Building and Evaluation of a PBPK Model for alfentanil in Adults

Version	**2.0-OSP9.0**
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Alfentanil-Model/releases/tag/v2.0
OSP Version	9.0
Qualification Framework Version	2.2

This evaluation report and the corresponding PK-Sim project file are filed at:

https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/

Table of Contents

1 Introduction

Alfentanil is a potent analgesic synthetic opioid. It is fast but short-acting and used for anesthesia during surgery. Alfentanil is metabolized solely by CYP3A4 (Phimmasone 2001). Like midazolam, alfentanil is not a substrate for P-gp (Wandel 2002) and less than 1% of an alfentanil dose is excreted unchanged in urine (Meuldermans 1988).

Although in clinical use alfentanil is always administered intravenously, some DDI studies published plasma concentration-time profiles of alfentanil following oral ingestion. The presented alfentanil model was established using clinical PK data of 8 publications, covering iv and oral administration and a dosing range from 0.015 to 0.075 mg/kg as well as absolute doses of 1 mg

IV and 4 mg PO. The established model is based on (Hanke 2018) and applies metabolism by CYP3A4 and glomerular filtration.

The herein presented model building and evaluation report evaluates the performance of the PBPK model for Alfentanil in (healthy) adults. The established Alfentanil PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (https://github.com/.../Compound-model).

2 Methods

2.1 Modeling Strategy

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

Variability of plasma proteins and CYP3A4 are integrated into PK-Sim® and 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 clinical data including selected single dose studies with intravenous and oral applications (solution) of alfentanil to find an appropriate structure to describe the pharmacokinetics in plasma. The mean PBPK model was developed using a typical European individual. The relative tissue specific expressions of enzymes predominantly being involved in the metabolism of alfentanil was taken from...

Unknown parameters (see below) 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.

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 / physico-chemical Data

A literature search was performed to collect available information on physiochemical properties of alfentanil. The obtained information from literature is summarized in the table below.

Parameter	Unit	Value	Source	Description
MW	g/mol	416.52		Molecular weight
pK_a		6.5 (base)	Jansson 2008	Acid dissociation constant
Solubility (pH)	mg/L	992.0 (6.5)	Baneyx 2014	Solubility
logP		2.1, 2.2	Baneyx 2014, Jansson 2008	Partition coefficient between octanol and water
fu	%	8.6, 10.0, 12.0	Baneyx 2014, Edginton 2008, Almond 2016	Fraction unbound in plasma

2.2.2 Clinical Data

A literature search was performed to collect available clinical data on alfentanil in healthy adults.

2.2.2.1 Model Building

The following studies were used for model building:

Publication	Arm / Treatment / Information used for model building
Ferrier 1985	Healthy subjects with a single iv dose of 0.05 mg/kg
Kharasch 1997	Healthy subjects with a single iv dose of 0.02 mg/kg
Kharasch 2004	Healthy subjects with a single iv dose of 0.015 mg/kg, healthy subjects with a single oral dose of 0.06 mg/kg
Kharasch 2011	Healthy subjects with a single iv dose of 0.015 mg/kg, healthy subjects with a single oral dose of 0.075 mg/kg
Kharasch 2011b	Healthy subjects with an iv dose of 1 mg, healthy subjects with an oral dose of 1 mg
Kharasch 2012	Healthy subjects with a single iv dose of 0.02 mg/kg
Meistelman 1987	Healthy subjects with a single dose of 0.02 mg/kg
Phimmasone 2001	Healthy subjects with a single dose of 0.015 mg/kg

2.3 Model Parameters and Assumptions

2.3.1 Absorption

Absorption observed in clinical studies can be fully explained by passive absorption.

2.3.2 Distribution

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built in PK-Sim, observed clinical data was best described by choosing the partition coefficient calculation by `Rodgers and Rowland` and cellular permeability calculation by `PK-Sim Standard`.

2.3.3 Metabolism and Elimination

Alfentanil is metabolized solely by CYP3A4.

The first model simulations showed that gut wall metabolization was too low in the PBPK model. In order to increase gut wall metabolization, the “mucosa permeability on basolateral side” was estimated. This may lead to higher gut wall concentrations and, in turn, to a higher gut wall elimination. This parameter
was preferred over other parameters such as relative CYP3A4 expression or fraction unbound (fu) in the gut wall as it is technically not limited to a maximum value of 100%.

2.3.4 Automated Parameter Identification

The parameter identification tool in PK-Sim has been used to estimate selected model parameters by adjusting to PK data of the clinical studies that were used in the model building process. This is the result of the final parameter identification.

Model Parameter	Optimized Value	Unit
lipophilicity	1.846	
intestinal permeability	5.737E-4	cm/min
(organ) permeability	6.875E-3	cm/min
mucosa permeability	5.415E-4	cm/min
intrinsic clearance CYP3A4	0.527	l/min

3 Results and Discussion

The PBPK model for alfentanil was developed and evaluated using publically available, clinical pharmacokinetic data from studies listed in Section 2.2.2.

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 and for model verification: Section 3.3.

3.1 Final input parameters

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

Compound: Alfentanil

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	992 mg/l	Publication-Hanke 2018	Baneyx 2014	True
Reference pH	6.5	Publication-Hanke 2018	Baneyx 2014	True
Lipophilicity	1.8463211883 Log Units	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28	Fit	True
Fraction unbound (plasma, reference value)	0.1	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28	Healthy	True
Permeability	0.0068752756625 cm/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28	Optimized	True
Specific intestinal permeability (transcellular)	0.00057373577138 cm/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28	Optimized	True
Is small molecule	Yes			
Molecular weight	416.52 g/mol	Publication-Drugbank		
Plasma protein binding partner	α1-acid glycoprotein			

Calculation methods

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

Processes

Metabolizing Enzyme: CYP3A4-1st order CL

Species: Human
Molecule: CYP3A4

Parameters

Name	Value	Value Origin
Intrinsic clearance	0.5272297928 l/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 4' on 2019-09-06 11:28

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	0.06	Publication-Hanke 2018

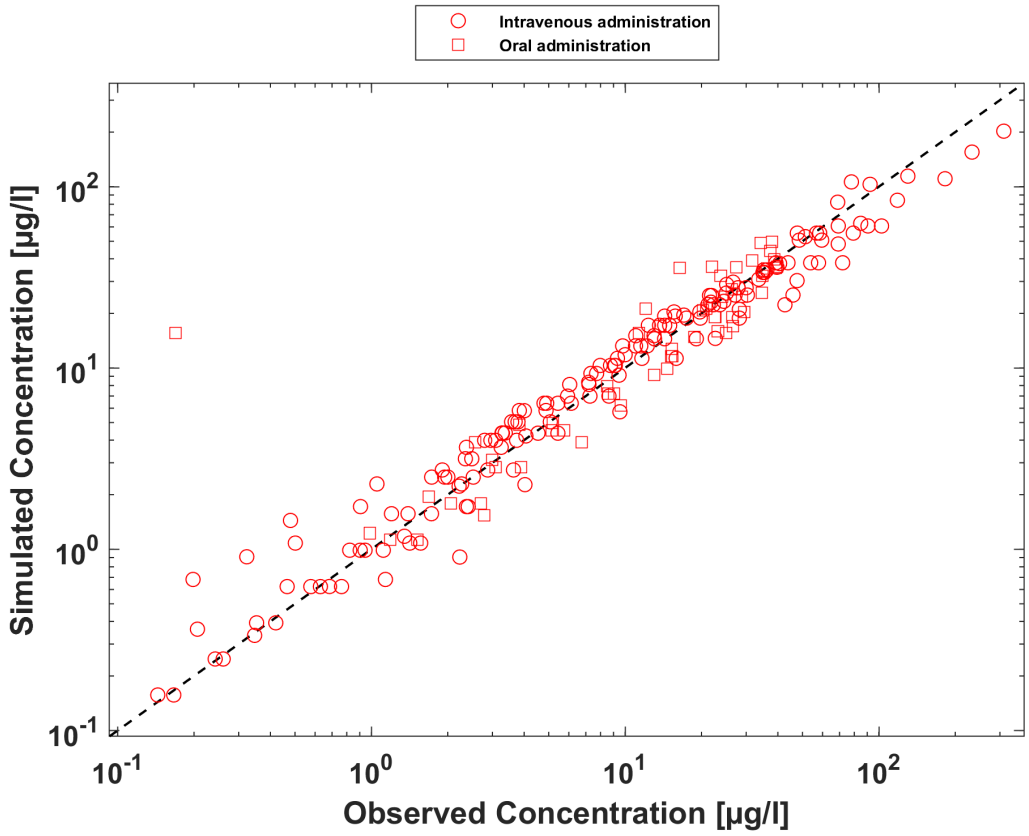
Formulation: Solution

Type: Dissolved

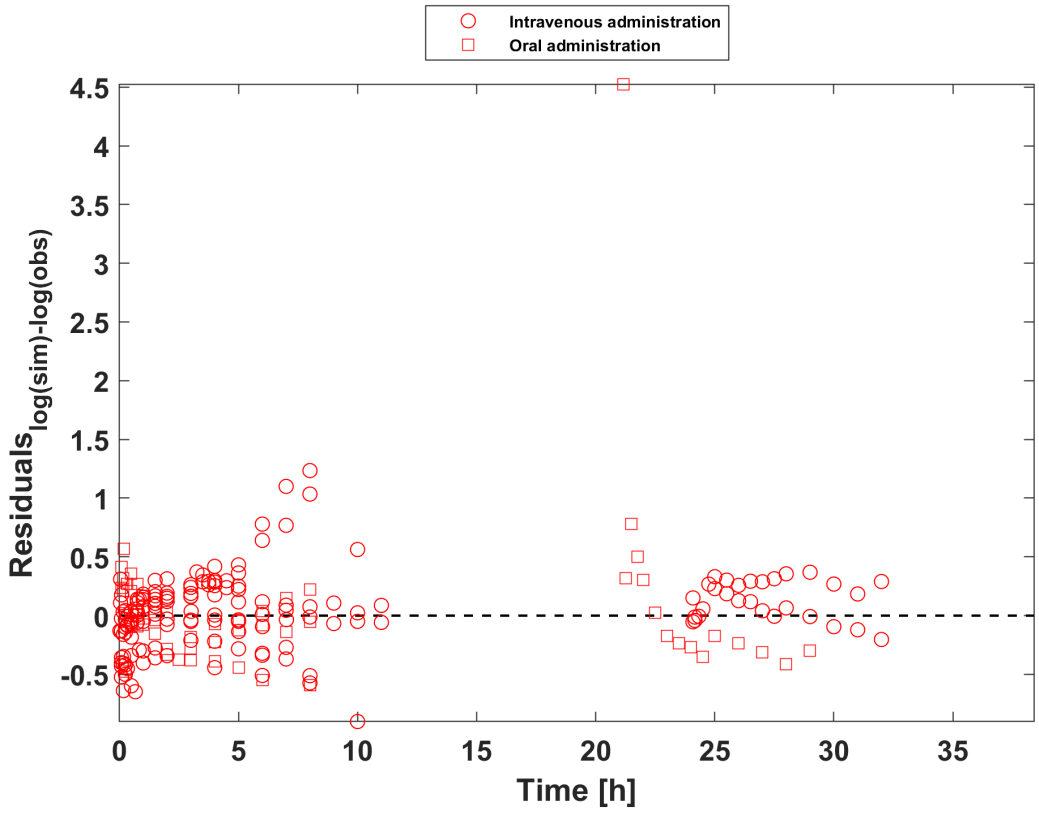
3.2 Diagnostics Plots

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

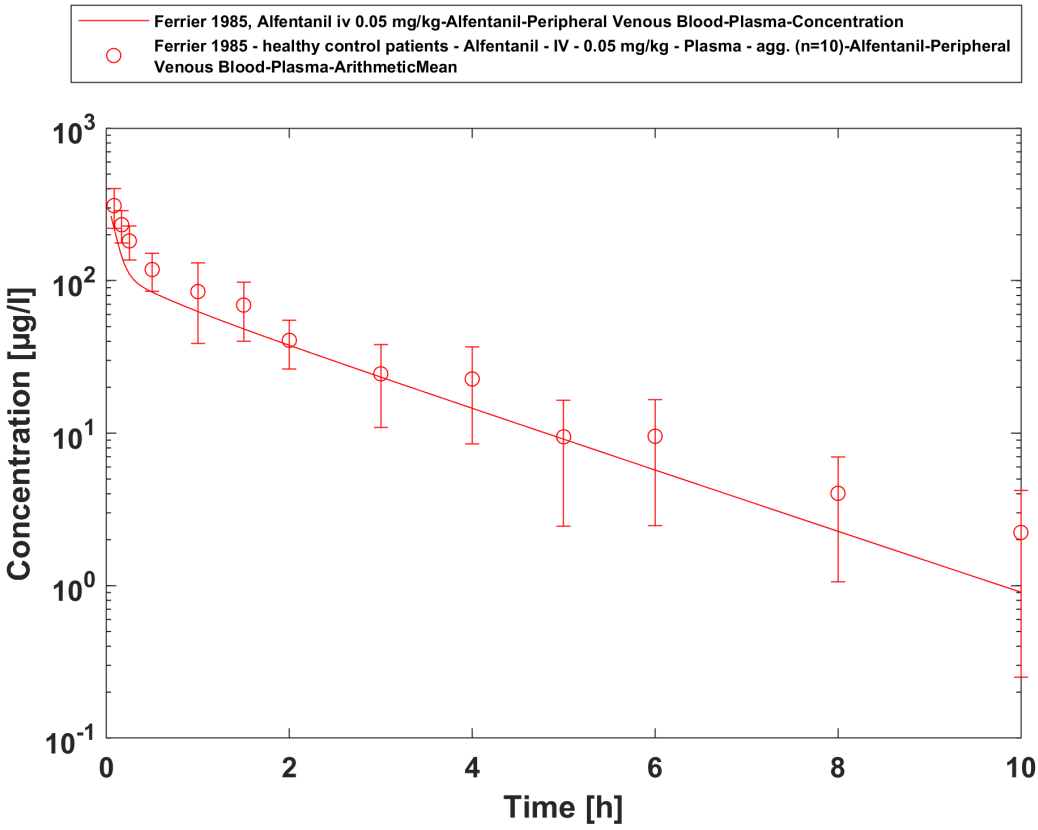


Goodness of fit plor for concentration in plasma

GMFE = 1.289924

3.3 Concentration-Time Profiles

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



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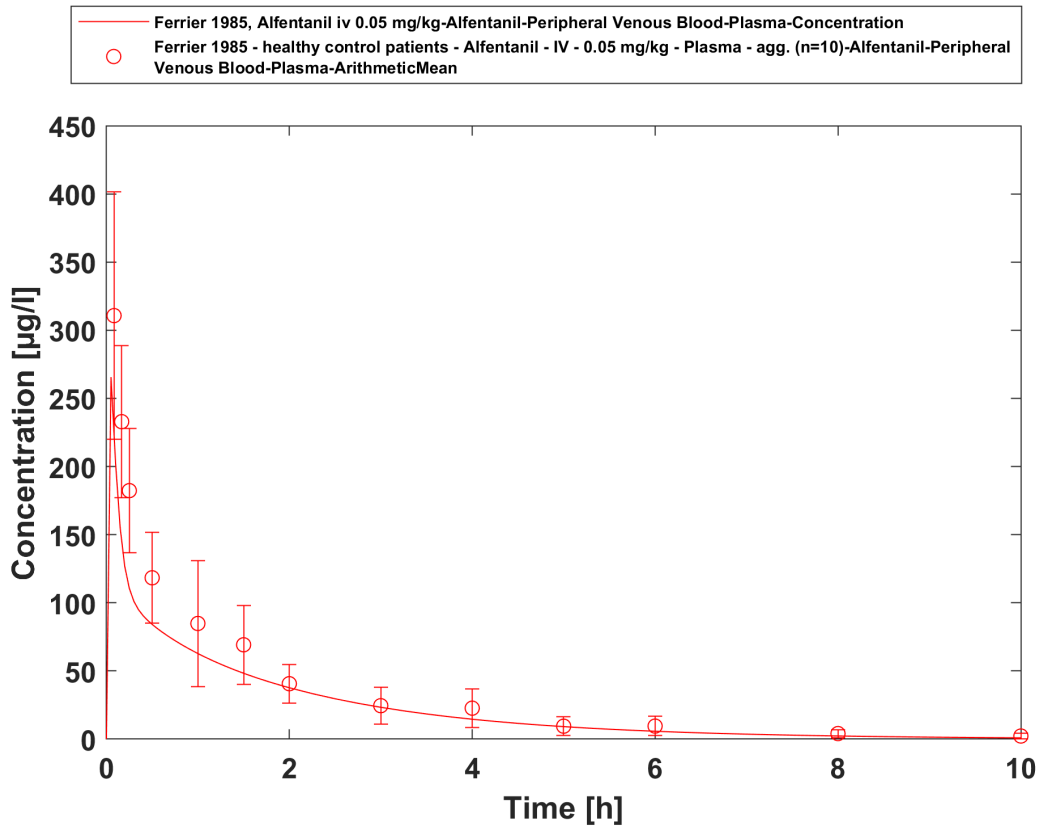

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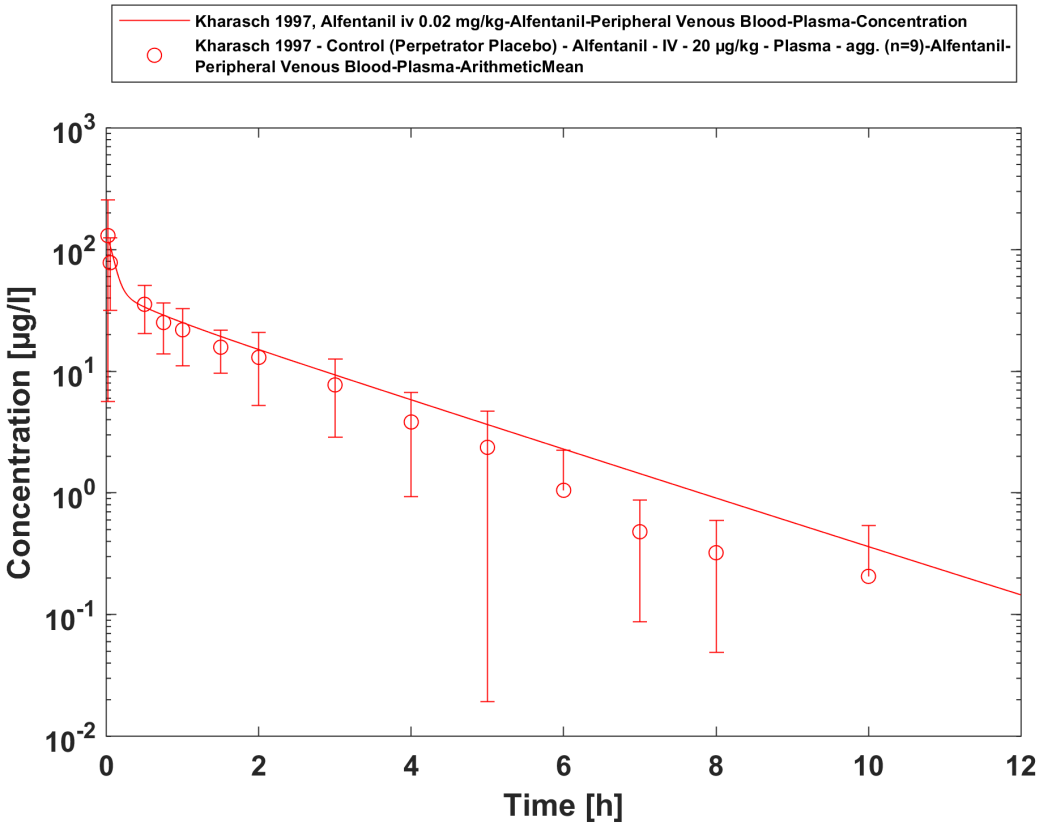

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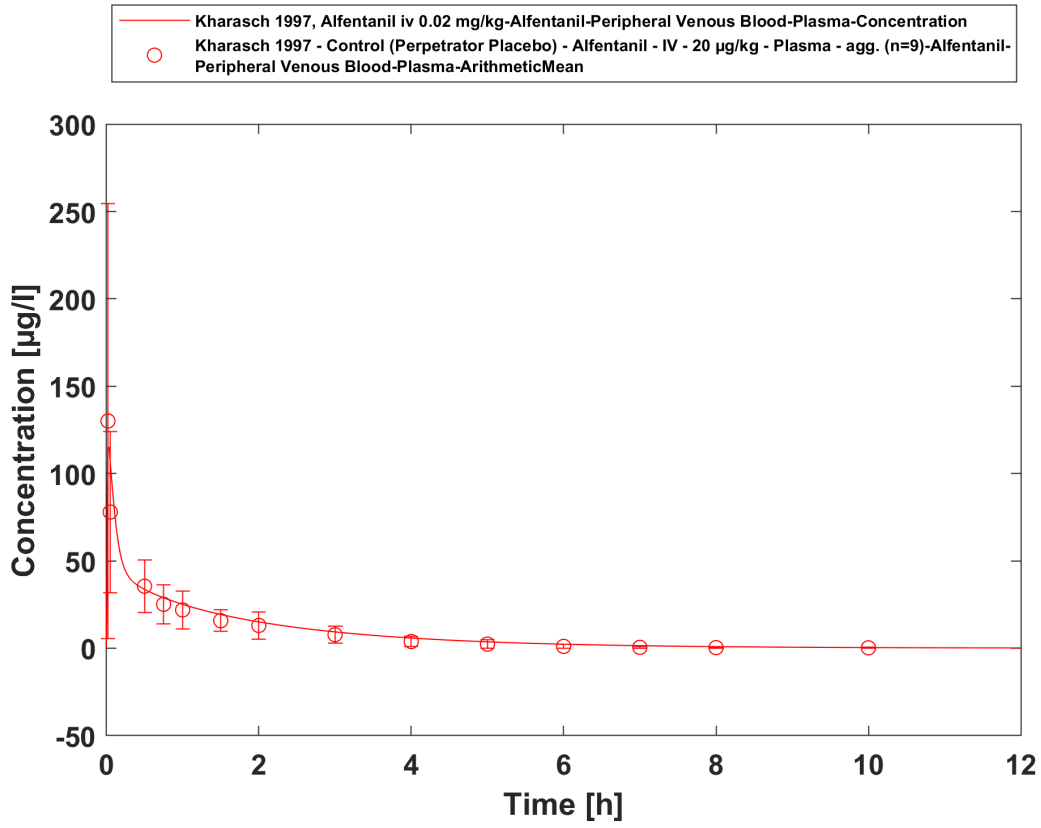

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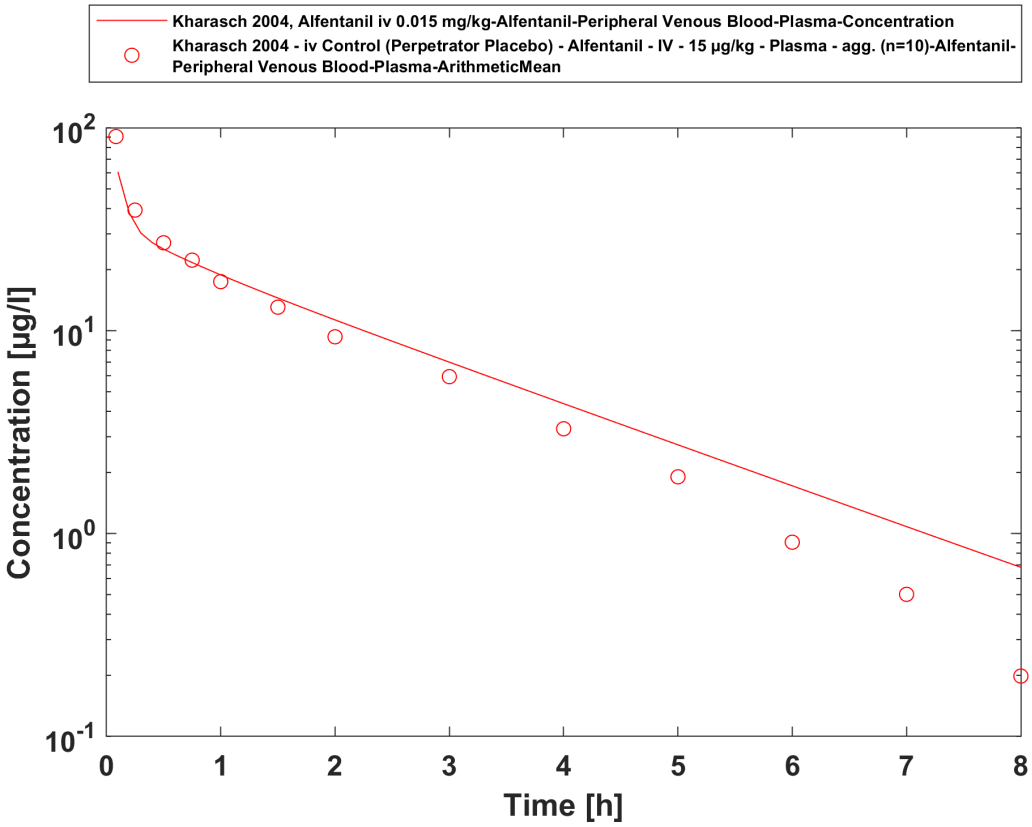

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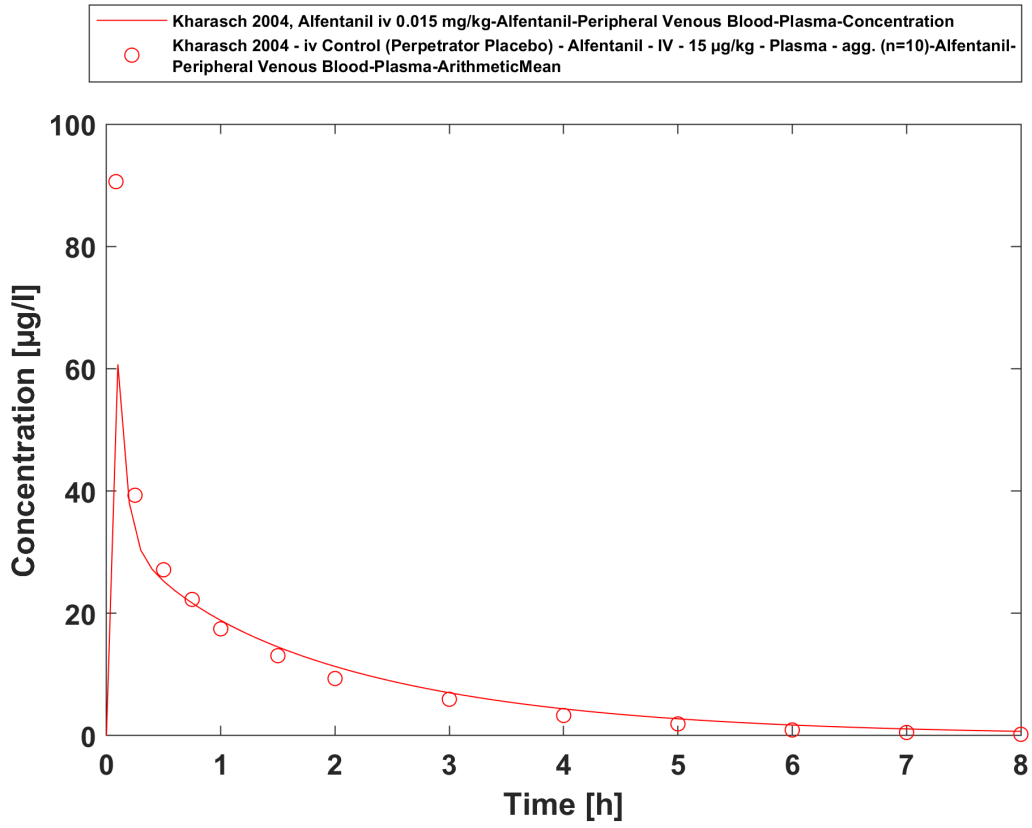

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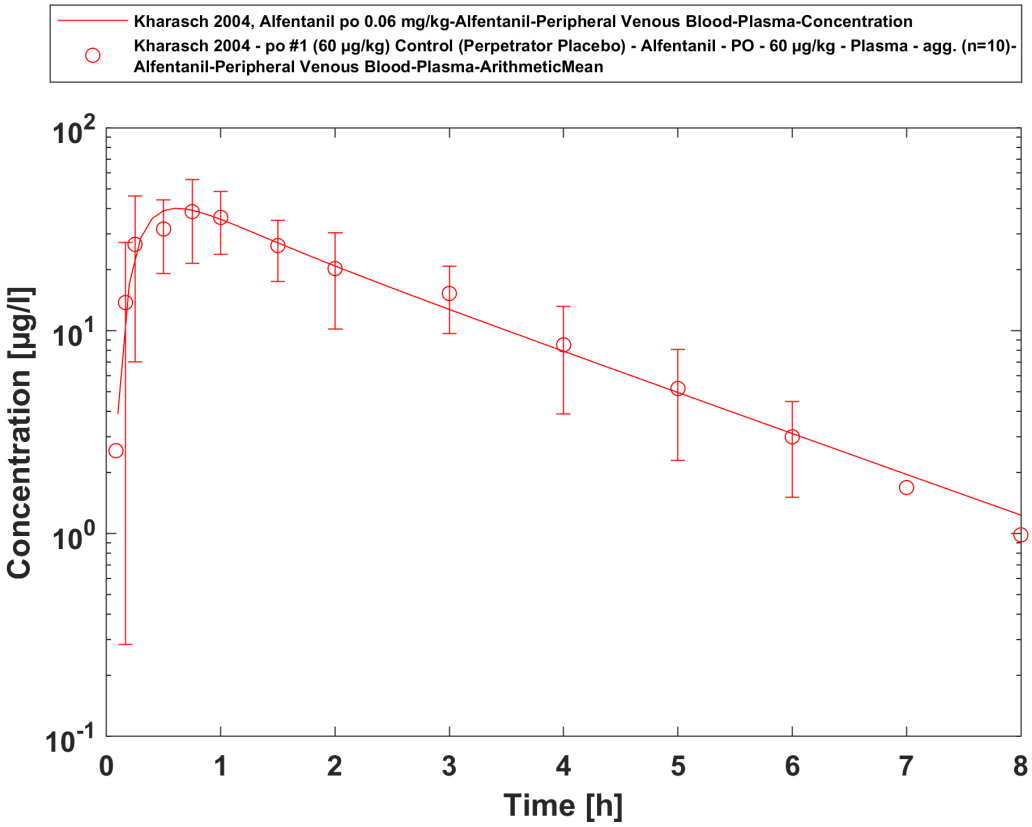

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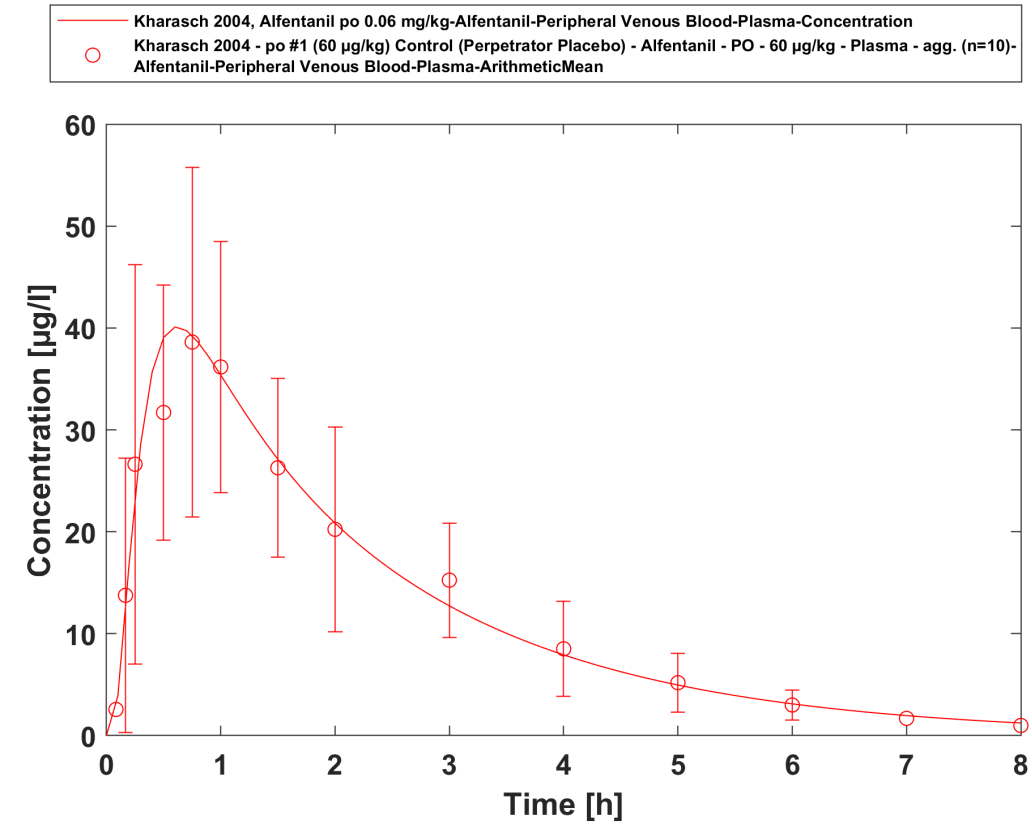

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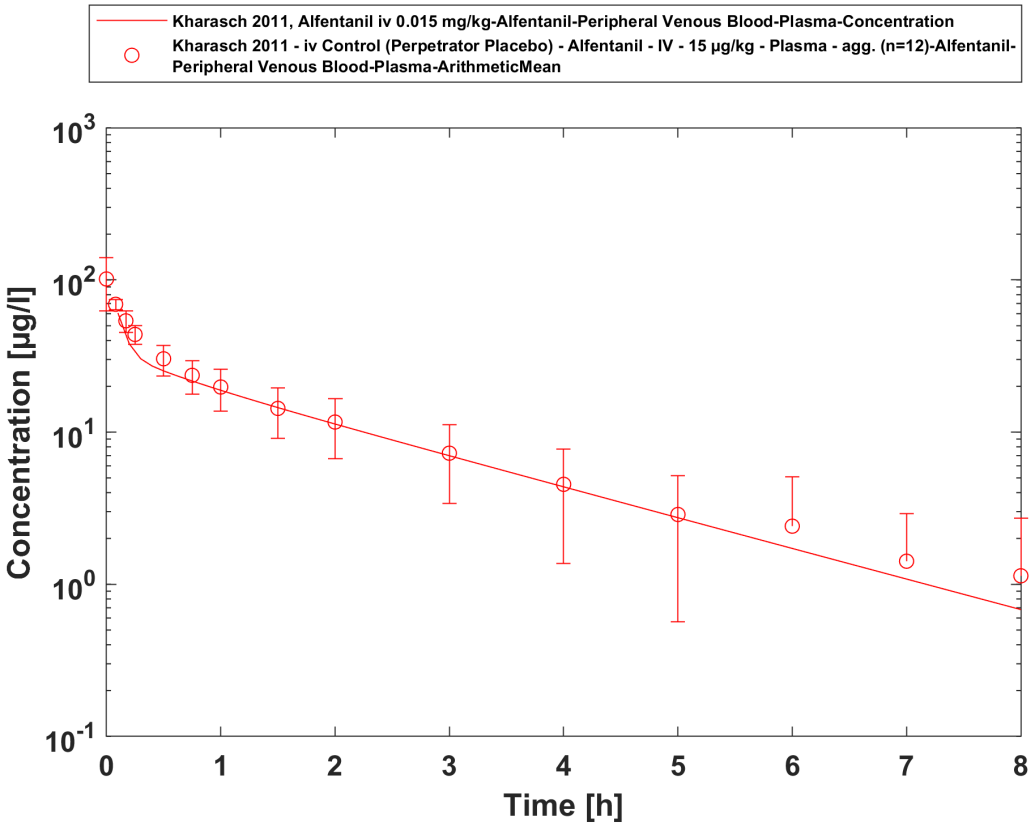

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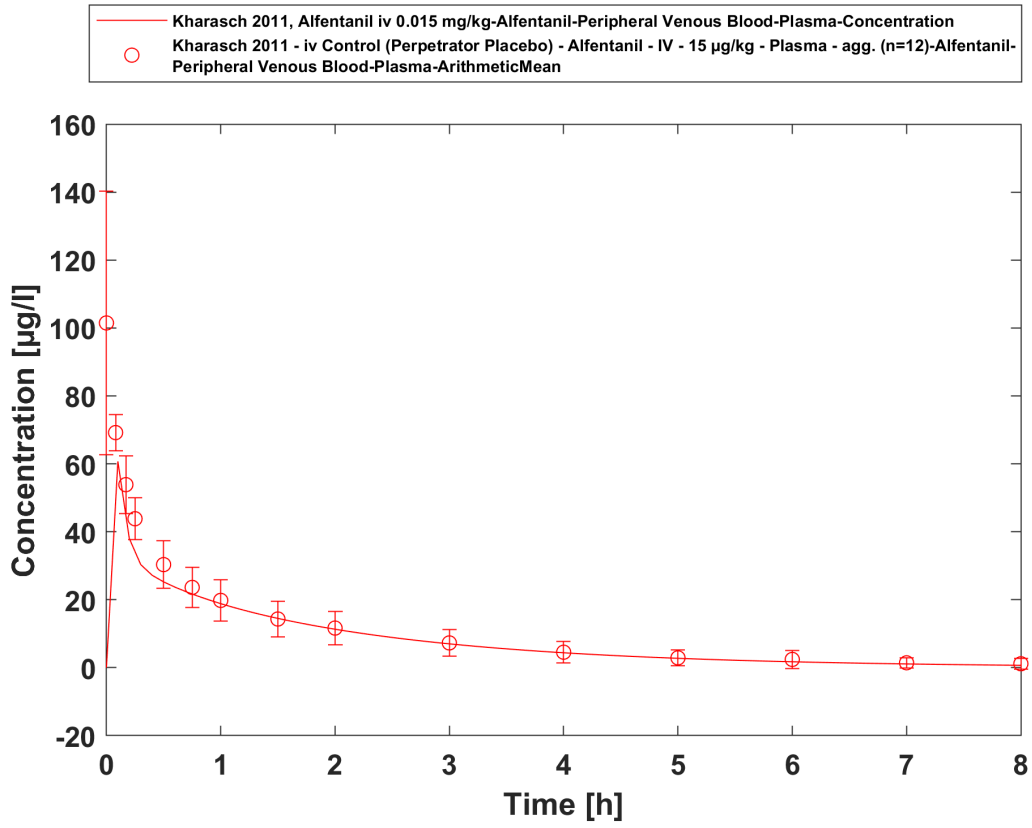

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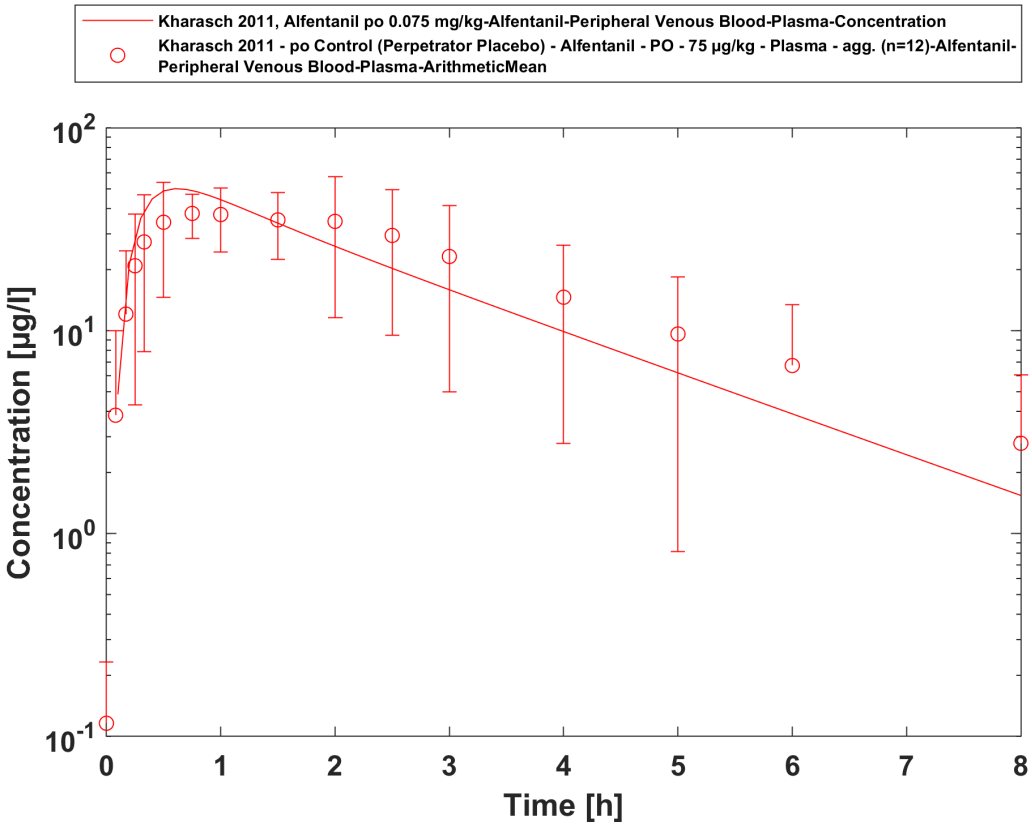

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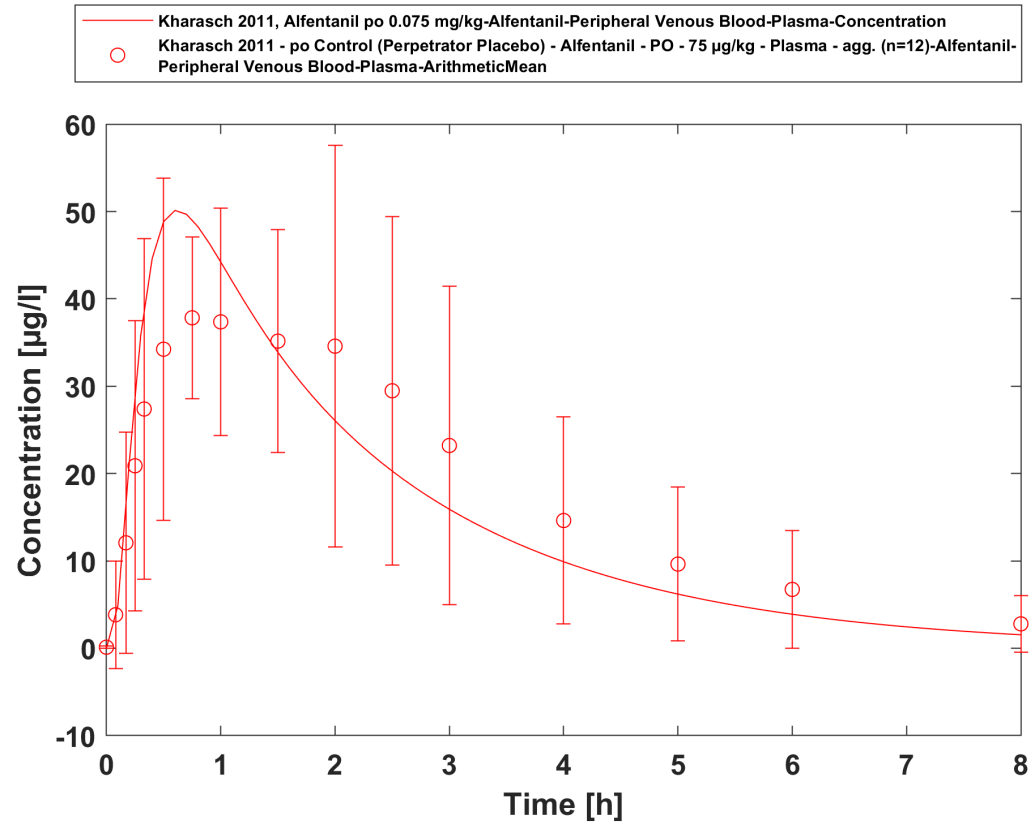

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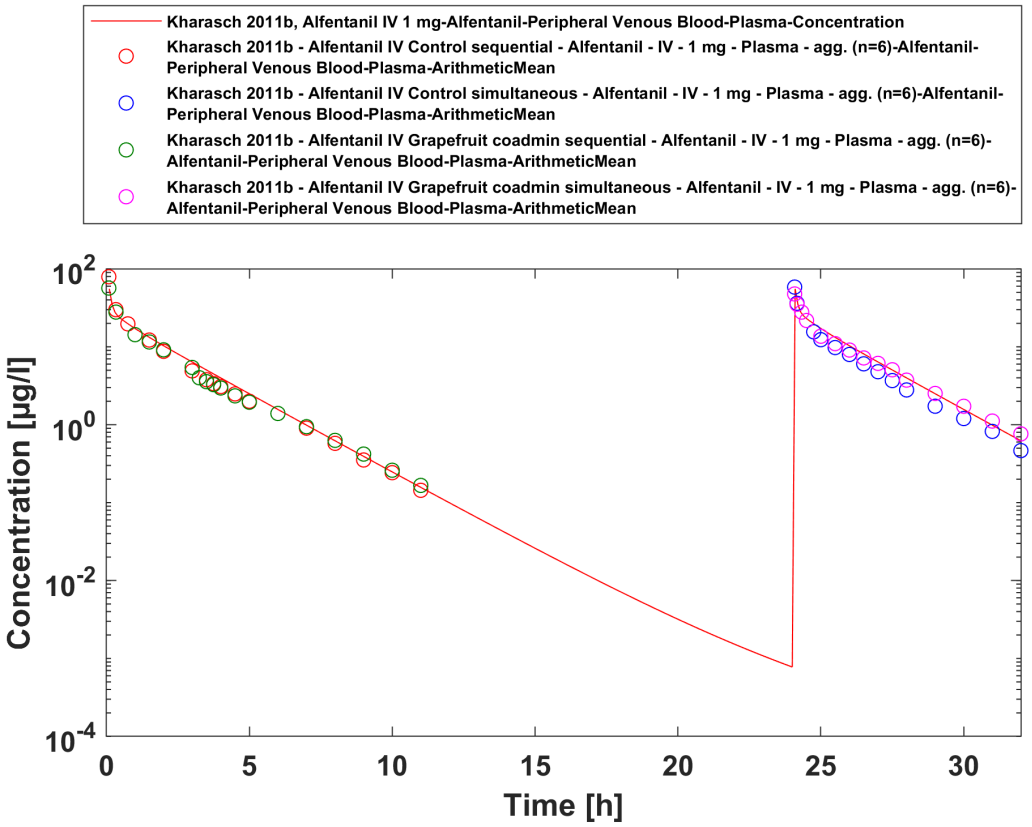

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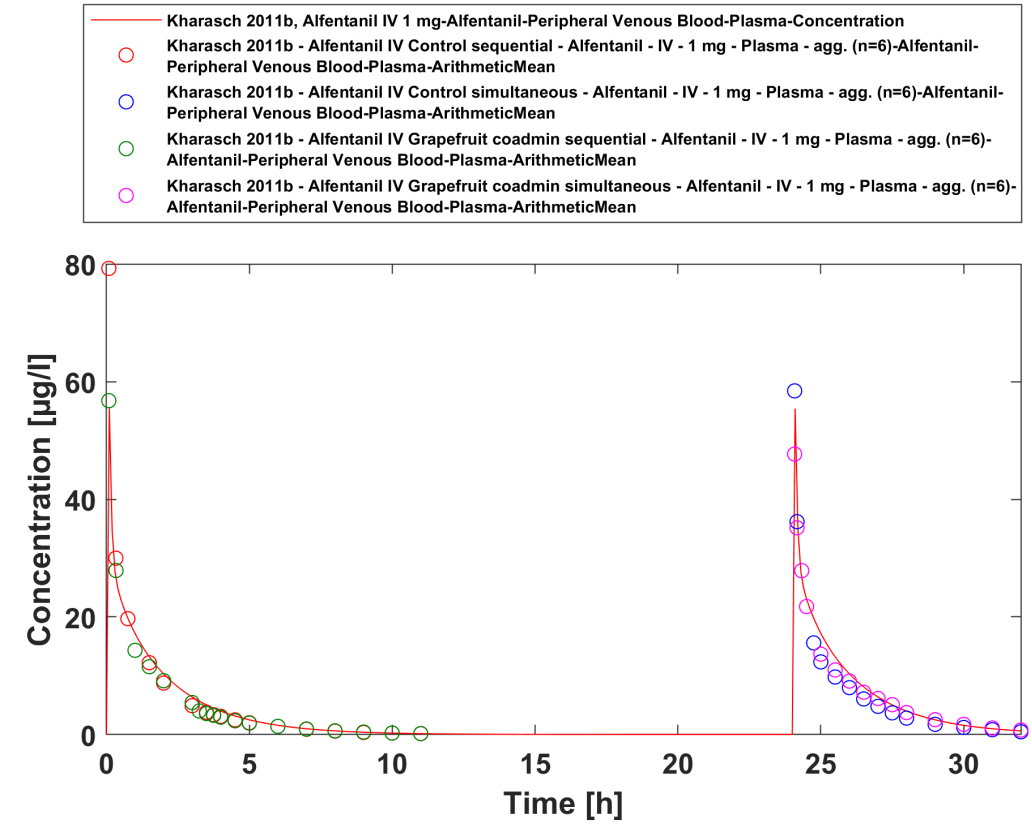

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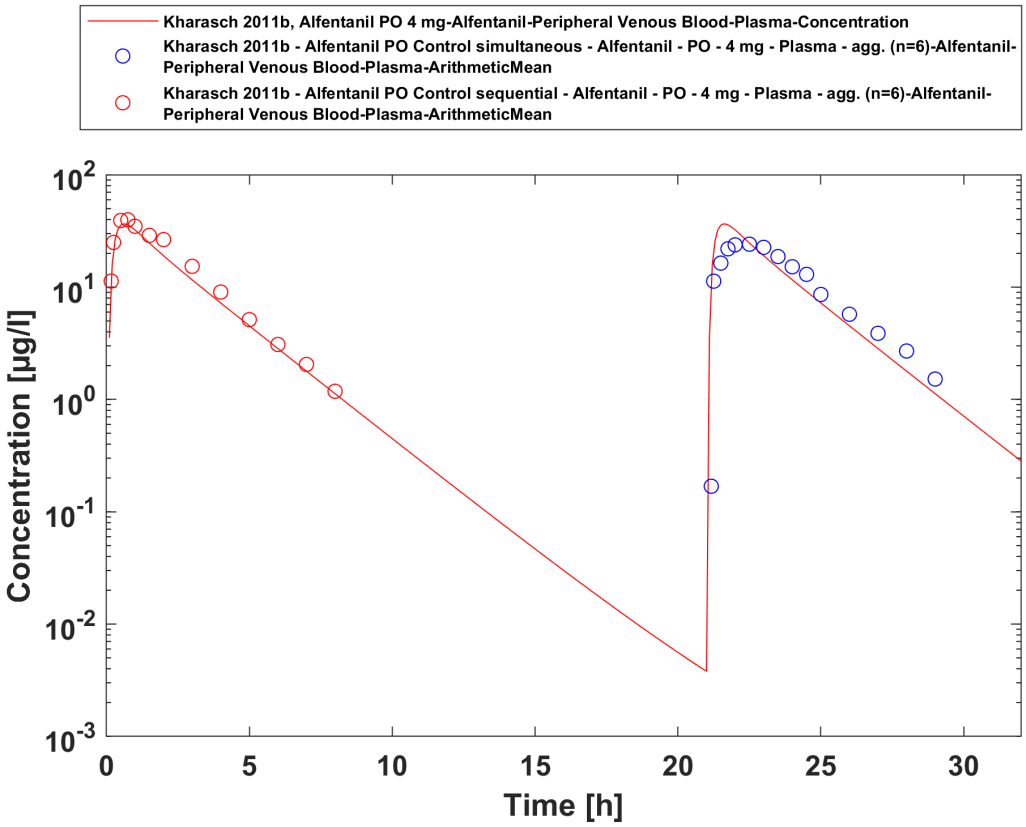

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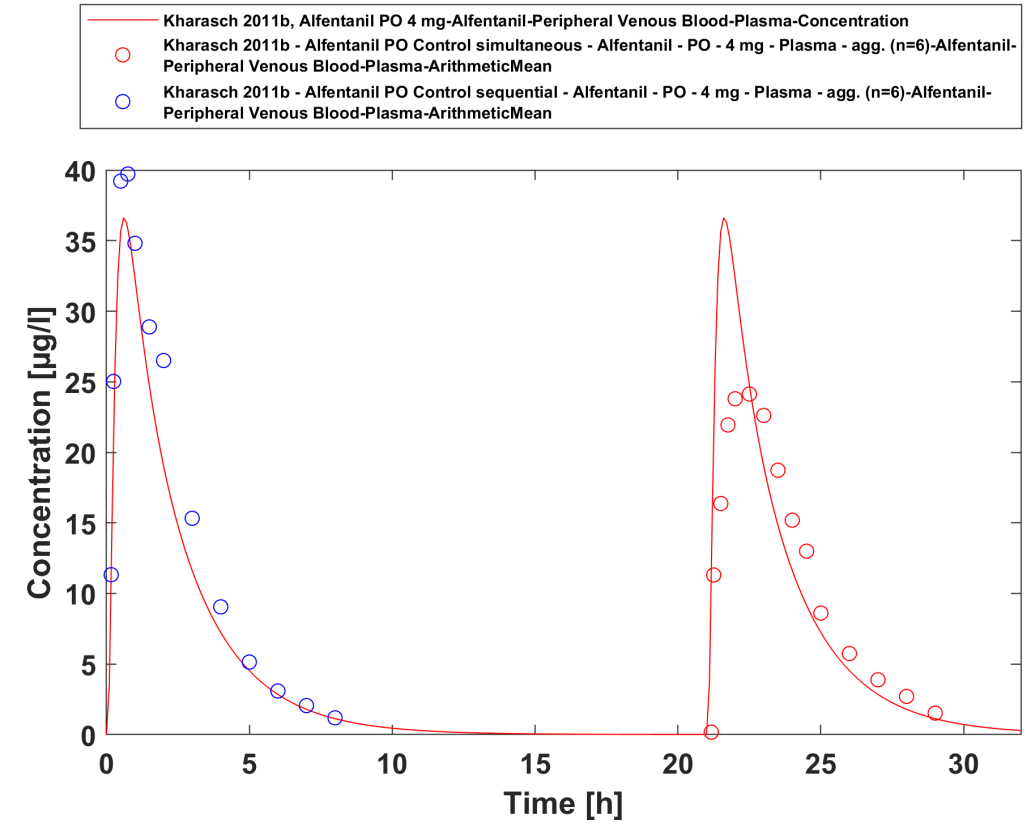

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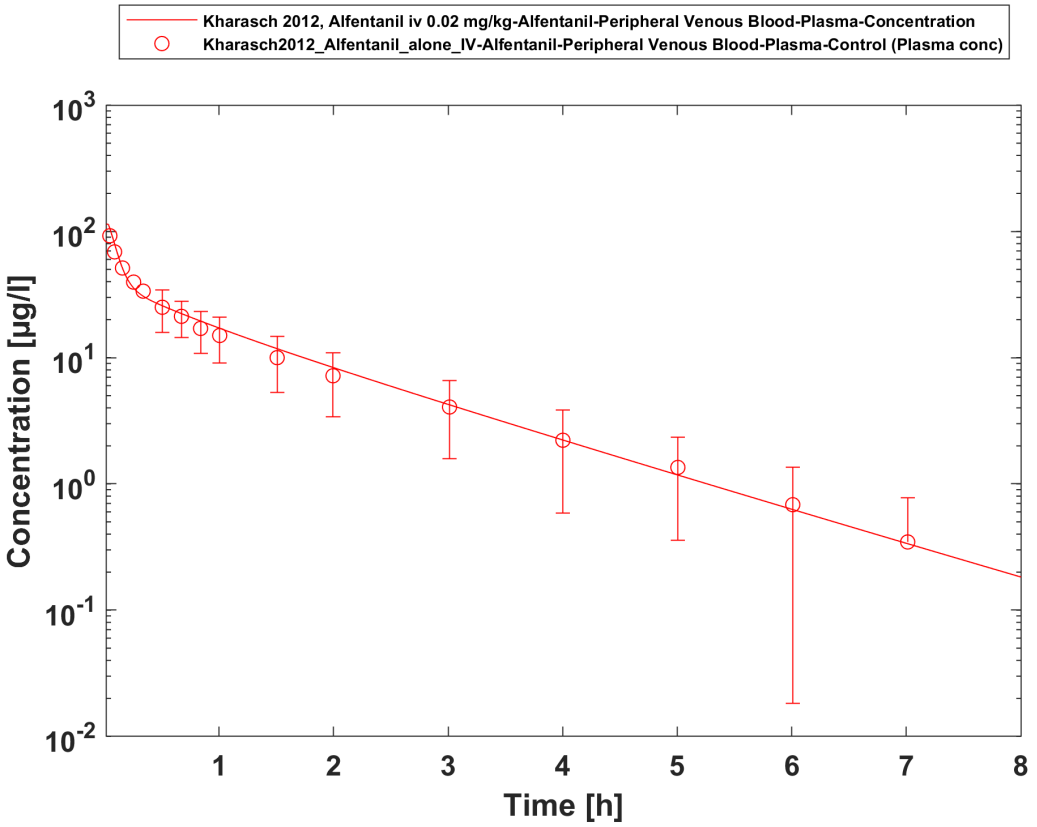

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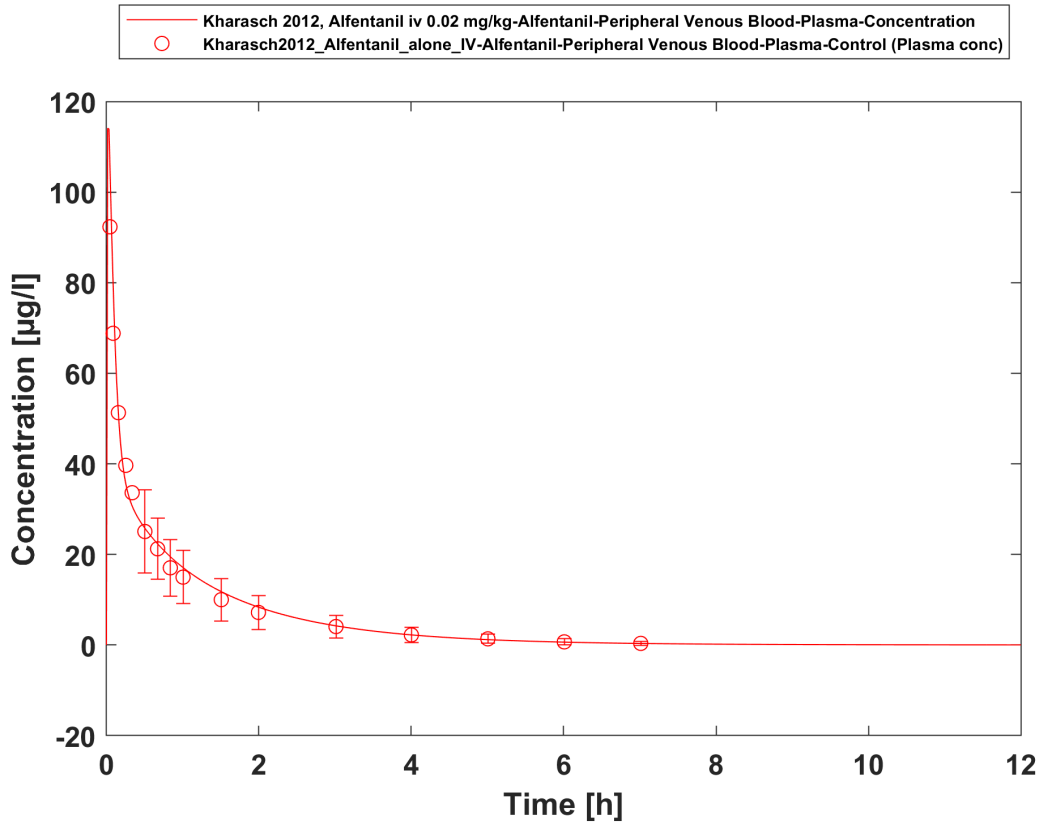

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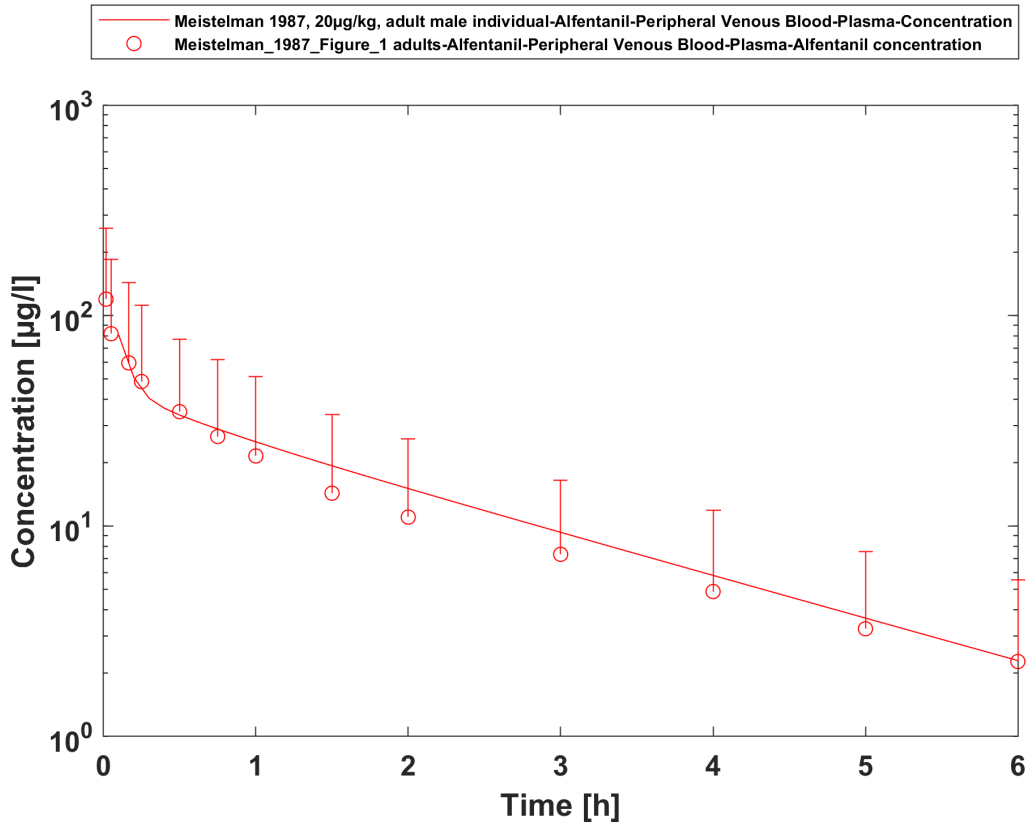

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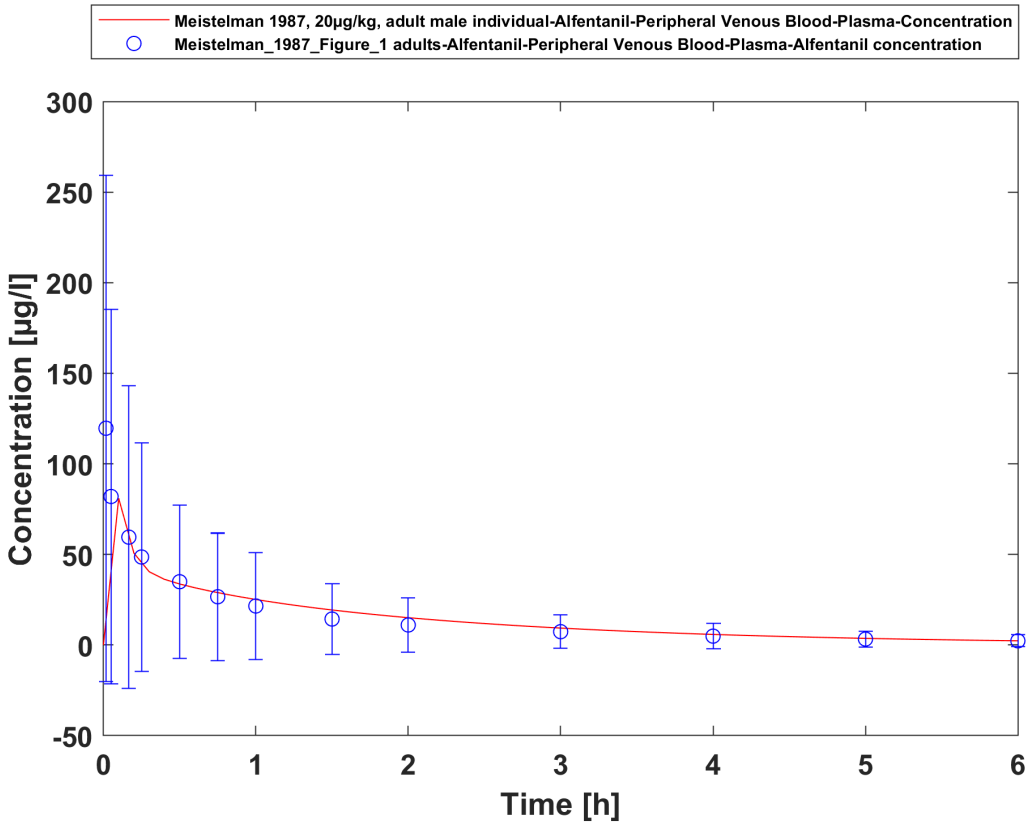

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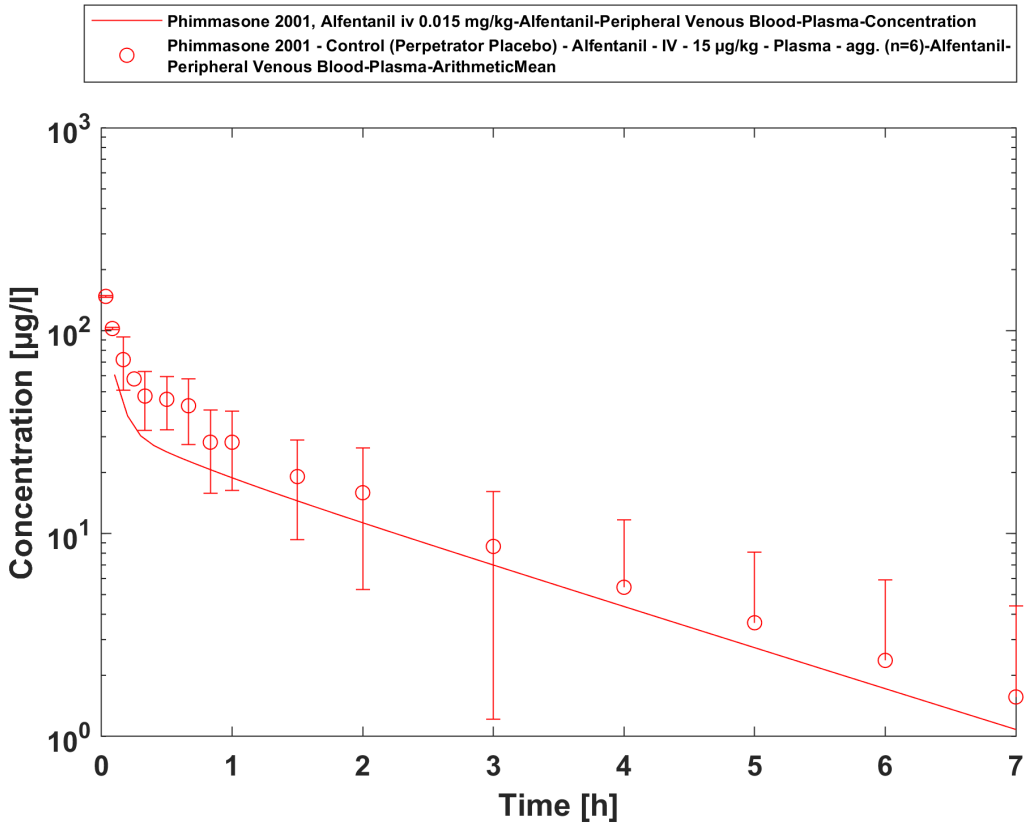

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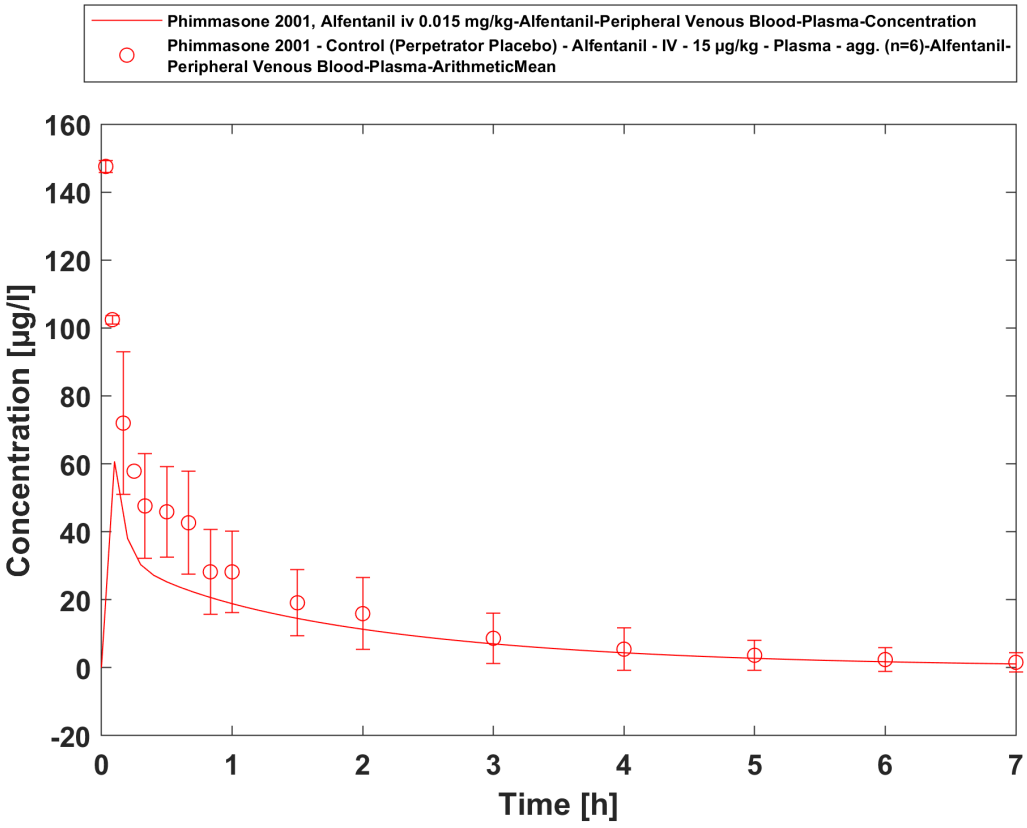

Time Profile Analysis 1

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of alfentanil after iv and oral administration of a variety of doses to healthy adults. Parameters that were optimized during parameter identification are in a close range to the measured or calculated values and, consistent with literature, no additional active processes were needed to reflect the PK of alfentanil.

In conclusion, the presented alfentanil PBPK model is well-suited to be applied in drug-drug-interaction scenarios to predict the interaction potential.

5 References

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