Building and evaluation of a PBPK model for raltegravir in adults

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1.1 Materials and Methods

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

Raltegravir (RAL), sold under the brand name Isentress, is an antiretroviral medication used to treat HIV/AIDS by blocking the establishment of post-integration HIV latency . It is also used as part of post exposure prophylaxis, to prevent HIV infection following potential exposure. Raltegravir is only taken orally and is mainly metabolized by UGT1A1 (~70%) **(Kassahun 2007**). The final raltegravir model applies metabolism by UGT1A1, and minor involved enzyme UGT1A9 and glomerular filtration and adequately described the pharmacokinetics of raltegravir in adults.

The raltegravir model is a whole-body PBPK model, allowing for dynamic translation between individuals with organs expressing UGT1A1. The raltegravir report demonstrates the level of confidence of the raltegravir PBPK model build with the OSP suite with regard to reliable predictions of Raltegravir PBPK adults during model-informed drug development. The presented raltegravir PBPK model as well as the respective evaluation plan and PBPK report are provided open-source and transparently documented (https://github.com/Incei/Raltegravir-Model).

1.1.1 Modelling strategy

Modelling strategy

The building of a PBPK model is well-described by Kuepfer et al. (**Kuepfer 2016**) The PBPK models are developed with clinical data of healthy adult subjects obtained from the literature, covering available dosing ranges for e.g. intravenous as well as oral administration, to capture both systemic clearance as well gut-wall metabolic clearance processes. Plasma concentrations following multiple-dose application, mass balance information and other clinical measurements need to be included for model development, if available. During model building, uncertainties in data-quality caused inaccurate in vitro assay-techniques regarding mass balance, as well as study differences may cause not being able to adequately describe the PK in adults for all reported studies.

Model performance of the PBPK model for raltegravir are then shown by means of diagnostics plots and predicted versus observed concentration-time profiles, of which the results support an adequate prediction of the PK in adults.

Anthropometric and Physiological Information

Regarding the relevant anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in adults was gathered from the literature and has been previously published (**PK-Sim Ontogeny Database Version 7.3**). The information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available 'PK-Sim® Ontogeny Database Version 7.3' (**Schlender 2016**) or otherwise referenced for the specific process.

1.1.2 Data used

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1.1.2.1 In vitro / physchem data

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

Parameter	Unit	Raltegravir literature	Description
MW	g/mol	586.2 (**drugbank.ca**)	Molecular weight
pKa		7.67 (**Moss 2012**)	Acid dissociation constant
Solubility (pH)	mg/L	Reference pH-dependent table (Moss 2013)	Solubility
logP		0.58 (**Moss 2012**)	Lipophilicity
fu		0.17 (**Laufer 2009**)	Fraction unbound
UGT1A1	µM	99 (**Kassahun 2007**)	Michaelis-Menten constant (Km)
UGT1A1	nmol/min/mg	0.89 (**Kassahun 2007**)	Vmax
UGT1A9	µM	296 (**Kassahun 2007**)	Michaelis-Menten constant (Km)
UGT1A9	nmol/min/mg	0.53 (**Kassahun 2007**)	Vmax

1.1.2.2 Clinical data

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

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

Iwamoto M, Wenning LA, Petry AS, Laethem M, De Smet M, Kost JT, Merschman SA, Strohmaier KM, Ramael S, Lasseter KC, Stone JA, Gottesdiener KM, Wagner JA. Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. Clin Pharmacol Ther. 2008 Feb;83(2):293-9. Epub 2007 Aug 22.

Iwamoto M, Wenning LA, Nguyen BY, Teppler H, Moreau AR, Rhodes RR, Hanley WD, Jin B, Harvey CM, Breidinger SA, Azrolan N, Farmer HF Jr, Isaacs RD, Chodakewitz JA, Stone JA, Wagner JA. Effects of omeprazole on plasma levels of raltegravir. Clin Infect Dis. 2009 Feb 15;48(4):489-92. doi: 10.1086/596503.

Markowitz M, Morales-Ramirez JO, Nguyen BY, Kovacs CM, Steigbigel RT, Cooper DA, Liporace R, Schwartz R, Isaacs R, Gilde LR, Wenning L, Zhao J, Teppler H. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. J Acquir Immune Defic Syndr. 2006 Dec 15;43(5):509-15.

Kassahun K, McIntosh I, Cui D, Hreniuk D, Merschman S, Lasseter K, Azrolan N, Iwamoto M, Wagner JA, Wenning LA. Metabolism and disposition in humans of raltegravir (MK-0518), an anti-AIDS drug targeting the human immunodeficiency virus 1 integrase enzyme. Drug Metab Dispos. 2007 Sep;35(9):1657-63. Epub 2007 Jun 25.

Rhee EG, Rizk ML, Brainard DM, Gendrano IN 3rd, Jin B, Wenning LA, Wagner JA, Iwamoto M. A pharmacokinetic comparison of adult and paediatric formulations of raltegravir in healthy adults. Antivir Ther. 2014;19(6):619-24. doi: 10.3851/IMP2765. Epub 2014 Mar 7.

Larissa A. Wenning,, William D. Hanley, Diana M. Brainard, Amelia S. Petry, Kalyan Ghosh, Bo Jin, Eric Mangin, Thomas C. Marbury, Jolene K. Berg, Jeffrey A. Chodakewitz, Julie A. Stone,1 Keith M. Gottesdiener, John A. Wagner, and Marian Iwamoto. Effect of Rifampin, a Potent Inducer of Drug-Metabolizing Enzymes, on the Pharmacokinetics of Raltegravir. Antimicrob Agents Chemother. 2009 Jul; 53(7): 2852–2856.

1.1.3 Model parameters and assumptions

1.1.3 Model parameters and assumptions

1.1.3.1 Absorption

As no intravenous data is currently available to study systemic clearance of raltegravir in vivo, only oral data was used for model building. For oral administration the following parameters play a role with regards to the absorption kinetics of a compound, which can be estimated with PBPK: solubility, lipophilicity and intestinal permeability. Moss et al. (**Moss 2013**) published values for raltegravir solubility in population groups with very low pH, low pH, medium pH, high pH and very high pH, after a single 400 mg dose of raltegravir. For the raltegravir PBPK

model we have applied the medium pH group for creating a pH dependent solubility profile throughout the intestinal tract. The lipophilicity as well as pKa of raltegravir was also published by Moss et al (**Moss 2012, Moss 2013**) to be 0.58 (as log partition coefficient between octanol and water (pH 7) and 6.67 (acid), respectively. These values were applied and fixed into the raltegravir PBPK model, without further optimization. Regarding intestinal transcellular permeability (Pint), Moss et al (Moss 2012) reported a range of apical to basolateral apparent permeability in Caco-2 monolayer at different pH values. Using published functions Pint can be calculated from Caco-2 cell membrane permeability measurements (Parrot et al. (**Parrot 2002**), Thelen et al. (**Thelen 2010**, Sun et al. (**Sun 2002**) and Sjögren et al. (**Sjögren 2013**). However as no reference/calibrator compound was available to correct for inter-study variability, these functions could not be applied, and it was decided to estimate the Pint from in vivo clinical data instead. Nevertheless, for plausibility check, a theoretical Pint was calculated using the aforementioned functions without correction, resulting in a range of Pint from 2.14E-04 to 1.47E-09 cm/min. The finally estimated (based on in vivo data) Pint falls within this range.

Table 2. Reported Caco-permeability and calculated theoretical effective permeability (intestinal transcellular permeability) values for raltegravir via different reported functions, lacking a reference compound for correcting inter-study variability.

Reference publication of reported function	Ph apical-basolateral	Peff (cm/min)	Reference compound available for correcting Inter study variability
Raltegravir Caco permeability (Moss 2012)	7.4	6.60E-6	-
Raltegravir Caco permeability (Moss 2012)	6.5	9.20E-6	-
Parrot 2002	7.4	2.14E-04	Not available
Thelen 2010	7.4	1.47E-09	Not available
Sjögren 2013	7.4	1.03606E-6	Not available
Sun 2002	7.4	2.77E-4	Not available
Sun 2002	6.5	2.86E-4	Not available
Simcyp (*)	6.5	4.62E-4	Not available

*Not published as paper, Simcyp applied an adapted version of Sun et al 2002

1.1.3.2 Distribution

Laufer et al. (**Laufer 2009**) published a fu in humans to be 0.17. Barau et al 2013 reported that raltegravir binds to serum albumin, and not alpha glycoprotein, and are built-in as such into the PBPK model.

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built in PK-Sim, observed clinical data was best described by choosing the partition coefficient calculation by Rodgers and Rowland, and cell permeability calculation by PK-Sim standard. Specific organ permeability normalized to surface area was automatically calculated by PK-Sim.

1.1.3.3 Metabolism and Elimination

Kassahun et al. (**Kassahun 2007**) studied the absorption, metabolism, and excretion of raltegravir in healthy volunteers after a single oral dose of 200 mg (200Ci) of [14C] raltegravir. Human liver microsomal incubations confirmed the dominat role of UGT metabolism for raltegravir. Additionally, data from incubations using cDNA-expressed UGTs indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation. Raltegravir was in particular converted to M2 by UGT1A1 and 1A9. The apparent Km values for the glucuronidation of raltegravir by UGT1A1 and UGT1A9 were 99 (standard deviation (SD): 16) and 296 (SD: 55) µM, respectively. The corresponding Vmax values (nmol/min/mg) were 0.89 (SD: 0.05) for UGT1A1, and 0.53 (SD: 0.06) for UGT1A9.

Based on this information, the reported in vitro Km values for UGT1A1 and 1A9 in the model. Reported Vmax values were of the dimension nmol/min/mg protein and thus not directly transferable into the PBPK model. Therefore, a unique scaling factor fUGT on the in vitro Vmax values was estimated to match observed in vivo data, and keeping the relative relationship between those in vitro values (0.89 and 0.53 nmol/min/mg) for UGT1A1 and UGT1A9 fixed according to:

$V_{max,UGT1A1} = fUGT * V_{max,in\text{-}vitro,UGT1A1}$

$V_{max,UGT1A9} = fUGT * V_{max,in\text{-}vitro,UGT1A9}$

It is especially important to fix the relative contribution of both enzymes as a ratio to ensure that, when scaling to other populations (e.g. children where both UGT's undergo a different ontogeny pattern, or patients who have differently reduced amounts of UGT1A1 vs 1A9) the relative contributions can be adequately scaled.

Finally, as ~9% of the dose is excreted in human urine as unchanged parent compound, GFR is introduced in the raltegravir PBPK model.

1.2 Results and Discussion

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The PBPK model **raltegravir** was developed with clinical pharmacokinetic data covering 4 different oral formulation and a dose range of 10-1600mg, including single dose (SD) as well as multiple dose (MD) clinical data.

As there were 4 different oral formulations available for model evaluation, all formulations require an estimation of the dissolution kinetics via a Weibull function. This function requires the estimation of 2 parameters, the dissolution time (time where 50% of the drug is dissolved), and dissolution shape (shape parameter of the Weibull function). Therefore, to minimize the amount of parameters for fitting, as a first step, the PK study data (lactose formulation) by Iwamoto et al. (**Iwamoto 2007**) was fitted which includes SD escalation and hast a broad dose-range (10mg-1600mg) to capture (non-) linearity. During the model-fitting, the following parameters were estimated (all other parameters were fixed to reported values):

· Vmax (as unique scaling factor Fugt, as described in section 1.1.3.3)
· Weibul function paramters: Dissolution time and dissolution shape
· Specific intestinal permeability (transcellular)

The fit resulted in an adequate description of all data. As there is no iv data available, it was not possible to clearly distinguish between clearance and absorption, resulting in a considerable correlation between Vmax and dissolution shape (Weibull). An attempt to fix Vmax to reported in vitro values, and only estimating absorption (lipophilicity and intestinal transcellular permeability) resulted in an underprediction of the clearance, and clearly indicated a need for increase in clearance. As described above, no reported intestinal permeability was found other than caco-permeability. Caco-permeability could not be translated to effective intestinal permeability without a reference compound. Therefore it was decided to continue with the model where both Pint and Vmax were estimated.

As a second step, clincial study data for all other formulations summarised in section 1.1.2 were included for model fitting, including film-coated tablets (100-400mg MD, 200-400mg SD), chewable tablets (400mg fasted + fed) and oral granules in suspension (400mg). In this step, only the Weibull functions were estimated with all other parameters fixed based on the first step. Finally, as the Weibull functions were highly correlated (as expected), only dissolution shape was estimated as a last step. The model results show that the PBPK model of raltegravir adequately described the date for all formulations and doses available.

1.2.1 Raltegravir final PK parameter tables

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

Compound: Raltegravir

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility table	40 mg/l	Publication-In Vitro-Moss 2013 Table 2	Moss 2013	True
Lipophilicity	0.58 Log Units	Parameter Identification-Parameter Identification	Moss 2012	True
Fraction unbound (plasma, reference value)	0.17	Publication-In Vitro-Laufer 2009	Measurement	True
Specific intestinal permeability (transcellular)	2.8204676221E-07 cm/s	Parameter Identification-Parameter Identification	Fit	True
F	1	Publication-Other-Drugbank.ca		
Is small molecule	Yes			
Molecular weight	444.4163 g/mol	Publication-Other-Drugbank.ca		
Plasma protein binding partner	Albumin			

Calculation methods

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

Processes

Systemic Process: Glomerular Filtration-Kassahun 2007

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-In Vitro-Kassahun 2007

Metabolizing Enzyme: UGT1A1-Kassahun 2007

Molecule: UGT1A1

Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	2.6516610638 nmol/min/mg mic. protein	Parameter Identification-Parameter Identification
Km	99 µM	Publication-In Vitro-Kassahun 2007

Metabolizing Enzyme: UGT1A9-Kassahun 2007

Molecule: UGT1A9

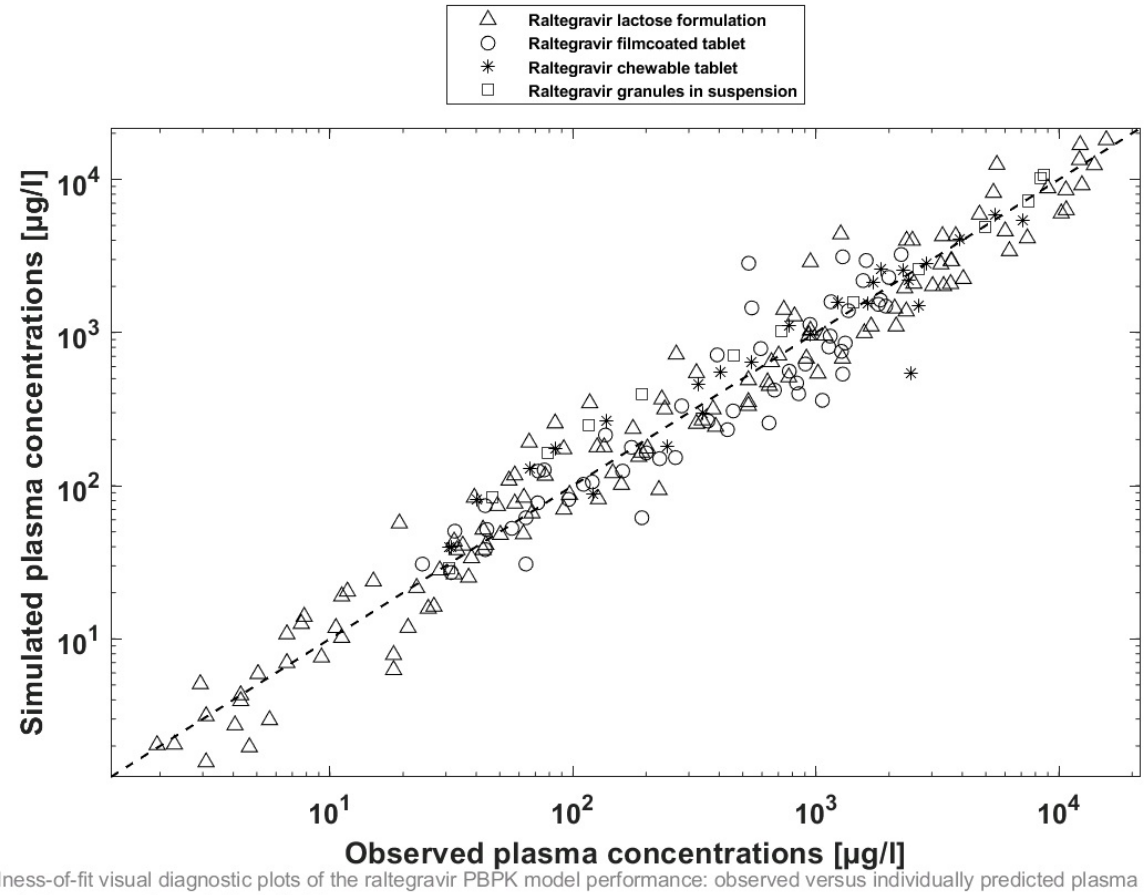
Parameters

Name	Value	Value Origin
In vitro Vmax for liver microsomes	1.5790790604 nmol/min/mg mic. protein	Parameter Identification-Parameter Identification
Km	296 µM	Publication-In Vitro-Kassahun 2007

1.2.2: Raltegravir Diagnostics Plots

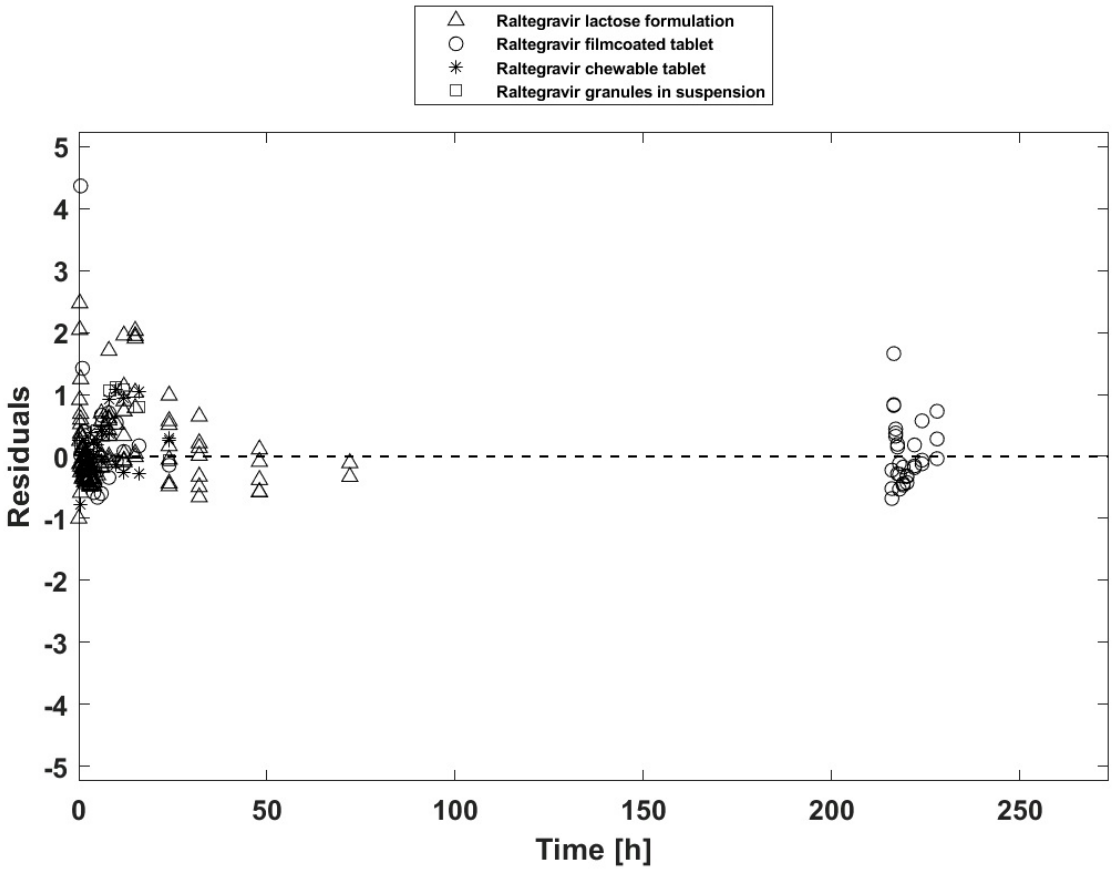
Raltegravir adult PBPK model performance

Below you find the input goodness-of-fit visual diagnostic plots for raltegravir PBPK model performance (observed versus individually simulated plasma concentration and weighted residuals versus time) of all data used for model building.



Goodness-of-fit visual diagnostic plots of the raltegravir PBPK model performance: observed versus individually predicted plasma concentration versus time of all adult data.

GMFE = 1.470261



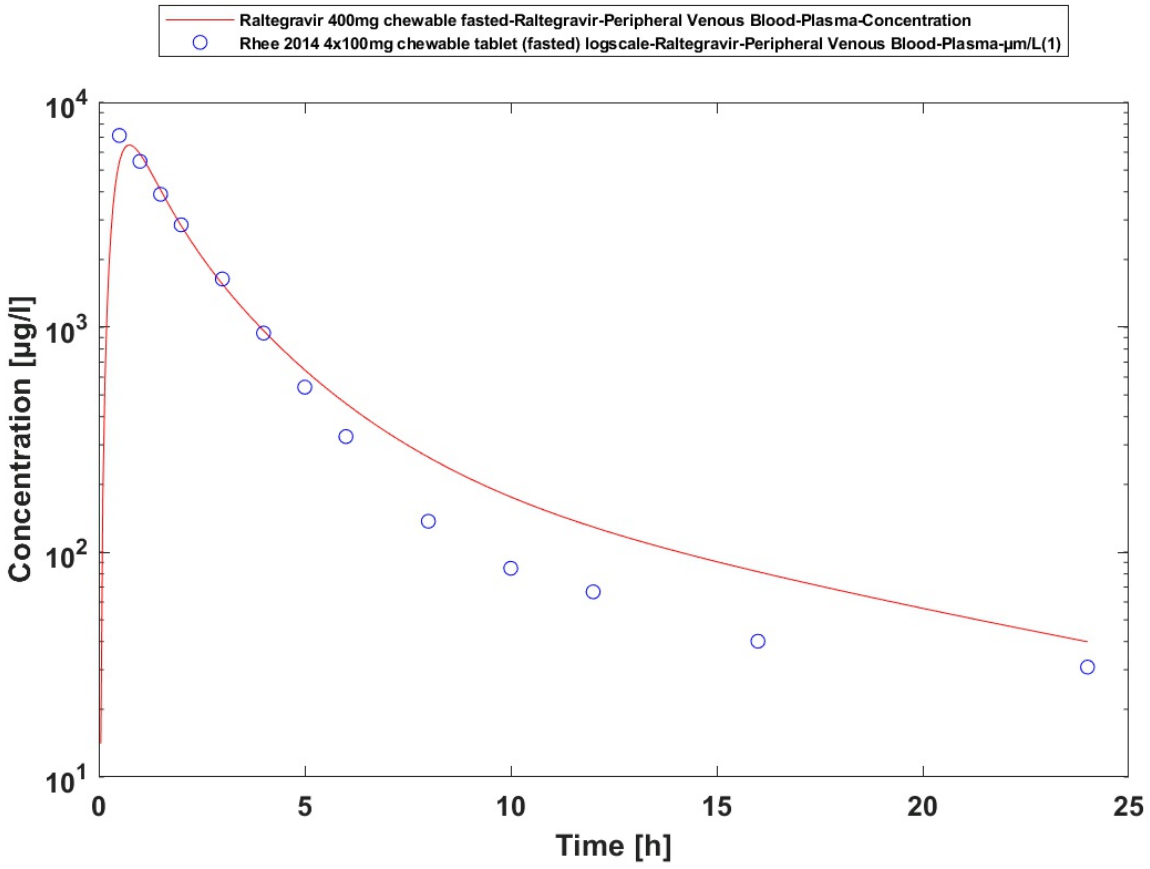
Goodness-of-fit visual diagnostic plots of the raltegravir PBPK model performance: weighted residuals versus time of all adult data.

GMFE = 1.470261

1.2.3: Raltegravir Concentration-Time profiles

Concentration-Time Profiles

Simulated versus observed plasma concentration-time profiles of all data are listed below.



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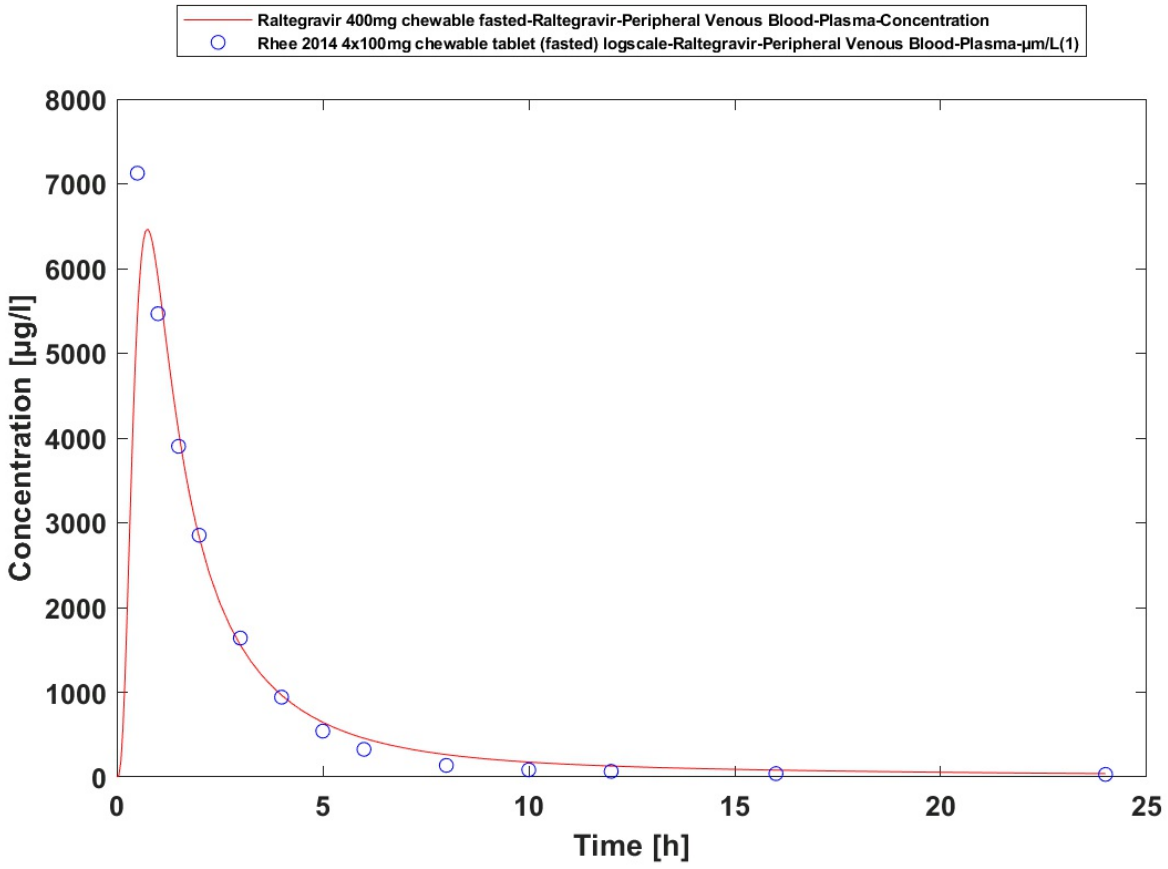

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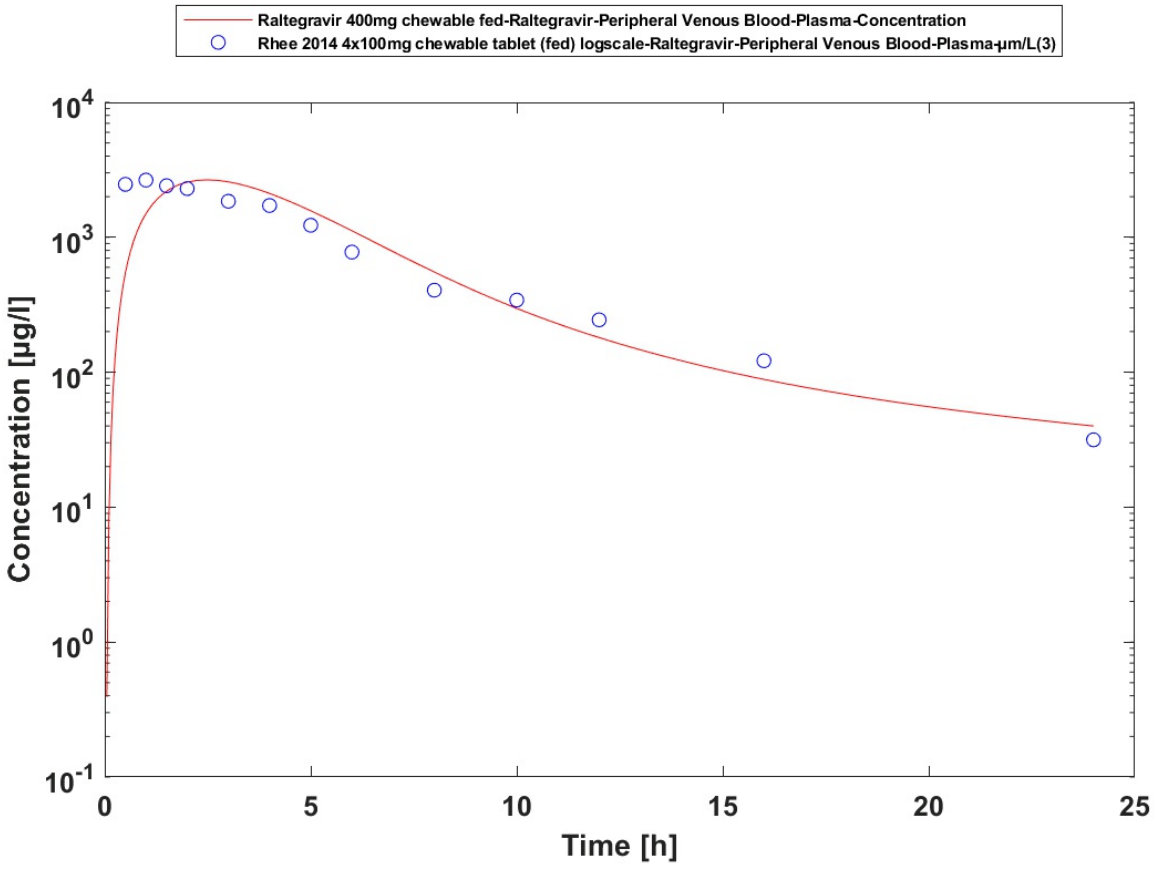

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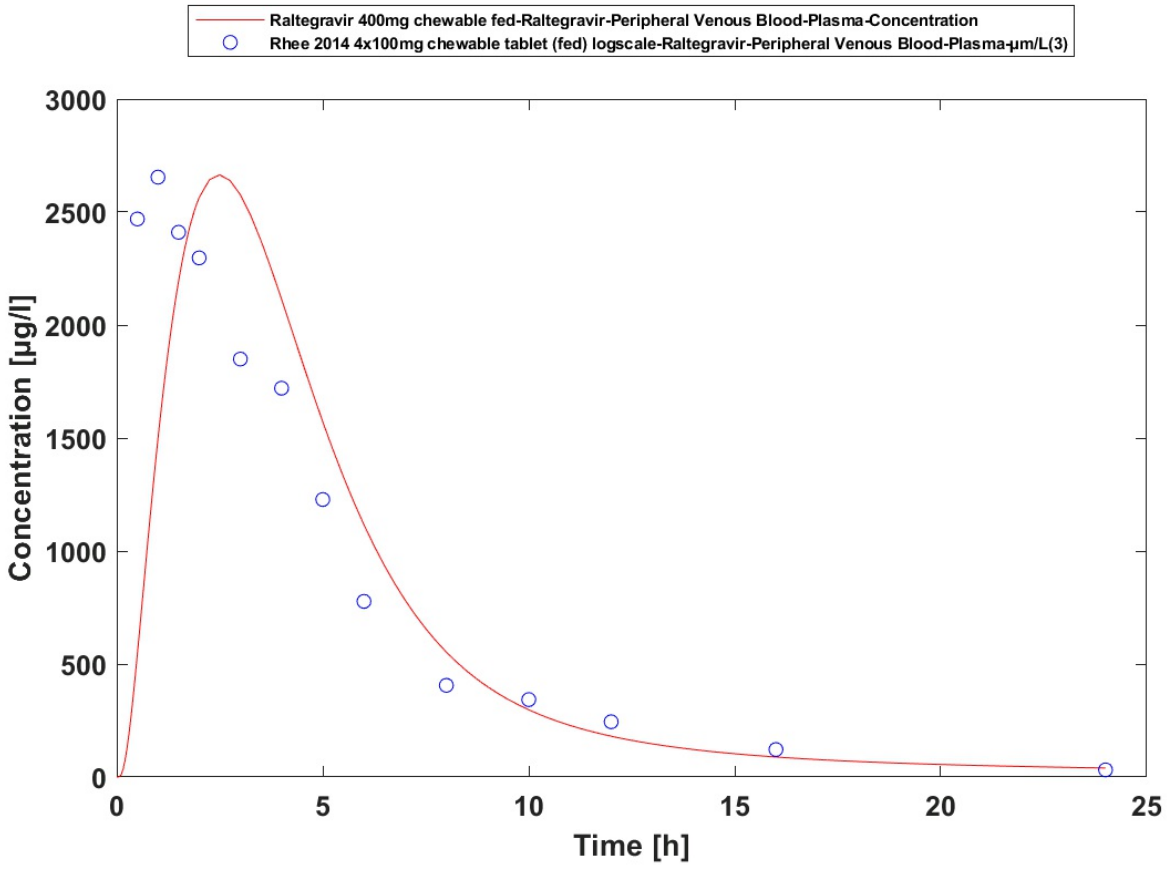

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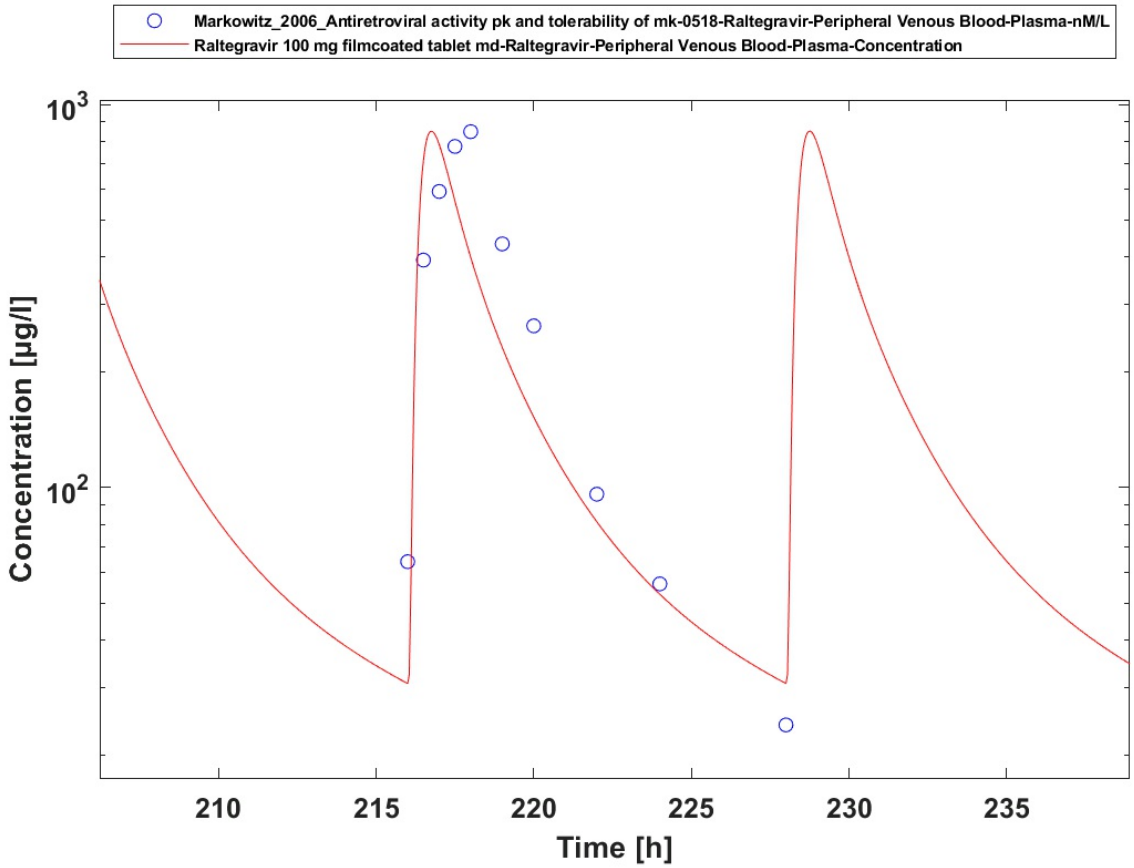

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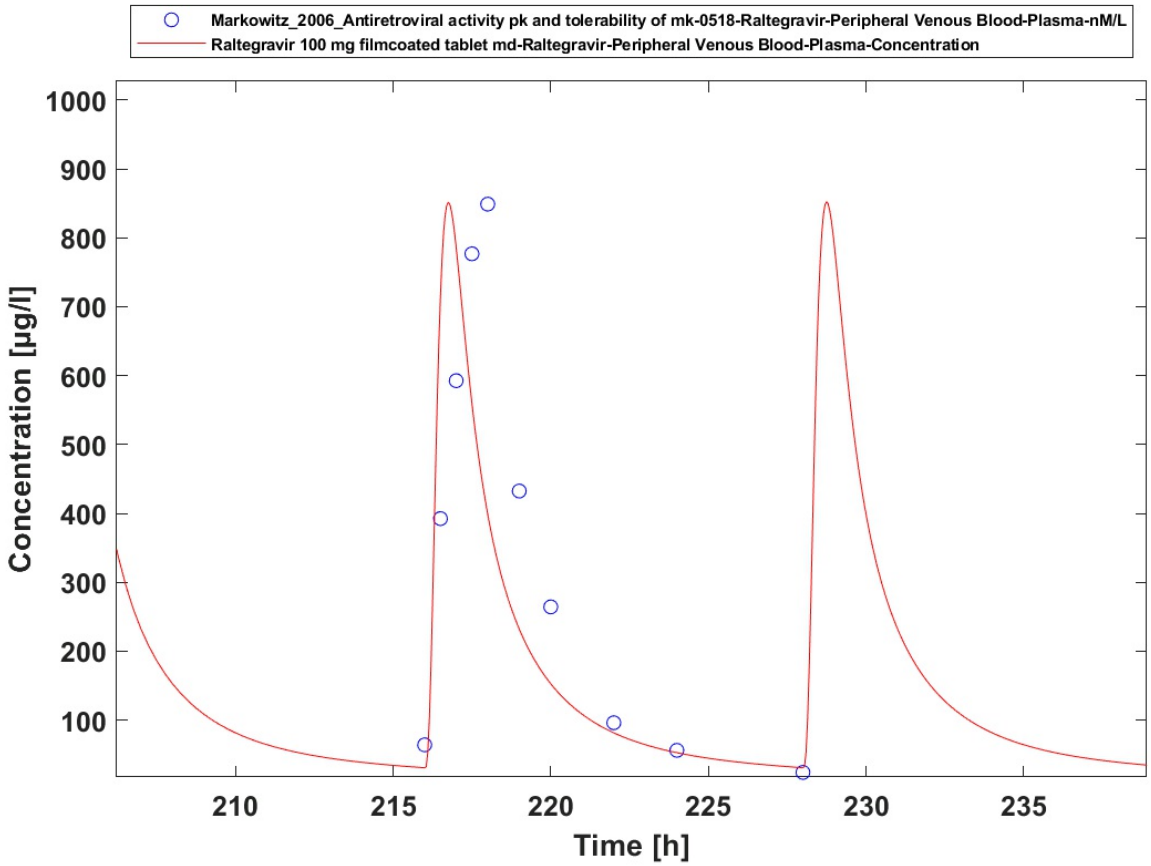

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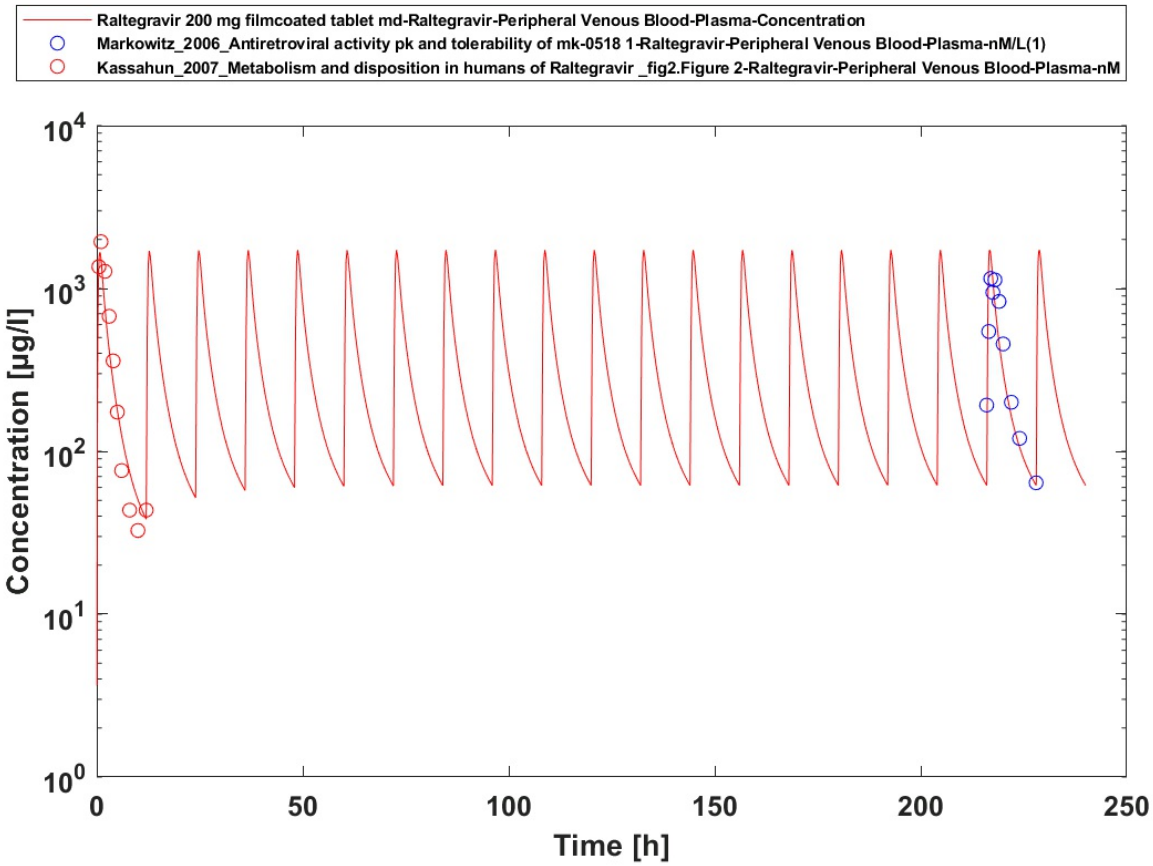

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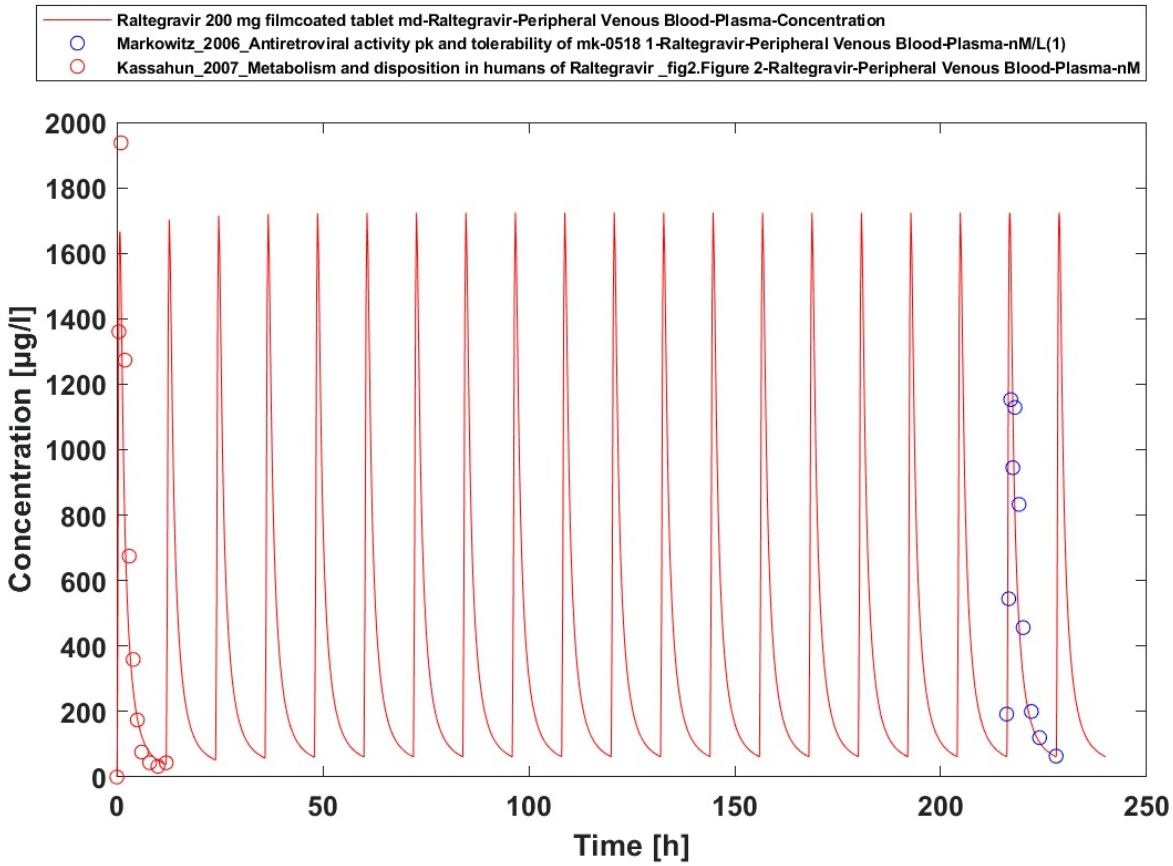

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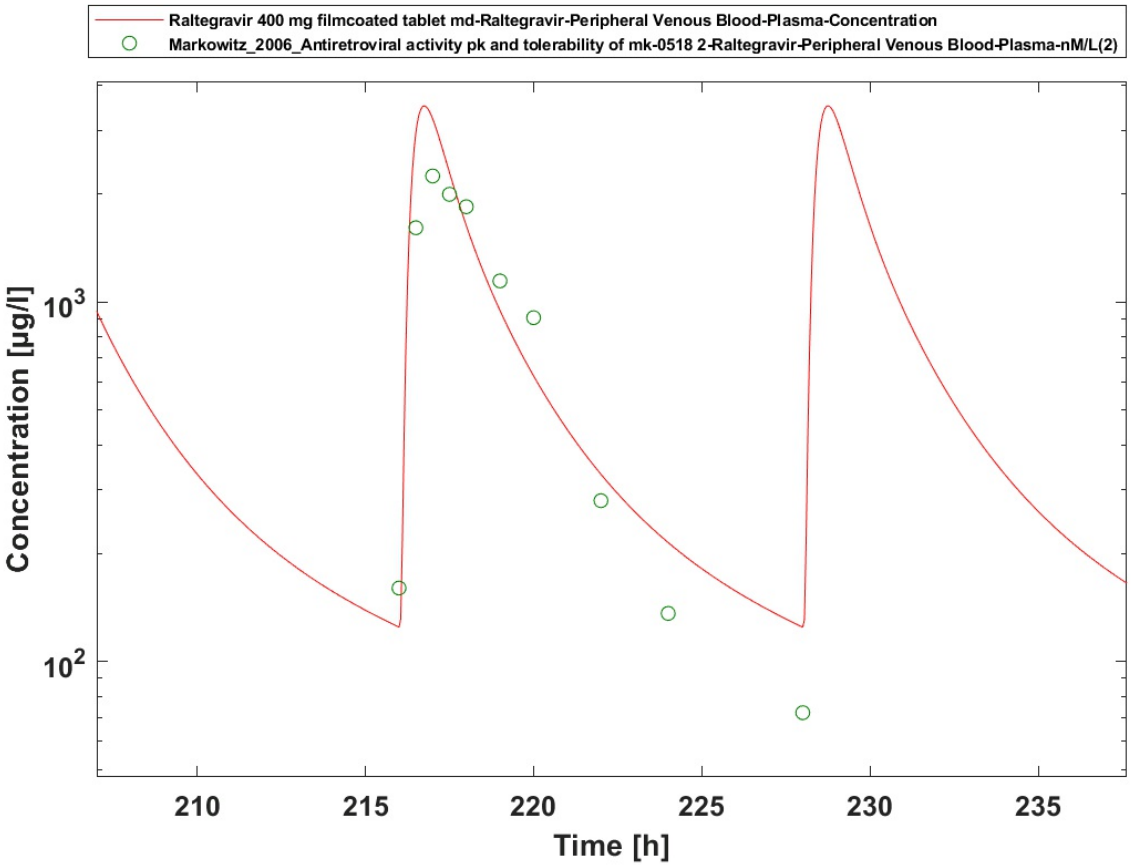

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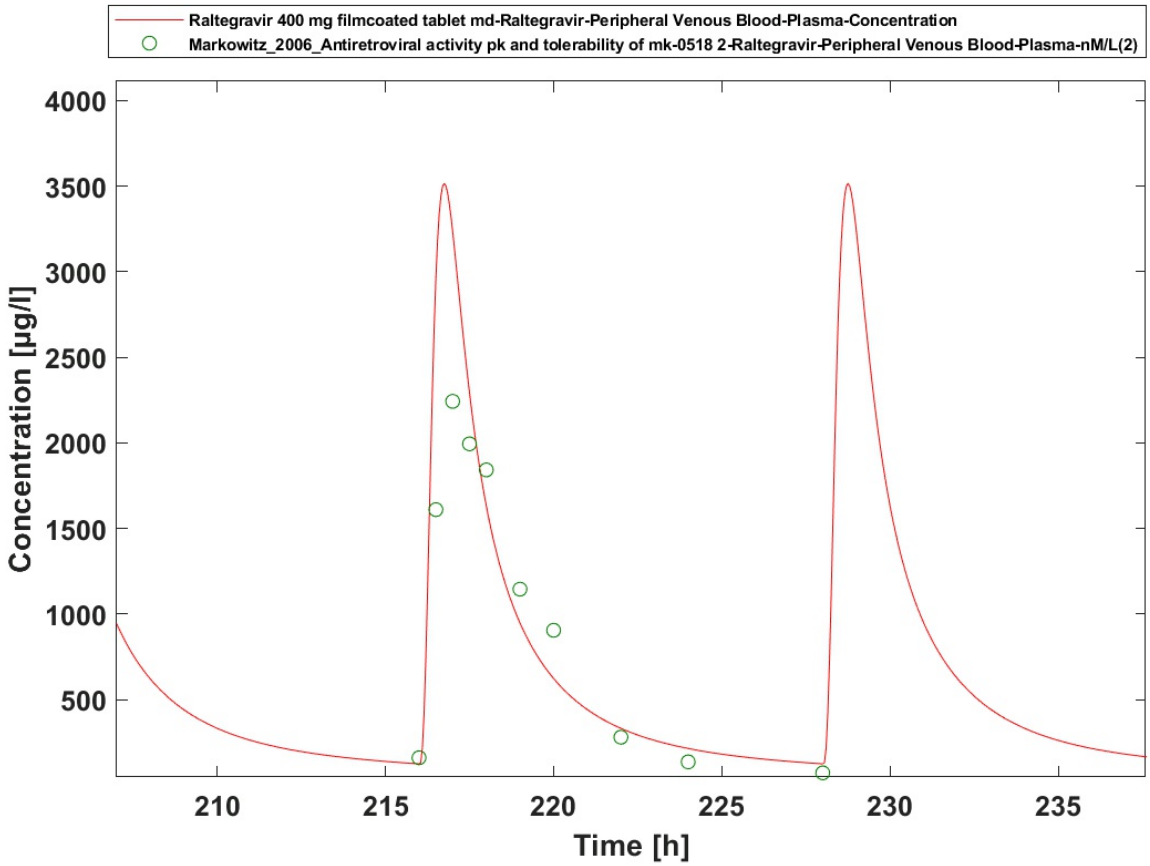

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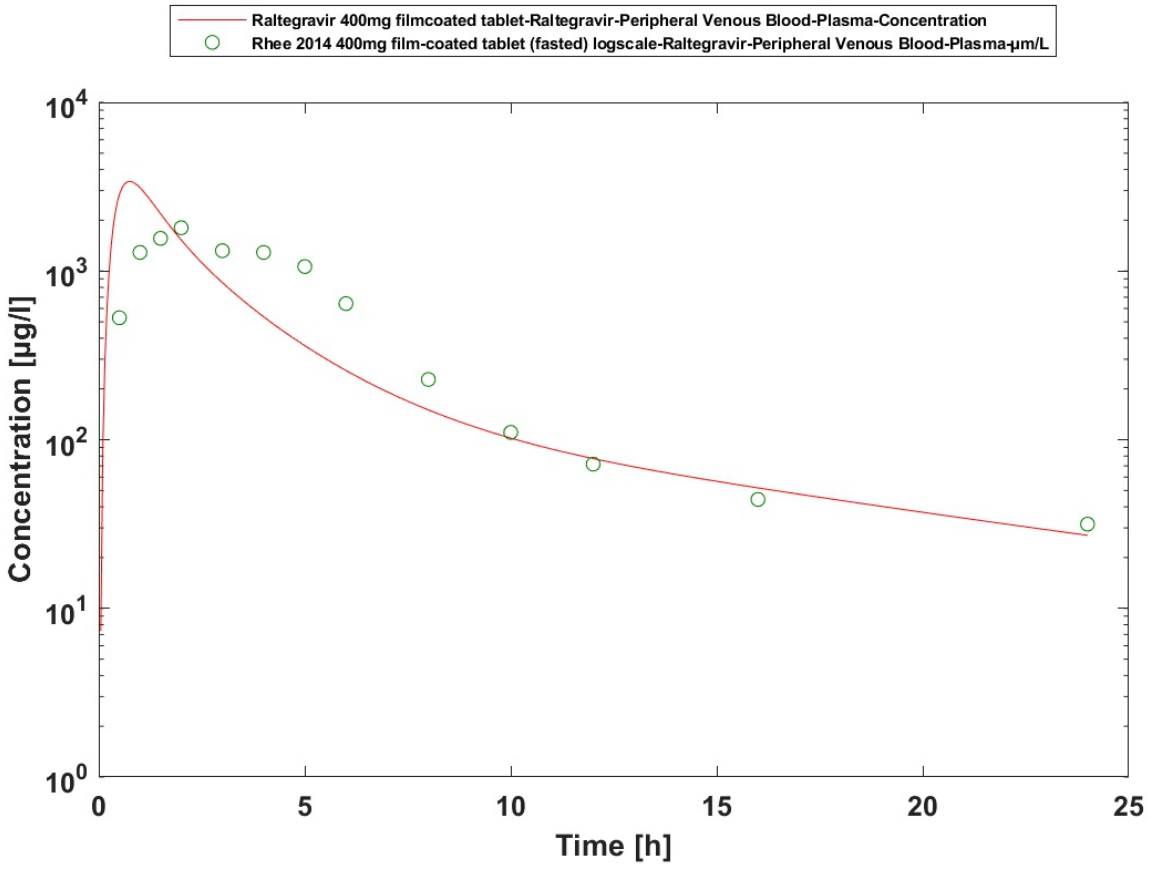

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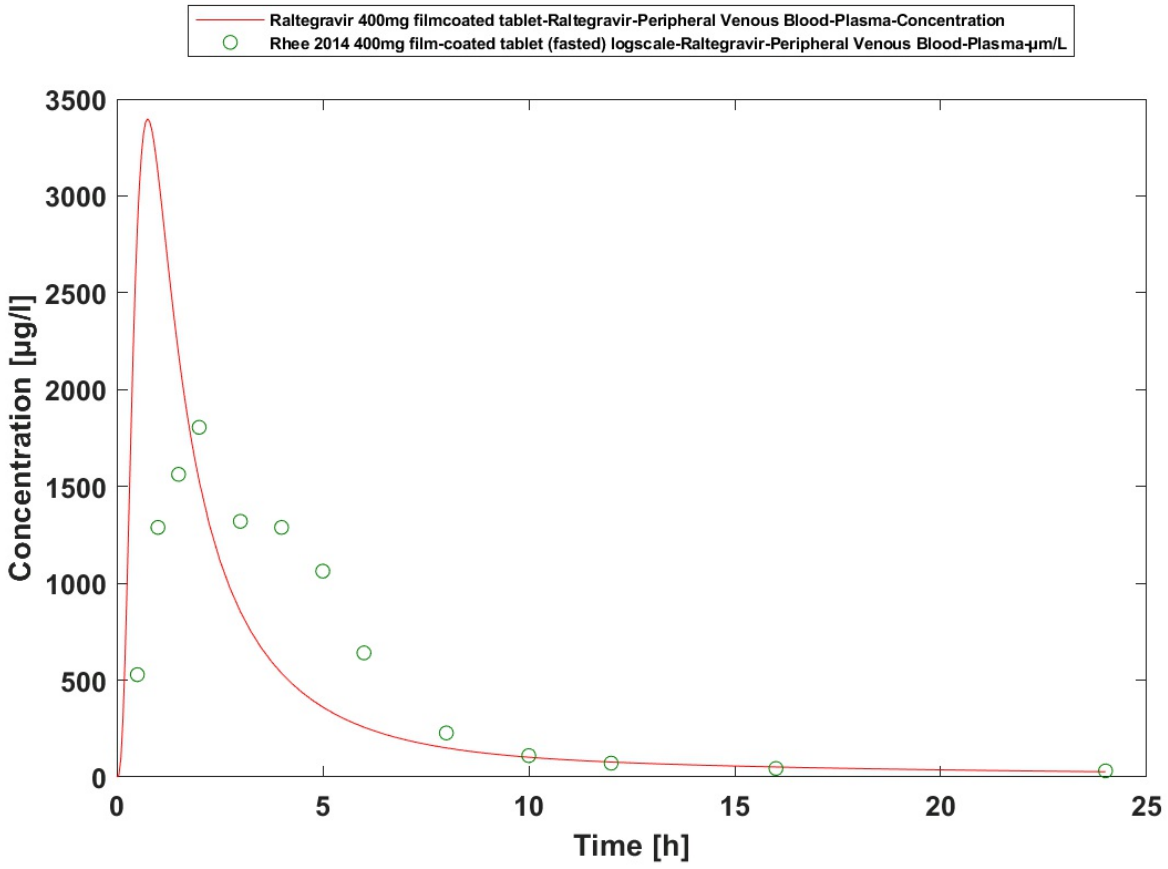

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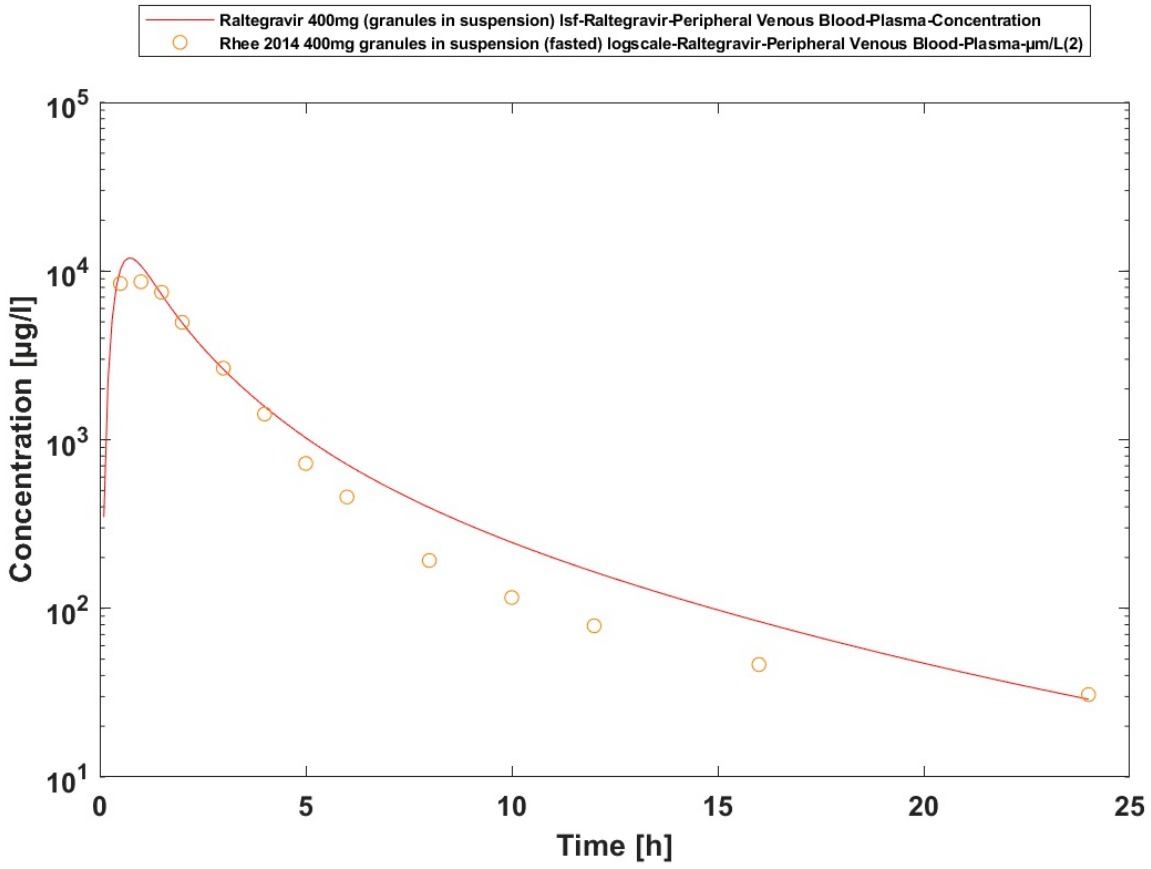

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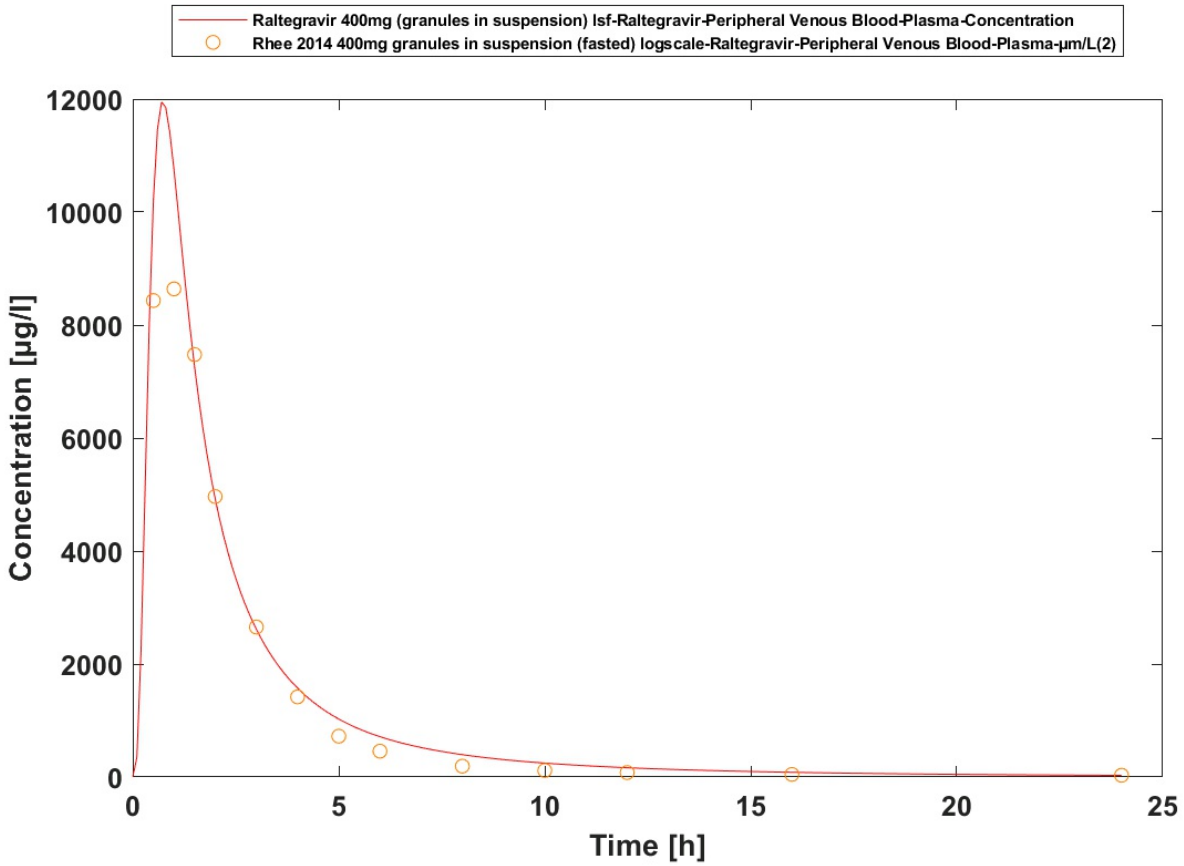
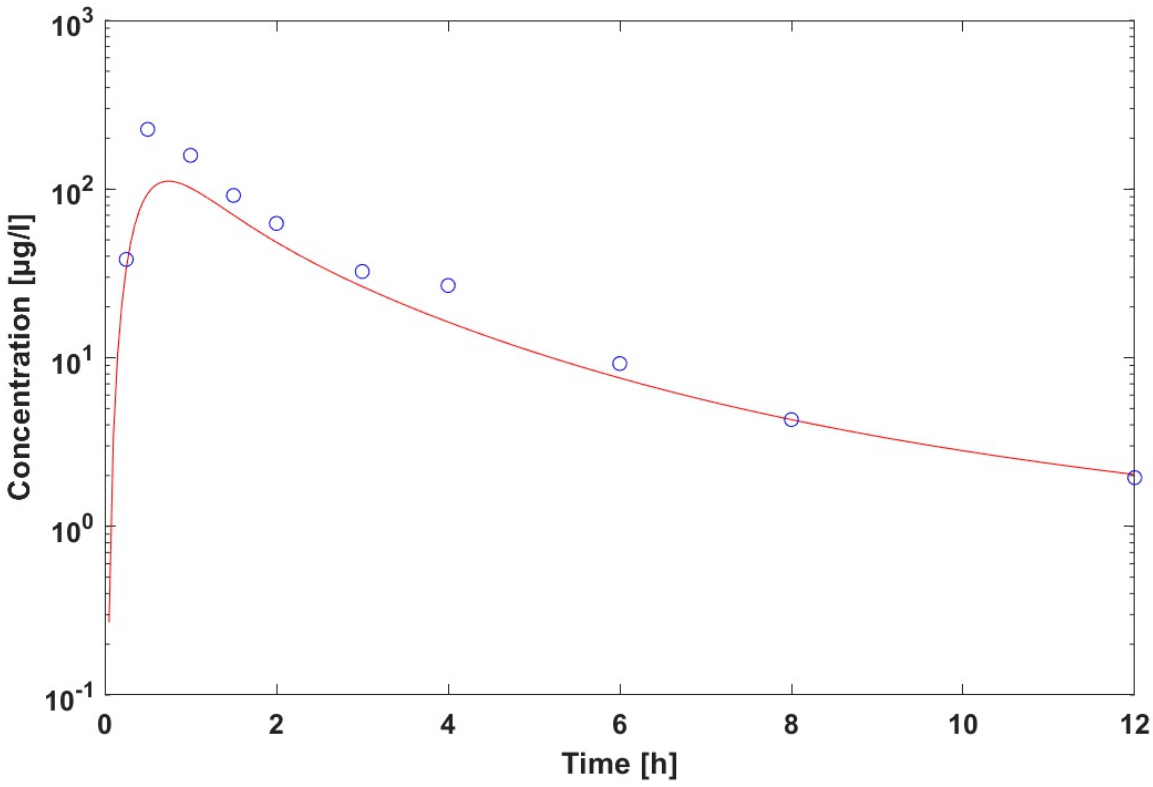


Time Profile Analysis 1

gravir-Peripheral Venous Blood-Plasma-Concentration
cokinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 9-Raltegravir-Peripheral Venous Blood-Plasma-nM



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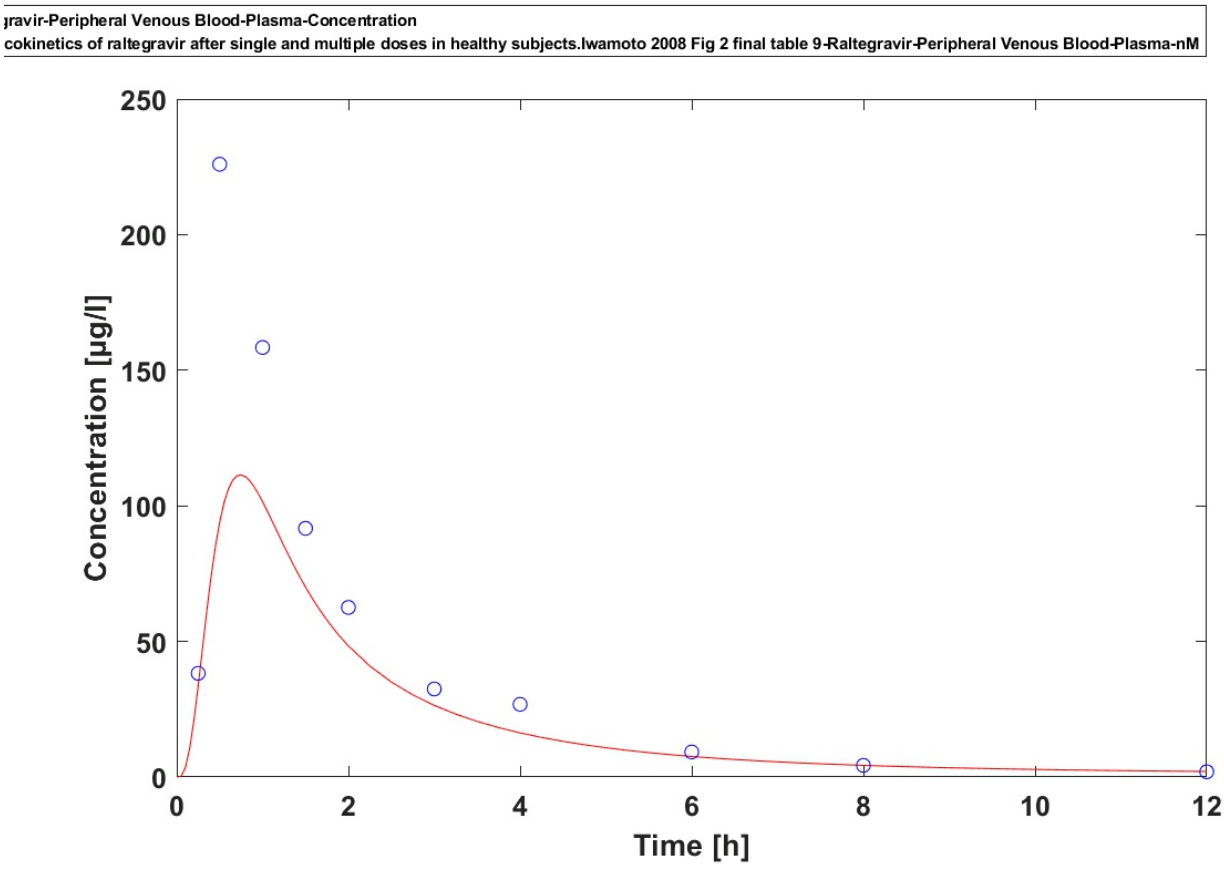
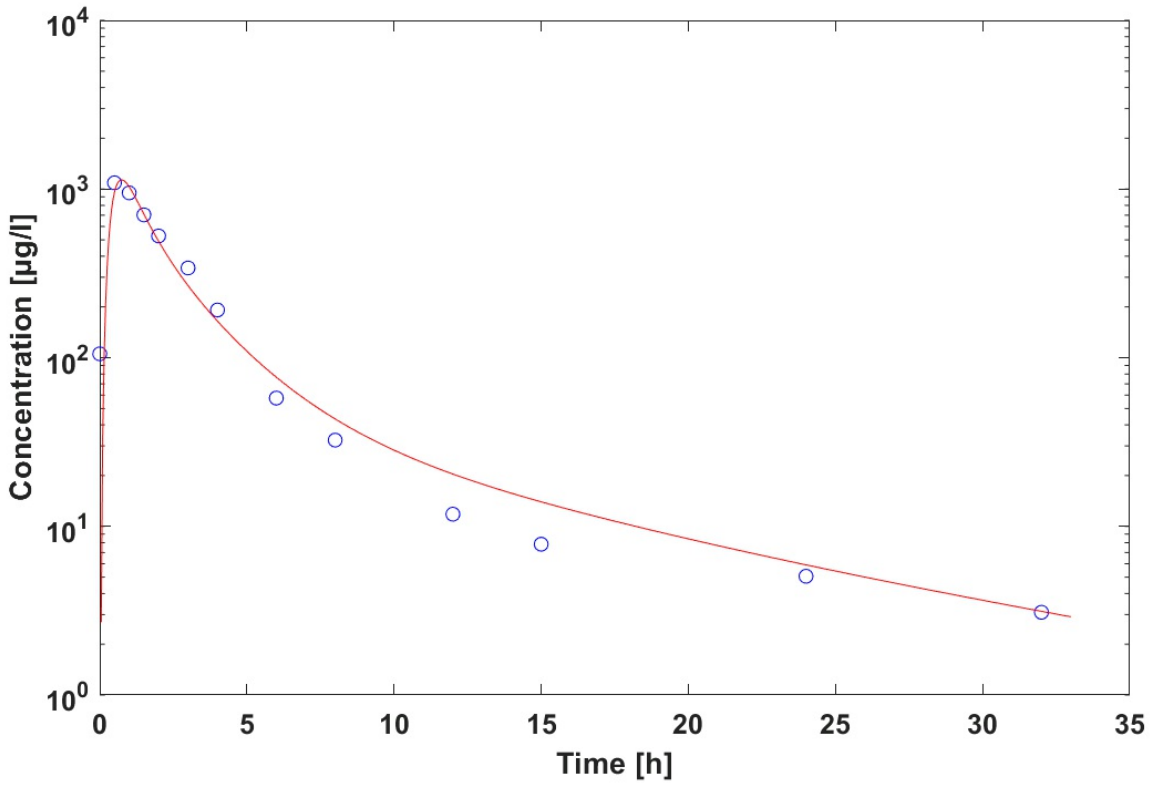


Time Profile Analysis 1

okinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 12-Raltegravir-Peripheral Venous Blood-Plasma-nM
ravir-Peripheral Venous Blood-Plasma-Concentration



Time Profile Analysis

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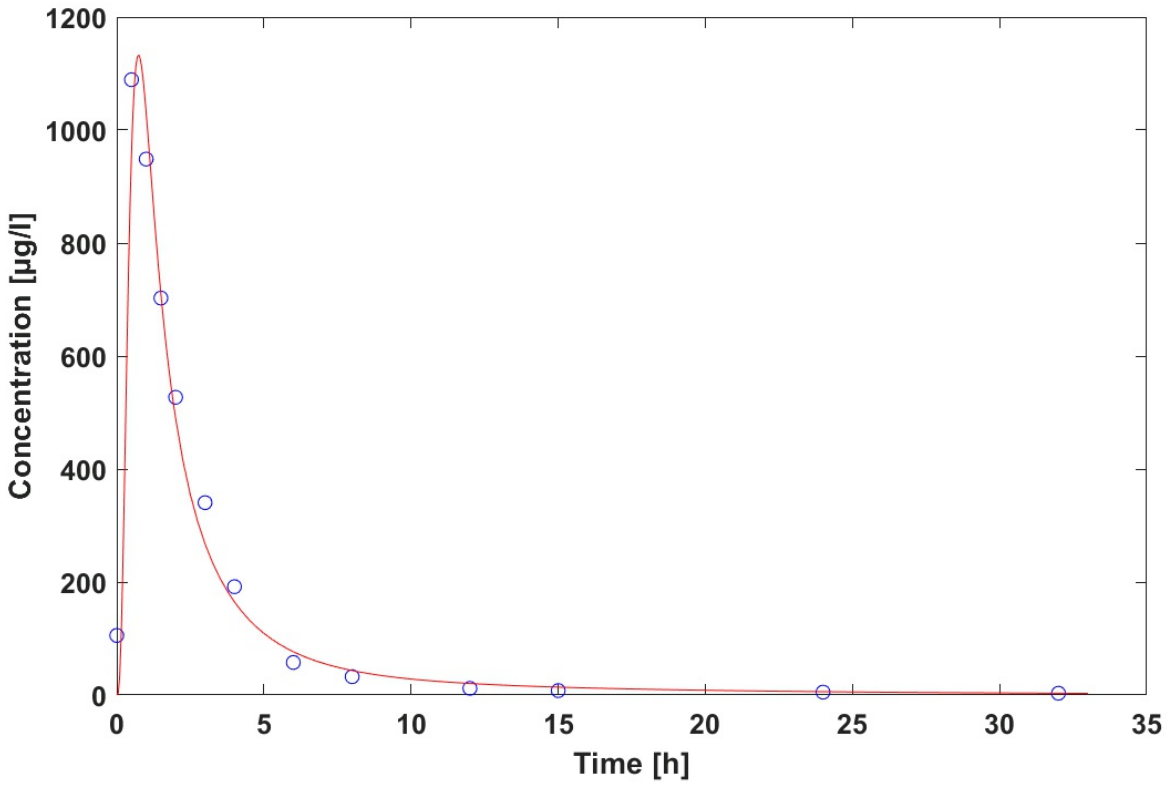
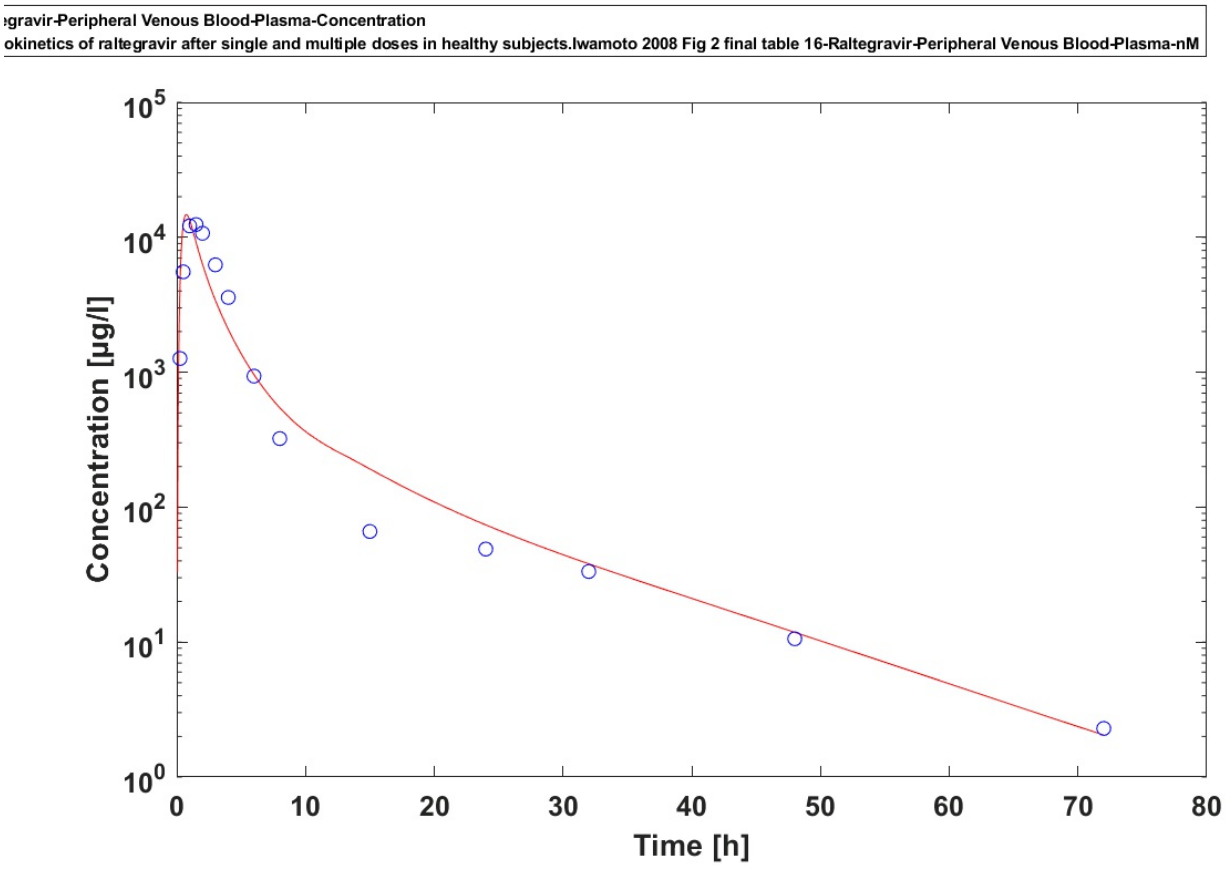
ravir-Peripheral Venous Blood-Plasma-Concentration



Time Profile Analysis 1



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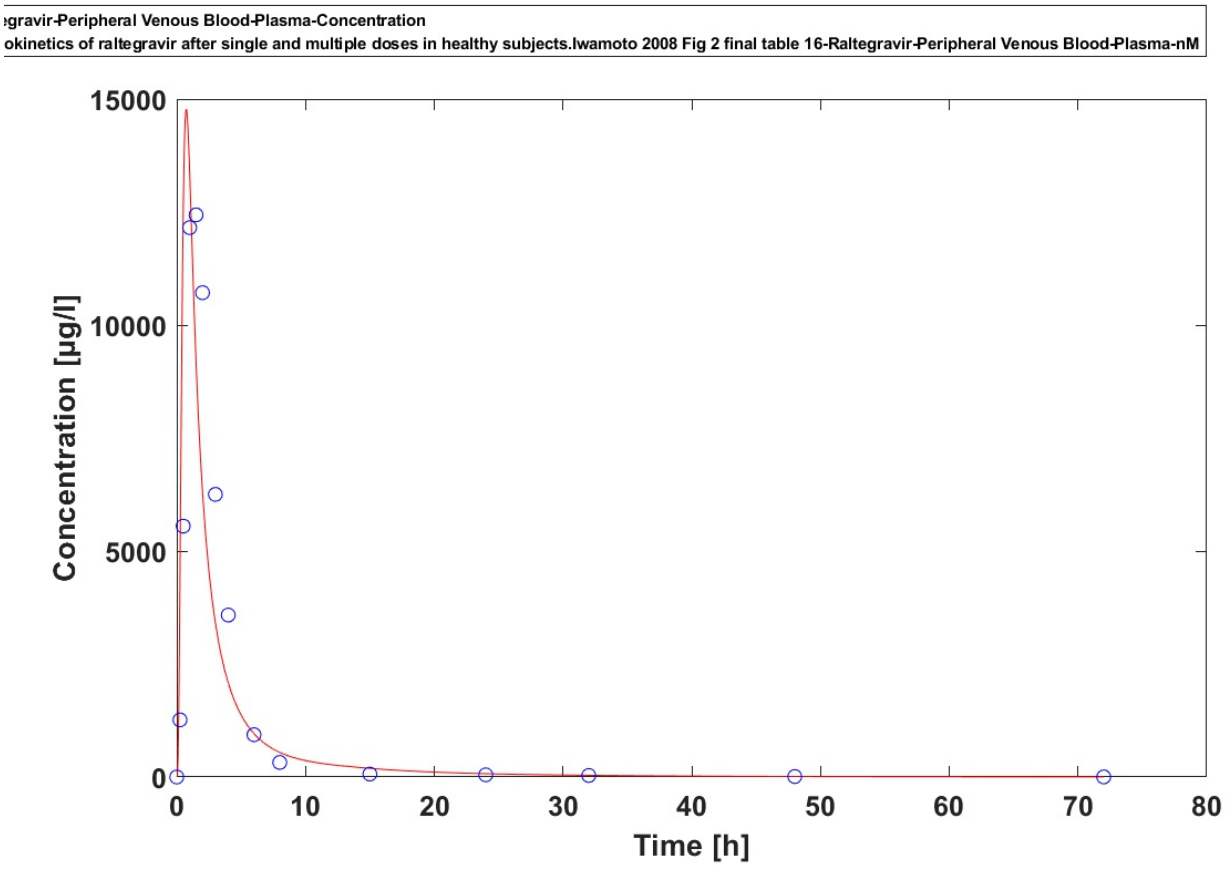
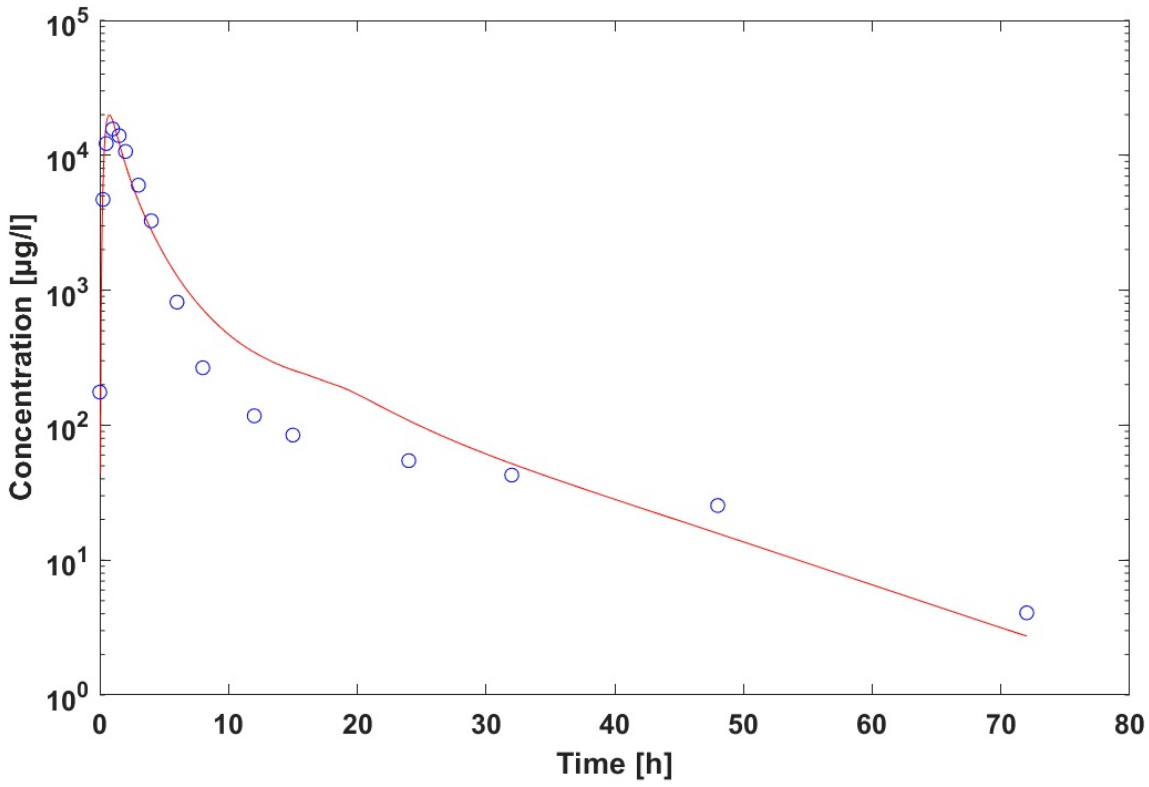


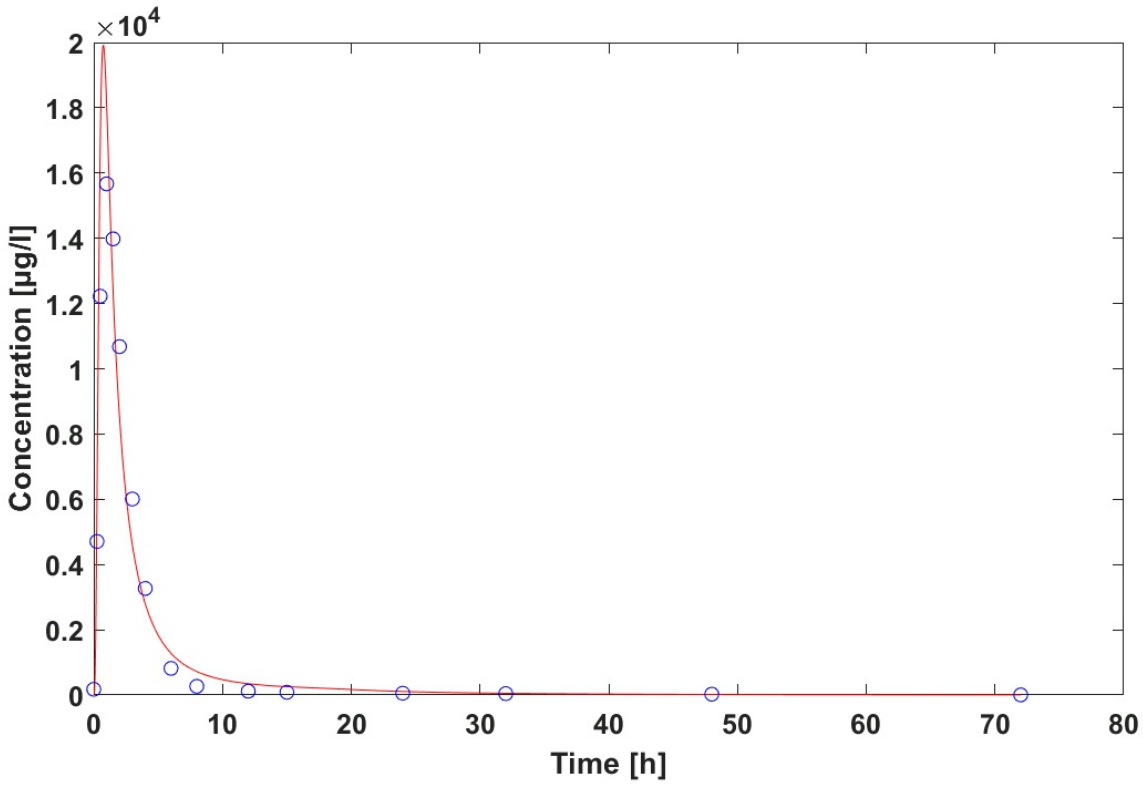
Time Profile Analysis 1

gravir-Peripheral Venous Blood-Plasma-Concentration
okinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 17-Raltegravir-Peripheral Venous Blood-Plasma-nM



Time Profile Analysis

gravir-Peripheral Venous Blood-Plasma-Concentration
okinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 17-Raltegravir-Peripheral Venous Blood-Plasma-nM



Time Profile Analysis 1

ɪravir-Peripheral Venous Blood-Plasma-Concentration
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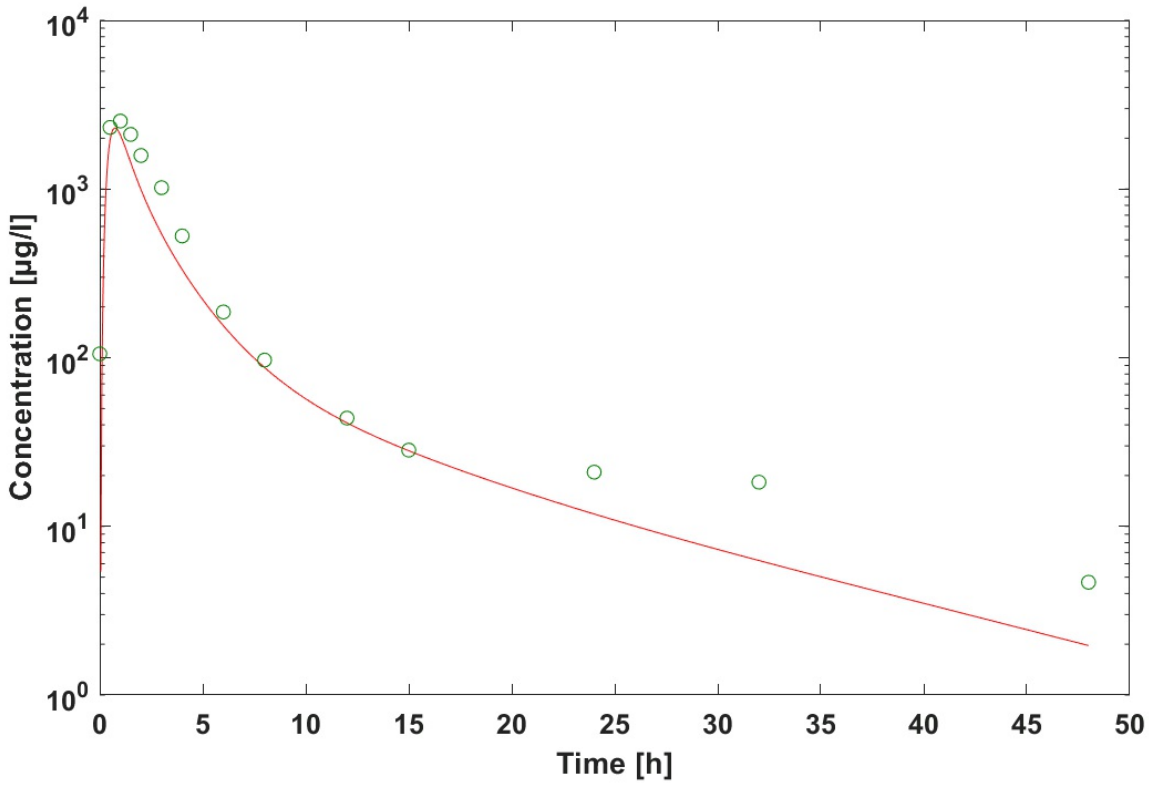
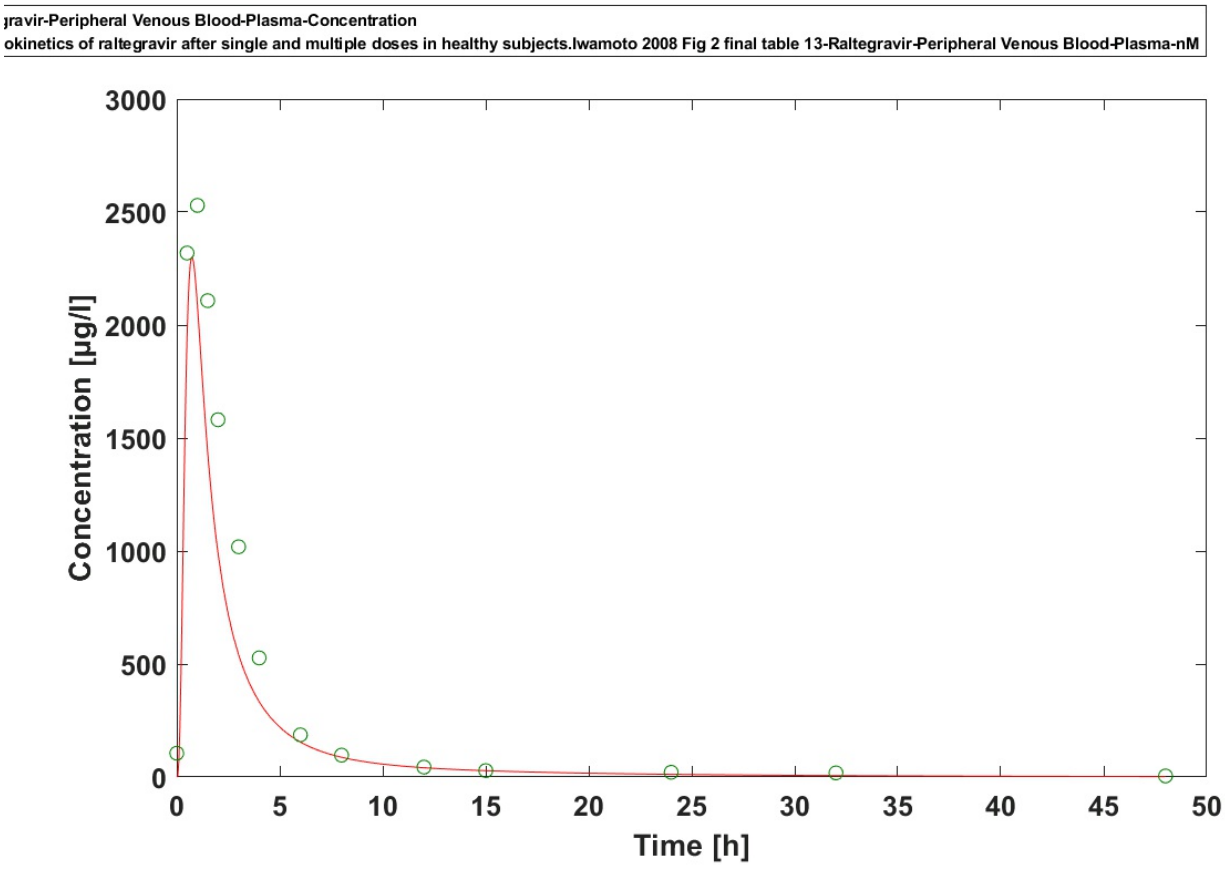


Time Profile Analysis



Time Profile Analysis 1

avir-Peripheral Venous Blood-Plasma-Concentration
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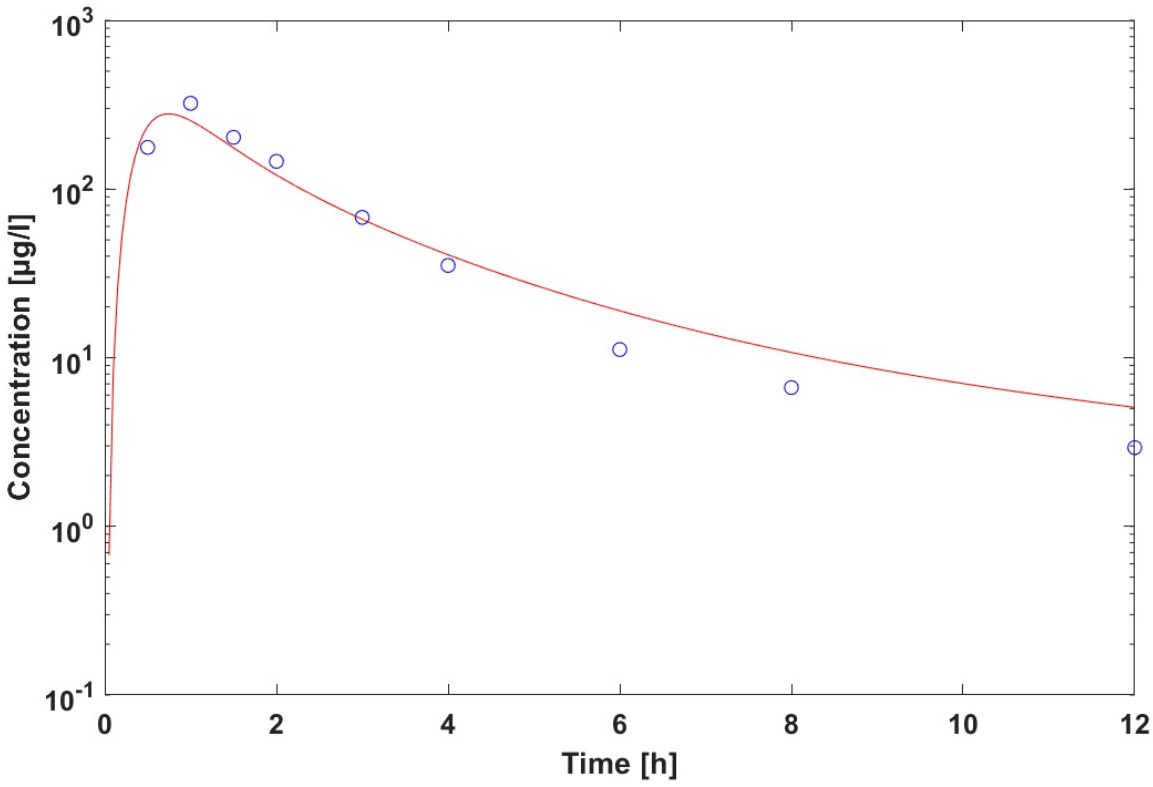
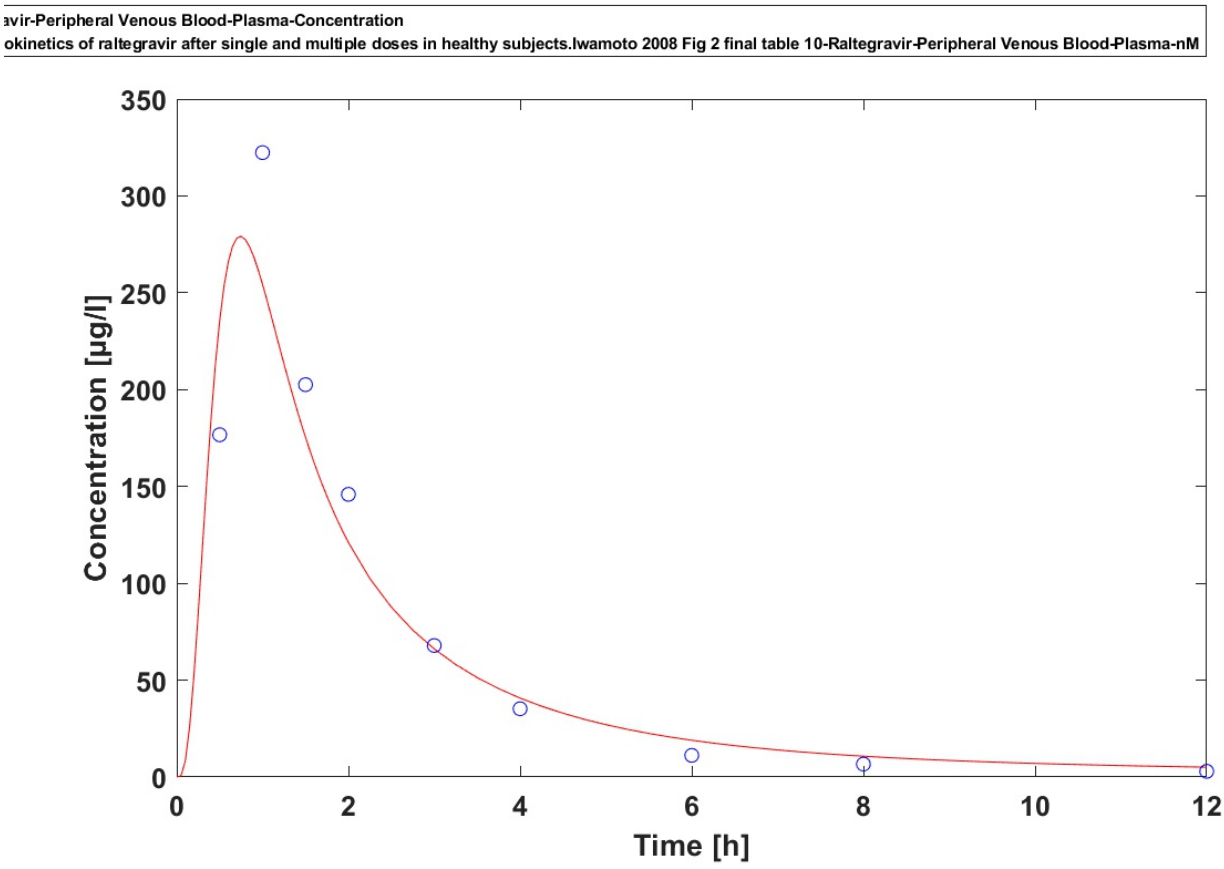
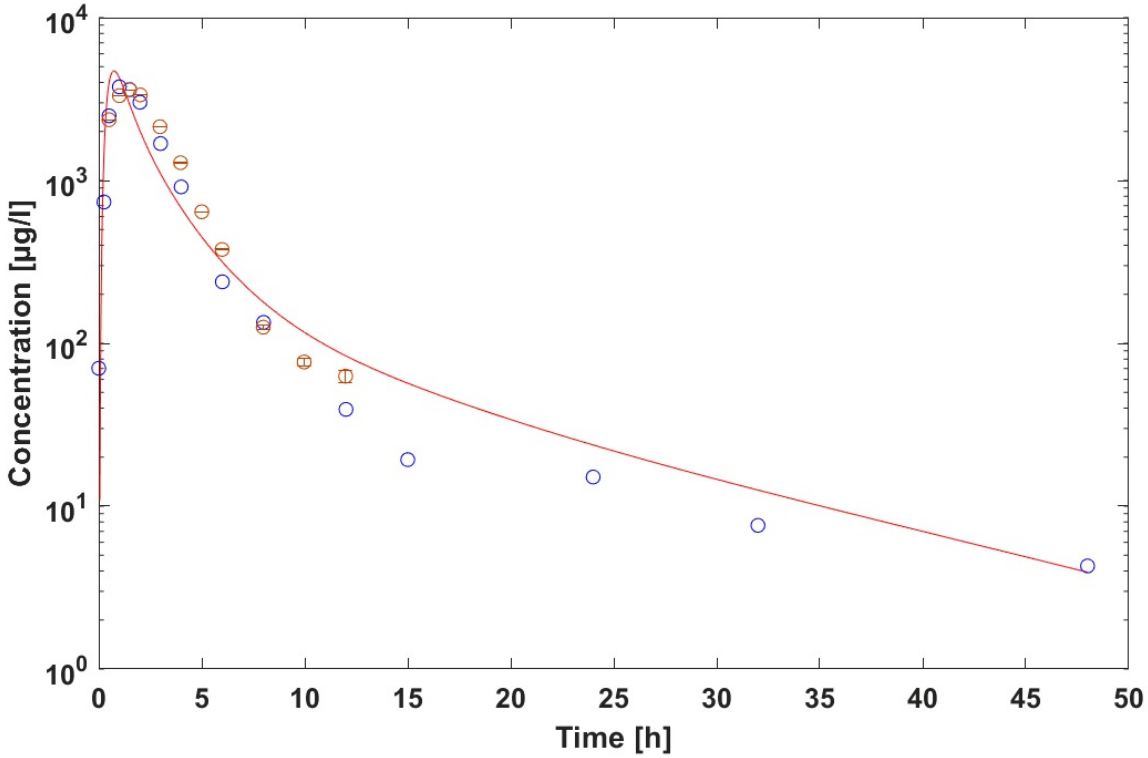


Time Profile Analysis



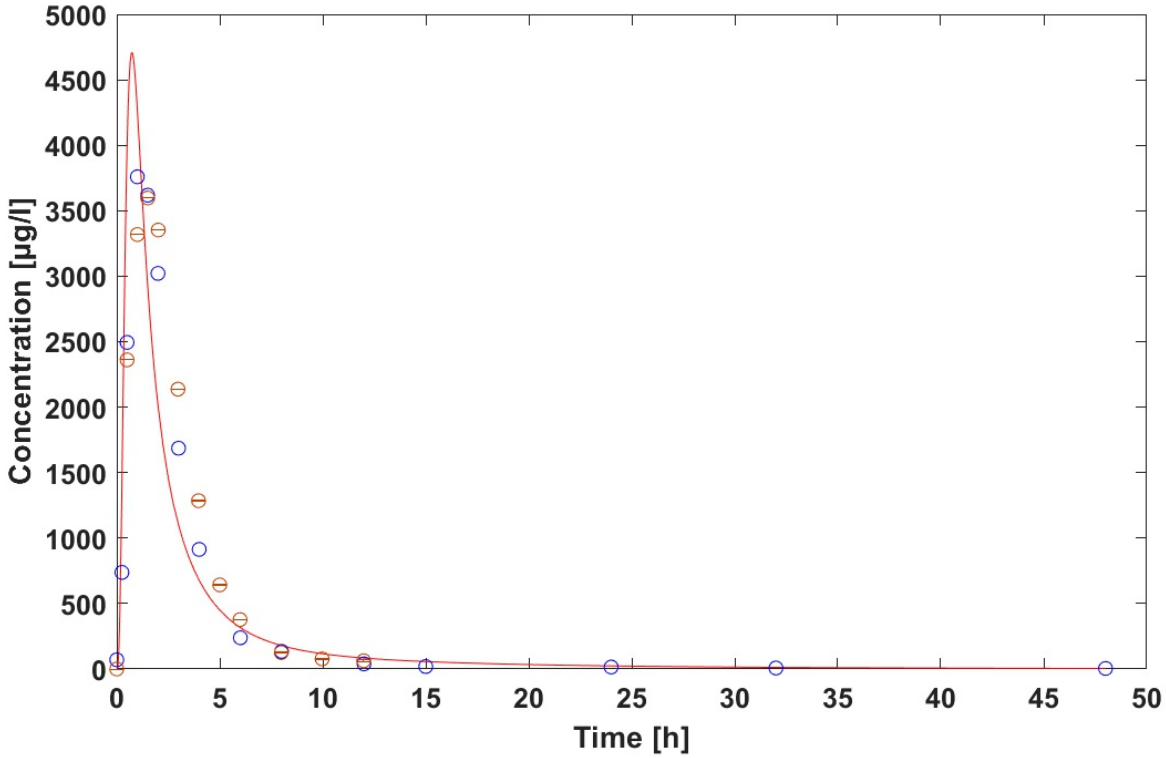
Time Profile Analysis 1

avir-Peripheral Venous Blood-Plasma-Concentration
okinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 14-Raltegravir-Peripheral Venous Blood-Plasma-nM
ıcer of Drug-Metabolizing Enzymes_figure 1a.Figure 1-Raltegravir-Peripheral Venous Blood-Plasma-µg/L



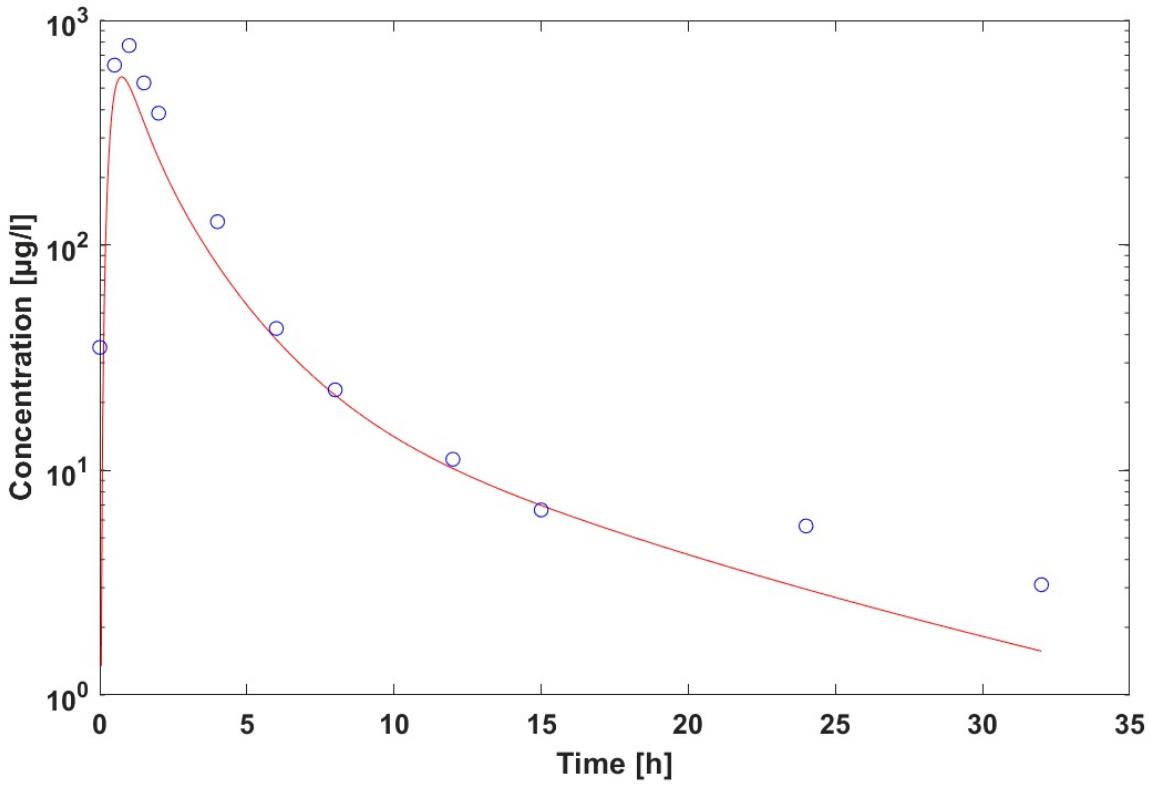
Time Profile Analysis

avir-Peripheral Venous Blood-Plasma-Concentration
okinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 14-Raltegravir-Peripheral Venous Blood-Plasma-nM
ıcer of Drug-Metabolizing Enzymes_figure 1a.Figure 1-Raltegravir-Peripheral Venous Blood-Plasma-µg/L

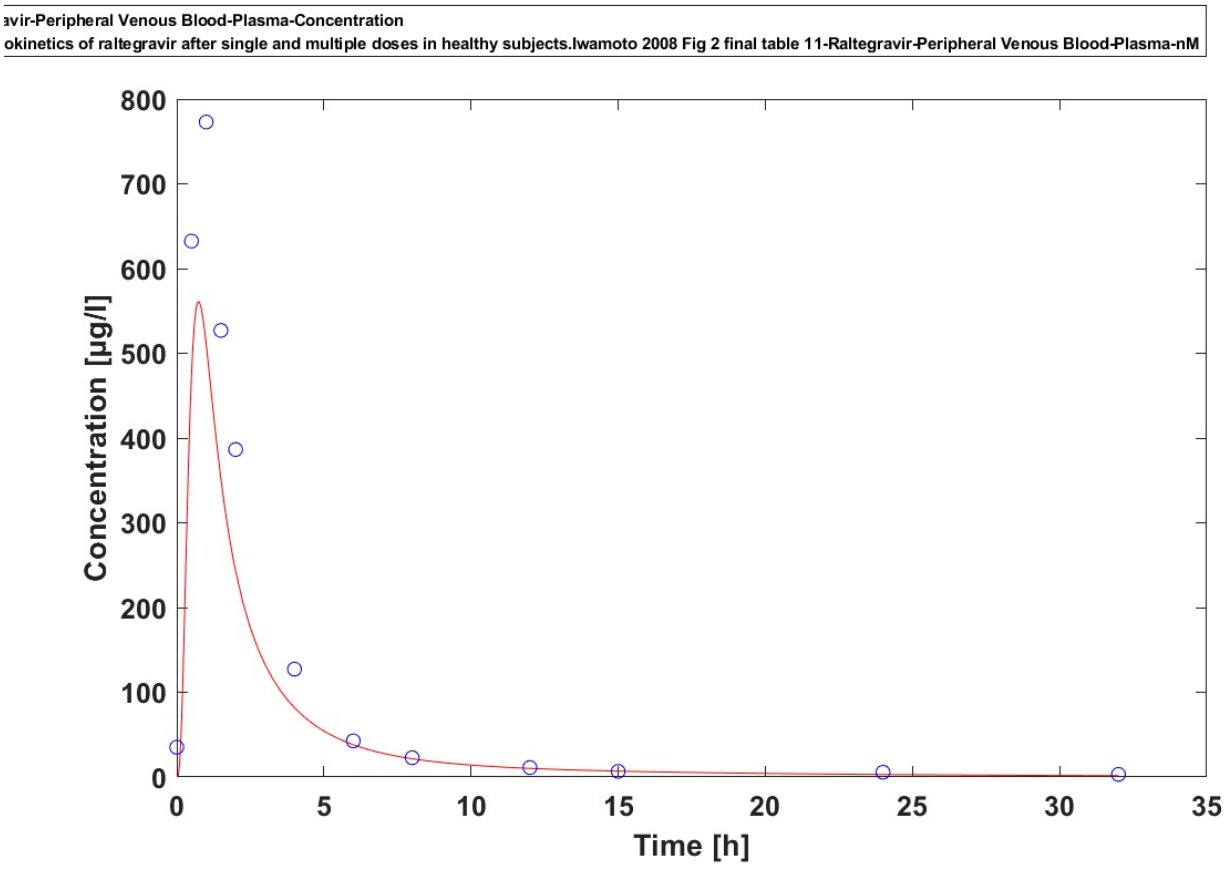


Time Profile Analysis 1

avir-Peripheral Venous Blood-Plasma-Concentration
okinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 11-Raltegravir-Peripheral Venous Blood-Plasma-nM

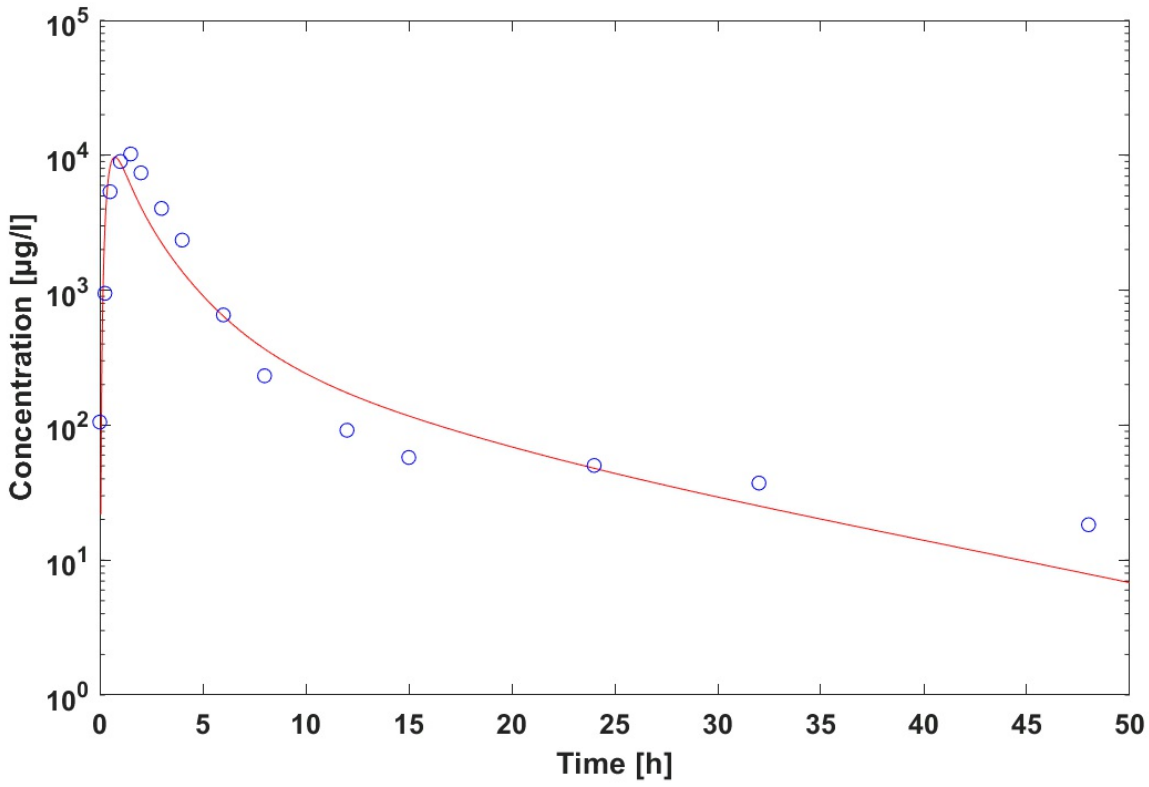


Time Profile Analysis



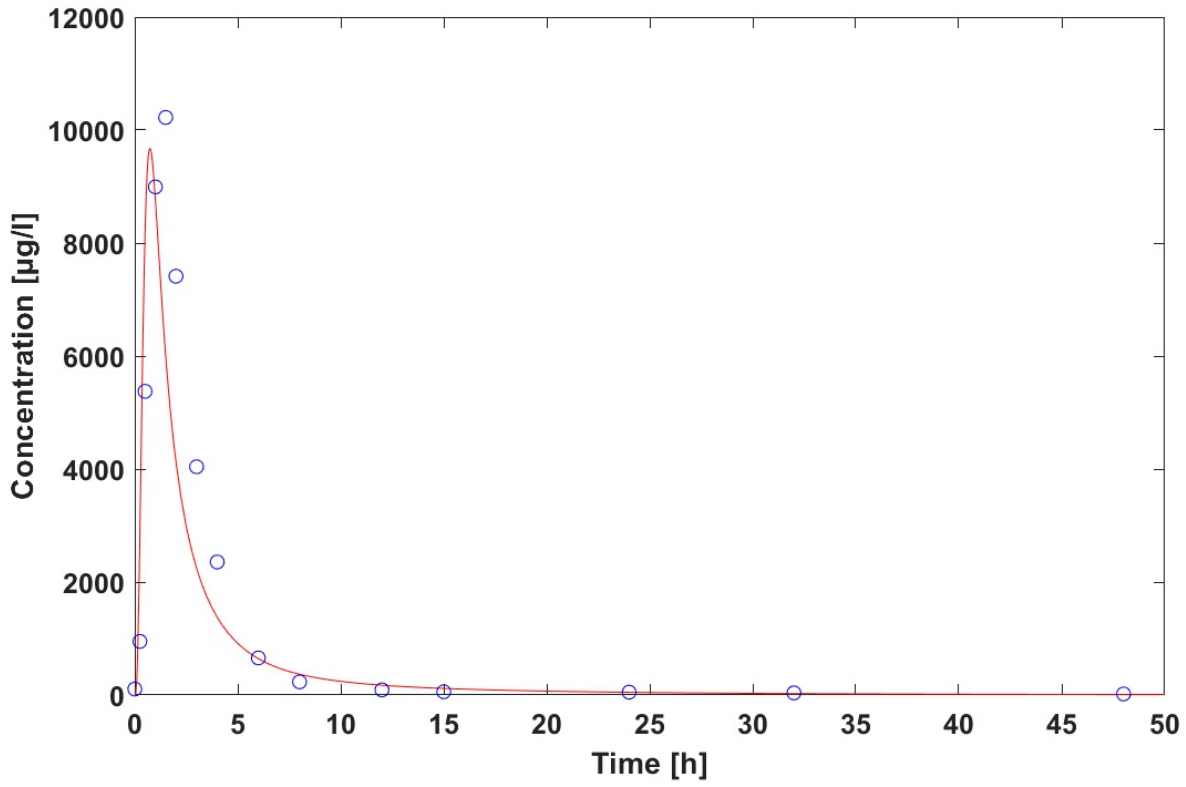
Time Profile Analysis 1

ravir-Peripheral Venous Blood-Plasma-Concentration
okinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 15-Raltegravir-Peripheral Venous Blood-Plasma-nM



Time Profile Analysis

ravir-Peripheral Venous Blood-Plasma-Concentration
okinetics of raltegravir after single and multiple doses in healthy subjects.Iwamoto 2008 Fig 2 final table 15-Raltegravir-Peripheral Venous Blood-Plasma-nM



Time Profile Analysis 1

1.3 Conclusion

1.3 Conclusions

The final raltegravir PBPK model applies metabolism by UGT1A1, UGT1A9 and glomerular filtration and adequately describes the pharmacokinetics of raltegravir in adults receiving SD, MD of Raltegravir ranging from 10mg to 1600mg, including four different oral formulations.

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

References

References

Iwamoto M, Wenning LA, Nguyen BY, Teppler H, Moreau AR, Rhodes RR, Hanley WD, Jin B, Harvey CM, Breidinger SA, Azrolan N, Farmer HF Jr, Isaacs RD, Chodakewitz JA, Stone JA, Wagner JA. Effects of omeprazole on plasma levels of raltegravir. Clin Infect Dis. 2009 Feb 15;48(4):489-92. doi: 10.1086/596503.

Iwamoto M, Wenning LA, Petry AS, Laethem M, De Smet M, Kost JT, Merschman SA, Strohmaier KM, Ramael S, Lasseter KC, Stone JA, Gottesdiener KM, Wagner JA. Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. Clin Pharmacol Ther. 2008 Feb;83(2):293-9. Epub 2007 Aug 22.

Kassahun K, McIntosh I, Cui D, Hreniuk D, Merschman S, Lasseter K, Azrolan N, Iwamoto M, Wagner JA, Wenning LA. Metabolism and disposition in humans of raltegravir (MK-0518), an anti-AIDS drug targeting the human immunodeficiency virus 1 integrase enzyme. Drug Metab Dispos. 2007 Sep;35(9):1657-63. Epub 2007 Jun 25.

Kuepfer L, Niederalt C, Wendl T, Schlender JF, Willmann S, Lippert J, Block M, Eissing T, Teutonico D. Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model.CPT Pharmacometrics Syst Pharmacol. 2016 Oct;5(10):516-531. doi: 10.1002/psp4.12134. Epub 2016 Oct 19.

Larissa A. Wenning,, William D. Hanley, Diana M. Brainard, Amelia S. Petry, Kalyan Ghosh, Bo Jin, Eric Mangin, Thomas C. Marbury, Jolene K. Berg, Jeffrey A. Chodakewitz, Julie A. Stone,1 Keith M. Gottesdiener, John A. Wagner, and Marian Iwamoto. Effect of Rifampin, a Potent Inducer of Drug-Metabolizing Enzymes, on the Pharmacokinetics of Raltegravir. Antimicrob Agents Chemother. 2009 Jul; 53(7): 2852–2856.

Laufer R, Paz OG, Di Marco A, Bonelli F, Monteagudo E, Summa V, Rowley M. Quantitative prediction of human clearance guiding the development of Raltegravir (MK-0518, isentress) and related HIV integrase inhibitors. Drug Metab Dispos. 2009 Apr;37(4):873-83. doi: 10.1124/dmd.108.023804. Epub 2009 Jan 14.

Markowitz M, Morales-Ramirez JO, Nguyen BY, Kovacs CM, Steigbigel RT, Cooper DA, Liporace R, Schwartz R, Isaacs R, Gilde LR, Wenning L, Zhao J, Teppler H. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. J Acquir Immune Defic Syndr. 2006 Dec 15;43(5):509-15.

Moss DM, Siccardi M, Back DJ, Owen A. Predicting intestinal absorption of raltegravir using a population-based ADME simulation. J Antimicrob Chemother. 2013 Jul;68(7):1627-34. doi: 10.1093/jac/dkt084. Epub 2013 Mar 20.

Moss DM, Siccardi M, Murphy M, Piperakis MM, Khoo SH, Back DJ, Owen A. Divalent metals and pH alter raltegravir disposition in vitro. Antimicrob Agents Chemother. 2012 Jun;56(6):3020-6. doi: 10.1128/AAC.06407-11. Epub 2012 Mar 26.

Parrott N, Lave T. Applications of physiologically based absorption models in drug discovery and development. Mol Pharm. 2008 Sep-Oct;5(5):760-75. doi: 10.1021/mp8000155. Epub 2008 Jun 12.

PK-Sim Ontogeny Database Version 7.3 (https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/38cf71b384cfc25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf)

Rhee EG, Rizk ML, Brainard DM, Gendrano IN 3rd, Jin B, Wenning LA, Wagner JA, Iwamoto M. A pharmacokinetic comparison of adult and paediatric formulations of raltegravir in healthy adults. Antivir Ther. 2014;19(6):619-24. doi: 10.3851/IMP2765. Epub 2014 Mar 7.

Schlender JF, Meyer M, Thelen K, Krauss M, Willmann S, Eissing T, Jaehde U. Development of a Whole-Body Physiologically Based Pharmacokinetic Approach to Assess the Pharmacokinetics of Drugs in Elderly Individuals. Clin Pharmacokinet. 2016 Dec;55(12):1573-1589.

Sjögren E, Westergren J, Grant I, Hanisch G, Lindfors L, Lennernäs H, Abrahamsson B, Tannergren C. In silico predictions of gastrointestinal drug absorption in pharmaceutical product development: application of the mechanistic absorption model GI-Sim. Eur J Pharm Sci. 2013 Jul 16;49(4):679-98. doi: 10.1016/j.ejps.2013.05.019. Epub 2013 May 29.

Sun D, Lennernas H, Welage LS, Barnett JL, Landowski CP, Foster D, Fleisher D, Lee KD, Amidon GL. , Comparison of human duodenum and Caco-2 gene expression profiles for 12,000 gene sequences tags and correlation with permeability of 26 drugs. Pharm Res. 2002 Oct;19(10):1400-16.

Thelen K, Coboeken K, Willmann S, Burghaus R, Dressman JB, Lippert J. Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part 1: oral solutions. J Pharm Sci. 2011 Dec;100(12):5324-45. doi: 10.1002/jps.22726. Epub 2011 Oct 12