Project
Fit-HV_manuscrit

bpasquiers

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Contents

Part I

Building Blocks

Chapter 1

Individuals

1.1 HV1

1.1.1 Biometrics

Population Properties

Population Properties	Value
Species	Human
Population	European (ICRP, 2002)
Gender	Male

Table 1.1: Population Properties

Individual Parameters

Individual Parameters	Value	Unit
Age	30.00	year(s)
Weight	73.00	kg
Height	176.00	cm
BMI	23.57	kg/m^2

Table 1.2: Individual Parameters

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 1.3: Calculation methods

1.1.2 Anatomy & Physiology

Default

1.1.3 Expression

1.1.3.1 Metabolizing Enzymes

None

1.1.3.2 Transport Proteins

None

1.1.3.3 Protein Binding Partners

VEGFA
Reference concentration: 3.00E-4 µmol/l
t1/2 (liver): 36.00 h
t1/2 (intestine): 23.00 h
Ontogeny/Variability like: Undefined
Localization: Interstitial, BloodCellsMembrane, VascMembraneTissueSide
Expression Levels

Relative expression	Name	Value
VEGFA	0.18	0.18 %
VEGFA	0.18	0.18 %

Table 1.4: Expression Levels

1.2 HV_chinese

1.2.1 Biometrics

Population Properties

Population Properties	Value
Species	Human
Population	Asian (Tanaka, 1996)
Gender	Male

Table 1.5: Population Properties

Individual Parameters

Individual Parameters	Value	Unit
Age	30.00	year(s)
Weight	60.03	kg
Height	169.96	cm
BMI	20.78	kg/m^2

Table 1.6: Individual Parameters

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 1.7: Calculation methods

1.2.2 Anatomy & Physiology

Default

1.2.3 Expression

1.2.3.1 Metabolizing Enzymes

None

1.2.3.2 Transport Proteins

None

1.2.3.3 Protein Binding Partners

VEGFA
Reference concentration: 3.00E-4 µmol/l
t1/2 (liver): 36.00 h
t1/2 (intestine): 23.00 h
Ontogeny/Variability like: Undefined
Localization: Interstitial, BloodCellsMembrane, VascMembraneTissueSide
Expression Levels

Relative expression	Name	Value
VEGFA	0.18	0.18 %
VEGFA	0.18	0.18 %

Table 1.8: Expression Levels

1.3 Patient1

1.3.1 Biometrics

Population Properties

Population Properties	Value
Species	Human
Population	European (ICRP, 2002)
Gender	Male

Table 1.9: Population Properties

Individual Parameters

Individual Parameters	Value	Unit
Age	30.00	year(s)
Weight	73.00	kg
Height	176.00	cm
BMI	23.57	kg/m^2

Table 1.10: Individual Parameters

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 1.11: Calculation methods

1.3.2 Anatomy & Physiology

Default

1.3.3 Expression

1.3.3.1 Metabolizing Enzymes

None

1.3.3.2 Transport Proteins

None

1.3.3.3 Protein Binding Partners

VEGFA
Reference concentration: 3.00E-3 µmol/l
t1/2 (liver): 36.00 h
t1/2 (intestine): 23.00 h
Ontogeny/Variability like: Undefined
Localization: Interstitial, BloodCellsMembrane, VascMembraneTissueSide
Expression Levels

Relative expression	Name	Value
VEGFA	0.18	0.18 %
VEGFA	0.18	0.18 %

Table 1.12: Expression Levels

1.4 Patient_ped

1.4.1 Biometrics

Population Properties

Population Properties	Value
Species	Human
Population	European (ICRP, 2002)
Gender	Male

Table 1.13: Population Properties

Individual Parameters

Individual Parameters	Value	Unit
Age	13.00	year(s)
Weight	46.40	kg
Height	155.40	cm
BMI	19.21	kg/m^2

Table 1.14: Individual Parameters

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 1.15: Calculation methods

1.4.2 Anatomy & Physiology

Default

1.4.3 Expression

1.4.3.1 Metabolizing Enzymes

None

1.4.3.2 Transport Proteins

None

1.4.3.3 Protein Binding Partners

VEGFA
Reference concentration: 3.86E-3 µmol/l
t1/2 (liver): 36.00 h
t1/2 (intestine): 23.00 h

Ontogeny/Variability like: Undefined
Localization: Interstitial, BloodCellsMembrane, VascMembraneTissueSide
Expression Levels

Relative expression	Name	Value
VEGFA	0.18	0.18 %
VEGFA	0.18	0.18 %

Table 1.16: Expression Levels

Chapter 2

Compounds

2.1 Bevacizumab_human

2.1.1 Basic Physico-chemistry

Is small molecule: No

2.1.1.1 Molecular weight

Parameter	Value	Unit
Molecular weight	150.00	kDa
Effective molecular weight	150000.00	g/mol
I	0	
F	0	
Cl	0	
Br	0	

Table 2.1: Molecular weight

2.1.1.2 Lipophilicity

Experiment	Lipophilicity [Log Units]
Measurement	−5.00

Table 2.2: Lipophilicity

Table 2.2 lists lipophilicity values for compound Bevacizumab_human.

2.1.1.3 Fraction unbound (plasma, reference value)

Experiment	Fraction Unbound	Species
Measurement	1.00	Human

Table 2.3: Fraction unbound (plasma, reference value)

Table 2.3 lists fraction unbound values for compound Bevacizumab_human.

2.1.1.4 Solubility

Experiment	Ref-pH	Solubility at Ref-pH [mg/l]	Solubility gain per charge
Measurement	7.00	9999.00	1000.00

Table 2.4: Solubility

Table 2.4 lists solubility values for compound Bevacizumab_human.

2.1.2 ADME

2.1.2.1 Absorption

Specific intestinal permeability

Experiment	Lipophilicity	Permeability [cm/min]
Calculated	Measurement	0

Table 2.5: Specific intestinal permeability

Table 2.5 lists intestinal permeability values for compound Bevacizumab_human.

2.1.2.2 Distribution

Specific organ permeability

Experiment	Lipophilicity	Permeability [cm/min]
Calculated	Measurement	0

Table 2.6: Specific organ permeability

Table 2.6 lists organ permeability values for compound Bevacizumab_human.

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 2.7: Calculation methods

VEGF 2-Paper 2
Process Type: Specific Binding

Parameter	Value	Unit
koff	3.10×10^{-5}	1/s
Kd	0.06	nmol/l

Table 2.8: Parameters

VEGFA-Paper
Process Type: Specific Binding

Parameter	Value	Unit
koff	3.10×10^{-5}	1/s
Kd	0.06	nmol/l

Table 2.9: Parameters

2.2 Bevacizumab

2.2.1 Basic Physico-chemistry

Is small molecule: No

2.2.1.1 Molecular weight

Parameter	Value	Unit
Molecular weight	150.00	kDa
Effective molecular weight	150000.00	g/mol
I	0	
F	0	
Cl	0	
Br	0	

Table 2.10: Molecular weight

2.2.1.2 Lipophilicity

Experiment	Lipophilicity [Log Units]
Measurement	−5.00

Table 2.11: Lipophilicity

Table 2.11 lists lipophilicity values for compound Bevacizumab.

2.2.1.3 Fraction unbound (plasma, reference value)

Experiment	Fraction Unbound	Species
Measurement	1.00	Human

Table 2.12: Fraction unbound (plasma, reference value)

Table 2.12 lists fraction unbound values for compound Bevacizumab.

2.2.1.4 Solubility

Experiment	Ref-pH	Solubility at Ref-pH [mg/l]	Solubility gain per charge
Measurement	7.00	9999.00	1000.00

Table 2.13: Solubility

Table 2.13 lists solubility values for compound Bevacizumab.

2.2.2 ADME

2.2.2.1 Absorption

Specific intestinal permeability

Experiment	Lipophilicity	Permeability [cm/min]
Calculated	Measurement	0

Table 2.14: Specific intestinal permeability

Table 2.14 lists intestinal permeability values for compound Bevacizumab.

2.2.2.2 Distribution

Specific organ permeability

Experiment	Lipophilicity	Permeability [cm/min]
Calculated	Measurement	0

Table 2.15: Specific organ permeability

Table 2.15 lists organ permeability values for compound Bevacizumab.

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 2.16: Calculation methods

VEGF 2-Paper 2
Process Type: Specific Binding

Parameter	Value	Unit
koff	3.10×10^{-5}	1/s
Kd	0.06	nmol/l

Table 2.17: Parameters

VEGFA-Paper
Process Type: Specific Binding

Parameter	Value	Unit
koff	3.10×10^{-5}	1/s
Kd	0.06	nmol/l

Table 2.18: Parameters

Chapter 3

Protocols

3.1 Perfusion 90 min_1mg/kg

Property	Value
Process Type	Simple protocol
Administration type	Intravenous Infusion
Dosing interval	Single

Table 3.1

Parameter	Value	Unit
Dose	1.00	mg/kg
Infusion time	90.00	min

Table 3.2: Parameters

3.2 Perfusion 90 min_3mg/kg

Property	Value
Process Type	Simple protocol
Administration type	Intravenous Infusion
Dosing interval	Single

Table 3.3

Parameter	Value	Unit
Dose	3.00	mg/kg
Infusion time	90.00	min

Table 3.4: Parameters

3.3 Perfusion 90 min_0.5mg/kg

Property	Value
Process Type	Simple protocol
Administration type	Intravenous Infusion
Dosing interval	Single

Table 3.5

Parameter	Value	Unit
Dose	0.50	mg/kg
Infusion time	90.00	min

Table 3.6: Parameters

3.4 Infusion 0.3mg/kg human

Schema 1

- Start time: 0 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 0.30 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 0.30 mg/kg
    - Infusion time: 90.00 min

Schema 2

- Start time: 28.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 0.30 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 0.30 mg/kg
    - Infusion time: 60.00 min

Schema 3

- Start time: 35.00 day(s)
- Number of Repetitions: 1.00

- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 0.30 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 0.30 mg/kg
    - Infusion time: 60.00 min

Schema 4

- Start time: 42.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 0.30 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 0.30 mg/kg
    - Infusion time: 60.00 min

3.5 Infusion 10mg/kg human

Schema 1

- Start time: 0 h
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 10.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 10.00 mg/kg
    - Infusion time: 90.00 min

Schema 2

- Start time: 28.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 10.00 mg/kg
  - Administration type: Intravenous Infusion

  - **Parameters**
    * Dose: 10.00 mg/kg
    * Infusion time: 60.00 min

Schema 3

- Start time: 35.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 10.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    * Dose: 10.00 mg/kg
    * Infusion time: 60.00 min

Schema 4

- Start time: 42.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 10.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    * Dose: 10.00 mg/kg
    * Infusion time: 60.00 min

3.6 Infusion 1mg/kg human

Schema 1

- Start time: 0 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 90.00 min
- **Dosing**
  - Start time: 0 h
  - Dose: 1.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    * Dose: 1.00 mg/kg
    * Infusion time: 90.00 min

Schema 3

- Start time: 28.00 day(s)

- Number of Repetitions: 1.00
- Time Between Repetitions: 90.00 min
- **Dosing**
  - Start time: 0 h
  - Dose: 1.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 1.00 mg/kg
    - Infusion time: 60.00 min

Schema 4

- Start time: 35.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 90.00 min
- **Dosing**
  - Start time: 0 h
  - Dose: 1.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 1.00 mg/kg
    - Infusion time: 60.00 min

Schema 5

- Start time: 42.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 90.00 min
- **Dosing**
  - Start time: 0 h
  - Dose: 1.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 1.00 mg/kg
    - Infusion time: 60.00 min

3.7 Infusion 3mg/kg human

Schema 1

- Start time: 0 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h

  - Dose: 3.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 3.00 mg/kg
    - Infusion time: 60.00 min

Schema 2

- Start time: 28.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 3.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 3.00 mg/kg
    - Infusion time: 60.00 min

Schema 3

- Start time: 35.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 3.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 3.00 mg/kg
    - Infusion time: 60.00 min

Schema 4

- Start time: 42.00 day(s)
- Number of Repetitions: 1.00
- Time Between Repetitions: 0 h
- **Dosing**
  - Start time: 0 h
  - Dose: 3.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 3.00 mg/kg
    - Infusion time: 60.00 min

3.8 5mpk_every2weeks

Schema 1

- Start time: 0 h
- Number of Repetitions: 7.00
- Time Between Repetitions: 14.00 day(s)
- **Dosing**
  - Start time: 0 h
  - Dose: 5.00 mg/kg
  - Administration type: Intravenous Infusion
  - **Parameters**
    - Dose: 5.00 mg/kg
    - Infusion time: 60.00 min

3.9 Infusion_5mg/kg

Property	Value
Process Type	Simple protocol
Administration type	Intravenous Infusion
Dosing interval	Single

Table 3.7

Parameter	Value	Unit
Dose	5.00	mg/kg
Infusion time	60.00	min

Table 3.8: Parameters

3.10 Infusion_15mg/kg

Property	Value
Process Type	Simple protocol
Administration type	Intravenous Infusion
Dosing interval	Single

Table 3.9

Parameter	Value	Unit
Dose	15.00	mg/kg
Infusion time	60.00	min

Table 3.10: Parameters

Part II

Simulations

Chapter 1

HV_1mg/kg

1.1 Used building blocks

Building Block	Name
Individual	HV1 (see section 1.1 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Perfusion 90 min_1mg/kg (see section 3.1 in Part I)

Table 1.1: Building Block

1.2 Simulation Properties

1.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 1.2: Calculation methods

1.2.2 Compounds

1.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	**Alternative in compound**	**Value**	**Unit**
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 1.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 1.4: Calculation methods

1.2.3 Processes

1.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

1.2.4 Administration

1.2.4.1 Bevacizumab

Simple protocol
Intravenous Infusion
Dosing interval: Single
Dose: 1.00 mg/kg
Infusion time: 90.00 min

1.3 Charts

1.3.1 Time Profile Analysis

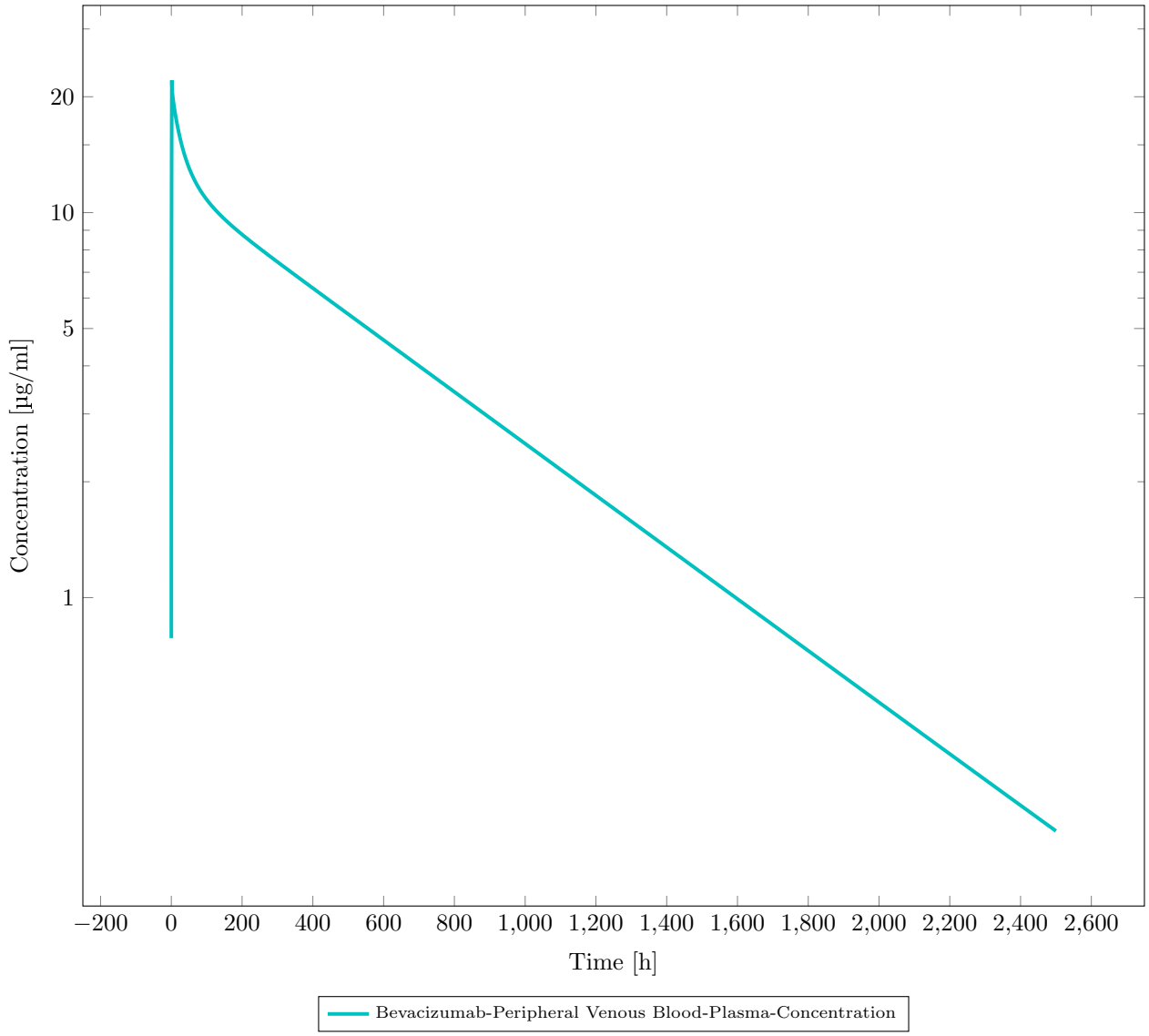

Figure 1.1

1.3.1.1 Global PK-Analyses

Parameter	Compound	Value	Unit
Vss (plasma)	Bevacizumab	78.17	ml/kg
Vd (plasma)	Bevacizumab	82.14	ml/kg
Vss (phys-chem)	Bevacizumab	623.05	ml/kg
Total plasma clearance	Bevacizumab	2.09×10^{-3}	ml/min/kg

Table 1.5: Global PK-Analyses

1.3.1.2 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	0.15	µmol/l
C_max_norm	2.20×10^{7}	mg/l
t_max	1.50	h
C_tEnd	1.65×10^{-3}	µmol/l
AUC_tEnd	3117.62	µmol*min/l
AUC_tEnd_norm	4.68×10^{14}	µg*min/l
AUC_inf	3182.35	µmol*min/l
AUC_inf_norm	4.77×10^{14}	µg*min/l
MRT	621.93	h
Half-Life	452.95	h
% AUC (tlast-∞)	0.02	
Total body clearance/F	2.09×10^{-3}	ml/min/kg
Vss (plasma)/F	78.17	ml/kg
Vd (plasma)/F	82.14	ml/kg

Table 1.6: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Beva_Demarchi2021_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim-Bevacizumab_human_sim-Measurement

Parameter	Value	Unit
C_max	0.15	µmol/l
C_max_norm	NaN	mg/l
t_max	4.86	h
C_tEnd	7.71×10^{-5}	µmol/l
AUC_tEnd	2942.18	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	2942.77	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	448.08	h
Half-Life	89.57	h
% AUC (tlast-∞)	2.03×10^{-4}	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 1.7: PK-Analyses for Beva_Demarchi2021_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim-Bevacizumab_human_sim-Measurement

Beva_Hetema2017_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim-Bevacizumab_human_sim-Measurement

Parameter	Value	Unit
C_max	0.16	µmol/l
C_max_norm	NaN	mg/l
t_max	0.64	h
C_tEnd	8.38×10^{-3}	µmol/l
AUC_tEnd	2638.13	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 1.8: PK-Analyses for Beva_Hetema2017_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim-Bevacizumab_human_sim-Measurement

Beva_Hummel2022_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim-Bevacizumab_human_sim-Measurement

Parameter	Value	Unit
C_max	0.17	µmol/l
C_max_norm	NaN	mg/l
t_max	1.50	h
C_tEnd	6.47×10^{-4}	µmol/l
AUC_tEnd	3230.16	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	3241.46	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	476.41	h
Half-Life	201.77	h
% AUC (tlast-∞)	3.49×10^{-3}	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 1.9: PK-Analyses for Beva_Hummel2022_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim-Bevacizumab_human_sim-Measurement

Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.1-Bevacizumab_human_sim-Measurement

Parameter	Value	Unit
C_max	0.17	µmol/l

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Parameter	Value	Unit
C_max_norm	NaN	mg/l
t_max	1.50	h
C_tEnd	1.18×10^{-3}	µmol/l
AUC_tEnd	2779.89	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	2821.02	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	532.48	h
Half-Life	404.25	h
% AUC (tlast-∞)	0.01	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 1.10: PK-Analyses for Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.1-Bevacizumab_human_sim-Measurement

Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.2-Bevacizumab_human_sim-Measurement

Parameter	Value	Unit
C_max	0.12	µmol/l
C_max_norm	NaN	mg/l
t_max	14.58	h
C_tEnd	2.20×10^{-4}	µmol/l
AUC_tEnd	2257.21	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 1.11: PK-Analyses for Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.2-Bevacizumab_human_sim-Measurement

Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.3-Bevacizumab_human_sim-Measurement

Parameter	Value	Unit
C_max	0.12	µmol/l

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Parameter	**Value**	**Unit**
C_max_norm	NaN	mg/l
t_max	14.58	h
C_tEnd	2.48×10^{-3}	µmol/l
AUC_tEnd	2995.12	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 1.12: PK-Analyses for Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.3-Bevacizumab_human_sim-Measurement

Chapter 2

HV_3mg/kg

2.1 Used building blocks

Building Block	Name
Individual	HV1 (see section 1.1 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Perfusion 90 min_3mg/kg (see section 3.2 in Part I)

Table 2.1: Building Block

2.2 Simulation Properties

2.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 2.2: Calculation methods

2.2.2 Compounds

2.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	**Alternative in compound**	**Value**	**Unit**
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 2.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 2.4: Calculation methods

2.2.3 Processes

2.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

2.2.4 Administration

2.2.4.1 Bevacizumab

Simple protocol
Intravenous Infusion
Dosing interval: Single
Dose: 3.00 mg/kg
Infusion time: 90.00 min

2.3 Charts

2.3.1 Time Profile Analysis

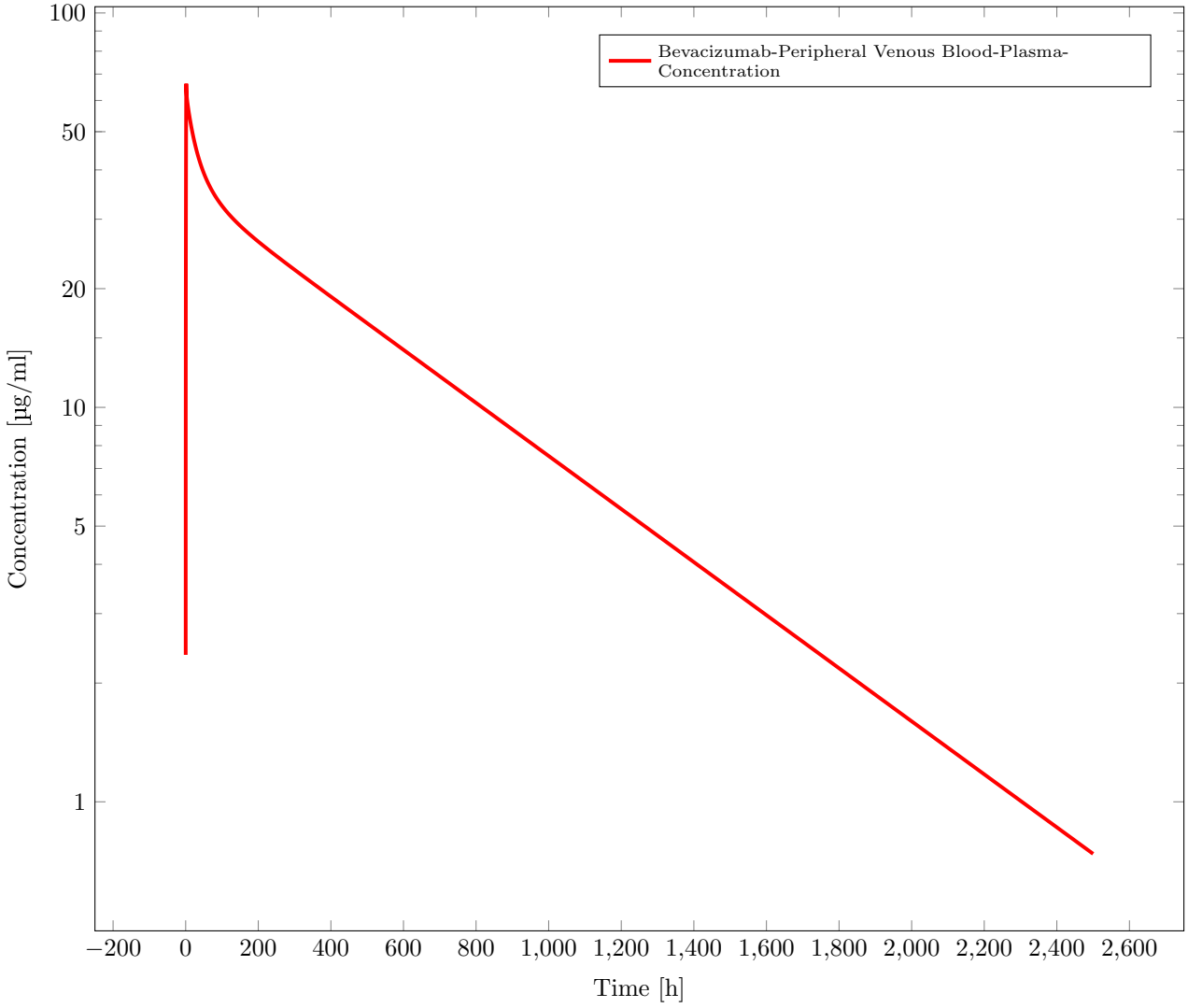

Figure 2.1

2.3.1.1 Global PK-Analyses

Parameter	Compound	Value	Unit
Vss (plasma)	Bevacizumab	78.05	ml/kg
Vd (plasma)	Bevacizumab	81.35	ml/kg
Vss (phys-chem)	Bevacizumab	623.05	ml/kg
Total plasma clearance	Bevacizumab	2.10×10^{-3}	ml/min/kg

Table 2.5: Global PK-Analyses

2.3.1.2 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	0.44	µmol/l
C_max_norm	2.21×10^{7}	mg/l
t_max	1.50	h
C_tEnd	4.92×10^{-3}	µmol/l
AUC_tEnd	9350.65	µmol*min/l
AUC_tEnd_norm	4.68×10^{14}	µg*min/l
AUC_inf	9541.60	µmol*min/l
AUC_inf_norm	4.77×10^{14}	µg*min/l
MRT	620.64	h
Half-Life	448.34	h
% AUC (tlast-∞)	0.02	
Total body clearance/F	2.10×10^{-3}	ml/min/kg
Vss (plasma)/F	78.05	ml/kg
Vd (plasma)/F	81.35	ml/kg

Table 2.6: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Beva_sinn2021_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim-Bevacizumab_human_-sim-Measurement

Parameter	Value	Unit
C_max	0.56	µmol/l
C_max_norm	NaN	mg/l
t_max	0.94	h
C_tEnd	6.84×10^{-3}	µmol/l
AUC_tEnd	13496.98	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	13722.24	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	569.85	h
Half-Life	380.52	h
% AUC (tlast-∞)	0.02	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 2.7: PK-Analyses for Beva_sinn2021_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim-Bevacizumab_human_sim-Measurement

Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.3-Bevacizumab_human_-sim-Measurement

Parameter	Value	Unit
C_max	0.39	µmol/l
C_max_norm	NaN	mg/l
t_max	47.73	h
C_tEnd	0.02	µmol/l
AUC_tEnd	12330.29	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 2.8: PK-Analyses for Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.3-Bevacizumab_human_sim-Measurement

Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.2-Bevacizumab_human_-sim-Measurement

Parameter	Value	Unit
C_max	0.27	µmol/l
C_max_norm	NaN	mg/l
t_max	47.73	h
C_tEnd	7.79×10^{-3}	µmol/l
AUC_tEnd	7591.91	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 2.9: PK-Analyses for Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.2-Bevacizumab_human_sim-Measurement

Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.1-Bevacizumab_human_-sim-Measurement

Parameter	Value	Unit
C_max	0.50	µmol/l

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Parameter	**Value**	**Unit**
C_max_norm	NaN	mg/l
t_max	1.50	h
C_tEnd	0.01	µmol/l
AUC_tEnd	11014.24	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 2.10: PK-Analyses for Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.1-Bevacizumab_human_sim-Measurement

Chapter 3

HV_0.5 mg/kg_chinese

3.1 Used building blocks

Building Block	Name
Individual	HV_chinese (see section 1.2 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Perfusion 90 min_0.5mg/kg (see section 3.3 in Part I)

Table 3.1: Building Block

3.2 Simulation Properties

3.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 3.2: Calculation methods

3.2.2 Compounds

3.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	**Alternative in compound**	**Value**	**Unit**
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 3.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 3.4: Calculation methods

3.2.3 Processes

3.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

3.2.4 Administration

3.2.4.1 Bevacizumab

Simple protocol
Intravenous Infusion
Dosing interval: Single
Dose: 0.50 mg/kg
Infusion time: 90.00 min

3.3 Charts

3.3.1 Time Profile Analysis

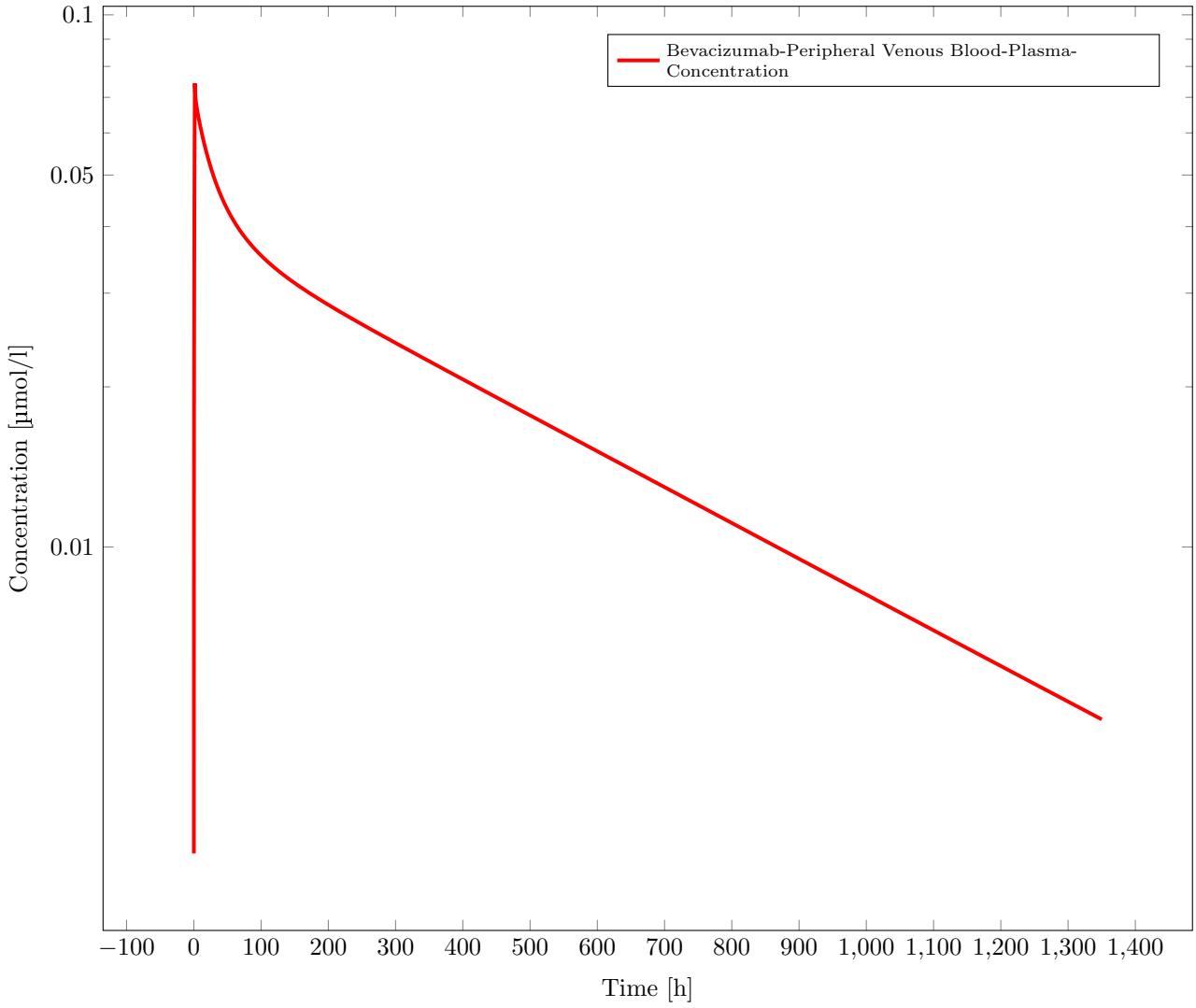

Figure 3.1

3.3.1.1 Global PK-Analyses

Parameter	Compound	Value	Unit
Vss (plasma)	Bevacizumab	79.80	ml/kg
Vd (plasma)	Bevacizumab	83.77	ml/kg
Vss (phys-chem)	Bevacizumab	616.73	ml/kg
Total plasma clearance	Bevacizumab	2.14×10^{-3}	ml/min/kg

Table 3.5: Global PK-Analyses

3.3.1.2 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	0.07	µmol/l
C_max_norm	2.23×10^{7}	mg/l
t_max	1.50	h
C_tEnd	4.74×10^{-3}	µmol/l
AUC_tEnd	1370.41	µmol*min/l
AUC_tEnd_norm	4.11×10^{14}	µg*min/l
AUC_inf	1555.93	µmol*min/l
AUC_inf_norm	4.67×10^{14}	µg*min/l
MRT	620.78	h
Half-Life	451.72	h
% AUC (tlast-∞)	0.12	
Total body clearance/F	2.14×10^{-3}	ml/min/kg
Vss (plasma)/F	79.80	ml/kg
Vd (plasma)/F	83.77	ml/kg

Table 3.6: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.1-Bevacizumab_human_sim-Measurement

Parameter	Value	Unit
C_max	0.04	µmol/l
C_max_norm	NaN	mg/l
t_max	2.00	h
C_tEnd	1.00×10^{-3}	µmol/l
AUC_tEnd	889.66	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 3.7: PK-Analyses for Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.1-Bevacizumab_human_sim-Measurement

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.2-Bevacizumab_human_sim-Measurement

Parameter	Value	Unit
C_max	0.04	µmol/l
C_max_norm	NaN	mg/l
t_max	2.00	h
C_tEnd	5.21×10^{-4}	µmol/l
AUC_tEnd	538.67	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 3.8: PK-Analyses for Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.2-Bevacizumab_human_sim-Measurement

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.3-Bevacizumab_human_-sim-Measurement

Parameter	Value	Unit
C_max	0.05	µmol/l
C_max_norm	NaN	mg/l
t_max	2.00	h
C_tEnd	7.56×10^{-4}	µmol/l
AUC_tEnd	1054.14	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 3.9: PK-Analyses for Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.3-Bevacizumab_human_sim-Measurement

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.4-Bevacizumab_human_-sim-Measurement

Parameter	Value	Unit
C_max	0.05	µmol/l

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Parameter	**Value**	**Unit**
C_max_norm	NaN	mg/l
t_max	2.00	h
C_tEnd	1.17×10^{-3}	µmol/l
AUC_tEnd	914.90	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 3.10: PK-Analyses for Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.4-Bevacizumab_human_sim-Measurement

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.5-Bevacizumab_human_-sim-Measurement

Parameter	**Value**	**Unit**
C_max	0.05	µmol/l
C_max_norm	NaN	mg/l
t_max	2.00	h
C_tEnd	1.08×10^{-3}	µmol/l
AUC_tEnd	766.72	µmol*min/l
AUC_tEnd_norm	NaN	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 3.11: PK-Analyses for Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.5-Bevacizumab_human_sim-Measurement

Chapter 4

Sim_Patient_1mg/kg

4.1 Used building blocks

Building Block	Name
Individual	Patient1 (see section 1.3 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Infusion 1mg/kg human (see section 3.6 in Part I)

Table 4.1: Building Block

4.2 Simulation Properties

4.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 4.2: Calculation methods

4.2.2 Compounds

4.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	**Alternative in compound**	**Value**	**Unit**
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 4.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 4.4: Calculation methods

4.2.3 Processes

4.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

4.2.4 Administration

4.2.4.1 Bevacizumab

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 1.00 mg/kg
Infusion time: 90.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 1.00 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 1.00 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 1.00 mg/kg
Infusion time: 60.00 min

4.3 Charts

4.3.1 Time Profile Analysis

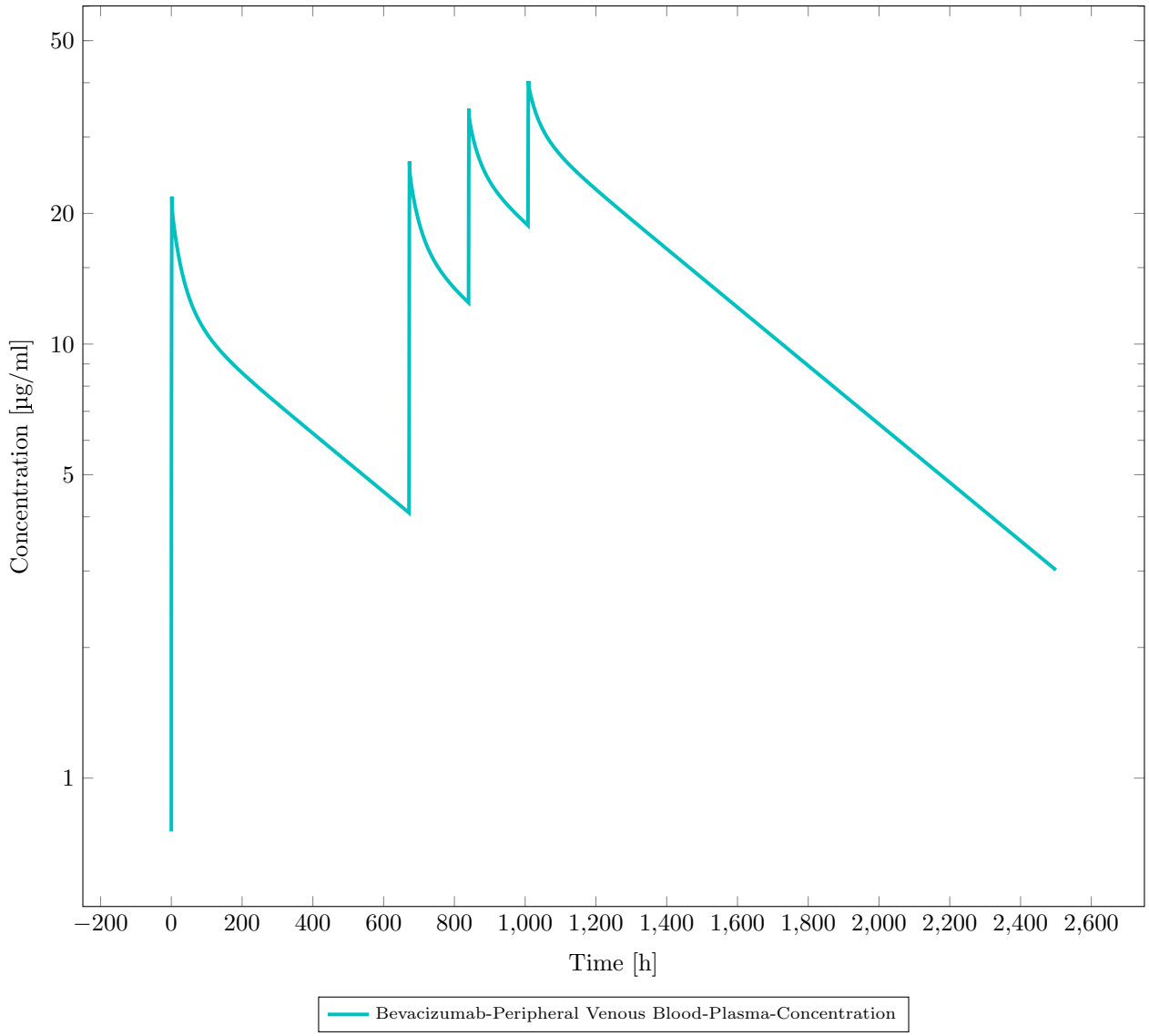

Figure 4.1

4.3.1.1 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	0.27	µmol/l
C_max_norm	1.01×10^7	mg/l
C_max_tD1-tD2	0.15	µmol/l
C_max_tD1-tD2_norm	2.19×10^7	mg/l
C_max_tDlast-tEnd	0.27	µmol/l
C_max_tDLast-tEnd_norm	4.04×10^7	mg/l
t_max	1009.40	h
t_max_tD1-tD2	1.50	h

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Parameter	**Value**	**Unit**
t_max_tDlast-tEnd	1009.40	h
C_trough_tD2	0.04	µmol/l
C_trough_tDlast	0.02	µmol/l
AUC_tD1-tD2	2060.15	µmol*min/l
AUC_tD1-tD2_norm	3.09×10^{14}	µg*min/l
AUC_tDlast-1_tDlast	1556.16	µmol*min/l
AUC_tDlast-1_tDlast_norm	2.33×10^{14}	µg*min/l
AUC_inf_tD1	0	µmol*min/l
AUC_inf_tD1_norm	0	µg*min/l
AUC_inf_tDLast	7984.57	µmol*min/l
AUC_inf_tDLast_norm	1.20×10^{15}	µg*min/l
MRT	NaN	h
Half-Life	−0.77	h
Half-Life_tDlast-tEnd	448.10	h

Table 4.5: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Beva_Gordon2001_patients_1mpk..Human.iv perfusion.1.Bevacizumab-Bevacizumab-Measurement

Parameter	**Value**	**Unit**
C_max	0.30	µmol/l
C_max_norm	1.14×10^{7}	mg/l
t_max	1006.87	h
C_tEnd	0.06	µmol/l
AUC_tEnd	10839.74	µmol*min/l
AUC_tEnd_norm	4.06×10^{14}	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 4.6: PK-Analyses for Beva_Gordon2001_patients_1mpk..Human.iv perfusion.1.Bevacizumab-Bevacizumab-Measurement

Chapter 5

Sim_Patient_3mg/kg

5.1 Used building blocks

Building Block	Name
Individual	Patient1 (see section 1.3 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Infusion 3mg/kg human (see section 3.7 in Part I)

Table 5.1: Building Block

5.2 Simulation Properties

5.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 5.2: Calculation methods

5.2.2 Compounds

5.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	**Alternative in compound**	**Value**	**Unit**
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 5.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 5.4: Calculation methods

5.2.3 Processes

5.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

5.2.4 Administration

5.2.4.1 Bevacizumab

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 3.00 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 3.00 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 3.00 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 3.00 mg/kg
Infusion time: 60.00 min

5.3 Charts

5.3.1 Time Profile Analysis

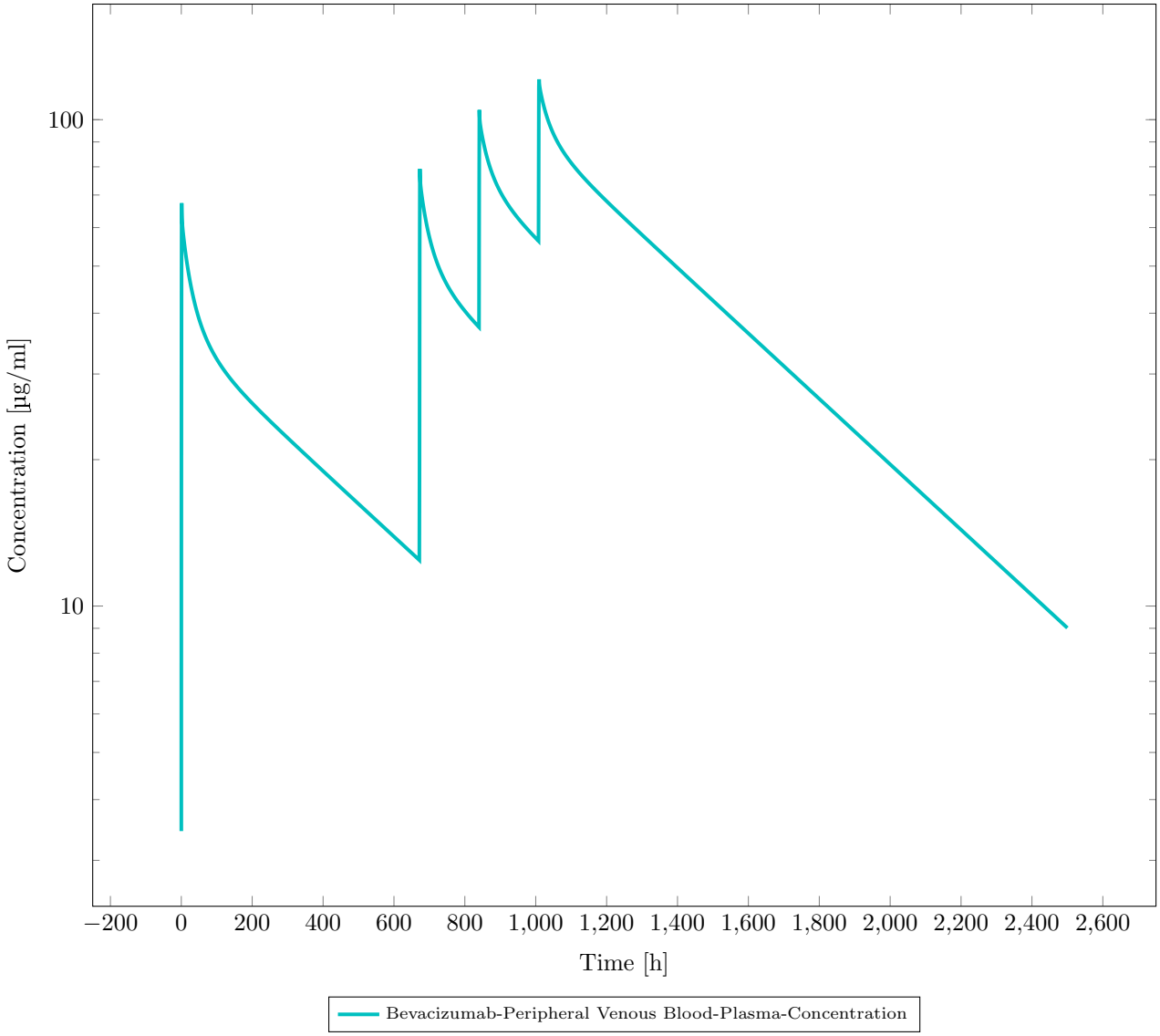

Figure 5.1

5.3.1.1 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	0.81	µmol/l
C_max_norm	1.01×10^7	mg/l
C_max_tD1-tD2	0.45	µmol/l
C_max_tD1-tD2_norm	2.25×10^7	mg/l
C_max_tDlast-tEnd	0.81	µmol/l
C_max_tDLast-tEnd_norm	4.04×10^7	mg/l
t_max	1009.40	h
t_max_tD1-tD2	1.00	h

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Parameter	**Value**	**Unit**
t_max_tDlast-tEnd	1009.40	h
C_trough_tD2	0.13	µmol/l
C_trough_tDlast	0.06	µmol/l
AUC_tD1-tD2	6267.91	µmol*min/l
AUC_tD1-tD2_norm	3.13×10^{14}	µg*min/l
AUC_tDlast-1_tDlast	4667.69	µmol*min/l
AUC_tDlast-1_tDlast_norm	2.33×10^{14}	µg*min/l
AUC_inf_tD1	0	µmol*min/l
AUC_inf_tD1_norm	0	µg*min/l
AUC_inf_tDLast	23890.55	µmol*min/l
AUC_inf_tDLast_norm	1.19×10^{15}	µg*min/l
MRT	NaN	h
Half-Life	−0.77	h
Half-Life_tDlast-tEnd	447.50	h

Table 5.5: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Beva_Gordon2001_patients_3mpk..Human.iv perfusion.3.Bevacizumab-Bevacizumab-Measurement

Parameter	**Value**	**Unit**
C_max	1.14	µmol/l
C_max_norm	1.42×10^{7}	mg/l
t_max	1008.57	h
C_tEnd	0.14	µmol/l
AUC_tEnd	34293.29	µmol*min/l
AUC_tEnd_norm	4.29×10^{14}	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 5.6: PK-Analyses for Beva_Gordon2001_patients_3mpk..Human.iv perfusion.3.Bevacizumab-Bevacizumab-Measurement

Chapter 6

Sim_Patient_10mg/kg

6.1 Used building blocks

Building Block	Name
Individual	Patient1 (see section 1.3 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Infusion 10mg/kg human (see section 3.5 in Part I)

Table 6.1: Building Block

6.2 Simulation Properties

6.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 6.2: Calculation methods

6.2.2 Compounds

6.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	Alternative in compound	Value	Unit
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 6.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 6.4: Calculation methods

6.2.3 Processes

6.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

6.2.4 Administration

6.2.4.1 Bevacizumab

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 10.00 mg/kg
Infusion time: 90.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 10.00 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 10.00 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 10.00 mg/kg
Infusion time: 60.00 min

6.3 Charts

6.3.1 Time Profile Analysis

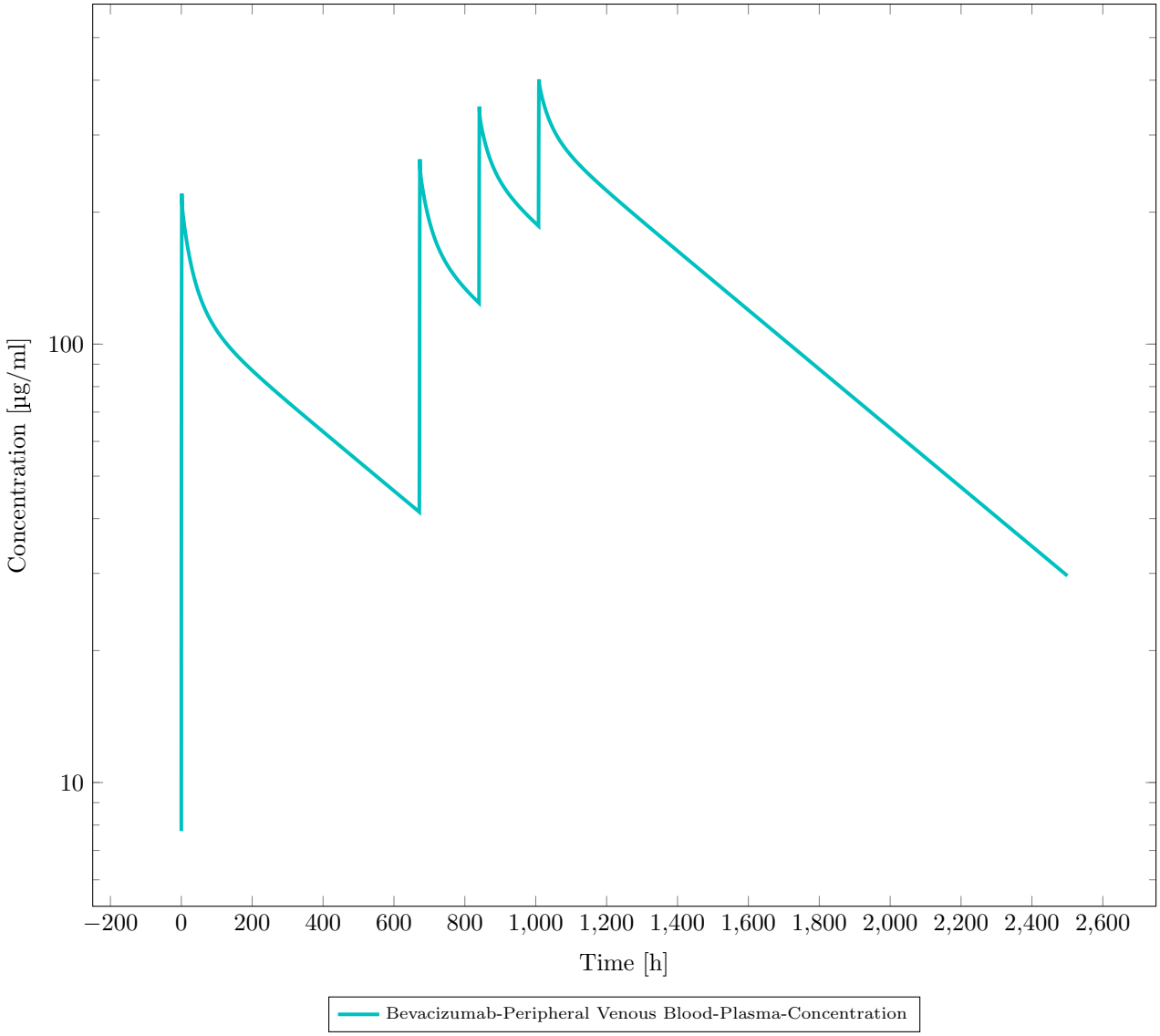

Figure 6.1

6.3.1.1 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	2.68	µmol/l
C_max_norm	1.00×10^7	mg/l
C_max_tD1-tD2	1.47	µmol/l
C_max_tD1-tD2_norm	2.20×10^7	mg/l
C_max_tDlast-tEnd	2.68	µmol/l
C_max_tDLast-tEnd_norm	4.02×10^7	mg/l
t_max	1009.40	h
t_max_tD1-tD2	1.50	h

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Parameter	**Value**	**Unit**
t_max_tDlast-tEnd	1009.40	h
C_trough_tD2	0.43	µmol/l
C_trough_tDlast	0.20	µmol/l
AUC_tD1-tD2	20891.18	µmol*min/l
AUC_tD1-tD2_norm	3.13×10^{14}	µg*min/l
AUC_tDlast-1_tDlast	15454.22	µmol*min/l
AUC_tDlast-1_tDlast_norm	2.32×10^{14}	µg*min/l
AUC_inf_tD1	0	µmol*min/l
AUC_inf_tD1_norm	0	µg*min/l
AUC_inf_tDLast	78648.48	µmol*min/l
AUC_inf_tDLast_norm	1.18×10^{15}	µg*min/l
MRT	NaN	h
Half-Life	−0.77	h
Half-Life_tDlast-tEnd	447.26	h

Table 6.5: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Beva_Gordon2001_patients_10mpk..Human.iv perfusion.10.Bevacizumab-Bevacizumab-Measurement

Parameter	**Value**	**Unit**
C_max	2.85	µmol/l
C_max_norm	1.07×10^{7}	mg/l
t_max	1006.87	h
C_tEnd	0.61	µmol/l
AUC_tEnd	111357.59	µmol*min/l
AUC_tEnd_norm	4.18×10^{14}	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 6.6: PK-Analyses for Beva_Gordon2001_patients_10mpk..Human.iv perfusion.10.Bevacizumab-Bevacizumab-Measurement

Chapter 7

Sim_Patient_5mg/kg

7.1 Used building blocks

Building Block	Name
Individual	Patient1 (see section 1.3 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	5mpk_every2weeks (see section 3.8 in Part I)

Table 7.1: Building Block

7.2 Simulation Properties

7.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 7.2: Calculation methods

7.2.2 Compounds

7.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	**Alternative in compound**	**Value**	**Unit**
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 7.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 7.4: Calculation methods

7.2.3 Processes

7.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

7.2.4 Administration

7.2.4.1 Bevacizumab

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 5.00 mg/kg
Infusion time: 60.00 min

7.3 Charts

7.3.1 Time Profile Analysis

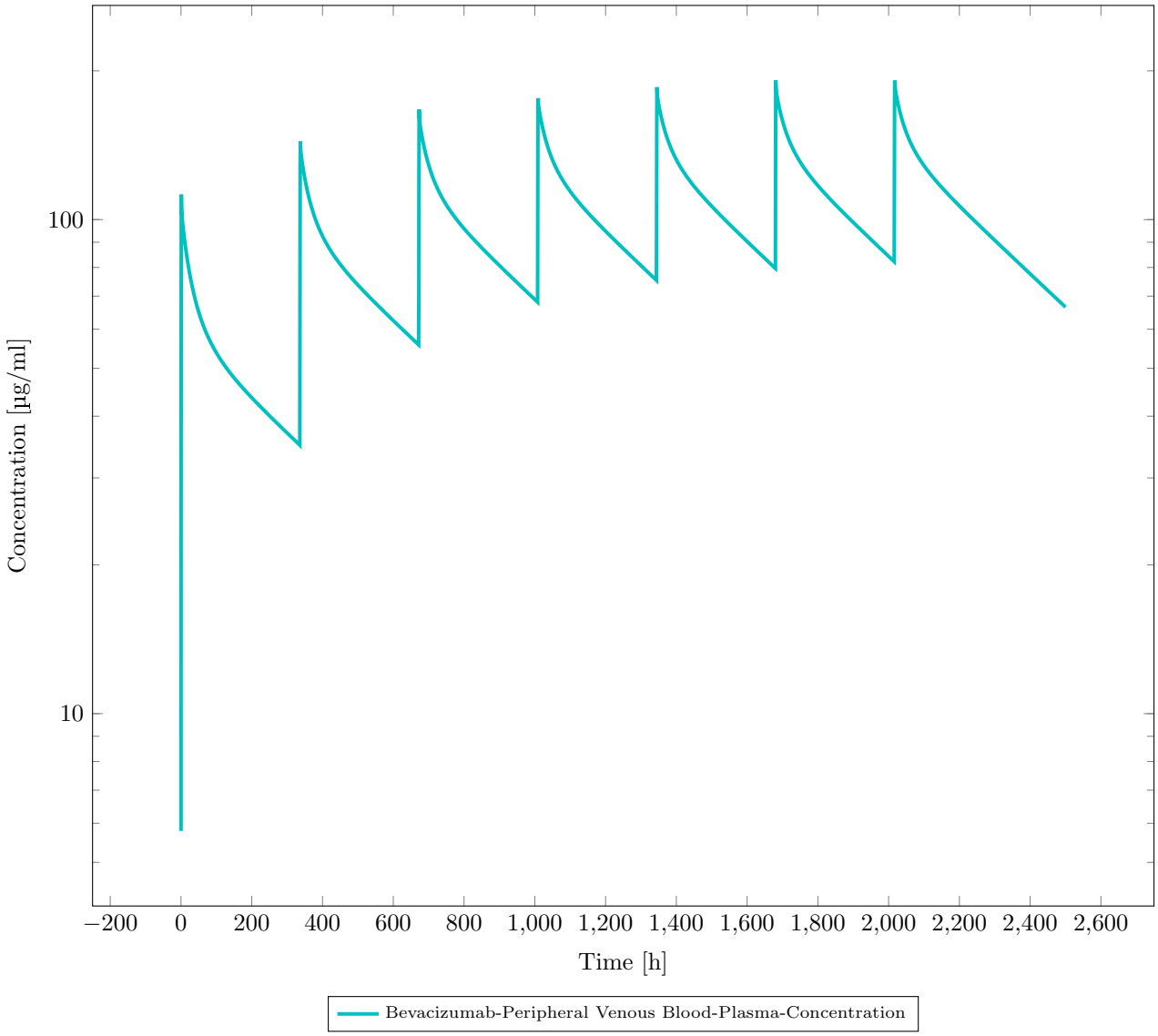

Figure 7.1

7.3.1.1 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	1.28	µmol/l
C_max_norm	5.46×10^6	mg/l
C_max_tD1-tD2	0.75	µmol/l
C_max_tD1-tD2_norm	2.25×10^7	mg/l
C_max_tDlast-tEnd	1.27	µmol/l
C_max_tDLast-tEnd_norm	3.82×10^7	mg/l
t_max	1680.99	h
t_max_tD1-tD2	1.00	h
t_max_tDlast-tEnd	2017.29	h

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Parameter	**Value**	**Unit**
C_trough_tD2	0.47	µmol/l
C_trough_tDlast	0.44	µmol/l
AUC_tD1-tD2	6810.80	µmol*min/l
AUC_tD1-tD2_norm	2.04×10^{14}	µg*min/l
AUC_tDlast-1_tDlast	15137.61	µmol*min/l
AUC_tDlast-1_tDlast_norm	4.54×10^{14}	µg*min/l
AUC_inf_tD1	0	µmol*min/l
AUC_inf_tD1_norm	0	µg*min/l
AUC_inf_tDLast	36960.51	µmol*min/l
AUC_inf_tDLast_norm	1.11×10^{15}	µg*min/l
MRT	NaN	h
Half-Life	−0.50	h
Half-Life_tDlast-tEnd	446.60	h

Table 7.5: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Beva_Romera2018_patients_5mpk..Human.iv perfusion.5.Bevacizumab-Bevacizumab-Measurement

Parameter	Value	Unit
C_max	1.27	µmol/l
C_max_norm	5.44×10^{6}	mg/l
t_max	2022.79	h
C_tEnd	0.52	µmol/l
AUC_tEnd	90708.27	µmol*min/l
AUC_tEnd_norm	3.89×10^{14}	µg*min/l
AUC_inf	107670.11	µmol*min/l
AUC_inf_norm	4.61×10^{14}	µg*min/l
MRT	1897.54	h
Half-Life	376.53	h
% AUC (tlast-∞)	0.16	
Total body clearance/F	2.17×10^{-3}	ml/min/kg
Vss (plasma)/F	246.73	ml/kg
Vd (plasma)/F	70.63	ml/kg

Table 7.6: PK-Analyses for Beva_Romera2018_patients_5mpk..Human.iv perfusion.5.Bevacizumab-Bevacizumab-Measurement

Chapter 8

Sim_Patient_0.3mg/kg

8.1 Used building blocks

Building Block	Name
Individual	Patient1 (see section 1.3 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Infusion 0.3mg/kg human (see section 3.4 in Part I)

Table 8.1: Building Block

8.2 Simulation Properties

8.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 8.2: Calculation methods

8.2.2 Compounds

8.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	**Alternative in compound**	**Value**	**Unit**
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 8.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 8.4: Calculation methods

8.2.3 Processes

8.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

8.2.4 Administration

8.2.4.1 Bevacizumab

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 0.30 mg/kg
Infusion time: 90.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 0.30 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 0.30 mg/kg
Infusion time: 60.00 min

Schema Item 1
Intravenous Infusion
Start time: 0 h
Dose: 0.30 mg/kg
Infusion time: 60.00 min

8.3 Charts

8.3.1 Time Profile Analysis

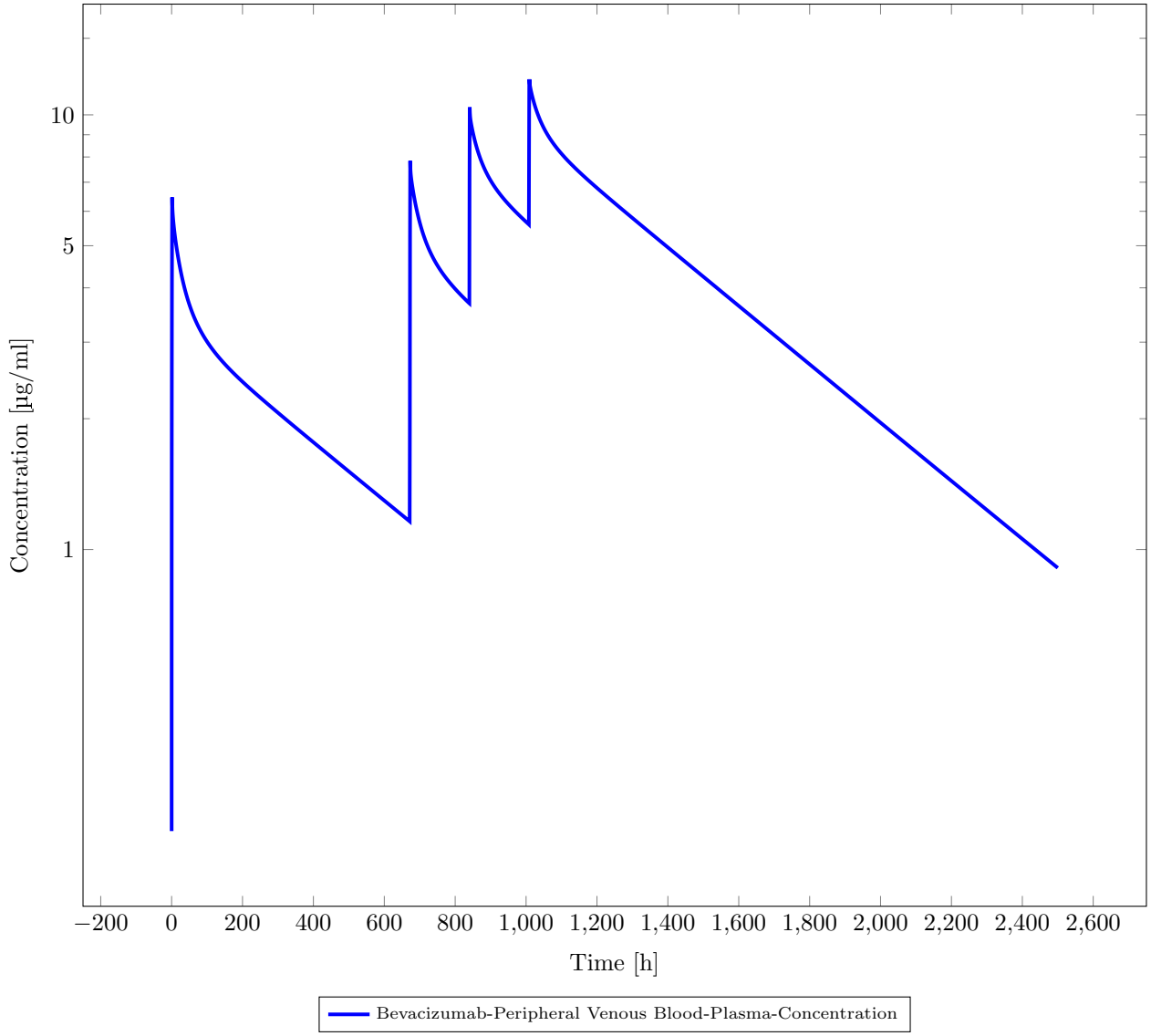

Figure 8.1

8.3.1.1 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	0.08	µmol/l
C_max_norm	1.01×10^7	mg/l
C_max_tD1-tD2	0.04	µmol/l
C_max_tD1-tD2_norm	2.15×10^7	mg/l
C_max_tDlast-tEnd	0.08	µmol/l
C_max_tDLast-tEnd_norm	4.02×10^7	mg/l
t_max	1009.40	h
t_max_tD1-tD2	1.50	h

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Parameter	**Value**	**Unit**
t_max_tDlast-tEnd	1009.40	h
C_trough_tD2	0.01	µmol/l
C_trough_tDlast	6.05×10^{-3}	µmol/l
AUC_tD1-tD2	585.81	µmol*min/l
AUC_tD1-tD2_norm	2.93×10^{14}	µg*min/l
AUC_tDlast-1_tDlast	463.83	µmol*min/l
AUC_tDlast-1_tDlast_norm	2.32×10^{14}	µg*min/l
AUC_inf_tD1	0	µmol*min/l
AUC_inf_tD1_norm	0	µg*min/l
AUC_inf_tDLast	2392.41	µmol*min/l
AUC_inf_tDLast_norm	1.20×10^{15}	µg*min/l
MRT	NaN	h
Half-Life	−0.73	h
Half-Life_tDlast-tEnd	453.27	h

Table 8.5: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Beva_Gordon2001_patients_0.3mpk..Human.iv perfusion.0.3.Bevacizumab-Bevacizumab-Measurement

Parameter	Value	Unit
C_max	0.07	µmol/l
C_max_norm	8.38×10^{6}	mg/l
t_max	1008.57	h
C_tEnd	3.12×10^{-3}	µmol/l
AUC_tEnd	2314.57	µmol*min/l
AUC_tEnd_norm	2.89×10^{14}	µg*min/l
AUC_inf	NaN	µmol*min/l
AUC_inf_norm	NaN	µg*min/l
MRT	NaN	h
Half-Life	Infinity	h
% AUC (tlast-∞)	NaN	
Total body clearance/F	NaN	ml/min/kg
Vss (plasma)/F	NaN	ml/kg
Vd (plasma)/F	NaN	ml/kg

Table 8.6: PK-Analyses for Beva_Gordon2001_patients_0.3mpk..Human.iv perfusion.0.3.Bevacizumab-Bevacizumab-Measurement

Chapter 9

Sim_patient_ped_5mg/kg

9.1 Used building blocks

Building Block	Name
Individual	Patient_ped (see section 1.4 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Infusion_5mg/kg (see section 3.9 in Part I)

Table 9.1: Building Block

9.2 Simulation Properties

9.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 9.2: Calculation methods

9.2.2 Compounds

9.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	Alternative in compound	Value	Unit
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 9.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 9.4: Calculation methods

9.2.3 Processes

9.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

9.2.4 Administration

9.2.4.1 Bevacizumab

Simple protocol
Intravenous Infusion
Dosing interval: Single
Dose: 5.00 mg/kg
Infusion time: 60.00 min

9.3 Charts

9.3.1 Time Profile Analysis

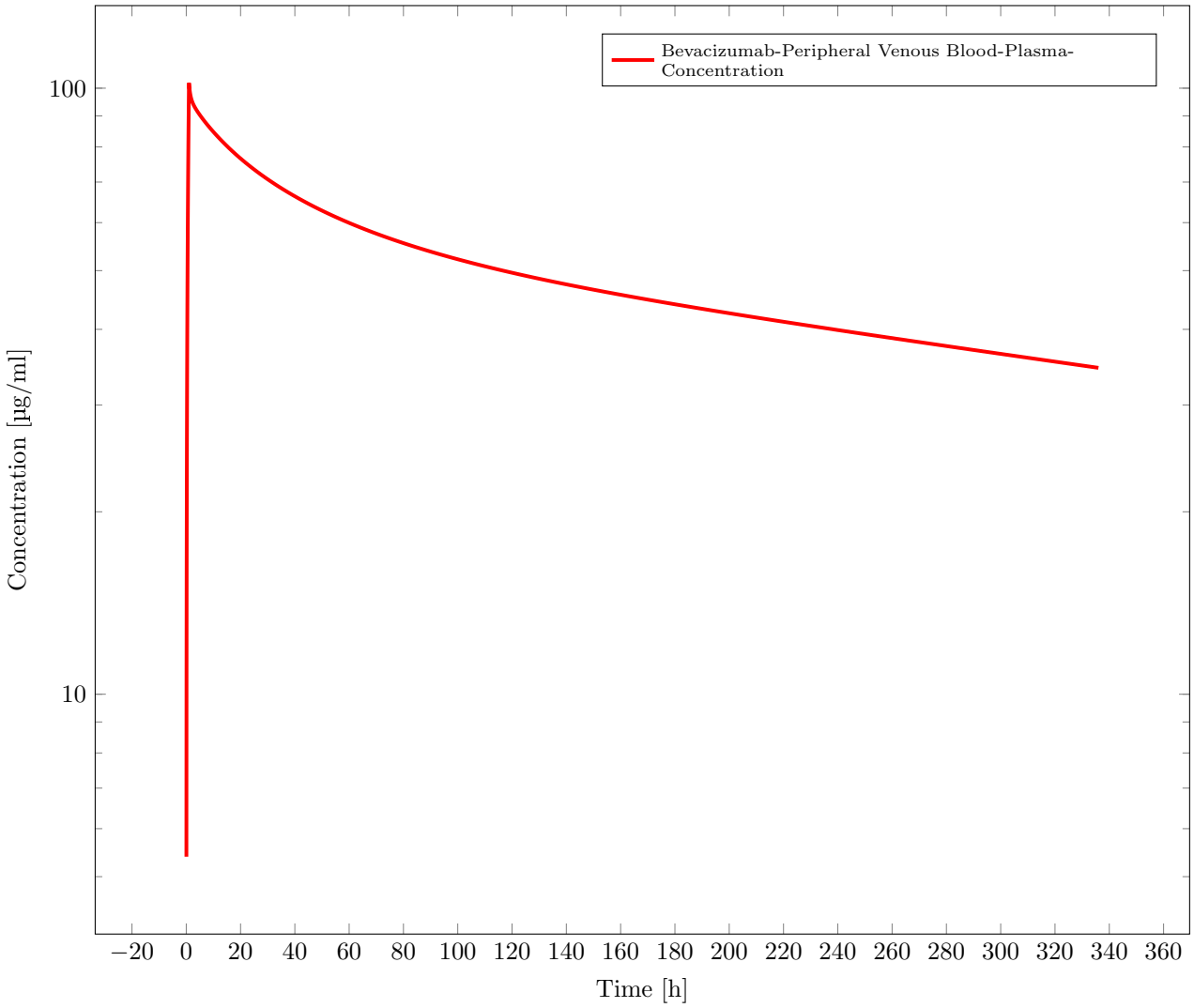

Figure 9.1

9.3.1.1 Global PK-Analyses

Parameter	Compound	Value	Unit
Vss (plasma)	Bevacizumab	82.20	ml/kg
Vd (plasma)	Bevacizumab	85.17	ml/kg
Vss (phys-chem)	Bevacizumab	650.79	ml/kg
Total plasma clearance	Bevacizumab	2.08×10^{-3}	ml/min/kg

Table 9.5: Global PK-Analyses

9.3.1.2 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	0.68	µmol/l
C_max_norm	2.04×10^{7}	mg/l
t_max	1.00	h
C_tEnd	0.23	µmol/l
AUC_tEnd	6586.24	µmol*min/l
AUC_tEnd_norm	1.98×10^{14}	µg*min/l
AUC_inf	16013.58	µmol*min/l
AUC_inf_norm	4.80×10^{14}	µg*min/l
MRT	658.14	h
Half-Life	472.66	h
% AUC (tlast-∞)	0.59	
Total body clearance/F	2.08×10^{-3}	ml/min/kg
Vss (plasma)/F	82.20	ml/kg
Vd (plasma)/F	85.17	ml/kg

Table 9.6: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Chapter 10

Sim_patient_ped_15mg/kg

10.1 Used building blocks

Building Block	Name
Individual	Patient_ped (see section 1.4 in Part I)
Compound	Bevacizumab (see section 2.2 in Part I)
Protocol	Infusion_15mg/kg (see section 3.10 in Part I)

Table 10.1: Building Block

10.2 Simulation Properties

10.2.1 Model Structure

Allow aging
No

Calculation methods

Category	Calculation methods
Endothelial surface areas	Organ vascularization
Body surface area	Mosteller

Table 10.2: Calculation methods

10.2.2 Compounds

10.2.2.1 Bevacizumab

Compound Configuration

Parameter	Alternative in compound	Value	Unit
Solubility	Measurement	9999.00	mg/l
Lipophilicity	Measurement	−5.00	Log Units
Fraction unbound (plasma, reference value)	Measurement	1.00	

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Parameter	**Alternative in compound**	**Value**	**Unit**
Specific organ permeability	Calculated	0	cm/min
Specific intestinal permeability	Calculated	0	cm/min

Table 10.3: Compound Configuration

Calculation methods

Category	Calculation methods
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Table 10.4: Calculation methods

10.2.3 Processes

10.2.3.1 Bevacizumab

Specific Binding
Mapping VEGFA with VEGFA-Paper

10.2.4 Administration

10.2.4.1 Bevacizumab

Simple protocol
Intravenous Infusion
Dosing interval: Single
Dose: 15.00 mg/kg
Infusion time: 60.00 min

10.3 Charts

10.3.1 Time Profile Analysis

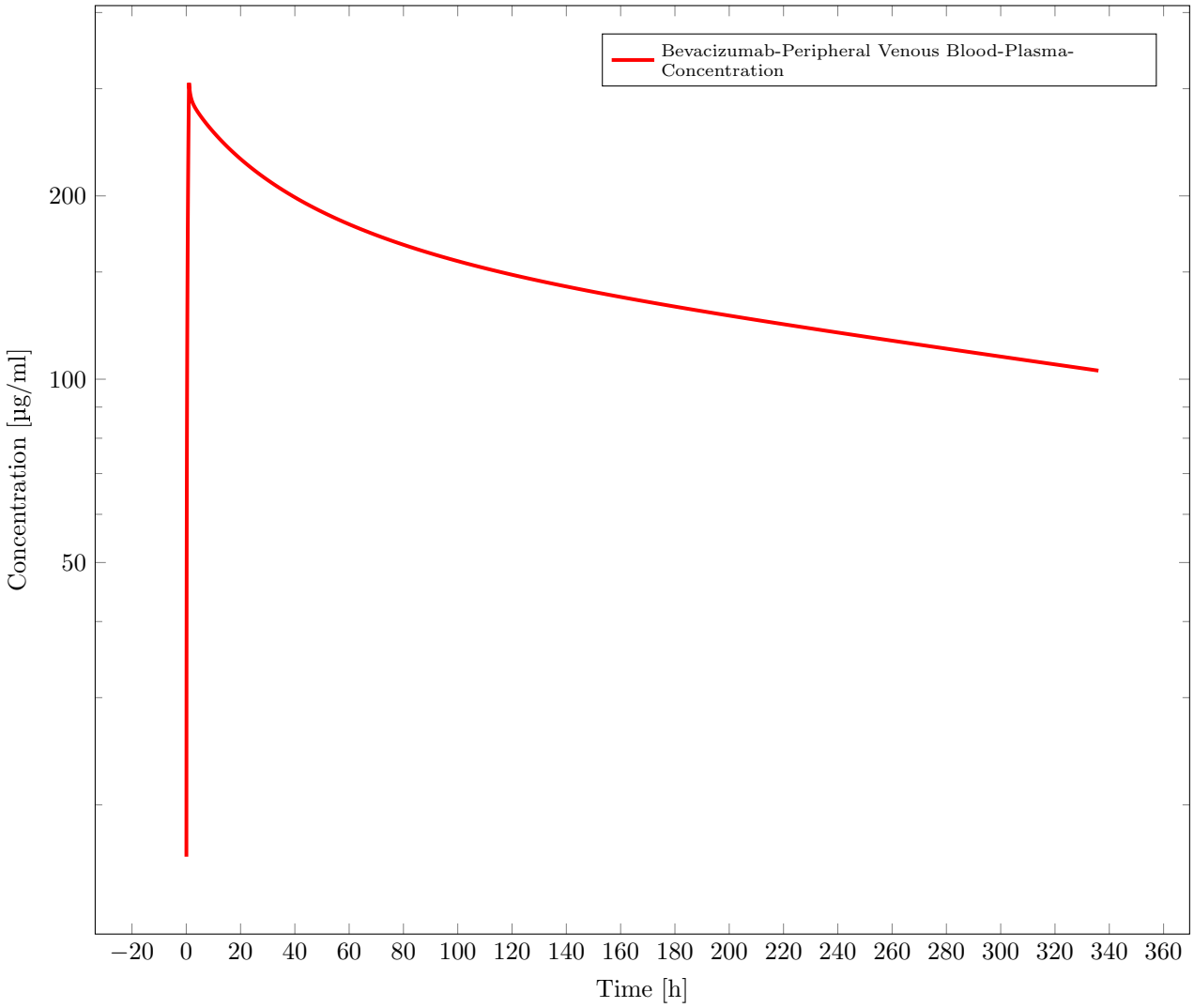

Figure 10.1

10.3.1.1 Global PK-Analyses

Parameter	Compound	Value	Unit
Vss (plasma)	Bevacizumab	82.32	ml/kg
Vd (plasma)	Bevacizumab	85.34	ml/kg
Vss (phys-chem)	Bevacizumab	650.79	ml/kg
Total plasma clearance	Bevacizumab	2.09×10^{-3}	ml/min/kg

Table 10.5: Global PK-Analyses

10.3.1.2 PK-Analyses

Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Parameter	Value	Unit
C_max	2.04	µmol/l
C_max_norm	2.04×10^{7}	mg/l
t_max	1.00	h
C_tEnd	0.69	µmol/l
AUC_tEnd	19721.20	µmol*min/l
AUC_tEnd_norm	1.97×10^{14}	µg*min/l
AUC_inf	47833.70	µmol*min/l
AUC_inf_norm	4.78×10^{14}	µg*min/l
MRT	656.31	h
Half-Life	471.61	h
% AUC (tlast-∞)	0.59	
Total body clearance/F	2.09×10^{-3}	ml/min/kg
Vss (plasma)/F	82.32	ml/kg
Vd (plasma)/F	85.34	ml/kg

Table 10.6: PK-Analyses for Bevacizumab-Peripheral Venous Blood-Plasma-Concentration

Part III

Observed Data

Chapter 1

Beva_Demarchi2021_HV_-1mpk..Human.iv perfusion.1.Bevacizumab_human_sim

Observed Data
Beva_Demarchi2021_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_Demarchi2021_HV_1mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 1
Molecule: Bevacizumab_human_sim

Time [h]	Measurement [µg/ml]
0	0.06
0.75	12.00
4.86	23.00
16.21	22.50
25.93	22.00
43.75	19.00
58.34	14.69
71.30	13.08
95.61	12.19
183.12	8.90
358.14	6.06
526.67	5.85
696.83	3.23
862.12	2.47
1030.65	1.84
1199.19	1.41
1534.64	0.76
1704.79	0.49
1871.71	0.27
2278.46	0.01

Table 1.1: Beva_Demarchi2021_HV_1mpk..Hu

Chapter 2

Beva_Hetema2017_HV_-1mpk..Human.iv perfusion.1.Bevacizumab_human_sim

Observed Data
Beva_Hetema2017_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_Hetema2017_HV_1mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 1
Molecule: Bevacizumab_human_sim

Time [h]	Measurement [µg/ml]
0.64	24.50
1.29	22.93
1.93	21.48
2.57	21.06
24.44	18.23
46.95	14.39
91.32	11.39
169.14	9.88
333.78	7.08
502.29	5.12
838.00	2.53
1179.50	1.26

Table 2.1: Beva_Hetema2017_HV_1mpk..Huma

Chapter 3

Beva_Hummel2022_HV_-1mpk..Human.iv perfusion.1.Bevacizumab_human_sim

Observed Data
Beva_Hummel2022_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_Hummel2022_HV_1mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 1
Molecule: Bevacizumab_human_sim

Time [h]	Measurement [µg/ml]
0.33	5.00
1.00	15.00
1.50	25.00
2.00	24.90
3.00	24.80
4.00	24.60
5.00	24.50
6.00	24.40
8.00	24.20
20.05	24.07
30.74	20.16
41.43	17.65
60.14	15.46
81.52	13.73
102.90	12.39
134.97	11.25
163.04	10.30
204.46	9.50
273.95	8.76
350.13	7.61
510.49	5.22
672.19	4.00

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Time [h]	**Measurement [µg/ml]**
1014.30	2.20
1348.39	1.15
1679.81	0.63
2013.90	0.31
2353.34	0.10

Table 3.1: Beva_Hummel2022_HV_1mpk..Huma

Chapter 4

Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.1

Observed Data
Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.1
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_wu2019_HV_1mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 1
Molecule: Bevacizumab_human_sim
Subject Id: 1

Time [h]	Measurement [µg/ml]
0.75	12.00
1.50	25.00
2.50	24.50
3.50	24.00
5.50	22.50
9.50	20.00
14.58	18.09
19.92	16.04
46.98	13.86
94.96	11.28
168.77	8.42
237.64	7.40
336.02	6.29
503.26	4.86
671.74	3.69
840.22	2.62
1007.47	1.97
1344.42	1.13
1680.16	0.60
2015.89	0.31
2351.62	0.18

Table 4.1: Beva_wu2019_HV_1mpk..Human.iv

Chapter 5

Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.2

Observed Data
Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.2
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_wu2019_HV_1mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 1
Molecule: Bevacizumab_human_sim
Subject Id: 2

Time [h]	**Measurement [µg/ml]**
14.58	18.09
19.92	16.04
46.98	13.86
94.96	11.28
168.77	8.42
237.64	7.40
336.02	4.99
503.26	3.92
671.74	2.98
840.22	2.04
1007.47	1.40
1344.42	0.74
1680.16	0.30
2015.89	0.10
2351.62	0.03

Table 5.1: Beva_wu2019_HV_1mpk..Human.iv

Chapter 6

Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.3

Observed Data
Beva_wu2019_HV_1mpk..Human.iv perfusion.1.Bevacizumab_human_sim.3
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_wu2019_HV_1mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 1
Molecule: Bevacizumab_human_sim
Subject Id: 3

Time [h]	**Measurement [µg/ml]**
14.58	18.09
19.92	16.04
46.98	13.86
94.96	11.28
168.77	8.42
237.64	7.40
336.02	7.66
503.26	5.92
671.74	4.35
840.22	3.14
1007.47	2.26
1344.42	1.35
1680.16	0.65
2015.89	0.53
2351.62	0.37

Table 6.1: Beva_wu2019_HV_1mpk..Human.iv

Chapter 7

Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.1

Observed Data
Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.1
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_shin2020_HV_3mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 3
Molecule: Bevacizumab_human_sim
Subject Id: 1

Time [h]	Measurement [µg/ml]
0.75	33.20
1.50	75.45
4.15	74.26
8.30	65.68
12.45	59.41
24.90	55.56
47.73	49.14
96.49	40.42
168.09	31.80
335.14	23.01
506.33	18.61
672.35	14.89
1006.44	9.21
1344.69	5.83
1679.83	3.69
2016.00	2.14

Table 7.1: Beva_shin2020_HV_3mpk..Human.

Chapter 8

Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.2

Observed Data
Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.2
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_shin2020_HV_3mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 3
Molecule: Bevacizumab_human_sim
Subject Id: 2

Time [h]	**Measurement [µg/ml]**
47.73	41.10
96.49	33.25
168.09	25.72
335.14	18.61
506.33	15.06
672.35	11.14
1006.44	6.59
1344.69	3.90
1679.83	2.11
2016.00	1.17

Table 8.1: Beva_shin2020_HV_3mpk..Human.

Chapter 9

Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.3

Observed Data
Beva_shin2020_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim.3
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_shin2020_HV_3mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 3
Molecule: Bevacizumab_human_sim
Subject Id: 3

Time [h]	**Measurement [µg/ml]**
47.73	58.75
96.49	45.96
168.09	37.59
335.14	27.20
506.33	22.50
672.35	18.61
1006.44	12.32
1344.69	7.79
1679.83	5.33
2016.00	3.21

Table 9.1: Beva_shin2020_HV_3mpk..Human.

Chapter 10

Beva_sinn2021_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim

Observed Data
Beva_sinn2021_HV_3mpk..Human.iv perfusion.3.Bevacizumab_human_sim
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_sinn2021_HV_3mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 3
Molecule: Bevacizumab_human_sim

Time [h]	Measurement [µg/ml]
0.94	83.47
2.00	83.00
3.00	82.50
4.00	82.00
5.00	81.00
6.00	80.50
8.00	76.00
19.75	73.15
36.67	64.10
52.65	57.75
78.04	51.32
106.25	49.56
132.57	46.24
159.84	43.43
184.29	41.08
222.84	38.06
301.82	33.59
473.88	24.06
639.37	17.84
984.44	10.60
1307.88	6.38
1840.06	2.70
2370.36	1.03

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Time [h]	**Measurement [µg/ml]**

Table 10.1: Beva_sinn2021_HV_3mpk..Human.

Chapter 11

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_-sim.1

Observed Data
Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.1
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_li2017_HV_0.5mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 0.5
Molecule: Bevacizumab_human_sim
Subject Id: 1

Time [h]	Measurement [mg/l]
2.00	6.74
6.00	6.50
16.73	6.30
24.00	6.00
39.03	4.70
64.13	4.55
114.31	3.64
161.71	3.40
329.00	2.45
663.57	1.32
833.64	0.86
1000.93	0.50
1168.22	0.25
1335.50	0.15

Table 11.1: Beva_li2017_HV_0.5mpk..Human.

Chapter 12

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_-sim.2

Observed Data
Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.2
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_li2017_HV_0.5mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 0.5
Molecule: Bevacizumab_human_sim
Subject Id: 2

Time [h]	Measurement [mg/l]
2.00	5.58
8.38	4.62
12.00	4.70
24.00	4.50
39.11	3.58
64.25	3.28
111.73	3.01
162.01	2.10
326.82	1.37
662.01	0.64
829.61	0.45
1000.00	0.23
1170.39	0.10
1337.99	0.08

Table 12.1: Beva_li2017_HV_0.5mpk..Human.

Chapter 13

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_-sim.3

Observed Data
Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.3
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_li2017_HV_0.5mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 0.5
Molecule: Bevacizumab_human_sim
Subject Id: 3

Time [h]	Measurement [mg/l]
2.00	8.14
5.50	7.52
19.27	6.40
24.00	6.30
41.28	6.19
66.06	5.21
112.84	4.92
162.39	4.01
330.28	3.26
663.30	1.35
833.94	0.90
999.08	0.51
1166.97	0.21
1337.61	0.11

Table 13.1: Beva_li2017_HV_0.5mpk..Human.

Chapter 14

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_-sim.4

Observed Data
Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.4
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_li2017_HV_0.5mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 0.5
Molecule: Bevacizumab_human_sim
Subject Id: 4

Time [h]	Measurement [mg/l]
2.00	7.52
5.51	6.26
13.79	6.05
24.00	6.00
41.36	4.76
66.18	4.55
113.05	4.01
162.68	3.42
330.88	2.51
664.52	1.18
835.48	0.88
1000.92	0.71
1169.12	0.36
1337.32	0.18

Table 14.1: Beva_li2017_HV_0.5mpk..Human.

Chapter 15

Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_-sim.5

Observed Data
Beva_li2017_HV_0.5mpk..Human.iv perfusion.0.5.Bevacizumab_human_sim.5
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_li2017_HV_0.5mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 0.5
Molecule: Bevacizumab_human_sim
Subject Id: 5

Time [h]	**Measurement [mg/l]**
2.00	6.85
2.75	5.70
19.27	5.32
24.00	5.20
41.28	4.74
66.06	3.95
115.60	3.40
165.14	3.03
330.28	1.89
663.30	0.98
833.94	0.71
1001.83	0.59
1169.72	0.36
1334.86	0.16

Table 15.1: Beva_li2017_HV_0.5mpk..Human.

Chapter 16

Beva_Gordon2001_patients_-3mpk..Human.iv perfusion.3.Bevacizumab

Observed Data
Beva_Gordon2001_patients_3mpk..Human.iv perfusion.3.Bevacizumab
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_Gordon2001_patients_3mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 3
Molecule: Bevacizumab

Time [h]	Measurement [µg/ml]
2.83	77.29
17.00	63.47
45.33	58.82
90.66	44.09
161.48	32.55
235.14	29.70
334.30	26.29
504.28	17.70
671.43	13.66
674.27	92.14
835.75	44.47
841.42	134.36
1005.73	57.44
1008.57	170.96
1056.73	110.13
1172.88	70.90
1345.70	44.94
1507.18	28.49
1728.16	21.64

Table 16.1: Beva_Gordon2001_patients_3mpk

Chapter 17

Beva_Gordon2001_patients_-0.3mpk..Human.iv perfusion.0.3.Bevacizumab

Observed Data
Beva_Gordon2001_patients_0.3mpk..Human.iv perfusion.0.3.Bevacizumab
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_Gordon2001_patients_0.3mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 0.3
Molecule: Bevacizumab

Time [h]	Measurement [µg/ml]
5.67	6.07
19.83	5.21
45.33	4.28
90.66	3.02
161.48	2.33
235.14	1.75
331.47	1.31
501.45	0.72
671.00	0.73
672.00	7.57
835.75	2.91
841.42	9.92
1005.73	3.99
1008.57	10.06
1056.73	8.91
1172.88	5.00
1342.87	2.94
1510.02	1.75
1728.16	0.47

Table 17.1: Beva_Gordon2001_patients_0.3m

Chapter 18

Beva_Gordon2001_patients_-1mpk..Human.iv perfusion.1.Bevacizumab

Observed Data
Beva_Gordon2001_patients_1mpk..Human.iv perfusion.1.Bevacizumab
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_Gordon2001_patients_1mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 1
Molecule: Bevacizumab

Time [h]	Measurement [µg/ml]
2.83	24.82
19.80	21.65
45.25	17.25
90.51	13.13
161.21	10.15
234.75	7.85
330.91	6.16
500.61	4.28
667.47	2.64
670.30	27.59
837.17	11.81
840.00	39.69
1004.04	18.33
1006.87	45.49
1054.95	31.62
1170.91	26.77
1340.61	16.74
1507.47	12.18
1725.25	8.99

Table 18.1: Beva_Gordon2001_patients_1mpk

Chapter 19

Beva_Gordon2001_patients_-10mpk..Human.iv perfusion.10.Bevacizumab

Observed Data
Beva_Gordon2001_patients_10mpk..Human.iv perfusion.10.Bevacizumab
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_Gordon2001_patients_10mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 10
Molecule: Bevacizumab

Time [h]	Measurement [µg/ml]
2.83	233.57
22.63	183.30
48.08	177.83
90.51	135.39
164.04	109.52
237.58	95.56
333.74	76.13
500.61	52.13
667.47	36.80
673.13	284.41
834.34	114.61
840.00	379.27
1004.04	188.94
1006.87	428.13
1054.95	396.90
1173.74	226.60
1343.43	175.15
1507.47	119.94
1725.25	91.31

Table 19.1: Beva_Gordon2001_patients_10mp

Chapter 20

Beva_Romera2018_patients_-5mpk..Human.iv perfusion.5.Bevacizumab

Observed Data
Beva_Romera2018_patients_5mpk..Human.iv perfusion.5.Bevacizumab
Source: J:\PhInC\Suivi_Echanges\Stage\Salih Benamara_2022\Gastro Plus\Bevacizumab_all_Raw_Data\Donne propres\Beva_Romera2018_patients_5mpk.csv
Sheet:
Species: Human
Route: iv perfusion
Dose: 5
Molecule: Bevacizumab

Time [h]	Measurement [µg/ml]
0.82	97.77
1.64	108.28
6.36	114.33
24.82	87.26
49.03	71.18
73.23	64.81
121.23	50.00
169.03	43.47
241.64	35.35
338.46	30.41
2016.62	173.72
2017.44	181.63
2022.79	190.56
2040.47	160.97
2064.94	146.43
2089.20	134.18
2138.35	118.37
2186.47	106.12
2257.20	93.37
2354.47	78.06

Table 20.1: Beva_Romera2018_patients_5mpk