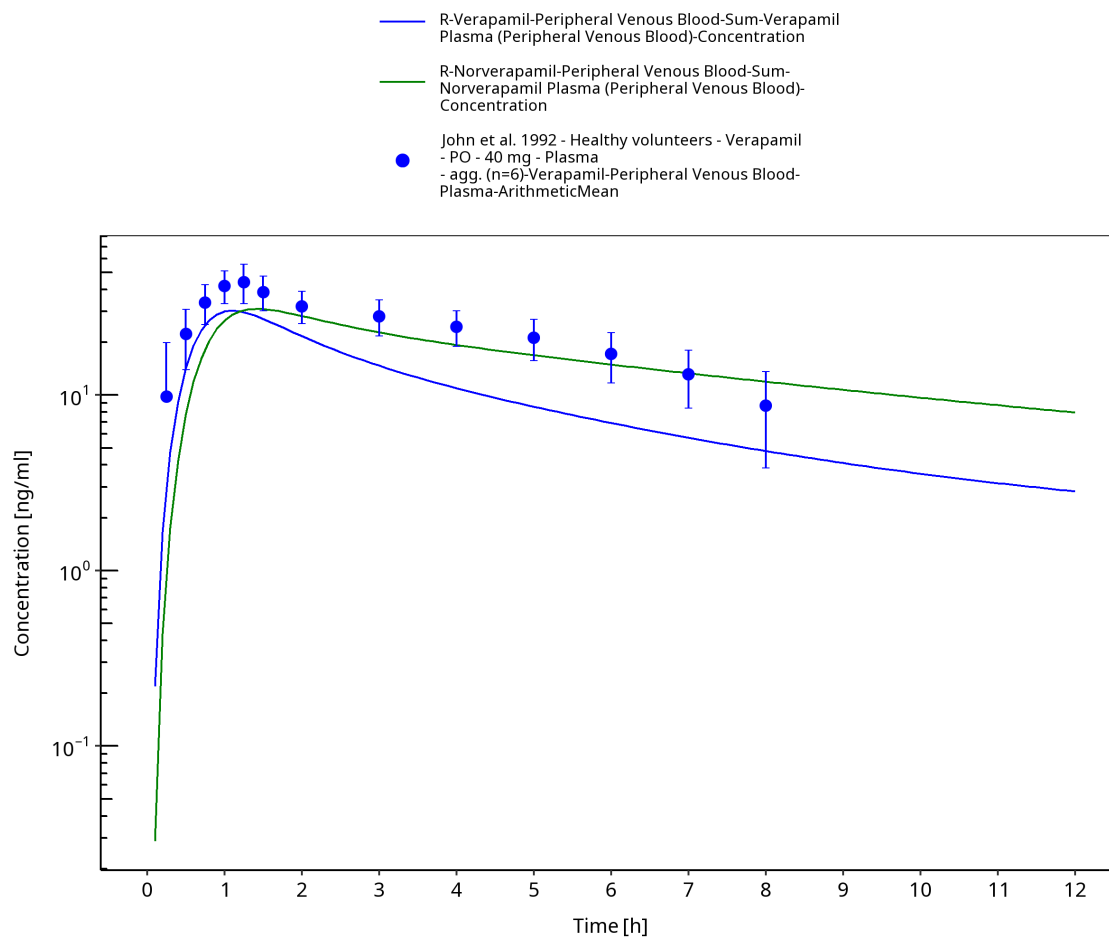
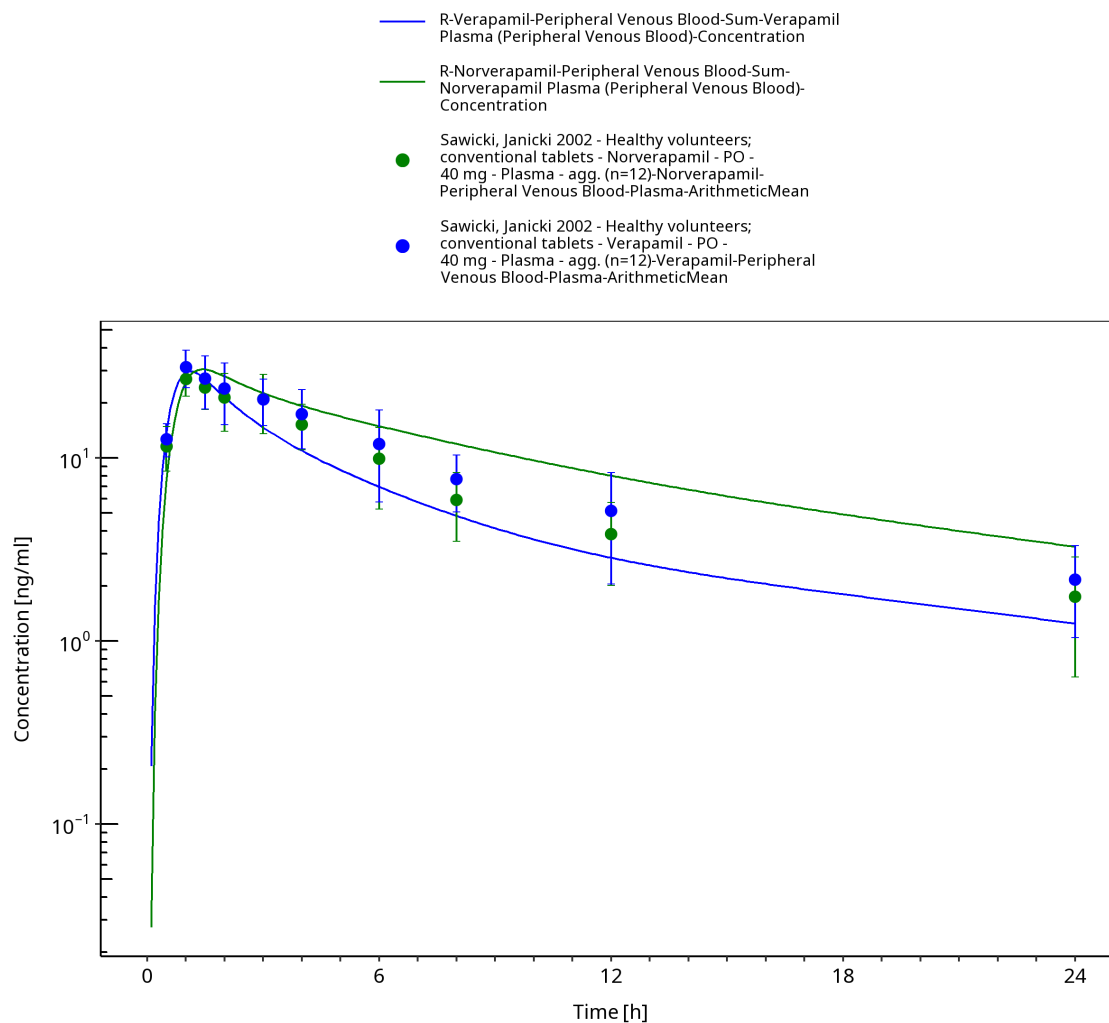


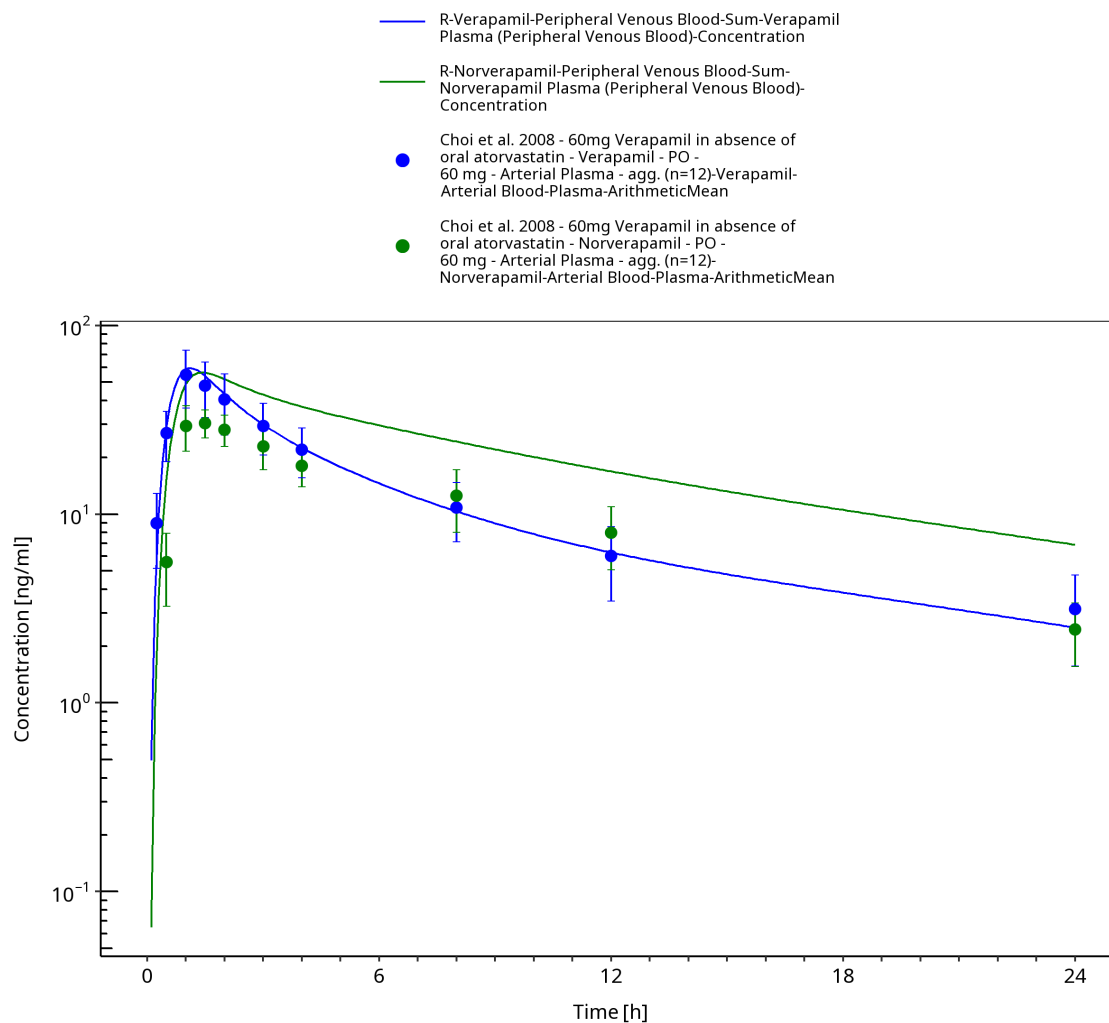
Figure 3-26: Time Profile Analysis



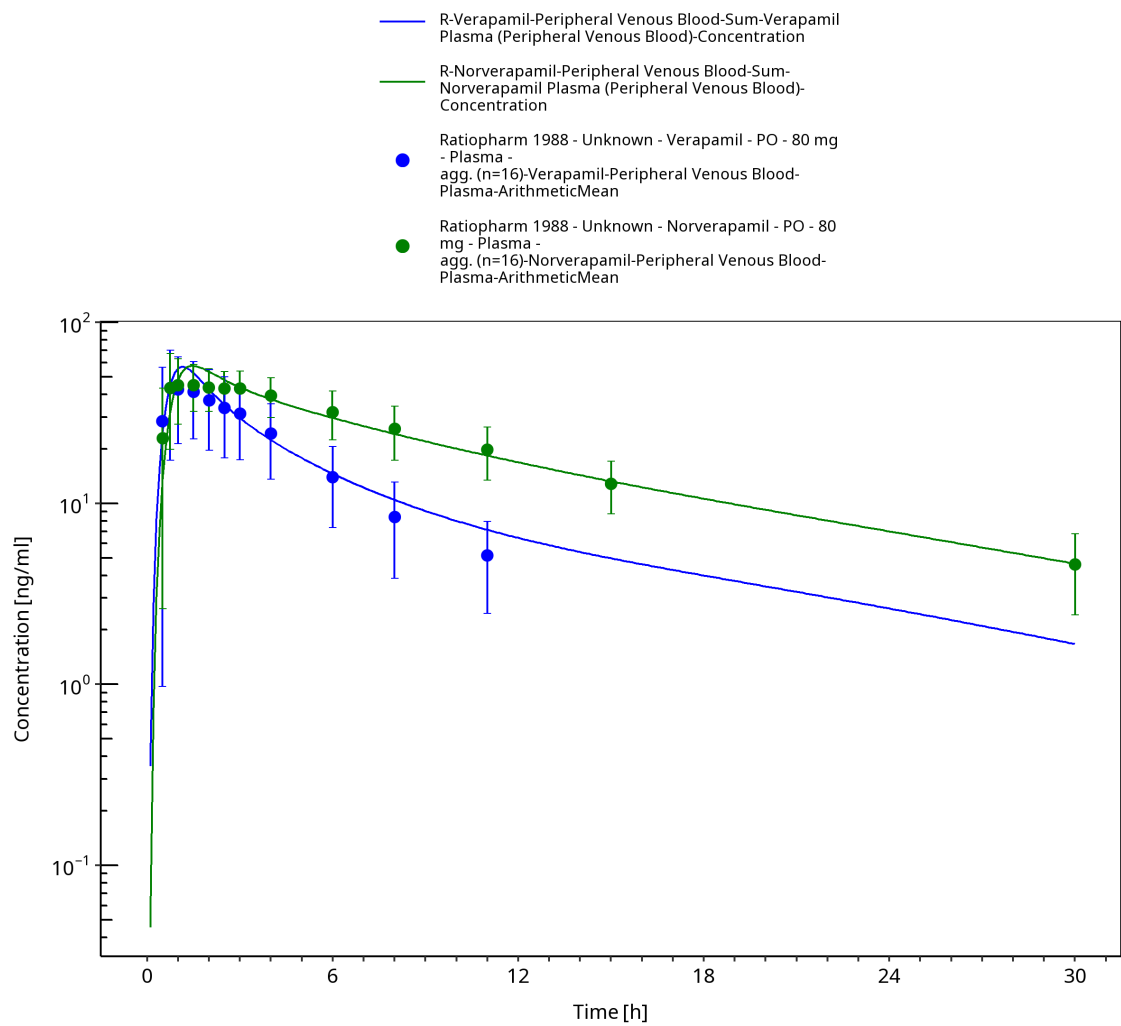
**Figure 3-27: Time Profile Analysis**



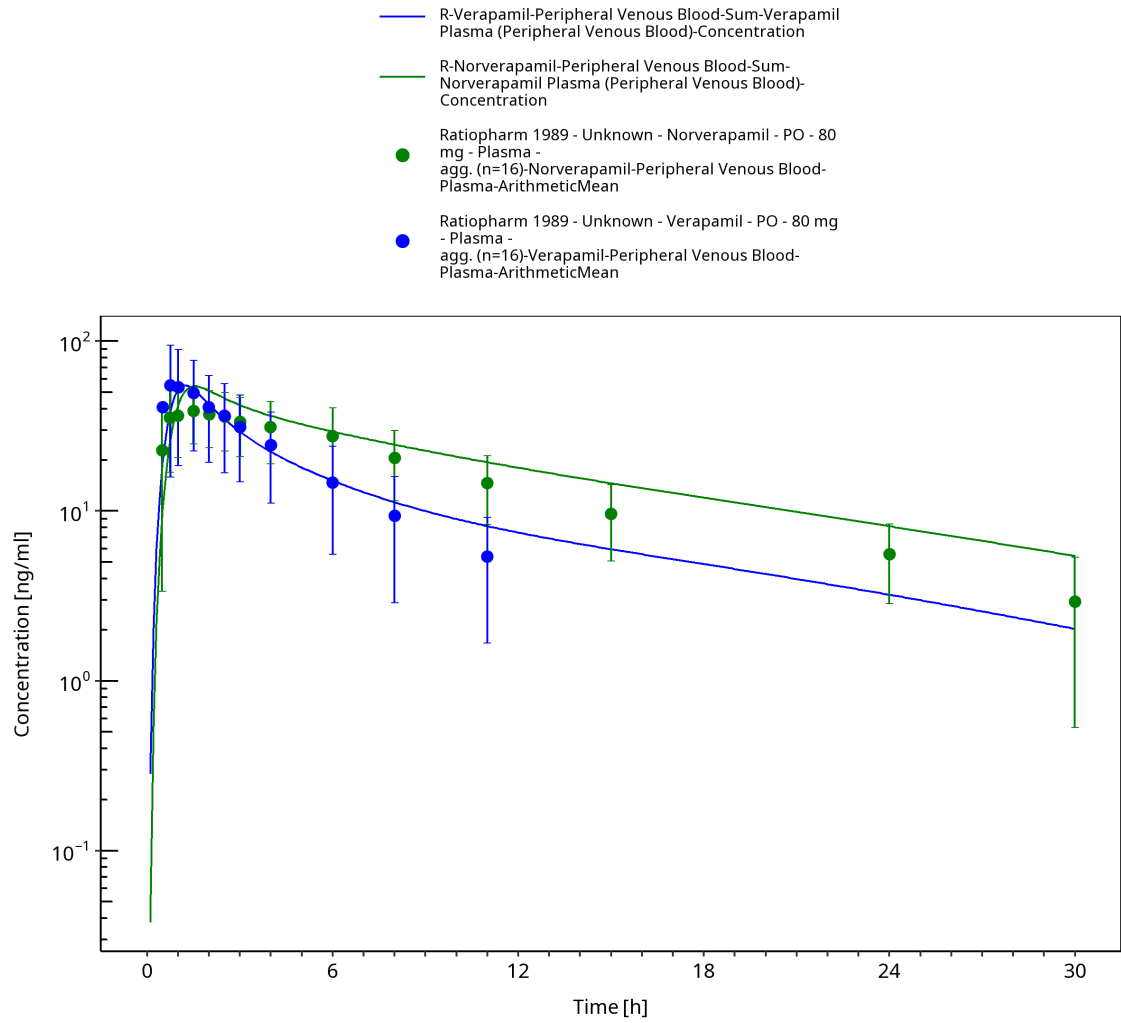
**Figure 3-28: Time Profile Analysis**



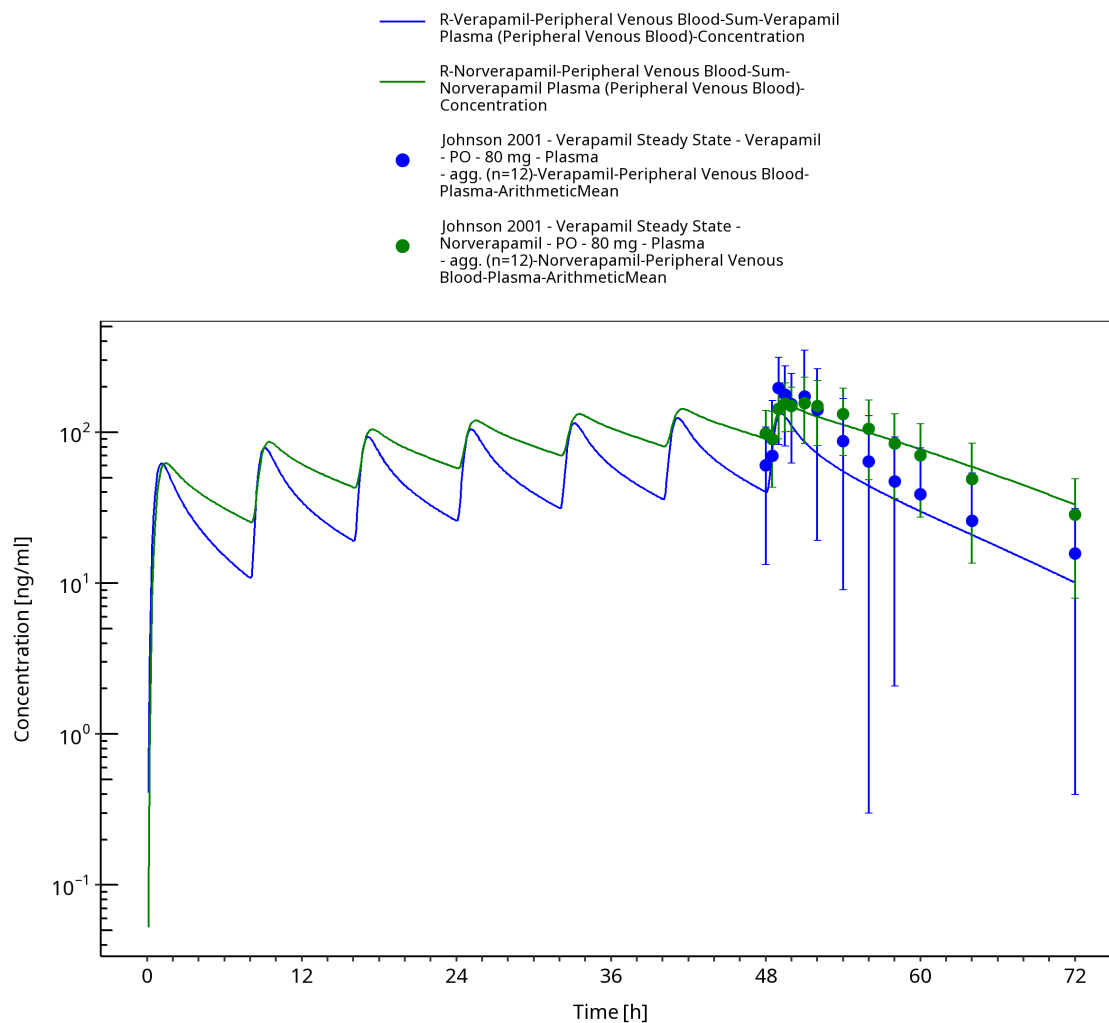
**Figure 3-29: Time Profile Analysis**



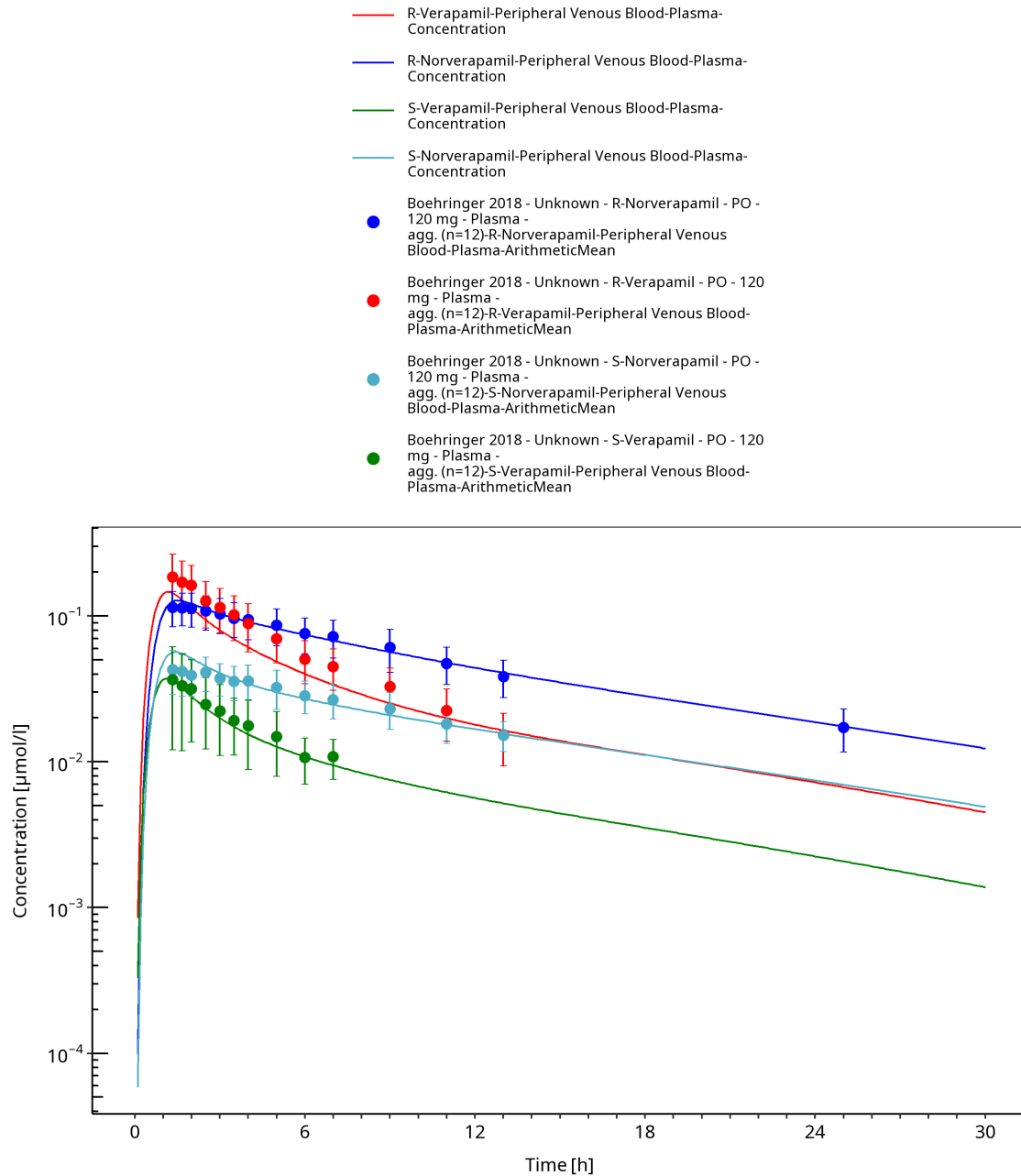
**Figure 3-30: Time Profile Analysis**



**Figure 3-31: Time Profile Analysis**



**Figure 3-32: Time Profile Analysis**



**Figure 3-33: Time Profile Analysis**

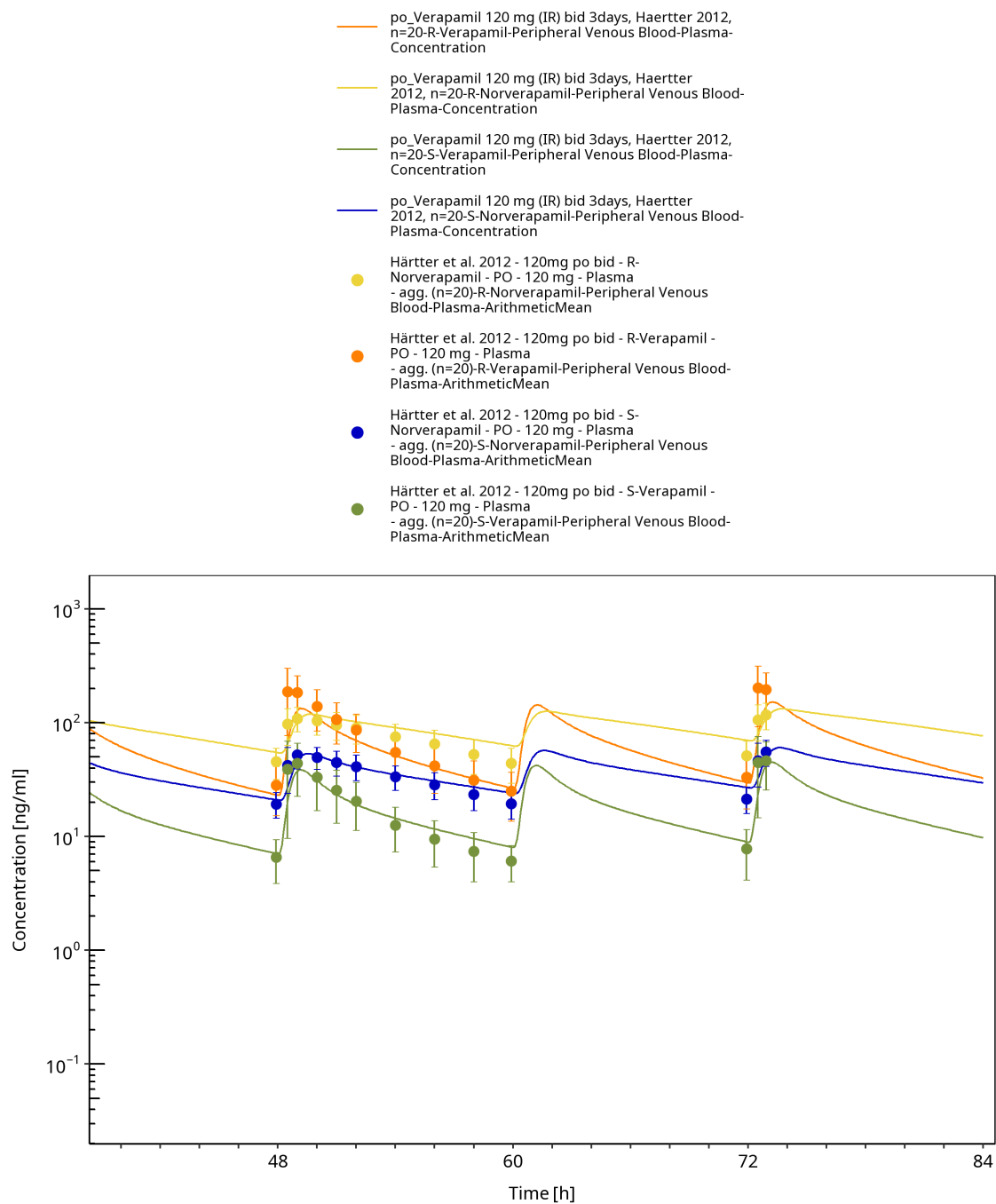
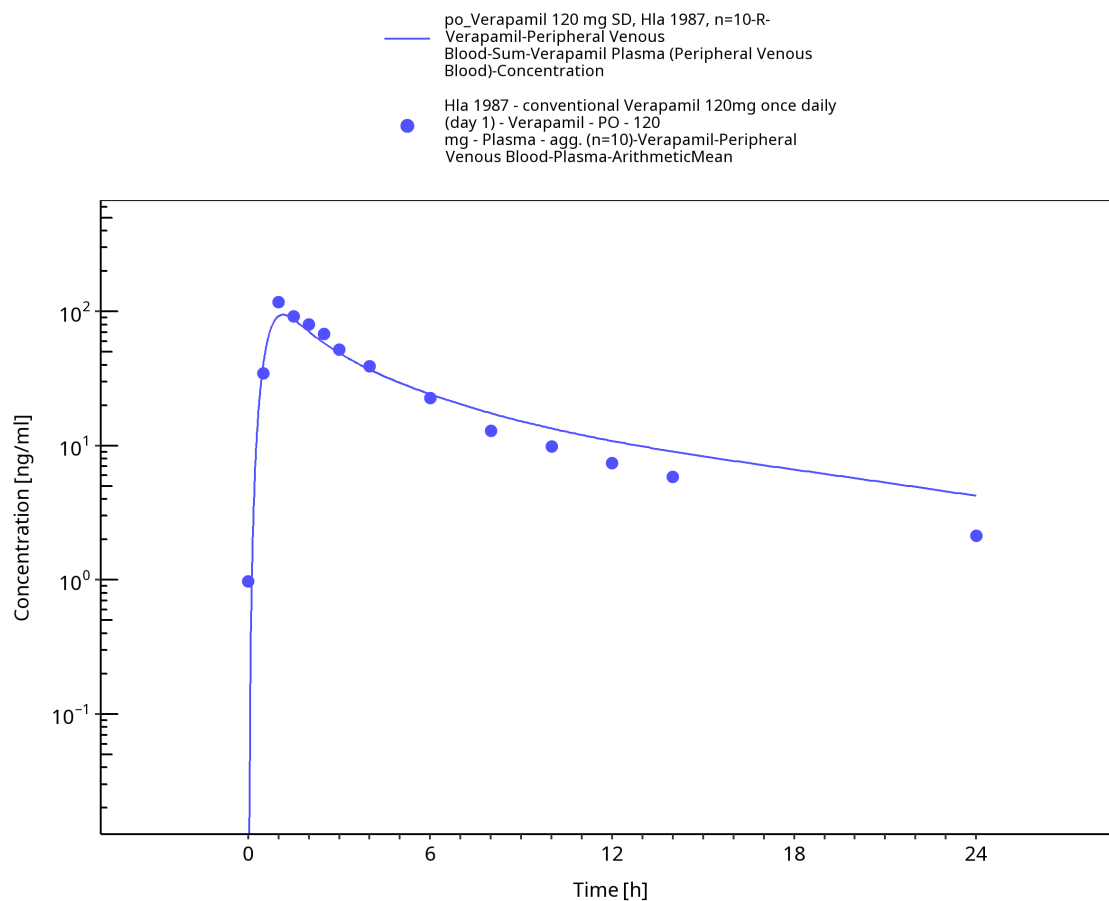
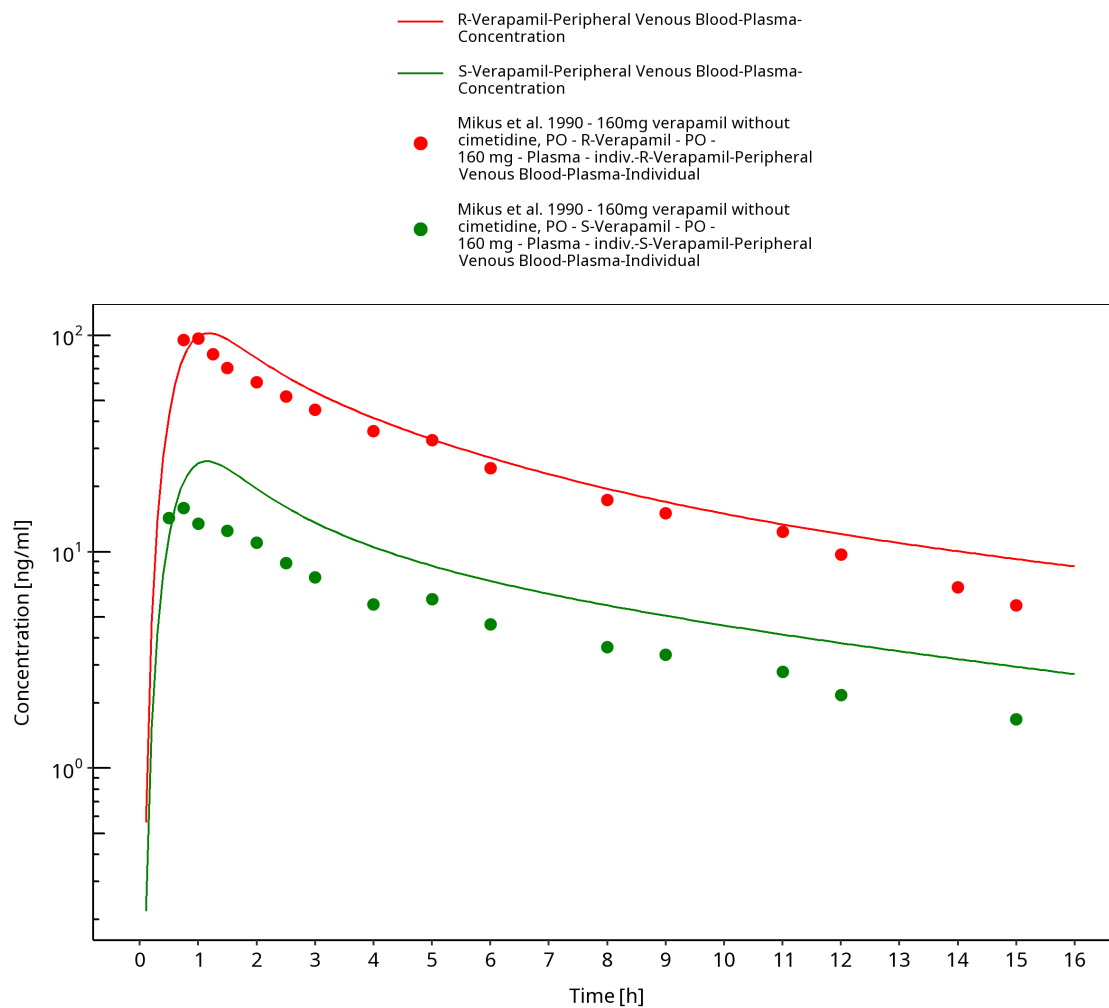


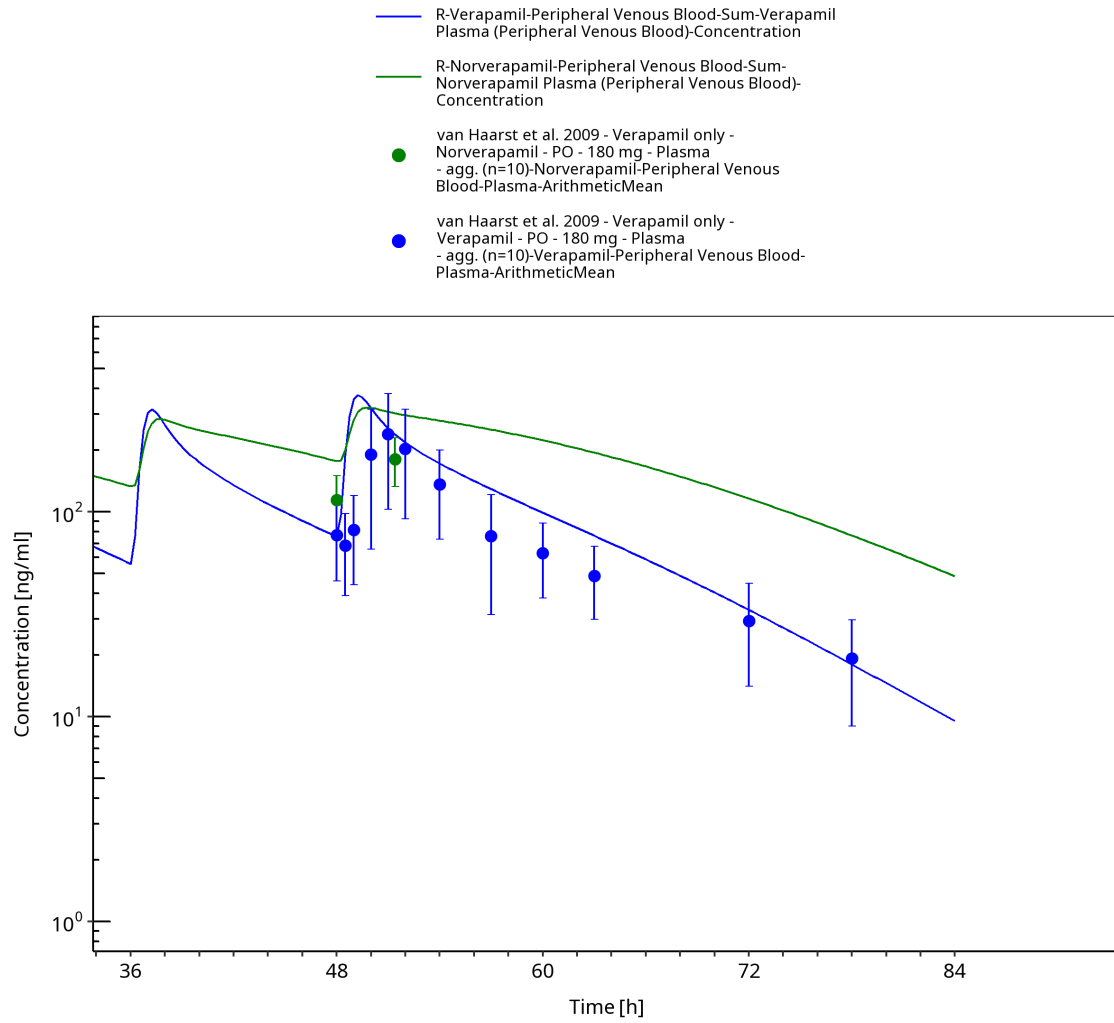
Figure 3-34: Time Profile Analysis



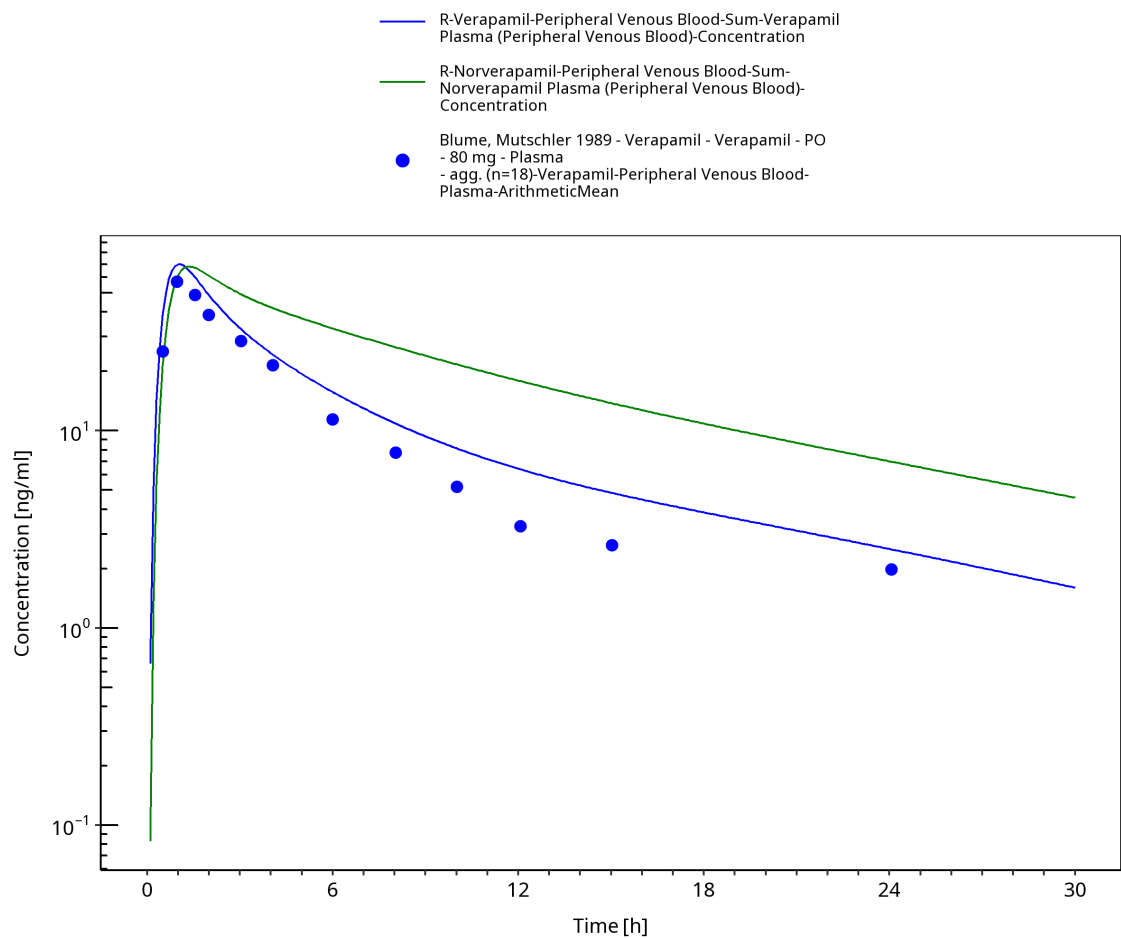
**Figure 3-35: Time Profile Analysis**



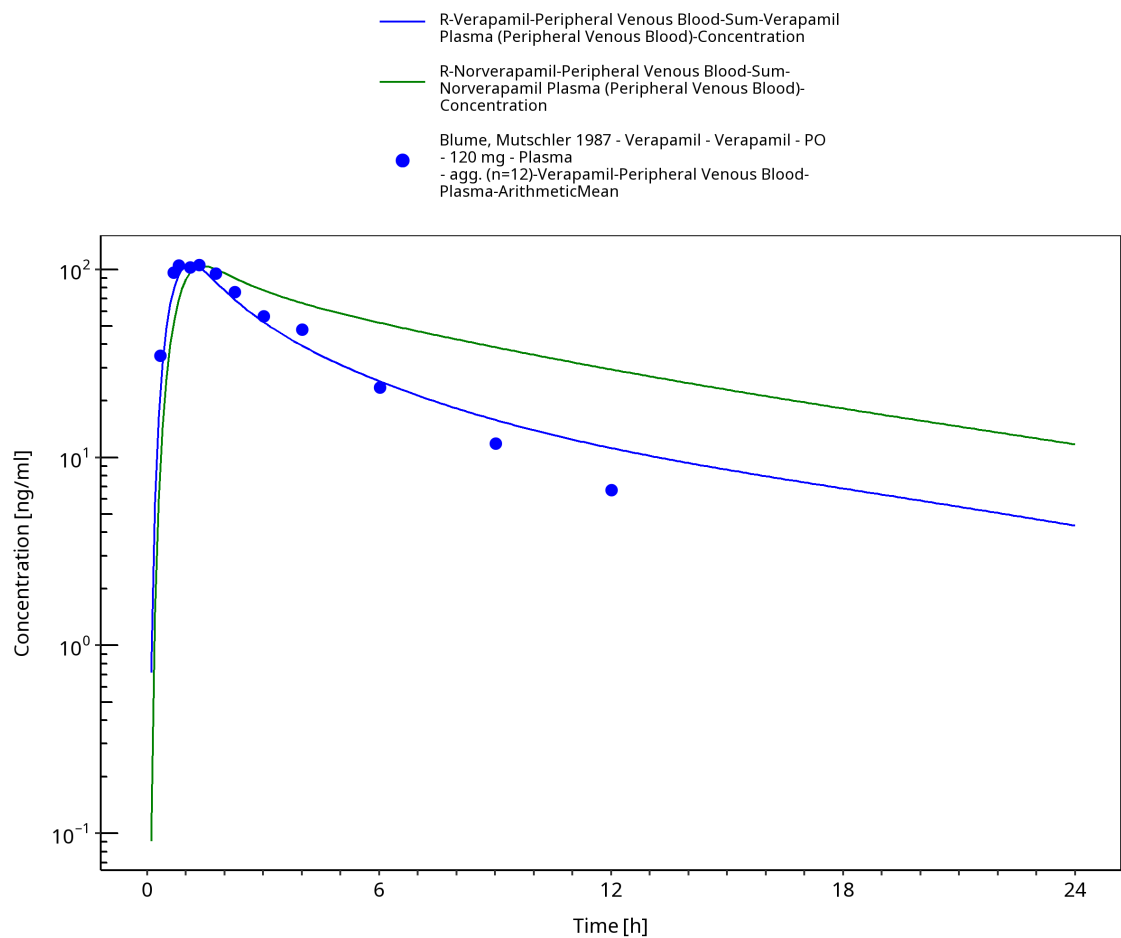
**Figure 3-36: Time Profile Analysis**



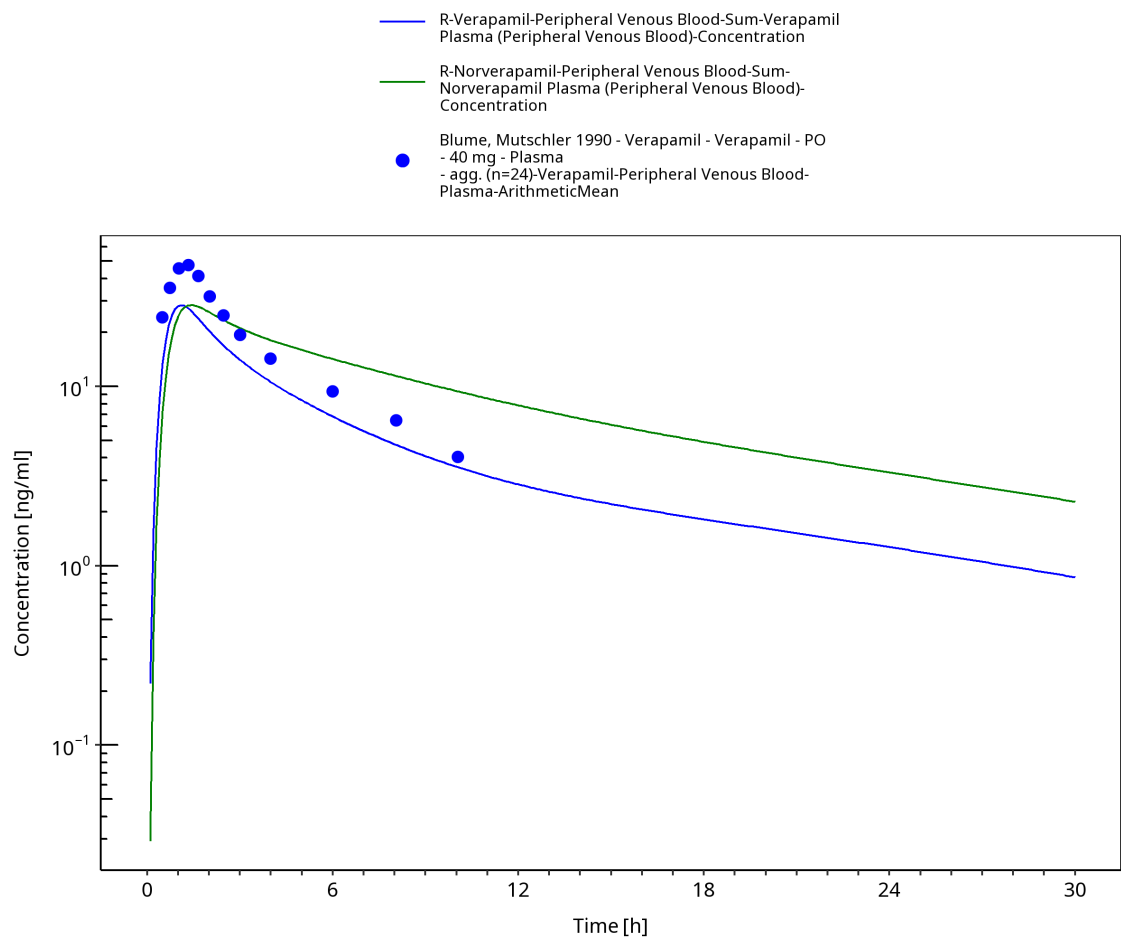
**Figure 3-37: Time Profile Analysis**



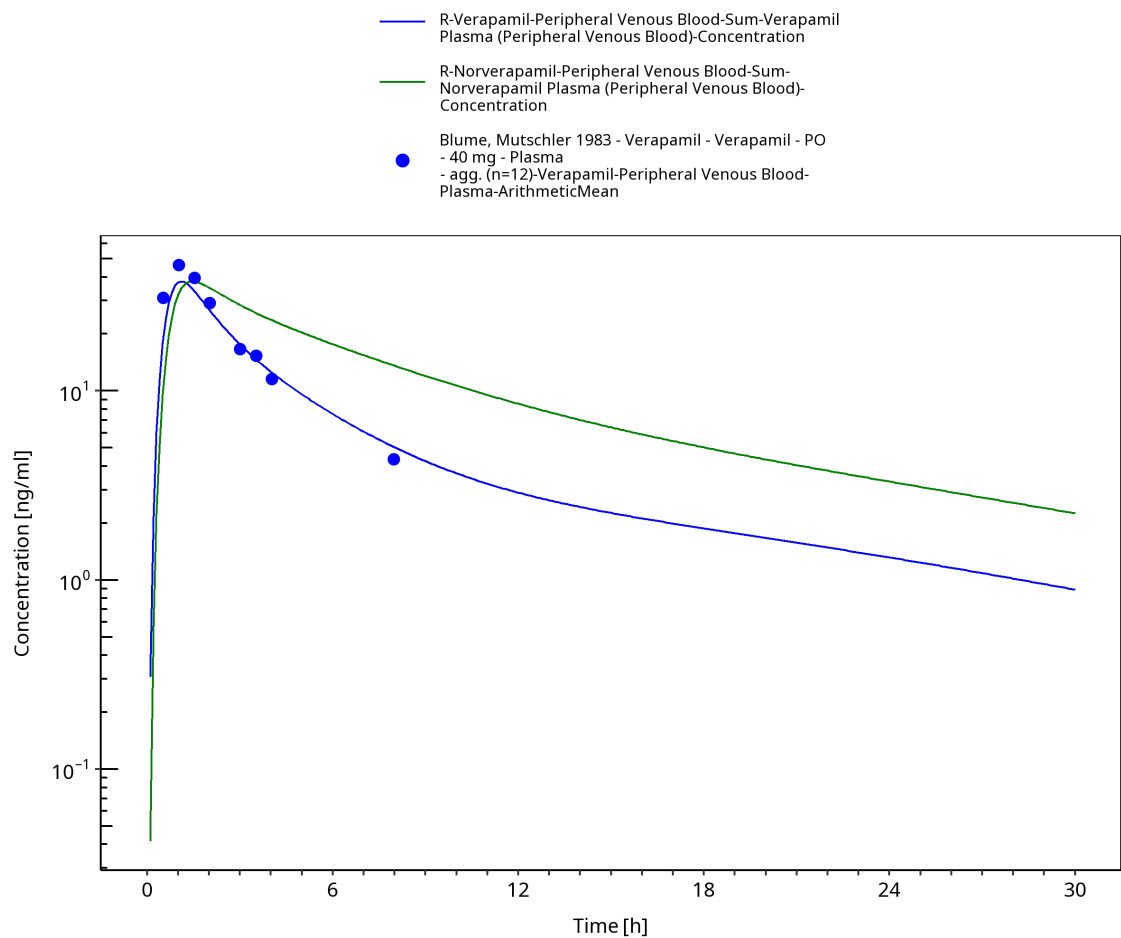
**Figure 3-38: Time Profile Analysis**



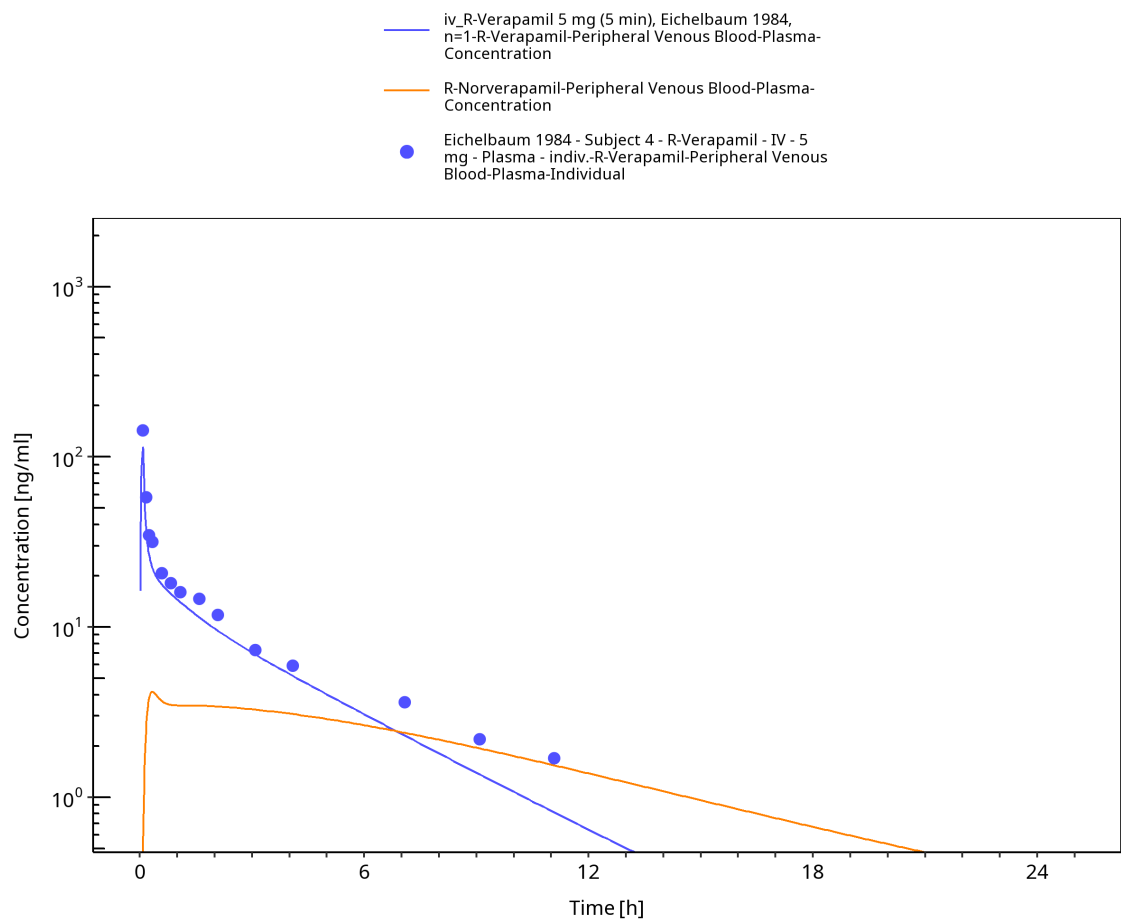
**Figure 3-39: Time Profile Analysis**



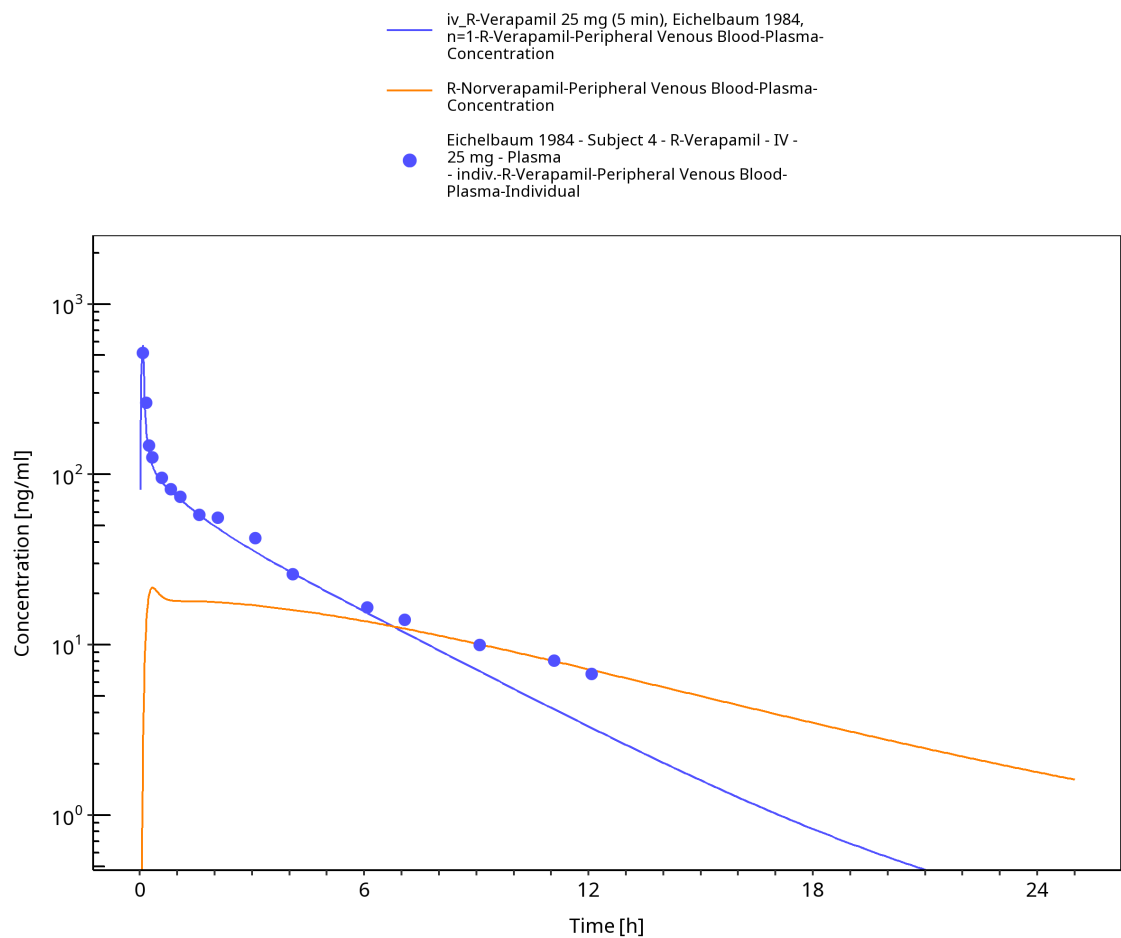
**Figure 3-40: Time Profile Analysis**



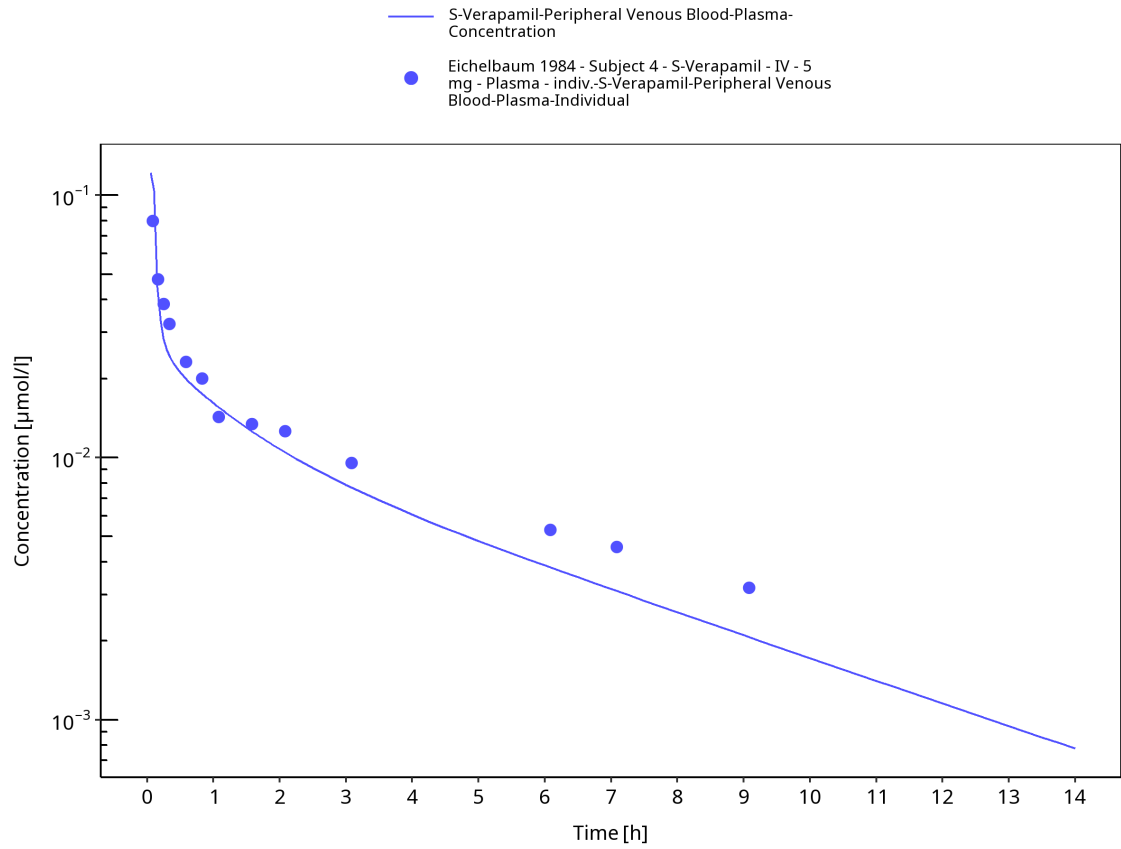
**Figure 3-41: Time Profile Analysis**



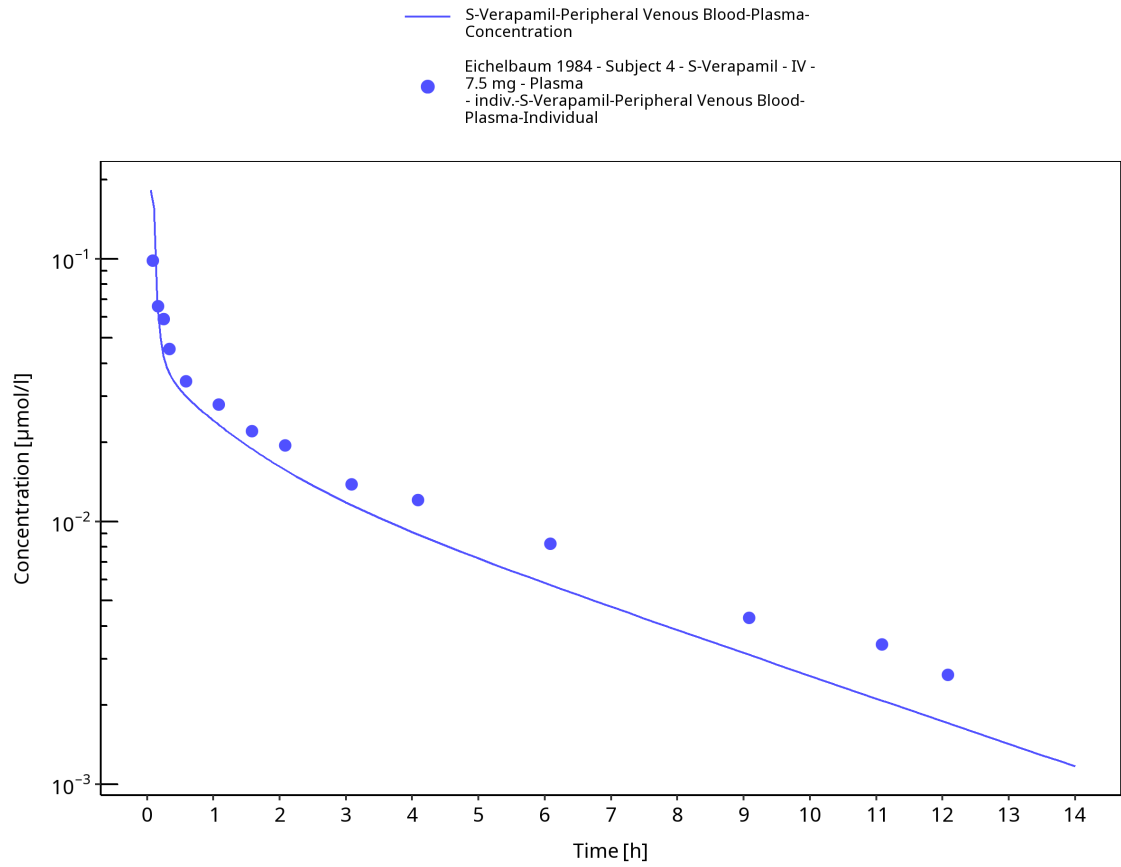
**Figure 3-42: Time Profile Analysis**



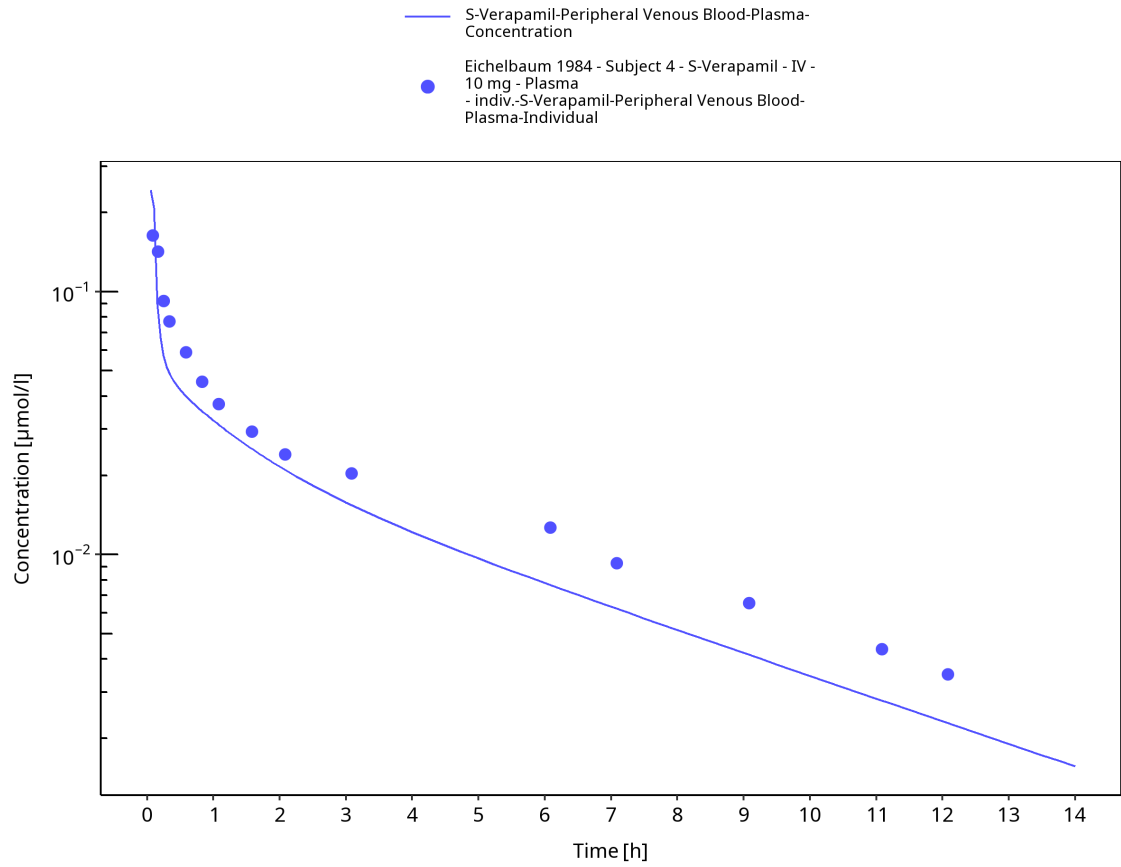
**Figure 3-43: Time Profile Analysis**



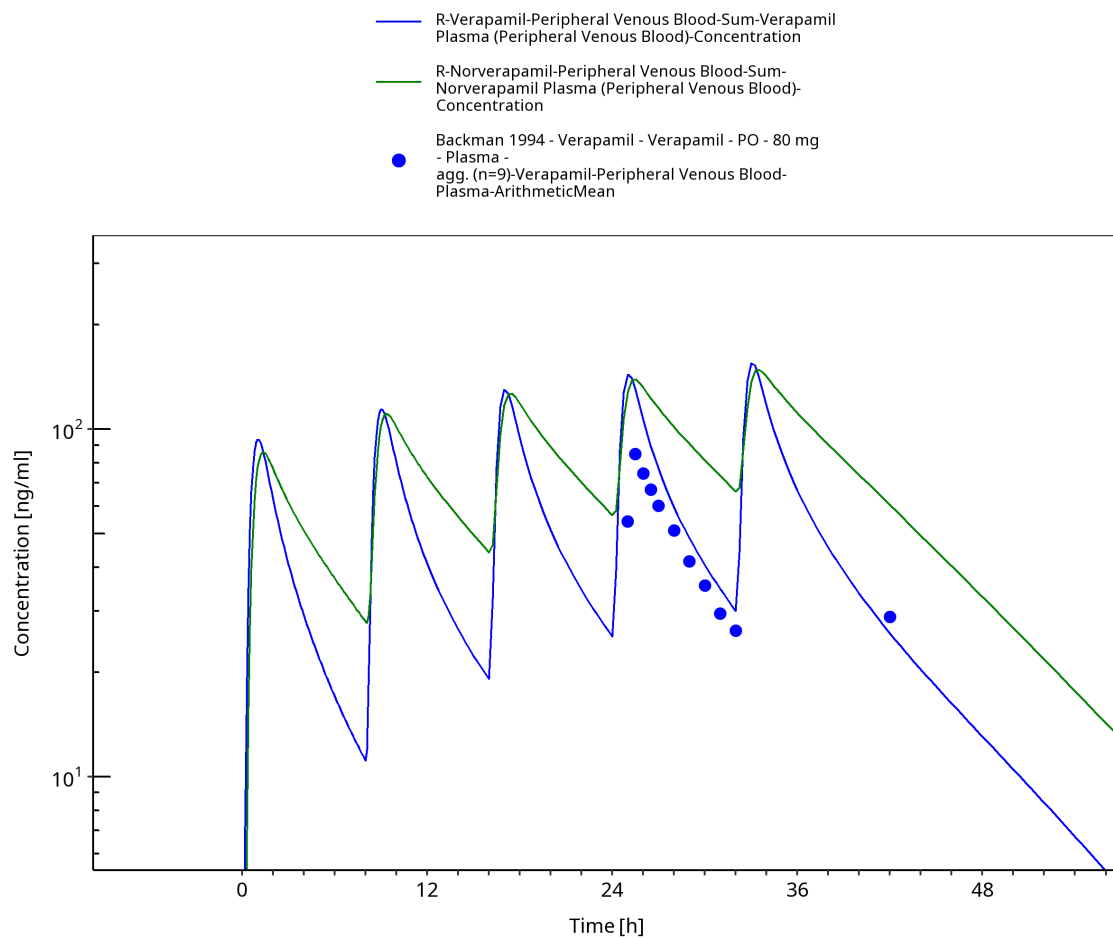
**Figure 3-44: Time Profile Analysis**



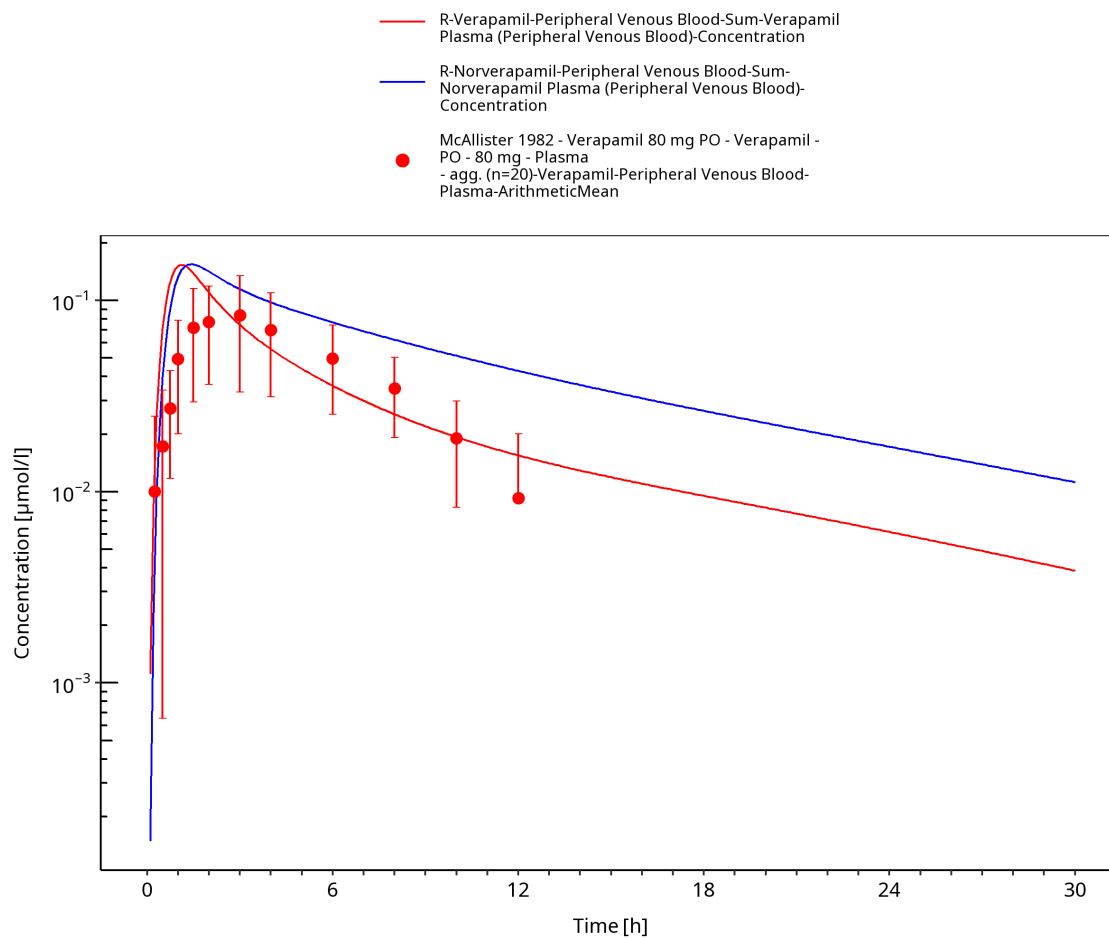
**Figure 3-45: Time Profile Analysis**



**Figure 3-46: Time Profile Analysis**



**Figure 3-47: Time Profile Analysis**



**Figure 3-48: Time Profile Analysis**

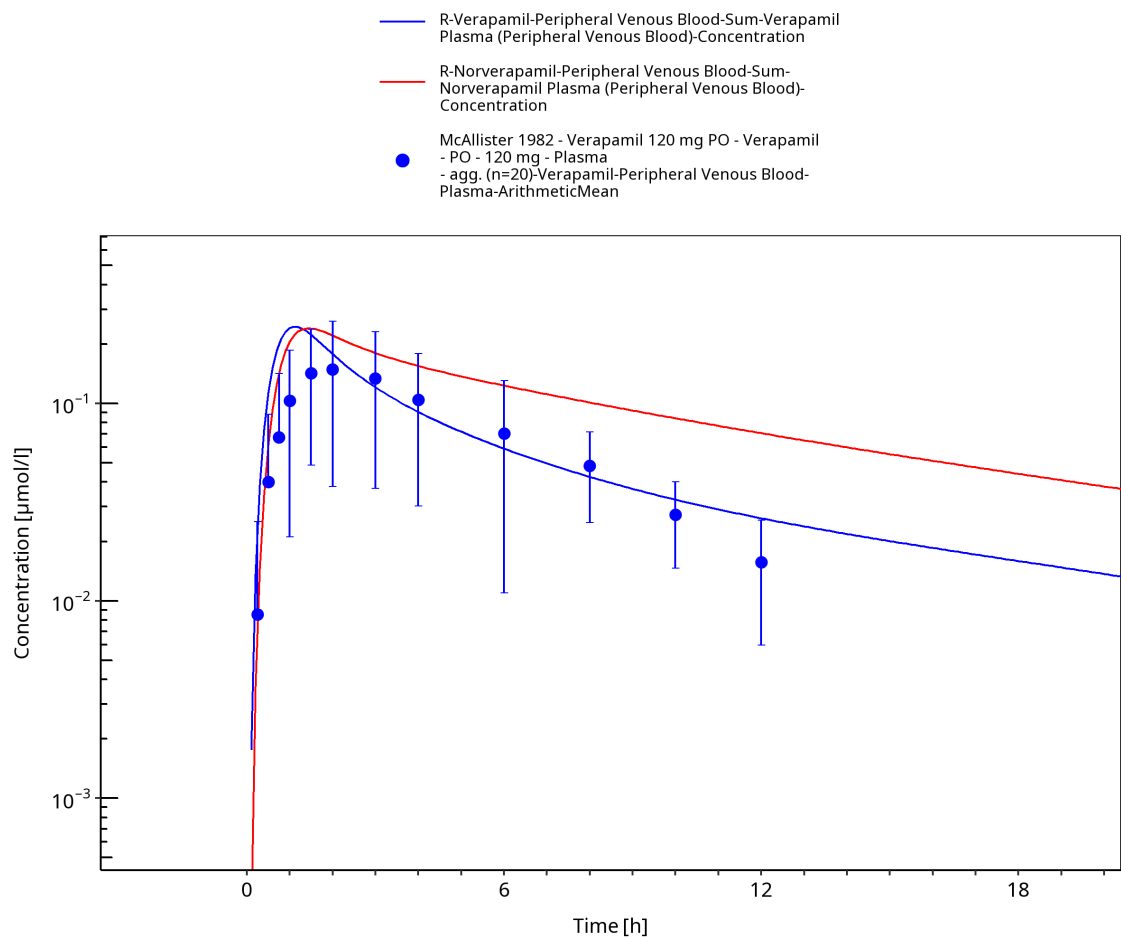
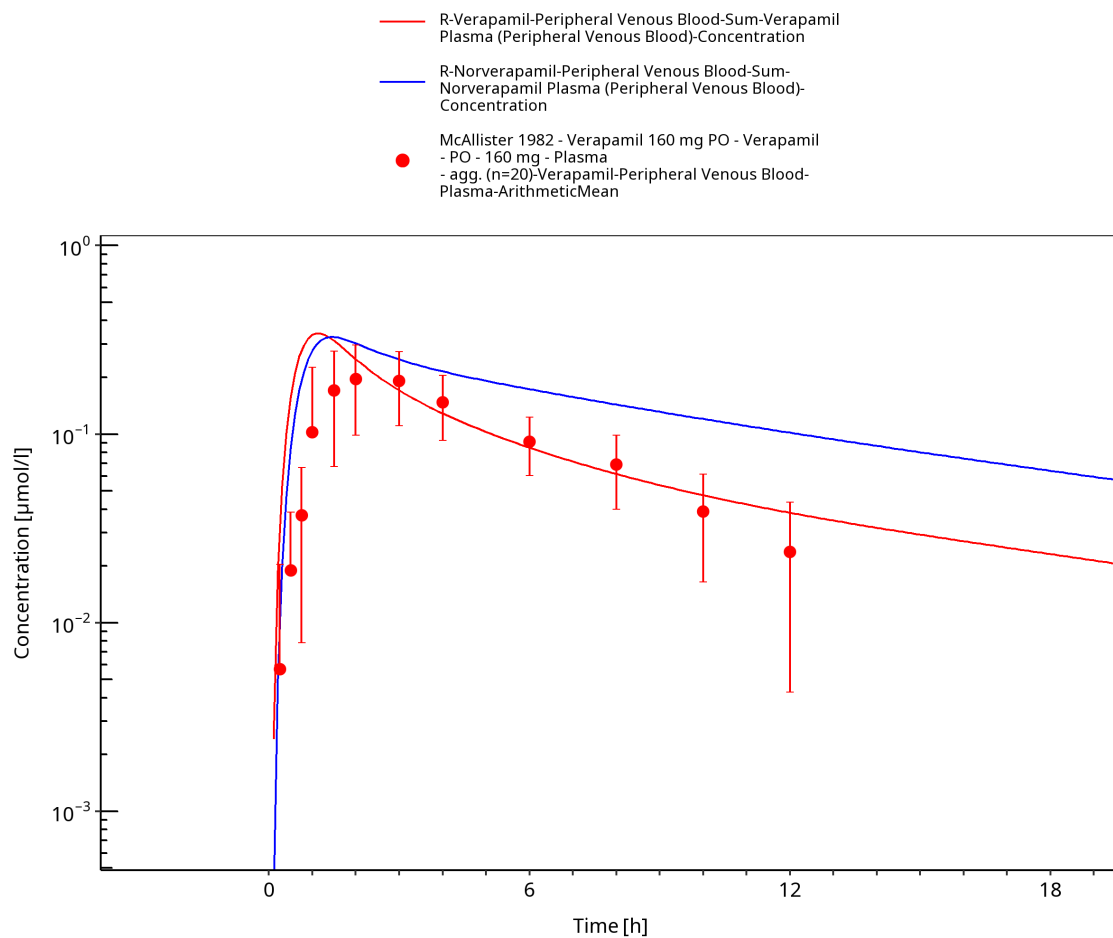
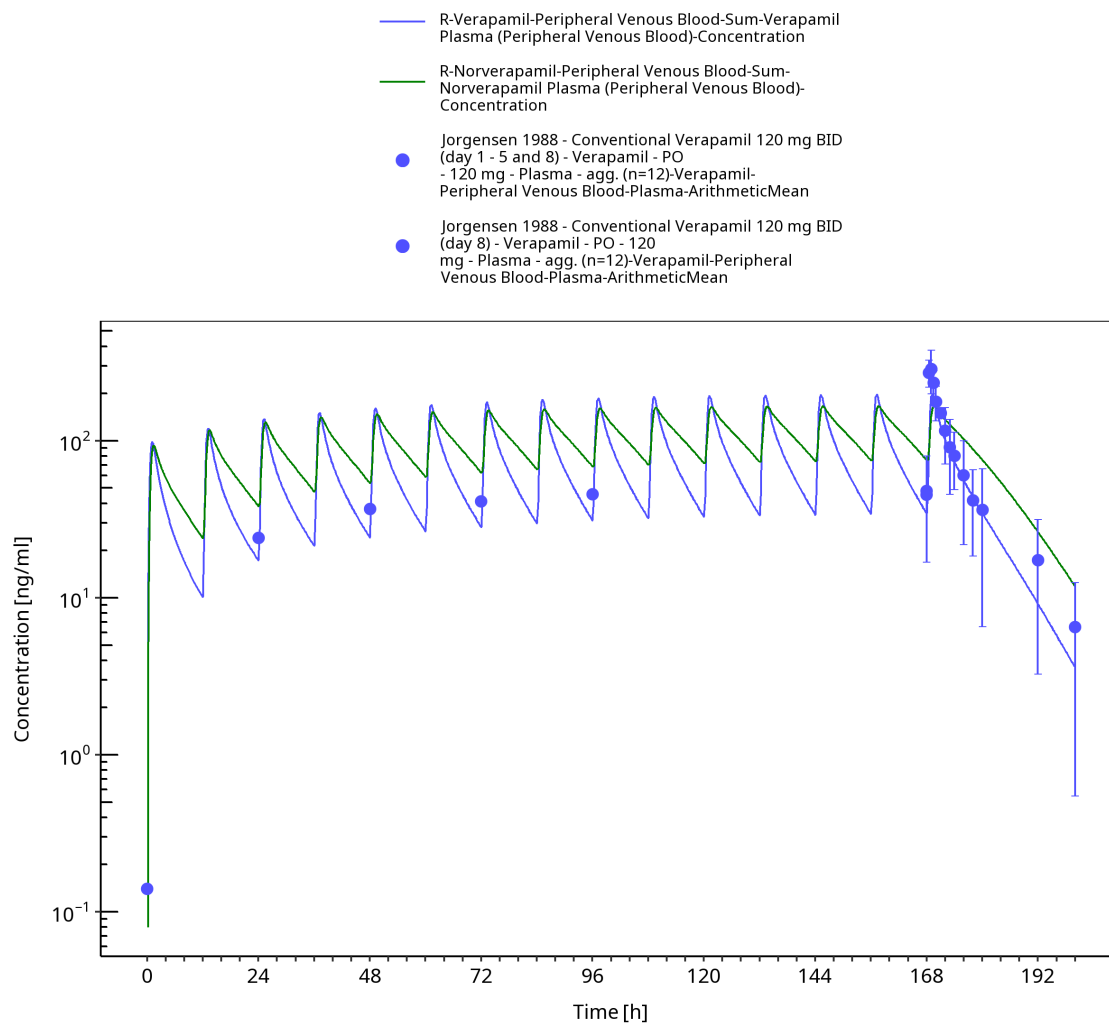


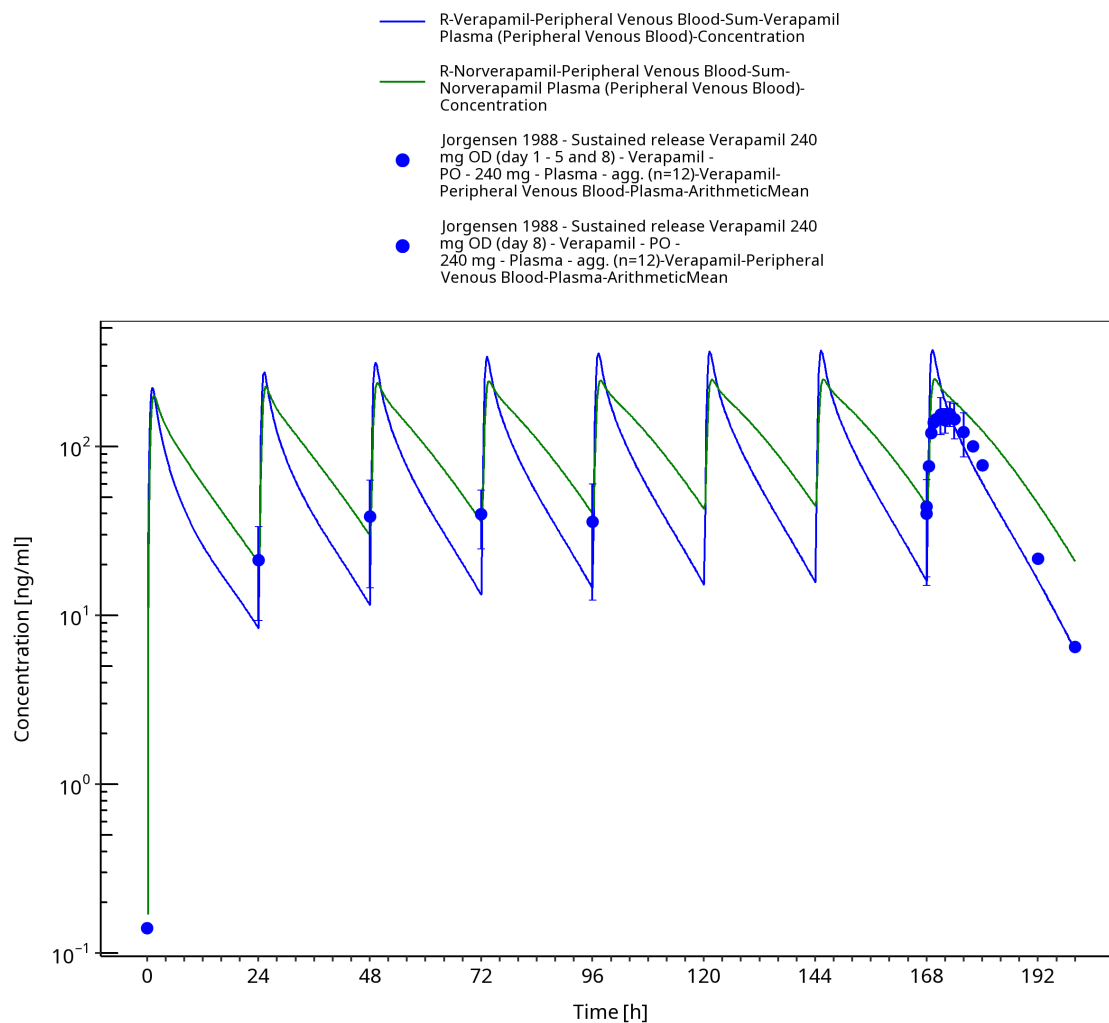
Figure 3-49: Time Profile Analysis



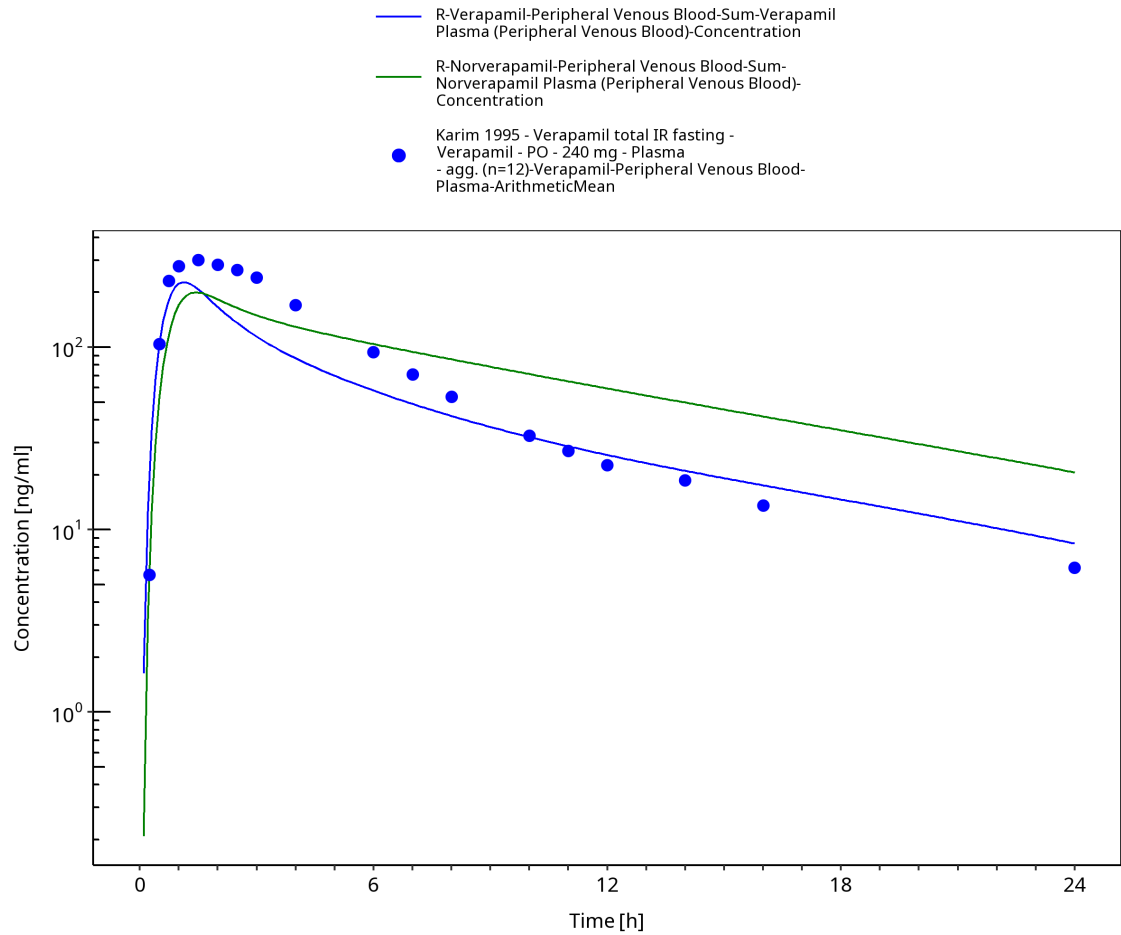
**Figure 3-50: Time Profile Analysis**



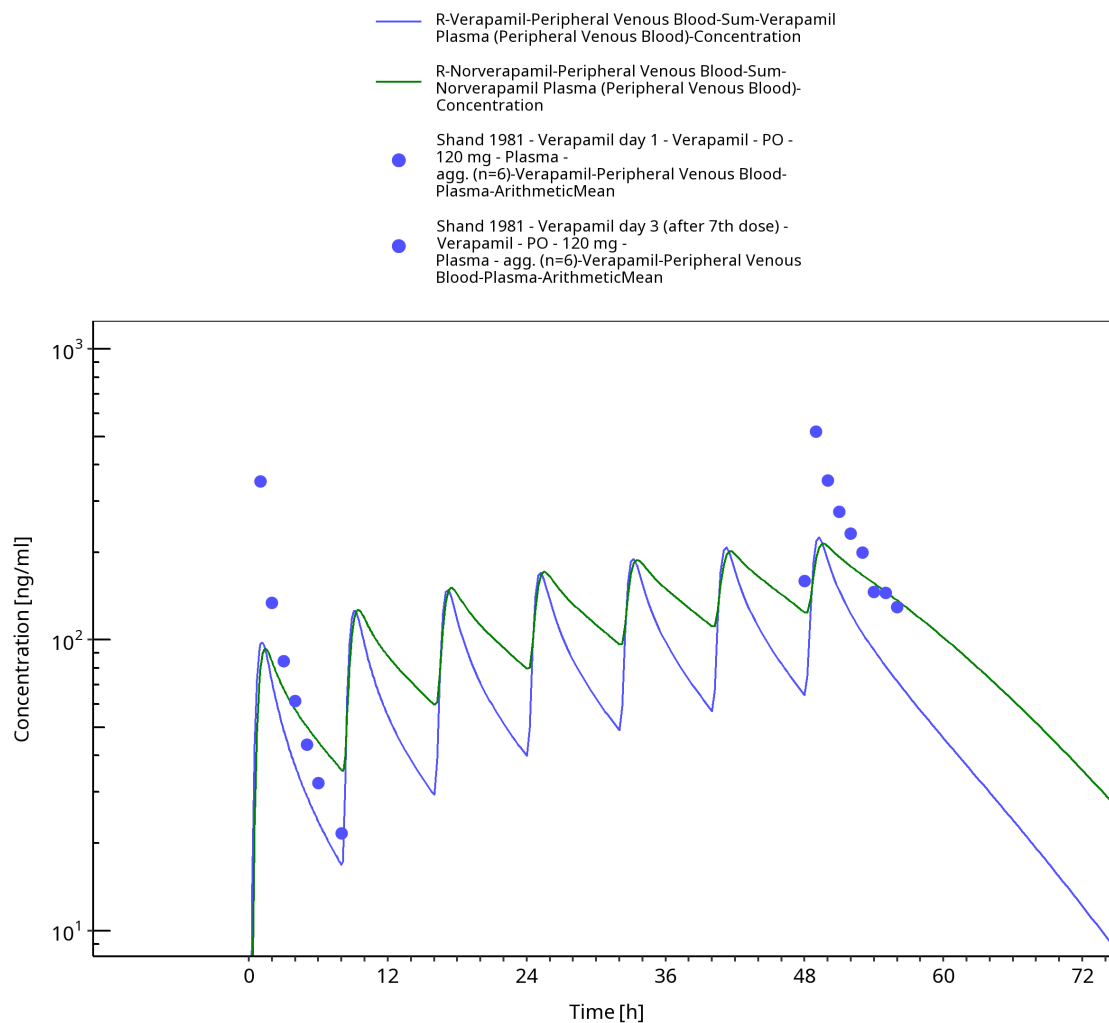
**Figure 3-51: Time Profile Analysis**



**Figure 3-52: Time Profile Analysis**



**Figure 3-53: Time Profile Analysis**



**Figure 3-54: Time Profile Analysis**

## 4 Conclusion

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The herein presented PBPK model adequately describes the pharmacokinetics of R-verapamil, S-verapamil, R-norverapamil and S-norverapamil after single and multiple administration of a variety of doses to healthy adults. Furthermore, mechanism-based CYP3A4 (auto-) inactivation on verapamil itself can be described well with the optimized parameterization.

## 5 References

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**Barbarash 1988** Barbarash RA, Bauman JL, Fischer JH, Kondos GT, Batenhorst RL. Near-total reduction in verapamil bioavailability by rifampin. *Electrocardiographic correlates.* *Chest.* 1988 Nov;94(5):954-9.

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**Blume 1990** Blume H, Mutschler E (1989) Bioäquivalenz: Qualitätsbewertung wirkstoffgleicher Fertigarzneimittel: Anleitung, Methoden, Materialien. Govi-Verlag

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