Building and evaluation of a PBPK model for COMPOUND in adults

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1 Introduction

The presented model building and evaluation report evaluates the performance of PBPK model for `COMPOUND` in adults.

The `COMPOUND` model is a whole-body PBPK model, allowing for ...

[...]

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

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.

Compound: COMPOUND

Parameters

Name	Value	Value Origin	Alternative	Default	
Solubility at reference pH	1 mg/l		Measurement	True	
Reference pH	7		Measurement	True	
Lipophilicity	0 Log Units		Measurement	True	
Fraction unbound (plasma, reference value)	1		Measurement	True	
Is small molecule	Yes				
Molecular weight	300 g/mol				
Plasma protein binding partner	Unknown				

Calculation methods

Name	Value	
Partition coefficients	PK-Sim Standard	
Cellular permeabilities	PK-Sim Standard	

Processes

Systemic Process: Glomerular Filtration-source_data

Species: Human

Parameters

Name	Value	Value Origin	
GFR fraction	1		

Formulation: Tablet

Type: Weibull

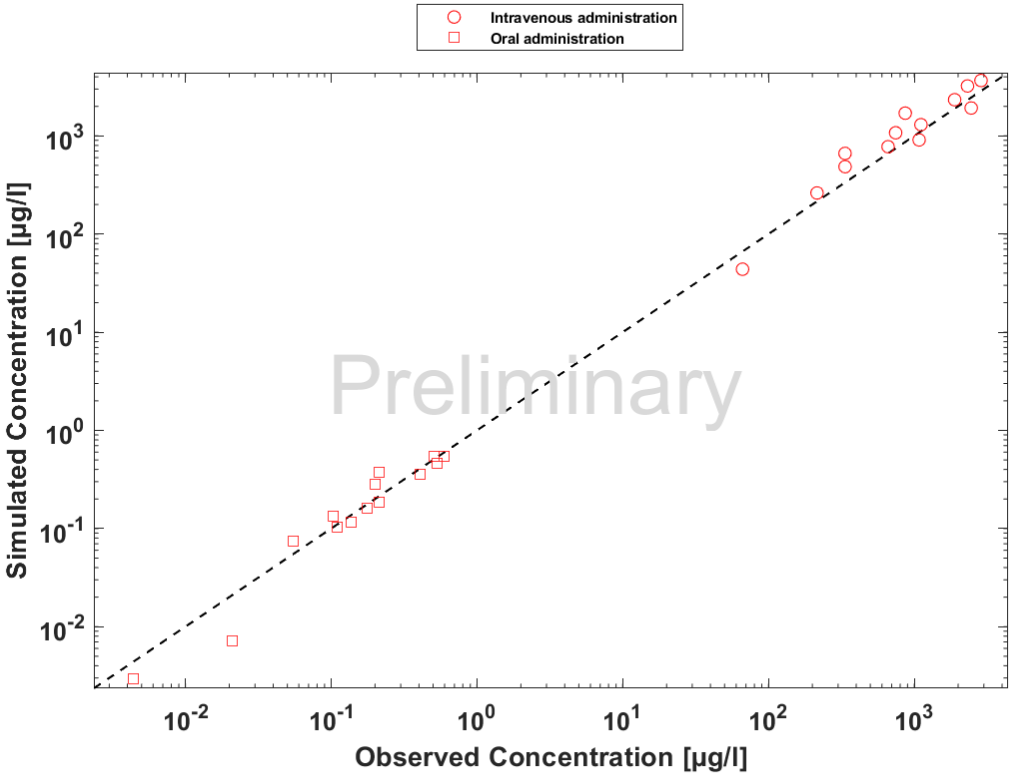
Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	240 min		
Lag time	0 min		
Dissolution shape	0.92		
Use as suspension	Yes		

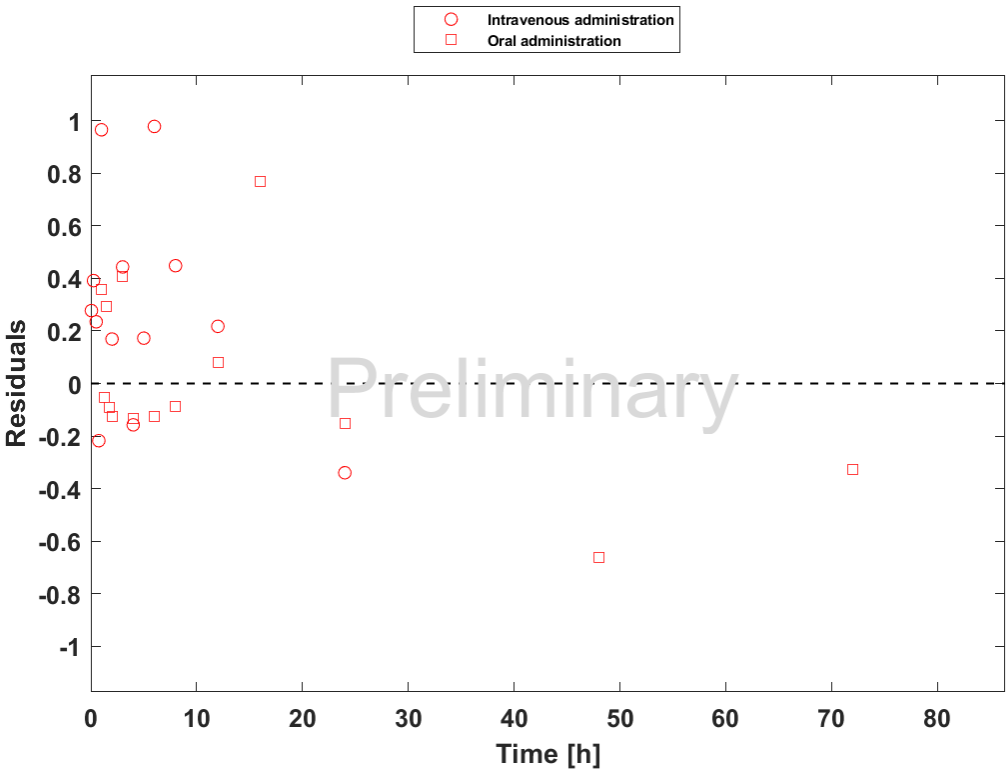
3.2 Diagnostics Plots

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

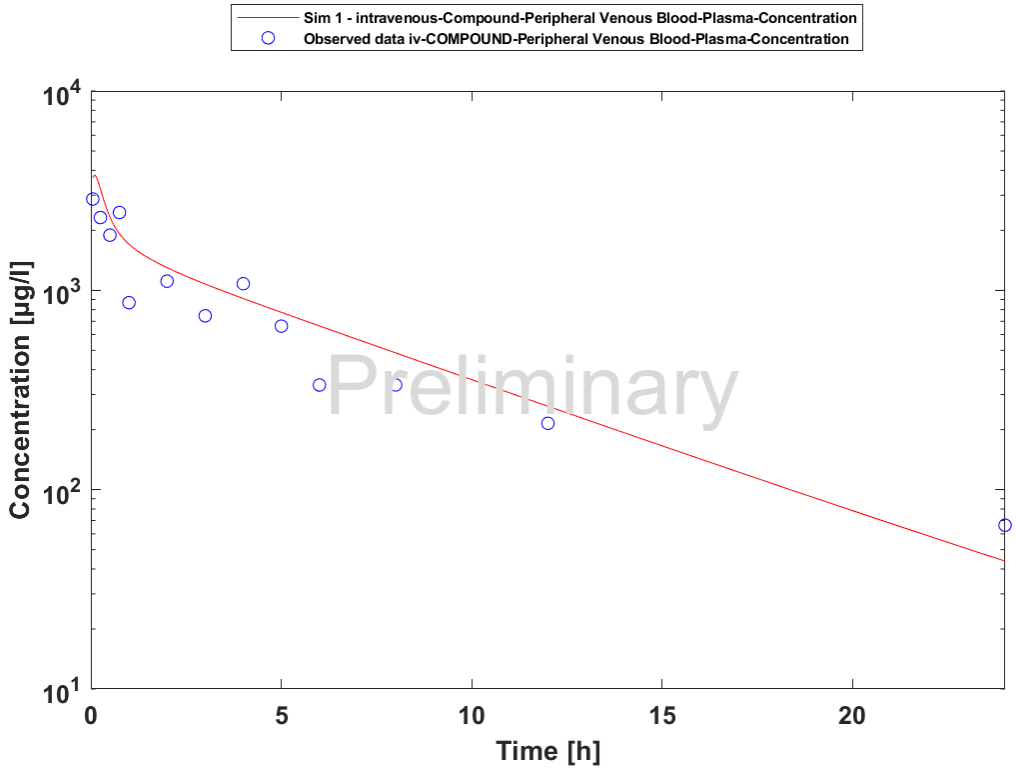


Goodness of fit plor for concentration in plasma

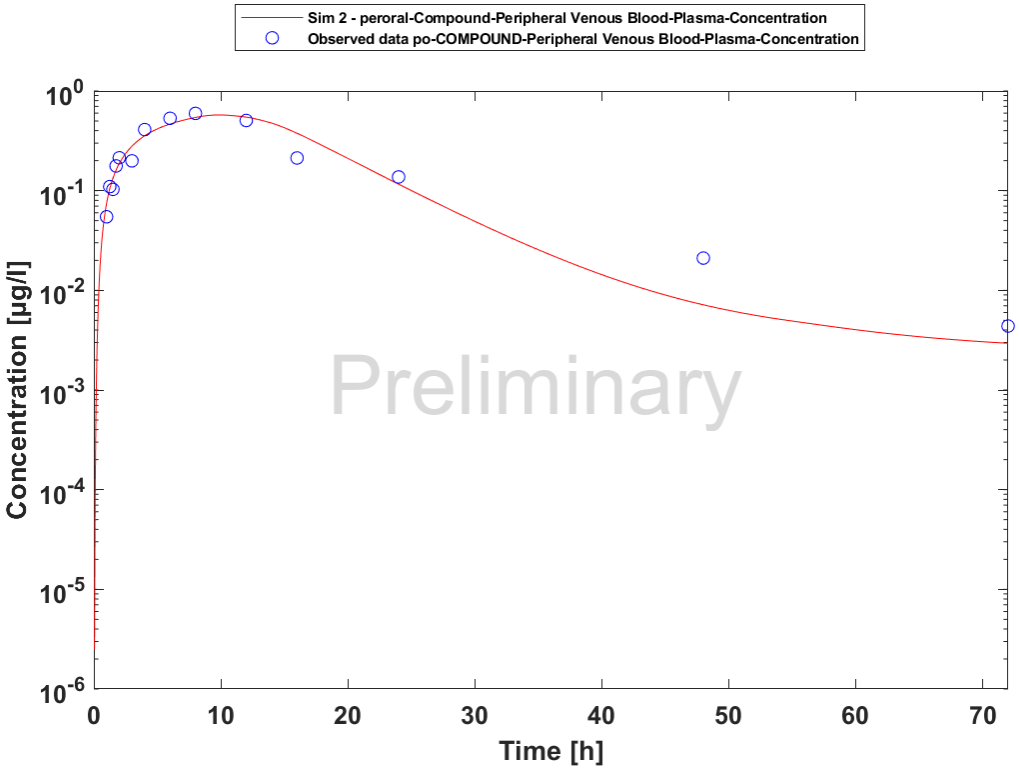
GMFE = 1.348334

3.3: Concentration-Time profiles

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



Sim 1 - intravenous



Sim 2 - peroral

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

Author YEAR Author A, Doe J, Doe K. Clinical study to investigate the pharmacokinetics of COMPOUND after intravenous and oral administration. Clin Pharmacol Ther. YEAR Feb;83(2):293-9.