Building and evaluation of a PBPK model for COMPOUND in adults

1 Introduction

Midazolam is a widely-used sedative, approved as premedication before surgical interventions. It is almost exclusively metabolized by CYP3A4, turning it into a sensitive probe and victim drug for the investigation of in vivo CYP3A4 activity. Midazolam shows substantial first pass metabolism, resulting in a bioavailability of under 50%. Less than 1% of a midazolam dose is excreted unchanged in urine.

The herein presented model represents an update of the midazolam model publisdhed by Hanke et al. (Hanke 2018). The model has been developed using in particular published pharmacokinetic clinical data by Hohmann et al. (Hohmann 2015), Hyland et al. 2009 (Hyland 2009) and Thummel et al. 1996 (Thummel 1996). It has then been evaluated by comparing observed data to simulations of a large number of clinical studies covering a dose range from 0.05 mg/kg to 20 mg after intravenous and oral administrations. Furthermore, it has been evaluated within a CYP3A4 DDI modeling network as a victim drug.

Model features include:

- CYP3A4 metabolism
- (direct) UGT1A4 metabolism
- excretion into urine via glomerular filtration
- a decrease in the permeability between the intracellular and interstitial space (parameters "P (intracellular->interstitial)" and "P (interstitial->intracellular)") in intestinal mucosa to optimize quantitatively the extent of gut wall metabolism
- and binding to a hypothetical binding partner in the brain to optimize a late redistribution phase in midazolam plasma concentrations.

The presented midazolam PBPK model as well as the respective evaluation plan and PBPK report are provided open-source (https://github.com/sfrechen/Midazolam-model).

2 Methods

2.1 Modeling strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. (Kuepfer 2016) Regarding the relevant anthropometric (height, weight) and physiological parameters (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). The information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

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 (Schlender 2016) or otherwise referenced for the specific process.

First, a base mean model was built using data from [...] to find an appropriate structure to describe the PK in plasma. The mean PBPK model was developed using a typical European individual. Unknown parameters 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.

Once the appropriate structural model was identified, additional parameters for different formulations were identified.

A final PBPK model was established and simulations were compared to the reported data to evaluate model appropriateness and to assess model qualification, by means of diagnostics plots and predicted versus observed concentration-time profiles, of which the results support an adequate prediction of the PK in adults.

[...]

2.2 Data used

2.2.1 In vitro / physico-chemical data

A literature search was performed to collect available information on physical chemical properties of `COMPOUND`. The obtained information from literature is summarized in the table below, and is used for model building.

Parameter	Unit	Value	Source	Description
MW	g/mol	300	Author YEAR	Molecular weight
pKa		7	Author YEAR	Acid dissociation constant
Solubility (pH)	mg/L	1	Author YEAR	Aqueous Solubility
logP		0	Author YEAR	Partition coefficient between octanol and water
fu	%	100	Author YEAR	Fraction unbound in plasma
...				...
...				...
...				...
...				...

2.2.2 Clinical data

A literature search was performed to collect available clinical data on `COMPOUND` in adults.

The following publications were found in adults for model building and evaluation:

Publication	Study description
Author YEAR	Clinical study to investigate the pharmacokinetics of COMPOUND after intravenous and oral administration
...	...
...	...
...	...

2.3 Model parameters and assumptions

2.3.1 Absorption

`DESCRIBE PROPERTIES OF THE MODEL`

2.3.2 Distribution

`DESCRIBE PROPERTIES OF THE MODEL`

2.3.3 Metabolism and Elimination

`DESCRIBE PROPERTIES OF THE MODEL`

3 Results and Discussion

The PBPK model `COMPOUND` was developed with clinical pharmacokinetic data covering ...

[...]

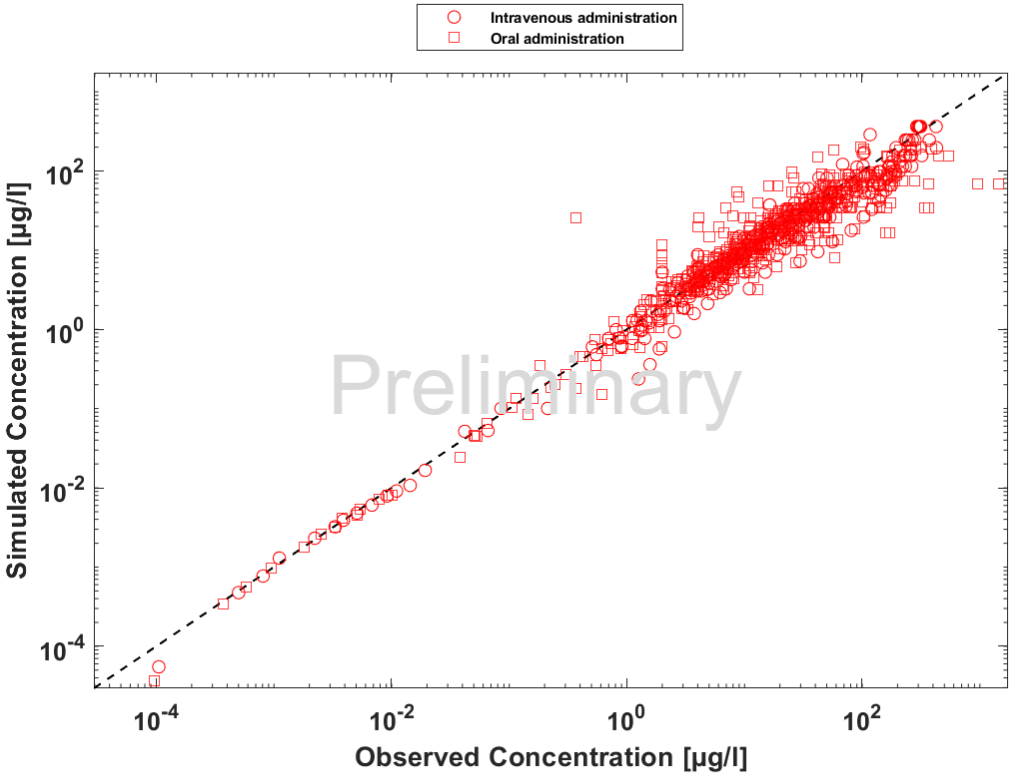
3.1 Final input parameters

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

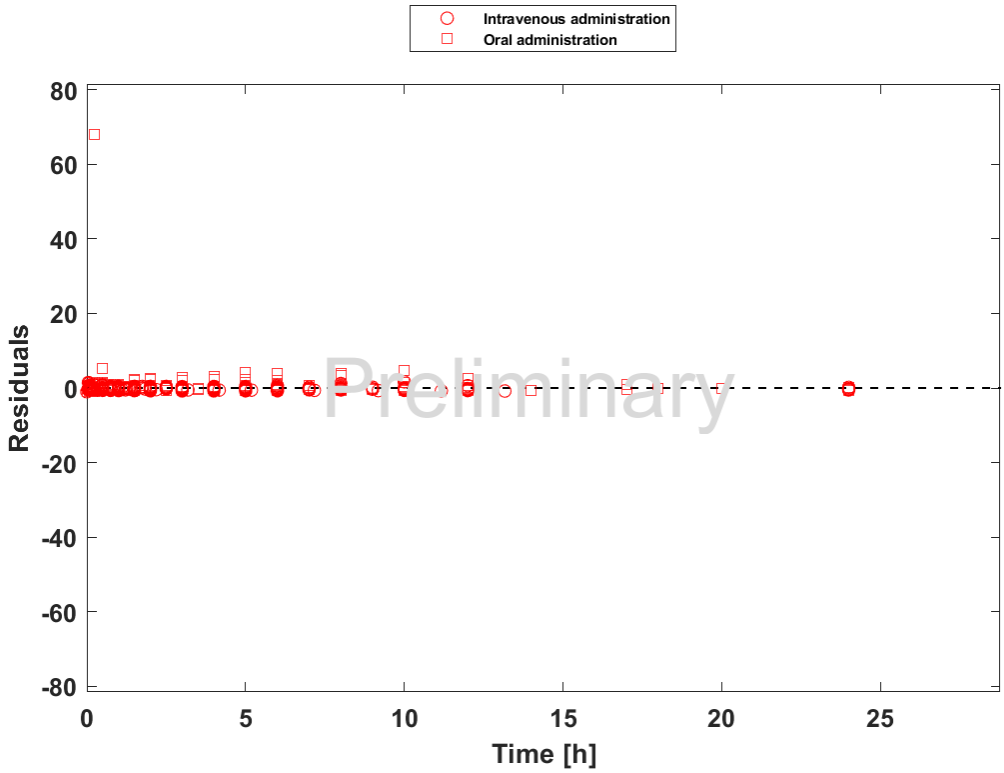
3.2 Diagnostics Plots

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.



Midazolam concentration in plasma/blood

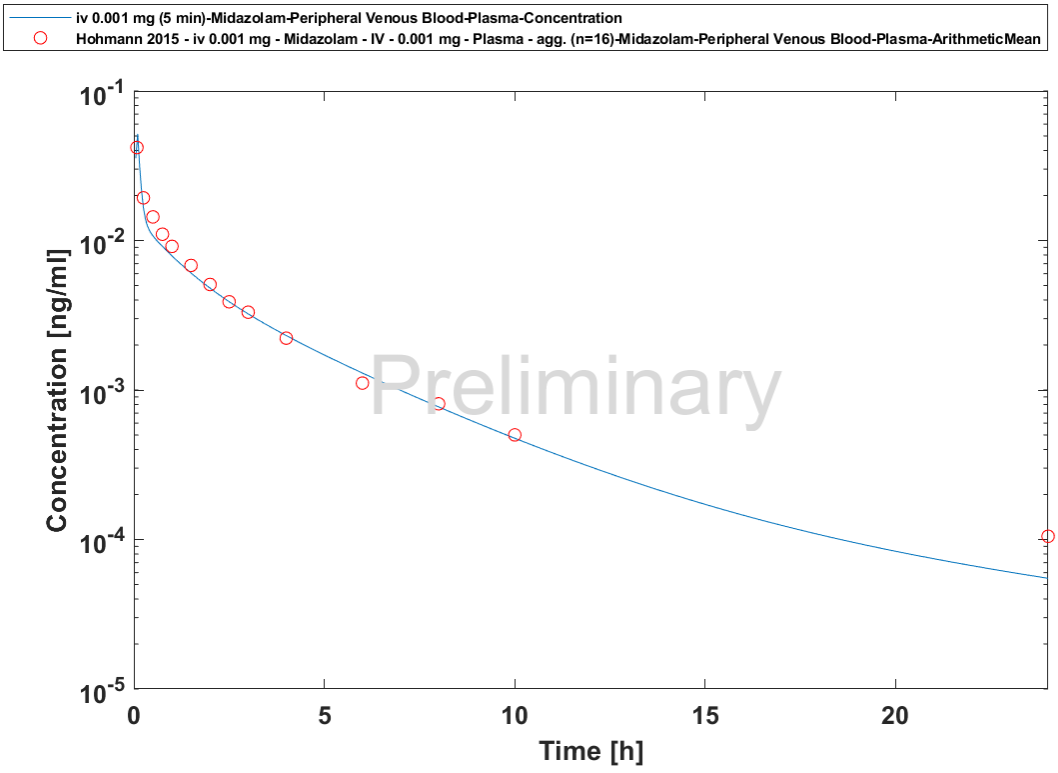


Midazolam concentration in plasma/blood

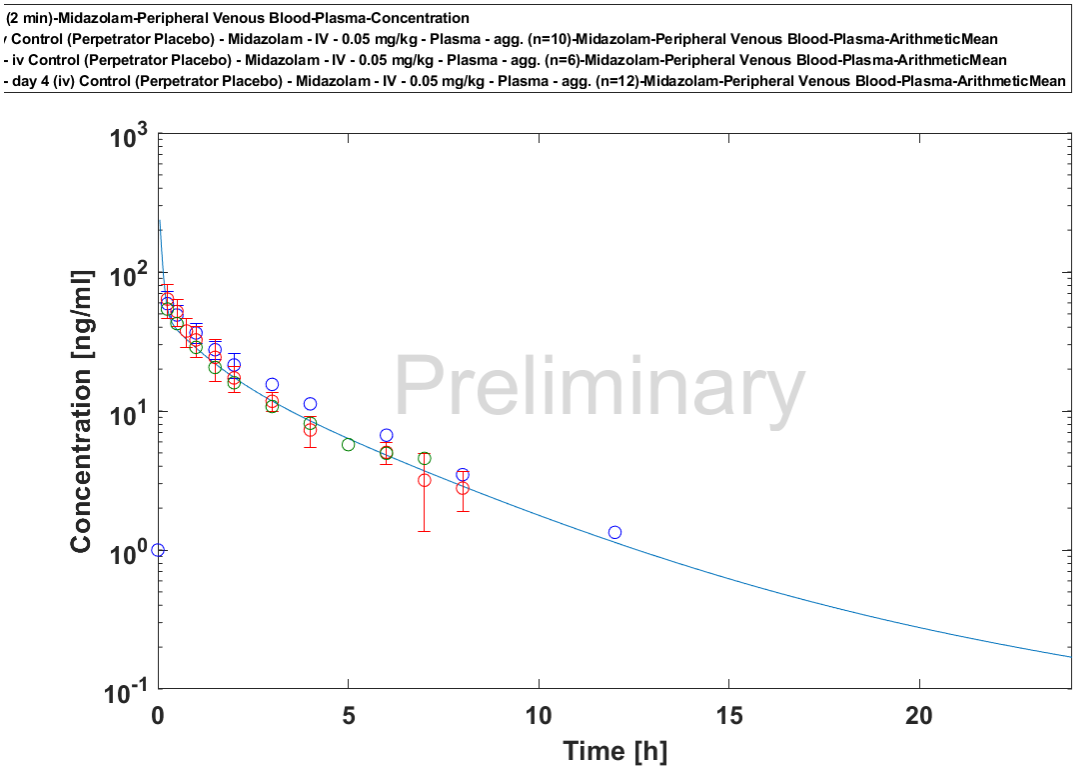
GMFE = 1.451824

3.3: Concentration-Time profiles

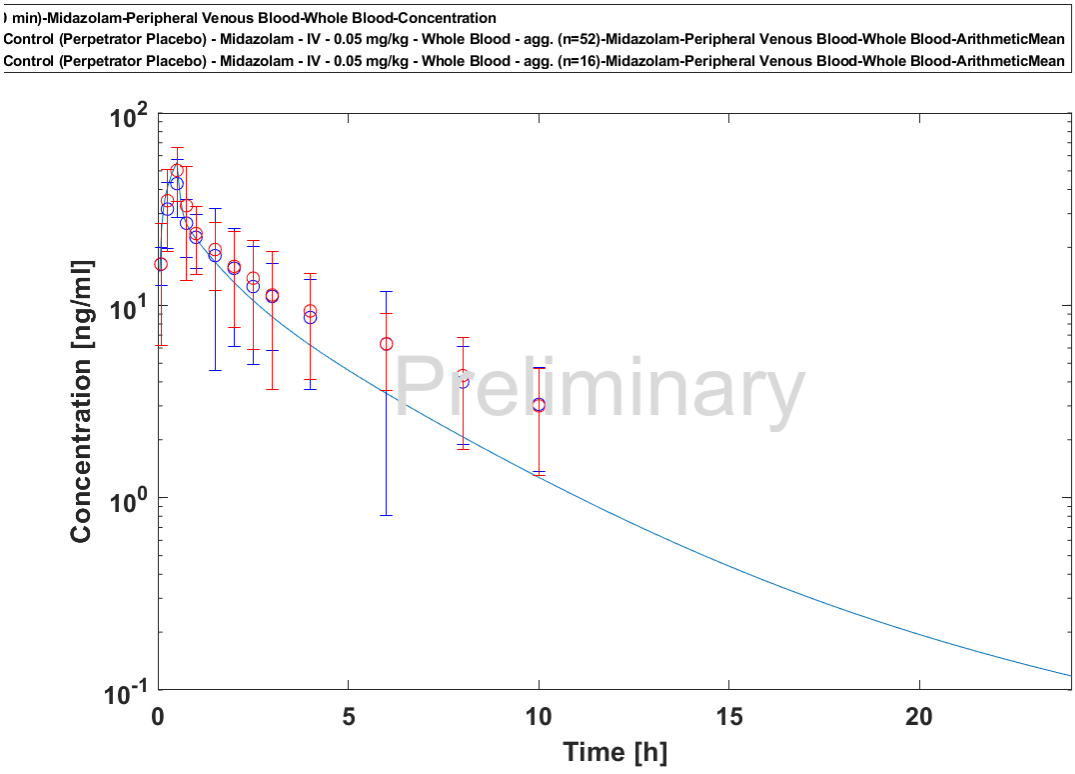
Simulated versus observed concentration-time profiles of all data listed in Section 2.2.2 are presented below.



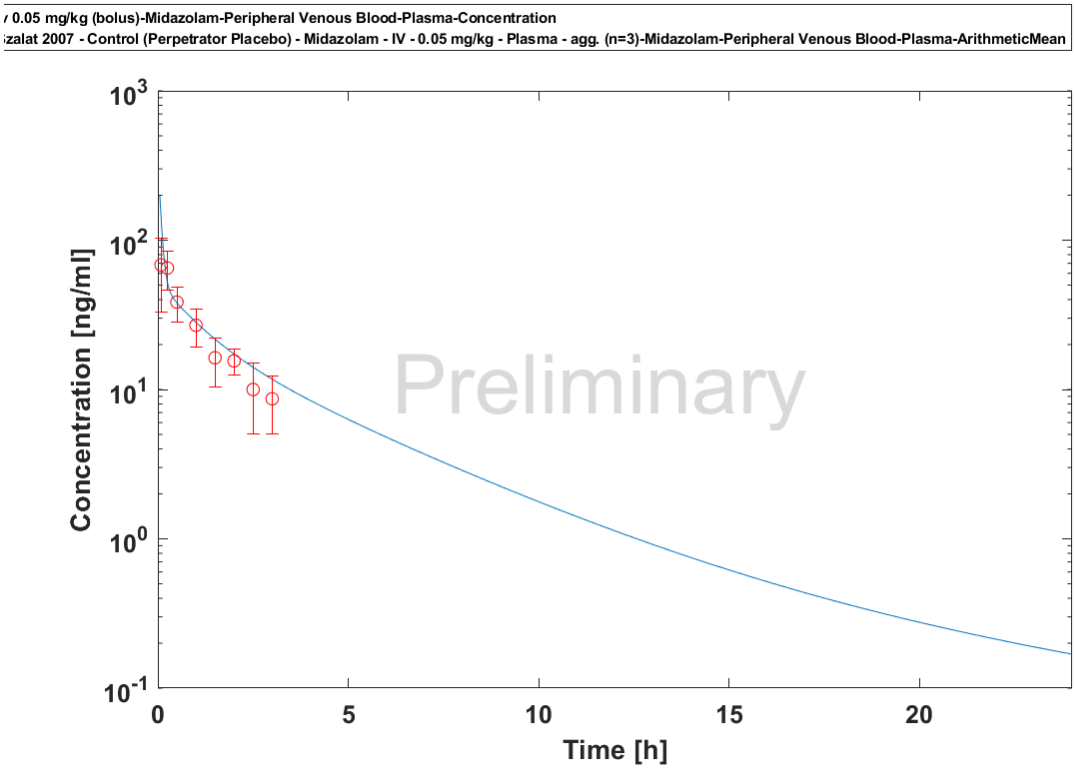
iv 0.001 mg (5 min) - Plasma



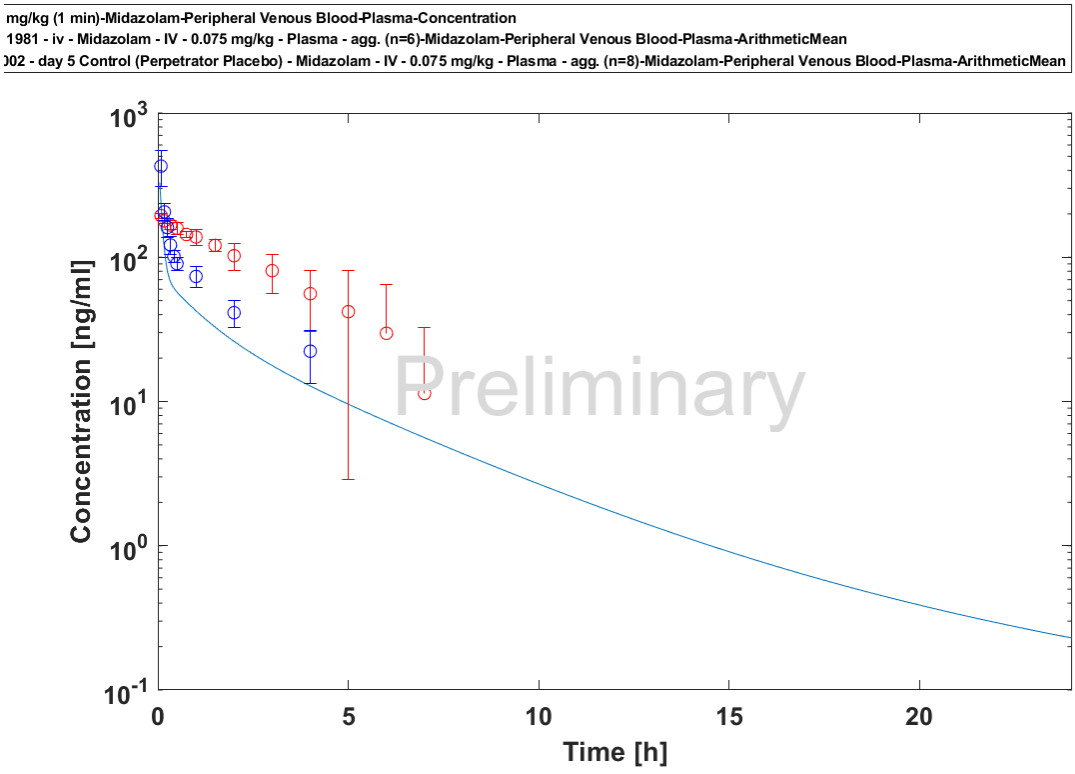
iv 0.05 mg/kg (2 min) - Plasma



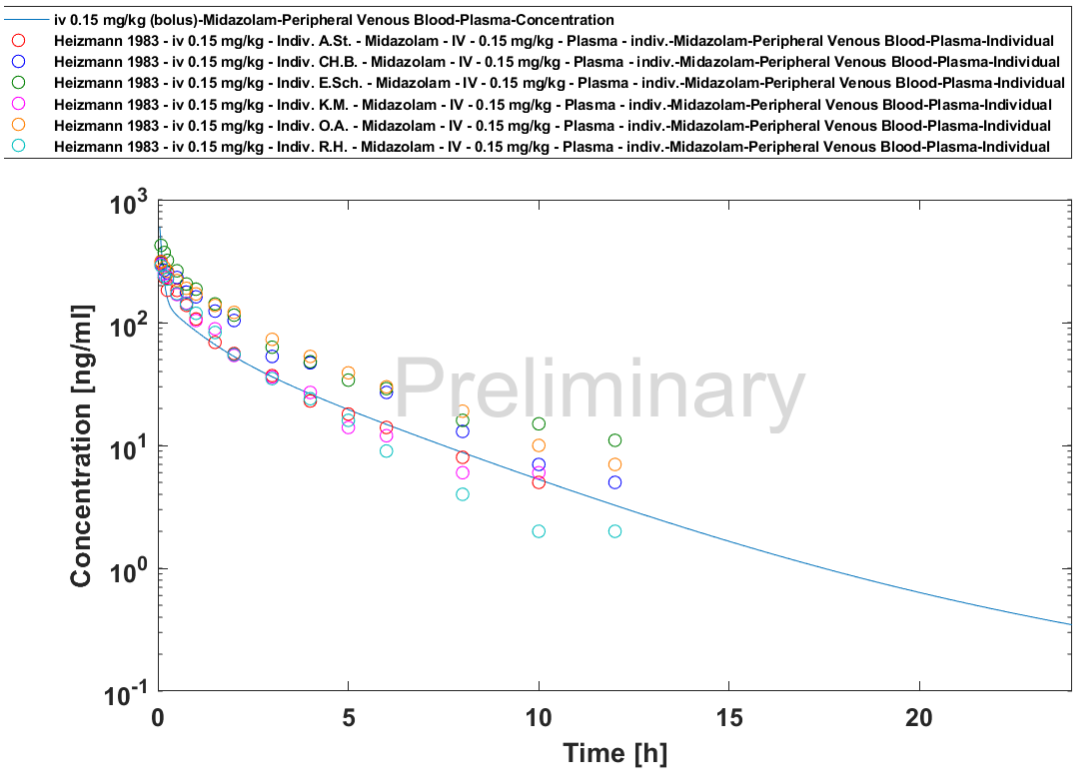
iv 0.05 mg/kg (30 min) - Whole blood



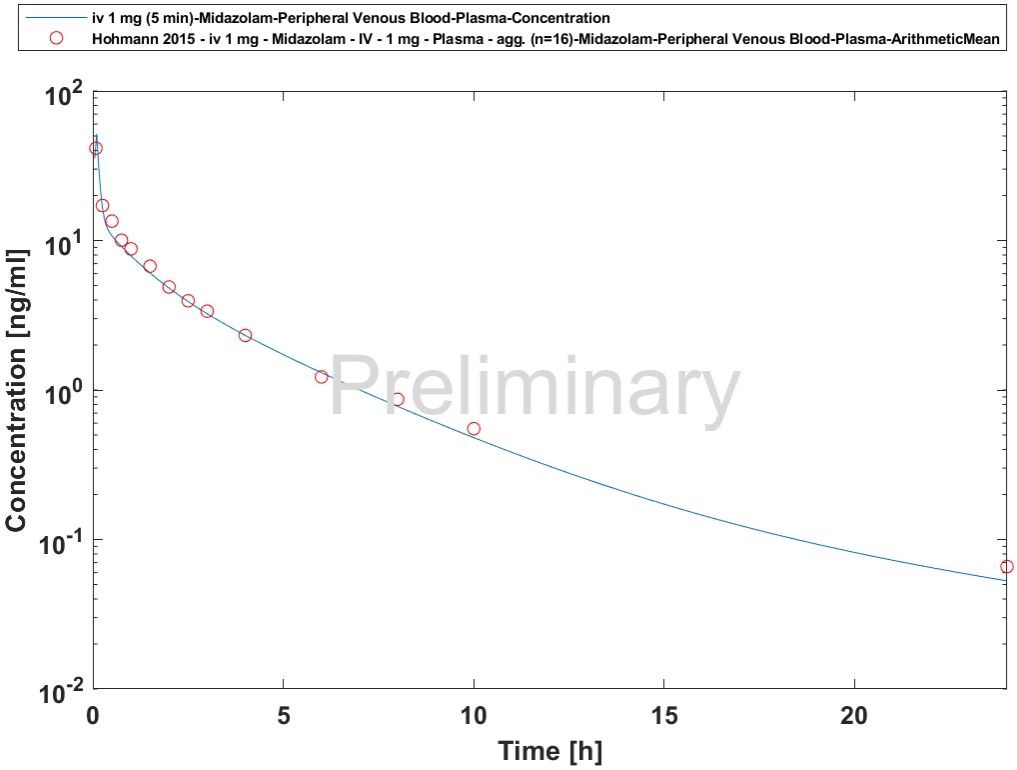
iv 0.05 mg/kg (bolus) - Plasma



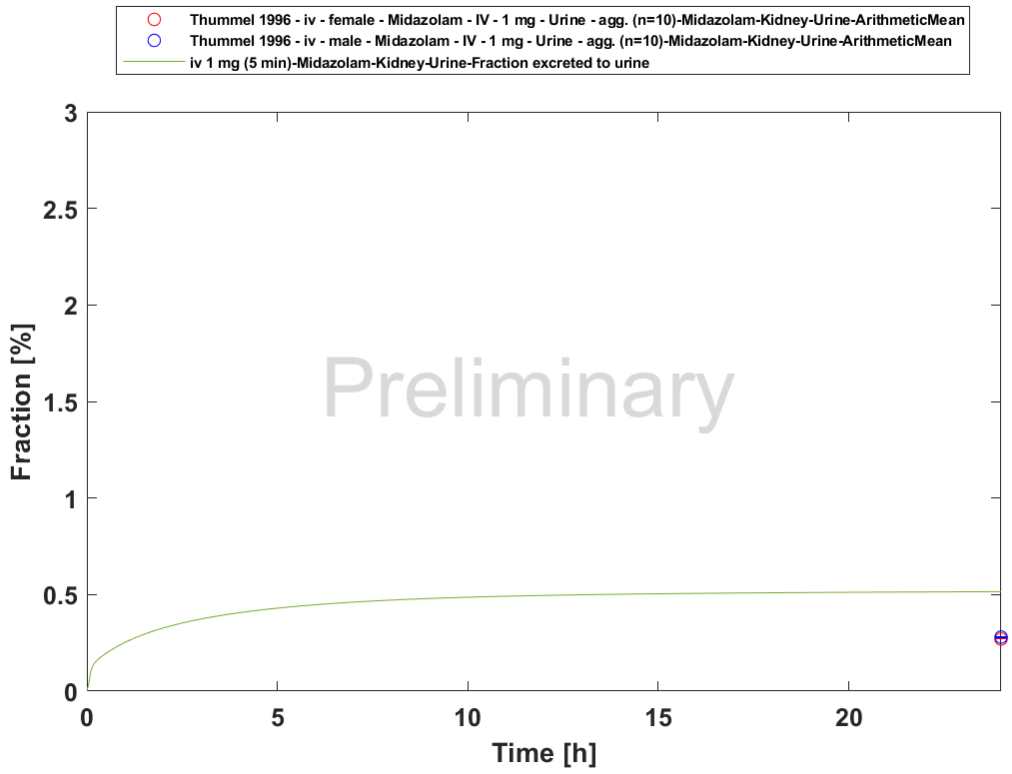
iv 0.075 mg/kg (1 min) - Plasma



iv 0.15 mg/kg (bolus) - Plasma

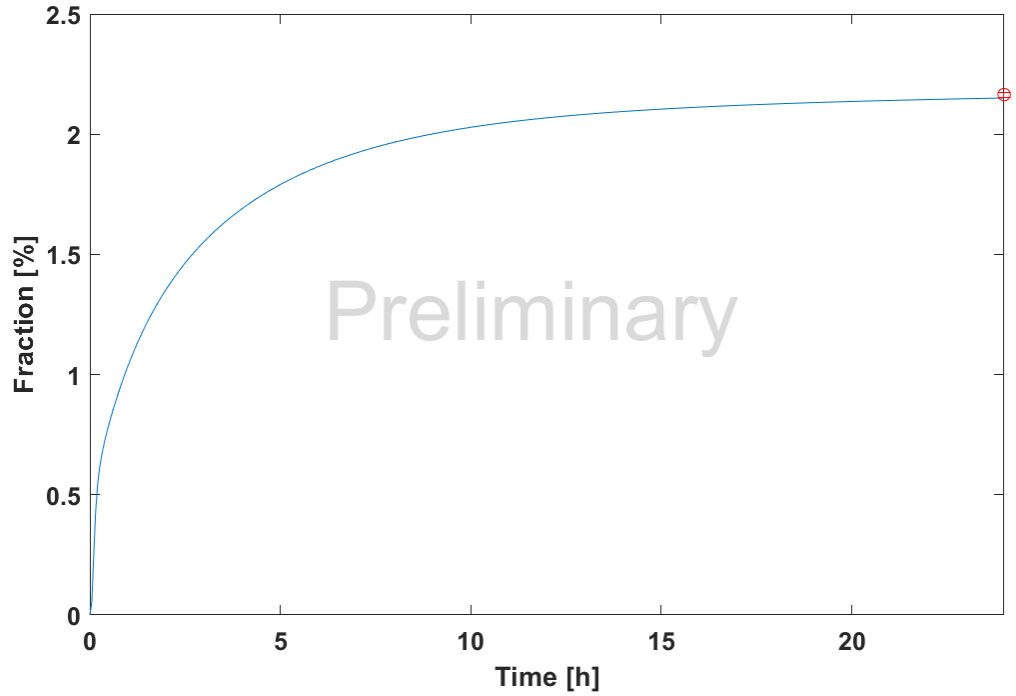


iv 1 mg (5 min) - Plasma



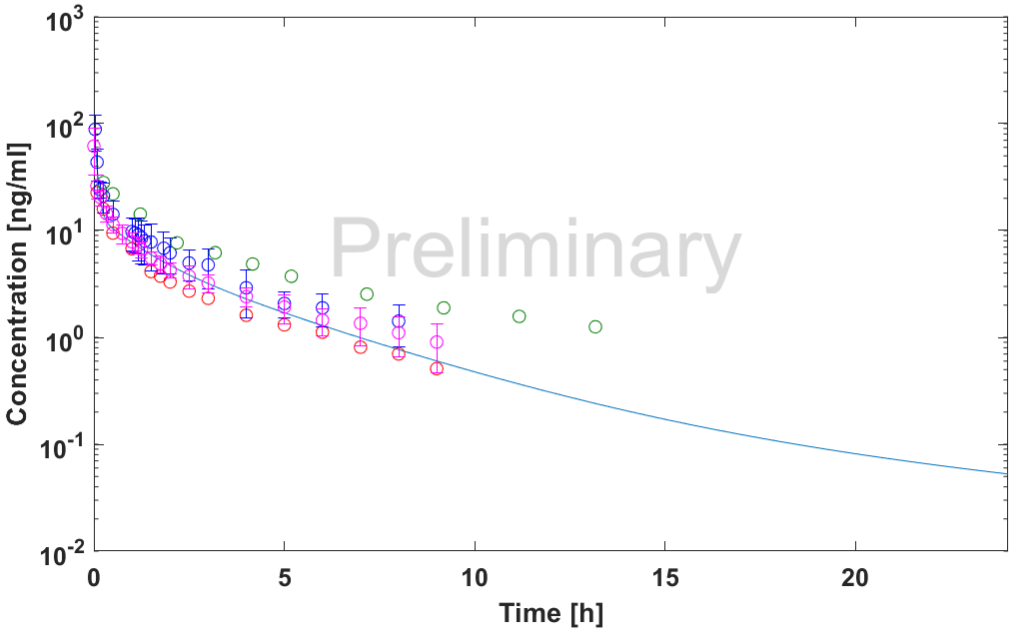
iv 1 mg (5 min) - Urine

min)-Midazolam-UGT1A4-Optimized Metabolite-Liver Periportal-Intracellular-Fraction of dose-Midazolam
09 - 1-mg i.v. dose (as fraction of dose) - Midazolam-N-Glucuronide - IV - 1 mg - Urine - agg. (n=6)-Midazolam-N-Glucuronide-Kidney-Urine-ArithmeticMean

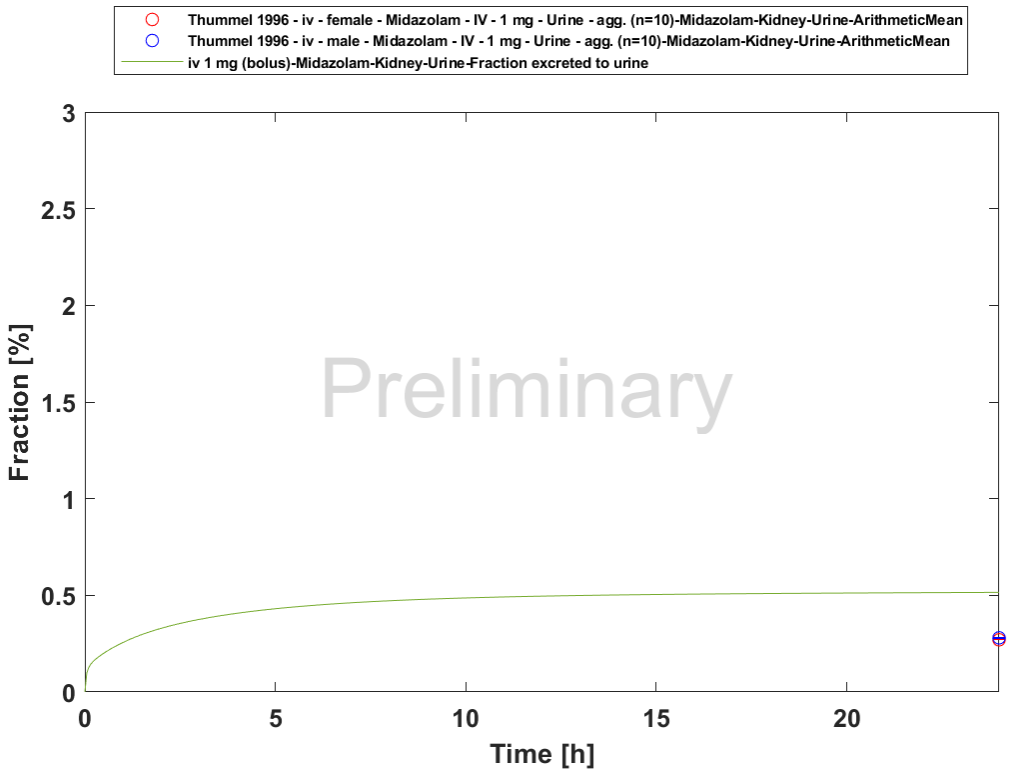


iv 1 mg (5 min) - fm UGT1A4

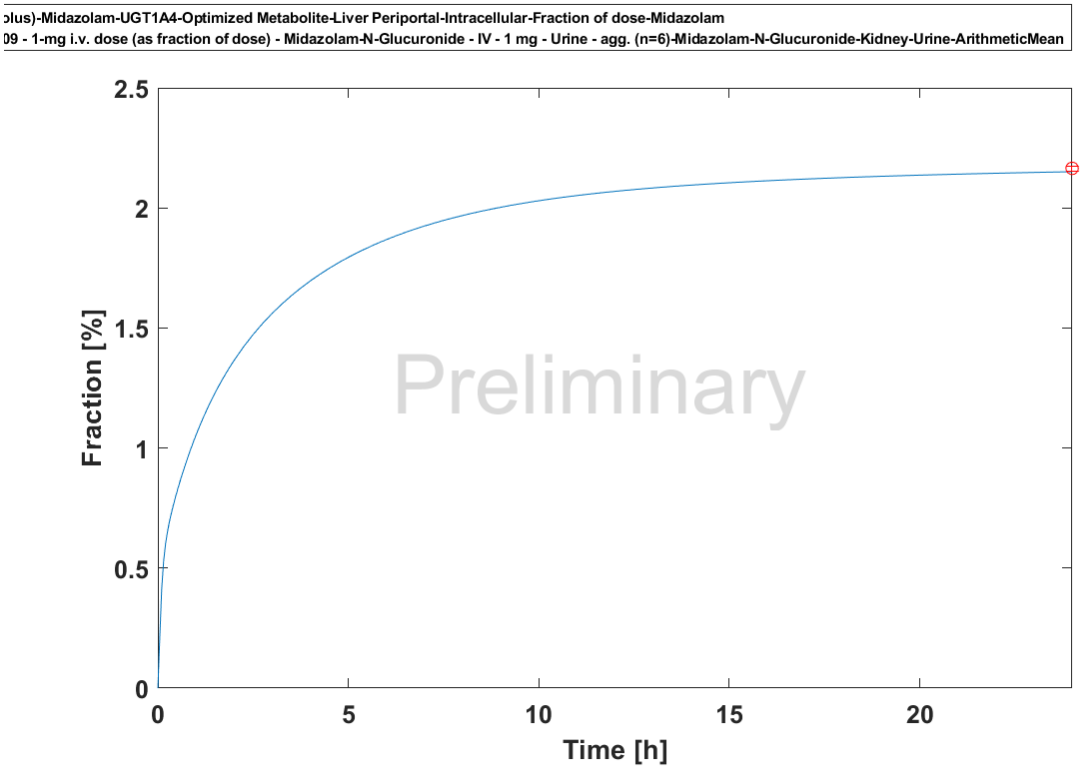
1 mg (bolus)-Midazolam-Peripheral Venous Blood-Plasma-Concentration
arasch 2004 - iv Control (Perpetrator Placebo) - Midazolam - IV - 1 mg - Plasma - agg. (n=10)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
immasone 2001 - Control (Perpetrator Placebo) - Midazolam - IV - 1 mg - Plasma - agg. (n=6)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
arasch 1997 - Control (Perpetrator Placebo) - Midazolam - IV - 1 mg - Plasma - typical (n=9)-Midazolam-Peripheral Venous Blood-Plasma-Individual
arasch 2011 - iv Control (Perpetrator Placebo) - Midazolam - IV - 1 mg - Plasma - agg. (n=12)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



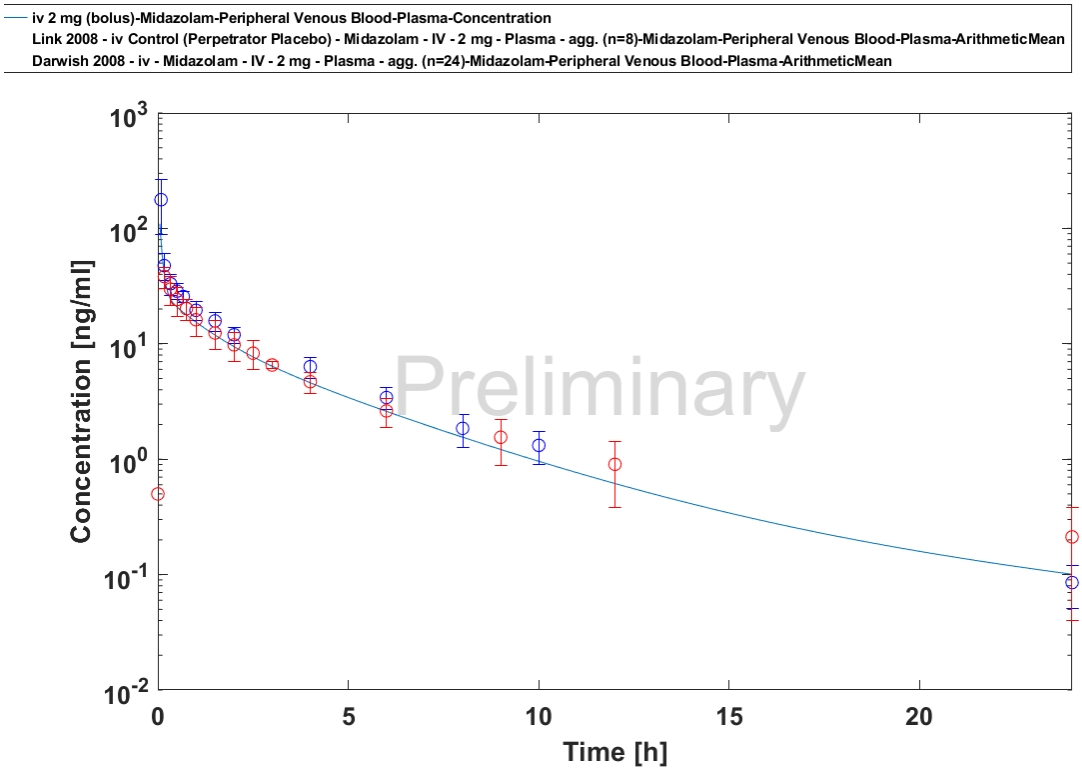
iv 1 mg (bolus) - Plasma



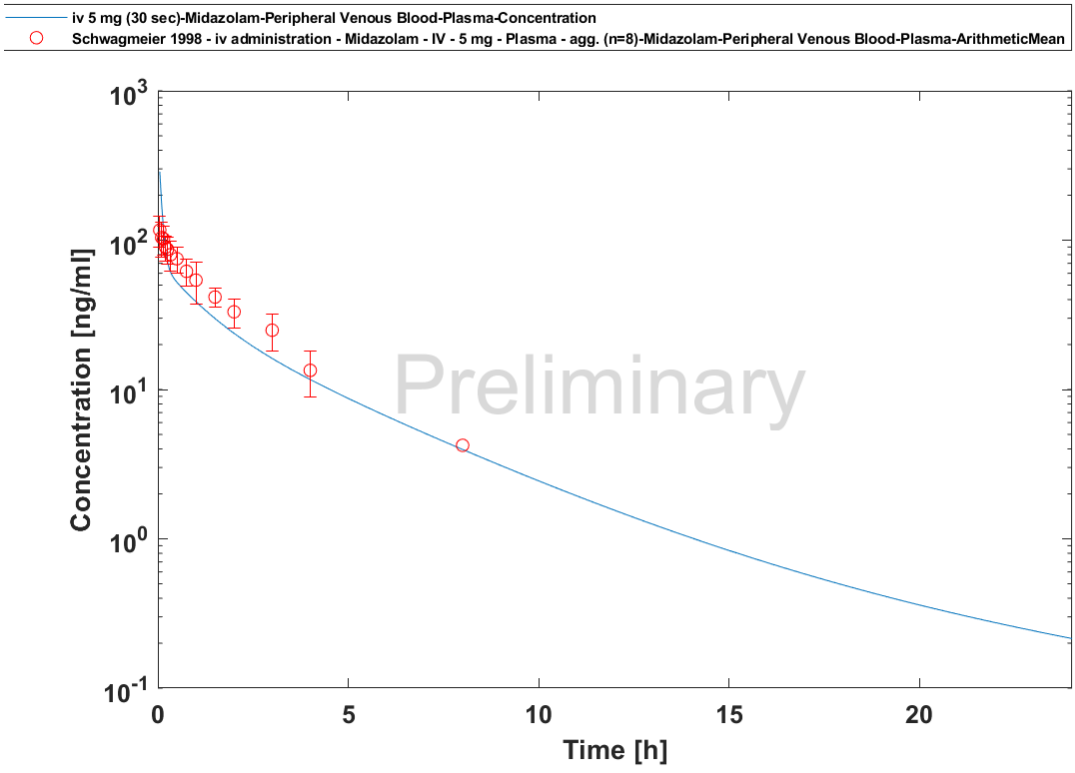
iv 1 mg (bolus) - Urine



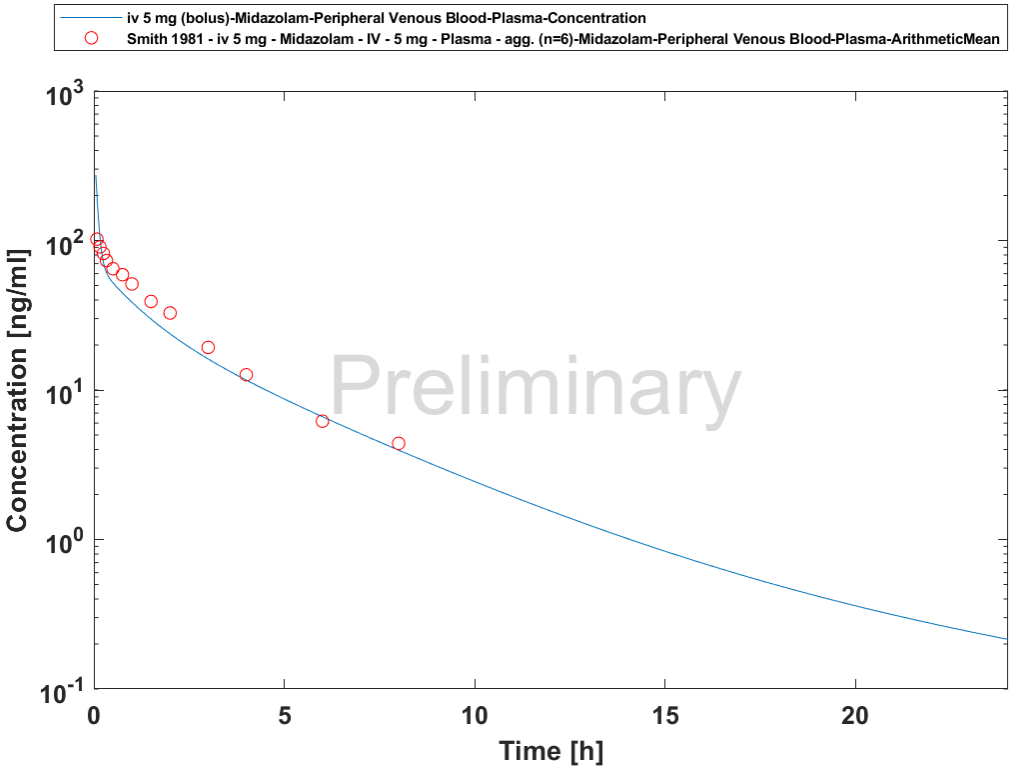
iv 1 mg (bolus) - fm UGT1A4



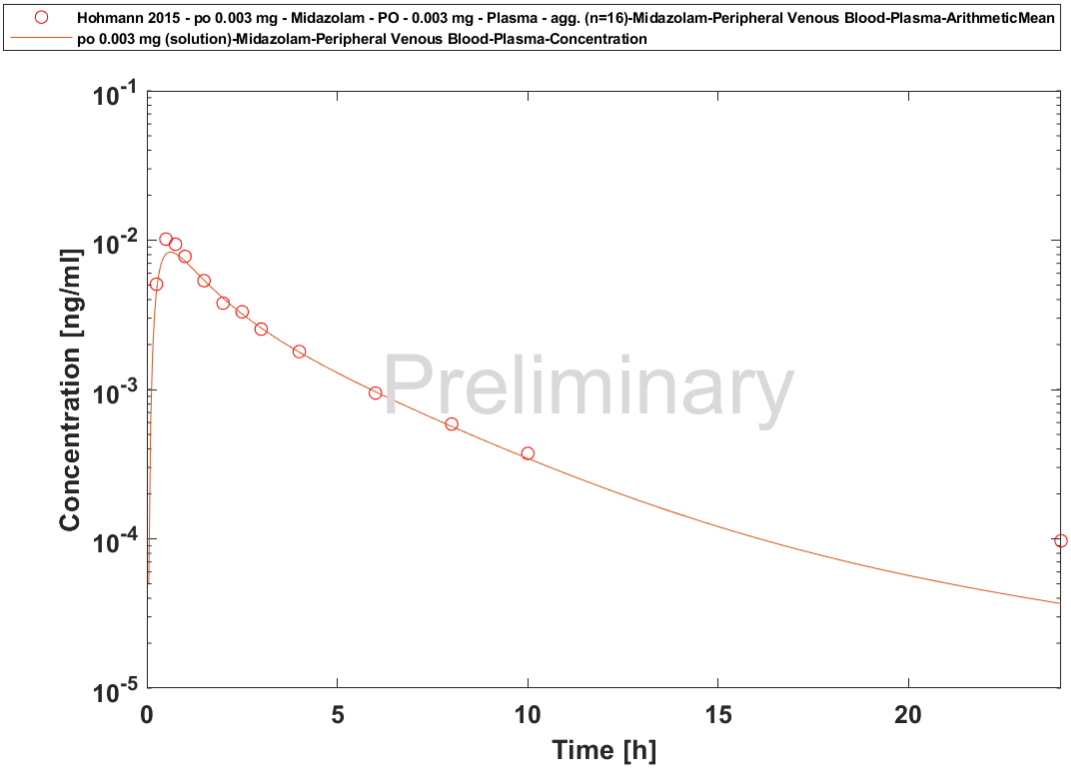
iv 2 mg (bolus) - Plasma



iv 5 mg (30 sec) - Plasma

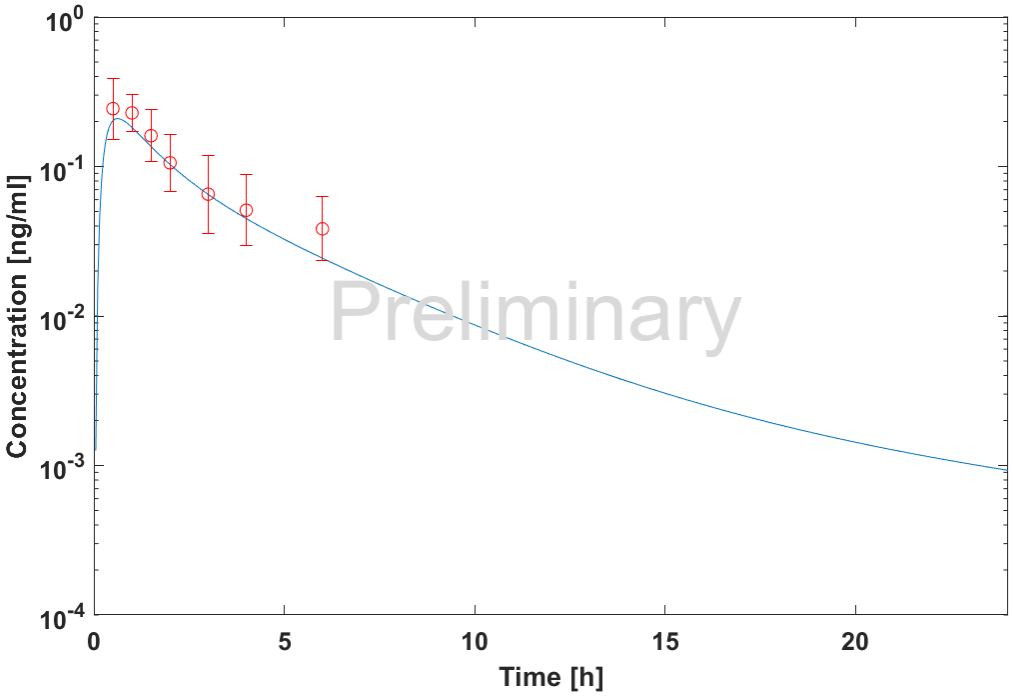


iv 5 mg (bolus) - Plasma



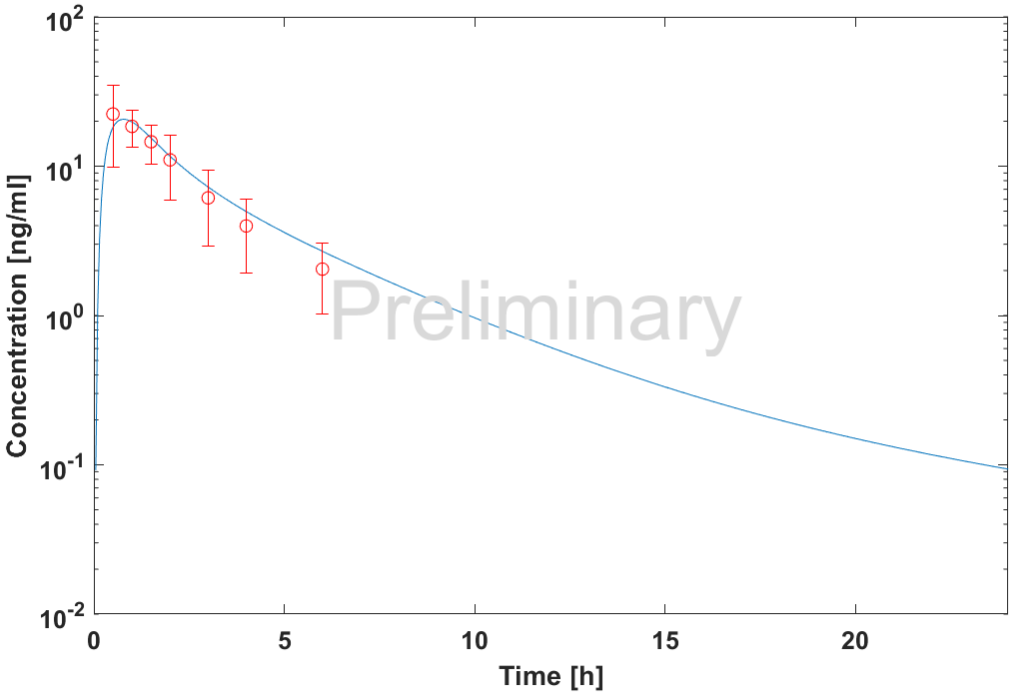
po 0.003 mg (solution) - Plasma

mg (solution)-Midazolam-Peripheral Venous Blood-Plasma-Concentration
- 0.075 mg Control (Perpetrator Placebo) - Midazolam - PO - 0.075 mg - Plasma - agg. (n=21)-Midazolam-Peripheral Venous Blood-Plasma-GeometricMean

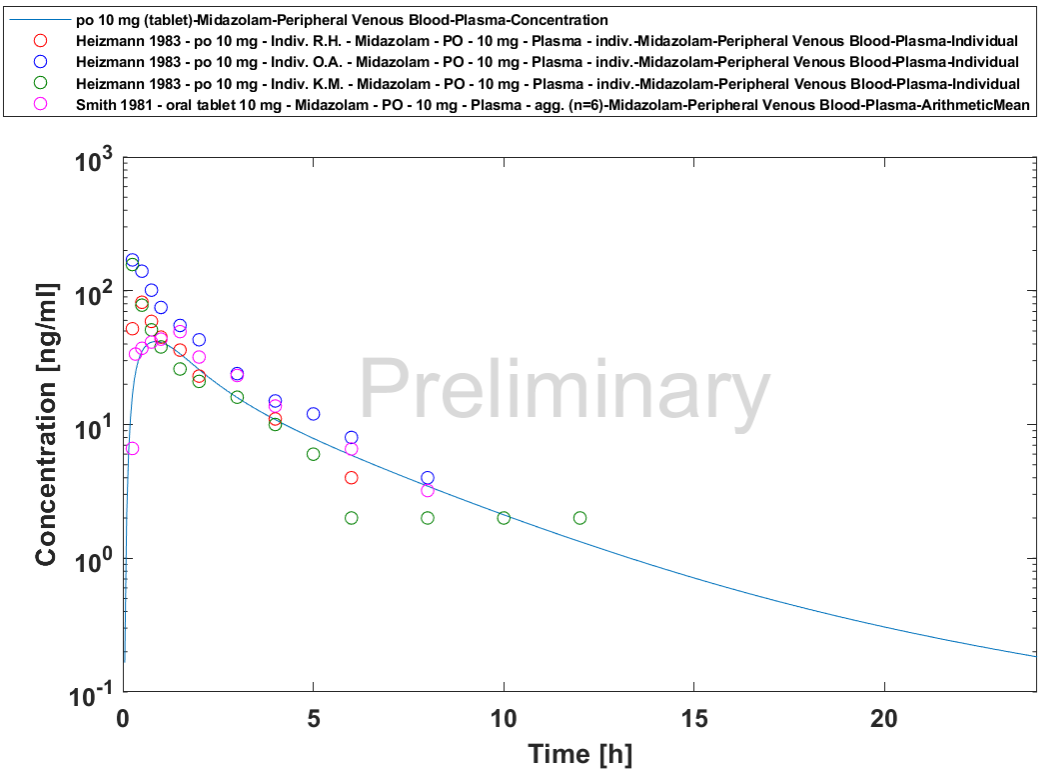


po 0.075 mg (solution) - Plasma

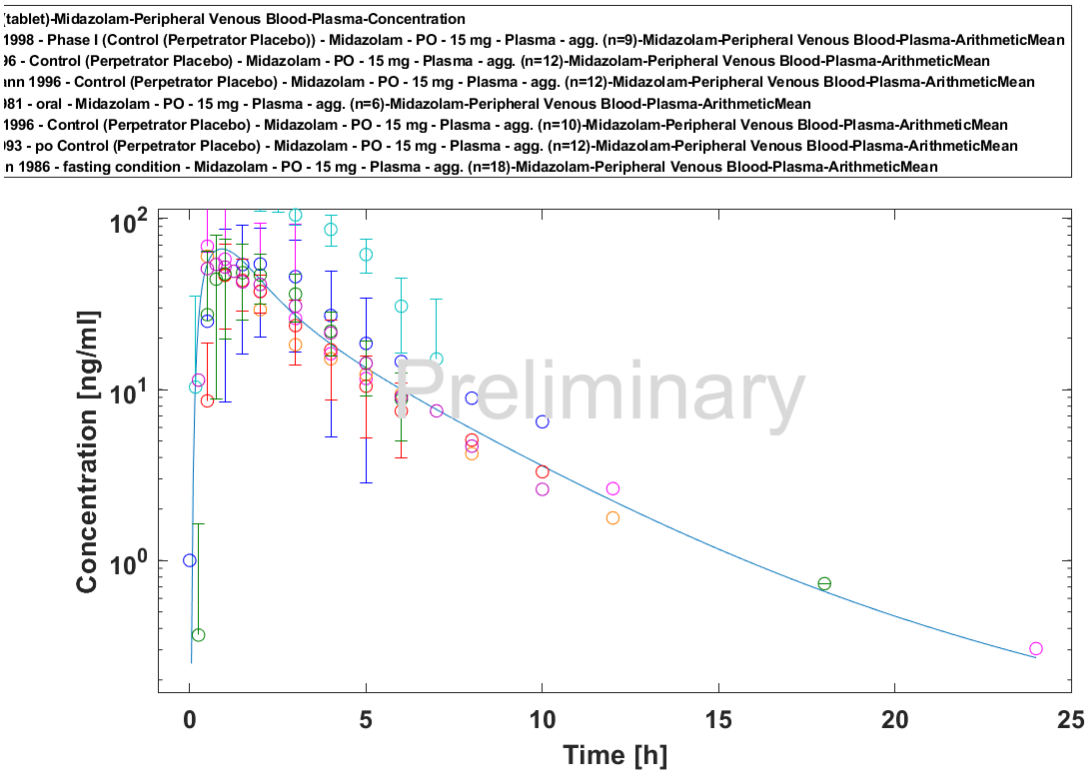
075 mg/kg (syrup)-Midazolam-Peripheral Venous Blood-Plasma-Concentration
g 2006 - Control (Perpetrator Placebo) - Midazolam - PO - 0.075 mg/kg - Plasma - agg. (n=18)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



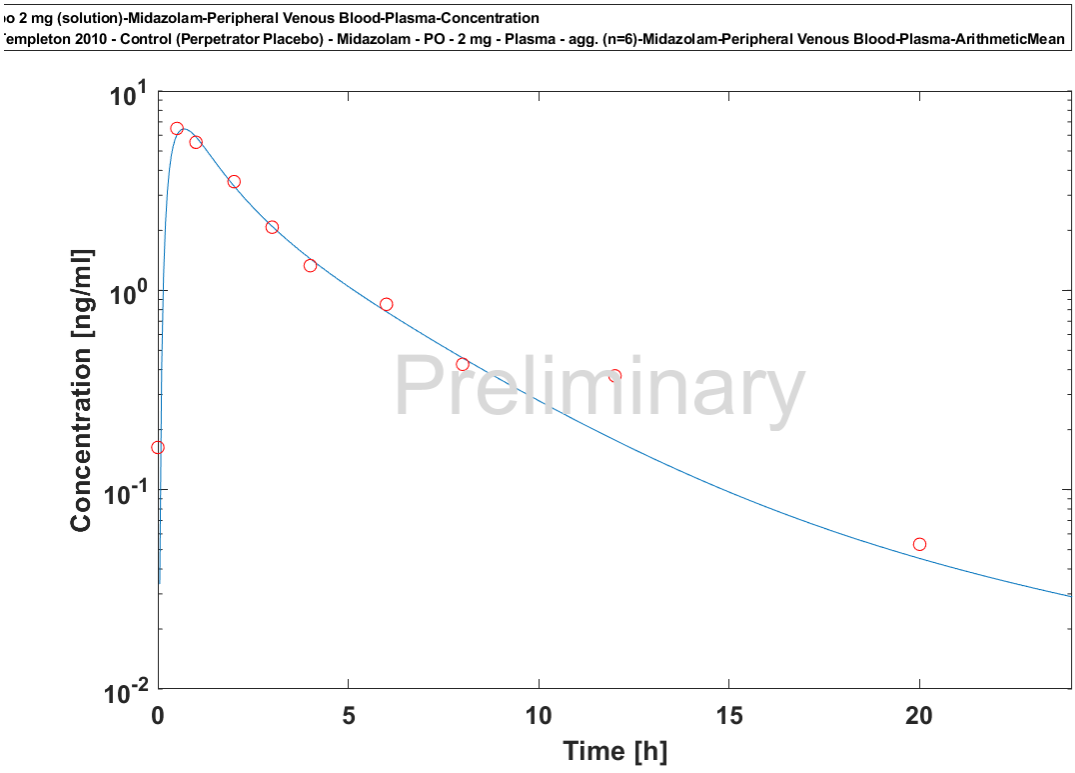
po 0.075 mg/kg (syrup) - Plasma



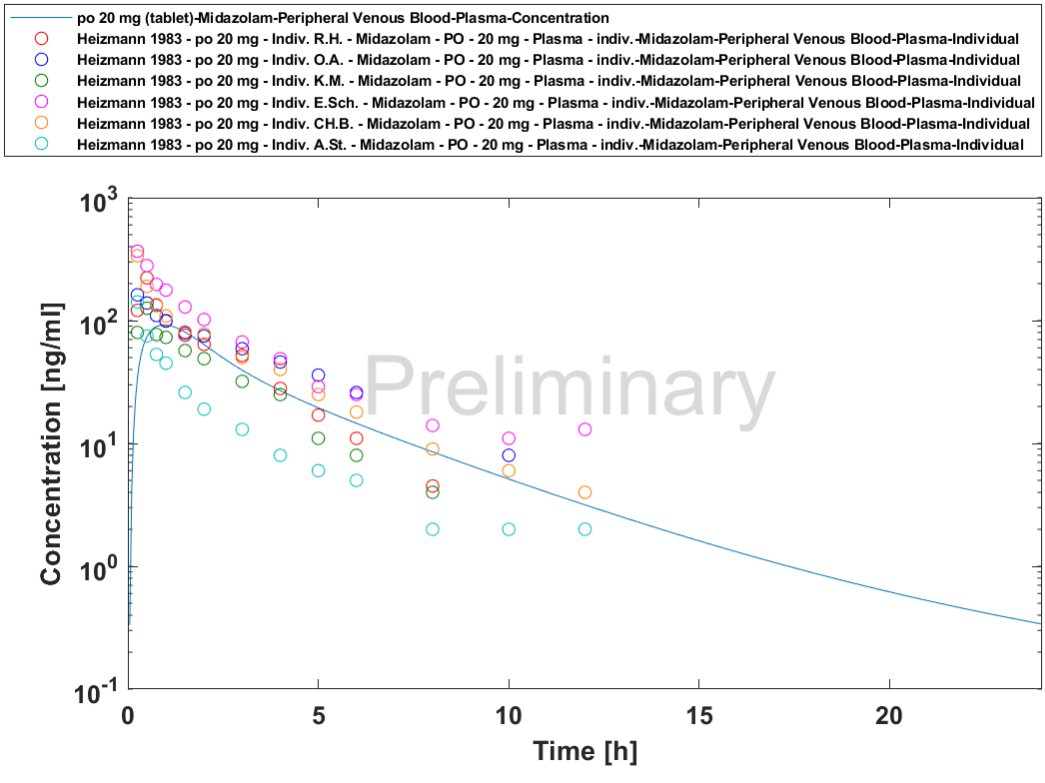
po 10 mg (tablet) - Plasma



po 15 mg (tablet) - Plasma

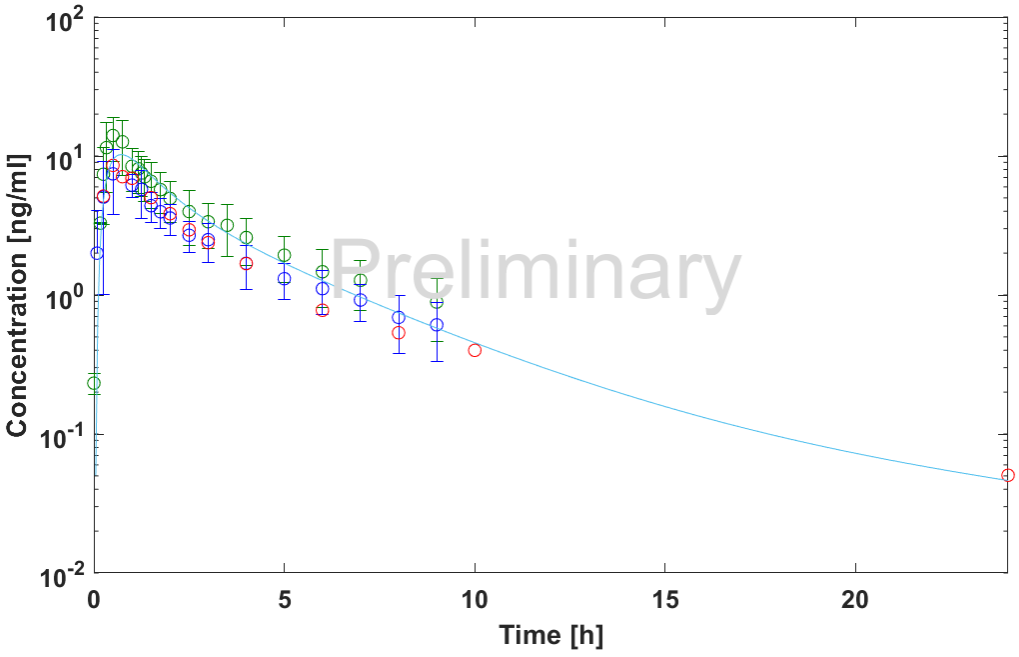


po 2 mg (solution) - Plasma



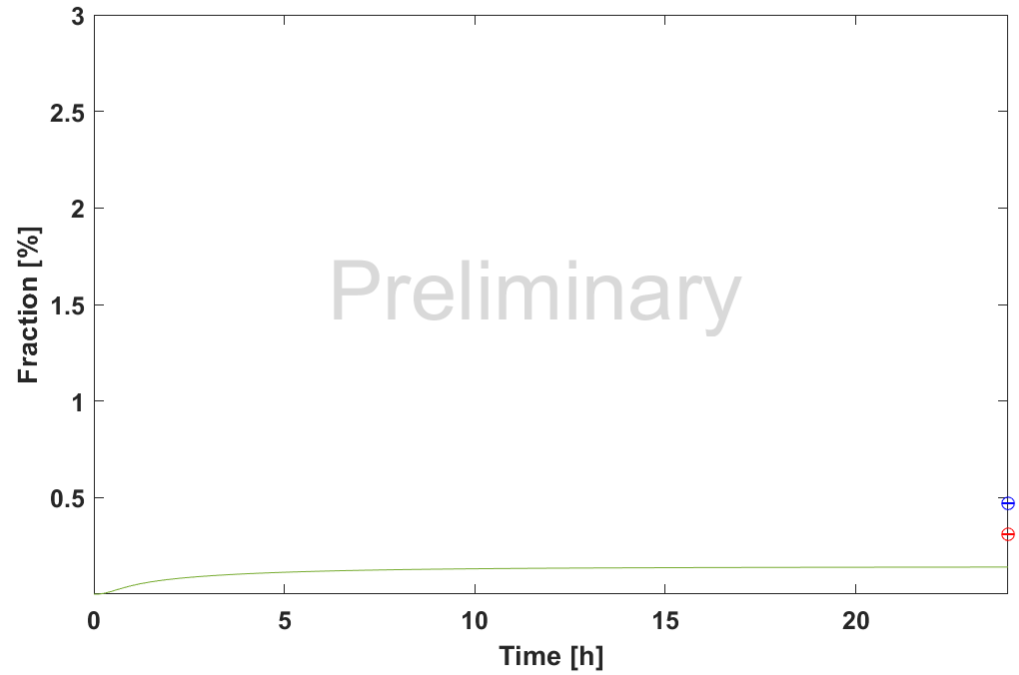
po 20 mg (tablet) - Plasma

ch 2011 - po Control (Perpetrator Placebo) - Midazolam - PO - 3 mg - Plasma - agg. (n=12)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
ch 2004 - po #1 Control (Perpetrator Placebo) - Midazolam - PO - 3 mg - Plasma - agg. (n=10)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
nn 2015 - po 3 mg - Midazolam - PO - 3 mg - Plasma - agg. (n=16)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
g (solution)-Midazolam-Peripheral Venous Blood-Plasma-Concentration



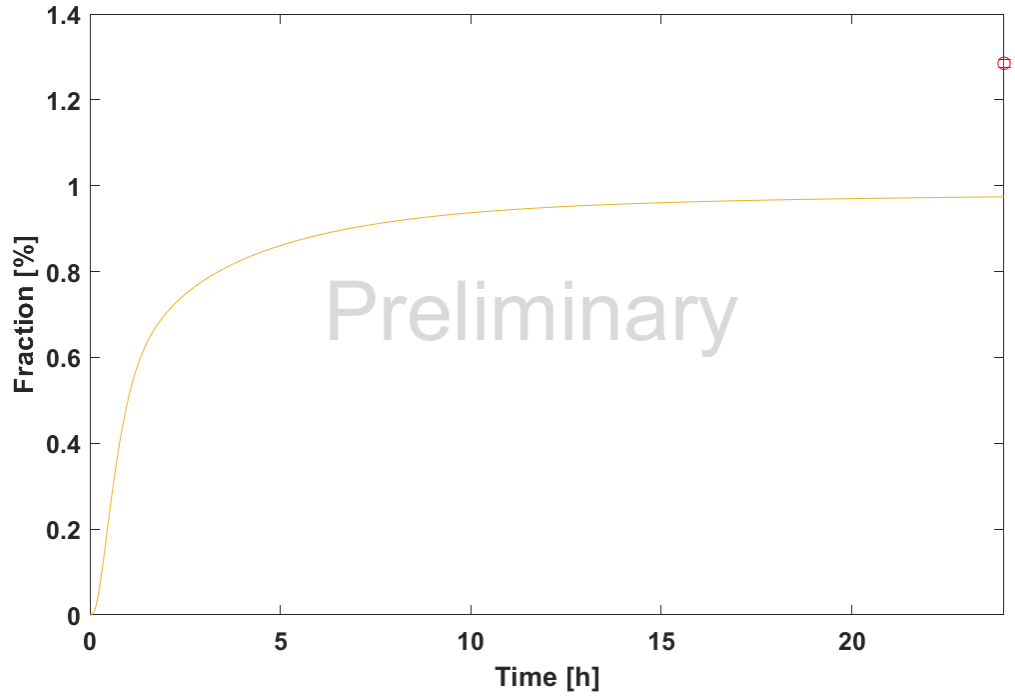
po 3 mg (solution) - Plasma

Thummel 1996 - po - male - Midazolam - PO - 2 mg - Urine - agg. (n=10)-Midazolam-Kidney-Urine-ArithmeticMean
Thummel 1996 - po - female - Midazolam - PO - 2 mg - Urine - agg. (n=10)-Midazolam-Kidney-Urine-ArithmeticMean
po 3 mg (solution)-Midazolam-Kidney-Urine-Fraction excreted to urine



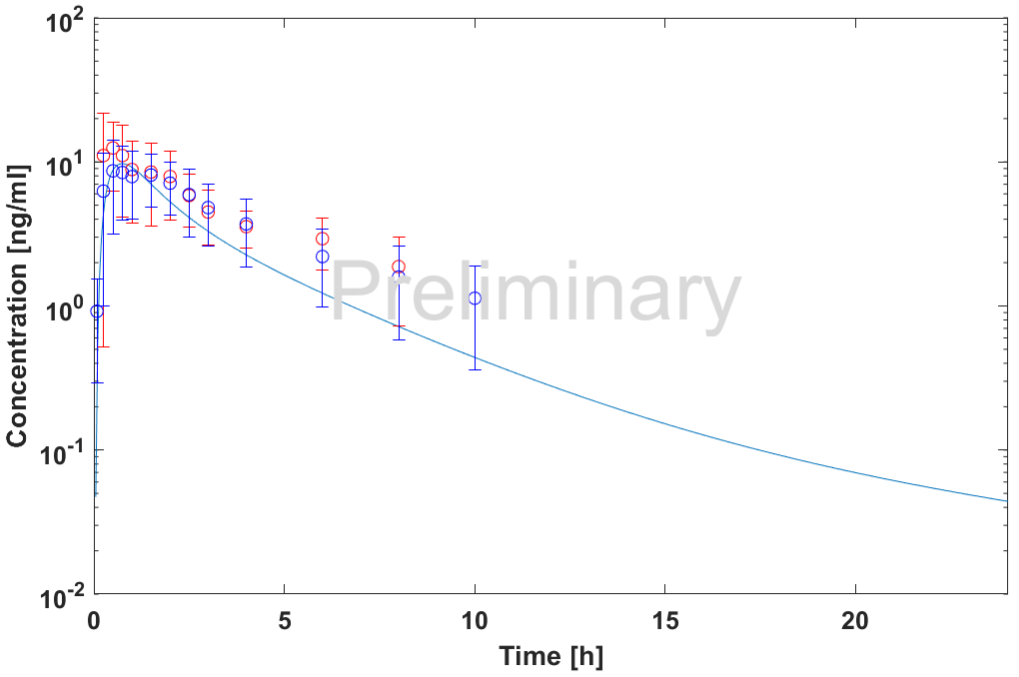
po 3 mg (solution) - Urine

) - 3-mg oral dose (as fraction of dose) - Midazolam-N-Glucuronide - PO - 3 mg - Urine - agg. (n=6)-Midazolam-N-Glucuronide-Kidney-Urine-ArithmeticMean
lution)-Midazolam-UGT1A4-Optimized Metabolite-Liver Periportal-Intracellular-Fraction of dose-Midazolam

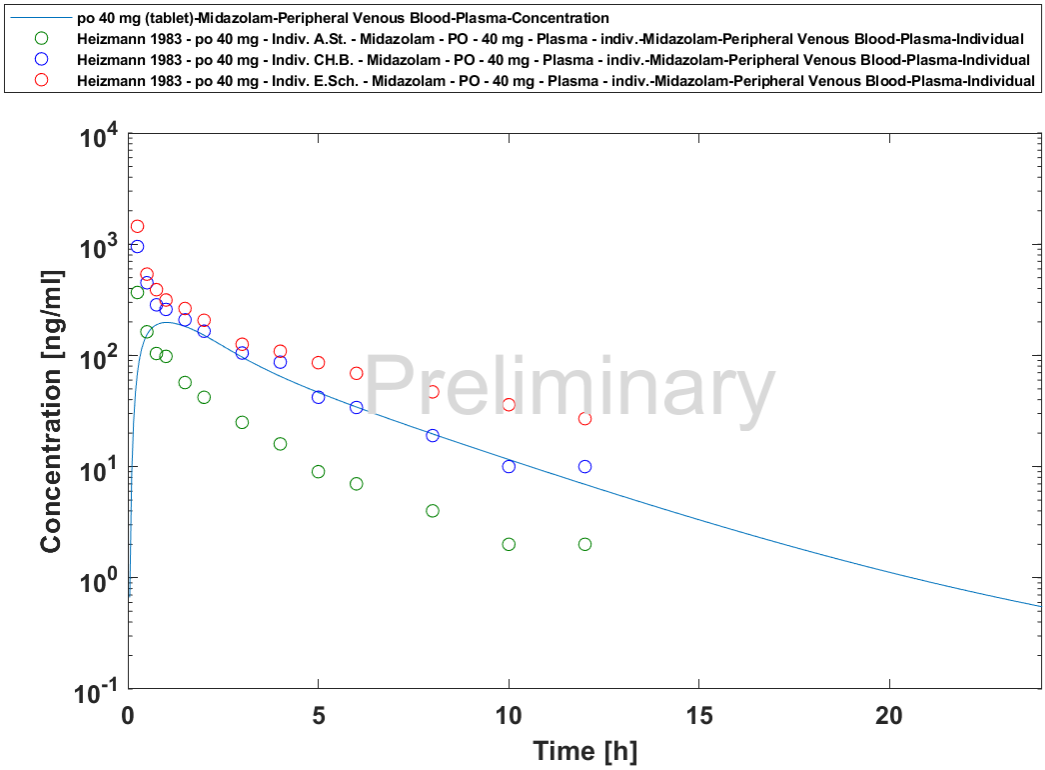


po 3 mg (solution) - fm UGT1A4

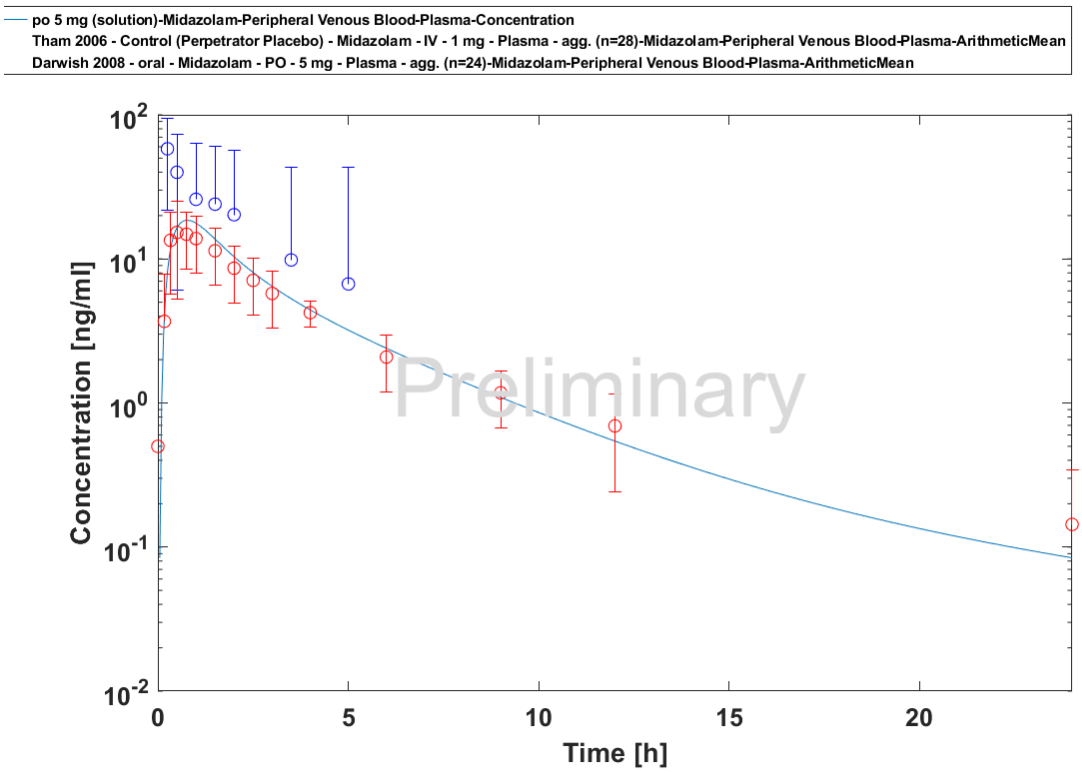
ution)-Midazolam-Peripheral Venous Blood-Whole Blood-Concentration
- po Control (Perpetrator Placebo) - Midazolam - PO - 4 mg - Whole Blood - agg. (n=16)-Midazolam-Peripheral Venous Blood-Whole Blood-ArithmeticMean
- po Control (Perpetrator Placebo) - Midazolam - PO - 4 mg - Whole Blood - agg. (n=52)-Midazolam-Peripheral Venous Blood-Whole Blood-ArithmeticMean



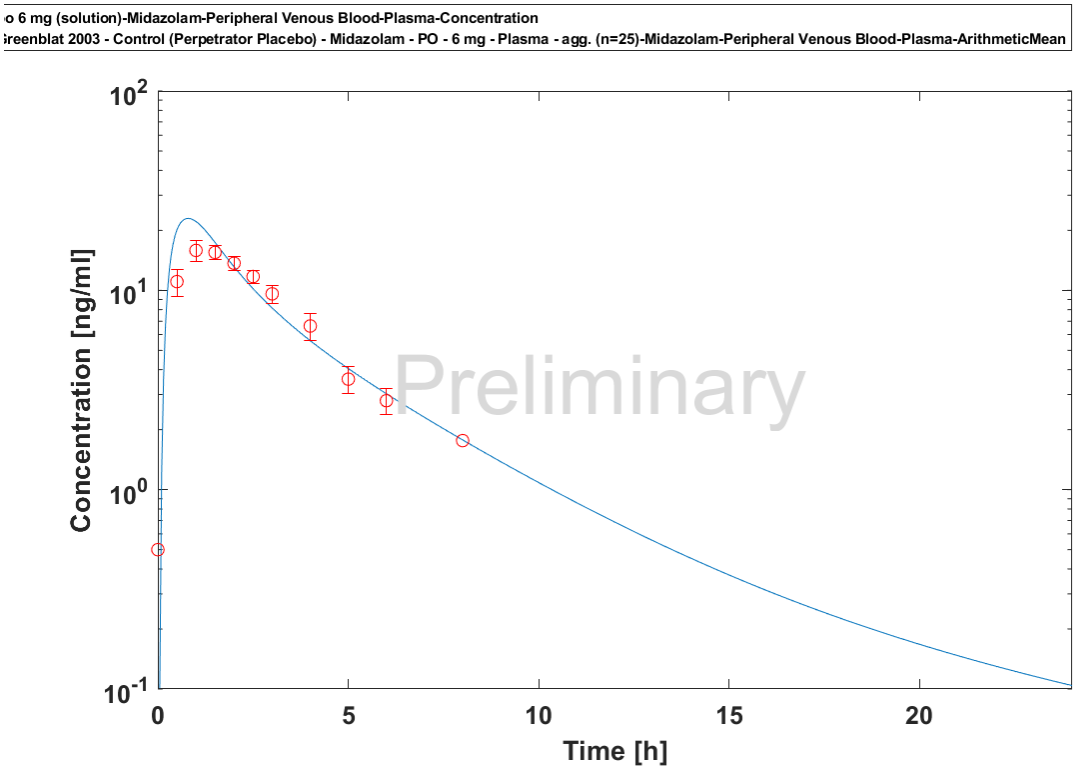
po 4 mg (solution) - Whole blood



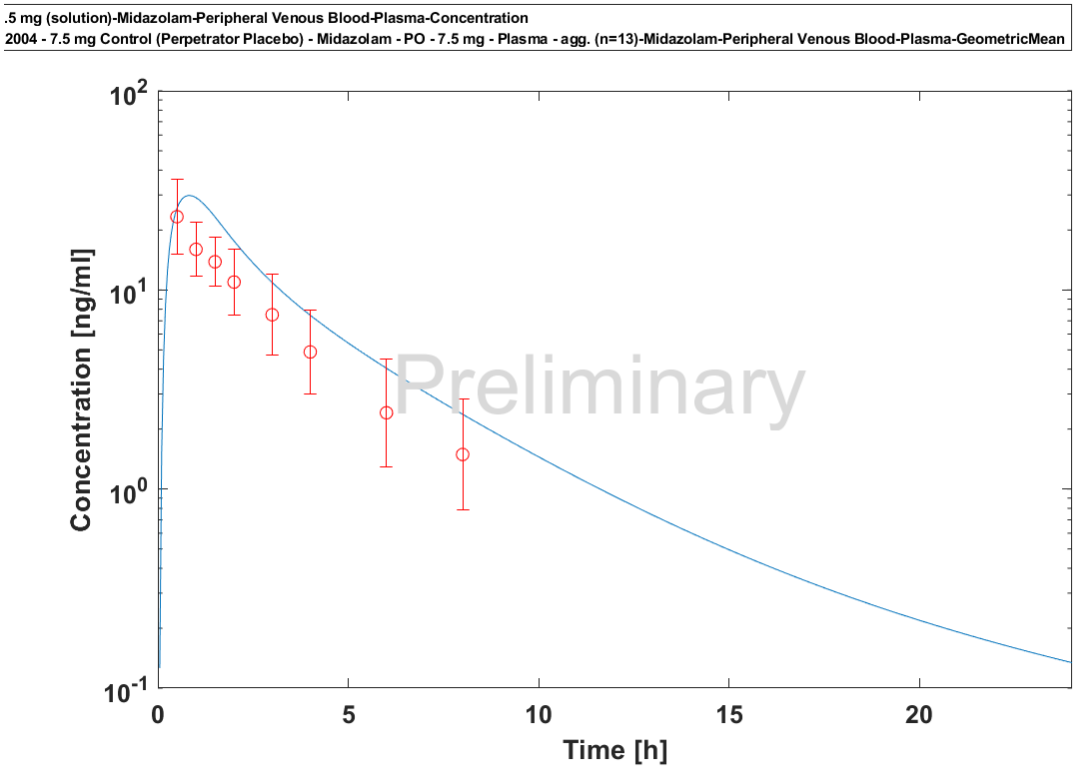
po 40 mg (tablet) - Plasma



po 5 mg (solution) - Plasma

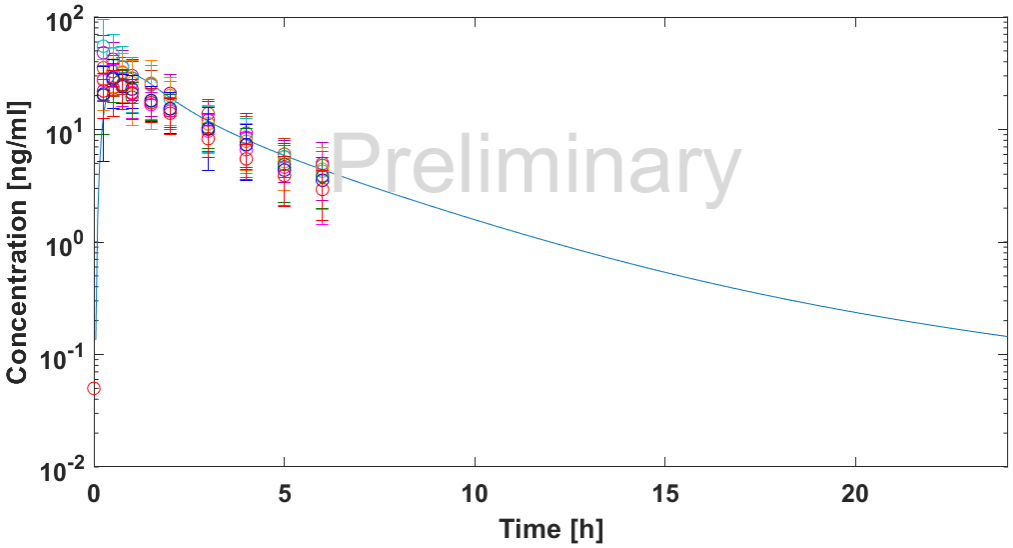


po 6 mg (solution) - Plasma



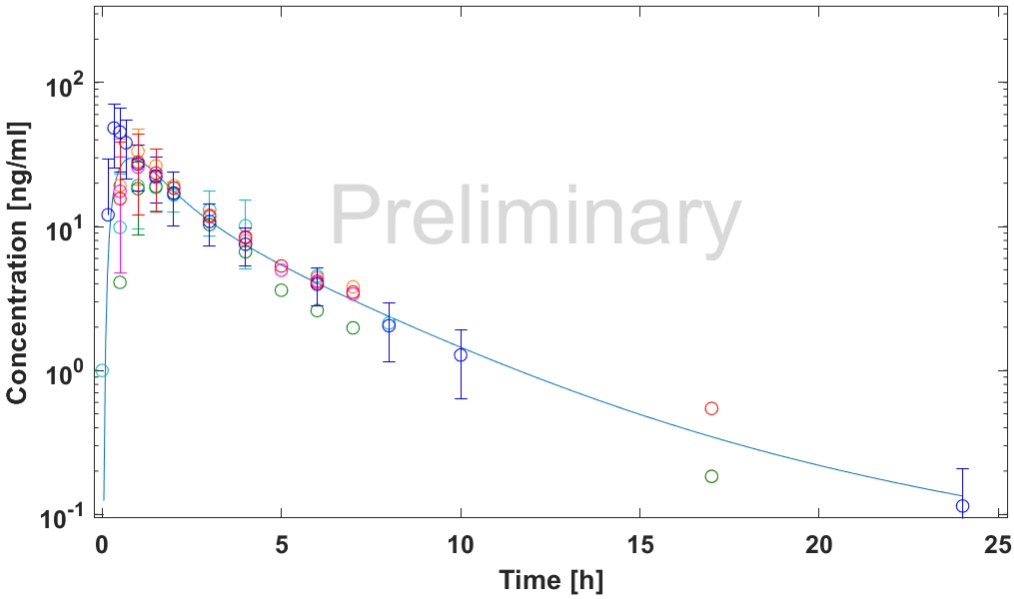
po 7.5 mg (solution) - Plasma

-Midazolam-Peripheral Venous Blood-Plasma-Concentration
ıtrol pre-Kava kava (Perpetrator Placebo) - Midazolam - PO - 8 mg - Plasma - agg. (n=16)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
ıtrol pre-Goldenseal (Perpetrator Placebo) - Midazolam - PO - 8 mg - Plasma - agg. (n=16)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
ıtrol pre-Clarithromycin (Perpetrator Placebo) - Midazolam - PO - 8 mg - Plasma - agg. (n=16)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
ıtrol pre-Rifampicin (Perpetrator Placebo) - Midazolam - PO - 8 mg - Plasma - agg. (n=16)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
rol pre-Milk thistle (Perpetrator Placebo) - Midazolam - PO - 8 mg - Plasma - agg. (n=19)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
rol pre-Black cohosh (Perpetrator Placebo) - Midazolam - PO - 8 mg - Plasma - agg. (n=19)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
rol pre-Clarithromycin (Perpetrator Placebo) - Midazolam - PO - 8 mg - Plasma - agg. (n=19)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
rol pre-Rifampicin (Perpetrator Placebo) - Midazolam - PO - 8 mg - Plasma - agg. (n=19)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean

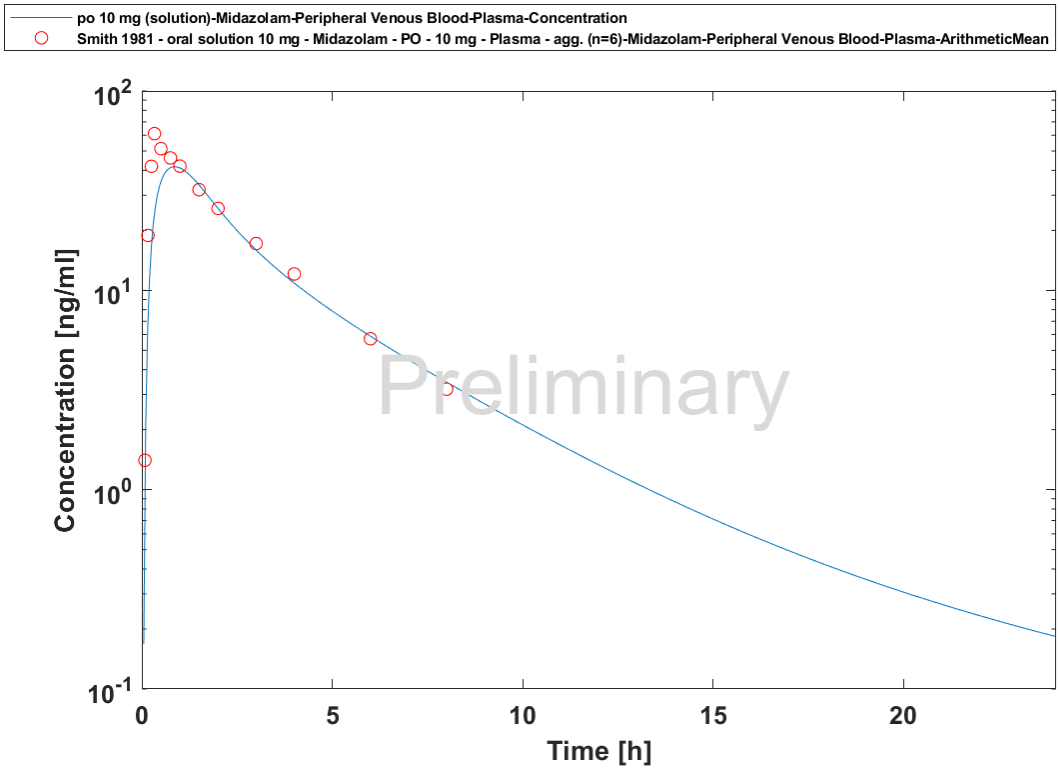


po 8 mg (solution) - Plasma

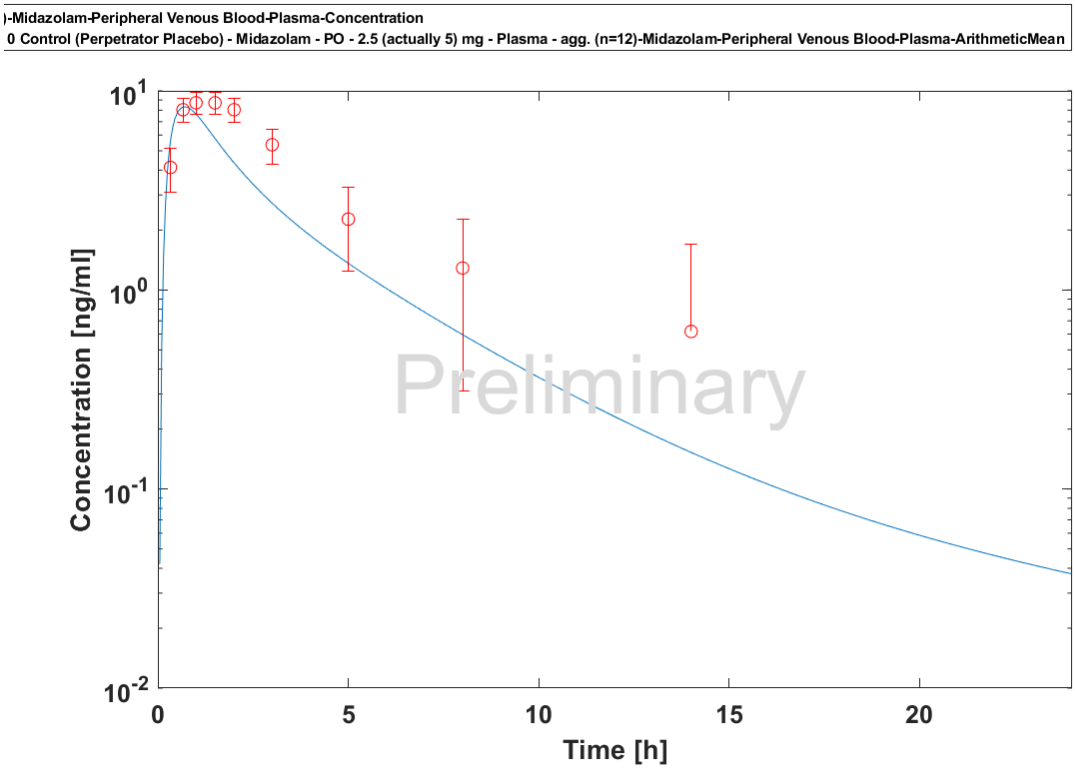
tablet)-Midazolam-Peripheral Venous Blood-Plasma-Concentration
· po Control (Perpetrator Placebo) - Midazolam - PO - 7.5 mg - Plasma - agg. (n=10)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
6 - day 6 (po) Control (Perpetrator Placebo) - Midazolam - PO - 7.5 mg - Plasma - agg. (n=12)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
6 - day 1 (po) Control (Perpetrator Placebo) - Midazolam - PO - 7.5 mg - Plasma - agg. (n=12)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
4 - po Control (Perpetrator Placebo) - Midazolam - PO - 7.5 mg - Plasma - agg. (n=9)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
po Control (Perpetrator Placebo) - Midazolam - PO - 7.5 mg - Plasma - agg. (n=8)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
5 - Control (Perpetrator Placebo) - Midazolam - PO - 7.5 mg - Plasma - agg. (n=12)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean



po 7.5 mg (tablet) - Plasma



po 10 mg (solution) - Plasma



po 2.5 mg (solution) - Plasma

4 Conclusion

The final `COMPOUND` PBPK model applies metabolism by .... and adequately describes the pharmacokinetics of `COMPOUND` in adults receiving [...] ranging from [...] mg, including [...] different oral formulations.

This model could be applied for the investigation of DDI, and translation to special populations such as pediatrics with regard to ... metabolism.

5 References

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OSP Database https://github.com/Open-Systems-Pharmacology/Database-for-observed-data