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

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1 Introduction

The presented model building and evaluation report evaluates the performance of a PBPK model for atazanavir in healthy adults.

Atazanavir, sold under the trade name Reyataz among others, is an azapeptide protease inhibitor and used as antiretroviral medication to treat and prevent HIV/AIDS. It is taken orally once a day at a dose of 300 mg, if co-administered with ritonavir 100 mg orally once a day, and 400 mg, if administered without ritonavir.

After oral administration, atazanavir is rapidly absorbed. A positive food effect has been observed, atazanavir is recommended to be taken with food. Protein binding is relatively high (86%) and independent of the concentration of serum proteins (**US Food and Drug Administration 2002**). Atazanavir undergoes extensive metabolism by CYP3A isoenzymes with a dose fraction excreted unchanged in urine of approximately 7% (**US Food and Drug Administration 2002**, **Le Tiec 2005**). Previous in vitro studies suggest that atazanavir is a mechanism-based inhibitor of CYP3A (**US Food and Drug Administration 2002**, **Perloff 2005**).

The atzanavir model is a whole-body PBPK model and is - together with the respective evaluation plan and PBPK report - transparently documented and provided open-source (https://github.com/AndreDlm/Atazanavir-Model).

2 Methods

2.1 Modeling strategy

The general workflow for building an adult PBPK model has been described by Kuepfer et al. (**Kuepfer 2016**).

First, a base mean model was built using plasma concentration-time profiles and the dose fraction excreted unchanged in urine following single dose administration of 400 mg po. The mean PK model was developed using a typical White American individual. Unknown parameters were identified using the Parameter Identification module provided in PK-Sim® and MoBi® (**Open Systems Pharmacology Documentation**). The following parameters were optimized:

- Dissolution shape
- Dissolution time (50% dissolved)
- Specific intestinal permeability (transcellular)
- GFR fraction
- CLspec/[Enzyme]

Structural model selection was mainly guided by visual inspection of the resulting description of PK data and biological plausibility. On the basis of in vitro findings, atazanavir has been suggested to be a mechanism-based inhibitor of CYP3A (**Perloff 2005**); however, no kinetic parameters have been reported for this interaction. Hence, to avoid non-identifiability issues,

mechanism-based inhibition of CYP3A was not considered during parameter identification of the mean base model for single dose administration. All models implemented in PK-Sim for estimating the intracellular-to-plasma partition coefficient and those for estimating the permeability between interstitial and intracellular space were tested in this step. Once an appropriate structural model was identified, a second parameter identification was conducted fixing all previously optimized parameter values (except the GFR fraction) and including additional PK data following multiple dose administration of 200 mg, 300 mg, 400 mg, and 800 mg po. Optimized parameters were:

- GFR fraction
- k_kinact_half
- k_inact

The PBPK models are developed based on clinical data of healthy adult subjects obtained from the literature, covering available dosing ranges for oral administration. Plasma concentration-time profiles following multiple-dose application and mass balance information on the urinary excretion of unchanged atazanavir were included in model development.

The performance of the PBPK model for atazanavir to describe observed PK is assessed by means of diagnostics plots and predicted versus observed concentration-time profiles, of which the results support an adequate simulation of the PK in healthy adults.

Relevant information on the anthropometry (height, weight) was gathered from the respective clinical study, if reported. Information on physiological parameters (e.g. blood flows, organ volumes, hematocrit) in adults was gathered from the literature and has been incorporated in PK-Sim® as described previously (**Willmann 2007**). The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available ‘PK-Sim® Ontogeny Database Version 7.3' (**PK-Sim Ontogeny Database Version 7.3**).

2.2 Data used

2.2.1 In vitro / physicochemical data

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

Parameter	Unit	Raltegravir literature	Description
MW	g/mol	704.9 (**drugbank.ca**)	Molecular weight
pKa (basic)		4.7 (**Berlin 2015**)	Acid dissociation constant
logP		2.12 (**Hyland 2008**)	Partition coefficient between octanol and water
fu		0.14 (**US Food and Drug Administration 2002**)	Fraction unbound

2.2.2 Clinical data

A literature search was performed to collect available PK data on atazanavir in healthy adults.

The following publications were found and used for model building and evaluation:

Publication	Study description
Acosta 2007	300 mg atazanavir BID
Agarwala 2003	400 mg atazanavir QD
Agarwala 2005a	400 mg atazanavir QD
Agarwala 2005b	400 mg atazanavir QD
Martin 2008	400 mg atazanavir QD
Zhu 2010	300 mg atazanavir QD
Zhu 2011	400 mg atazanavir QD
US Food and Drug Administration 2002	AI424-004 (p. 94): 400 mg atazanavir single dose; AI424-014 (p. 77): 400 mg atazanavir single dose; AI424-015 (p. 81): 400 mg atazanavir single dose; AI424-028 (p. 128): 200, 400, and 800 mg atazanavir QD; AI424-029 (p. 47): 400 mg [14C]atazanavir single dose; AI424-040 (p. 64): 200, 400, and 800 mg atazanavir QD; AI424-056 (p. 134): 300 mg atazanavir QD; AI424-076 (p. 178): 400 and 800 mg atazanavir QD

2.3 Model parameters and assumptions

2.3.1 Dissolution and absorption

No PK data were available following intravenous administration of atazanavir allowing informing distribution and systemic clearance independently of dissolution and absorption. Consequently, only PK data following oral administration of atazanavir as capsule were used for model building. It was assumed that solubility is not a critical parameter for dissolution of atazanvir capsules in the GI tract; in the models, solubility was therefore fixed to a very high value (50 mg/mL) to prevent solubility being a limiting factor of dissolution. Although the equilibrium solubility of atazanavir in the biorelevant media FaSSIF and FeSSIF has been observed to be rather low (2.74 µg/mL and 4.13 µg/mL in FaSSIF and FeSSIF, respectively), dissolution of atazanavir capsules in these media yields concentrations that are considerably higher than this threshold during the complete measurement period of at least 3 h (**Berlin 2015**). In the model, dissolution was described by a Weibull function; and the two Weibull parameters, dissolution shape and Dissolution time (50% dissolved), were fitted together with the specific intestinal permeability (transcellular) to observed PK data as described in section **2.1**.

2.3.2 Distribution

With a fraction unbound in humans of 0.14, atazanavir is extensively protein-bound. The extent of protein binding has been reported to be independent of the concentration of serum proteins (**US Food and Drug Administration 2002**). The observed PK data were found to be best described using the model for estimating intracellular-to-plasma partition coefficients by Rodgers et al. (**Rodgers 2005**, **Rodgers 2006**) and the cellular permeability automatically calculated by PK-Sim® (**Open Systems Pharmacology Documentation**).

2.3.3 Elimination

Atazanavir is extensively metabolized via CYP3A isoenzymes (**Le Tiec 2005**). Metabolism was modeled as linear process mediated by CYP3A4 ('in vitro clearance - first order'). The gene expression profile of CYP3A4 was loaded from the internal PK-Sim® database using the expression data quantified by RT-PCR (**Open Systems Pharmacology Documentation**).

Following oral administration of 400 mg [14C]atazanavir to healthy males, approximately 7% of the radioactive dose were recovered as unchanged drug in the urine (**US Food and Drug Administration 2002**). Renal excretion of the unchanged drug was modeled as glomerular

filtration process. The GFR fraction was then, together with the specific clearance via CYP3A4 normalized to the enzyme concentration (CLspec/[Enzyme]), fitted to observed PK data as described in section **2.1**.

2.3.2 Autoinhibition

Findings from in vitro studies indicate that atazanavir irreversibly inhibits CYP3A (**US Food and Drug Administration 2002**, **Perloff 2005**). Since no kinetic values were reported for this mechanism-based inhibition, relevant parameters in the model (k_kinact_half and k_inact) were fitted as described in section **2.1**.

3 Results and Discussion

The results of the first parameter identification including PK data after single dose administration (see section **2.1**) described the observed PK reasonably. However, since no PK data following IV administration was available, a moderate correlation was observed between the fitted dissolution time (50% dissolved) and GFR fraction. PK profiles in fed state were generally well described, while the model overestimated Cmax in fasted state. Since atazanavir must be taken with food, the overestimation of Cmax in fasted state was considered inconsequential for further model applications which encompassed all fed state PK.

As described in section **2.1**, the second parameter identification was conducted in the basis of PK data after single and multiple dose administration and included autoinhibition of CYP3A4-mediated clearance. An attempt to fix k_kinact_half to a very high value (100 µmol/L) to ensure linear inhibition kinetics while fitting k_inact and the GFR faction resulted in a slightly worse description of the observed PK in the terminal phase. Hence, both k_kinact_half and k_inact were fitted together with the GFR fraction. This resulted in a strong correlation between the former two parameters, but also in a reduction of the total error from 4.76 (k_kinact_half fixed to 100 µmol/L) to 3.55 (k_kinact_half fitted). Furthermore, the introduction of irreversible CYP3A4 inhibition led to a slightly worse description of clearance of the single dose PK data. Due to the lack of data from in vitro studies, neither of the two parameters could be fixed to observed values, though, and it was decided to both fit k_kinact_half and k_inact. Results showed that the observed PK profiles were in adequate agreement with the simulated PK, although the PK after administration of the lowest and highest dose (200 and 800 mg) was somewhat less accurately described. Importantly, the PK after administration of 300 mg and 400 mg - the only two approved doses - could be adequately captured, though.

3.1 Atazanavir final PK parameter tables

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

Compound: Atazanavir

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	50000 mg/l	Assumption	Assumption	True
Reference pH	7	Assumption	Assumption	True
Lipophilicity	2.12 Log Units	Publication-Hyland 2008, PMID: 18647303	Measurement	True
Fraction unbound (plasma, reference value)	0.14	Publication-Rajoli 2015, PMID: 25523214	Measurement	True
Specific intestinal permeability (transcellular)	9.8649602504E-06 cm/min	Parameter Identification	Optimized	True
Is small molecule	Yes			
Molecular weight	704.8555 g/mol	Internet-drugbank.ca		
Plasma protein binding partner	Unknown			

Calculation methods

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

Processes

Metabolizing Enzyme: CYP3A4-Optimized

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
Enzyme concentration	1 µmol/l	
Specific clearance	0 1/min	
CLspec/[Enzyme]	1.0383524966 l/µmol/min	Parameter Identification

Systemic Process: Glomerular Filtration-Clinical Pharmacology Review

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	2.014495446	Parameter Identification

Inhibition: CYP3A4-Perloff2005

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
kinact	0.0033009852632 1/min	Parameter Identification
K_kinact_half	0.1292581489 µmol/l	Parameter Identification

Inhibition: UGT1A1-InternalData

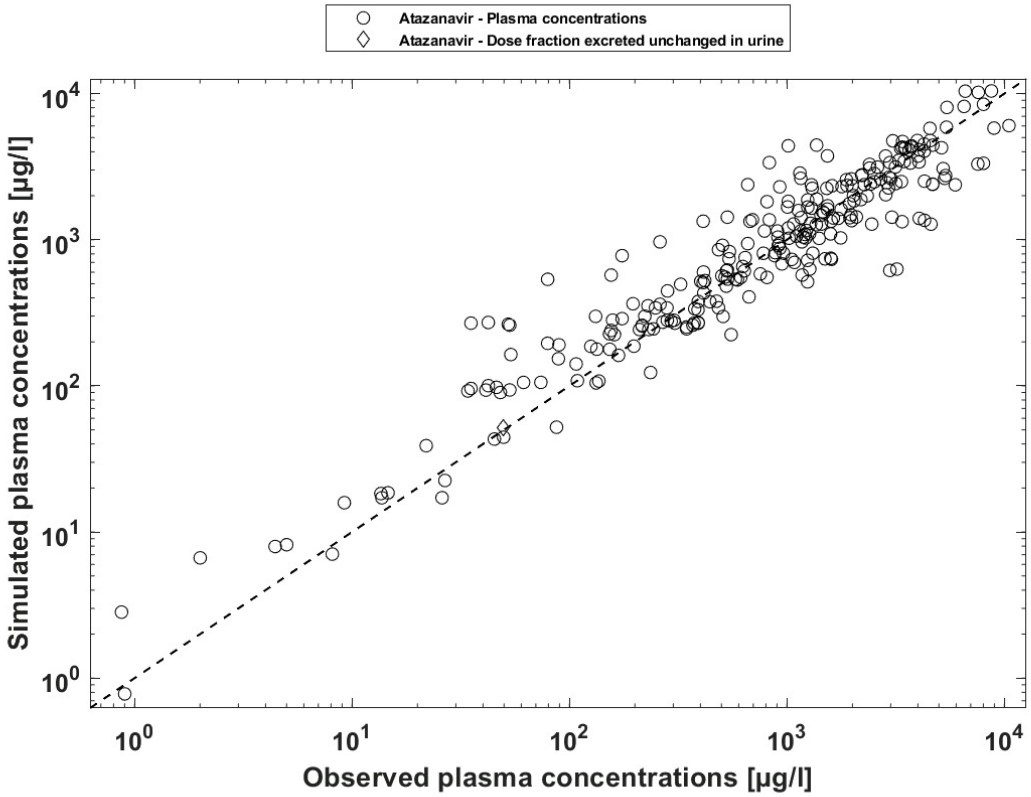
Molecule: UGT1A1

Parameters

Name	Value	Value Origin
Ki_c	0.1672 µmol/l	In Vitro-Calculated from reported Ki and fu,mic
Ki_u	0.7524 µmol/l	In Vitro-Calculated from reported Ki, fu,mic and alpha

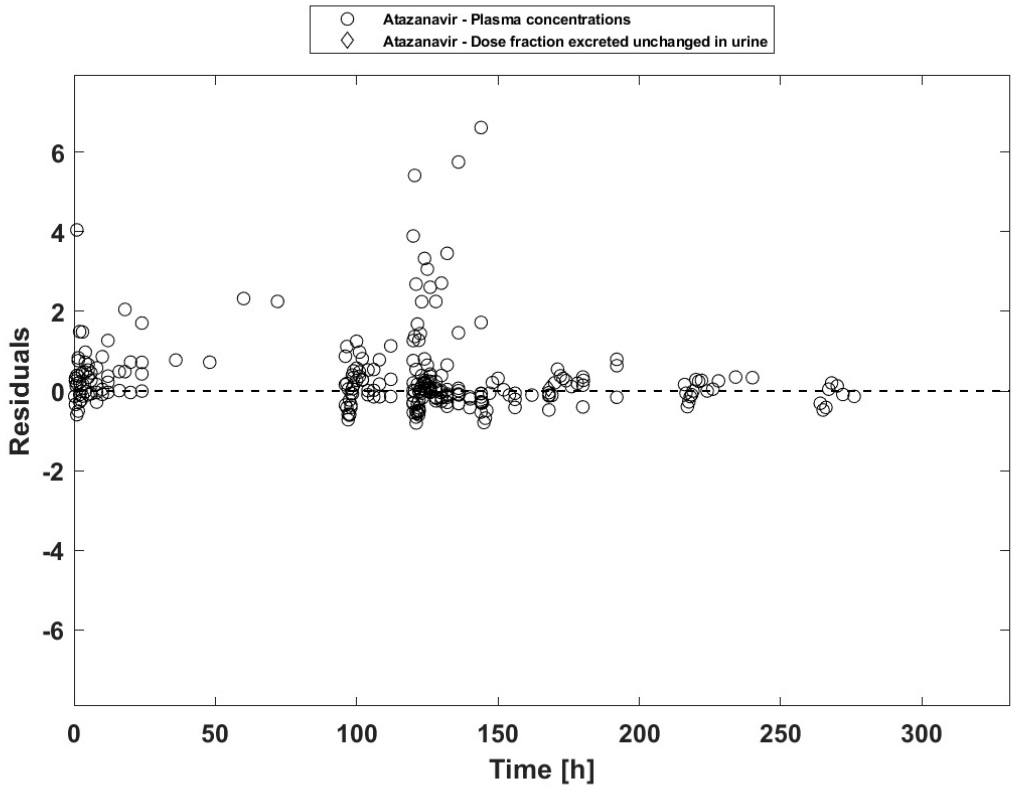
3.2 Atazanavir Diagnostics Plots

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



Goodness-of-fit visual diagnostic plots for atazanavir PBPK model performance: observed versus simulated plasma concentrations

GMFE = 1.496554

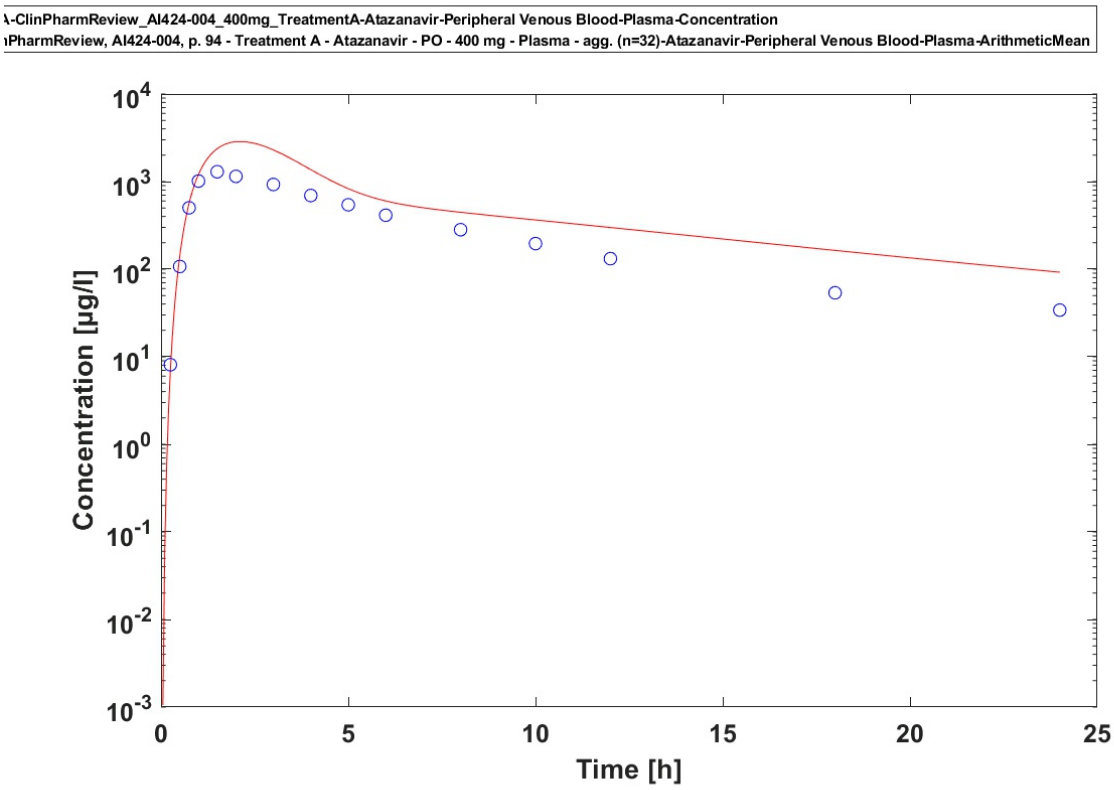


Goodness-of-fit visual diagnostic plots for atazanavir PBPK model performance: weighted residuals versus time

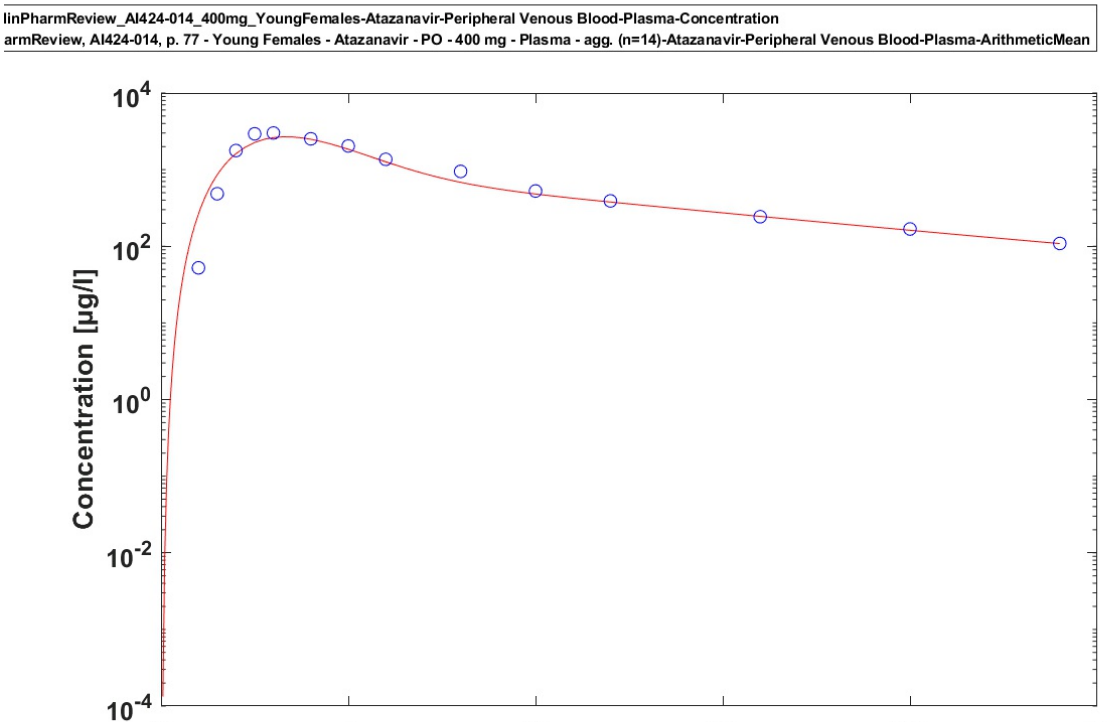
GMFE = 1.496554

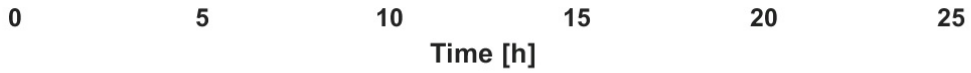
3.3 Atazanavir Concentration-Time profiles

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



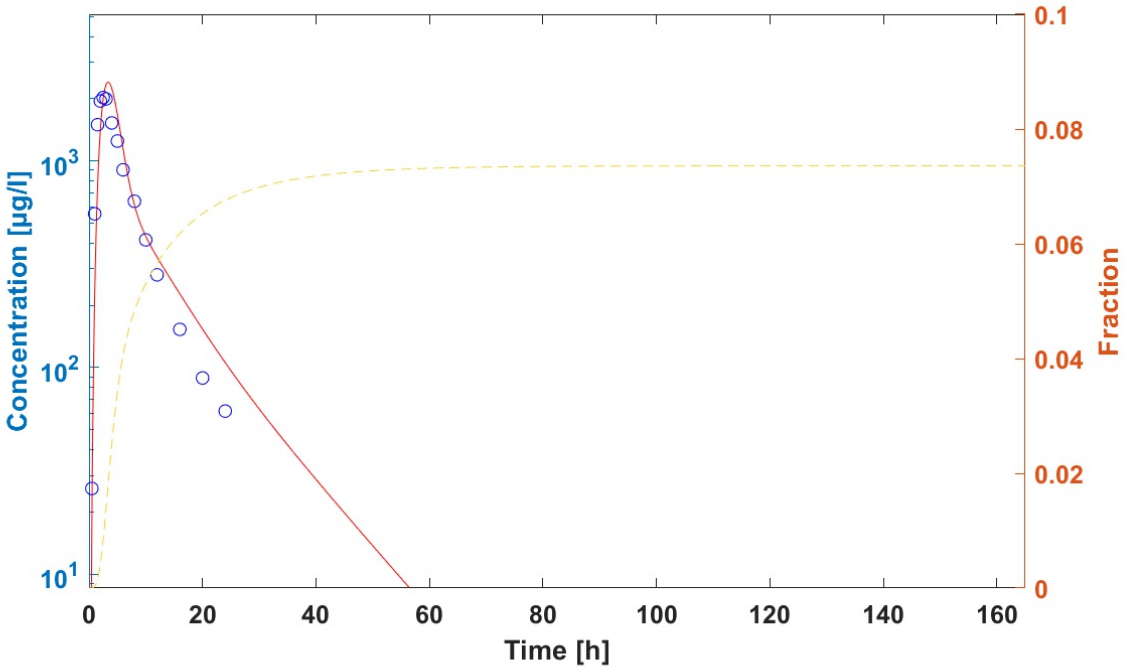
Time Profile Analysis





Time Profile Analysis

-ClinPharmReview_AI424-014_400mg_YoungMales-Atazanavir-Peripheral Venous Blood-Plasma-Concentration
-ClinPharmReview_AI424-014_400mg_YoungMales-Atazanavir-Kidney-Urine-Fraction excreted to urine
PharmReview, AI424-029, p. 47 - Urinary radioactivity - Atazanavir - PO - 400 - Urine - agg. (n=12)-Atazanavir-Kidney-Urine-ArithmeticMean
PharmReview, AI424-014, p. 77 - Young Males - Atazanavir - PO - 400 mg - Plasma - agg. (n=15)-Atazanavir-Peripheral Venous Blood-Plasma-ArithmeticMean



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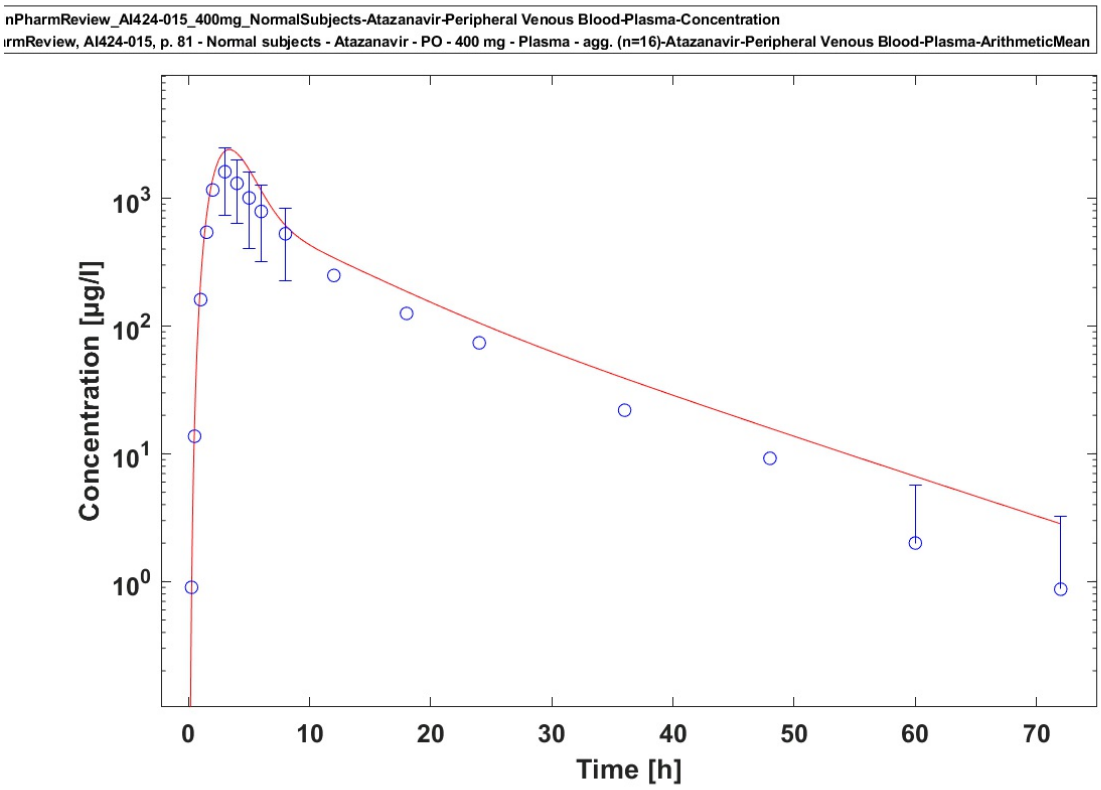

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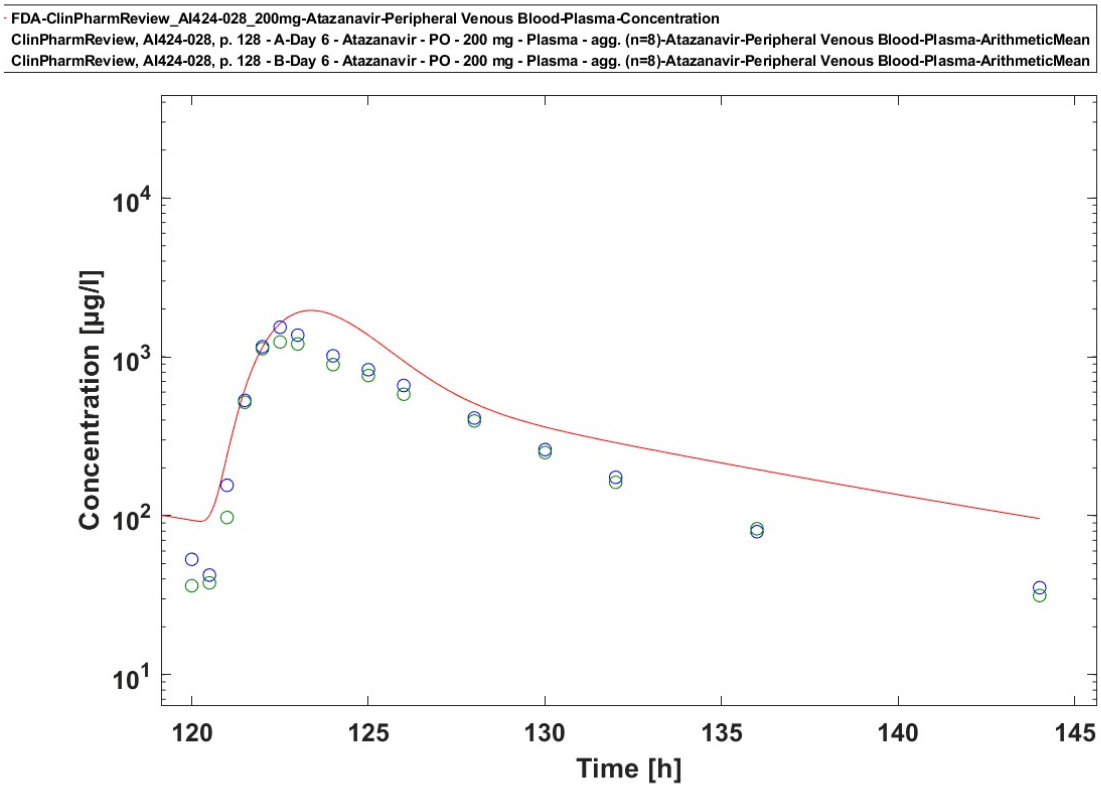

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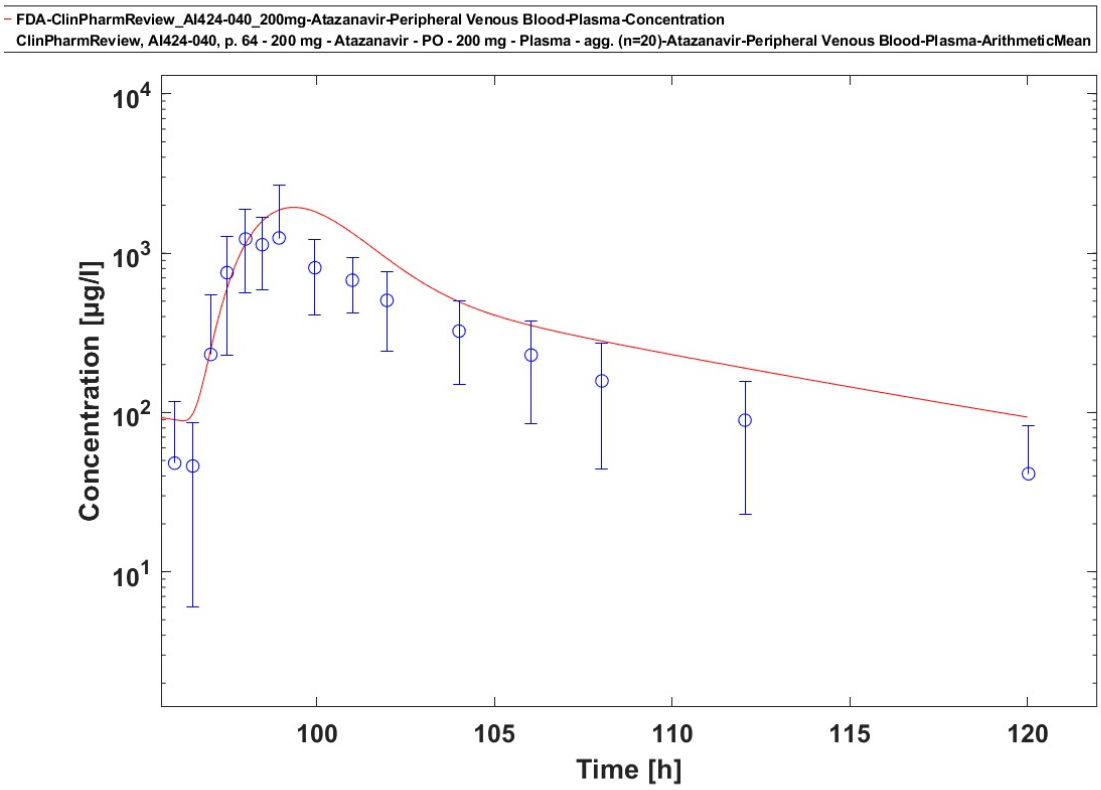

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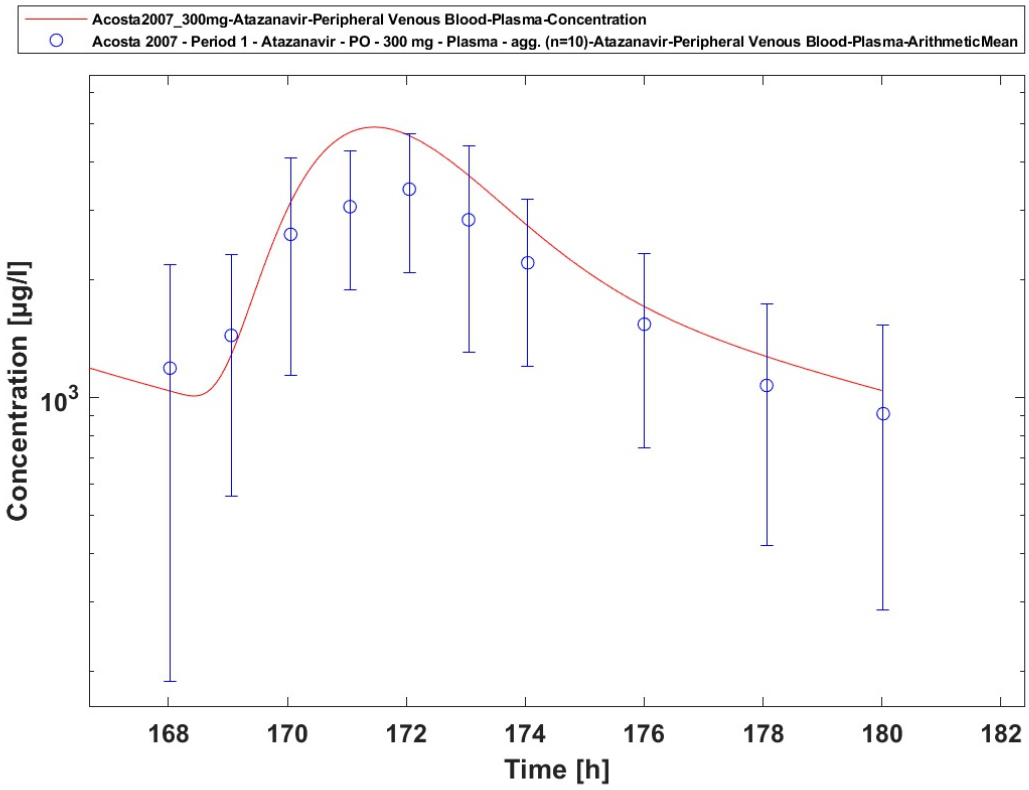

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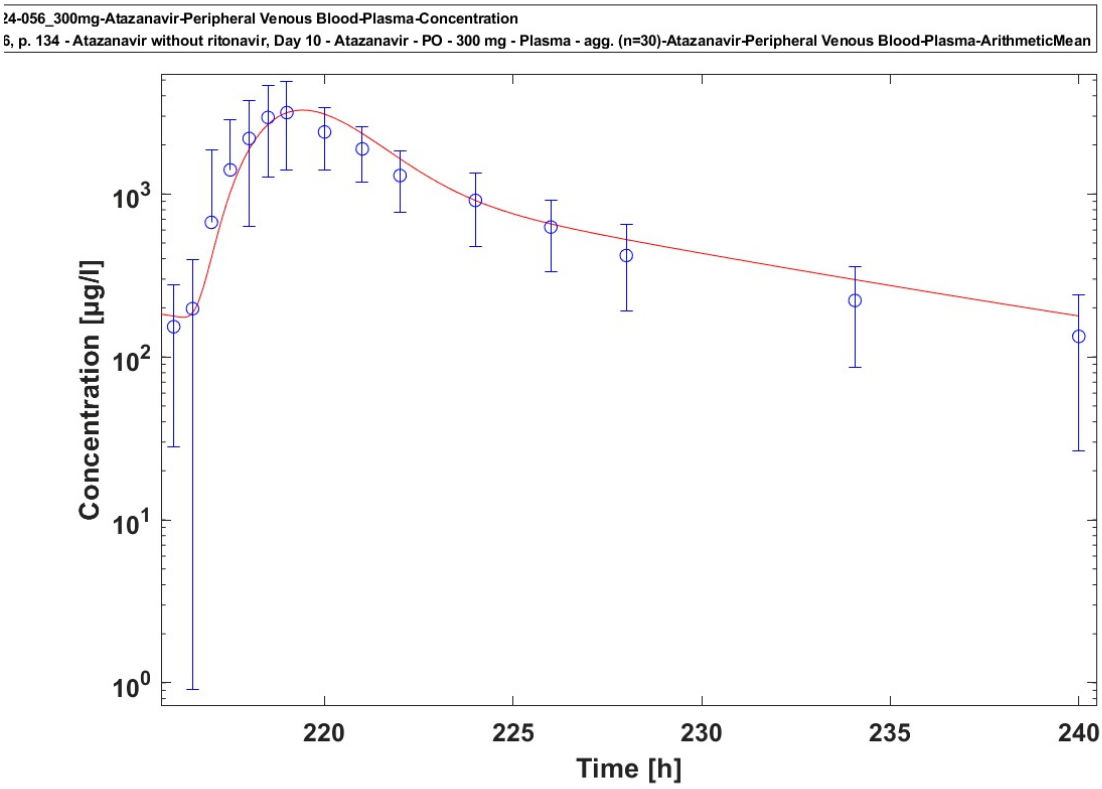

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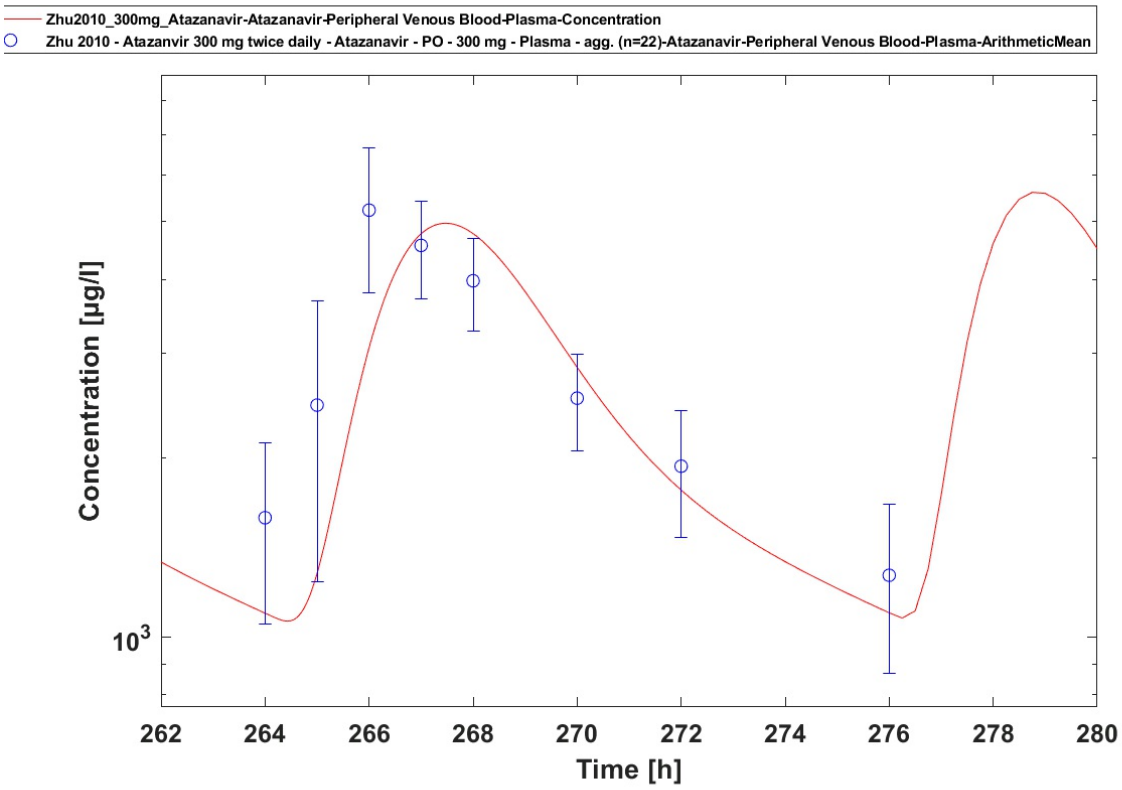

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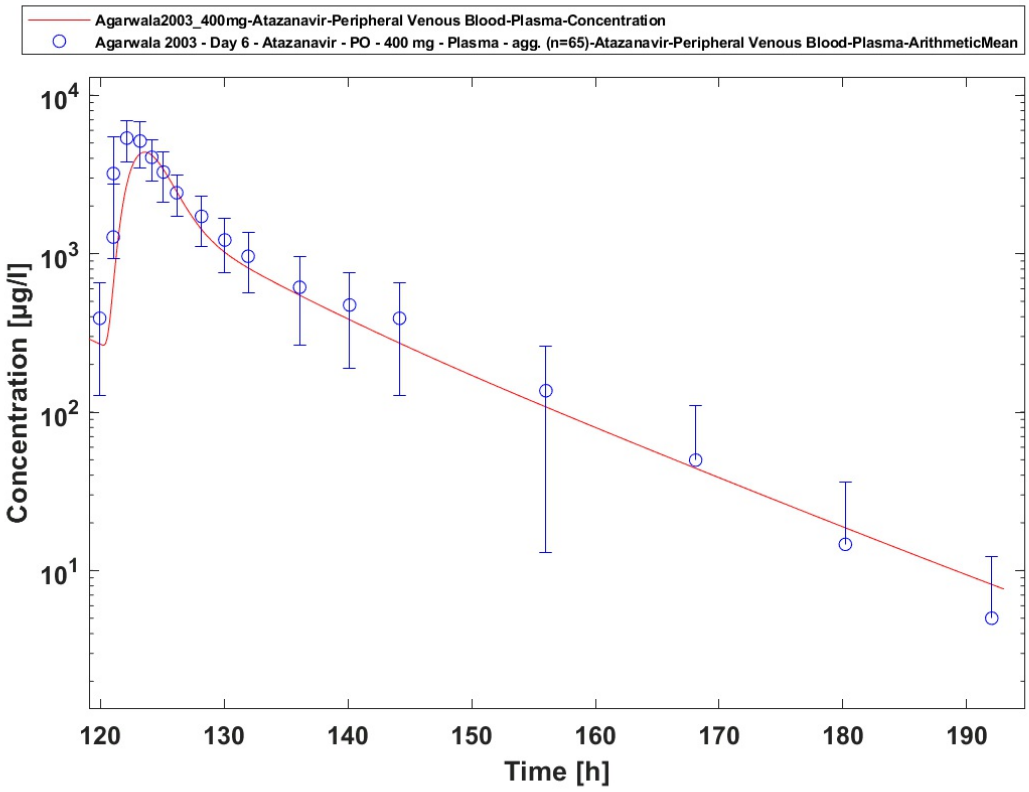

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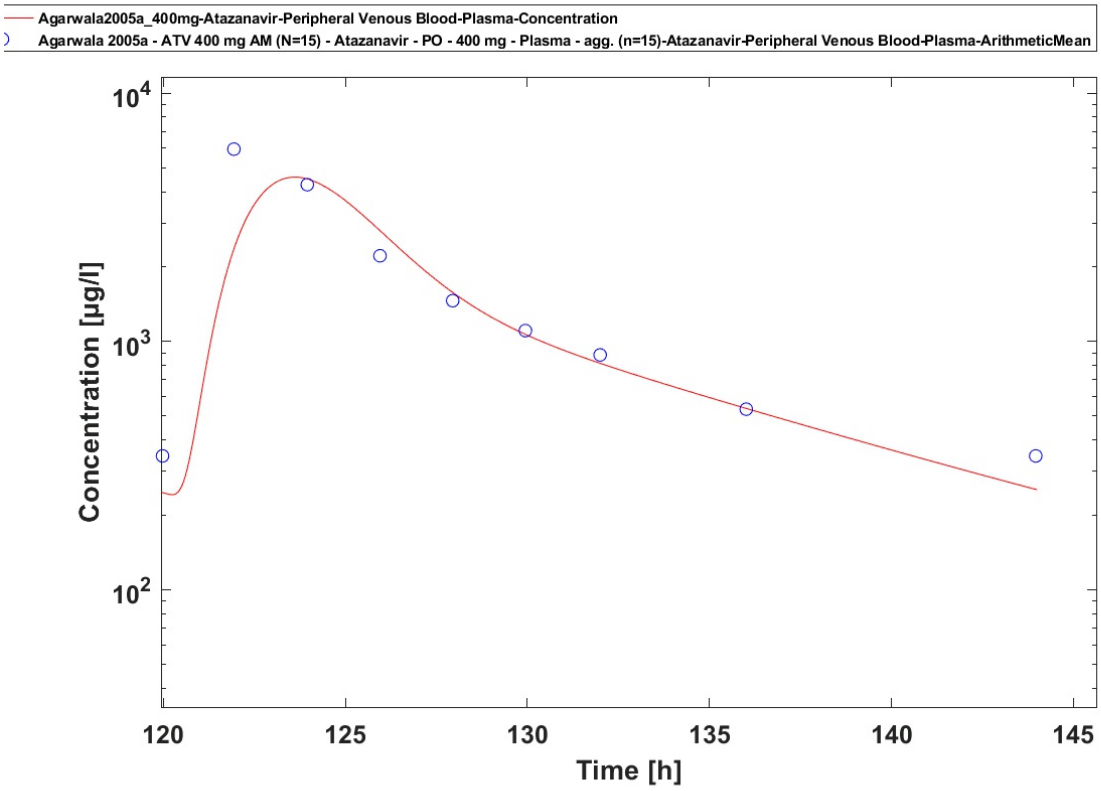

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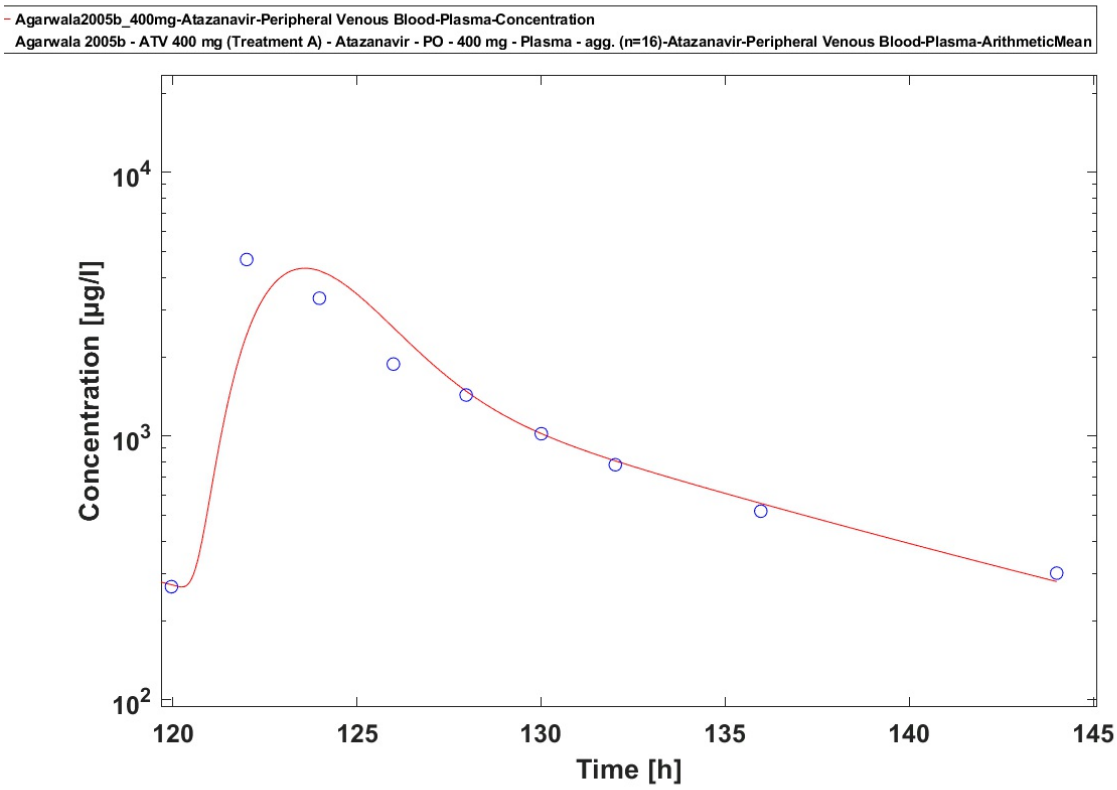

Time Profile Analysis

FDA-ClinPharmReview_AI424-028_400mg-Atazanavir-Peripheral Venous Blood-Plasma-Concentration
ClinPharmReview, AI424-028, p. 128 - D-Day 6 - Atazanavir - PO - 400 mg - Plasma - agg. (n=8)-Atazanavir-Peripheral Venous Blood-Plasma-ArithmeticMean
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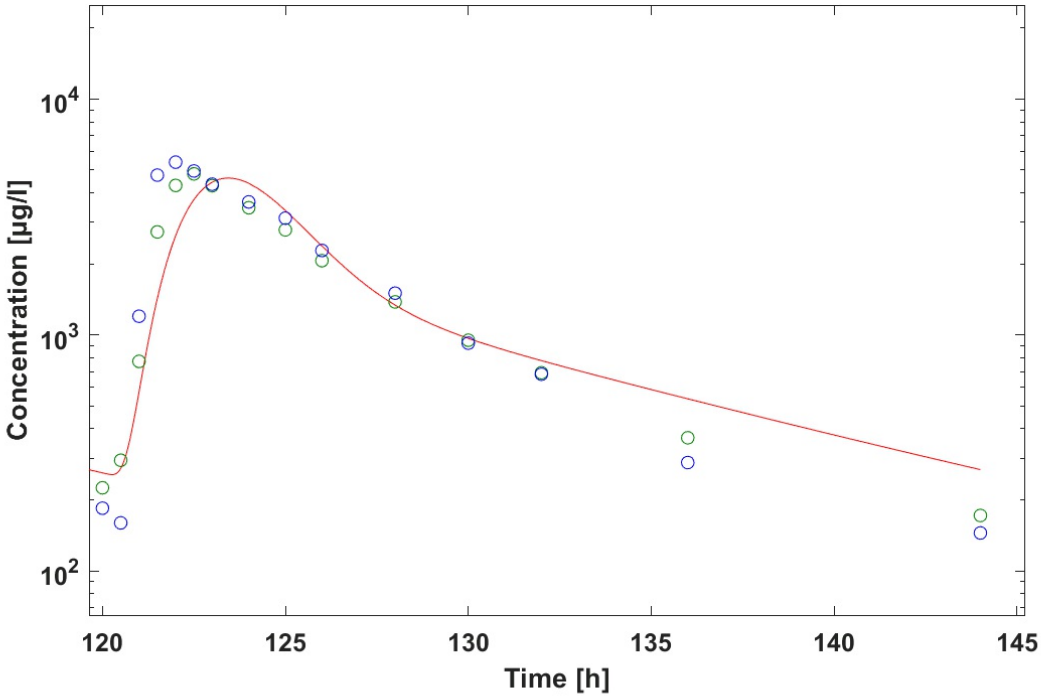

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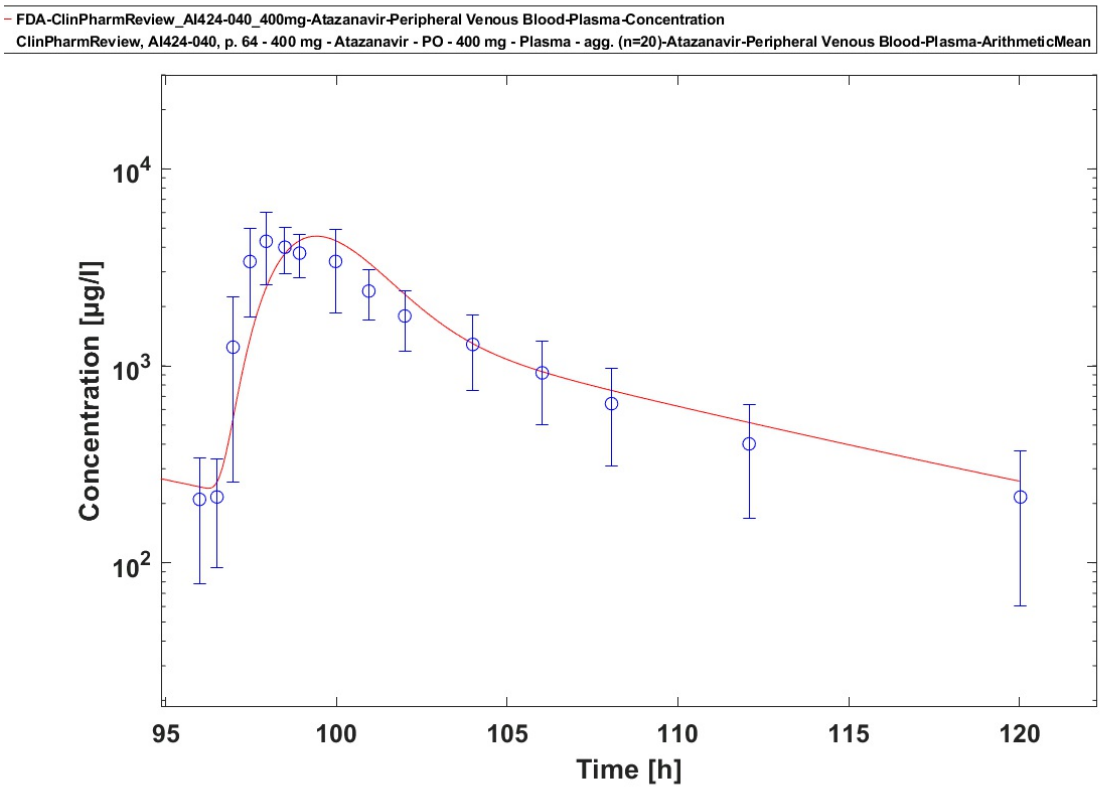

Time Profile Analysis

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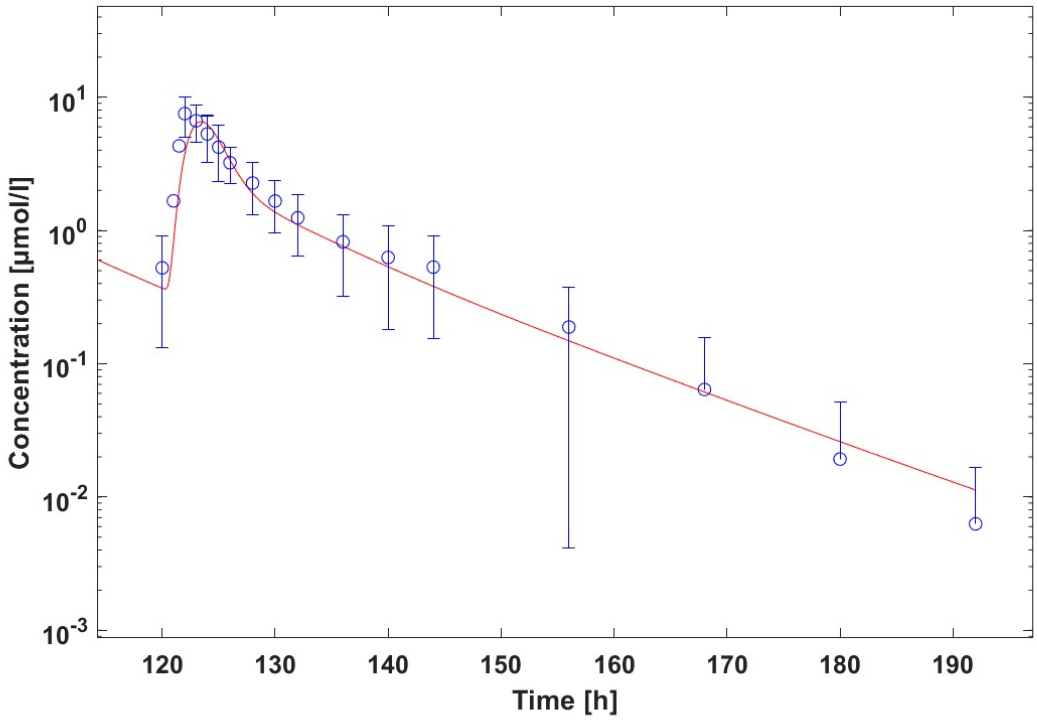

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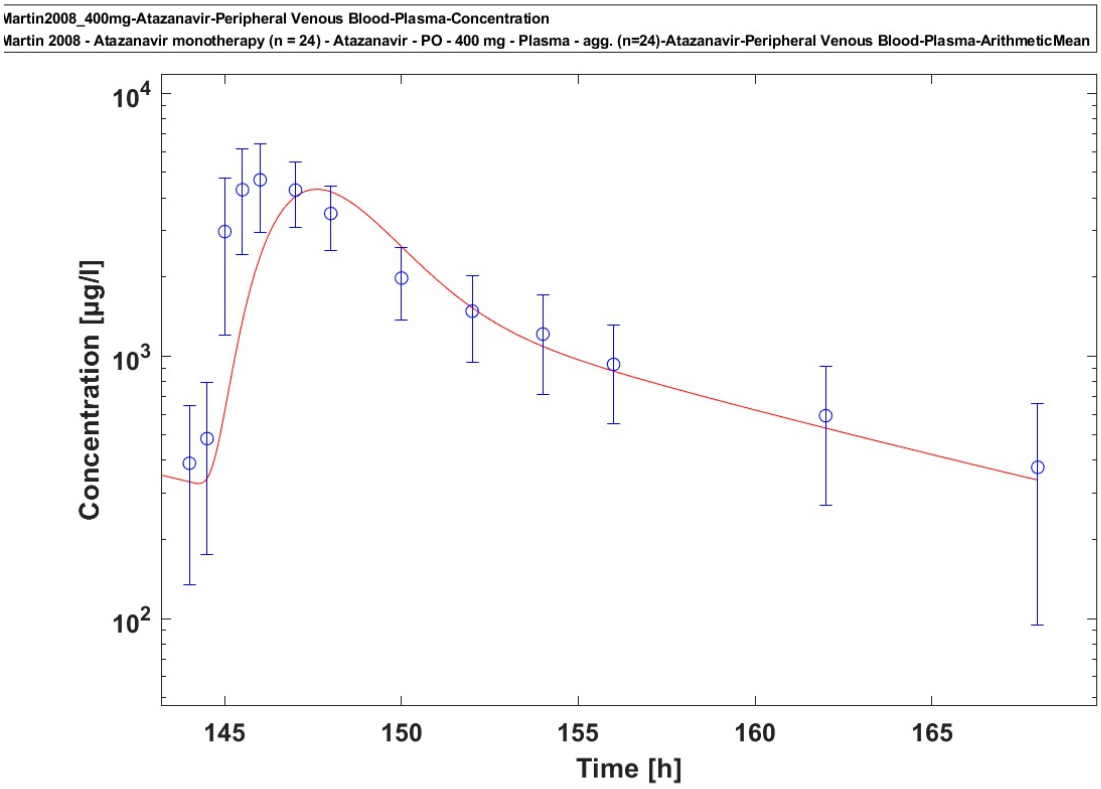

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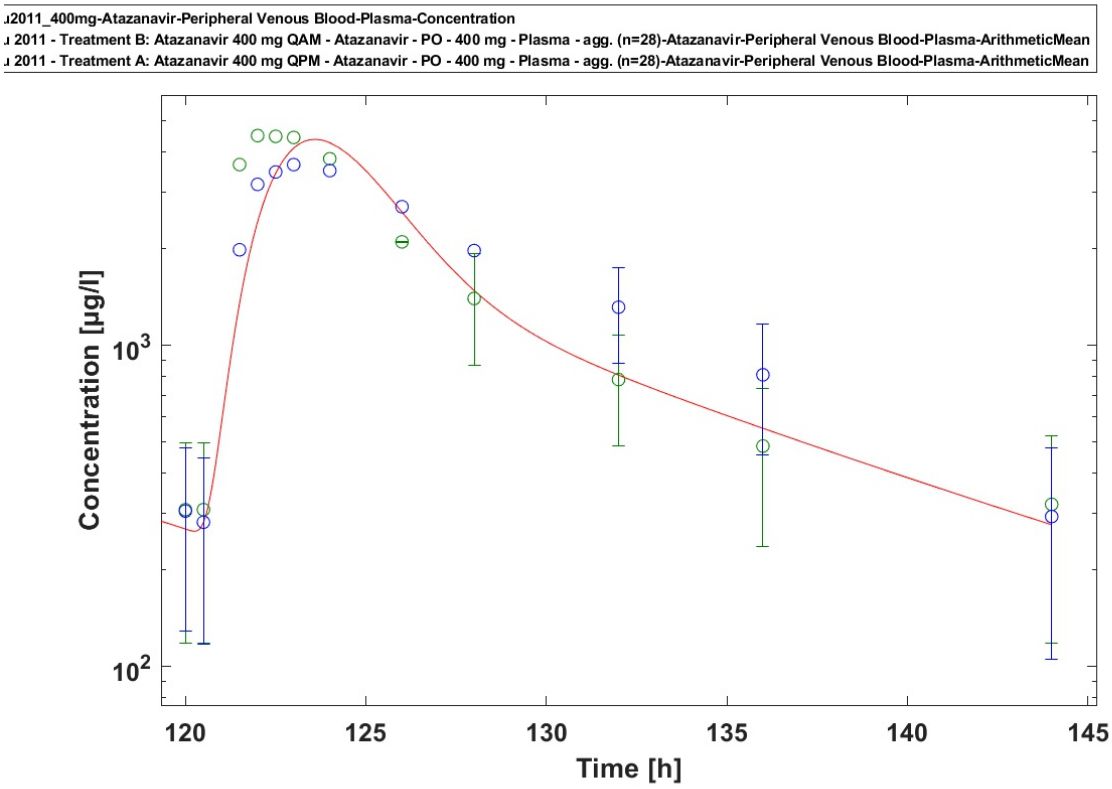

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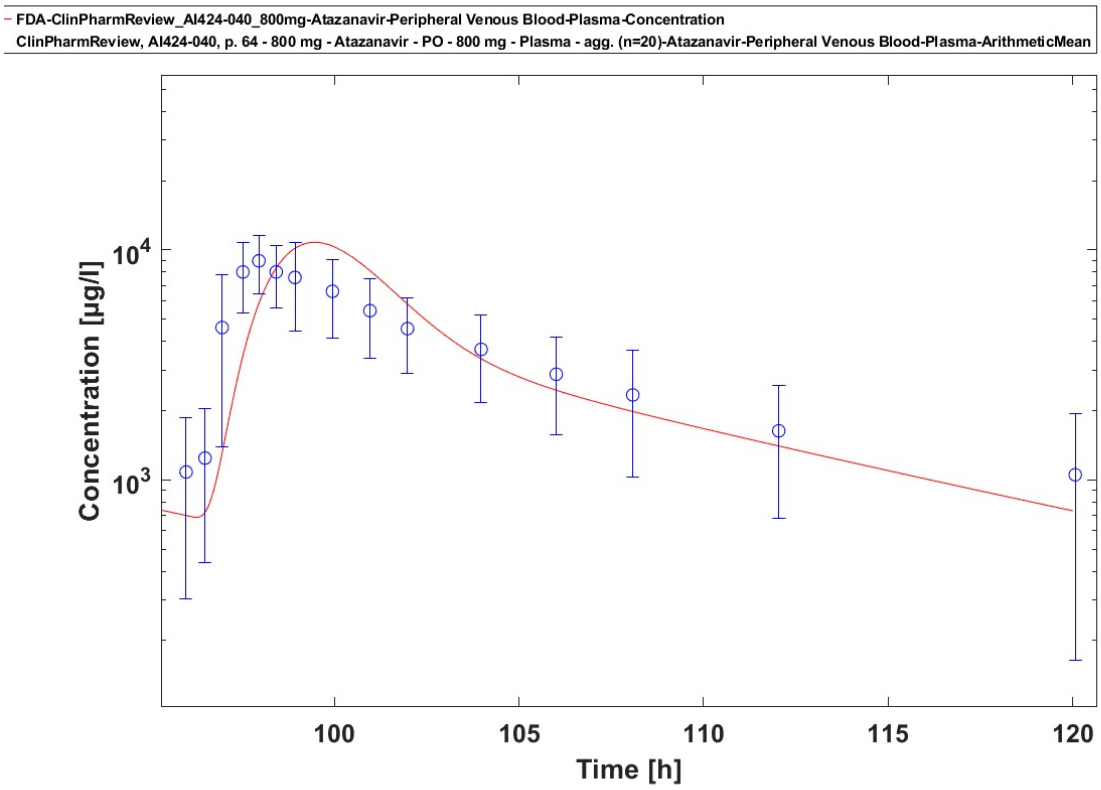

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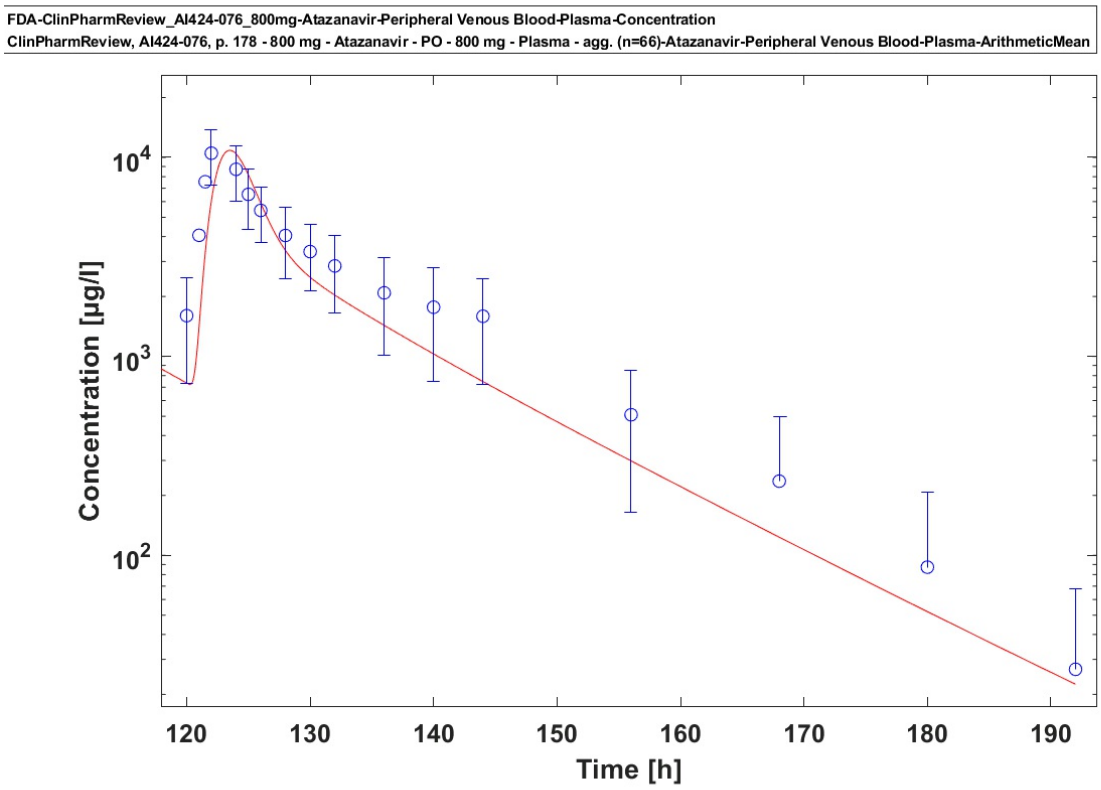

Time Profile Analysis

4 Conclusion

The final atazanavir PBPK model applies metabolism by CYP3A4, glomerular filtration and mechanism-based inhibition of CYP3A4. While the latter process has not been evaluated using another victim compound, it should only be regarded preliminary and further work is needed before this model can be applied to predict CYP3A4 DDIs. Overall, the model adequately describes the oral pharmacokinetics of atazanavir in healthy adults receiving approved atazanavir doses of 300 mg and 400 mg.

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