PRECLINICAL PHARMACOKINETIC REPORT

Developmental Biology and Solid Tumor Program

P-PKSR Study 18260-82776

STUDY TITLE:

PHARMACOKINETICS AND EFFICACY OF THE SPLEEN TYROSINE KINASE INHIBITOR R406 (TAMATINIB) AFTER OCULAR DELIVERY FOR RETINOBLASTOMA

SHORT TITLE:	**Ocular PK of (Fos)tamatinib – WNL TLFs**
TEST ARTICLE:	Fostamatinib (R788) – Phosphate prodrug of tamatinib Tamatinib (R406) – Free base, phenylsulfonate, and palmitate
SECTION:	Nonclinical Pharmacokinetics (Non-GLP)
PRINCIPAL INVESTIGATOR(S):	Dyer, Michael A <Michael.Dyer@STJUDE.ORG>
SJCRH SRM2 O/R:	18260-82776 Preclinical Pharmacokinetic Shared Resource 18176-82422 18176-82421 18156-82375
REFERENCE STUDY NUMBERS:	NA
IN VIVO SCIENTIST(S):	Pritchard, Eleanor
BIOANALYTICAL SCIENTIST:	Yang, Lei <Lei.Yang@STJUDE.ORG>
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REPORT FORMAT:	WinNonlin Output TLFs
REPORT STATUS:	FINAL
DATE:	2020-04-29
PUBLICATION:	Pritchard EM et al. Pharmacokinetics and Efficacy of the Spleen Tyrosine Kinase Inhibitor R406 after Ocular Delivery for Retinoblastoma. Pharm Res. 2014 Jun 7;31(11):3060–72.

Quality Statement

This non-GLP study was conducted using sound scientific principles and established techniques in accordance with the relevant guidelines and standard operating procedures (SOPs) of St. Jude Children's Research Hospital (SJCRH), Memphis, TN, USA. Data were provided in processed formats from the listed In Vivo Scientist and Bioanalytical Scientist to the Preclinical Pharmacokinetic Shared Resource (P-PKSR) for analysis. This report reflects the analysis of the data provided.

These results represent part of an early phase preclinical pharmacology program. This study has been conducted to provide preliminary insights into the pharmacokinetic (PK) properties of the compound(s) in the indicated preclinical model(s). This study and its results are not intended to provide a comprehensive PK evaluation of the compound(s). The applied bioanalytical method was validated/qualified to support this specific study and discovery-style sample analyses.

Substantial study-to-study and inter-animal variability in preclinical PK exists. Such variability depends upon the in vivo scientists' experience, variations in compound purity and formulation, animal strains, sex and age, and other situational fixed effects (i.e. husbandry conditions, chow constituents, presence or absence of disease, concomitant drugs). As such, the actual PK, plasma or tissue compound concentrations, or equivalent dose in other studies or preclinical models may vary significantly from that reported herein.

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Table 1: Putative Final R406 Mean Ct Data for NCA Analysis (Provided by In Vivo Scientist, Generated by Bioanalytical Scientist)

DATE	DOSE	ROUTE	MATRIX	Time (hr)	Mean_Concentration (nMol/L)	SD	GRP	SRM
4/12/2012	R406 Ph Cosol	OC	Vitreous	0.50	82.00	57.26	1.00	18175-82415
4/12/2012	R406 Ph Cosol	OC	Vitreous	1.00	281.57	247.56	1.00	18175-82415
4/12/2012	R406 Ph Cosol	OC	Vitreous	2.00	170.00	176.77	1.00	18175-82415
4/12/2012	R406 Ph Cosol	OC	Vitreous	4.00	247.80	129.53	1.00	18175-82415
4/12/2012	R788 PO	PO	Plasma	0.50	2009.67	1053.57	2.00	18156-82375
4/12/2012	R788 PO	PO	Plasma	1.00	388.50	149.46	2.00	18156-82375
4/12/2012	R788 PO	PO	Plasma	2.00	117.67	60.91	2.00	18156-82375
4/12/2012	R788 PO	PO	Plasma	4.00	26.33	16.36	2.00	18156-82375
4/12/2012	R788 PO	PO	Vitreous	0.50	164.00	117.80	2.00	18156-82375
4/12/2012	R788 PO	PO	Vitreous	1.00	41.33	7.09	2.00	18156-82375
4/12/2012	R788 PO	PO	Vitreous	2.00	24.83	15.67	2.00	18156-82375
5/12/2012	R406 Emu	OC	Plasma	0.50	112.33	92.51	3.00	18176-82417
5/12/2012	R406 Emu	OC	Plasma	1.00	32.67	12.66	3.00	18176-82417
5/12/2012	R406 Emu	OC	Plasma	2.00	30.00	4.58	3.00	18176-82417
5/12/2012	R406 Emu	OC	Plasma	4.00	15.33	5.86	3.00	18176-82417
5/12/2012	R406 Emu	OC	Plasma	8.00	7.33	1.53	3.00	18176-82417
5/12/2012	R406 Emu	OC	Plasma	24.00	6.50	0.87	3.00	18176-82417
5/12/2012	R406 Emu	OC	Vitreous	0.50	33.67	17.79	3.00	18176-82417
5/12/2012	R406 Emu	OC	Vitreous	1.00	28.67	20.82	3.00	18176-82417
5/12/2012	R406 Emu	OC	Vitreous	2.00	20.67	15.14	3.00	18176-82417
5/12/2012	R406 Emu	OC	Vitreous	4.00	15.67	7.23	3.00	18176-82417
5/12/2012	R406 Emu	OC	Vitreous	8.00	37.00	25.46	3.00	18176-82417

Ocular PK of (Fos)tamatinib – WNL TLFs

DATE	DOSE	ROUTE	MATRIX	Time (hr)	Mean_Concentration (nMol/L)	SD	GRP	SRM
5/12/2012	R406 Emu	OC	Vitreous	24.00			3.00	18176-82417
5/12/2012	R406 Ph Cosol	OC	Plasma	0.50	79.00	34.70	4.00	18176-82416
5/12/2012	R406 Ph Cosol	OC	Plasma	1.00	13.67	3.51	4.00	18176-82416
5/12/2012	R406 Ph Cosol	OC	Vitreous	0.50	41.33	31.21	4.00	18176-82416
5/12/2012	R406 Ph Cosol	OC	Vitreous	1.00	13.33	6.81	4.00	18176-82416
5/12/2012	R406 Ph Cosol	OC	Vitreous	2.00	6.00	1.00	4.00	18176-82416
7/20/2012	R406 Emu	OC	Plasma	0.50	118.60	34.24	5.00	18176-82419
7/20/2012	R406 Emu	OC	Plasma	1.00	65.88	13.66	5.00	18176-82419
7/20/2012	R406 Emu	OC	Plasma	2.00	20.11	11.81	5.00	18176-82419
7/20/2012	R406 Emu	OC	Vitreous	0.50	169.13	62.19	5.00	18176-82419
7/20/2012	R406 Emu	OC	Vitreous	1.00	74.12	32.51	5.00	18176-82419
7/20/2012	R406 Emu	OC	Vitreous	2.00	105.22	141.93	5.00	18176-82419
7/20/2012	R406 Emu	OC	Vitreous	4.00	131.79	205.95	5.00	18176-82419
7/20/2012	R406 Ph Cosol	OC	Plasma	0.50	22.28	16.20	6.00	18176-82418
7/20/2012	R406 Ph Cosol	OC	Vitreous	0.50			6.00	18176-82418
7/24/2012	R406 Ph DMSO	OC	Plasma	0.50	370.23	90.15	7.00	18176-82420
7/24/2012	R406 Ph DMSO	OC	Plasma	1.00	45.62	23.33	7.00	18176-82420
7/24/2012	R406 Ph DMSO	OC	Plasma	2.00	43.88	18.04	7.00	18176-82420
7/24/2012	R406 Ph DMSO	OC	Plasma	4.00	12.86	4.87	7.00	18176-82420
7/24/2012	R406 Ph DMSO	OC	Vitreous	0.50	892.18	606.51	7.00	18176-82420
7/24/2012	R406 Ph DMSO	OC	Vitreous	1.00	282.43	140.64	7.00	18176-82420
7/24/2012	R406 Ph DMSO	OC	Vitreous	2.00	561.82	154.47	7.00	18176-82420
7/24/2012	R406 Ph DMSO	OC	Vitreous	4.00	456.52	407.60	7.00	18176-82420
7/24/2012	R406 Ph DMSO	OC	Vitreous	8.00	60.85	44.62	7.00	18176-82420
8/29/2012	R788 Cosol	OC	Plasma	0.50	574.20	135.70	8.00	18176-82421
8/29/2012	R788 Cosol	OC	Plasma	1.00	75.11	18.41	8.00	18176-82421
8/29/2012	R788 Cosol	OC	Vitreous	0.50	968.56	68.92	8.00	18176-82421
8/29/2012	R788 Cosol	OC	Vitreous	1.00	175.89	39.99	8.00	18176-82421
8/29/2012	R788 Cosol	OC	Vitreous	2.00	60.43	20.87	8.00	18176-82421
8/29/2012	R788 Cosol	OC	Vitreous	4.00	17.06	9.97	8.00	18176-82421
8/29/2012	R788 Cosol	OC	Vitreous	8.00	36.32	27.45	8.00	18176-82421
9/27/2012	R788 Suspension	OC	Plasma	0.50	2906.58	1650.57	9.00	18176-82422
9/27/2012	R788 Suspension	OC	Plasma	1.00	369.62	391.94	9.00	18176-82422
9/27/2012	R788 Suspension	OC	Plasma	2.00	43.70	14.99	9.00	18176-82422
9/27/2012	R788 Suspension	OC	Plasma	4.00	25.68	5.48	9.00	18176-82422
9/27/2012	R788 Suspension	OC	Vitreous	0.50	267.27	132.38	9.00	18176-82422
9/27/2012	R788 Suspension	OC	Vitreous	1.00	103.81	120.99	9.00	18176-82422
9/27/2012	R788 Suspension	OC	Vitreous	2.00	116.79	132.15	9.00	18176-82422
9/27/2012	R788 Suspension	OC	Vitreous	4.00	69.21	19.77	9.00	18176-82422
9/27/2012	R788 Suspension	OC	Vitreous	8.00			9.00	18176-82422
3/18/2013	R788 IVit	OC	Vitreous	0.50	1212.82	409.50	10.00	18260-82776
3/18/2013	R788 IVit	OC	Vitreous	1.00	546.90	645.91	10.00	18260-82776
3/18/2013	R788 IVit	OC	Vitreous	2.00	149.94	103.86	10.00	18260-82776
3/18/2013	R788 IVit	OC	Vitreous	4.00	22.51	10.14	10.00	18260-82776

Table 2: NCA Parameter Estimates.

MATRIX	DATE	DOSE	ROUTE	Tmax	Cmax	Tlast	AUClast	MRTlast	AUC0-4
Plasma	4/12/2012	R788 PO	PO	0.50	2009.67	4.00	1499.04	0.84	1499.04
Plasma	5/12/2012	R406 Emu	OC	0.50	112.33	24.00	297.00	7.28	141.00
Plasma	5/12/2012	R406 Ph Cosol	OC	0.50	79.00	1.00	42.92	0.54	
Plasma	7/20/2012	R406 Emu	OC	0.50	118.60	2.00	118.76	0.83	
Plasma	7/20/2012	R406 Ph Cosol	OC	0.50	22.28	0.50	5.57	0.50	
Plasma	7/24/2012	R406 Ph DMSO	OC	0.50	370.23	4.00	298.01	1.04	298.01
Plasma	8/29/2012	R788 Cosol	OC	0.50	574.20	1.00	305.88	0.53	
Plasma	9/27/2012	R788 Suspension	OC	0.50	2906.58	4.00	1821.73	0.68	1821.73
Vitreous	4/12/2012	R406 Ph Cosol	OC	1.00	281.57	4.00	754.98	2.30	754.98
Vitreous	4/12/2012	R788 PO	PO	0.50	164.00	2.00	125.42	0.77	143.86
Vitreous	5/12/2012	R406 Emu	OC	8.00	37.00	8.00	190.33	4.58	85.00
Vitreous	5/12/2012	R406 Ph Cosol	OC	0.50	41.33	2.00	33.67	0.78	

MATRIX	DATE	DOSE	ROUTE	Tmax	Cmax	Tlast	AUClast	MRTlast	AUC0-4
Vitreous	7/20/2012	R406 Emu	OC	0.50	169.13	4.00	429.78	2.19	429.78
Vitreous	7/20/2012	R406 Ph Cosol	OC						
Vitreous	7/24/2012	R406 Ph DMSO	OC	0.50	892.18	8.00	2991.91	2.87	1957.17
Vitreous	8/29/2012	R788 Cosol	OC	0.50	968.56	8.00	830.66	1.61	723.90
Vitreous	9/27/2012	R788 Suspension	OC	0.50	267.27	4.00	455.89	1.69	455.89
Vitreous	3/18/2013	R788 IVit	OC	0.50	1212.82	4.00	1264.01	0.99	1264.01

NOTE: AUClast values reported in manuscript were either AUClast or AUC0-4, depending on the precision or execution of terminal phase slope regression.

Table 3: Terminal Slope Settings

MATRIX	DATE	DOSE	ROUTE	Start Time	End Time	Fit Method	Selection
Plasma	4/12/2012	R788 PO	PO	1.00	4.00	TimeRange	User
Plasma	5/12/2012	R406 Emu	OC	2.00	24.00	TimeRange	User
Plasma	5/12/2012	R406 Ph Cosol	OC			BestFit	System
Plasma	7/20/2012	R406 Emu	OC			BestFit	System
Plasma	7/20/2012	R406 Ph Cosol	OC			BestFit	System
Plasma	7/24/2012	R406 Ph DMSO	OC	1.00	4.00	BestFit	System
Plasma	8/29/2012	R788 Cosol	OC			BestFit	System
Plasma	9/27/2012	R788 Suspension	OC	1.00	4.00	BestFit	System
Vitreous	4/12/2012	R406 Ph Cosol	OC	1.00	4.00	TimeRange	User
Vitreous	4/12/2012	R788 PO	PO	0.50	2.00	TimeRange	User
Vitreous	5/12/2012	R406 Emu	OC			BestFit	System
Vitreous	5/12/2012	R406 Ph Cosol	OC			BestFit	System
Vitreous	7/20/2012	R406 Emu	OC			BestFit	System
Vitreous	7/20/2012	R406 Ph Cosol	OC			BestFit	System
Vitreous	7/24/2012	R406 Ph DMSO	OC	2.00	8.00	BestFit	System
Vitreous	8/29/2012	R788 Cosol	OC	1.00	8.00	BestFit	System
Vitreous	9/27/2012	R788 Suspension	OC	1.00	4.00	BestFit	System
Vitreous	3/18/2013	R788 IVit	OC	1.00	4.00	BestFit	System

Listing 1: Phoenix WNL NCA Settings

```
Date: Apr 30, 2020 8:52:28 AM Local
/********************************* Begin Mappings *********************************/
Main : New Project.Data.R406 Putative Final Data
       Sort : DATE, DOSE, ROUTE, MATRIX
       Time : Time [hr]
       Concentration : Mean_Concentration [nMol/L]
       Carry :

Dosing : <None>

Slopes : (Internal)

Partial Areas : (Internal)

Therapeutic Response : <None>

Units : (Internal)

Parameter Names : (Internal)

/********************************* End Mappings   *********************************/



Phoenix Build 8.2.0.4383
Plasma Model
Title =
Linear Trapezoidal Linear Interpolation
Sparse = False
Weighting = Uniform Weighting; 0
Dose Type = Extravascular
Dose Unit =
Dose Normalization = None
Slope Settings
       MATRIX=Plasma, DATE=4/12/2012, DOSE=R788 PO, ROUTE=PO, Start Time=1, End Time=4,
Exclusions=, Fit Method=TimeRange, Selection=User
       MATRIX=Plasma, DATE=5/12/2012, DOSE=R406 Emu, ROUTE=OC, Start Time=2, End Time=24,
Exclusions=, Fit Method=TimeRange, Selection=User
       MATRIX=Plasma, DATE=5/12/2012, DOSE=R406 Ph Cosol, ROUTE=OC, Start Time=, End Time=,
Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Plasma, DATE=7/20/2012, DOSE=R406 Emu, ROUTE=OC, Start Time=, End Time=,
Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Plasma, DATE=7/20/2012, DOSE=R406 Ph Cosol, ROUTE=OC, Start Time=, End Time=,
Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Plasma, DATE=7/24/2012, DOSE=R406 Ph DMSO, ROUTE=OC, Start Time=1, End Time=4,
Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Plasma, DATE=8/29/2012, DOSE=R788 Cosol, ROUTE=OC, Start Time=, End Time=,
Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Plasma, DATE=9/27/2012, DOSE=R788 Suspension, ROUTE=OC, Start Time=1, End
Time=4, Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Vitreous, DATE=4/12/2012, DOSE=R406 Ph Cosol, ROUTE=OC, Start Time=1, End
Time=4, Exclusions=, Fit Method=TimeRange, Selection=User
       MATRIX=Vitreous, DATE=4/12/2012, DOSE=R788 PO, ROUTE=PO, Start Time=0.5, End Time=2,
Exclusions=, Fit Method=TimeRange, Selection=User
       MATRIX=Vitreous, DATE=5/12/2012, DOSE=R406 Emu, ROUTE=OC, Start Time=, End Time=,
Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Vitreous, DATE=5/12/2012, DOSE=R406 Ph Cosol, ROUTE=OC, Start Time=, End
Time=, Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Vitreous, DATE=7/20/2012, DOSE=R406 Emu, ROUTE=OC, Start Time=, End Time=,
```

```
Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Vitreous, DATE=7/20/2012, DOSE=R406 Ph Cosol, ROUTE=OC, Start Time=, End
Time=, Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Vitreous, DATE=7/24/2012, DOSE=R406 Ph DMSO, ROUTE=OC, Start Time=2, End
Time=8, Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Vitreous, DATE=8/29/2012, DOSE=R788 Cosol, ROUTE=OC, Start Time=1, End Time=8,
Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Vitreous, DATE=9/27/2012, DOSE=R788 Suspension, ROUTE=OC, Start Time=1, End
Time=4, Exclusions=, Fit Method=BestFit, Selection=System
       MATRIX=Vitreous, DATE=3/18/2013, DOSE=R788 IVit, ROUTE=OC, Start Time=1, End Time=4,
Exclusions=, Fit Method=BestFit, Selection=System
```

Listing 2: Phoenix WNL NCA Full Output

```
WinNonlin 8.2.0.4383
DATE=4/12/2012,DOSE=R406 Ph Cosol,ROUTE=OC,MATRIX=Vitreous

                                                    Date:    4/30/2020
                                                    Time:    08:52:22


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                      8.2.0.4383
                                Core Version 11Oct2017

Settings
--------
Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:   4
Dose time:      0.00
Dose amount:        0.00
Calculation method:  Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  User-specified lambda_z range,  Log regression
User's lambda_z bounds:      1.00,      4.00


Summary Table
-------------
      Time          Conc.       Pred.     Residual       AUC        AUMC       Weight
-------------------------------------------------------------------------------------
     0.0000 @     0.0000                              0.0000     0.0000
     0.5000        82.00                               20.50      10.25
      1.000 *      281.6       231.0       50.58      111.4      90.89        1.000
      2.000 *      170.0       228.8      -58.79      337.2      401.7        1.000
      4.000 *      247.8       224.4       23.36      755.0      1733.        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                                                4
Dose                                                0.0000
Rsq                                                 0.0031
Rsq_adjusted                                       -0.9938
Corr_XY                                            -0.0558
No_points_lambda_z                                       3
Lambda_z                                            0.0096
Lambda_z_intercept                                  5.4520
Lambda_z_lower                                      1.0000
Lambda_z_upper                                      4.0000
HL_Lambda_z                                        72.3290
Span                                                0.0415
Tlag                                                0.0000
Tmax                                                1.0000
Cmax                                              281.5667
Cmax_D                                             Missing
Tlast                                               4.0000
Clast                                             247.8000
```

Clast_pred	224.4436
AUClast	754.9750
AUClast_D	Missing
AUCall	754.9750
AUCINF_obs	26612.5675
AUCINF_D_obs	Missing
AUC_%Extrap_obs	97.1631
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	24175.3591
AUCINF_D_pred	Missing
AUC_%Extrap_pred	96.8771
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	1732.8750
AUMCINF_obs	2803367.8062
AUMC_%Extrap_obs	99.9382
AUMCINF_pred	2539299.5969
AUMC_%Extrap_pred	99.9318
MRTlast	2.2953
MRTINF_obs	105.3400
MRTINF_pred	105.0367
AUC0_4	754.9750

WinNonlin 8.2.0.4383
DATE=4/12/2012,DOSE=R788 PO,ROUTE=PO,MATRIX=Plasma

Date: 4/30/2020
Time: 08:52:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 4
Dose time: 0.00
Dose amount: 0.00
Calculation method: Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: User-specified lambda_z range, Log regression
User's lambda_z bounds: 1.00, 4.00

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000 @	0.0000			0.0000	0.0000	
0.5000	2010.			502.4	251.2	
1.000 *	388.5	342.0	46.47	1102.	599.5	1.000
2.000 *	117.7	142.4	-24.78	1355.	911.5	1.000
4.000 *	26.33	24.71	1.625	1499.	1252.	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	4
Dose	0.0000
Rsq	0.9844
Rsq_adjusted	0.9688
Corr_XY	-0.9922
No_points_lambda_z	3
Lambda_z	0.8759
Lambda_z_intercept	6.7108
Lambda_z_lower	1.0000
Lambda_z_upper	4.0000
HL_Lambda_z	0.7913
Span	3.7910
Tlag	0.0000
Tmax	0.5000
Cmax	2009.6667
Cmax_D	Missing
Tlast	4.0000
Clast	26.3333
Clast_pred	24.7081
AUClast	1499.0417
AUClast_D	Missing
AUCall	1499.0417
AUCINF_obs	1529.1054
AUCINF_D_obs	Missing
AUC_%Extrap_obs	1.9661
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	1527.2499
AUCINF_D_pred	Missing
AUC_%Extrap_pred	1.8470
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	1252.1250
AUMCINF_obs	1406.7023
AUMC_%Extrap_obs	10.9886
AUMCINF_pred	1397.1622
AUMC_%Extrap_pred	10.3808
MRTlast	0.8353
MRTINF_obs	0.9200
MRTINF_pred	0.9148
AUC0_4	1499.0417

WinNonlin 8.2.0.4383
DATE=4/12/2012,DOSE=R788 PO,ROUTE=PO,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383

Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 3
Dose time: 0.00
Dose amount: 0.00
Calculation method: Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: User-specified lambda_z range, Log regression
User's lambda_z bounds: 0.50, 2.00

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000 @	0.0000			0.0000	0.0000	
0.5000 *	164.0	119.0	45.03	41.00	20.50	1.000
1.000 *	41.33	66.90	-25.56	92.33	51.33	1.000
2.000 *	24.83	21.15	3.682	125.4	96.83	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	3
Dose	0.0000
Rsq	0.8109
Rsq_adjusted	0.6219
Corr_XY	-0.9005
No_points_lambda_z	3
Lambda_z	1.1515
Lambda_z_intercept	5.3546
Lambda_z_lower	0.5000
Lambda_z_upper	2.0000
HL_Lambda_z	0.6020
Span	2.4918
Tlag	0.0000
Tmax	0.5000
Cmax	164.0000
Cmax_D	Missing
Tlast	2.0000
Clast	24.8333
Clast_pred	21.1511
AUClast	125.4167
AUClast_D	Missing
AUCall	125.4167
AUCINF_obs	146.9835
AUCINF_D_obs	Missing
AUC_%Extrap_obs	14.6730
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	143.7857
AUCINF_D_pred	Missing

AUC_%Extrap_pred	12.7753
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	96.8333
AUMCINF_obs	158.6971
AUMC_%Extrap_obs	38.9823
AUMCINF_pred	149.5242
AUMC_%Extrap_pred	35.2390
MRTlast	0.7721
MRTINF_obs	1.0797
MRTINF_pred	1.0399
AUC0_4	143.8618

WinNonlin 8.2.0.4383
DATE=5/12/2012,DOSE=R406 Emu,ROUTE=OC,MATRIX=Plasma

Date: 4/30/2020
Time: 08:52:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 6
Dose time: 0.00
Dose amount: 0.00
Calculation method: Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: User-specified lambda_z range, Log regression
User's lambda_z bounds: 2.00, 24.00

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000 @	0.0000			0.0000	0.0000	
0.5000	112.3			28.08	14.04	
1.000	32.67			64.33	36.25	
2.000 *	30.00	18.35	11.65	95.67	82.58	1.000
4.000 *	15.33	16.44	-1.112	141.0	203.9	1.000
8.000 *	7.333	13.21	-5.877	186.3	443.9	1.000
24.00 *	6.500	5.501	0.9990	297.0	2161.	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	6
Dose	0.0000

Rsq	0.5908
Rsq_adjusted	0.3862
Corr_XY	-0.7686
No_points_lambda_z	4
Lambda_z	0.0548
Lambda_z_intercept	3.0190
Lambda_z_lower	2.0000
Lambda_z_upper	24.0000
HL_Lambda_z	12.6591
Span	1.7379
Tlag	0.0000
Tmax	0.5000
Cmax	112.3333
Cmax_D	Missing
Tlast	24.0000
Clast	6.5000
Clast_pred	5.5010
AUClast	297.0000
AUClast_D	Missing
AUCall	297.0000
AUCINF_obs	415.7113
AUCINF_D_obs	Missing
AUC_%Extrap_obs	28.5562
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	397.4654
AUCINF_D_pred	Missing
AUC_%Extrap_pred	25.2765
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	2161.2500
AUMCINF_obs	7178.3773
AUMC_%Extrap_obs	69.8922
AUMCINF_pred	6407.2482
AUMC_%Extrap_pred	66.2687
MRTlast	7.2769
MRTINF_obs	17.2677
MRTINF_pred	16.1203
AUC0_4	141.0000

WinNonlin 8.2.0.4383
DATE=5/12/2012,DOSE=R406 Emu,ROUTE=OC,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 5
Dose time: 0.00
Dose amount: 0.00
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	33.67			8.417	4.208	
1.000	28.67			24.00	15.58	
2.000	20.67			48.67	50.58	
4.000	15.67			85.00	154.6	
8.000	37.00			190.3	871.9	

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

*) Starred values were included in the estimation of Lambda_z.

*** Warning 14530: Lambda_z could not be estimated.
No parameters could be extrapolated to infinity.

Final Parameters

N_Samples	5
Dose	0.0000
Rsq	Missing
Rsq_adjusted	Missing
Corr_XY	Missing
No_points_lambda_z	0
Lambda_z	Missing
Lambda_z_intercept	Missing
Lambda_z_lower	Missing
Lambda_z_upper	Missing
HL_Lambda_z	Missing
Span	Missing
Tlag	0.0000
Tmax	8.0000
Cmax	37.0000
Cmax_D	Missing
Tlast	8.0000
Clast	37.0000
Clast_pred	Missing
AUClast	190.3333
AUClast_D	Missing
AUCall	190.3333
AUCINF_obs	Missing
AUCINF_D_obs	Missing
AUC_%Extrap_obs	Missing
Vz_F_obs	Missing
Cl_F_obs	Missing
AUCINF_pred	Missing
AUCINF_D_pred	Missing
AUC_%Extrap_pred	Missing
Vz_F_pred	Missing
Cl_F_pred	Missing
AUMClast	871.9167
AUMCINF_obs	Missing

AUMC_%Extrap_obs	Missing
AUMCINF_pred	Missing
AUMC_%Extrap_pred	Missing
MRTlast	4.5810
MRTINF_obs	Missing
MRTINF_pred	Missing
AUC0_4	85.0000

WinNonlin 8.2.0.4383
DATE=5/12/2012,DOSE=R406 Ph Cosol,ROUTE=OC,MATRIX=Plasma

Date: 4/30/2020
Time: 08:52:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 2
Dose time: 0.00
Dose amount: 0.00
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	79.00			19.75	9.875	
1.000	13.67			42.92	23.17	

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

*) Starred values were included in the estimation of Lambda_z.

*** Warning 14530: Lambda_z could not be estimated.
No parameters could be extrapolated to infinity.

Final Parameters

N_Samples	2
Dose	0.0000
Rsq	Missing
Rsq_adjusted	Missing
Corr_XY	Missing
No_points_lambda_z	0
Lambda_z	Missing
Lambda_z_intercept	Missing
Lambda_z_lower	Missing

Lambda_z_upper	Missing
HL_Lambda_z	Missing
Span	Missing
Tlag	0.0000
Tmax	0.5000
Cmax	79.0000
Cmax_D	Missing
Tlast	1.0000
Clast	13.6667
Clast_pred	Missing
AUClast	42.9167
AUClast_D	Missing
AUCall	42.9167
AUCINF_obs	Missing
AUCINF_D_obs	Missing
AUC_%Extrap_obs	Missing
Vz_F_obs	Missing
Cl_F_obs	Missing
AUCINF_pred	Missing
AUCINF_D_pred	Missing
AUC_%Extrap_pred	Missing
Vz_F_pred	Missing
Cl_F_pred	Missing
AUMClast	23.1667
AUMCINF_obs	Missing
AUMC_%Extrap_obs	Missing
AUMCINF_pred	Missing
AUMC_%Extrap_pred	Missing
MRTlast	0.5398
MRTINF_obs	Missing
MRTINF_pred	Missing
AUC0_4	Missing

WinNonlin 8.2.0.4383
DATE=5/12/2012,DOSE=R406 Ph Cosol,ROUTE=OC,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 3
Dose time: 0.00
Dose amount: 0.00
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	41.33	10.33	5.167
1.000	13.33	24.00	13.67
2.000	6.000	33.67	26.33

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

*) Starred values were included in the estimation of Lambda_z.

*** Warning 14530: Lambda_z could not be estimated.
No parameters could be extrapolated to infinity.

Final Parameters

N_Samples	3
Dose	0.0000
Rsq	Missing
Rsq_adjusted	Missing
Corr_XY	Missing
No_points_lambda_z	0
Lambda_z	Missing
Lambda_z_intercept	Missing
Lambda_z_lower	Missing
Lambda_z_upper	Missing
HL_Lambda_z	Missing
Span	Missing
Tlag	0.0000
Tmax	0.5000
Cmax	41.3333
Cmax_D	Missing
Tlast	2.0000
Clast	6.0000
Clast_pred	Missing
AUClast	33.6667
AUClast_D	Missing
AUCall	33.6667
AUCINF_obs	Missing
AUCINF_D_obs	Missing
AUC_%Extrap_obs	Missing
Vz_F_obs	Missing
Cl_F_obs	Missing
AUCINF_pred	Missing
AUCINF_D_pred	Missing
AUC_%Extrap_pred	Missing
Vz_F_pred	Missing
Cl_F_pred	Missing
AUMClast	26.3333
AUMCINF_obs	Missing
AUMC_%Extrap_obs	Missing
AUMCINF_pred	Missing
AUMC_%Extrap_pred	Missing
MRTlast	0.7822
MRTINF_obs	Missing
MRTINF_pred	Missing
AUC0_4	Missing

```
WinNonlin 8.2.0.4383
DATE=7/20/2012,DOSE=R406 Emu,ROUTE=OC,MATRIX=Plasma

                                                    Date:    4/30/2020
                                                    Time:    08:52:26


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                    8.2.0.4383
                                Core Version 11Oct2017

Settings
--------
Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:   3
Dose time:      0.00
Dose amount:         0.00
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        118.6                               29.65      14.83
      1.000        65.88                               75.77      46.12
      2.000        20.11                               118.8      99.17


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

*) Starred values were included in the estimation of Lambda_z.


*** Warning 14530: Lambda_z could not be estimated.
No parameters could be extrapolated to infinity.

Final Parameters
----------------
N_Samples                                            3
Dose                                            0.0000
Rsq                                            Missing
Rsq_adjusted                                   Missing
Corr_XY                                        Missing
No_points_lambda_z                                   0
Lambda_z                                       Missing
Lambda_z_intercept                             Missing
Lambda_z_lower                                 Missing
Lambda_z_upper                                 Missing
HL_Lambda_z                                    Missing
Span                                           Missing
Tlag                                            0.0000
Tmax                                            0.5000
Cmax                                          118.6040
Cmax_D                                         Missing
Tlast                                           2.0000
```

Clast	20.1063
Clast_pred	Missing
AUClast	118.7644
AUClast_D	Missing
AUCall	118.7644
AUCINF_obs	Missing
AUCINF_D_obs	Missing
AUC_%Extrap_obs	Missing
Vz_F_obs	Missing
Cl_F_obs	Missing
AUCINF_pred	Missing
AUCINF_D_pred	Missing
AUC_%Extrap_pred	Missing
Vz_F_pred	Missing
Cl_F_pred	Missing
AUMClast	99.1666
AUMCINF_obs	Missing
AUMC_%Extrap_obs	Missing
AUMCINF_pred	Missing
AUMC_%Extrap_pred	Missing
MRTlast	0.8350
MRTINF_obs	Missing
MRTINF_pred	Missing
AUC0_4	Missing

WinNonlin 8.2.0.4383
DATE=7/20/2012,DOSE=R406 Emu,ROUTE=OC,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 4
Dose time: 0.00
Dose amount: 0.00
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	169.1			42.28	21.14	
1.000	74.12			103.1	60.81	
2.000	105.2			192.8	203.1	
4.000	131.8			429.8	940.7	

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

*) Starred values were included in the estimation of Lambda_z.

*** Warning 14530: Lambda_z could not be estimated.
No parameters could be extrapolated to infinity.

Final Parameters

N_Samples	4
Dose	0.0000
Rsq	Missing
Rsq_adjusted	Missing
Corr_XY	Missing
No_points_lambda_z	0
Lambda_z	Missing
Lambda_z_intercept	Missing
Lambda_z_lower	Missing
Lambda_z_upper	Missing
HL_Lambda_z	Missing
Span	Missing
Tlag	0.0000
Tmax	0.5000
Cmax	169.1297
Cmax_D	Missing
Tlast	4.0000
Clast	131.7948
Clast_pred	Missing
AUClast	429.7762
AUClast_D	Missing
AUCall	429.7762
AUCINF_obs	Missing
AUCINF_D_obs	Missing
AUC_%Extrap_obs	Missing
Vz_F_obs	Missing
Cl_F_obs	Missing
AUCINF_pred	Missing
AUCINF_D_pred	Missing
AUC_%Extrap_pred	Missing
Vz_F_pred	Missing
Cl_F_pred	Missing
AUMClast	940.7075
AUMCINF_obs	Missing
AUMC_%Extrap_obs	Missing
AUMCINF_pred	Missing
AUMC_%Extrap_pred	Missing
MRTlast	2.1888
MRTINF_obs	Missing
MRTINF_pred	Missing
AUC0_4	429.7762

WinNonlin 8.2.0.4383
DATE=7/20/2012,DOSE=R406 Ph Cosol,ROUTE=OC,MATRIX=Plasma

Date: 4/30/2020
Time: 08:52:22

```
                WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                             8.2.0.4383
                        Core Version 11Oct2017

Settings
--------
Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:   1
Dose time:      0.00
Dose amount:        0.00
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        22.28                           5.570      2.785


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

*) Starred values were included in the estimation of Lambda_z.


*** Warning 14530: Lambda_z could not be estimated.
No parameters could be extrapolated to infinity.

Final Parameters
----------------
N_Samples                                          1
Dose                                          0.0000
Rsq                                          Missing
Rsq_adjusted                                 Missing
Corr_XY                                      Missing
No_points_lambda_z                                 0
Lambda_z                                     Missing
Lambda_z_intercept                           Missing
Lambda_z_lower                               Missing
Lambda_z_upper                               Missing
HL_Lambda_z                                  Missing
Span                                         Missing
Tlag                                          0.0000
Tmax                                          0.5000
Cmax                                         22.2793
Cmax_D                                       Missing
Tlast                                         0.5000
Clast                                        22.2793
Clast_pred                                   Missing
AUClast                                       5.5698
AUClast_D                                    Missing
AUCall                                        5.5698
AUCINF_obs                                   Missing
AUCINF_D_obs                                 Missing
AUC_%Extrap_obs                              Missing
Vz_F_obs                                     Missing
```

Cl_F_obs	Missing
AUCINF_pred	Missing
AUCINF_D_pred	Missing
AUC_%Extrap_pred	Missing
Vz_F_pred	Missing
Cl_F_pred	Missing
AUMClast	2.7849
AUMCINF_obs	Missing
AUMC_%Extrap_obs	Missing
AUMCINF_pred	Missing
AUMC_%Extrap_pred	Missing
MRTlast	0.5000
MRTINF_obs	Missing
MRTINF_pred	Missing
AUC0_4	Missing

WinNonlin 8.2.0.4383
DATE=7/20/2012,DOSE=R406 Ph Cosol,ROUTE=OC,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 0
Dose time: 0.00
Dose amount: 0.00
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
No data used.						

Final Parameters

N_Samples	0
Flag_N_Samples	Insufficient
Dose	0.0000
Rsq	Missing
Rsq_adjusted	Missing
Flag_Rsq_adjusted	Missing
Corr_XY	Missing
No_points_lambda_z	Missing
Lambda_z	Missing
Lambda_z_intercept	Missing
Lambda_z_lower	Missing
Lambda_z_upper	Missing

HL_Lambda_z	Missing
Span	Missing
Tlag	Missing
Tmax	Missing
Cmax	Missing
Cmax_D	Missing
Tlast	Missing
Clast	Missing
Clast_pred	Missing
AUClast	Missing
AUClast_D	Missing
AUCall	Missing
AUCINF_obs	Missing
AUCINF_D_obs	Missing
AUC_%Extrap_obs	Missing
Vz_F_obs	Missing
Cl_F_obs	Missing
AUCINF_pred	Missing
AUCINF_D_pred	Missing
AUC_%Extrap_pred	Missing
Vz_F_pred	Missing
Cl_F_pred	Missing
AUMClast	Missing
AUMCINF_obs	Missing
AUMC_%Extrap_obs	Missing
AUMCINF_pred	Missing
AUMC_%Extrap_pred	Missing
MRTlast	Missing
MRTINF_obs	Missing
MRTINF_pred	Missing
AUC0_4	Missing

WinNonlin 8.2.0.4383
DATE=7/24/2012,DOSE=R406 Ph DMSO,ROUTE=OC,MATRIX=Plasma

Date: 4/30/2020
Time: 08:52:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 4
Dose time: 0.00
Dose amount: 0.00
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		370.2			92.56	46.28	
1.000	*	45.62	53.76	-8.141	196.5	104.0	1.000
2.000	*	43.88	34.30	9.578	241.3	170.7	1.000
4.000	*	12.86	13.96	-1.100	298.0	309.9	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	4
Dose	0.0000
Rsq	0.9090
Rsq_adjusted	0.8181
Corr_XY	-0.9534
No_points_lambda_z	3
Lambda_z	0.4495
Lambda_z_intercept	4.4341
Lambda_z_lower	1.0000
Lambda_z_upper	4.0000
HL_Lambda_z	1.5422
Span	1.9453
Tlag	0.0000
Tmax	0.5000
Cmax	370.2293
Cmax_D	Missing
Tlast	4.0000
Clast	12.8603
Clast_pred	13.9606
AUClast	298.0112
AUClast_D	Missing
AUCall	298.0112
AUCINF_obs	326.6240
AUCINF_D_obs	Missing
AUC_%Extrap_obs	8.7602
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	329.0719
AUCINF_D_pred	Missing
AUC_%Extrap_pred	9.4389
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	309.8529
AUMCINF_obs	487.9643
AUMC_%Extrap_obs	36.5009
AUMCINF_pred	503.2023
AUMC_%Extrap_pred	38.4238
MRTlast	1.0397
MRTINF_obs	1.4940
MRTINF_pred	1.5292
AUC0_4	298.0112

WinNonlin 8.2.0.4383
DATE=7/24/2012,DOSE=R406 Ph DMSO,ROUTE=OC,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 5
Dose time: 0.00
Dose amount: 0.00
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	892.2			223.0	111.5	
1.000	282.4			516.7	293.7	
2.000 *	561.8	706.1	-144.3	938.8	996.7	1.000
4.000 *	456.5	324.0	132.5	1957.	3946.	1.000
8.000 *	60.85	68.21	-7.368	2992.	8572.	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	5
Dose	0.0000
Rsq	0.9393
Rsq_adjusted	0.8787
Corr_XY	-0.9692
No_points_lambda_z	3
Lambda_z	0.3895
Lambda_z_intercept	7.3388
Lambda_z_lower	2.0000
Lambda_z_upper	8.0000
HL_Lambda_z	1.7795
Span	3.3718
Tlag	0.0000
Tmax	0.5000
Cmax	892.1753
Cmax_D	Missing
Tlast	8.0000
Clast	60.8467
Clast_pred	68.2145
AUClast	2991.9132
AUClast_D	Missing

AUCall	2991.9132
AUCINF_obs	3148.1220
AUCINF_D_obs	Missing
AUC_%Extrap_obs	4.9620
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	3167.0370
AUCINF_D_pred	Missing
AUC_%Extrap_pred	5.5296
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	8572.1733
AUMCINF_obs	10222.8703
AUMC_%Extrap_obs	16.1471
AUMCINF_pred	10422.7496
AUMC_%Extrap_pred	17.7552
MRTlast	2.8651
MRTINF_obs	3.2473
MRTINF_pred	3.2910
AUC0_4	1957.1719

WinNonlin 8.2.0.4383
DATE=8/29/2012,DOSE=R788 Cosol,ROUTE=OC,MATRIX=Plasma

Date: 4/30/2020
Time: 08:52:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 2
Dose time: 0.00
Dose amount: 0.00
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	574.2			143.6	71.78	
1.000	75.11			305.9	162.3	

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

*) Starred values were included in the estimation of Lambda_z.

*** Warning 14530: Lambda_z could not be estimated.

No parameters could be extrapolated to infinity.

Final Parameters

N_Samples	2
Dose	0.0000
Rsq	Missing
Rsq_adjusted	Missing
Corr_XY	Missing
No_points_lambda_z	0
Lambda_z	Missing
Lambda_z_intercept	Missing
Lambda_z_lower	Missing
Lambda_z_upper	Missing
HL_Lambda_z	Missing
Span	Missing
Tlag	0.0000
Tmax	0.5000
Cmax	574.2047
Cmax_D	Missing
Tlast	1.0000
Clast	75.1097
Clast_pred	Missing
AUClast	305.8798
AUClast_D	Missing
AUCall	305.8798
AUCINF_obs	Missing
AUCINF_D_obs	Missing
AUC_%Extrap_obs	Missing
Vz_F_obs	Missing
Cl_F_obs	Missing
AUCINF_pred	Missing
AUCINF_D_pred	Missing
AUC_%Extrap_pred	Missing
Vz_F_pred	Missing
Cl_F_pred	Missing
AUMClast	162.3286
AUMCINF_obs	Missing
AUMC_%Extrap_obs	Missing
AUMCINF_pred	Missing
AUMC_%Extrap_pred	Missing
MRTlast	0.5307
MRTINF_obs	Missing
MRTINF_pred	Missing
AUC0_4	Missing

WinNonlin 8.2.0.4383
DATE=8/29/2012,DOSE=R788 Cosol,ROUTE=OC,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

```
--------
Model: Plasma Data, Extravascular Administration
Number of nonmissing observations:  5
Dose time:      0.00
Dose amount:        0.00
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        968.6                              242.1      121.1
      1.000 *      175.9       85.06      90.84       528.3      286.1       1.000
      2.000 *      60.43       70.45     -10.02       646.4      434.5       1.000
      4.000 *      17.06       48.33     -31.27       723.9      623.6       1.000
      8.000 *      36.32       22.74      13.58       830.7      1341.       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                                                5
Dose                                                     0.0000
Rsq                                                      0.3550
Rsq_adjusted                                             0.0324
Corr_XY                                                 -0.5958
No_points_lambda_z                                       4
Lambda_z                                                 0.1884
Lambda_z_intercept                                       4.6318
Lambda_z_lower                                           1.0000
Lambda_z_upper                                           8.0000
HL_Lambda_z                                              3.6783
Span                                                     1.9031
Tlag                                                     0.0000
Tmax                                                     0.5000
Cmax                                                   968.5560
Cmax_D                                                 Missing
Tlast                                                    8.0000
Clast                                                   36.3233
Clast_pred                                              22.7422
AUClast                                                830.6629
AUClast_D                                              Missing
AUCall                                                 830.6629
AUCINF_obs                                            1023.4184
AUCINF_D_obs                                           Missing
AUC_%Extrap_obs                                         18.8345
Vz_F_obs                                                 0.0000
Cl_F_obs                                                 0.0000
AUCINF_pred                                            951.3478
AUCINF_D_pred                                          Missing
AUC_%Extrap_pred                                        12.6857
Vz_F_pred                                                0.0000
```

Cl_F_pred	0.0000
AUMClast	1341.2101
AUMCINF_obs	3906.1417
AUMC_%Extrap_obs	65.6641
AUMCINF_pred	2947.1228
AUMC_%Extrap_pred	54.4909
MRTlast	1.6146
MRTINF_obs	3.8168
MRTINF_pred	3.0978
AUC0_4	723.9026

WinNonlin 8.2.0.4383
DATE=9/27/2012,DOSE=R788 Suspension,ROUTE=OC,MATRIX=Plasma

Date: 4/30/2020
Time: 08:52:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 4
Dose time: 0.00
Dose amount: 0.00
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	2907.			726.6	363.3	
1.000 *	369.6	216.7	153.0	1546.	819.0	1.000
2.000 *	43.70	97.36	-53.67	1752.	1048.	1.000
4.000 *	25.68	19.66	6.019	1822.	1238.	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	4
Dose	0.0000
Rsq	0.7494
Rsq_adjusted	0.4988
Corr_XY	-0.8657
No_points_lambda_z	3
Lambda_z	0.7999

Lambda_z_intercept	6.1782
Lambda_z_lower	1.0000
Lambda_z_upper	4.0000
HL_Lambda_z	0.8665
Span	3.4620
Tlag	0.0000
Tmax	0.5000
Cmax	2906.5783
Cmax_D	Missing
Tlast	4.0000
Clast	25.6797
Clast_pred	19.6609
AUClast	1821.7263
AUClast_D	Missing
AUCall	1821.7263
AUCINF_obs	1853.8298
AUCINF_D_obs	Missing
AUC_%Extrap_obs	1.7317
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	1846.3054
AUCINF_D_pred	Missing
AUC_%Extrap_pred	1.3313
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	1237.6632
AUMCINF_obs	1406.2114
AUMC_%Extrap_obs	11.9860
AUMCINF_pred	1366.7073
AUMC_%Extrap_pred	9.4420
MRTlast	0.6794
MRTINF_obs	0.7585
MRTINF_pred	0.7402
AUC0_4	1821.7263

WinNonlin 8.2.0.4383
DATE=9/27/2012,DOSE=R788 Suspension,ROUTE=OC,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 4
Dose time: 0.00
Dose amount: 0.00
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		267.3			66.82	33.41	
1.000	*	103.8	115.7	-11.88	159.6	92.77	1.000
2.000	*	116.8	99.26	17.52	269.9	261.5	1.000
4.000	*	69.21	73.07	-3.854	455.9	771.9	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	4
Dose	0.0000
Rsq	0.7271
Rsq_adjusted	0.4541
Corr_XY	-0.8527
No_points_lambda_z	3
Lambda_z	0.1532
Lambda_z_intercept	4.9042
Lambda_z_lower	1.0000
Lambda_z_upper	4.0000
HL_Lambda_z	4.5247
Span	0.6630
Tlag	0.0000
Tmax	0.5000
Cmax	267.2687
Cmax_D	Missing
Tlast	4.0000
Clast	69.2143
Clast_pred	73.0685
AUClast	455.8887
AUClast_D	Missing
AUCall	455.8887
AUCINF_obs	907.7032
AUCINF_D_obs	Missing
AUC_%Extrap_obs	49.7756
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	932.8623
AUCINF_D_pred	Missing
AUC_%Extrap_pred	51.1301
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	771.8945
AUMCINF_obs	5528.4899
AUMC_%Extrap_obs	86.0379
AUMCINF_pred	5793.3581
AUMC_%Extrap_pred	86.6762
MRTlast	1.6932
MRTINF_obs	6.0906
MRTINF_pred	6.2103
AUC0_4	455.8887

WinNonlin 8.2.0.4383
DATE=3/18/2013,DOSE=R788 IVit,ROUTE=OC,MATRIX=Vitreous

Date: 4/30/2020
Time: 08:52:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.2.0.4383
Core Version 11Oct2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 4
Dose time: 0.00
Dose amount: 0.00
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	1213.			303.2	151.6	
1.000 *	546.9	495.4	51.46	743.1	439.9	1.000
2.000 *	149.9	173.9	-23.96	1092.	863.3	1.000
4.000 *	22.51	21.42	1.085	1264.	1253.	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	4
Dose	0.0000
Rsq	0.9934
Rsq_adjusted	0.9867
Corr_XY	-0.9967
No_points_lambda_z	3
Lambda_z	1.0470
Lambda_z_intercept	7.2524
Lambda_z_lower	1.0000
Lambda_z_upper	4.0000
HL_Lambda_z	0.6621
Span	4.5314
Tlag	0.0000
Tmax	0.5000
Cmax	1212.8200
Cmax_D	Missing
Tlast	4.0000
Clast	22.5100
Clast_pred	21.4247

Ocular PK of (Fos)tamatinib – WNL TLFs

AUClast	1264.0050
AUClast_D	Missing
AUCall	1264.0050
AUCINF_obs	1285.5053
AUCINF_D_obs	Missing
AUC_%Extrap_obs	1.6725
Vz_F_obs	0.0000
Cl_F_obs	0.0000
AUCINF_pred	1284.4687
AUCINF_D_pred	Missing
AUC_%Extrap_pred	1.5932
Vz_F_pred	0.0000
Cl_F_pred	0.0000
AUMClast	1253.2400
AUMCINF_obs	1359.7768
AUMC_%Extrap_obs	7.8349
AUMCINF_pred	1354.6404
AUMC_%Extrap_pred	7.4854
MRTlast	0.9915
MRTINF_obs	1.0578
MRTINF_pred	1.0546
AUC0_4	1264.0050

Figure 1: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

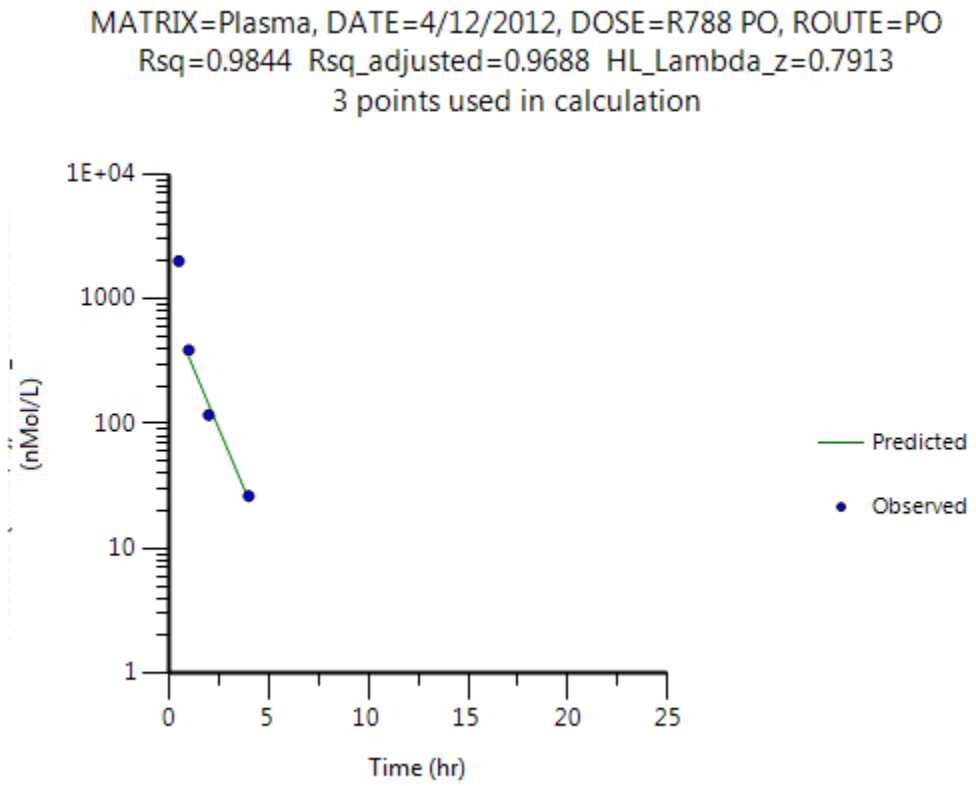

Figure 2: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

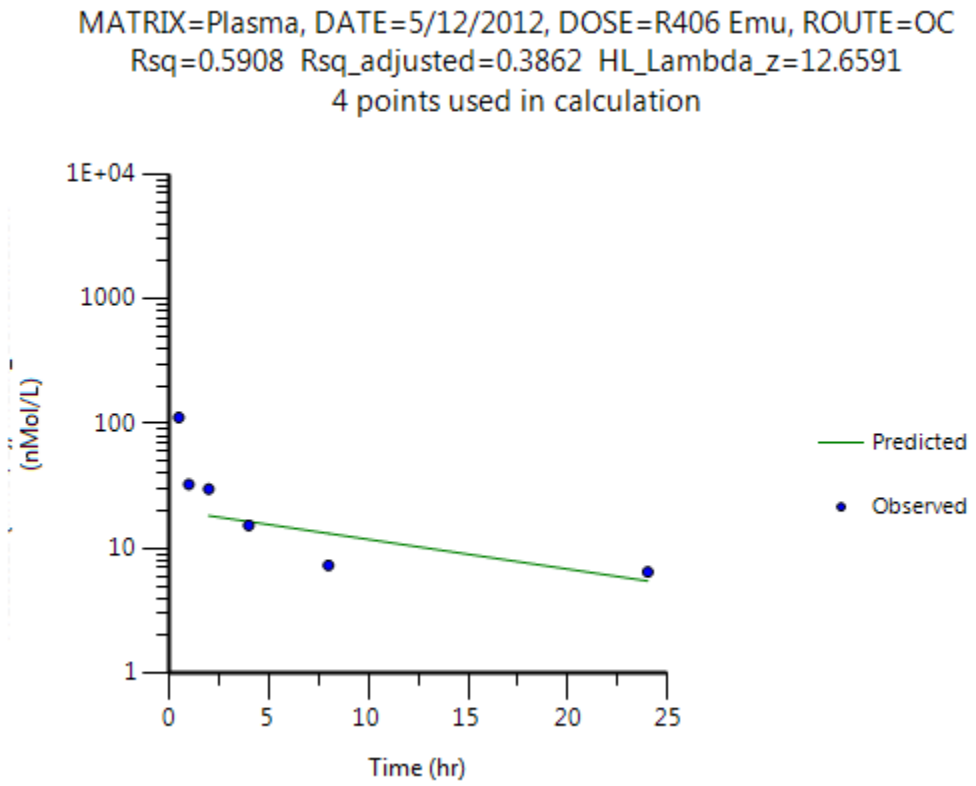

Figure 3: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

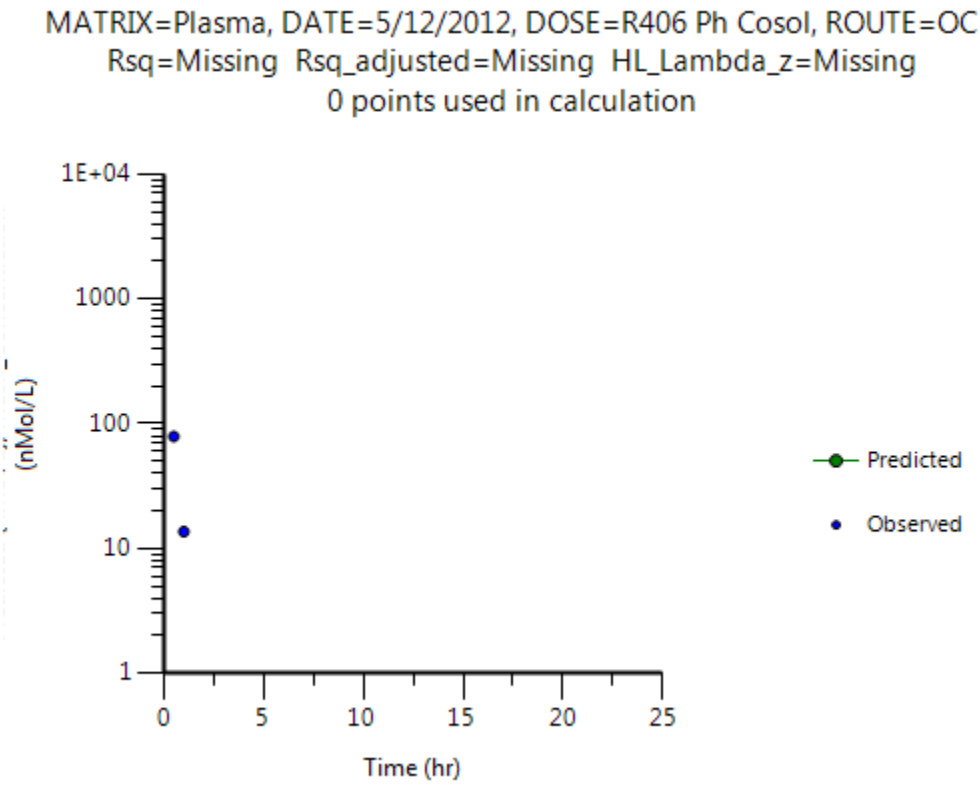

Figure 4: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

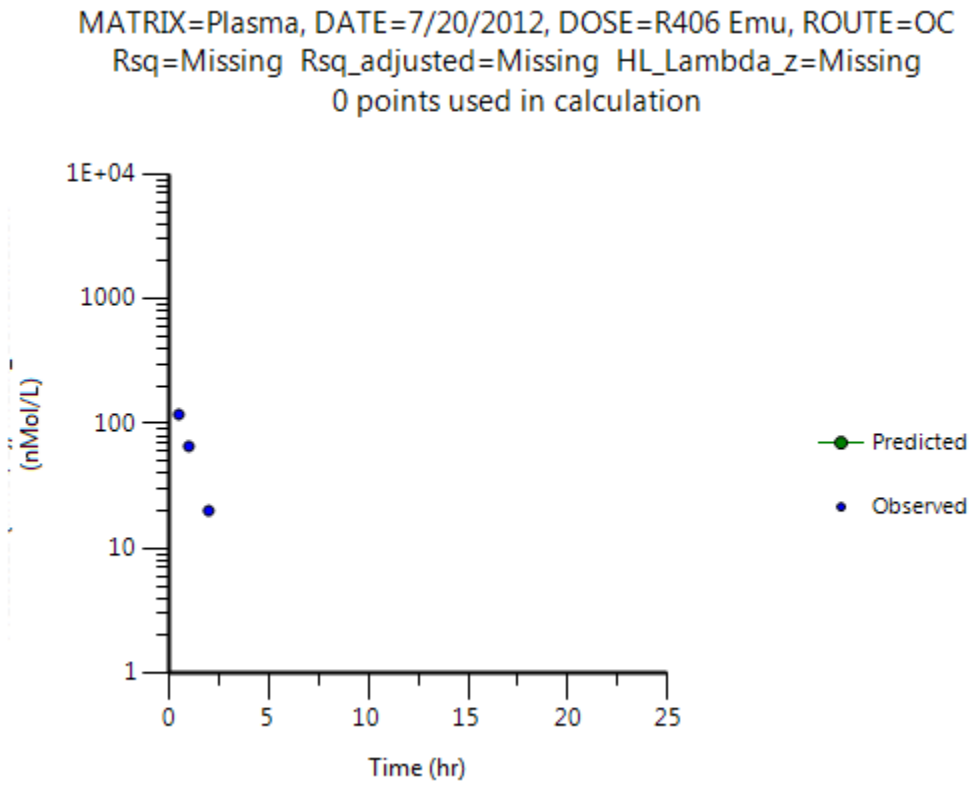

Figure 5: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

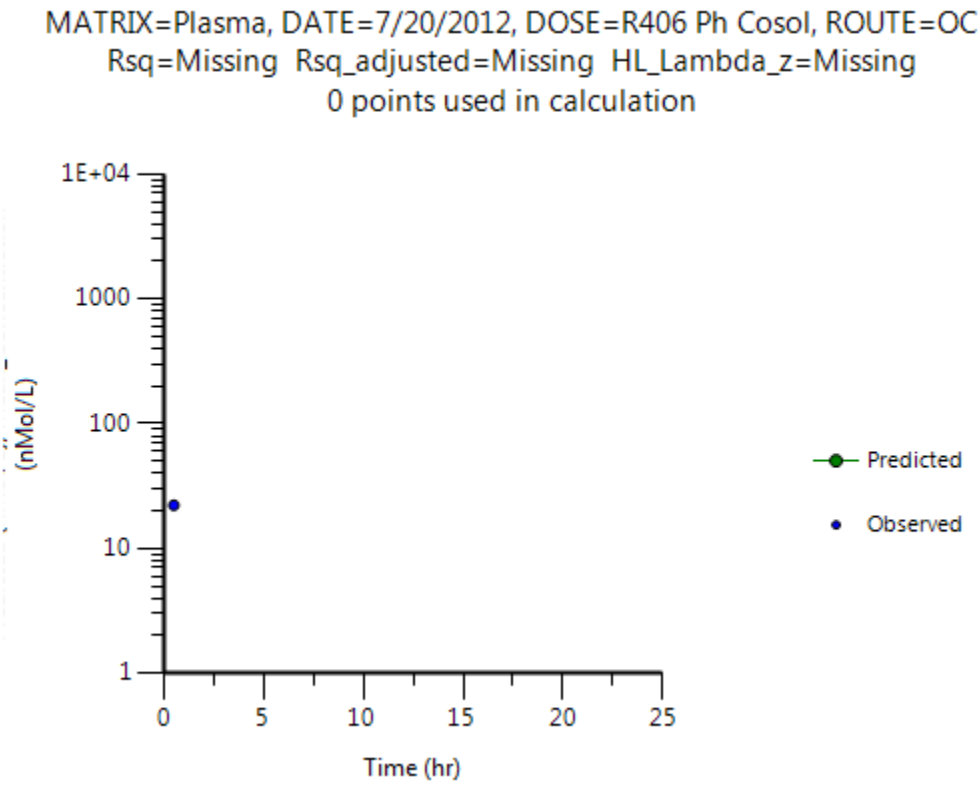

Figure 6: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

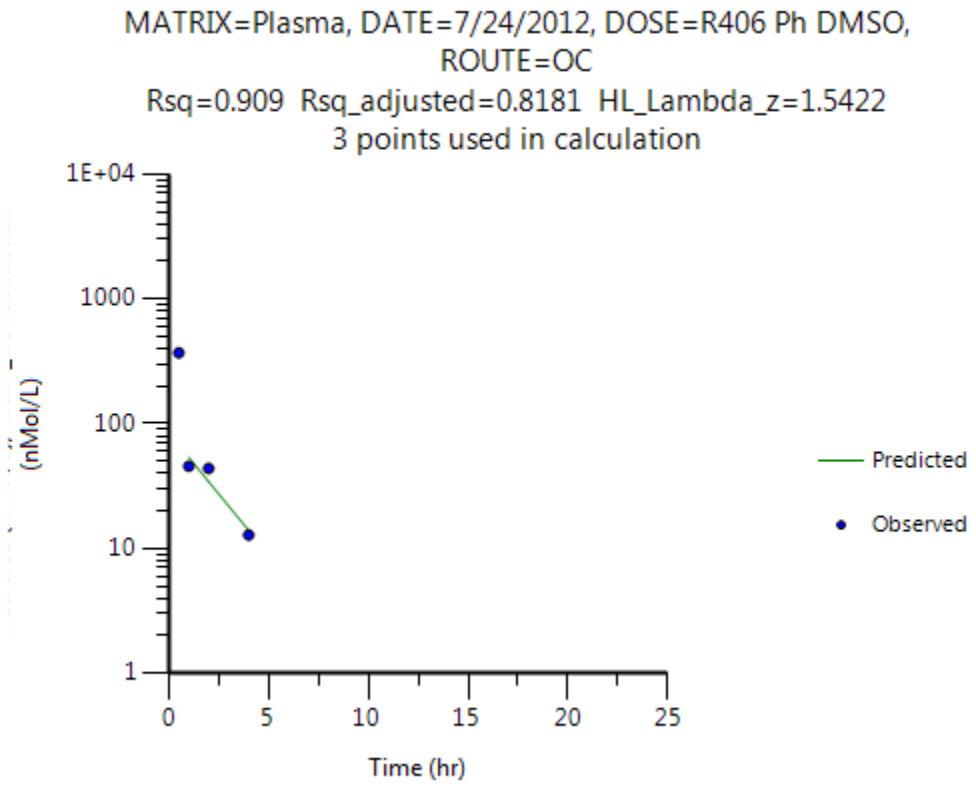

Figure 7: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

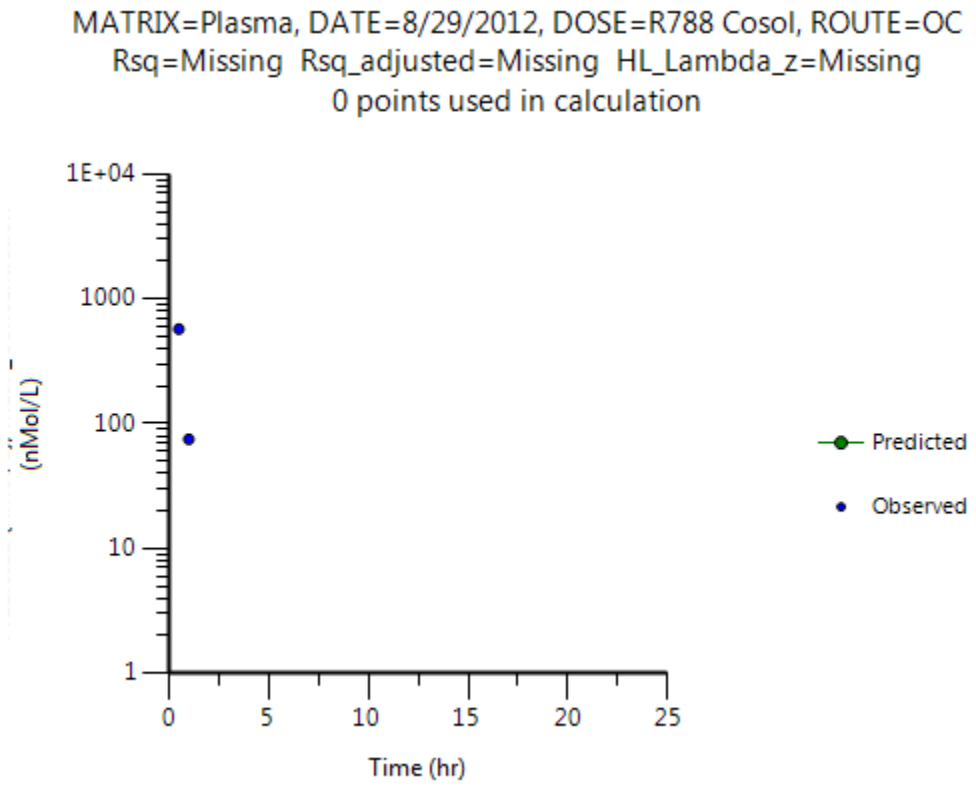

Figure 8: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

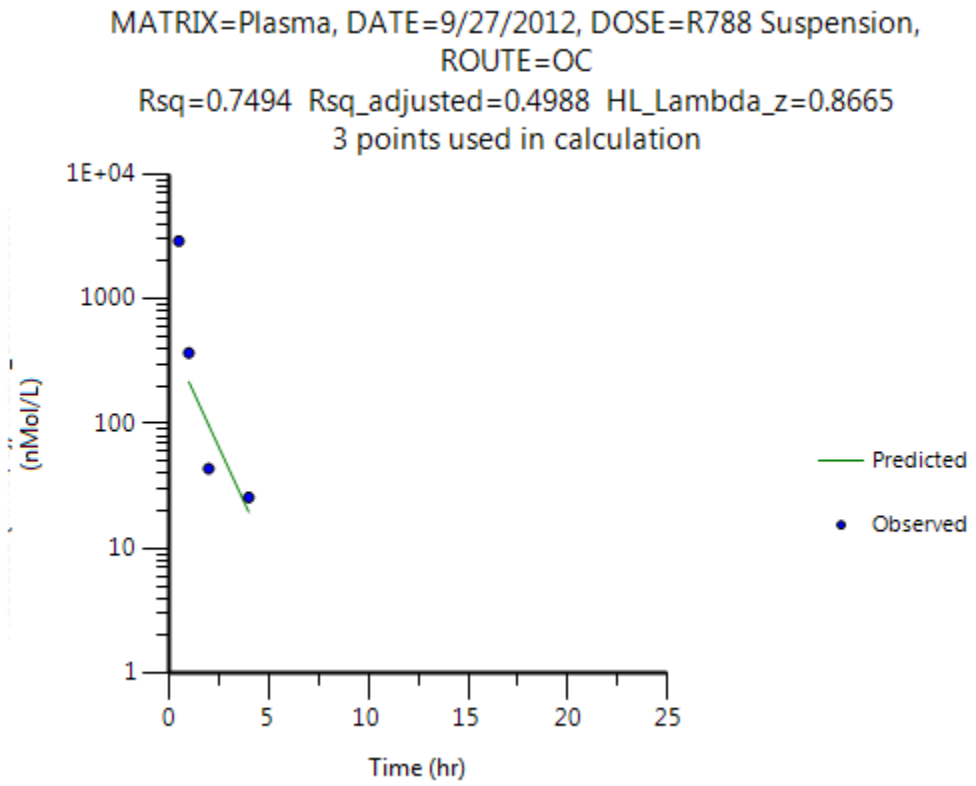

Figure 9: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

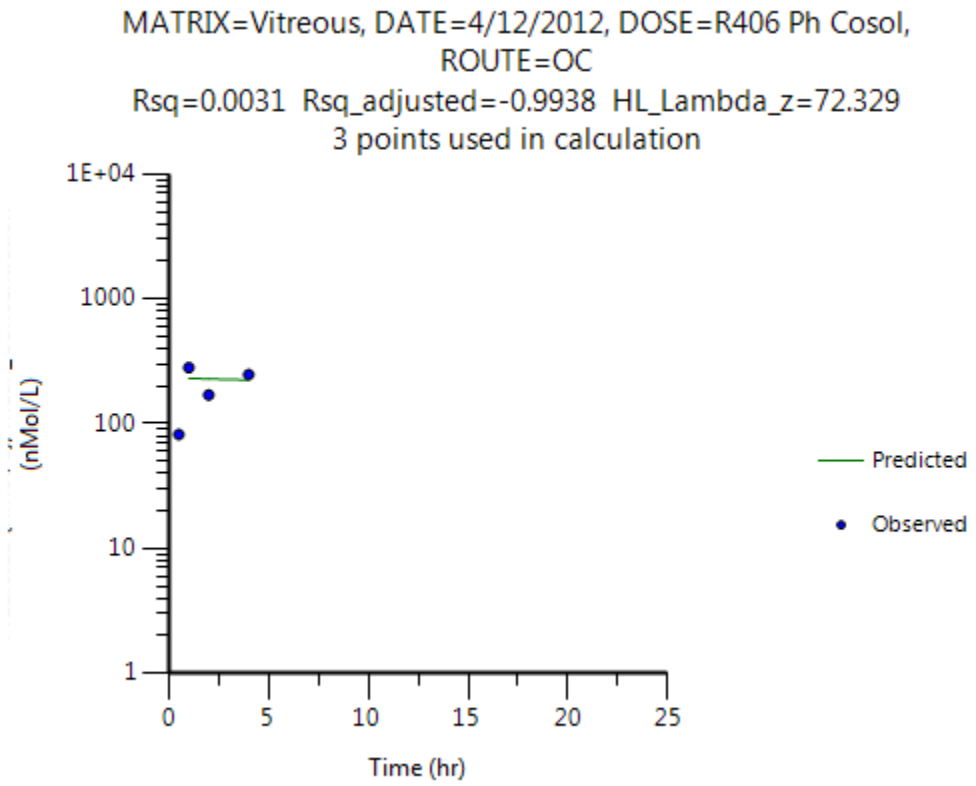

Figure 10: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

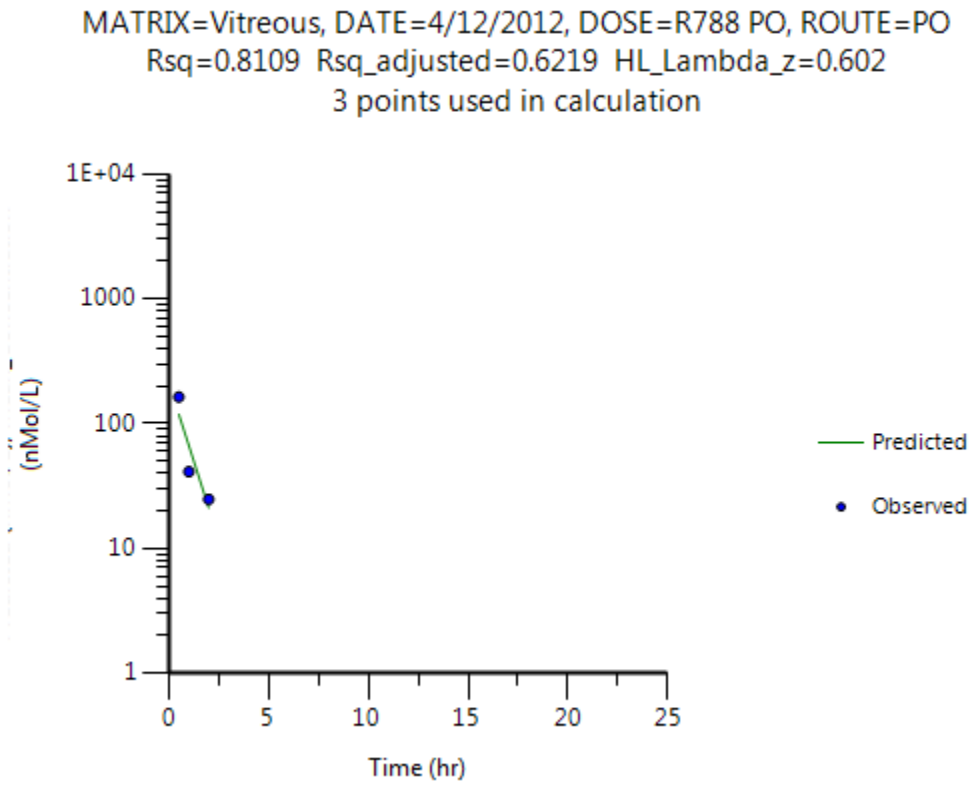

Figure 11: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

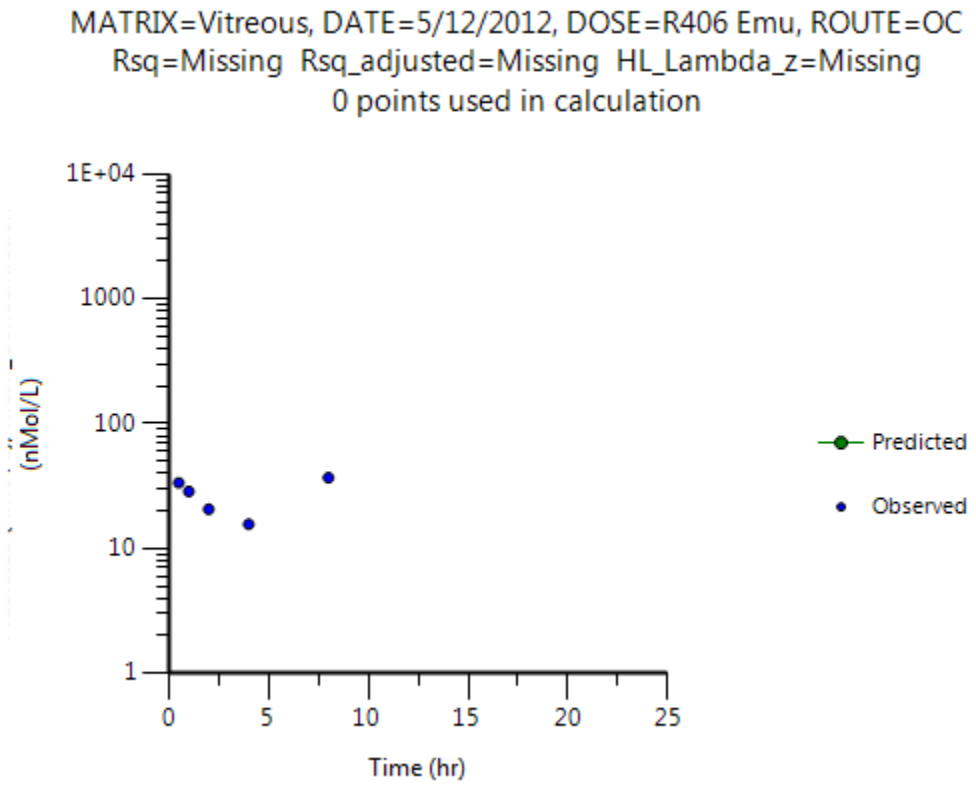

Figure 12: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

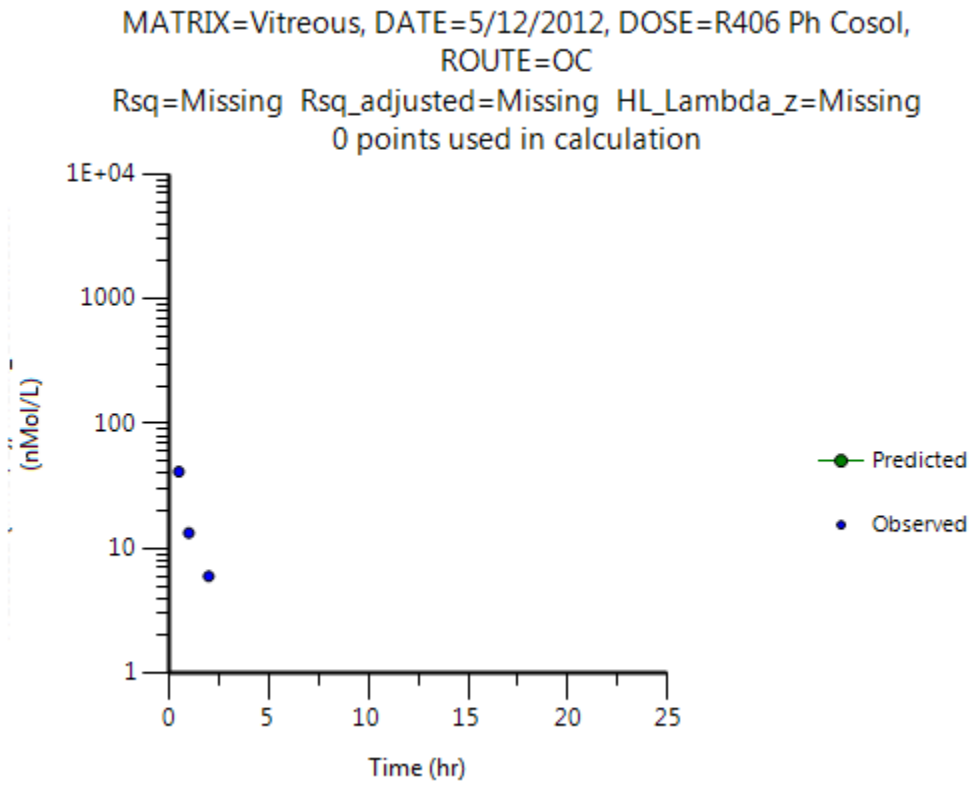

Figure 13: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

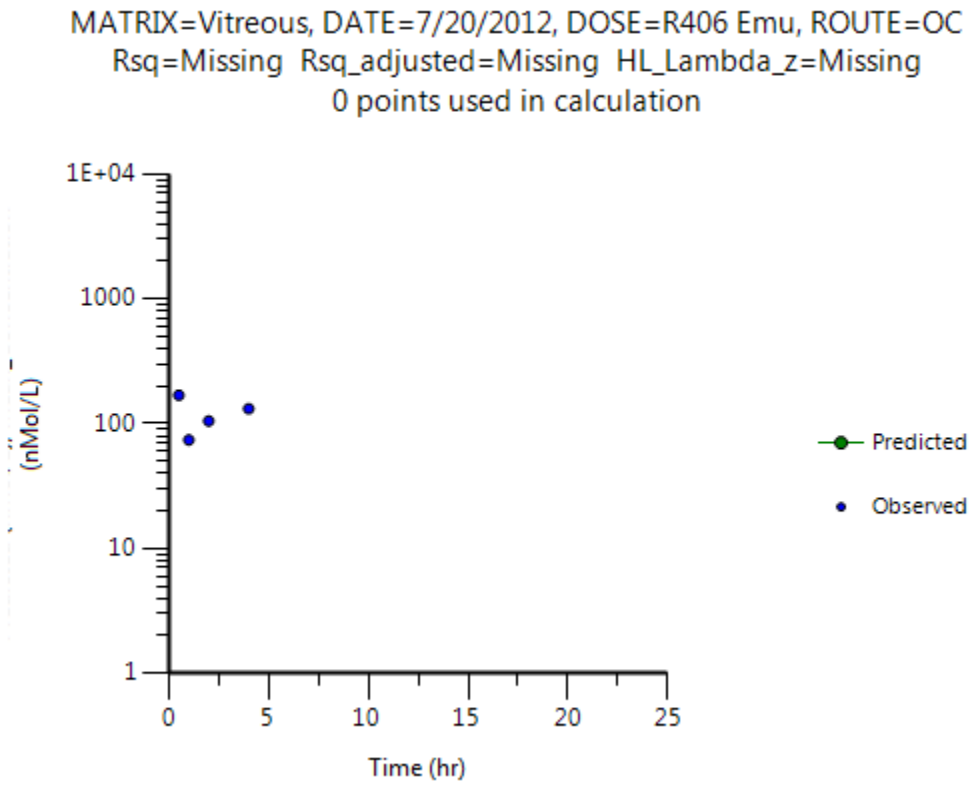

Figure 14: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

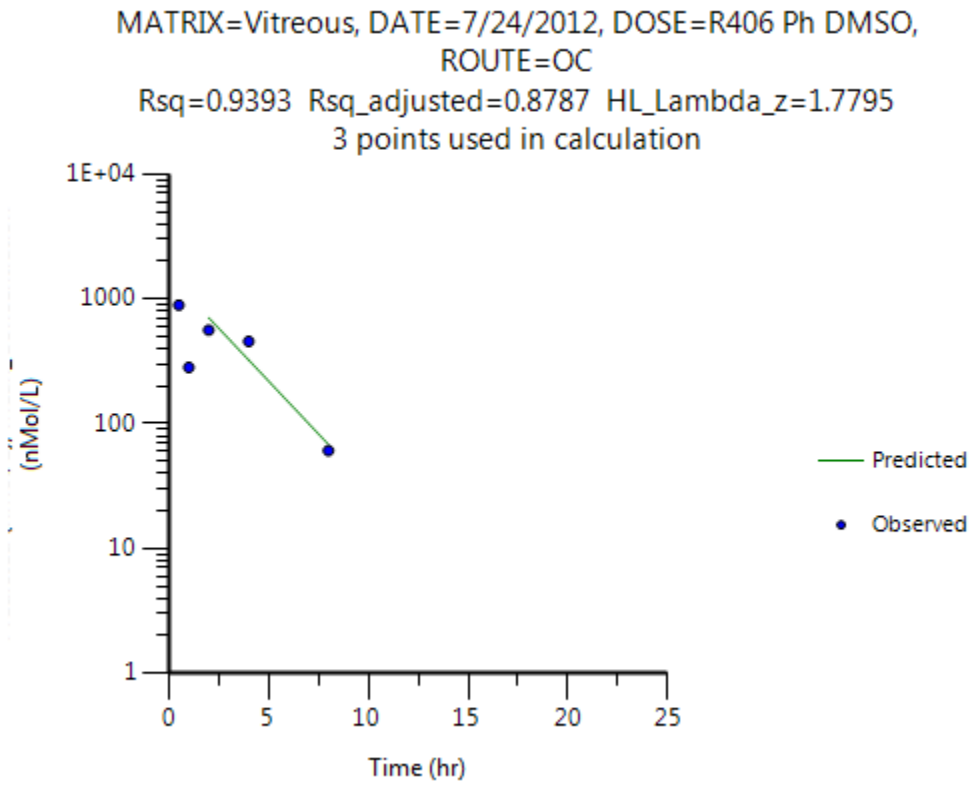

Figure 15: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

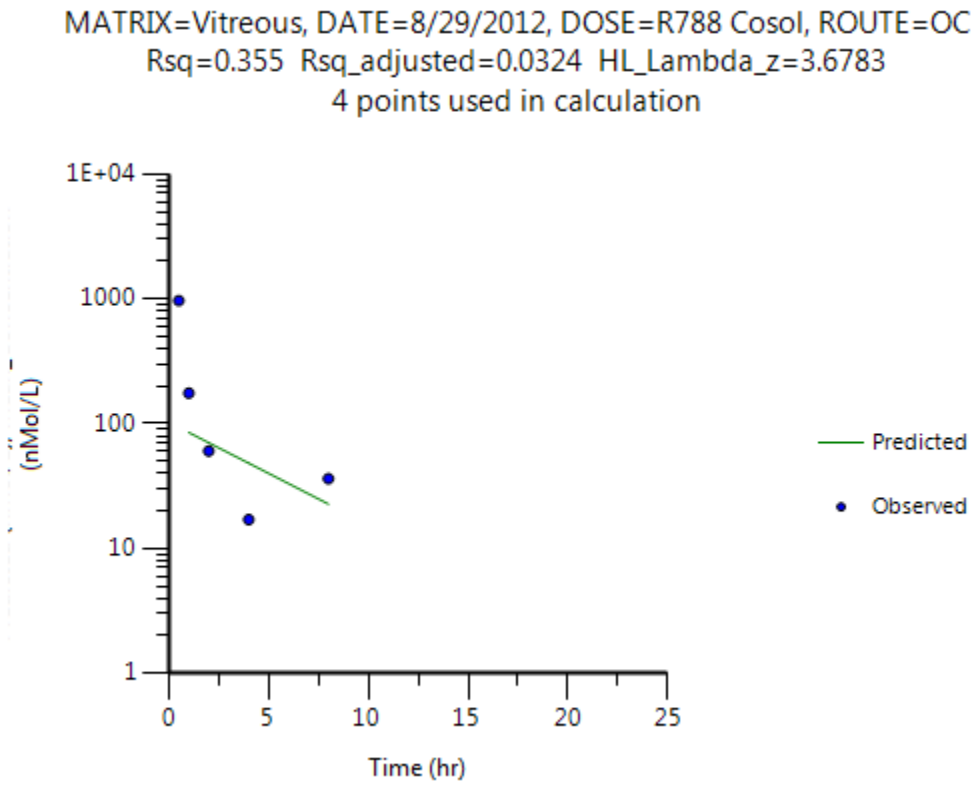

Figure 16: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions

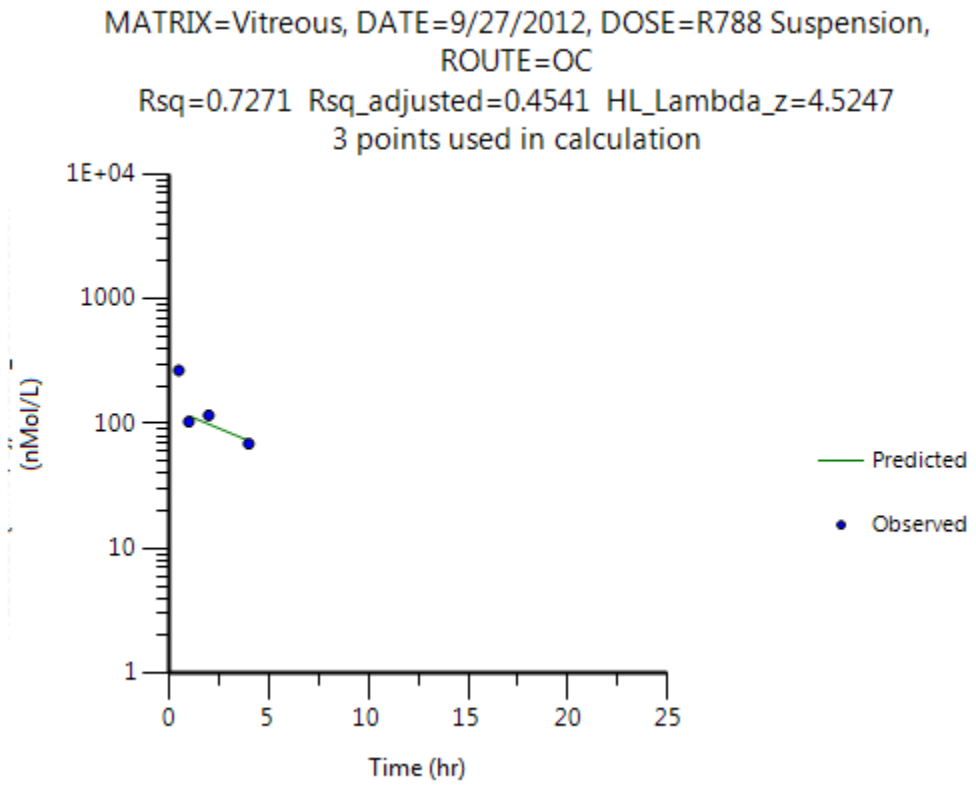

Figure 17: NCA Obs Y and Pred Y vs X Plots with Terminal Regressions