

Building and Evaluation of a PBPK Model for Carbamazepine in Adults

Version	1.1-OSP11.1
based on <i>Model Snapshot</i> and <i>Evaluation Plan</i>	1.1 (https://github.com/Open-Systems-Pharmacology/Carbamazepine-Model/releases/tag/v1.1)
OSP Version	11.1
Qualification Framework Version	2.3

Table of Contents

- [1 Introduction](#)
- [2 Methods](#)
 - [2.1 Modeling Strategy](#)
 - [2.2 Data](#)
 - [2.3 Model Parameters and Assumptions](#)
- [3 Results and Discussion](#)
 - [3.1 Final input parameters](#)
 - [3.2 Diagnostics Plots](#)
 - [3.3 Concentration-Time Profiles](#)
- [4 Conclusion](#)
- [5 References](#)

1 Introduction

Carbamazepine, sold under the trade name Tegretol® among others, is an anticonvulsant medication used primarily to treat epilepsy and neuropathic pain. Other indications include schizophrenia where it is used as an adjunctive treatment along with other medications, and bipolar disorder where it is used as a second-line agent. Carbamazepine is typically taken by mouth on empty stomach or together with meals, depending on the administered formulation.

Carbamazepine is extensively metabolized by various enzymes including CYP2B6, 2C8, 3A4, and UGT2B7 (Kerr 1994, Pelkonen 2001, Staines 2004). Following oral administration the major dose fraction (approx.) is metabolized to carbamazepine-10,11-epoxide (Eichelbaum 1985, Tomson 1983). This reaction is mainly catalyzed by CYP3A4, with some contribution from CYP2C8 (Kerr 1994). After oral administration, a minor fraction of the dose (approximately 1 - 3%) is excreted unchanged in urine (Bernus 1994, Morselli 1975), while approximately 1% of the dose can be recovered as unchanged drug in the bile (Terhaag 1978).

Carbamazepine is classified by the U.S. Food and Drug Administration (FDA) as a strong CYP3A4 and CYP2B6 inducer (<https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions>) and hence induces its own metabolism.

The herein presented model was developed independently of the model reported by Fuhr et al. (Fuhr 2021). The main difference between the two models pertains to the metabolite carbamazepine-10,11-epoxide, which is included as separate compound in the model by Fuhr et al. (Fuhr 2021), but not modeled in the herein presented model. Another structural model differences concerns the enzymatic elimination pathways of carbamazepine; the model by Fuhr et al. (Fuhr 2021) includes five different metabolism pathways, whereas the herein presented model includes three different metabolism pathways. Additionally, the parameterization of CYP2B6 and 3A4 induction differs between the two models.

2 Methods

2.1 Modeling Strategy

The general workflow for building an adult PBPK model has been described by Kuepfer et al. ([Kuepfer 2016](#)). Relevant information on the anthropometry (height, weight) was gathered from the respective clinical study, if reported. Information on physiological parameters (e.g. blood flows, organ volumes, hematocrit) in adults was gathered from the literature and has been incorporated in PK-Sim® as described previously ([Willmann 2007](#)). The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available 'PK-Sim® Ontogeny Database Version 7.3' ([PK-Sim Ontogeny Database Version 7.3](#)).

The PBPK model was developed based on publicly available pharmacokinetic data of adult healthy subjects covering a carbamazepine dose range from 10 to 800 mg following intravenous administration or oral administration as liquid oral dosage form, immediate release (IR) tablet or extended release (XR) formulations in the fasted state. The carbamazepine PBPK model includes metabolism by CYP2B6, CYP3A4, and UGT2B7, unchanged renal excretion, and induction of CYP2B6 and 3A4 by carbamazepine. Pharmacokinetics of carbamazepine following administration in the fed state was not considered in the herein presented model. Furthermore, the metabolite carbamazepine-10,11-epoxide was not modeled as separate compound.

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. Several parameter identifications were conducted to optimize unknown parameters. In a first step, lipophilicity and enzymatic clearances (catalyzed by CYP3A4, CYP2B6 and UGT2B7) were optimized using observed plasma concentration-time profile data following administration of carbamazepine intravenously or orally as syrup. In a second parameter identification, enzymatic clearances were refined and optimized together with the glomerular filtration rate fraction of carbamazepine and the dissolution kinetics of the IR tablet using observed plasma concentration-time profiles and the dose fraction excreted unchanged in urine after single dose administration of various doses as IR tablet. Subsequently, the EC₅₀ value of CYP3A4 induction was optimized using observed plasma concentration-time profile data after multiple dose administration of carbamazepine. In a final parameter identification, the dissolution kinetics and carbamazepine solubility of XR formulations were optimized.

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 performed to collect available information on physicochemical properties of carbamazepine and carbamazepine-10,11-epoxide. The information is summarized in the table below.

Parameter	Unit	Value	Source	Description
MW	g/mol	236.27	DrugBank DB00564	Molecular weight
logP (calculated)		1.54	Austin 2002	Partition coefficient between octanol and water
logP (calculated)		2.1	DrugBank DB00564	Partition coefficient between octanol and water
logP (calculated)		2.45	Fenet 2012	Partition coefficient between octanol and water
logP (calculated)		2.77	DrugBank DB00564	Partition coefficient between octanol and water
pK _a		11.83		Logarithm of the acid dissociation constant
Solubility (pH)	µg/mL	336 (6.2)	Annaert 2010	Solubility in human intestinal fluid
Solubility (pH)	µg/mL	283 (7.0)	Söderlind 2010	Solubility in human intestinal fluid
Solubility (pH)	µg/mL	306 (6.9)	Clarysse 2011	Solubility in fasted human intestinal fluid
f _u		0.25	Pynnonen 1977	Fraction unbound in plasma of healthy subjects
f _u		0.243 ± 0.013 [0.225 - 0.258] ^a	Morselli 1975	Fraction unbound in plasma of healthy male subjects
f _u		0.239	Di Salle 1974	Fraction unbound in plasma of normal subjects
f _u		0.237 ± 0.031 ^b	Vinçon 1987	Fraction unbound in plasma of epileptic patients
f _u		0.182 ± 0.05 [0.103 - 0.297] ^a	Hooper 1975	Fraction unbound in plasma of normal subjects
K _m CYP2B6	µM	420	Pearce 2002	CYP2B6 Michaelis-Menten constant
V _{max} CYP2B6	pmol/min/pmol rec enzyme	0.429	Pearce 2002	in vitro metabolic rate constant for recombinant CYP2B6
K _m CYP2C8	µM	757	Cazali 2003	CYP2C8 Michaelis-Menten constant
V _{max} CYP2C8	pmol/min/pmol rec enzyme	0.673	Cazali 2003	in vitro metabolic rate constant for recombinant CYP2C8
K _m CYP3A4 ^c	µM	282	Pearce 2002	CYP3A4 Michaelis-Menten constant
K _m CYP3A4 (→CBZE) ^d	µM	248	Huang 2004	CYP3A4 Michaelis-Menten constant
K _m UGT2B7	µM	214	Staines 2004	UGT2B7 Michaelis-Menten constant
V _{max} UGT2B7	pmol/min/mg mic enzyme	0.79	Staines 2004	in vitro metabolic rate constant for microsomal enzymes

Parameter	Unit	Value	Source	Description
Microsomal UGT2B7	pmol/mg mic protein	82.9	Achour 2014	Content of UGT2B7 proteins in liver microsomes
Intestinal permeability	cm/min	0.0258	Lennernäs 2007	Transcellular intestinal permeability

^a denotes mean ± standard deviation [range]

^b denotes mean ± standard deviation

^c refers to CYP3A4-mediated reaction forming other metabolites than carbamazepine-10,11-epoxide

^d refers to CYP3A4-mediated reaction forming carbamazepine-10,11-epoxide

2.2.2 Clinical Data

A literature search was conducted to collect available data on carbamazepine pharmacokinetics in healthy adult subjects after intravenous or oral administration in the fasted state.

The following studies were used for model building:

Publication	Arm / Treatment / Information used for model building
Bernus 1994	Healthy subjects receiving two oral doses of 600 mg carbamazepine as IR tablet (only pharmacokinetic data following the first dose were used for model building)
Gérardin 1976	Healthy subjects receiving a single oral dose of 100 mg carbamazepine as IR tablet
Gérardin 1990	Healthy subjects receiving a single oral dose of 100 mg [¹⁵ N]-carbamazepine as suspension concomitantly with a single intravenous dose of 10 mg carbamazepine
McLean 2001	Healthy subjects receiving a single oral dose of 400 mg carbamazepine as XR formulation in fasted state
Møller 2001	Healthy subjects receiving a multiple oral doses of carbamazepine, starting at 100 mg and escalating to 400 mg
Wada 1978	Healthy subjects receiving a single oral dose of 200 mg carbamazepine as syrup and IR tablet

The following studies were used for model evaluation:

Publication	Arm / Treatment / Information used for model building
Barzaghi 1987	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Bedada 2015	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Bedada 2016	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Bernus 1994	Healthy subjects receiving two oral doses of 600 mg carbamazepine (only pharmacokinetic data following the second were used for model evaluation)
Bianchetti 1987	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Burstein 2000	Healthy subjects receiving a multiple oral doses of carbamazepine, starting at 100 mg and escalating to 400 mg
Caraco 1995	Healthy lean subjects receiving a single oral dose of 200 mg carbamazepine
Cawello 2000	Healthy subjects receiving a multiple oral doses of carbamazepine, starting at 100 mg and escalating to 200 mg
Cotter 1977	Healthy subject receiving a single oral dose of 800 mg carbamazepine
Dalton 1985a	Healthy subjects receiving a single oral dose of 600 mg carbamazepine
Dalton 1985b	Healthy subjects receiving a single oral dose of 600 mg carbamazepine
Eichelbaum 1985	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Elqidra 2004	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
European Patent Application EP 1044681 A2	Healthy subjects receiving a single oral dose of 400 and 600 mg carbamazepine
Gérardin 1976	Healthy subjects receiving a single oral dose of 200, and 600 mg carbamazepine
Ji 2008	Healthy subjects receiving a multiple oral doses of carbamazepine, starting at 200 mg and escalating to 400 mg
Kayali 1994	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Kim 2005	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Kovacević 2009	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Levy 1975	Healthy subjects receiving a single oral carbamazepine dose of 6 mg/kg body weight
Meyer 1996	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Meyer 1998	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Miles 1989	Healthy subjects receiving a multiple oral doses of 300 and 400 mg carbamazepine
Morselli 1975	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Pynnonen 1977	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Rawlins 1975	Healthy subject receiving a single oral dose of 50, 100, and 200 mg carbamazepine
Saint-Salvi 1987	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Stevens 1998	Healthy subjects receiving multiple oral doses of 400 mg carbamazepine
Strandjord 1975	Healthy subjects receiving a single oral dose of 400 mg carbamazepine
Sumi 1987	Healthy subjects receiving a single oral dose of 200 mg carbamazepine
Tomson 1983	Healthy subject receiving a single oral doses of 200 mg carbamazepine

Publication	Arm / Treatment / Information used for model building
US Patent Application - US 2009/0169619 A1	Healthy subjects receiving a single oral dose of 300 mg carbamazepine
Wong 1983	Healthy subjects receiving a single oral dose of 400 mg carbamazepine

2.3 Model Parameters and Assumptions

2.3.1 Absorption

Absorption of carbamazepine from the gastrointestinal tract can be fully explained by passive diffusion; active uptake by drug transporters does not seem to play a role. Intestinal permeability was observed to be not a rate-limiting step in drug absorption. The solubility of carbamazepine following administration of the IR tablet was fixed to the mean value (308 mg/L at a pH of 6.7) reported by several studies in fasted human intestinal fluid ([Annaert 2010](#), [Söderlind 2010](#), [Clarysse 2011](#)).

2.3.2 Distribution

Plasma protein binding of carbamazepine was fixed to 75.7% as reported by Morselli et al. for healthy subjects ([Morselli 1975](#)). The distribution of carbamazepine throughout the body was found to be best described by the partition coefficient calculation by [Rodgers and Rowlands](#) and cellular permeability calculation by [PK-sim Standard](#).

2.3.3 Metabolism, Excretion and Induction

Metabolism

Carbamazepine metabolism is complex involving multiple enzymes with more than 30 metabolites identified ([Lertratanangkoon 1982](#)). Several *in vitro* studies suggest involvement of CYP1A2, 2A6, 2B6, 2C8, 2E1, 3A4, and UGT2B7 in carbamazepine metabolism ([Cazali 2003](#), [Kerr 1994](#), [Pearce 2002](#), [Pelkonen 2001](#), [Staines 2004](#)).

In various *in vitro* assays, the biotransformation to the main metabolite, carbamazepine-10,11-epoxide, appears to be mainly catalyzed by CYP3A4 with minimal contribution by CYP2C8 ([Cazali 2003](#), [Egnell 2003](#), [Kerr 1994](#)). For example, Egnell et al. report that, at equimolar amounts of recombinantly expressed CYP enzymes, the activity of CYP3A4 towards carbamazepine was more than 20-fold higher than that of CYP2C8 ([Egnell 2003](#)). Therefore, carbamazepine epoxidation was modeled via CYP3A4 only.

Further oxidative metabolism pathways include 2- and 3-hydroxylation. The formation of 2-hydroxycarbamazepine is mediated by several CYP enzymes *in vitro* (including CYP1A2, 2A6, 2B6, 2E1, and 3A4); though, the contribution of any of these isoforms does not exceed 50% of the total formation ([Pearce 2002](#)). In experiments with liver slices, 2-hydroxylation appears to be a minor elimination pathway (1-2 % of total clearance) as reported by Pelkonen et al. ([Pelkonen 2001](#)). Hence, 2-hydroxylation was not accounted for in the PBPK model.

The formation of 3-hydroxycarbamazepine also appears to constitute a minor metabolism pathway ([Pelkonen 2001](#)); still, in human liver microsomes, 3-hydroxycarbamazepine was formed at rates ~25 times greater than those of 2-hydroxycarbamazepine ([Pearce 2002](#)). The responsible enzyme for 3-hydroxylation *in vitro* seems to be CYP2B6, although a minor contribution by CYP1A2, 2A6, and 3A4 cannot be ruled out ([Pearce 2002](#)). In the PBPK model, 3-hydroxylation was implemented as CYP2B6-mediated reaction.

N-glucuronidation of carbamazepine in human liver microsomes and baculovirus-infected insect cells expressing human UGTs was also observed with UGT2B7 appearing to be the responsible enzyme for this reaction ([Staines 2004](#)). Thus, the PBPK model also includes UGT2B7-mediated N-glucuronidation of carbamazepine.

In summary, the following three metabolic pathways, each mediated by a specific enzyme, were implemented in the PBPK model:

- 10,11-epoxidation via CYP3A4
- 3-hydroxylation via CYP2B6
- N-glucuronidation via UGT2B7

Since no clinical mass balance data were found for these three pathways, the following clearance kinetics in human liver microsomes reported for each pathway were initially implemented in the PBPK model:

Biotransformation pathway	K _m [μM]	V _{max} [pmol/min/mg microsomal protein]	Source
10,11-epoxidation	808	726	Sakamoto 2013
3-hydroxylation	235	49.0	Pearce 2002
N-glucuronidation	234	3.5	Staines 2004

The following enzymatic content in human liver microsomes was assumed:

Enzyme	Enzyme content [pmol/mg microsomal protein]	Source
CYP3A4	108	Rodrigues 1999
CYP2B6	39	Rodrigues 1999
UGT2B7	82.9	Achour 2014

The expression profiles for these enzymes were loaded from the 'PK-Sim® Ontogeny Database Version 7.3' ([PK-Sim Ontogeny Database Version 7.3](#)) using RT-PCR as data source for each enzyme.

Upon implementation of these enzyme clearance pathways, it was seen that total clearance was slightly overestimated in the PBPK model. Therefore, the k_{cat} values of each enzyme were optimized during parameter identification; to respect the initial mass balance of these biotransformation reactions as reported in human liver microsomes, the k_{cat} values were not fitted independently but were varied together by the same factor.

Excretion

A minor fraction of the carbamazepine dose (approximately 1%) is excreted unchanged in urine ([Bernus 1994](#), [Morselli 1975](#)). In the model, unchanged renal excretion was implemented as glomerular filtration with the parameter GFR fraction being fitted to the clinical excretion data reported by Bernus et al. ([Bernus 1994](#)).

Induction

Carbamazepine induces CYP2B6 and 3A4 via the CAR- and PXR-pathway ([Faucette 2007](#), [Williamson 2016](#)). CYP2B6 induction was informed based on *in vitro* experiments conducted by Faucette et al. ([Faucette 2004](#)). These authors reported the induction of CYP2B6 activity at various carbamazepine concentrations in three preparations of primary human hepatocytes. The reported data suggest linear induction in the tested carbamazepine concentration range. A

linear-mixed effects model was fitted to the reported data; the fitted slope was 0.149. To implement a linear induction in the PBPK model, the EC₅₀ value of the E_{max} model was set to an arbitrarily high value (1000 µM) and E_{max} was then calculated as product of the fitted slope value and EC₅₀ resulting in a value of 149.

CYP3A4 induction was initially parameterized based on internal *in vitro* experiments and calibrated with rifampicin induction data as described by Almond et al. ([Almond 2016](#)). This resulted in an EC₅₀ of 63.0 µM and an E_{max} of 5.39. Simulated carbamazepine plasma concentrations in steady-state indicated that the induction was underestimated; therefore, the calibrated EC₅₀ value was optimized during parameter identification, while the calibrated E_{max} value was kept fixed.

2.3.4 Automated Parameter Identification

The parameter identification tool in PK-Sim® has been used to estimate the model parameters described above. The result of the parameter identifications is shown in the table below:

Model Parameter	Optimized Value	Unit
Lipophilicity	2.01	
kcat (CYP3A4)	5.01	1/min
kcat (CYP2B6)	0.936	1/min
kcat (UGT2B7)	0.0669	1/min
GFR fraction	0.0240	
EC50 (CYP3A4)	27.2	µM
Dissolution time (50% dissolved) (IR tablet, fasted)	109	min
Dissolution shape (IR tablet, fasted)	0.689	
Dissolution time (50% dissolved) (XR formulation, fasted)	315	min
Dissolution shape (XR formulation, fasted)	1.23	
Solubility at ref pH -- for XR formulations only	546	mg/L

3 Results and Discussion

The PBPK model for carbamazepine was developed and evaluated using publicly 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: Carbamazepine

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	308.3333 mg/l	Publication-Mean value of the following FaHIF solubility data reported in the literature: 336 µg/mL, pH 6.2 (Annaert 2010; DOI: 10.1016/j.ejps.2009.10.005); 283 µg/mL, pH 7.0 (Söderlind 2010; DOI: 10.1021/mp100144v); 306 mg/mL, pH 6.9 (Clarysse 2011; DOI: 10.1016/j.ejps.2011.04.016)	IR tablet (FaHIF)	True
Reference pH	6.7	Publication-Mean value of the following FaHIF solubility data reported in the literature: 336 µg/mL, pH 6.2 (Annaert 2010; DOI: 10.1016/j.ejps.2009.10.005); 283 µg/mL, pH 7.0 (Söderlind 2010; DOI: 10.1021/mp100144v); 306 mg/mL, pH 6.9 (Clarysse 2011; DOI: 10.1016/j.ejps.2011.04.016)	IR tablet (FaHIF)	True
Solubility at reference pH	546.0199756643 mg/l	Parameter Identification-Parameter Identification-Value updated from '004-2_from-003-1_XRtablet_fasted_solubility_FINAL' on 2022-03-24 12:41	XR tablet (fitted)	False
Reference pH	6.7	Parameter Identification-Parameter Identification-Value updated from '004-2_from-003-1_XRtablet_fasted_solubility_FINAL' on 2022-03-16 18:25	XR tablet (fitted)	False
Lipophilicity	2.0067753065 Log Units	Parameter Identification-Parameter Identification-Value updated from '001-5-3_CYP3A4_MM-kinetics_WithoutTablet' on 2022-02-21 16:49	Optimized	True
Fraction unbound (plasma, reference value)	0.243	Publication-Morselli 1975 (DOI: 10.1007/978-3-642-85921-2_16)	Morselli 1975	True
Is small molecule	Yes			
Molecular weight	236.2686 g/mol	Internet-DrugBank (https://go.drugbank.com/drugs/DB00564)		
Plasma protein binding partner	Albumin			

Calculation methods

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

Processes

Induction: CYP3A4-DMPK

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
EC50	27.193363407 μmol/l	Parameter Identification-Parameter Identification-Value updated from '003-1_from002-3-6_EC50' on 2022-02-24 10:23
Emax	5.3929777775	Publication-In Vitro-DMPK measurement (internal data); the measured Emax was calibrated with rifampicin by using the Emax implemented in the rifampicin OSP model v1.2 according the method described by Almond 2016 (DOI: 10.1124/dmd.115.066845)

Systemic Process: Glomerular Filtration-Glomerular Filtration

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	0.0240108793	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18

Metabolizing Enzyme: UGT2B7-N-Glucuronidation_Staines2004

Molecule: UGT2B7

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	3.5 pmol/min/mg mic. protein	Publication-In Vitro-Staines 2004 (DOI: 10.1124/jpet.104.073114)
Content of CYP proteins in liver microsomes	82.9 pmol/mg mic. protein	Publication-In Vitro-Achour 2014 (DOI: 10.1124/dmd.113.055632)
Km	234 μmol/l	Publication-In Vitro-Staines 2004 (DOI: 10.1124/jpet.104.073114)
kcat	0.0668699322 1/min	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18

Metabolizing Enzyme: CYP2B6-3-Hydroxylation_Pearce2002

Molecule: CYP2B6

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	49 pmol/min/mg mic. protein	Publication-In Vitro-Pearce 2002 (DOI: 10.1124/dmd.30.11.1170)
Content of CYP proteins in liver microsomes	39 pmol/mg mic. protein	Publication-In Vitro-Rodrigues 1999 (DOI: 10.1016/s0006-2952(98)00268-8)
Km	235 μmol/l	Publication-Pearce 2002 (DOI: 10.1124/dmd.30.11.1170)
kcat	0.9361790504 1/min	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18

Metabolizing Enzyme: CYP3A4-Epoxidation_Sakamoto2013

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	726 pmol/min/mg mic. protein	Publication-In Vitro-Sakamoto 2013 (DOI: 10.1248/bpb.b13-00569)
Km	808 μmol/l	Publication-In Vitro-Sakamoto 2013 (DOI: 10.1248/bpb.b13-00569)
kcat	5.0088763476 1/min	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18

Induction: CYP2B6-Faucette2004

Molecule: CYP2B6

Parameters

Name	Value	Value Origin
EC50	1000 μmol/l	Publication-Set to an arbitrarily high value to enable linear induction as suggested by Faucette 2004 (DOI: 10.1124/dmd.32.3.348); see evaluation report for details
Emax	148.7284	Publication-Linear-mixed effects model fitted to reported data by Faucette 2004 (DOI: 10.1124/dmd.32.3.348); see evaluation report for details

Formulation: CBZ_capsuleXR_fasted (Carbatrol)

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	315.2431776804 min	Parameter Identification-Parameter Identification-Value updated from '004-2_from-003-1_XRtablet_fasted_solubility_FINAL' on 2022-03-24 12:41
Lag time	0 min	
Dissolution shape	1.2290186648	Parameter Identification-Parameter Identification-Value updated from '004-2_from-003-1_XRtablet_fasted_solubility_FINAL' on 2022-03-24 12:41
Use as suspension	Yes	

Formulation: CBZ_tabletIR_fasted (Tegretol)

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	109.3089775422 min	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18
Lag time	0 min	
Dissolution shape	0.6890123758	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18
Use as suspension	Yes	

Formulation: Solution

Type: Dissolved

Compound: [15N]-Carbamazepine

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	308.3333 mg/l	Publication-Mean value of the following FaHIF solubility data reported in the literature: 336 µg/mL, pH 6.2 (Annaert 2010; DOI: 10.1016/j.ejps.2009.10.005); 283 µg/mL, pH 7.0 (Söderlind 2010; DOI: 10.1021/mp100144v); 306 mg/mL, pH 6.9 (Clarysse 2011; DOI: 10.1016/j.ejps.2011.04.016)	IR tablet (FaHIF)	True
Reference pH	6.7	Publication-Mean value of the following FaHIF solubility data reported in the literature: 336 µg/mL, pH 6.2 (Annaert 2010; DOI: 10.1016/j.ejps.2009.10.005); 283 µg/mL, pH 7.0 (Söderlind 2010; DOI: 10.1021/mp100144v); 306 mg/mL, pH 6.9 (Clarysse 2011; DOI: 10.1016/j.ejps.2011.04.016)	IR tablet (FaHIF)	True
Solubility at reference pH	546.0199756643 mg/l	Parameter Identification-Parameter Identification-Value updated from '004-2_from-003-1_XRtablet_fasted_solubility_FINAL' on 2022-03-24 12:41	XR tablet (fitted)	False
Reference pH	6.7	Parameter Identification-Parameter Identification-Value updated from '004-2_from-003-1_XRtablet_fasted_solubility_FINAL' on 2022-03-16 18:25	XR tablet (fitted)	False
Lipophilicity	2.0067753065 Log Units	Parameter Identification-Parameter Identification-Value updated from '001-5-3_CYP3A4_MM-kinetics_WithoutTablet' on 2022-02-21 16:49	Optimized	True
Fraction unbound (plasma, reference value)	0.243	Publication-Morselli 1975 (DOI: 10.1007/978-3-642-85921-2_16)	Morselli 1975	True
Is small molecule	Yes			
Molecular weight	236.2686 g/mol	Internet-DrugBank (https://go.drugbank.com/drugs/DB00564)		
Plasma protein binding partner	Albumin			

Calculation methods

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

Processes

Induction: CYP3A4-DMPK

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
EC50	27.193363407 µmol/l	Parameter Identification-Parameter Identification-Value updated from '003-1_from002-3-6_EC50' on 2022-02-24 10:23
Emax	5.3929777775	Publication-In Vitro-DMPK measurement (internal data); the measured Emax was calibrated with rifampicin by using the Emax implemented in the rifampicin OSP model v1.2 according the method described by Almond 2016 (DOI: 10.1124/dmd.115.066845)

Systemic Process: Glomerular Filtration-Glomerular Filtration

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	0.0240108793	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18

Metabolizing Enzyme: UGT2B7-N-Glucuronidation_Staines2004

Molecule: UGT2B7

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	3.5 pmol/min/mg mic. protein	Publication-In Vitro-Staines 2004 (DOI: 10.1124/jpet.104.073114)
Content of CYP proteins in liver microsomes	82.9 pmol/mg mic. protein	Publication-In Vitro-Achour 2014 (DOI: 10.1124/dmd.113.055632)
Km	234 μmol/l	Publication-In Vitro-Staines 2004 (DOI: 10.1124/jpet.104.073114)
kcat	0.0668699322 1/min	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18

Metabolizing Enzyme: CYP2B6-3-Hydroxylation_Pearce2002

Molecule: CYP2B6

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	49 pmol/min/mg mic. protein	Publication-In Vitro-Pearce 2002 (DOI: 10.1124/dmd.30.11.1170)
Content of CYP proteins in liver microsomes	39 pmol/mg mic. protein	Publication-In Vitro-Rodrigues 1999 (DOI: 10.1016/s0006-2952(98)00268-8)
Km	235 μmol/l	Publication-Pearce 2002 (DOI: 10.1124/dmd.30.11.1170)
kcat	0.9361790504 1/min	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18

Metabolizing Enzyme: CYP3A4-Epoxidation_Sakamoto2013

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	726 pmol/min/mg mic. protein	Publication-In Vitro-Sakamoto 2013 (DOI: 10.1248/bpb.b13-00569)
Km	808 µmol/l	Publication-In Vitro-Sakamoto 2013 (DOI: 10.1248/bpb.b13-00569)
kcat	5.0088763476 1/min	Parameter Identification-Parameter Identification-Value updated from '002-3-6_from001-5-3_IRtablet-sd_Pint-FIX_FINAL' on 2022-02-23 17:18

Induction: CYP2B6-Faucette2004

Molecule: CYP2B6

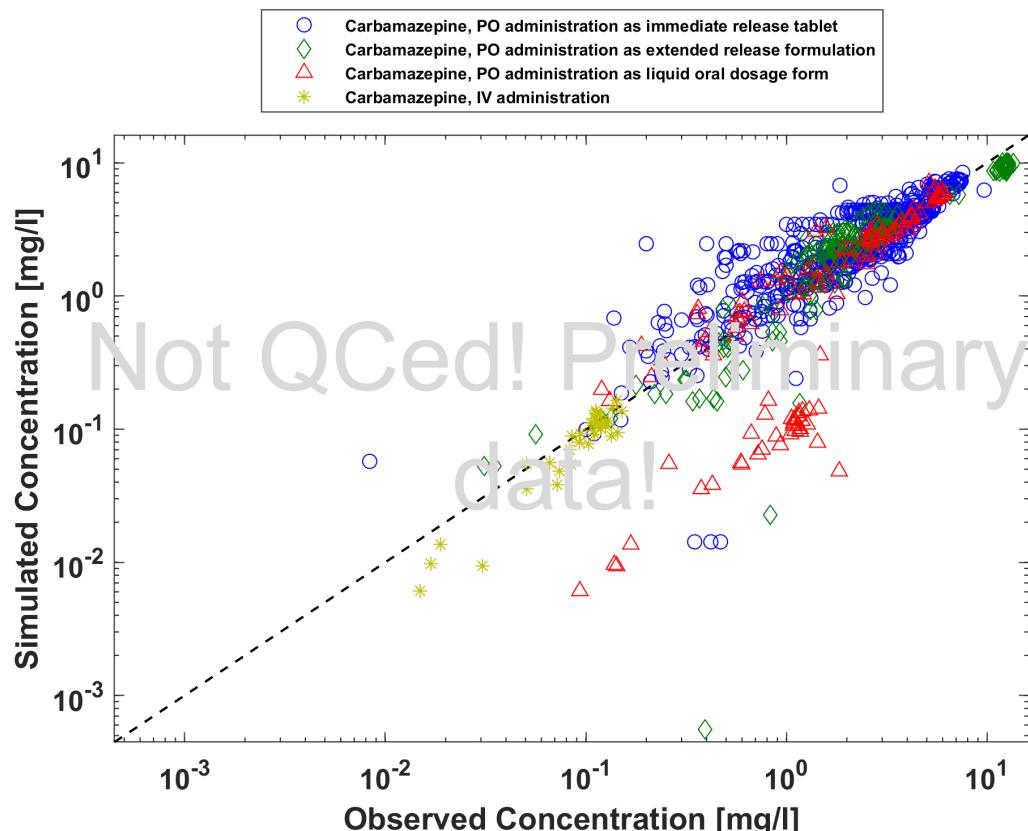
Parameters

Name	Value	Value Origin
EC50	1000 µmol/l	Publication-Set to an arbitrarily high value to enable linear induction as suggested by Faucette 2004 (DOI: 10.1124/dmd.32.3.348); see evaluation report for details
Emax	148.7284	Publication-Linear-mixed effects model fitted to reported data by Faucette 2004 (DOI: 10.1124/dmd.32.3.348); see evaluation report for details

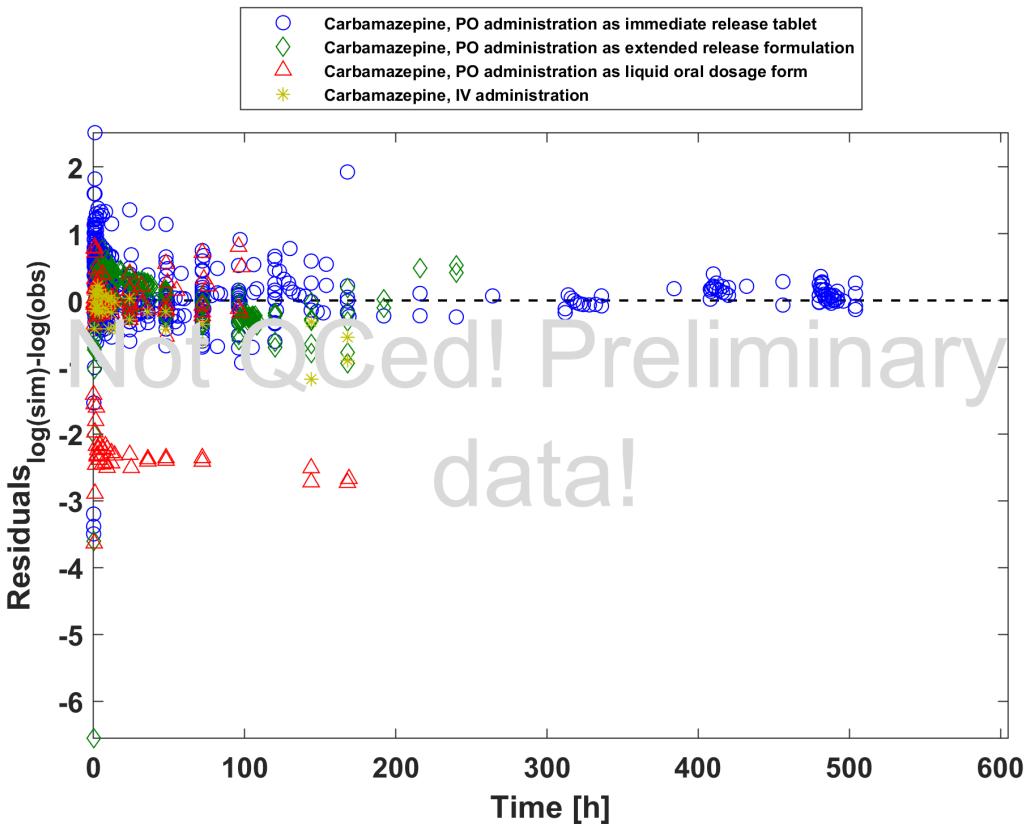
3.2 Diagnostics Plots

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 simulated versus observed plasma concentration, the second weighted residuals versus time.



Goodness of fit plot for concentration in plasma

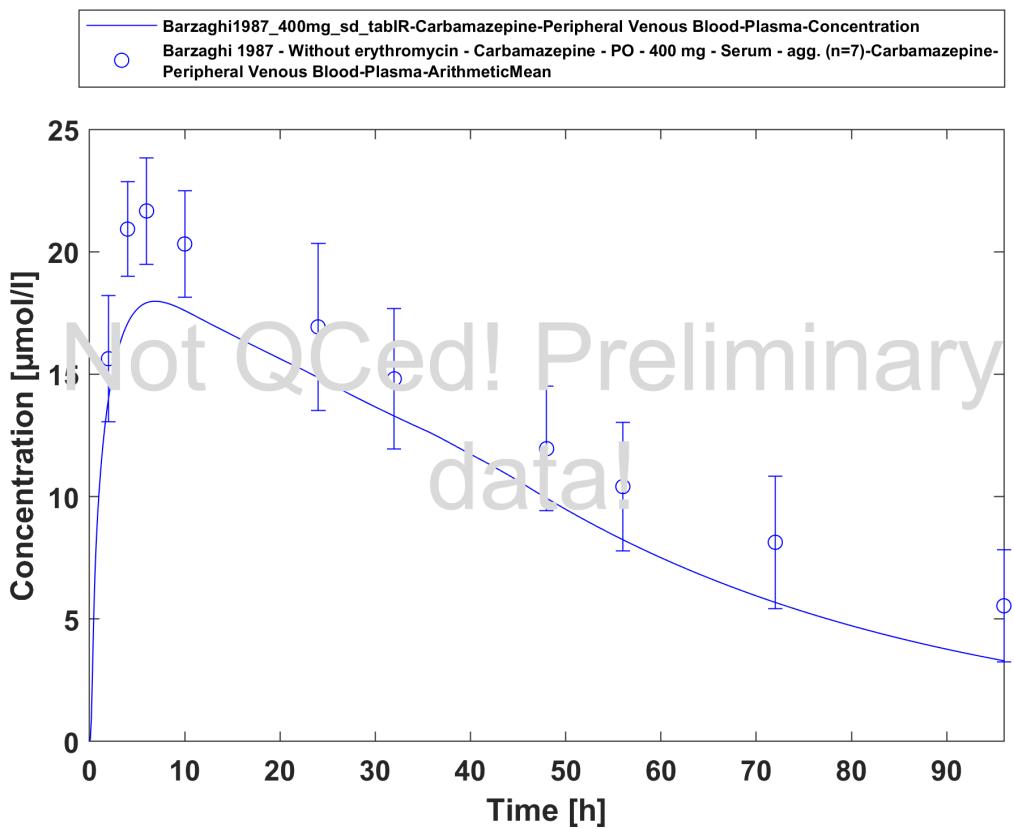


Goodness of fit plot for concentration in plasma

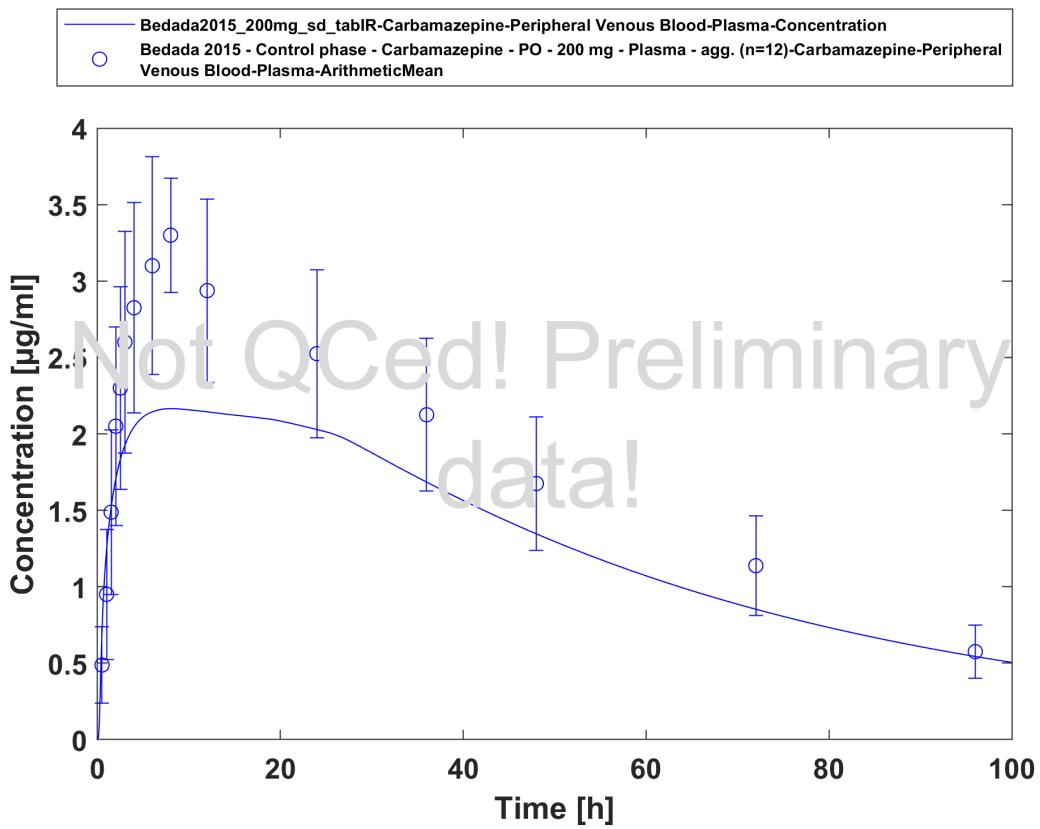
GMFE = 1.486311

3.3 Concentration-Time Profiles

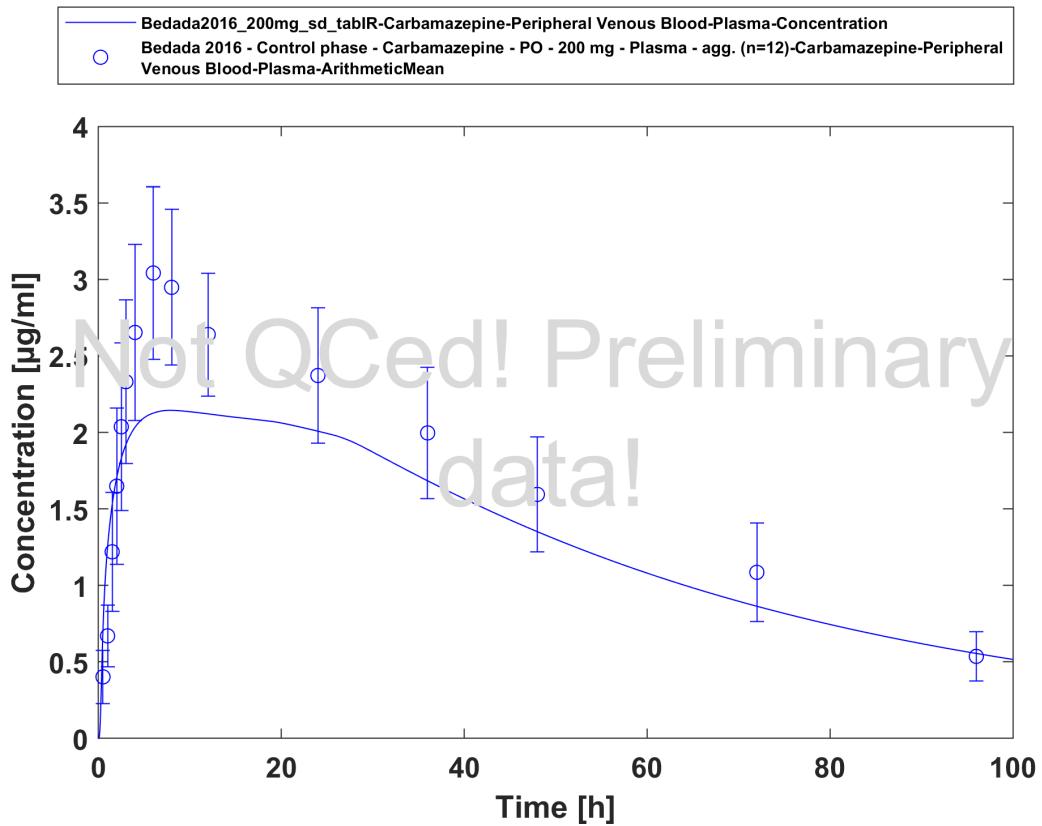
Simulated versus observed concentration-time profiles of all data listed in [Section 2.2.2](#) are presented below.



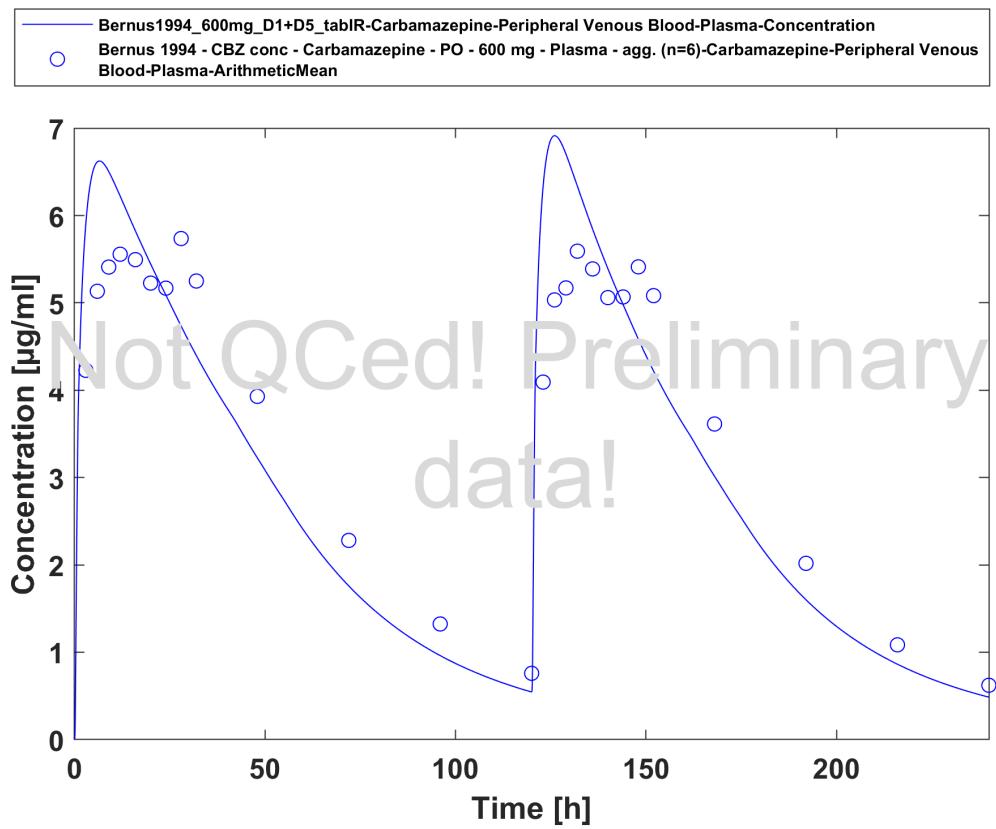
Barzaghi1987_400mg_sd_tablR_fed



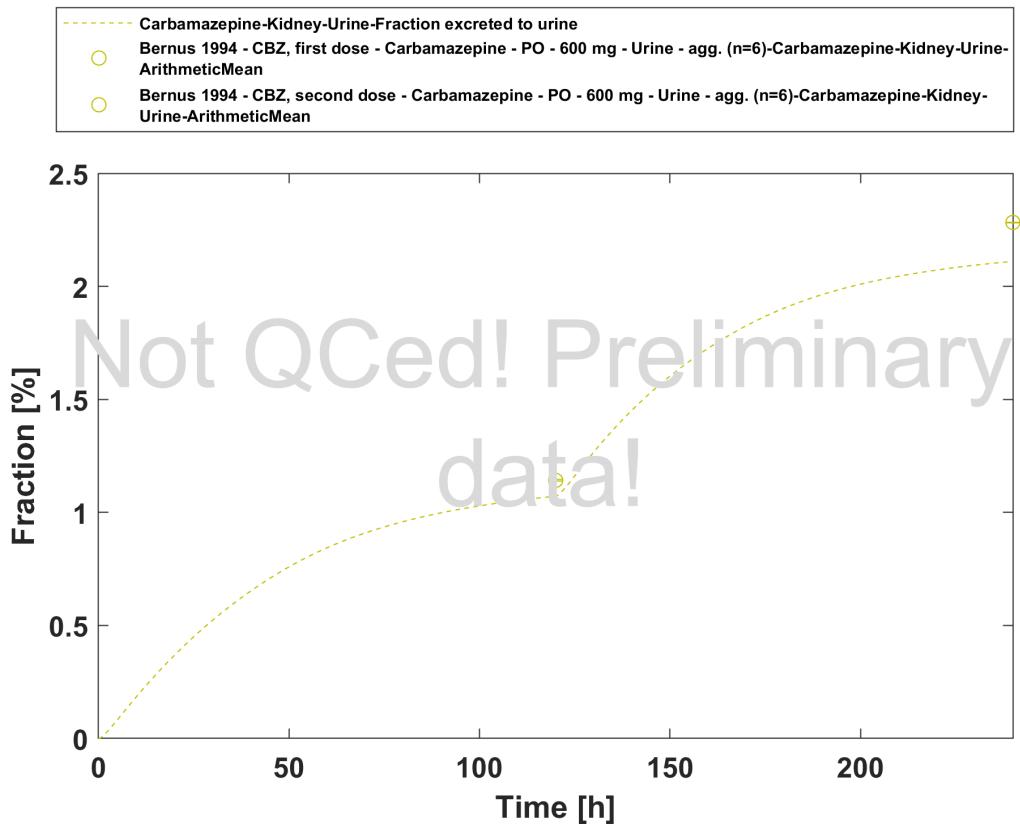
Bedada2015_200mg_sd_tablR



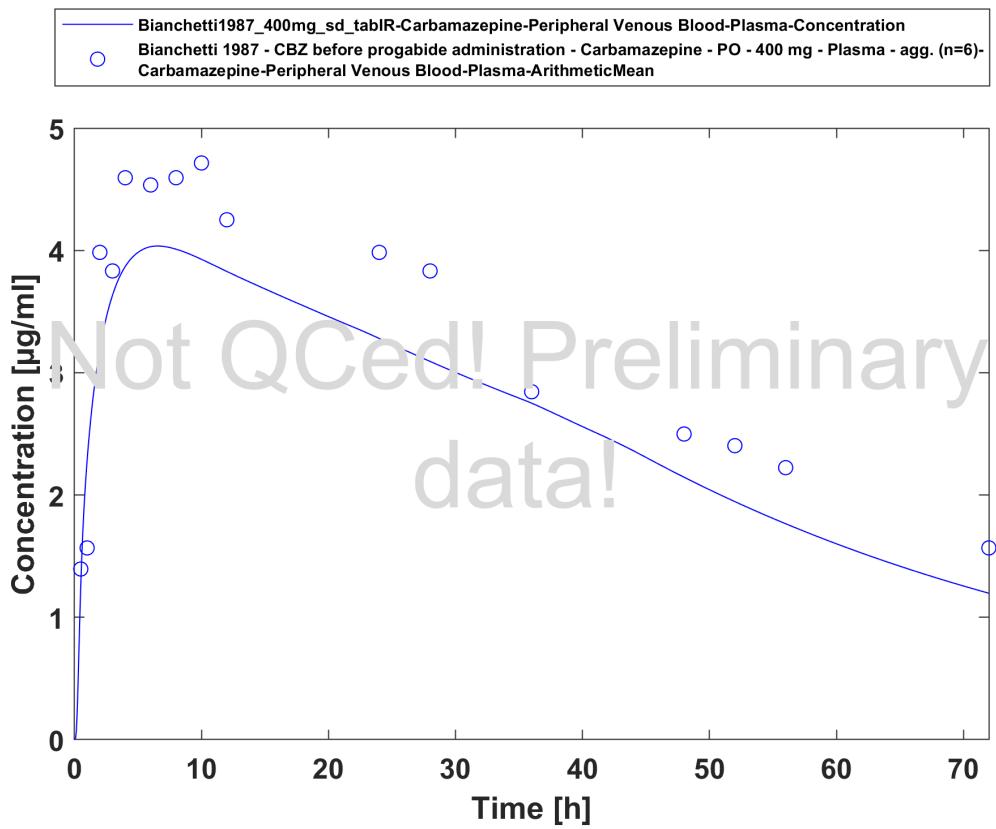
Bedada2016_200mg_sd_tabIR



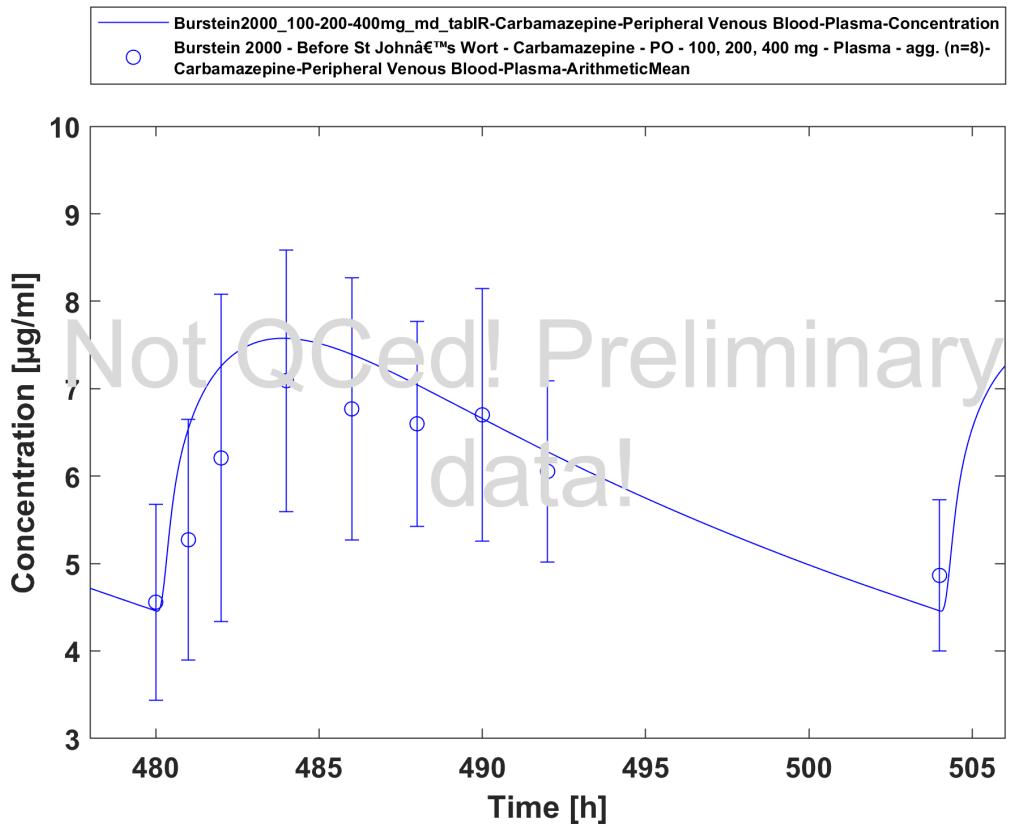
Bernus1994_600mg_D1+D5_tabIR - plasma



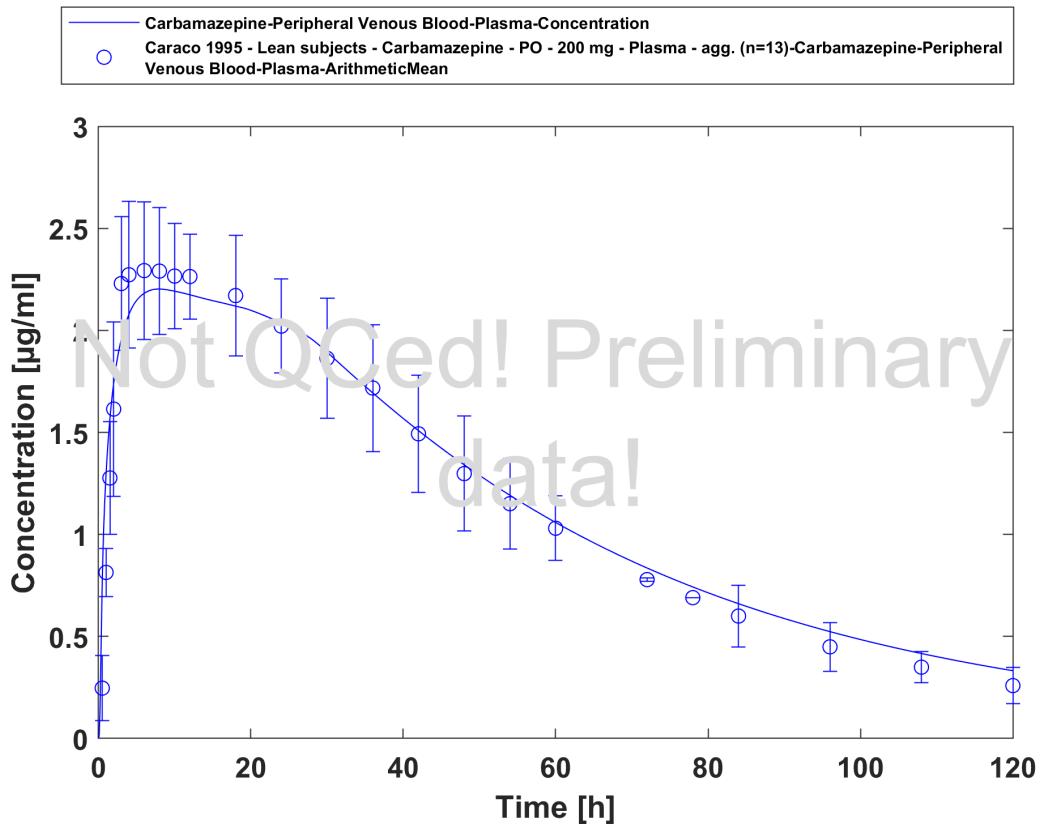
Bernus1994_600mg_D1+D5_tablR - urine



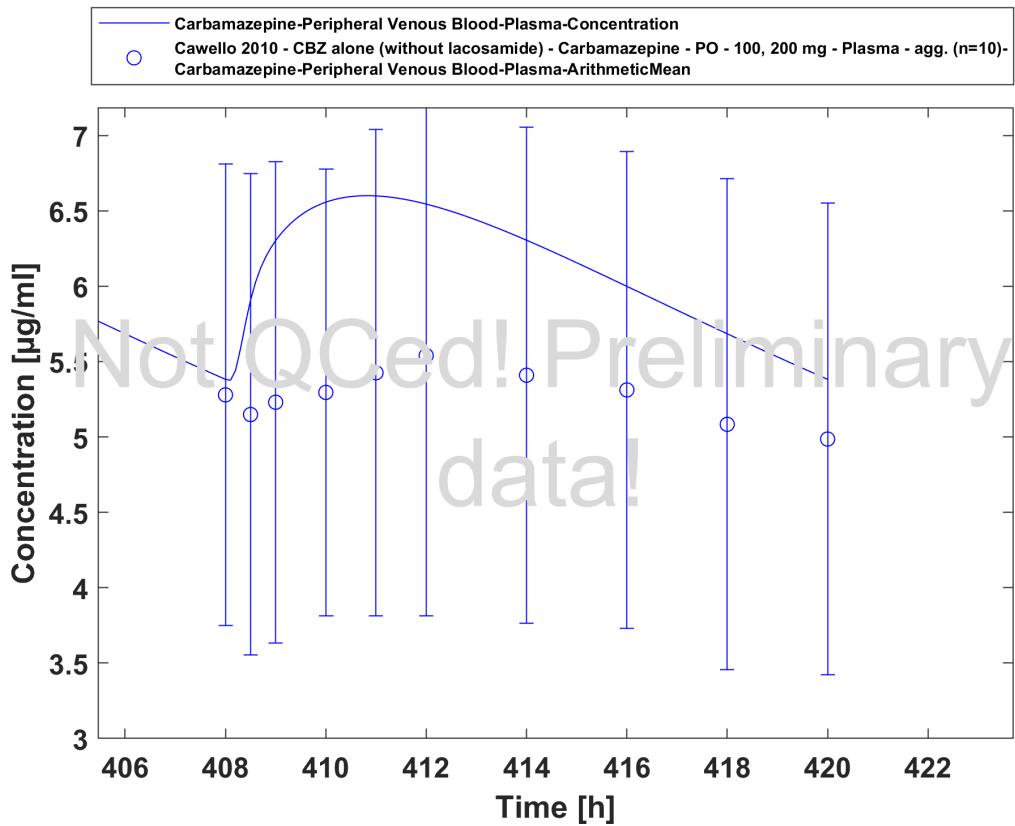
Bianchetti1987_400mg_sd_tablR_fed



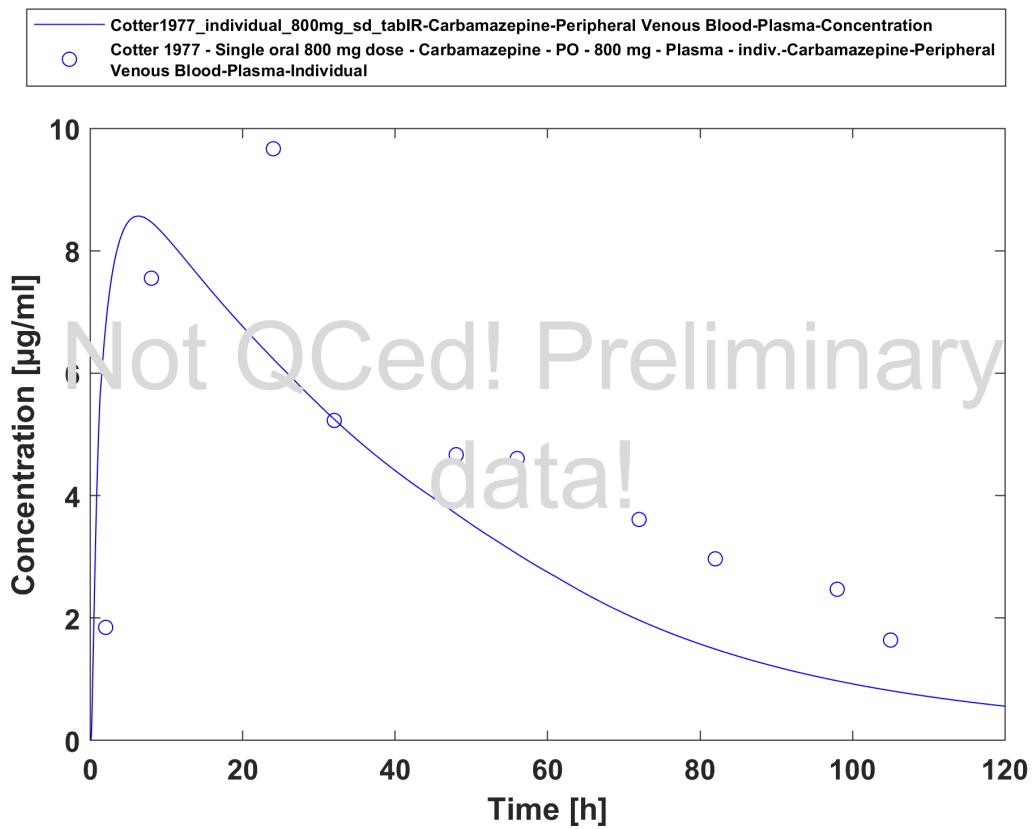
Burstein2000_100-200-400mg_md_tabIR



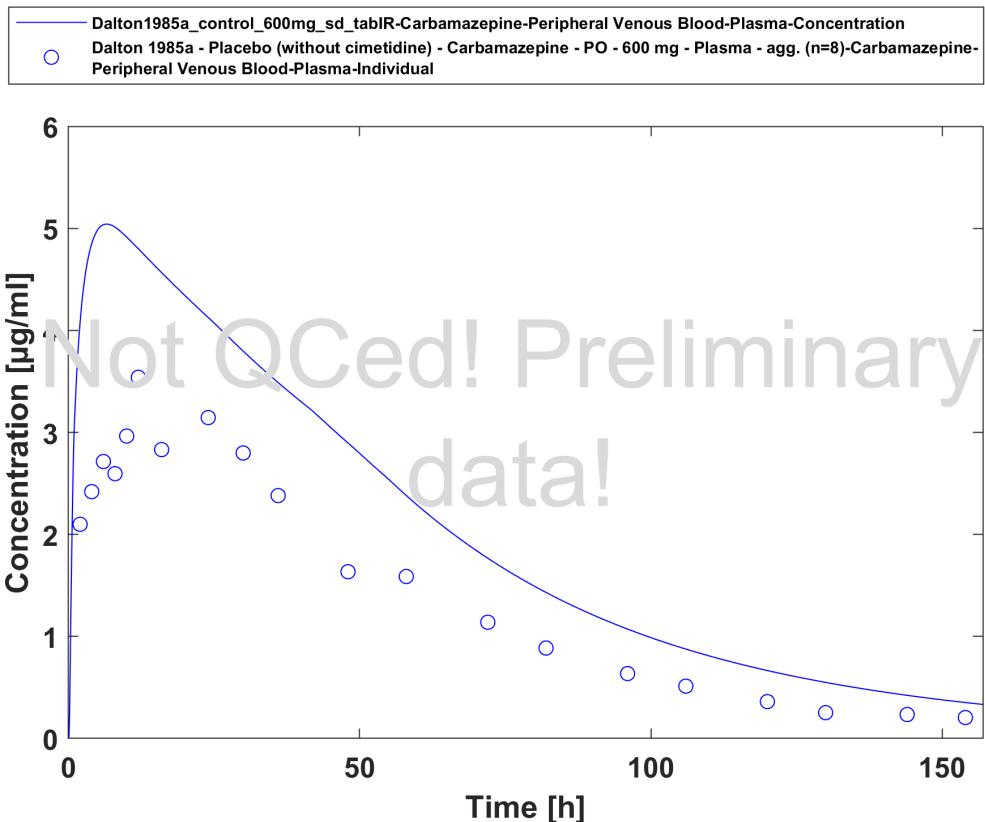
Time Profile Analysis



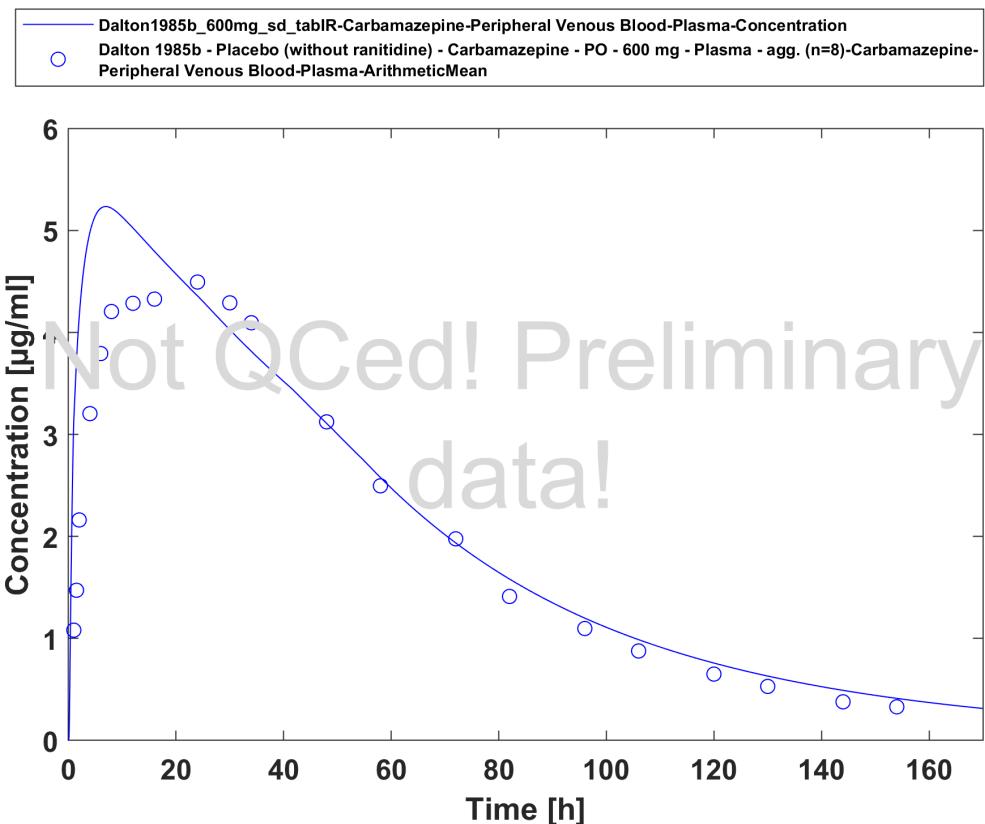
Time Profile Analysis



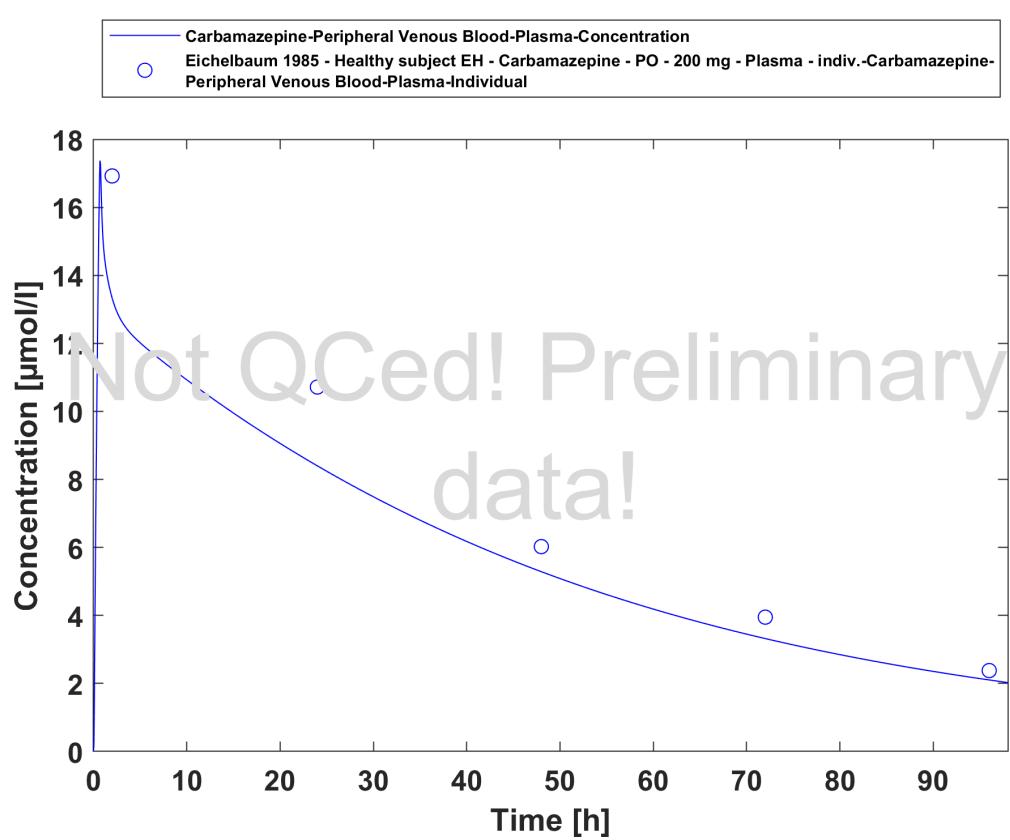
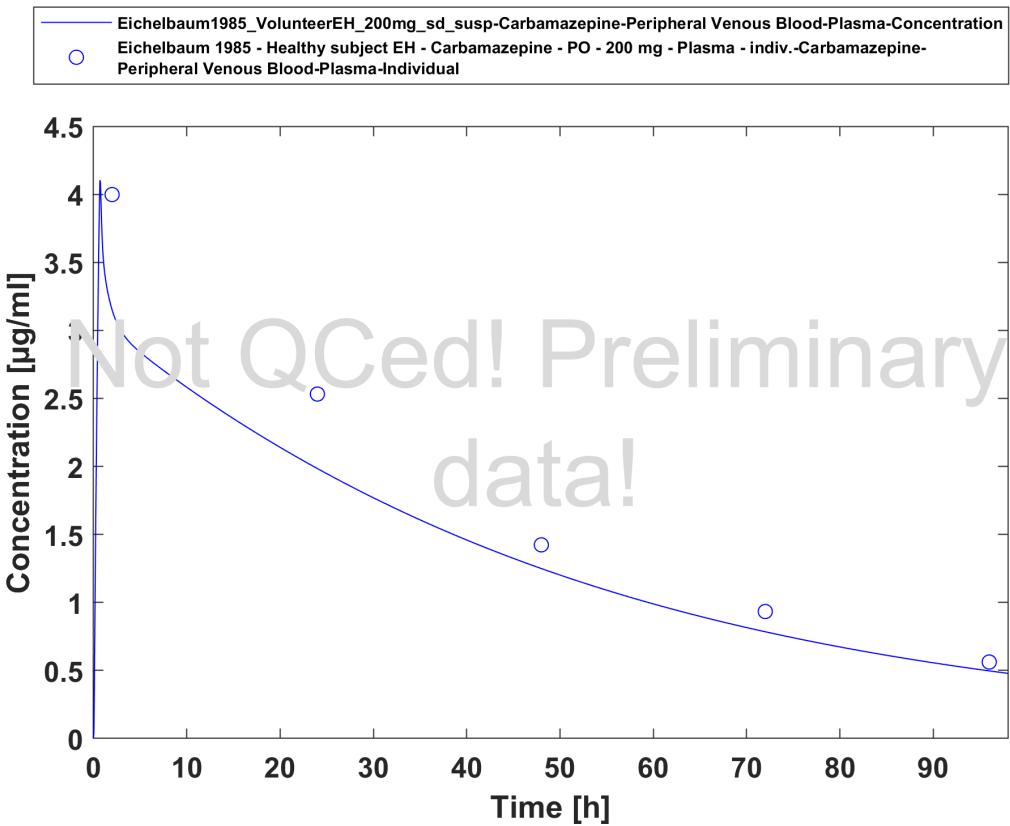
Cotter1977_individual_800mg_sd_tabIR

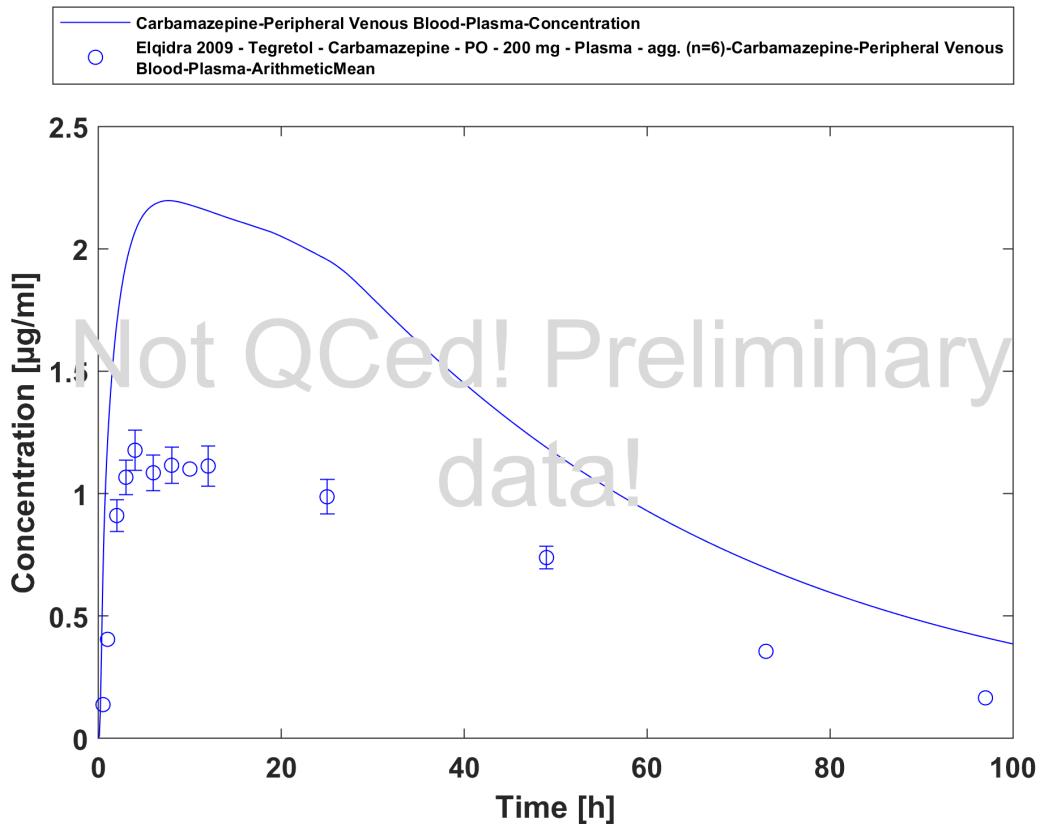


Dalton1985_control_600mg_sd_tabIR

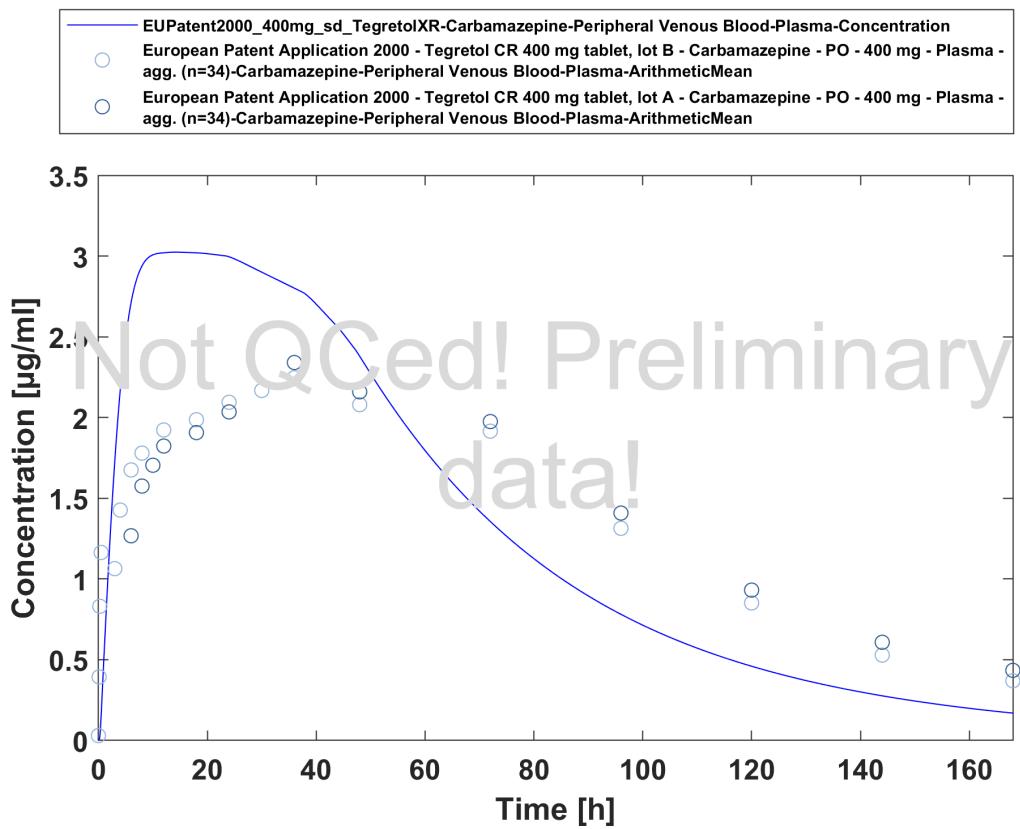


Dalton1985a_600mg_sd_tabIR

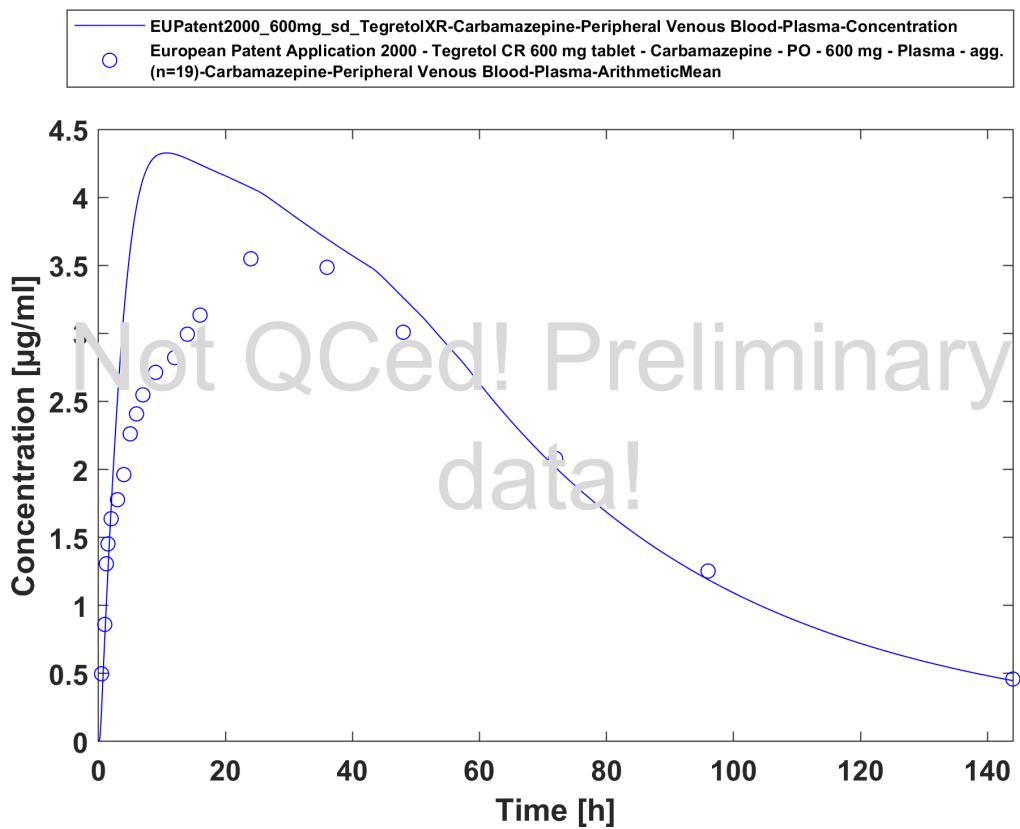




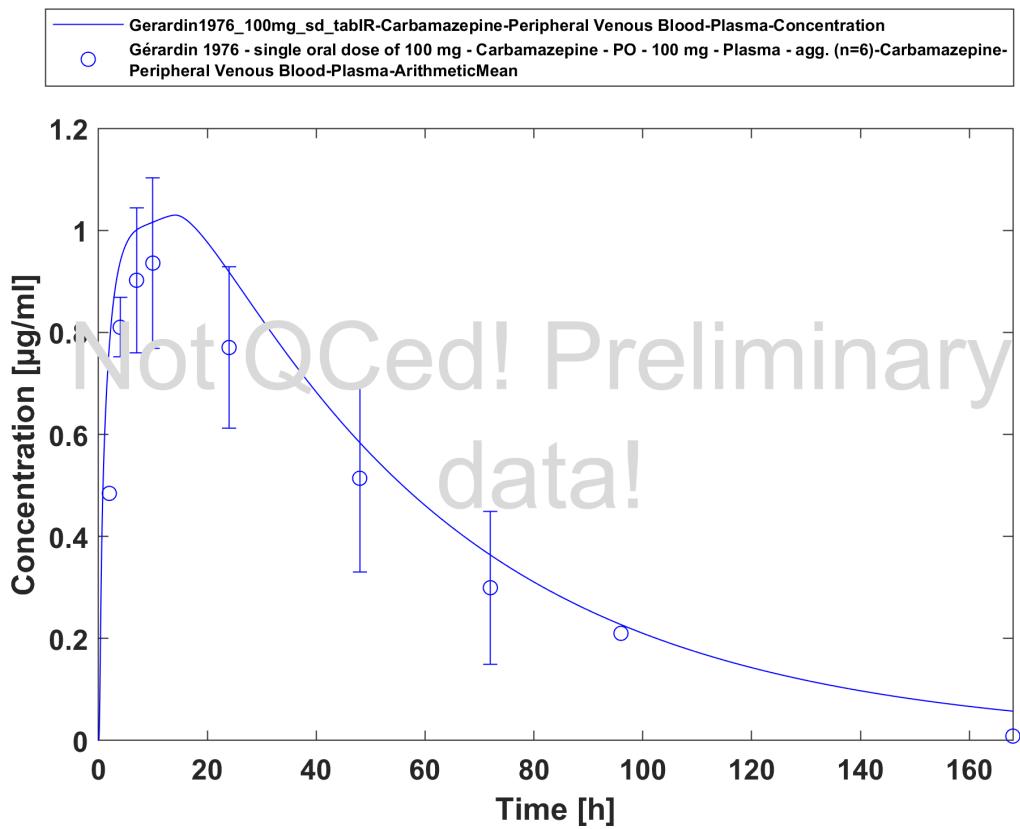
Time Profile Analysis



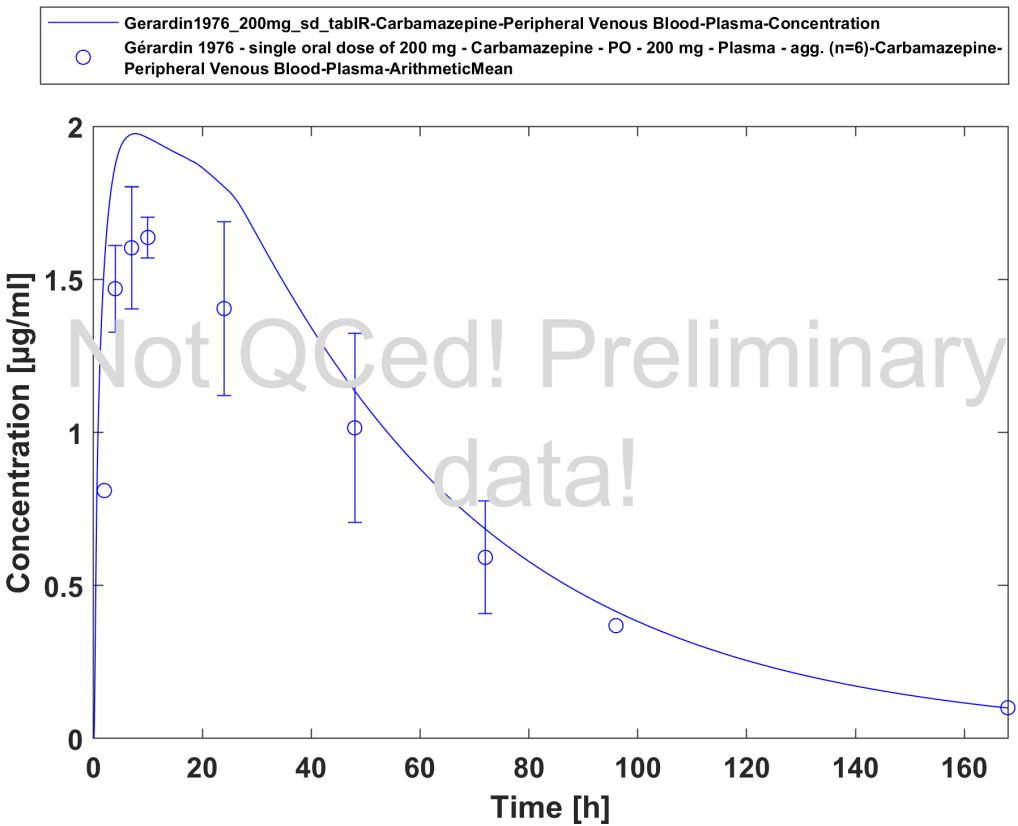
EUPatent2005_400mg_sd_TegretolXR



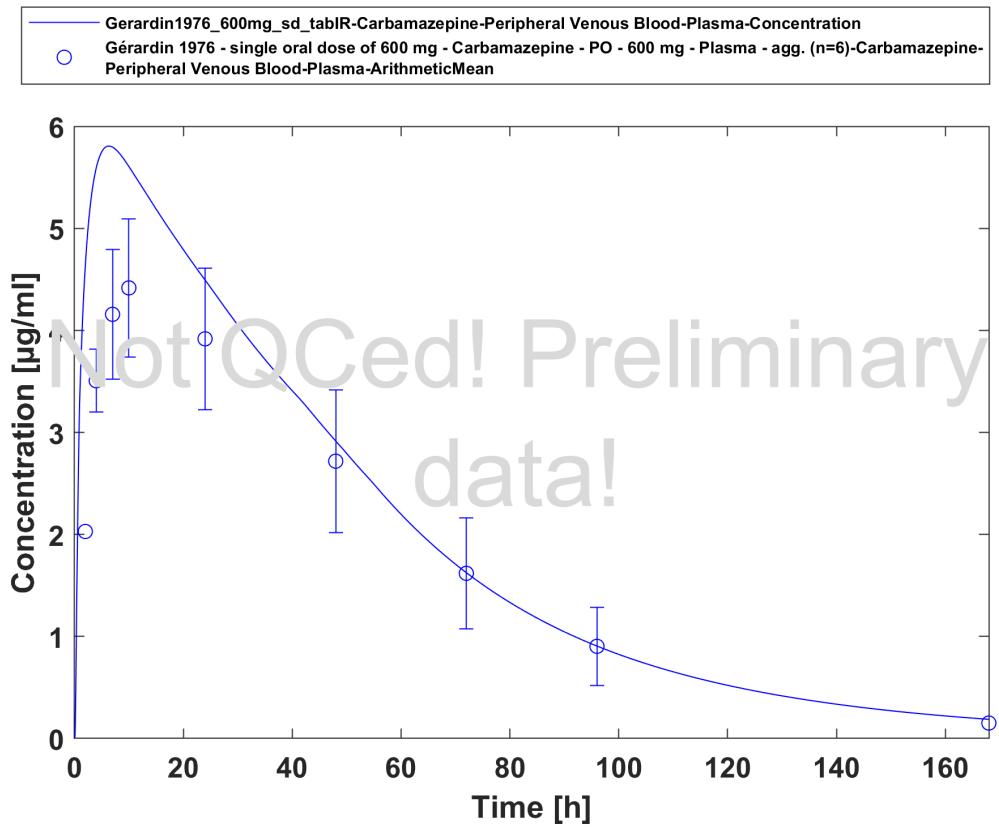
EUPatent2005_600mg_sd_TegretolXR



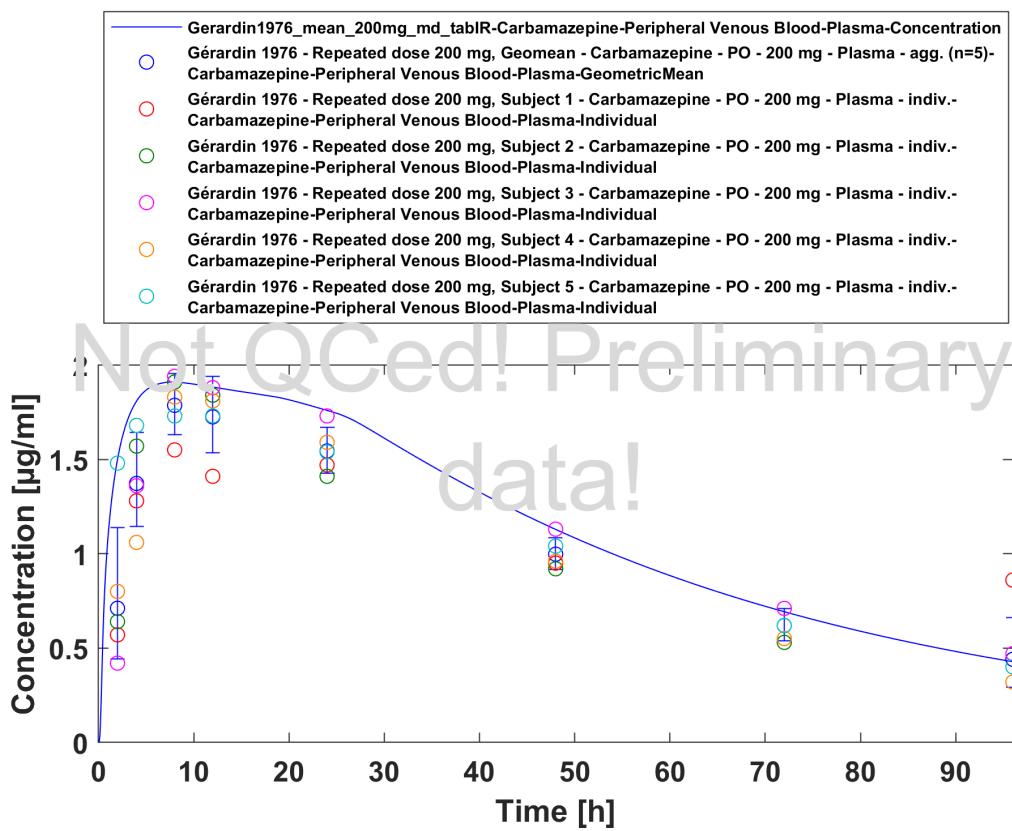
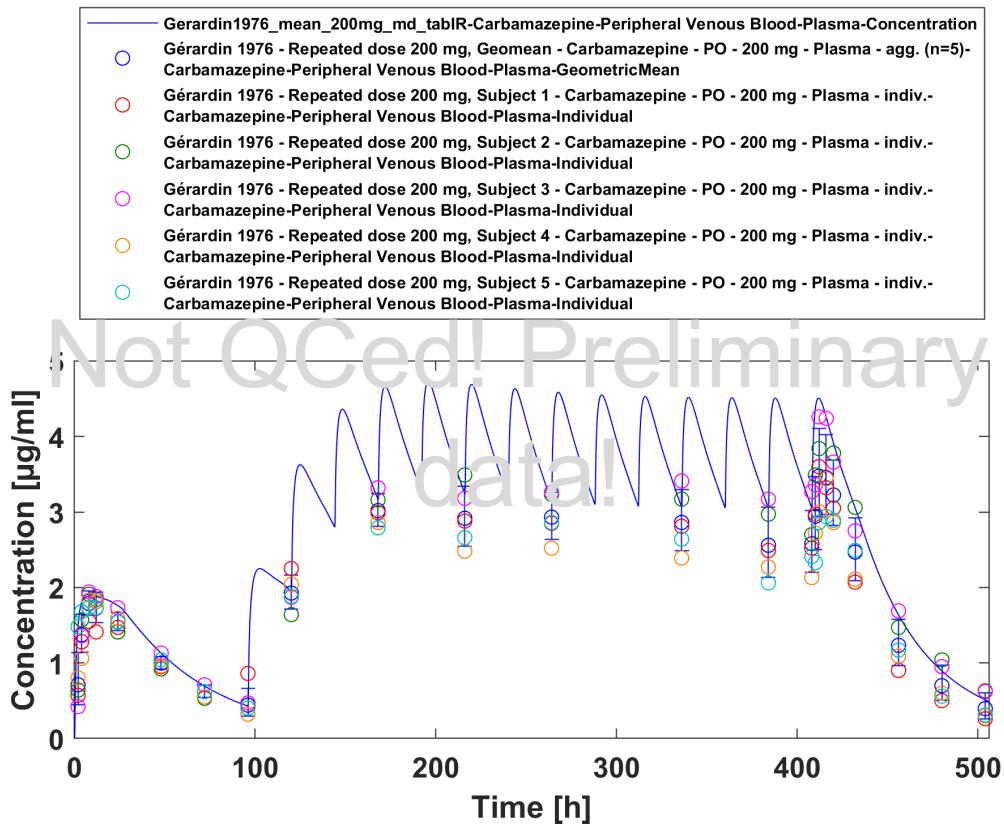
Time Profile Analysis

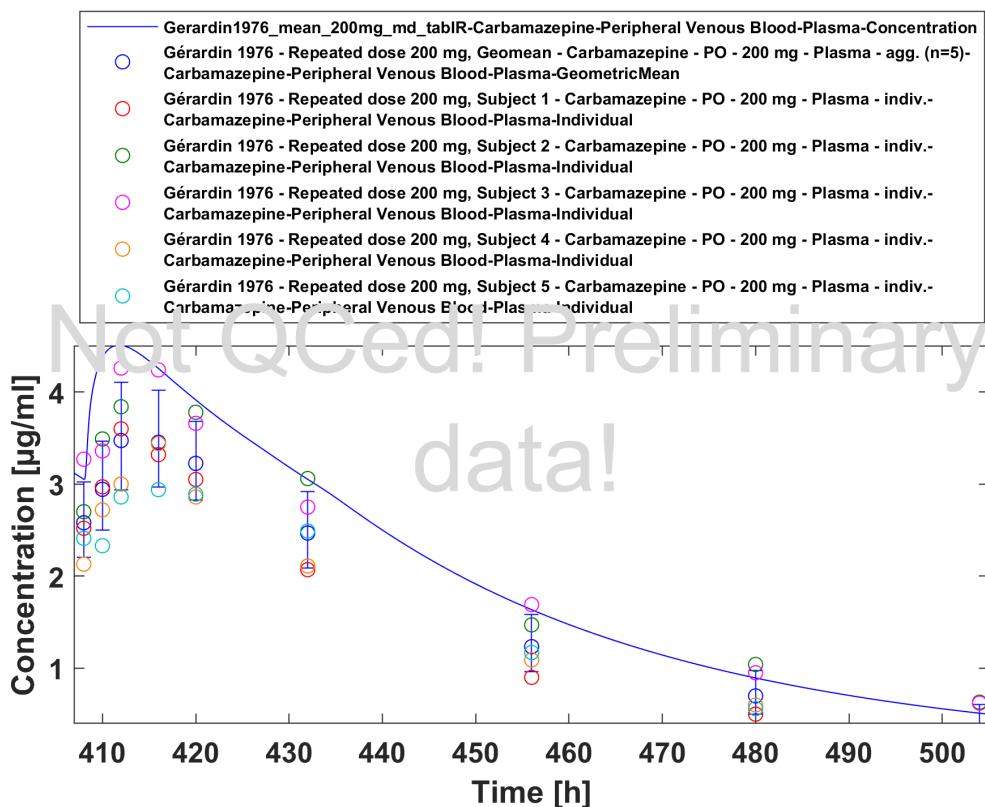


Geradin1976_200mg_sd_tablR

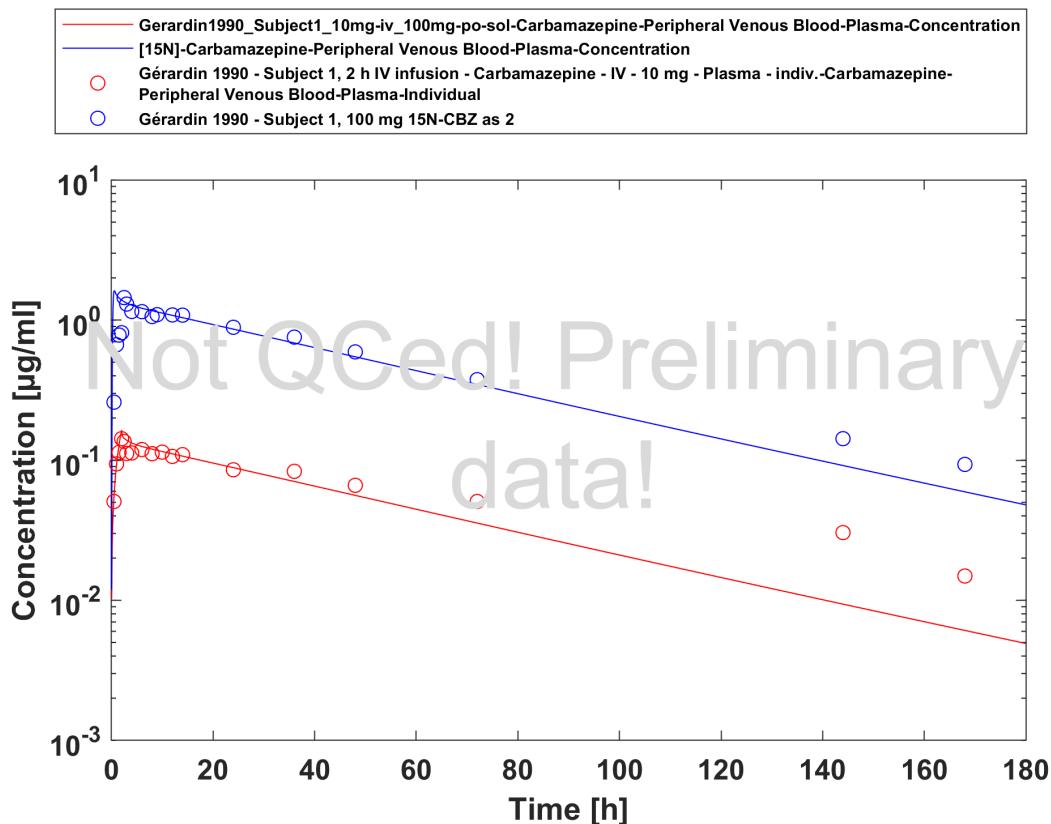


Time Profile Analysis

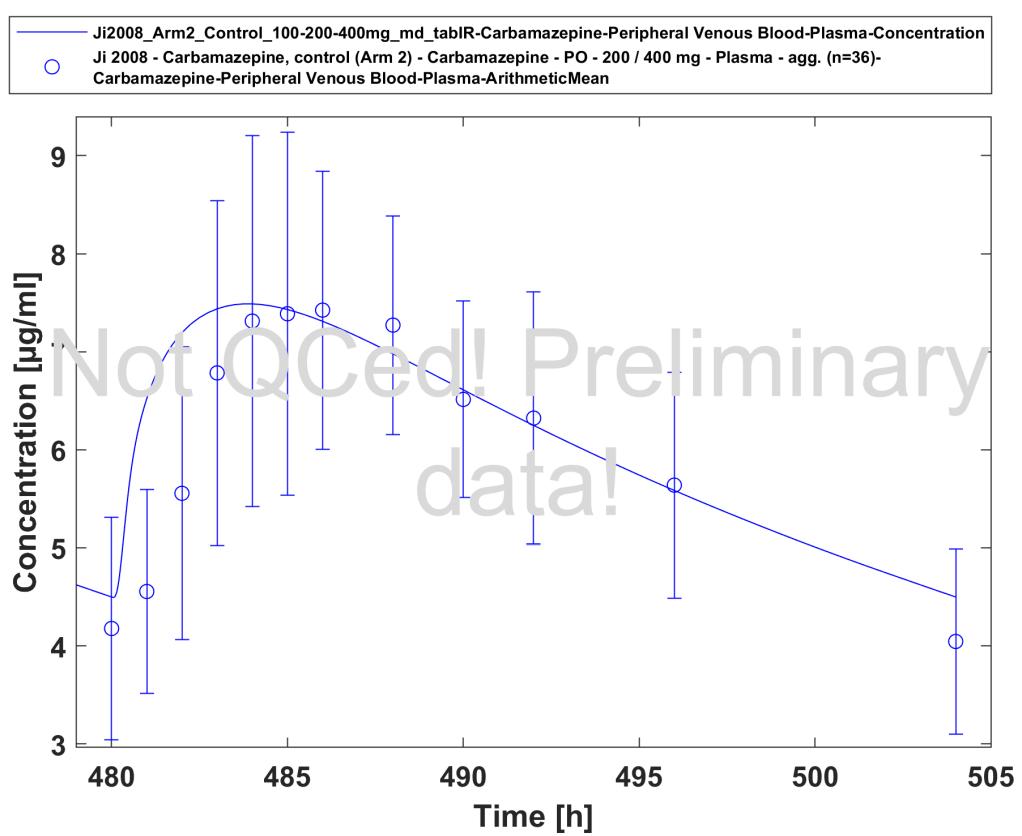
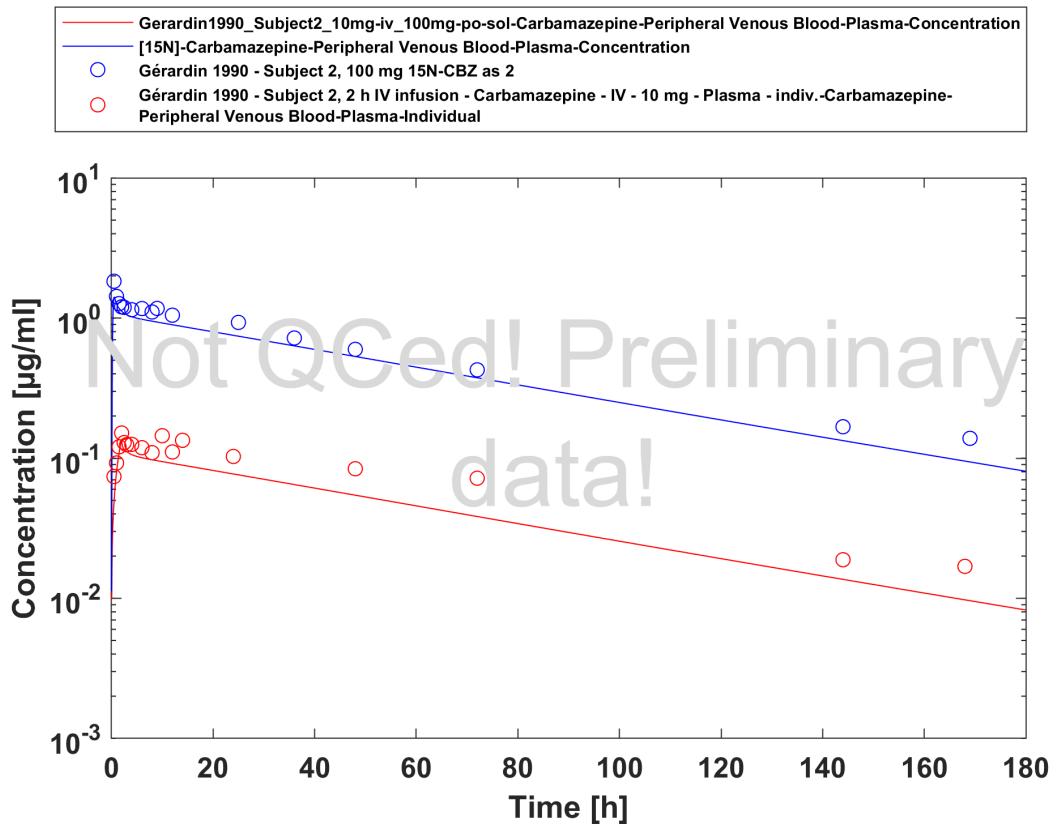


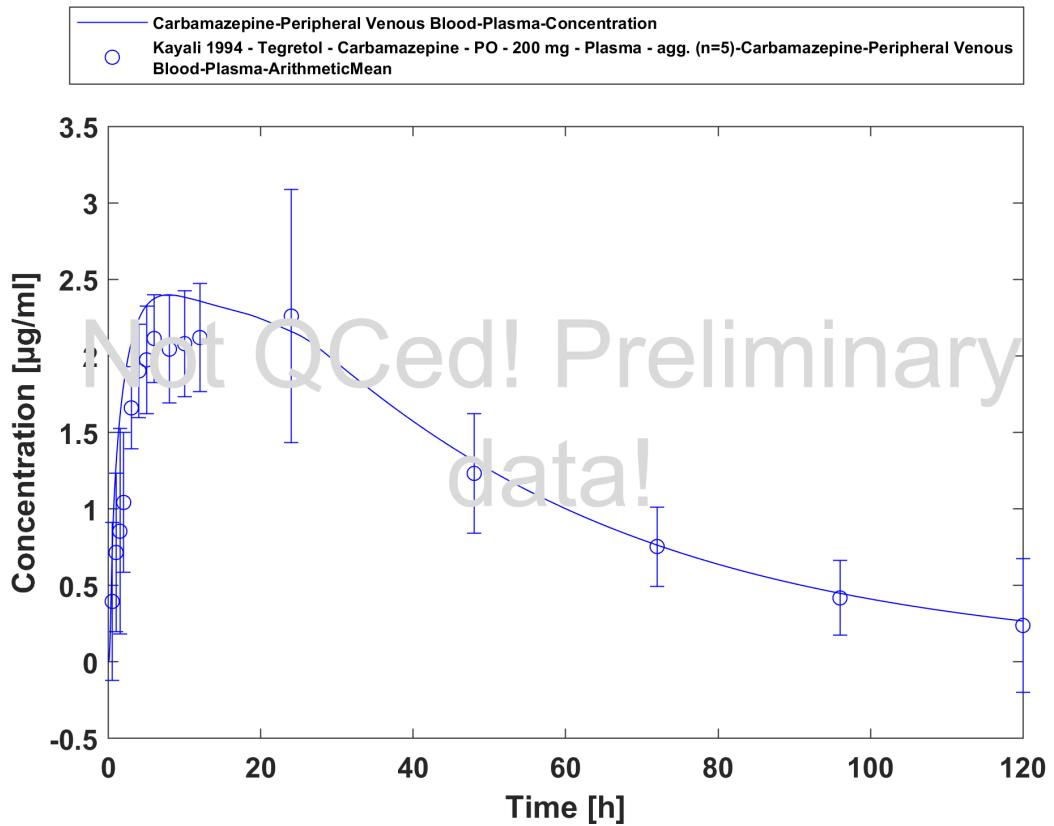


Gérardin1976_mean_200mg_md_tablR - last dose

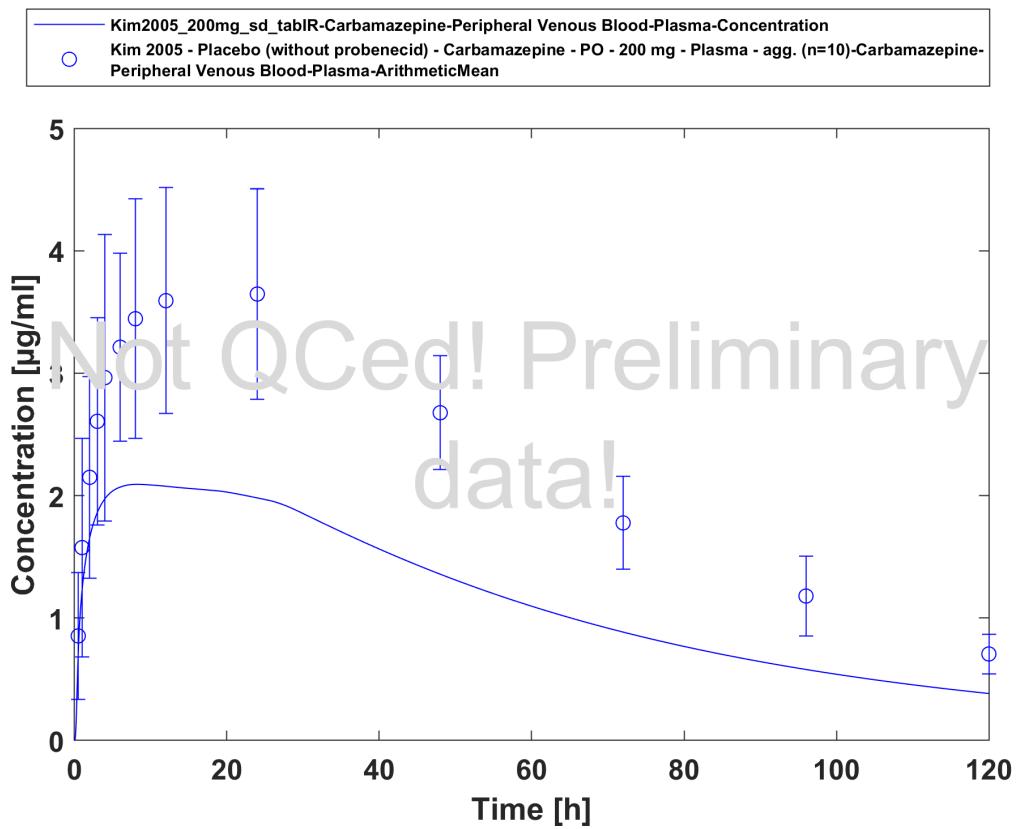


Gérardin1990_Subject1_100mg-iv_100mg-po-sol

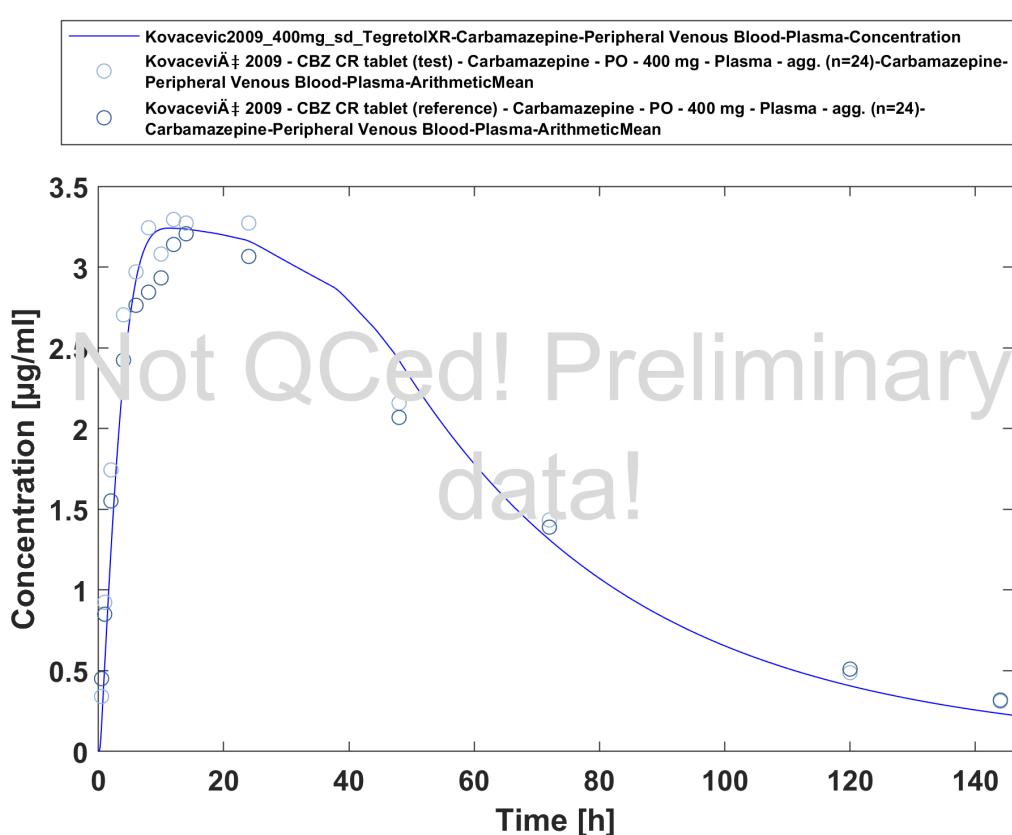
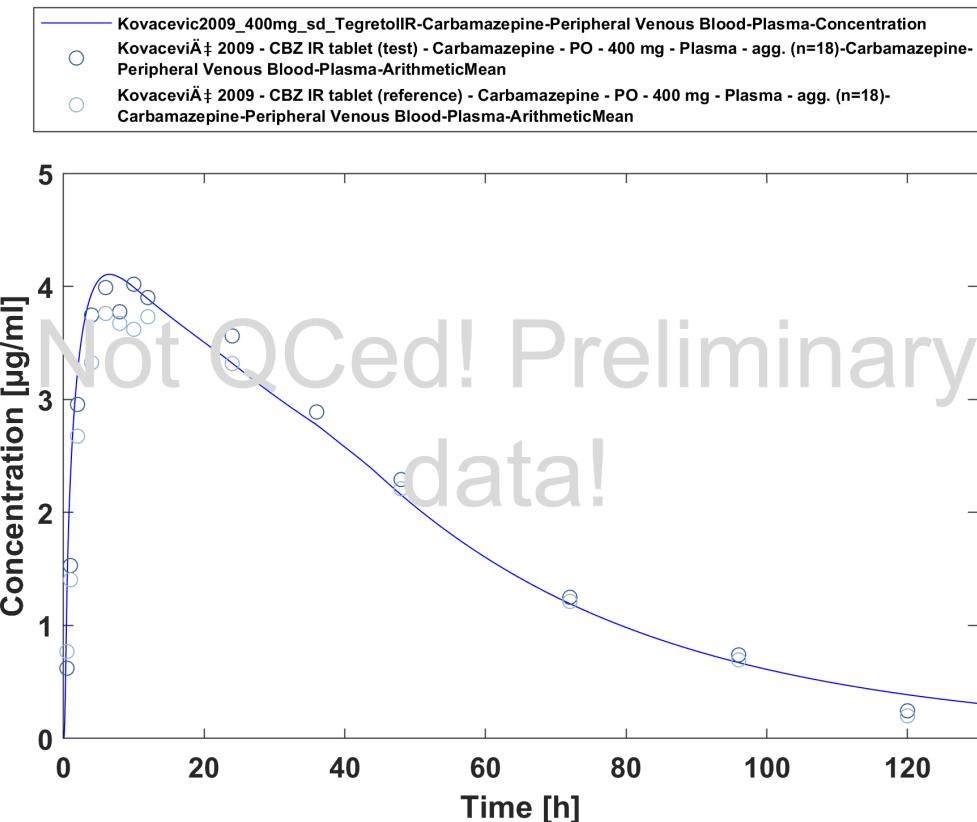


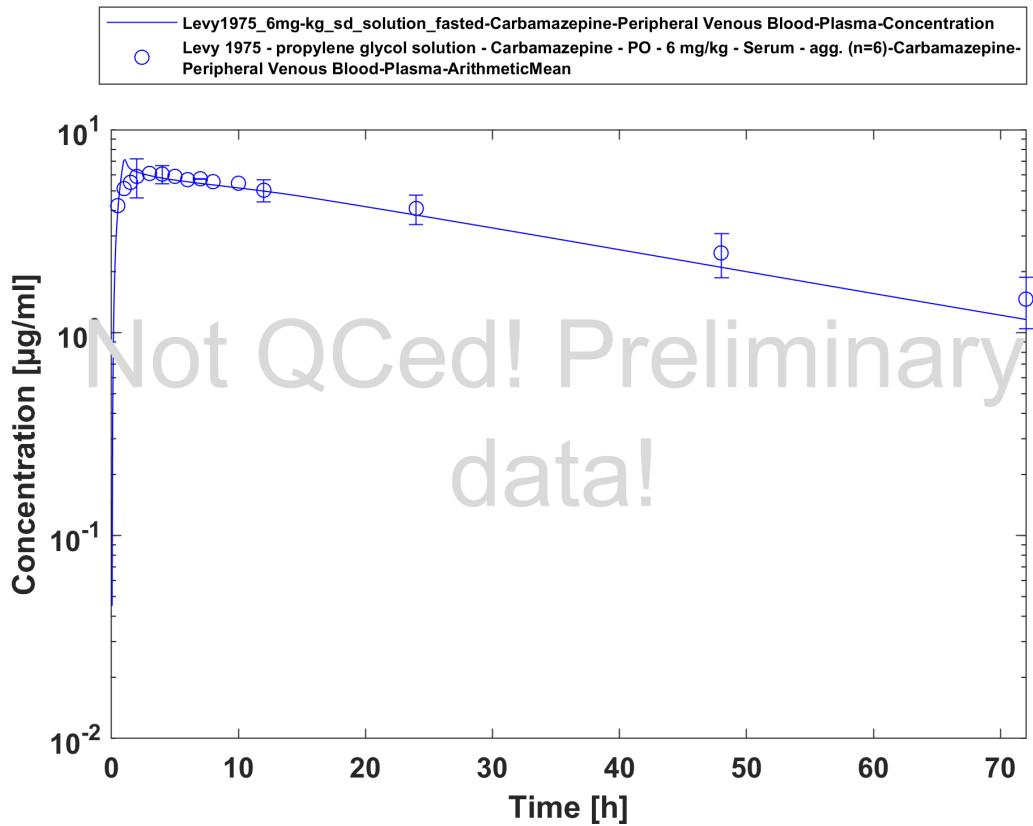


Time Profile Analysis

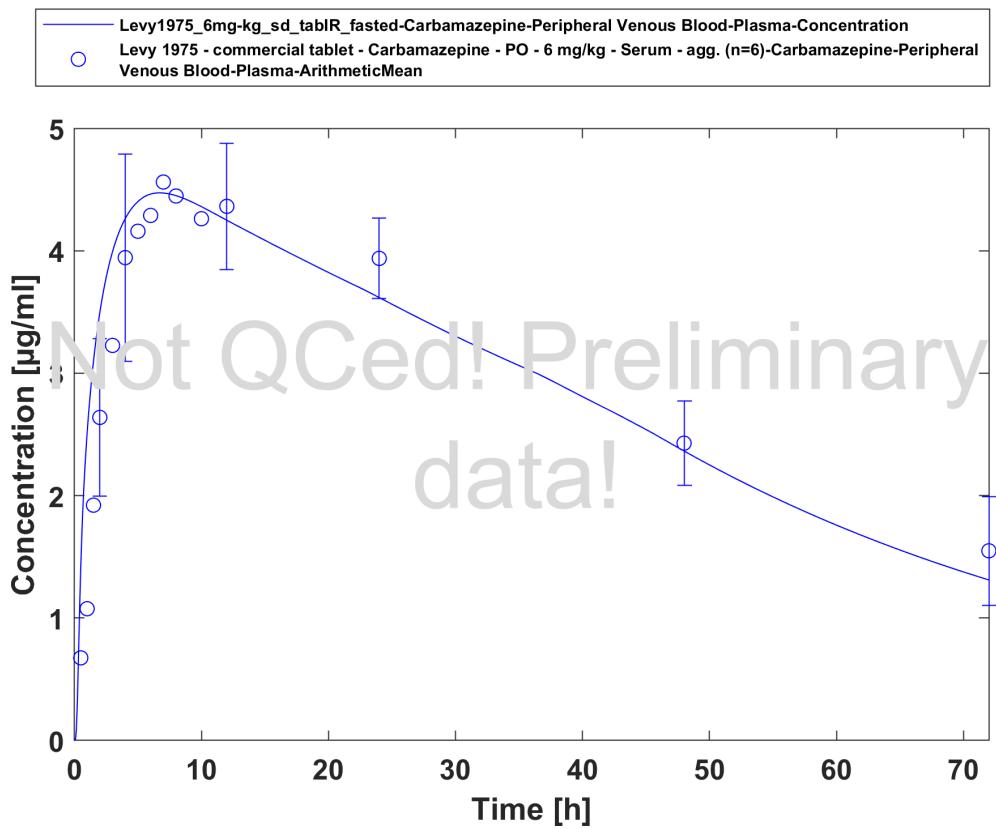


Kim2005_200mg_sd_tablR

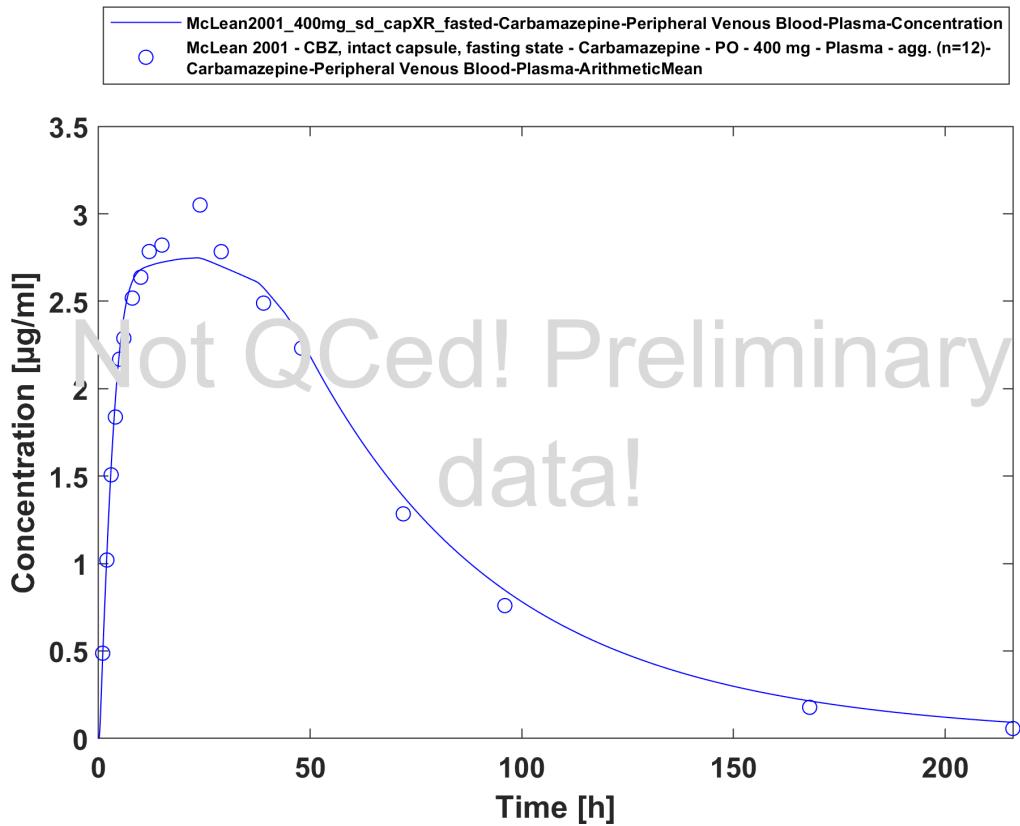




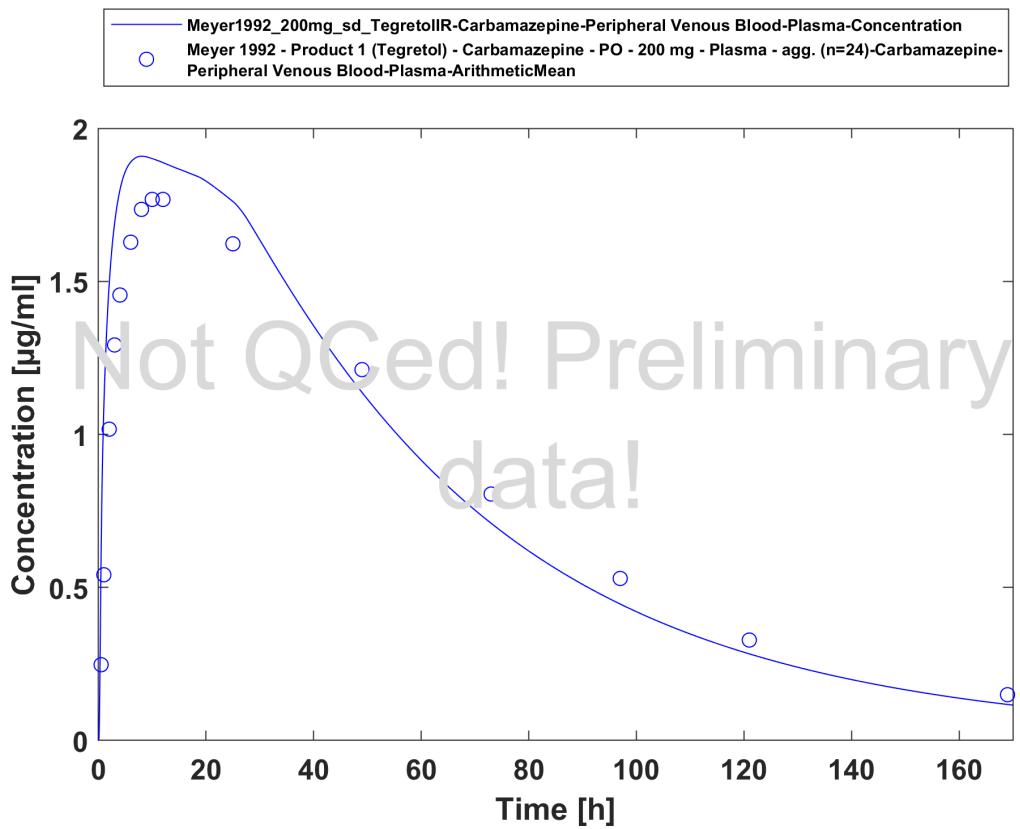
Levy1975_6mg-kg_sd_solution_fasted



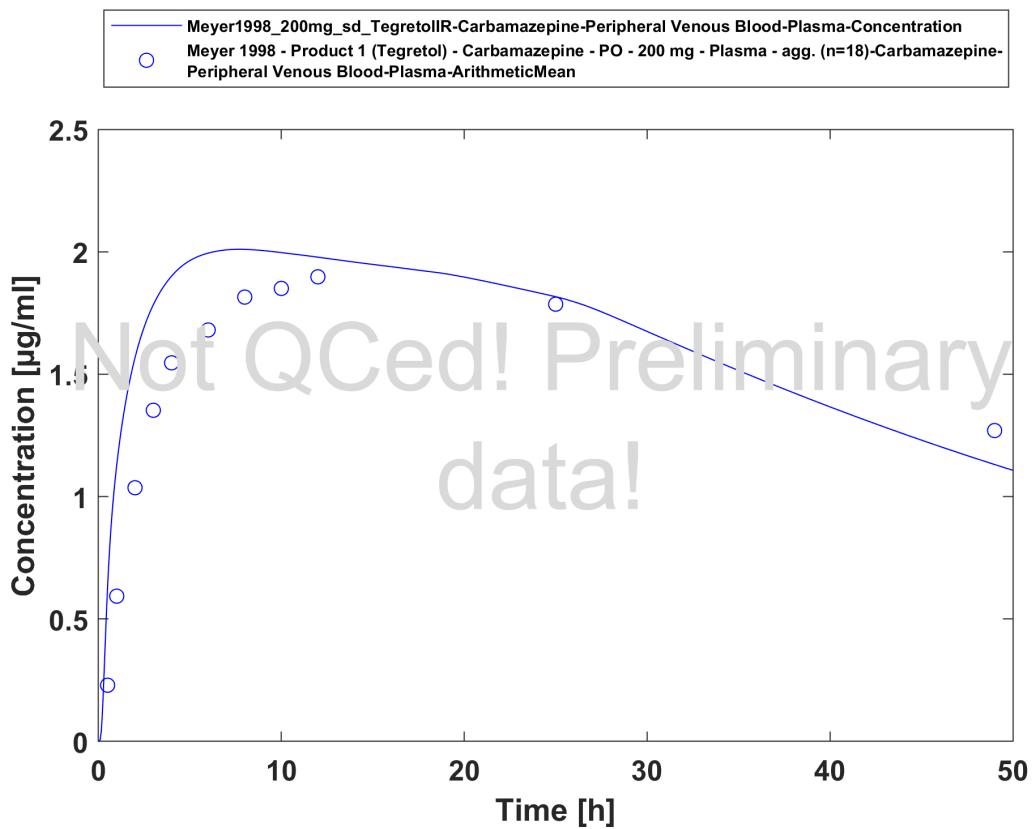
Levy1975_6mg-kg_sd_tablR_fasted



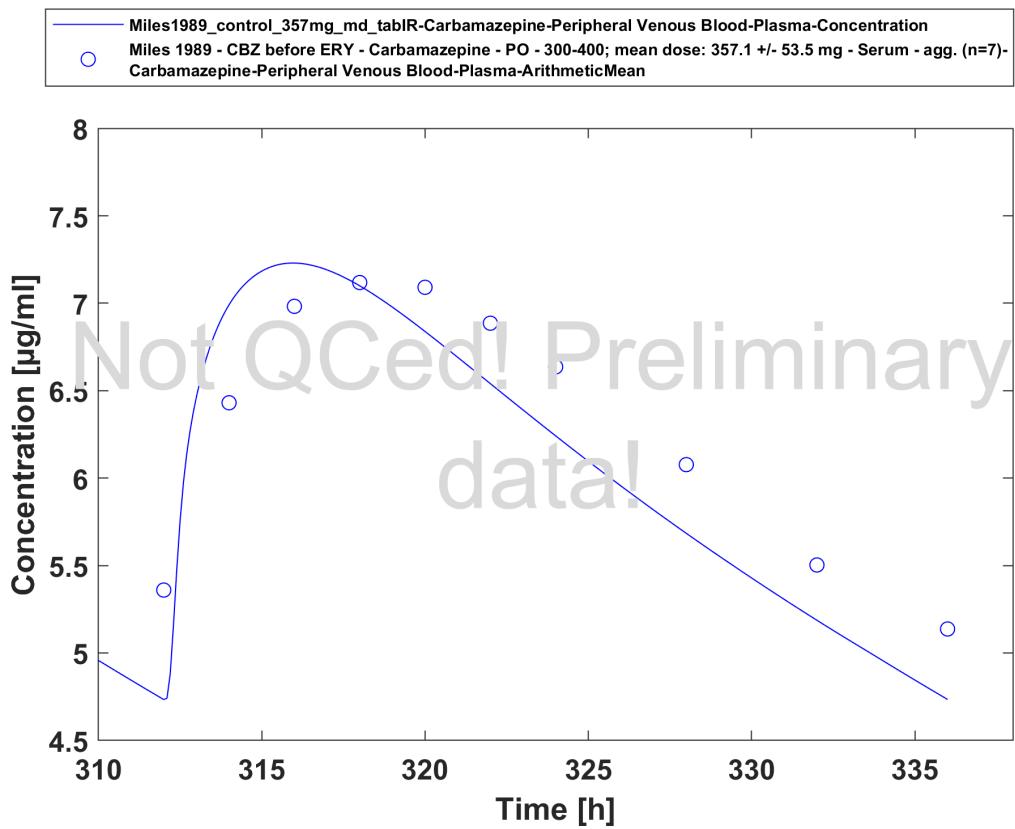
McLean2001_400mg_sd_capXR_fasted



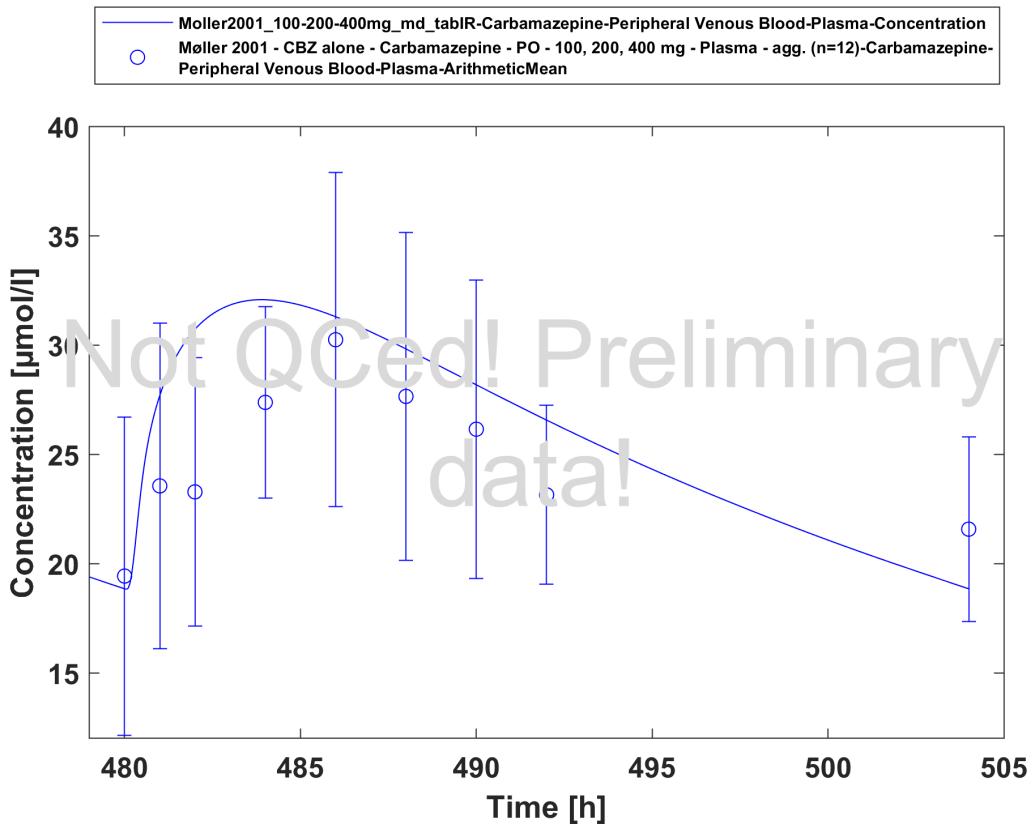
Time Profile Analysis



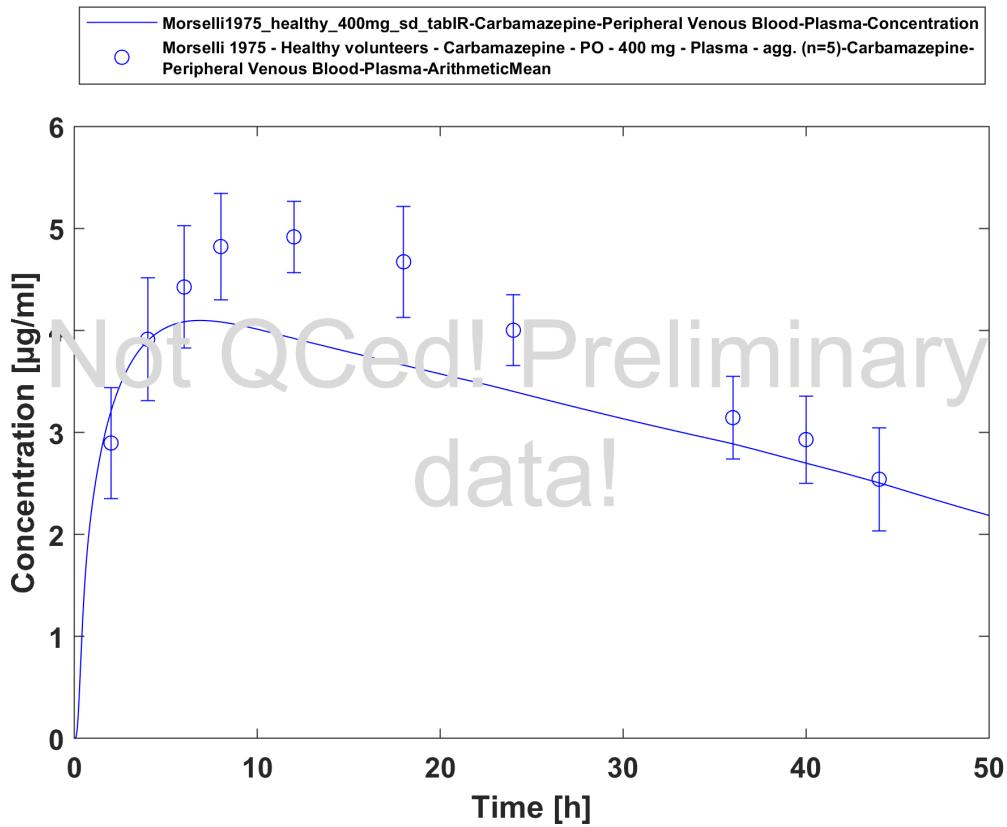
Time Profile Analysis



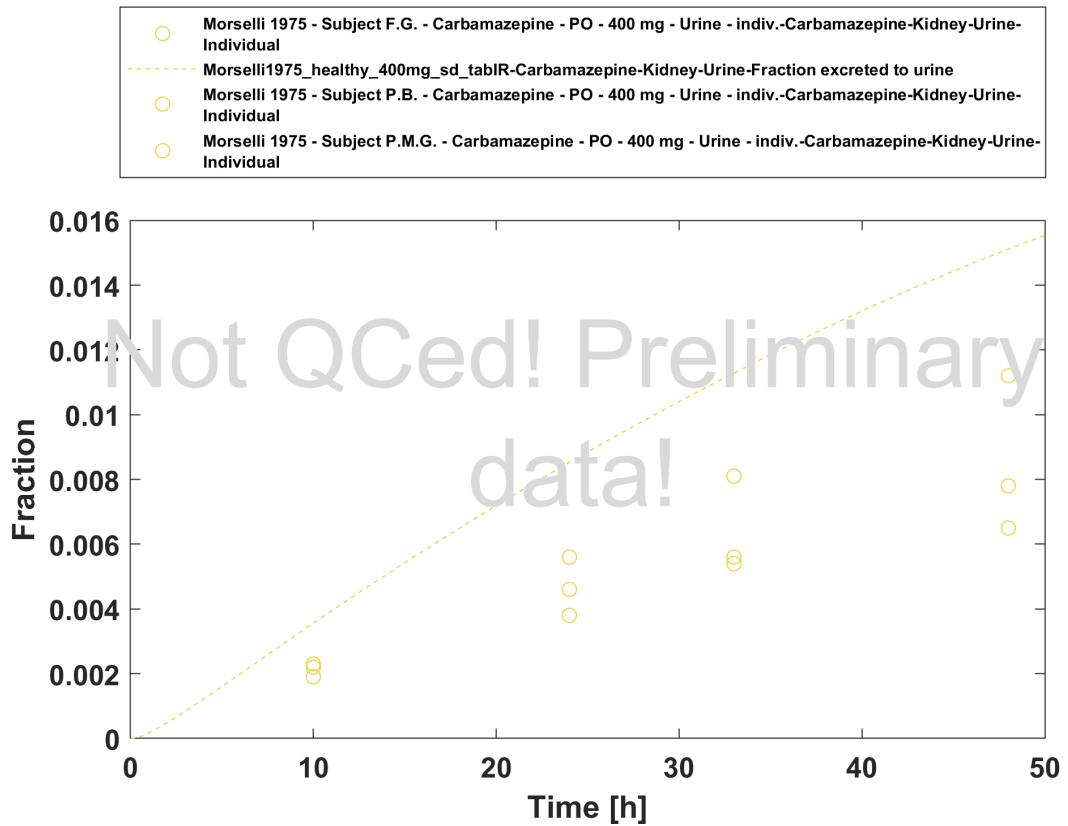
Miles1989_control_357_md_tabIR



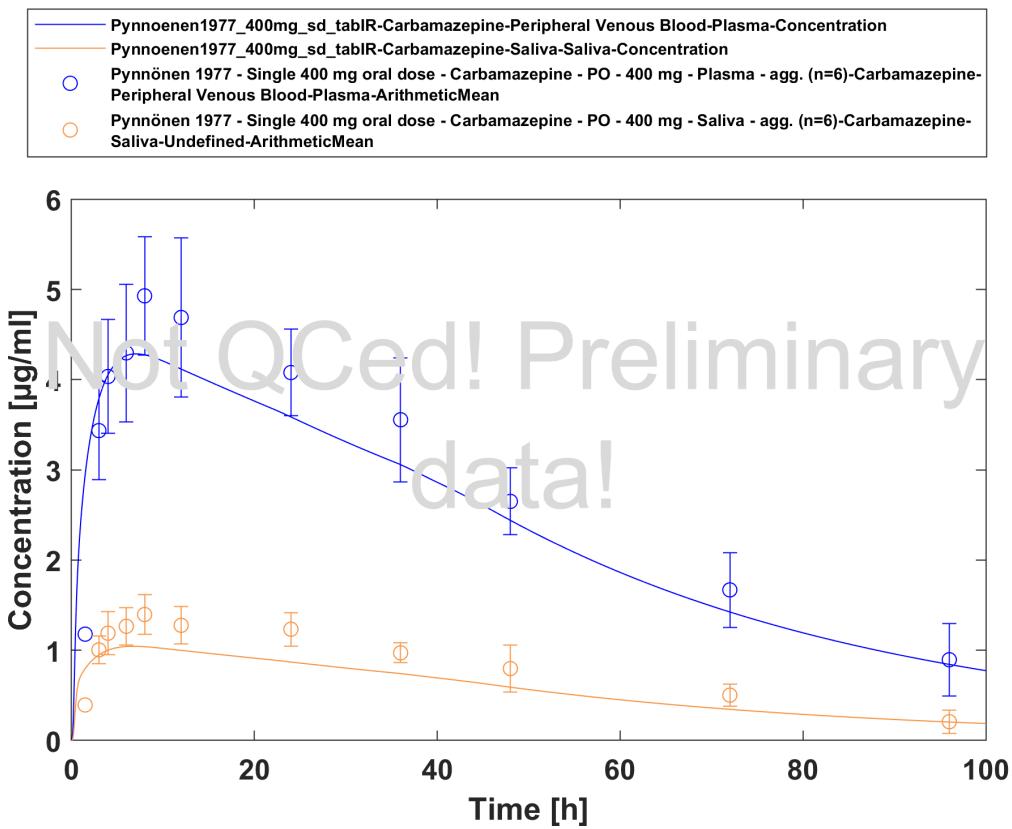
Moller2001_100-200-400mg_md_tabIR



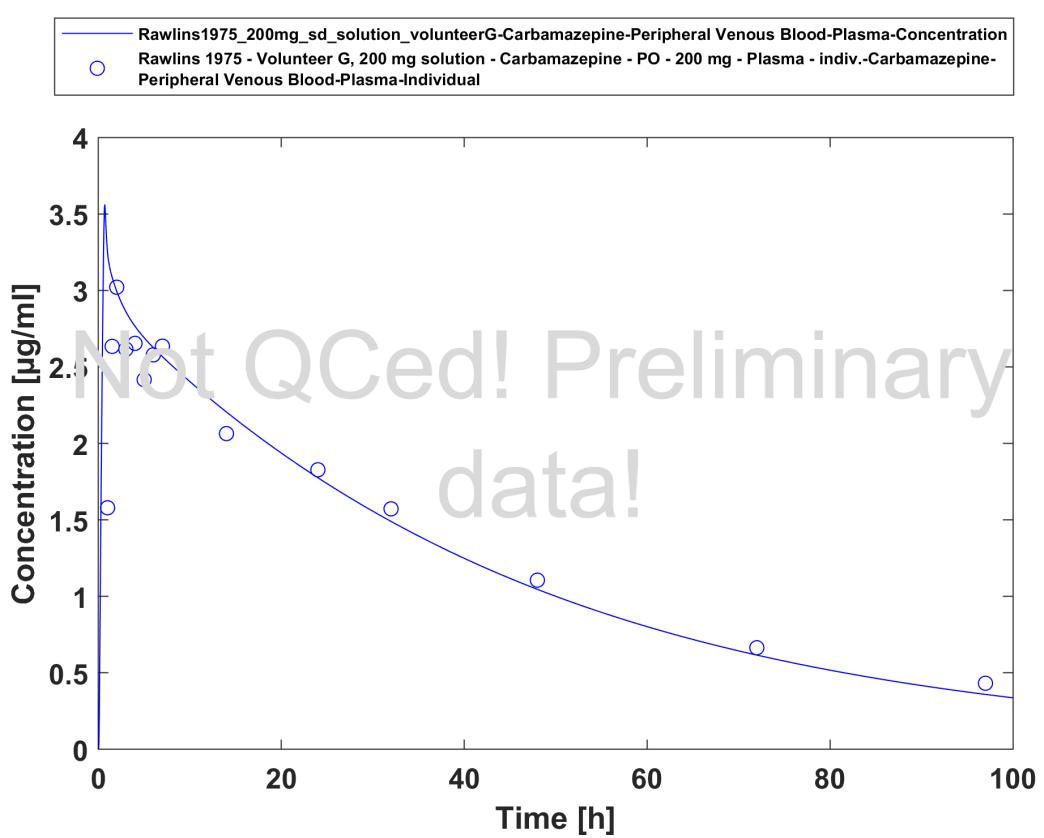
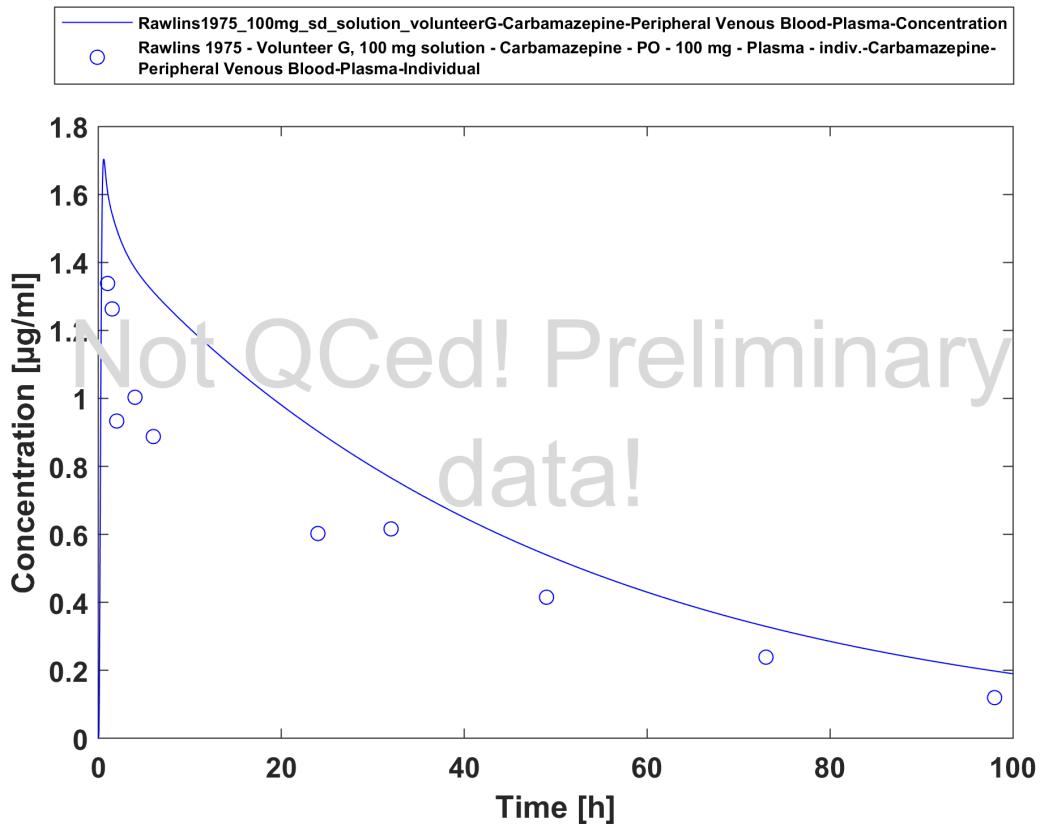
Morselli1975_healthy_400mg_sd_tabIR_plasma

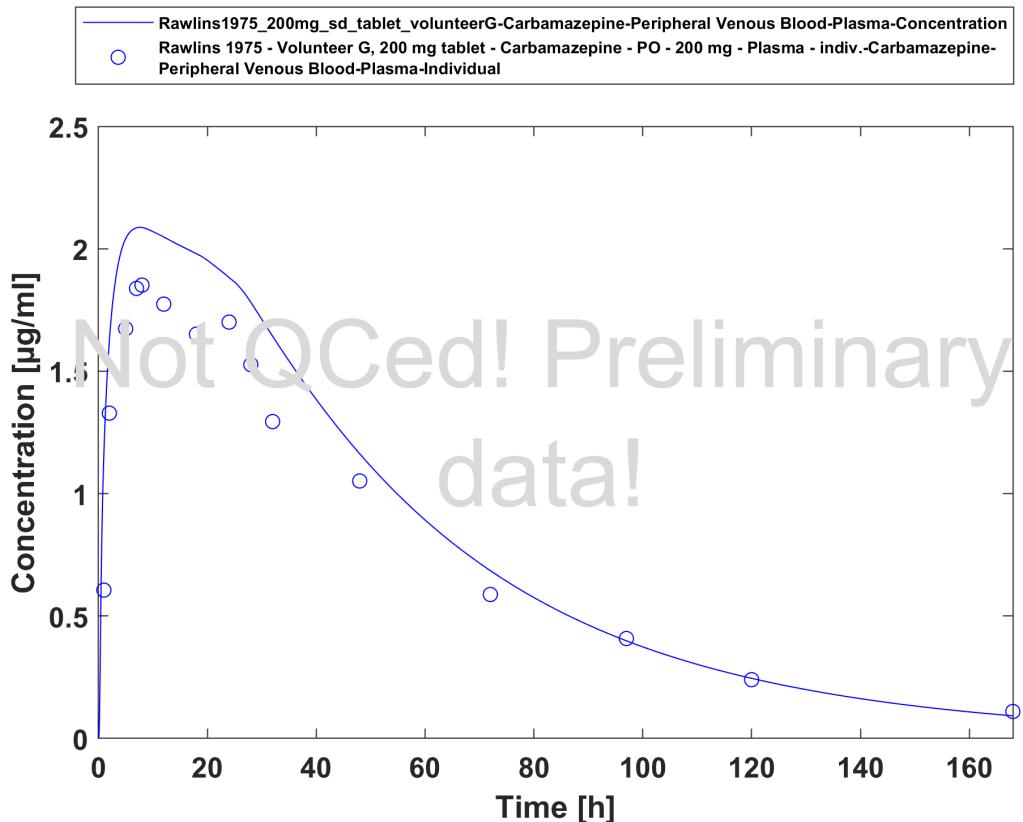


Morselli1975_healthy_400mg_sd_tabIR_urine

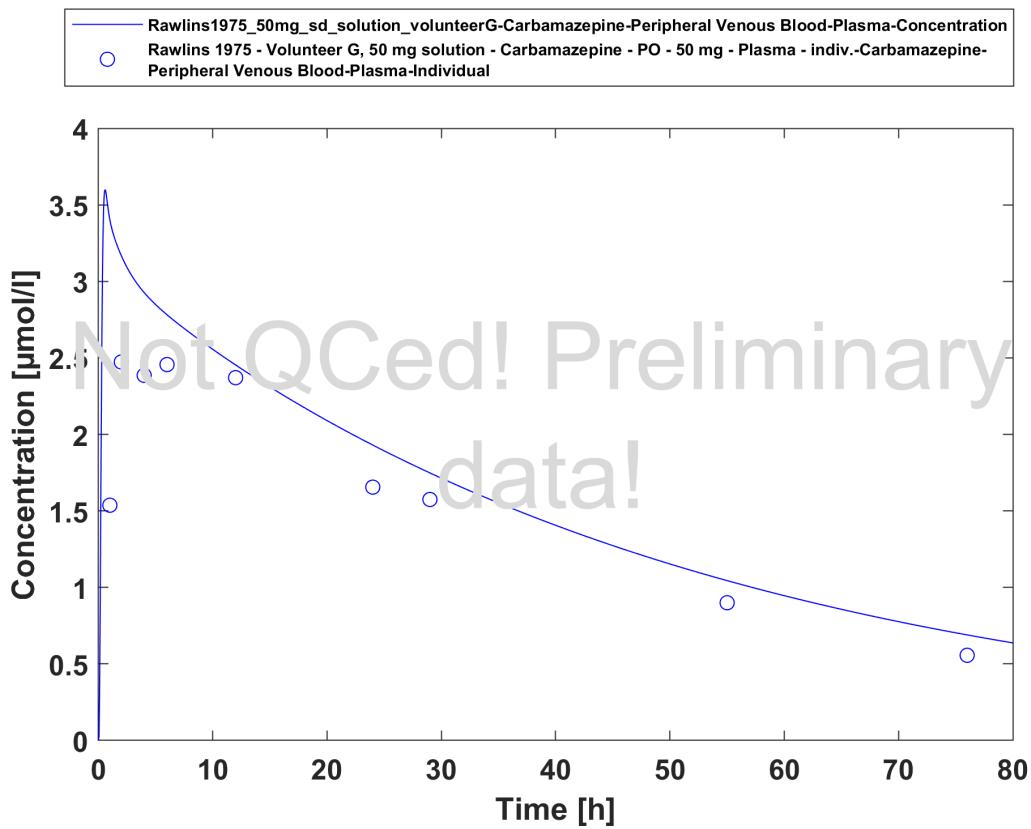


Pynnoenen1977_400mg_sd_tabIR

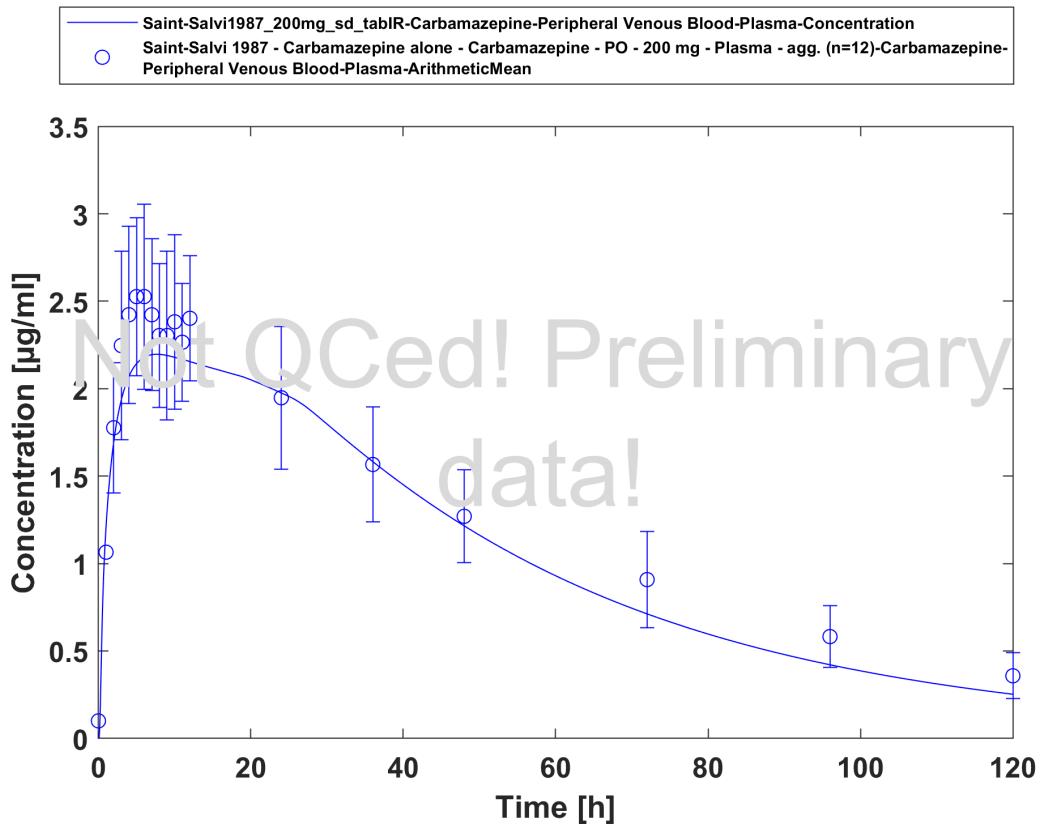




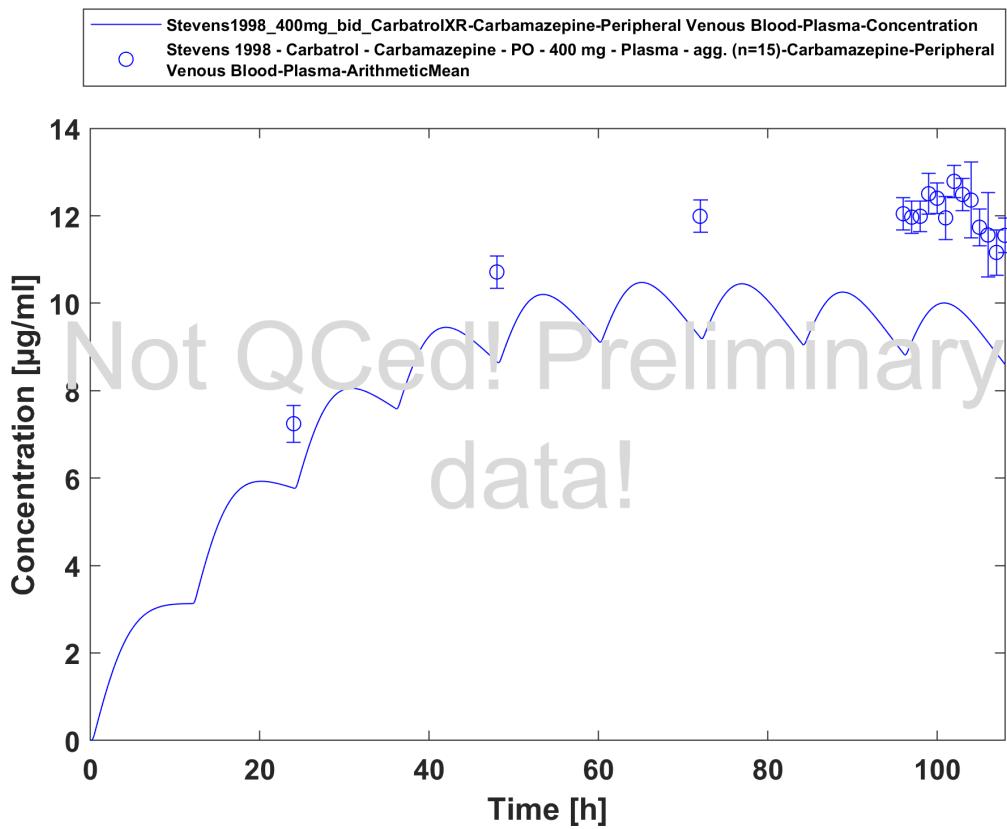
Rawlins1975_200mg_sd_sol



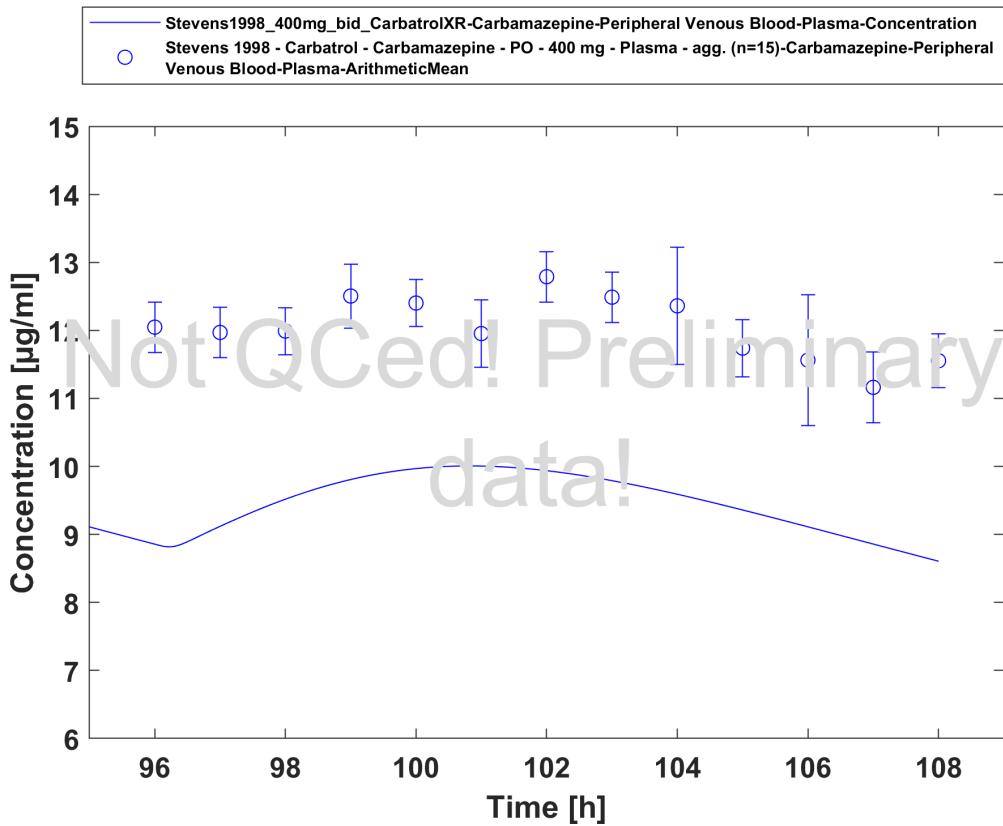
Rawlins1975_50mg_sd_sol



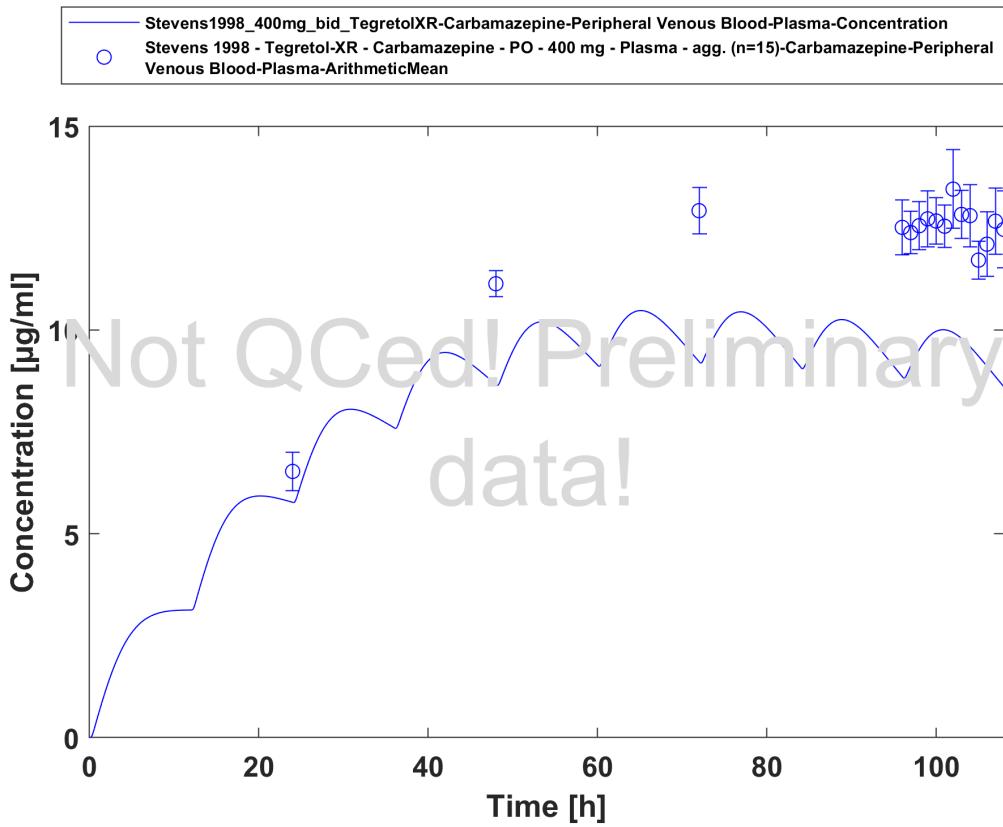
SaintSalvi1987_200mg_sd_tabIR



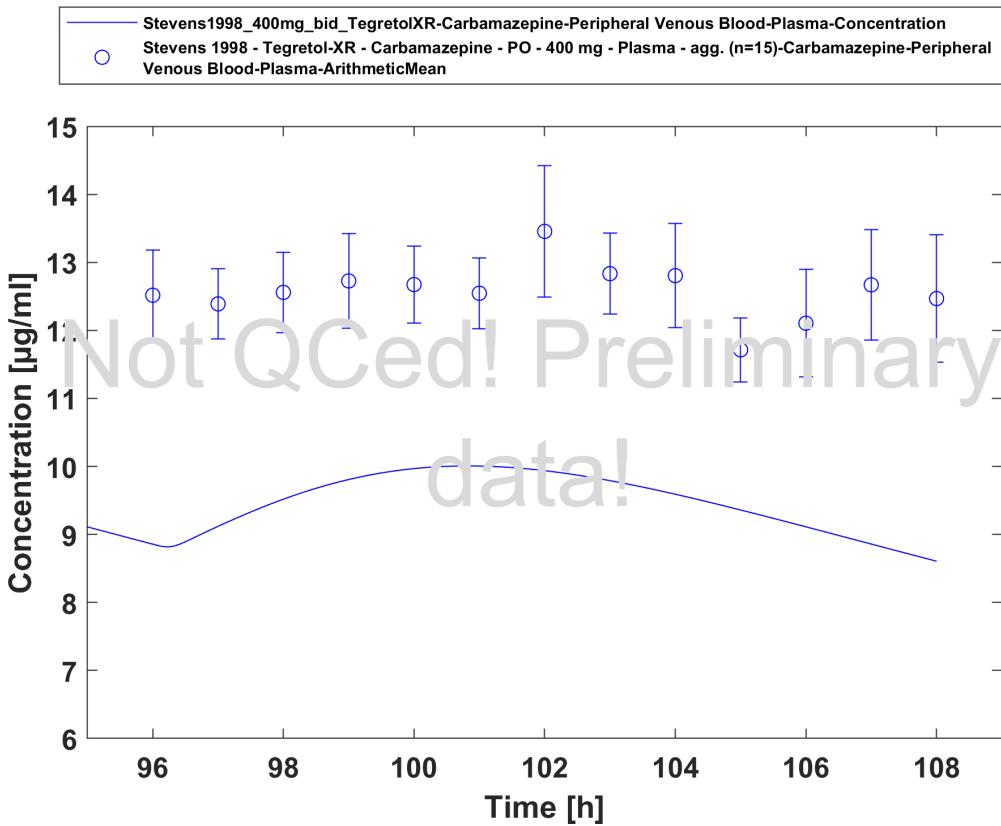
Stevens1998_400mg_bid_CarbatrolXR



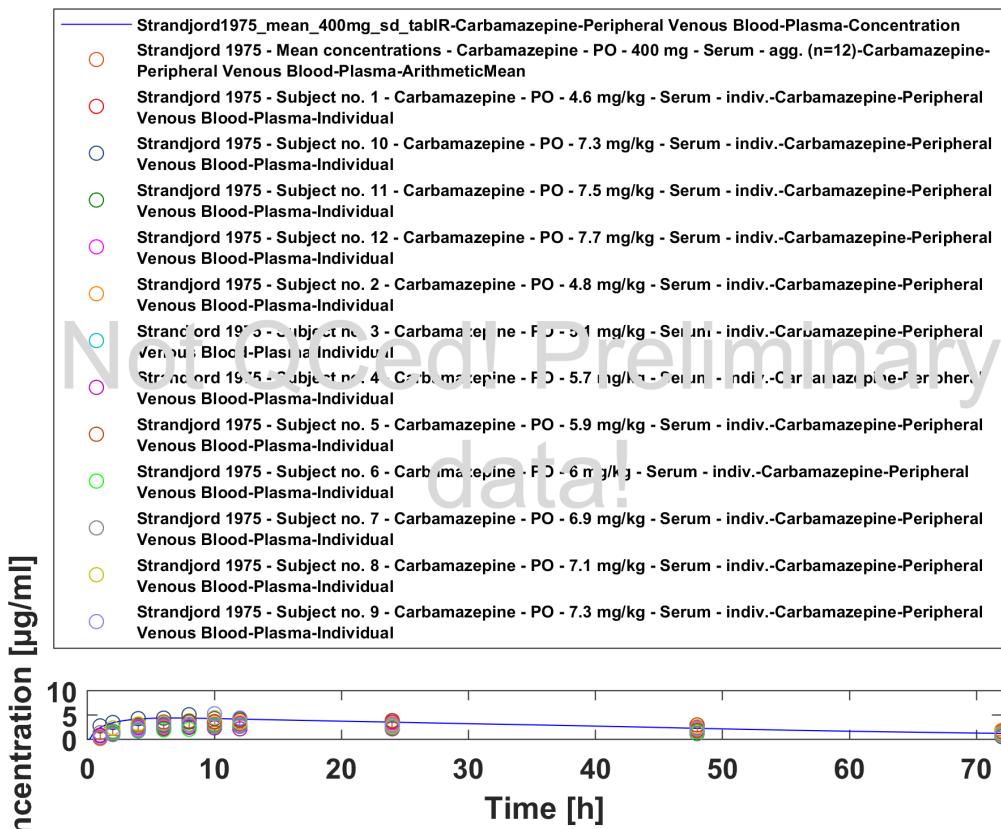
Stevens1998_400mg_bid_Carbamazepine-Peripheral Venous Blood-Plasma-Concentration 1 - last dose



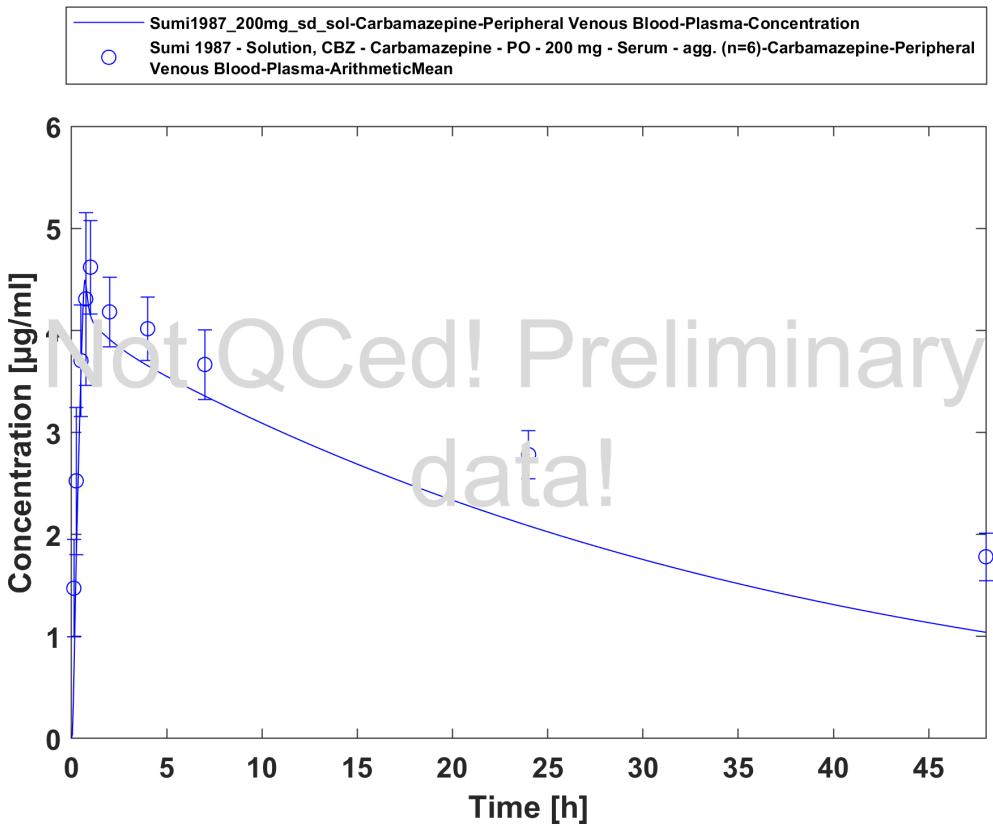
Stevens1998_400mg_bid_TegretolXR



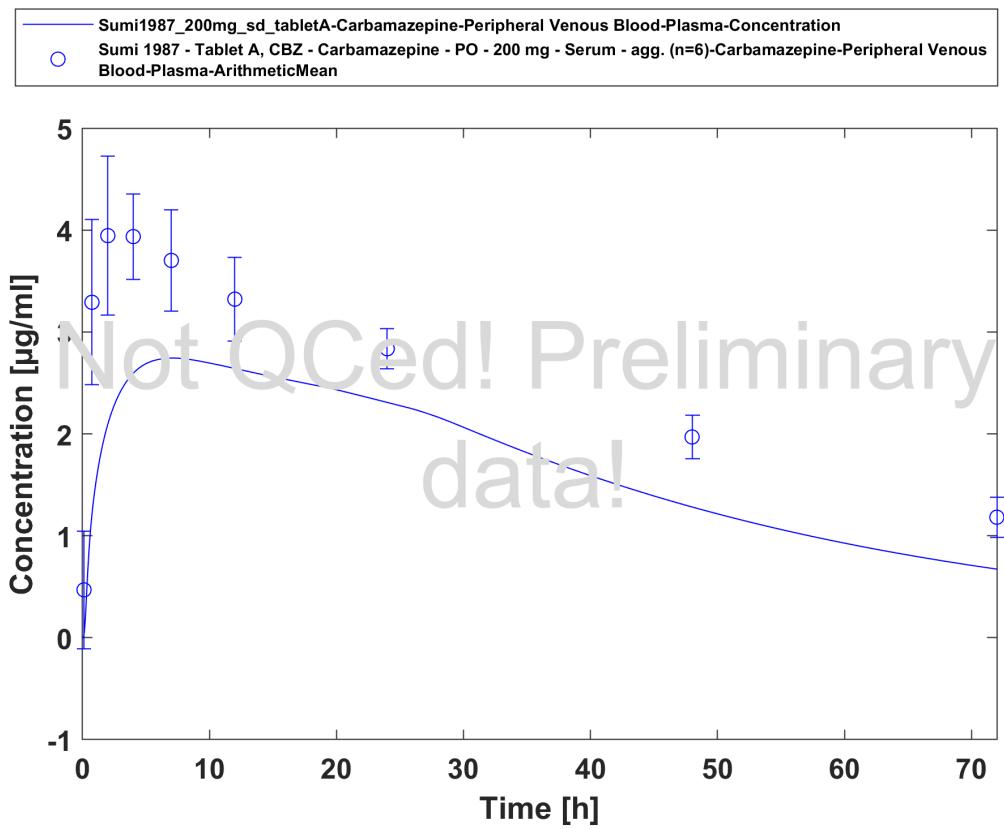
Stevens1998_400mg_bid_TegretolXR 1 - last dose



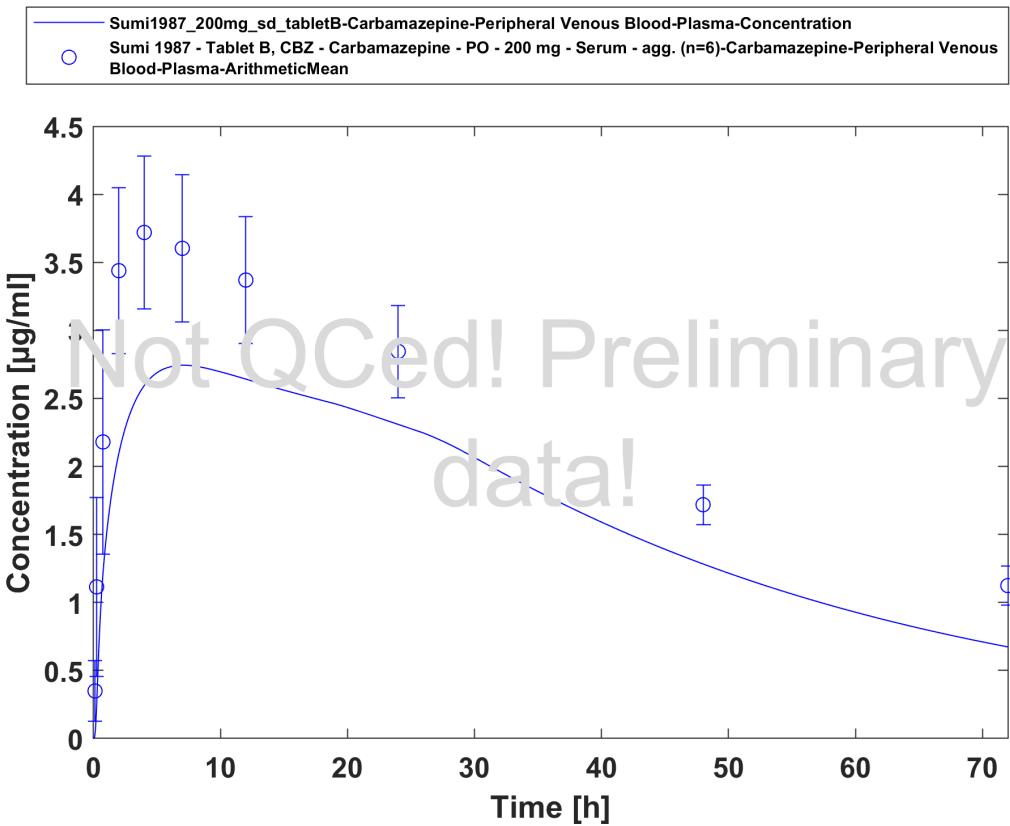
Strandjord1975_mean_400mg_sd_tablR



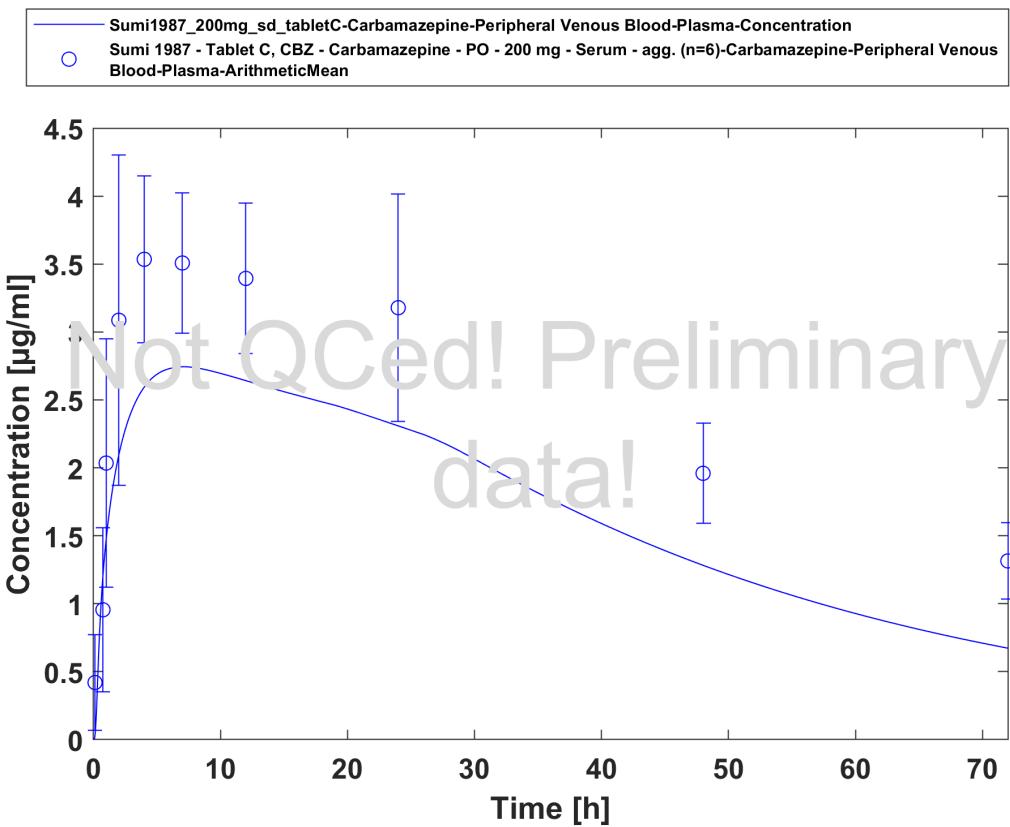
Time Profile Analysis



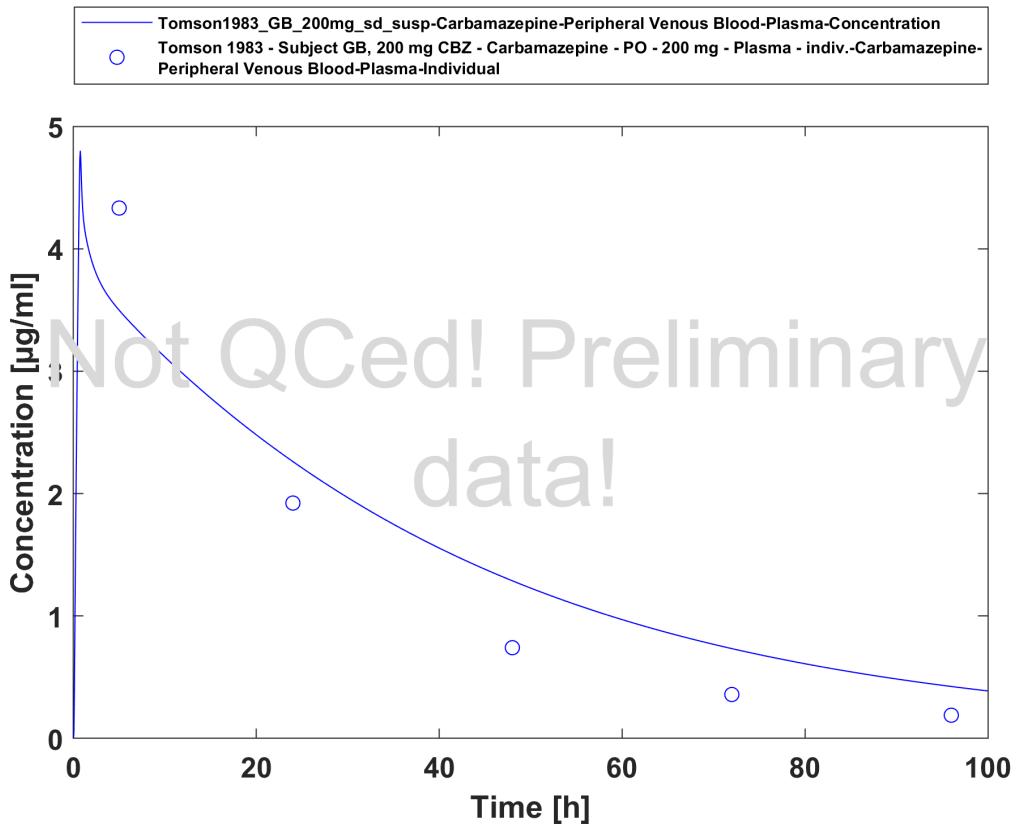
Time Profile Analysis



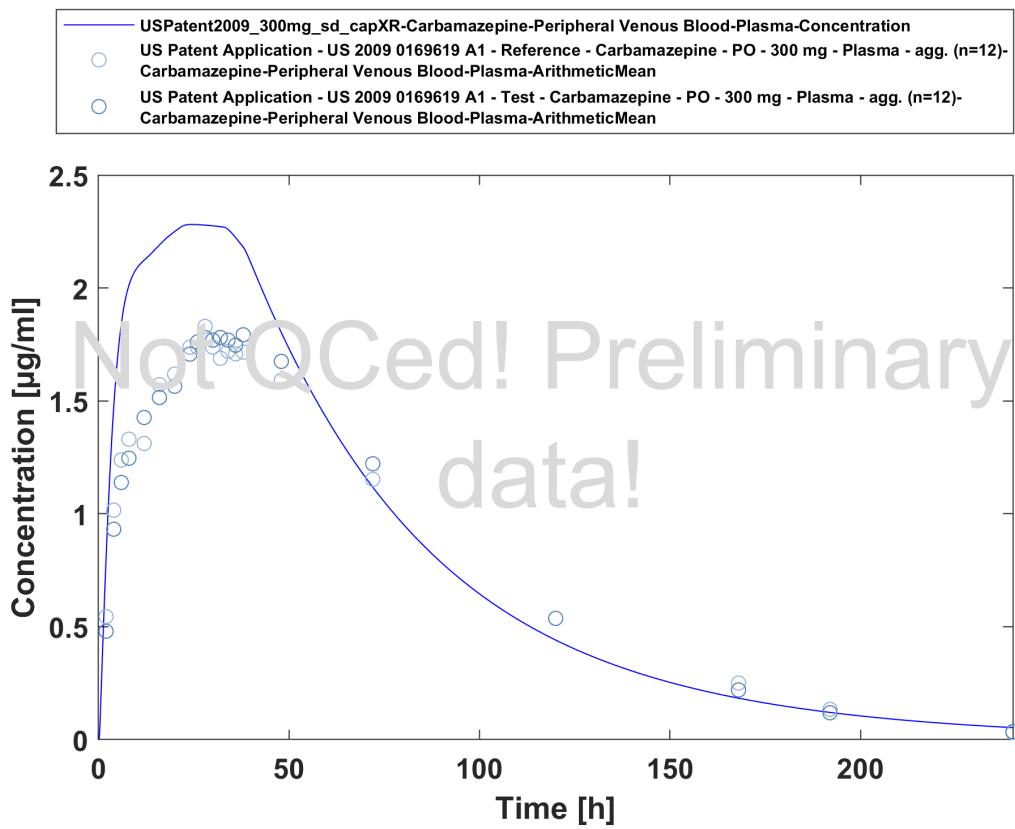
Time Profile Analysis



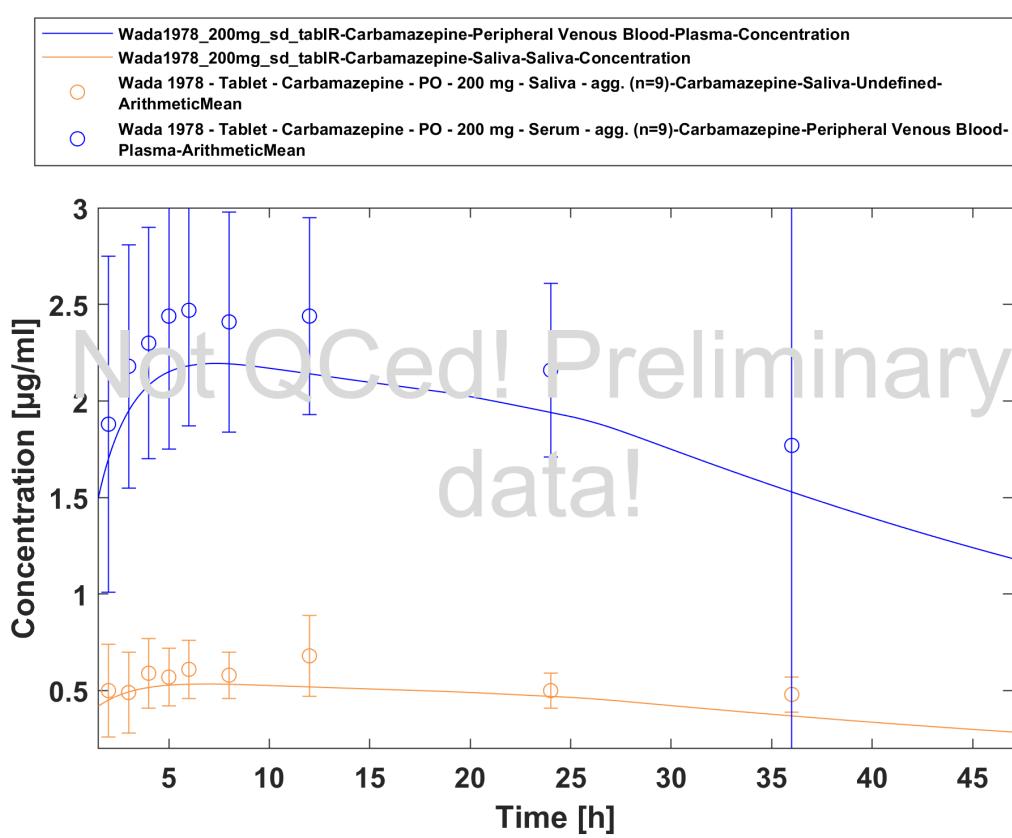
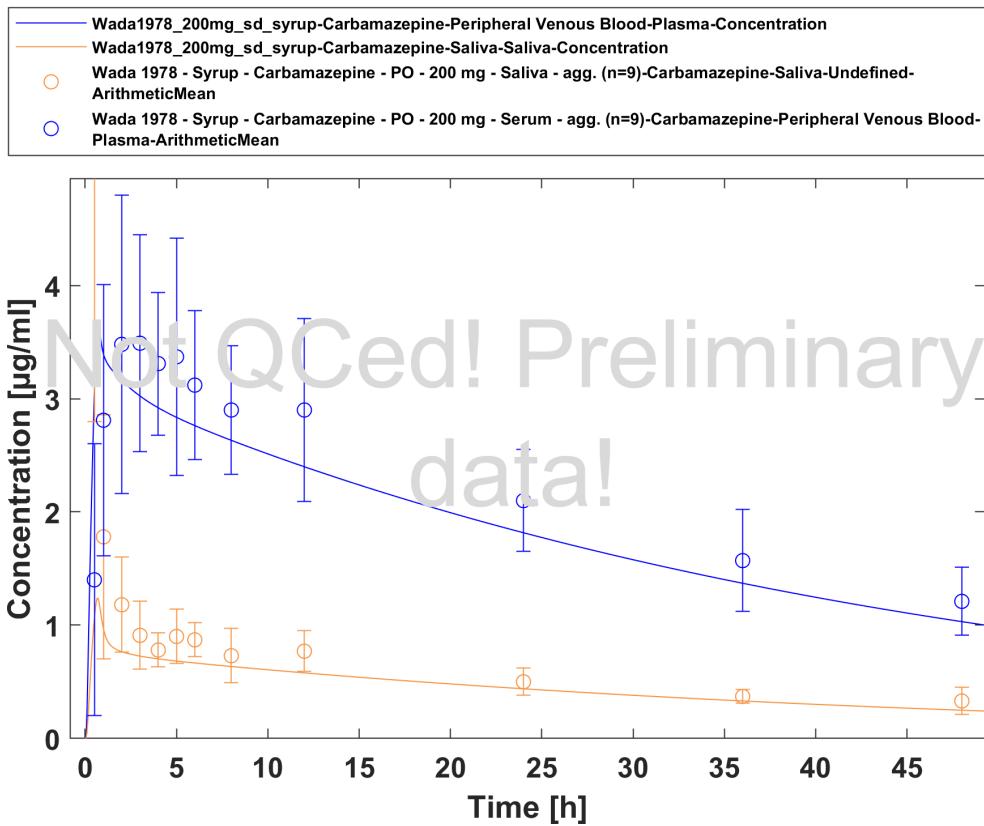
Time Profile Analysis



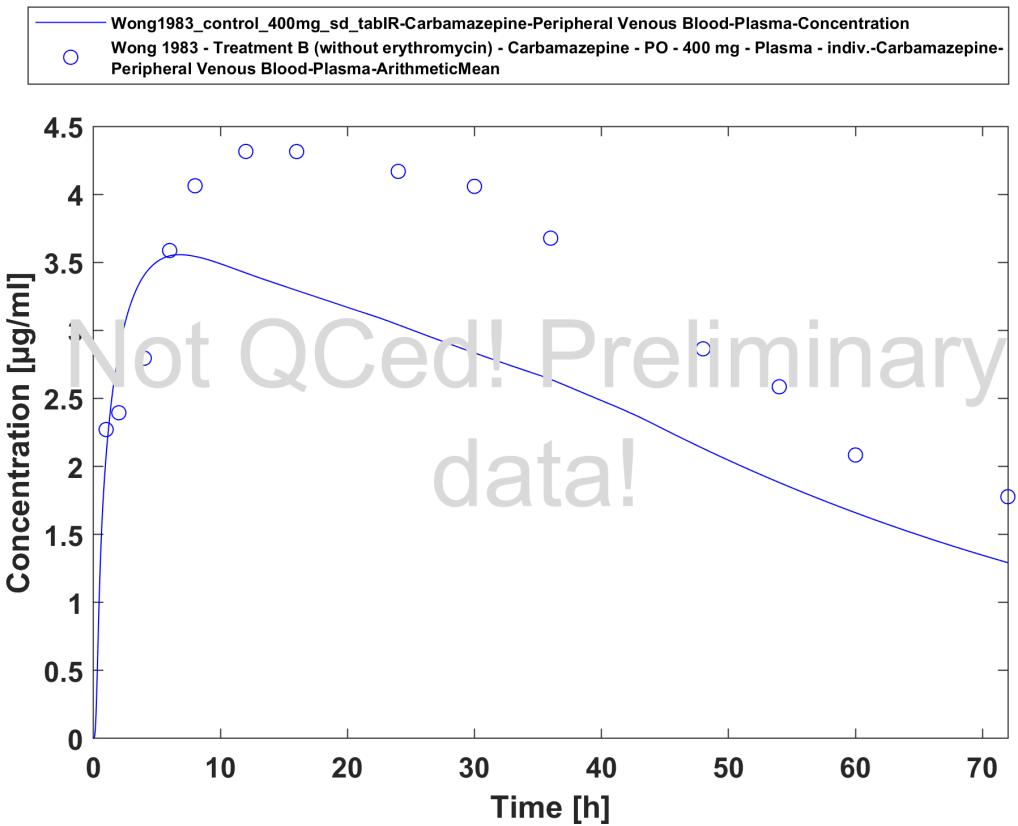
Tomson1983_GB_200mg_sd_susp



USPatent2009_300mg_sd_capXR



Wada1978_200mg_sd_tabIR



Wong1983_control_400mg_sd_tablR

4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of carbamazepine after single and multiple oral administration of various doses to healthy adults.

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

5 References

- Achour 2014** Achour, B., Russell, M. R., Barber, J., & Rostami-Hodjegan, A. (2014). Simultaneous quantification of the abundance of several cytochrome P450 and uridine 5'-diphospho-glucuronosyltransferase enzymes in human liver microsomes using multiplexed targeted proteomics. *Drug metabolism and disposition*, 42(4), 500-510.
- Almond 2016** Almond, L. M., Mukadam, S., Gardner, I., Okialda, K., Wong, S., Hatley, O., ... & Kenny, J. R. (2016). Prediction of drug-drug interactions arising from CYP3A induction using a physiologically based dynamic model. *Drug Metabolism and Disposition*, 44(6), 821-832.
- Annaert 2010** Annaert, P., Brouwers, J., Bijnens, A., Lammert, F., Tack, J., & Augustijns, P. (2010). Ex vivo permeability experiments in excised rat intestinal tissue and in vitro solubility measurements in aspirated human intestinal fluids support age-dependent oral drug absorption. *European journal of pharmaceutical sciences*, 39(1-3), 15-22.
- Austin 2002** Austin, R. P., Barton, P., Cockroft, S. L., Wenlock, M. C., & Riley, R. J. (2002). The influence of nonspecific microsomal binding on apparent intrinsic clearance, and its prediction from physicochemical properties. *Drug Metabolism and Disposition*, 30(12), 1497-1503.
- Barzaghi 1987** Barzaghi, N., Gatti, G., Crema, F., Monteleone, M., Amione, C., Leone, L., & Perucca, E. (1987). Inhibition by erythromycin of the conversion of carbamazepine to its active 10, 11-epoxide metabolite. *British journal of clinical pharmacology*, 24(6), 836-838.
- Bedada 2015** Bedada, S. K., & Nearati, P. (2015). Effect of resveratrol on the pharmacokinetics of carbamazepine in healthy human volunteers. *Phytotherapy Research*, 29(5), 701-706.
- Bedada 2016** Bedada, S. K., Appani, R., & Boga, P. K. (2017). Effect of piperine on the metabolism and pharmacokinetics of carbamazepine in healthy volunteers. *Drug research*, 67(01), 46-51.
- Bernus 1994** Bernus, I., Dickinson, R. G., Hooper, W. D., & Eadie, M. J. (1994). Early stage autoinduction of carbamazepine metabolism in humans. *European journal of clinical pharmacology*, 47(4), 355-360.
- Bianchetti 1987** Bianchetti, G., Padovani, P., Thenot, J. P., Thiercelin, J. F., & Morselli, P. L. (1987). Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia*, 28(1), 68-73.
- Burstein 2000** Burstein, A. H., Horton, R. L., Dunn, T., Alfaro, R. M., Piscitelli, S. C., & Theodore, W. (2000). Lack of effect of St John's Wort on carbamazepine pharmacokinetics in healthy volunteers. *Clinical Pharmacology & Therapeutics*, 68(6), 605-612.
- Caraco 1995** Caraco, Y., Zylber-Katz, E., Berry, E. M., & Levy, M. (1995). Carbamazepine pharmacokinetics in obese and lean subjects. *Annals of Pharmacotherapy*, 29(9), 843-847.
- Cawello 2010** Cawello, W., Nickel, B., & Eggert-Formella, A. (2010). No pharmacokinetic interaction between lacosamide and carbamazepine in healthy volunteers. *The Journal of Clinical Pharmacology*, 50(4), 459-471.
- Cazali 2003** Cazali, N., Tran, A., Treluyer, J. M., Rey, E., d'Athis, P., Vincent, J., & Pons, G. (2003). Inhibitory effect of stiripentol on carbamazepine and saquinavir metabolism in human. *British journal of clinical pharmacology*, 56(5), 526-536.
- Clarysse 2011** Clarysse, S., Brouwers, J., Tack, J., Annaert, P., & Augustijns, P. (2011). Intestinal drug solubility estimation based on simulated intestinal fluids: comparison with solubility in human intestinal fluids. *European journal of pharmaceutical sciences*, 43(4), 260-269.

Cotter 1977 Cotter, L. M., Eadie, M. J., Hooper, W. D., Lander, C. M., Smith, G. A., & Tyrer, J. H. (1977). The pharmacokinetics of carbamazepine. *European journal of clinical pharmacology*, 12(6), 451-456.

Dalton 1985a Dalton, M. J., Powell, J. R., & Messenheimer Jr, J. A. (1985). The Influence of Cimetidine on Single-Dose Carbamazepine Pharmacokinetics. *Epilepsia*, 26(2), 127-130.

Dalton 1985b Dalton, M. J., Powell, J. R., Messenheimer Jr, J. A., Nazario, M., & Mallet, L. (1985). Ranitidine Does Not Alter Single-Dose Carbamazepin Pharmacokinetics in Healthy Adults. *Drug intelligence & clinical pharmacy*, 19(12), 941-944.

Di Salle 1974 Di Salle, E., Pacifici, G. M., & Morselli, P. L. (1974). Studies on plasma protein binding of carbamazepine. *Pharmacological research communications*, 6(2), 193-202.

Drugbank DB00564. URL: <https://www.drugbank.ca/drugs/DB00564>, accessed on 12-14-2020.

Drugbank DBMET00291. URL: <https://www.drugbank.ca/metabolites/DBMET00291>, accessed on 12-16-2020.

Egnell 2003 Egnell, A. C., Houston, B., & Boyer, S. (2003). In vivo CYP3A4 heteroactivation is a possible mechanism for the drug interaction between felbamate and carbamazepine. *Journal of Pharmacology and Experimental Therapeutics*, 305(3), 1251-1262.

Eichelbaum 1985 Eichelbaum, M., Tomson, T., Tybring, G., & Bertilsson, L. (1985). Carbamazepine metabolism in man. *Clinical pharmacokinetics*, 10(1), 80-90.

Elqidra 2004 Elqidra, R., Ünlü, N., Capan, Y., Sahin, G., Dalkara, T., & Hincal, A. A. (2004). Effect of polymorphism on in vitro-in vivo properties of carbamazepine conventional tablets. *Journal of Drug Delivery Science and Technology*, 14(2), 147-153.

European Patent Application EP 1044681 A2 European Patent Application 2000, EP 1044681 A2, Application no. 00650026.8. URL: <https://patentimages.storage.googleapis.com/0c/45/b7/d2be4fa9d24371/EP1044681A2.pdf>, accessed on 12-01-2022.

Faucette 2004 Faucette, S. R., Wang, H., Hamilton, G. A., Jolley, S. L., Gilbert, D., Lindley, C., ... & LeCluyse, E. L. (2004). Regulation of CYP2B6 in primary human hepatocytes by prototypical inducers. *Drug Metabolism and Disposition*, 32(3), 348-358.

Faucette 2007 Faucette, S. R., Zhang, T. C., Moore, R., Sueyoshi, T., Omiecinski, C. J., LeCluyse, E. L., ... & Wang, H. (2007). Relative activation of human pregnane X receptor versus constitutive androstane receptor defines distinct classes of CYP2B6 and CYP3A4 inducers. *Journal of Pharmacology and Experimental Therapeutics*, 320(1), 72-80.

Fenet 2012 Fenet, H., Mathieu, O., Mahjoub, O., Li, Z., Hillaire-Buys, D., Casellas, C., & Gomez, E. (2012). Carbamazepine, carbamazepine epoxide and dihydroxycarbamazepine sorption to soil and occurrence in a wastewater reuse site in Tunisia. *Chemosphere*, 88(1), 49-54.

Fuhr 2021 Fuhr, L. M., Marok, F. Z., Hanke, N., Selzer, D., & Lehr, T. (2021). Pharmacokinetics of the CYP3A4 and CYP2B6 Inducer Carbamazepine and Its Drug–Drug Interaction Potential: A Physiologically Based Pharmacokinetic Modeling Approach. *Pharmaceutics*, 13(2), 270.

Gérardin 1976 Gérardin, A. P., Abadie, F. V., Campestrini, J. A., & Theobald, W. (1976). Pharmacokinetics of carbamazepine in normal humans after single and repeated oral doses. *Journal of pharmacokinetics and biopharmaceutics*, 4(6), 521-535.

Gérardin 1990 Gérardin, A., Dubois, J. P., Moppert, J., & Geller, L. (1990). Absolute bioavailability of carbamazepine after oral administration of a 2% syrup. *Epilepsia*, 31(3), 334-338.

Hooper 1975 Hooper, W. D., Dubetz, D. K., Bochner, F., Cotter, L. M., Smith, G. A., Eadie, M. J., & Tyrer, J. H. (1975). Plasma protein binding of carbamazepine. *Clinical Pharmacology & Therapeutics*, 17(4), 433-440.

Huang 2004 Huang, W., Lin, Y. S., McConn, D. J., Calamia, J. C., Totah, R. A., Isoherranen, N., ... & Thummel, K. E. (2004). Evidence of significant contribution from CYP3A5 to hepatic drug metabolism. *Drug metabolism and disposition*, 32(12), 1434-1445.

Ji 2008 Ji, P., Damle, B., Xie, J., Unger, S. E., Grasela, D. M., & Kaul, S. (2008). Pharmacokinetic interaction between efavirenz and carbamazepine after multiple-dose administration in healthy subjects. *The Journal of Clinical Pharmacology*, 48(8), 948-956.

Kayali 1994 Kayali, A., Tuglular, I., & Ertas, M. (1994). Pharmacokinetics of carbamazepine Part I: a new bioequivalency parameter based on a relative bioavailability trial. *European journal of drug metabolism and pharmacokinetics*, 19(4), 319-325.

Kerr 1994 Kerr, B. M., Thummel, K. E., Wurden, C. J., Klein, S. M., Kroetz, D. L., Gonzalez, F. J., & Levy, R. (1994). Human liver carbamazepine metabolism: role of CYP3A4 and CYP2C8 in 10, 11-epoxide formation. *Biochemical pharmacology*, 47(11), 1969-1979.

Kim 2005 Kim, K. A., Oh, S. O., Park, P. W., & Park, J. Y. (2005). Effect of probenecid on the pharmacokinetics of carbamazepine in healthy subjects. *European journal of clinical pharmacology*, 61(4), 275-280.

Kovacević 2009 Kovacević, I., Parojcic, J., Homsek, I., Tubic-Grozdanis, M., & Langguth, P. (2009). Justification of biowaiver for carbamazepine, a low soluble high permeable compound, in solid dosage forms based on IVIVC and gastrointestinal simulation. *Molecular pharmaceutics*, 6(1), 40-47.

Kuepfer 2016 Kuepfer, L., Niederalt, C., Wendl, T., Schlender, J. F., Willmann, S., Lippert, J., ... & Teutonico, D. (2016). Applied concepts in PBPK modeling: how to build a PBPK/PD model. *CPT: pharmacometrics & systems pharmacology*, 5(10), 516-531.

Lertratanangkoon 1982 Lertratanangkoon, K., & Horning, M. G. (1982). Metabolism of carbamazepine. *Drug Metabolism and Disposition*, 10(1), 1-10.

Lennernäs 2007 Lennernäs, H. (2007). Intestinal permeability and its relevance for absorption and elimination. *Xenobiotica*, 37(10-11), 1015-1051.

Levy 1975 Levy, R. H., Pitlick, W. H., Troupin, A. S., Green, J. R., & Neal, J. M. (1975). Pharmacokinetics of carbamazepine in normal man. *Clinical Pharmacology & Therapeutics*, 17(6), 657-668.

McLean 2001 McLean, A., Browne, S., Zhang, Y., Slaughter, E., Halstenson, C., & Couch, R. (2001). The influence of food on the bioavailability of a twice-daily controlled release carbamazepine formulation. *The Journal of Clinical Pharmacology*, 41(2), 183-186.

Meyer 1992 Meyer, M. C., Straughn, A. B., Jarvi, E. J., Wood, G. C., Pelsor, F. R., & Shah, V. P. (1992). The bioinequivalence of carbamazepine tablets with a history of clinical failures. *Pharmaceutical Research*, 9(12), 1612-1616.

Meyer 1998 Meyer, M. C., Straughn, A. B., Mhatre, R. M., Shah, V. P., Williams, R. L., & Lesko, L. J. (1998). The relative bioavailability and in vivo-in vitro correlations for four marketed carbamazepine tablets. *Pharmaceutical research*, 15(11), 1787-1791.

Meyer 2012 Meyer, M., Schneckener, S., Ludewig, B., Kuepfer, L., & Lippert, J. (2012). Using expression data for quantification of active processes in physiologically based pharmacokinetic modeling. *Drug Metabolism and Disposition*, 40(5), 892-901.

- Miles 1989** Miles, M. V., & Tennison, M. B. (1989). Erythromycin effects on multiple-dose carbamazepine kinetics. *Therapeutic drug monitoring*, 11(1), 47-52.
- Møller 2001** Møller, S. E., Larsen, F., Khan, A. Z., & Rolan, P. E. (2001). Lack of effect of citalopram on the steady-state pharmacokinetics of carbamazepine in healthy male subjects. *Journal of clinical psychopharmacology*, 21(5), 493-499.
- Morselli 1975** Morselli, P. L., Gerna, M., De Maio, D., Zanda, G., Viani, F., & Garattini, S. (1975). Pharmacokinetic studies on carbamazepine in volunteers and in epileptic patients. In: *Clinical pharmacology of anti-epileptic drugs* (pp. 166-180). Springer, Berlin, Heidelberg.
- Nishimura 2003** Nishimura, M., Yaguti, H., Yoshitsugu, H., Naito, S., & Satoh, T. (2003). Tissue Distribution of mRNA Expression of Human Cytochrome P450 Isoforms Assessed by High-Sensitivity Real-Time Reverse Transcription PCR. *Yakugaku zasshi*, 123(5), 369-375.
- Pearce 2002** Pearce, R. E., Vakkalagadda, G. R., & Leeder, J. S. (2002). Pathways of carbamazepine bioactivation in vitro I. Characterization of human cytochromes P450 responsible for the formation of 2- and 3-hydroxylated metabolites. *Drug metabolism and disposition*, 30(11), 1170-1179.
- Pelkonen 2001** Pelkonen, O., Myllynen, P., Taavitsainen, P., Boobis, A. R., Watts, P., Lake, B. G., ... & Lewis, D. F. V. (2001). Carbamazepine: a 'blind' assessment of CYP-associated metabolism and interactions in human liver-derived in vitro systems. *Xenobiotica*, 31(6), 321-343.
- PK-Sim Ontogeny Database Version 7.3** URL: <https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/38cf71b384fcf25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf>, accessed on 12-01-2022.
- Pynnonen 1977** Pynnonen, S. (1977). The pharmacokinetics of carbamazepine in plasma and saliva of man. *Acta pharmacologica et toxicologica*, 41(5), 465-471.
- Rawlins 1975** Rawlins, M. D., Collste, P., Bertilsson, L., & Palmer, L. (1975). Distribution and elimination kinetics of carbamazepine in man. *European journal of clinical pharmacology*, 8(2), 91-96.
- Rodrigues 1999** Rodrigues, A. D. (1999). Integrated cytochrome P450 reaction phenotyping: attempting to bridge the gap between cDNA-expressed cytochromes P450 and native human liver microsomes. *Biochemical pharmacology*, 57(5), 465-480.
- Saint-Salvi 1987** Saint-Salvi, B., Tremblay, D., Surjus, A., & Lefebvre, M. A. (1987). A Study of the Interaction of Roxithromycin with Theophylline and Carbarmazepine. *Journal of Antimicrobial Chemotherapy*, 20(suppl_B), 121-129.
- Sakamoto 2013** Sakamoto, M., Itoh, T., & Fujiwara, R. (2013). Prediction of in vivo carbamazepine 10, 11-epoxidation from in vitro metabolic studies with human liver microsomes: importance of its sigmoidal kinetics. *Biological and Pharmaceutical Bulletin*, 36(12), 1959-1963.
- Söderlind 2010** Söderlind, E., Karlsson, E., Carlsson, A., Kong, R., Lenz, A., Lindborg, S., & Sheng, J. J. (2010). Simulating fasted human intestinal fluids: understanding the roles of lecithin and bile acids. *Molecular pharmaceutics*, 7(5), 1498-1507.
- Staines 2004** Staines, A. G., Coughtrie, M. W., & Burchell, B. (2004). N-glucuronidation of carbamazepine in human tissues is mediated by UGT2B7. *Journal of Pharmacology and Experimental Therapeutics*, 311(3), 1131-1137.
- Stevens 1998** Stevens, R. E., Limsakun, T., Evans, G., & Mason, J. D. H. (1998). Controlled, multidose, pharmacokinetic evaluation of two extended-release carbamazepine formulations (Carbatrol and Tegretol-XR). *Journal of pharmaceutical sciences*, 87(12), 1531-1534.

Strandjord 1975 Strandjord, R. E., & Johannessen, S. I. (1975). A preliminary study of serum carbamazepine levels in healthy subjects and in patients with epilepsy. In: *Clinical pharmacology of anti-epileptic drugs* (pp. 181-188). Springer, Berlin, Heidelberg.

Sumi 1987 Sumi, M., Watari, N., Umezawa, O., & Kaneniwa, N. (1987). Pharmacokinetic study of carbamazepine and its epoxide metabolite in humans. *Journal of pharmacobio-dynamics*, 10(11), 652-661.

Terhaag 1978 Terhaag, B., Richter, K., & Dietrich, H. (1978). Concentration behavior of carbamazepine in bile and plasma of man. *International journal of clinical pharmacology and biopharmacy*, 16(12), 607-609.

Tomaszewska 2013 Tomaszewska, I. (2013). In vitro and Physiologically Based Pharmacokinetic models for pharmaceutical cocrystals. Doctoral dissertation, University of Bath. https://purehost.bath.ac.uk/ws/portalfiles/portal/187934939/UnivBath_PhD_2013_I_Tomaszewska.pdf, accessed on 12-01-2022.

Tomson 1983 Tomson, T., Tybring, G., & Bertilsson, L. (1983). Single-dose kinetics and metabolism of carbamazepine-10, 11-epoxide. *Clinical Pharmacology & Therapeutics*, 33(1), 58-65.

US Patent Application - US 2009/0169619 A1. United States Patent Application 2009, Publication no.: US 2009/0169619 A1. <https://patentimages.storage.googleapis.com/66/d4/30/f3588f44ab2b6f/US20090169619A1.pdf>, accessed on 12-01-2022.

US Patent Application - US 2014/0302138 A1. United States Patent Application 2014, Publication no.: US 2014/0302138 A1. <https://patentimages.storage.googleapis.com/57/d9/18/0d8cbfa046681d/US20140302138A1.pdf>, accessed on 12-01-2022.

Vinçon 1987 Vinçon, G., Albin, H., Demotes-Mainard, F., Guyot, M., Bistue, C., & Loiseau, P. (1987). Effects of josamycin on carbamazepine kinetics. *European journal of clinical pharmacology*, 32(3), 321-323.

Wada 1978 Wada, J. A., Troupin, A. S., Friel, P., Remick, R., Leal, K., & Pearmain, J. (1978). Pharmacokinetic comparison of tablet and suspension dosage forms of carbamazepine. *Epilepsia*, 19(3), 251-255.

Williamson 2016 Williamson, B., Lorbeer, M., Mitchell, M. D., Brayman, T. G., & Riley, R. J. (2016). Evaluation of a novel PXR-knockout in HepaRG™ cells. *Pharmacology research & perspectives*, 4(5), e00264.

Willmann 2007 Willmann, S., Höhn, K., Edginton, A., Sevestre, M., Solodenko, J., Weiss, W., ... & Schmitt, W. (2007). Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. *Journal of pharmacokinetics and pharmacodynamics*, 34(3), 401-431.

Wong 1983 Wong, Y. Y., Ludden, T. M., & Bell, R. D. (1983). Effect of erythromycin on carbamazepine kinetics. *Clinical Pharmacology & Therapeutics*, 33(4), 460-464.