# MetidaNCA validation report

Vladimir Arnautov

2021-07-16

## 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
- ≥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:

"0.1.4"

# 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. 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 String | Description 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 |
| Rsq | r square |
| ARsq | 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 | Clearence |
| Vzinf | Volume of distribution |
| AUCtau | AUC in Tau range |
| AUMCtau | AUC in Tau range |
| MRTtauinf | MRT based on Tau |
| Cltau | Clearence in Tau range |
| Vztau | Volume of distribution in Tau range |

## 4.2 Results

### 4.2.1 Linear-trapezoidal rule; Extravascular

#### Cmax

| Subjct Float64 | Value Float64 | Reference Float64 | Difference 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 Float64 | Value Float64 | Reference Float64 | Difference 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 |

#### AUMClast

| Subjct | Value | Reference | Difference |
|---|---|---|---|
| Float64 | Float64 | Float64 | 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 | 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 |

#### Rsq

| Subjct | Value | Reference | Difference |
|---|---|---|---|
| Float64 | Float64 | Float64 | 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 |
|---|---|---|---|

| 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 | Value | Reference | Difference |
|---|---|---|---|
| Any | Any | Any | 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 | Value | Reference | Difference |
|---|---|---|---|
| Any | Any | Any | 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 | Value | Reference | Difference |
|---|---|---|---|
| Any | Any | Any | 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 | Value | Reference | Difference |
|---|---|---|---|
| Any | Any | Any | 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 | Value | Reference | Difference |
|---|---|---|---|
| Any | Any | Any | 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 | Value | Reference | Difference |
|---|---|---|---|
| Any | Any | Any | 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 | Value | Reference | Difference |
|---|---|---|---|
| Any | Any | Any | 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 |

```
 10   5.99545     5.99545          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 |
| Rsq | 0.7861 |
| Rsq_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

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 | 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 |
| 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 | 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 |
| Rsq | 0.7861 |
| Rsq_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 |
| 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 | 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_z.

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 |
| 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 | 0.2500 |
| 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 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 @ | 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 |
| 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 | 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 |
| 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 | 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 |
| 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 | 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
---

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 |