

MetidaNCA validation report

Vladimir Arnautov

2024-07-31

Contents

| | | |
|----------|---|-----------|
| 1 | Introduction and package description | 2 |
| 1.1 | Validation purpose | 2 |
| 1.2 | Requirements | 2 |
| 1.3 | Developer software life cycle | 2 |
| 1.3.1 | Versions | 2 |
| 1.4 | Build support | 3 |
| 1.4.1 | Tier 1 | 3 |
| 2 | Installation | 4 |
| 2.1 | System information | 4 |
| 2.2 | Installation method | 4 |
| 2.3 | Version check | 4 |
| 3 | Operation qualification | 4 |
| 3.1 | Coverage | 4 |
| 3.2 | Data | 4 |
| 3.3 | Testing results | 4 |
| 4 | Performance qualification | 5 |
| 4.1 | Parameter's names description | 5 |
| 4.2 | Output example | 6 |
| 4.3 | Results | 8 |
| 4.3.1 | Linear-trapezoidal rule; Extravascular; Dosetime 0.0; No Tau; Dose 100 | 8 |
| 4.3.2 | Linear-Up Log-Down; Extravascular; Dosetime 0.25; Tau 9; Dose 100 | 12 |
| 4.3.3 | Linear-trapezoidal rule; Intravascular; Dosetime 0.0; Tau 12; Dose 120 | 16 |
| 4.3.4 | Linear/Log Trapezoidal rule; Extravascular; Dosetime 0.0; Tau 12; Dose 120 | 20 |
| 4.3.5 | Urine data; Linear-trapezoidal rule; Extravascular; Dosetime 0.0; Dose 100 | 24 |
| 4.3.6 | Pharmacodynamics data; Linear-trapezoidal rule | 25 |
| 5 | Glossary | 26 |
| 6 | Reference | 26 |
| 7 | Appendix 1 | 27 |

| | | |
|----------|-----------------------------------|-----------|
| 7.0.1 | Testing PK dataset. | 27 |
| 7.0.2 | Testing urine PK dataset. | 31 |
| 7.0.3 | Testing PD dataset. | 32 |
| 8 | Appendix 2 | 33 |
| 8.0.1 | Reference output. | 33 |

1 Introduction and package description

This is Non-compartment anlysis software. The package is designed for batch processing of pharmacokinetic data.

See documentation:

- Dev: <https://pharmcat.github.io/MetidaNCA.jl/dev/>
- Stable: <https://pharmcat.github.io/MetidaNCA.jl/stable/>

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 1.6 (or higher) installed for Operating System/OS Version/Architecture in Tier 1 list

Tier 1: Julia is guaranteed to build from source and pass all tests on these platforms when built with the default options. Official binaries are always available and CI is run on every commit to ensure support is actively maintained.

1.3 Developer software life cycle

- Development stage
- Testing procedures development
- Performing testing procedures on local machine
- Push to development branch
- Make pull request to main 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.0 - minor release (may include breaking changes if $X = 0$)
- X.0.0 - major release (breaking changes, changes in public API)
- 0.#.# - no stable public API
- 1.#.# or higher - stable public API

1.4 Build support

1.4.1 Tier 1

- `julia-version`: 1.6, 1.7, 1.8
- `julia-arch`: x64
- `os`: ubuntu-latest, macOS-latest, windows-latest

2 Installation

2.1 System information

- Julia version: v“1.8.5”
- Current machine: “x86_64-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 check performed before merging into JuliaRegistries/General repository (see Automatic merging of pull requests).

Current package version: “0.5.12”

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. Testing procedures can be found in `test` directory.

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")
```

4 Performance qualification

Purpose of this testing procedures to demonstrate performance for some critical tasks. Results from MetidaNCA compared with Phoenix WinNonlin 8.0 results, see Appendix 2.

4.1 Parameter's names description

Table 1: Parameter description

| Name | Description |
|------------|-------------------------------------|
| 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 | AUMC in Tau range |
| MRTtauinf | MRT based on Tau |
| Cltau | Clearance in Tau range |
| Vztau | Volume of distribution in Tau range |

4.2 Output example

Import data:

```
pkdata2 = CSV.File(  
  joinpath(dirname(pathof(MetidaNCA)), "..", "test", "csv", "pkdata2.csv")  
) |> DataFrame  
ds = pkimport(pkdata2, :Time, :Concentration, [:Subject, :Formulation]);  
dosetime = DoseTime(dose = 100, time = 0))  
sort!(ds, :Subject)
```

Execute NCA:

```
MetidaNCA.nca!(ds[1], adm = :ev, calcm = :lint, verbose = 1)
```

Non-compartmental Pharmacokinetic Analysis

Subject: Subject => 1; Formulation => T;

Settings:

Method: lint; Dose: 100; Dose time: 0

| Time | Conc. | AUC | AUC (cum.) | AUMC | AUMC (cum.) | Info |
|------|-------|-------|---------------|-----------|----------------|------|
| 0 | 0 | 0 | 0 | 0 | 0 | D |
| 0.5 | 178.9 | 44.74 | 44.74 | 22.37 | 22.37 | |
| 1 | 190.9 | 92.45 | 137.2 | 70.09 | 92.45 | |
| 1.5 | 164.9 | 88.95 | 226.1 | 109.6 | 202 | |
| 2 | 140 | 76.22 | 302.4 | 131.8 | 333.8 | |
| 2.5 | 129.6 | 67.39 | 369.8 | 151 | 484.8 | |
| 3 | 131.4 | 65.24 | 435 | 179.5 | 664.3 | |
| 4 | 150.9 | 141.1 | 576.1 | 498.8 | 1163 | |
| 5 | 121.2 | 136 | 712.1 | 604.8 | 1768 | |
| 6 | 139.2 | 130.2 | 842.4 | 720.8 | 2489 | |
| 8 | 128.5 | 267.7 | 1110 | 1864 | 4352 | |
| 10 | 143.2 | 271.8 | 1382 | 2461 | 6813 | E |
| 12 | 145 | 288.2 | 1670 | 3172 | 9985 | E |
| 24 | 133.2 | 1669 | 3339 | 2.961e+04 | 3.96e+04 | E |
| 48 | 137.3 | 3245 | 6584 | 1.174e+05 | 1.57e+05 | E |
| 72 | 112.8 | 3001 | 9585 | 1.766e+05 | 3.336e+05 | E |

Cdose: 0.0, Dose time: 0

Kel start: 10.0; end: 72.0

PK/PD subject NCA result

| Parameter | Value |
|-----------|---------|
| Rsqn | 3.0 |
| Vzlast | 3.08222 |
| Tmax | 1.0 |

| | |
|-------------|-------------|
| ARsq | 0.714769 |
| AUClast | 9585.42 |
| MRTinf | 293.162 |
| AUCinf_pred | 44242.6 |
| LZ | -0.00338474 |
| LZint | 5.00849 |
| Obsnum | 16.0 |
| Clast | 112.846 |
| Dose | 100.0 |
| Tlag | 0.0 |
| Cdose | 0.0 |
| Vssinf | 0.682964 |
| AUCall | 9585.42 |

 15 rows omitted

4.3 Results

4.3.1 Linear-trapezoidal rule; Extravascular; Dosetime 0.0; No Tau; Dose 100

Code:

```
nca!(ds, adm = :ev, calcm = :lint)
```

Table 2: Plasma data results, Linear-trapezoidal rule, Extravascular

| Parameter | Subject | Value | Reference | Difference |
|--------------|---------|---------|-----------|------------|
| <i>Cmax</i> | 1 | 190.869 | 190.869 | 0.0 |
| <i>Cmax</i> | 2 | 261.177 | 261.177 | 0.0 |
| <i>Cmax</i> | 3 | 105.345 | 105.345 | 0.0 |
| <i>Cmax</i> | 4 | 208.542 | 208.542 | 0.0 |
| <i>Cmax</i> | 5 | 169.334 | 169.334 | 0.0 |
| <i>Cmax</i> | 6 | 154.648 | 154.648 | 0.0 |
| <i>Cmax</i> | 7 | 153.254 | 153.254 | 0.0 |
| <i>Cmax</i> | 8 | 138.327 | 138.327 | 0.0 |
| <i>Cmax</i> | 9 | 167.347 | 167.347 | 0.0 |
| <i>Cmax</i> | 10 | 125.482 | 125.482 | 0.0 |
| <i>Tmax</i> | 1 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 2 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 3 | 1.5 | 1.5 | 0.0 |
| <i>Tmax</i> | 4 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 5 | 4.0 | 4.0 | 0.0 |
| <i>Tmax</i> | 6 | 2.5 | 2.5 | 0.0 |
| <i>Tmax</i> | 7 | 2.5 | 2.5 | 0.0 |
| <i>Tmax</i> | 8 | 4.0 | 4.0 | 0.0 |
| <i>Tmax</i> | 9 | 3.0 | 3.0 | 0.0 |
| <i>Tmax</i> | 10 | 2.0 | 2.0 | 0.0 |
| <i>Cdose</i> | 1 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 2 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 3 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 4 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 5 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 6 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 7 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 8 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 9 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 10 | 0.0 | 0.0 | 0.0 |
| <i>Clast</i> | 1 | 112.846 | 112.846 | 0.0 |
| <i>Clast</i> | 2 | 85.241 | 85.241 | 0.0 |
| <i>Clast</i> | 3 | 67.901 | 67.901 | 0.0 |
| <i>Clast</i> | 4 | 97.625 | 97.625 | 0.0 |
| <i>Clast</i> | 5 | 110.778 | 110.778 | 0.0 |
| <i>Clast</i> | 6 | 69.501 | 69.501 | 0.0 |
| <i>Clast</i> | 7 | 58.051 | 58.051 | 0.0 |
| <i>Clast</i> | 8 | 74.437 | 74.437 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|-----------------|---------|----------|-----------|------------|
| <i>Clast</i> | 9 | 93.44 | 93.44 | 0.0 |
| <i>Clast</i> | 10 | 42.191 | 42.191 | 0.0 |
| <i>AUClast</i> | 1 | 9585.42 | 9585.42 | 0.0 |
| <i>AUClast</i> | 2 | 10112.2 | 10112.2 | 0.0 |
| <i>AUClast</i> | 3 | 5396.55 | 5396.55 | 0.0 |
| <i>AUClast</i> | 4 | 9317.84 | 9317.84 | 0.0 |
| <i>AUClast</i> | 5 | 9561.26 | 9561.26 | 0.0 |
| <i>AUClast</i> | 6 | 6966.6 | 6966.6 | 0.0 |
| <i>AUClast</i> | 7 | 7029.57 | 7029.57 | 0.0 |
| <i>AUClast</i> | 8 | 7110.67 | 7110.67 | 0.0 |
| <i>AUClast</i> | 9 | 8315.08 | 8315.08 | 0.0 |
| <i>AUClast</i> | 10 | 5620.89 | 5620.89 | 0.0 |
| <i>AUMClast</i> | 1 | 333582.0 | 333582.0 | 0.0 |
| <i>AUMClast</i> | 2 | 298701.0 | 298701.0 | 0.0 |
| <i>AUMClast</i> | 3 | 186032.0 | 186032.0 | 0.0 |
| <i>AUMClast</i> | 4 | 313956.0 | 313956.0 | 0.0 |
| <i>AUMClast</i> | 5 | 315182.0 | 315182.0 | 0.0 |
| <i>AUMClast</i> | 6 | 226977.0 | 226977.0 | 0.0 |
| <i>AUMClast</i> | 7 | 219798.0 | 219798.0 | 0.0 |
| <i>AUMClast</i> | 8 | 240526.0 | 240526.0 | 0.0 |
| <i>AUMClast</i> | 9 | 277614.0 | 277614.0 | 0.0 |
| <i>AUMClast</i> | 10 | 154893.0 | 154893.0 | 0.0 |
| <i>AUCall</i> | 1 | 9585.42 | 9585.42 | 0.0 |
| <i>AUCall</i> | 2 | 10112.2 | 10112.2 | 0.0 |
| <i>AUCall</i> | 3 | 5396.55 | 5396.55 | 0.0 |
| <i>AUCall</i> | 4 | 9317.84 | 9317.84 | 0.0 |
| <i>AUCall</i> | 5 | 9561.26 | 9561.26 | 0.0 |
| <i>AUCall</i> | 6 | 6966.6 | 6966.6 | 0.0 |
| <i>AUCall</i> | 7 | 7029.57 | 7029.57 | 0.0 |
| <i>AUCall</i> | 8 | 7110.67 | 7110.67 | 0.0 |
| <i>AUCall</i> | 9 | 8315.08 | 8315.08 | 0.0 |
| <i>AUCall</i> | 10 | 5620.89 | 5620.89 | 0.0 |
| <i>Rsq</i> | 1 | 0.786077 | 0.786077 | 0.0 |
| <i>Rsq</i> | 2 | 0.992764 | 0.992764 | 0.0 |
| <i>Rsq</i> | 3 | 0.813589 | 0.813589 | 0.0 |
| <i>Rsq</i> | 4 | 0.918859 | 0.918859 | 0.0 |
| <i>Rsq</i> | 5 | 0.85336 | 0.85336 | 0.0 |
| <i>Rsq</i> | 6 | 0.950119 | 0.950119 | 0.0 |
| <i>Rsq</i> | 7 | 0.970312 | 0.970312 | 0.0 |
| <i>Rsq</i> | 8 | 0.947969 | 0.947969 | 0.0 |
| <i>Rsq</i> | 9 | 0.947538 | 0.947538 | 0.0 |
| <i>Rsq</i> | 10 | 0.880923 | 0.880923 | 0.0 |
| <i>ARsq</i> | 1 | 0.714769 | 0.714769 | 0.0 |
| <i>ARsq</i> | 2 | 0.990351 | 0.990351 | 0.0 |
| <i>ARsq</i> | 3 | 0.776307 | 0.776307 | 0.0 |
| <i>ARsq</i> | 4 | 0.837717 | 0.837717 | 0.0 |
| <i>ARsq</i> | 5 | 0.82892 | 0.82892 | 0.0 |
| <i>ARsq</i> | 6 | 0.925179 | 0.925179 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|-----------------------------|---------|------------|------------|------------|
| <i>ARsq</i> | 7 | 0.960416 | 0.960416 | 0.0 |
| <i>ARsq</i> | 8 | 0.921954 | 0.921954 | 0.0 |
| <i>ARsq</i> | 9 | 0.921307 | 0.921307 | 0.0 |
| <i>ARsq</i> | 10 | 0.863912 | 0.863912 | 0.0 |
| <i>Kel</i> | 1 | 0.00338474 | 0.00338474 | 0.0 |
| <i>Kel</i> | 2 | 0.0141063 | 0.0141063 | 0.0 |
| <i>Kel</i> | 3 | 0.00329143 | 0.00329143 | 0.0 |
| <i>Kel</i> | 4 | 0.00769534 | 0.00769534 | 0.0 |
| <i>Kel</i> | 5 | 0.00681333 | 0.00681333 | 0.0 |
| <i>Kel</i> | 6 | 0.00769228 | 0.00769228 | 0.0 |
| <i>Kel</i> | 7 | 0.012459 | 0.012459 | 0.0 |
| <i>Kel</i> | 8 | 0.00893008 | 0.00893008 | 0.0 |
| <i>Kel</i> | 9 | 0.00564586 | 0.00564586 | 0.0 |
| <i>Kel</i> | 10 | 0.0171897 | 0.0171897 | 0.0 |
| <i>HL</i> | 1 | 204.786 | 204.786 | 0.0 |
| <i>HL</i> | 2 | 49.1374 | 49.1374 | 0.0 |
| <i>HL</i> | 3 | 210.591 | 210.591 | 0.0 |
| <i>HL</i> | 4 | 90.0736 | 90.0736 | 0.0 |
| <i>HL</i> | 5 | 101.734 | 101.734 | 0.0 |
| <i>HL</i> | 6 | 90.1095 | 90.1095 | 0.0 |
| <i>HL</i> | 7 | 55.6345 | 55.6345 | 0.0 |
| <i>HL</i> | 8 | 77.6194 | 77.6194 | 0.0 |
| <i>HL</i> | 9 | 122.771 | 122.771 | 0.0 |
| <i>HL</i> | 10 | 40.3233 | 40.3233 | 0.0 |
| <i>Clast_{pred}</i> | 1 | 117.306 | 117.306 | 0.0 |
| <i>Clast_{pred}</i> | 2 | 82.5367 | 82.5367 | 0.0 |
| <i>Clast_{pred}</i> | 3 | 66.9311 | 66.9311 | 0.0 |
| <i>Clast_{pred}</i> | 4 | 100.768 | 100.768 | 0.0 |
| <i>Clast_{pred}</i> | 5 | 105.298 | 105.298 | 0.0 |
| <i>Clast_{pred}</i> | 6 | 71.9399 | 71.9399 | 0.0 |
| <i>Clast_{pred}</i> | 7 | 61.1727 | 61.1727 | 0.0 |
| <i>Clast_{pred}</i> | 8 | 75.6043 | 75.6043 | 0.0 |
| <i>Clast_{pred}</i> | 9 | 93.7618 | 93.7618 | 0.0 |
| <i>Clast_{pred}</i> | 10 | 38.8109 | 38.8109 | 0.0 |
| <i>AUCinf</i> | 1 | 42925.0 | 42925.0 | 0.0 |
| <i>AUCinf</i> | 2 | 16154.9 | 16154.9 | 0.0 |
| <i>AUCinf</i> | 3 | 26026.2 | 26026.2 | 0.0 |
| <i>AUCinf</i> | 4 | 22004.1 | 22004.1 | 0.0 |
| <i>AUCinf</i> | 5 | 25820.3 | 25820.3 | 0.0 |
| <i>AUCinf</i> | 6 | 16001.8 | 16001.8 | 0.0 |
| <i>AUCinf</i> | 7 | 11689.0 | 11689.0 | 0.0 |
| <i>AUCinf</i> | 8 | 15446.2 | 15446.2 | 0.0 |
| <i>AUCinf</i> | 9 | 24865.2 | 24865.2 | 0.0 |
| <i>AUCinf</i> | 10 | 8075.32 | 8075.32 | 0.0 |
| <i>AUCpct</i> | 1 | 77.6694 | 77.6694 | 0.0 |
| <i>AUCpct</i> | 2 | 37.405 | 37.405 | 0.0 |
| <i>AUCpct</i> | 3 | 79.2649 | 79.2649 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|----------------|---------|------------|------------|------------|
| <i>AUCpct</i> | 4 | 57.6541 | 57.6541 | 0.0 |
| <i>AUCpct</i> | 5 | 62.97 | 62.97 | 0.0 |
| <i>AUCpct</i> | 6 | 56.4636 | 56.4636 | 0.0 |
| <i>AUCpct</i> | 7 | 39.8614 | 39.8614 | 0.0 |
| <i>AUCpct</i> | 8 | 53.9649 | 53.9649 | 0.0 |
| <i>AUCpct</i> | 9 | 66.5594 | 66.5594 | 0.0 |
| <i>AUCpct</i> | 10 | 30.3942 | 30.3942 | 0.0 |
| <i>MRTlast</i> | 1 | 34.801 | 34.801 | 0.0 |
| <i>MRTlast</i> | 2 | 29.5388 | 29.5388 | 0.0 |
| <i>MRTlast</i> | 3 | 34.4724 | 34.4724 | 0.0 |
| <i>MRTlast</i> | 4 | 33.6941 | 33.6941 | 0.0 |
| <i>MRTlast</i> | 5 | 32.9644 | 32.9644 | 0.0 |
| <i>MRTlast</i> | 6 | 32.5808 | 32.5808 | 0.0 |
| <i>MRTlast</i> | 7 | 31.2676 | 31.2676 | 0.0 |
| <i>MRTlast</i> | 8 | 33.8261 | 33.8261 | 0.0 |
| <i>MRTlast</i> | 9 | 33.3868 | 33.3868 | 0.0 |
| <i>MRTlast</i> | 10 | 27.5567 | 27.5567 | 0.0 |
| <i>MRTinf</i> | 1 | 293.162 | 293.162 | 0.0 |
| <i>MRTinf</i> | 2 | 71.9379 | 71.9379 | 0.0 |
| <i>MRTinf</i> | 3 | 305.041 | 305.041 | 0.0 |
| <i>MRTinf</i> | 4 | 130.7 | 130.7 | 0.0 |
| <i>MRTinf</i> | 5 | 149.967 | 149.967 | 0.0 |
| <i>MRTinf</i> | 6 | 128.241 | 128.241 | 0.0 |
| <i>MRTinf</i> | 7 | 79.4983 | 79.4983 | 0.0 |
| <i>MRTinf</i> | 8 | 114.857 | 114.857 | 0.0 |
| <i>MRTinf</i> | 9 | 176.978 | 176.978 | 0.0 |
| <i>MRTinf</i> | 10 | 58.7464 | 58.7464 | 0.0 |
| <i>Clinf</i> | 1 | 0.00232964 | 0.00232964 | 0.0 |
| <i>Clinf</i> | 2 | 0.00619006 | 0.00619006 | 0.0 |
| <i>Clinf</i> | 3 | 0.00384228 | 0.00384228 | 0.0 |
| <i>Clinf</i> | 4 | 0.00454461 | 0.00454461 | 0.0 |
| <i>Clinf</i> | 5 | 0.00387293 | 0.00387293 | 0.0 |
| <i>Clinf</i> | 6 | 0.00624931 | 0.00624931 | 0.0 |
| <i>Clinf</i> | 7 | 0.00855509 | 0.00855509 | 0.0 |
| <i>Clinf</i> | 8 | 0.00647408 | 0.00647408 | 0.0 |
| <i>Clinf</i> | 9 | 0.00402168 | 0.00402168 | 0.0 |
| <i>Clinf</i> | 10 | 0.0123834 | 0.0123834 | 0.0 |
| <i>Vzinf</i> | 1 | 0.688278 | 0.688278 | 0.0 |
| <i>Vzinf</i> | 2 | 0.438815 | 0.438815 | 0.0 |
| <i>Vzinf</i> | 3 | 1.16736 | 1.16736 | 0.0 |
| <i>Vzinf</i> | 4 | 0.590566 | 0.590566 | 0.0 |
| <i>Vzinf</i> | 5 | 0.568434 | 0.568434 | 0.0 |
| <i>Vzinf</i> | 6 | 0.812414 | 0.812414 | 0.0 |
| <i>Vzinf</i> | 7 | 0.686662 | 0.686662 | 0.0 |
| <i>Vzinf</i> | 8 | 0.724974 | 0.724974 | 0.0 |
| <i>Vzinf</i> | 9 | 0.712323 | 0.712323 | 0.0 |
| <i>Vzinf</i> | 10 | 0.720395 | 0.720395 | 0.0 |

4.3.2 Linear-Up Log-Down; Extravascular; Dosetime 0.25; Tau 9; Dose 100

Code:

```
setdosetime!(ds, DoseTime(dose = 100, time = 0.25, tau = 9))
nca!(ds, adm = :ev, calcm = :luld)
```

Table 3: Plasma data results, Linear-Up Log-Down, Extravascular

| Parameter | Subject | Value | Reference | Difference |
|--------------|---------|---------|-----------|------------|
| <i>Cmax</i> | 1 | 190.869 | 190.869 | 0.0 |
| <i>Cmax</i> | 2 | 261.177 | 261.177 | 0.0 |
| <i>Cmax</i> | 3 | 105.345 | 105.345 | 0.0 |
| <i>Cmax</i> | 4 | 208.542 | 208.542 | 0.0 |
| <i>Cmax</i> | 5 | 169.334 | 169.334 | 0.0 |
| <i>Cmax</i> | 6 | 154.648 | 154.648 | 0.0 |
| <i>Cmax</i> | 7 | 153.254 | 153.254 | 0.0 |
| <i>Cmax</i> | 8 | 138.327 | 138.327 | 0.0 |
| <i>Cmax</i> | 9 | 167.347 | 167.347 | 0.0 |
| <i>Cmax</i> | 10 | 125.482 | 125.482 | 0.0 |
| <i>Tmax</i> | 1 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 2 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 3 | 1.5 | 1.5 | 0.0 |
| <i>Tmax</i> | 4 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 5 | 4.0 | 4.0 | 0.0 |
| <i>Tmax</i> | 6 | 2.5 | 2.5 | 0.0 |
| <i>Tmax</i> | 7 | 2.5 | 2.5 | 0.0 |
| <i>Tmax</i> | 8 | 4.0 | 4.0 | 0.0 |
| <i>Tmax</i> | 9 | 3.0 | 3.0 | 0.0 |
| <i>Tmax</i> | 10 | 2.0 | 2.0 | 0.0 |
| <i>Cdose</i> | 1 | 121.239 | 121.239 | 0.0 |
| <i>Cdose</i> | 2 | 62.222 | 62.222 | 0.0 |
| <i>Cdose</i> | 3 | 49.849 | 49.849 | 0.0 |
| <i>Cdose</i> | 4 | 52.421 | 52.421 | 0.0 |
| <i>Cdose</i> | 5 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 6 | 57.882 | 57.882 | 0.0 |
| <i>Cdose</i> | 7 | 19.95 | 19.95 | 0.0 |
| <i>Cdose</i> | 8 | 22.724 | 22.724 | 0.0 |
| <i>Cdose</i> | 9 | 105.438 | 105.438 | 0.0 |
| <i>Cdose</i> | 10 | 13.634 | 13.634 | 0.0 |
| <i>Clast</i> | 1 | 112.846 | 112.846 | 0.0 |
| <i>Clast</i> | 2 | 85.241 | 85.241 | 0.0 |
| <i>Clast</i> | 3 | 67.901 | 67.901 | 0.0 |
| <i>Clast</i> | 4 | 97.625 | 97.625 | 0.0 |
| <i>Clast</i> | 5 | 110.778 | 110.778 | 0.0 |
| <i>Clast</i> | 6 | 69.501 | 69.501 | 0.0 |
| <i>Clast</i> | 7 | 58.051 | 58.051 | 0.0 |
| <i>Clast</i> | 8 | 74.437 | 74.437 | 0.0 |
| <i>Clast</i> | 9 | 93.44 | 93.44 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|----------------|---------|----------|-----------|------------|
| <i>Clast</i> | 10 | 42.191 | 42.191 | 0.0 |
| <i>AUClast</i> | 1 | 9566.6 | 9566.6 | 0.0 |
| <i>AUClast</i> | 2 | 10054.3 | 10054.3 | 0.0 |
| <i>AUClast</i> | 3 | 5392.46 | 5392.46 | 0.0 |
| <i>AUClast</i> | 4 | 9297.1 | 9297.1 | 0.0 |
| <i>AUClast</i> | 5 | 9519.18 | 9519.18 | 0.0 |
| <i>AUClast</i> | 6 | 6948.99 | 6948.99 | 0.0 |
| <i>AUClast</i> | 7 | 6988.77 | 6988.77 | 0.0 |
| <i>AUClast</i> | 8 | 7058.82 | 7058.82 | 0.0 |
| <i>AUClast</i> | 9 | 8302.37 | 8302.37 | 0.0 |
| <i>AUClast</i> | 10 | 5486.84 | 5486.84 | 0.0 |
| <i>AUCtau</i> | 1 | 1268.28 | 1268.28 | 0.0 |
| <i>AUCtau</i> | 2 | 1831.82 | 1831.82 | 0.0 |
| <i>AUCtau</i> | 3 | 754.649 | 754.649 | 0.0 |
| <i>AUCtau</i> | 4 | 1336.48 | 1336.48 | 0.0 |
| <i>AUCtau</i> | 5 | 1310.9 | 1310.9 | 0.0 |
| <i>AUCtau</i> | 6 | 1114.24 | 1114.24 | 0.0 |
| <i>AUCtau</i> | 7 | 1079.37 | 1079.37 | 0.0 |
| <i>AUCtau</i> | 8 | 766.62 | 766.62 | 0.0 |
| <i>AUCtau</i> | 9 | 1219.63 | 1219.63 | 0.0 |
| <i>AUCtau</i> | 10 | 970.306 | 970.306 | 0.0 |
| <i>AUMCtau</i> | 1 | 5477.2 | 5477.2 | 0.0 |
| <i>AUMCtau</i> | 2 | 8367.57 | 8367.57 | 0.0 |
| <i>AUMCtau</i> | 3 | 3455.35 | 3455.35 | 0.0 |
| <i>AUMCtau</i> | 4 | 6014.65 | 6014.65 | 0.0 |
| <i>AUMCtau</i> | 5 | 6609.79 | 6609.79 | 0.0 |
| <i>AUMCtau</i> | 6 | 5064.72 | 5064.72 | 0.0 |
| <i>AUMCtau</i> | 7 | 4976.96 | 4976.96 | 0.0 |
| <i>AUMCtau</i> | 8 | 2863.01 | 2863.01 | 0.0 |
| <i>AUMCtau</i> | 9 | 5386.88 | 5386.88 | 0.0 |
| <i>AUMCtau</i> | 10 | 4713.48 | 4713.48 | 0.0 |
| <i>AUCall</i> | 1 | 9566.6 | 9566.6 | 0.0 |
| <i>AUCall</i> | 2 | 10054.3 | 10054.3 | 0.0 |
| <i>AUCall</i> | 3 | 5392.46 | 5392.46 | 0.0 |
| <i>AUCall</i> | 4 | 9297.1 | 9297.1 | 0.0 |
| <i>AUCall</i> | 5 | 9519.18 | 9519.18 | 0.0 |
| <i>AUCall</i> | 6 | 6948.99 | 6948.99 | 0.0 |
| <i>AUCall</i> | 7 | 6988.77 | 6988.77 | 0.0 |
| <i>AUCall</i> | 8 | 7058.82 | 7058.82 | 0.0 |
| <i>AUCall</i> | 9 | 8302.37 | 8302.37 | 0.0 |
| <i>AUCall</i> | 10 | 5486.84 | 5486.84 | 0.0 |
| <i>Rsqr</i> | 1 | 0.786077 | 0.786077 | 0.0 |
| <i>Rsqr</i> | 2 | 0.992764 | 0.992764 | 0.0 |
| <i>Rsqr</i> | 3 | 0.813589 | 0.813589 | 0.0 |
| <i>Rsqr</i> | 4 | 0.918859 | 0.918859 | 0.0 |
| <i>Rsqr</i> | 5 | 0.85336 | 0.85336 | 0.0 |
| <i>Rsqr</i> | 6 | 0.950119 | 0.950119 | 0.0 |
| <i>Rsqr</i> | 7 | 0.970312 | 0.970312 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|-----------------------------|---------|------------|------------|------------|
| <i>Rsq</i> | 8 | 0.947969 | 0.947969 | 0.0 |
| <i>Rsq</i> | 9 | 0.947538 | 0.947538 | 0.0 |
| <i>Rsq</i> | 10 | 0.880923 | 0.880923 | 0.0 |
| <i>ARsq</i> | 1 | 0.714769 | 0.714769 | 0.0 |
| <i>ARsq</i> | 2 | 0.990351 | 0.990351 | 0.0 |
| <i>ARsq</i> | 3 | 0.776307 | 0.776307 | 0.0 |
| <i>ARsq</i> | 4 | 0.837717 | 0.837717 | 0.0 |
| <i>ARsq</i> | 5 | 0.82892 | 0.82892 | 0.0 |
| <i>ARsq</i> | 6 | 0.925179 | 0.925179 | 0.0 |
| <i>ARsq</i> | 7 | 0.960416 | 0.960416 | 0.0 |
| <i>ARsq</i> | 8 | 0.921954 | 0.921954 | 0.0 |
| <i>ARsq</i> | 9 | 0.921307 | 0.921307 | 0.0 |
| <i>ARsq</i> | 10 | 0.863912 | 0.863912 | 0.0 |
| <i>Kel</i> | 1 | 0.00338474 | 0.00338474 | 0.0 |
| <i>Kel</i> | 2 | 0.0141063 | 0.0141063 | 0.0 |
| <i>Kel</i> | 3 | 0.00329143 | 0.00329143 | 0.0 |
| <i>Kel</i> | 4 | 0.00769534 | 0.00769534 | 0.0 |
| <i>Kel</i> | 5 | 0.00681333 | 0.00681333 | 0.0 |
| <i>Kel</i> | 6 | 0.00769228 | 0.00769228 | 0.0 |
| <i>Kel</i> | 7 | 0.012459 | 0.012459 | 0.0 |
| <i>Kel</i> | 8 | 0.00893008 | 0.00893008 | 0.0 |
| <i>Kel</i> | 9 | 0.00564586 | 0.00564586 | 0.0 |
| <i>Kel</i> | 10 | 0.0171897 | 0.0171897 | 0.0 |
| <i>HL</i> | 1 | 204.786 | 204.786 | 0.0 |
| <i>HL</i> | 2 | 49.1374 | 49.1374 | 0.0 |
| <i>HL</i> | 3 | 210.591 | 210.591 | 0.0 |
| <i>HL</i> | 4 | 90.0736 | 90.0736 | 0.0 |
| <i>HL</i> | 5 | 101.734 | 101.734 | 0.0 |
| <i>HL</i> | 6 | 90.1095 | 90.1095 | 0.0 |
| <i>HL</i> | 7 | 55.6345 | 55.6345 | 0.0 |
| <i>HL</i> | 8 | 77.6194 | 77.6194 | 0.0 |
| <i>HL</i> | 9 | 122.771 | 122.771 | 0.0 |
| <i>HL</i> | 10 | 40.3233 | 40.3233 | 0.0 |
| <i>Clast_{pred}</i> | 1 | 117.306 | 117.306 | 0.0 |
| <i>Clast_{pred}</i> | 2 | 82.5367 | 82.5367 | 0.0 |
| <i>Clast_{pred}</i> | 3 | 66.9311 | 66.9311 | 0.0 |
| <i>Clast_{pred}</i> | 4 | 100.768 | 100.768 | 0.0 |
| <i>Clast_{pred}</i> | 5 | 105.298 | 105.298 | 0.0 |
| <i>Clast_{pred}</i> | 6 | 71.9399 | 71.9399 | 0.0 |
| <i>Clast_{pred}</i> | 7 | 61.1727 | 61.1727 | 0.0 |
| <i>Clast_{pred}</i> | 8 | 75.6043 | 75.6043 | 0.0 |
| <i>Clast_{pred}</i> | 9 | 93.7618 | 93.7618 | 0.0 |
| <i>Clast_{pred}</i> | 10 | 38.8109 | 38.8109 | 0.0 |
| <i>AUCinf</i> | 1 | 42906.2 | 42906.2 | 0.0 |
| <i>AUCinf</i> | 2 | 16097.0 | 16097.0 | 0.0 |
| <i>AUCinf</i> | 3 | 26022.1 | 26022.1 | 0.0 |
| <i>AUCinf</i> | 4 | 21983.3 | 21983.3 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|-----------------|---------|-----------|-----------|------------|
| <i>AUCinf</i> | 5 | 25778.2 | 25778.2 | 0.0 |
| <i>AUCinf</i> | 6 | 15984.1 | 15984.1 | 0.0 |
| <i>AUCinf</i> | 7 | 11648.2 | 11648.2 | 0.0 |
| <i>AUCinf</i> | 8 | 15394.4 | 15394.4 | 0.0 |
| <i>AUCinf</i> | 9 | 24852.5 | 24852.5 | 0.0 |
| <i>AUCinf</i> | 10 | 7941.27 | 7941.27 | 0.0 |
| <i>AUCpct</i> | 1 | 77.7035 | 77.7035 | 0.0 |
| <i>AUCpct</i> | 2 | 37.5395 | 37.5395 | 0.0 |
| <i>AUCpct</i> | 3 | 79.2774 | 79.2774 | 0.0 |
| <i>AUCpct</i> | 4 | 57.7084 | 57.7084 | 0.0 |
| <i>AUCpct</i> | 5 | 63.0727 | 63.0727 | 0.0 |
| <i>AUCpct</i> | 6 | 56.5258 | 56.5258 | 0.0 |
| <i>AUCpct</i> | 7 | 40.001 | 40.001 | 0.0 |
| <i>AUCpct</i> | 8 | 54.1467 | 54.1467 | 0.0 |
| <i>AUCpct</i> | 9 | 66.5935 | 66.5935 | 0.0 |
| <i>AUCpct</i> | 10 | 30.9073 | 30.9073 | 0.0 |
| <i>MRTtauin</i> | 1 | 299.792 | 299.792 | 0.0 |
| <i>MRTtauin</i> | 2 | 74.655 | 74.655 | 0.0 |
| <i>MRTtauin</i> | 3 | 305.92 | 305.92 | 0.0 |
| <i>MRTtauin</i> | 4 | 143.538 | 143.538 | 0.0 |
| <i>MRTtauin</i> | 5 | 173.022 | 173.022 | 0.0 |
| <i>MRTtauin</i> | 6 | 124.653 | 124.653 | 0.0 |
| <i>MRTtauin</i> | 7 | 92.7359 | 92.7359 | 0.0 |
| <i>MRTtauin</i> | 8 | 175.462 | 175.462 | 0.0 |
| <i>MRTtauin</i> | 9 | 178.811 | 178.811 | 0.0 |
| <i>MRTtauin</i> | 10 | 69.5163 | 69.5163 | 0.0 |
| <i>Cltau</i> | 1 | 0.0788472 | 0.0788472 | 0.0 |
| <i>Cltau</i> | 2 | 0.0545905 | 0.0545905 | 0.0 |
| <i>Cltau</i> | 3 | 0.132512 | 0.132512 | 0.0 |
| <i>Cltau</i> | 4 | 0.0748234 | 0.0748234 | 0.0 |
| <i>Cltau</i> | 5 | 0.0762832 | 0.0762832 | 0.0 |
| <i>Cltau</i> | 6 | 0.0897472 | 0.0897472 | 0.0 |
| <i>Cltau</i> | 7 | 0.0926469 | 0.0926469 | 0.0 |
| <i>Cltau</i> | 8 | 0.130443 | 0.130443 | 0.0 |
| <i>Cltau</i> | 9 | 0.081992 | 0.081992 | 0.0 |
| <i>Cltau</i> | 10 | 0.10306 | 0.10306 | 0.0 |
| <i>Vztau</i> | 1 | 23.2949 | 23.2949 | 0.0 |
| <i>Vztau</i> | 2 | 3.86993 | 3.86993 | 0.0 |
| <i>Vztau</i> | 3 | 40.2597 | 40.2597 | 0.0 |
| <i>Vztau</i> | 4 | 9.7232 | 9.7232 | 0.0 |
| <i>Vztau</i> | 5 | 11.1962 | 11.1962 | 0.0 |
| <i>Vztau</i> | 6 | 11.6672 | 11.6672 | 0.0 |
| <i>Vztau</i> | 7 | 7.43617 | 7.43617 | 0.0 |
| <i>Vztau</i> | 8 | 14.6071 | 14.6071 | 0.0 |
| <i>Vztau</i> | 9 | 14.5225 | 14.5225 | 0.0 |
| <i>Vztau</i> | 10 | 5.99545 | 5.99545 | 0.0 |

4.3.3 Linear-trapezoidal rule; Intravascular; Dosetime 0.0; Tau 12; Dose 120

Code:

```
setdosetime!(ds, DoseTime(dose = 120, time = 0.0, tau = 12))
nca!(ds, adm = :iv, calcm = :lint)
```

Table 4: Plasma data results, Linear-trapezoidal rule, Intravascular

| Parameter | Subject | Value | Reference | Difference |
|--------------|---------|---------|-----------|------------|
| <i>Cmax</i> | 1 | 190.869 | 190.869 | 0.0 |
| <i>Cmax</i> | 2 | 261.177 | 261.177 | 0.0 |
| <i>Cmax</i> | 3 | 105.345 | 105.345 | 0.0 |
| <i>Cmax</i> | 4 | 208.542 | 208.542 | 0.0 |
| <i>Cmax</i> | 5 | 169.334 | 169.334 | 0.0 |
| <i>Cmax</i> | 6 | 154.648 | 154.648 | 0.0 |
| <i>Cmax</i> | 7 | 153.254 | 153.254 | 0.0 |
| <i>Cmax</i> | 8 | 138.327 | 138.327 | 0.0 |
| <i>Cmax</i> | 9 | 167.347 | 167.347 | 0.0 |
| <i>Cmax</i> | 10 | 125.482 | 125.482 | 0.0 |
| <i>Tmax</i> | 1 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 2 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 3 | 1.5 | 1.5 | 0.0 |
| <i>Tmax</i> | 4 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 5 | 4.0 | 4.0 | 0.0 |
| <i>Tmax</i> | 6 | 2.5 | 2.5 | 0.0 |
| <i>Tmax</i> | 7 | 2.5 | 2.5 | 0.0 |
| <i>Tmax</i> | 8 | 4.0 | 4.0 | 0.0 |
| <i>Tmax</i> | 9 | 3.0 | 3.0 | 0.0 |
| <i>Tmax</i> | 10 | 2.0 | 2.0 | 0.0 |
| <i>Cdose</i> | 1 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 2 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 3 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 4 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 5 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 6 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 7 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 8 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 9 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 10 | 0.0 | 0.0 | 0.0 |
| <i>Clast</i> | 1 | 112.846 | 112.846 | 0.0 |
| <i>Clast</i> | 2 | 85.241 | 85.241 | 0.0 |
| <i>Clast</i> | 3 | 67.901 | 67.901 | 0.0 |
| <i>Clast</i> | 4 | 97.625 | 97.625 | 0.0 |
| <i>Clast</i> | 5 | 110.778 | 110.778 | 0.0 |
| <i>Clast</i> | 6 | 69.501 | 69.501 | 0.0 |
| <i>Clast</i> | 7 | 58.051 | 58.051 | 0.0 |
| <i>Clast</i> | 8 | 74.437 | 74.437 | 0.0 |
| <i>Clast</i> | 9 | 93.44 | 93.44 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|----------------|---------|----------|-----------|------------|
| <i>Clast</i> | 10 | 42.191 | 42.191 | 0.0 |
| <i>AUClast</i> | 1 | 9585.42 | 9585.42 | 0.0 |
| <i>AUClast</i> | 2 | 10112.2 | 10112.2 | 0.0 |
| <i>AUClast</i> | 3 | 5396.55 | 5396.55 | 0.0 |
| <i>AUClast</i> | 4 | 9317.84 | 9317.84 | 0.0 |
| <i>AUClast</i> | 5 | 9561.26 | 9561.26 | 0.0 |
| <i>AUClast</i> | 6 | 6966.6 | 6966.6 | 0.0 |
| <i>AUClast</i> | 7 | 7029.57 | 7029.57 | 0.0 |
| <i>AUClast</i> | 8 | 7110.67 | 7110.67 | 0.0 |
| <i>AUClast</i> | 9 | 8315.08 | 8315.08 | 0.0 |
| <i>AUClast</i> | 10 | 5620.89 | 5620.89 | 0.0 |
| <i>AUCtau</i> | 1 | 1670.1 | 1670.1 | 0.0 |
| <i>AUCtau</i> | 2 | 2380.27 | 2380.27 | 0.0 |
| <i>AUCtau</i> | 3 | 980.346 | 980.346 | 0.0 |
| <i>AUCtau</i> | 4 | 1711.04 | 1711.04 | 0.0 |
| <i>AUCtau</i> | 5 | 1738.46 | 1738.46 | 0.0 |
| <i>AUCtau</i> | 6 | 1410.0 | 1410.0 | 0.0 |
| <i>AUCtau</i> | 7 | 1436.56 | 1436.56 | 0.0 |
| <i>AUCtau</i> | 8 | 1105.07 | 1105.07 | 0.0 |
| <i>AUCtau</i> | 9 | 1638.19 | 1638.19 | 0.0 |
| <i>AUCtau</i> | 10 | 1293.71 | 1293.71 | 0.0 |
| <i>AUMCtau</i> | 1 | 9984.82 | 9984.82 | 0.0 |
| <i>AUMCtau</i> | 2 | 14630.1 | 14630.1 | 0.0 |
| <i>AUMCtau</i> | 3 | 6024.5 | 6024.5 | 0.0 |
| <i>AUMCtau</i> | 4 | 10299.7 | 10299.7 | 0.0 |
| <i>AUMCtau</i> | 5 | 11466.1 | 11466.1 | 0.0 |
| <i>AUMCtau</i> | 6 | 8467.36 | 8467.36 | 0.0 |
| <i>AUMCtau</i> | 7 | 9003.02 | 9003.02 | 0.0 |
| <i>AUMCtau</i> | 8 | 6457.01 | 6457.01 | 0.0 |
| <i>AUMCtau</i> | 9 | 10095.8 | 10095.8 | 0.0 |
| <i>AUMCtau</i> | 10 | 8367.3 | 8367.3 | 0.0 |
| <i>AUCall</i> | 1 | 9585.42 | 9585.42 | 0.0 |
| <i>AUCall</i> | 2 | 10112.2 | 10112.2 | 0.0 |
| <i>AUCall</i> | 3 | 5396.55 | 5396.55 | 0.0 |
| <i>AUCall</i> | 4 | 9317.84 | 9317.84 | 0.0 |
| <i>AUCall</i> | 5 | 9561.26 | 9561.26 | 0.0 |
| <i>AUCall</i> | 6 | 6966.6 | 6966.6 | 0.0 |
| <i>AUCall</i> | 7 | 7029.57 | 7029.57 | 0.0 |
| <i>AUCall</i> | 8 | 7110.67 | 7110.67 | 0.0 |
| <i>AUCall</i> | 9 | 8315.08 | 8315.08 | 0.0 |
| <i>AUCall</i> | 10 | 5620.89 | 5620.89 | 0.0 |
| <i>Rsqr</i> | 1 | 0.786077 | 0.786077 | 0.0 |
| <i>Rsqr</i> | 2 | 0.992764 | 0.992764 | 0.0 |
| <i>Rsqr</i> | 3 | 0.813589 | 0.813589 | 0.0 |
| <i>Rsqr</i> | 4 | 0.918859 | 0.918859 | 0.0 |
| <i>Rsqr</i> | 5 | 0.863677 | 0.863677 | 0.0 |
| <i>Rsqr</i> | 6 | 0.950119 | 0.950119 | 0.0 |
| <i>Rsqr</i> | 7 | 0.970312 | 0.970312 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|-----------------------------|---------|------------|------------|------------|
| <i>Rsq</i> | 8 | 0.947969 | 0.947969 | 0.0 |
| <i>Rsq</i> | 9 | 0.947538 | 0.947538 | 0.0 |
| <i>Rsq</i> | 10 | 0.879699 | 0.879699 | 0.0 |
| <i>ARsq</i> | 1 | 0.714769 | 0.714769 | 0.0 |
| <i>ARsq</i> | 2 | 0.990351 | 0.990351 | 0.0 |
| <i>ARsq</i> | 3 | 0.776307 | 0.776307 | 0.0 |
| <i>ARsq</i> | 4 | 0.837717 | 0.837717 | 0.0 |
| <i>ARsq</i> | 5 | 0.844202 | 0.844202 | 0.0 |
| <i>ARsq</i> | 6 | 0.925179 | 0.925179 | 0.0 |
| <i>ARsq</i> | 7 | 0.960416 | 0.960416 | 0.0 |
| <i>ARsq</i> | 8 | 0.921954 | 0.921954 | 0.0 |
| <i>ARsq</i> | 9 | 0.921307 | 0.921307 | 0.0 |
| <i>ARsq</i> | 10 | 0.867669 | 0.867669 | 0.0 |
| <i>Kel</i> | 1 | 0.00338474 | 0.00338474 | 0.0 |
| <i>Kel</i> | 2 | 0.0141063 | 0.0141063 | 0.0 |
| <i>Kel</i> | 3 | 0.00329143 | 0.00329143 | 0.0 |
| <i>Kel</i> | 4 | 0.00769534 | 0.00769534 | 0.0 |
| <i>Kel</i> | 5 | 0.00685799 | 0.00685799 | 0.0 |
| <i>Kel</i> | 6 | 0.00769228 | 0.00769228 | 0.0 |
| <i>Kel</i> | 7 | 0.012459 | 0.012459 | 0.0 |
| <i>Kel</i> | 8 | 0.00893008 | 0.00893008 | 0.0 |
| <i>Kel</i> | 9 | 0.00564586 | 0.00564586 | 0.0 |
| <i>Kel</i> | 10 | 0.0165438 | 0.0165438 | 0.0 |
| <i>HL</i> | 1 | 204.786 | 204.786 | 0.0 |
| <i>HL</i> | 2 | 49.1374 | 49.1374 | 0.0 |
| <i>HL</i> | 3 | 210.591 | 210.591 | 0.0 |
| <i>HL</i> | 4 | 90.0736 | 90.0736 | 0.0 |
| <i>HL</i> | 5 | 101.072 | 101.072 | 0.0 |
| <i>HL</i> | 6 | 90.1095 | 90.1095 | 0.0 |
| <i>HL</i> | 7 | 55.6345 | 55.6345 | 0.0 |
| <i>HL</i> | 8 | 77.6194 | 77.6194 | 0.0 |
| <i>HL</i> | 9 | 122.771 | 122.771 | 0.0 |
| <i>HL</i> | 10 | 41.8978 | 41.8978 | 0.0 |
| <i>Clast_{pred}</i> | 1 | 117.306 | 117.306 | 0.0 |
| <i>Clast_{pred}</i> | 2 | 82.5367 | 82.5367 | 0.0 |
| <i>Clast_{pred}</i> | 3 | 66.9311 | 66.9311 | 0.0 |
| <i>Clast_{pred}</i> | 4 | 100.768 | 100.768 | 0.0 |
| <i>Clast_{pred}</i> | 5 | 105.196 | 105.196 | 0.0 |
| <i>Clast_{pred}</i> | 6 | 71.9399 | 71.9399 | 0.0 |
| <i>Clast_{pred}</i> | 7 | 61.1727 | 61.1727 | 0.0 |
| <i>Clast_{pred}</i> | 8 | 75.6043 | 75.6043 | 0.0 |
| <i>Clast_{pred}</i> | 9 | 93.7618 | 93.7618 | 0.0 |
| <i>Clast_{pred}</i> | 10 | 39.4088 | 39.4088 | 0.0 |
| <i>AUCinf</i> | 1 | 42925.0 | 42925.0 | 0.0 |
| <i>AUCinf</i> | 2 | 16154.9 | 16154.9 | 0.0 |
| <i>AUCinf</i> | 3 | 26026.2 | 26026.2 | 0.0 |
| <i>AUCinf</i> | 4 | 22004.1 | 22004.1 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|-----------------|---------|-----------|-----------|------------|
| <i>AUCinf</i> | 5 | 25714.4 | 25714.4 | 0.0 |
| <i>AUCinf</i> | 6 | 16001.8 | 16001.8 | 0.0 |
| <i>AUCinf</i> | 7 | 11689.0 | 11689.0 | 0.0 |
| <i>AUCinf</i> | 8 | 15446.2 | 15446.2 | 0.0 |
| <i>AUCinf</i> | 9 | 24865.2 | 24865.2 | 0.0 |
| <i>AUCinf</i> | 10 | 8171.16 | 8171.16 | 0.0 |
| <i>AUCpct</i> | 1 | 77.6694 | 77.6694 | 0.0 |
| <i>AUCpct</i> | 2 | 37.405 | 37.405 | 0.0 |
| <i>AUCpct</i> | 3 | 79.2649 | 79.2649 | 0.0 |
| <i>AUCpct</i> | 4 | 57.6541 | 57.6541 | 0.0 |
| <i>AUCpct</i> | 5 | 62.8175 | 62.8175 | 0.0 |
| <i>AUCpct</i> | 6 | 56.4636 | 56.4636 | 0.0 |
| <i>AUCpct</i> | 7 | 39.8614 | 39.8614 | 0.0 |
| <i>AUCpct</i> | 8 | 53.9649 | 53.9649 | 0.0 |
| <i>AUCpct</i> | 9 | 66.5594 | 66.5594 | 0.0 |
| <i>AUCpct</i> | 10 | 31.2106 | 31.2106 | 0.0 |
| <i>MRTtauin</i> | 1 | 302.403 | 302.403 | 0.0 |
| <i>MRTtauin</i> | 2 | 75.5906 | 75.5906 | 0.0 |
| <i>MRTtauin</i> | 3 | 312.721 | 312.721 | 0.0 |
| <i>MRTtauin</i> | 4 | 148.341 | 148.341 | 0.0 |
| <i>MRTtauin</i> | 5 | 172.093 | 172.093 | 0.0 |
| <i>MRTtauin</i> | 6 | 130.191 | 130.191 | 0.0 |
| <i>MRTtauin</i> | 7 | 91.9083 | 91.9083 | 0.0 |
| <i>MRTtauin</i> | 8 | 161.574 | 161.574 | 0.0 |
| <i>MRTtauin</i> | 9 | 176.305 | 176.305 | 0.0 |
| <i>MRTtauin</i> | 10 | 70.2607 | 70.2607 | 0.0 |
| <i>Cltau</i> | 1 | 0.0718519 | 0.0718519 | 0.0 |
| <i>Cltau</i> | 2 | 0.0504145 | 0.0504145 | 0.0 |
| <i>Cltau</i> | 3 | 0.122406 | 0.122406 | 0.0 |
| <i>Cltau</i> | 4 | 0.070133 | 0.070133 | 0.0 |
| <i>Cltau</i> | 5 | 0.0690266 | 0.0690266 | 0.0 |
| <i>Cltau</i> | 6 | 0.0851065 | 0.0851065 | 0.0 |
| <i>Cltau</i> | 7 | 0.0835329 | 0.0835329 | 0.0 |
| <i>Cltau</i> | 8 | 0.10859 | 0.10859 | 0.0 |
| <i>Cltau</i> | 9 | 0.0732516 | 0.0732516 | 0.0 |
| <i>Cltau</i> | 10 | 0.0927567 | 0.0927567 | 0.0 |
| <i>Vztau</i> | 1 | 21.2282 | 21.2282 | 0.0 |
| <i>Vztau</i> | 2 | 3.57389 | 3.57389 | 0.0 |
| <i>Vztau</i> | 3 | 37.1892 | 37.1892 | 0.0 |
| <i>Vztau</i> | 4 | 9.11369 | 9.11369 | 0.0 |
| <i>Vztau</i> | 5 | 10.0651 | 10.0651 | 0.0 |
| <i>Vztau</i> | 6 | 11.0639 | 11.0639 | 0.0 |
| <i>Vztau</i> | 7 | 6.70465 | 6.70465 | 0.0 |
| <i>Vztau</i> | 8 | 12.1601 | 12.1601 | 0.0 |
| <i>Vztau</i> | 9 | 12.9744 | 12.9744 | 0.0 |
| <i>Vztau</i> | 10 | 5.60675 | 5.60675 | 0.0 |

4.3.4 Linear/Log Trapezoidal rule; Extravascular; Dosetime 0.0; Tau 12; Dose 120

Code:

```
setdosetime!(ds, DoseTime(dose = 120, time = 0.0, tau = 12))
nca!(ds, adm = :ev, calcm = :logt)
```

Table 5: Plasma data results, Linear/Log Trapezoidal rule, Extravascular

| Parameter | Subject | Value | Reference | Difference |
|--------------|---------|---------|-----------|------------|
| <i>Cmax</i> | 1 | 190.869 | 190.869 | 0.0 |
| <i>Cmax</i> | 2 | 261.177 | 261.177 | 0.0 |
| <i>Cmax</i> | 3 | 105.345 | 105.345 | 0.0 |
| <i>Cmax</i> | 4 | 208.542 | 208.542 | 0.0 |
| <i>Cmax</i> | 5 | 169.334 | 169.334 | 0.0 |
| <i>Cmax</i> | 6 | 154.648 | 154.648 | 0.0 |
| <i>Cmax</i> | 7 | 153.254 | 153.254 | 0.0 |
| <i>Cmax</i> | 8 | 138.327 | 138.327 | 0.0 |
| <i>Cmax</i> | 9 | 167.347 | 167.347 | 0.0 |
| <i>Cmax</i> | 10 | 125.482 | 125.482 | 0.0 |
| <i>Tmax</i> | 1 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 2 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 3 | 1.5 | 1.5 | 0.0 |
| <i>Tmax</i> | 4 | 1.0 | 1.0 | 0.0 |
| <i>Tmax</i> | 5 | 4.0 | 4.0 | 0.0 |
| <i>Tmax</i> | 6 | 2.5 | 2.5 | 0.0 |
| <i>Tmax</i> | 7 | 2.5 | 2.5 | 0.0 |
| <i>Tmax</i> | 8 | 4.0 | 4.0 | 0.0 |
| <i>Tmax</i> | 9 | 3.0 | 3.0 | 0.0 |
| <i>Tmax</i> | 10 | 2.0 | 2.0 | 0.0 |
| <i>Cdose</i> | 1 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 2 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 3 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 4 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 5 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 6 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 7 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 8 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 9 | 0.0 | 0.0 | 0.0 |
| <i>Cdose</i> | 10 | 0.0 | 0.0 | 0.0 |
| <i>Clast</i> | 1 | 112.846 | 112.846 | 0.0 |
| <i>Clast</i> | 2 | 85.241 | 85.241 | 0.0 |
| <i>Clast</i> | 3 | 67.901 | 67.901 | 0.0 |
| <i>Clast</i> | 4 | 97.625 | 97.625 | 0.0 |
| <i>Clast</i> | 5 | 110.778 | 110.778 | 0.0 |
| <i>Clast</i> | 6 | 69.501 | 69.501 | 0.0 |
| <i>Clast</i> | 7 | 58.051 | 58.051 | 0.0 |
| <i>Clast</i> | 8 | 74.437 | 74.437 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|----------------|---------|----------|-----------|------------|
| <i>Clast</i> | 9 | 93.44 | 93.44 | 0.0 |
| <i>Clast</i> | 10 | 42.191 | 42.191 | 0.0 |
| <i>AUClast</i> | 1 | 9572.86 | 9572.86 | 0.0 |
| <i>AUClast</i> | 2 | 10054.0 | 10054.0 | 0.0 |
| <i>AUClast</i> | 3 | 5391.53 | 5391.53 | 0.0 |
| <i>AUClast</i> | 4 | 9296.22 | 9296.22 | 0.0 |
| <i>AUClast</i> | 5 | 9518.65 | 9518.65 | 0.0 |
| <i>AUClast</i> | 6 | 6948.58 | 6948.58 | 0.0 |
| <i>AUClast</i> | 7 | 6987.06 | 6987.06 | 0.0 |
| <i>AUClast</i> | 8 | 7064.78 | 7064.78 | 0.0 |
| <i>AUClast</i> | 9 | 8298.96 | 8298.96 | 0.0 |
| <i>AUClast</i> | 10 | 5485.65 | 5485.65 | 0.0 |
| <i>AUCtau</i> | 1 | 1668.36 | 1668.36 | 0.0 |
| <i>AUCtau</i> | 2 | 2379.57 | 2379.57 | 0.0 |
| <i>AUCtau</i> | 3 | 979.109 | 979.109 | 0.0 |
| <i>AUCtau</i> | 4 | 1709.79 | 1709.79 | 0.0 |
| <i>AUCtau</i> | 5 | 1738.24 | 1738.24 | 0.0 |
| <i>AUCtau</i> | 6 | 1408.16 | 1408.16 | 0.0 |
| <i>AUCtau</i> | 7 | 1432.02 | 1432.02 | 0.0 |
| <i>AUCtau</i> | 8 | 1080.02 | 1080.02 | 0.0 |
| <i>AUCtau</i> | 9 | 1630.98 | 1630.98 | 0.0 |
| <i>AUCtau</i> | 10 | 1292.83 | 1292.83 | 0.0 |
| <i>AUMCtau</i> | 1 | 9973.81 | 9973.81 | 0.0 |
| <i>AUMCtau</i> | 2 | 14631.1 | 14631.1 | 0.0 |
| <i>AUMCtau</i> | 3 | 6022.93 | 6022.93 | 0.0 |
| <i>AUMCtau</i> | 4 | 10308.0 | 10308.0 | 0.0 |
| <i>AUMCtau</i> | 5 | 11473.1 | 11473.1 | 0.0 |
| <i>AUMCtau</i> | 6 | 8471.1 | 8471.1 | 0.0 |
| <i>AUMCtau</i> | 7 | 8982.04 | 8982.04 | 0.0 |
| <i>AUMCtau</i> | 8 | 6271.74 | 6271.74 | 0.0 |
| <i>AUMCtau</i> | 9 | 10040.8 | 10040.8 | 0.0 |
| <i>AUMCtau</i> | 10 | 8361.79 | 8361.79 | 0.0 |
| <i>AUCall</i> | 1 | 9572.86 | 9572.86 | 0.0 |
| <i>AUCall</i> | 2 | 10054.0 | 10054.0 | 0.0 |
| <i>AUCall</i> | 3 | 5391.53 | 5391.53 | 0.0 |
| <i>AUCall</i> | 4 | 9296.22 | 9296.22 | 0.0 |
| <i>AUCall</i> | 5 | 9518.65 | 9518.65 | 0.0 |
| <i>AUCall</i> | 6 | 6948.58 | 6948.58 | 0.0 |
| <i>AUCall</i> | 7 | 6987.06 | 6987.06 | 0.0 |
| <i>AUCall</i> | 8 | 7064.78 | 7064.78 | 0.0 |
| <i>AUCall</i> | 9 | 8298.96 | 8298.96 | 0.0 |
| <i>AUCall</i> | 10 | 5485.65 | 5485.65 | 0.0 |
| <i>Rsq</i> | 1 | 0.786077 | 0.786077 | 0.0 |
| <i>Rsq</i> | 2 | 0.992764 | 0.992764 | 0.0 |
| <i>Rsq</i> | 3 | 0.813589 | 0.813589 | 0.0 |
| <i>Rsq</i> | 4 | 0.918859 | 0.918859 | 0.0 |
| <i>Rsq</i> | 5 | 0.85336 | 0.85336 | 0.0 |
| <i>Rsq</i> | 6 | 0.950119 | 0.950119 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|-----------------------------|---------|------------|------------|------------|
| <i>Rsq</i> | 7 | 0.970312 | 0.970312 | 0.0 |
| <i>Rsq</i> | 8 | 0.947969 | 0.947969 | 0.0 |
| <i>Rsq</i> | 9 | 0.947538 | 0.947538 | 0.0 |
| <i>Rsq</i> | 10 | 0.880923 | 0.880923 | 0.0 |
| <i>ARsq</i> | 1 | 0.714769 | 0.714769 | 0.0 |
| <i>ARsq</i> | 2 | 0.990351 | 0.990351 | 0.0 |
| <i>ARsq</i> | 3 | 0.776307 | 0.776307 | 0.0 |
| <i>ARsq</i> | 4 | 0.837717 | 0.837717 | 0.0 |
| <i>ARsq</i> | 5 | 0.82892 | 0.82892 | 0.0 |
| <i>ARsq</i> | 6 | 0.925179 | 0.925179 | 0.0 |
| <i>ARsq</i> | 7 | 0.960416 | 0.960416 | 0.0 |
| <i>ARsq</i> | 8 | 0.921954 | 0.921954 | 0.0 |
| <i>ARsq</i> | 9 | 0.921307 | 0.921307 | 0.0 |
| <i>ARsq</i> | 10 | 0.863912 | 0.863912 | 0.0 |
| <i>Kel</i> | 1 | 0.00338474 | 0.00338474 | 0.0 |
| <i>Kel</i> | 2 | 0.0141063 | 0.0141063 | 0.0 |
| <i>Kel</i> | 3 | 0.00329143 | 0.00329143 | 0.0 |
| <i>Kel</i> | 4 | 0.00769534 | 0.00769534 | 0.0 |
| <i>Kel</i> | 5 | 0.00681333 | 0.00681333 | 0.0 |
| <i>Kel</i> | 6 | 0.00769228 | 0.00769228 | 0.0 |
| <i>Kel</i> | 7 | 0.012459 | 0.012459 | 0.0 |
| <i>Kel</i> | 8 | 0.00893008 | 0.00893008 | 0.0 |
| <i>Kel</i> | 9 | 0.00564586 | 0.00564586 | 0.0 |
| <i>Kel</i> | 10 | 0.0171897 | 0.0171897 | 0.0 |
| <i>HL</i> | 1 | 204.786 | 204.786 | 0.0 |
| <i>HL</i> | 2 | 49.1374 | 49.1374 | 0.0 |
| <i>HL</i> | 3 | 210.591 | 210.591 | 0.0 |
| <i>HL</i> | 4 | 90.0736 | 90.0736 | 0.0 |
| <i>HL</i> | 5 | 101.734 | 101.734 | 0.0 |
| <i>HL</i> | 6 | 90.1095 | 90.1095 | 0.0 |
| <i>HL</i> | 7 | 55.6345 | 55.6345 | 0.0 |
| <i>HL</i> | 8 | 77.6194 | 77.6194 | 0.0 |
| <i>HL</i> | 9 | 122.771 | 122.771 | 0.0 |
| <i>HL</i> | 10 | 40.3233 | 40.3233 | 0.0 |
| <i>Clast_{pred}</i> | 1 | 117.306 | 117.306 | 0.0 |
| <i>Clast_{pred}</i> | 2 | 82.5367 | 82.5367 | 0.0 |
| <i>Clast_{pred}</i> | 3 | 66.9311 | 66.9311 | 0.0 |
| <i>Clast_{pred}</i> | 4 | 100.768 | 100.768 | 0.0 |
| <i>Clast_{pred}</i> | 5 | 105.298 | 105.298 | 0.0 |
| <i>Clast_{pred}</i> | 6 | 71.9399 | 71.9399 | 0.0 |
| <i>Clast_{pred}</i> | 7 | 61.1727 | 61.1727 | 0.0 |
| <i>Clast_{pred}</i> | 8 | 75.6043 | 75.6043 | 0.0 |
| <i>Clast_{pred}</i> | 9 | 93.7618 | 93.7618 | 0.0 |
| <i>Clast_{pred}</i> | 10 | 38.8109 | 38.8109 | 0.0 |
| <i>AUCinf</i> | 1 | 42912.5 | 42912.5 | 0.0 |
| <i>AUCinf</i> | 2 | 16096.8 | 16096.8 | 0.0 |
| <i>AUCinf</i> | 3 | 26021.2 | 26021.2 | 0.0 |

| Parameter | Subject | Value | Reference | Difference |
|-----------------|---------|-----------|-----------|------------|
| <i>AUCinf</i> | 4 | 21982.5 | 21982.5 | 0.0 |
| <i>AUCinf</i> | 5 | 25777.7 | 25777.7 | 0.0 |
| <i>AUCinf</i> | 6 | 15983.7 | 15983.7 | 0.0 |
| <i>AUCinf</i> | 7 | 11646.4 | 11646.4 | 0.0 |
| <i>AUCinf</i> | 8 | 15400.3 | 15400.3 | 0.0 |
| <i>AUCinf</i> | 9 | 24849.1 | 24849.1 | 0.0 |
| <i>AUCinf</i> | 10 | 7940.08 | 7940.08 | 0.0 |
| <i>AUCpct</i> | 1 | 77.6921 | 77.6921 | 0.0 |
| <i>AUCpct</i> | 2 | 37.5401 | 37.5401 | 0.0 |
| <i>AUCpct</i> | 3 | 79.2802 | 79.2802 | 0.0 |
| <i>AUCpct</i> | 4 | 57.7107 | 57.7107 | 0.0 |
| <i>AUCpct</i> | 5 | 63.074 | 63.074 | 0.0 |
| <i>AUCpct</i> | 6 | 56.5272 | 56.5272 | 0.0 |
| <i>AUCpct</i> | 7 | 40.0069 | 40.0069 | 0.0 |
| <i>AUCpct</i> | 8 | 54.1257 | 54.1257 | 0.0 |
| <i>AUCpct</i> | 9 | 66.6026 | 66.6026 | 0.0 |
| <i>AUCpct</i> | 10 | 30.9119 | 30.9119 | 0.0 |
| <i>MRTtauin</i> | 1 | 302.635 | 302.635 | 0.0 |
| <i>MRTtauin</i> | 2 | 75.3237 | 75.3237 | 0.0 |
| <i>MRTtauin</i> | 3 | 313.068 | 313.068 | 0.0 |
| <i>MRTtauin</i> | 4 | 148.311 | 148.311 | 0.0 |
| <i>MRTtauin</i> | 5 | 172.558 | 172.558 | 0.0 |
| <i>MRTtauin</i> | 6 | 130.226 | 130.226 | 0.0 |
| <i>MRTtauin</i> | 7 | 91.8667 | 91.8667 | 0.0 |
| <i>MRTtauin</i> | 8 | 164.918 | 164.918 | 0.0 |
| <i>MRTtauin</i> | 9 | 176.985 | 176.985 | 0.0 |
| <i>MRTtauin</i> | 10 | 68.1676 | 68.1676 | 0.0 |
| <i>Cltau</i> | 1 | 0.0719271 | 0.0719271 | 0.0 |
| <i>Cltau</i> | 2 | 0.0504294 | 0.0504294 | 0.0 |
| <i>Cltau</i> | 3 | 0.12256 | 0.12256 | 0.0 |
| <i>Cltau</i> | 4 | 0.0701841 | 0.0701841 | 0.0 |
| <i>Cltau</i> | 5 | 0.0690354 | 0.0690354 | 0.0 |
| <i>Cltau</i> | 6 | 0.0852177 | 0.0852177 | 0.0 |
| <i>Cltau</i> | 7 | 0.0837976 | 0.0837976 | 0.0 |
| <i>Cltau</i> | 8 | 0.111109 | 0.111109 | 0.0 |
| <i>Cltau</i> | 9 | 0.0735756 | 0.0735756 | 0.0 |
| <i>Cltau</i> | 10 | 0.0928198 | 0.0928198 | 0.0 |
| <i>Vztau</i> | 1 | 21.2504 | 21.2504 | 0.0 |
| <i>Vztau</i> | 2 | 3.57495 | 3.57495 | 0.0 |
| <i>Vztau</i> | 3 | 37.2362 | 37.2362 | 0.0 |
| <i>Vztau</i> | 4 | 9.12034 | 9.12034 | 0.0 |
| <i>Vztau</i> | 5 | 10.1324 | 10.1324 | 0.0 |
| <i>Vztau</i> | 6 | 11.0783 | 11.0783 | 0.0 |
| <i>Vztau</i> | 7 | 6.72589 | 6.72589 | 0.0 |
| <i>Vztau</i> | 8 | 12.4421 | 12.4421 | 0.0 |
| <i>Vztau</i> | 9 | 13.0318 | 13.0318 | 0.0 |
| <i>Vztau</i> | 10 | 5.39972 | 5.39972 | 0.0 |

4.3.5 Urine data; Linear-trapezoidal rule; Extravascular; Dosetime 0.0; Dose 100

Code:

```
upkds = upkimport(upkdata, :st, :et, :conc, :vol, :subj;
dosetime = MetidaNCA.DoseTime(dose = 100))
MetidaNCA.nca!(upkds)
```

Table 6: Urine data results

| Parameter | Value | Reference | Difference |
|----------------|----------|-----------|------------|
| <i>AUCall</i> | 17.125 | 17.125 | 0.0 |
| <i>Prec</i> | 16.0 | 16.0 | 0.0 |
| <i>Tmax</i> | 1.5 | 1.5 | 0.0 |
| <i>Rlast</i> | 0.333333 | 0.333333 | 0.0 |
| <i>AR</i> | 16.0 | 16.0 | 0.0 |
| <i>ARsq</i> | 0.810983 | 0.810983 | 0.0 |
| <i>HL</i> | 5.15526 | 5.15526 | 0.0 |
| <i>AUClast</i> | 17.125 | 17.125 | 0.0 |
| <i>AUCinf</i> | 19.6042 | 19.6042 | 0.0 |
| <i>Vol</i> | 11.0 | 11.0 | 0.0 |
| <i>AUCpct</i> | 12.6461 | 12.6461 | 0.0 |
| <i>Kel</i> | 0.134454 | 0.134454 | 0.0 |
| <i>Maxrate</i> | 4.0 | 4.0 | 0.0 |
| <i>Rsq</i> | 0.905492 | 0.905492 | 0.0 |

4.3.6 Pharmacodynamics data; Linear-trapezoidal rule

Code:

```
pd = MetidaNCA.pdimport(pddata, :time, :obs;  
bl = 3.0, th = 1.5, id = Dict(:subj => 1))  
pdres = MetidaNCA.nca!(pd)
```

Table 7: Pharmacodynamics data results

| Parameter | Value | Reference | Difference |
|----------------|---------|-----------|------------|
| <i>Tmax</i> | 5.0 | 5.0 | 0.0 |
| <i>TBBL</i> | 5.51905 | 5.51905 | 0.0 |
| <i>TIMEBTW</i> | 2.28095 | 2.28095 | 0.0 |
| <i>AUCBTW</i> | 6.92619 | 6.92619 | 0.0 |
| <i>AUCBBL</i> | 8.73571 | 8.73571 | 0.0 |
| <i>TBTH</i> | 3.2381 | 3.2381 | 0.0 |
| <i>AUCNETT</i> | 12.15 | 12.15 | 0.0 |
| <i>Rmax</i> | 8.0 | 8.0 | 0.0 |
| <i>AUCABL</i> | 7.38571 | 7.38571 | 0.0 |
| <i>AUCATH</i> | 13.9595 | 13.9595 | 0.0 |
| <i>TATH</i> | 5.7619 | 5.7619 | 0.0 |
| <i>AUCNETB</i> | -1.35 | -1.35 | 0.0 |
| <i>AUCBTH</i> | 1.80952 | 1.80952 | 0.0 |
| <i>TABL</i> | 3.48095 | 3.48095 | 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

7.0.1 Testing PK dataset.

| Subject | Formulation | Time | Concentration |
|---------|-------------|------|---------------|
| 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 | |
| | ----- | | ----- | | ----- | | ----- | |

7.0.2 Testing urine PK dataset.

| subj | conc | st | et | vol |
|------|------|----|----|-----|
| 1 | 1 | 0 | 1 | 1 |
| 1 | 2 | 1 | 2 | 2 |
| 1 | 2 | 2 | 6 | 3 |
| 1 | 1 | 6 | 12 | 3 |
| 1 | 1 | 12 | 18 | 2 |

7.0.3 Testing PD dataset.

| subj | time | obs |
|------|------|-----|
| 1 | 0.0 | 0 |
| 1 | 1.0 | 1 |
| 1 | 2.0 | 4 |
| 1 | 2.5 | 7 |
| 1 | 3.0 | 5 |
| 1 | 3.3 | 4 |
| 1 | 3.6 | 3 |
| 1 | 4.0 | 2 |
| 1 | 5.0 | 8 |
| 1 | 6.0 | 1 |
| 1 | 7.0 | 2 |
| 1 | 8.0 | 1 |
| 1 | 9.0 | 1 |

8 Appendix 2

8.0.1 Reference output.

Avialible at <https://github.com/PharmCat/MetidaNCA.jl/tree/main/docs/src/pdf>.

See Appendix 2.1.pdf,

Appendix 2.2.pdf,

Appendix 2.3.pdf,

Appendix 2.4.pdf,

Appendix 2.5.pdf.