

## Pediatric Qualification Package: CYP2C8 Ontogeny

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# Chapter 1: Introduction to Pediatric Translation

The presented qualification report evaluates the predictive performance of the OSP suite to predict cytochrome P450 2C8 (CYP2C8)-mediated drug clearance in children.

Therefore, PBPK models of specific *in vivo* probe substances covering children aged below 6 months up to adolescents were built and evaluated. All models are whole-body PBPK models, allowing for dynamic pediatric translation in organs expressing CYP2C8. The qualification report demonstrates the level of confidence of the OSP suite with regard to reliable PBPK predictions of age-related CYP2C8-mediated drug clearance during model-informed drug development. The presented PBPK models as well as the respective qualification plan and qualification report are provided open-source and transparently documented (<https://github.com/Open-Systems-Pharmacology/Pediatric-Qualification-Package-CYP2C8>).

## Translation of Adult PBPK to Children

Using a developed and validated (adult) PBPK model for an *in vivo* probe substance, a pediatric PBPK model can be established for children by translating physiology, clearance processes (as parameterized in the adult model) and age-dependent protein binding including the variability therein.[1]

The PBPK models are developed with clinical data of healthy adult subjects obtained from the literature, covering available dosing ranges for e.g. intravenous as well as oral administration, to capture both systemic clearance as well gut-wall metabolic clearance processes. For orally administered drugs, the same formulations that are used in children should ideally be included in the model for adults. Plasma concentrations following multiple-dose application, mass balance information and other clinical measurements need to be included for model development, if available. During model translation from adults to children for a specific substance, uncertainties in data-quality caused by impact of disease or the target study population, inaccurate *in vitro* assay-techniques regarding mass balance, as well as study differences may cause not being able to adequately predict the PK in children for all reported studies.

Prediction performance of the PBPK model for these probe substances in children are then shown by means of e.g. predicted versus observed area under the plasma concentration (AUC)-ratio plots, of which the results support an adequate prediction of the ontogeny function for the application of PBPK model translation of adult PBPK to children.

For qualification purpose, during the translation of adult PBPK to children the following assumptions and considerations were made:

- when translating an adult model to children, it was assumed that the metabolism and excretion pathways are qualitatively the same in children and in adults.
- no further changes to input parameters other than those for the physiology and protein binding. All other parameters (e.g. lipophilicity, intestinal permeability, solubility) were kept unchanged.

## Anthropometric and Physiological Information

Regarding the age-dependencies of the relevant anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in children was gathered from the literature and has been previously published [2]. The information was incorporated into PK-Sim® and was used as default values for the simulations in children.

The CYP2C8 ontogeny function is reported by Upadhyay et al. [3] and was integrated into PK-Sim. The ontogeny of CYP2C8 reaches 15% of adult activity at birth, peaks at 260% of adult activity around the age of 14 months and reaches adult activity by the age of 5 to 6 years. The applied ontogeny and variability of other active processes that are integrated into PK-Sim® for translation to children, are described in the publicly available 'PK-Sim® Ontogeny Database Version 7.3' [4] or otherwise referenced for the specific process.

## Qualification of CYP2C8 enzyme ontogeny

To qualify the OSP suite for the pediatric translation of the pharmacokinetics of new drugs that are metabolized by CYP2C8, the following set of probe substances was included:

- Montelukast [4]
- Paclitaxel [5]

## References

[1] Maharaj AR, Barrett JS, Edginton AN. A workflow example of PBPK modeling to support pediatric research and development: case study with lorazepam. *The AAPS journal*. 2013;15(2): 455-464.

- [2] Edginton AN, Schmitt W, Willmann S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. *Clin Pharmacokinet*. 2006;45(10):1013-34.
- [3] Upreti VV, Wahlstrom JL. Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling. *J Clin Pharmacol*. 2016 Mar;56(3):266-83. doi: 10.1002/jcph.585. Epub 2015 Oct 9.
- [4] OSPSuite.Documentation/PK-Sim Ontogeny Database Version 7.3.pdf
- [5] Montelukast-Model, Whole-body PBPK model of Montelukast. <https://github.com/Open-Systems-Pharmacology/Montelukast-Model>
- [6] Paclitaxel-Model, Whole-body PBPK model of Paclitaxel. <https://github.com/Open-Systems-Pharmacology/Paclitaxel-Model>

## Chapter 2: Pediatric translation qualification

### Evaluation of Pediatric translation

All pediatric translations are pure retrospective predictions, no pediatric pharmacokinetic studies were used to inform model parameters. All parameters necessary to model the pediatric populations, such as demographics (age, weight, height), as well as dosing formulation information were taken from the respective pediatrics studies from literature in order to evaluate their predictive performance.

The models were evaluated by ratio plots of area under the plasma concentration-time curve (AUC), or clearance (CL) values resulting from our predictions to the values observed during clinical studies, and by comparison of concentration-time profiles if available. As a quantitative measure of the descriptive and predictive performance of each model, the geometric mean fold error was calculated according to Eq. 1:

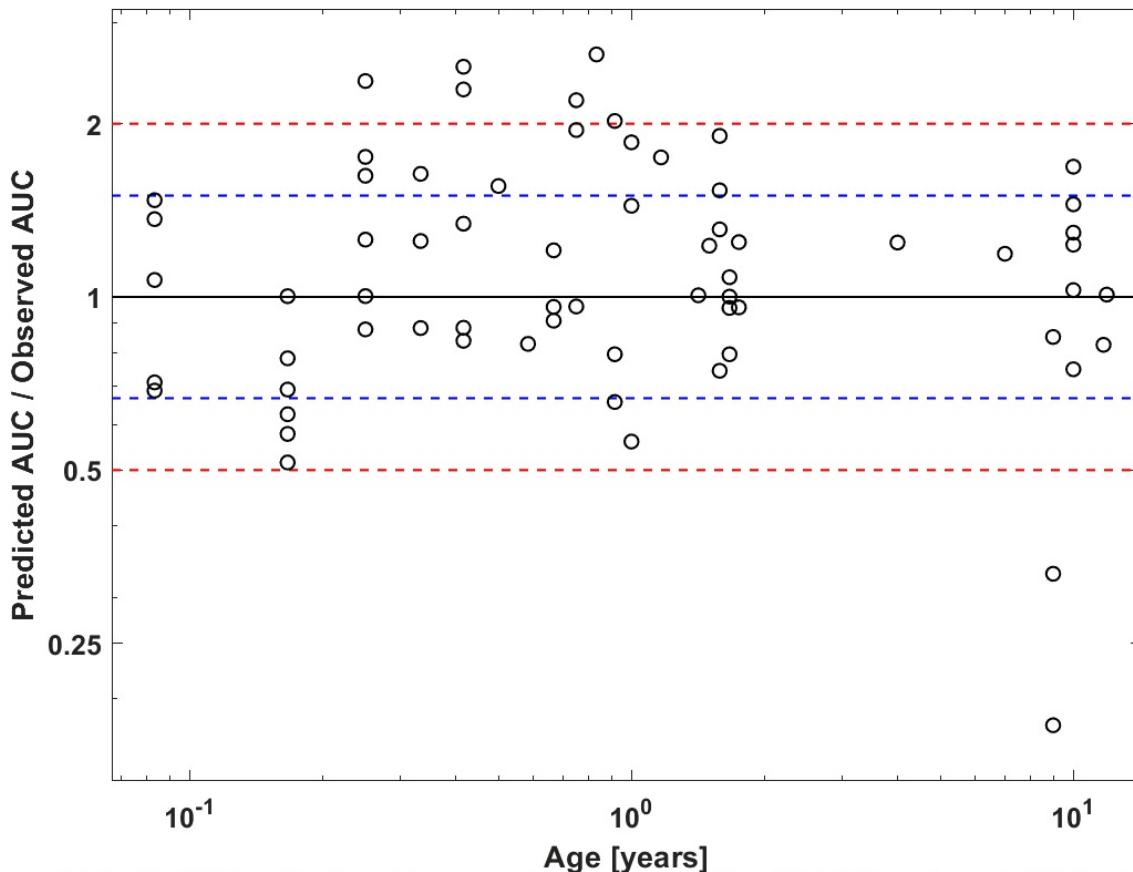
$$\text{Eq. 1: GMFE} = 10^{(\sum |\log_{10}(\text{pred PK parameter}/\text{obs PK parameter})|)/n}$$

with GMFE = geometric mean fold error of all AUC or CL predictions of the respective model, pred PK parameter = predicted AUC or CL, obs PK parameter = observed AUC or CL, and n = number of observed values.

The ratios of predicted over observed mean AUC or CL values from all compound were also plotted across all age groups in the figure below. As illustrated, most of the prediction were within the 0.5 to 2.0 range (2-fold error).

In the next sections the demographics as well as the evaluation results of the predictive performance of the specific compound PBPK models in children can be found.

GMFE = 1.435241



Overall predictivity of the PBPK models. Open circles represent mean ratios of PBPK predicted AUC over observed AUC of all drugs in children 1 month to 11.9 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error, respectively.

## Chapter 2.1: Montelukast PK Ratio tables and Figures

### Montelukast model

Montelukast PBPK predictions in children were evaluated using pharmacokinetic (PK) data reported in the following studies:

- Knorr B, Holland S, Rogers JD, Nguyen HH, Reiss TF. Montelukast adult (10-mg film-coated tablet) and pediatric (5-mg chewable tablet) dose selections. *J Allergy Clin Immunol.* 2000 Sep;106(3 Suppl):S171-8.
- Friesen CA, Keams GL, Andre L, Neustrom M, Roberts CC, Abdel-Rahman SM. Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with duodenal eosinophilia. *J Pediatr Gastroenterol Nutr.* 2004 Mar;38(3):343-51.
- Keams GL, Lu S, Maganti L, Li XS, Migoya E, Ahmed T, Knorr B, Reiss TF. Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol.* 2008 Apr;48(4):502-11. doi: 10.1177/0091270008314251. Epub 2008 Feb 22.
- Knorr B, Nguyen HH, Keams GL, Villaran C, Boza ML, Reiss TF, Rogers JD, Zhang J, Larson P, Spielberg S. Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. *J Clin Pharmacol.* 2001 Jun;41(6):612-9.
- Knorr B, Larson P, Nguyen HH, Holland S, Reiss TF, Chervinsky P, Blake K, van Nispen CH, Noonan G, Freeman A, Haesen R, Michiels N, Rogers JD, Amin RD, Zhao J, Xu X, Seidenberg BC, Gertz BJ, Spielberg S. Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol.* 1999 Aug;39(8):786-93.
- Knorr B, Maganti L, Ramakrishnan R, Tozzi CA, Migoya E, Keams G. Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. *J Clin Pharmacol.* 2006 Jun;46(6):620-7.
- Migoya E1, Keams GL, Hartford A, Zhao J, van Adelsberg J, Tozzi CA, Knorr B, Deutsch P. Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. *J Clin Pharmacol.* 2004 May;44(5):487-94.

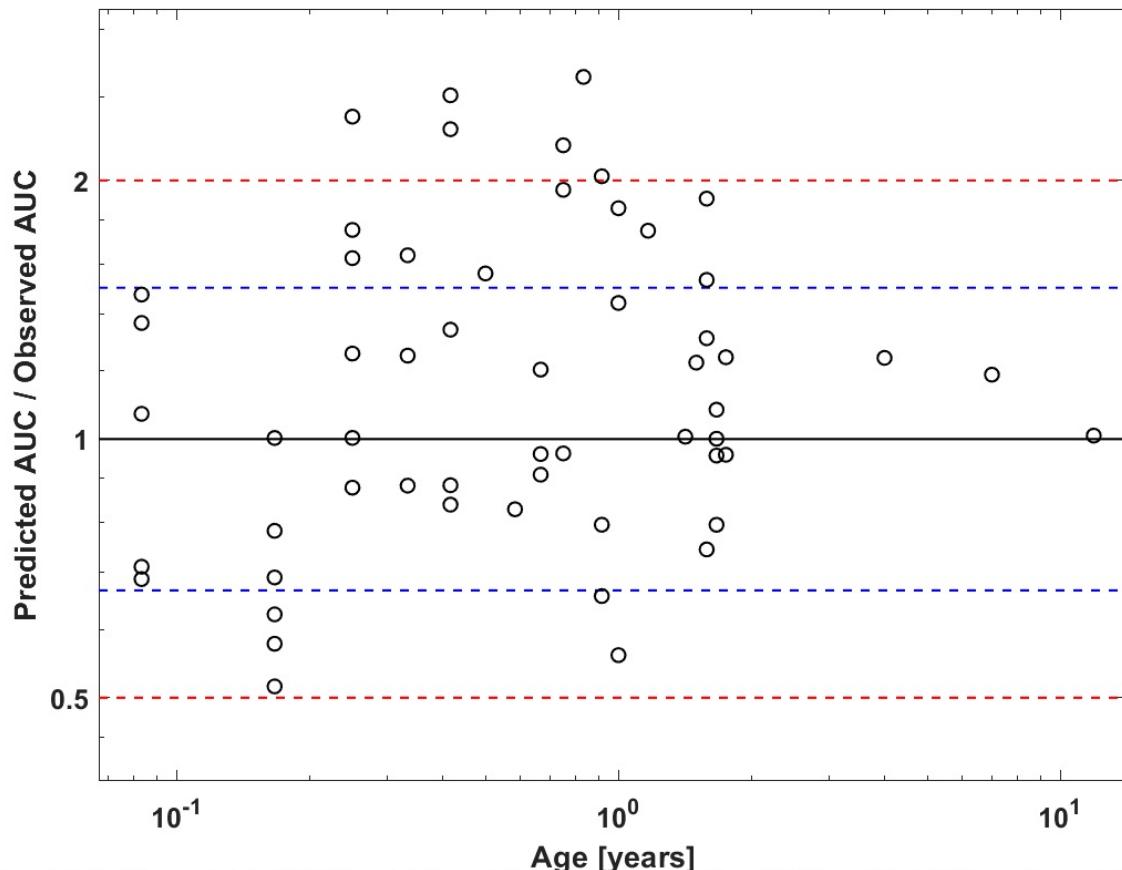
The pediatric PBPK model predicted the clearance values of montelukast observed in pediatric studies reasonably across all available age groups, ranging from 1 month to 11.9 years old. The ratios of mean predicted over observed area under the observed plasma concentrations (AUC) are illustrated in the table below as well as in the predicted versus observed AUC ratio plot, showing that most predictions in children were within 2-fold error of observed values.

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [ng*h/ml]	Observed AUC [ng*h/ml]	Pred/Obs AUC Ratio
Kearns 2008	0.083333	4.0417	20846.6261	30336.98	0.68717
Kearns 2008	0.083333	4.0417	20846.6261	29350.14	0.71027
Kearns 2008	0.083333	4.0417	20846.6261	19481.8	1.0701
Kearns 2008	0.083333	4.0417	20846.6261	15271.04	1.3651
Kearns 2008	0.083333	4.0417	20846.6261	14152.63	1.473
Kearns 2008	0.166667	4.5833	10046.0462	19490.31	0.51544
Kearns 2008	0.166667	4.5833	10046.0462	17384.8	0.57786
Kearns 2008	0.166667	4.5833	10046.0462	16069.03	0.62518
Kearns 2008	0.166667	4.5833	10046.0462	14555.88	0.69017
Kearns 2008	0.166667	4.5833	10046.0462	12845.36	0.78208
Kearns 2008	0.166667	4.5833	10046.0462	10016.44	1.003
Kearns 2008	0.25	5.125	8802.0653	10024.69	0.87804
Kearns 2008	0.25	5.125	8802.0653	8774.445	1.0031
Kearns 2008	0.25	5.125	8802.0653	6998.658	1.2577

Kearns 2008	0.25	5.125	8802.0653	5419.723	1.6241
Kearns 2008	0.25	5.125	8802.0653	5024.989	1.7517
Kearns 2008	0.25	5.125	8802.0653	3709.209	2.373
Kearns 2008	0.33333	5.6667	8681.5721	9835.066	0.88272
Kearns 2008	0.33333	5.6667	8681.5721	6941.125	1.2507
Kearns 2008	0.41667	6.2083	8698.7013	10369.89	0.83884
Kearns 2008	0.41667	6.2083	8698.7013	9843.322	0.88372
Kearns 2008	0.41667	6.2083	8698.7013	6488.084	1.3407
Kearns 2008	0.41667	6.2083	8698.7013	3791.252	2.2944
Kearns 2008	0.41667	6.2083	8698.7013	3462.049	2.5126
Kearns 2008	0.5	6.75	9614.0712	6167.911	1.5587
Kearns 2008	0.58333	7.2917	9805.1252	11833.5	0.82859
Kearns 2008	0.66667	7.8333	9987.473	10986.76	0.90905
Kearns 2008	0.66667	7.8333	9987.473	10394.92	0.9608
Kearns 2008	0.66667	7.8333	9987.473	8289.154	1.2049
Kearns 2008	0.75	8.375	10137.9085	10534.24	0.96238
Kearns 2008	0.75	8.375	10137.9085	4612.969	2.1977
Kearns 2008	0.83333	8.9167	10286.7404	3897.288	2.6395
Kearns 2008	0.91667	9.4583	10426.5483	15879.4	0.65661
Kearns 2008	0.91667	9.4583	10426.5483	13116.26	0.79493
Kearns 2008	0.91667	9.4583	10426.5483	5155.535	2.0224
Kearns 2008	1	10	10563.8754	18848.16	0.56047
Kearns 2008	1	10	10563.8754	7334.827	1.4402
Kearns 2008	1	10	10563.8754	5690.103	1.8565
Kearns 2008	1.1667	10.375	10779.508	6167.137	1.7479
Kearns 2008	1.4167	10.9375	11130.8768	11060.03	1.0064
Kearns 2008	1.5833	11.3125	11324.8461	15221.25	0.74402
Kearns 2008	1.5833	11.3125	11324.8461	8642.352	1.3104

Kearns 2008	1.5833	11.3125	11324.8461	7392.36	1.532
Kearns 2008	1.5833	11.3125	11324.8461	5945.002	1.9049
Kearns 2008	1.6667	11.5	11424.5764	14374.25	0.79479
Kearns 2008	1.6667	11.5	11424.5764	11940.31	0.95681
Kearns 2008	1.6667	11.5	11424.5764	11414	1.0009
Kearns 2008	1.6667	11.5	11424.5764	10558.23	1.0821
Kearns 2008	1.75	11.6875	11520.1405	12013.84	0.95891
Kearns 2008	1.75	11.6875	11520.1405	9250.706	1.2453
Friesen 2004	11.9	40.55	4428.2699	4387.2	1.0094
Knorr 1999	7	26	3480.9817	2929	1.1885
Knorr 2001	4	17	3382.7648	2721	1.2432
Knorr 2006	0.33333	6.8	5964.2914	3644.3	1.6366
Miyoga 2004	1.5	9	4454.641	3629.2	1.2274
Miyoga 2004	0.75	9	4819.0955	2470.9	1.9503

GMFE = 1.403891

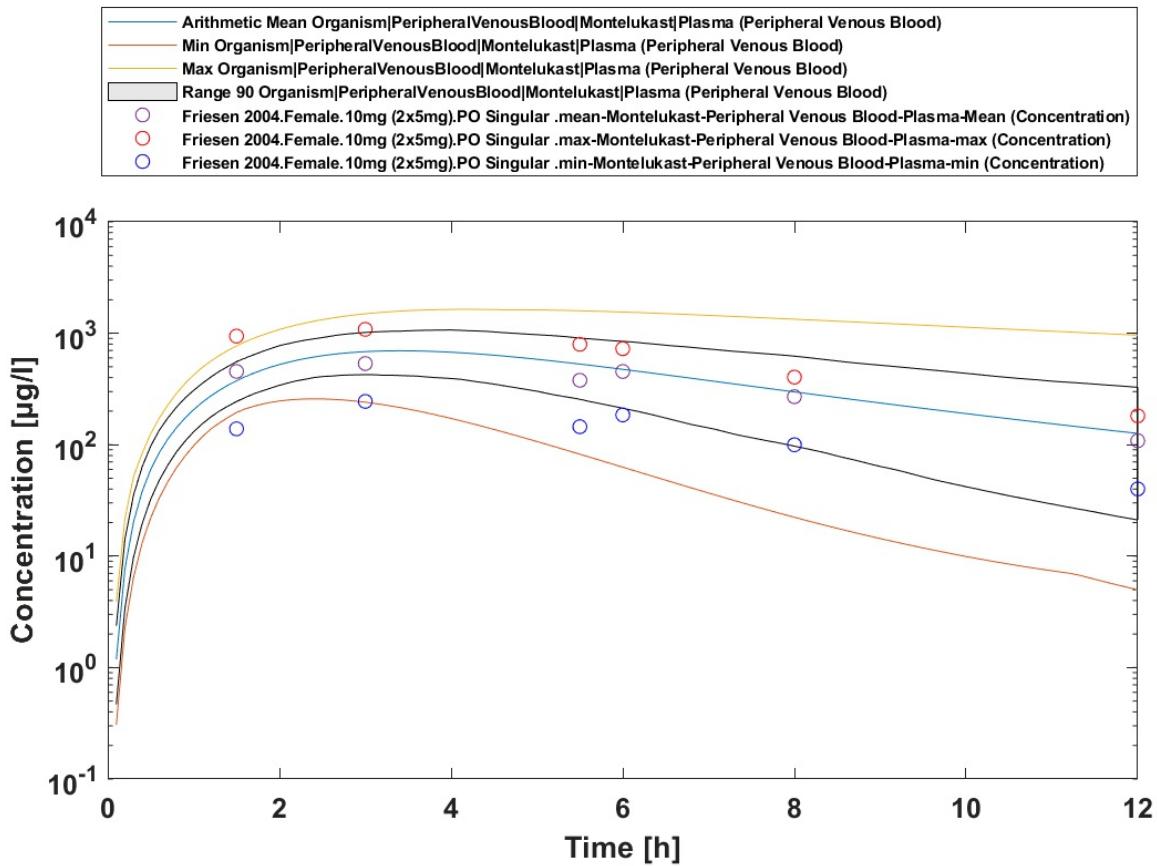


Overall predictivity of the montelukast PBPK model. Open circles represent mean ratios of PBPK predicted AUC over observed AUC of montelukast in children 1 month to 11.9 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error, respectively.

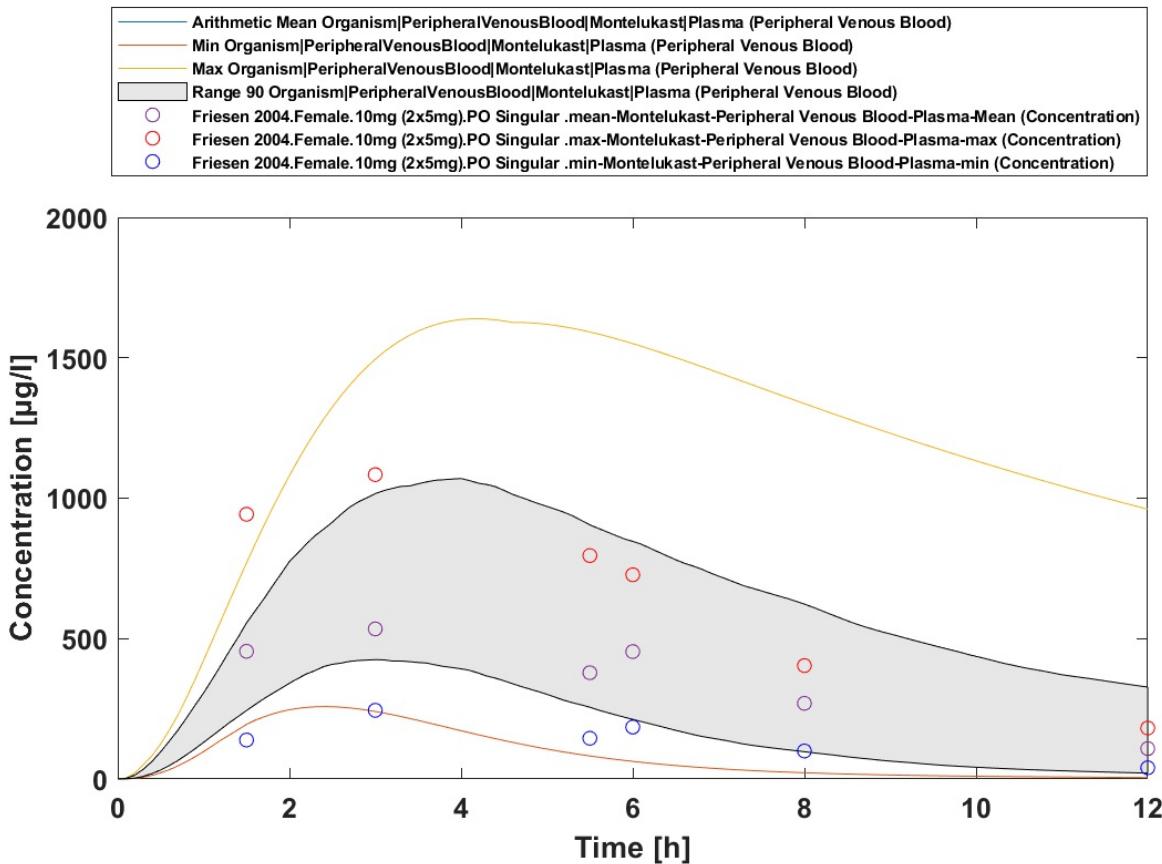
## Chapter 2.2: Montelukast Concentration-Time profiles in Children

### Concentration-Time Profiles

Predicted versus observed plasma concentration-time profiles are listed below. Only simulations where observed data was available for comparison are shown. Depending if the observed data were individual data or aggregated data, individual predictions or population predictions including variability are shown, respectively.



Time Profile Analysis



Time Profile Analysis 1

## Chapter 2.3: Paclitaxel PK Ratio tables and Figures

### Paclitaxel model

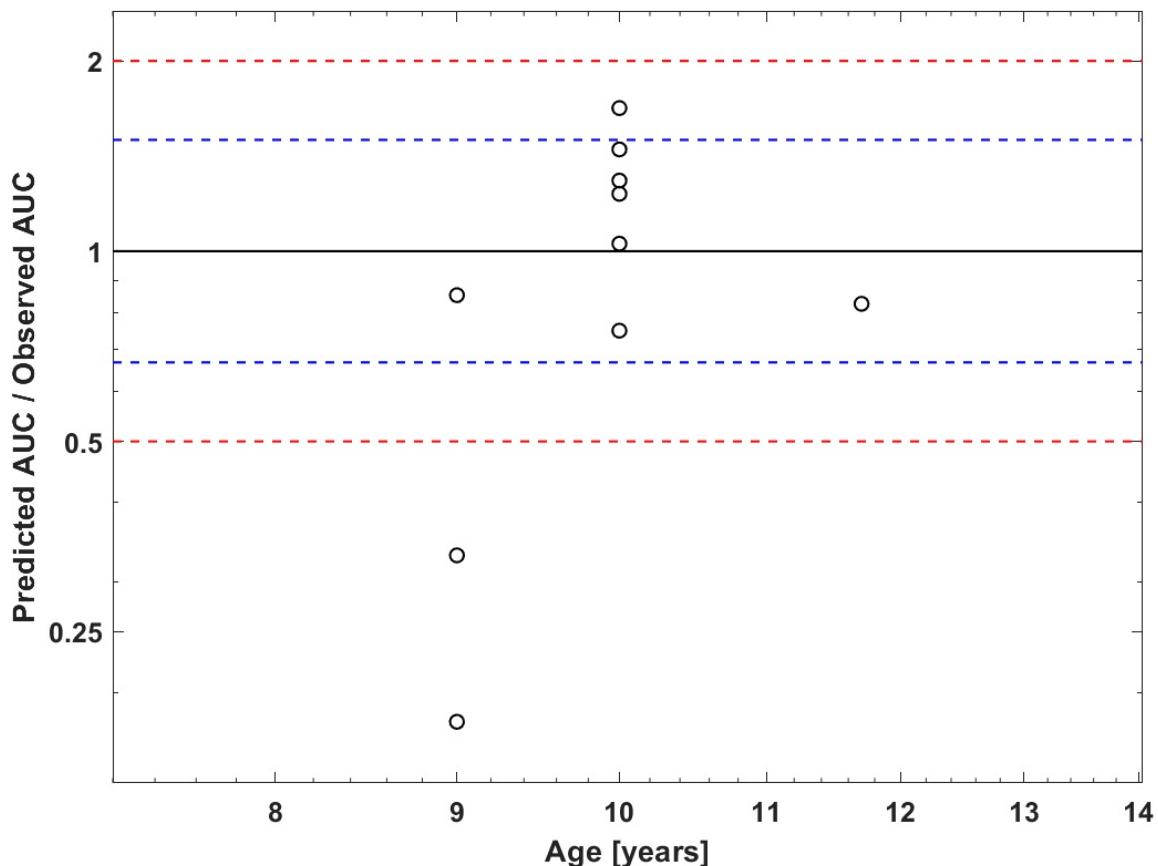
Paclitaxel PBPK predictions in children were evaluated using pharmacokinetic (PK) data reported in the following studies:

- Doz F, Gentet JC, Pein F, Frappaz D, Chastagner P, Moretti S, Vassal G, Arditti J, Tellingen OV, Iliadis A, Catalin J. Phase I trial and pharmacological study of a 3-hour paclitaxel infusion in children with refractory solid tumours: a SFOP study. Br J Cancer. 2001 Mar;84(5):604-10.
- Horton TM, Ames MM, Reid JM, Kralio MD, Pendergrass T, Mosher R, Reaman GH, Seibel NL; Children's Oncology Group. A Phase 1 and pharmacokinetic clinical trial of paclitaxel for the treatment of refractory leukemia in children: a Children's Oncology Group study. Pediatr Blood Cancer. 2008 Apr;50(4):788-92.
- Sonneichsen DS, Hurwitz CA, Pratt CB, Shuster JJ, Relling MV. Saturable pharmacokinetics and paclitaxel pharmacodynamics in children with solid tumors. J Clin Oncol. 1994 Mar;12(3):532-8.

The pediatric PBPK model predicted the clearance values of paclitaxel observed in pediatric studies reasonably across all available age groups, ranging from 9 to 11.7 years old. The ratios of mean predicted over observed area under the observed plasma concentrations (AUC) are illustrated in the table below as well as in the predicted versus observed AUC ratio plot, showing that most predictions in children were within 2-fold error of observed values.

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [mmol*h/l]	Observed AUC [mmol*h/l]	Pred/Obs AUC Ratio
Doz 2001	9	29.4	0.028792	0.0338	0.85185
Doz 2001	9	29.4	0.023373	0.0708	0.33013
Doz 2001	9	29.4	0.028209	0.1567	0.18002
Horton 2008	10	32	0.016842	0.01	1.6842
Horton 2008	10	32	0.020211	0.0164	1.2324
Horton 2008	10	32	0.024253	0.0236	1.0277
Horton 2008	10	32	0.026947	0.0186	1.4488
Horton 2008	10	32	0.028968	0.0224	1.2932
Horton 2008	10	32	0.026947	0.036	0.74854
Sonnichsen 1994	11.7	45.5	0.024764	0.03	0.82548

GMFE = 1.624194

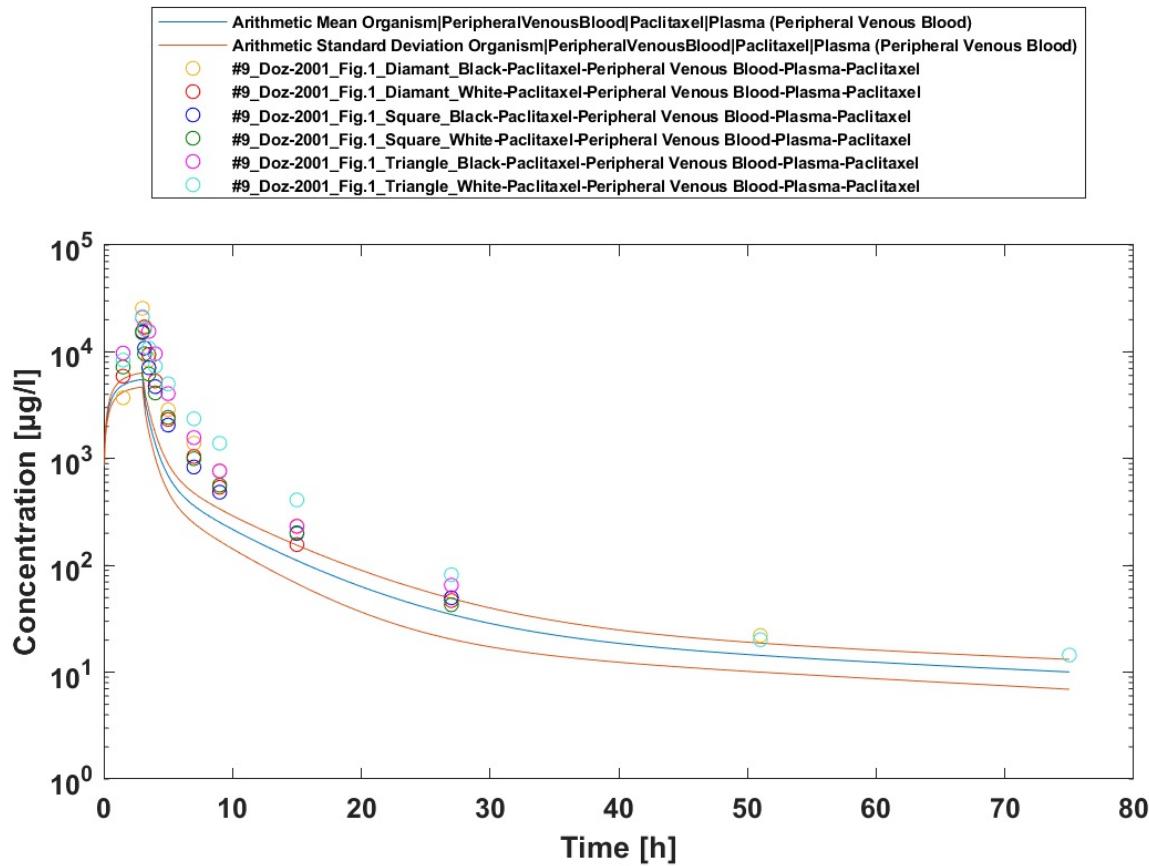


Overall predictivity of the paclitaxel PBPK model. Open circles represent mean ratios of PBPK predicted AUC over observed AUC of paclitaxel in children 9 years to 11.7 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error, respectively.

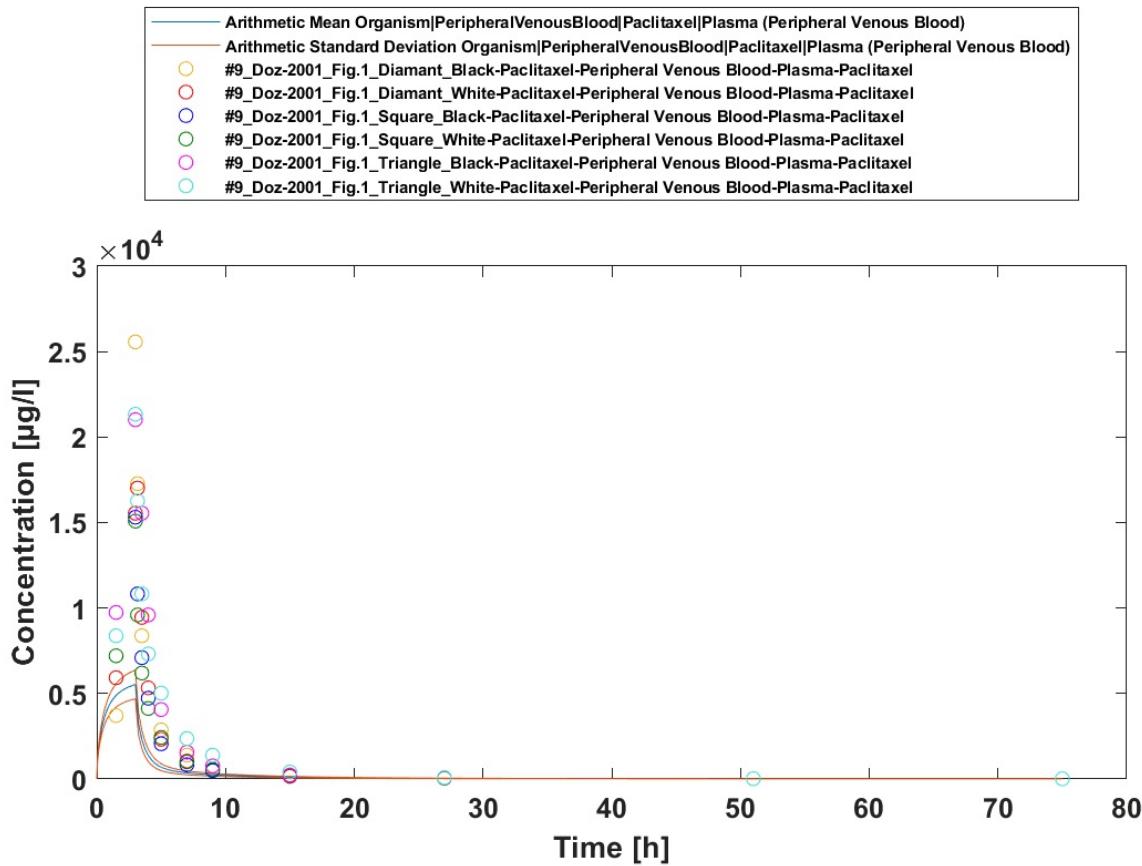
## Chapter 2.4: Paclitaxel Concentration-Time profiles in Children

### Concentration-Time Profiles

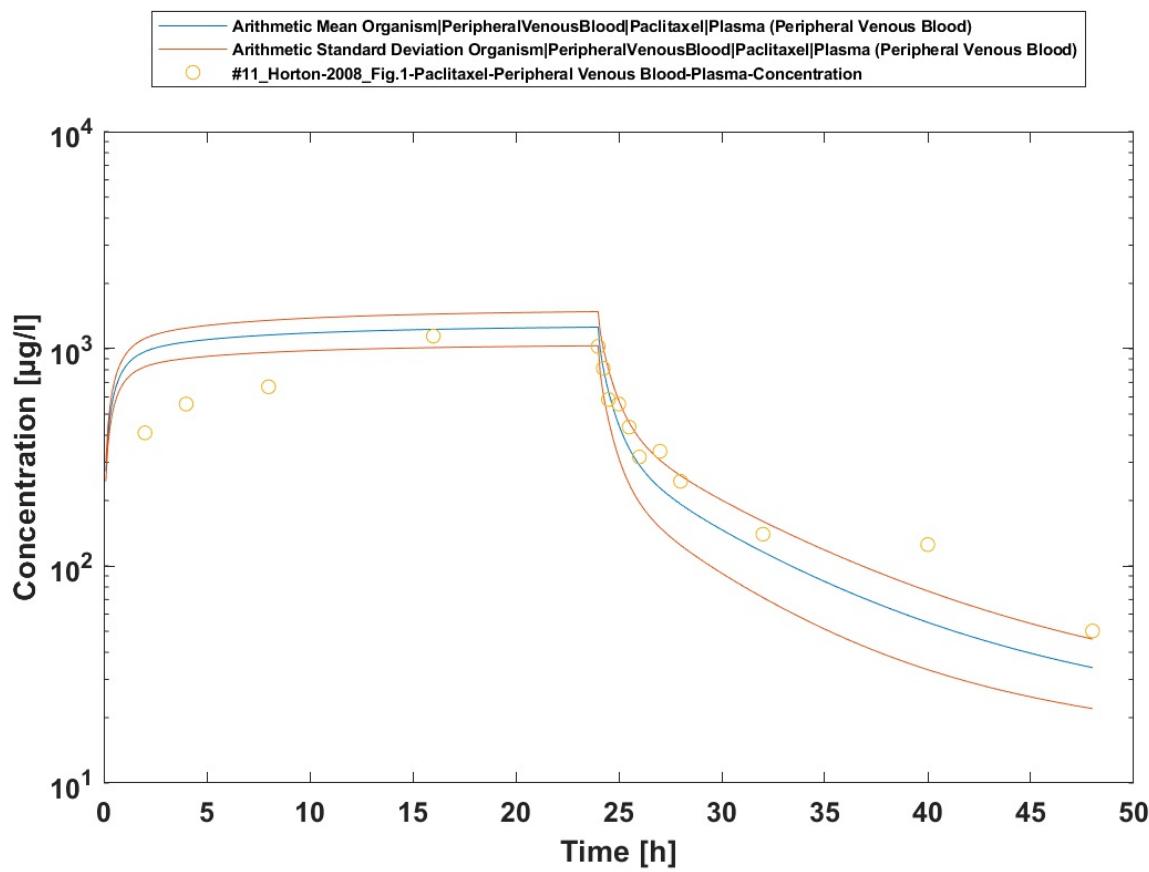
Predicted versus observed plasma concentration-time profiles are listed below. Only simulations where observed data was available for comparison are shown. Depending if the observed data were individual data or aggregated data, individual predictions or population predictions including variability are shown, respectively.



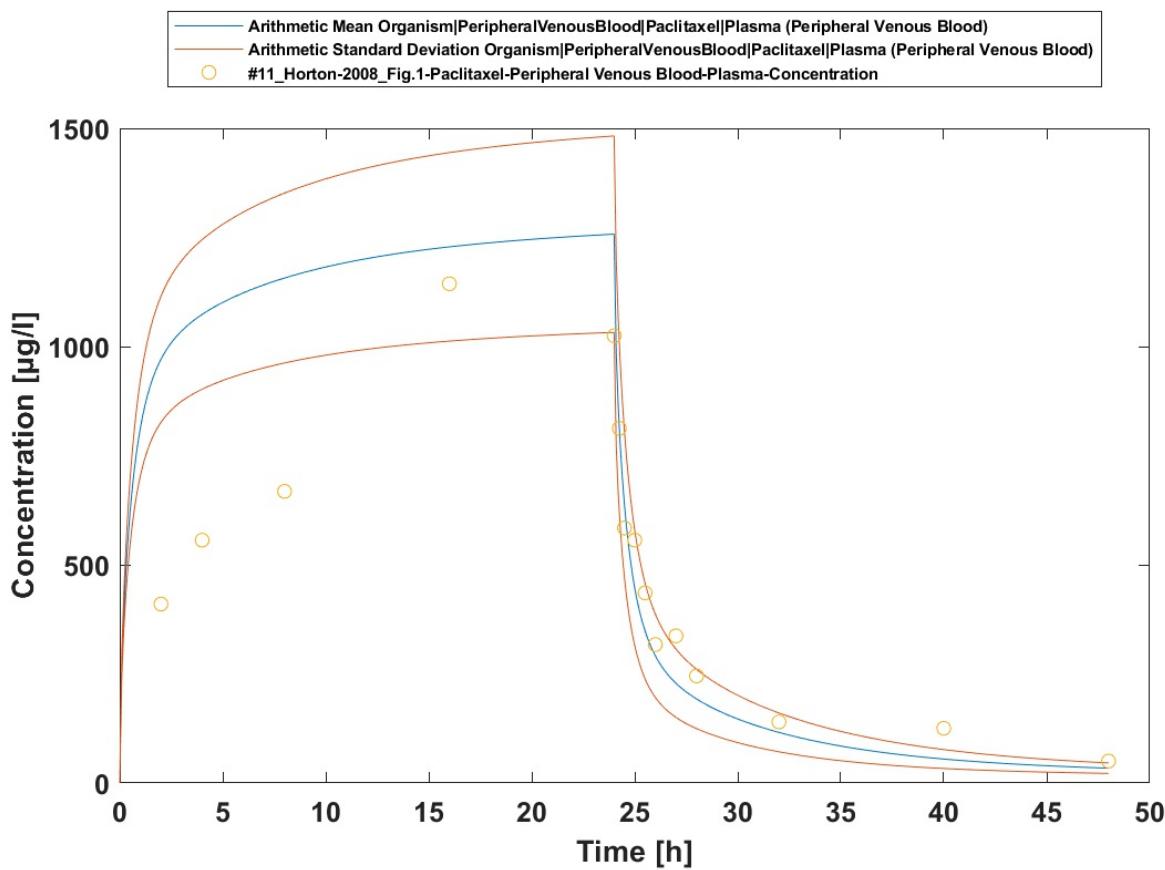
Time Profile Analysis



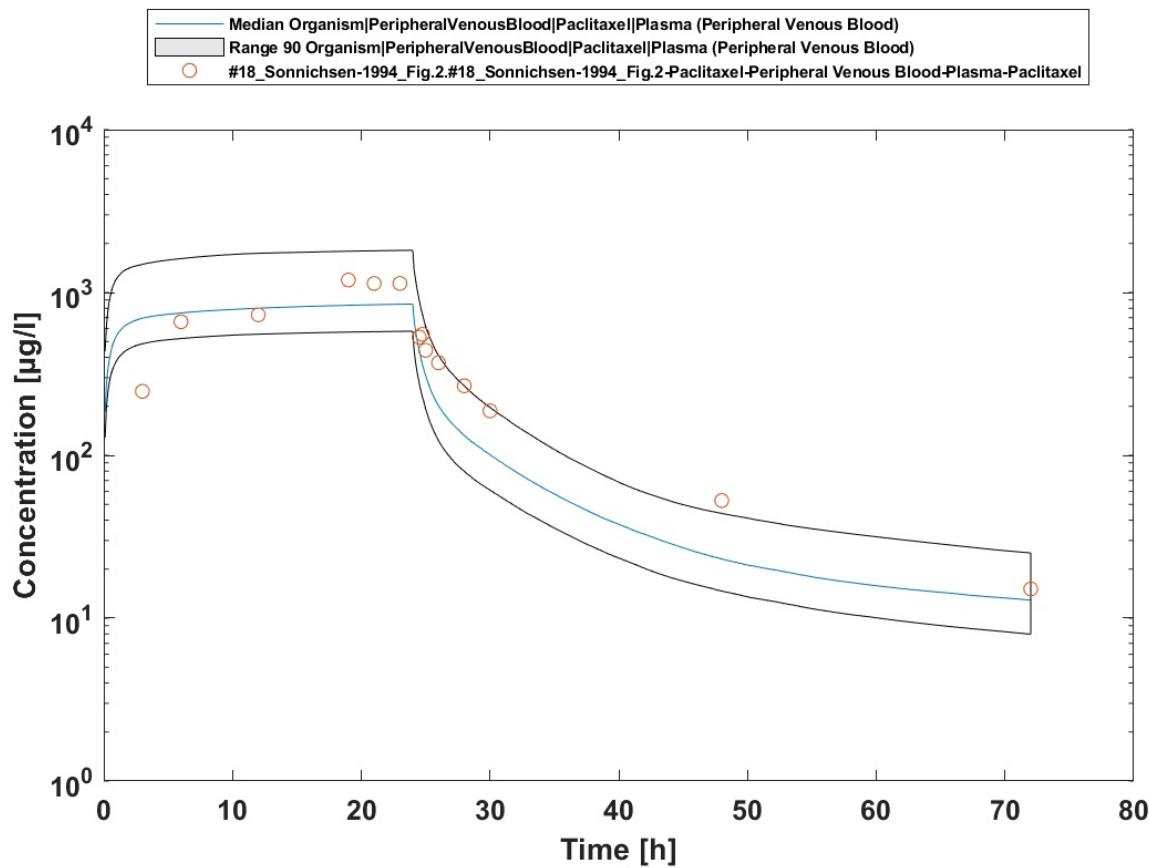
Time Profile Analysis 1



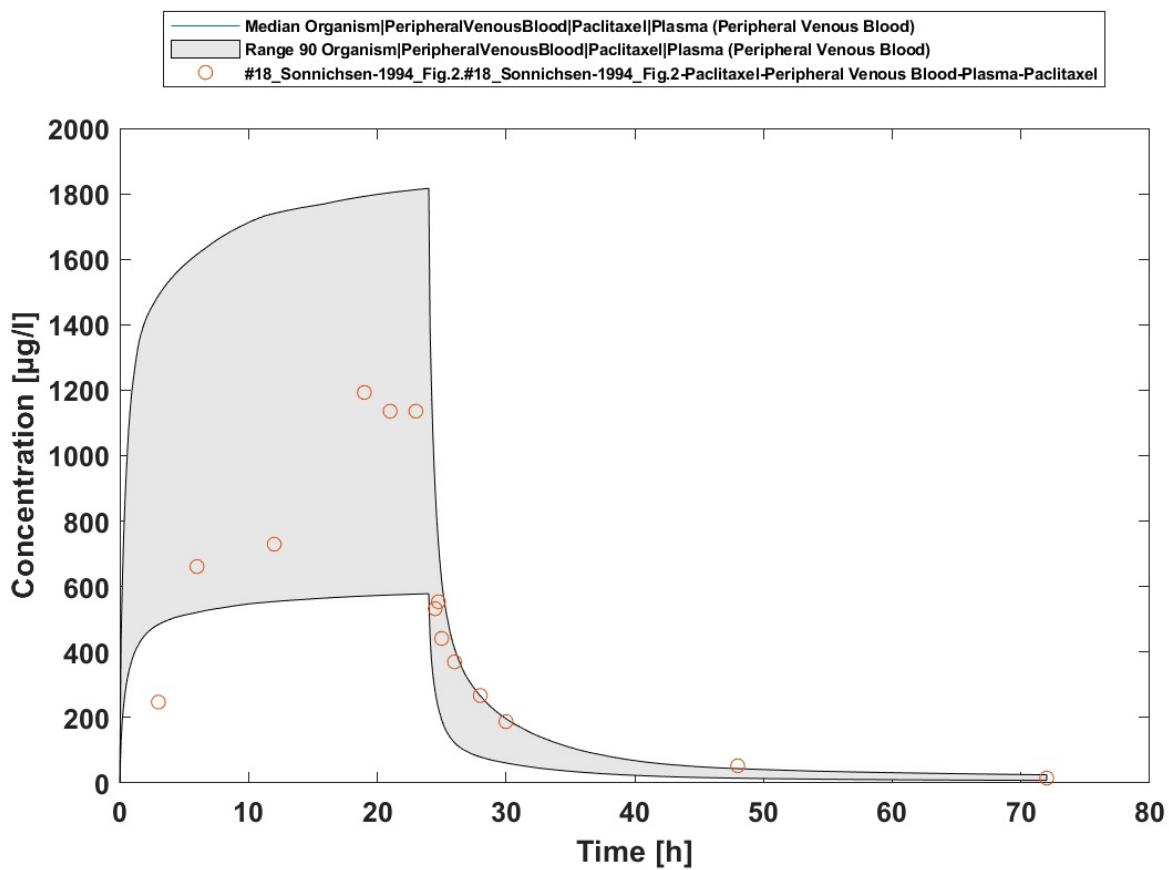
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1

# Chapter 3: Adult PBPK model performance

## Evaluation of Adult PBPK models

The PBPK models of **montelukast** and **paclitaxel** were developed with clinical pharmacokinetic data covering at least administrations given in children. Plasma concentrations following intravenous administration, oral administration, multiple dose application, fractions excreted to urine or bile and other clinical measurements were included for model development whenever available.

### Chapter 3.1: Montelukast Input Tables

#### Montelukast adult PBPK model

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%) [1]. 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 the drug already reached maximal permeability levels. The final montelukast model applies metabolism by CYP2C8, and minor involved enzymes CYP3A4/5 (16%) CYP2C9 (12%) and glomerular filtration [1-3] and adequately described the pharmacokinetics of montelukast in adults.

The montelukast model was developed using data of the following publications:

- Bovill JG, Sebel PS, Blackburn CL, Oei-Lim V, Heykants JJ. The pharmacokinetics of sufentanil in surgical patients. *Anesthesiology*. 1984 Nov;61(5):502-6. (<https://www.ncbi.nlm.nih.gov/pubmed/6238552>)
- Knorr B, Holland S, Rogers JD, Nguyen HH, Reiss TF. Montelukast adult (10-mg film-coated tablet) and pediatric (5-mg chewable tablet) dose selections. *J Allergy Clin Immunol*. 2000 Sep;106(3 Suppl):S171-8. (<https://www.ncbi.nlm.nih.gov/pubmed/10984399>)
- Zhao JJ, Rogers JD, Holland SD, Larson P, Amin RD, Haesen R, Freeman A, Seiberling M, Merz M, Cheng H. Pharmacokinetics and bioavailability of montelukast sodium (MK-0476) in healthy young and elderly volunteers. *Biopharm Drug Dispos*. 1997 Dec;18(9):769-77. (<https://www.ncbi.nlm.nih.gov/pubmed/9429741>)
- Fey C, Thyroff-Friesinger U, Jones S. Bioequivalence of two formulations of montelukast sodium 4 mg oral granules in healthy adults. *Clin Transl Allergy*. 2014 Sep 18;4:29. doi: 10.1186/2045-7022-4-29. eCollection 2014. <https://www.ncbi.nlm.nih.gov/pubmed/25250173>
- Cheng H, Leff JA, Amin R, Gertz BJ, De Smet M, Noonan N, Rogers JD, Malbecq W, Meisner D, Somers G. Pharmacokinetics, bioavailability, and safety of montelukast sodium (MK-0476) in healthy males and females. *Pharm Res*. 1996 Mar;13(3):445-8. <https://www.ncbi.nlm.nih.gov/pubmed/8692739>

#### References

- [1] Marzolini C, Rajoli R, Battegay M, Elzi L, Back D, Siccardi M. Efavirenz Involving Simultaneous Inducing and Inhibitory Effects on Cytochromes. *Clin Pharmacokinet*. 2017 Apr;56(4):409-420. doi: 10.1007/s40262-016-0447-7.
- [2] Filppula AM, Laitila J, Neuvonen PJ, Backman JT. Reevaluation of the microsomal metabolism of montelukast: major contribution by CYP2C8 at clinically relevant concentrations. *Drug Metab Dispos*. 2011 May;39(5):904-11. doi: 10.1124/dmd.110.037689. Epub 2011 Feb 2.
- [3] Zhou W, Johnson TN, Bui KH, Cheung SYA, Li J, Xu H, Al-Huniti N, Zhou D. Predictive Performance of Physiologically Based Pharmacokinetic (PBPK) Modeling of Drugs Extensively Metabolized by Major Cytochrome P450s in Children. *Clin Pharmacol Ther*. 2018 Jul;104(1):188-200. doi: 10.1002/cpt.905. Epub 2017 Nov 20.

The compound properties used for input 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

**Systemic Process: Total Hepatic Clearance-Literatur (Cheng 1996)**

Species: Human

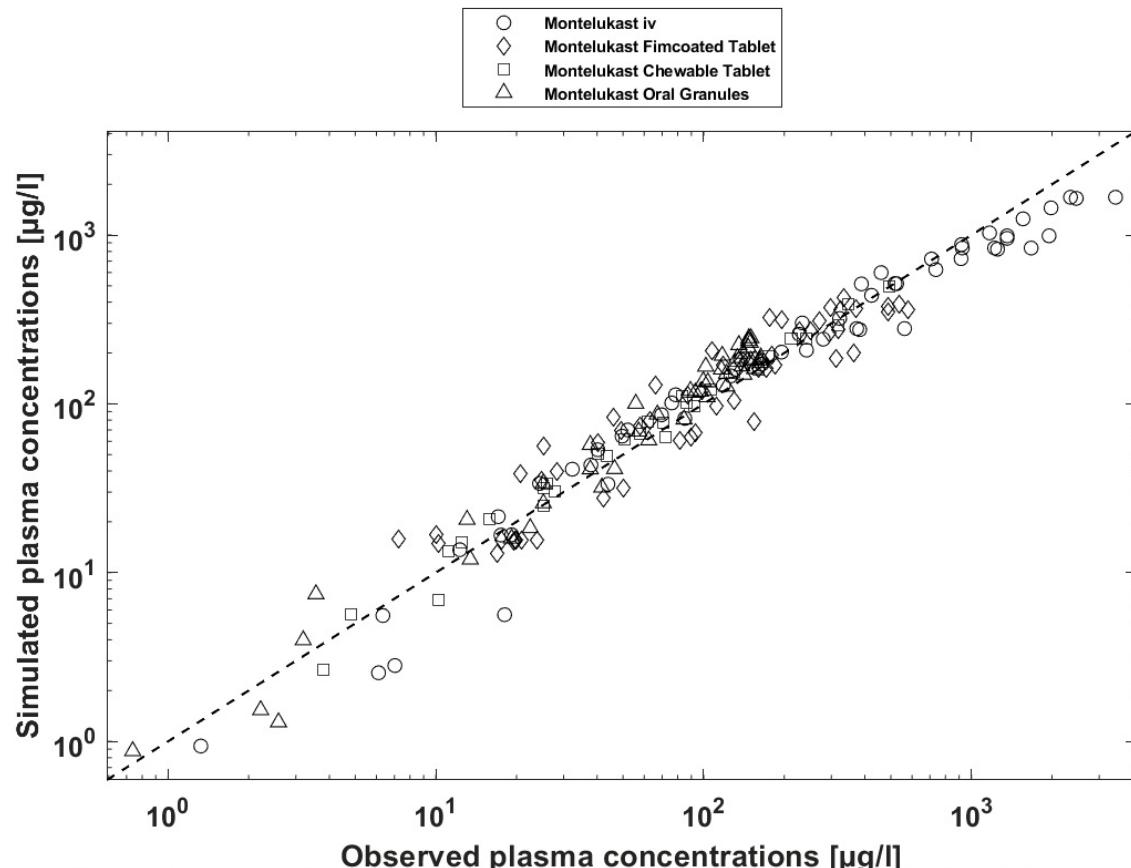
**Parameters**

Name	Value	Value Origin
Body weight	76.5 kg	Publication-In Vivo-Cheng 1996
Fraction unbound (experiment)	0.0018	
Lipophilicity (experiment)	7.9 Log Units	
Plasma clearance	0.608496732 ml/min/kg	Publication-In Vivo-Cheng 1996

**Chapter 3.2: Montelukast Diagnostics Plots**

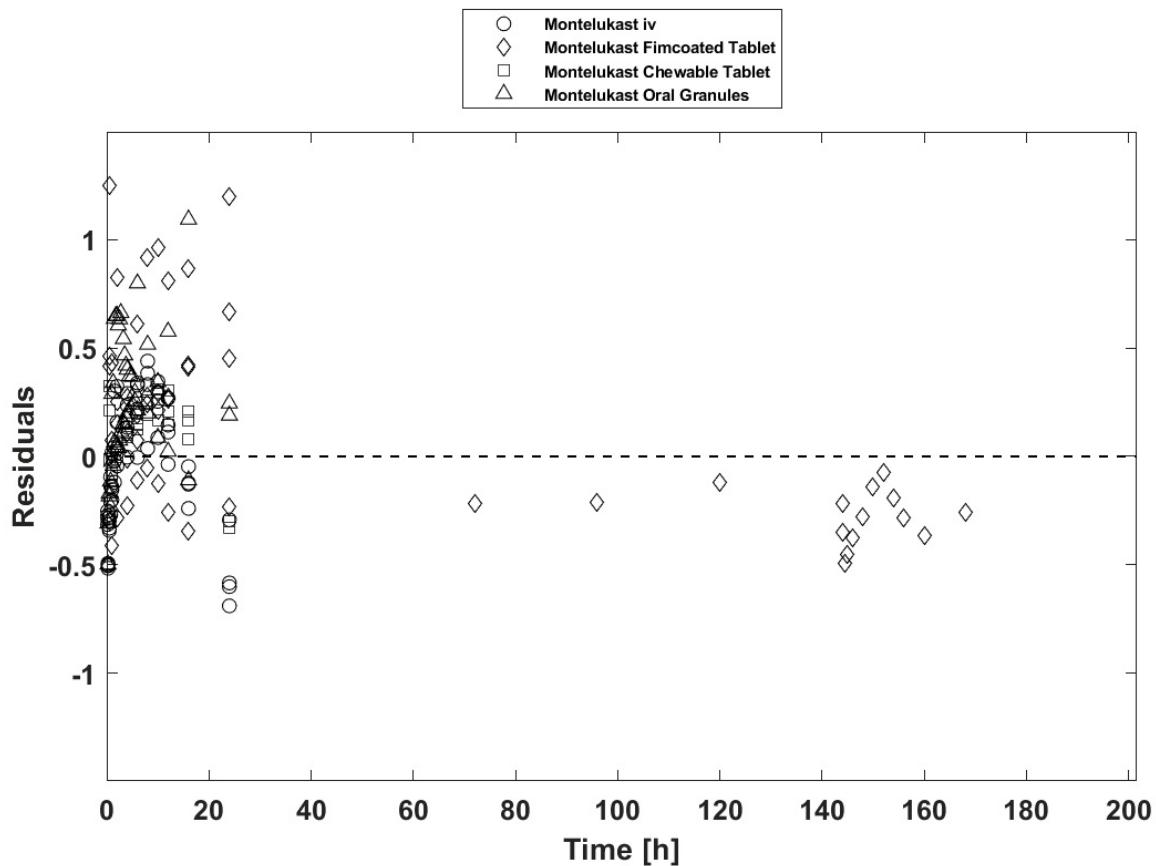
## Montelukast adult PBPK model performance

Below you find the input goodness-of-fit visual diagnostic plots for montelukast PBPK model performance (observed versus individually predicted plasma concentration and weighted residuals versus time) of all adult data.



Goodness-of-fit visual diagnostic plots for montelukast PBPK model performance: observed versus individually predicted plasma concentration versus time of all adult data.

GMFE = 1.311214



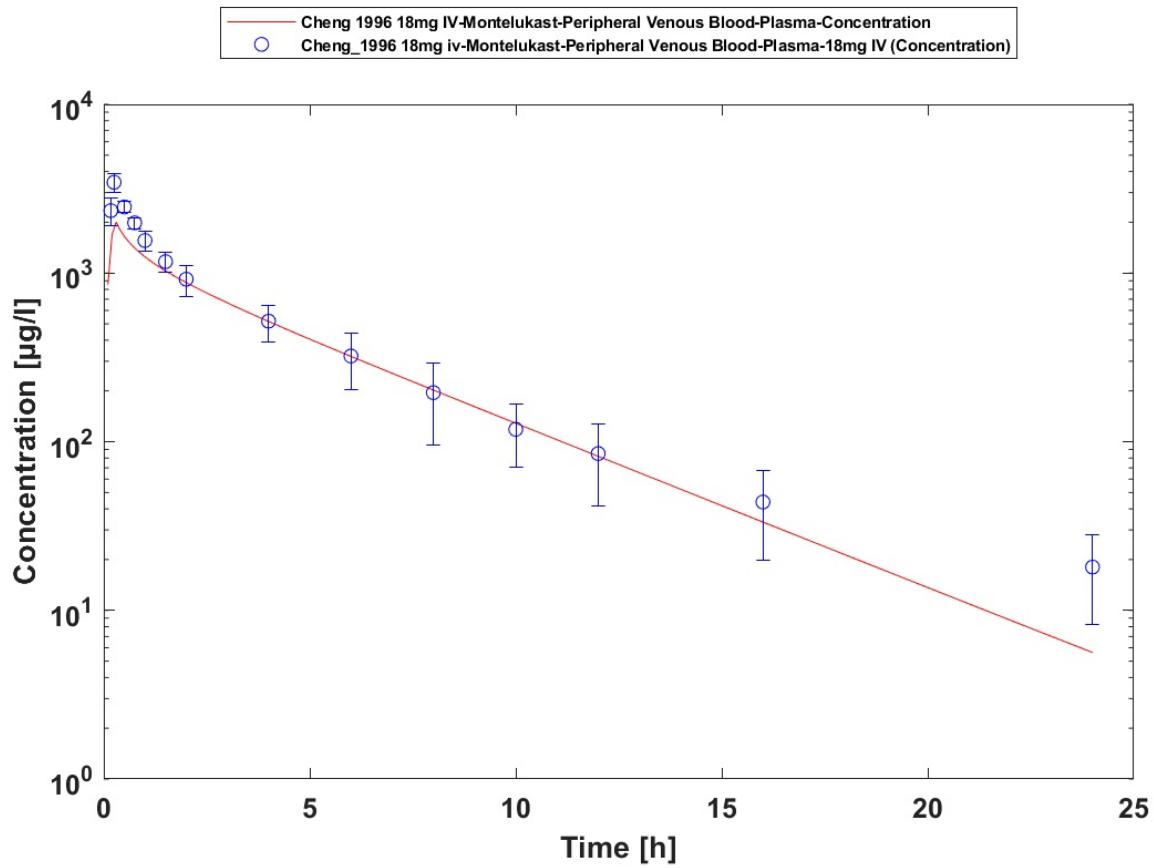
Goodness-of-fit visual diagnostic plots for montelukast PBPK model performance: weighted residuals versus time of all adult data.

GMFE = 1.311214

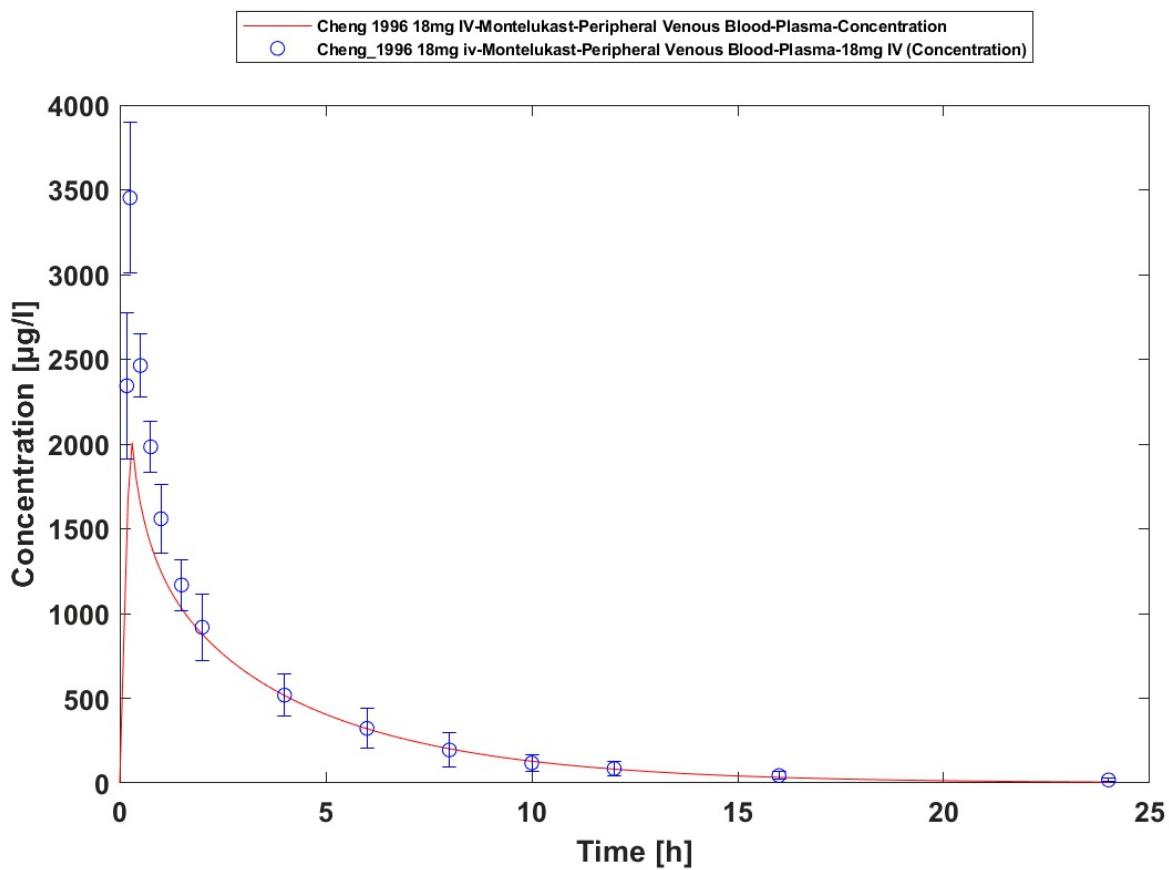
### Chapter 3.3: Montelukast Concentration-Time profiles in Adults

#### Concentration-Time Profiles

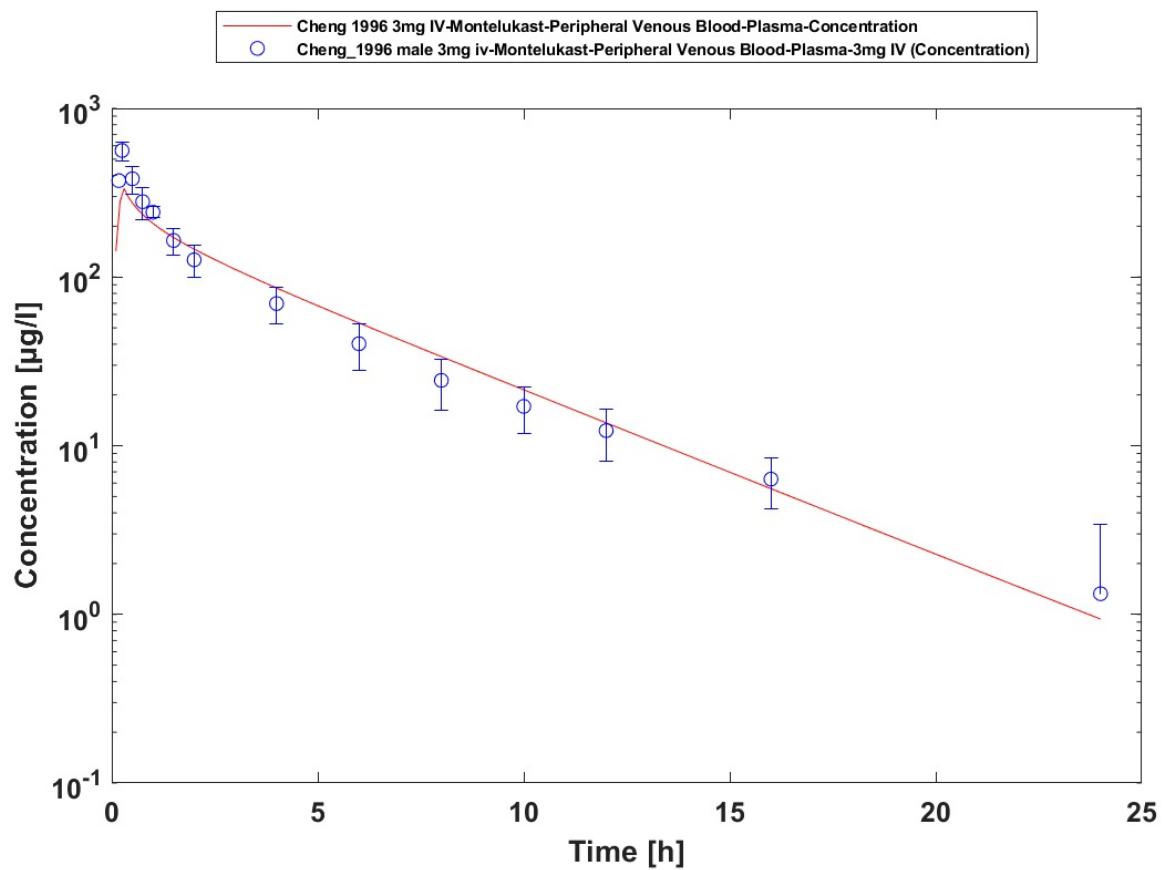
Simulated versus observed plasma concentration-time profiles of all data are listed below.



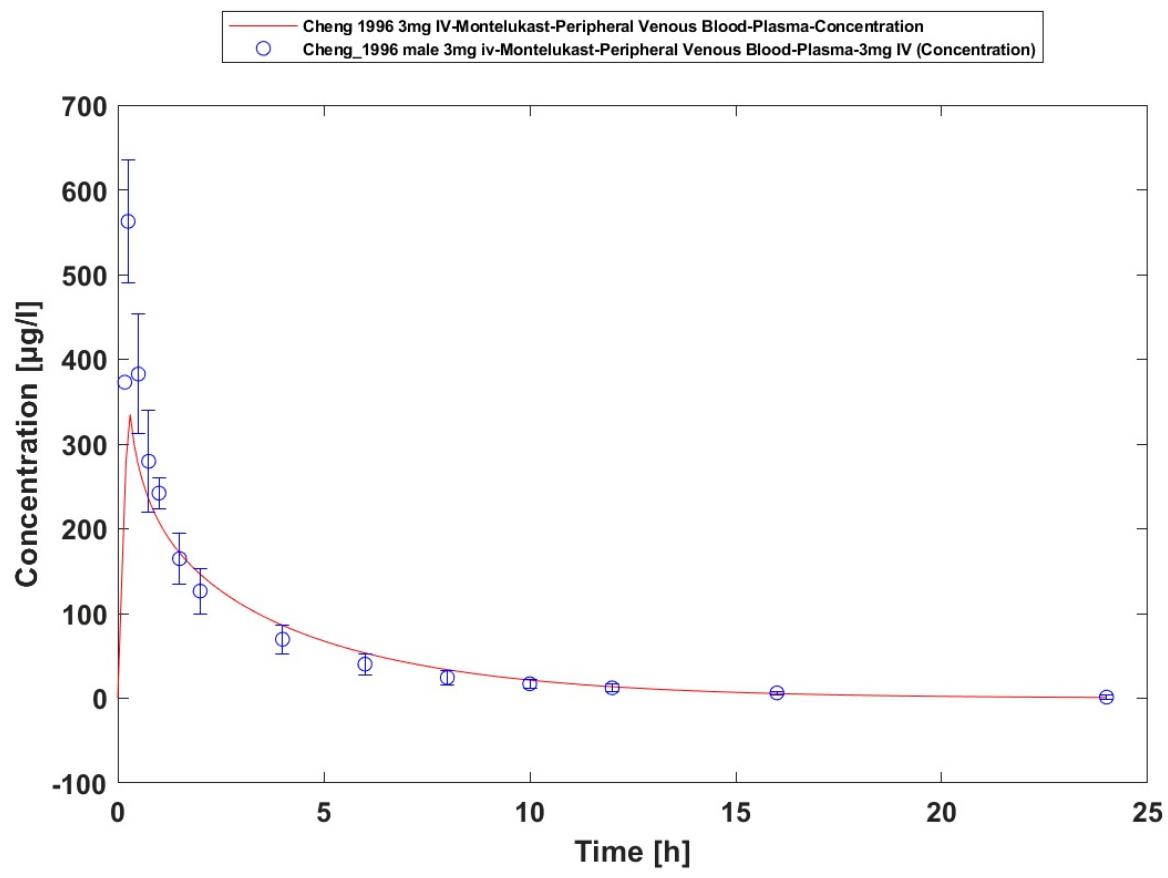
Time Profile Analysis



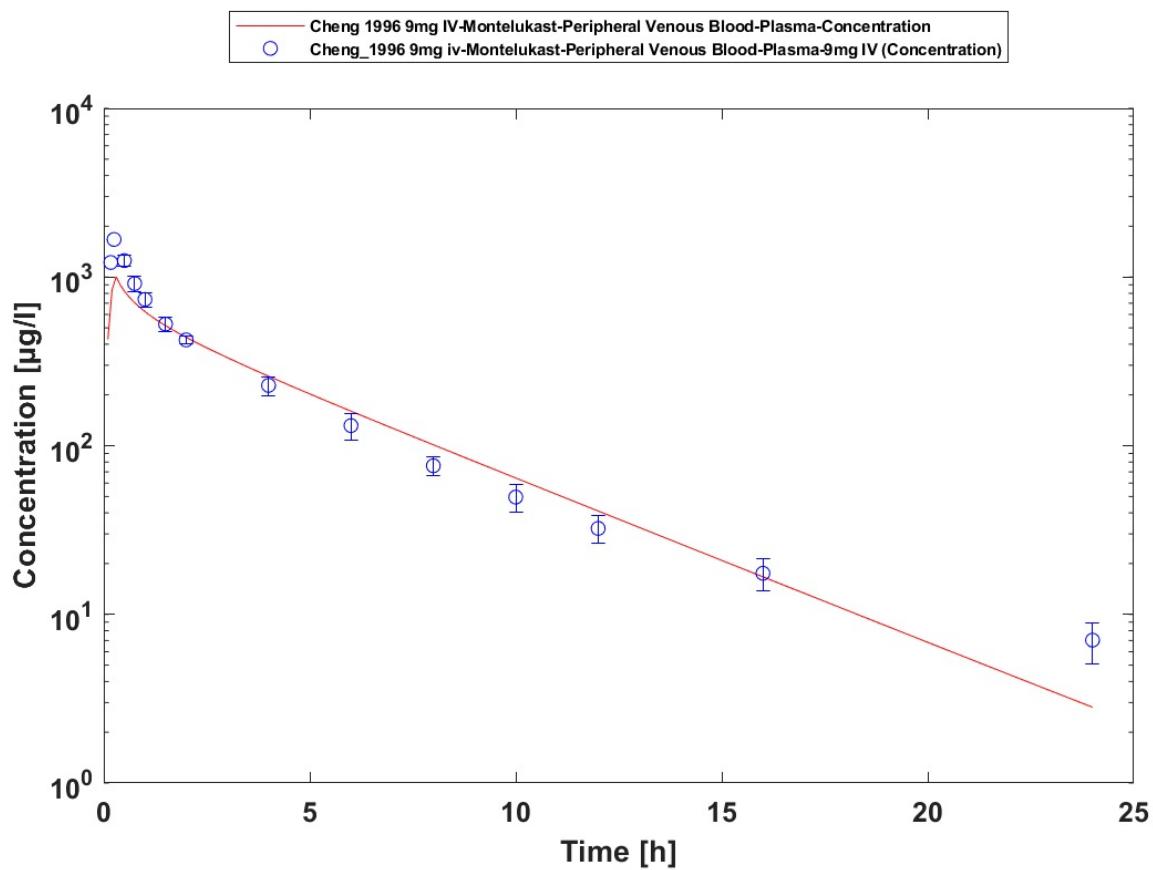
Time Profile Analysis 1



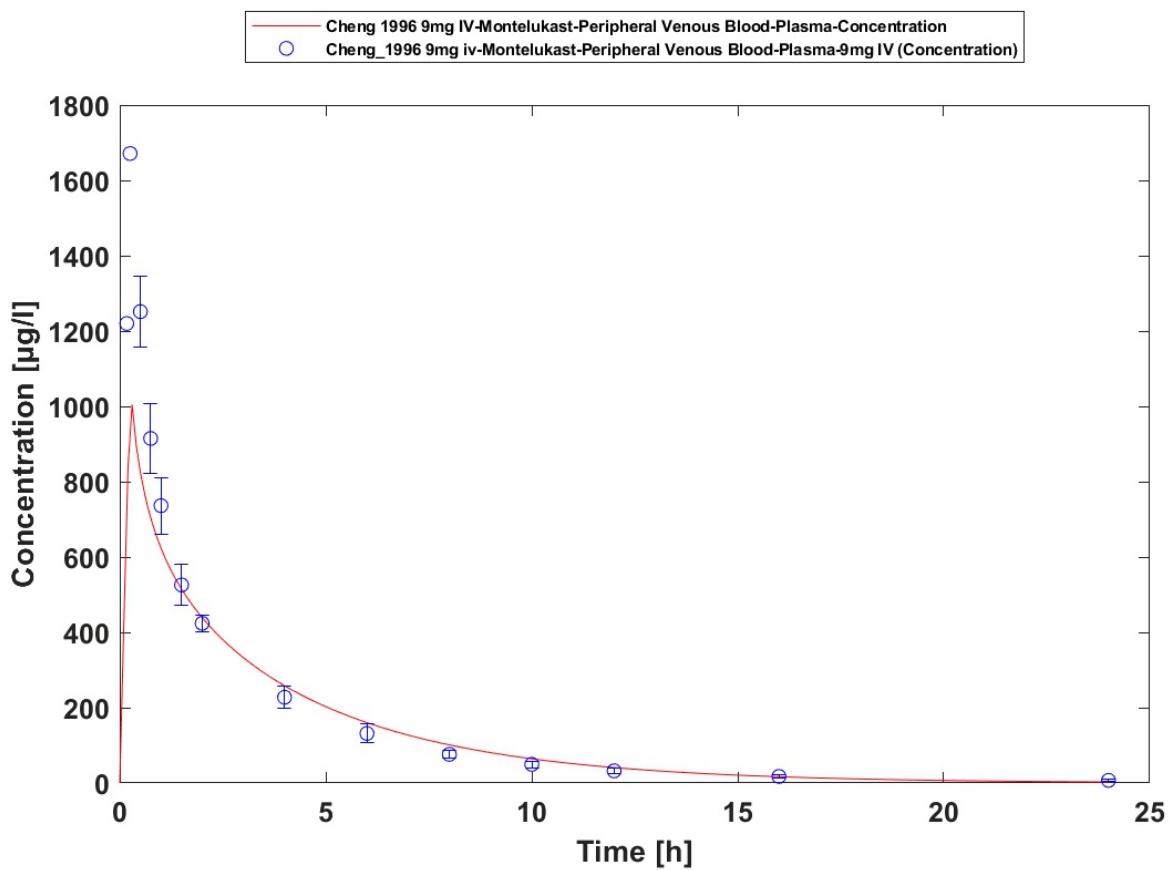
Time Profile Analysis



Time Profile Analysis 1

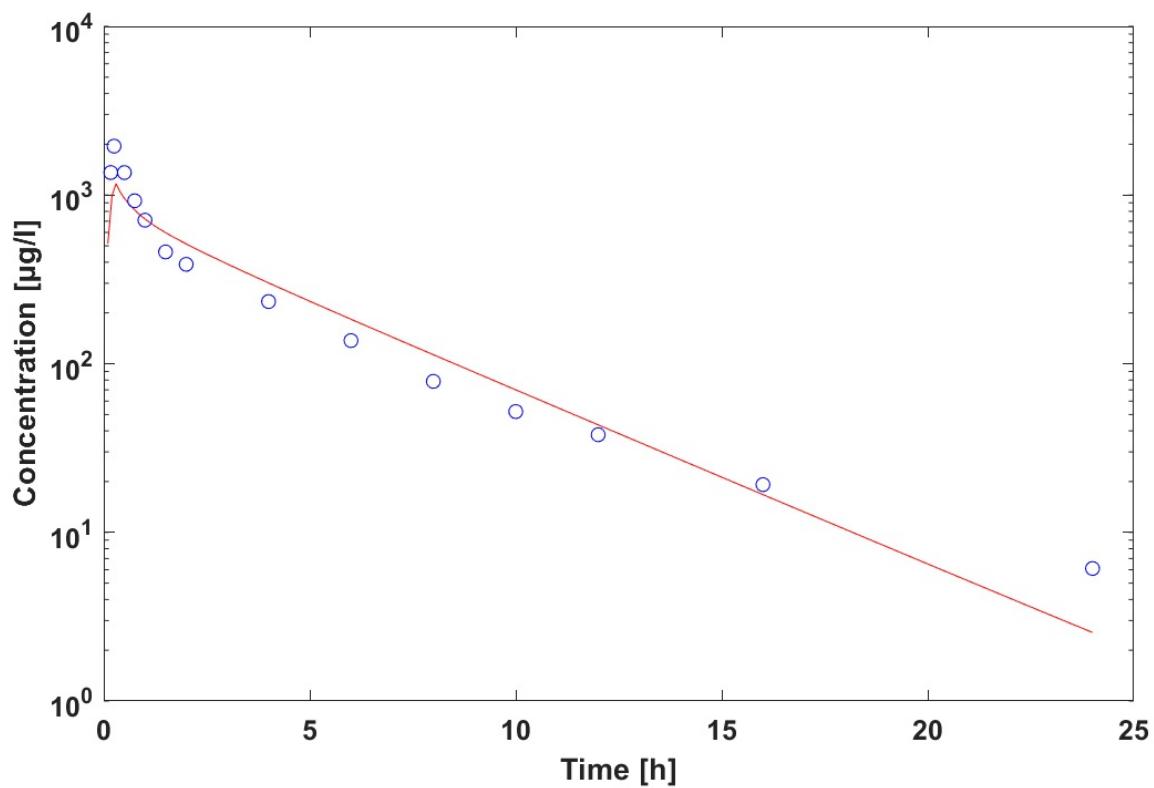


Time Profile Analysis

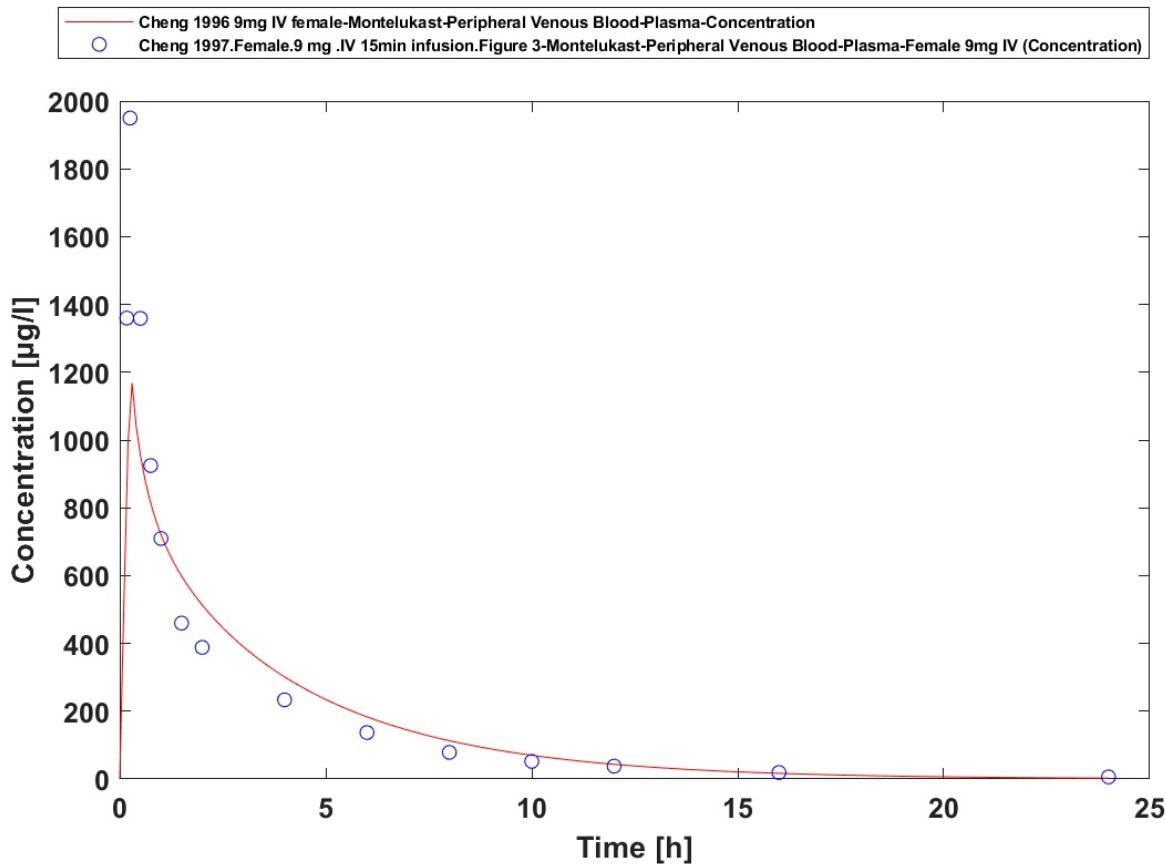


Time Profile Analysis 1

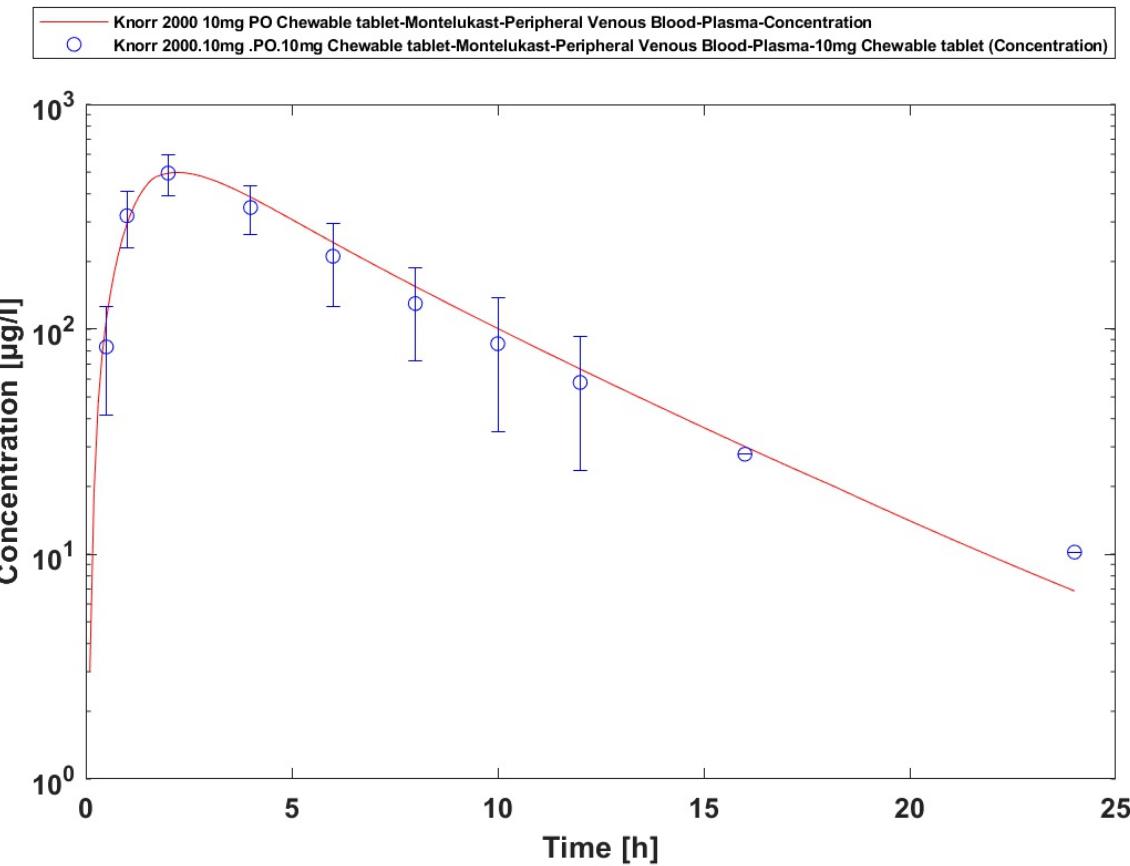
Cheng 1996 9mg IV female-Montelukast-Peripheral Venous Blood-Plasma-Concentration  
Cheng 1997.Female.9 mg .IV 15min infusion.Figure 3-Montelukast-Peripheral Venous Blood-Plasma-Female 9mg IV (Concentration)

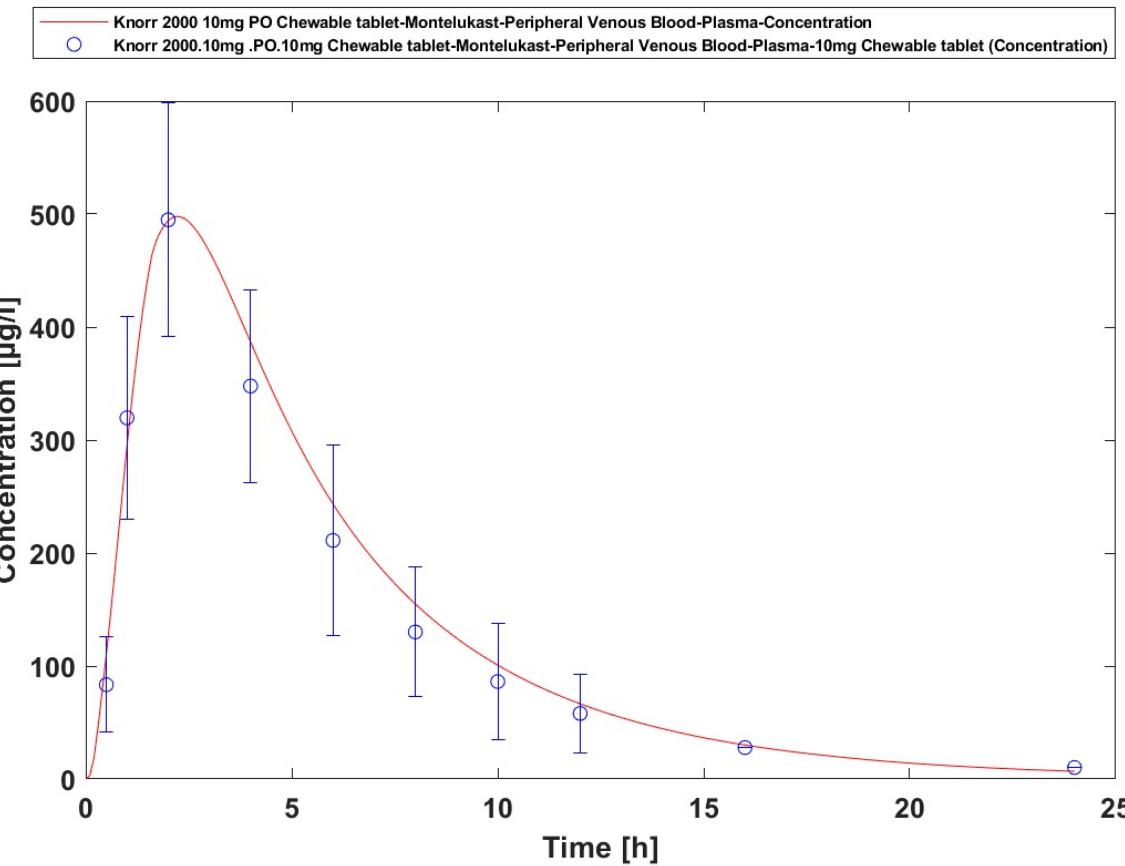


Time Profile Analysis

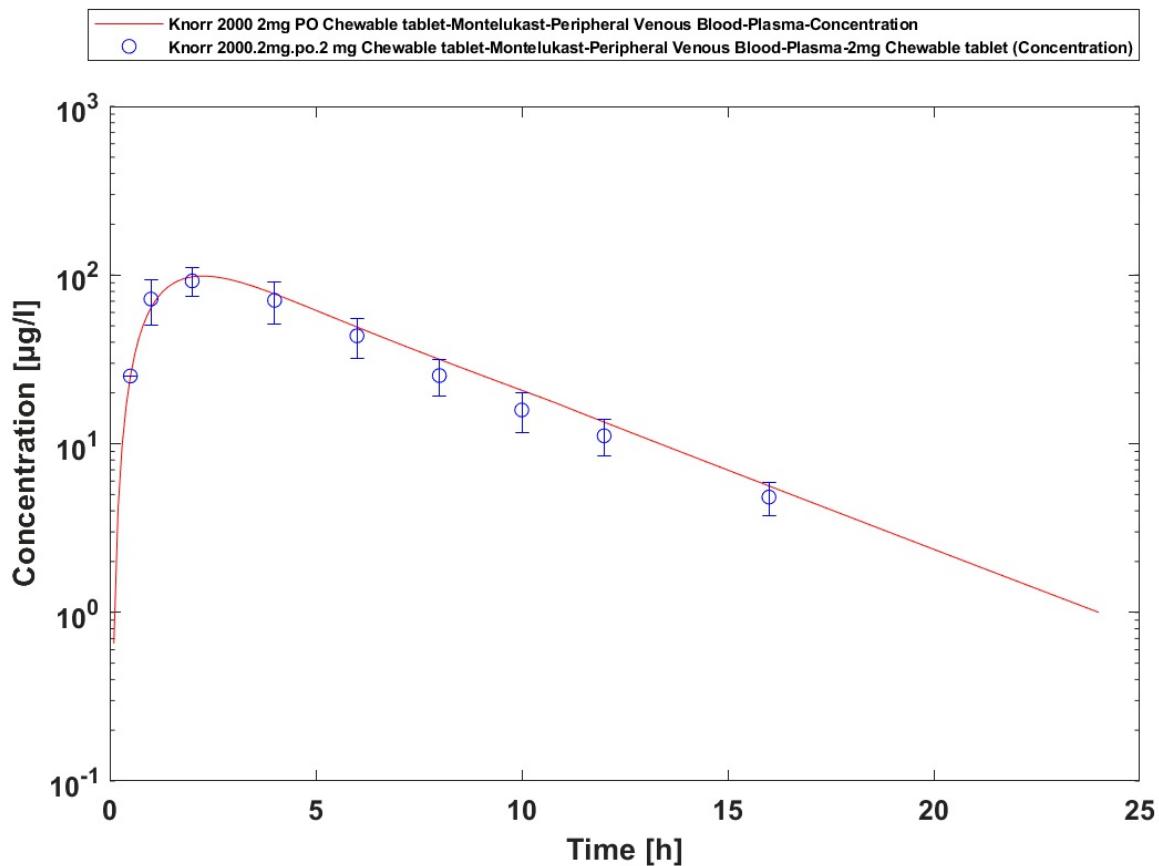


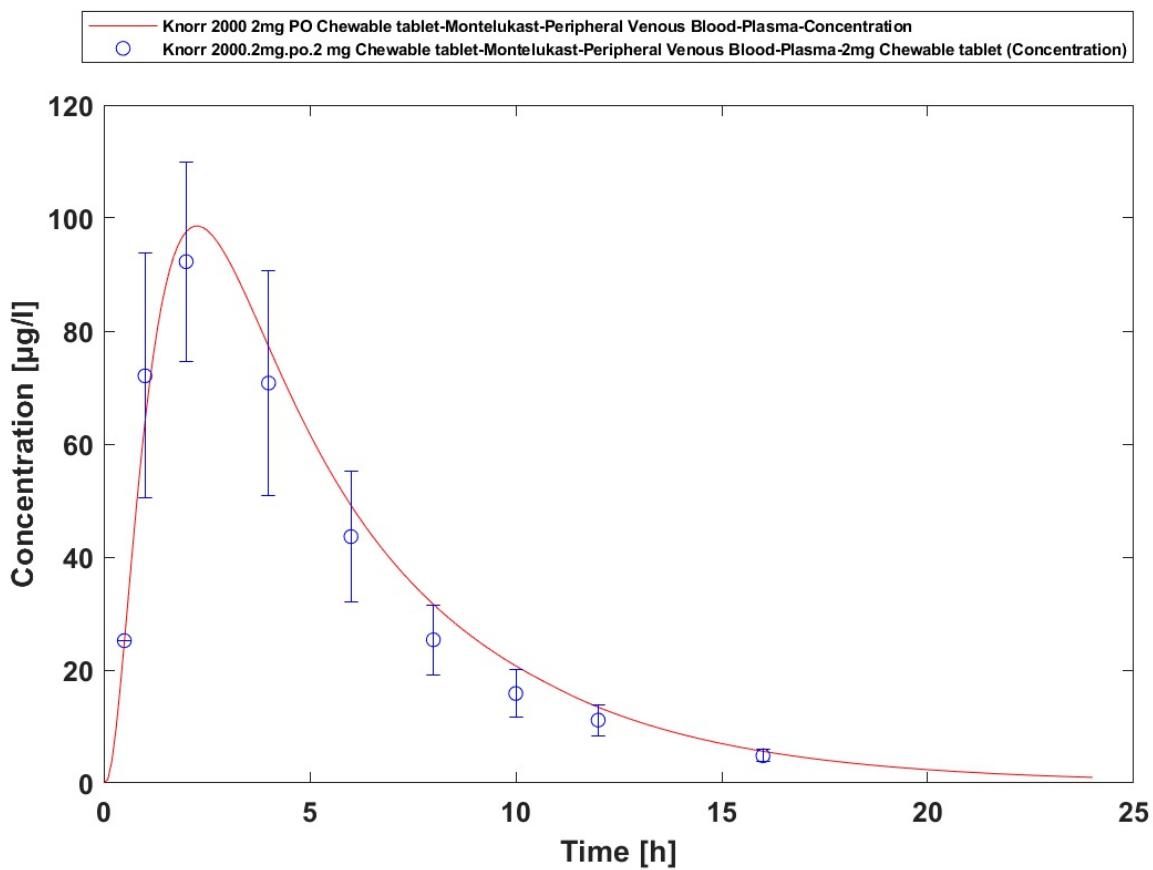
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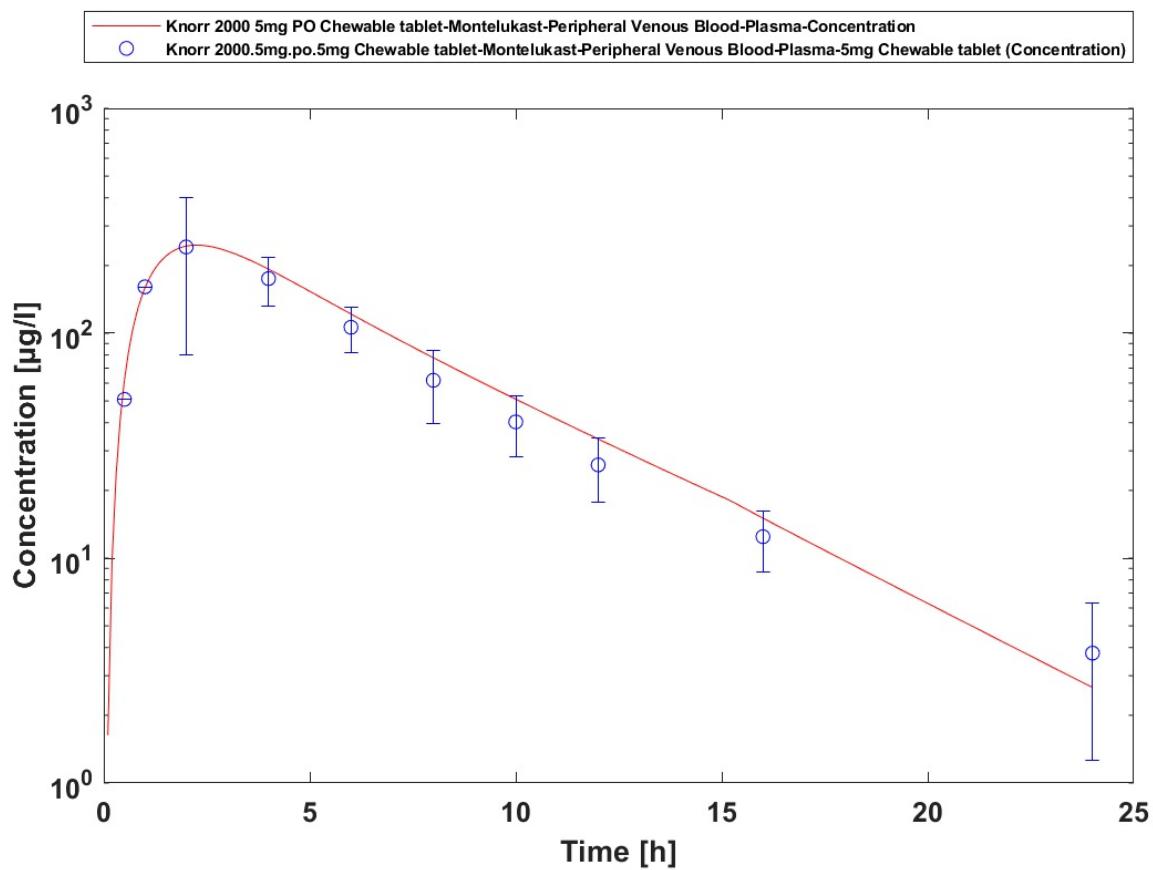


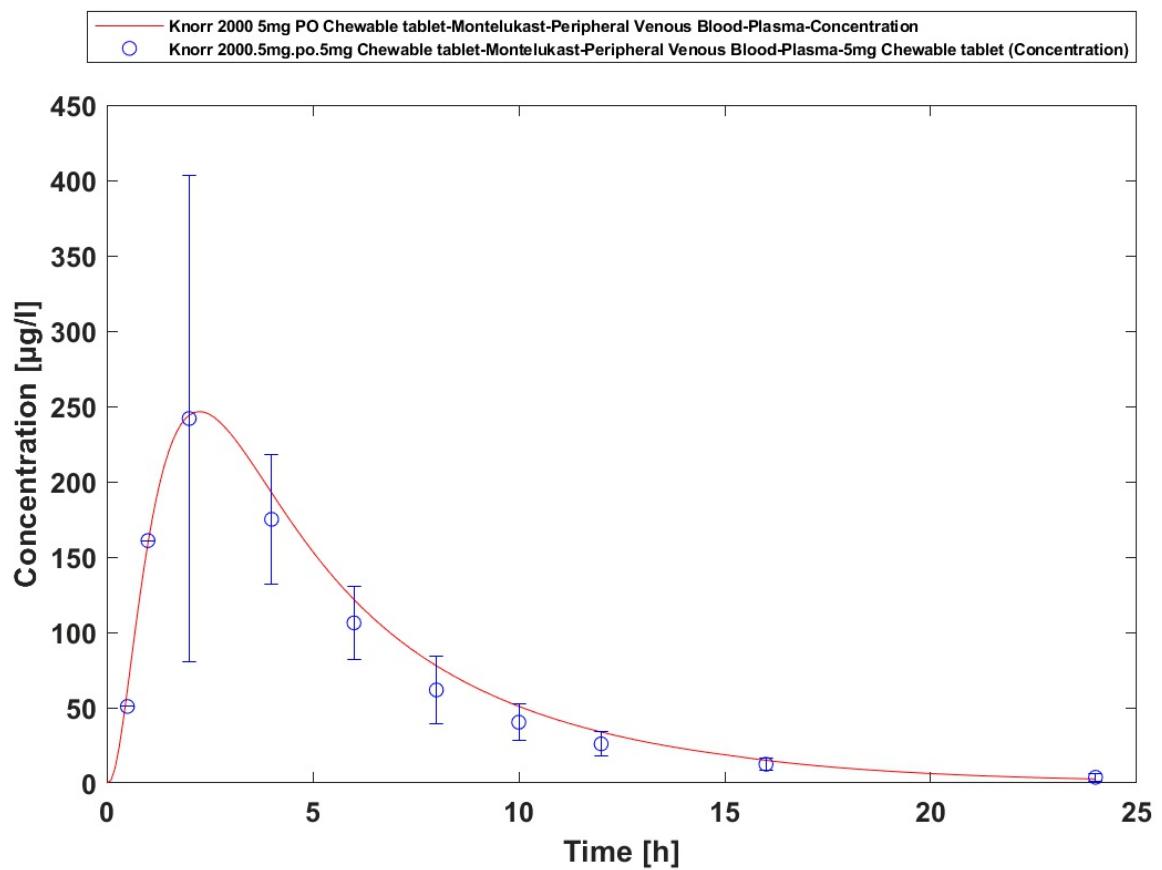


Time Profile Analysis 1

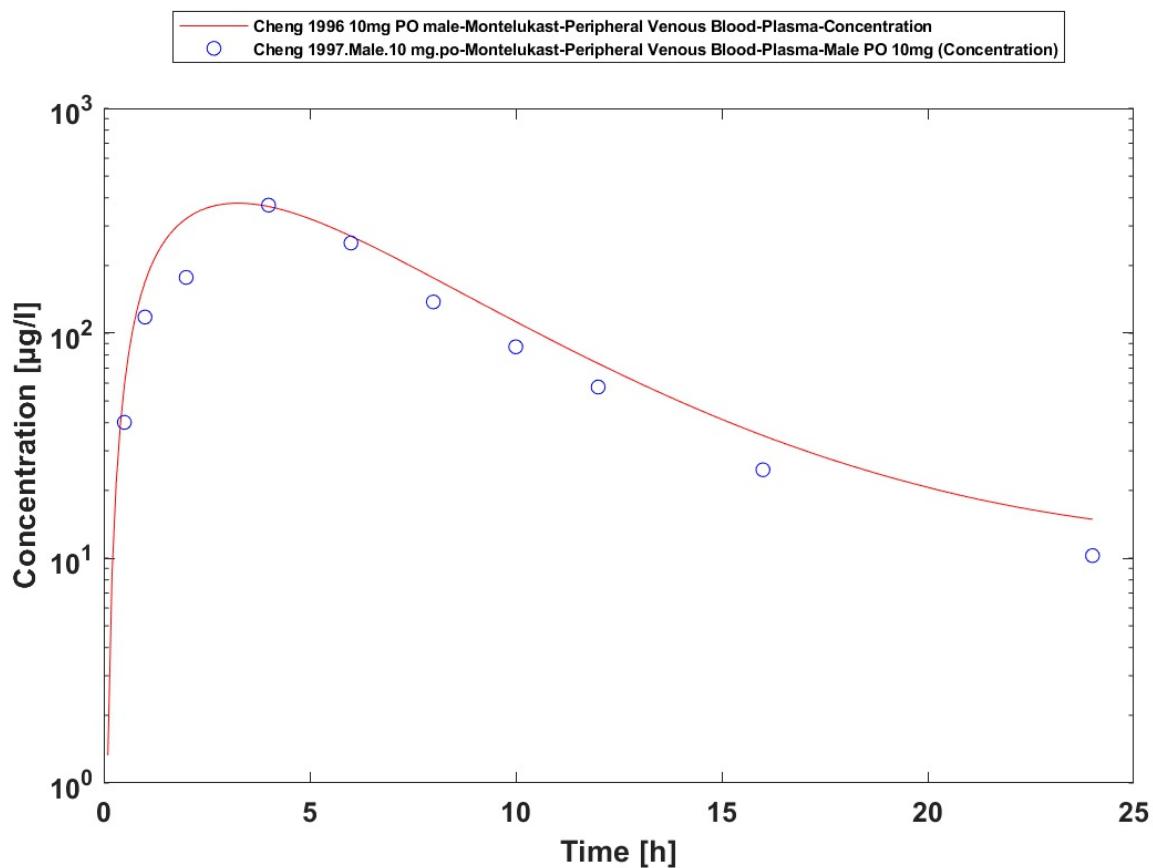




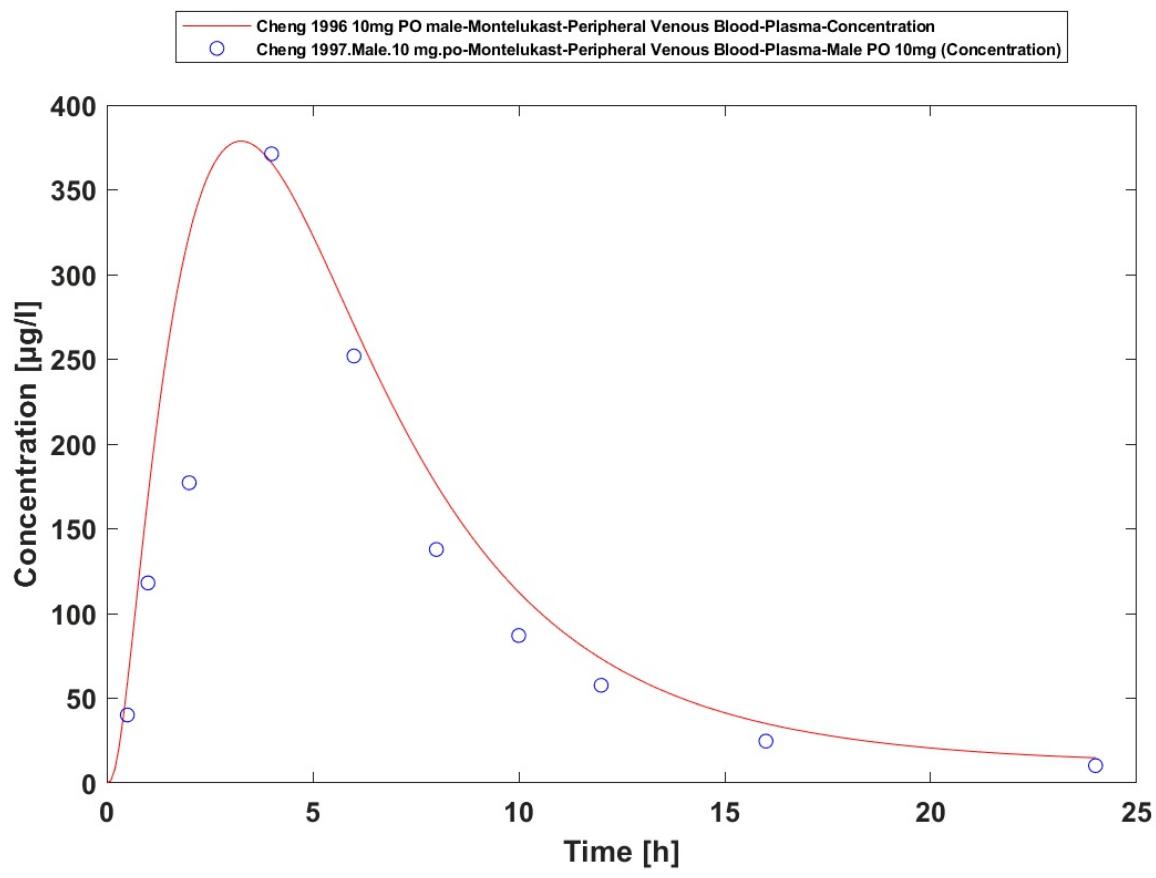




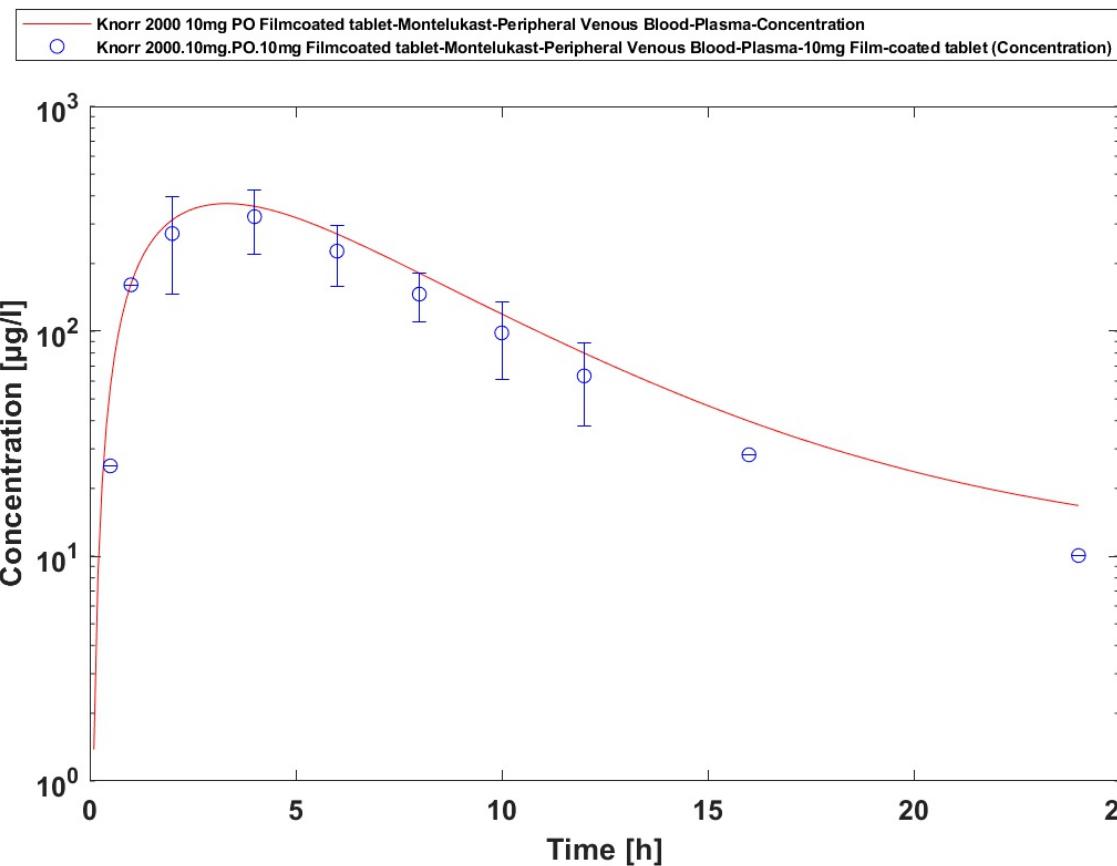
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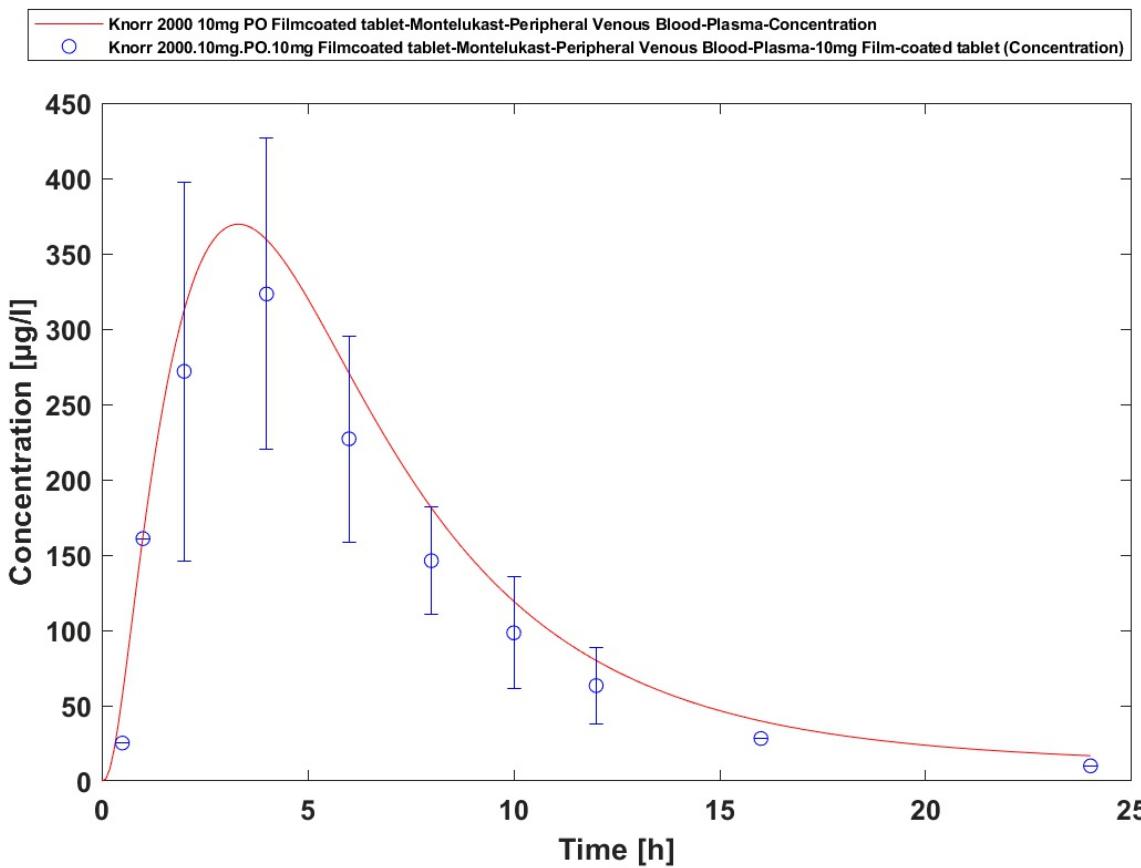
Time Profile Analysis



Time Profile Analysis 1

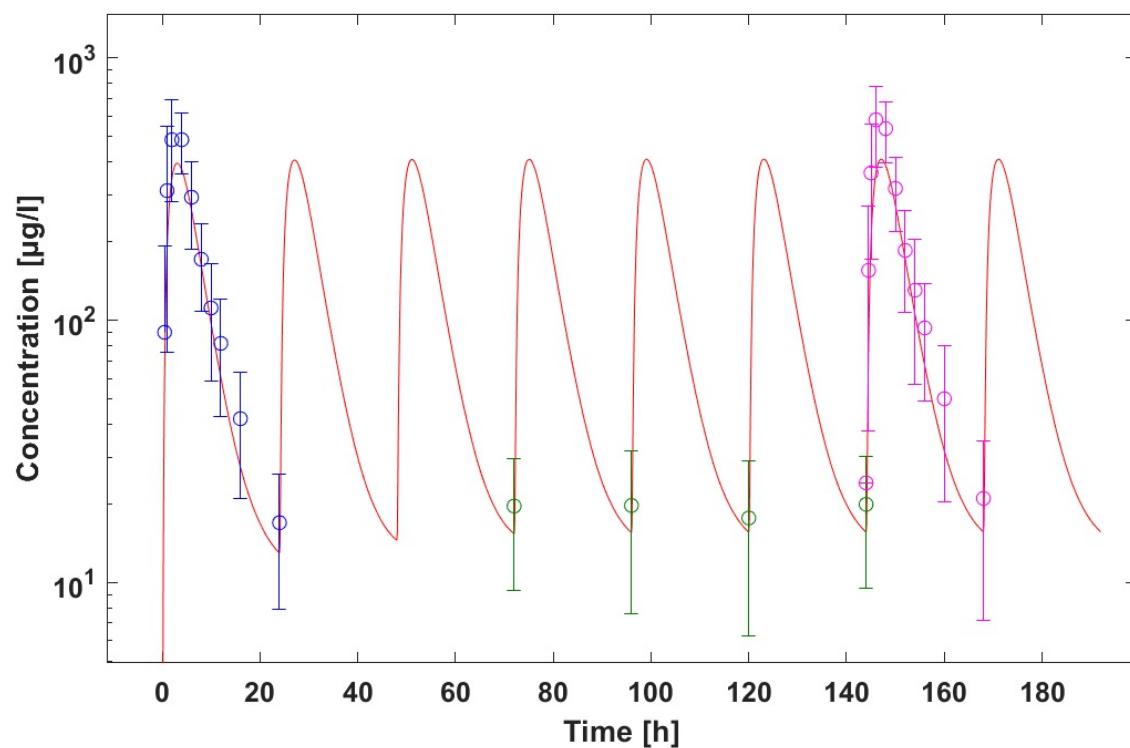


Time Profile Analysis



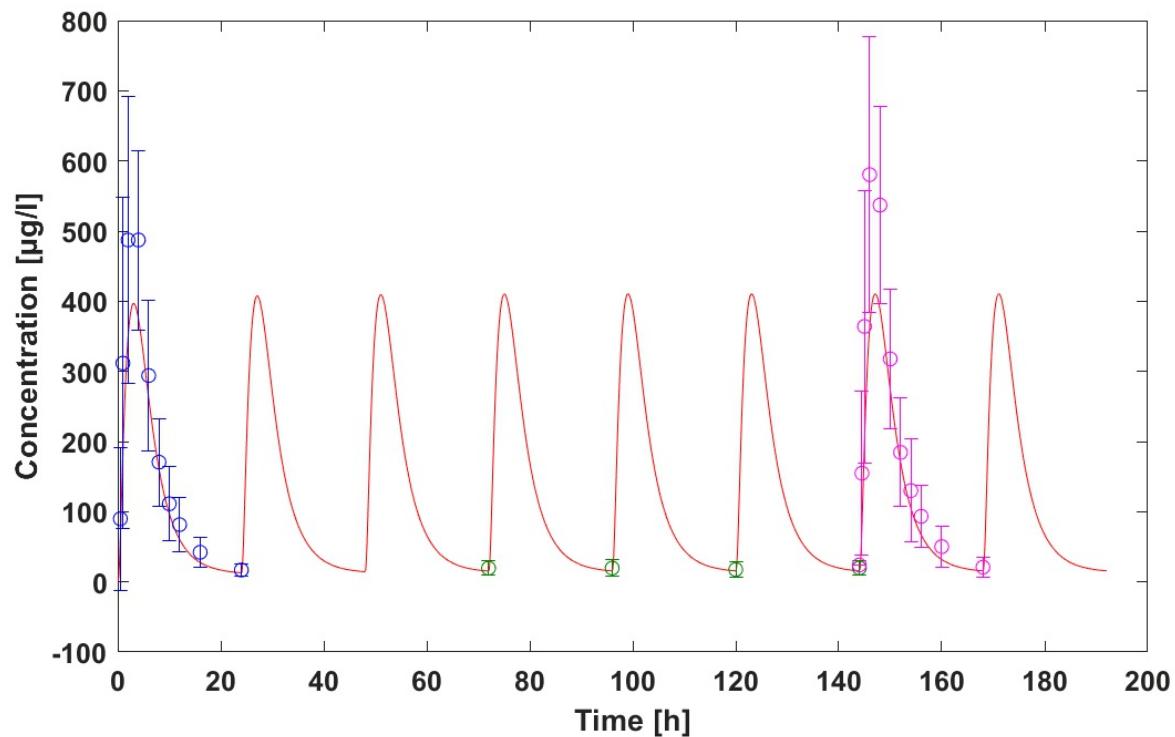
Time Profile Analysis 1

heral Venous Blood-Plasma-Concentration  
nontelukas sodium (mk-0476) in healthy young and elderly volunteers-Montelukast-Peripheral Venous Blood-Plasma-Mean plasma conc. (Concentration)  
montelukas sodium (mk-0476) in healthy young and elderly volunteers-Montelukast-Peripheral Venous Blood-Plasma-concentration values (Concentration)  
nontelukas sodium (mk-0476) in healthy young and elderly volunteers 1-Montelukast-Peripheral Venous Blood-Plasma-concentration values (Concentration)



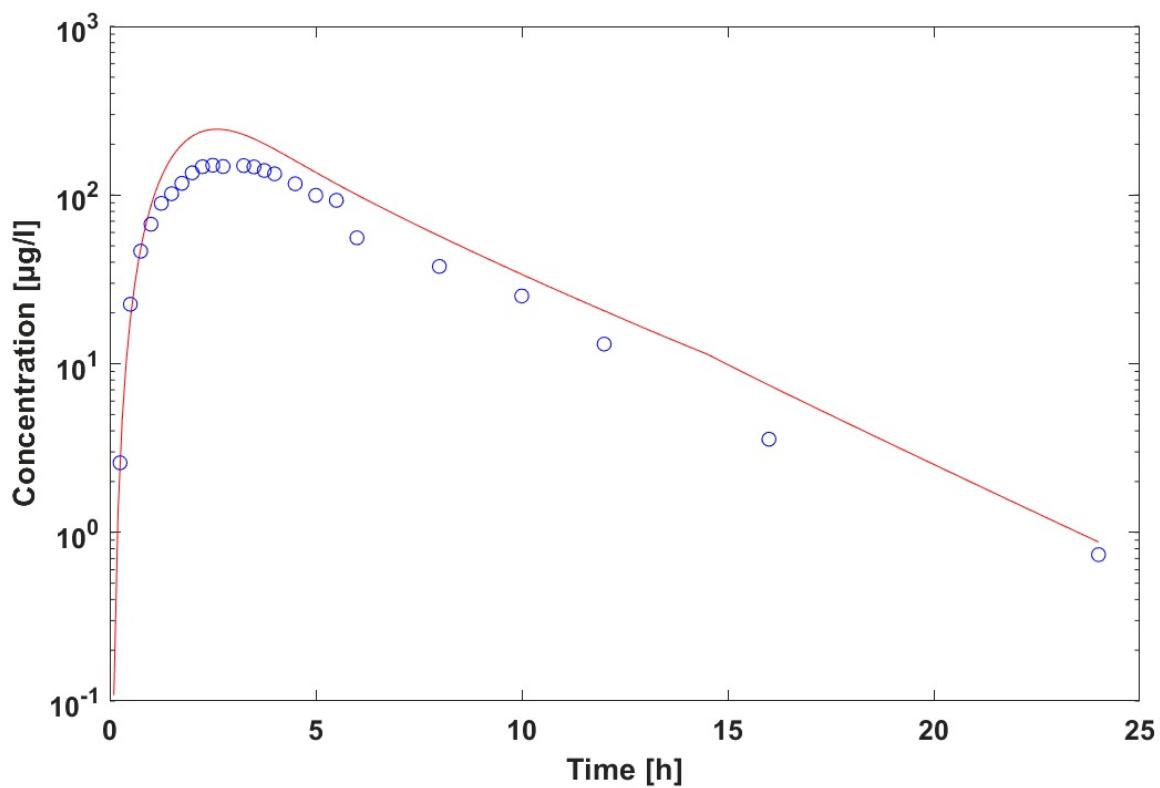
Time Profile Analysis

heral Venous Blood-Plasma-Concentration  
montelukas sodium (mk-0476) in healthy young and elderly volunteers-Montelukast-Peripheral Venous Blood-Plasma-Mean plasma conc. (Concentration)  
montelukas sodium (mk-0476) in healthy young and elderly volunteers-Montelukast-Peripheral Venous Blood-Plasma-concentration values (Concentration)  
montelukas sodium (mk-0476) in healthy young and elderly volunteers 1-Montelukast-Peripheral Venous Blood-Plasma-concentration values (Concentration)



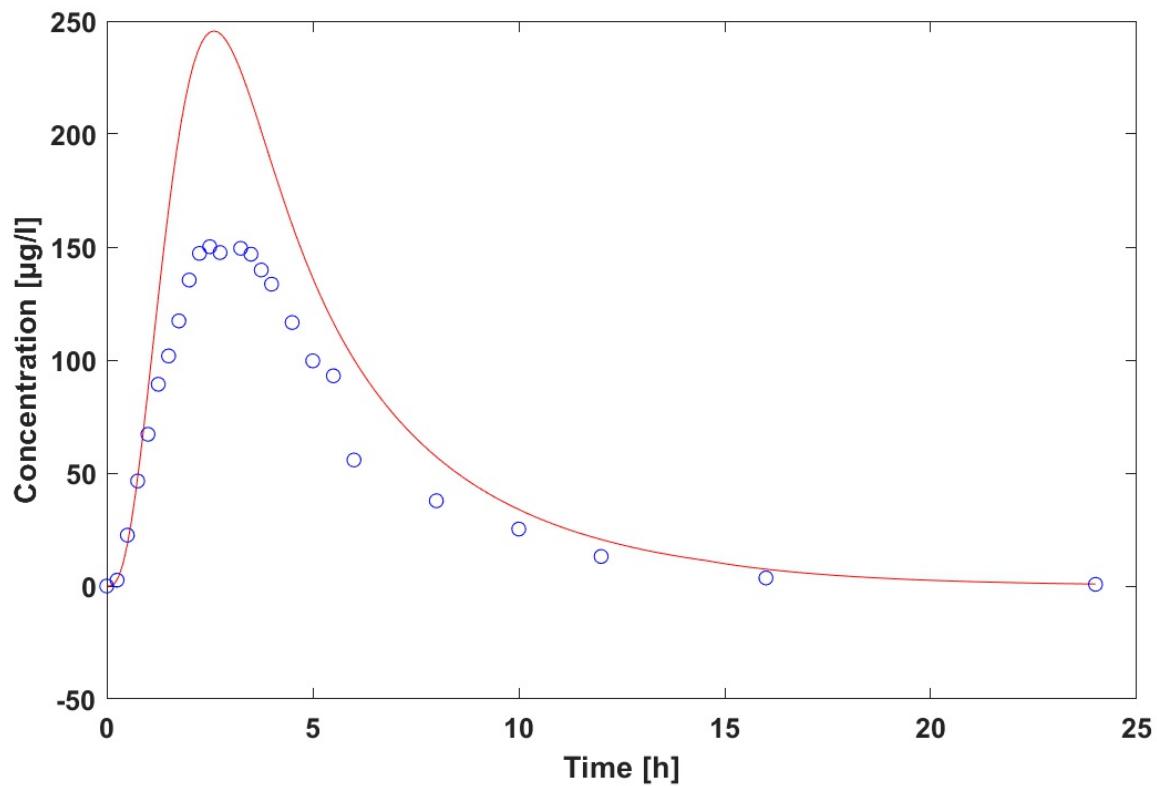
Time Profile Analysis 1

— Fey 2014 4mg PO Sandoz oral granules (for reporting)-Montelukast-Peripheral Venous Blood-Plasma-Concentration  
○ Fey 2014 .Male.4mg.PO oral granules.Adult Sandoz 4mg granules-Montelukast-Peripheral Venous Blood-Plasma-Sandoz 4mg granules (Concentration)



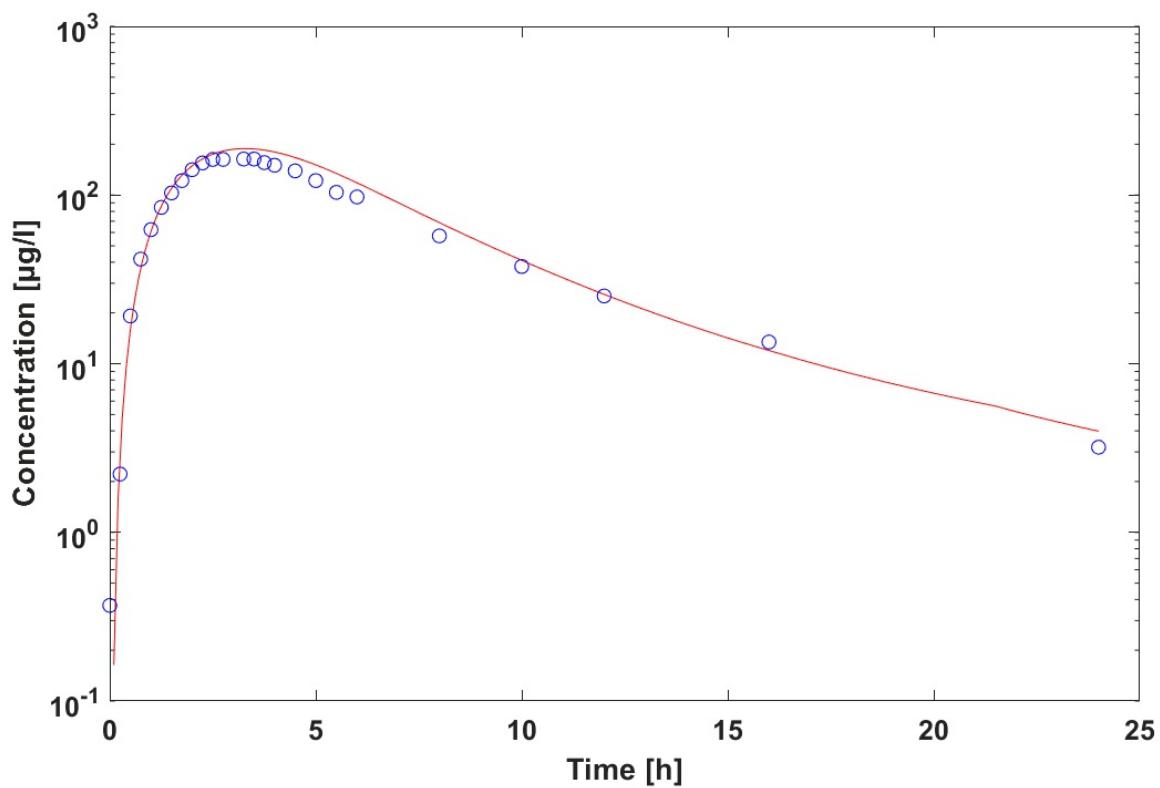
Time Profile Analysis

— Fey 2014 4mg PO Sandoz oral granules (for reporting)-Montelukast-Peripheral Venous Blood-Plasma-Concentration  
) Fey 2014 .Male.4mg.PO oral granules.Adult Sandoz 4mg granules-Montelukast-Peripheral Venous Blood-Plasma-Sandoz 4mg granules (Concentration)



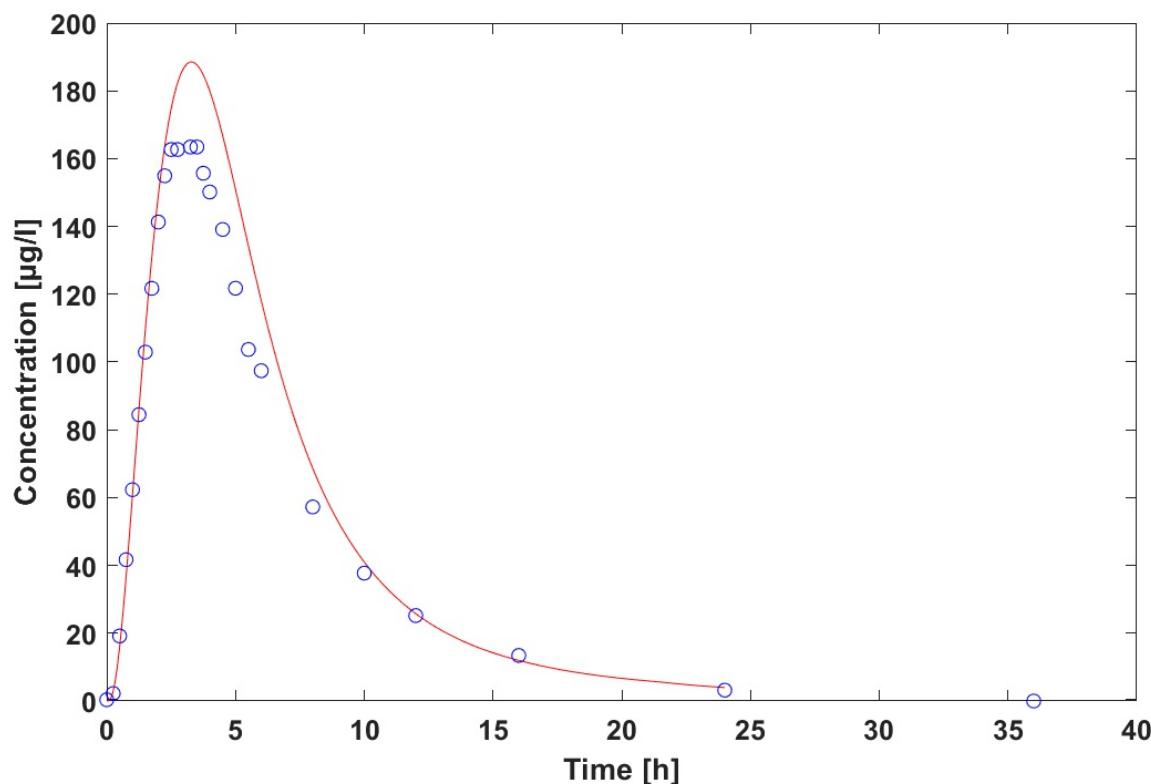
Time Profile Analysis 1

4 4mg PO Singular oral mini granules (for reporting)-Montelukast-Peripheral Venous Blood-Plasma-Concentration  
4 .Male.4mg.PO oral granules.Adultt Singular mini 4mg granules-Montelukast-Peripheral Venous Blood-Plasma-Singulair mini 4mg granules (Concentration)



Time Profile Analysis

4 4mg PO Singular oral mini granules (for reporting)-Montelukast-Peripheral Venous Blood-Plasma-Concentration  
 4 .Male.4mg.PO oral granules.Adult Singulair mini 4mg granules-Montelukast-Peripheral Venous Blood-Plasma-Singulair mini 4mg granules (Concentration)



Time Profile Analysis 1

## Chapter 3.4: Paclitaxel Input Tables

### Paclitaxel model

Paclitaxel is antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. It is applied as chemotherapy medication for treating a number of types of cancer. It is administered intravenously. Paclitaxel is mainly metabolized by CYP2C8 [1]. The final Paclitaxel model applies metabolism by CYP2C8, and CYP3A4,[1] and glomerular filtration [2]. As paclitaxel is highly lipophilic and freely enters the cell without a transporter.[1] Although *in vitro* it is indicated that OATP transporters are involved, this is considered minor and is not included in the model. During model building and the estimation of *in vivo* clearances of the enzymes, in order to keep the mass balance information as published *in vitro*, the enzyme-clearances were estimated as factor to the *in vitro* values with the same ratio. The paclitaxel PBPK model adequately described the pharmacokinetics of paclitaxel in adults.

The paclitaxel model was developed using data of the following publications:

- Diamond JR, Wu B, Agarwal N, Bowles DW, Lam ET, Werner TL, Rasmussen E, Gamelin E, Soto F, Friberg G, Sun YN, Sharma S. Pharmacokinetic drug-drug interaction study of the angiopoietin-1/angiopoietin-2-inhibiting peptibody trebananib (AMG 386) and paclitaxel in patients with advanced solid tumors. *Invest New Drugs*. 2015 Jun;33(3):691-9. doi: 10.1007/s10637-015-0236-4. Epub 2015 Apr 21.  
<https://link.springer.com/article/10.1007%2Fs10637-015-0236-4>
- Huizing MT, Keung AC, Rosing H, van der Kuij V, ten Bokkel Huinink WW, Mandjes IM, Dubbelman AC, Pinedo HM, Beijnen JH. Pharmacokinetics of paclitaxel and metabolites in a randomized comparative study in platinum-pretreated ovarian cancer patients. *J Clin Oncol*. 1993 Nov;11(11):2127-35.  
<https://ascopubs.org/doi/abs/10.1200/JCO.1993.11.11.2127>
- Huizing MT, Vermorken JB, Rosing H, ten Bokkel Huinink WW, Mandjes I, Pinedo HM, Beijnen JH. Pharmacokinetics of paclitaxel and

three major metabolites in patients with advanced breast carcinoma refractory to anthracycline therapy treated with a 3-hour paclitaxel infusion: a European Cancer Centre (ECC) trial. Ann Oncol. 1995 Sep;6(7):699-704  
<https://www.ncbi.nlm.nih.gov/pubmed/8664192>

- Ibrahim NK, Desai N, Legha S, Soon-Shiong P, Theriault RL, Rivera E, Esmaeli B, Ring SE, Bedikian A, Hortobagyi GN, Ellerhorst JA. Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clin Cancer Res. 2002 May;8(5):1038-44.  
<http://clincancerres.aacrjournals.org/content/8/5/1038.long>
- Sparreboom A, Scripture CD, Trieu V, Williams PJ, De T, Yang A, Beals B, Figg WD, Hawkins M, Desai N. Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). Clin Cancer Res. 2005 Jun 1;11(11):4136-43.  
<http://clincancerres.aacrjournals.org/content/11/11/4136.long>

## References

- [1] Bristol-Myers-Squibb (2015) Taxol product label. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/020262s049lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf)
- [2] Willmann S, Höhn K, Edginton A, Sevestre M, Solodenko J, Weiss W, Lippert J, Schmitt W. Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. J Pharmacokinet Pharmacodyn. 2007 Jun;34(3):401-31. Epub 2007 Mar 13.

The compound properties used for input are illustrated below.

# Compound: Paclitaxel

## Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	0.1 mg/l	Database-Wikipedia 0.1 to 30 mg/L in water	Measurement	True
Reference pH	7	Database-Wikipedia 0.1 to 30 mg/L in water	Measurement	True
Lipophilicity	3.53 Log Units	Parameter Identification-Parameter Identification	Fit	True
Fraction unbound (plasma, reference value)	0.03	Publication- Marzolini 2017: Brouwer 2000, range 0.036-0.079, conc dependent, see Fig. 3	Marzolini 2017	True
Is small molecule	Yes			
Molecular weight	853.92 g/mol	Publication-Wikipedia & Marzolini 2017		
Plasma protein binding partner	Albumin			

## Calculation methods

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

## Processes

### Systemic Process: Glomerular Filtration-Marzolini2017

Species: Human

#### Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Marzolini 2017, Table 1, fraction excreted range: 0.013-0.126

### Metabolizing Enzyme: CYP3A4-Fit

Molecule: CYP3A4

#### Parameters

Name	Value	Value Origin
In vitro CL/recombinant enzyme	40.62257 $\mu\text{l}/\text{min}/\text{pmol}$ rec. enzyme	Parameter Identification-Parameter Identification

### Metabolizing Enzyme: CYP2C8-Fit

Molecule: CYP2C8

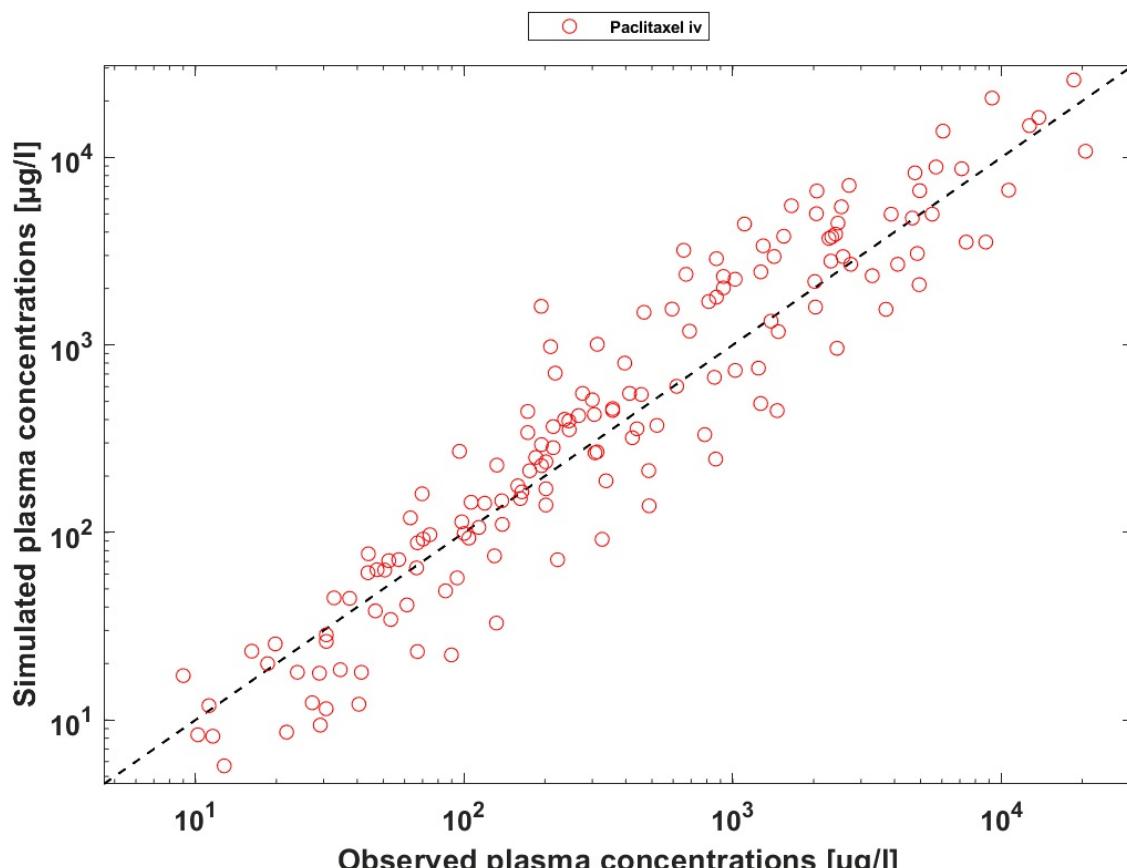
#### Parameters

Name	Value	Value Origin
In vitro CL/recombinant enzyme	359.18904 $\mu\text{l}/\text{min}/\text{pmol}$ rec. enzyme	Parameter Identification-Parameter Identification

## Chapter 3.5: Paclitaxel Diagnostics Plots

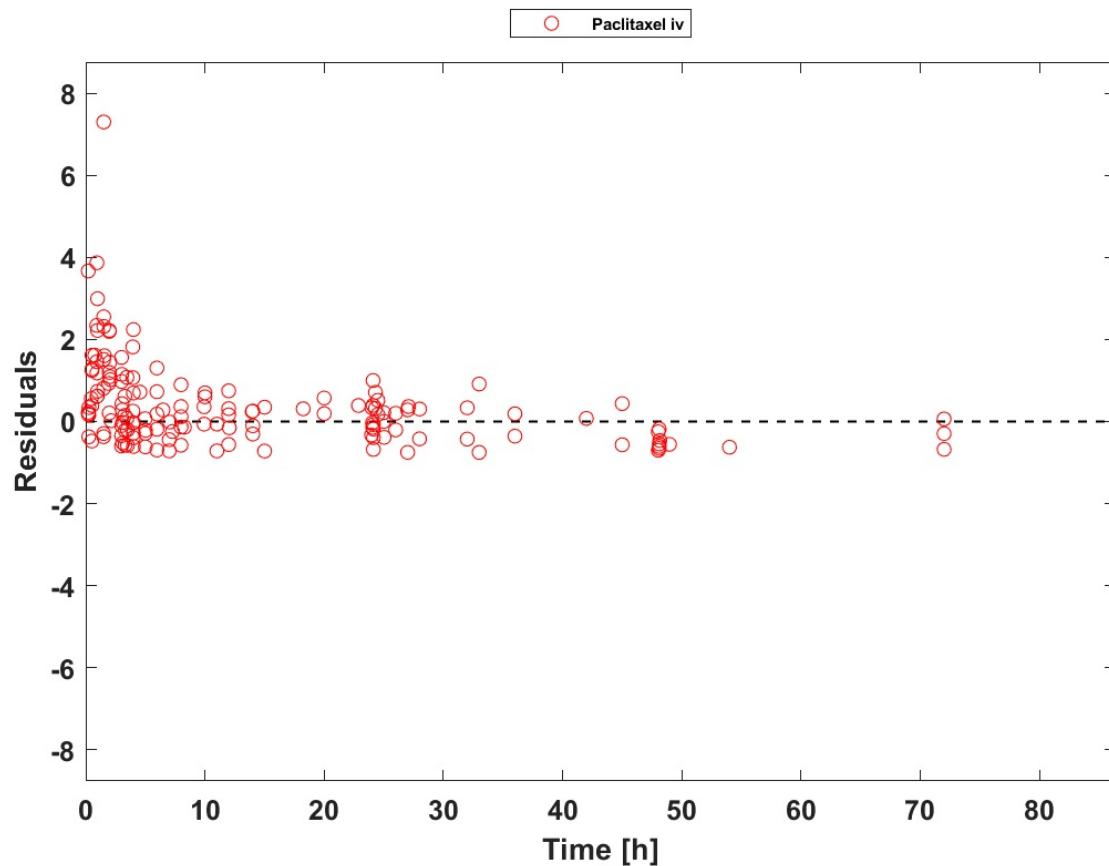
### Paclitaxel adult PBPK model performance

Below you find the input goodness-of-fit visual diagnostic plots for paclitaxel PBPK model performance (observed versus individually simulated plasma concentration and weighted residuals versus time) of all adult data.



Goodness-of-fit visual diagnostic plots for paclitaxel PBPK model performance: observed versus individually predicted plasma concentration versus time of all adult data.

GMFE = 1.738689



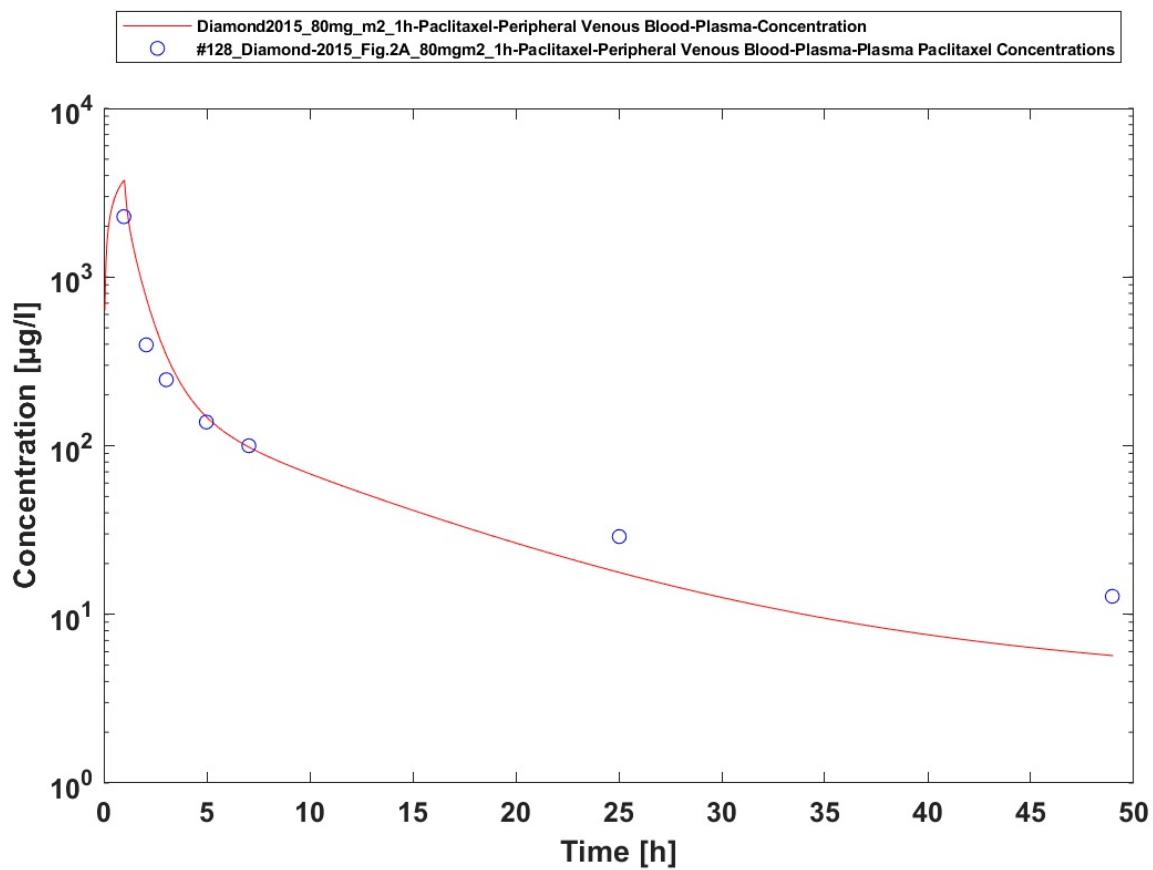
Goodness-of-fit visual diagnostic plots for paclitaxel PBPK model performance: weighted residuals versus time of all adult data.

GMFE = 1.738689

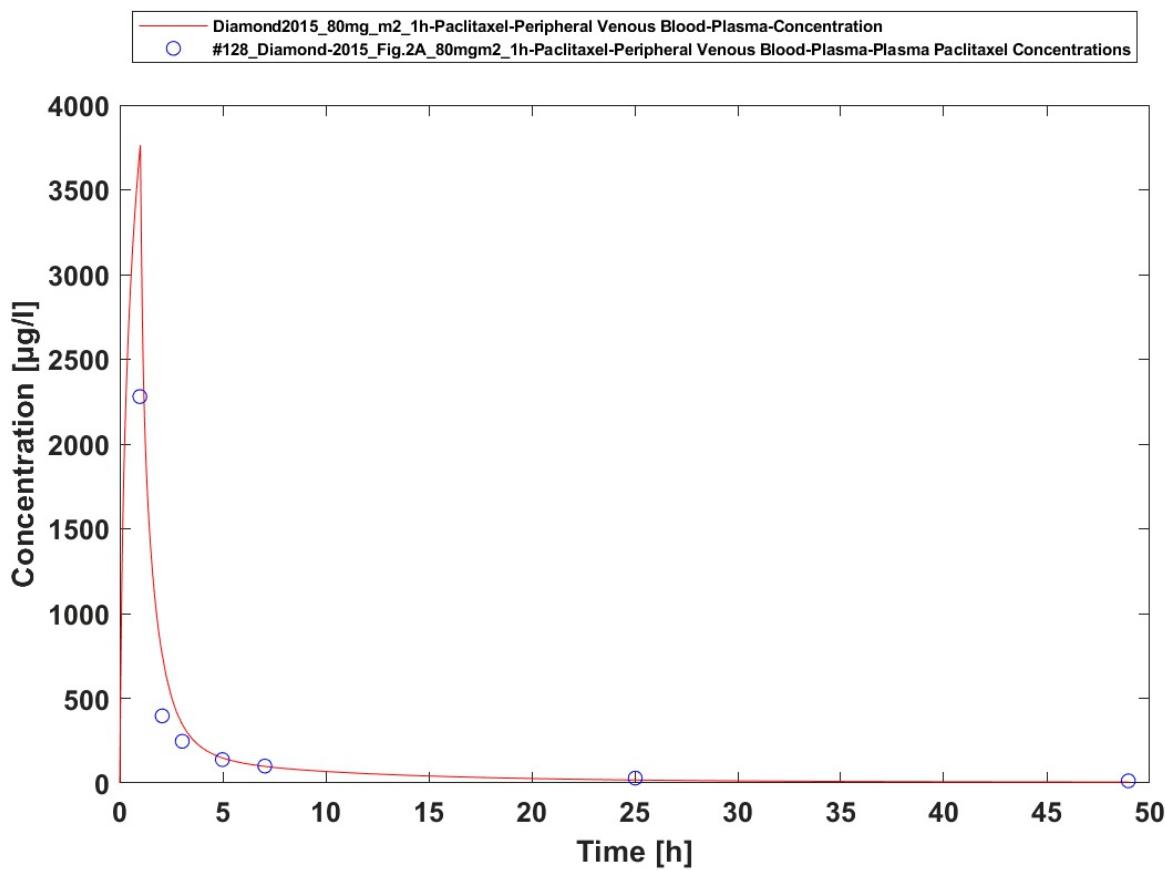
## Chapter 3.6: Paclitaxel Concentration-Time profiles in Adults

### Concentration-Time Profiles

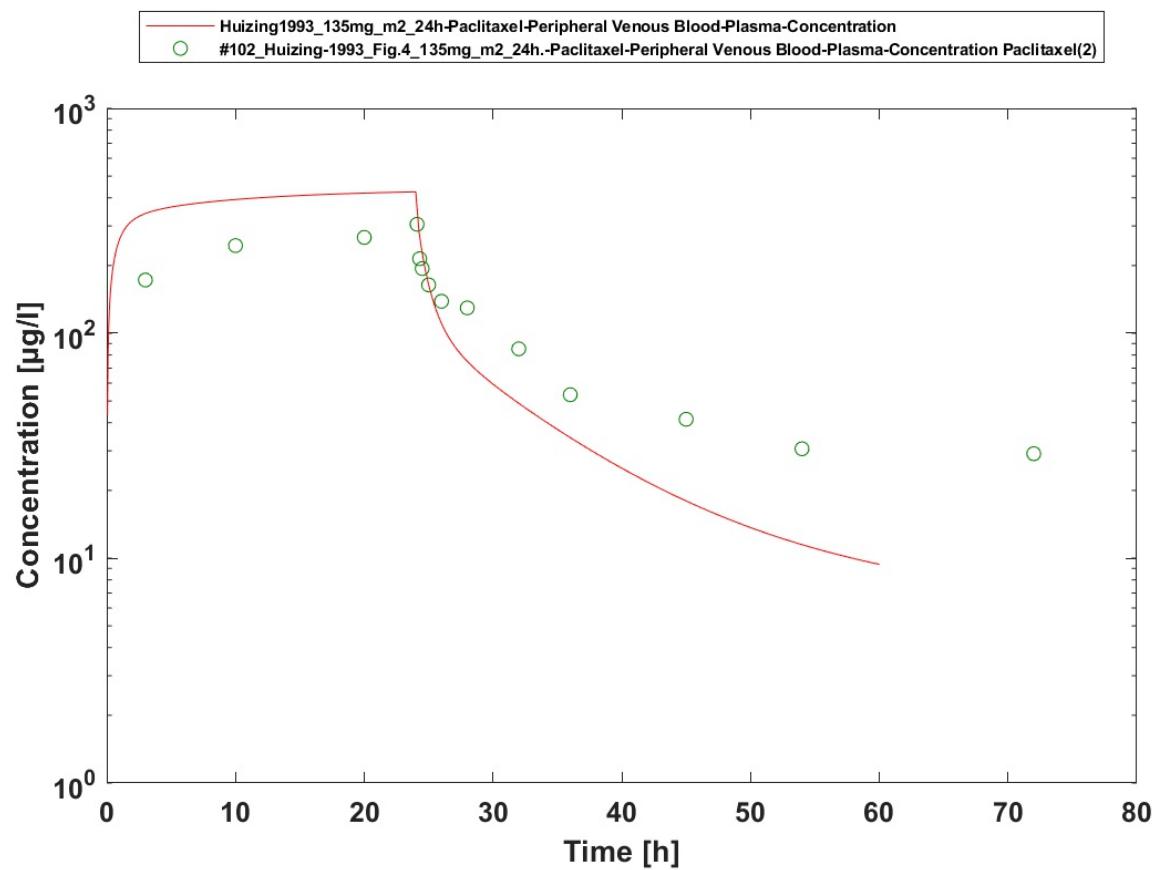
Simulated versus observed plasma concentration-time profiles of all data are listed below.

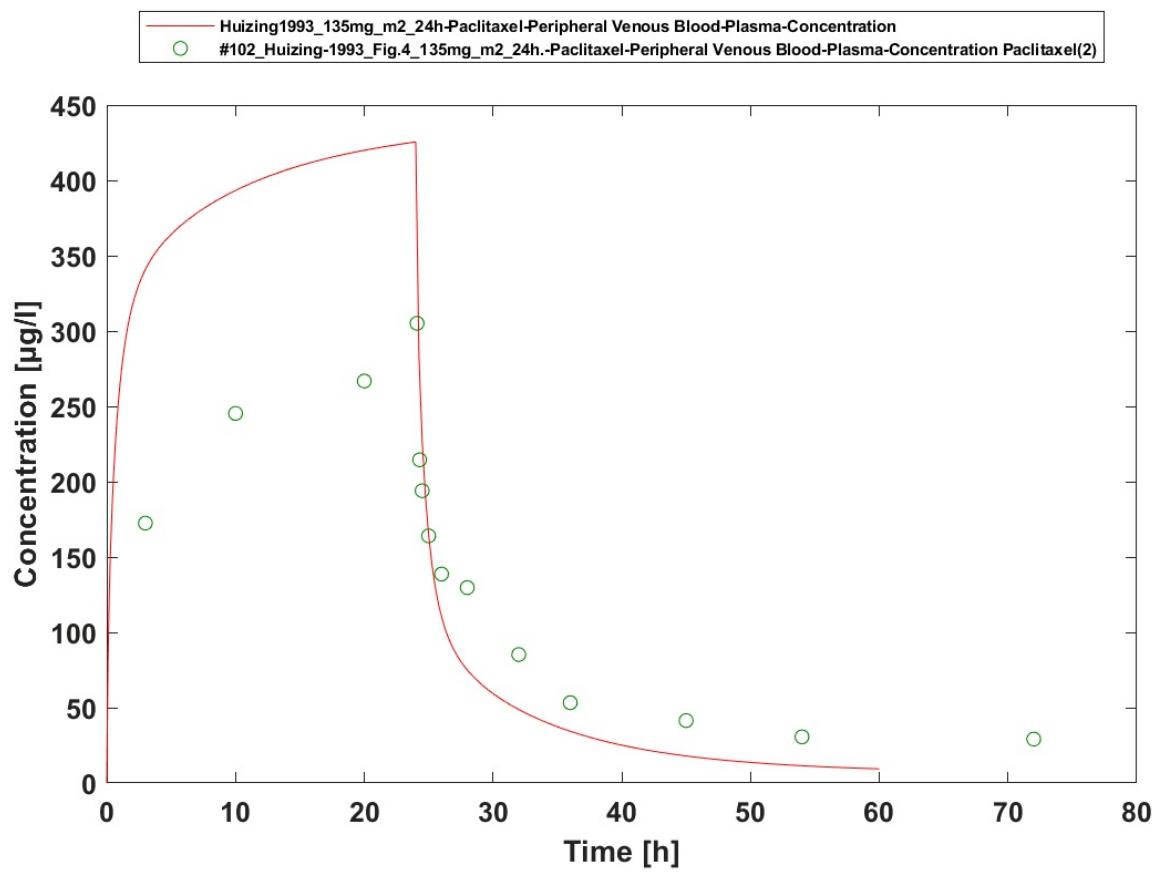


Time Profile Analysis

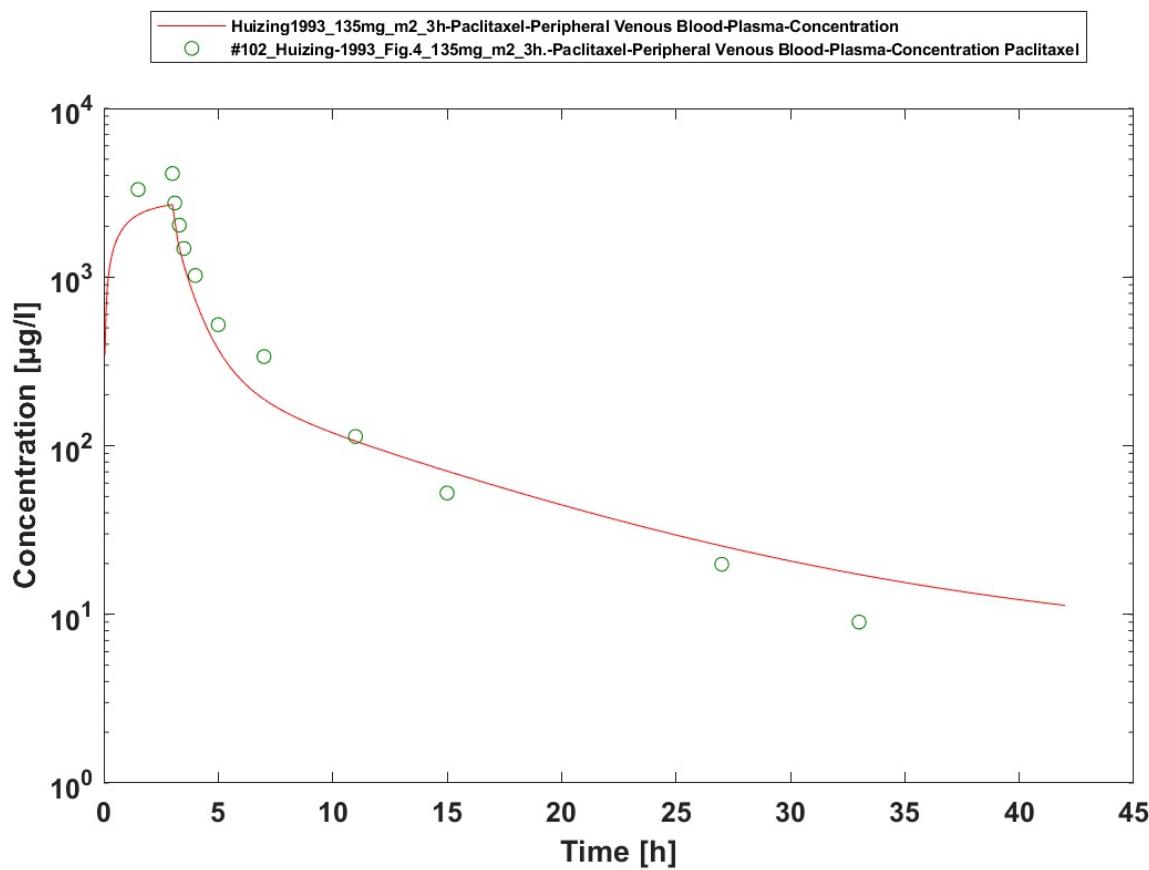


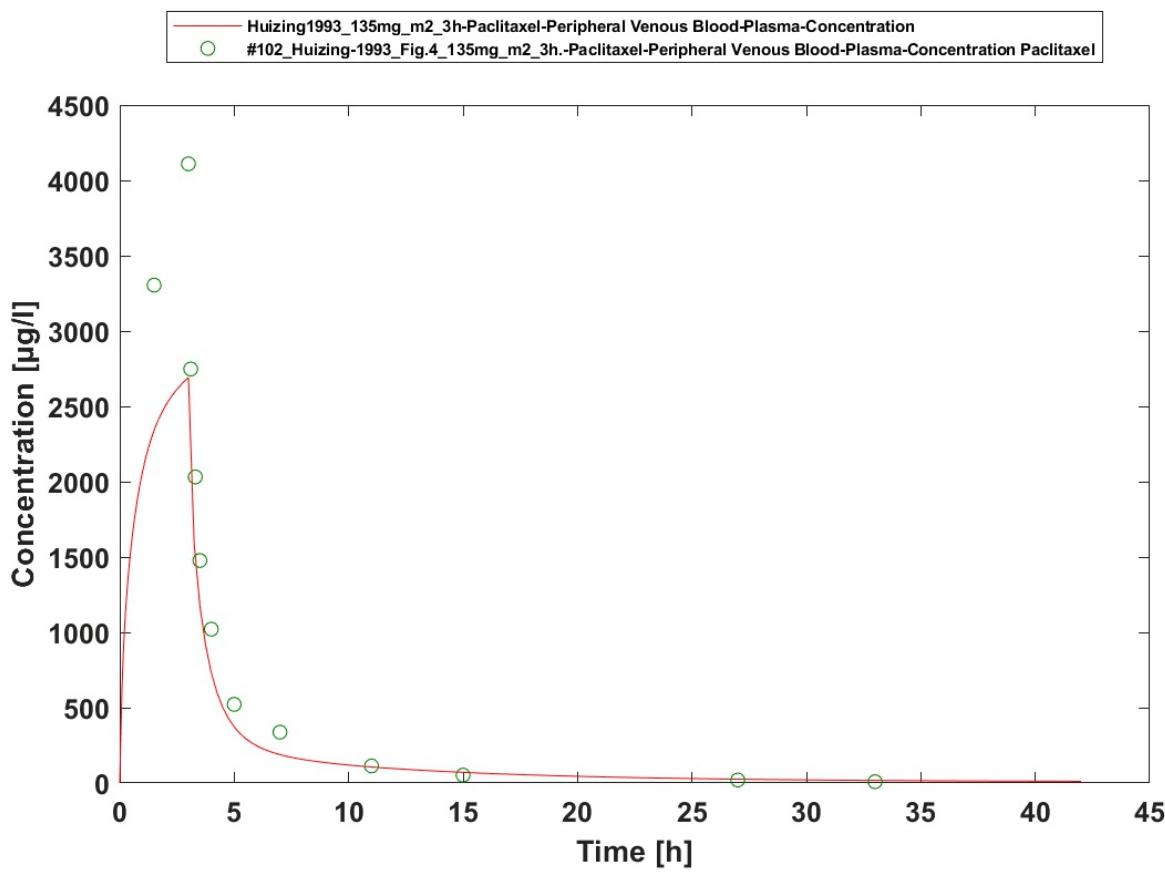
Time Profile Analysis 1

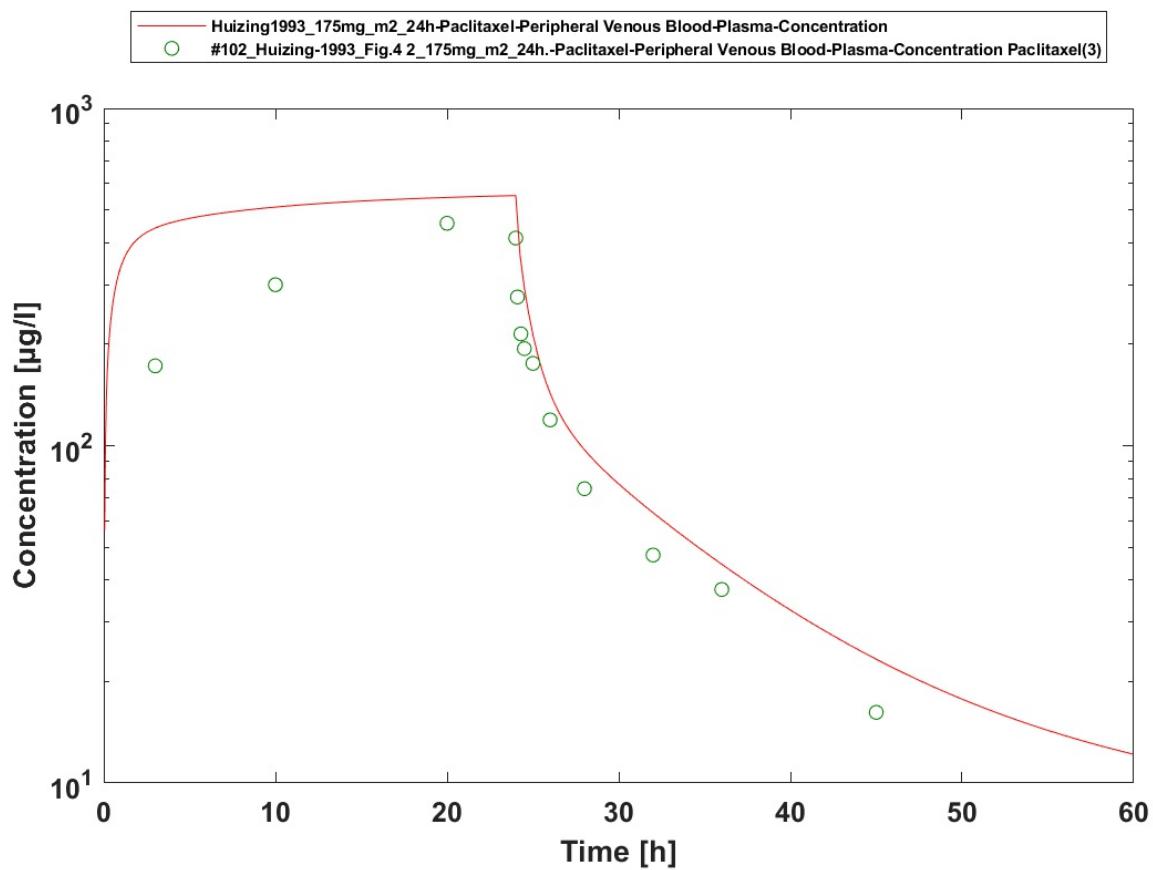


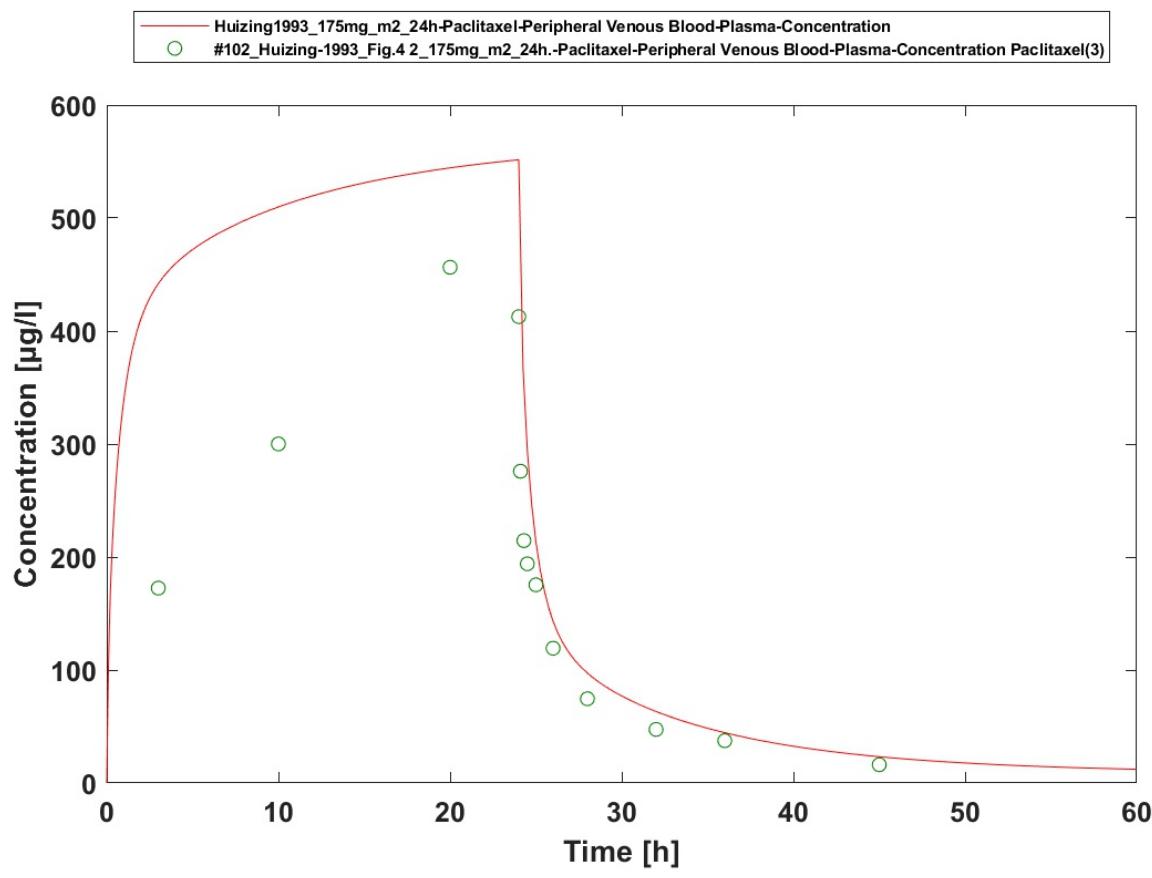


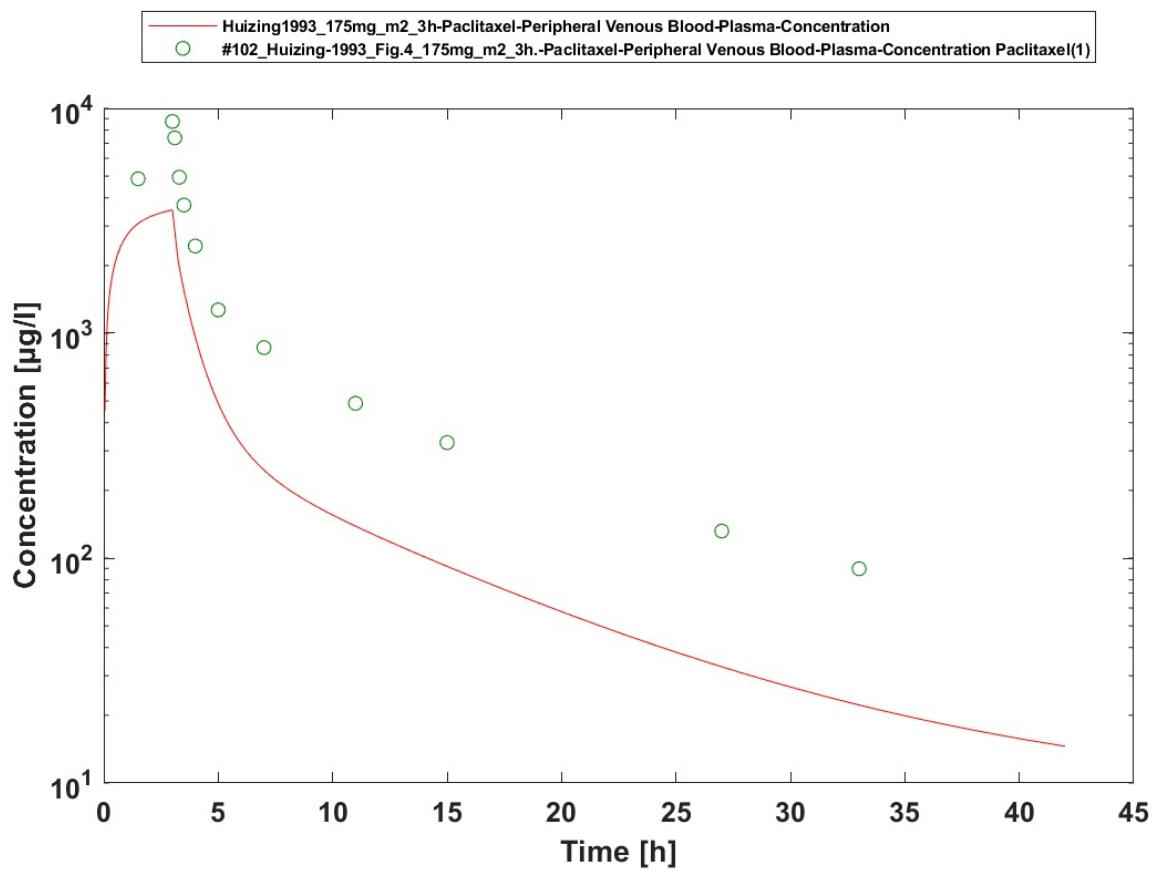
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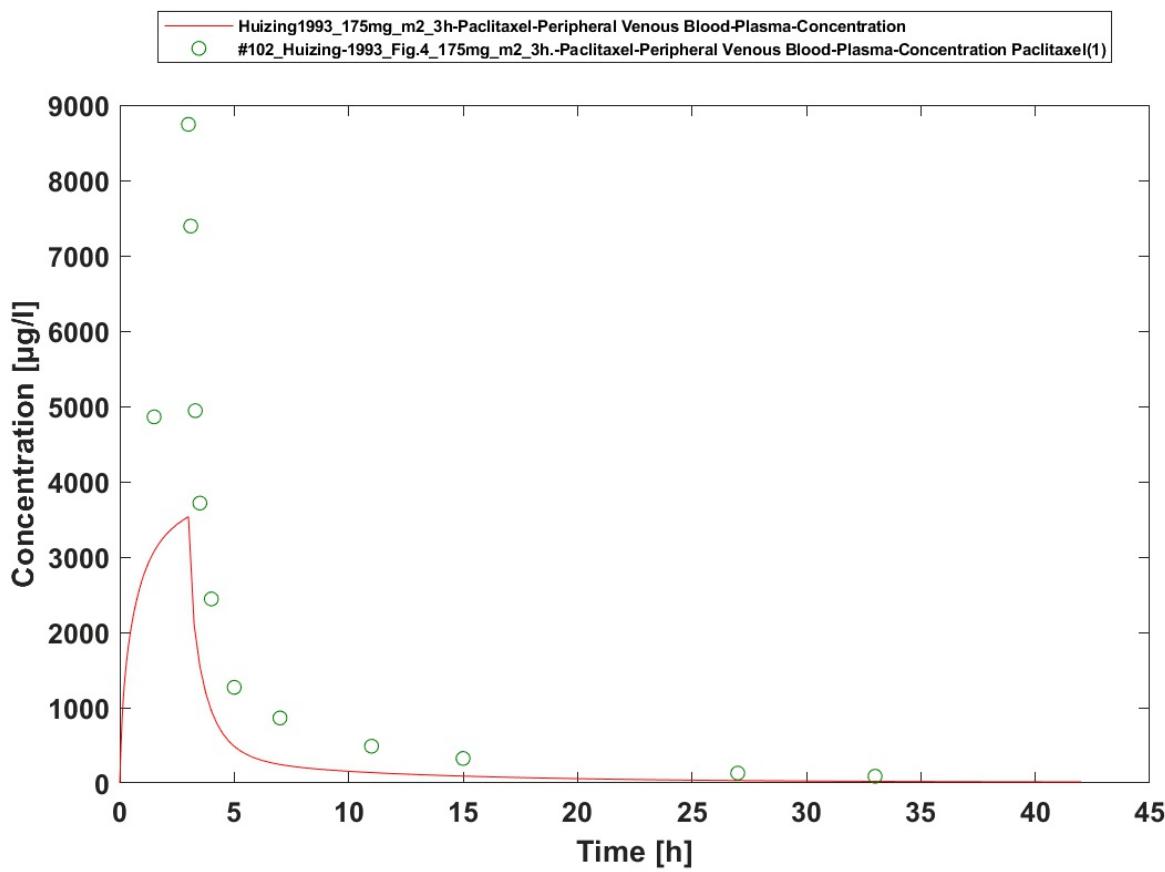




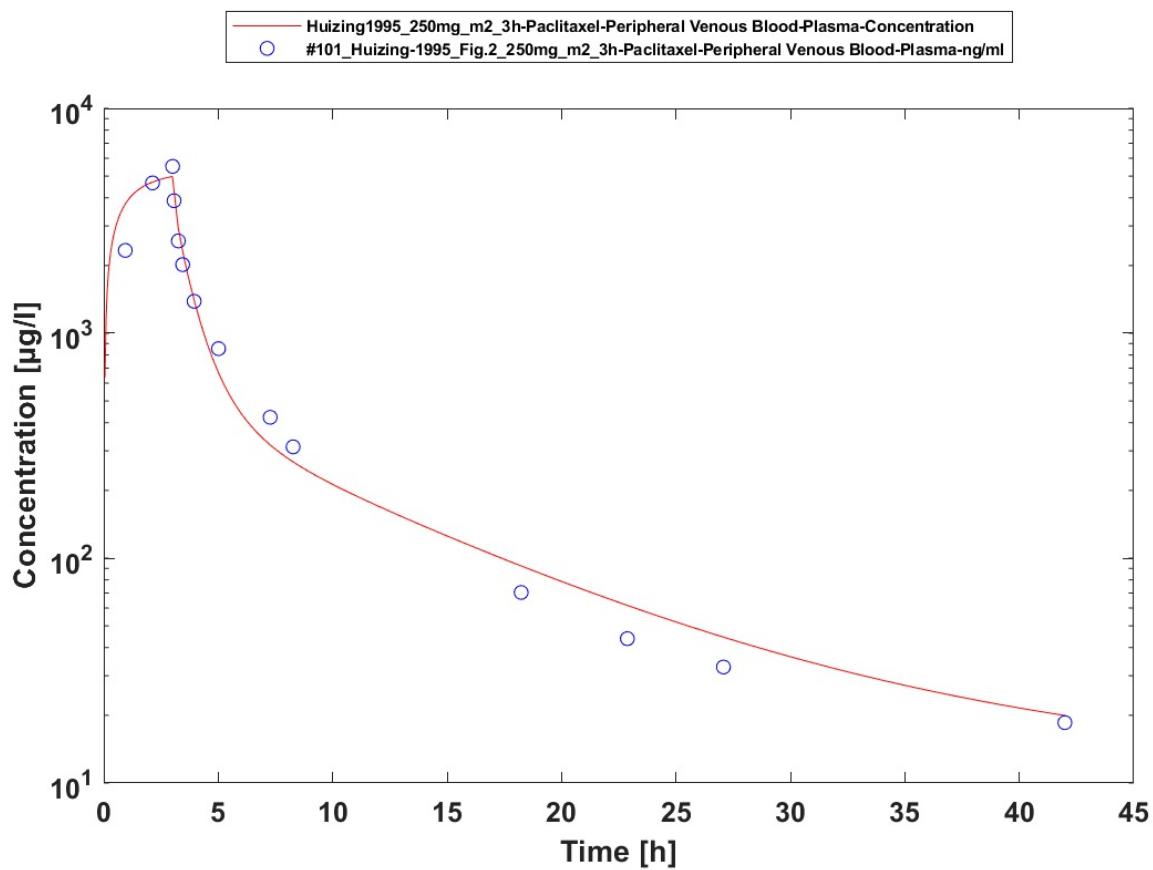




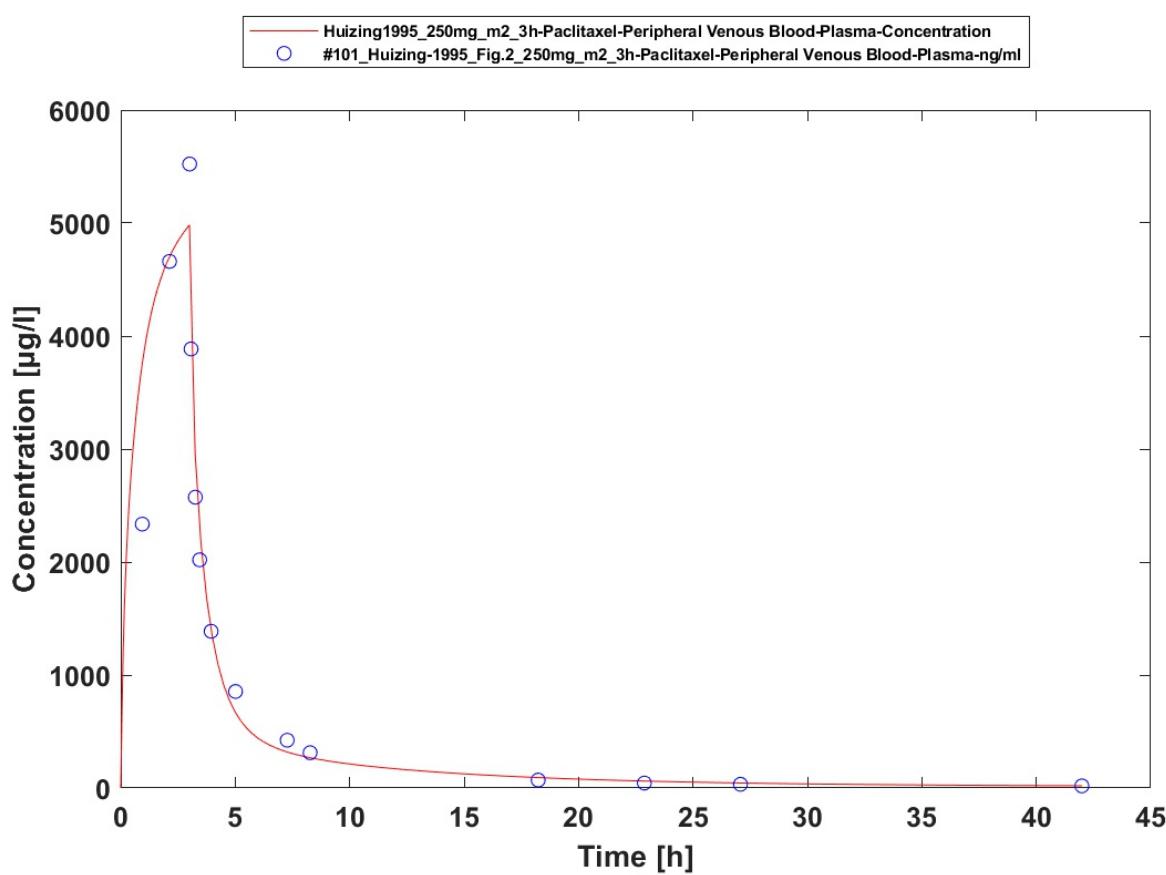
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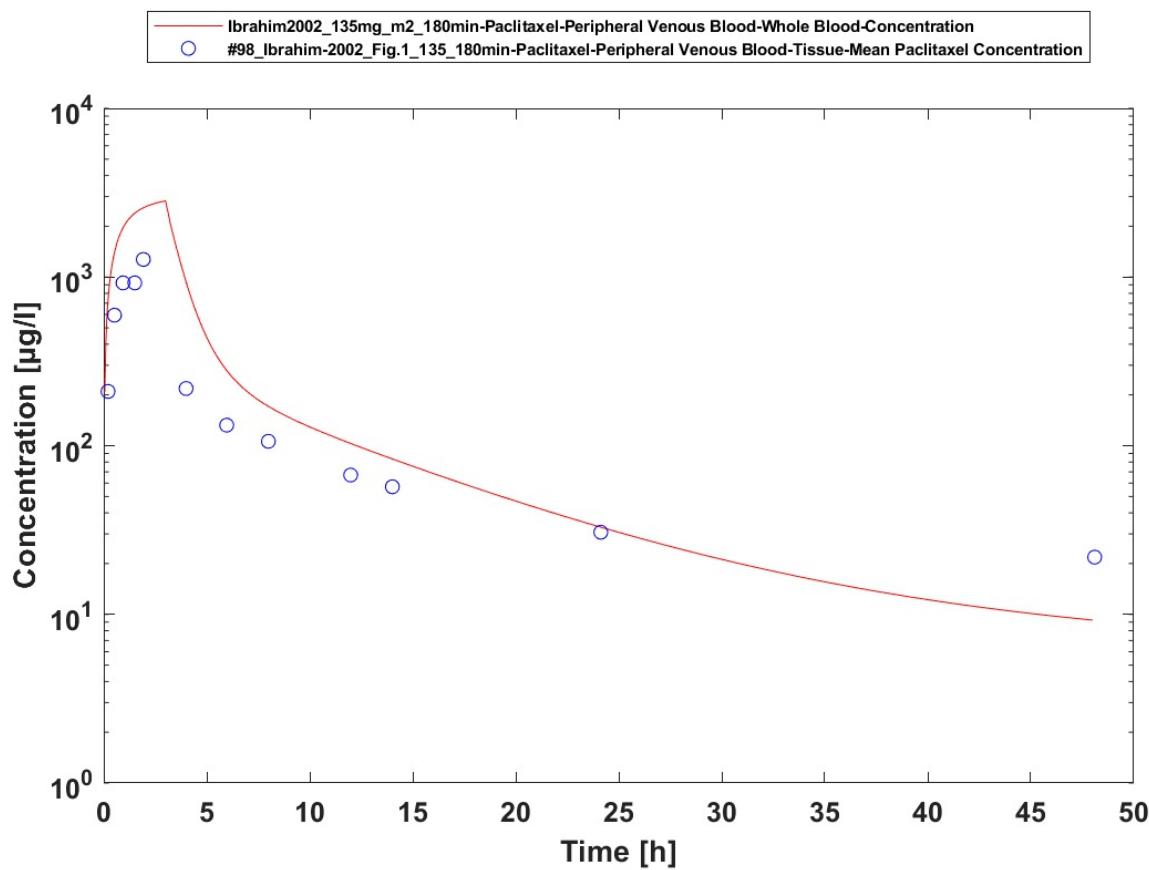
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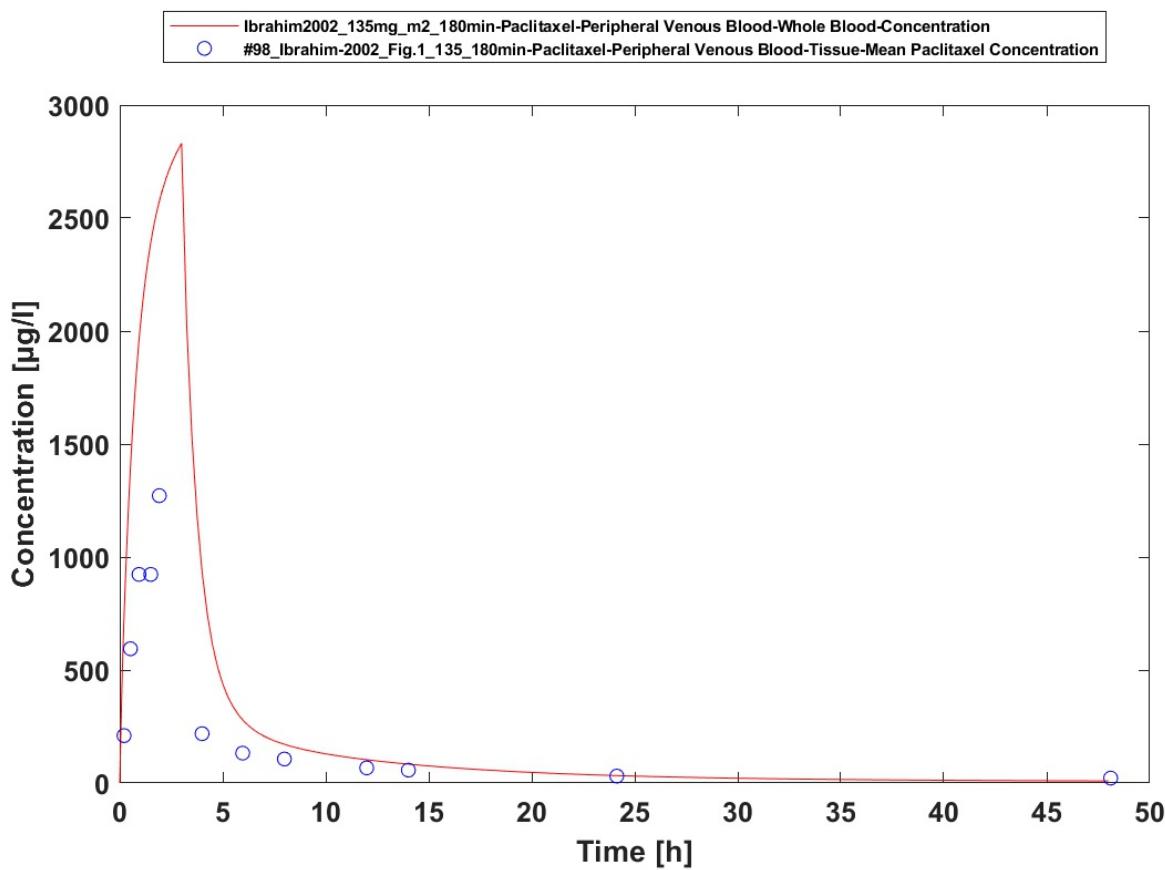


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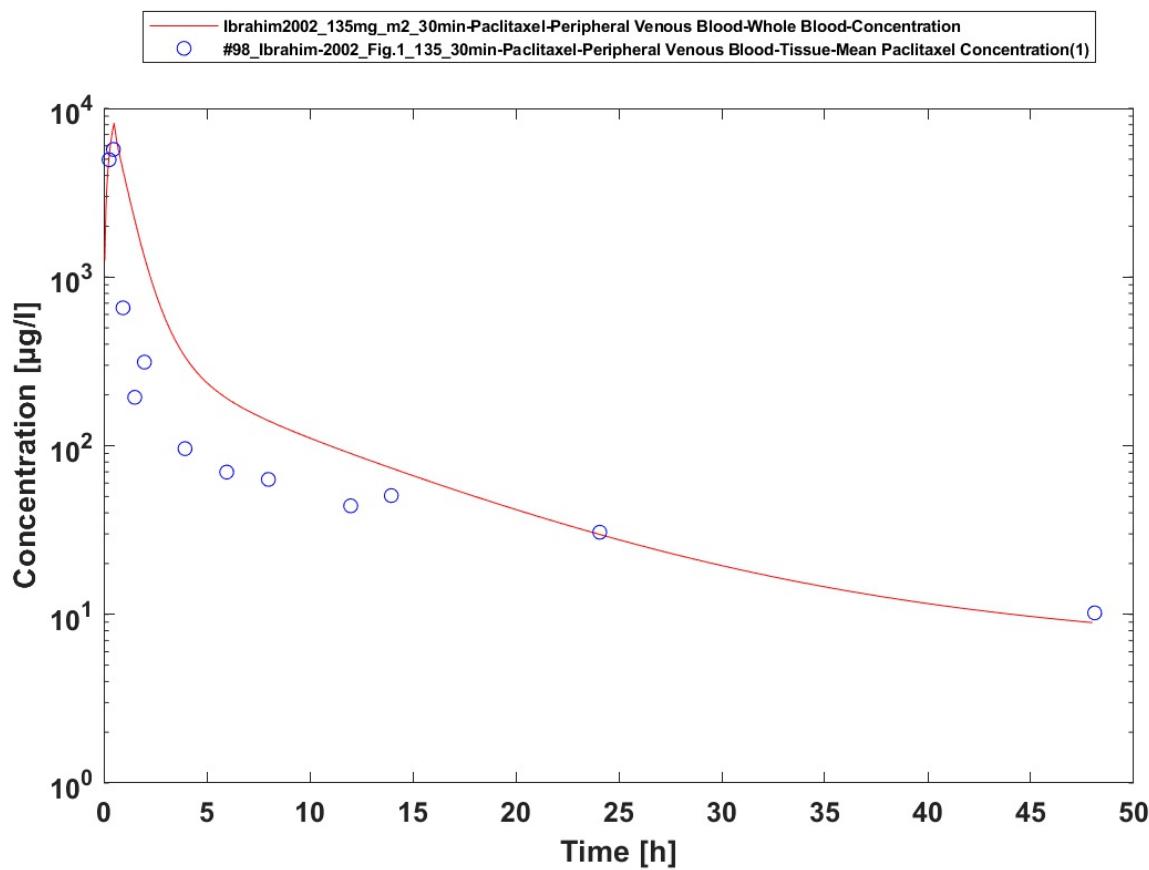


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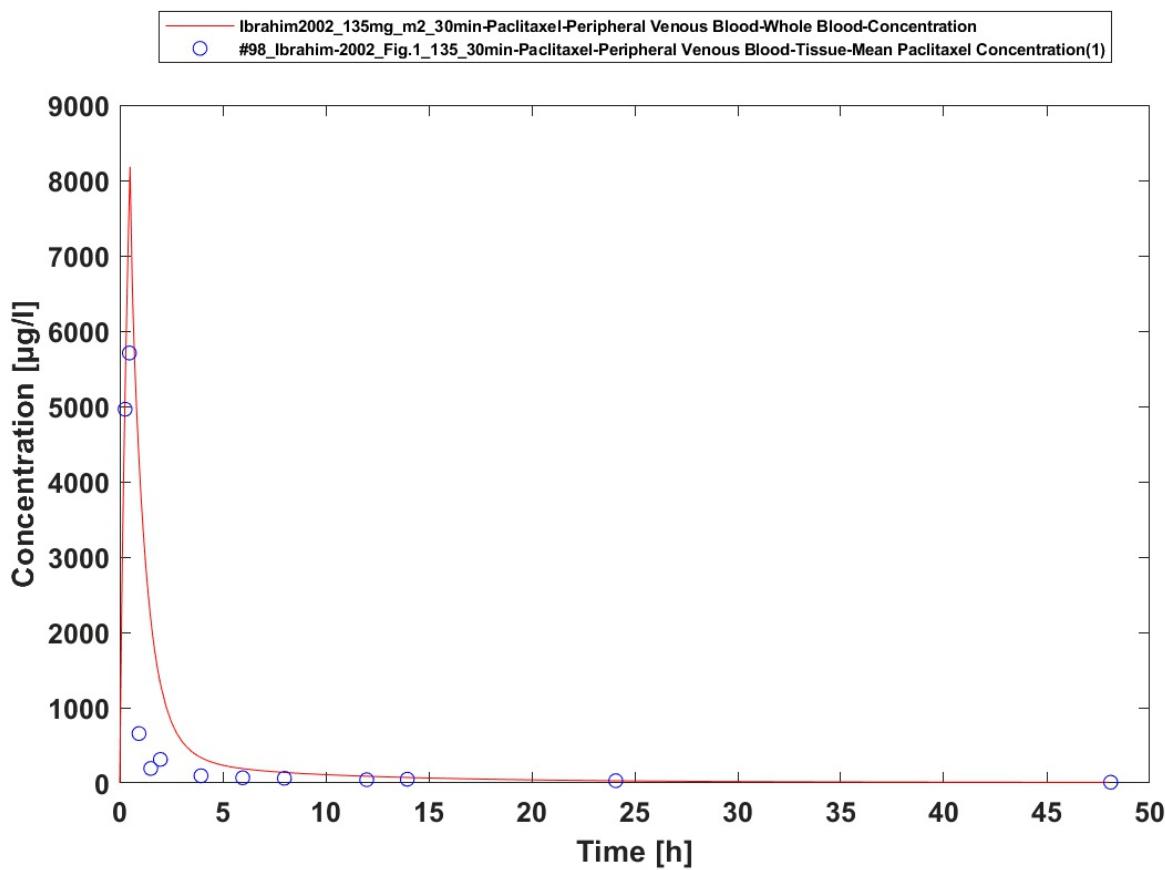




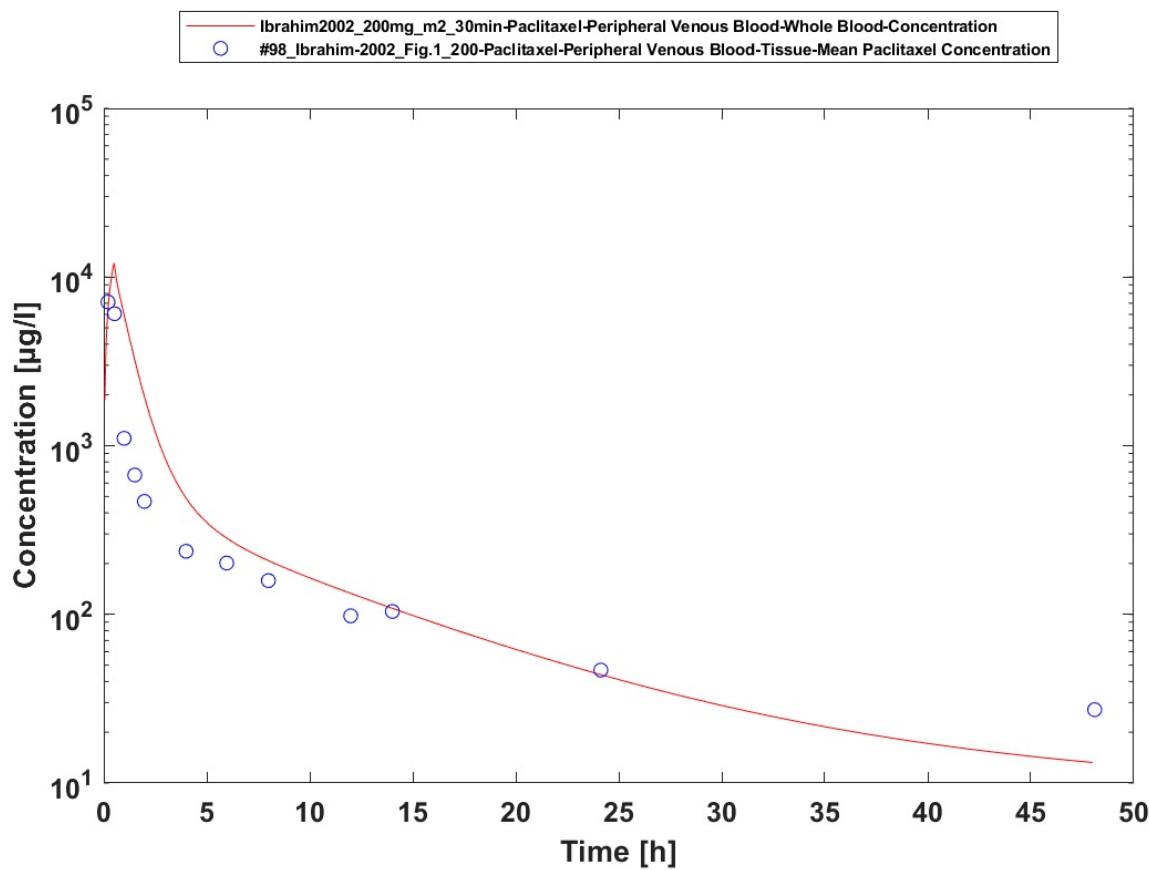
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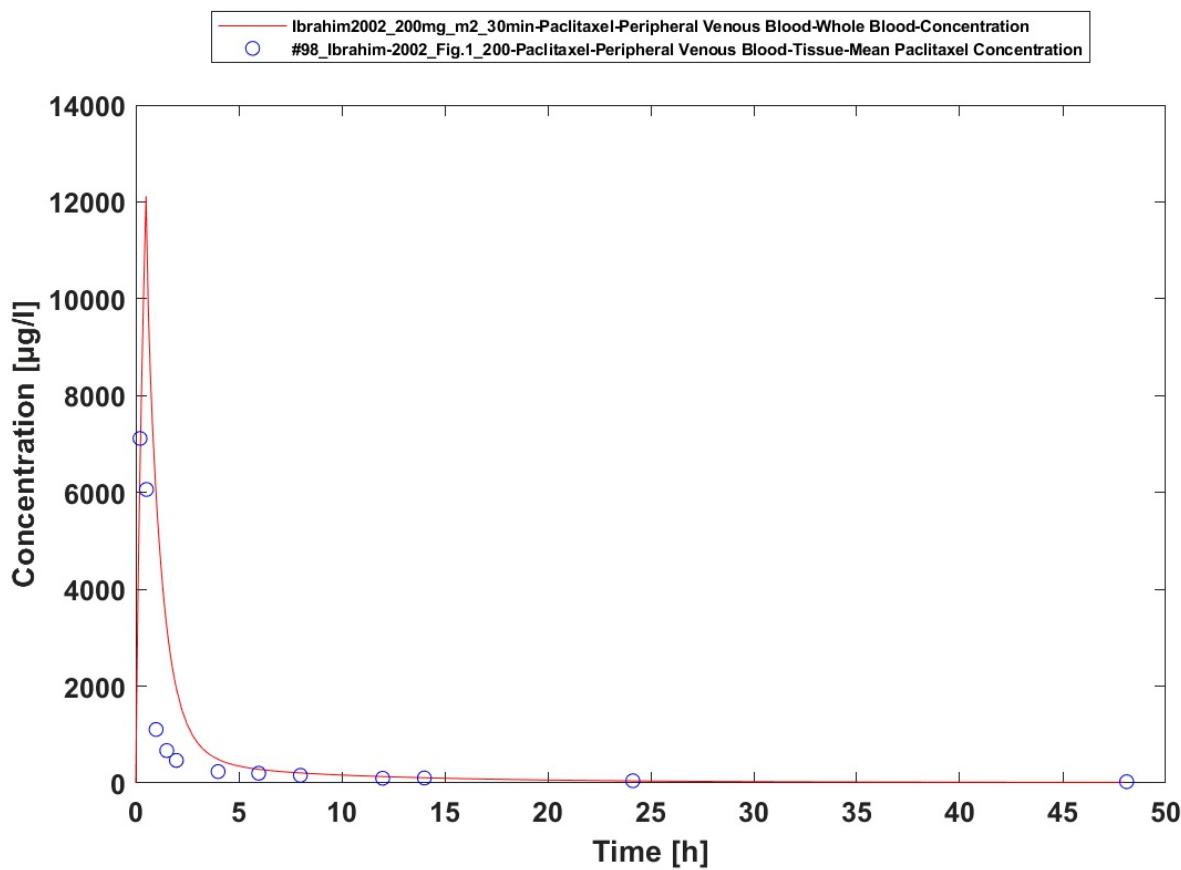
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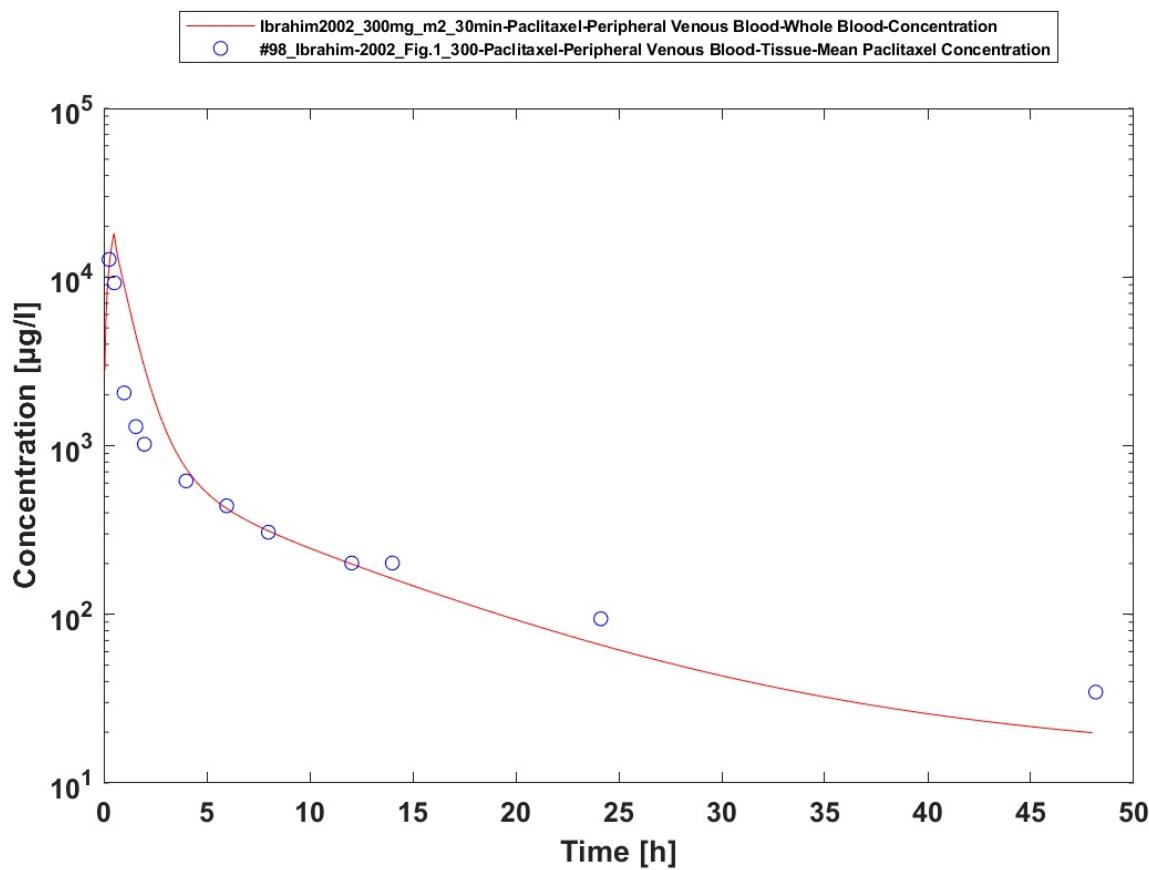
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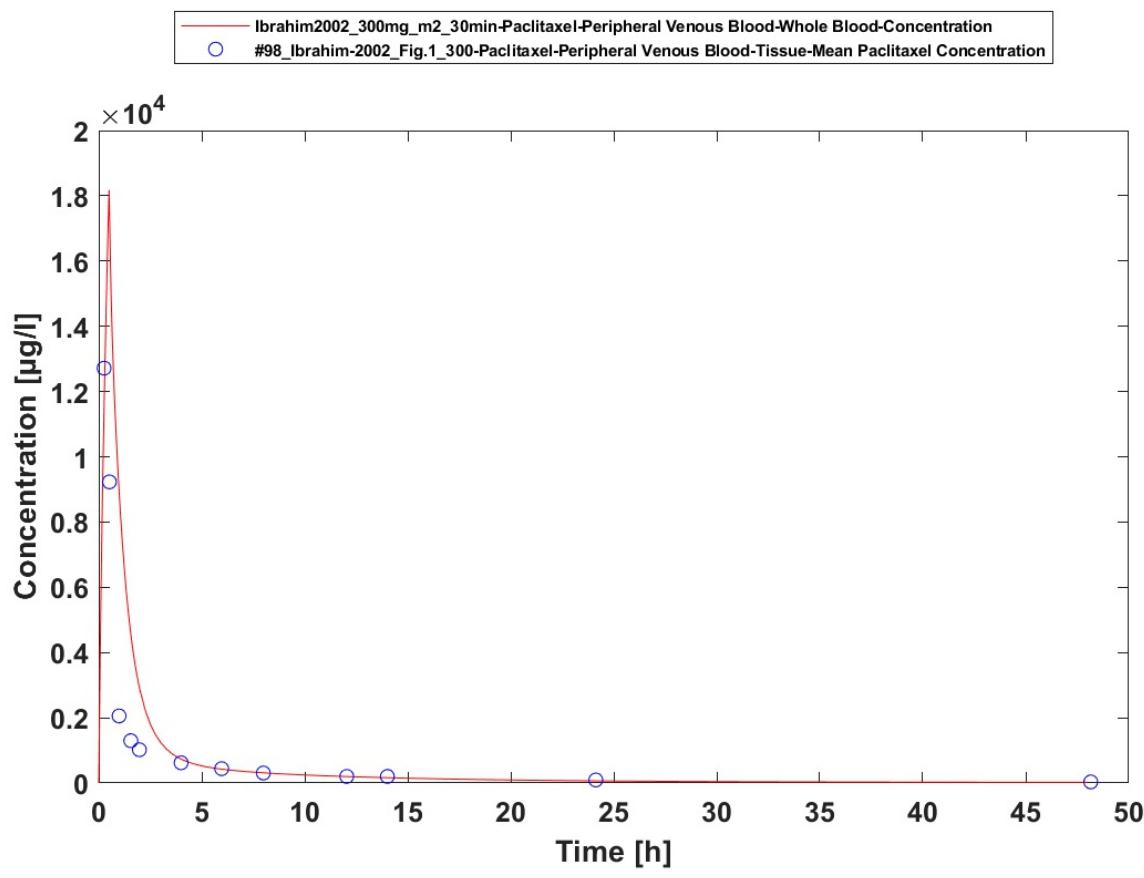
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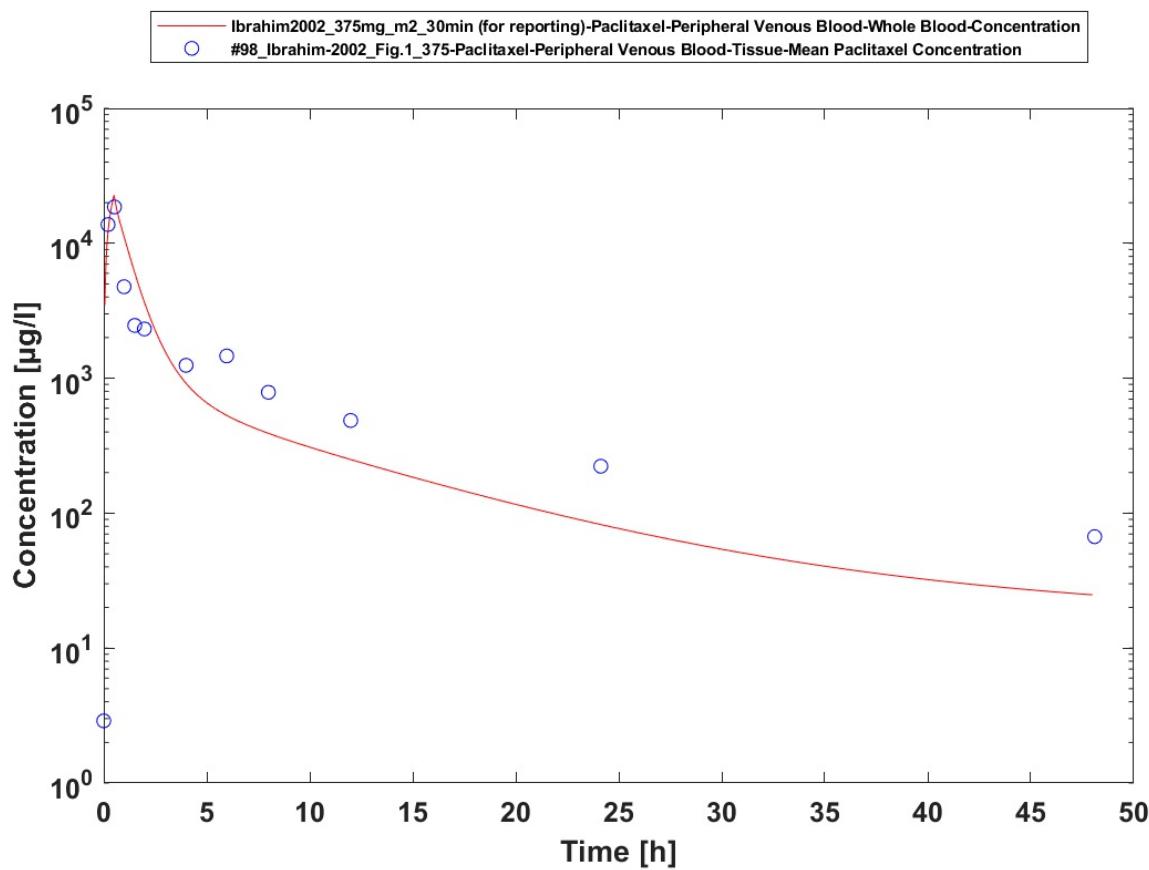
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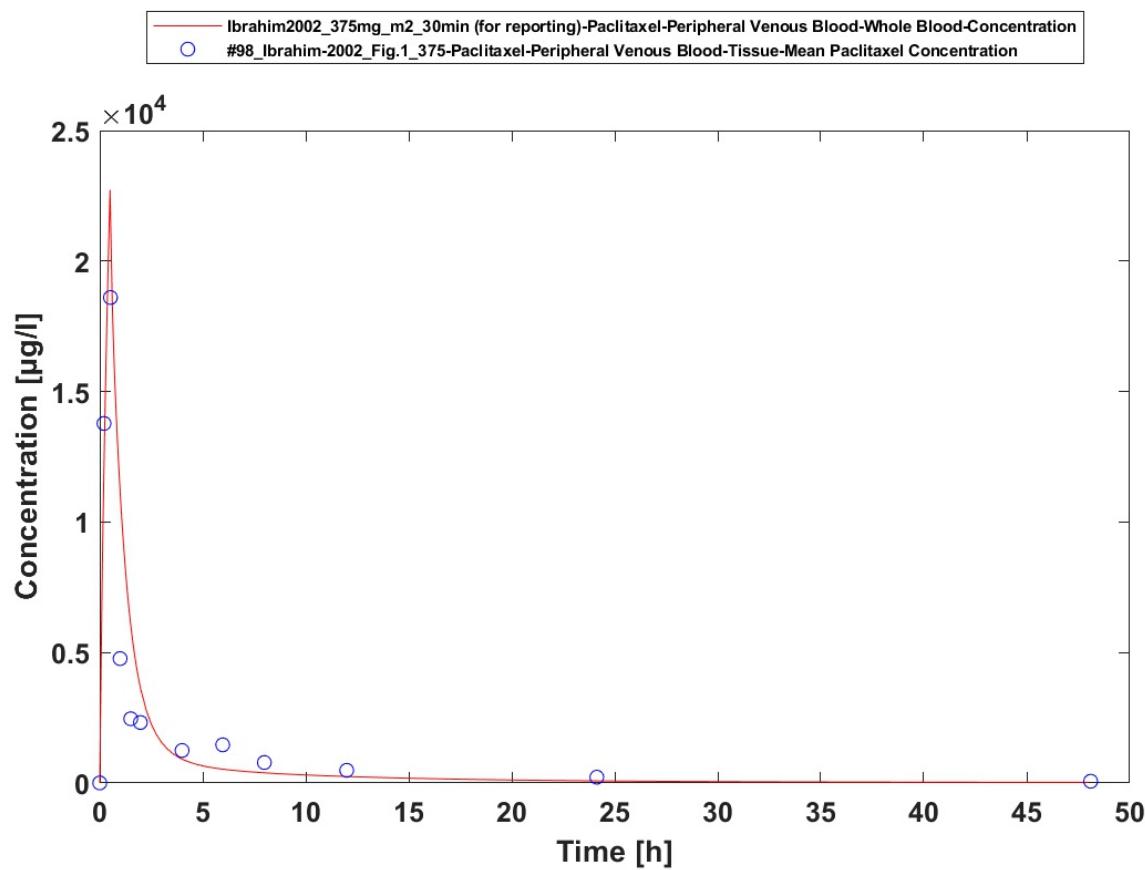
Time Profile Analysis



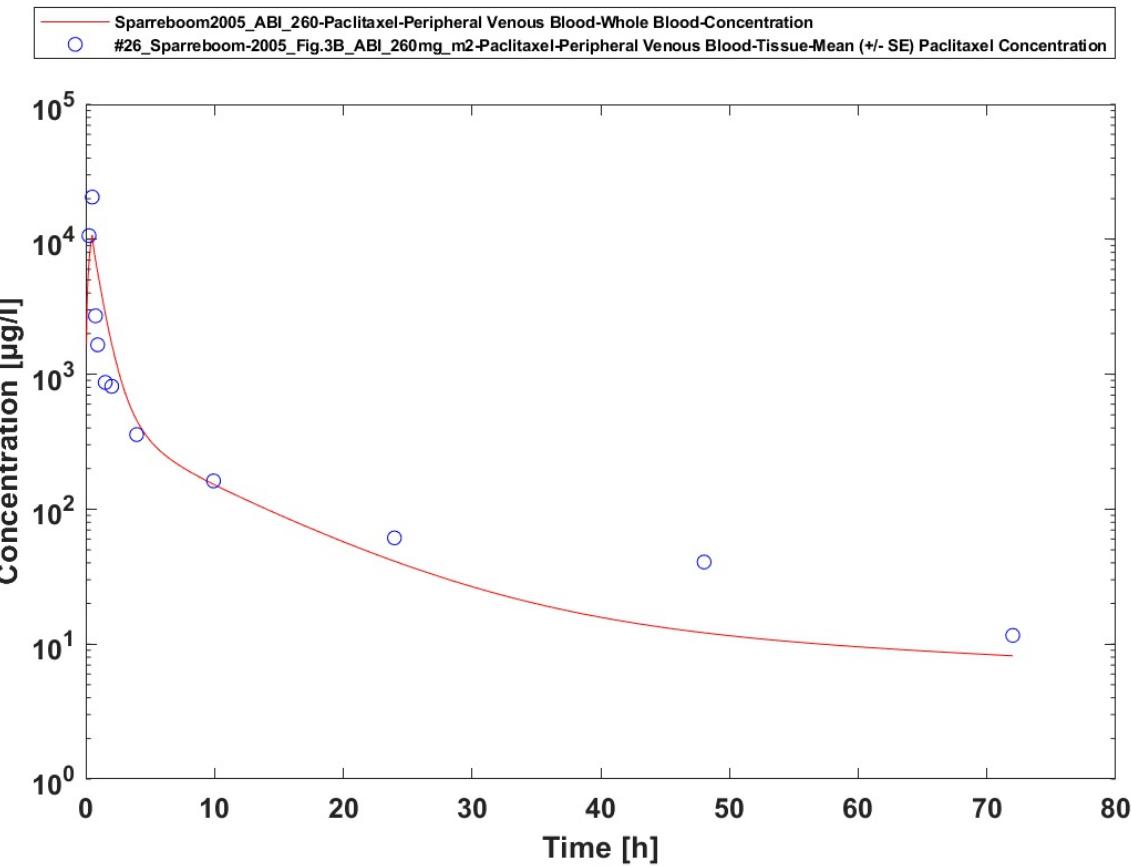
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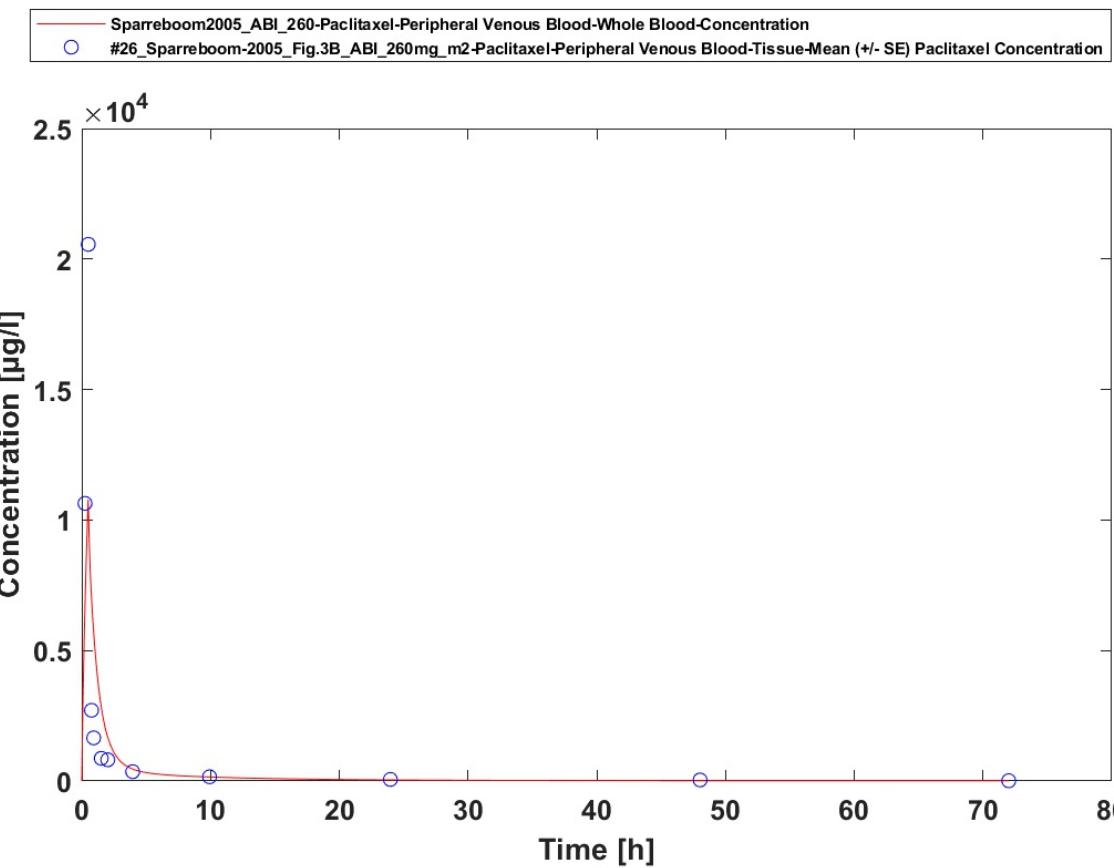
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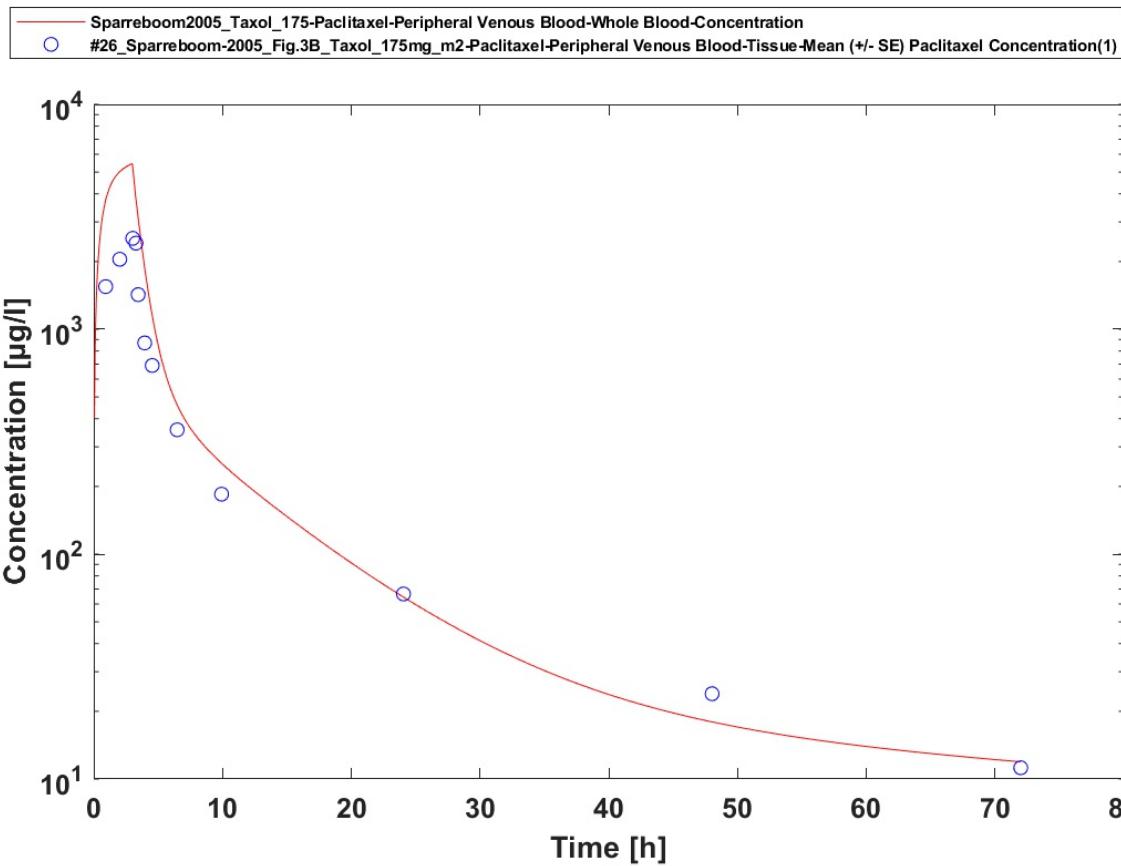
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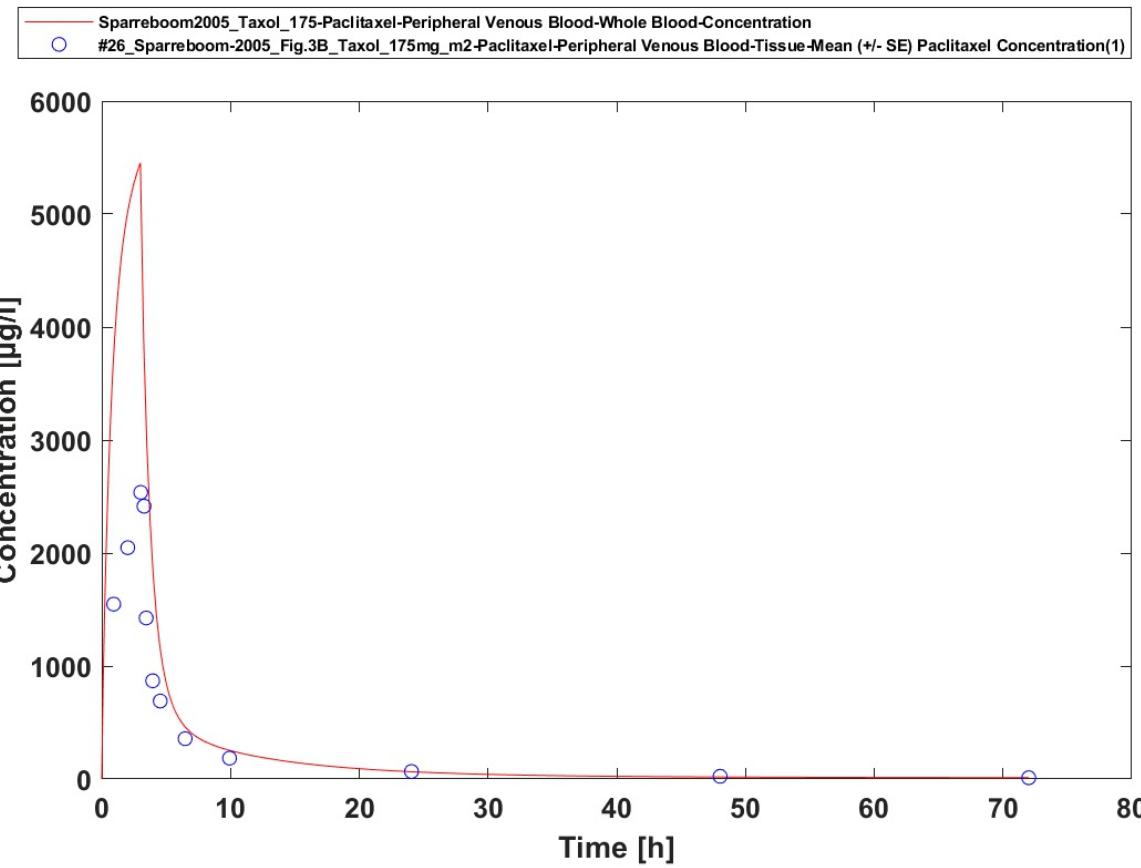
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1