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

Version	0.1
OSP Version	8.0
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Table of Contents

1 Introduction

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

Alprazolam, sold under the trade names Xanax and Solanax, among others, belongs to the group of benzodiazepines and is commonly used in short term management of anxiety disorders. It is generally administered orally as immediate release or extended release tablet, but other forms are also available, e.g. solution or sublingual tablet.

Following oral administration, alprazolam is rapidly absorbed with an absolute bioavailability ranging from 80% to 100% (Greenblatt 1993). Absorption is independent of the dose and the relative bioavailability of solid and liquid dosage forms has been observed to be similar (Dawson 1984). Alprazolam is widely distributed throughout the body and its free fraction in plasma, averaging around 30%, is not influenced by total alprazolam concentrations within the tested range of 0.01 to 10 mg/L (Moschitto 1983). Alprazolam is extensively metabolized to various metabolites (von Moltke 1993). The two major metabolites, α-hydroxy-alprazolam and 4-hydroxy-alprazolam, are formed through oxidation catalyzed by CYP3A (Eberts 1980, von Moltke 1993). Within 72 h of a 2 mg oral dose of ^{14}C-alprazolam, 20% of the dose have been observed to be excreted unchanged in urine (Eberts 1980). Alprazolam displays dose linear pharmacokinetics and does not accumulate during multiple dose treatment (Dawson 1984, Greenblatt 1993).

The presented alprazolam PBPK model was developed for intravenous (IV) administration and oral (PO) administration of the immediate release tablet given in fasted state in healthy, non-obese adults; extended-release formulations and administration in fed state were not addressed here. The PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (https://github.com/Open-Systems-Pharmacology/Alprazolam-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). 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).

The PBPK model was developed based on clinical data of healthy, non-obese, adult subjects obtained from the literature, covering different single doses of alprazolam administered intravenously or orally as immediate release tablet in the fasted state. Sustained release formulations of alprazolam were not considered here. Mass balance information on urinary excretion of unchanged ^{14}C-alprazolam after PO administration was also accounted for during the model building process.

Unknown parameters were simultaneously optimized using all available PK data, in particular:

- 10 data sets following single IV administration of 6 different doses of alprazolam (0.25 mg, 0.5 mg, 1 mg, 1.576 mg, 2 mg, 4 mg)
- 16 data sets following single PO administration of 3 different doses of alprazolam as immediate release tablet and ^{14}C-alprazolam (0.5 mg, 1 mg, 2 mg)

Structural model selection was mainly guided by visual inspection of the resulting description of data and biological plausibility. The following parameters were identified using the Parameter Identification module provided in PK-Sim® and MoBi® (Open Systems Pharmacology Documentation):

- `Dissolution time (50% dissolved)`
- `Dissolution shape`
- `Specific intestinal permeability`
- `Mucosa permeability (interstitial<->intracellular)`
- `Lipophilicity`
- `Metabolizing Enzyme - CYP3A4 - kact`
- `GFR fraction`

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 / physicochemical data

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

Parameter	Unit	Literature	Description
Molecular weight	g/mol	308.765 (drugbank.ca)	Molecular weight
pK_a (basic)		2.40 (Cho 1983, Raymond 1986); 2.48 ± 0.01 (Manchester 2018)	Acid dissociation constant

Parameter	Unit	Literature	Description
logP		2.19 (Machatha 2004); 2.92 (Capobianco 1994)	Partition coefficient between octanol and water
logD		3.06 (Greenblatt 1983)	Partition coefficient between octanol and water at physiological pH
f_u		0.20 (Eberts 1980); 0.233 ± 0.028[a] (Schmith 1991); 0.270 ± 0.017[a] (Scavone 1988); 0.284 ± 0.017[a] (Scavone 1988); 0.290 ± 0.025[a] (Juhl 1984); 0.298 [0.259 - 0.316][b] (Abernethy 1983); 0.311 ± 0.026[a] (Ochs 1986); 0.316[c] (Moschitto 1983)	Fraction unbound in human plasma of healthy adults
Water solubility (pH 1.2)	mg/L	12 (drugbank.ca)	Estimated solubility in water at pH 1.2
Water solubility (pH 7.0)	mg/L	40 (drugbank.ca)	Estimated solubility in water at pH 7.0
Water solubility	mg/L	73 (Loftsson 2006)	Experimentally measured solubility in water at 22°C - 24°C

[a] mean ± SD

[b] mean [range]

[c] mean

2.2.2 Clinical data

A literature search was carried out to collect alprazolam PK data in healthy adults.

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

Publication	Study description
Adams 1984	IV administration of 0.25 mg and 4 mg
Bertz 1997	IV administration of 2 mg
Eberts 1980	PO administration of 2 mg ^{14}C-alprazolam
Eller 1990	PO administration of 1 mg
Fleishaker 1989	IV administration of 1 mg
Friedman 1991	PO administration of 1 mg
Greenblatt 1988	PO administration of 1 mg
Greenblatt 1992	PO administration of 1 mg
Greenblatt 1998	PO administration of 1 mg
Greenblatt 2000	PO administration of 1 mg
Juhl 1984	PO administration of 1 mg
Kaplan 1998	PO administration of 1 mg
Kirkwood 1991	PO administration of 1 mg
Kroboth 1988	IV administration of 0.5 mg, 1 mg followed by 72 µg over 8 h, and 2 mg
Lin 1988	IV administration of 0.5 mg and PO administration of 0.5 mg
Schmider 1999	PO administration of 1 mg
Schmith 1991	PO administration of 0.5 mg and 2 mg
Smith 1984	IV administration of 1 mg and PO administration of 1 mg
Venkatakrishnan 2005	IV administration of 1 mg
Wennerholm 2005	PO administration of 1 mg

2.3 Model Parameters and Assumptions

2.3.1 Dissolution and absorption

Dissolution of the immediate release tablet of alprazolam was described by a Weibull function with the two parameters `Dissolution shape` and `Dissolution time (50% dissolved)` being fitted to observed PK data. Sustained release formulations of alprazolam were not considered here. Although alprazolam is sparingly soluble in water, no solubility limitation was observed in the model using a solubility value of 40 mg/L (pH 7.0). `Specific intestinal permeability (transcellular)` was also optimized to better match the observed PK data.

2.3.2 Distribution

In the model, the `fraction unbound (plasma, reference value)` was set to 0.233 which is the average value measured in young male subjects (Schmith 1991). Slightly higher values around 0.30 have been reported for mid-aged subjects (Juhl 1984, Ochs 1986) which have not been applied in the current model. `Lipophilicity` was optimized within the range of reported values for logP or logD (1.26 - 2.19, Greenblatt 1983, Machatha 2004) to better match the observed PK data. The observed PK data were found to be best described using the model for estimating intracellular-to-plasma partition coefficients according to the method by `Rodgers and Rowland` (Rodgers 2005, Rodgers 2006). Cellular permeabilities were automatically calculated using the method `PK-Sim Standard` (Open Systems Pharmacology Documentation).

2.3.3 Elimination

Alprazolam is extensively metabolized via CYP3A to give two major metabolites, α-hydroxy-alprazolam and 4-hydroxy-alprazolam. In the model, these two biotransformation pathways were described by Michaelis-Menten kinetics. The `Km` values for each pathway were fixed to reported literature values, namely 269 μmol/L for the α-OH pathway and 704 μmol/L for the 4-OH pathway (Hirota 2001), and the `kcat` values were optimized to better match the observed PK data while keeping the ratio between both values constant (by selecting the option `Use as Factor`). 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 ^{14}C-alprazolam, 20% of the dose have been recovered unchanged in urine (Eberts 1980). This information was accounted for in the model by implementing a glomerular filtration process and optimizing the `GFR fraction` to match the observed dose fraction excreted unchanged in urine.

3 Results and Discussion

The PBPK model for alprazolam was developed and verified with clinical pharmacokinetic data.

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: Section 3.3.

3.1 Final input parameters

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

Compound: Alprazolam

Parameters

Name	Value	Value Origin	Alternative	Default	
Solubility at reference pH	40 mg/l		Measurement	True	
Reference pH	7		Measurement	True	
Lipophilicity	2.0756837827 Log Units	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2019-10-21 16:26	Optimized	True	
Fraction unbound (plasma, reference value)	0.233	Publication-In Vivo-PMID: 1880224	Measurement	True	
Specific intestinal permeability (transcellular)	0.1369893967 cm/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2019-10-21 16:26	Optimized	True	
Cl	1				
Is small molecule	Yes				
Molecular weight	308.765 g/mol				
Plasma protein binding partner	Unknown				

Calculation methods

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

Processes

Metabolizing Enzyme: CYP3A4-alpha-OH pathway

Molecule: CYP3A4

Parameters

Name	Value	Value Origin	
In vitro Vmax for liver microsomes	0.131 nmol/min/mg mic. protein	Publication-In Vitro-PMID: 11745908	
Km	269 µmol/l	Publication-In Vitro-PMID: 11745908	
kcat	0.7777214266 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2019-10-21 16:26	

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

Name	Value	Value Origin	
GFR fraction	0.5426032482	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2019-10-21 16:26	

Metabolizing Enzyme: CYP3A4-4-OH pathway

Molecule: CYP3A4

Parameters

Name	Value	Value Origin	
In vitro Vmax for liver microsomes	2.23 nmol/min/mg mic. protein	Publication-In Vitro-PMID: 11745908	
Km	704 µmol/l	Publication-In Vitro-PMID: 11745908	
kcat	13.2390746671 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2019-10-21 16:26	

Formulation: Weibull_Xanax

Type: Weibull

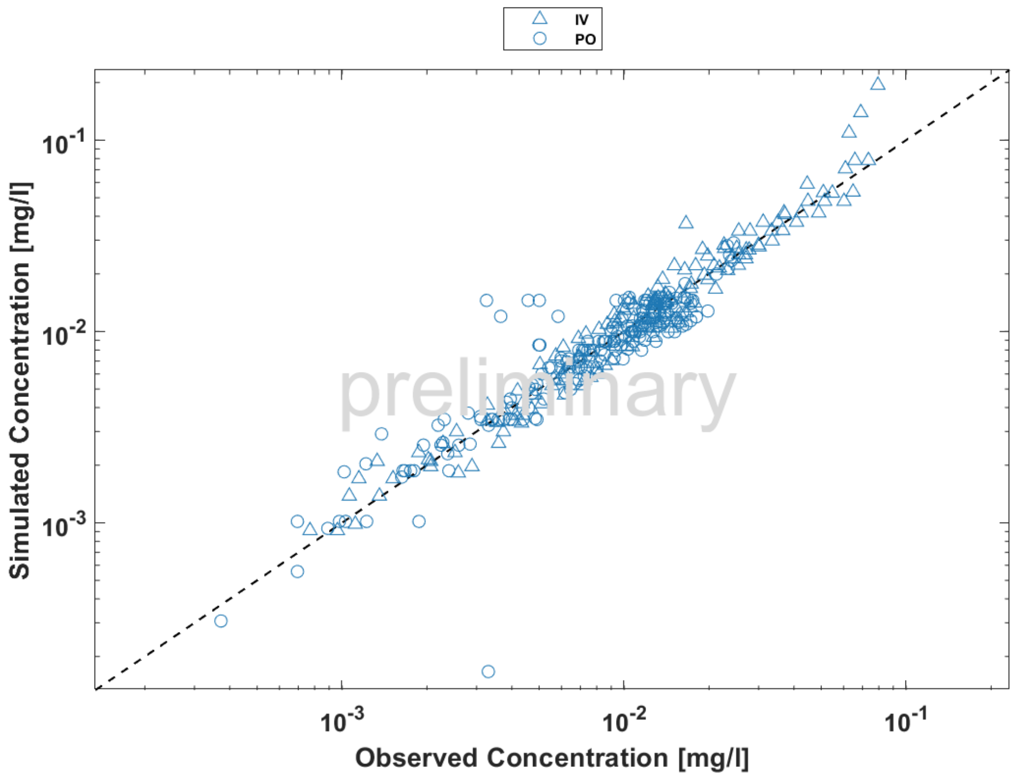
Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	0.001438691456 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2019-10-21 16:26	
Lag time	0 min		
Dissolution shape	0.7012076697	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification' on 2019-10-21 16:26	
Use as suspension	Yes		

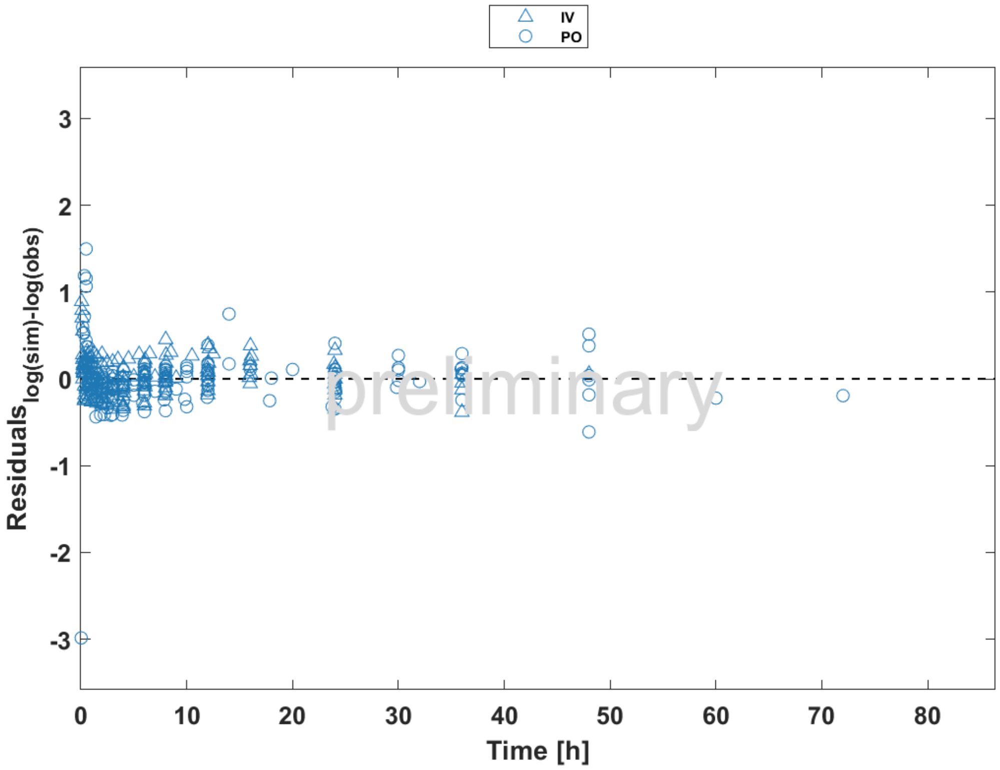
3.2 Diagnostics Plots

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 plot for concentration in plasma

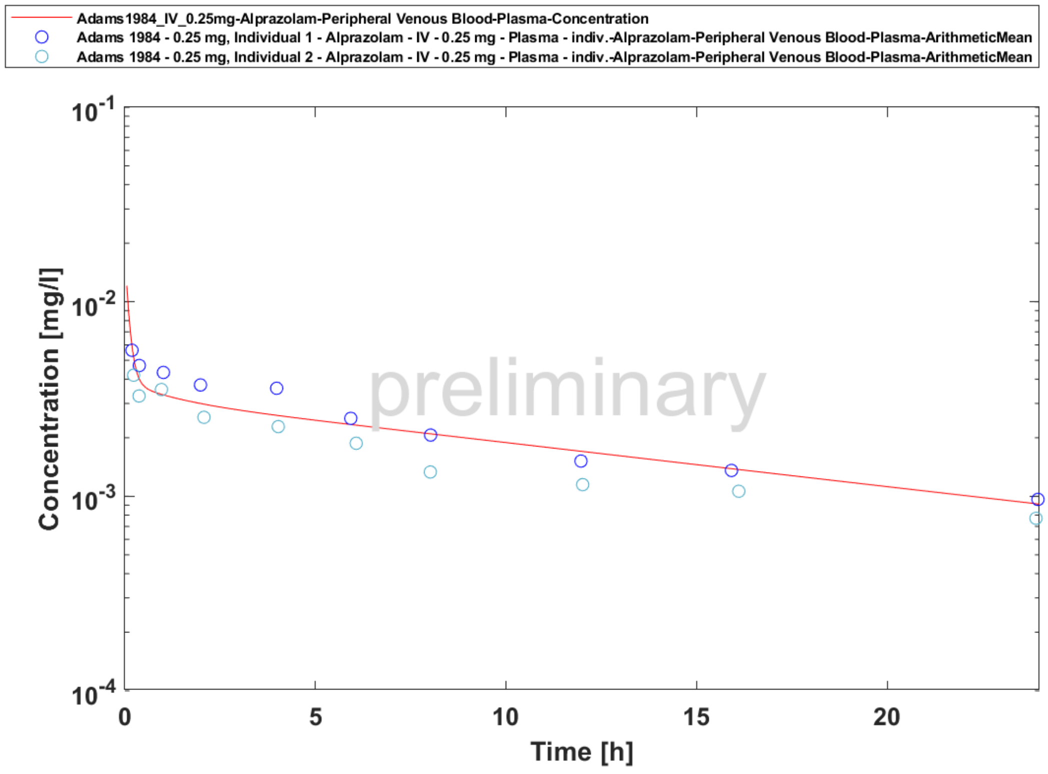


Goodness of fit plot for concentration in plasma

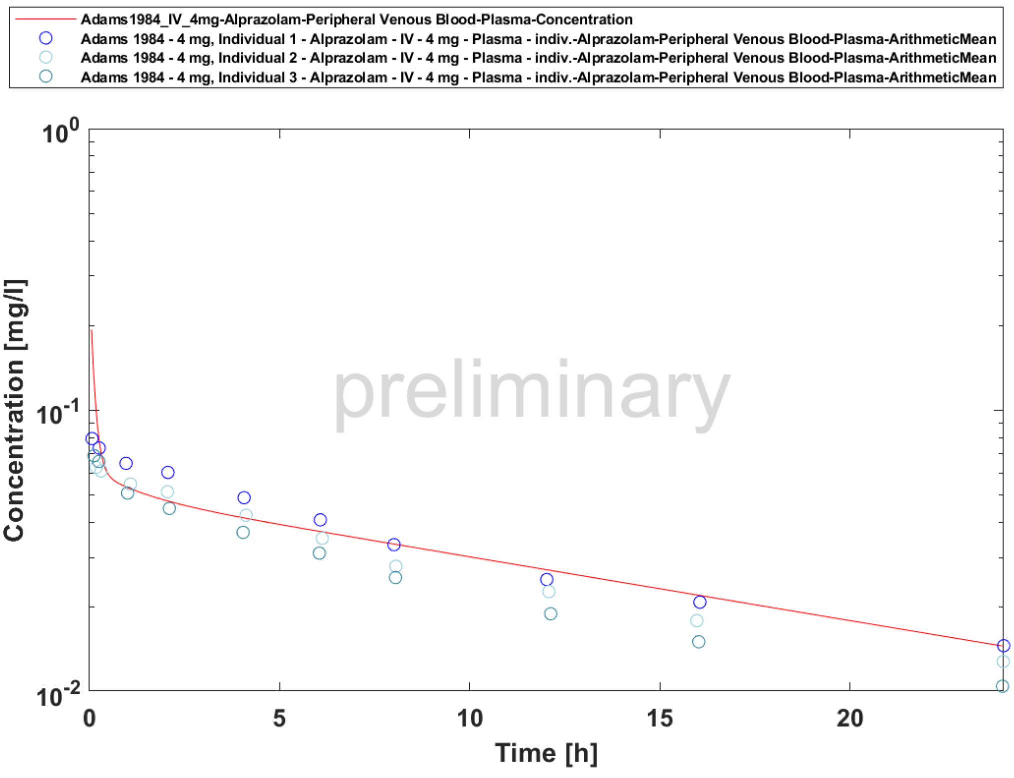
GMFE = 1.198649

3.3: Concentration-Time Profiles

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



Time Profile Analysis



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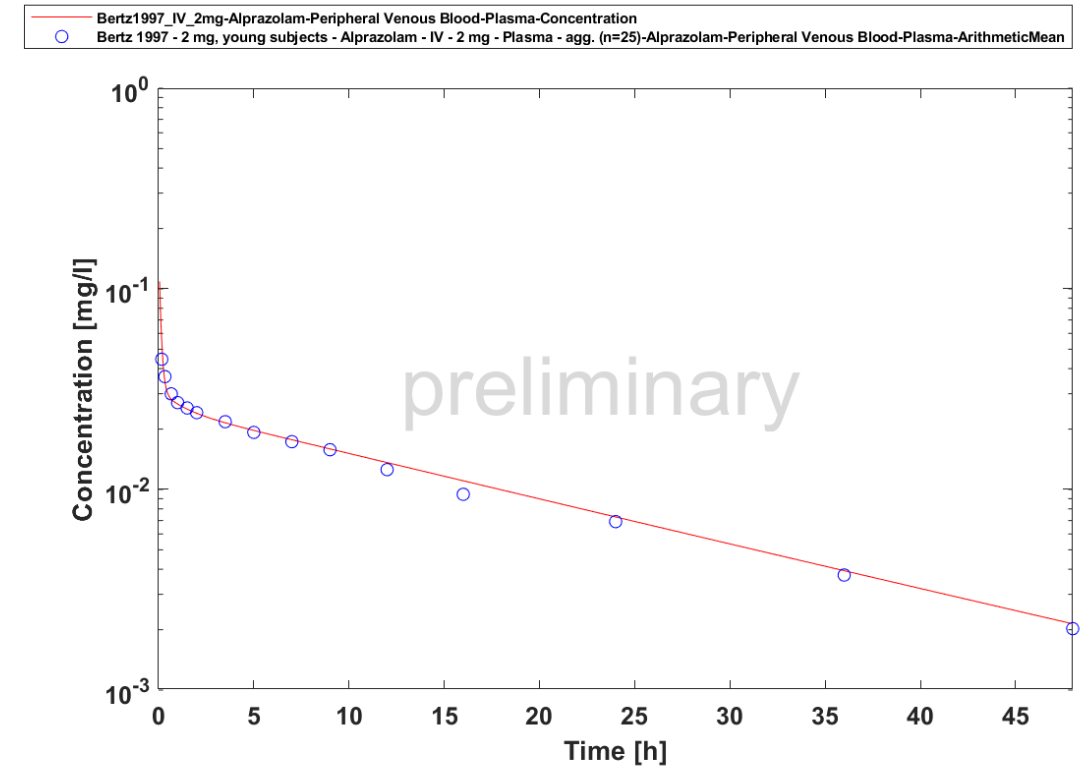

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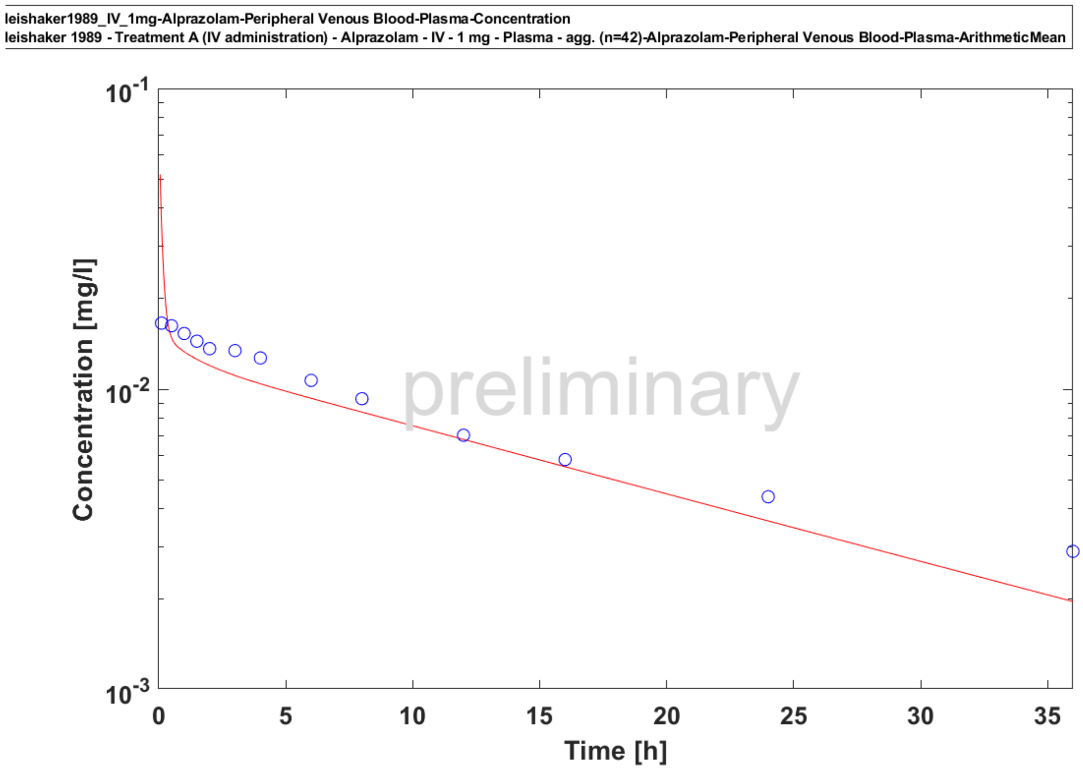

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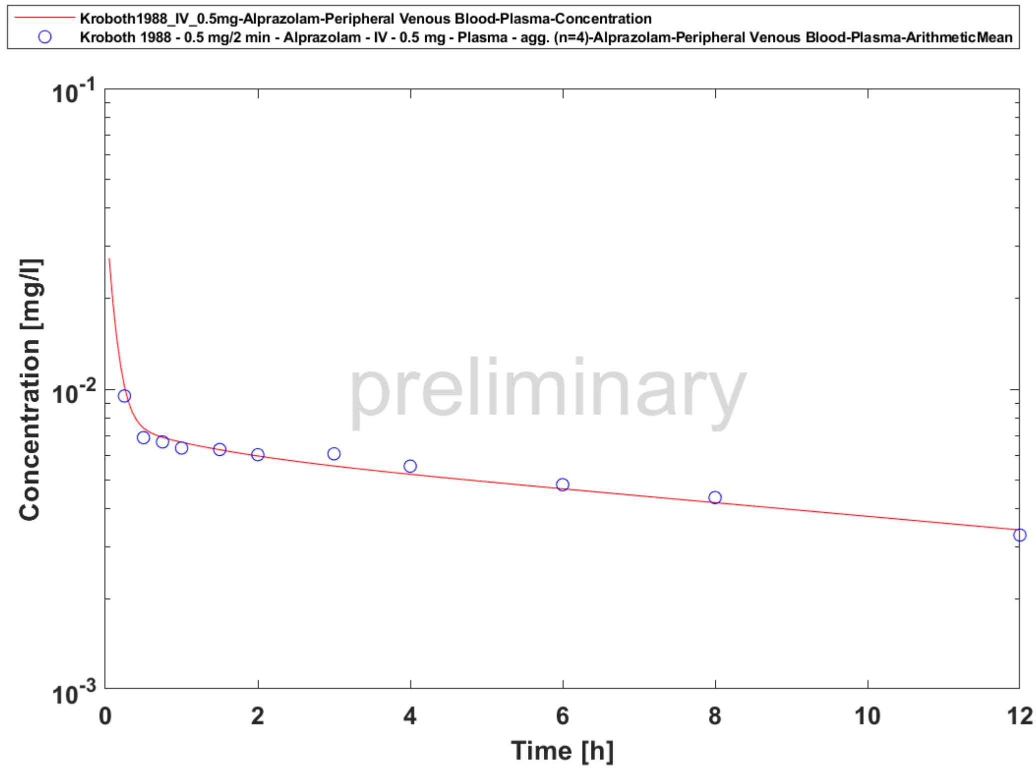

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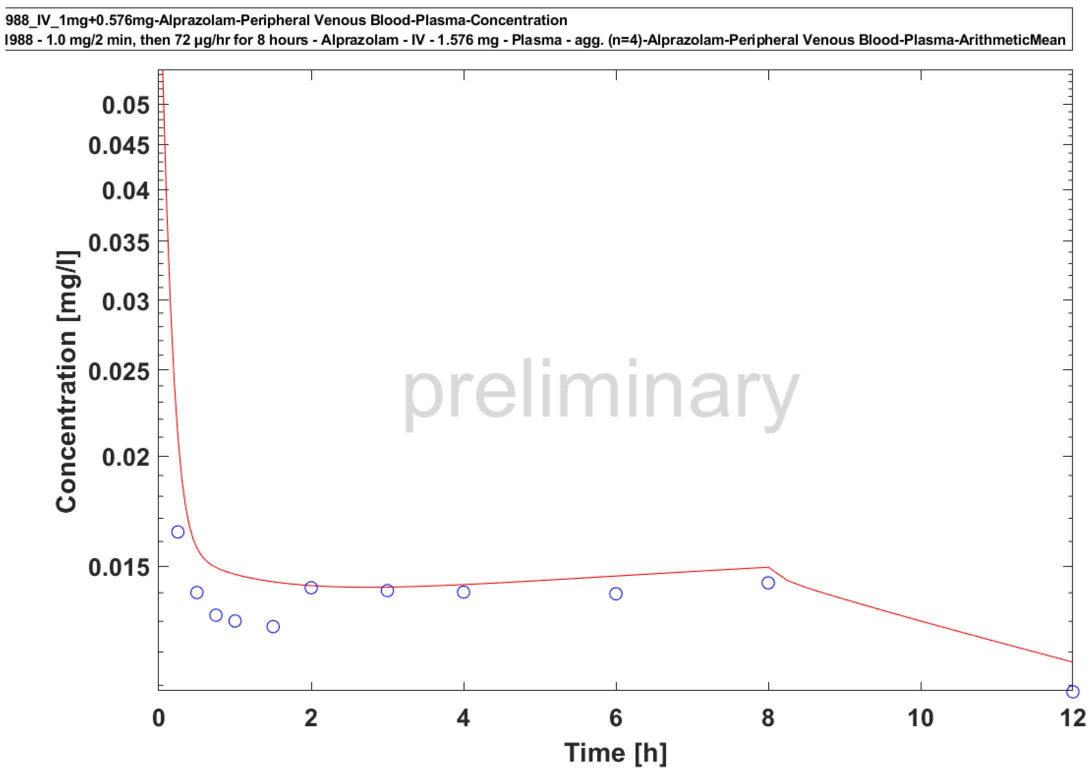

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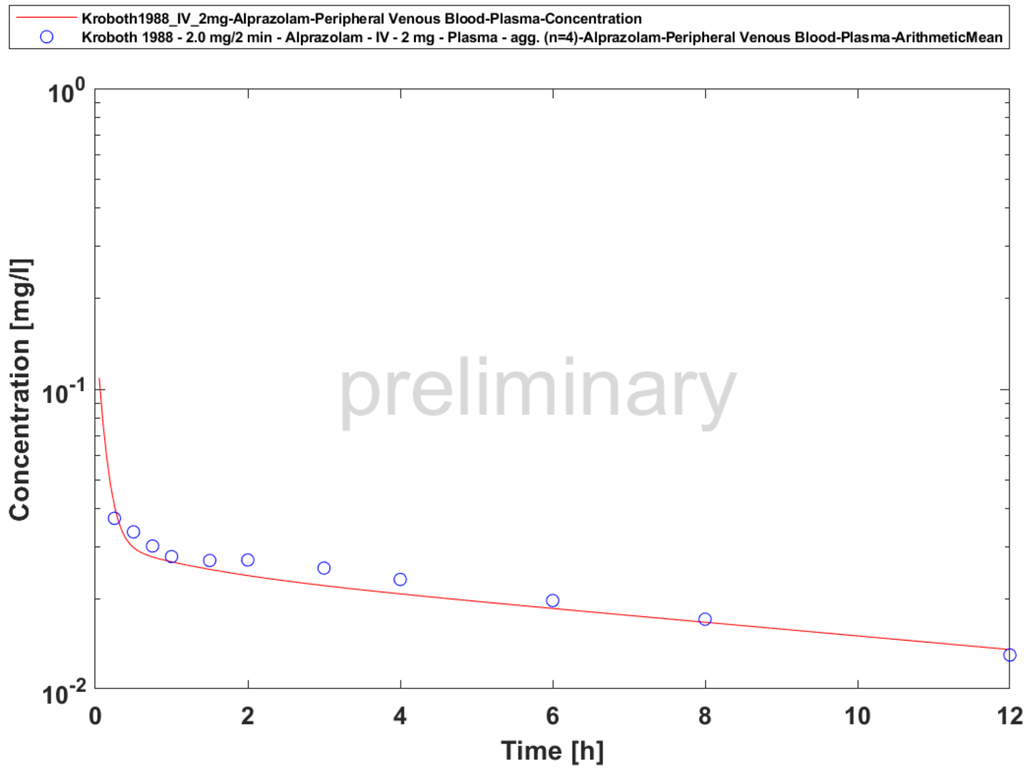

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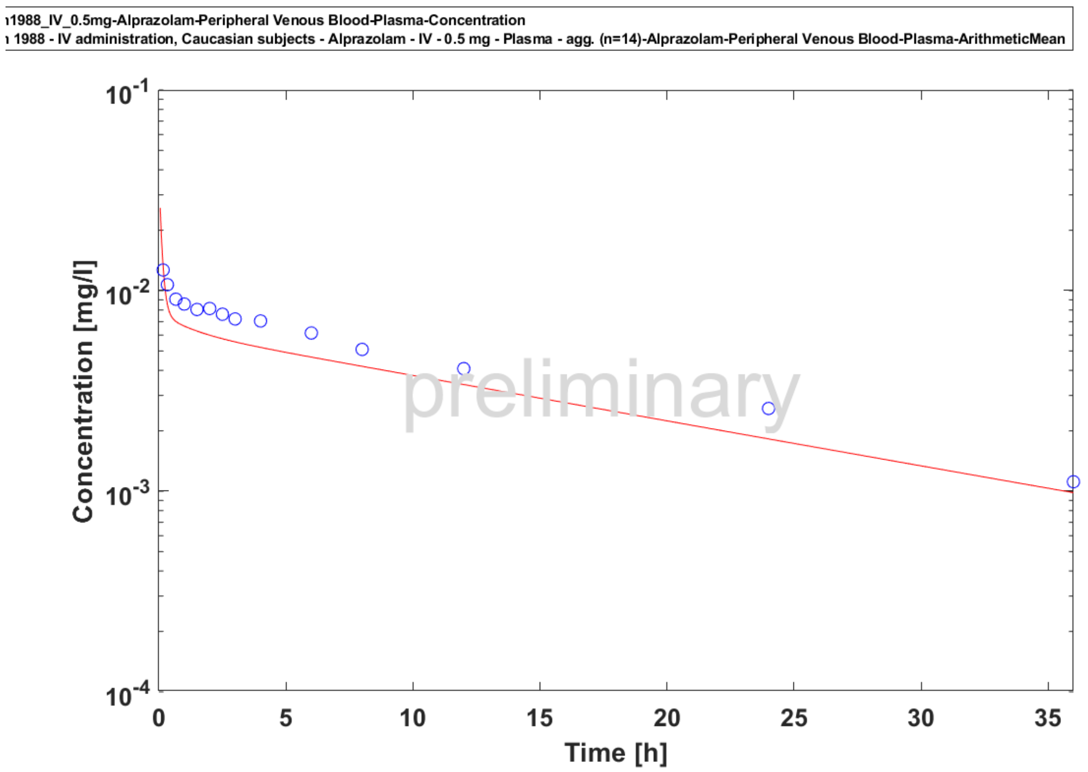

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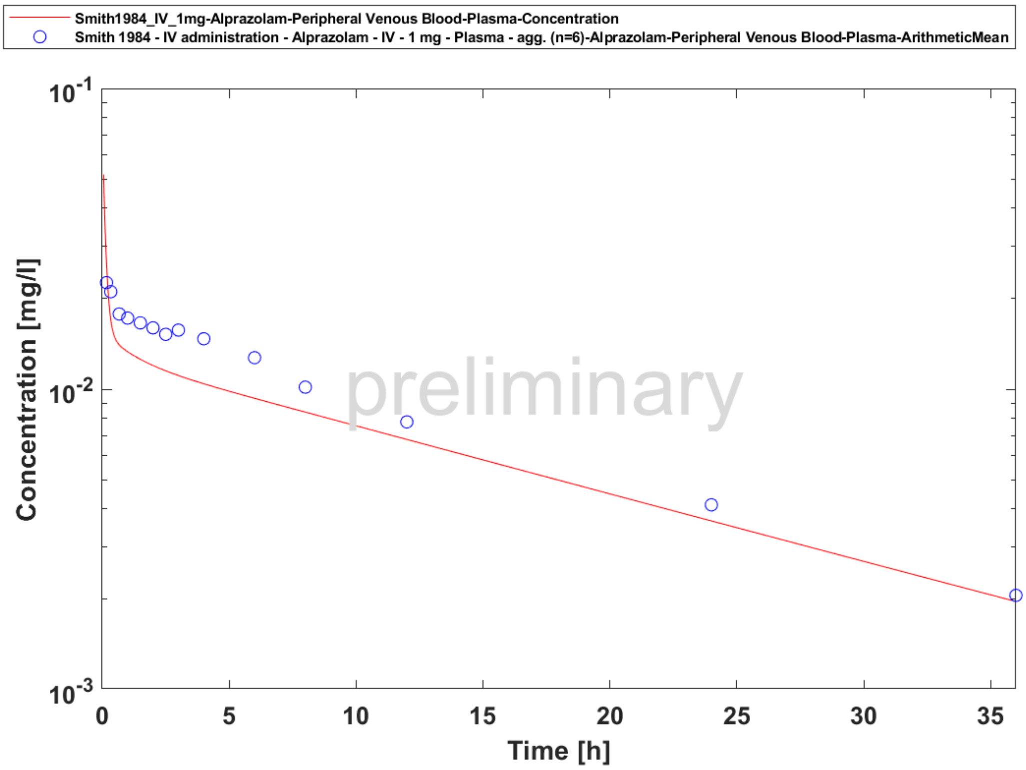
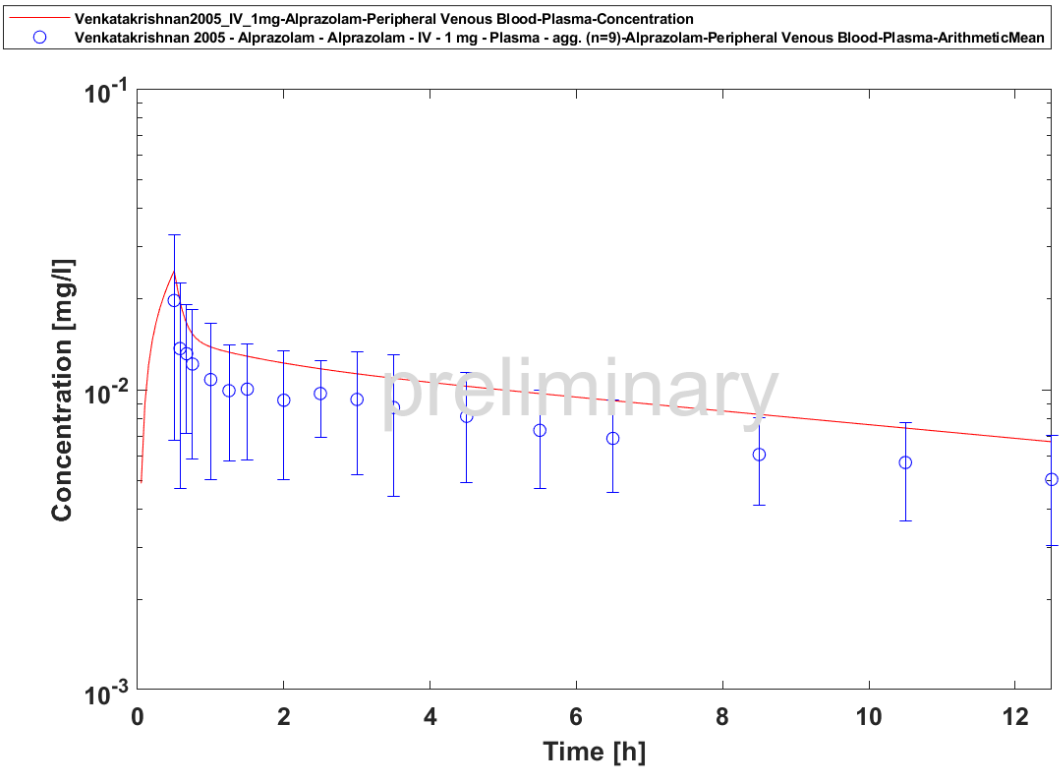


Time Profile Analysis



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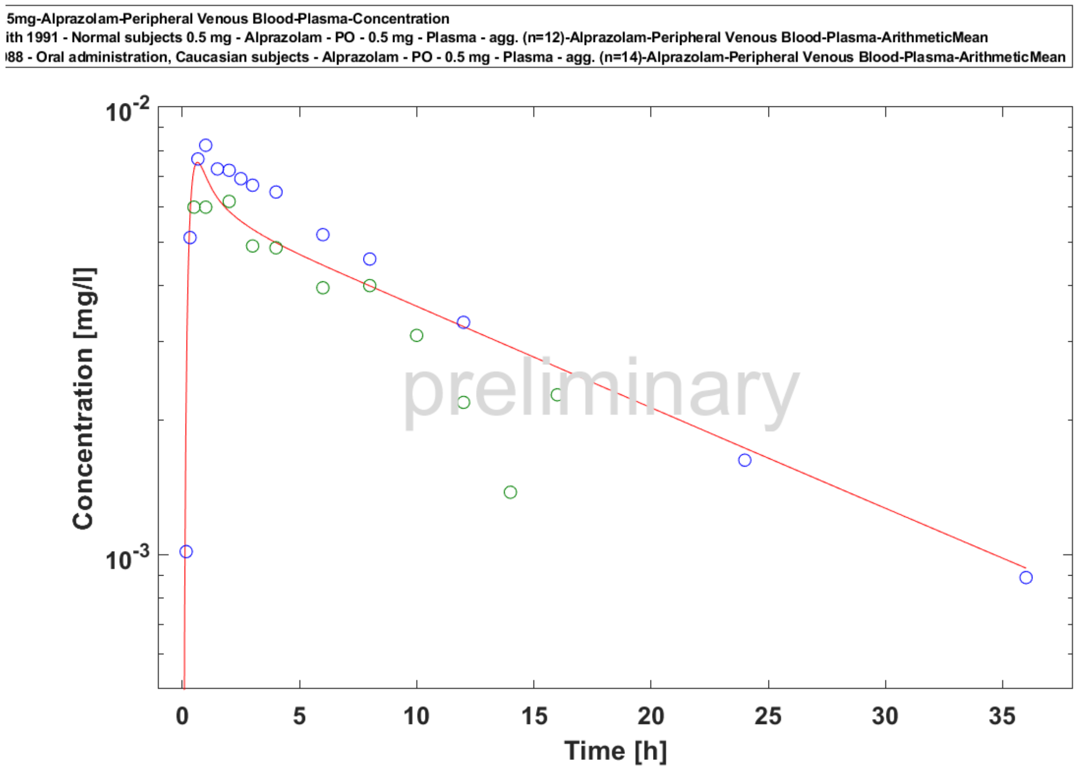

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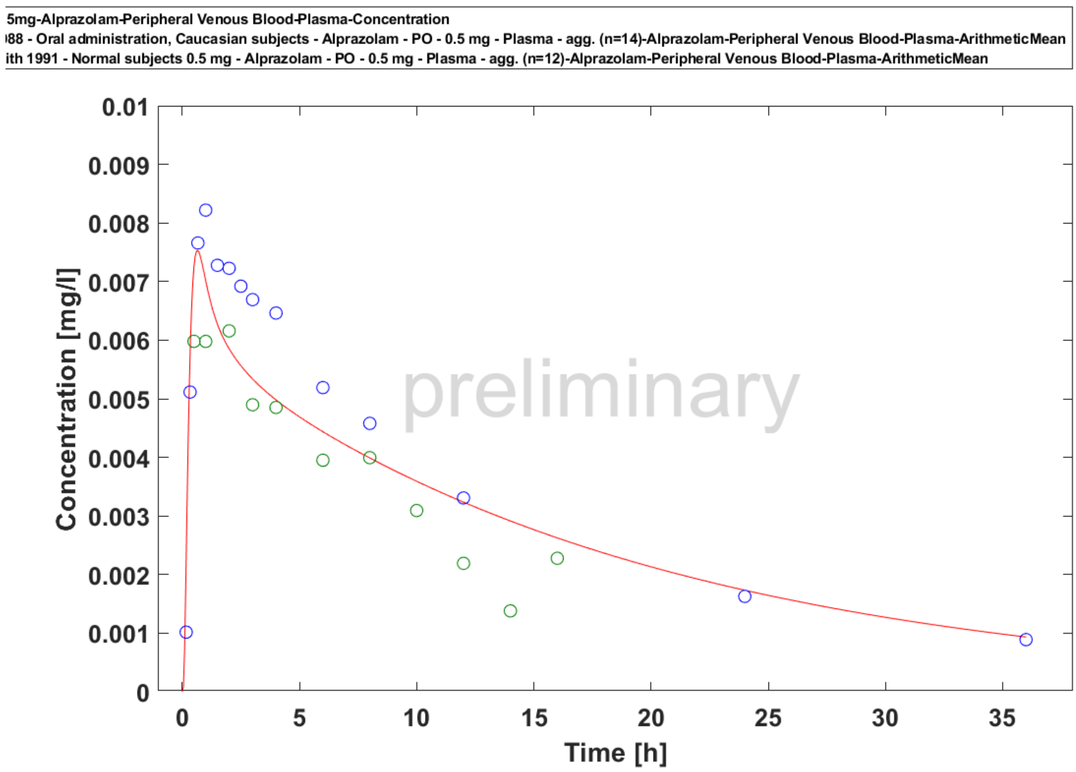
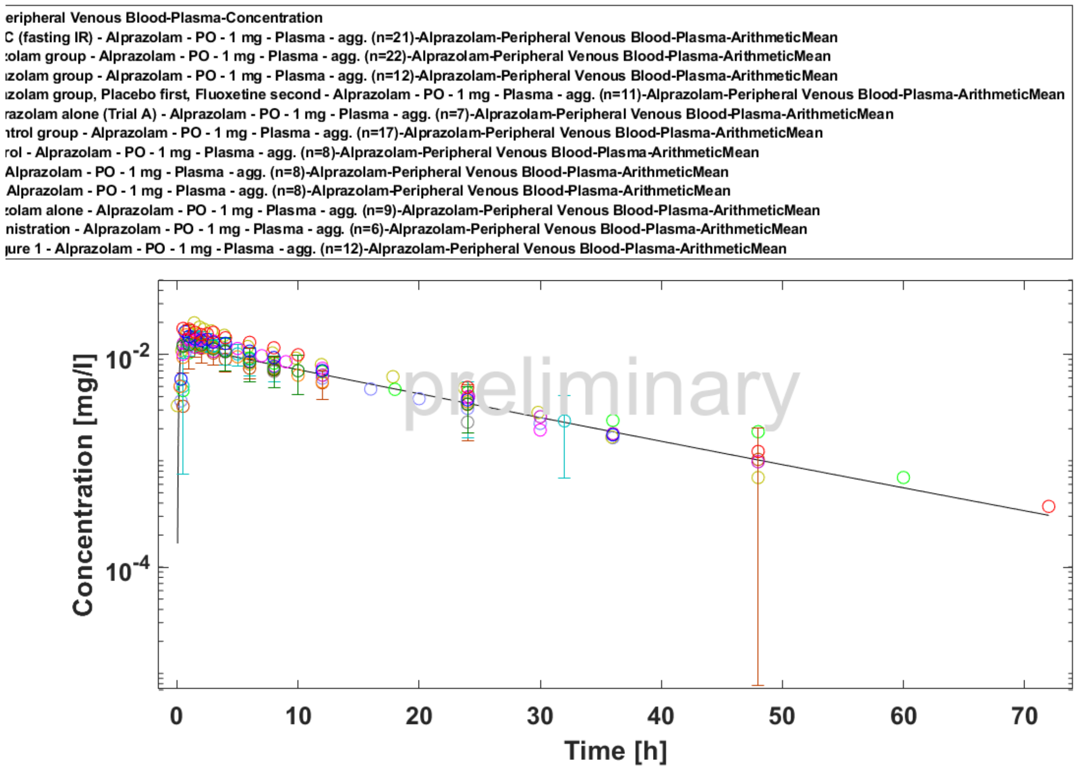


Time Profile Analysis 1



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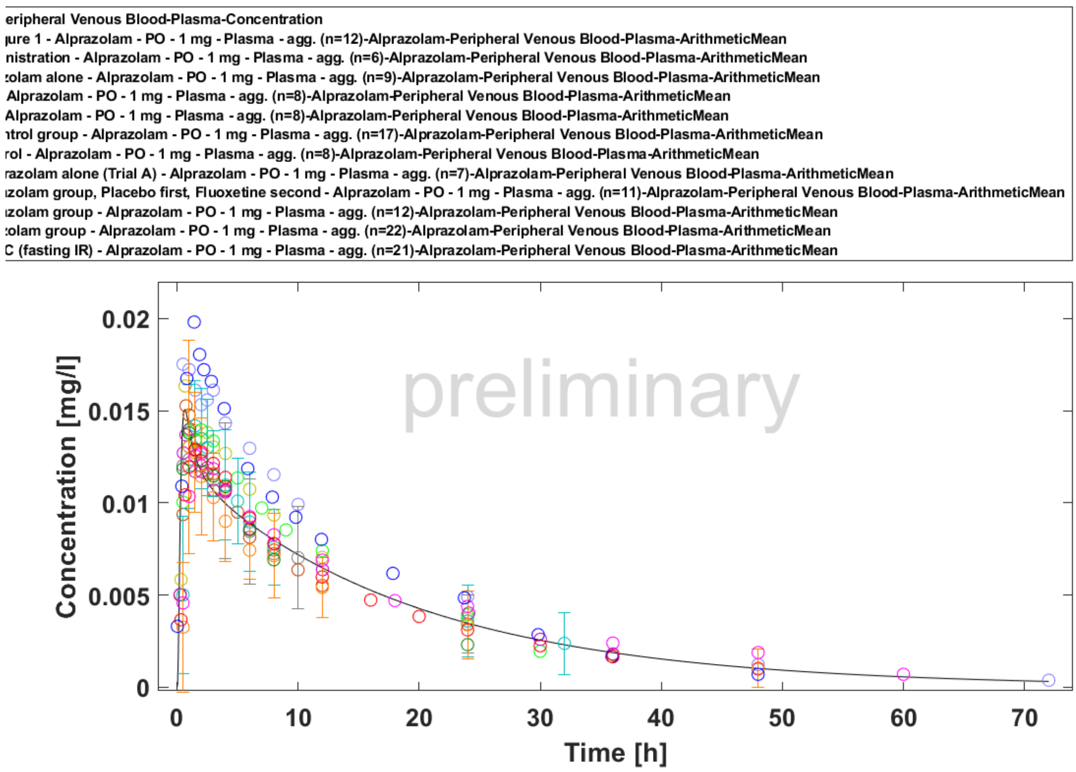
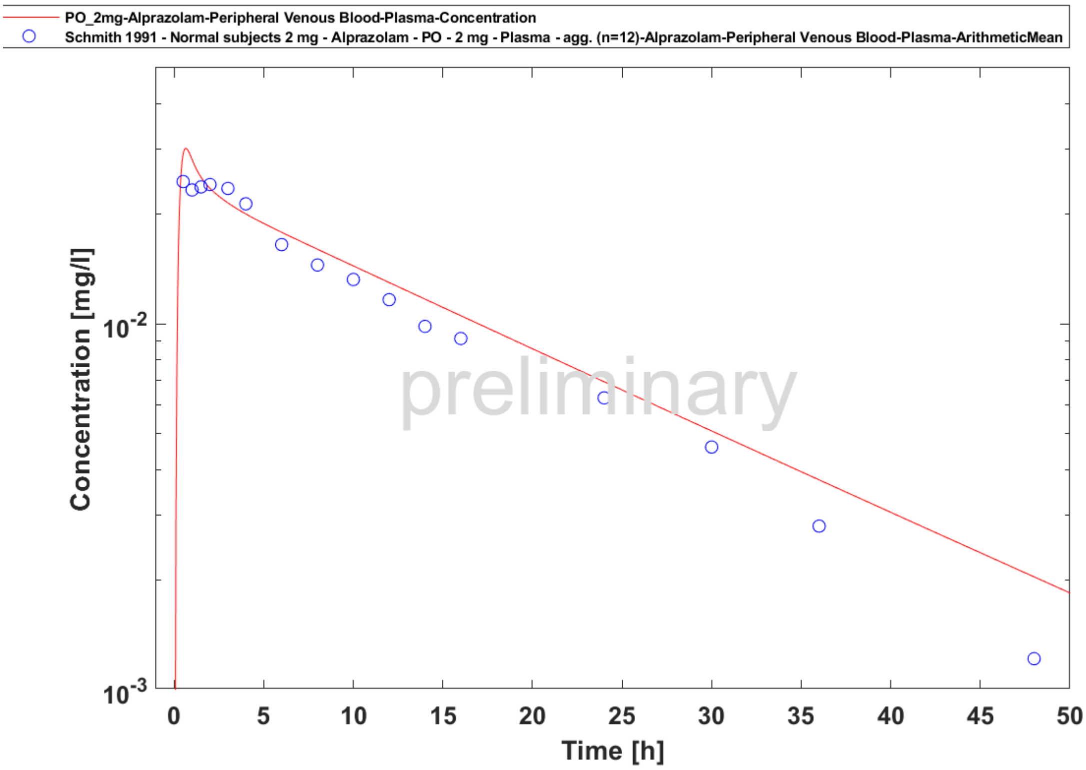
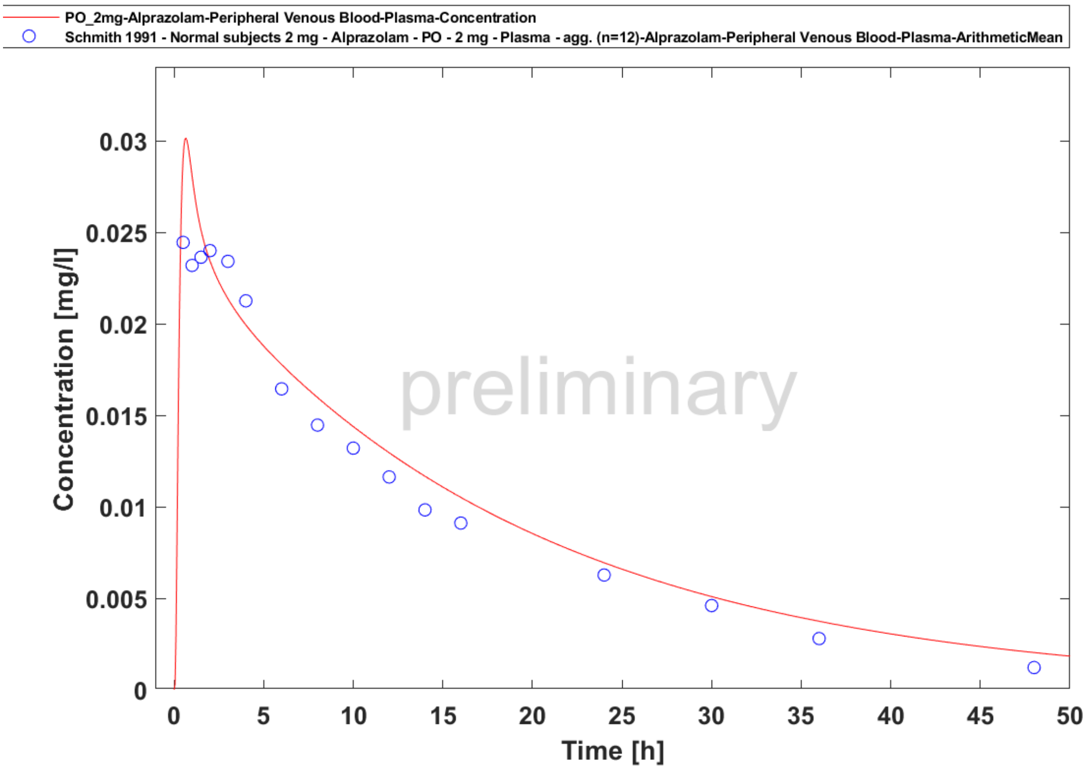


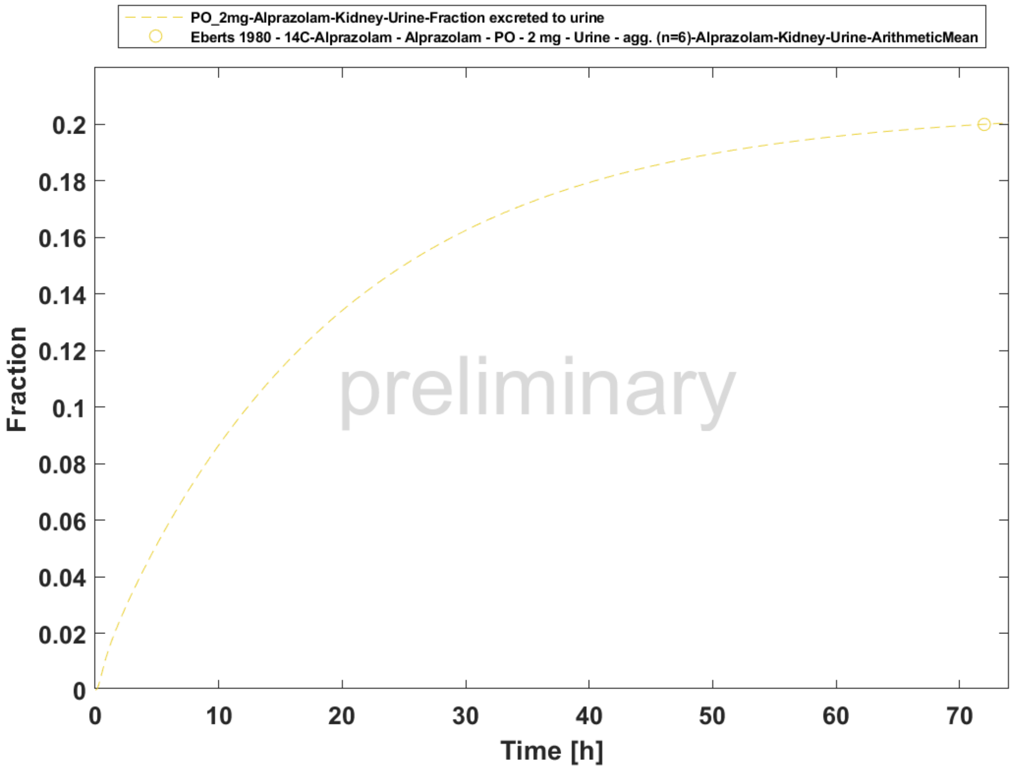
Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis 2

4 Conclusion

The final alprazolam PBPK model applies metabolism by CYP3A4, modelled as two separate pathways catalyzed by the same enzyme yielding α-hydroxy-alprazolam and 4-hydroxy-alprazolam as metabolites, and glomerular filtration. Overall, the model adequately describes the pharmacokinetics of alprazolam in healthy, non-obese adults receiving different single doses of alprazolam via the IV route or oral route as immediate release tablet in the fasted state.

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