Building and Evaluation of a PBPK Model for Efavirenz in Adults

Version	**1.0**
OSP Version	8.0
Author	Thomas Wendl (TWendl)

Table of Contents

1 Introduction

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

Its major metabolizing enzyme is CYP2B6, but also CYP3A4, CYP3A5, CYP1A2 and CYP2A6 play a role (Ward 2003, Ogburn 2010). CYP2B6 polymorphism is a major determinant of clinical efavirenz disposition and dose adjustment. Efavirenz activates the pregnane X receptor (PXR) and induces its target gene expression. As a consequence, some cytochrome P450 genes are upregulated, and, e.g. higher CYP3A4 (Shou 2008) and CYP2B6 (Ke 2016) activity levels can be measured.

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

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

The herein presented model building and evaluation report evaluates the performance of the PBPK model for efavirenz in (healthy) adults. The established efavirenz PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (https://github.com/.../Compound-model).

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by e.g. Kuepfer et al. (Kuepfer 2016). The relevant anthropometric (height, weight) and physiological information (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in adults was gathered from the literature and has been previously published (PK-Sim Ontogeny Database Version 7.3). 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 (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 oral applications of efavirenz (Sustiva) to find an appropriate structure to describe the pharmacokinetics in plasma. The mean PBPK model was developed using a typical European individual adjusted to the demography of the respective study population. The relative tissue specific expressions of enzymes predominantly being involved in the metabolism of efavirenz were derived from RT-PCR data from Nishimura 2003.

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

2.2.1 In vitro / physico-chemical Data

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

Parameter	Unit	Value	Source	Description
MW	g/mol	315.675	https://www.drugbank.ca/	Molecular weight
pK_a	10.1	(base)	Rabel 1996	Acid dissociation constant
Solubility (pH)	mg/L	11.5 (6.4)	Cristofoletti 2013	Water solubility
logP		2.07, 4.6	Almond 2005, https://www.drugbank.ca/	Partition coefficient between octanol and water
logD		5.1	Janneh 2009	Partition coefficient between octanol and buffer solution
fu		0.006 [0.004 - 0.015]	Almond 2005	Fraction unbound in plasma
Emax (CYP3A4)		7.27, 3.15 (average 5.21)	Shou 2008	Maximum induction effect
EC50 (CYP3A4)	µmol/l	12.5, 2.18 (average 7.34)	Shou 2008	Concentration at half maximum induction
Emax (CYP2B6)		5.1	Ke 2016	Maximum induction effect
EC50 (CYP2B6)	µmol/l	5.1	Ke 2016	Concentration at half maximum induction

2.2.2 Clinical Data

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

2.2.2.1 Model Building

The following studies were used for model building:

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

2.2.2.2 Midazolam interaction studies used to parameterize CYP3A4 interaction

The following studies were used for parameterization of CYP3A4 interaction:

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

2.2.2.3 Verification of interaction using Alfentanil interaction studies

The following study was used to verify CYP3A4 interaction:

Publication	Arm / Treatment / Information used for model building
Kharasch 2012	Healthy subjects receiving a single iv dose of 0.015 mg/kg alfentanil following multiple doses of 600 mg efavirenz

2.3 Model Parameters and Assumptions

2.3.1 Absorption

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

2.3.2 Distribution

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built in PK-Sim, observed clinical data was best described by choosing the partition coefficient calculation by `Schmitt` and cellular permeability calculation by `PK-Sim Standard`.

2.3.3 Metabolism, Elimination and Induction

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

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

2.3.4 Automated Parameter Identification

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

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

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

3 Results and Discussion

The PBPK model for efavirenz was developed and evaluated using publically available, clinical pharmacokinetic data from studies listed in Section 2.2.2.

The next sections show:

1. the final model parameters for the building blocks: Section 3.1.
2. the overall goodness of fit: Section 3.2.
3. simulated vs. observed concentration-time profiles for the clinical studies used for model building and for model verification: Section 3.3.

3.1 Final input parameters

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

Compound: Efavirenz

Parameters

Name	Value	Value Origin	Alternative	Default	

Name	Value	Value Origin	Alternative	Default	
Solubility at reference pH	39.9217804729 mg/l	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02	Measurement	True	
Reference pH	0		Measurement	True	
Lipophilicity	3.4369753585 Log Units	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02	Optimized	True	
Fraction unbound (plasma, reference value)	0.0059553692487	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02	Measurement	True	
Specific intestinal permeability (transcellular)	2.9720579005E-05 cm/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02	Optimized	True	
Cl	1				

Name	Value	Value Origin	Alternative	Default	
F	3				
Is small molecule	Yes				
Molecular weight	315.675 g/mol				
Plasma protein binding partner	Albumin				

Calculation methods

Name	Value	
Partition coefficients	Schmitt	
Cellular permeabilities	PK-Sim Standard	

Processes

Metabolizing Enzyme: CYP2B6-Ward2003

Molecule: CYP2B6
Metabolite: 8-OH efavirenz

Parameters

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

Metabolizing Enzyme: CYP1A2-Ward2003

Molecule: CYP1A2
Metabolite: 8-OH efavirenz

Parameters

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

Metabolizing Enzyme: CYP3A4-Ward2003

Molecule: CYP3A4
Metabolite: 8-OH efavirenz

Parameters

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

Metabolizing Enzyme: CYP3A5-Ward2003

Molecule: CYP3A5
Metabolite: 8-OH efavirenz

Parameters

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

Metabolizing Enzyme: CYP2A6-Ogburn2010

Molecule: CYP2A6
Metabolite: 8-OH efavirenz

Parameters

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

Metabolizing Enzyme: CYP2B6-CYP2B6*1/6*

Molecule: CYP2B6
Metabolite: 8-OH efavirenz

Parameters

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

Metabolizing Enzyme: CYP2B6-CYP2B6*6/6*

Molecule: CYP2B6
Metabolite: 8-OH efavirenz

Parameters

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

Induction: CYP3A4-Shou2008

Molecule: CYP3A4

Parameters

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

Induction: CYP2B6-Ke2016

Molecule: CYP2B6

Parameters

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

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

Name	Value	Value Origin	
GFR fraction	1		

Formulation: Sustiva

Type: Weibull

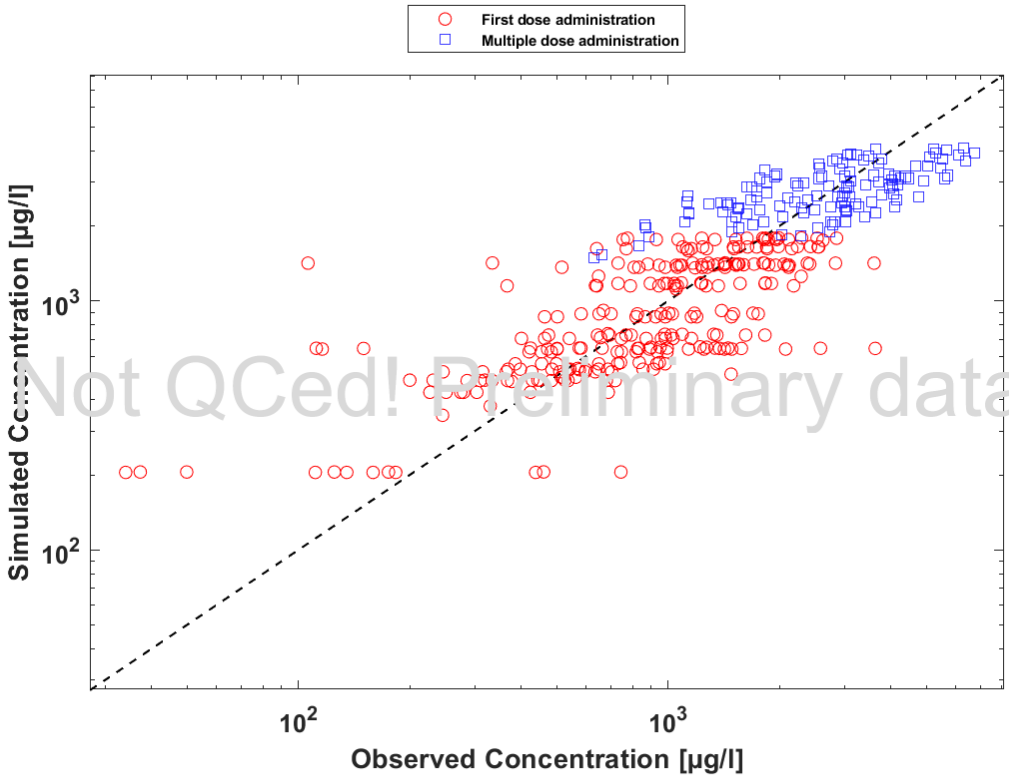
Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	60 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02	
Lag time	0 min		
Dissolution shape	0.2720936819	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 7 (Mida)' on 2019-10-11 09:02	
Use as suspension	Yes		

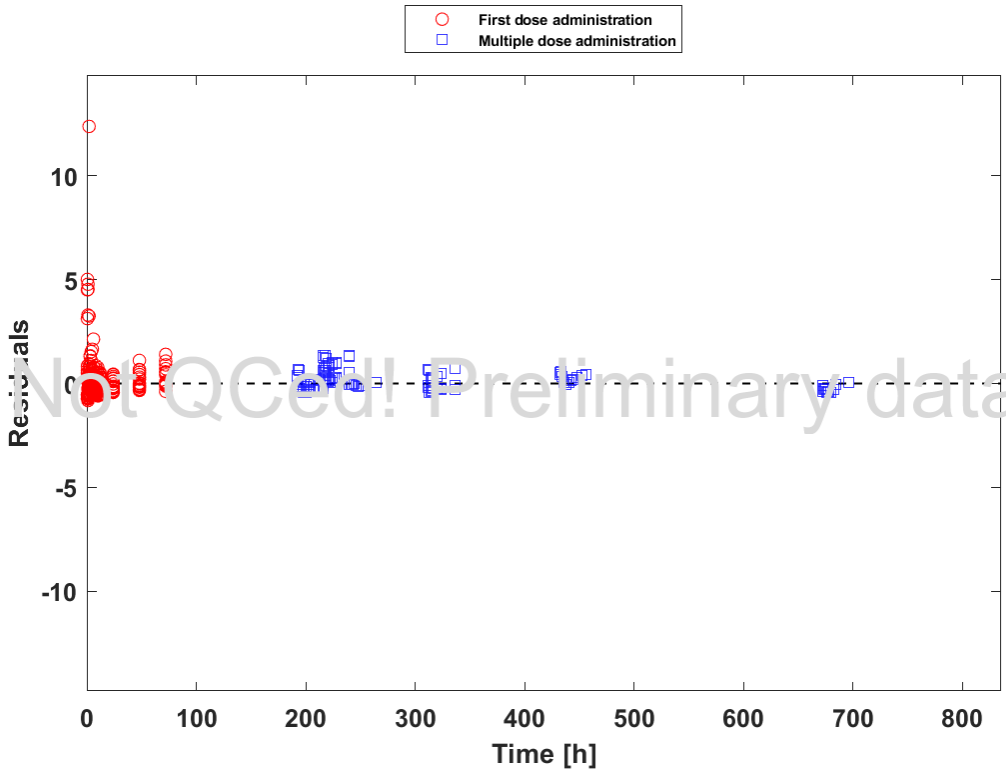
3.2 Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data used presented in Section 2.2.2.

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



Goodness of fit plor for concentration in plasma



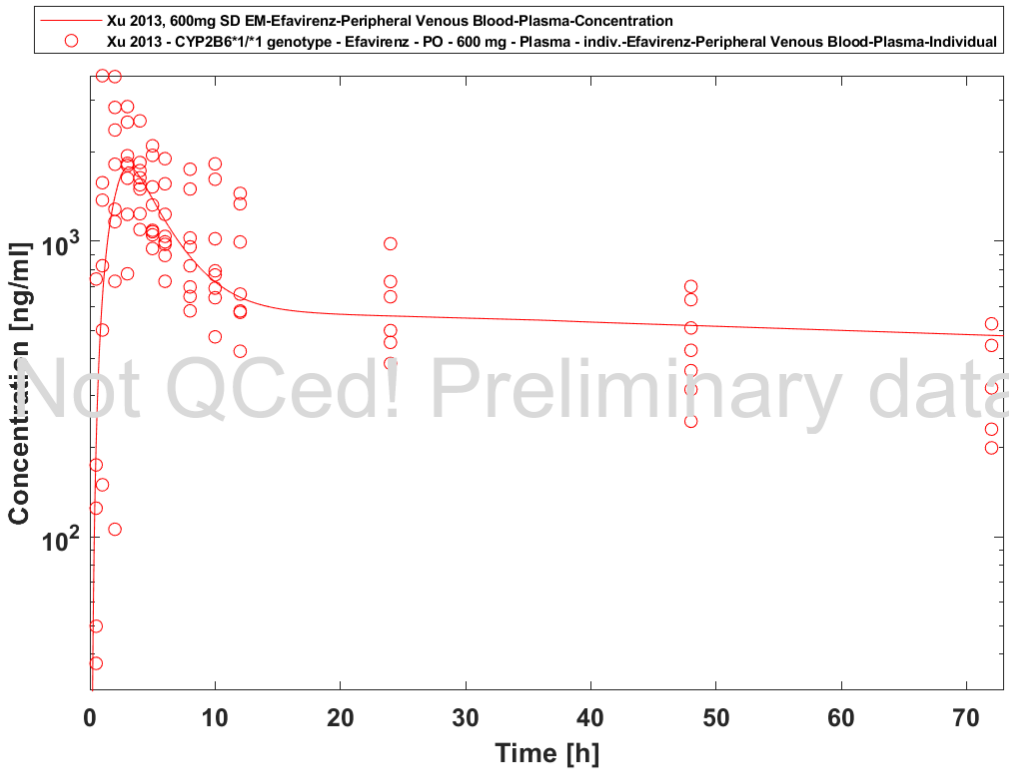
Goodness of fit plor for concentration in plasma

GMFE = 1.445153

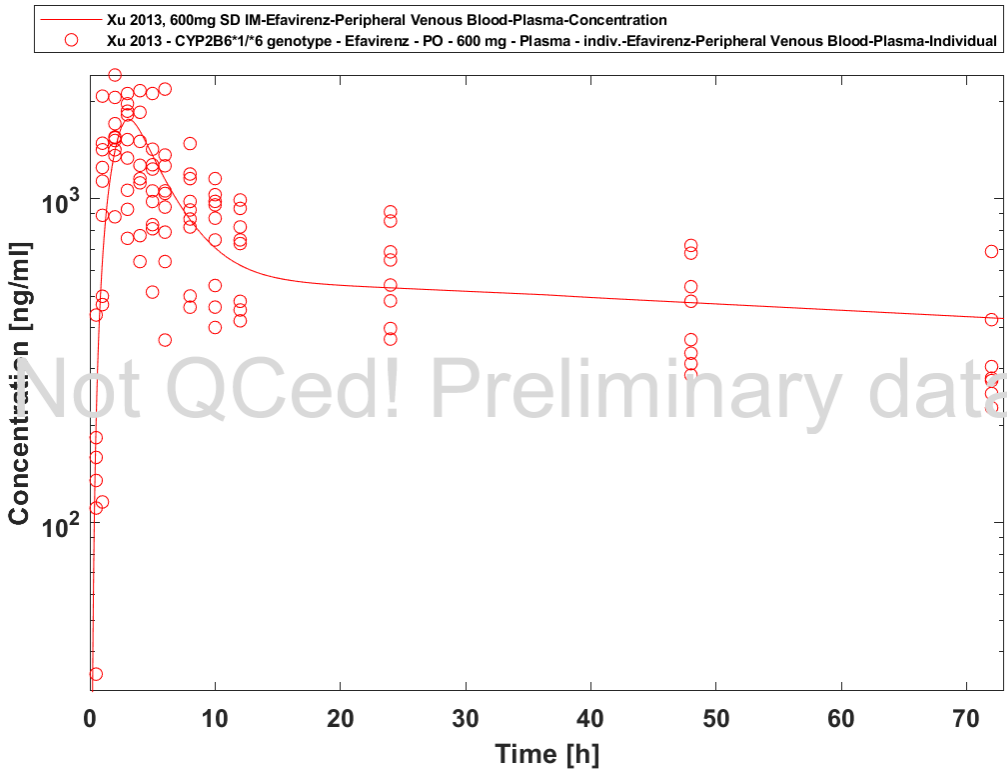
3.3: Concentration-Time Profiles

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

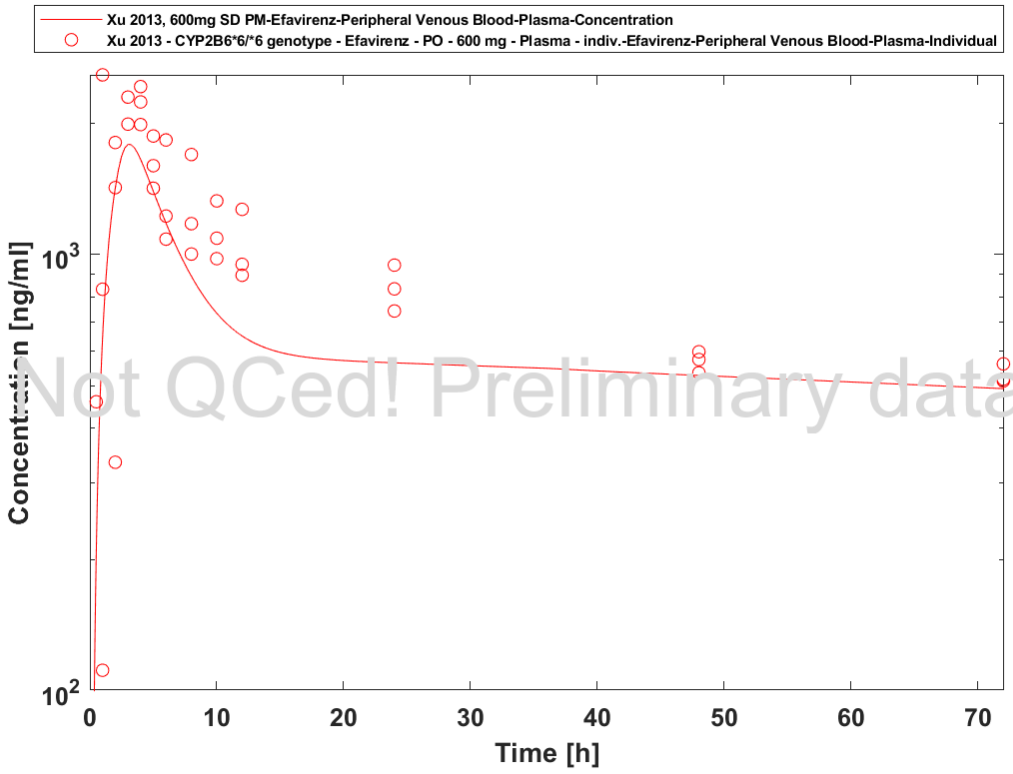
3.3.1 Model Building



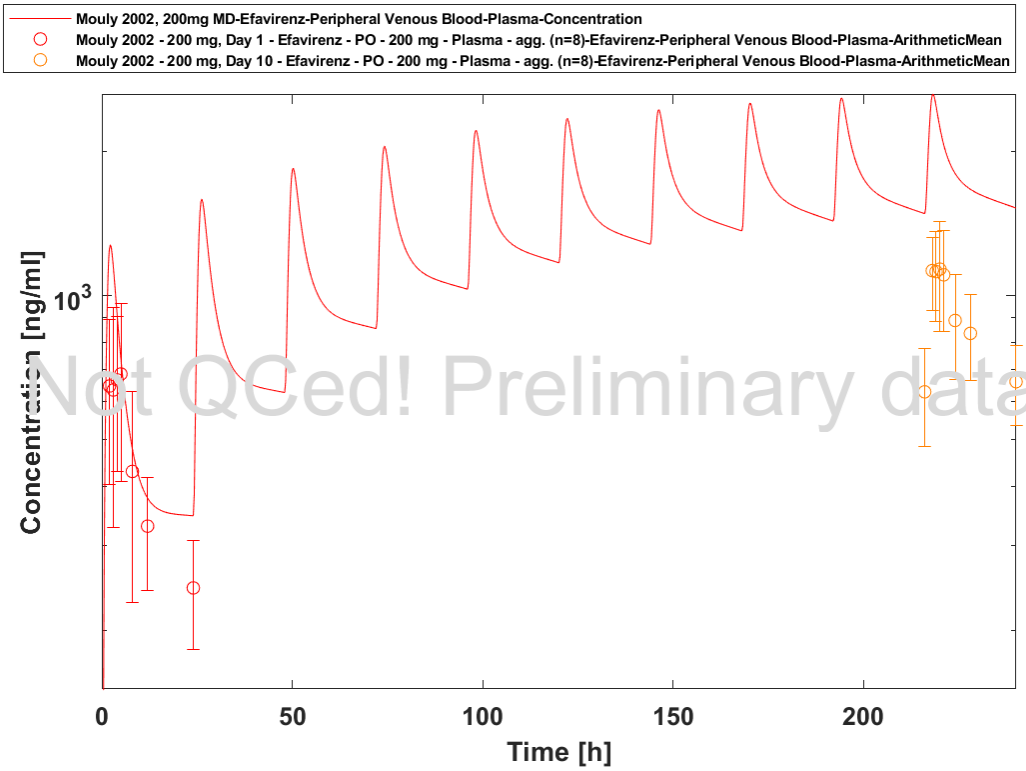
Time Profile Analysis



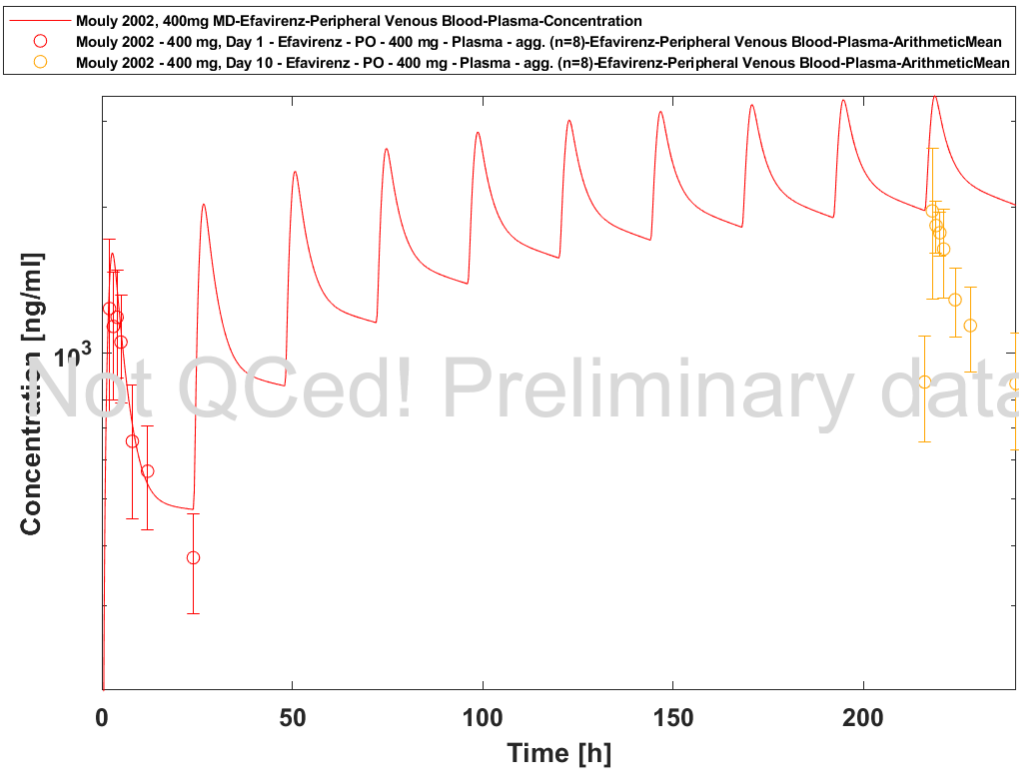
Time Profile Analysis



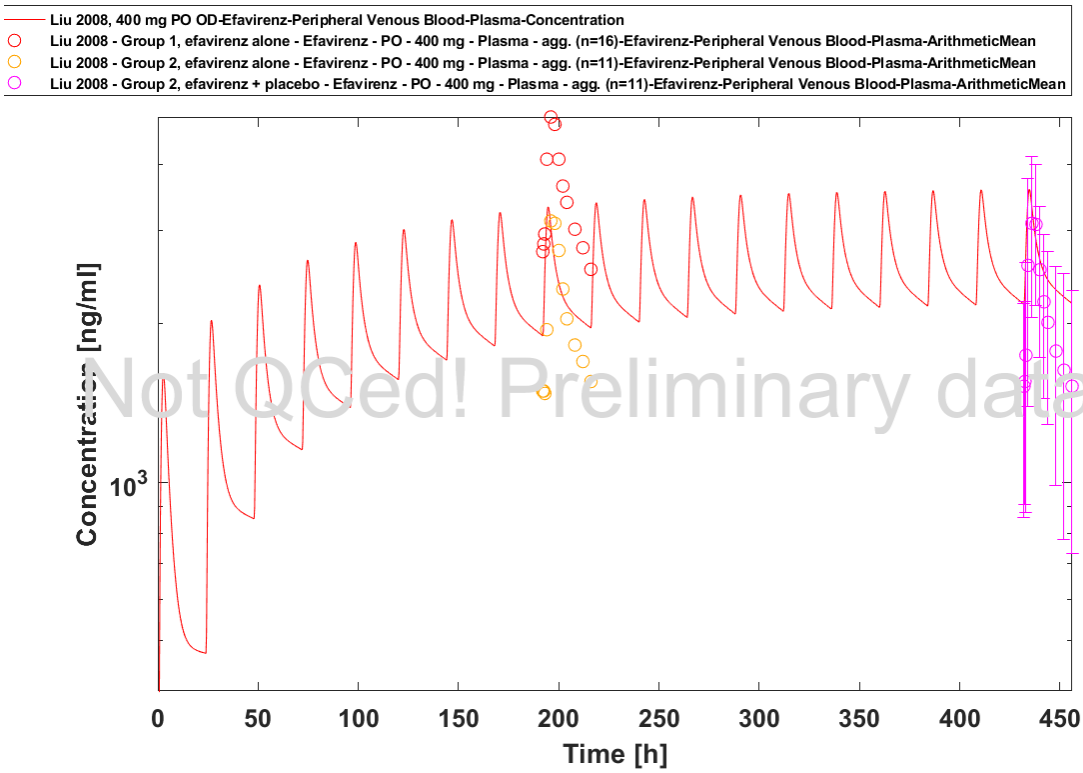
Time Profile Analysis



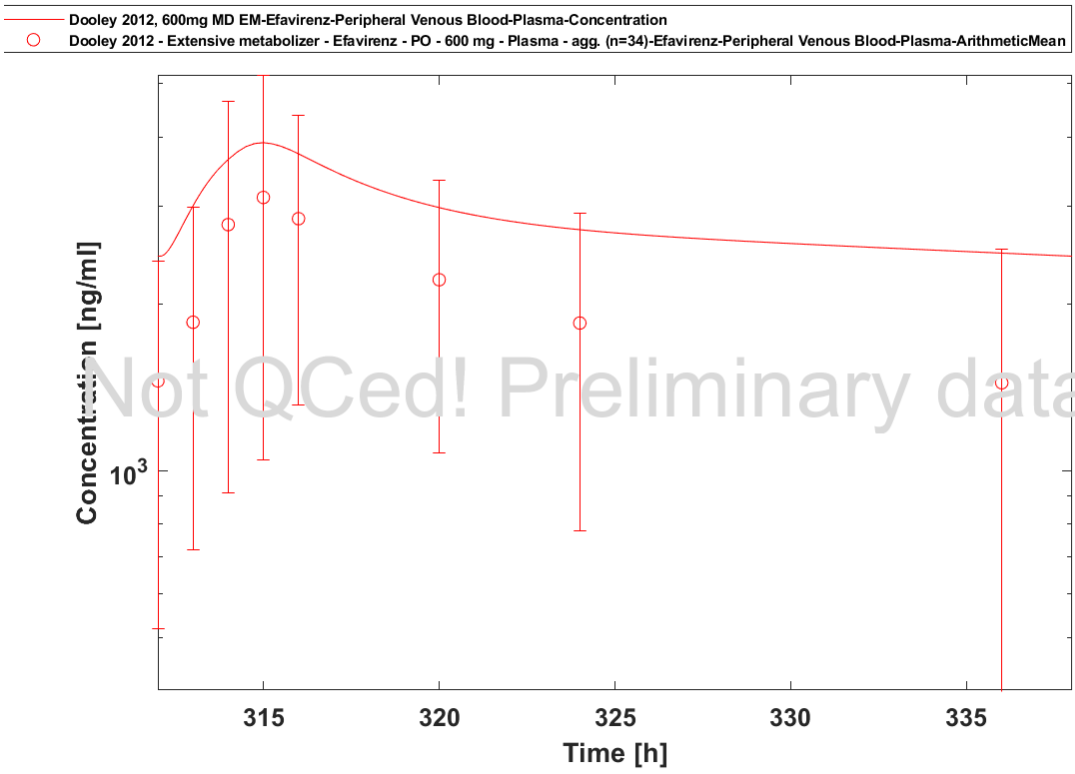
Time Profile Analysis



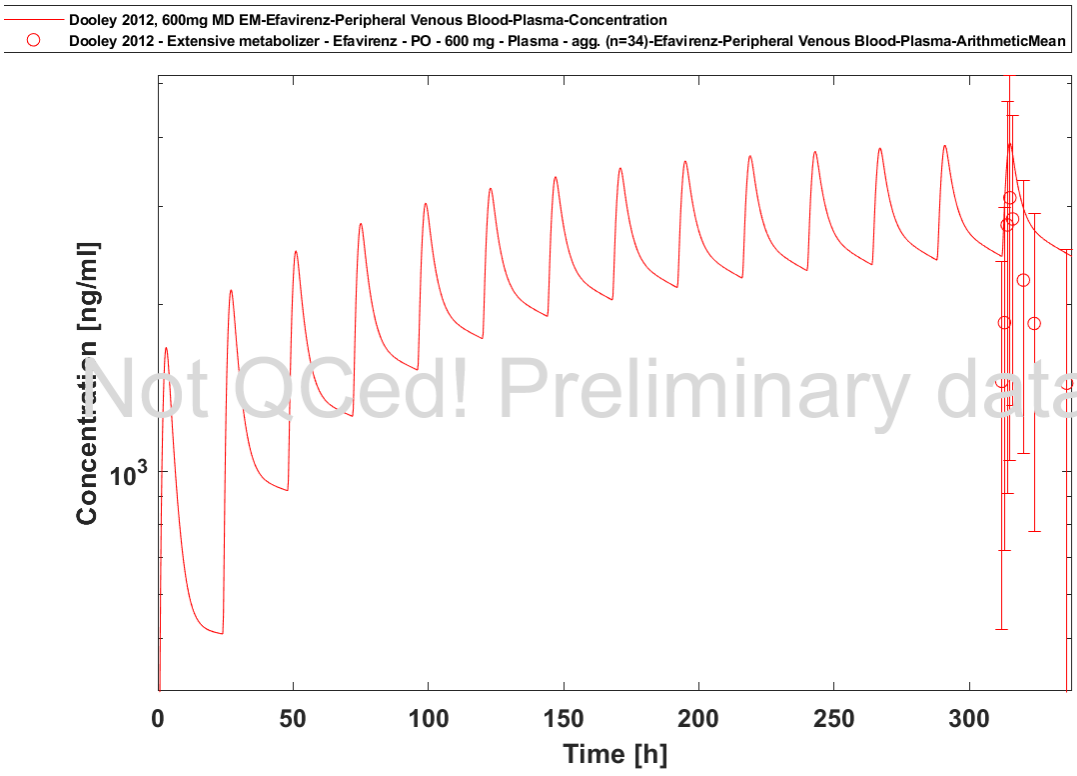
Time Profile Analysis



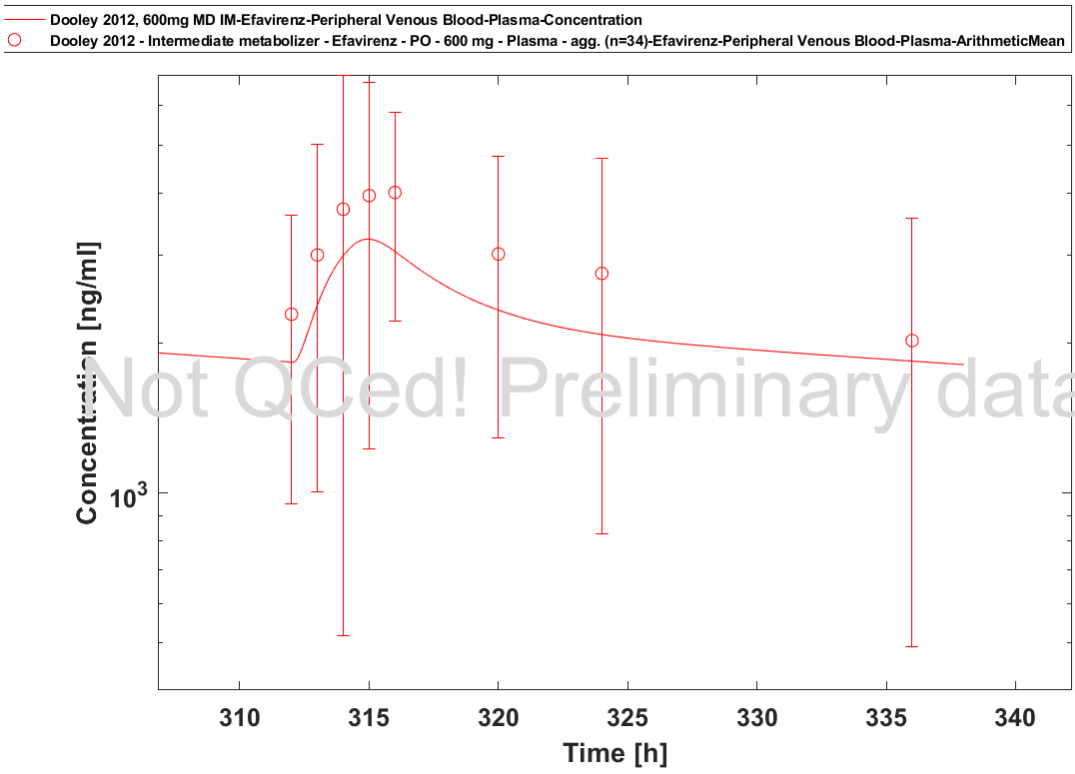
Time Profile Analysis



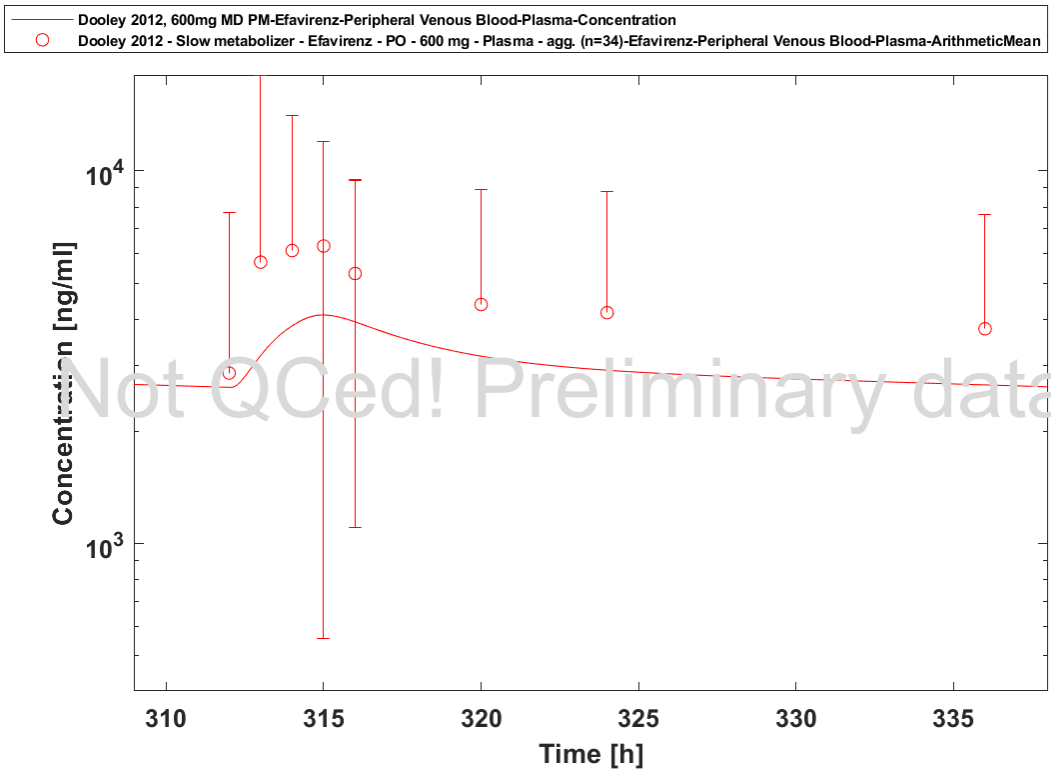
Time Profile Analysis



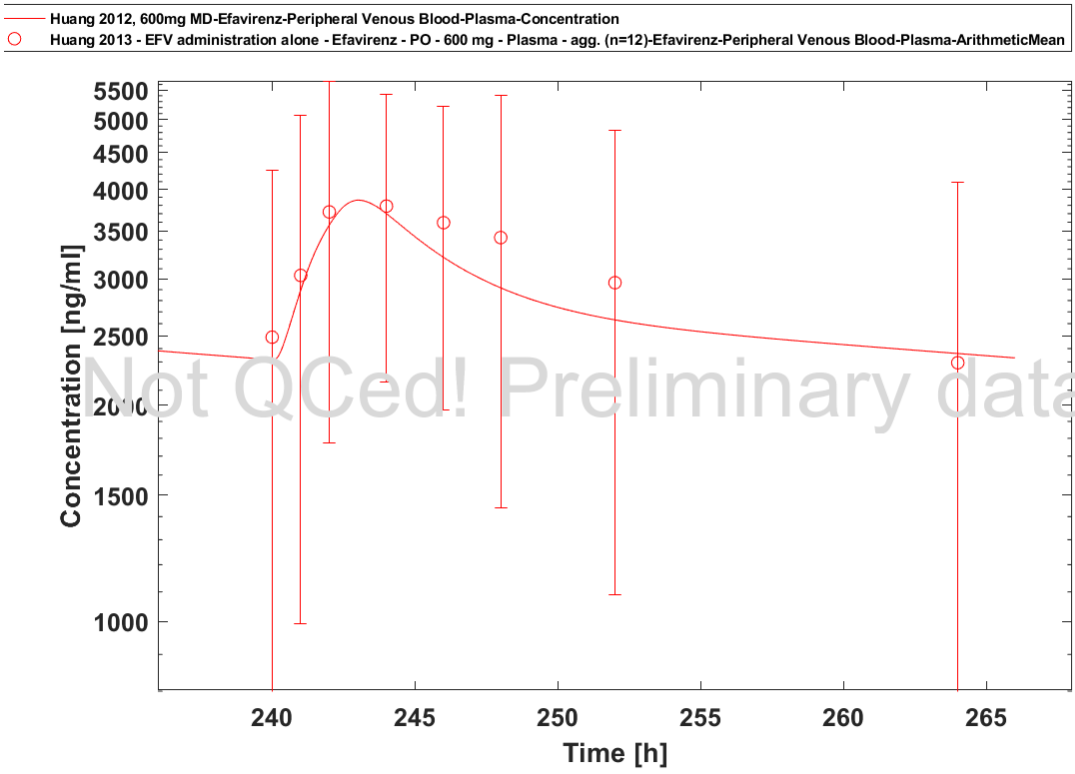
Time Profile Analysis 1



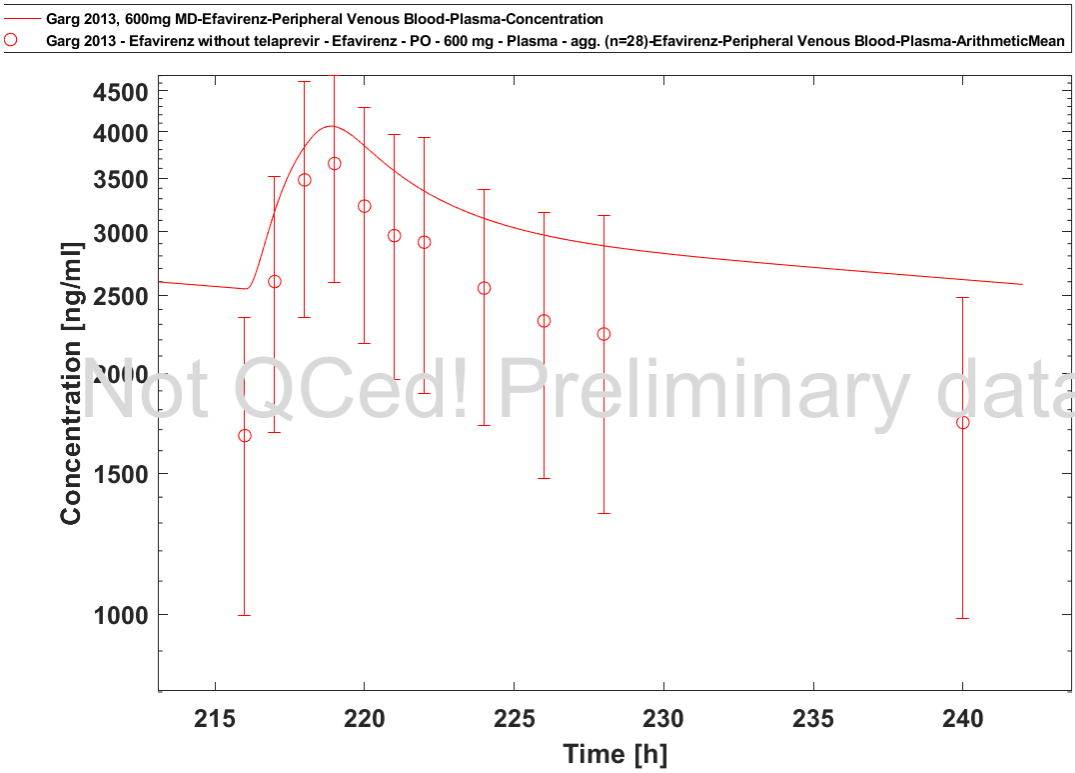
Time Profile Analysis



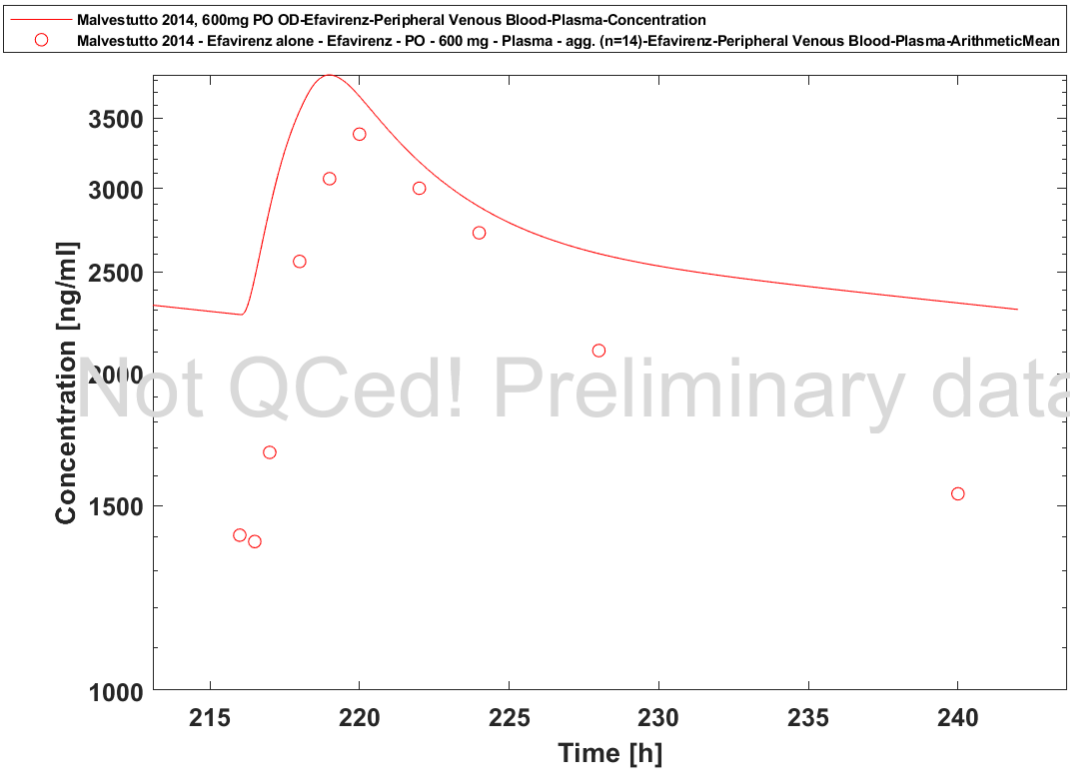
Time Profile Analysis



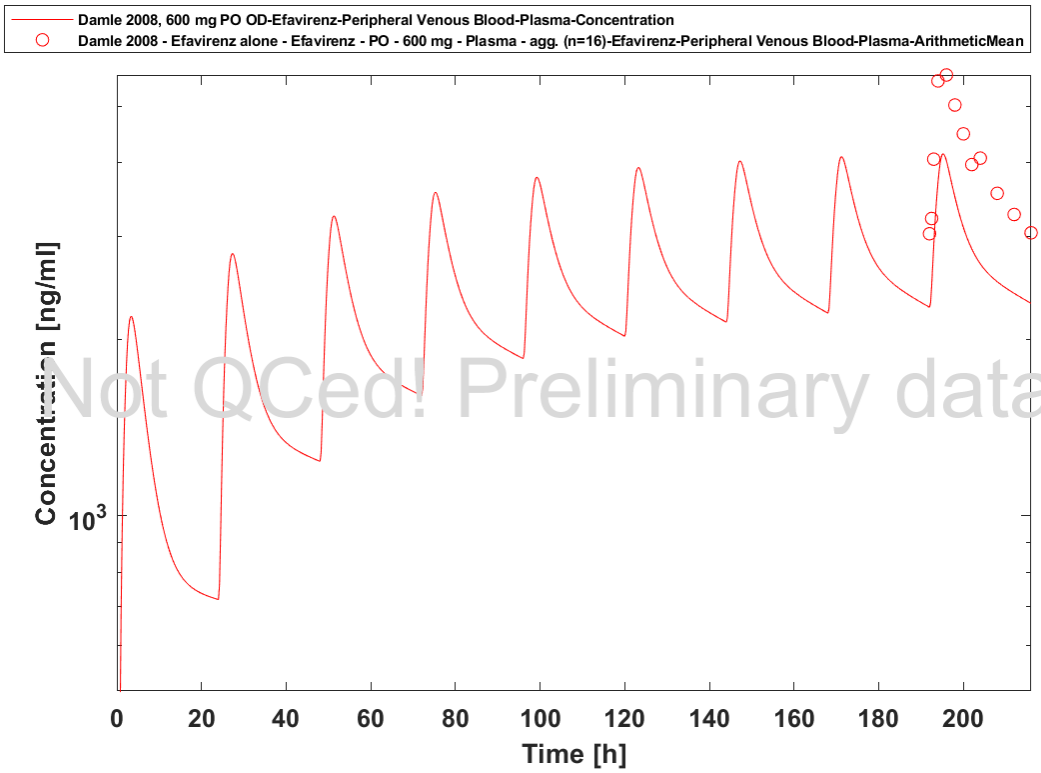
Time Profile Analysis



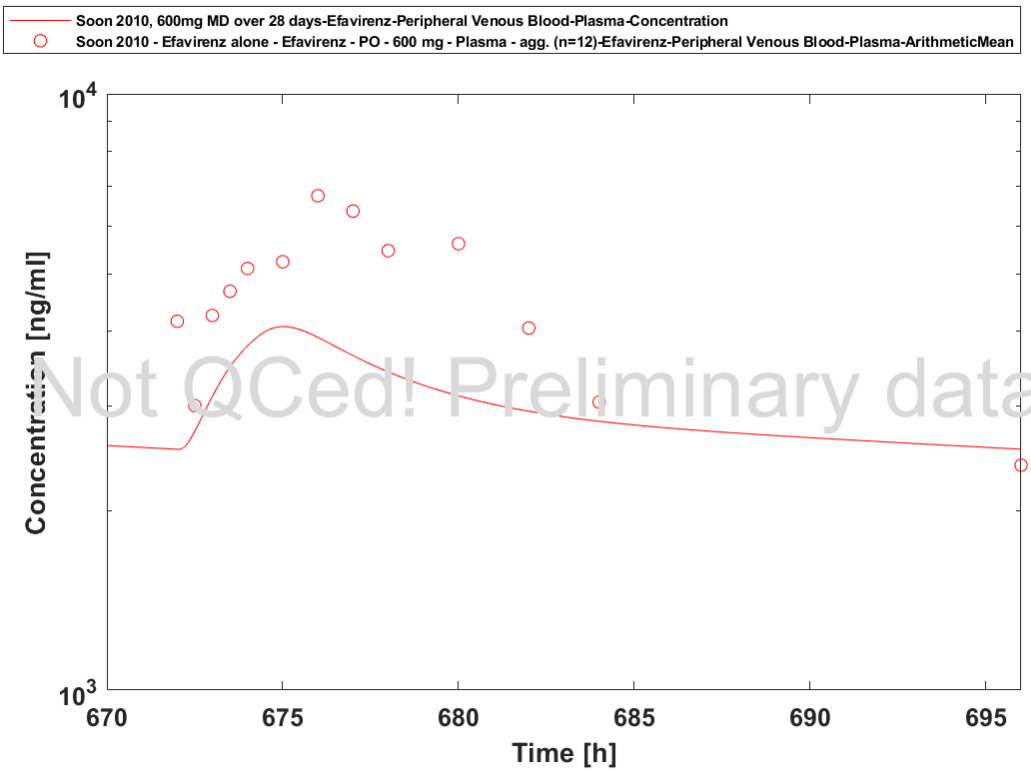
Time Profile Analysis



Time Profile Analysis

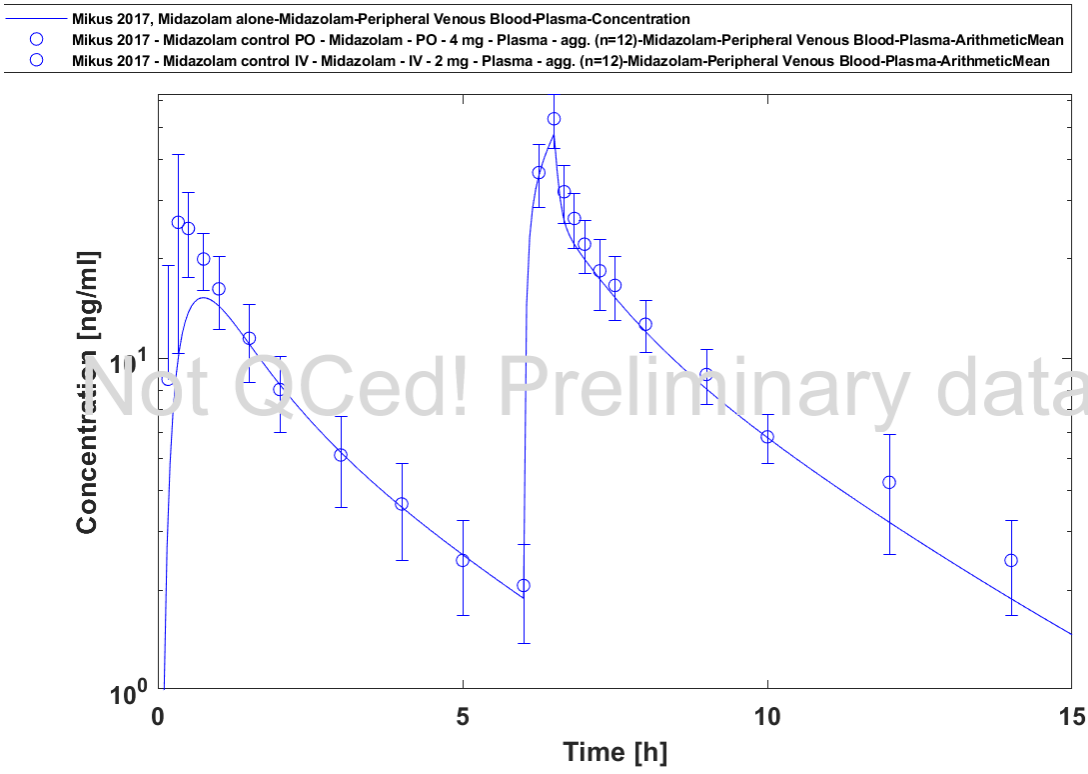


Time Profile Analysis

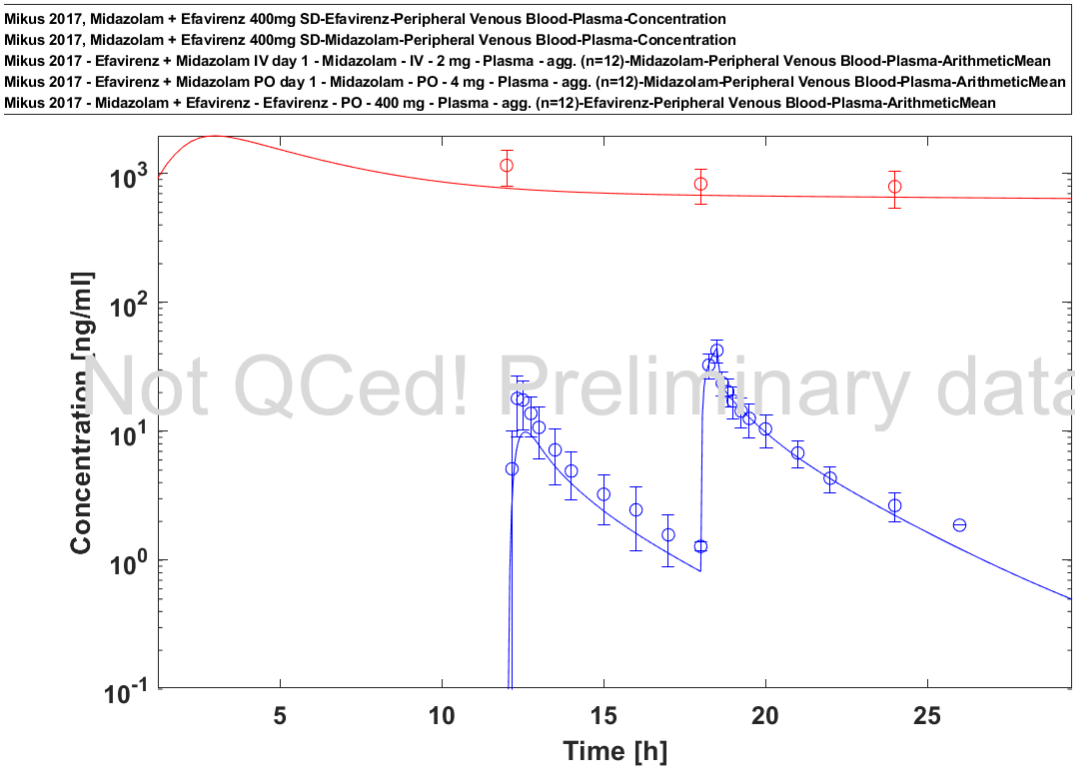


Time Profile Analysis

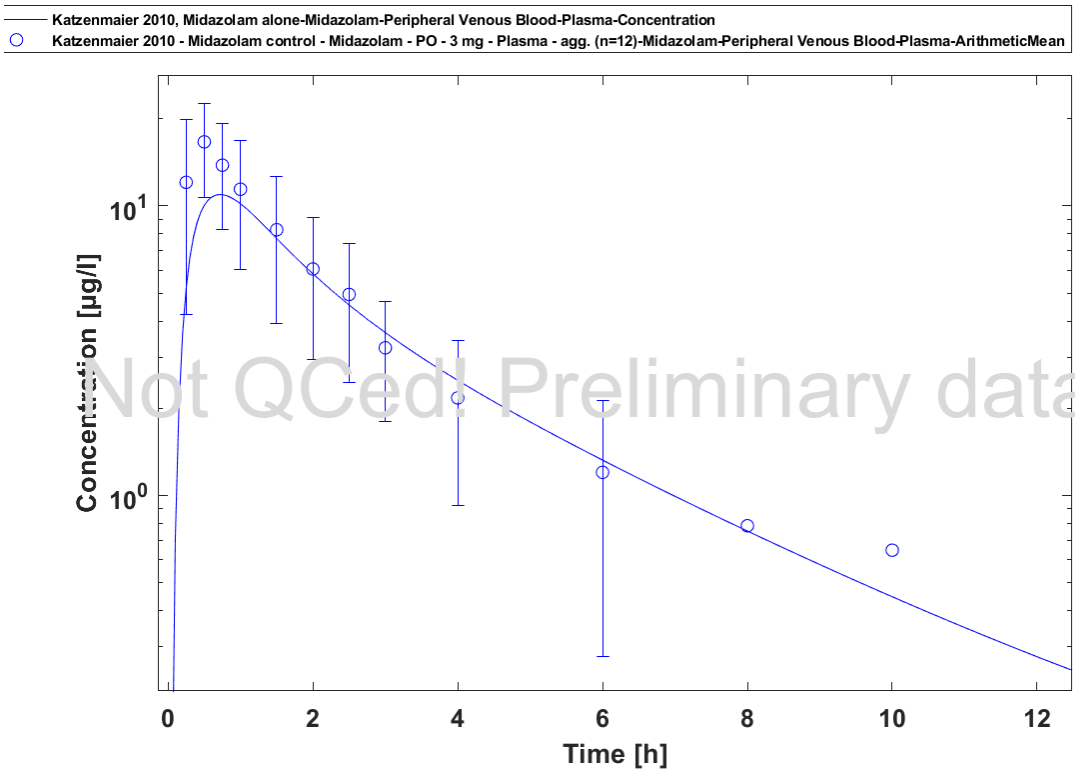
3.3.2 Fitted interaction with Midazolam



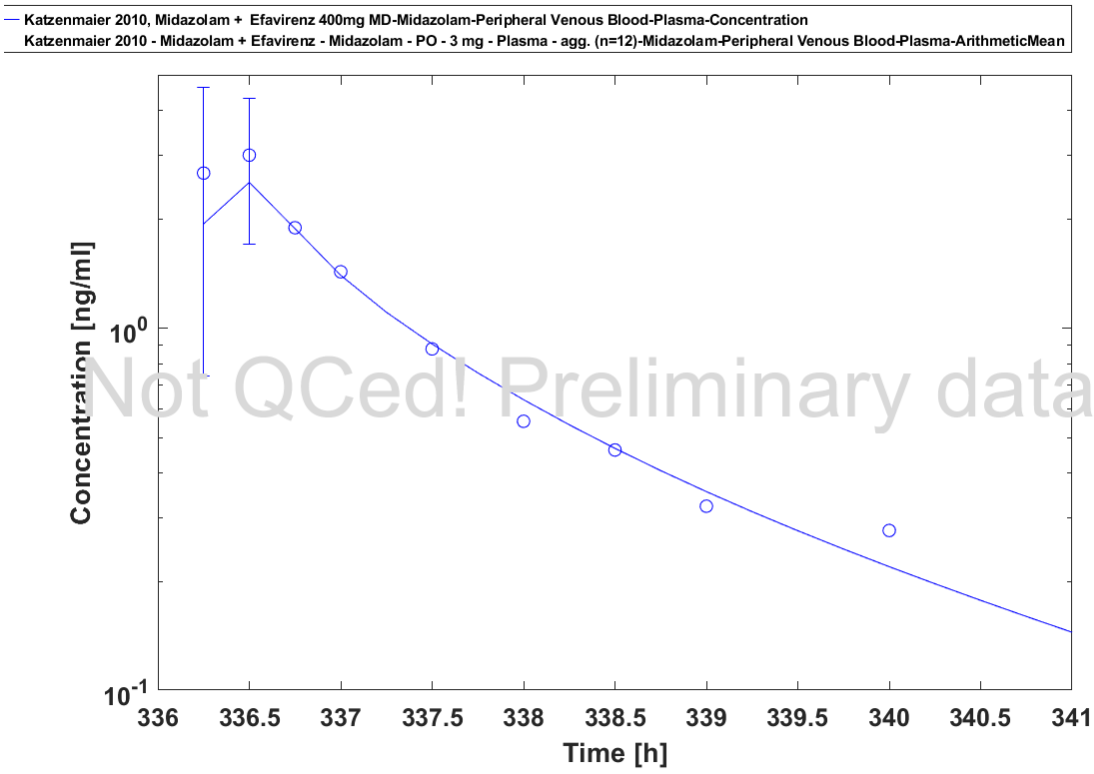
Time Profile Analysis



Time Profile Analysis

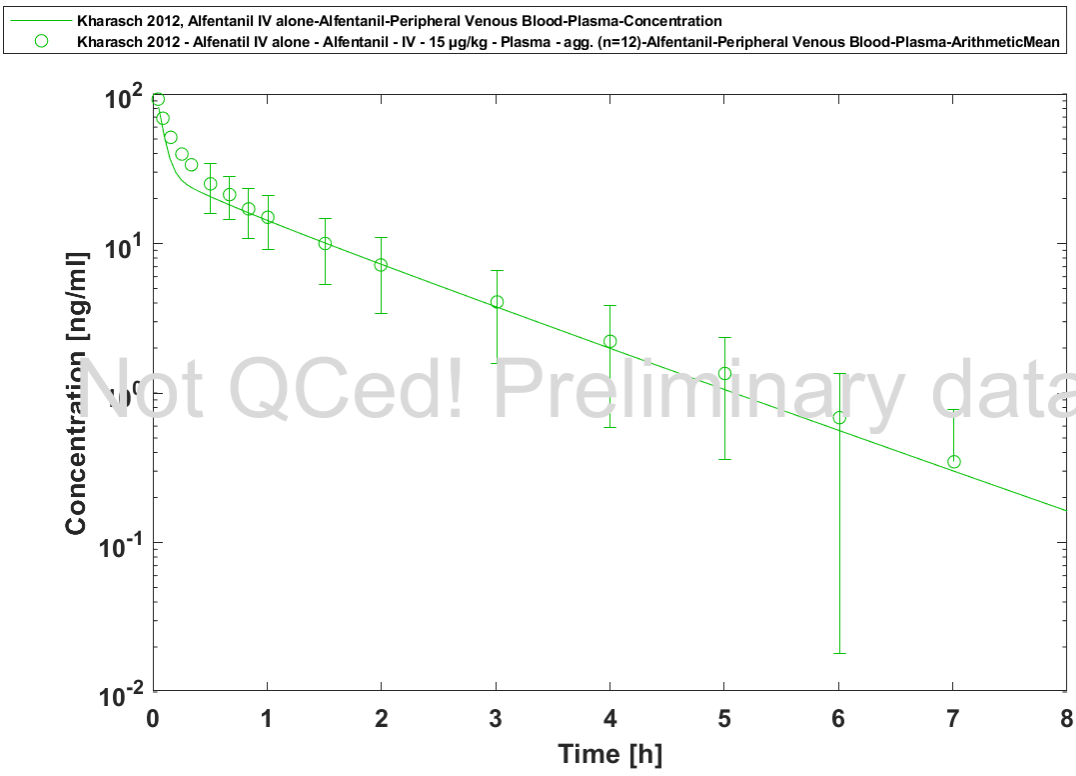


Time Profile Analysis

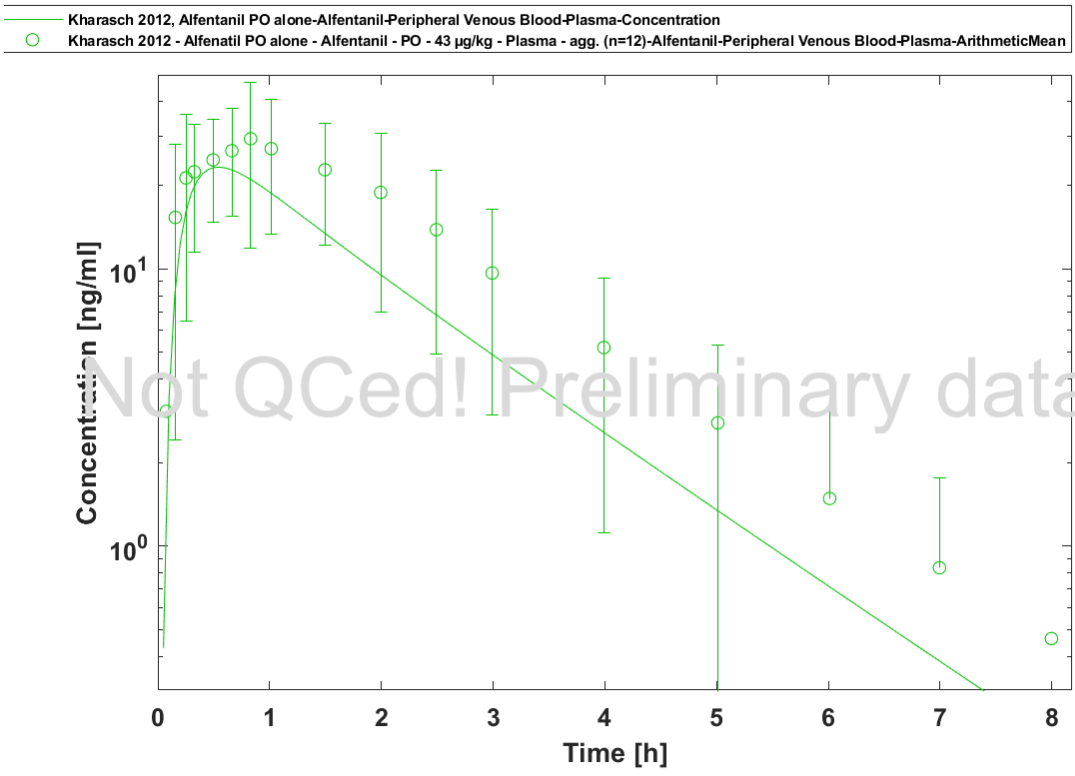


Time Profile Analysis

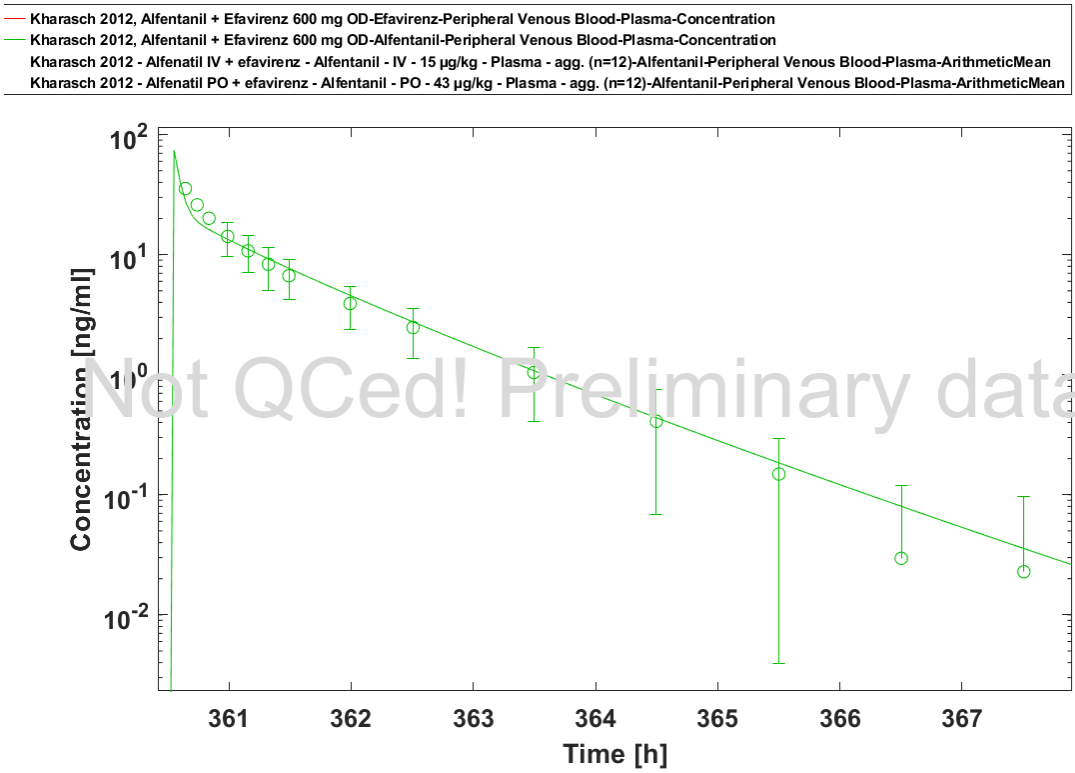
3.3.3 Model Verification: Interaction with Alfentanil



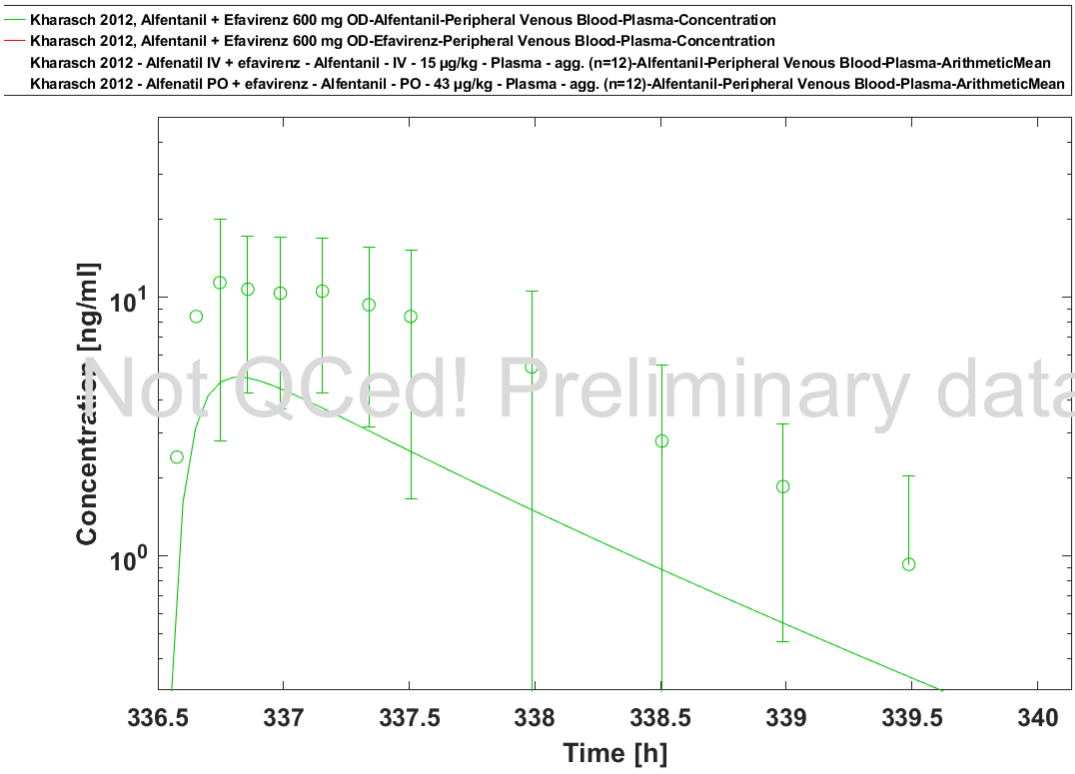
Time Profile Analysis



Time Profile Analysis



Time Profile Analysis



Time Profile Analysis 1

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of efavirenz after single and multiple administration of a variety of doses to healthy adults. Furthermore, CYP3A4 induction on alfentanil can be described well with the optimized parameterization.

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

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

5 References

Kuepfer 2016 Kuepfer L, Niederalt C, Wendl T, Schlender JF, Willmann S, Lippert J, Block M, Eissing T, Teutonico D. Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model.CPT Pharmacometrics Syst Pharmacol. 2016 Oct;5(10):516-531. doi: 10.1002/psp4.12134. Epub 2016 Oct 19.

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

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

Hanke 2018 Hanke N, Frechen S, Moj D, Britz H, Eissing T, Wendl T, Lehr T. PBPK Models for CYP3A4 and P-gp DDI Prediction: A Modeling Network of Rifampicin, Itraconazole, Clarithromycin, Midazolam, Alfentanil, and Digoxin. CPT Pharmacometrics Syst Pharmacol. 2018 Oct;7(10):647-659. doi: 10.1002/psp4.12343. Epub 2018 Sep 7.

Ward 2003 Ward BA, Gorski JC, Jones DR, Hall SD, Flockhart DA, Desta Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther. 2003 Jul;306(1):287-300. Epub 2003 Apr 3. PubMed PMID: 12676886.

Ogburn 2010 Ogburn ET, Jones DR, Masters AR, Xu C, Guo Y, Desta Z. Efavirenz primary and secondary metabolism in vitro and in vivo: identification of novel metabolic pathways and cytochrome P450 2A6 as the principal catalyst of efavirenz 7-hydroxylation. Drug Metab Dispos. 2010 Jul;38(7):1218-29. doi: 10.1124/dmd.109.031393. Epub 2010 Mar 24. PubMed PMID: 20335270; PubMed Central PMCID: PMC2908985.

Mikus 2017 Mikus G, Heinrich T, Bödigheimer J, Röder C, Matthee AK, Weiss J, Burhenne J, Haefeli WE. Semisimultaneous Midazolam Administration to Evaluate the Time Course of CYP3A Activation by a Single Oral Dose of Efavirenz. J Clin Pharmacol. 2017 Jul;57(7):899-905. doi: 10.1002/jcph.879. Epub 2017 Feb 14. PubMed PMID: 28194792.

Katzenmaier 2010 Katzenmaier S, Markert C, Mikus G. Proposal of a new limited sampling strategy to predict CYP3A activity using a partial AUC of midazolam. Eur J Clin Pharmacol. 2010 Nov;66(11):1137-41. doi: 10.1007/s00228-010-0878-2. Epub 2010 Aug 3. PubMed PMID: 20680253.

Kharasch 2012 Kharasch ED, Whittington D, Ensign D, Hoffer C, Bedynek PS, Campbell S, Stubbert K, Crafford A, London A, Kim T. Mechanism of efavirenz influence on methadone pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2012 Apr;91(4):673-84. doi: 10.1038/clpt.2011.276. Epub 2012 Mar 7.

Nishimura 2003 Nishimura, M., Yaguti, H., Yoshitsugu, H., Naito, S. & Satoh, T. Tissue distribution of mRNA expression of human cytochrome P450 isoforms assessed by high-sensitivity real-time reverse transcription PCR. J. Pharm. Soc. Japan 123, 369–75 (2003).

Rabel 1996 Rabel SR, Maurin MB, Rowe SM, Hussain M. Determination of the pKa and pH-solubility behavior of an ionizable cyclic carbamate, (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-
(trifluoromethyl)-2H-3,1-benzoxazin-2-one (DMP 266). Pharm Dev Technol. 1996 Apr;1(1):91-5. PubMed PMID: 9552335.

Cristofoletti 2013 Cristofoletti R, Nair A, Abrahamsson B, Groot DW, Kopp S, Langguth P, Polli JE, Shah VP, Dressman JB. Biowaiver monographs for immediate release solid oral dosage forms: efavirenz. J Pharm Sci. 2013 Feb;102(2):318-29. doi: 10.1002/jps.23380. Epub 2012 Nov 22. Review. PubMed PMID: 23175470.

Almond 2005 Almond LM, Hoggard PG, Edirisinghe D, Khoo SH, Back DJ. Intracellular and plasma pharmacokinetics of efavirenz in HIV-infected individuals. J Antimicrob Chemother. 2005 Oct;56(4):738-44. Epub 2005 Sep 1. PubMed PMID: 16141277.

Janneh 2009 Janneh O, Chandler B, Hartkoorn R, Kwan WS, Jenkinson C, Evans S, Back DJ, Owen A, Khoo SH. Intracellular accumulation of efavirenz and nevirapine is independent of P-glycoprotein activity in cultured CD4 T cells and primary human lymphocytes. J Antimicrob Chemother. 2009 Nov;64(5):1002-7. doi: 10.1093/jac/dkp335. Epub 2009 Sep 11. PubMed PMID: 19748977.

Shou 2008 Shou M, Hayashi M, Pan Y, Xu Y, Morrissey K, Xu L, Skiles GL. Modeling, prediction, and in vitro in vivo correlation of CYP3A4 induction. Drug Metab Dispos. 2008 Nov;36(11):2355-70. doi: 0.1124/dmd.108.020602. Epub 2008 Jul 31. PubMed PMID: 18669588.

Ke 2016 Ke A, Barter Z, Rowland-Yeo K, Almond L. Towards a Best Practice Approach in PBPK Modeling: Case Example of Developing a Unified Efavirenz Model Accounting for Induction of CYPs 3A4 and 2B6. CPT Pharmacometrics Syst Pharmacol. 2016 Jul;5(7):367-76. doi: 10.1002/psp4.12088. Epub 2016 Jul 20. PubMed PMID: 27435752; PubMed Central PMCID: PMC4961080.

Mouly 2002 Mouly S, Lown KS, Kornhauser D, Joseph JL, Fiske WD, Benedek IH, Watkins PB. Hepatic but not intestinal CYP3A4 displays dose-dependent induction by efavirenz in humans. Clin Pharmacol Ther. 2002 Jul;72(1):1-9. PubMed PMID: 12151999.

Xu 2013 Xu C, Quinney SK, Guo Y, Hall SD, Li L, Desta Z. CYP2B6 pharmacogenetics-based in vitro-in vivo extrapolation of efavirenz clearance by physiologically based pharmacokinetic modeling. Drug Metab Dispos. 2013 Dec;41(12):2004-11. doi: 10.1124/dmd.113.051755. Epub 2013 Jul 11. PubMed PMID: 23846872; PubMed Central PMCID: PMC3834132.

Dooley 2012 Dooley KE, Park JG, Swindells S, Allen R, Haas DW, Cramer Y, Aweeka F, Wiggins I, Gupta A, Lizak P, Qasba S, van Heeswijk R, Flexner C; ACTG 5267 Study Team. Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS Clinical Trials Group Study A5267. J Acquir Immune Defic Syndr. 2012 Apr 15;59(5):455-62. doi: 10.1097/QAI.0b013e3182410503. PubMed PMID: 22126739; PubMed Central PMCID: PMC3302922.

Garg 2013 Garg V, Chandorkar G, Yang Y, Adda N, McNair L, Alves K, Smith F, van Heeswijk RP. The effect of CYP3A inhibitors and inducers on the pharmacokinetics of telaprevir in healthy volunteers. Br J Clin Pharmacol. 2013 Feb;75(2):431-9. doi: 10.1111/j.1365-2125.2012.04345.x. PubMed PMID: 22642697; PubMed Central PMCID: PMC3579258.

Huang 2012 Huang L, Parikh S, Rosenthal PJ, Lizak P, Marzan F, Dorsey G, Havlir D, Aweeka FT. Concomitant efavirenz reduces pharmacokinetic exposure to the antimalarial drug artemether-lumefantrine in healthy volunteers. J Acquir Immune Defic Syndr. 2012 Nov 1;61(3):310-6. doi: 10.1097/QAI.0b013e31826ebb5c. PubMed PMID: 22918158; PubMed Central PMCID: PMC3511816.

Kharasch 2012 Kharasch ED, Whittington D, Ensign D, Hoffer C, Bedynek PS, Campbell S, Stubbert K, Crafford A, London A, Kim T. Mechanism of efavirenz influence on methadone pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2012 Apr;91(4):673-84. doi: 10.1038/clpt.2011.276. Epub 2012 Mar 7. PubMed PMID: 22398970; PubMed Central PMCID: PMC3600645.