

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

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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 erythromycin in healthy adults.

Erythromycin a macrolide antibiotic used for the treatment of a number of bacterial infections, including respiratory tract infections, skin infections, chlamydia infections, and others.

Erythromycin is available in the form of various salts and formulations, for example as:

- erythromycin lactobionate for injection
- erythromycin base in enteric-coated capsules or tablets for oral administration
- erythromycin stearate in filmcoated tablets for oral administration
- erythromycin ethylsuccinate in suspension or in filmcoated tablets for oral administration

In its free form as base, erythromycin is easily hydrolyzed in acidic aqueous solution ([Mordi 2000](#)). Therefore, orally administered erythromycin is given in the form of enteric-coated formulations or as more acid-stable salts or esters of erythromycin (e.g. erythromycin ethylsuccinate). Once in the small intestine, erythromycin is rapidly absorbed displaying a highly variable bioavailability ([Chun 1977](#), [Mather 1981](#)). Erythromycin diffuses in most tissues and accumulates in leukocytes and phagocytes ([Miller 1984](#), [Carlier 1987](#)). About 70% of erythromycin is bound to plasma proteins ([Barre 1987](#)). Erythromycin has been shown to be a substrate for various transporters including P-gp and OATP1B1. The latter has been shown to critically affect erythromycin disposition ([Lancaster 2012](#)). Erythromycin is extensively metabolized through N-demethylation catalyzed by CYP3A. Metabolism via CYP4F11 has also been suggested ([Kalsotra 2004](#)). Biliary excretion also appears to play an important role in erythromycin clearance ([Acocella 1968](#), [Chelvan 1979](#)), but its contribution to total elimination remains unknown. The dose fraction excreted unchanged in urine is minimal and highly variable; reported fractions range from  $0.018 \pm 0.005$  to  $0.171 \pm 0.11$  (mean  $\pm$  SD) ([Pasic 1987](#), [Austin 1980](#)). Erythromycin is a moderate inhibitor of CYP3A4 and listed by the FDA as clinical index inhibitor for CYP3A.

The presented erythromycin PBPK model as well as the respective evaluation plan and evaluation report are provided open-source (<https://github.com/Open-Systems-Pharmacology/Erythromycin-Model>).

# 2 Methods

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## 2.1 Modeling Strategy

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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 adult subjects obtained from the literature, covering different formulation types and erythromycin salts. Multiple doses and dosing schedules following intravenous (IV) and oral (PO) administration were included in model building. Mass balance information on urinary excretion of unchanged erythromycin after IV administration was also accounted for during the model building process.

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

- 4 data sets following single IV administration of 4 different doses of erythromycin (125 mg, 250 mg, 300 mg, 500 mg) as erythromycin lactobionate
- 6 data sets following single and multiple PO administration of 3 different doses of erythromycin (250 mg, 500 mg, 1000 mg) as film-coated tablets containing erythromycin stearate
- 2 data sets following single PO administration of 500 mg erythromycin as enteric-coated tablets containing erythromycin as base
- 2 data sets following single and multiple PO administration of 2 different doses of erythromycin (250 mg, 500 mg) as enteric-coated capsules containing pellets of erythromycin as base

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 shape** (for the film-coated tablet containing erythromycin stearate)
- **Dissolution time (50% dissolved)** (for the film-coated tablet containing erythromycin stearate)
- **Dissolution lag time** (for the enteric-coated tablet containing erythromycin as base)
- **Dissolution shape** (for the enteric-coated tablet containing erythromycin as base)
- **Dissolution time (50% dissolved)** (for the enteric-coated tablet containing erythromycin as base)
- **Solubility at reference pH** (for the enteric-coated tablet containing erythromycin as base)
- **Dissolution lag time** (for the enteric-coated capsule containing pellets of erythromycin as base)
- **Dissolution shape** (for the enteric-coated capsule containing pellets of erythromycin as base)
- **Dissolution time (50% dissolved)** (for the enteric-coated capsule containing pellets of erythromycin as base)

- Specific intestinal permeability (transcellular)
- Transport Protein - OATP1B1 -  $k_{act}$
- Metabolizing Enzyme - CYP3A4 -  $k_{act}$
- Total Hepatic Clearance - Specific clearance
- 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	733.9 ( <a href="#">drugbank.ca</a> )	Molecular weight
pK <sub>a</sub> (basic)		8.8 ( <a href="#">Lien 1974</a> ); 8.88 ( <a href="#">McFarland 1997</a> )	Acid dissociation constant
logP		2.48 ( <a href="#">Lien 1974</a> ); 2.92 ( <a href="#">Capobianco 1994</a> ); 3.06 ( <a href="#">McFarland 1997</a> )	Partition coefficient between octanol and water
f <sub>u</sub>		0.27 ± 0.05 <sup>a</sup> ( <a href="#">Sun 2010</a> ); 0.28 ± 0.04 <sup>a</sup> ( <a href="#">Iliopoulou 1982</a> ); 0.305 ± 0.028 <sup>a</sup> ( <a href="#">Barre 1987</a> ); 0.326 ( <a href="#">Xu 2009</a> )	Fraction unbound in human plasma
Water solubility (erythromycin lactobionate)	mg/L	200000 ( <a href="#">U.S. Patent 2,761,859</a> )	Solubility of erythromycin lactobionate in water
Water solubility (erythromycin stearate)	mg/L	182 ( <a href="#">Jones 1969</a> )	Solubility of erythromycin stearate in water
Water solubility (erythromycin base)	mg/L	2100 ( <a href="#">Manna 1998</a> )	Solubility of free erythromycin as base in water

<sup>a</sup> mean ± SD

### 2.2.2 In vitro data on mechanism-based inhibition of CYP3A

A literature search was carried out to collect quantitative information the mechanism-based inhibition of CYP3A by erythromycin, in particular measured values for K<sub>i</sub> and k<sub>inact</sub>. The gathered information is summarized in the table below and is used for model building.

Victim compound	In vitro system	Enzyme	$K_i$ [ $\mu$ M]	$k_{inact}$ [ $\text{min}^{-1}$ ]	Concentration range of erythromycin [ $\mu$ M]	Concentration of victim compound [ $\mu$ M]	Reference
testosterone	rec cDNA CYP3A4	CYP3A4	1.04	0.0293	0 - 20	100	<a href="#">Akiyoshi 2013</a>
testosterone	rec cDNA CYP3A4	CYP3A4	1.21	0.0164	0 - 20	100	<a href="#">Akiyoshi 2013</a>
testosterone	rec cDNA CYP3A4	CYP3A4	0.415	0.0159	0 - 20	100	<a href="#">Akiyoshi 2013</a>
testosterone	rec cDNA CYP3A4	CYP3A4	2.24	0.0293	0 - 20	100	<a href="#">Akiyoshi 2013</a>
testosterone	rec cDNA CYP3A4	CYP3A4	0.753	0.0248	0 - 20	100	<a href="#">Akiyoshi 2013</a>
midazolam	rec cDNA CYP3A4	CYP3A	9.5	0.16	50-fold range	10	<a href="#">Atkinson 2005</a>
midazolam	rec cDNA CYP3A4	CYP3A	8.82	0.12	50-fold range	10	<a href="#">Atkinson 2005</a>
midazolam	rec cDNA CYP3A4	CYP3A	8.3	0.09	50-fold range	10	<a href="#">Atkinson 2005</a>
testosterone	rec cDNA CYP3A4	CYP3A	9.5	0.06	4 - 200	16.7	<a href="#">Atkinson 2005</a>
triazolam	HLM	CYP3A	5.4	0.069		400	<a href="#">Aueviriyavit 2010</a>
testosterone	rec cDNA CYP3A4	CYP3A4	5.3	0.12	5 - 20	200	<a href="#">Chan 2000</a>
midazolam	cryopreserved HEP	CYP3A	60	0.081	3 - 300	30	<a href="#">Chen 2011</a>
midazolam	cryopreserved HEP	CYP3A	67.9	0.079	3 - 300	30	<a href="#">Chen 2011</a>
midazolam	rec cDNA CYP3A4	CYP3A4	0.762	0.0648	0.1 - 30	4	<a href="#">Ishikawa 2017</a>
testosterone	rec cDNA CYP3A4	CYP3A4	1.00	0.0604	0.1 - 30	150	<a href="#">Ishikawa 2017</a>
nifedipine	rec cDNA CYP3A4	CYP3A4	0.794	0.0766	0.1 - 30	6	<a href="#">Ishikawa 2017</a>
triazolam	HLM	CYP3A4	15.9	0.062	3 - 100	300	<a href="#">Kanamitsu 2000</a>
triazolam	HLM	CYP3A4	17.4	0.055	3 - 100	300	<a href="#">Kanamitsu 2000</a>
triazolam	rec cDNA CYP3A4	CYP3A4	19.1	0.173	3 - 100	300	<a href="#">Kanamitsu 2000</a>
triazolam	rec cDNA CYP3A4	CYP3A4	18.9	0.097	3 - 100	300	<a href="#">Kanamitsu 2000</a>
testosterone	HLM	CYP3A4	29.4	0.0271		250	<a href="#">Kosaka 2017</a>
testosterone	HLM	CYP3A4	30	0.040	0.3 - 300		<a href="#">Kozakai 2013</a>
midazolam	HLM	CYP3A4	12	0.035	0.3 - 300		<a href="#">Kozakai 2013</a>
midazolam	HLM	CYP3A4	20	0.033	0.3 - 300		<a href="#">Kozakai 2013</a>
midazolam	cryopreserved HEP	CYP3A	25.15	0.08	0.13 - 100	30	<a href="#">Mao 2011</a>

Victim compound	In vitro system	Enzyme	$K_i$ [μM]	$k_{inact}$ [min <sup>-1</sup> ]	Concentration range of erythromycin [μM]	Concentration of victim compound [μM]	Reference
midazolam	HLM	CYP3A	10.8	0.032			<a href="#">Mao 2016</a>
midazolam	cryopreserved HEP	CYP3A	30.7	0.05	0 - 300	20	<a href="#">Mao 2016</a>
midazolam	cryopreserved HEP	CYP3A	59.2	0.062	0 - 100	5	<a href="#">Mao 2016</a>
midazolam	cryopreserved HEP	CYP3A	80.3	0.052	0 - 100	20	<a href="#">Mao 2016</a>
midazolam	rec cDNA CYP3A4	CYP3A4	7.47	0.042	2 - 50	8	<a href="#">McConn 2004</a>
midazolam	HLM	CYP3A4	10.9	0.046	2 - 100	8	<a href="#">McConn 2004</a>
midazolam	primary HEP	CYP3A	11	0.07	0.1 - 10	3	<a href="#">McGinnity, 2006</a>
midazolam	HLM	CYP3A4	10	0.036	0 - 25		<a href="#">Obach 2007</a>
testosterone	HLM	CYP3A4	9.8	0.039	0 - 25	500	<a href="#">Obach 2007</a>
testosterone	rec cDNA CYP3A4	CYP3A4	0.92	0.058	5 - 100	250	<a href="#">Polasek 2006</a>
testosterone	HLM	CYP3A4	12.8	0.037	5 - 100	250	<a href="#">Polasek 2006</a>
midazolam	rec cDNA CYP3A4	CYP3A4	5.1	0.30	0.5 - 50	100	<a href="#">Ring 2005</a>
testosterone	rec cDNA CYP3A4	CYP3A4	0.92	0.058			<a href="#">Teng 2010</a>
testosterone	HLM	CYP3A4	4.579	0.0115			<a href="#">Teng 2010</a>
domperidone	HLM	CYP3A4	18.4	0.022	2.5 - 200	500	<a href="#">Ung 2009</a>
domperidone	rec cDNA CYP3A4	CYP3A4	4.1	0.026	2.5 - 200	500	<a href="#">Ung 2009</a>
midazolam	HLM	CYP3A4	12.1	0.0215	0 - 100	25	<a href="#">Watanabe 2007</a>
nifedipine	HLM	CYP3A4	11.3	0.0295	0 - 100	50	<a href="#">Watanabe 2007</a>
testosterone	HLM	CYP3A4	10.9	0.0352	0 - 100	200	<a href="#">Watanabe 2007</a>
midazolam	HLM	CYP3A	1.48	0.017	0.5 - 500	20	<a href="#">Xu 2009</a>
midazolam	cryopreserved HEP	CYP3A	20.0	0.016	0.5 - 500	20	<a href="#">Xu 2009</a>
midazolam	cryopreserved HEP	CYP3A	109	0.055	0.5 - 500	20	<a href="#">Xu 2009</a>
midazolam	HLM	CYP3A	81.8	0.0665	20 - 400	10	<a href="#">Yamano 2001</a>
midazolam	HLM	CYP3A	15.7	0.1			<a href="#">Zhang 2006</a>
testosterone	rec cDNA CYP3A4	CYP3A4	5	0.34	1 - 50	200	<a href="#">Zhang 2009</a>
testosterone	HLM	CYP3A4	15.7	0.09	1 - 50	200	<a href="#">Zhang 2009</a>



Victim compound	In vitro system	Enzyme	$K_i$ [ $\mu\text{M}$ ]	$k_{\text{inact}}$ [ $\text{min}^{-1}$ ]	Concentration range of erythromycin [ $\mu\text{M}$ ]	Concentration of victim compound [ $\mu\text{M}$ ]	Reference
midazolam	HLM	CYP3A4	26.5	0.041	2.5 - 50	10	<a href="#">Zimmerlin 2011</a>

*Note:* Abbreviations: HEP: human hepatocytes; HLM: human liver microsomes; rec cDNA CYP3A4: human recombinant c-DNA CYP3A4 enzymes (e.g. supersomes, baculovirus-insect cell system, E. coli transfected cells)

### 2.2.3 Clinical data

A literature search was carried out to collect available PK data on erythromycin in healthy adults.

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

Publication	Study description
<a href="#">Austin 1980</a>	IV administration of 125 mg, 250 mg, 500 mg, and 900 mg as erythromycin lactobionate; single dose
<a href="#">Barre 1987</a>	IV administration of 500 mg as erythromycin lactobionate; single dose
<a href="#">Huppertz 2011</a>	IV administration of 1000 mg as erythromycin lactobionate; single dose
<a href="#">Pasic 1987</a>	IV administration of 300 mg as erythromycin lactobionate; single dose
<a href="#">Sun 2010</a>	IV administration of 125 mg and PO administration of 250 mg (salt and formulation type not specified); single dose
<a href="#">Iliopoulou 1982</a>	PO administration of 500 mg as film-coated tablet containing erythromycin stearate; multiple dose
<a href="#">Josefsson 1982</a>	PO administration of 500 mg as film-coated tablet containing erythromycin stearate and 250 mg, 500 mg, 1000 mg as enteric coated capsules containing pellets of erythromycin base; single dose
<a href="#">Kavi 1988</a>	PO administration of 500 mg as film-coated tablet containing erythromycin stearate; single dose
<a href="#">Malmborg 1978</a>	PO administration of 500 mg as film-coated tablet containing erythromycin stearate; multiple dose
<a href="#">Miglioli 1990</a>	PO administration of 1000 mg erythromycin stearate; multiple dose
<a href="#">Posti 1983</a>	PO administration of 500 mg as film-coated tablets containing erythromycin stearate, as enteric-coated tablets containing erythromycin base, and as enteric-coated tablets containing erythromycin stearate; single dose
<a href="#">Schreiner 1984</a>	PO administration of 500 mg as film-coated tablets containing erythromycin stearate and as enteric-coated capsule containing pellets of erythromycin base; single dose
<a href="#">Yakatan 1980</a>	PO administration of 250 mg as film-coated tablet containing erythromycin stearate, as enteric-coated tablet containing erythromycin base, and as enteric-coated capsules containing erythromycin estolate; single and multiple dose
<a href="#">Birkett 1990</a>	PO administration of 250 mg as enteric-coated capsules containing pellets of erythromycin base; single dose
<a href="#">Kivistö 1997</a>	PO administration of 500 mg as enteric-coated capsules containing erythromycin base; multiple dose
<a href="#">DiSanto 1981</a>	PO administration of 500 mg as unprotected tablets containing erythromycin base, as film-coated tablets containing erythromycin base, as enteric-coated tablets containing erythromycin base and as film-coated tablets containing erythromycin stearate; single and multiple dose
<a href="#">Kroboth 1982</a>	PO administration of 500 mg as enteric-coated tablets containing erythromycin base; single dose

## 2.3 Model Parameters and Assumptions

### 2.3.1 Dissolution and absorption

Development of an adequate absorption model for erythromycin was complicated by the large intersubject variability in the absorption kinetics of erythromycin ([Chun 1977](#), [Mather 1981](#)). Additionally, multiple formulation types are available entailing different absorption kinetics ([Chun 1977](#), [Yakatan 1980](#), [Mather 1981](#)). The herein presented model was developed for the following oral dosage forms:

- film-coated tablets containing erythromycin stearate
- enteric-coated tablets containing erythromycin as free base
- enteric-coated capsules containing pellets of erythromycin as free base

It was assumed that the solubility of erythromycin as stearate in the film-coated tablets and as free base pellets in enteric-coated capsules is high and was therefore fixed to a value of 500 mg/L. Solubility of erythromycin base in enteric-coated tablets was optimized to capture the relatively lower  $C_{\max}$  value of this formulation observed in the herein used *in vivo* PK studies. For all three formulations types, dissolution kinetics was described by a Weibull function with different parameter values for each formulation type. Optimized parameters were the `Dissolution shape` and `Dissolution time (50% dissolved)`. Additionally, for the enteric-coated formulations, a `lag time` was applied in the model to account for the passage through the stomach, while the film-coated tablet was assumed to dissolve immediately upon entering the stomach, i.e. no lag time was applied here. `Specific intestinal permeability (transcellular)` was the same for all formulations and simultaneously optimized with the other parameters.

### 2.3.2 Distribution

With an average fraction unbound in human plasma of approximately 0.30, erythromycin is moderately protein-bound. In the developed model, the `fraction unbound (plasma, reference value)` was set to 0.305 which is the value reported by [Barre 1987](#). Lipophilicity was fixed to a value of 2.82 which is the average of three experimentally measured values reported in the literature ([Lien 1974](#), [Capobianco 1994](#), [McFarland 1997](#)). 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 `Charge dependent Schmitt` ([Open Systems Pharmacology Documentation](#)). Active transfer of erythromycin by OATP1B1 was modeled as Michaelis-Menten kinetics using an `Influx` transporter type; the `Km` value of 13.2  $\mu\text{M}$  was taken from the literature ([Lancaster 2012](#)) and `kcat` was optimized. The gene expression profile of OATP1B1 (default symbol for the gene: LST-3TM12) was loaded from the internal PK-Sim® database using the expression data quantified by RT-PCR ([Open Systems Pharmacology Documentation](#)).

### 2.3.3 Elimination

Erythromycin is extensively metabolized via N-demethylation catalyzed by CYP3A. Kinetics of this biotransformation was described by a Michaelis-Menten process with `kcat` being optimized and `Km` fixed to a value of 70  $\mu\text{M}$ , the average of reported values in the literature ([Riley 1997](#), [Wang 1997](#)). 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](#)).

Although it has also been observed that erythromycin is metabolized via CYP4F11 ([Kalsotra 2004](#)), this elimination pathway was not accounted for in the model because its contribution to overall elimination was assumed to be low. In humans, CYP4F11 is mainly expressed in the liver and to a much lesser extent in the kidney ([Cui 2000](#)) and the CYP4F family makes up approximately 15% of all hepatic CYP enzymes ([Michaels 2014](#)). The  $K_m$  and  $V_{max}$  values for the CYP4F11-mediated biotransformation reported by [Kalsotra 2004](#) are similar to those measured for CYP3A4 ([Riley 1997](#), [Wang 1997](#)), suggesting that the relative mass balance of these two metabolism pathways mainly depends on the absolute amount of each enzyme in the liver. While no information on total CYP4F11 in the human liver could be found in the literature, CYP4F11 expression in the liver of cynomolgus monkeys was observed to be approximately 6-fold lower than that of CYP3A4 ([Uehara 2015](#)). Hence, it was assumed that CYP4F11-mediated metabolism of erythromycin can be neglected in humans.

Additional elimination pathways suggested for erythromycin are acid-catalyzed degradation (hydrolysis) the acidic milieu of the stomach ([Mordi 2000](#)) and biliary excretion ([Acocella 1968](#), [Chelvan 1979](#)), but no quantitative information on the mass balance of these pathways could be found in the literature. Additionally, mechanism-based inhibition of CYP3A4 by erythromycin might constitute another clearance process which was neither considered in the model. However, a `total hepatic clearance` process was implemented in the model which could at least partly account for other elimination pathways not explicitly accounted for in the model.

The reported dose fractions of erythromycin undergo unchanged renal excretion after IV administration range from  $0.018 \pm 0.005$  to  $0.171 \pm 0.11$  (mean  $\pm$  SD) ([Pasic 1987](#), [Austin 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 fractions excreted unchanged in urine.

## 2.3.2 Autoinhibition

There is abundant evidence from *in vitro* studies that erythromycin irreversibly inhibits CYP3A (e.g. [Larrey 1983](#)) and the FDA lists erythromycin as moderate index inhibitor for CYP3A. Ample data quantifying the mechanism-based inhibition of CYP3A4 by erythromycin was collected from the literature (see section [2.2.2](#)). The data listed in the Table in section [2.2.2](#) can be statistically summarized as follows:

Parameter [unit]	Min	Q1	Geometric mean	Median	Arithmetic mean	Q3	Max
$K_i$ [ $\mu\text{M}$ ]	0.420	4.89	8.71	10.9	18.4	19.3	109
$k_{inact}$ [ $\text{min}^{-1}$ ]	0.0115	0.0314	0.0504	0.0535	0.0664	0.0772	0.340

In the PBPK model, `ki` and `kinact` were fixed to the geometric mean values tabulated above.

# 3 Results and Discussion

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The PBPK model for erythromycin 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 and for model verification: [Section 3.3](#).

## 3.1 Final input parameters

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

# Compound: Erythromycin

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## Parameters

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Name	Value	Value Origin	Alternative	Default	
Solubility at reference pH	500 mg/l	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	Erythromycin stearate film-coated tablet	True	
Reference pH	7	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	Erythromycin stearate film-coated tablet	True	
Solubility at reference pH	500 mg/l	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	Erythromycin base enteric coated pellets	False	
Reference pH	7	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	Erythromycin base enteric coated pellets	False	
Solubility at reference pH	200 mg/ml	Publication-In Vitro-Hoffhine, Jr Charles E. "Aqueous soluble salts of erythromycin." U.S. Patent 2,761,859, issued September 4, 1956.	Erythromycin lactobionate	False	

Name	Value	Value Origin	Alternative	Default	
Reference pH	7	Publication-In Vitro-Hoffhine, Jr Charles E. "Aqueous soluble salts of erythromycin." U.S. Patent 2,761,859, issued September 4, 1956.	Erythromycin lactobionate	False	
Solubility at reference pH	2.5002520571 mg/l	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	Erythromycin base enteric coated tablet	False	
Reference pH	7		Erythromycin base enteric coated tablet	False	
Lipophilicity	2.82 Log Units	Publication-In Vitro-Average of reported values in the literature (PMID: 9135031, PMID: 18611609, and: Lien, E. J., Kuwahara, J., & Koda, R. T. (1974). Diffusion of drugs into prostatic fluid and milk. Drug Intelligence & Clinical Pharmacy, 8(8), 470-475. <a href="http://journals.sagepub.com/doi/abs/10.1177/106002807400800803">http://journals.sagepub.com/doi/abs/10.1177/106002807400800803</a> )	Literature (average value)	True	

Name	Value	Value Origin	Alternative	Default	
Fraction unbound (plasma, reference value)	0.305	Publication-In Vivo-PMID: 3606934	Barre 1987	True	
Specific intestinal permeability (transcellular)	0.00057882652836 cm/min	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	Fitted	True	
Is small molecule	Yes				
Molecular weight	733.927 g/mol	Internet-drugbank.ca			
Plasma protein binding partner	Unknown				

# Calculation methods

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Name	Value	
Partition coefficients	Rodgers and Rowland	
Cellular permeabilities	Charge dependent Schmitt	

## Processes

### Metabolizing Enzyme: CYP3A4-Biotransformation\_fitted

Molecule: CYP3A4

#### Parameters

Name	Value	Value Origin	
In vitro Vmax for liver microsomes	345 pmol/min/mg mic. protein	Publication-In Vitro-PMID: 9566442	
Km	70 $\mu$ M	Publication-In Vitro-Average of reported values in the literature (PMID: 9107550 and PMID: 9566442)	
kcat	6.477728756 1/min	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	

### Systemic Process: Glomerular Filtration-fitted

Species: Human

#### Parameters

Name	Value	Value Origin	
GFR fraction	1.3151947529	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	

### Inhibition: CYP3A4-MBI

Molecule: CYP3A4

#### Parameters

Name	Value	Value Origin	
kinact	0.05044312 1/min	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	
K_kinact_half	8.705192 $\mu$ mol/l	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	

### Transport Protein: OATP1B1-fitted

Molecule: OATP1B1

#### Parameters

Name	Value	Value Origin	
Transporter concentration	1 $\mu\text{mol/l}$		
Vmax	11.66 $\text{pmol/ml/min}$	Publication-In Vitro-PMID: 22990751	
Km	13.2 $\mu\text{mol/l}$	Publication-In Vitro-PMID: 22990751	
kcat	18.3753550107 $1/\text{min}$	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	

## Systemic Process: Total Hepatic Clearance-fitted

Species: Human

### Parameters

Name	Value	Value Origin	
Fraction unbound (experiment)	0.305		
Lipophilicity (experiment)	2.48 Log Units		
Plasma clearance	0 $\text{ml/min/kg}$		
Specific clearance	3.1542129297 $1/\text{min}$	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:46	

# Formulation: Erythromycin\_Weibull\_enteric-coated- pellets

---

Type: Weibull

## Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	3.4504159922 min	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:29	
Lag time	107.7187470594 min	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:29	
Dissolution shape	1.1678641251	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:29	
Use as suspension	Yes		



# Formulation: Erythromycin\_Weibull\_enteric-coated-tablet

---

Type: Weibull

## Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	121.1893502595 min	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:29	
Lag time	66.1803696499 min	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:29	
Dissolution shape	1.5167999313	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:29	
Use as suspension	Yes		

# Formulation: Erythromycin\_Weibull\_filmtablet

---

Type: Weibull

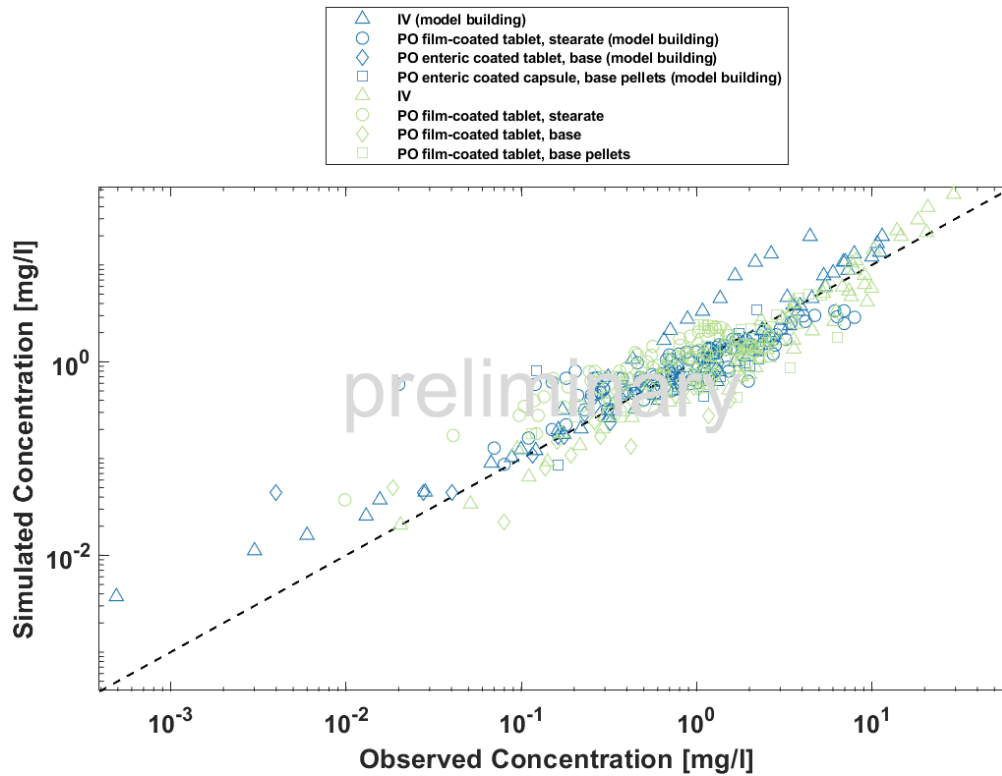
## Parameters

Name	Value	Value Origin	
Dissolution time (50% dissolved)	27.6449832276 min	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:29	
Lag time	0 min	Other-Assumption	
Dissolution shape	0.3779018493	Parameter Identification-Parameter Identification-Value updated from '001' on 2019-10-01 13:29	
Use as suspension	Yes		

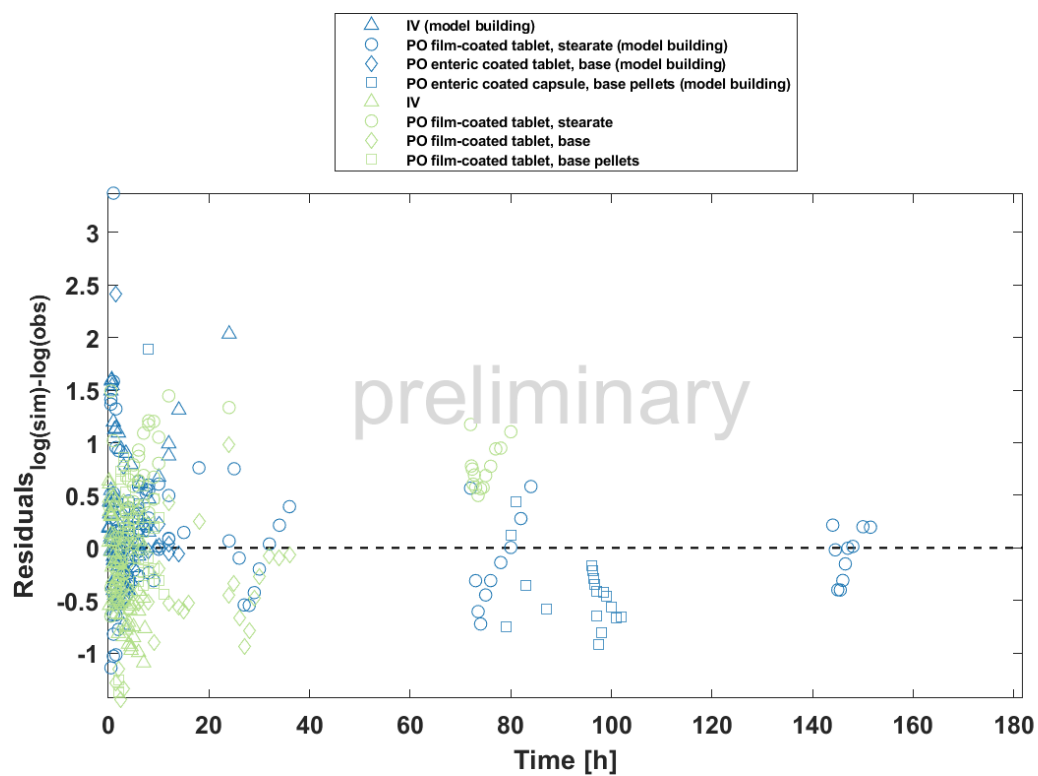
## 3.2 Diagnostics Plots

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

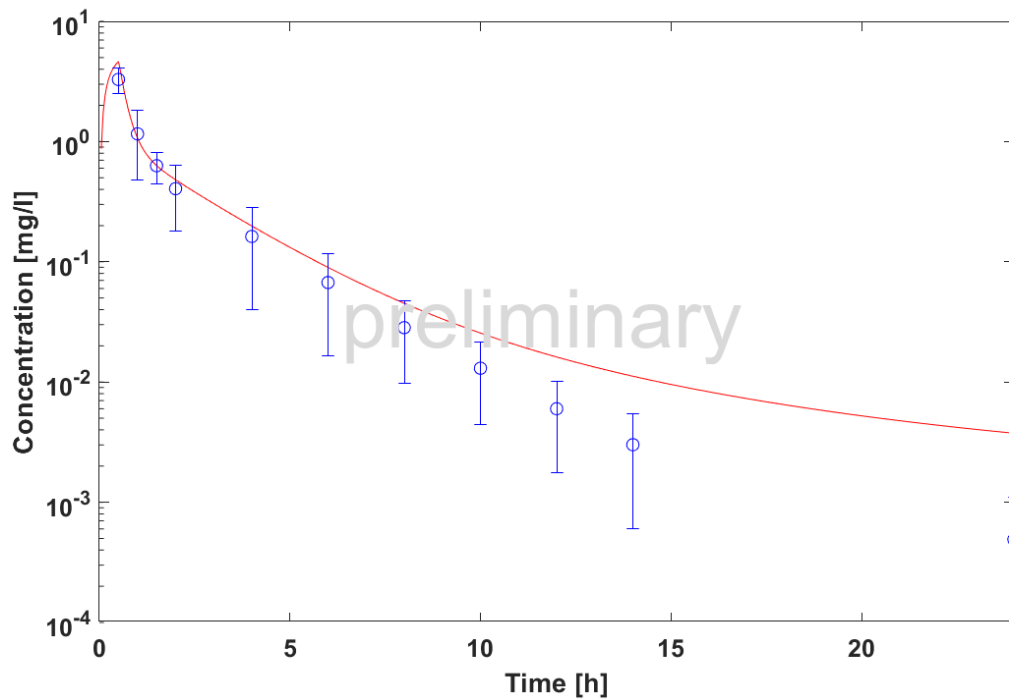
GMFE = 1.579291

## 3.3: Concentration-Time Profiles

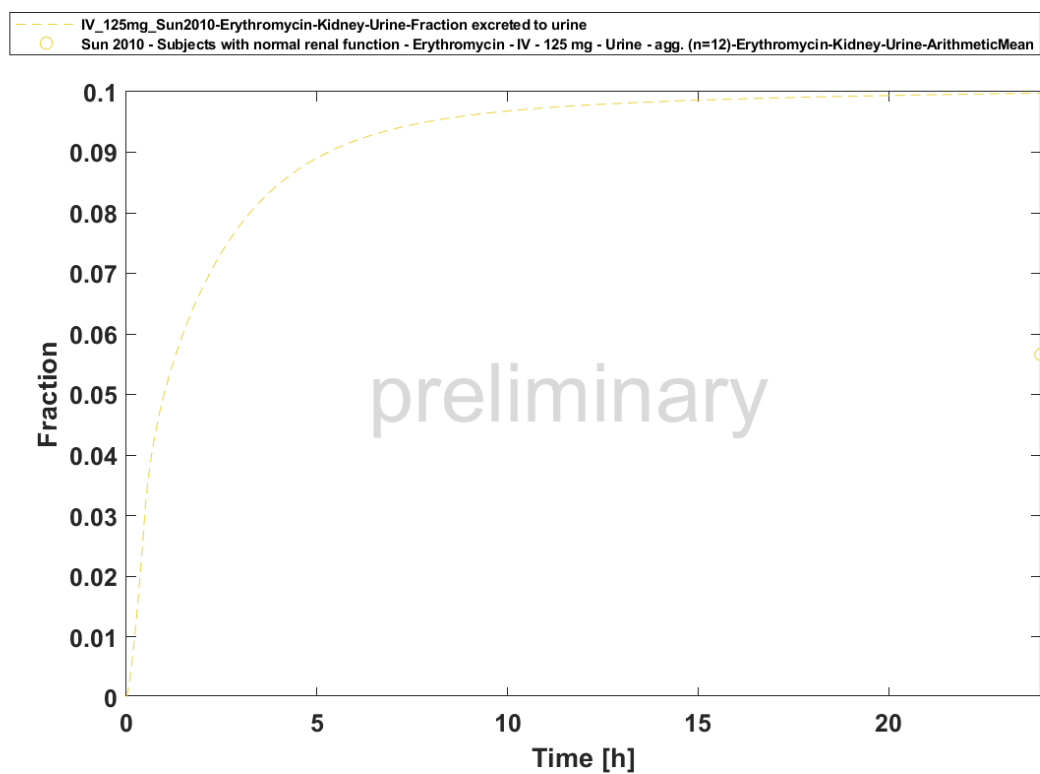
Simulated versus observed concentration-time profiles of all data listed in [Section 2.2.2](#) are presented below.

### 3.3.1 Model Building

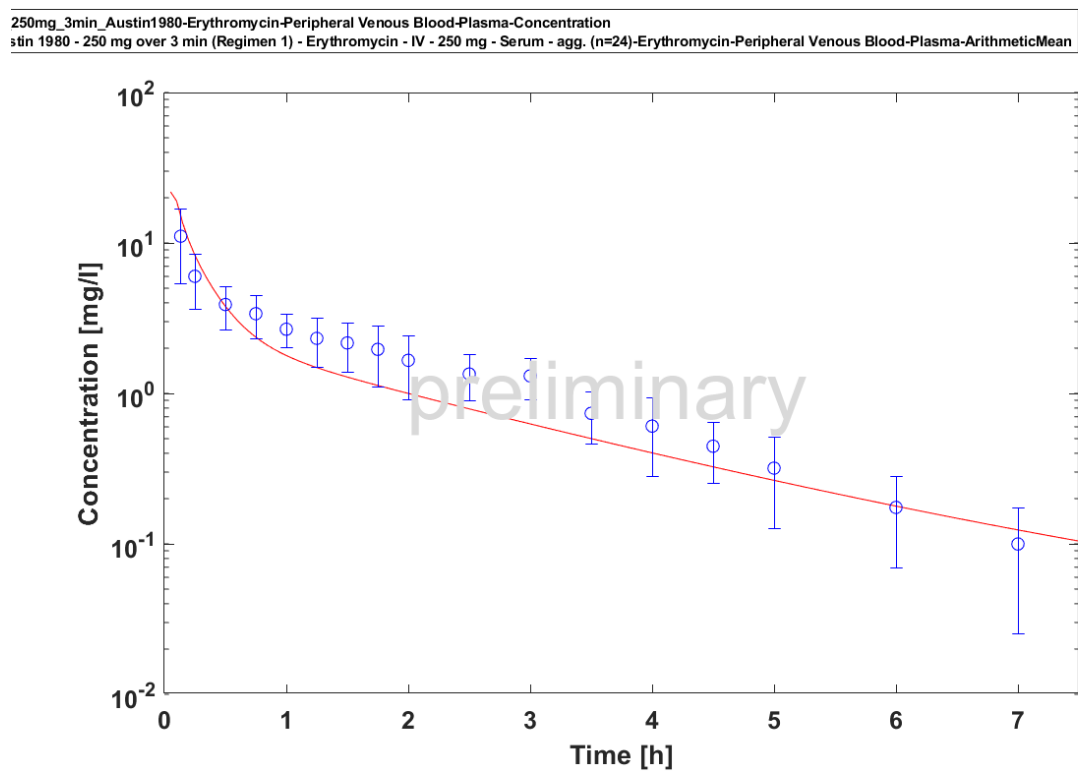
img\_Sun2010-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
010 - Subjects with normal renal function - Erythromycin - IV - 125 mg - Plasma - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis



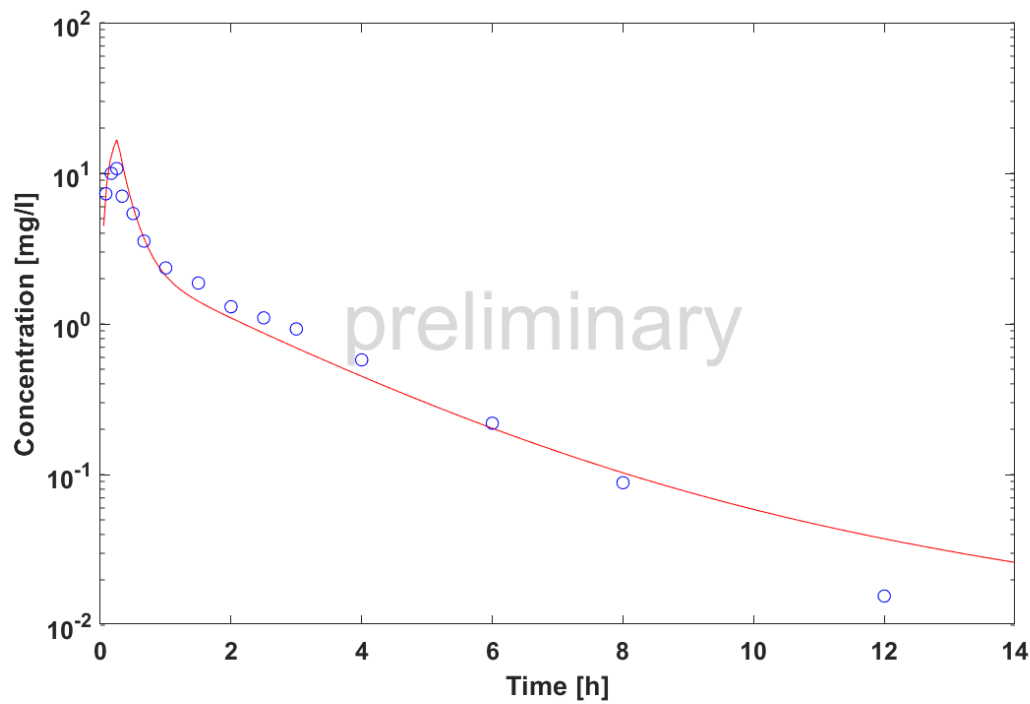
Time Profile Analysis 1



Time Profile Analysis

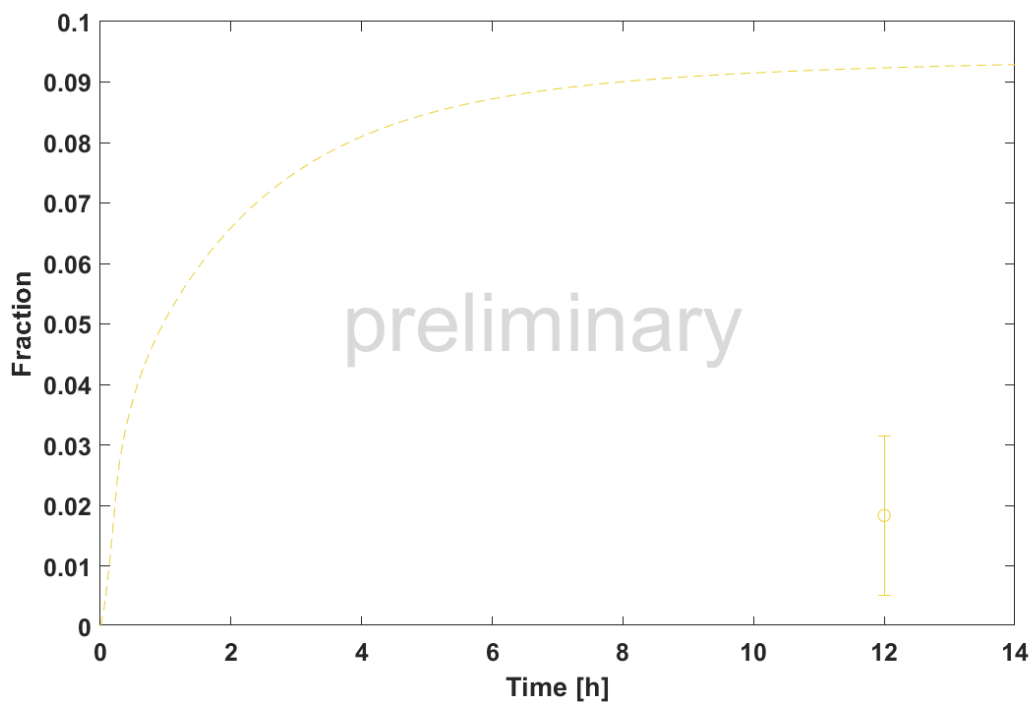


sic1987-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
Without oral theophylline co-administration - Erythromycin - IV - 300 mg - Serum - agg. (n=8)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



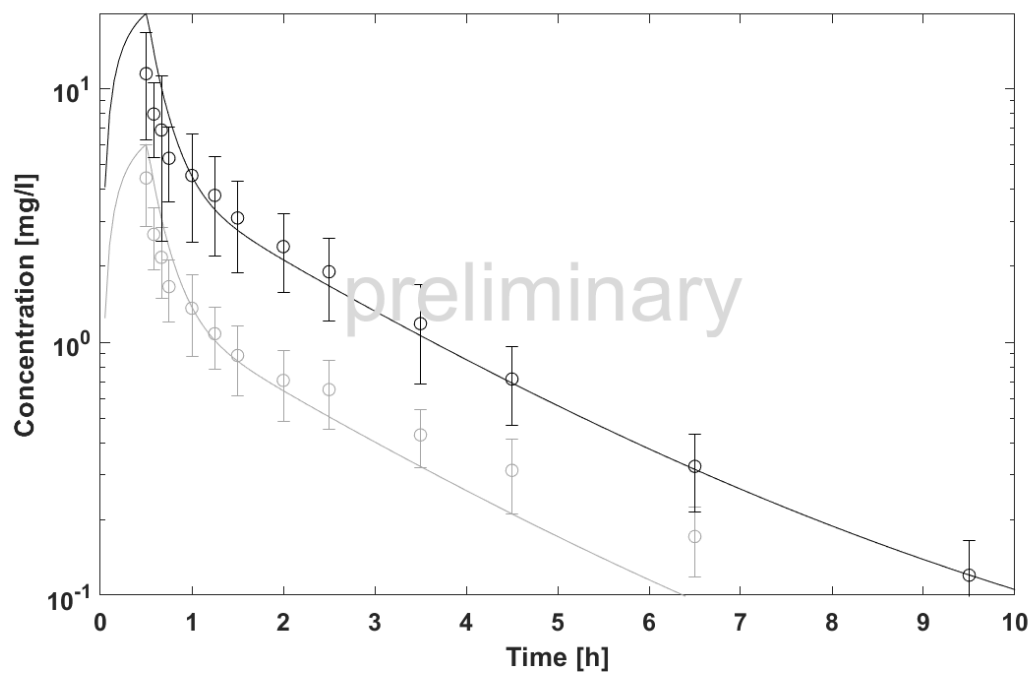
Time Profile Analysis

IV\_300mg\_Pasic1987-Erythromycin-Kidney-Urine-Fraction excreted to urine  
Pasic 1987 - Without oral theophylline co-administration - Erythromycin - IV - 300 mg - Urine - agg. (n=8)-Erythromycin-Kidney-Urine-ArithmeticMean



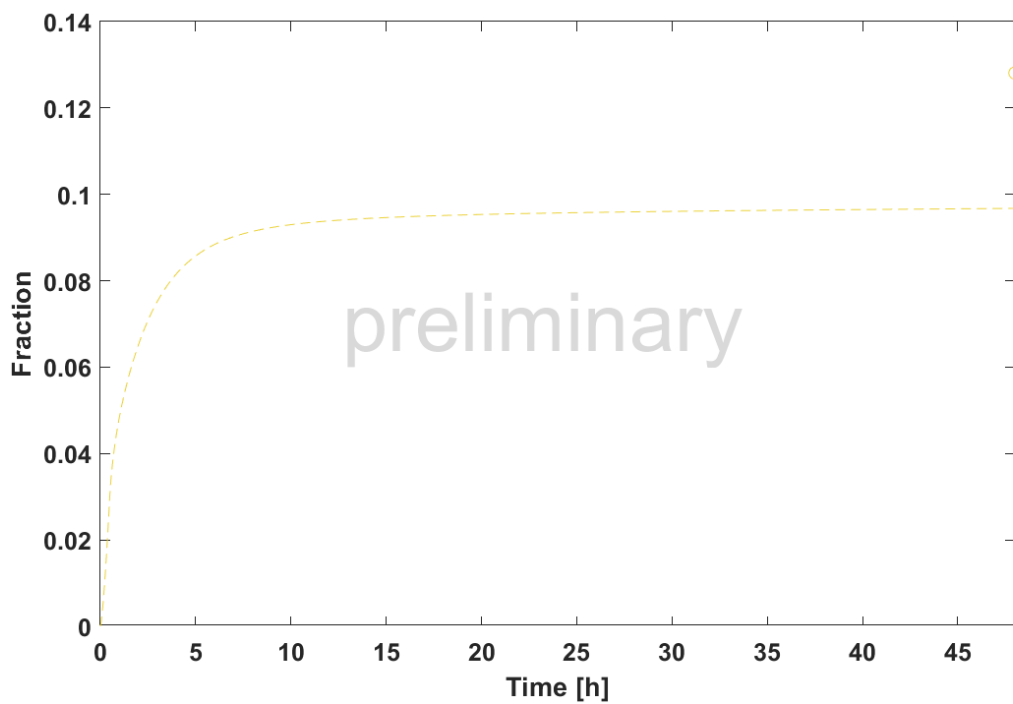
Time Profile Analysis 1

e1987-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
e1987-Erythromycin-Peripheral Venous Blood-Plasma Unbound-Concentration  
3 mg over 30 min, unbound concentrations - Erythromycin - IV - 500 mg - Serum - agg. (n=6)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
3 mg over 30 min, total concentrations - Erythromycin - IV - 500 mg - Serum - agg. (n=6)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



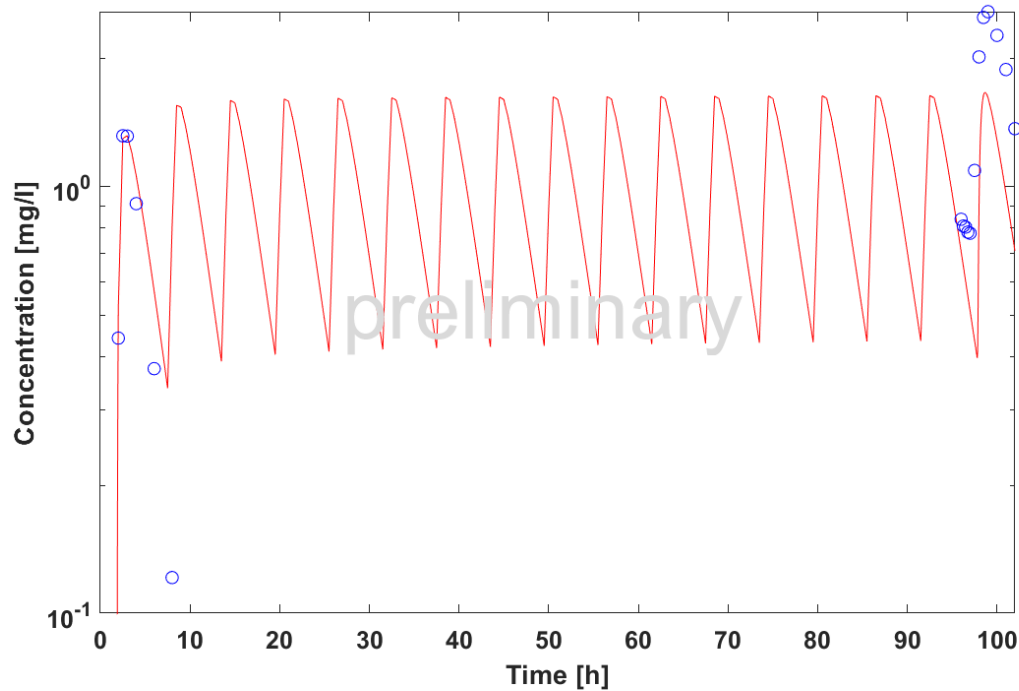
Time Profile Analysis

IV\_500mg\_Barre1987-Erythromycin-Kidney-Urine-Fraction excreted to urine  
Barre 1987 - 500 mg over 30 min, total concentrations - Erythromycin - IV - 500 mg - Urine - agg. (n=6)-Erythromycin-Kidney-Urine-ArithmeticMean



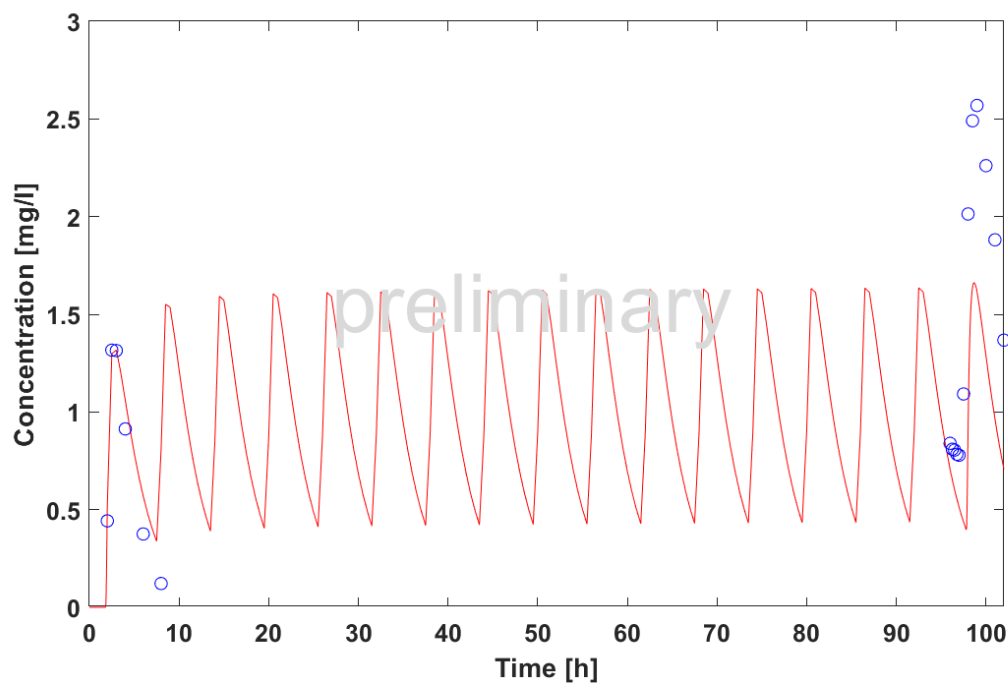
Time Profile Analysis 1

rkett1990-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
10 - 250 mg erythromycin, single dose - Erythromycin - PO - 250 mg - Plasma - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
10 - 250 mg erythromycin, multiple dose - Erythromycin - PO - 250 mg - Plasma - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



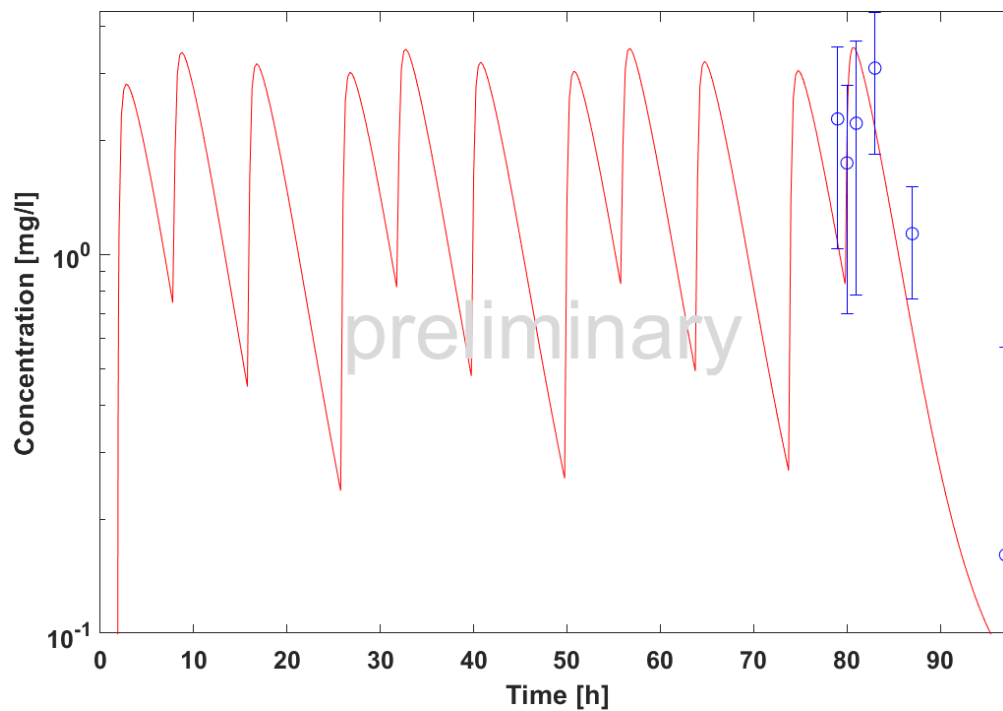
Time Profile Analysis

rkett1990-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
10 - 250 mg erythromycin, single dose - Erythromycin - PO - 250 mg - Plasma - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
10 - 250 mg erythromycin, multiple dose - Erythromycin - PO - 250 mg - Plasma - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



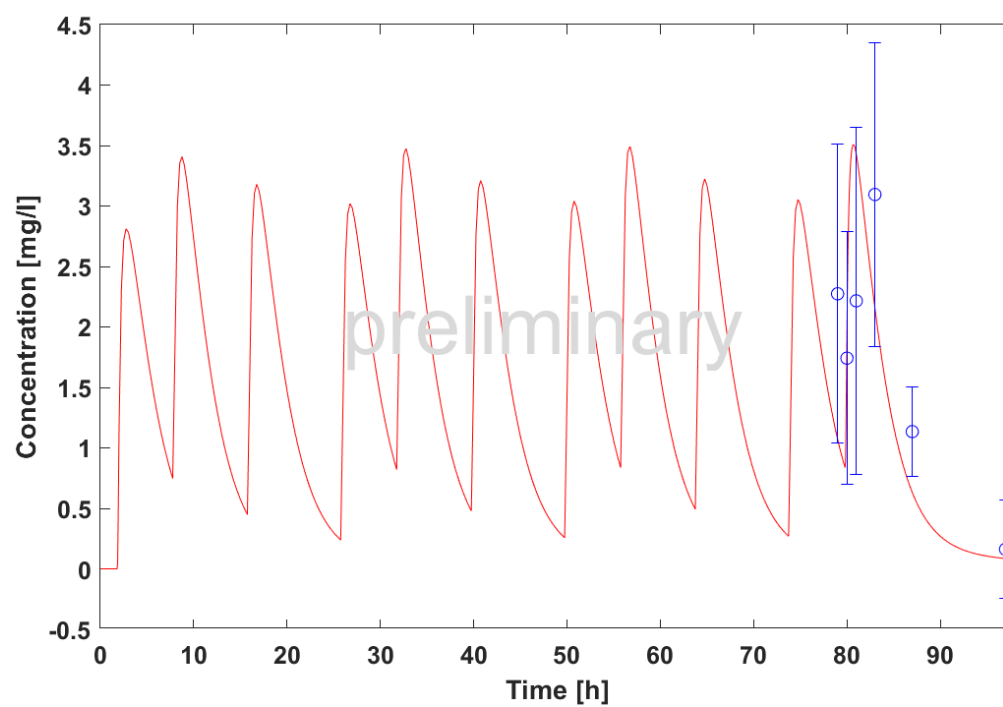
Time Profile Analysis 1

ig\_Kivistö1997\_pellets\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
tö 1997 - with Perpetrator (Erythromycin) - Erythromycin - PO - 500 mg - Plasma - agg. (n=8)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



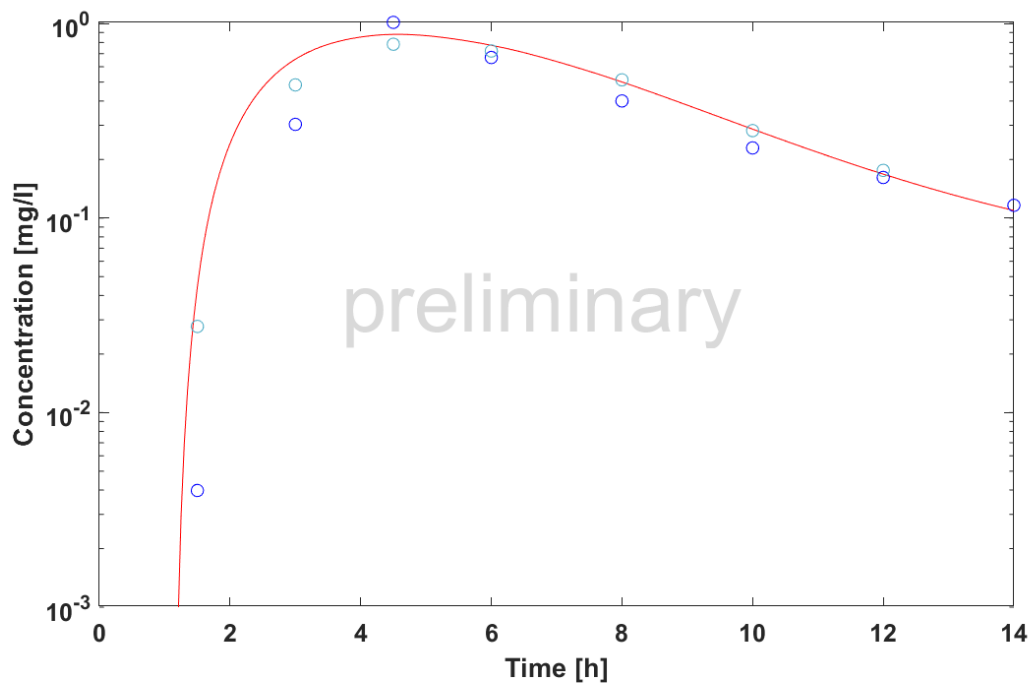
Time Profile Analysis

ig\_Kivistö1997\_pellets\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
tö 1997 - with Perpetrator (Erythromycin) - Erythromycin - PO - 500 mg - Plasma - agg. (n=8)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



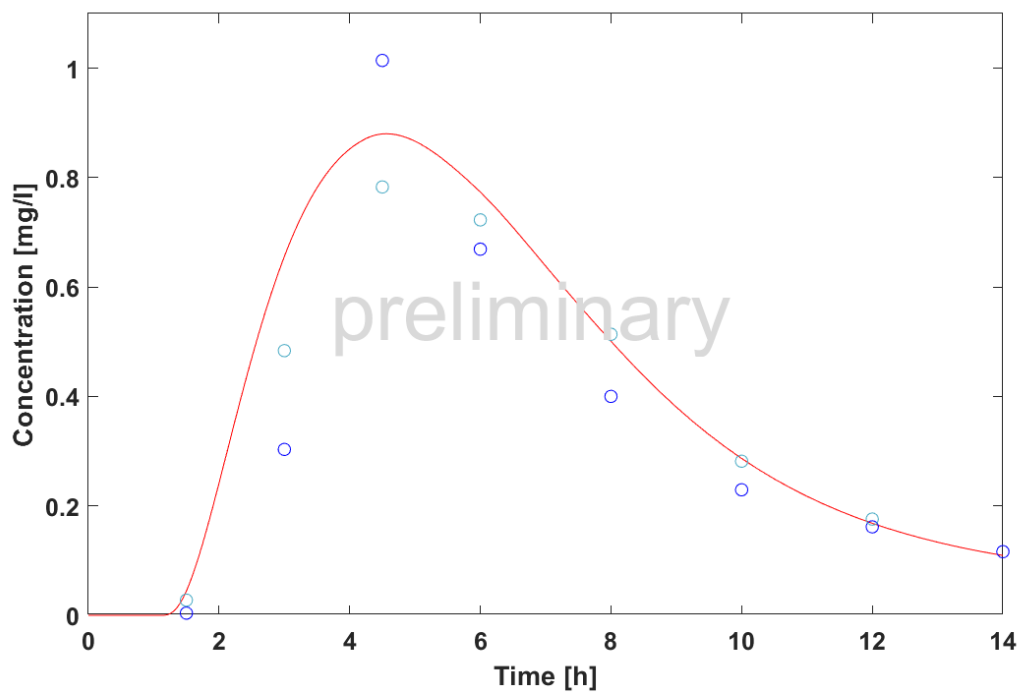
Time Profile Analysis 1

Peripheral Venous Blood-Plasma-Concentration  
ric-coated erythromycin tablets (study 1) - Erythromycin - PO - 500 mg - Serum - agg. (n=21)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
ed erythromycin tablets (study 2) - Erythromycin - PO - 500 mg - Serum - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



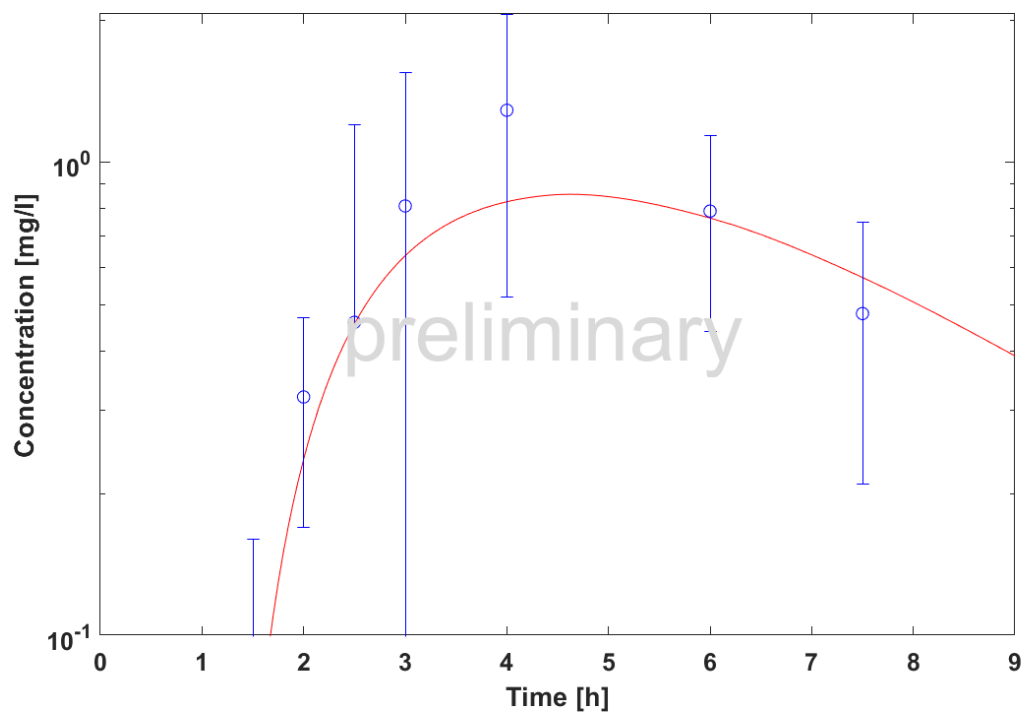
Time Profile Analysis

Peripheral Venous Blood-Plasma-Concentration  
ric-coated erythromycin tablets (study 1) - Erythromycin - PO - 500 mg - Serum - agg. (n=21)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
ed erythromycin tablets (study 2) - Erythromycin - PO - 500 mg - Serum - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



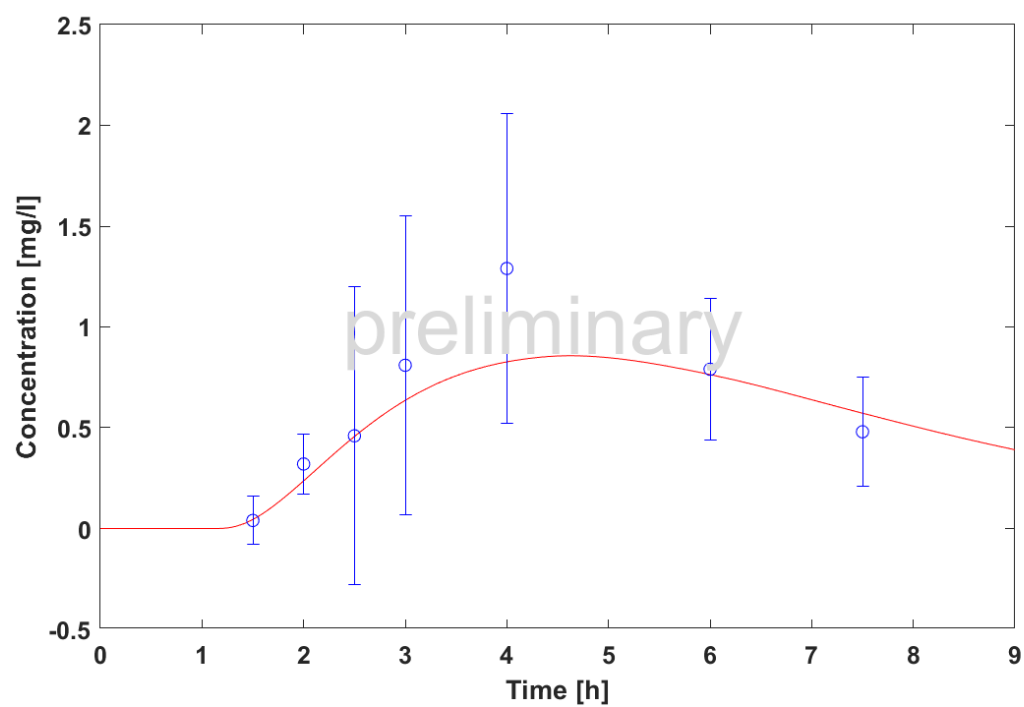
Time Profile Analysis 1

omycin-Peripheral Venous Blood-Plasma-Concentration  
(enteric-coated tablets, ery base), fasted - Erythromycin - PO - 500 mg - Serum - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



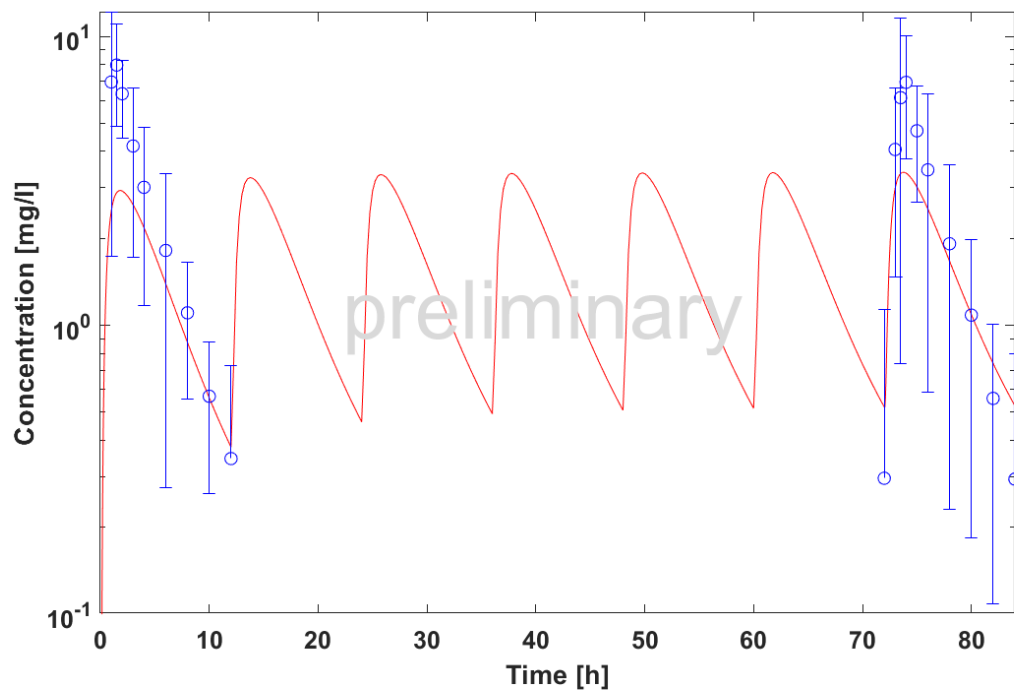
Time Profile Analysis

omycin-Peripheral Venous Blood-Plasma-Concentration  
(enteric-coated tablets, ery base), fasted - Erythromycin - PO - 500 mg - Serum - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



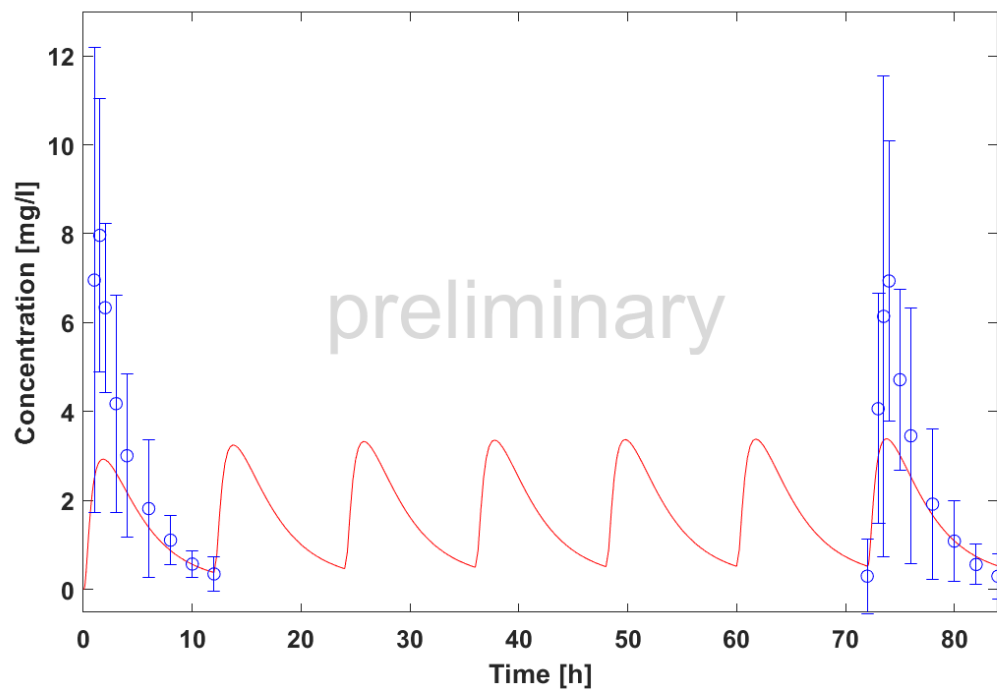
Time Profile Analysis 1

1000mg\_Miglioli1990\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
Miglioli 1990 - First dose, young subjects - Erythromycin - PO - 1 g - Serum - agg. (n=8)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
Miglioli 1990 - Seventh dose, young subjects - Erythromycin - PO - 1 g - Serum - agg. (n=8)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean

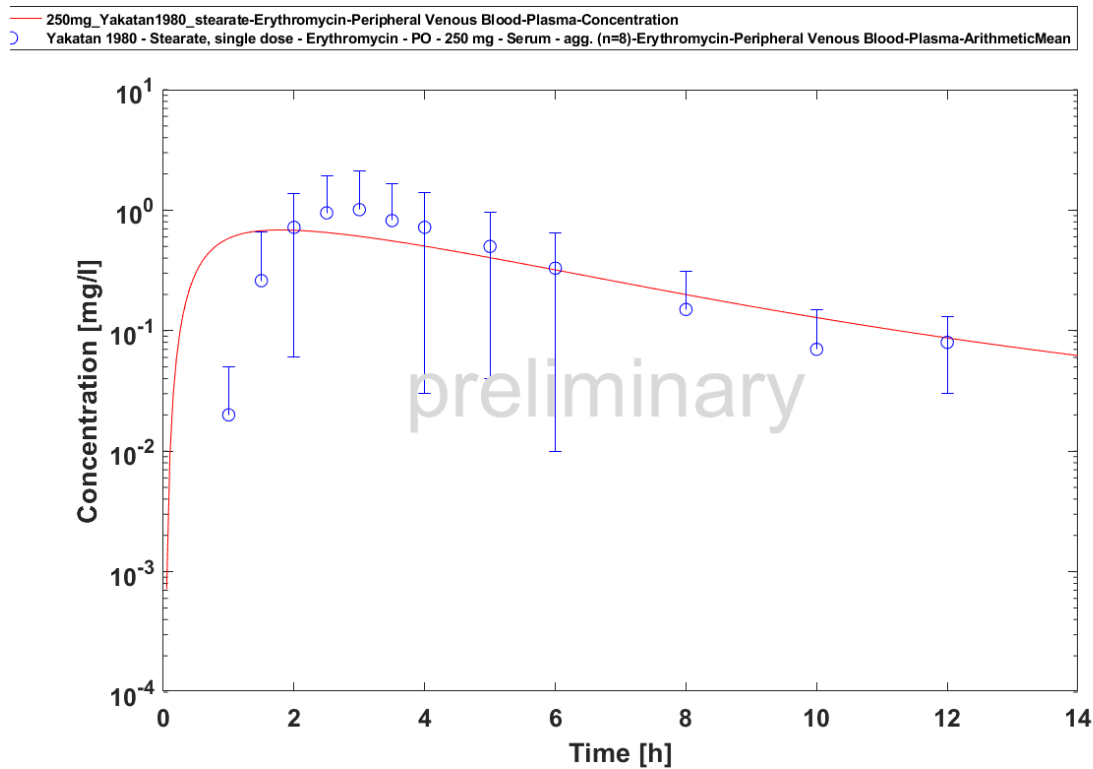


Time Profile Analysis

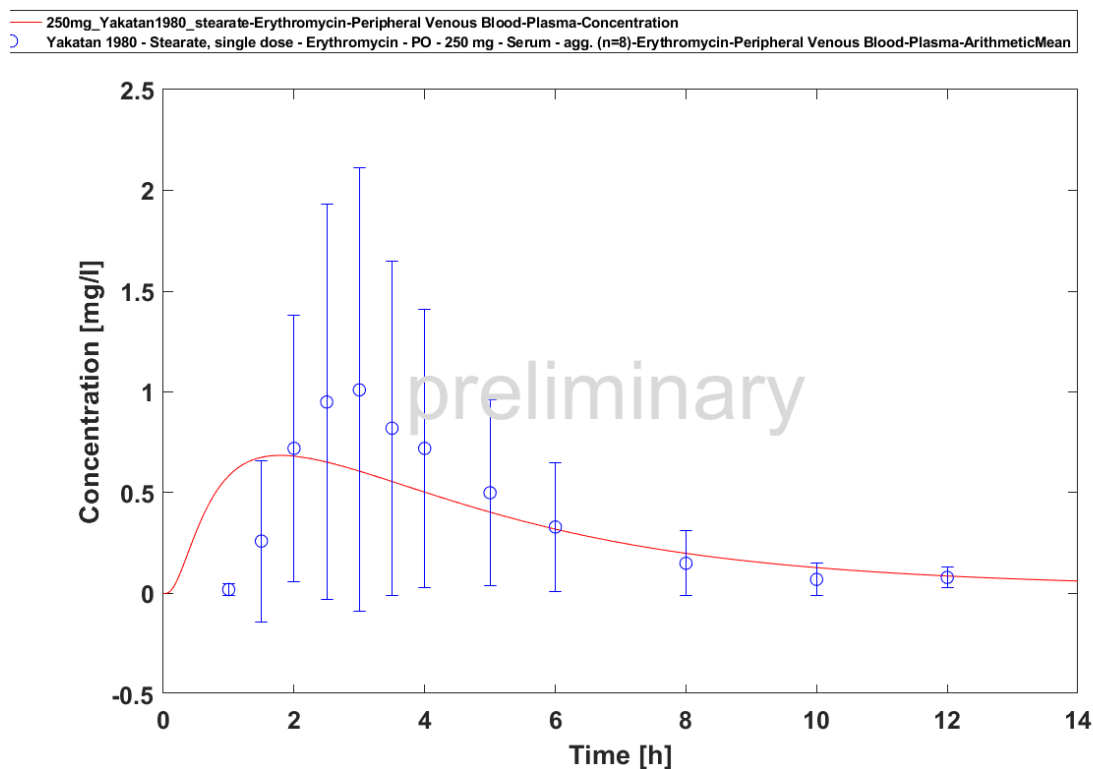
1000mg\_Miglioli1990\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
Miglioli 1990 - First dose, young subjects - Erythromycin - PO - 1 g - Serum - agg. (n=8)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
Miglioli 1990 - Seventh dose, young subjects - Erythromycin - PO - 1 g - Serum - agg. (n=8)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis 1



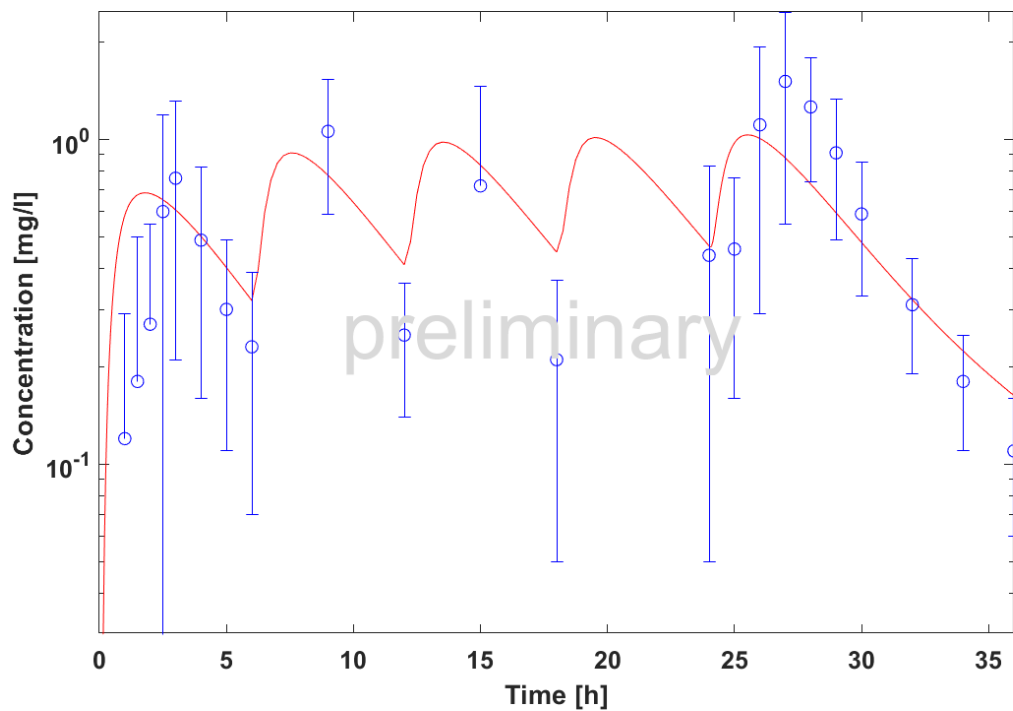
Time Profile Analysis



Time Profile Analysis 1

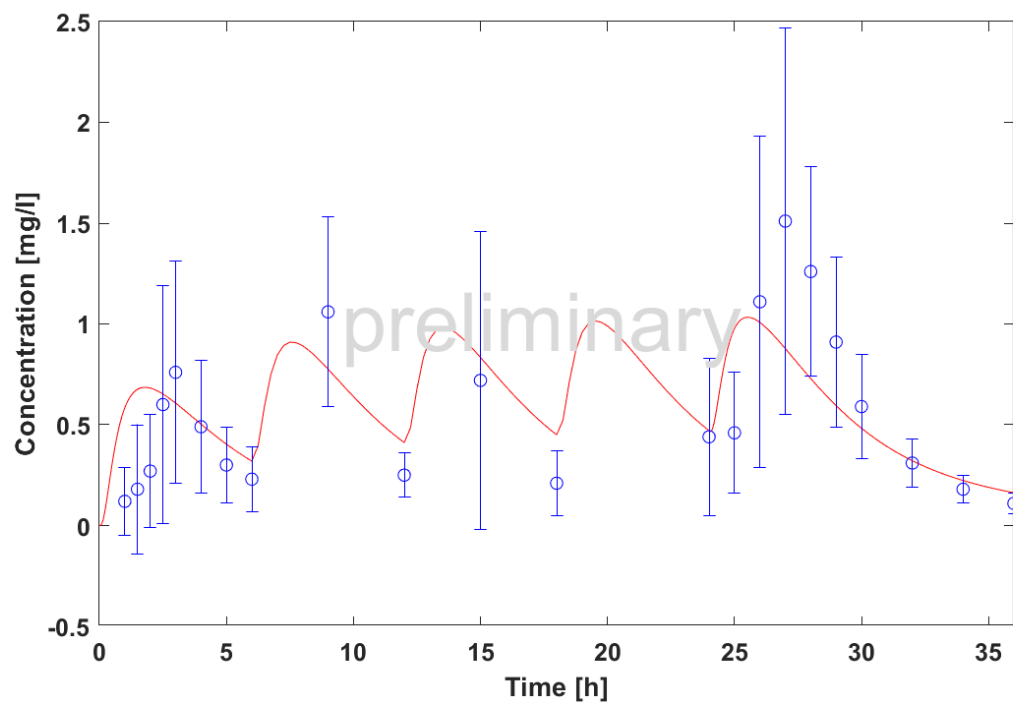


ig\_Yakatan1980\_stearate\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
tan 1980 - Stearate, five doses, every 6 h - Erythromycin - PO - 250 mg - Serum - agg. (n=24)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



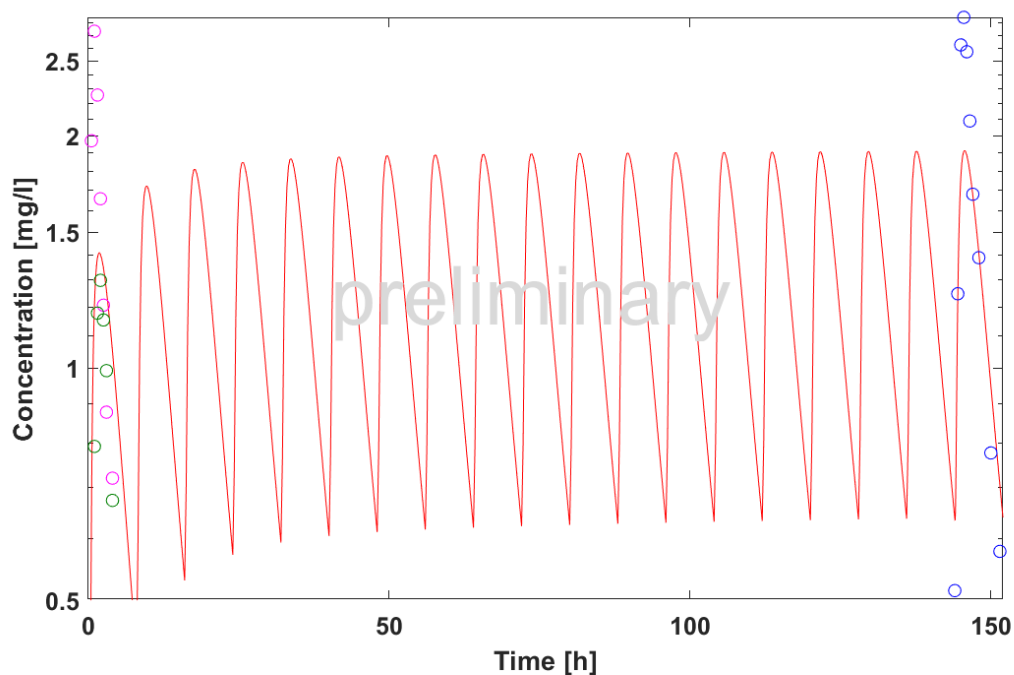
Time Profile Analysis

ig\_Yakatan1980\_stearate\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
tan 1980 - Stearate, five doses, every 6 h - Erythromycin - PO - 250 mg - Serum - agg. (n=24)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



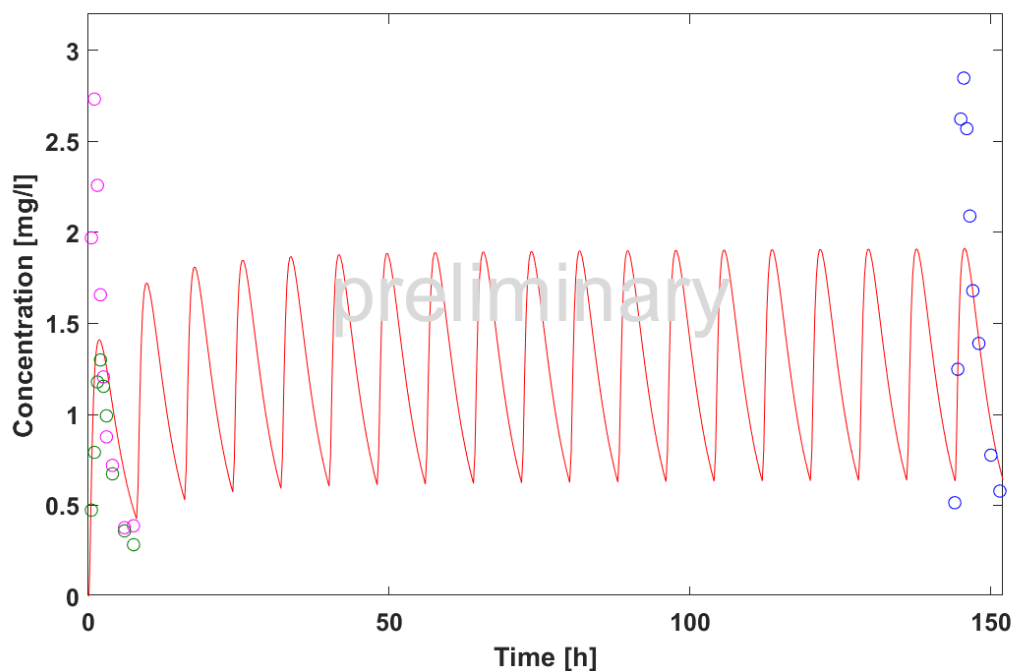
Time Profile Analysis 1

178\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
single dose before standardized breakfast - Erythromycin - PO - 500 mg - Plasma - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
single dose after overnight fast - Erythromycin - PO - 500 mg - Plasma - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
Day 7, every 8 h - Erythromycin - PO - 500 mg - Plasma - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



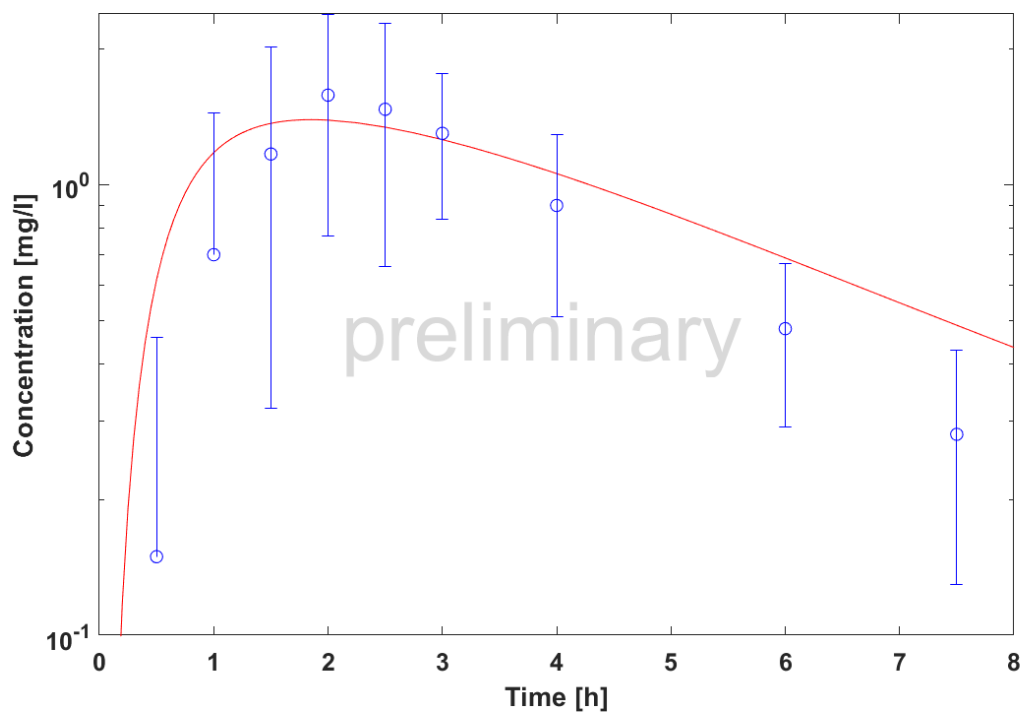
Time Profile Analysis

178\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
single dose before standardized breakfast - Erythromycin - PO - 500 mg - Plasma - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
single dose after overnight fast - Erythromycin - PO - 500 mg - Plasma - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
Day 7, every 8 h - Erythromycin - PO - 500 mg - Plasma - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



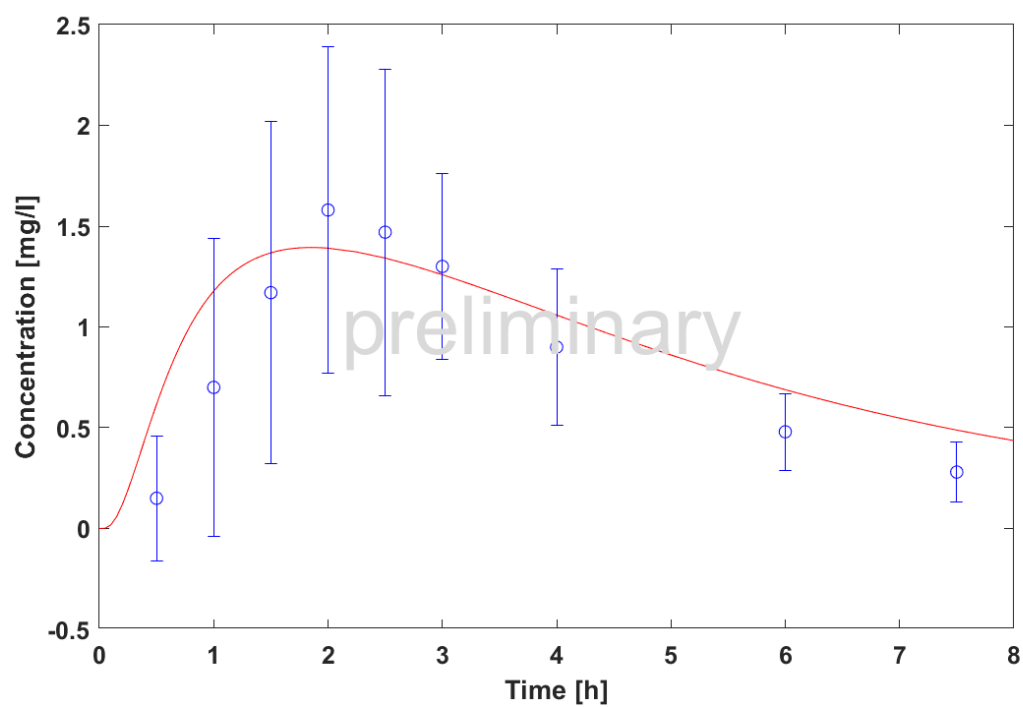
Time Profile Analysis 1

hromycin-Peripheral Venous Blood-Plasma-Concentration  
1 (film-coated tabet, ery stearate), fasted - Erythromycin - PO - 500 mg - Serum - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



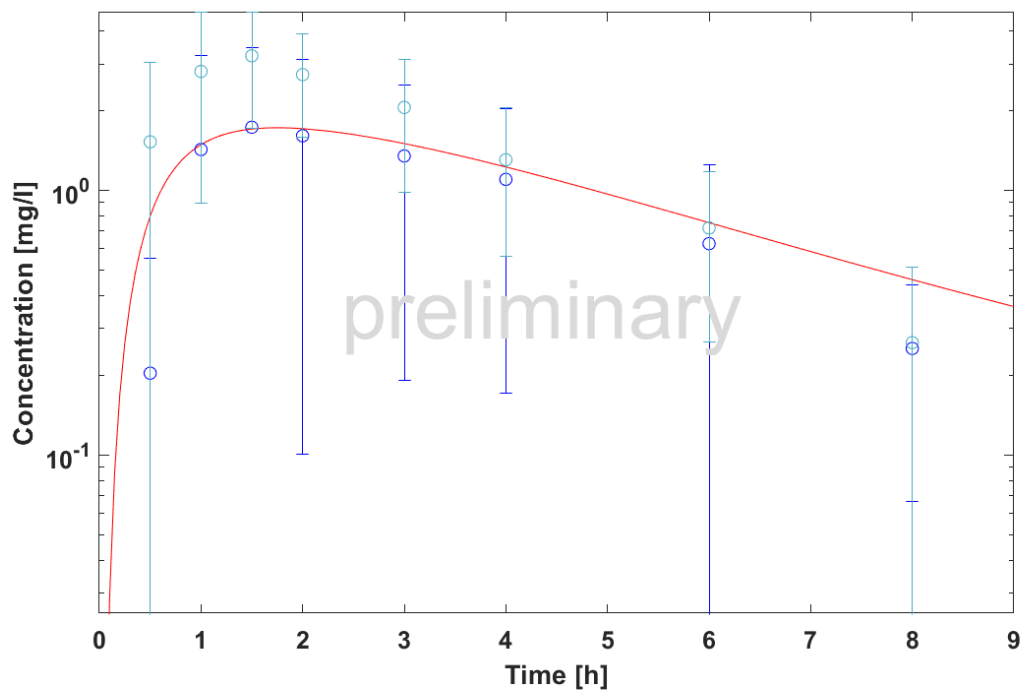
Time Profile Analysis

hromycin-Peripheral Venous Blood-Plasma-Concentration  
1 (film-coated tabet, ery stearate), fasted - Erythromycin - PO - 500 mg - Serum - agg. (n=15)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



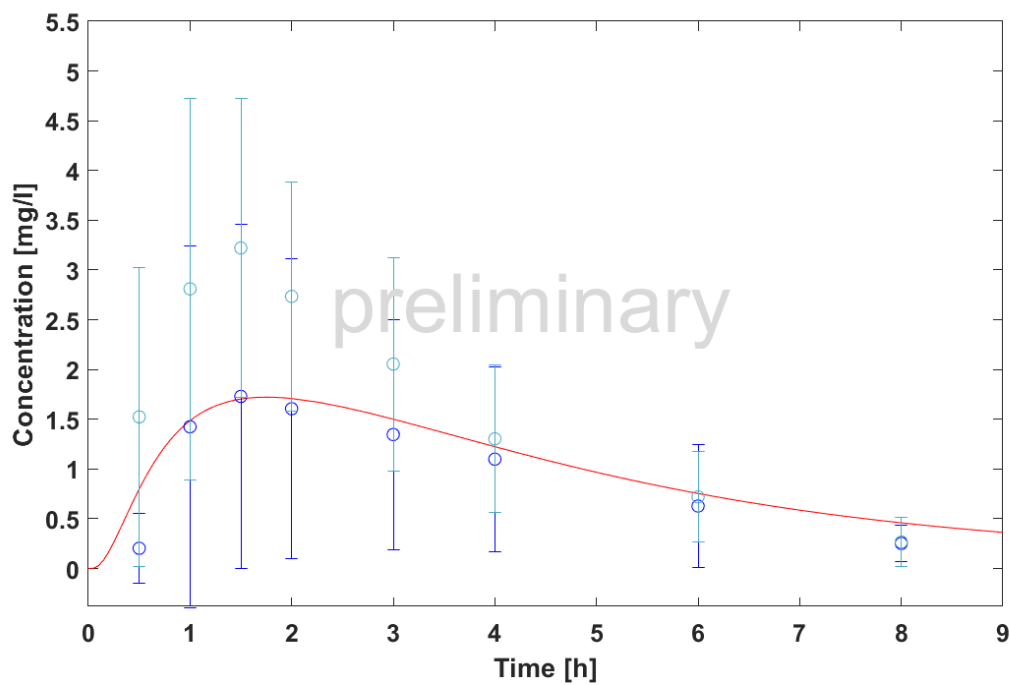
Time Profile Analysis 1

ythromycin-Peripheral Venous Blood-Plasma-Concentration  
(film-coated tablet, ery stearate), study 2 - Erythromycin - PO - 500 mg - Serum - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
(film-coated tablet, ery stearate), study 2 - Erythromycin - PO - 500 mg - Serum - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis

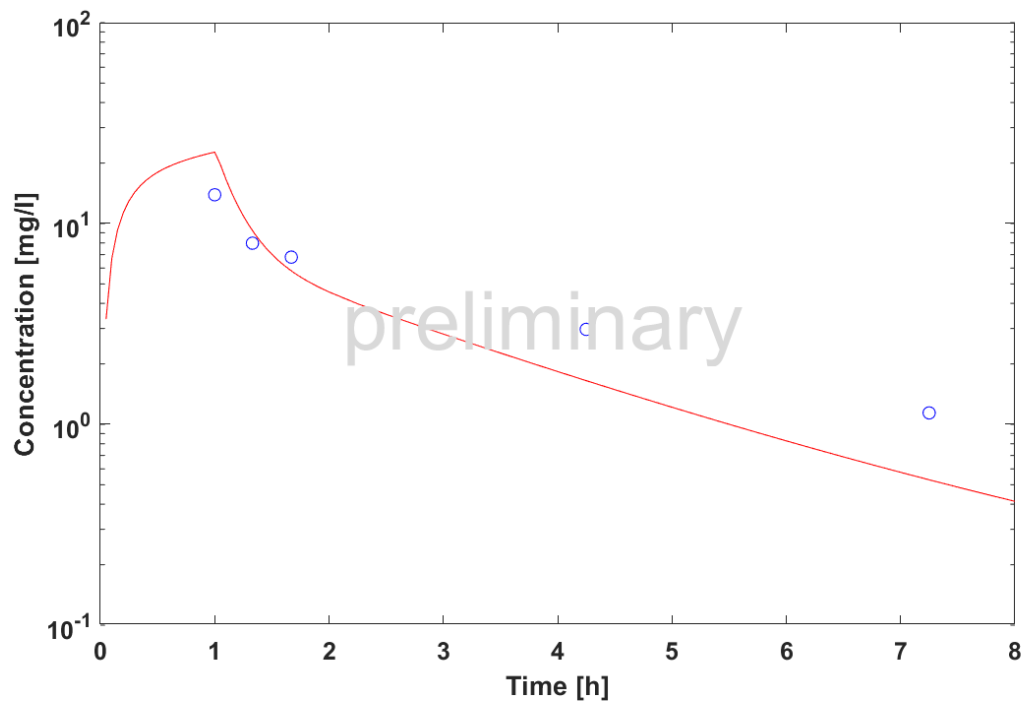
ythromycin-Peripheral Venous Blood-Plasma-Concentration  
(film-coated tablet, ery stearate), study 2 - Erythromycin - PO - 500 mg - Serum - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
(film-coated tablet, ery stearate), study 2 - Erythromycin - PO - 500 mg - Serum - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis 1

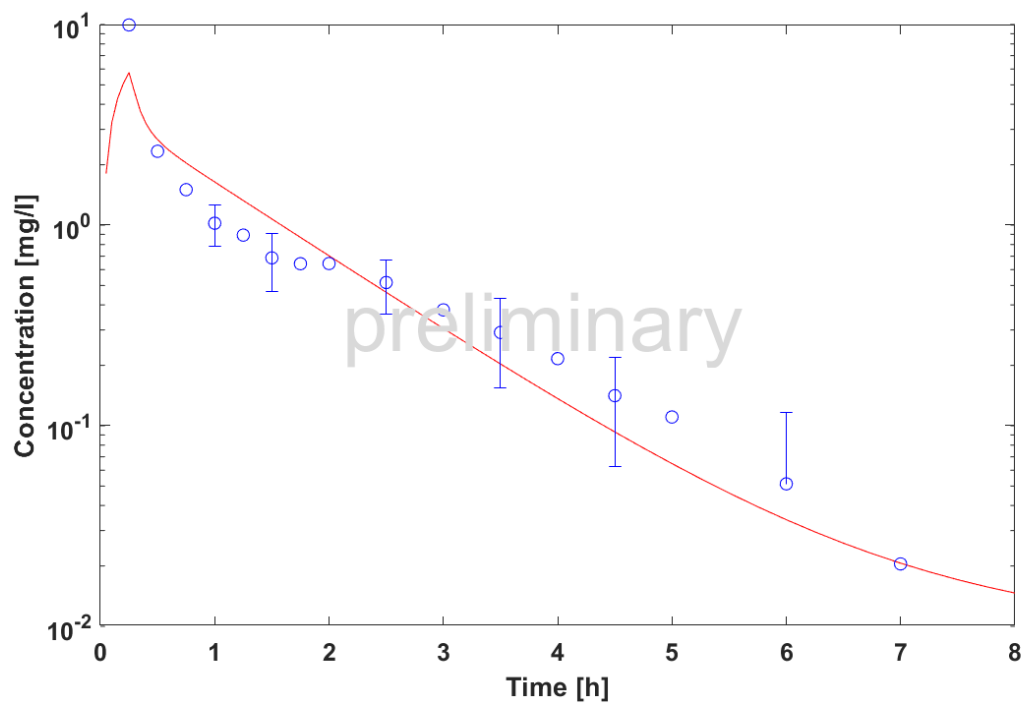
### 3.3.2 Model Verification

mg\_Huppertz2011-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
z 2011 - Treatment group, erythromycin - Erythromycin - IV - 1000 mg - Plasma - agg. (n=12)-Erythromycin-Peripheral Venous Blood-Plasma-GeometricMean

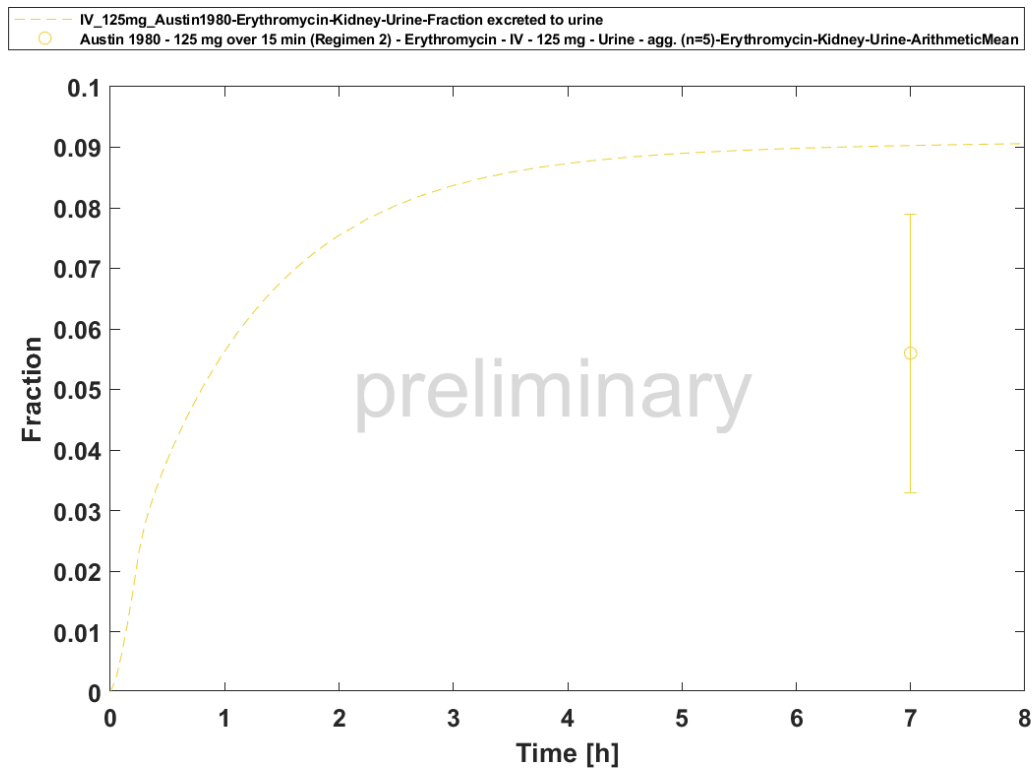


Time Profile Analysis

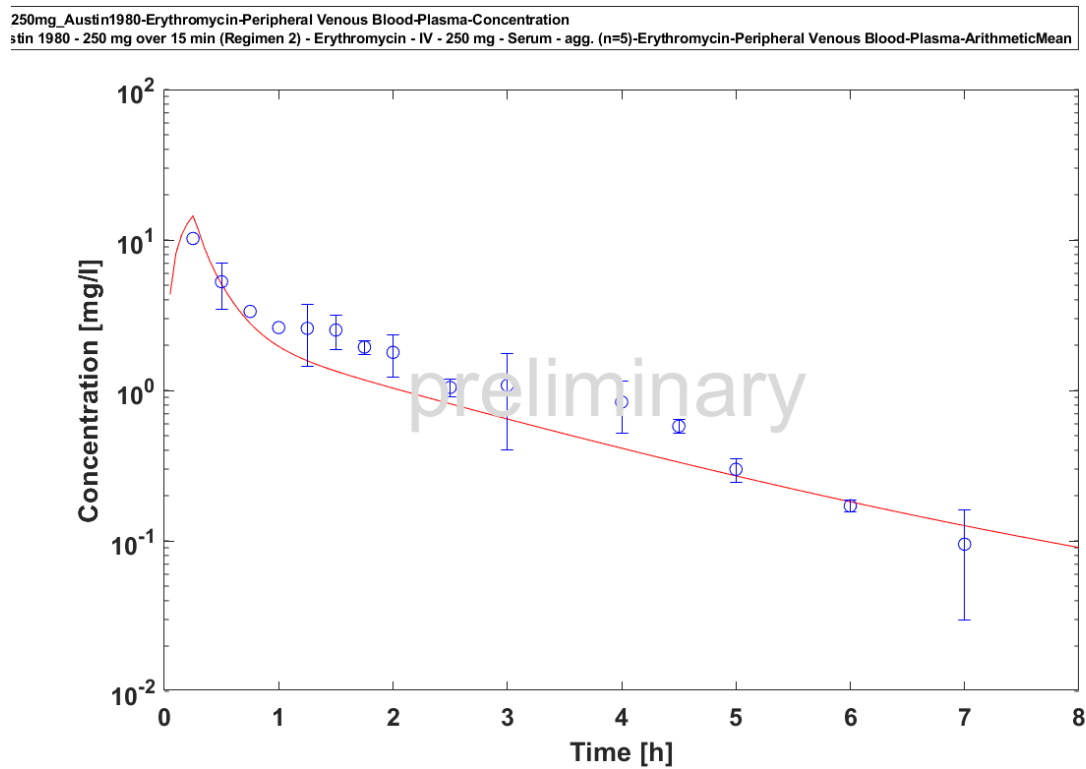
125mg\_Austin1980-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
stin 1980 - 125 mg over 15 min (Regimen 2) - Erythromycin - IV - 125 mg - Serum - agg. (n=5)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



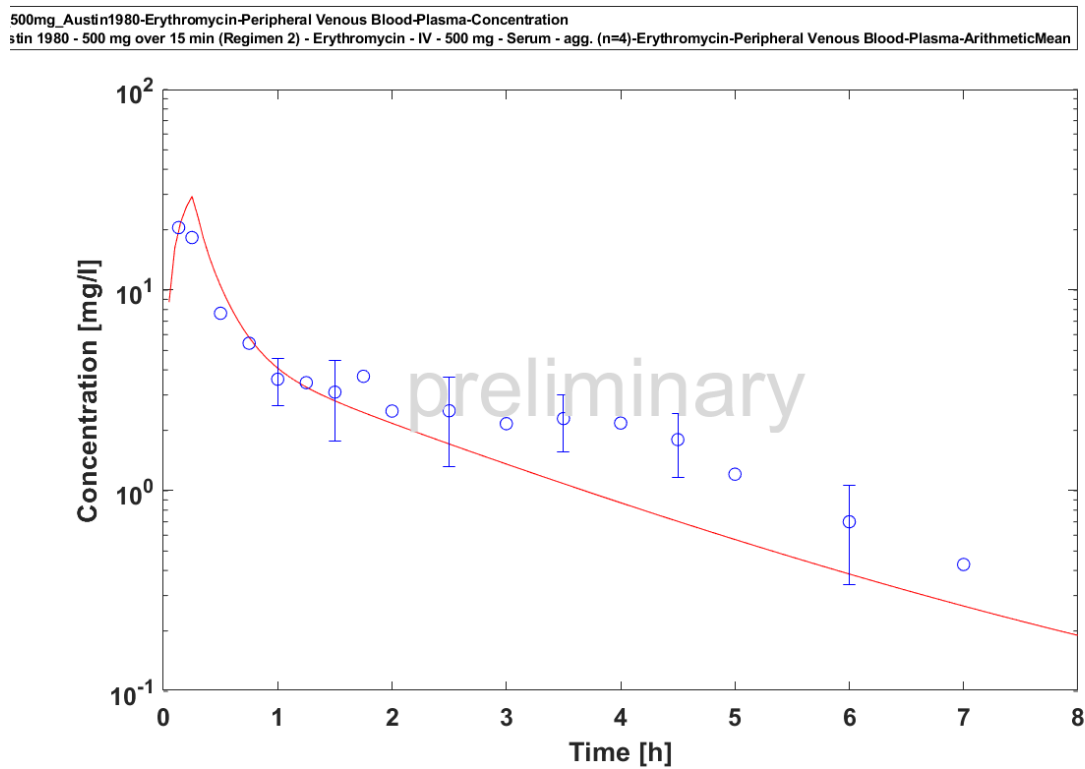
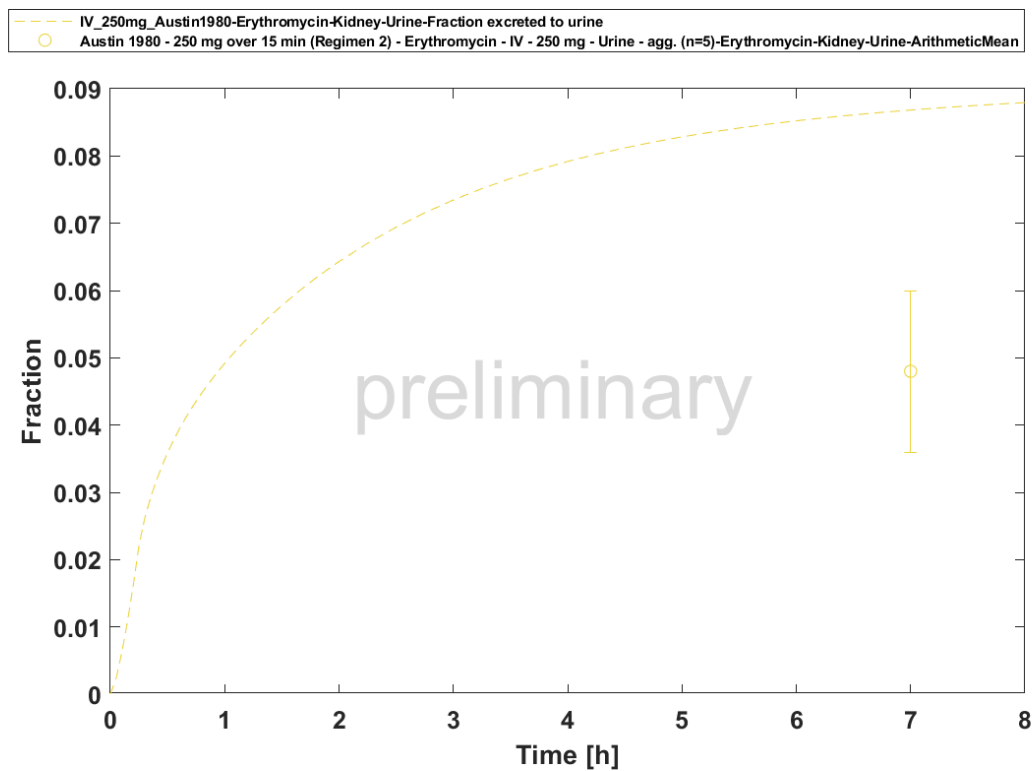
Time Profile Analysis

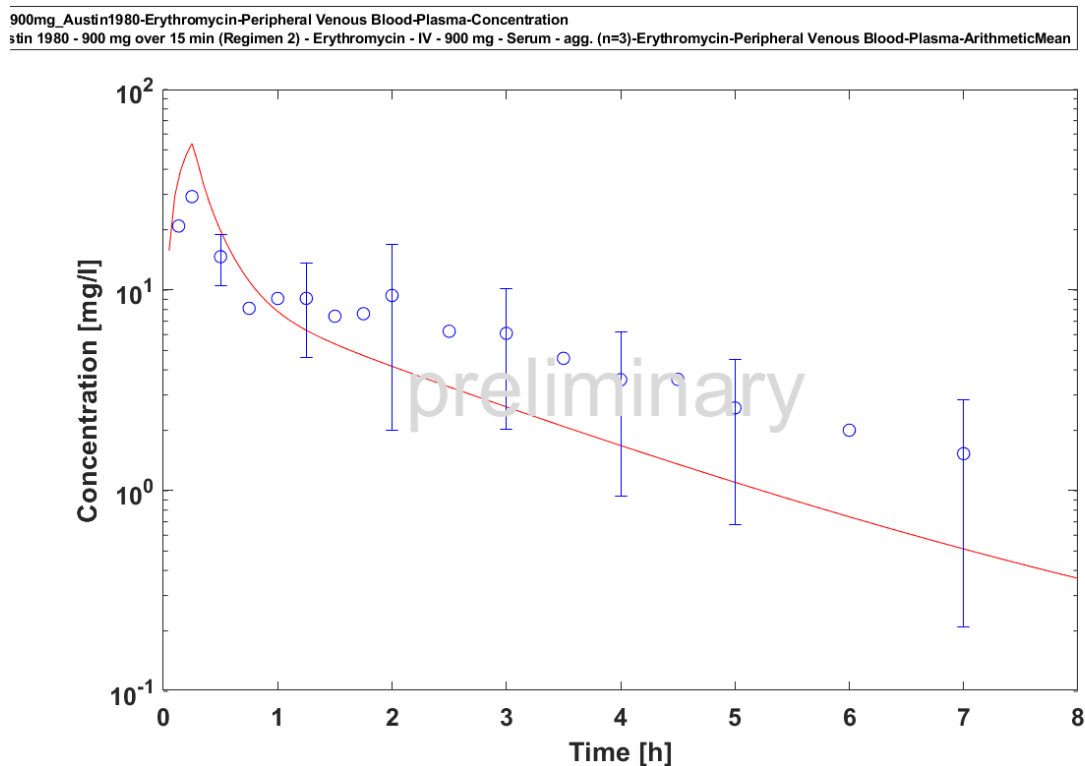
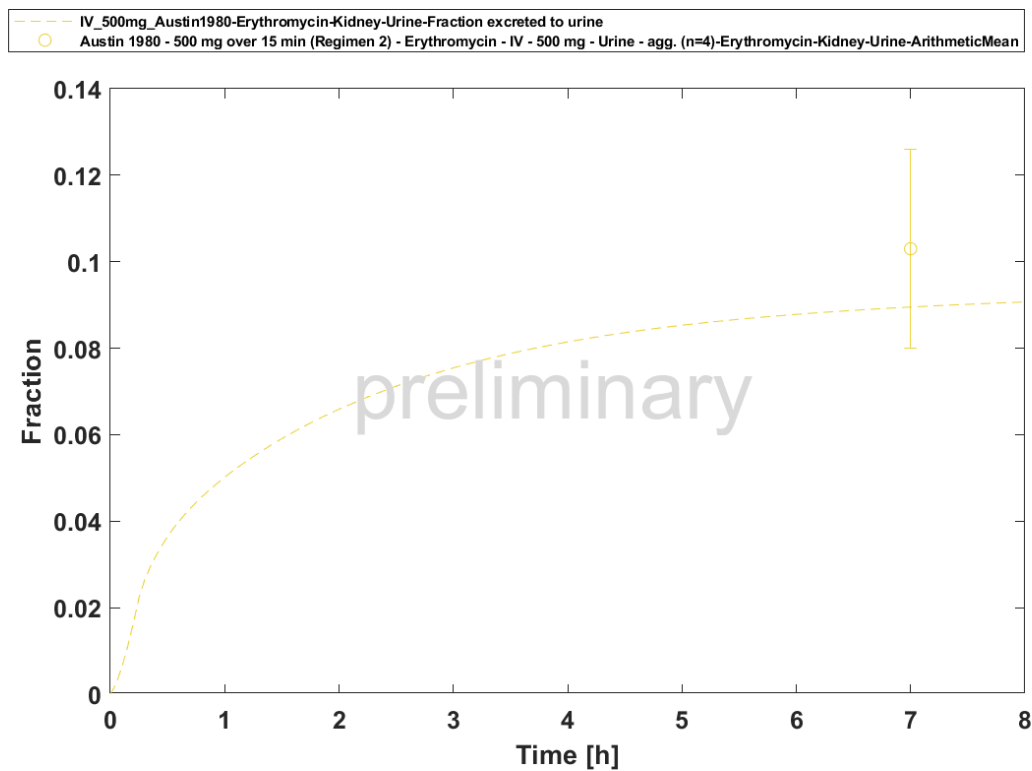


Time Profile Analysis 1

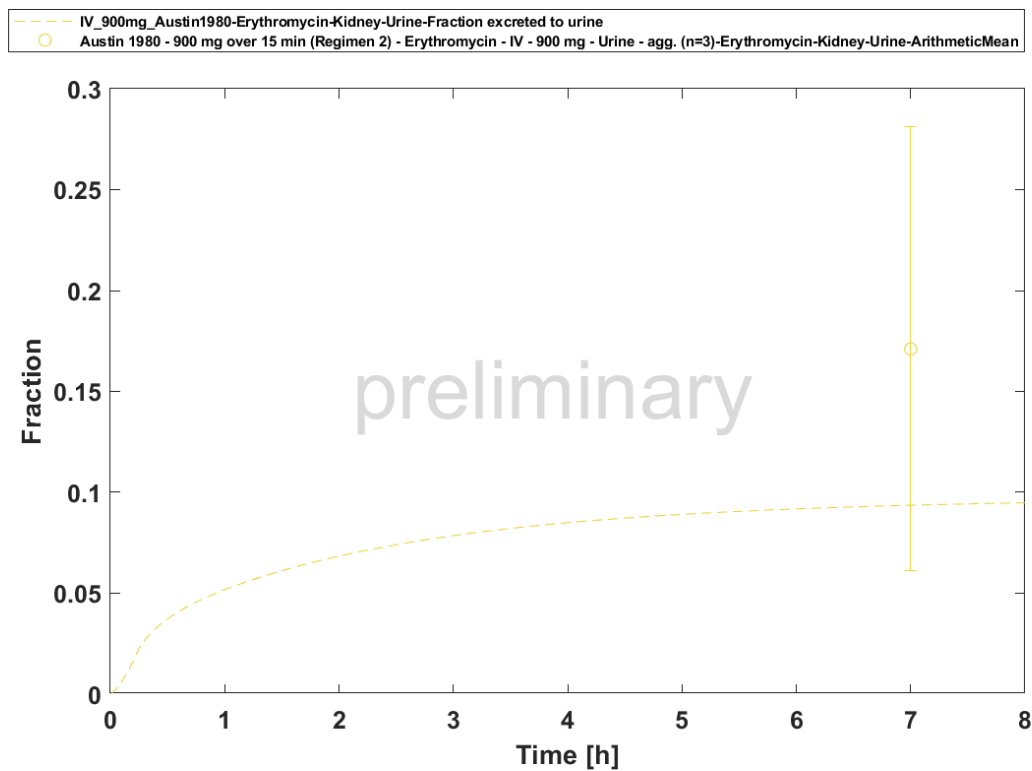


Time Profile Analysis

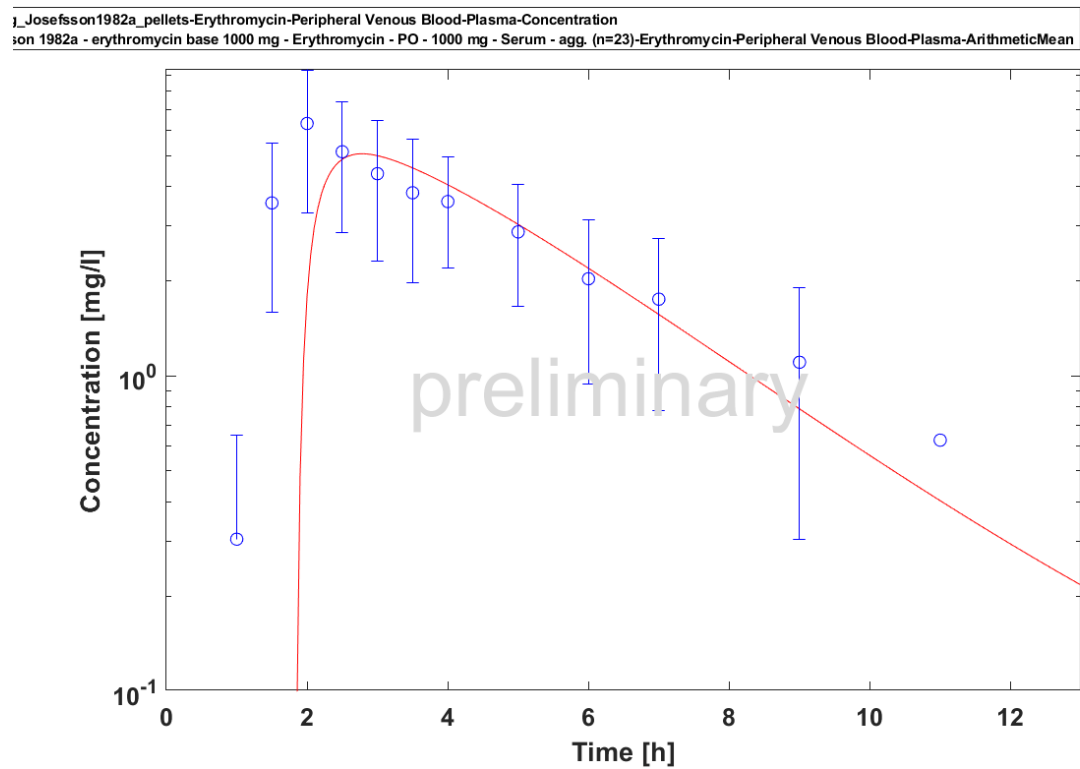






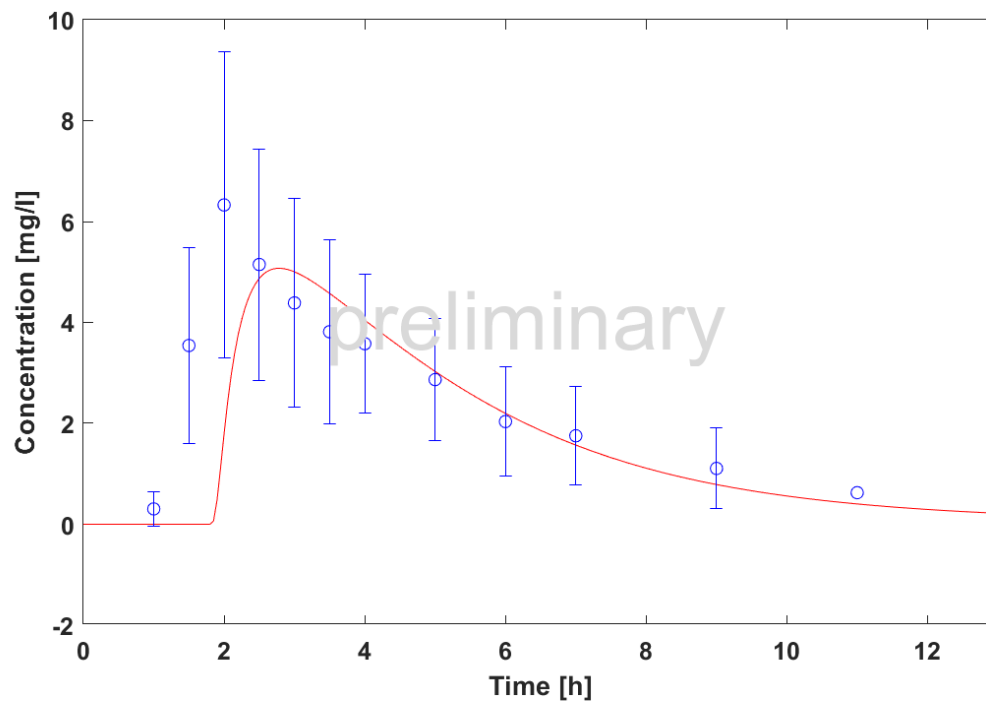


Time Profile Analysis 1



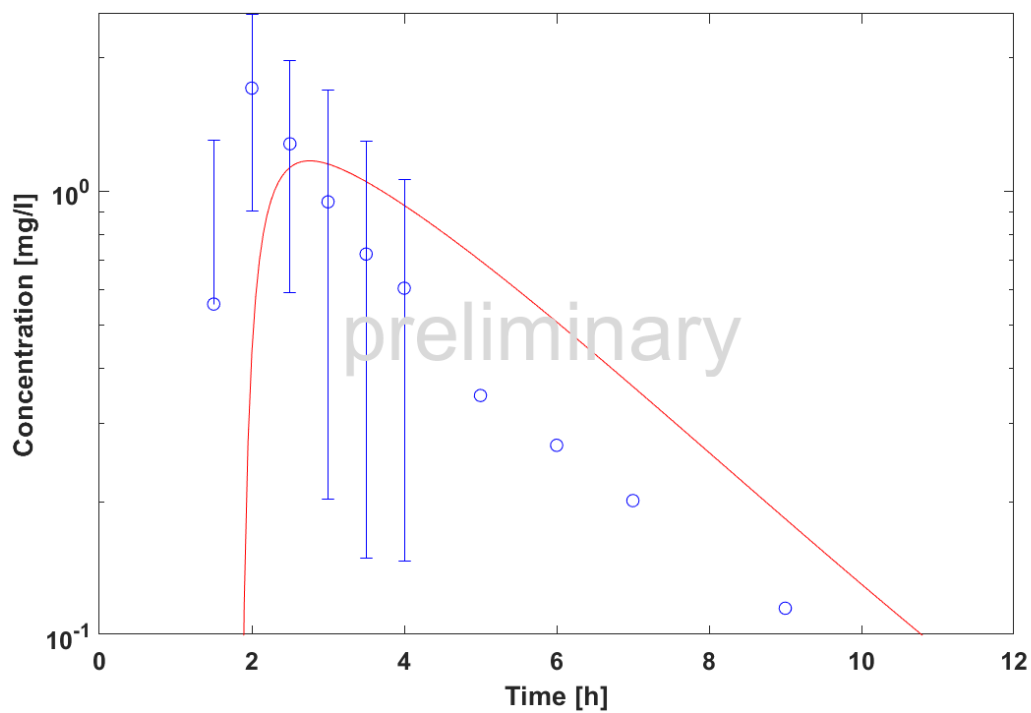
Time Profile Analysis

ig\_Josefsson1982a\_pellets-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
 Josefsson 1982a - erythromycin base 1000 mg - Erythromycin - PO - 1000 mg - Serum - agg. (n=23)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



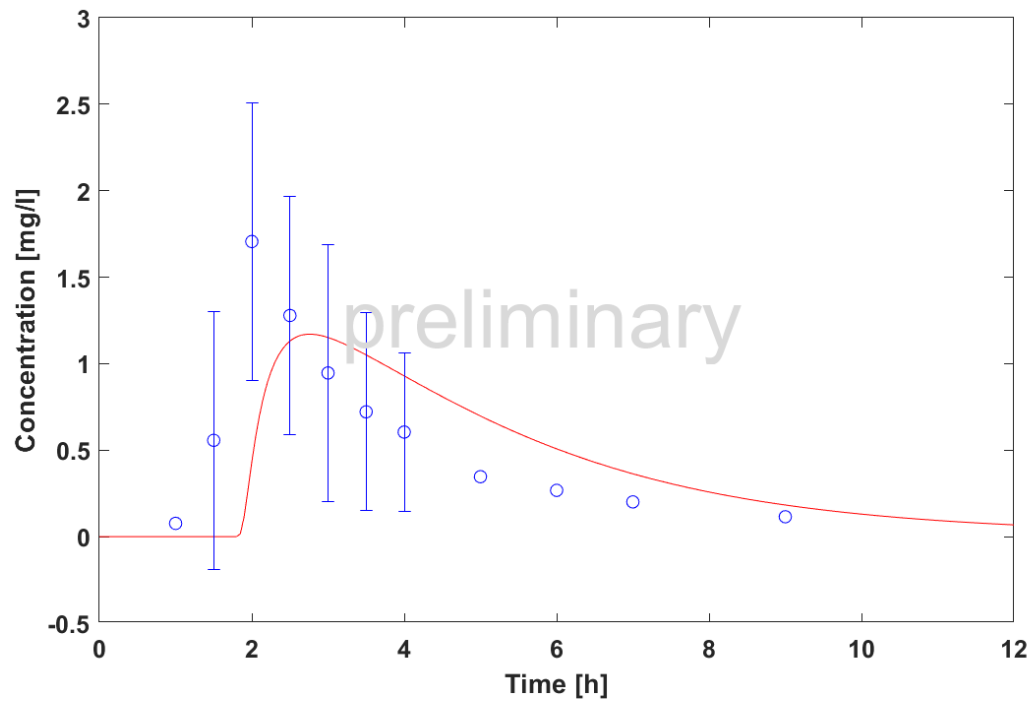
Time Profile Analysis 1

ig\_Josefsson1982a\_pellets-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
 Josefsson 1982a - erythromycin base 250 mg - Erythromycin - PO - 250 mg - Serum - agg. (n=23)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



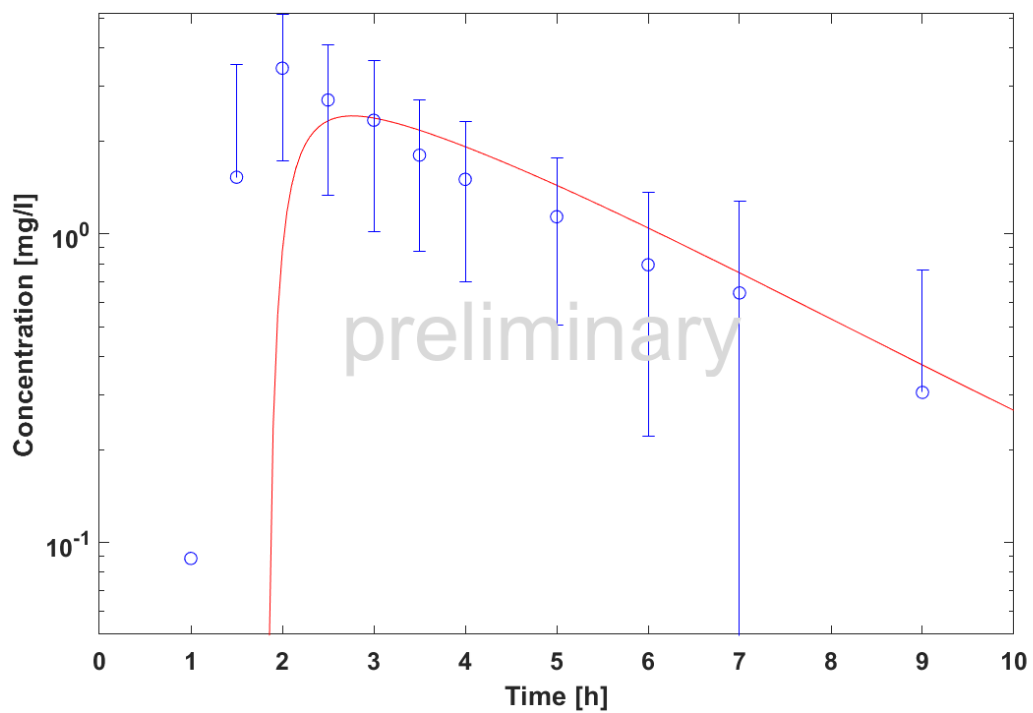
Time Profile Analysis

ig\_Josefsson1982a\_pellets-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
fsson 1982a - erythromycin base 250 mg - Erythromycin - PO - 250 mg - Serum - agg. (n=23)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



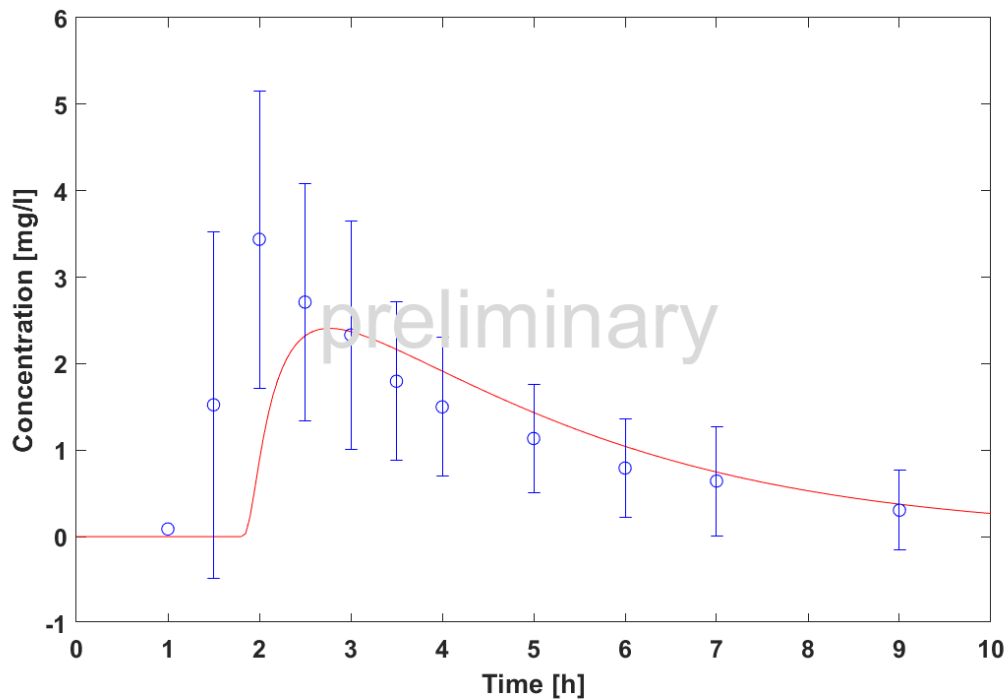
Time Profile Analysis 1

ig\_Josefsson1982a\_pellets-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
fsson 1982a - erythromycin base 500 mg - Erythromycin - PO - 500 mg - Serum - agg. (n=23)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



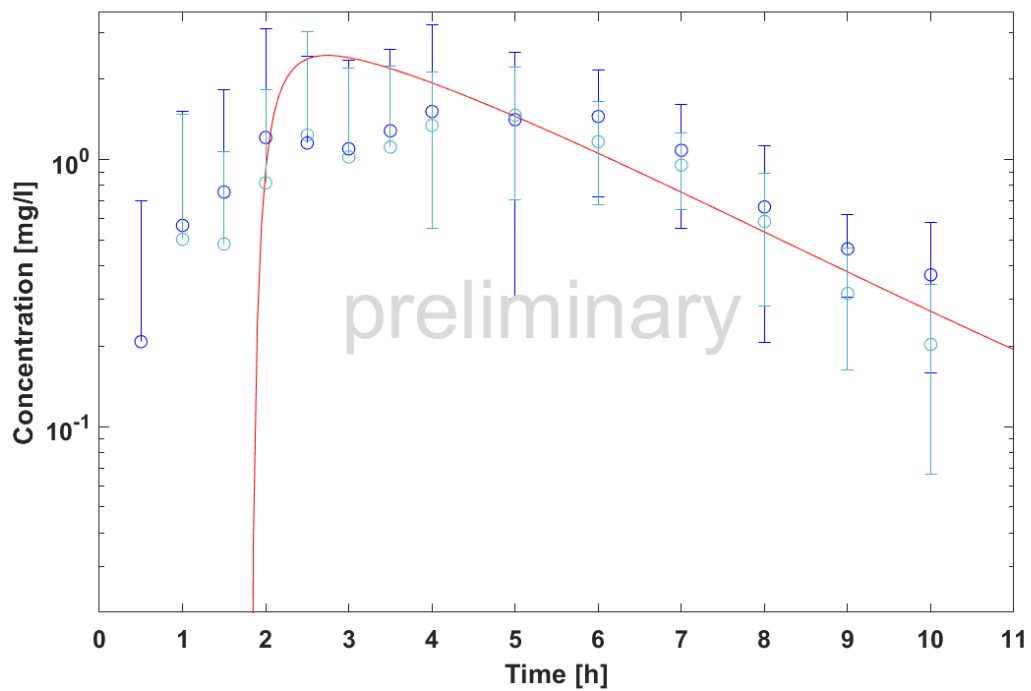
Time Profile Analysis

ig\_Josefsson1982a\_pellets-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
 fsson 1982a - erythromycin base 500 mg - Erythromycin - PO - 500 mg - Serum - agg. (n=23)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



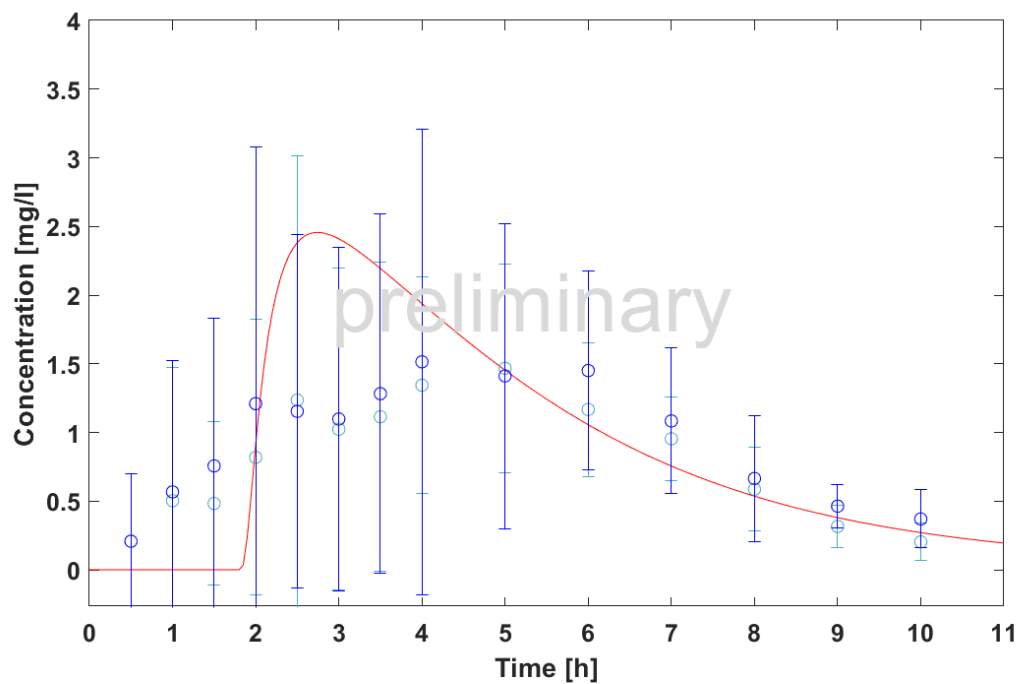
Time Profile Analysis 1

reiner1984\_pellets-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
 384 - Part I, base (enteric-coated pellets) - Erythromycin - PO - 500 mg - Serum - agg. (n=14)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
 384 - Part II, base (enteric-coated pellets) - Erythromycin - PO - 500 mg - Serum - agg. (n=10)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



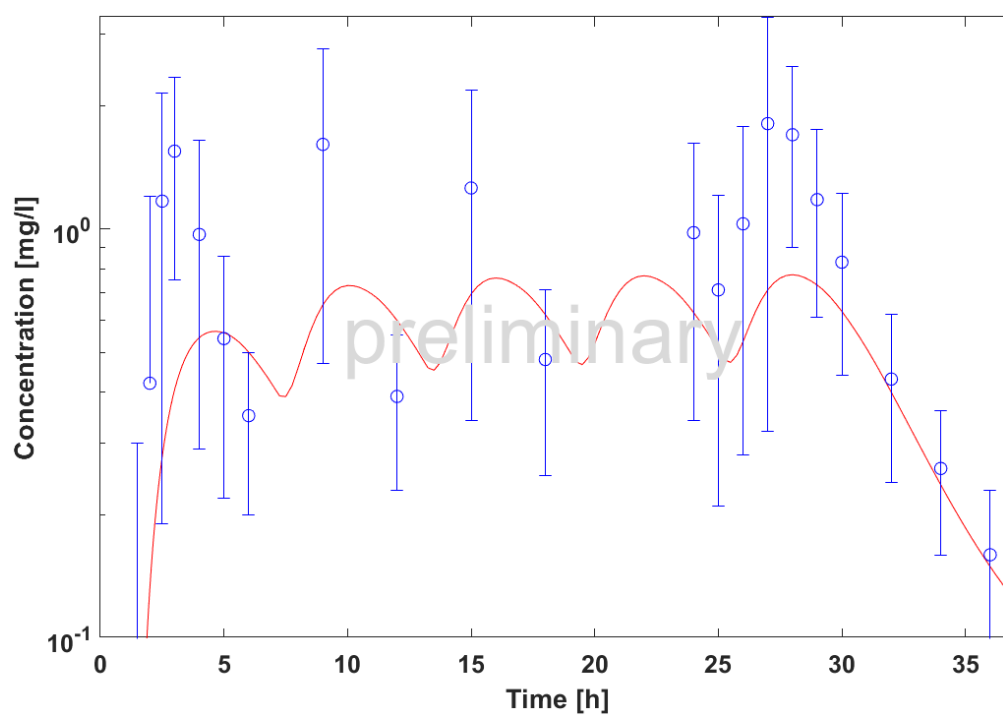
Time Profile Analysis

reiner1984\_pellets-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
384 - Part II, base (enteric-coated pellets) - Erythromycin - PO - 500 mg - Serum - agg. (n=10)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
384 - Part I, base (enteric-coated pellets) - Erythromycin - PO - 500 mg - Serum - agg. (n=14)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



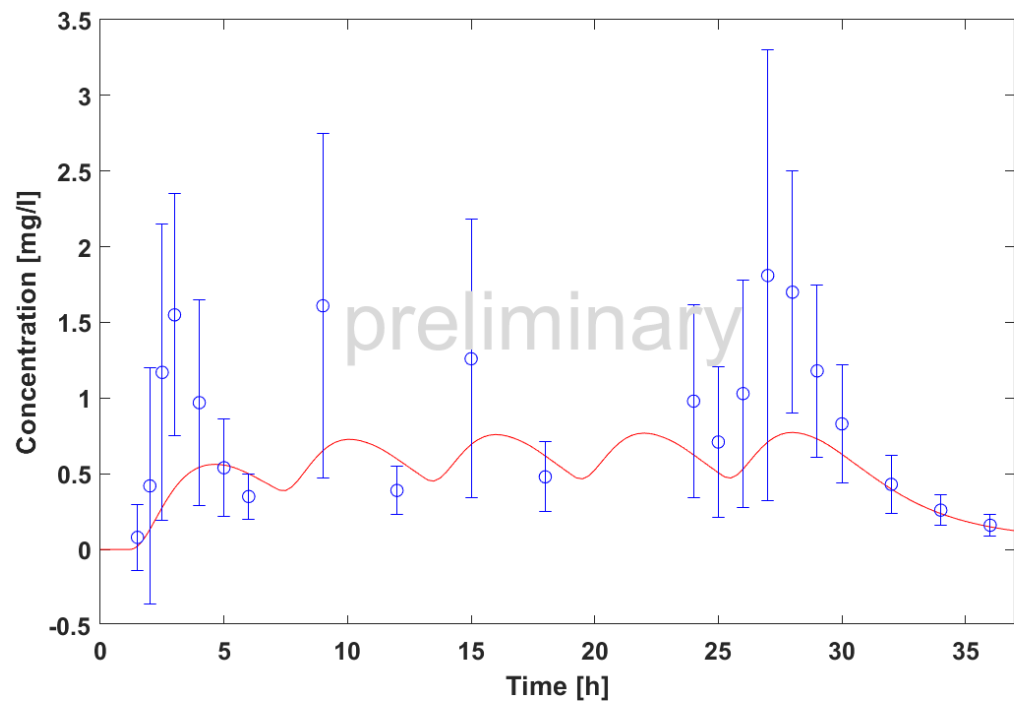
Time Profile Analysis 1

50mg\_Yakatan1980\_base\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
akatan 1980 - Base, five doses, every 6 h - Erythromycin - PO - 250 mg - Serum - agg. (n=24)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



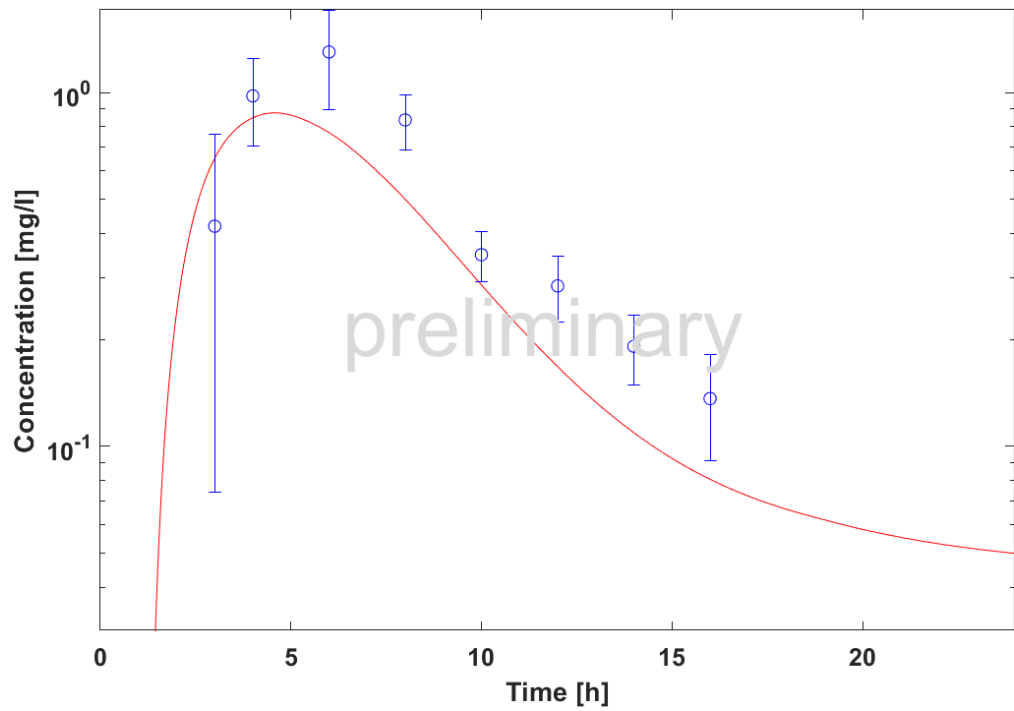
Time Profile Analysis

50mg\_Yakatan1980\_base\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
akatan 1980 - Base, five doses, every 6 h - Erythromycin - PO - 250 mg - Serum - agg. (n=24)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



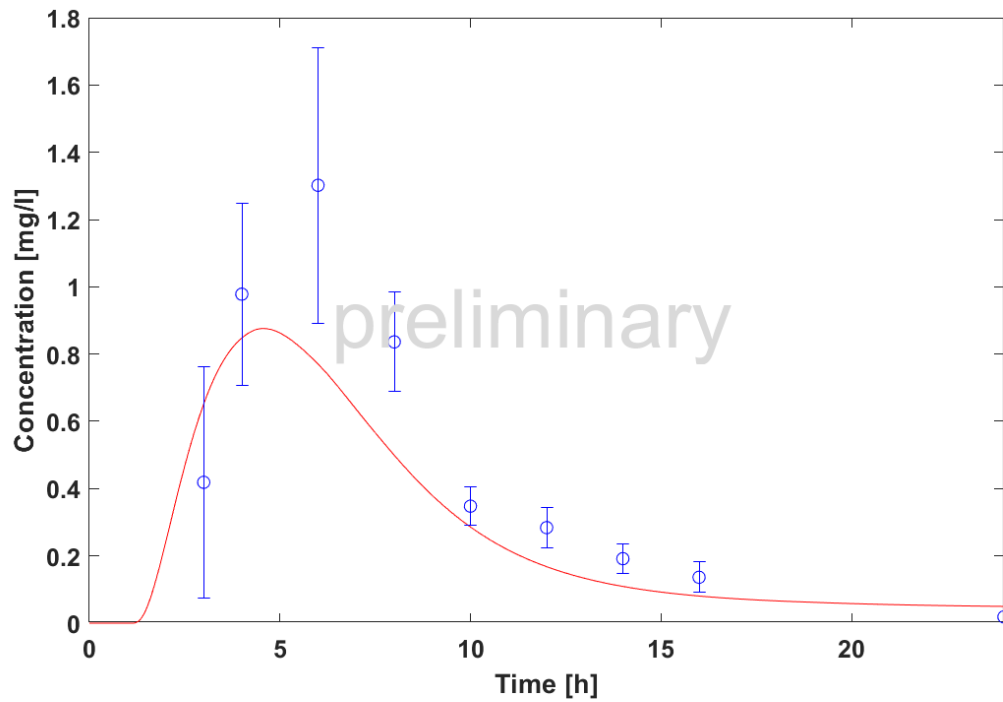
Time Profile Analysis 1

500mg\_Kroboth1982-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
Kroboth 1982 - Normal subjects - Erythromycin - PO - 500 mg - Serum - agg. (n=6)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



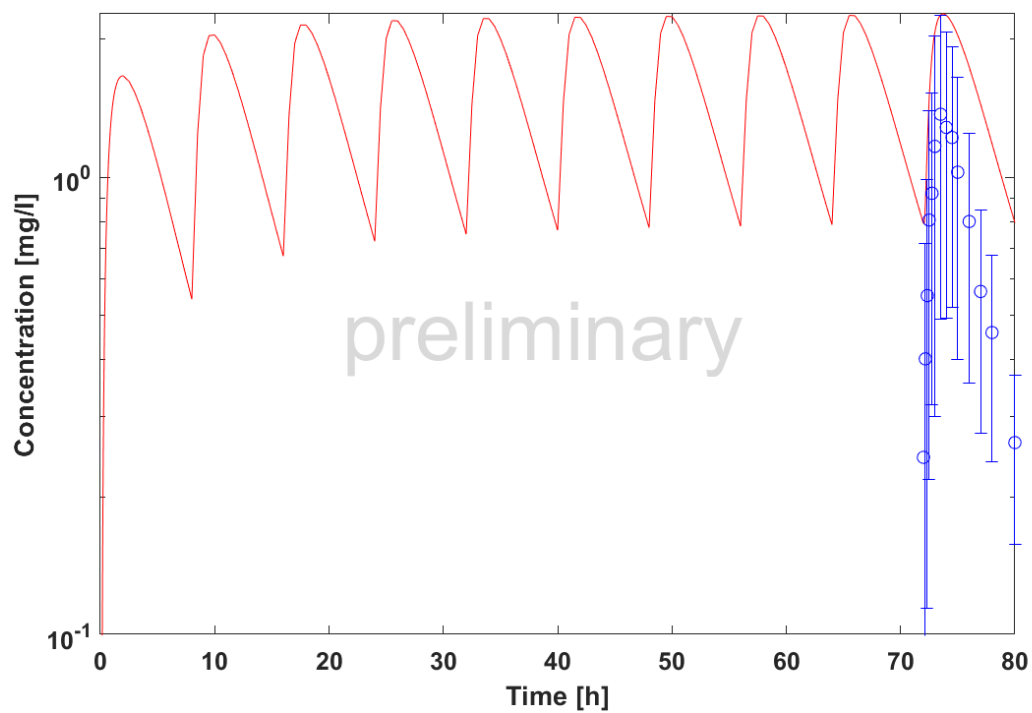
Time Profile Analysis

500mg\_Kroboth1982-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
○ Kroboth 1982 - Normal subjects - Erythromycin - PO - 500 mg - Serum - agg. (n=6)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



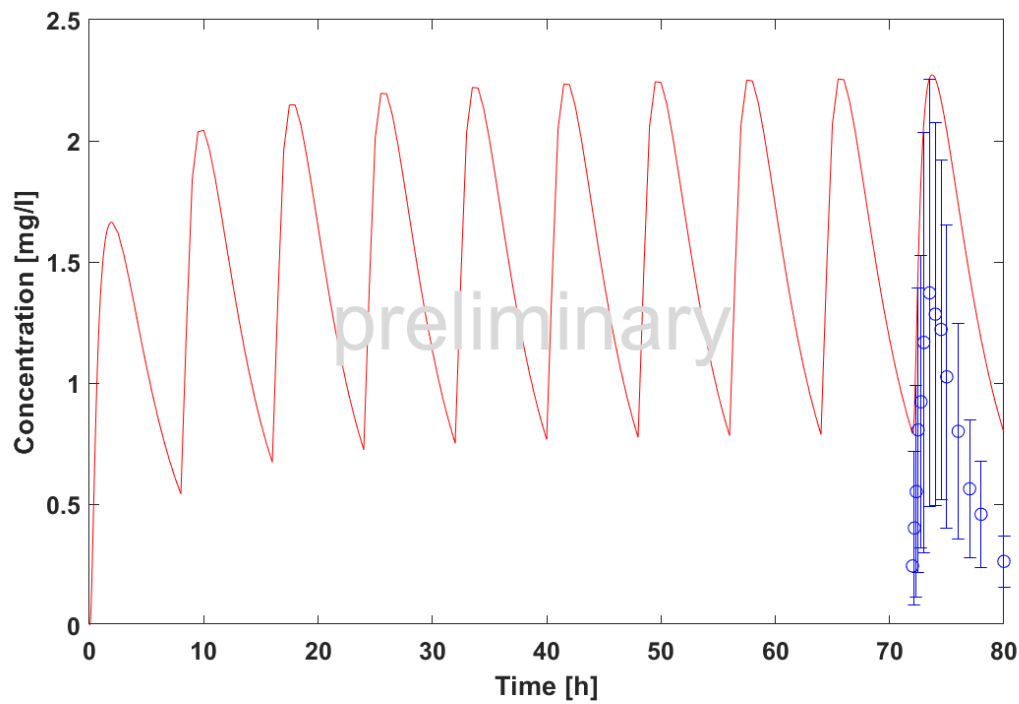
Time Profile Analysis 1

2\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
th day, before theophylline administration - Erythromycin - PO - 500 mg - Serum - agg. (n=6)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



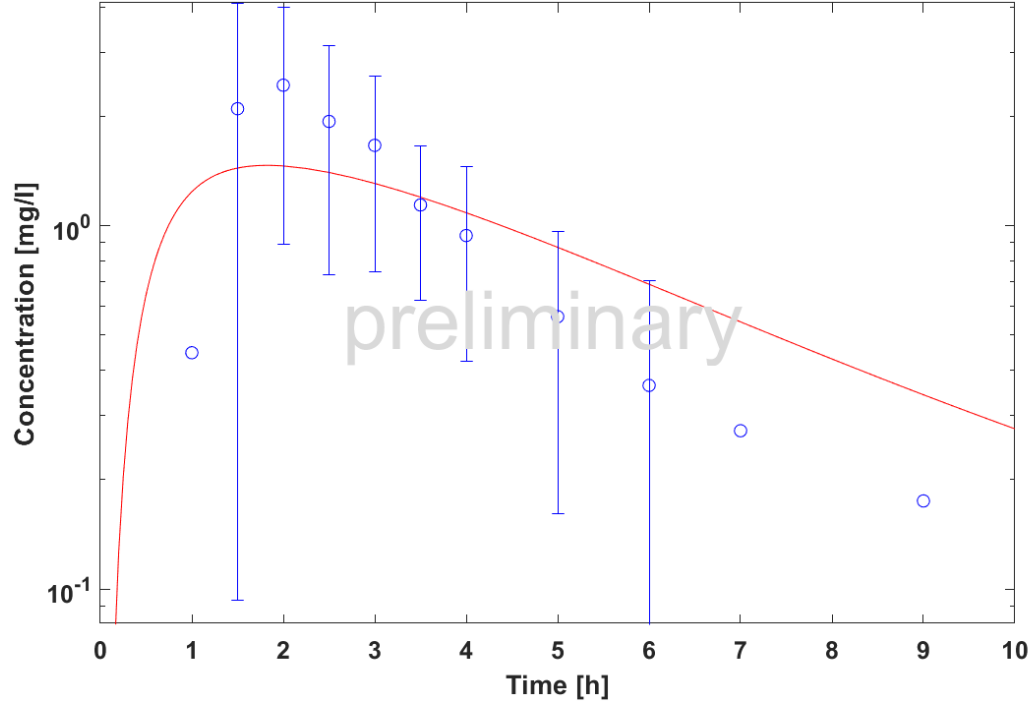
Time Profile Analysis

2\_MD-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
th day, before theophylline administration - Erythromycin - PO - 500 mg - Serum - agg. (n=6)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis 1

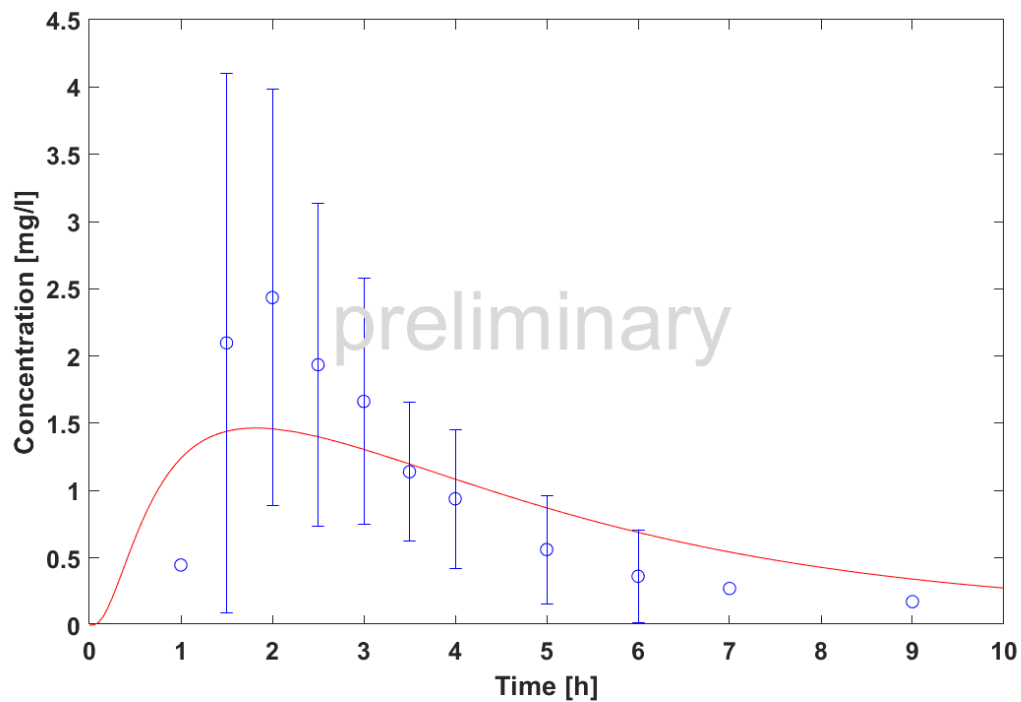
Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
Erythromycin stearate 500 mg (base equivalent) - Erythromycin - PO - 500 mg - Serum - agg. (n=23)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis

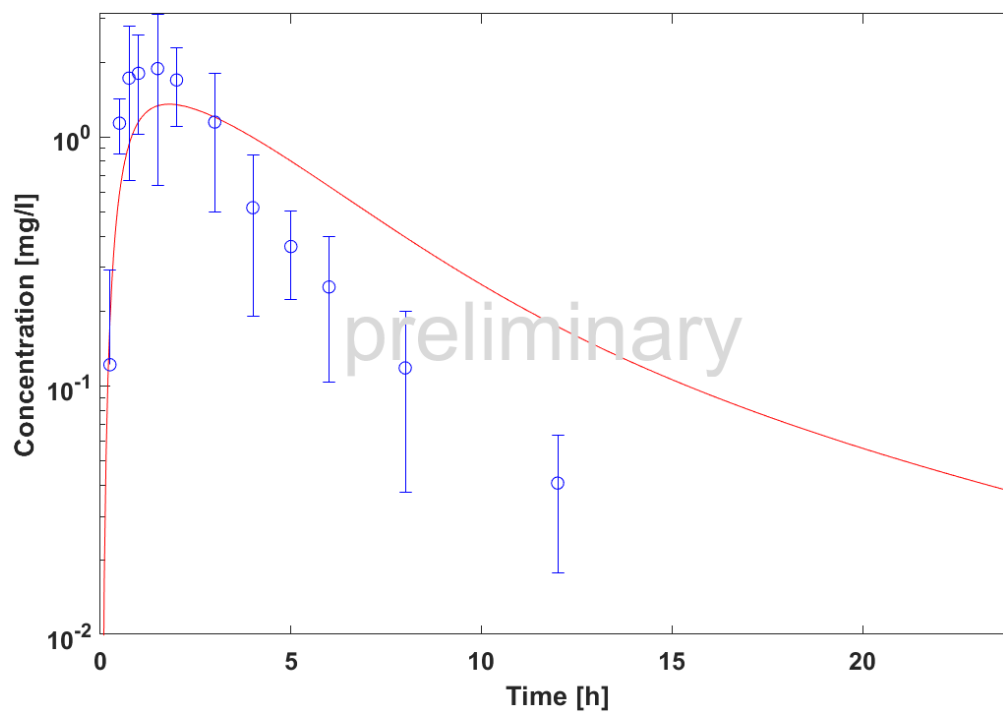


Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
 mycin stearate 500 mg (base equivalent) - Erythromycin - PO - 500 mg - Serum - agg. (n=23)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean

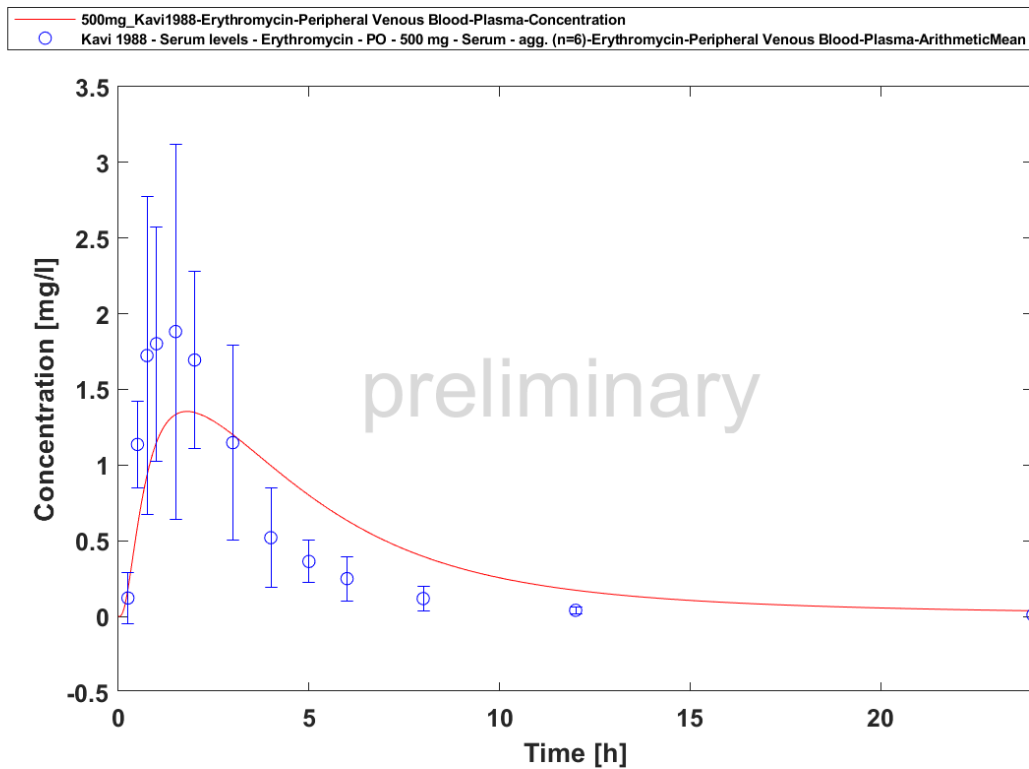


Time Profile Analysis 1

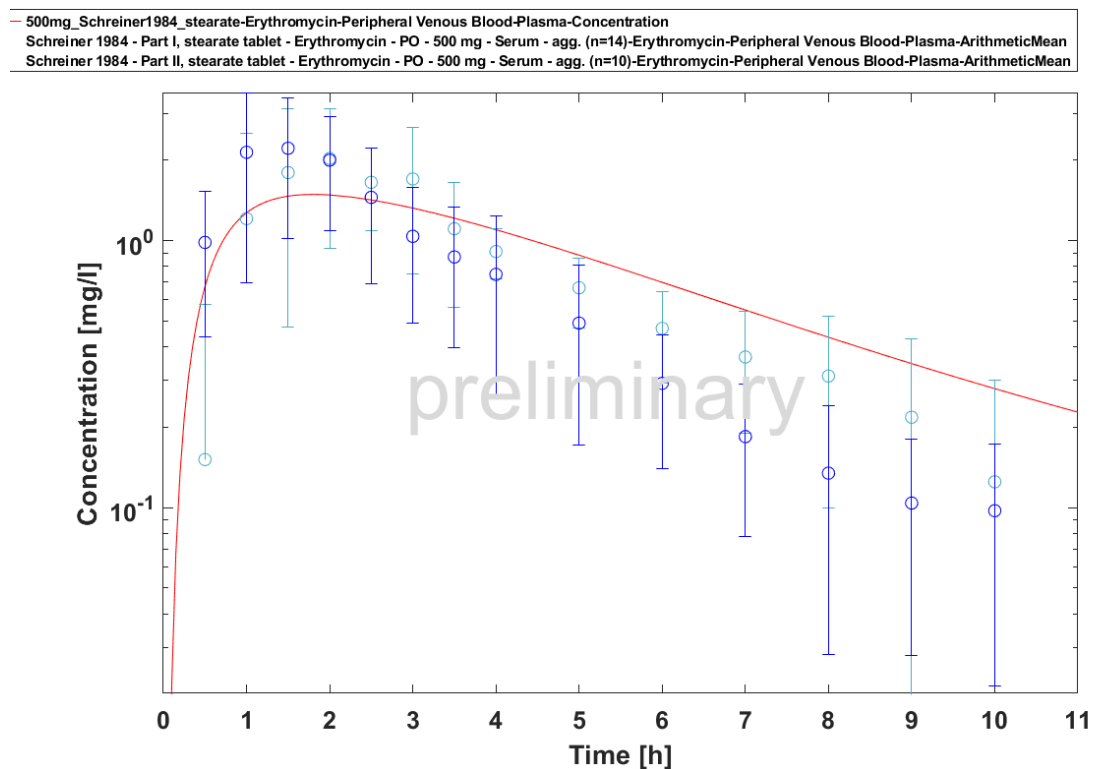
500mg\_Kavi1988-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
 Kavi 1988 - Serum levels - Erythromycin - PO - 500 mg - Serum - agg. (n=6)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis

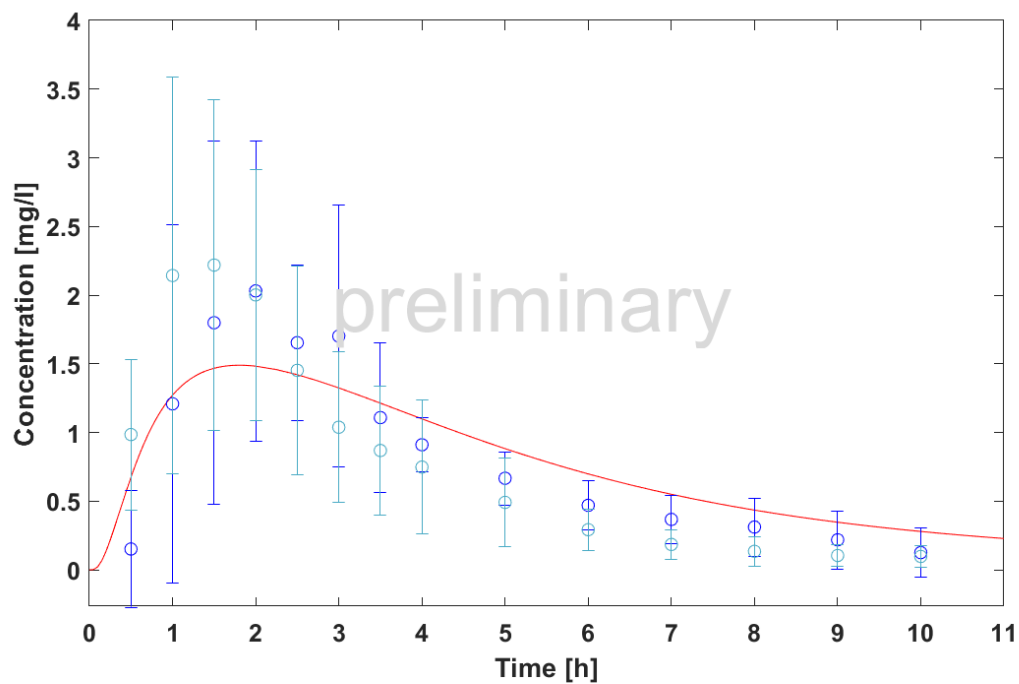


Time Profile Analysis 1



Time Profile Analysis

500mg\_Schreiner1984\_stearate-Erythromycin-Peripheral Venous Blood-Plasma-Concentration  
Schreiner 1984 - Part I, stearate tablet - Erythromycin - PO - 500 mg - Serum - agg. (n=14)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean  
Schreiner 1984 - Part II, stearate tablet - Erythromycin - PO - 500 mg - Serum - agg. (n=10)-Erythromycin-Peripheral Venous Blood-Plasma-ArithmeticMean



Time Profile Analysis 1

## 4 Conclusion

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The final erythromycin PBPK model applies metabolism by CYP3A4, hepatic plasma clearance, glomerular filtration and mechanism-based inhibition of CYP3A4. Overall, the model adequately describes the oral pharmacokinetics of erythromycin in healthy adults receiving different single or multiple doses of several oral dosage forms.

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