

# MetidaNCA validation report

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2021-07-14

## 1 Introduction and package description

Non-compartment anlysis software.

See documentation: <https://pharmcat.github.io/MetidaNCA.jl/dev/>

### 1.1 Validation purpose

The main validation purpose is confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

### 1.2 Requirements

- Julia 1.5.\* (or higher) installed
- Julia packages from dependence list installed (see [Project.toml](#))

### 1.3 Developer software life cycle

- Development stage
- Testing procedures development
- Performing testing procedures on local machine
- Push to master branch
- Performing testing procedures with GitHub Actions
- Make pull request to the official registry of general Julia packages (if nessesary)
- Make release (if previous completed)

### 1.3.1 Versions

- X.Y.Z - patch release (no breaking changes)
- X.Y.# - minor release (may include breaking changes)
- X.#.# - major release (breaking changes, changes in public API)
- 0.#.# - no stable public API
- $\geq 1.\#.\#$  - stable public API

## 1.4 Build support

### 1.4.1 Tier 1

- julia-version: 1.5, 1.6
- julia-arch: x64
- os: ubuntu-18.04, macos-10.15, windows-2019

## 2 Installation

### 2.1 System information

- Julia version: v"1.4.2"
- Current machine: "x86\_64-pc-linux-gnu"

### 2.2 Installation method

MetidaNCA.jl can be installed by executing the following command in REPL.

```
import Pkg; Pkg.add("MetidaNCA")
```

### 2.3 Version check

The installation process is checking within each testing job via GitHub Actions. Also GitHub Action [chek](#) performed before merging into JuliaRegistries/General repository (see [Automatic merging of pull requests](#)).

Current package version:

"0.1.3"

## 3 Operation qualification

This part of validation based on testing procedures entails running software products under known conditions with defined inputs and documented outcomes that can be compared to their predefined expectations. All documented public API included in testing procedures and part of critical internal methods.

### 3.1 Coverage

Code coverage report available on [Codecov.io](https://codecov.io). Test procedures include all public API methods check.

- Coverage goal:  $\geq 90.0\%$

### 3.2 Data

Validation data available in the repository and included in the package. See Appendix 1.

### 3.3 Testing results

```
Pkg.test("MetidaNCA")
```

Test Summary:		Pass	Total
Simple test		3	3
Test Summary:		Pass	Total
Linear trapezoidal, Dose 100, Dosetime 0, no tau		18	18
Test Summary:		Pass	Total
Linear up Log down, Dose 100, Dosetime 0.25, tau 9		17	17
Test Summary:		Pass	Total
Linear up Log down, Dose 120, Dosetime 0, tau 12		17	17
Test Summary:		Pass	Total
Log trapezoidal ATM, Dose 120, Dosetime 0, tau 12		5	5
Test Summary:		Pass	Total
Linear up Log down ATM, Dose 120, Dosetime 0, tau 12		4	4
Test Summary:		Pass	Total
Linear trapezoidal, Dose 100, Dosetime 2.0, tau 10		15	15
Test Summary:		Pass	Total
Linear trapezoidal, Dose 100, Dosetime 0.0, tau 100		15	15
Test Summary:		Pass	Total
Linear trapezoidal, Dose 120, Dosetime 0.0, tau 12		4	4
Test Summary:		Pass	Total
set-get*! tests		7	7
Test Summary:			
applylimitrule!		No tests	
Test Summary:			
kel		No tests	
Test Summary:			
Output		No tests	

## 4 Performance qualification

Purpose of this testing procedures to demonstrate performance for some critical tasks.

## 4.1 Parameter's names description

Name	Description
String	String
Cmax	Maximum concentration
Tmax	Time at Cmax
Cdose	Concentration at dose time
Clast	Last non-zero concentration
AUClast	AUC to Clast
AUMClast	AUMC to Clast
AUCall	AUC with all values
Rsqr	r square
ARsqr	Adjusted r square
Kel	Terminal elimination constant
HL	Half live or T1/2
LZint	Intercept
Clast_pred	Predicted Clast
AUCinf	AUC extrapolated to infinity
AUCpct	Percentage AUClast from AUCinf
MRTlast	Mean Residence Time (last)
MRTinf	Mean Residence Time (inf)
Clinf	Clearance
Vzinf	Volume of distribution
AUCtau	AUC in Tau range
AUMCtau	AUC in Tau range
MRTtauinf	MRT based on Tau
Cltau	Clearance in Tau range
Vztau	Volume of distribution in Tau range

## 4.2 Results

### 4.2.1 Linear-trapezoidal rule; Extravascular

#### Cmax

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	190.869	190.869	0.0
2.0	261.177	261.177	0.0
3.0	105.345	105.345	0.0
4.0	208.542	208.542	0.0
5.0	169.334	169.334	0.0
6.0	154.648	154.648	0.0
7.0	153.254	153.254	0.0
8.0	138.327	138.327	0.0
9.0	167.347	167.347	0.0
10.0	125.482	125.482	0.0

#### Tmax

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64

1.0	1.0	1.0	0.0
2.0	1.0	1.0	0.0
3.0	1.5	1.5	0.0
4.0	1.0	1.0	0.0
5.0	4.0	4.0	0.0
6.0	2.5	2.5	0.0
7.0	2.5	2.5	0.0
8.0	4.0	4.0	0.0
9.0	3.0	3.0	0.0
10.0	2.0	2.0	0.0

#### Cdose

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	0.0	0.0	0.0
2.0	0.0	0.0	0.0
3.0	0.0	0.0	0.0
4.0	0.0	0.0	0.0
5.0	0.0	0.0	0.0
6.0	0.0	0.0	0.0
7.0	0.0	0.0	0.0
8.0	0.0	0.0	0.0
9.0	0.0	0.0	0.0
10.0	0.0	0.0	0.0

#### Clast

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	112.846	112.846	0.0
2.0	85.241	85.241	0.0
3.0	67.901	67.901	0.0
4.0	97.625	97.625	0.0
5.0	110.778	110.778	0.0
6.0	69.501	69.501	0.0
7.0	58.051	58.051	0.0
8.0	74.437	74.437	0.0
9.0	93.44	93.44	0.0
10.0	42.191	42.191	0.0

#### AUClast

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	9585.42	9585.42	0.0
2.0	10112.2	10112.2	0.0
3.0	5396.55	5396.55	0.0
4.0	9317.84	9317.84	0.0
5.0	9561.26	9561.26	0.0
6.0	6966.6	6966.6	0.0
7.0	7029.57	7029.57	0.0

8.0	7110.67	7110.67	0.0
9.0	8315.08	8315.08	0.0
10.0	5620.89	5620.89	0.0

#### AUMClas

Subjct Float64	Value Float64	Reference Float64	Difference Float64
1.0	333582.0	333582.0	0.0
2.0	298701.0	298701.0	0.0
3.0	186032.0	186032.0	0.0
4.0	313956.0	313956.0	0.0
5.0	315182.0	315182.0	0.0
6.0	226977.0	226977.0	0.0
7.0	219798.0	219798.0	0.0
8.0	240526.0	240526.0	0.0
9.0	277614.0	277614.0	0.0
10.0	154893.0	154893.0	0.0

#### AUCall

Subjct Float64	Value Float64	Reference Float64	Difference Float64
1.0	9585.42	9585.42	0.0
2.0	10112.2	10112.2	0.0
3.0	5396.55	5396.55	0.0
4.0	9317.84	9317.84	0.0
5.0	9561.26	9561.26	0.0
6.0	6966.6	6966.6	0.0
7.0	7029.57	7029.57	0.0
8.0	7110.67	7110.67	0.0
9.0	8315.08	8315.08	0.0
10.0	5620.89	5620.89	0.0

#### Rsq

Subjct Float64	Value Float64	Reference Float64	Difference Float64
1.0	0.786077	0.786077	0.0
2.0	0.992764	0.992764	0.0
3.0	0.813589	0.813589	0.0
4.0	0.918859	0.918859	0.0
5.0	0.85336	0.85336	0.0
6.0	0.950119	0.950119	0.0
7.0	0.970312	0.970312	0.0
8.0	0.947969	0.947969	0.0
9.0	0.947538	0.947538	0.0
10.0	0.880923	0.880923	0.0

#### ARsq

Subjct	Value	Reference	Difference
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Float64	Float64	Float64	Float64
1.0	0.714769	0.714769	0.0
2.0	0.990351	0.990351	0.0
3.0	0.776307	0.776307	0.0
4.0	0.837717	0.837717	0.0
5.0	0.82892	0.82892	0.0
6.0	0.925179	0.925179	0.0
7.0	0.960416	0.960416	0.0
8.0	0.921954	0.921954	0.0
9.0	0.921307	0.921307	0.0
10.0	0.863912	0.863912	0.0

#### Kel

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	0.00338474	0.00338474	0.0
2.0	0.0141063	0.0141063	0.0
3.0	0.00329143	0.00329143	0.0
4.0	0.00769534	0.00769534	0.0
5.0	0.00681333	0.00681333	0.0
6.0	0.00769228	0.00769228	0.0
7.0	0.012459	0.012459	0.0
8.0	0.00893008	0.00893008	0.0
9.0	0.00564586	0.00564586	0.0
10.0	0.0171897	0.0171897	0.0

#### HL

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	204.786	204.786	0.0
2.0	49.1374	49.1374	0.0
3.0	210.591	210.591	0.0
4.0	90.0736	90.0736	0.0
5.0	101.734	101.734	0.0
6.0	90.1095	90.1094	0.0001
7.0	55.6345	55.6345	0.0
8.0	77.6194	77.6194	0.0
9.0	122.771	122.771	0.0
10.0	40.3233	40.3233	0.0

#### Clast\_pred

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	117.306	117.306	0.0
2.0	82.5367	82.5367	0.0
3.0	66.9311	66.9311	0.0
4.0	100.768	100.768	0.0
5.0	105.298	105.298	0.0
6.0	71.9399	71.9399	0.0

7.0	61.1727	61.1727	0.0
8.0	75.6043	75.6043	0.0
9.0	93.7618	93.7618	0.0
10.0	38.8109	38.8109	0.0

#### AUCinf

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	42925.0	42925.0	0.0
2.0	16154.9	16154.9	0.0
3.0	26026.2	26026.2	0.0
4.0	22004.1	22004.1	0.0
5.0	25820.3	25820.3	0.0
6.0	16001.8	16001.8	0.0
7.0	11689.0	11689.0	0.0
8.0	15446.2	15446.2	0.0
9.0	24865.2	24865.2	0.0
10.0	8075.32	8075.32	0.0

#### AUCpct

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	77.6694	77.6694	0.0
2.0	37.405	37.405	0.0
3.0	79.2649	79.2649	0.0
4.0	57.6541	57.6541	0.0
5.0	62.97	62.97	0.0
6.0	56.4636	56.4636	0.0
7.0	39.8614	39.8614	0.0
8.0	53.9649	53.9649	0.0
9.0	66.5594	66.5594	0.0
10.0	30.3942	30.3942	0.0

#### MRTlast

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	34.801	34.801	0.0
2.0	29.5388	29.5388	0.0
3.0	34.4724	34.4724	0.0
4.0	33.6941	33.6941	0.0
5.0	32.9644	32.9644	0.0
6.0	32.5808	32.5808	0.0
7.0	31.2676	31.2676	0.0
8.0	33.8261	33.8261	0.0
9.0	33.3868	33.3868	0.0
10.0	27.5567	27.5567	0.0

#### MRTinf



Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	293.162	293.162	0.0
2.0	71.9379	71.9379	0.0
3.0	305.041	305.041	0.0
4.0	130.7	130.7	0.0
5.0	149.967	149.967	0.0
6.0	128.241	128.241	0.0
7.0	79.4983	79.4983	0.0
8.0	114.857	114.857	0.0
9.0	176.978	176.978	0.0
10.0	58.7464	58.7464	0.0

#### Clinf

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	0.00232964	0.00232964	0.0
2.0	0.00619006	0.00619006	0.0
3.0	0.00384228	0.00384228	0.0
4.0	0.00454461	0.00454461	0.0
5.0	0.00387293	0.00387293	0.0
6.0	0.00624931	0.00624931	0.0
7.0	0.00855509	0.00855509	0.0
8.0	0.00647408	0.00647408	0.0
9.0	0.00402168	0.00402168	0.0
10.0	0.0123834	0.0123834	0.0

#### Vzinf

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	0.688278	0.688278	0.0
2.0	0.438815	0.438815	0.0
3.0	1.16736	1.16736	0.0
4.0	0.590566	0.590566	0.0
5.0	0.568434	0.568434	0.0
6.0	0.812414	0.812414	0.0
7.0	0.686662	0.686662	0.0
8.0	0.724974	0.724974	0.0
9.0	0.712323	0.712323	0.0
10.0	0.720395	0.720395	0.0

## 4.2.2 Linear-Up Log-Down; Extravascular; Dosetime 0.25; Tau 9

#### Cmax

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	190.869	190.869	0.0
2	261.177	261.177	0.0
3	105.345	105.345	0.0

4	208.542	208.542	0.0
5	169.334	169.334	0.0
6	154.648	154.648	0.0
7	153.254	153.254	0.0
8	138.327	138.327	0.0
9	167.347	167.347	0.0
10	125.482	125.482	0.0

#### Tmax

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	1.0	1.0	0.0
2	1.0	1.0	0.0
3	1.5	1.5	0.0
4	1.0	1.0	0.0
5	4.0	4.0	0.0
6	2.5	2.5	0.0
7	2.5	2.5	0.0
8	4.0	4.0	0.0
9	3.0	3.0	0.0
10	2.0	2.0	0.0

#### Cdose

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	121.239	121.239	0.0
2	62.222	62.222	0.0
3	49.849	49.849	0.0
4	52.421	52.421	0.0
5	0.0	0.0	0.0
6	57.882	57.882	0.0
7	19.95	19.95	0.0
8	22.724	22.724	0.0
9	105.438	105.438	0.0
10	13.634	13.634	0.0

#### Clast

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	112.846	112.846	0.0
2	85.241	85.241	0.0
3	67.901	67.901	0.0
4	97.625	97.625	0.0
5	110.778	110.778	0.0
6	69.501	69.501	0.0
7	58.051	58.051	0.0
8	74.437	74.437	0.0
9	93.44	93.44	0.0
10	42.191	42.191	0.0

#### AUClast

Subjct Any	Value Any	Reference Any	Difference Any
1	9566.6	9566.6	0.0
2	10054.3	10054.3	0.0
3	5392.46	5392.46	0.0
4	9297.1	9297.1	0.0
5	9519.18	9519.18	0.0
6	6948.99	6948.99	0.0
7	6988.77	6988.77	0.0
8	7058.82	7058.82	0.0
9	8302.37	8302.37	0.0
10	5486.84	5486.84	0.0

#### AUCtau

Subjct Any	Value Any	Reference Any	Difference Any
1	1268.28	1268.28	0.0
2	1831.82	1831.82	0.0
3	754.649	754.649	0.0
4	1336.48	1336.48	0.0
5	1310.9	1310.9	0.0
6	1114.24	1114.24	0.0
7	1079.37	1079.37	0.0
8	766.62	766.62	0.0
9	1219.63	1219.63	0.0
10	970.306	970.306	0.0

#### AUMCtau

Subjct Any	Value Any	Reference Any	Difference Any
1	5477.2	5477.2	0.0
2	8367.57	8367.57	0.0
3	3455.35	3455.35	0.0
4	6014.65	6014.65	0.0
5	6609.79	6609.79	0.0
6	5064.72	5064.72	0.0
7	4976.96	4976.96	0.0
8	2863.01	2863.01	0.0
9	5386.88	5386.88	0.0
10	4713.48	4713.48	0.0

#### AUCall

Subjct Any	Value Any	Reference Any	Difference Any
1	9566.6	9566.6	0.0
2	10054.3	10054.3	0.0

3	5392.46	5392.46	0.0
4	9297.1	9297.1	0.0
5	9519.18	9519.18	0.0
6	6948.99	6948.99	0.0
7	6988.77	6988.77	0.0
8	7058.82	7058.82	0.0
9	8302.37	8302.37	0.0
10	5486.84	5486.84	0.0

#### Rsq

Subjct Any	Value Any	Reference Any	Difference Any
1	0.786077	0.786077	0.0
2	0.992764	0.992764	0.0
3	0.813589	0.813589	0.0
4	0.918859	0.918859	0.0
5	0.85336	0.85336	0.0
6	0.950119	0.950119	0.0
7	0.970312	0.970312	0.0
8	0.947969	0.947969	0.0
9	0.947538	0.947538	0.0
10	0.880923	0.880923	0.0

#### ARsq

Subjct Any	Value Any	Reference Any	Difference Any
1	0.714769	0.714769	0.0
2	0.990351	0.990351	0.0
3	0.776307	0.776307	0.0
4	0.837717	0.837717	0.0
5	0.82892	0.82892	0.0
6	0.925179	0.925179	0.0
7	0.960416	0.960416	0.0
8	0.921954	0.921954	0.0
9	0.921307	0.921307	0.0
10	0.863912	0.863912	0.0

#### Kel

Subjct Any	Value Any	Reference Any	Difference Any
1	0.00338474	0.00338474	0.0
2	0.0141063	0.0141063	0.0
3	0.00329143	0.00329143	0.0
4	0.00769534	0.00769534	0.0
5	0.00681333	0.00681333	0.0
6	0.00769228	0.00769228	0.0
7	0.012459	0.012459	0.0
8	0.00893008	0.00893008	0.0
9	0.00564586	0.00564586	0.0
10	0.0171897	0.0171897	0.0

#### HL

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	204.786	204.786	0.0
2	49.1374	49.1374	0.0
3	210.591	210.591	0.0
4	90.0736	90.0736	0.0
5	101.734	101.734	0.0
6	90.1095	90.1095	0.0
7	55.6345	55.6345	0.0
8	77.6194	77.6194	0.0
9	122.771	122.771	0.0
10	40.3233	40.3233	0.0

#### Clast\_pred

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	117.306	117.306	0.0
2	82.5367	82.5367	0.0
3	66.9311	66.9311	0.0
4	100.768	100.768	0.0
5	105.298	105.298	0.0
6	71.9399	71.9399	0.0
7	61.1727	61.1727	0.0
8	75.6043	75.6043	0.0
9	93.7618	93.7618	0.0
10	38.8109	38.8109	0.0

#### AUCinf

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	42906.2	42906.2	0.0
2	16097.0	16097.0	0.0
3	26022.1	26022.1	0.0
4	21983.3	21983.3	0.0
5	25778.2	25778.2	0.0
6	15984.1	15984.1	0.0
7	11648.2	11648.2	0.0
8	15394.4	15394.4	0.0
9	24852.5	24852.5	0.0
10	7941.27	7941.27	0.0

#### AUCpct

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	77.7035	77.7035	0.0

2	37.5395	37.5395	0.0
3	79.2774	79.2774	0.0
4	57.7084	57.7084	0.0
5	63.0727	63.0727	0.0
6	56.5258	56.5258	0.0
7	40.001	40.001	0.0
8	54.1467	54.1467	0.0
9	66.5935	66.5935	0.0
10	30.9073	30.9073	0.0

#### MRTtauinf

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	299.792	299.792	0.0
2	74.655	74.655	0.0
3	305.92	305.92	0.0
4	143.538	143.538	0.0
5	173.022	173.022	0.0
6	124.653	124.653	0.0
7	92.7359	92.7359	0.0
8	175.462	175.462	0.0
9	178.811	178.811	0.0
10	69.5163	69.5163	0.0

#### Cltau

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	0.0788472	0.0788472	0.0
2	0.0545905	0.0545905	0.0
3	0.132512	0.132512	0.0
4	0.0748234	0.0748234	0.0
5	0.0762832	0.0762832	0.0
6	0.0897472	0.0897472	0.0
7	0.0926469	0.0926469	0.0
8	0.130443	0.130443	0.0
9	0.081992	0.081992	0.0
10	0.10306	0.10306	0.0

#### Vztau

Subjct	Value	Reference	Difference
Any	Any	Any	Any
1	23.2949	23.2949	0.0
2	3.86993	3.86993	0.0
3	40.2597	40.2597	0.0
4	9.7232	9.7232	0.0
5	11.1962	11.1962	0.0
6	11.6672	11.6672	0.0
7	7.43617	7.43617	0.0
8	14.6071	14.6071	0.0
9	14.5225	14.5225	0.0

## 5 Glossary

- Installation qualification (IQ) - Establishing confidence that process equipment and ancillary systems are compliant with appropriate codes and approved design intentions, and that manufacturer's recommendations are suitably considered.
- Operational qualification (OQ) Establishing confidence that process equipment and sub-systems are capable of consistently operating within established limits and tolerances.
- Product performance qualification (PQ) - Establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality and safety.
- Repository - GitHub repository: <https://github.com/PharmCat/MetidaNCA.jl>
- Master branch - main branch on GitHub ([link](#)).
- Current machine - pc that used for validation report generating.

## 6 Reference

- [General Principles of Software Validation; Final Guidance for Industry and FDA Staff](#)
- [Guidance for Industry Process Validation: General Principles and Practices](#)
- [Glossary of Computer System Software Development Terminology](#)

## 7 Appendix 1

Subject	Formulation	Time	Concentration
Int64	String	Float64	Float64
1	T	0.0	0.0
1	T	0.5	178.949
1	T	1.0	190.869
1	T	1.5	164.927
1	T	2.0	139.962
1	T	2.5	129.59
1	T	3.0	131.369
1	T	4.0	150.854
1	T	5.0	121.239
1	T	6.0	139.229
1	T	8.0	128.52
1	T	10.0	143.243
1	T	12.0	144.964
1	T	24.0	133.16
1	T	48.0	137.271
1	T	72.0	112.846

	2		R		0.0		0.0	
	2		R		0.5		62.222	
	2		R		1.0		261.177	
	2		R		1.5		234.063	
	2		R		2.0		234.091	
	2		R		2.5		222.881	
	2		R		3.0		213.896	
	2		R		4.0		196.026	
	2		R		5.0		199.634	
	2		R		6.0		196.037	
	2		R		8.0		213.352	
	2		R		10.0		200.088	
	2		R		12.0		196.035	
	2		R		24.0		160.338	
	2		R		48.0		110.28	
	2		R		72.0		85.241	
	3		R		0.0		0.0	
	3		R		0.5		49.849	
	3		R		1.0		77.367	
	3		R		1.5		105.345	
	3		R		2.0		100.943	
	3		R		2.5		72.746	
	3		R		3.0		69.985	
	3		R		4.0		93.565	
	3		R		5.0		91.981	
	3		R		6.0		82.71	
	3		R		8.0		84.205	
	3		R		10.0		85.342	
	3		R		12.0		76.027	
	3		R		24.0		81.259	
	3		R		48.0		70.107	
	3		R		72.0		67.901	
	4		R		0.0		0.0	
	4		R		0.5		52.421	
	4		R		1.0		208.542	
	4		R		1.5		188.923	
	4		R		2.0		165.177	
	4		R		2.5		146.996	
	4		R		3.0		152.701	
	4		R		4.0		154.345	
	4		R		5.0		128.398	
	4		R		6.0		149.807	
	4		R		8.0		151.066	
	4		R		10.0		136.819	
	4		R		12.0		132.257	
	4		R		24.0		141.247	
	4		R		48.0		129.138	
	4		R		72.0		97.625	
	5		T		0.0		0.0	
	5		T		0.5		0.0	
	5		T		1.0		9.545	
	5		T		1.5		153.964	
	5		T		2.0		152.34	
	5		T		2.5		151.452	
	5		T		3.0		161.312	
	5		T		4.0		169.334	
	5		T		5.0		162.907	
	5		T		6.0		166.651	
	5		T		8.0		168.668	



	5		T		10.0		155.103	
	5		T		12.0		154.066	
	5		T		24.0		162.974	
	5		T		48.0		109.814	
	5		T		72.0		110.778	
	6		T		0.0		0.0	
	6		T		0.5		57.882	
	6		T		1.0		100.498	
	6		T		1.5		138.651	
	6		T		2.0		147.287	
	6		T		2.5		154.648	
	6		T		3.0		122.316	
	6		T		4.0		132.857	
	6		T		5.0		126.067	
	6		T		6.0		140.466	
	6		T		8.0		115.542	
	6		T		10.0		102.16	
	6		T		12.0		113.751	
	6		T		24.0		101.049	
	6		T		48.0		92.55	
	6		T		72.0		69.501	
	7		R		0.0		0.0	
	7		R		0.5		19.95	
	7		R		1.0		128.405	
	7		R		1.5		136.807	
	7		R		2.0		113.109	
	7		R		2.5		153.254	
	7		R		3.0		123.606	
	7		R		4.0		142.655	
	7		R		5.0		112.347	
	7		R		6.0		139.919	
	7		R		8.0		105.513	
	7		R		10.0		134.408	
	7		R		12.0		123.37	
	7		R		24.0		110.511	
	7		R		48.0		90.291	
	7		R		72.0		58.051	
	8		R		0.0		0.0	
	8		R		0.5		136.91	
	8		R		1.0		126.646	
	8		R		1.5		118.5	
	8		R		2.0		134.926	
	8		R		2.5		113.213	
	8		R		3.0		130.896	
	8		R		4.0		138.327	
	8		R		5.0		22.724	
	8		R		6.0		53.774	
	8		R		8.0		55.107	
	8		R		10.0		102.871	
	8		R		12.0		134.133	
	8		R		24.0		108.021	
	8		R		48.0		98.466	
	8		R		72.0		74.437	
	9		T		0.0		0.0	
	9		T		0.5		113.362	
	9		T		1.0		128.273	
	9		T		1.5		125.395	
	9		T		2.0		146.933	
	9		T		2.5		140.559	

	9		T		3.0		167.347	
	9		T		4.0		157.504	
	9		T		5.0		141.35	
	9		T		6.0		140.282	
	9		T		8.0		105.438	
	9		T		10.0		164.843	
	9		T		12.0		135.58	
	9		T		24.0		117.125	
	9		T		48.0		109.745	
	9		T		72.0		93.44	
	10		R		0.0		0.0	
	10		R		0.5		13.634	
	10		R		1.0		62.561	
	10		R		1.5		112.655	
	10		R		2.0		125.482	
	10		R		2.5		116.255	
	10		R		3.0		112.674	
	10		R		4.0		116.986	
	10		R		5.0		119.81	
	10		R		6.0		107.557	
	10		R		8.0		120.479	
	10		R		10.0		124.171	
	10		R		12.0		106.476	
	10		R		24.0		116.508	
	10		R		48.0		45.204	
	10		R		72.0		42.191	
	-----							

## 8 Appendix 2

### 8.1 Reference values 1: Linear-trapezoidal rule; Extravascular

WinNonlin 8.0.0.3176  
Subject=1,Formulation=T

Date: 9/09/2019  
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.0.0.3176  
Core Version 22August2017

#### Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 16  
Dose time: 0.00  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal with Linear Interpolation  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

# Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	178.9			44.74	22.37	
1.000	190.9			137.2	92.45	
1.500	164.9			226.1	202.0	
2.000	140.0			302.4	333.8	
2.500	129.6			369.8	484.8	
3.000	131.4			435.0	664.3	
4.000	150.9			576.1	1163.	
5.000	121.2			712.1	1768.	
6.000	139.2			842.4	2489.	
8.000	128.5			1110.	4352.	
10.00 *	143.2	144.7	-1.453	1382.	6813.	1.000
12.00 *	145.0	143.7	1.244	1670.	9985.	1.000
24.00 *	133.2	138.0	-4.840	3339.	3.960e+04	1.000
48.00 *	137.3	127.2	10.04	6584.	1.570e+05	1.000
72.00 *	112.8	117.3	-4.460	9585.	3.336e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

## Final Parameters

N_Samples	16
Dose	100.0000
Rsqr	0.7861
Rsqr_adjusted	0.7148
Corr_XY	-0.8866
No_points_lambda_z	5
Lambda_z	0.0034
Lambda_z_intercept	5.0085
Lambda_z_lower	10.0000
Lambda_z_upper	72.0000
HL_Lambda_z	204.7857
Span	0.3028
Tlag	0.0000
Tmax	1.0000
Cmax	190.8690
Cmax_D	1.9087
Tlast	72.0000
Clast	112.8460
Clast_pred	117.3058
AUClast	9585.4218
AUClast_D	95.8542

AUCall	9585.4218
AUCINF_obs	42925.0191
AUCINF_D_obs	429.2502
AUC_%Extrap_obs	77.6694
Vz_F_obs	0.6883
Cl_F_obs	0.0023
AUCINF_pred	44242.6313
AUCINF_D_pred	442.4263
AUC_%Extrap_pred	78.3344
Vz_F_pred	0.6678
Cl_F_pred	0.0023
AUMClast	333582.4808
AUMCINF_obs	12583994.9366
AUMC_%Extrap_obs	97.3492
AUMCINF_pred	13068142.7409
AUMC_%Extrap_pred	97.4474
MRTlast	34.8010
MRTINF_obs	293.1622
MRTINF_pred	295.3744

WinNonlin 8.0.0.3176  
Subject=2,Formulation=R

Date: 9/09/2019  
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.0.0.3176  
Core Version 22August2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 16  
Dose time: 0.00  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal with Linear Interpolation  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	

0.5000	62.22			15.56	7.778	
1.000	261.2			96.41	80.85	
1.500	234.1			220.2	233.9	
2.000	234.1			337.3	438.7	
2.500	222.9			451.5	695.1	
3.000	213.9			560.7	994.8	
4.000	196.0			765.7	1708.	
5.000	199.6			963.5	2599.	
6.000	196.0			1161.	3686.	
8.000	213.4			1571.	6569.	
10.00 *	200.1	197.9	2.174	1984.	1.028e+04	1.000
12.00 *	196.0	192.4	3.626	2380.	1.463e+04	1.000
24.00 *	160.3	162.4	-2.108	4519.	5.183e+04	1.000
48.00 *	110.3	115.8	-5.512	7766.	1.615e+05	1.000
72.00 *	85.24	82.54	2.704	1.011e+04	2.987e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

-----

N_Samples	16
Dose	100.0000
Rsq	0.9928
Rsq_adjusted	0.9904
Corr_XY	-0.9964
No_points_lambda_z	5
Lambda_z	0.0141
Lambda_z_intercept	5.4289
Lambda_z_lower	10.0000
Lambda_z_upper	72.0000
HL_Lambda_z	49.1374
Span	1.2618
Tlag	0.0000
Tmax	1.0000
Cmax	261.1770
Cmax_D	2.6118
Tlast	72.0000
Clast	85.2410
Clast_pred	82.5367
AUClast	10112.1755
AUClast_D	101.1218
AUCall	10112.1755
AUCINF_obs	16154.9301
AUCINF_D_obs	161.5493
AUC_%Extrap_obs	37.4050
Vz_F_obs	0.4388
Cl_F_obs	0.0062

AUCINF_pred	15963.2209
AUCINF_D_pred	159.6322
AUC_%Extrap_pred	36.6533
Vz_F_pred	0.4441
Cl_F_pred	0.0063
AUMClast	298701.3885
AUMCINF_obs	1162152.0263
AUMC_%Extrap_obs	74.2976
AUMCINF_pred	1134758.6551
AUMC_%Extrap_pred	73.6771
MRTlast	29.5388
MRTINF_obs	71.9379
MRTINF_pred	71.0858

WinNonlin 8.0.0.3176  
Subject=3,Formulation=R

Date: 9/09/2019  
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.0.0.3176  
Core Version 22August2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 16  
Dose time: 0.00  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal with Linear Interpolation  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	49.85			12.46	6.231	
1.000	77.37			44.27	31.80	
1.500	105.3			89.94	90.65	
2.000	100.9			141.5	180.6	
2.500	72.75			184.9	276.6	
3.000	69.99			220.6	374.5	

4.000	93.57			302.4	666.6	
5.000	91.98			395.2	1084.	
6.000 *	82.71	83.17	-0.4609	482.5	1562.	1.000
8.000 *	84.21	82.63	1.580	649.4	2732.	1.000
10.00 *	85.34	82.08	3.259	819.0	4259.	1.000
12.00 *	76.03	81.54	-5.518	980.3	6024.	1.000
24.00 *	81.26	78.39	2.872	1924.	2.320e+04	1.000
48.00 *	70.11	72.43	-2.326	3740.	8.698e+04	1.000
72.00 *	67.90	66.93	0.9699	5397.	1.860e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

-----

N_Samples	16
Dose	100.0000
Rsq	0.8136
Rsq_adjusted	0.7763
Corr_XY	-0.9020
No_points_lambda_z	7
Lambda_z	0.0033
Lambda_z_intercept	4.4406
Lambda_z_lower	6.0000
Lambda_z_upper	72.0000
HL_Lambda_z	210.5915
Span	0.3134
Tlag	0.0000
Tmax	1.5000
Cmax	105.3450
Cmax_D	1.0535
Tlast	72.0000
Clast	67.9010
Clast_pred	66.9311
AUClast	5396.5498
AUClast_D	53.9655
AUCall	5396.5498
AUCINF_obs	26026.1826
AUCINF_D_obs	260.2618
AUC_%Extrap_obs	79.2649
Vz_F_obs	1.1674
Cl_F_obs	0.0038
AUCINF_pred	25731.4952
AUCINF_D_pred	257.3150
AUC_%Extrap_pred	79.0275
Vz_F_pred	1.1807
Cl_F_pred	0.0039
AUMClast	186032.0553

AUMCINF_obs	7939045.7669
AUMC_%Extrap_obs	97.6567
AUMCINF_pred	7828296.5609
AUMC_%Extrap_pred	97.6236
MRTlast	34.4724
MRTINF_obs	305.0407
MRTINF_pred	304.2301

WinNonlin 8.0.0.3176  
Subject=4,Formulation=R

Date: 9/09/2019  
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.0.0.3176  
Core Version 22August2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 16  
Dose time: 0.00  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal with Linear Interpolation  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	52.42			13.11	6.553	
1.000	208.5			78.35	65.24	
1.500	188.9			177.7	188.2	
2.000	165.2			266.2	341.7	
2.500	147.0			344.3	516.1	
3.000	152.7			419.2	722.5	
4.000	154.3			572.7	1260.	
5.000	128.4			714.1	1890.	
6.000	149.8			853.2	2660.	
8.000	151.1			1154.	4768.	
10.00	136.8			1442.	7344.	
12.00	132.3			1711.	1.030e+04	



24.00 *	141.2	145.8	-4.547	3352.	4.016e+04	1.000
48.00 *	129.1	121.2	7.930	6597.	1.552e+05	1.000
72.00 *	97.63	100.8	-3.143	9318.	3.140e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

# Final Parameters

-----

N_Samples	16
Dose	100.0000
Rsq	0.9189
Rsq_adjusted	0.8377
Corr_XY	-0.9586
No_points_lambda_z	3
Lambda_z	0.0077
Lambda_z_intercept	5.1669
Lambda_z_lower	24.0000
Lambda_z_upper	72.0000
HL_Lambda_z	90.0736
Span	0.5329
Tlag	0.0000
Tmax	1.0000
Cmax	208.5420
Cmax_D	2.0854
Tlast	72.0000
Clast	97.6250
Clast_pred	100.7679
AUClast	9317.8358
AUClast_D	93.1784
AUCall	9317.8358
AUCINF_obs	22004.0779
AUCINF_D_obs	220.0408
AUC_%Extrap_obs	57.6541
Vz_F_obs	0.5906
Cl_F_obs	0.0045
AUCINF_pred	22412.4980
AUCINF_D_pred	224.1250
AUC_%Extrap_pred	58.4257
Vz_F_pred	0.5798
Cl_F_pred	0.0045
AUMClast	313955.9048
AUMCINF_obs	2875926.0451
AUMC_%Extrap_obs	89.0833
AUMCINF_pred	2958405.9609
AUMC_%Extrap_pred	89.3877
MRTlast	33.6941
MRTINF_obs	130.6997

MRTINF\_pred

131.9980

WinNonlin 8.0.0.3176

Subject=5,Formulation=T

Date: 9/09/2019

Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

8.0.0.3176

Core Version 22August2017

Settings

-----

Model: Plasma Data, Extravascular Administration

Number of nonmissing observations: 16

Dose time: 0.00

Dose amount: 100.00

Calculation method: Linear Trapezoidal with Linear Interpolation

Weighting for lambda\_z calculations: Uniform weighting

Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

-----

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
1.000	9.545			2.386	2.386	
1.500	154.0			43.26	62.51	
2.000	152.3			119.8	196.4	
2.500	151.5			195.8	367.2	
3.000	161.3			274.0	582.9	
4.000	169.3			439.3	1164.	
5.000 *	162.9	166.2	-3.309	605.4	1909.	1.000
6.000 *	166.7	165.1	1.563	770.2	2817.	1.000
8.000 *	168.7	162.9	5.815	1106.	5166.	1.000
10.00 *	155.1	160.6	-5.546	1429.	8066.	1.000
12.00 *	154.1	158.5	-4.409	1738.	1.147e+04	1.000
24.00 *	163.0	146.0	16.94	3641.	4.603e+04	1.000
48.00 *	109.8	124.0	-14.19	6914.	1.562e+05	1.000
72.00 *	110.8	105.3	5.480	9561.	3.152e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

# Final Parameters

N_Samples	16
Dose	100.0000
Rsq	0.8534
Rsq_adjusted	0.8289
Corr_XY	-0.9238
No_points_lambda_z	8
Lambda_z	0.0068
Lambda_z_intercept	5.1474
Lambda_z_lower	5.0000
Lambda_z_upper	72.0000
HL_Lambda_z	101.7340
Span	0.6586
Tlag	0.5000
Tmax	4.0000
Cmax	169.3340
Cmax_D	1.6933
Tlast	72.0000
Clast	110.7780
Clast_pred	105.2983
AUClast	9561.2600
AUClast_D	95.6126
AUCall	9561.2600
AUCINF_obs	25820.2749
AUCINF_D_obs	258.2027
AUC_%Extrap_obs	62.9700
Vz_F_obs	0.5684
Cl_F_obs	0.0039
AUCINF_pred	25016.0160
AUCINF_D_pred	250.1602
AUC_%Extrap_pred	61.7794
Vz_F_pred	0.5867
Cl_F_pred	0.0040
AUMClast	315181.5625
AUMCINF_obs	3872185.0137
AUMC_%Extrap_obs	91.8604
AUMCINF_pred	3696236.3722
AUMC_%Extrap_pred	91.4729
MRTlast	32.9644
MRTINF_obs	149.9668
MRTINF_pred	147.7548

WinNonlin 8.0.0.3176

Subject=6,Formulation=T

Date: 9/09/2019  
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.0.0.3176  
Core Version 22August2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 16  
Dose time: 0.00  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal with Linear Interpolation  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	57.88			14.47	7.235	
1.000	100.5			54.07	39.60	
1.500	138.7			113.9	116.7	
2.000	147.3			185.3	242.4	
2.500	154.6			260.8	412.6	
3.000	122.3			330.1	601.0	
4.000	132.9			457.6	1050.	
5.000	126.1			587.1	1631.	
6.000	140.5			720.4	2368.	
8.000	115.5			976.4	4135.	
10.00	102.2			1194.	6081.	
12.00 *	113.8	114.1	-0.3825	1410.	8467.	1.000
24.00 *	101.0	104.1	-3.021	2699.	3.121e+04	1.000
48.00 *	92.55	86.53	6.024	5022.	1.136e+05	1.000
72.00 *	69.50	71.94	-2.439	6967.	2.270e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

Final Parameters

-----  
N\_Samples 16  
Dose 100.0000

Rsq	0.9501
Rsq_adjusted	0.9252
Corr_XY	-0.9747
No_points_lambda_z	4
Lambda_z	0.0077
Lambda_z_intercept	4.8297
Lambda_z_lower	12.0000
Lambda_z_upper	72.0000
HL_Lambda_z	90.1095
Span	0.6659
Tlag	0.0000
Tmax	2.5000
Cmax	154.6480
Cmax_D	1.5465
Tlast	72.0000
Clast	69.5010
Clast_pred	71.9399
AUClast	6966.5980
AUClast_D	69.6660
AUCall	6966.5980
AUCINF_obs	16001.7597
AUCINF_D_obs	160.0176
AUC_%Extrap_obs	56.4636
Vz_F_obs	0.8124
Cl_F_obs	0.0062
AUCINF_pred	16318.8233
AUCINF_D_pred	163.1882
AUC_%Extrap_pred	57.3094
Vz_F_pred	0.7966
Cl_F_pred	0.0061
AUMClast	226977.0608
AUMCINF_obs	2052083.8596
AUMC_%Extrap_obs	88.9392
AUMCINF_pred	2116130.8466
AUMC_%Extrap_pred	89.2740
MRTlast	32.5808
MRTINF_obs	128.2411
MRTINF_pred	129.6742

WinNonlin 8.0.0.3176  
Subject=7, Formulation=R

Date: 9/09/2019  
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

### Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 16  
Dose time: 0.00  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal with Linear Interpolation  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

### Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	19.95			4.988	2.494	
1.000	128.4			42.08	37.09	
1.500	136.8			108.4	120.5	
2.000	113.1			170.9	228.3	
2.500	153.3			237.4	380.7	
3.000	123.6			306.7	569.2	
4.000	142.7			439.8	1040.	
5.000	112.3			567.3	1606.	
6.000	139.9			693.4	2307.	
8.000	105.5			938.9	3990.	
10.00 *	134.4	132.4	1.964	1179.	6178.	1.000
12.00 *	123.4	129.2	-5.814	1437.	9003.	1.000
24.00 *	110.5	111.2	-0.7336	2840.	3.380e+04	1.000
48.00 *	90.29	82.49	7.798	5249.	1.176e+05	1.000
72.00 *	58.05	61.17	-3.122	7030.	2.198e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

### Final Parameters

-----  
N\_Samples 16  
Dose 100.0000  
Rsq 0.9703  
Rsq\_adjusted 0.9604  
Corr\_XY -0.9850  
No\_points\_lambda\_z 5  
Lambda\_z 0.0125  
Lambda\_z\_intercept 5.0107

Lambda_z_lower	10.0000
Lambda_z_upper	72.0000
HL_Lambda_z	55.6345
Span	1.1144
Tlag	0.0000
Tmax	2.5000
Cmax	153.2540
Cmax_D	1.5325
Tlast	72.0000
Clast	58.0510
Clast_pred	61.1727
AUClast	7029.5735
AUClast_D	70.2957
AUCall	7029.5735
AUCINF_obs	11688.9527
AUCINF_D_obs	116.8895
AUC_%Extrap_obs	39.8614
Vz_F_obs	0.6867
Cl_F_obs	0.0086
AUCINF_pred	11939.5116
AUCINF_D_pred	119.3951
AUC_%Extrap_pred	41.1234
Vz_F_pred	0.6723
Cl_F_pred	0.0084
AUMClast	219797.7073
AUMCINF_obs	929251.3075
AUMC_%Extrap_obs	76.3468
AUMCINF_pred	967402.2944
AUMC_%Extrap_pred	77.2796
MRTlast	31.2676
MRTINF_obs	79.4983
MRTINF_pred	81.0253

WinNonlin 8.0.0.3176  
Subject=8,Formulation=R

Date: 9/09/2019  
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.0.0.3176  
Core Version 22August2017

Settings

-----

Model: Plasma Data, Extravascular Administration

Number of nonmissing observations: 16  
 Dose time: 0.00  
 Dose amount: 100.00  
 Calculation method: Linear Trapezoidal with Linear Interpolation  
 Weighting for lambda\_z calculations: Uniform weighting  
 Lambda\_z method: Find best fit for lambda\_z, Log regression

#### Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	136.9			34.23	17.11	
1.000	126.6			100.1	65.89	
1.500	118.5			161.4	142.0	
2.000	134.9			224.8	253.9	
2.500	113.2			286.8	392.1	
3.000	130.9			347.8	561.0	
4.000	138.3			482.4	1034.	
5.000	22.72			563.0	1368.	
6.000	53.77			601.2	1586.	
8.000	55.11			710.1	2349.	
10.00	102.9			868.1	3819.	
12.00 *	134.1	129.2	4.939	1105.	6457.	1.000
24.00 *	108.0	116.1	-8.045	2558.	3.167e+04	1.000
48.00 *	98.47	93.68	4.791	5036.	1.195e+05	1.000
72.00 *	74.44	75.60	-1.167	7111.	2.405e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

N_Samples	16
Dose	100.0000
Rsqr	0.9480
Rsqr_adjusted	0.9220
Corr_XY	-0.9736
No_points_lambda_z	4
Lambda_z	0.0089
Lambda_z_intercept	4.9685
Lambda_z_lower	12.0000
Lambda_z_upper	72.0000
HL_Lambda_z	77.6194
Span	0.7730
Tlag	0.0000
Tmax	4.0000



Cmax	138.3270
Cmax_D	1.3833
Tlast	72.0000
Clast	74.4370
Clast_pred	75.6043
AUClast	7110.6745
AUClast_D	71.1067
AUCall	7110.6745
AUCINF_obs	15446.2103
AUCINF_D_obs	154.4621
AUC_%Extrap_obs	53.9649
Vz_F_obs	0.7250
Cl_F_obs	0.0065
AUCINF_pred	15576.9232
AUCINF_D_pred	155.7692
AUC_%Extrap_pred	54.3512
Vz_F_pred	0.7189
Cl_F_pred	0.0064
AUMClast	240526.0538
AUMCINF_obs	1774106.9508
AUMC_%Extrap_obs	86.4424
AUMCINF_pred	1798155.6519
AUMC_%Extrap_pred	86.6237
MRTlast	33.8261
MRTINF_obs	114.8571
MRTINF_pred	115.4372

WinNonlin 8.0.0.3176  
Subject=9,Formulation=T

Date: 9/09/2019  
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.0.0.3176  
Core Version 22August2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 16  
Dose time: 0.00  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal with Linear Interpolation  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

# Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	113.4			28.34	14.17	
1.000	128.3			88.75	60.41	
1.500	125.4			152.2	139.5	
2.000	146.9			220.2	260.0	
2.500	140.6			292.1	421.3	
3.000	167.3			369.1	634.7	
4.000	157.5			531.5	1201.	
5.000	141.4			681.0	1869.	
6.000	140.3			821.8	2643.	
8.000	105.4			1067.	4328.	
10.00	164.8			1338.	6820.	
12.00 *	135.6	131.6	4.014	1638.	1.010e+04	1.000
24.00 *	117.1	122.9	-5.823	3154.	3.672e+04	1.000
48.00 *	109.7	107.4	2.377	5877.	1.337e+05	1.000
72.00 *	93.44	93.76	-0.3218	8315.	2.776e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

## Final Parameters

N_Samples	16
Dose	100.0000
Rsq	0.9475
Rsq_adjusted	0.9213
Corr_XY	-0.9734
No_points_lambda_z	4
Lambda_z	0.0056
Lambda_z_intercept	4.9473
Lambda_z_lower	12.0000
Lambda_z_upper	72.0000
HL_Lambda_z	122.7708
Span	0.4887
Tlag	0.0000
Tmax	3.0000
Cmax	167.3470
Cmax_D	1.6735
Tlast	72.0000
Clast	93.4400
Clast_pred	93.7618
AUClast	8315.0803

AUClast_D	83.1508
AUCall	8315.0803
AUCINF_obs	24865.2460
AUCINF_D_obs	248.6525
AUC_%Extrap_obs	66.5594
Vz_F_obs	0.7123
Cl_F_obs	0.0040
AUCINF_pred	24922.2366
AUCINF_D_pred	249.2224
AUC_%Extrap_pred	66.6359
Vz_F_pred	0.7107
Cl_F_pred	0.0040
AUMClast	277613.9778
AUMCINF_obs	4400604.1747
AUMC_%Extrap_obs	93.6915
AUMCINF_pred	4414801.7328
AUMC_%Extrap_pred	93.7117
MRTlast	33.3868
MRTINF_obs	176.9781
MRTINF_pred	177.1431

WinNonlin 8.0.0.3176  
Subject=10,Formulation=R

Date: 9/09/2019  
Time: 18:03:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.0.0.3176  
Core Version 22August2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 16  
Dose time: 0.00  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal with Linear Interpolation  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
-----						

0.0000	0.0000			0.0000	0.0000	
0.5000	13.63			3.409	1.704	
1.000	62.56			22.46	19.05	
1.500	112.7			66.26	76.93	
2.000	125.5			125.8	181.9	
2.500	116.3			186.2	317.3	
3.000	112.7			243.5	474.5	
4.000 *	117.0	124.9	-7.925	358.3	877.5	1.000
5.000 *	119.8	122.8	-2.972	476.7	1411.	1.000
6.000 *	107.6	120.7	-13.13	590.4	2033.	1.000
8.000 *	120.5	116.6	3.868	818.4	3642.	1.000
10.00 *	124.2	112.7	11.50	1063.	5848.	1.000
12.00 *	106.5	108.9	-2.386	1294.	8367.	1.000
24.00 *	116.5	88.57	27.94	2632.	3.281e+04	1.000
48.00 *	45.20	58.63	-13.43	4572.	9.240e+04	1.000
72.00 *	42.19	38.81	3.380	5621.	1.549e+05	1.000

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

-----

N_Samples	16
Dose	100.0000
Rsq	0.8809
Rsq_adjusted	0.8639
Corr_XY	-0.9386
No_points_lambda_z	9
Lambda_z	0.0172
Lambda_z_intercept	4.8964
Lambda_z_lower	4.0000
Lambda_z_upper	72.0000
HL_Lambda_z	40.3233
Span	1.6864
Tlag	0.0000
Tmax	2.0000
Cmax	125.4820
Cmax_D	1.2548
Tlast	72.0000
Clast	42.1910
Clast_pred	38.8109
AUClast	5620.8945
AUClast_D	56.2089
AUCall	5620.8945
AUCINF_obs	8075.3242
AUCINF_D_obs	80.7532
AUC_%Extrap_obs	30.3942
Vz_F_obs	0.7204

Cl_F_obs	0.0124
AUCINF_pred	7878.6869
AUCINF_D_pred	78.7869
AUC_%Extrap_pred	28.6570
Vz_F_pred	0.7384
Cl_F_pred	0.0127
AUMClast	154893.0605
AUMCINF_obs	474396.5944
AUMC_%Extrap_obs	67.3495
AUMCINF_pred	448799.4879
AUMC_%Extrap_pred	65.4872
MRTlast	27.5567
MRTINF_obs	58.7464
MRTINF_pred	56.9637

## 8.2 Reference values 2: Linear-up Log-Down rule; Extravascular

WinNonlin 8.2.0.4383  
Subject=1,Formulation=T

Date: 2/11/2020  
Time: 22:58:06

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 11Oct2017

### Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 15  
Steady state interval Tau: 9.00  
Dose time: 0.25  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal Rule for for Increasing Values,  
Log Trapezoidal Rule for Decreasing Values  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

### Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.2500 @	121.2			0.0000	0.0000	
0.5000	178.9			37.52	5.592	
1.000	190.9			130.0	52.56	

1.500	164.9			218.8	140.8	
2.000	140.0			294.8	254.4	
2.500	129.6			362.2	388.9	
3.000	131.4			427.4	552.1	
4.000	150.9			568.5	1016.	
5.000	121.2			704.0	1589.	
6.000	139.2			834.3	2277.	
8.000	128.5			1102.	4080.	
10.00 *	143.2	144.7	-1.453	1374.	6473.	1.000
12.00 *	145.0	143.7	1.244	1662.	9573.	1.000
24.00 *	133.2	138.0	-4.840	3330.	3.903e+04	1.000
48.00 *	137.3	127.2	10.04	6575.	1.556e+05	1.000
72.00 *	112.8	117.3	-4.460	9567.	3.332e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

-----

N_Samples	15
Dose	100.0000
Rsqr	0.7861
Rsqr_adjusted	0.7148
Corr_XY	-0.8866
No_points_lambda_z	5
Lambda_z	0.0034
Lambda_z_intercept	5.0085
Lambda_z_lower	10.0000
Lambda_z_upper	72.0000
HL_Lambda_z	204.7857
Span	0.3028
Tlag	0.0000
Tmax	1.0000
Cmax	190.8690
Cmax_D	1.9087
Tlast	72.0000
Clast	112.8460
Clast_pred	117.3058
AUClast	9566.5968
AUClast_D	95.6660
AUCall	9566.5968
AUCINF_obs	42906.1941
AUCINF_D_obs	429.0619
AUC_%Extrap_obs	77.7035
AUCINF_pred	44223.8063
AUCINF_D_pred	442.2381

AUC_%Extrap_pred	78.3678
Tmin	5.0000
Cmin	121.2390
Ctau	137.7219
Cavg	140.9195
Swing	0.5743
Swing_Tau	0.3859
Fluctuation%	49.4112
Fluctuation%_Tau	37.7145
CLss_F	0.0788
MRTINF_obs	299.7917
MRTINF_pred	309.1418
Vz_F	23.2949
Accumulation_Index	33.3296
AUC_TAU	1268.2756
AUC_TAU_D	12.6828
AUC_TAU_%Extrap	0.0000
AUMC_TAU	5477.2042

WinNonlin 8.2.0.4383  
Subject=2,Formulation=R

Date: 2/11/2020  
Time: 22:58:06

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 11Oct2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 15  
Steady state interval Tau: 9.00  
Dose time: 0.25  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal Rule for for Increasing Values,  
Log Trapezoidal Rule for Decreasing Values  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
-----						

0.2500 @	62.22			0.0000	0.0000	
0.5000	62.22			15.56	1.944	
1.000	261.2			96.41	54.80	
1.500	234.1			220.1	177.9	
2.000	234.1			337.1	353.5	
2.500	222.9			451.4	581.7	
3.000	213.9			560.5	854.5	
4.000	196.0			765.4	1519.	
5.000	199.6			963.2	2360.	
6.000	196.0			1161.	3399.	
8.000	213.4			1570.	6179.	
10.00 *	200.1	197.9	2.174	1984.	9791.	1.000
12.00 *	196.0	192.4	3.626	2380.	1.405e+04	1.000
24.00 *	160.3	162.4	-2.108	4511.	5.145e+04	1.000
48.00 *	110.3	115.8	-5.512	7721.	1.638e+05	1.000
72.00 *	85.24	82.54	2.704	1.005e+04	3.020e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

-----

N_Samples	15
Dose	100.0000
Rsqr	0.9928
Rsqr_adjusted	0.9904
Corr_XY	-0.9964
No_points_lambda_z	5
Lambda_z	0.0141
Lambda_z_intercept	5.4289
Lambda_z_lower	10.0000
Lambda_z_upper	72.0000
HL_Lambda_z	49.1374
Span	1.2618
Tlag	0.0000
Tmax	1.0000
Cmax	261.1770
Cmax_D	2.6118
Tlast	72.0000
Clast	85.2410
Clast_pred	82.5367
AUClast	10054.2865
AUClast_D	100.5429
AUCall	10054.2865
AUCINF_obs	16097.0411
AUCINF_D_obs	160.9704



AUC_%Extrap_obs	37.5395
AUCINF_pred	15905.3319
AUCINF_D_pred	159.0533
AUC_%Extrap_pred	36.7867
Tmin	0.5000
Cmin	62.2220
Ctau	204.9625
Cavg	203.5356
Swing	3.1975
Swing_Tau	0.2743
Fluctuation%	97.7495
Fluctuation%_Tau	27.6190
CLss_F	0.0546
MRTINF_obs	74.6550
MRTINF_pred	73.7131
Vz_F	3.8699
Accumulation_Index	8.3873
AUC_TAU	1831.8205
AUC_TAU_D	18.3182
AUC_TAU_%Extrap	0.0000
AUMC_TAU	8367.5709

WinNonlin 8.2.0.4383  
Subject=3,Formulation=R

Date: 2/11/2020  
Time: 22:58:06

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 11Oct2017

Settings

-----

Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 15  
Steady state interval Tau: 9.00  
Dose time: 0.25  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal Rule for for Increasing Values,  
Log Trapezoidal Rule for Decreasing Values  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.2500 @	49.85			0.0000	0.0000	
0.5000	49.85			12.46	1.558	
1.000	77.37			44.27	19.18	
1.500	105.3			89.94	66.61	
2.000	100.9			141.5	143.9	
2.500	72.75			184.5	229.4	
3.000	69.99			220.2	318.5	
4.000	93.57			302.0	590.2	
5.000	91.98			394.8	984.3	
6.000 *	82.71	83.17	-0.4609	482.0	1442.	1.000
8.000 *	84.21	82.63	1.580	648.9	2570.	1.000
10.00 *	85.34	82.08	3.259	818.5	4055.	1.000
12.00 *	76.03	81.54	-5.518	979.7	5784.	1.000
24.00 *	81.26	78.39	2.872	1923.	2.272e+04	1.000
48.00 *	70.11	72.43	-2.326	3737.	8.701e+04	1.000
72.00 *	67.90	66.93	0.9699	5392.	1.858e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda<sub>z</sub>.

#### Final Parameters

N_Samples	15
Dose	100.0000
Rsq	0.8136
Rsq_adjusted	0.7763
Corr_XY	-0.9020
No_points_lambda_z	7
Lambda_z	0.0033
Lambda_z_intercept	4.4406
Lambda_z_lower	6.0000
Lambda_z_upper	72.0000
HL_Lambda_z	210.5915
Span	0.3134
Tlag	0.0000
Tmax	1.5000
Cmax	105.3450
Cmax_D	1.0535
Tlast	72.0000
Clast	67.9010
Clast_pred	66.9311
AUClast	5392.4572
AUClast_D	53.9246

AUCall	5392.4572
AUCINF_obs	26022.0900
AUCINF_D_obs	260.2209
AUC_%Extrap_obs	79.2774
AUCINF_pred	25727.4026
AUCINF_D_pred	257.2740
AUC_%Extrap_pred	79.0400
Tmin	0.5000
Cmin	49.8490
Ctau	84.9156
Cavg	83.8499
Swing	1.1133
Swing_Tau	0.2406
Fluctuation%	66.1849
Fluctuation%_Tau	24.3642
CLss_F	0.1325
MRTINF_obs	305.9200
MRTINF_pred	302.4055
Vz_F	40.2597
Accumulation_Index	34.2602
AUC_TAU	754.6494
AUC_TAU_D	7.5465
AUC_TAU_%Extrap	0.0000
AUMC_TAU	3455.3464

WinNonlin 8.2.0.4383  
Subject=4,Formulation=R

Date: 2/11/2020  
Time: 22:58:06

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 11Oct2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 15  
Steady state interval Tau: 9.00  
Dose time: 0.25  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal Rule for for Increasing Values,  
Log Trapezoidal Rule for Decreasing Values  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

# Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.2500 @	52.42			0.0000	0.0000	
0.5000	52.42			13.11	1.638	
1.000	208.5			78.35	44.02	
1.500	188.9			177.6	142.9	
2.000	165.2			266.0	275.0	
2.500	147.0			344.0	430.5	
3.000	152.7			418.9	618.2	
4.000	154.3			572.4	1118.	
5.000	128.4			713.4	1715.	
6.000	149.8			852.5	2450.	
8.000	151.1			1153.	4482.	
10.00	136.8			1441.	6995.	
12.00	132.3			1710.	9885.	
24.00 *	141.2	145.8	-4.547	3351.	3.934e+04	1.000
48.00 *	129.1	121.2	7.930	6594.	1.547e+05	1.000
72.00 *	97.63	100.8	-3.143	9297.	3.147e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

## Final Parameters

N_Samples	15
Dose	100.0000
Rsq	0.9189
Rsq_adjusted	0.8377
Corr_XY	-0.9586
No_points_lambda_z	3
Lambda_z	0.0077
Lambda_z_intercept	5.1669
Lambda_z_lower	24.0000
Lambda_z_upper	72.0000
HL_Lambda_z	90.0736
Span	0.5329
Tlag	0.0000
Tmax	1.0000
Cmax	208.5420
Cmax_D	2.0854
Tlast	72.0000
Clast	97.6250

Clast_pred	100.7679
AUClast	9297.0963
AUClast_D	92.9710
AUCall	9297.0963
AUCINF_obs	21983.3385
AUCINF_D_obs	219.8334
AUC_%Extrap_obs	57.7084
AUCINF_pred	22391.7586
AUCINF_D_pred	223.9176
AUC_%Extrap_pred	58.4798
Tmin	0.5000
Cmin	52.4210
Ctau	141.9970
Cavg	148.4979
Swing	2.9782
Swing_Tau	0.4686
Fluctuation%	105.1335
Fluctuation%_Tau	44.8121
CLss_F	0.0748
MRTINF_obs	143.5384
MRTINF_pred	146.2888
Vz_F	9.7232
Accumulation_Index	14.9445
AUC_TAU	1336.4809
AUC_TAU_D	13.3648
AUC_TAU_%Extrap	0.0000
AUMC_TAU	6014.6460

WinNonlin 8.2.0.4383  
Subject=5,Formulation=T

Date: 2/11/2020  
Time: 22:58:07

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 11Oct2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 15  
Steady state interval Tau: 9.00  
Dose time: 0.25  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal Rule for for Increasing Values,

Log Trapezoidal Rule for Decreasing Values  
 Weighting for lambda\_z calculations: Uniform weighting  
 Lambda\_z method: Find best fit for lambda\_z, Log regression

#### Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.2500 @	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
1.000	9.545			2.386	1.790	
1.500	154.0			43.26	51.69	
2.000	152.3			119.8	166.5	
2.500	151.5			195.8	318.4	
3.000	161.3			274.0	514.5	
4.000	169.3			439.3	1054.	
5.000 *	162.9	166.2	-3.309	605.4	1759.	1.000
6.000 *	166.7	165.1	1.563	770.2	2625.	1.000
8.000 *	168.7	162.9	5.815	1105.	4891.	1.000
10.00 *	155.1	160.6	-5.546	1429.	7717.	1.000
12.00 *	154.1	158.5	-4.409	1738.	1.104e+04	1.000
24.00 *	163.0	146.0	16.94	3640.	4.513e+04	1.000
48.00 *	109.8	124.0	-14.19	6872.	1.581e+05	1.000
72.00 *	110.8	105.3	5.480	9519.	3.164e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

N_Samples	15
Dose	100.0000
Rsqr	0.8534
Rsqr_adjusted	0.8289
Corr_XY	-0.9238
No_points_lambda_z	8
Lambda_z	0.0068
Lambda_z_intercept	5.1474
Lambda_z_lower	5.0000
Lambda_z_upper	72.0000
HL_Lambda_z	101.7340
Span	0.6586
Tlag	0.2500
Tmax	4.0000
Cmax	169.3340

Cmax_D	1.6933
Tlast	72.0000
Clast	110.7780
Clast_pred	105.2983
AUClast	9519.1809
AUClast_D	95.1918
AUCall	9519.1809
AUCINF_obs	25778.1958
AUCINF_D_obs	257.7820
AUC_%Extrap_obs	63.0727
AUCINF_pred	24973.9369
AUCINF_D_pred	249.7394
AUC_%Extrap_pred	61.8835
Tmin	0.5000
Cmin	0.0000
Ctau	160.0571
Cavg	145.6561
Swing	Missing
Swing_Tau	0.0580
Fluctuation%	116.2561
Fluctuation%_Tau	6.3691
CLss_F	0.0763
MRTINF_obs	173.0221
MRTINF_pred	167.5004
Vz_F	11.1962
Accumulation_Index	16.8130
AUC_TAU	1310.9045
AUC_TAU_D	13.1090
AUC_TAU_%Extrap	0.0000
AUMC_TAU	6609.7883

WinNonlin 8.2.0.4383  
Subject=6,Formulation=T

Date: 2/11/2020  
Time: 22:58:07

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 110ct2017

Settings

-----  
Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 15  
Steady state interval Tau: 9.00

Dose time: 0.25  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal Rule for for Increasing Values,  
Log Trapezoidal Rule for Decreasing Values  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

#### Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.2500 @	57.88			0.0000	0.0000	
0.5000	57.88			14.47	1.809	
1.000	100.5			54.07	24.27	
1.500	138.7			113.9	86.44	
2.000	147.3			185.3	194.2	
2.500	154.6			260.8	345.6	
3.000	122.3			329.7	517.3	
4.000	132.9			457.3	934.6	
5.000	126.1			586.8	1484.	
6.000	140.5			720.0	2187.	
8.000	115.5			975.2	3902.	
10.00	102.2			1193.	5800.	
12.00 *	113.8	114.1	-0.3825	1409.	8132.	1.000
24.00 *	101.0	104.1	-3.021	2696.	3.083e+04	1.000
48.00 *	92.55	86.53	6.024	5018.	1.134e+05	1.000
72.00 *	69.50	71.94	-2.439	6949.	2.277e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

N_Samples	15
Dose	100.0000
Rsqr	0.9501
Rsqr_adjusted	0.9252
Corr_XY	-0.9747
No_points_lambda_z	4
Lambda_z	0.0077
Lambda_z_intercept	4.8297
Lambda_z_lower	12.0000
Lambda_z_upper	72.0000
HL_Lambda_z	90.1095
Span	0.6659



Tlag	0.0000
Tmax	2.5000
Cmax	154.6480
Cmax_D	1.5465
Tlast	72.0000
Clast	69.5010
Clast_pred	71.9399
AUClast	6948.9856
AUClast_D	69.4899
AUCall	6948.9856
AUCINF_obs	15984.1474
AUCINF_D_obs	159.8415
AUC_%Extrap_obs	56.5258
AUCINF_pred	16301.2109
AUCINF_D_pred	163.0121
AUC_%Extrap_pred	57.3714
Tmin	0.5000
Cmin	57.8820
Ctau	106.9863
Cavg	123.8045
Swing	1.6718
Swing_Tau	0.4455
Fluctuation%	78.1603
Fluctuation%_Tau	38.4976
CLss_F	0.0897
MRTINF_obs	124.6534
MRTINF_pred	127.2144
Vz_F	11.6672
Accumulation_Index	14.9503
AUC_TAU	1114.2404
AUC_TAU_D	11.1424
AUC_TAU_%Extrap	0.0000
AUMC_TAU	5064.7238

WinNonlin 8.2.0.4383  
Subject=7,Formulation=R

Date: 2/11/2020  
Time: 22:58:07

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 11Oct2017

Settings  
-----

Model: Plasma Data, Extravascular Administration  
 Number of nonmissing observations: 15  
 Steady state interval Tau: 9.00  
 Dose time: 0.25  
 Dose amount: 100.00  
 Calculation method: Linear Trapezoidal Rule for for Increasing Values,  
 Log Trapezoidal Rule for Decreasing Values  
 Weighting for lambda\_z calculations: Uniform weighting  
 Lambda\_z method: Find best fit for lambda\_z, Log regression

#### Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.2500 @	19.95			0.0000	0.0000	
0.5000	19.95			4.988	0.6234	
1.000	128.4			42.08	25.95	
1.500	136.8			108.4	92.77	
2.000	113.1			170.7	185.7	
2.500	153.3			237.3	321.4	
3.000	123.6			306.2	493.2	
4.000	142.7			439.3	930.6	
5.000	112.3			566.2	1467.	
6.000	139.9			692.4	2136.	
8.000	105.5			936.2	3771.	
10.00 *	134.4	132.4	1.964	1176.	5899.	1.000
12.00 *	123.4	129.2	-5.814	1434.	8665.	1.000
24.00 *	110.5	111.2	-0.7336	2836.	3.339e+04	1.000
48.00 *	90.29	82.49	7.798	5237.	1.183e+05	1.000
72.00 *	58.05	61.17	-3.122	6989.	2.214e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

#### Final Parameters

N_Samples	15
Dose	100.0000
Rsqr	0.9703
Rsqr_adjusted	0.9604
Corr_XY	-0.9850
No_points_lambda_z	5
Lambda_z	0.0125
Lambda_z_intercept	5.0107
Lambda_z_lower	10.0000

Lambda_z_upper	72.0000
HL_Lambda_z	55.6345
Span	1.1144
Tlag	0.0000
Tmax	2.5000
Cmax	153.2540
Cmax_D	1.5325
Tlast	72.0000
Clast	58.0510
Clast_pred	61.1727
AUClast	6988.7726
AUClast_D	69.8877
AUCall	6988.7726
AUCINF_obs	11648.1518
AUCINF_D_obs	116.4815
AUC_%Extrap_obs	40.0010
AUCINF_pred	11898.7107
AUCINF_D_pred	118.9871
AUC_%Extrap_pred	41.2645
Tmin	0.5000
Cmin	19.9500
Ctau	123.5724
Cavg	119.9297
Swing	6.6819
Swing_Tau	0.2402
Fluctuation%	111.1518
Fluctuation%_Tau	24.7492
CLss_F	0.0926
MRTINF_obs	92.7359
MRTINF_pred	94.8251
Vz_F	7.4362
Accumulation_Index	9.4275
AUC_TAU	1079.3669
AUC_TAU_D	10.7937
AUC_TAU_%Extrap	0.0000
AUMC_TAU	4976.9637

WinNonlin 8.2.0.4383  
Subject=8,Formulation=R

Date: 2/11/2020  
Time: 22:58:07

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 11Oct2017

## Settings

```

-----
Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 15
Steady state interval Tau: 9.00
Dose time: 0.25
Dose amount: 100.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
                    Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

```

## Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.2500 @	22.72			0.0000	0.0000	
0.5000	136.9			19.95	4.278	
1.000	126.6			85.81	36.99	
1.500	118.5			147.1	98.09	
2.000	134.9			210.4	194.1	
2.500	113.2			272.3	317.4	
3.000	130.9			333.3	471.1	
4.000	138.3			467.9	910.5	
5.000	22.72			531.9	1173.	
6.000	53.77			570.2	1382.	
8.000	55.11			679.1	2118.	
10.00	102.9			837.1	3548.	
12.00 *	134.1	129.2	4.939	1074.	6127.	1.000
24.00 *	108.0	116.1	-8.045	2521.	3.150e+04	1.000
48.00 *	98.47	93.68	4.791	4997.	1.196e+05	1.000
72.00 *	74.44	75.60	-1.167	7059.	2.416e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

## Final Parameters

```

-----
N_Samples                15
Dose                     100.0000
Rsq                      0.9480
Rsq_adjusted             0.9220
Corr_XY                  -0.9736
No_points_lambda_z       4

```

Lambda_z	0.0089
Lambda_z_intercept	4.9685
Lambda_z_lower	12.0000
Lambda_z_upper	72.0000
HL_Lambda_z	77.6194
Span	0.7730
Tlag	0.0000
Tmax	4.0000
Cmax	138.3270
Cmax_D	1.3833
Tlast	72.0000
Clast	74.4370
Clast_pred	75.6043
AUClast	7058.8190
AUClast_D	70.5882
AUCall	7058.8190
AUCINF_obs	15394.3548
AUCINF_D_obs	153.9435
AUC_%Extrap_obs	54.1467
AUCINF_pred	15525.0677
AUCINF_D_pred	155.2507
AUC_%Extrap_pred	54.5328
Tmin	5.0000
Cmin	22.7240
Ctau	84.9595
Cavg	85.1800
Swing	5.0873
Swing_Tau	0.6282
Fluctuation%	135.7161
Fluctuation%_Tau	62.6526
CLss_F	0.1304
MRTINF_obs	175.4619
MRTINF_pred	176.9964
Vz_F	14.6071
Accumulation_Index	12.9490
AUC_TAU	766.6202
AUC_TAU_D	7.6662
AUC_TAU_%Extrap	0.0000
AUMC_TAU	2863.0052

WinNonlin 8.2.0.4383  
Subject=9,Formulation=T

Date: 2/11/2020  
Time: 22:58:08

## WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

8.2.0.4383

Core Version 11Oct2017

## Settings

-----

Model: Plasma Data, Extravascular Administration

Number of nonmissing observations: 15

Steady state interval Tau: 9.00

Dose time: 0.25

Dose amount: 100.00

Calculation method: Linear Trapezoidal Rule for for Increasing Values,

Log Trapezoidal Rule for Decreasing Values

Weighting for lambda\_z calculations: Uniform weighting

Lambda\_z method: Find best fit for lambda\_z, Log regression

## Summary Table

-----

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
-----						
0.2500 @	105.4			0.0000	0.0000	
0.5000	113.4			27.35	3.543	
1.000	128.3			87.76	34.68	
1.500	125.4			151.2	98.03	
2.000	146.9			219.3	201.5	
2.500	140.6			291.1	345.1	
3.000	167.3			368.1	539.2	
4.000	157.5			530.5	1066.	
5.000	141.4			679.7	1699.	
6.000	140.3			820.6	2438.	
8.000	105.4			1065.	4074.	
10.00	164.8			1335.	6499.	
12.00 *	135.6	131.6	4.014	1634.	9708.	1.000
24.00 *	117.1	122.9	-5.823	3148.	3.635e+04	1.000
48.00 *	109.7	107.4	2.377	5869.	1.333e+05	1.000
72.00 *	93.44	93.76	-0.3218	8302.	2.779e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

## Final Parameters

-----

N\_Samples

15

Dose

100.0000

Rsqr

0.9475

Rsqr_adjusted	0.9213
Corr_XY	-0.9734
No_points_lambda_z	4
Lambda_z	0.0056
Lambda_z_intercept	4.9473
Lambda_z_lower	12.0000
Lambda_z_upper	72.0000
HL_Lambda_z	122.7708
Span	0.4887
Tlag	0.0000
Tmax	3.0000
Cmax	167.3470
Cmax_D	1.6735
Tlast	72.0000
Clast	93.4400
Clast_pred	93.7618
AUClast	8302.3681
AUClast_D	83.0237
AUCall	8302.3681
AUCINF_obs	24852.5338
AUCINF_D_obs	248.5253
AUC_%Extrap_obs	66.5935
AUCINF_pred	24909.5245
AUCINF_D_pred	249.0952
AUC_%Extrap_pred	66.6699
Tmin	8.0000
Cmin	105.4380
Ctau	142.5661
Cavg	135.5147
Swing	0.5872
Swing_Tau	0.1738
Fluctuation%	45.6844
Fluctuation%_Tau	18.2865
CLss_F	0.0820
MRTINF_obs	178.8105
MRTINF_pred	179.2311
Vz_F	14.5225
Accumulation_Index	20.1843
AUC_TAU	1219.6319
AUC_TAU_D	12.1963
AUC_TAU_%Extrap	0.0000
AUMC_TAU	5386.8832

WinNonlin 8.2.0.4383  
Subject=10,Formulation=R

Date: 2/11/2020

Time: 22:58:08

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM  
8.2.0.4383  
Core Version 11Oct2017

Settings

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Model: Plasma Data, Extravascular Administration  
Number of nonmissing observations: 15  
Steady state interval Tau: 9.00  
Dose time: 0.25  
Dose amount: 100.00  
Calculation method: Linear Trapezoidal Rule for for Increasing Values,  
Log Trapezoidal Rule for Decreasing Values  
Weighting for lambda\_z calculations: Uniform weighting  
Lambda\_z method: Find best fit for lambda\_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.2500 @	13.63			0.0000	0.0000	
0.5000	13.63			3.409	0.4261	
1.000	62.56			22.46	13.01	
1.500	112.7			66.26	59.94	
2.000	125.5			125.8	150.0	
2.500	116.3			186.2	270.7	
3.000	112.7			243.4	413.7	
4.000 *	117.0	124.9	-7.925	358.3	787.9	1.000
5.000 *	119.8	122.8	-2.972	476.7	1292.	1.000
6.000 *	107.6	120.7	-13.13	590.2	1887.	1.000
8.000 *	120.5	116.6	3.868	818.3	3439.	1.000
10.00 *	124.2	112.7	11.50	1063.	5584.	1.000
12.00 *	106.5	108.9	-2.386	1293.	8052.	1.000
24.00 *	116.5	88.57	27.94	2631.	3.216e+04	1.000
48.00 *	45.20	58.63	-13.43	4439.	9.341e+04	1.000
72.00 *	42.19	38.81	3.380	5487.	1.559e+05	1.000

@) Note - the concentration at dose time was added for extrapolation purposes.

\*) Starred values were included in the estimation of Lambda\_z.

Final Parameters



N_Samples	15
Dose	100.0000
Rsq	0.8809
Rsq_adjusted	0.8639
Corr_XY	-0.9386
No_points_lambda_z	9
Lambda_z	0.0172
Lambda_z_intercept	4.8964
Lambda_z_lower	4.0000
Lambda_z_upper	72.0000
HL_Lambda_z	40.3233
Span	1.6864
Tlag	0.0000
Tmax	2.0000
Cmax	125.4820
Cmax_D	1.2548
Tlast	72.0000
Clast	42.1910
Clast_pred	38.8109
AUClast	5486.8389
AUClast_D	54.8684
AUCall	5486.8389
AUCINF_obs	7941.2686
AUCINF_D_obs	79.4127
AUC_%Extrap_obs	30.9073
AUCINF_pred	7744.6313
AUCINF_D_pred	77.4463
AUC_%Extrap_pred	29.1530
Tmin	0.5000
Cmin	13.6340
Ctau	122.7865
Cavg	107.8118
Swing	8.2036
Swing_Tau	0.0220
Fluctuation%	103.7437
Fluctuation%_Tau	2.5002
CLss_F	0.1031
MRTINF_obs	69.5163
MRTINF_pred	67.6924
Vz_F	5.9955
Accumulation_Index	6.9767
AUC_TAU	970.3063
AUC_TAU_D	9.7031
AUC_TAU_%Extrap	0.0000
AUMC_TAU	4713.4797