

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

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Version	0.1
OSP Version	8.0
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# 1 Introduction

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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,  $\alpha$ -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  $^{14}\text{C}$ -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 (Xanax) or extended-release formulation (Solanax) given in fasted state in healthy, non-obese adults; 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 via the intravenous (IV) or oral (PO) route in the fasted state. Several oral dosage forms were included in the model building process, such as Xanax® and Solanax® tablets. Comparison of the reported alprazolam plasma concentration-time profiles following administration of Xanax® and Solanax® tablets indicated that the latter oral dosage form yields a larger  $t_{\max}$  than the Xanax® immediate release formulation. Therefore, different dissolution kinetics were developed for these two oral dosage forms. The reported PK profiles following administration of Solanax® tablets were measured in Japanese subjects ([Yasui 1996](#), [Yasui 1998](#), [Yasui 2000](#)). To account for ethnicity-related differences in anatomical and physiological model parameters, the European Standard Individual used per default in the simulations was scaled to a Japanese individual and the reference concentration of CYP3A4 in this individual was optimized to better match the clinical data. Finally, mass balance information on urinary excretion of unchanged  $^{14}\text{C}$ -alprazolam after PO administration reported by Eberts et al. ([Eberts 1980](#)) was also accounted for during the model building process.

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

- 2 plasma concentration-time profiles following single IV administration of 0.25 mg
- 2 plasma concentration-time profiles following single IV administration of 0.5 mg
- 3 plasma concentration-time profiles following single IV administration of 1 mg
- 1 plasma concentration-time profile following single IV administration of 1 mg followed by 1.576 mg over 8 h
- 2 plasma concentration-time profiles following single IV administration of 2 mg
- 3 plasma concentration-time profiles following single IV administration of 4 mg
- 2 plasma concentration-time profiles following single PO administration of 0.5 mg
- 3 plasma concentration-time profiles following single PO administration of Solanax® tablets containing 0.8 mg alprazolam to Japanese subjects
- 12 plasma concentration-time profiles following single PO administration of 1 mg
- 1 plasma concentration-time profile following single PO administration of 2 mg
- 1 dose fraction excreted unchanged in urine following single PO administration of 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
- Reference concentration CYP3A4 (only for Japanese subjects)
- 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 erythromycin. 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 ( <a href="#">drugbank.ca</a> )	Molecular weight
pK <sub>a</sub> (basic)		2.40 ( <a href="#">Cho 1983</a> , <a href="#">Raymond 1986</a> ); 2.48 ± 0.01 ( <a href="#">Manchester 2018</a> )	Acid dissociation constant
logP		2.19 ( <a href="#">Machatha 2004</a> ); 2.92 ( <a href="#">Capobianco 1994</a> )	Partition coefficient between octanol and water
logD		3.06 ( <a href="#">Greenblatt 1983</a> )	Partition coefficient between octanol and water at physiological pH
f <sub>u</sub>		0.20 ( <a href="#">Eberts 1980</a> ); 0.233 ± 0.028 <sup>a</sup> ( <a href="#">Schmith 1991</a> ); 0.270 ± 0.017 <sup>a</sup> ( <a href="#">Scavone 1988</a> ); 0.284 ± 0.017 <sup>a</sup> ( <a href="#">Scavone 1988</a> ); 0.290 ± 0.025 <sup>a</sup> ( <a href="#">Juhl 1984</a> ); 0.298 [0.259 - 0.316] <sup>b</sup> ( <a href="#">Abernethy 1983</a> ); 0.311 ± 0.026 <sup>a</sup> ( <a href="#">Ochs 1986</a> ); 0.316 <sup>c</sup> ( <a href="#">Moschitto 1983</a> )	Fraction unbound in human plasma of healthy adults
Water solubility (pH 1.2)	mg/L	12 ( <a href="#">drugbank.ca</a> )	Estimated solubility in water at pH 1.2

Parameter	Unit	Literature	Description
Water solubility (pH 7.0)	mg/L	40 ( <a href="#">drugbank.ca</a> )	Estimated solubility in water at pH 7.0
Water solubility	mg/L	73 ( <a href="#">Loftsson 2006</a> )	Experimentally measured solubility in water at 22°C - 24°C

<sup>a</sup> mean ± SD

<sup>b</sup> mean [range]

<sup>c</sup> 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
<a href="#">Adams 1984</a>	IV administration of 0.25 mg and 4 mg
<a href="#">Bertz 1997</a>	IV administration of 2 mg (young subjects group)
<a href="#">Eberts 1980</a>	PO administration of 2 mg <sup>14</sup> C-alprazolam (no plasma concentration-time profile was reported, but the dose fraction excreted unchanged in urine was quantified)
<a href="#">Eller 1990</a>	PO administration of 1 mg (Treatment C: IR tablet in fasted state)
<a href="#">Fleishaker 1989</a>	IV administration of 1 mg (Treatment A)
<a href="#">Fleishaker 1994</a>	PO administration of 1 mg four times daily at irregular time intervals for 4 days (Control phase)
<a href="#">Friedman 1991</a>	PO administration of 1 mg
<a href="#">Greenblatt 1988</a>	PO administration of 1 mg
<a href="#">Greenblatt 1992</a>	PO administration of 1 mg (Control phase)
<a href="#">Greenblatt 1998</a>	PO administration of 1 mg (Trial A)
<a href="#">Greenblatt 2000</a>	PO administration of 1 mg (Control group)
<a href="#">Juhl 1984</a>	PO administration of 1 mg (Healthy control group)
<a href="#">Kaplan 1998</a>	PO administration of 1 mg (young subjects group)
<a href="#">Kirkwood 1991</a>	PO administration of 1 mg
<a href="#">Kroboth 1988</a>	IV administration of 0.5 mg, 1 mg followed by 72 µg over 8 h, and 2 mg
<a href="#">Lin 1988</a>	IV administration of 0.5 mg and PO administration of 0.5 mg
<a href="#">Schmider 1999</a>	PO administration of 1 mg (Control phase)
<a href="#">Schmith 1991</a>	PO administration of 0.5 mg and 2 mg (normal subjects group)
<a href="#">Smith 1984</a>	IV administration of 1 mg and PO administration of 1 mg
<a href="#">Venkatakrishnan 2005</a>	IV administration of 1 mg
<a href="#">Wennerholm 2005</a>	PO administration of 1 mg
<a href="#">Yasui 1996</a>	PO administration of 0.8 mg (Control phase)
<a href="#">Yasui 1998</a>	PO administration of 0.8 mg (Control phase)
<a href="#">Yasui 2000</a>	PO administration of 0.8 mg (Control phase)

## 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. As described in [Section 2.1](#), different dissolution kinetics were developed for Xanax<sup>®</sup> and Solanax<sup>®</sup> formulations to allow a slower dissolution of the latter yielding a larger  $t_{max}$ . 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,  $\alpha$ -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  $\mu\text{mol/L}$  for the  $\alpha$ -OH pathway and 704  $\mu\text{mol/L}$  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<sup>®</sup> database using the expression data quantified by RT-PCR ([Open Systems Pharmacology Documentation](#)). As described in [Section 2.1](#), the European Standard Individual used per default in the simulations was scaled to a Japanese individual with the `Reference concentration CYP3A4` being fitted to observed data reported by Yasui et al. ([Yasui 1996](#), [Yasui 1998](#), [Yasui 2000](#)) to account for ethnicity-related differences in anatomical and physiological model parameters.

Following oral administration of <sup>14</sup>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	2.0799268917 Log Units	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3.4' on 2020-03-25 13:19	Optimized	True	
Fraction unbound (plasma, reference value)	0.233	Publication-In Vivo-PMID: 1880224	Measurement	True	
Specific intestinal permeability (transcellular)	7.6146060669 cm/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3.4' on 2020-03-25 13:19	Optimized	True	
Cl	1				

Name	Value	Value Origin	Alternative	Default	
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	0.8066945978 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3.4' on 2020-03-25 13:19	

### Systemic Process: Glomerular Filtration-GFR

Species: Human

#### Parameters

Name	Value	Value Origin	
GFR fraction	0.5461456402	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3.4' on 2020-03-25 13:19	

### 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	13.7322820855	Parameter Identification-Parameter Identification-Value updated	

kcat	1/min	from 'Parameter Identification 3.4' on 2020-03-25 13:19	
Name	Value	Value Origin	

## Formulation: Solanax

Type: Weibull

### Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	35.8519725483 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3.4' on 2020-03-25 13:19	
Lag time	0 min		
Dissolution shape	0.92	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3.4' on 2020-03-25 13:19	
Use as suspension	Yes		

## Formulation: Xanax\_IR

Type: Weibull

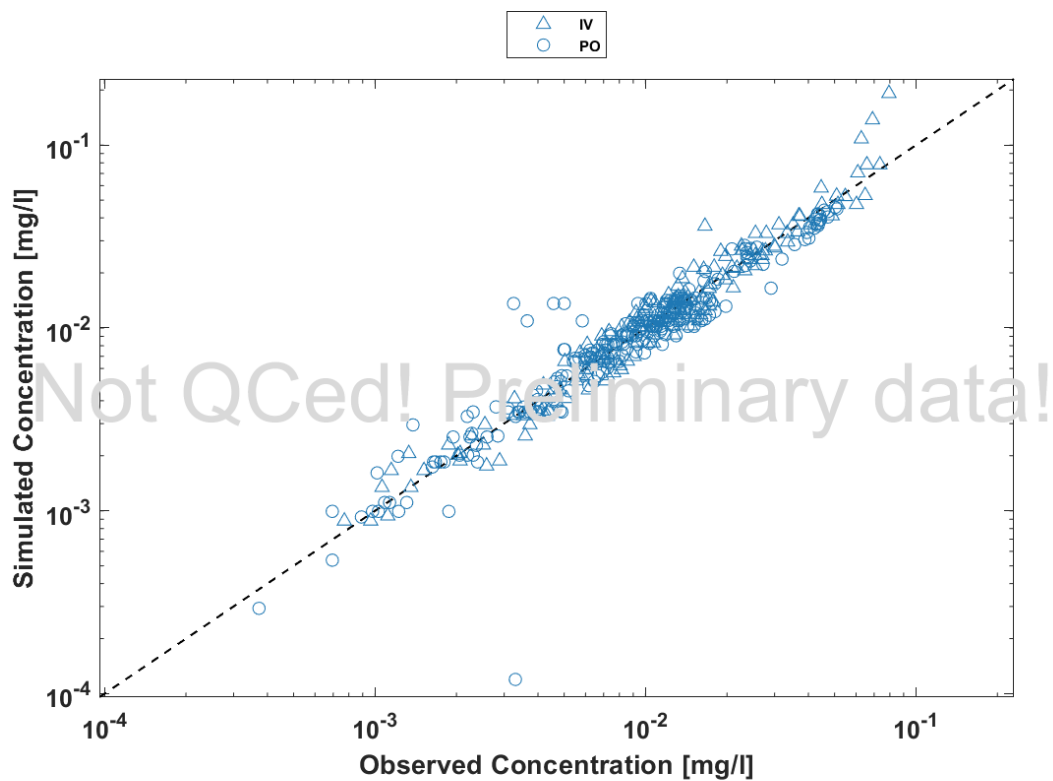
### Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	12.1060809908 min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3.4' on 2020-03-25 13:19	
Lag time	0 min		
Dissolution shape	0.92	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3.4' on 2020-03-25 13:19	
Use as suspension	Yes		

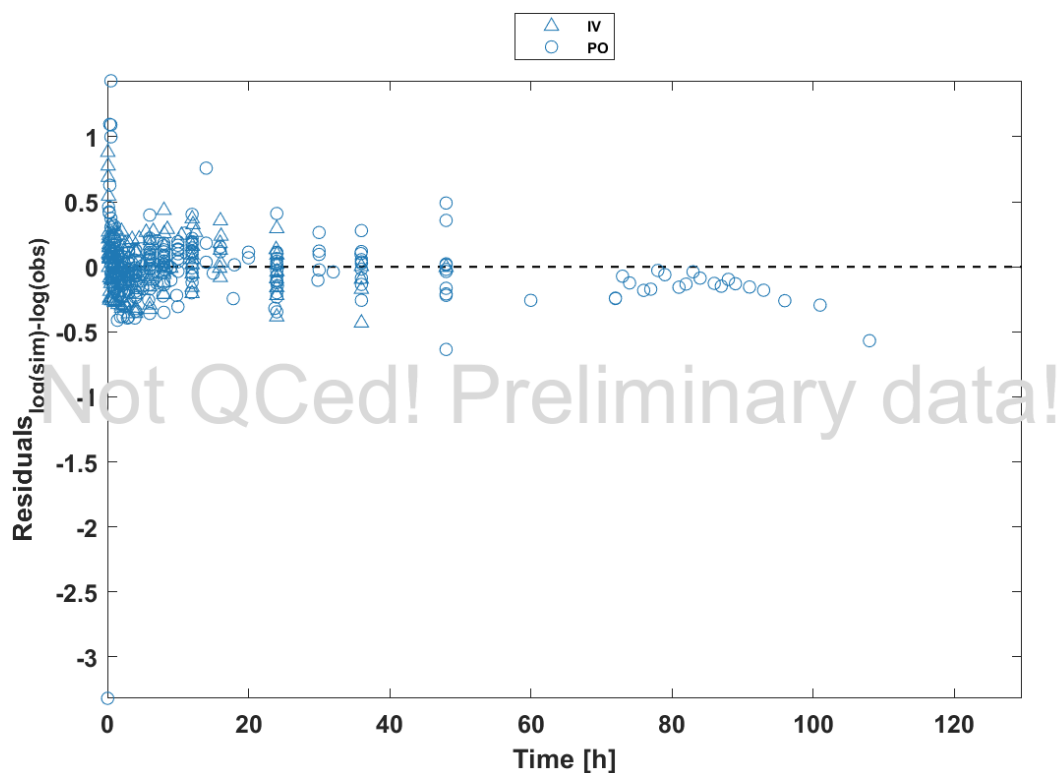
## 3.2 Diagnostics Plots

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

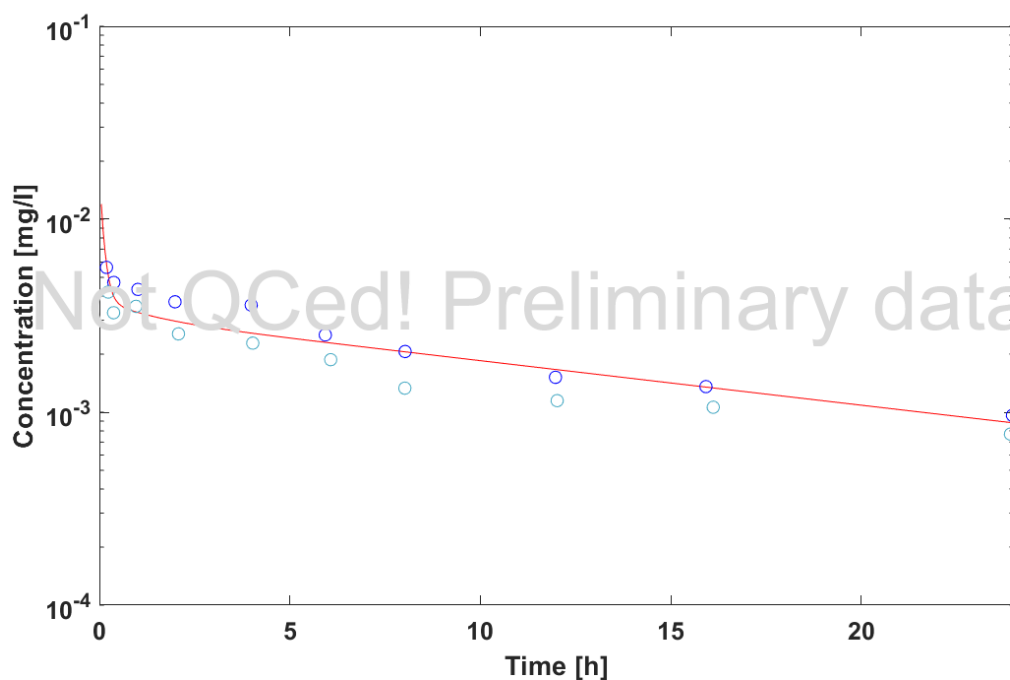
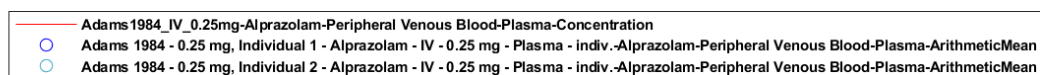


Goodness of fit plot for concentration in plasma

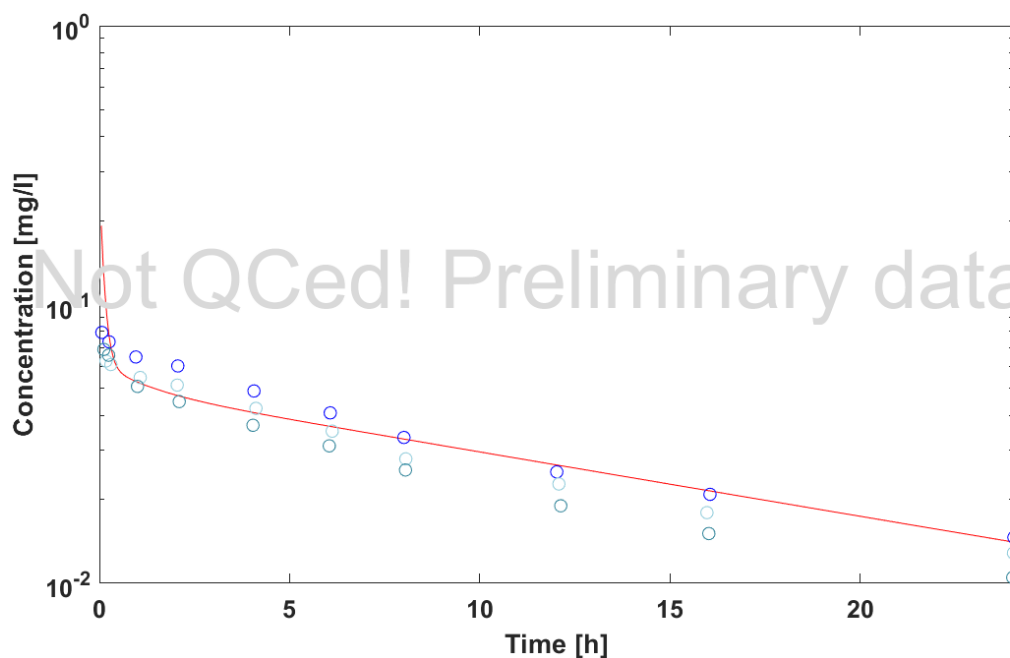
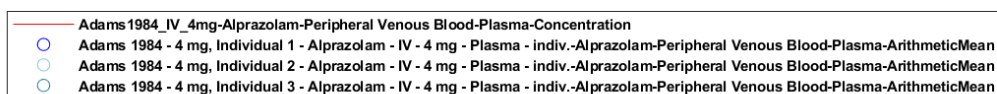
GMFE = 1.181425

### 3.3: Concentration-Time Profiles

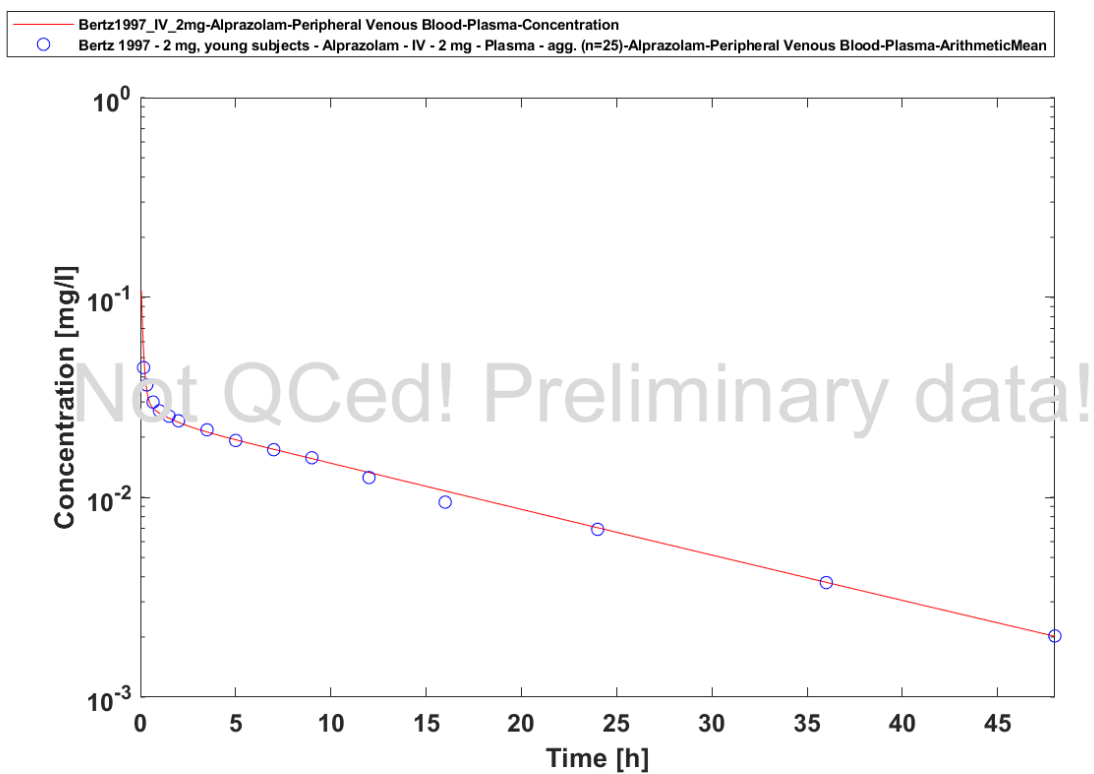
Simulated versus observed concentration-time profiles of all data listed in [Section 2.2.2](#) are presented below.



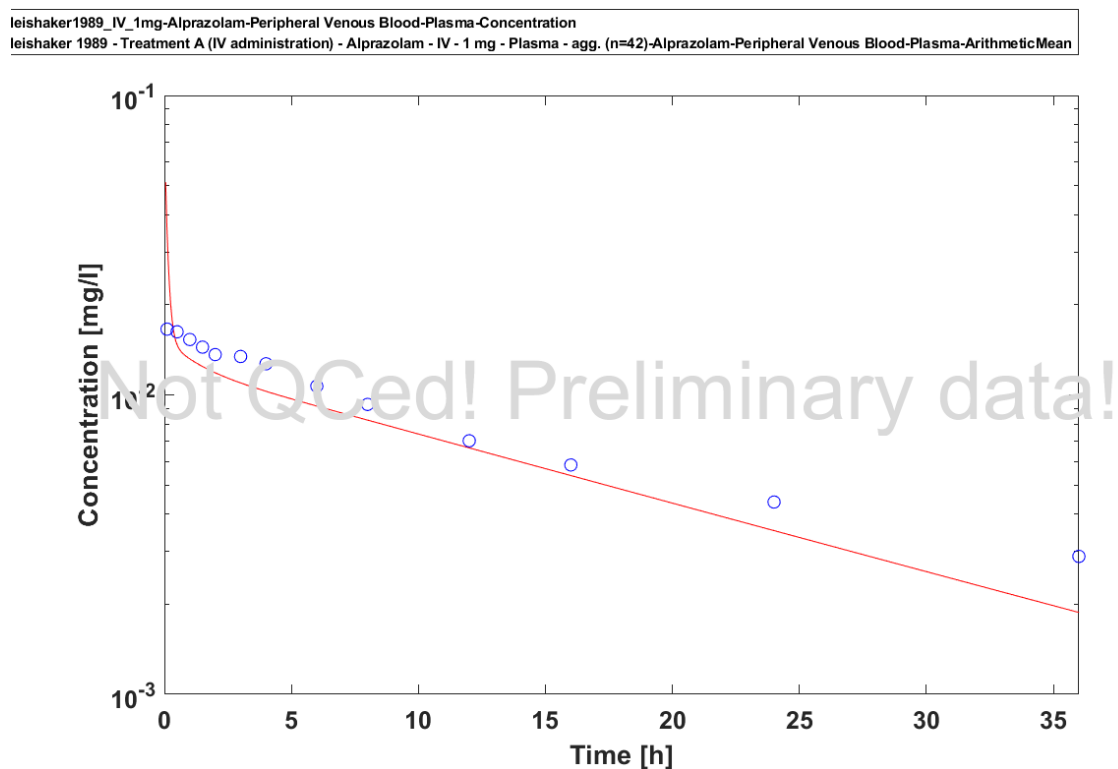
Time Profile Analysis



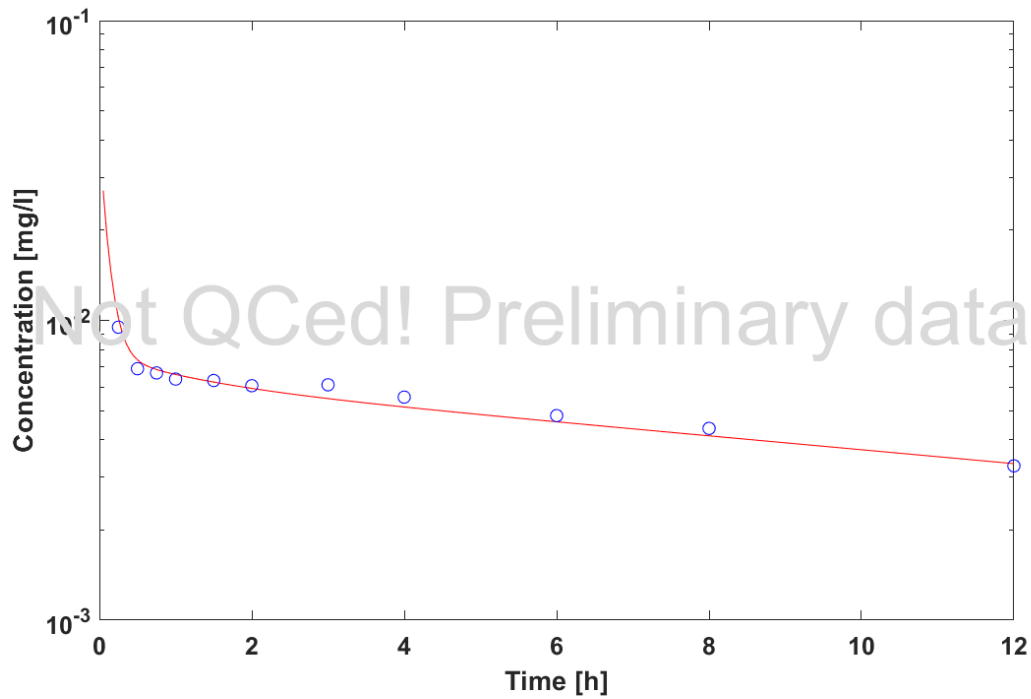
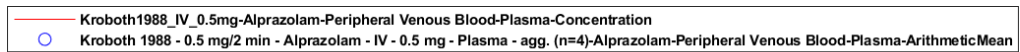
Time Profile Analysis



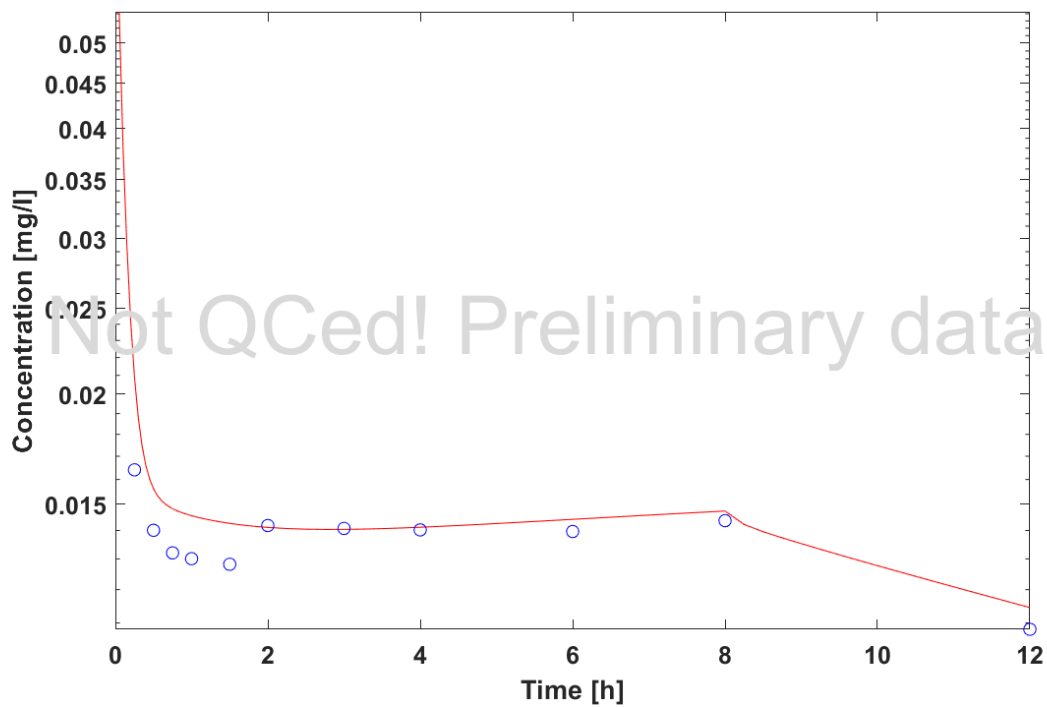
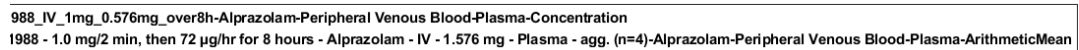
Time Profile Analysis



Time Profile Analysis

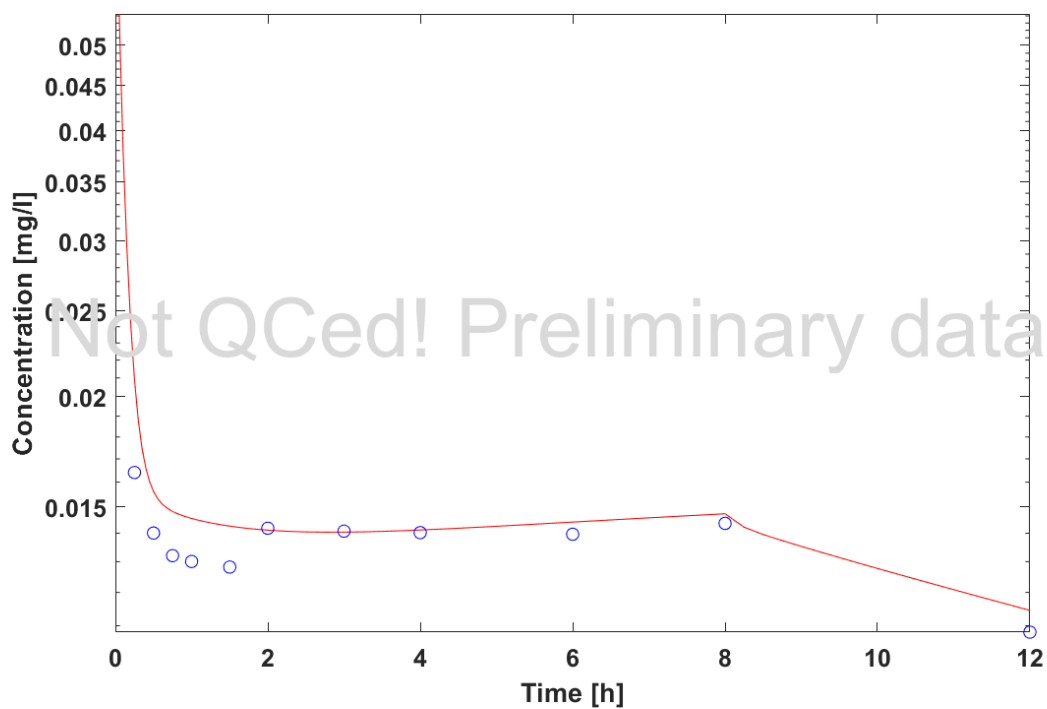


Time Profile Analysis



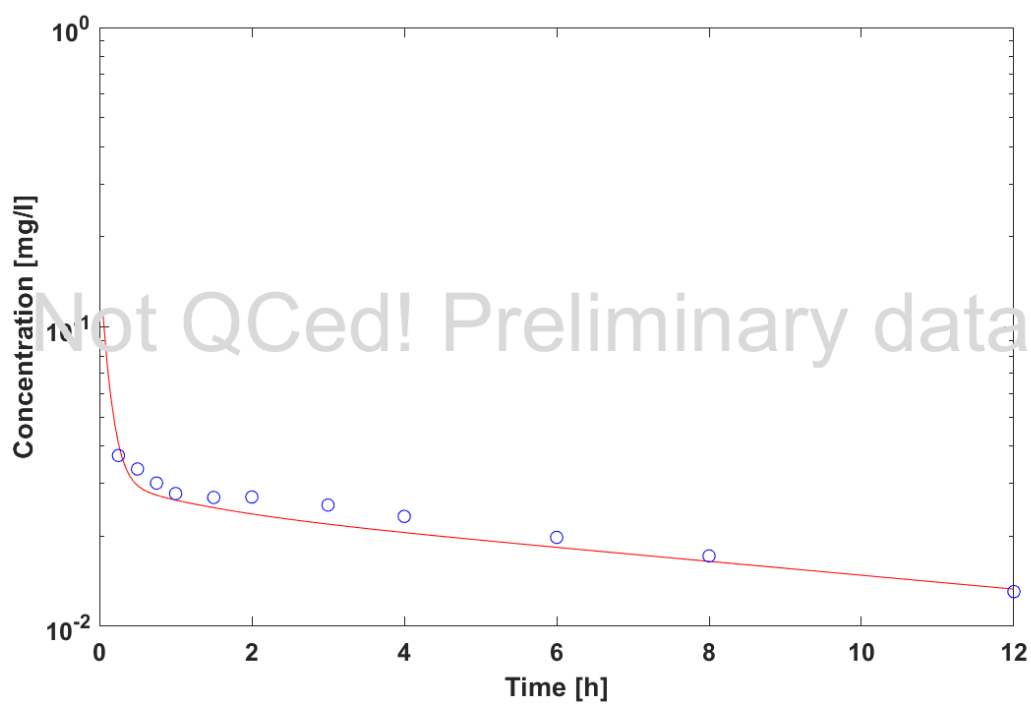
Time Profile Analysis

988\_IV\_1mg\_0.576mg\_over8h-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
1988 - 1.0 mg/2 min, then 72 µg/hr for 8 hours - Alprazolam - IV - 1.576 mg - Plasma - agg. (n=4)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis

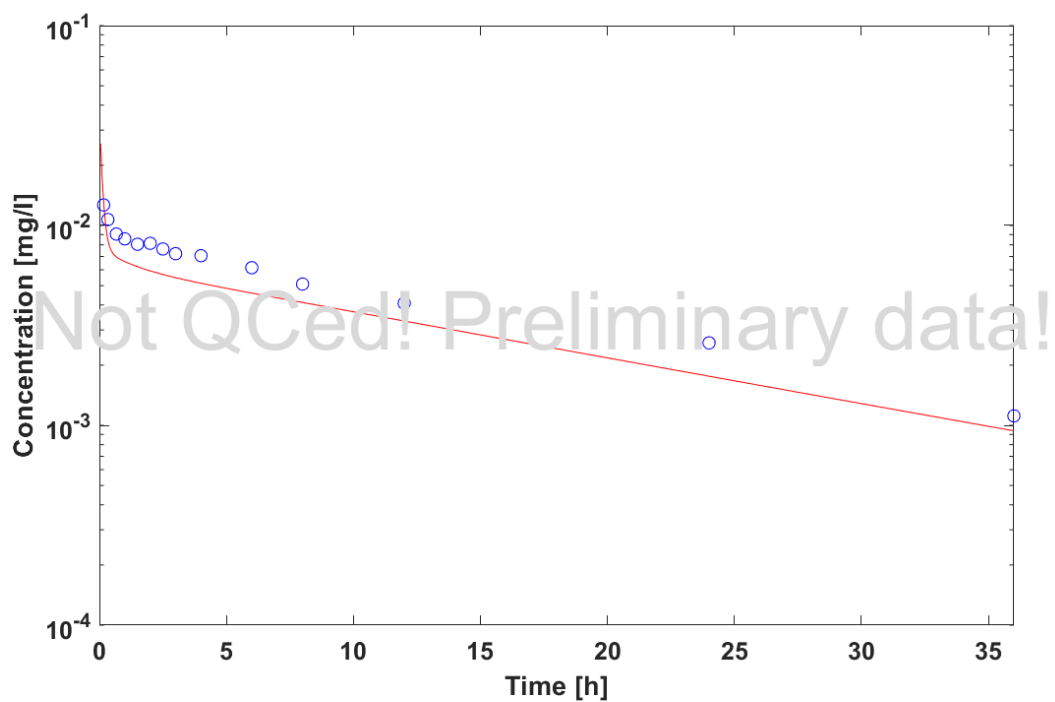
Kroboth1988\_IV\_2mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
Kroboth 1988 - 2.0 mg/2 min - Alprazolam - IV - 2 mg - Plasma - agg. (n=4)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis

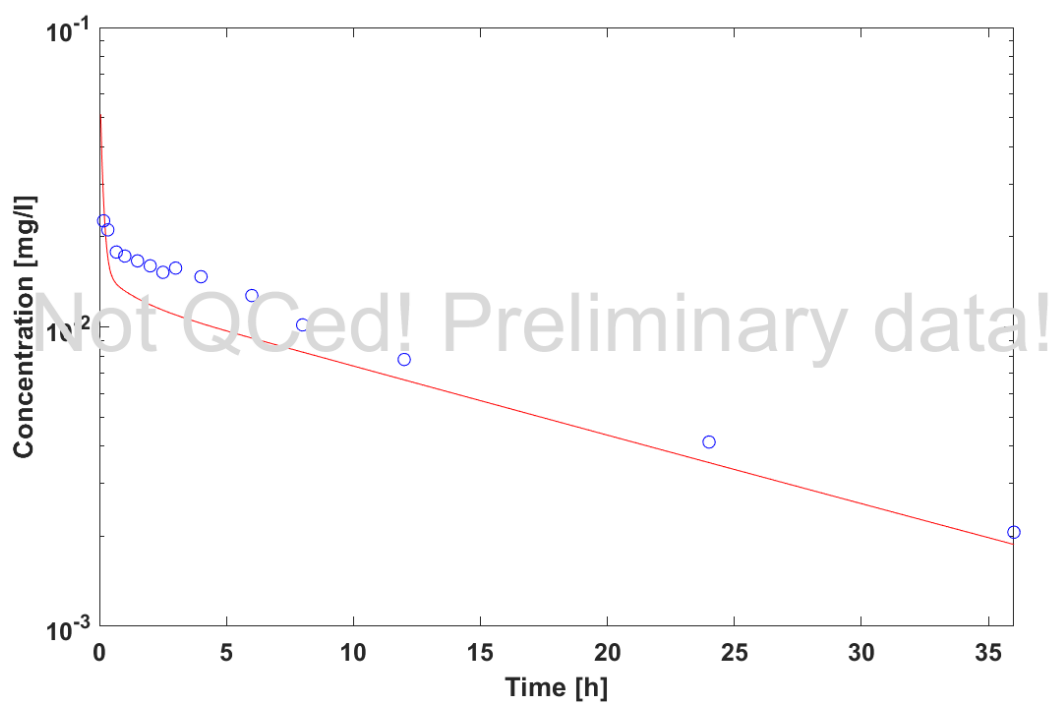


1988\_IV\_0.5mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
1988 - IV administration, Caucasian subjects - Alprazolam - IV - 0.5 mg - Plasma - agg. (n=14)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



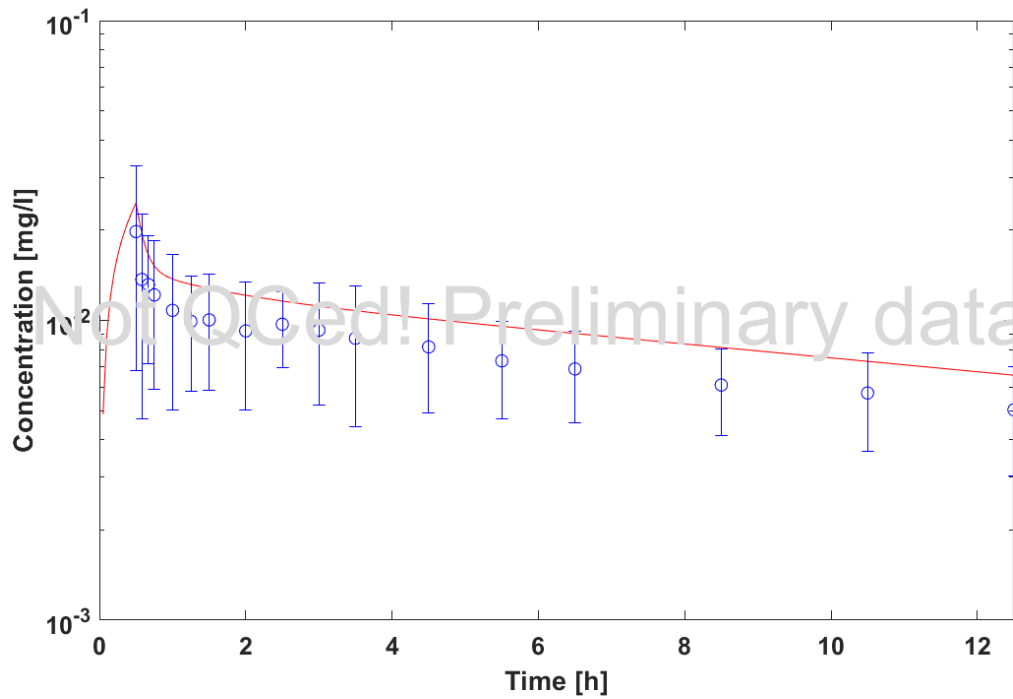
Time Profile Analysis

Smith1984\_IV\_1mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
Smith 1984 - IV administration - Alprazolam - IV - 1 mg - Plasma - agg. (n=6)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



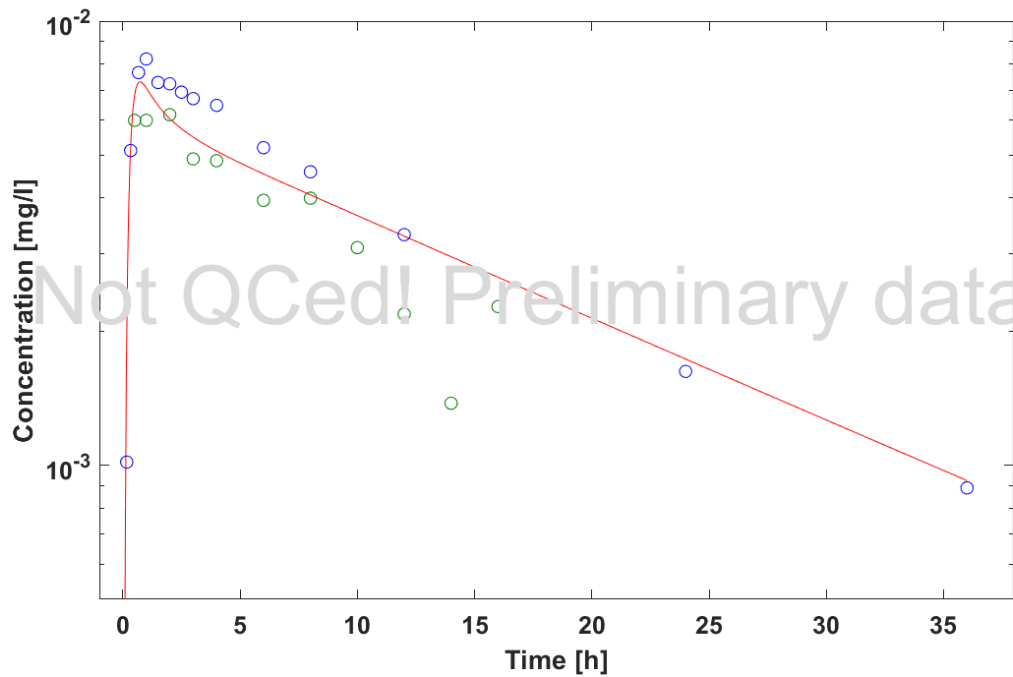
Time Profile Analysis

— Venkatakrishnan2005\_IV\_1mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
○ Venkatakrishnan 2005 - Alprazolam - Alprazolam - IV - 1 mg - Plasma - agg. (n=9)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



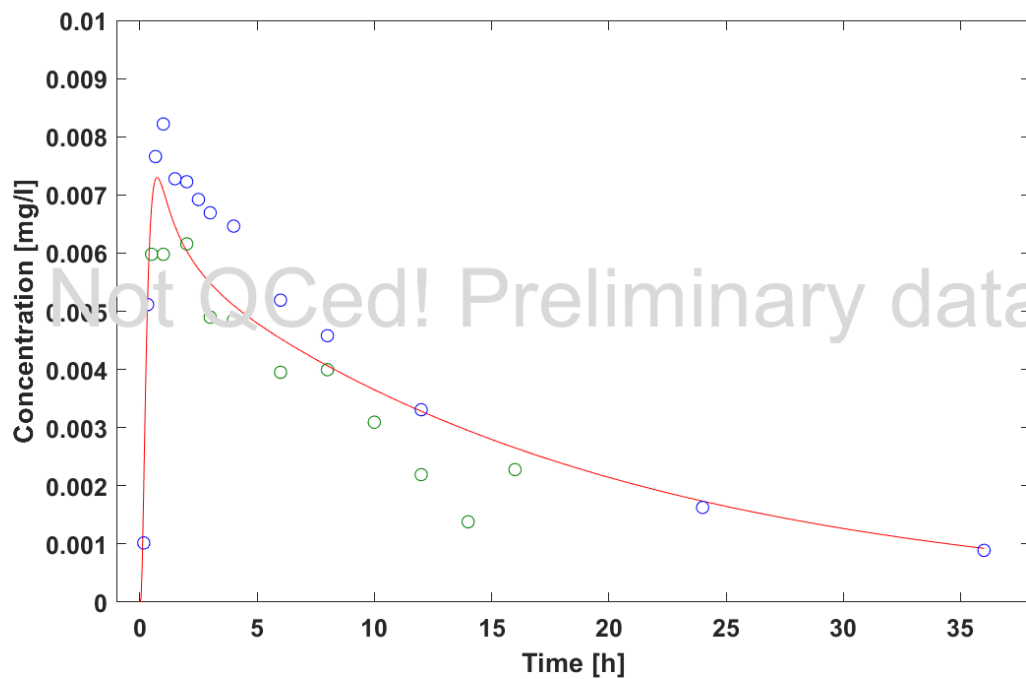
Time Profile Analysis

.5mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
 ith 1991 - Normal subjects 0.5 mg - Alprazolam - PO - 0.5 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 188 - Oral administration, Caucasian subjects - Alprazolam - PO - 0.5 mg - Plasma - agg. (n=14)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



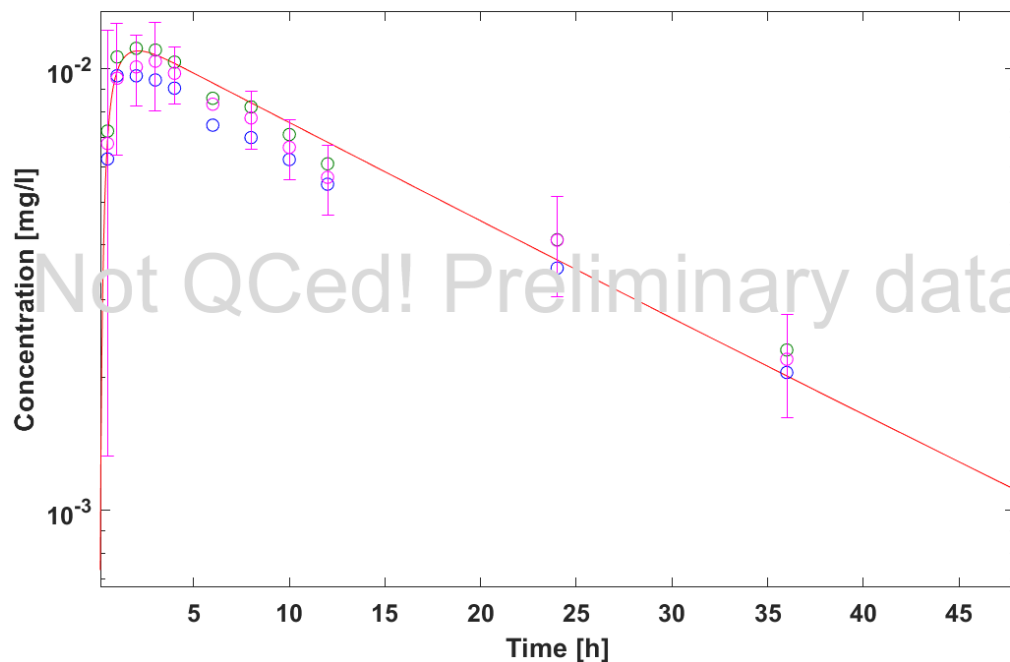
Time Profile Analysis

0.5mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
 188 - Oral administration, Caucasian subjects - Alprazolam - PO - 0.5 mg - Plasma - agg. (n=14)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 ith 1991 - Normal subjects 0.5 mg - Alprazolam - PO - 0.5 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



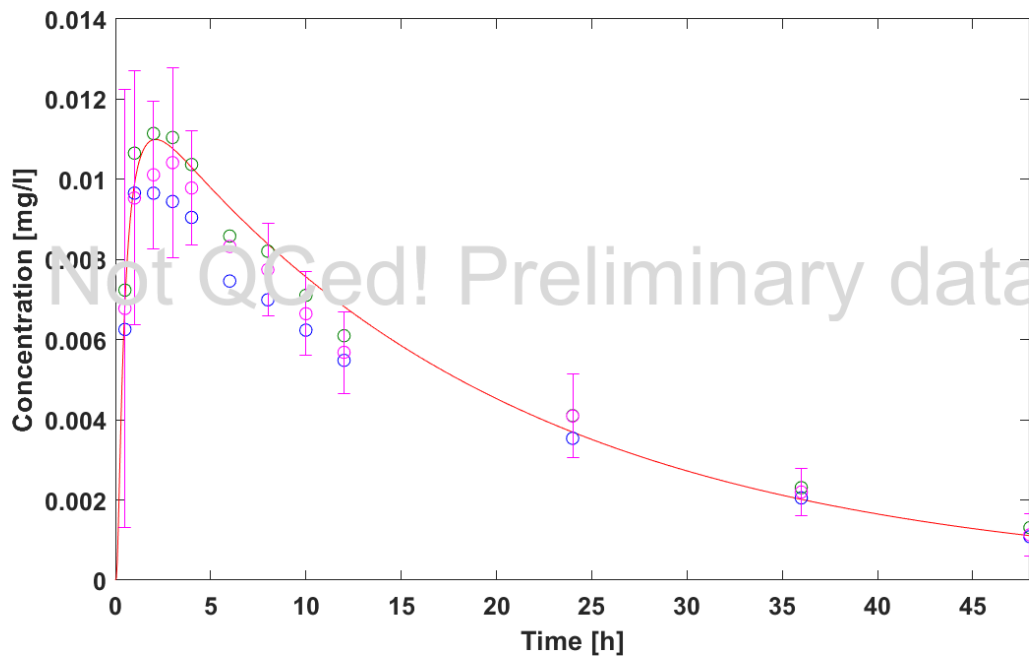
Time Profile Analysis 1

PO\_0.8mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
 Yasui 1998 - Alprazolam with placebo - Alprazolam - PO - 0.8 mg - Plasma - agg. (n=10)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Yasui 1996 - Treatment with placebo - Alprazolam - PO - 0.8 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Yasui 2000 - Alprazolam with water - Alprazolam - PO - 0.8 mg - Plasma - agg. (n=8)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



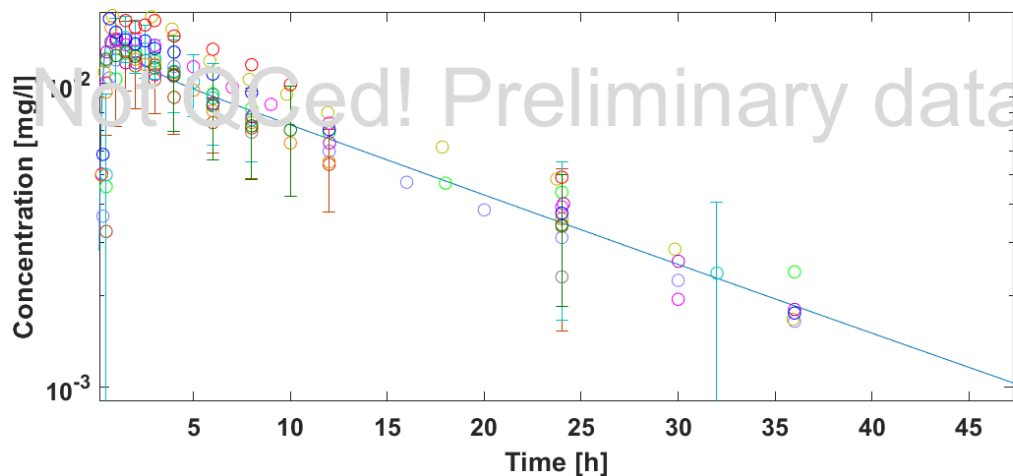
Time Profile Analysis

PO\_0.8mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration  
 Yasui 1996 - Treatment with placebo - Alprazolam - PO - 0.8 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Yasui 1998 - Alprazolam with placebo - Alprazolam - PO - 0.8 mg - Plasma - agg. (n=10)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Yasui 2000 - Alprazolam with water - Alprazolam - PO - 0.8 mg - Plasma - agg. (n=8)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis 1

Peripheral Venous Blood-Plasma-Concentration  
 C (fasting IR) - Alprazolam - PO - 1 mg - Plasma - agg. (n=21)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam group - Alprazolam - PO - 1 mg - Plasma - agg. (n=22)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam group - Alprazolam - PO - 1 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam group, Placebo first, Fluoxetine second - Alprazolam - PO - 1 mg - Plasma - agg. (n=11)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam alone (Trial A) - Alprazolam - PO - 1 mg - Plasma - agg. (n=7)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam alone (Trial B) - Alprazolam - PO - 1 mg - Plasma - agg. (n=17)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam alone (Trial C) - Alprazolam - PO - 1 mg - Plasma - agg. (n=8)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam - PO - 1 mg - Plasma - agg. (n=8)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam - PO - 1 mg - Plasma - agg. (n=8)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam alone - Alprazolam - PO - 1 mg - Plasma - agg. (n=9)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam alone (Trial A) - Alprazolam - PO - 1 mg - Plasma - agg. (n=6)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean  
 Alprazolam alone (Trial B) - Alprazolam - PO - 1 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis

Peripheral Venous Blood-Plasma-Concentration

Figure 1 - Alprazolam - PO - 1 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Administration - Alprazolam - PO - 1 mg - Plasma - agg. (n=6)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Alprazolam alone - Alprazolam - PO - 1 mg - Plasma - agg. (n=9)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Alprazolam - PO - 1 mg - Plasma - agg. (n=8)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Alprazolam - PO - 1 mg - Plasma - agg. (n=8)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Control group - Alprazolam - PO - 1 mg - Plasma - agg. (n=17)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Control - Alprazolam - PO - 1 mg - Plasma - agg. (n=8)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

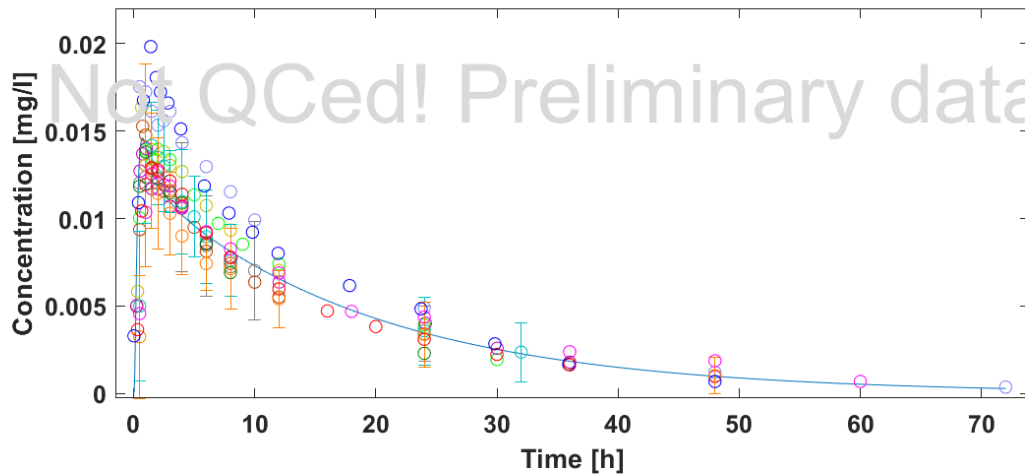
Alprazolam alone (Trial A) - Alprazolam - PO - 1 mg - Plasma - agg. (n=7)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Alprazolam group, Placebo first, Fluoxetine second - Alprazolam - PO - 1 mg - Plasma - agg. (n=11)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Alprazolam group - Alprazolam - PO - 1 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

Alprazolam group - Alprazolam - PO - 1 mg - Plasma - agg. (n=22)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

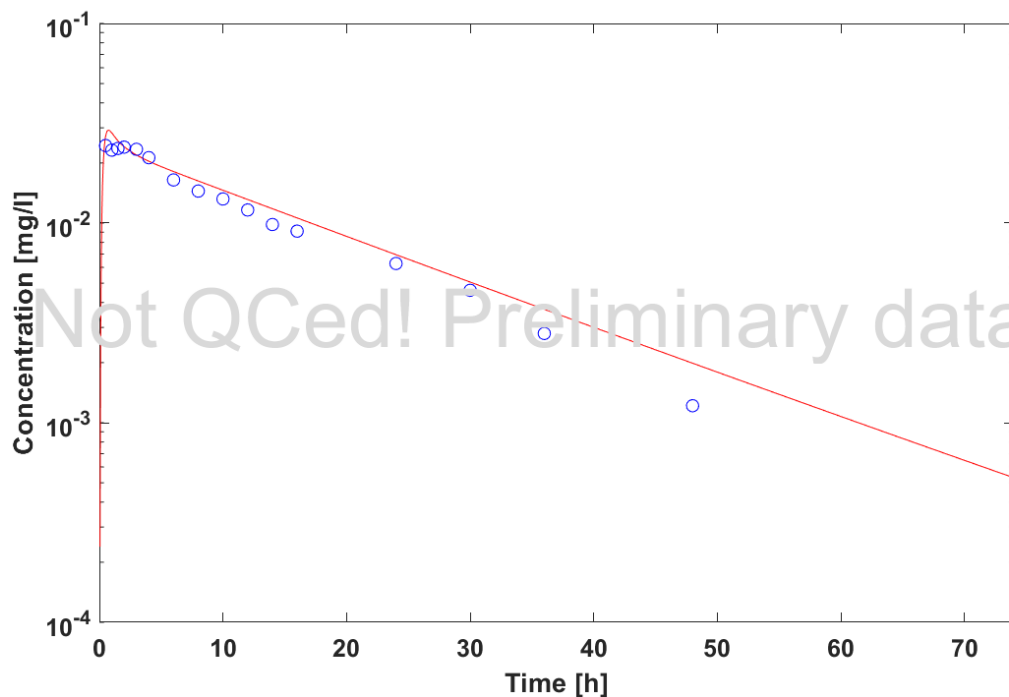
C (fasting IR) - Alprazolam - PO - 1 mg - Plasma - agg. (n=21)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



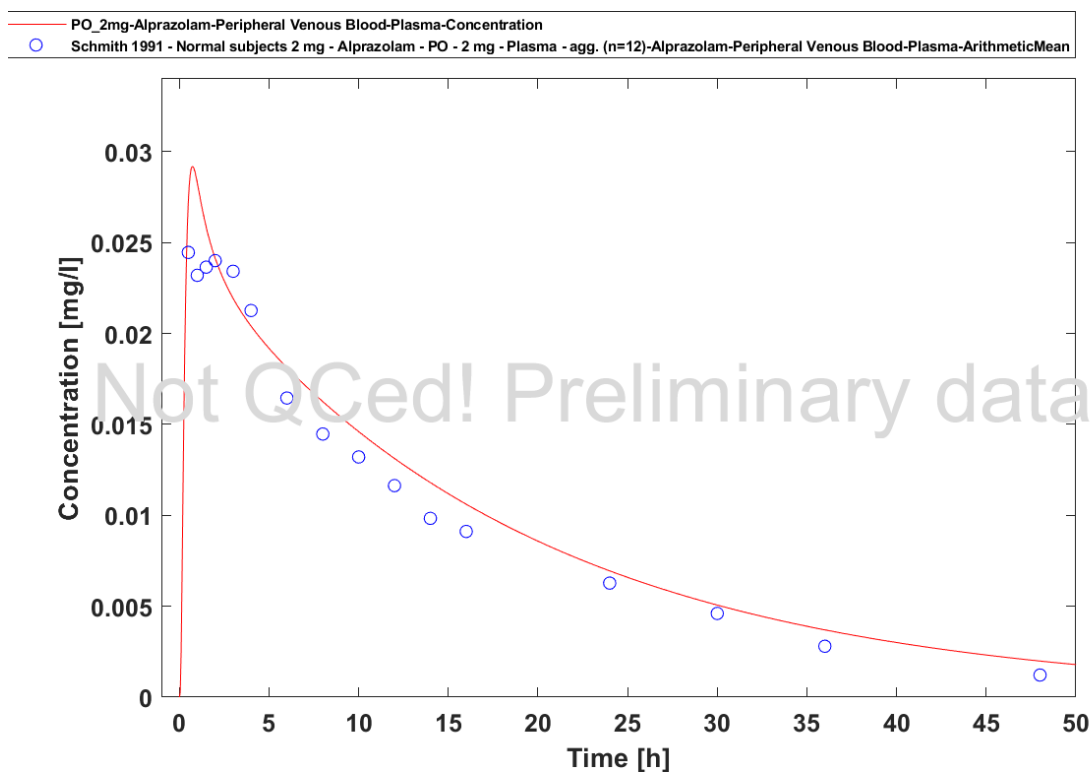
Time Profile Analysis 1

PO\_2mg-Alprazolam-Peripheral Venous Blood-Plasma-Concentration

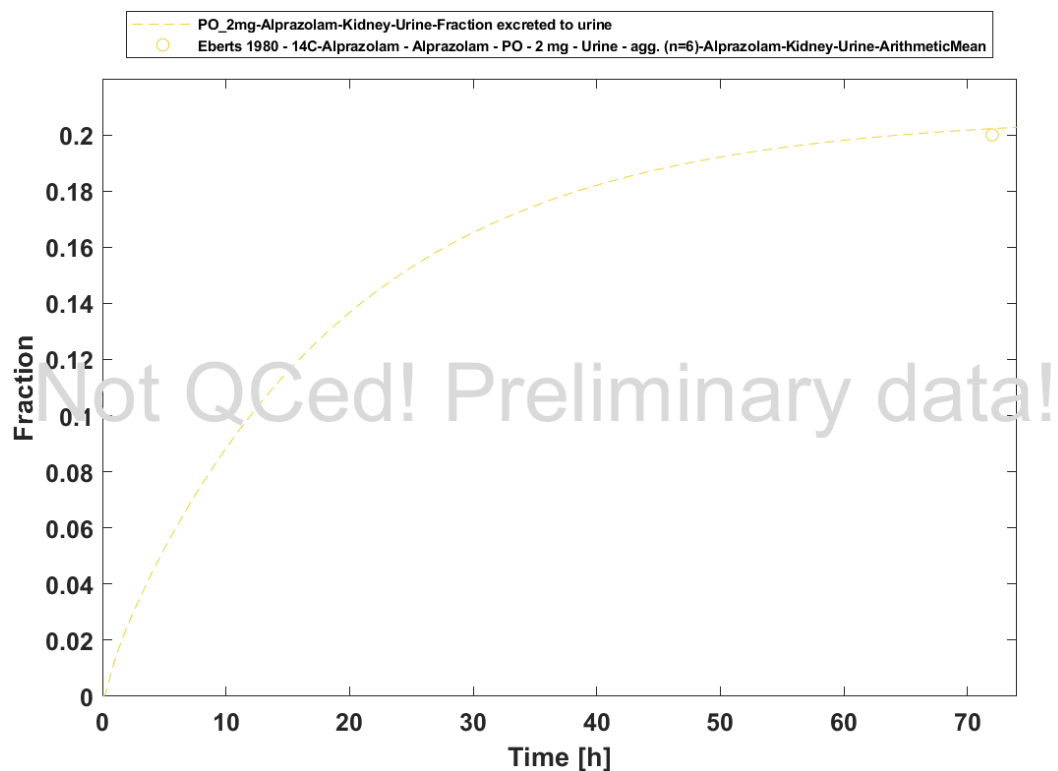
○ Schmith 1991 - Normal subjects 2 mg - Alprazolam - PO - 2 mg - Plasma - agg. (n=12)-Alprazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



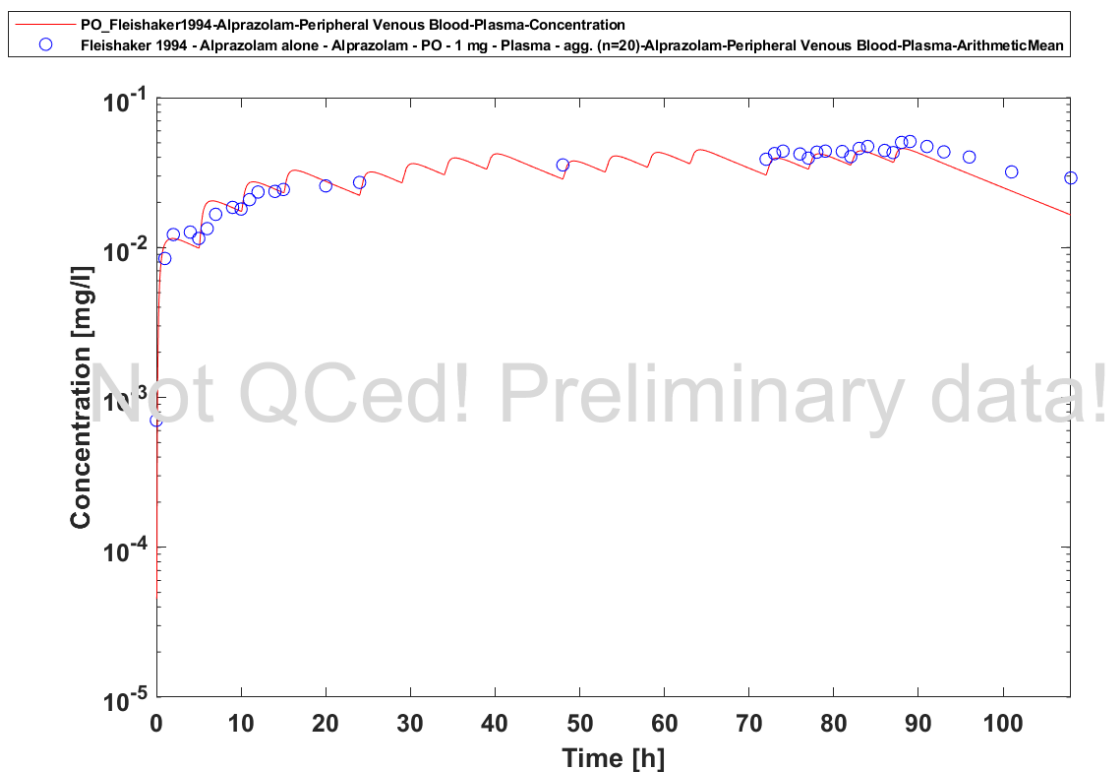
Time Profile Analysis



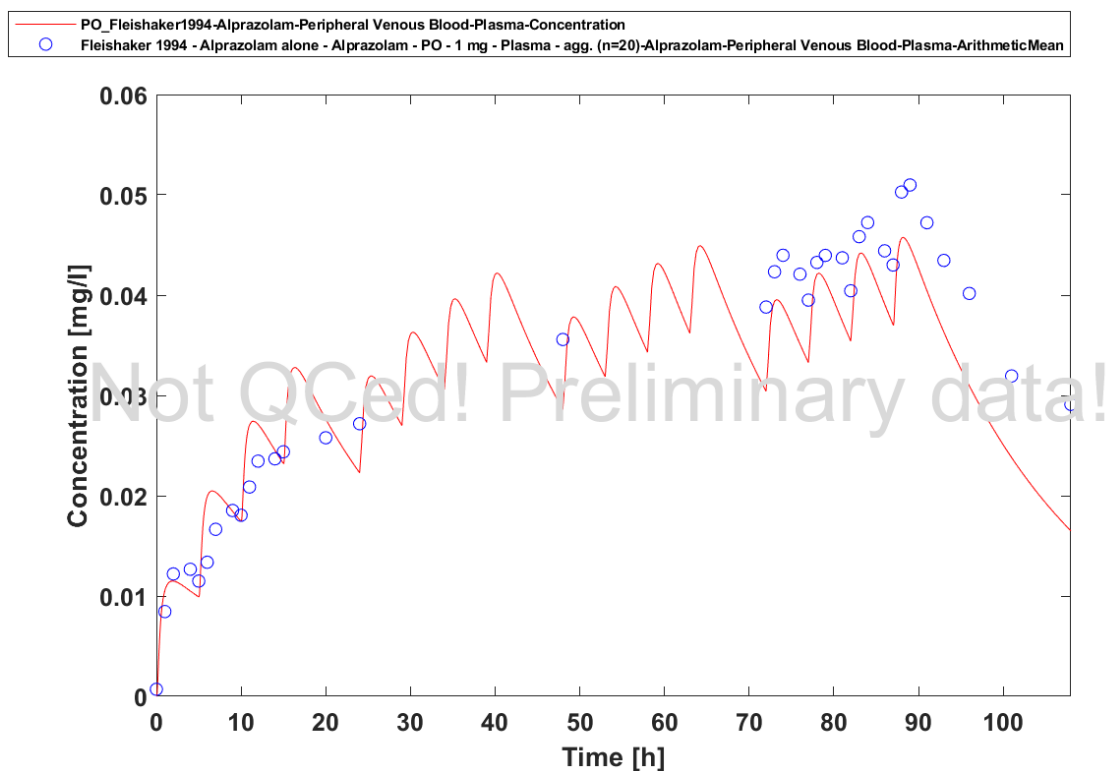
Time Profile Analysis 1



Time Profile Analysis 2



Time Profile Analysis



Time Profile Analysis 1

## 4 Conclusion

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The final alprazolam PBPK model applies metabolism by CYP3A4, modelled as two separate pathways catalyzed by the same enzyme yielding  $\alpha$ -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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