

Appendix 16.1.9

Documentation of Statistical Methods

[Integrated Analysis Plan Version 1.0, 22 November 2019](#)

[Statistical Analysis Output](#)

[WinNonlin Core Output](#)

[WinNonlin Plots](#)

Integrated Analysis Plan

Clinical Trial Protocol Identification No.

MS200095_0038

Title

An open-label, single-dose, randomized, 2-period, 2-sequence cross-over, single-center Phase I trial in healthy subjects to assess the bioequivalence of tepotinib tablet formulation 3 administered as 5 tablets of 100 mg versus 2 tablets of 250 mg dose strength

Trial Phase

I

Investigational Medicinal Product(s)

Tepotinib (MSC2156119J)

Clinical Trial Protocol Version

05 Sep 2019 / Version 1.0

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Integrated Analysis Plan Date and Version

22 Nov 2019 / Final Version 1.0

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Signature Page**Integrated Analysis Plan: MS200095_0038**

An open-label, single-dose, randomized, 2-period, 2-sequence cross-over, single-center Phase I trial in healthy subjects to assess the bioequivalence of tepotinib tablet formulation 3 administered as 5 tablets of 100 mg versus 2 tablets of 250 mg dose strength

Approval of the IAP by all Merck Data Analysis Responsibles is documented within Cara. With the approval within Cara, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

Merck responsible**Date****Signature**

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Via Cara approval process

Via Cara approval process

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2 List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
ANOVA	Analysis of VARIANCE
BMI	Body Mass Index
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CV%	Coefficient of Variation
ECG	Electrocardiogram
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
LCI	Lower Confidence Interval Bound
LLOQ	Lower Limit of Quantification
Max	Maximum
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QTcF	Corrected QT interval per Fridericia's formula

SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
SEM	Standard Error of the Mean
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TF3	Tablet Formulation 3
UCI	Upper Confidence Interval Bound
ULOQ	Upper Limit of Quantification

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
Final 1.0	22-NOV-2019	PI [REDACTED], Nuvisan	Original Document

4 Purpose of the Integrated Analysis Plan

The purpose of this integrated analysis plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for protocol MS200095_0038. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objectives	<ul style="list-style-type: none"> To demonstrate bioequivalence between 5 tablets of the 100 mg dose strength of tepotinib tablet formulation 3 (TF3, test treatment) and 2 tablets of the 250 mg dose strength of TF3 (reference treatment) after single dose administration in healthy subjects under fasting conditions 	Primary Endpoints: <ul style="list-style-type: none"> Area under the plasma concentration-time curve (AUC) from time zero (=dosing time) to the last sampling time at which the concentration is at or above the lower limit of quantification (AUC_{0-t}). AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$). Maximum plasma concentration (C_{max}) of tepotinib observed from time zero to 168 h postdose of each period. 	16.1.1
Secondary Objectives	<ul style="list-style-type: none"> To further investigate the Pharmacokinetic (PK) of tepotinib. To further assess the safety and tolerability of tepotinib TF3 under fasting conditions. 	Secondary endpoints: <ul style="list-style-type: none"> Time to reach C_{max} (t_{max}), terminal half-life ($t_{1/2}$), apparent total body clearance considering the fraction of dose absorbed (CL/f) and apparent volume of distribution during terminal phase (V_z/f) of tepotinib observed from time zero to 168 h postdose of each period. Occurrence of treatment-emergent adverse events (TEAEs; incidence, frequency, intensity and causality), occurrence of changes in safety laboratory assessments, 12-lead electrocardiograms (ECGs) and vital signs. 	16.1.2 15
Exploratory Objectives	<ul style="list-style-type: none"> To investigate the PK of tepotinib metabolites. To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of tepotinib (if applicable). 	Exploratory Endpoints: <ul style="list-style-type: none"> PK profiles of tepotinib metabolites: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$ of tepotinib metabolites observed from time zero to 168 h postdose of each period. Genetic variants and mutations in genes that potentially influence PK of tepotinib. 	16.1.3 16.2

6 Overview of Planned Analyses

6.1 Interim Analysis

No interim analysis is planned for this trial.

6.2 Final Analysis

The final, planned analyses identified in the Clinical Trial Protocol and in this IAP will be performed after the last subject has completed the last visit, i.e. end of trial visit/early termination visit with all trial data in-house, all data queries resolved, and the database locked.

Nodatabase can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The statistical methods as described in the protocol were adopted.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the trial data or that might significantly affect a subject's rights, safety, or well-being.

No formal data review meeting will be held. However, the following deviations will be identified and confirmed before the database is locked: Important protocol deviations include

- Deviations from the inclusion and exclusion criteria
- Concomitant medication violations (see Section 6.5.1 of the protocol)
- Use of prohibited medicines (see Section 6.5.2 of the protocol)
- Subjects that receive incorrect treatment or dose
- Sample processing errors that may lead to inaccurate bioanalytical results
- Vomiting or diarrhea following oral dosing (these instances will be discussed on a case-by-case basis)
- Deviation from Good Clinical Practice
- Non-compliance to trial procedures or deviations from trial procedures likely to affect the primary endpoints (e.g. subject develops withdrawal criteria whilst on the trial but is not withdrawn)
- Deviation from trial medication compliance in terms of medical conditions and/or adverse events (AEs) that may have interfered with drug disposition or with respect to factors likely to affect the primary endpoints

All important protocol deviations will be documented in Clinical Data Interchange Standard Consortium (CDISC) Study Data Tabulation Model (SDTM) datasets whether identified through sites monitoring or medical review.

8.2 Definition of Analysis Sets

Analysis Set	Description
Screening	All subjects who signed informed consent.
Safety	The Safety Analysis Set will include all subjects who have received at least 1 dose of planned Investigational Medicinal Product (IMP) and have had 1 subsequent safety assessment.
PK	The PK Analysis Set will include all subjects without any relevant protocol deviations with respect to PK and absence of factors likely to affect the comparability of PK results, with adequate trial medication compliance, and who have valid primary endpoints for both treatments.

Relevant decisions will be made before database lock.

9 General Specifications for Data Analyses

Statistical analyses will be performed using the computer program package SAS[®] System for Windows[™] (Version 9.4 or later; SAS Institute, Cary, North Carolina, USA).

The results of this trial will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized overall and/or by treatment and/or by scheduled time point, as appropriate.

For demographic, baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (i.e. number and percentage of observations, number and percentage of missing observations, mean, standard deviation [SD], median, the first and third quartile [Q1 and Q3], minimum [Min], and maximum [Max]) and categorical data will be summarized by means of frequency tables (i.e. count and percentages), if not stated otherwise. Mean, Median, Q1, Q3, Min, Max will have the same precision as the SDTM data (decimal places). SD will be presented with one decimal place more than the mean. For subject disposition and demographic tables the denominator will be the number of subjects in the analysis set. Counts of missing observations will be included as a separate category.

Concentrations of tepotinib and its metabolites in plasma will be presented in tables and descriptively summarized by treatment and nominal time point using n, arithmetic mean, SD, standard error of the mean (SEM), median, minimum, maximum and CV%. Values below the lower limit of quantification (LLOQ) will be taken as zero for descriptive statistics of PK concentrations. Descriptive statistics of PK parameters will additionally show the geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%), and the 95% CI for the GeoMean.

Graphical displays will be given, where appropriate. PK variables will be calculated and listed for all subjects who provide sufficient concentration-time data. Invalid data and their exclusion from statistical analysis will be discussed with the sponsor and flagged accordingly in the listings.

If not otherwise specified, 'baseline' refers to the last scheduled measurement before administration of the first drug in each period.

However, if a subject is missing the baseline collection, the previous non-missing evaluation could become the baseline value (e.g. from screening/admission). If no baseline or previous to baseline evaluations exist, then the baseline value will be treated as missing.

The following calculations and derivations, as applicable, will be used:

- Change from baseline: post-baseline visit value - baseline value
- Duration of AE (in days hh:mm) = end date and time - start date and time of the AE, if missing time for either the beginning or end then = end date – start date + 1; in case of multiple records for the same AE, the duration will be calculated over all these records
- Days hh:mm from dosing = start date and time of the event - date and time dose administration (for TEAEs); if missing time for either the dosing or event then = event start date – date of dose administration + 1
- Rel. Day in period of AE = start date of the event – date of First Admin in period + 1 (for AEs on or after the day of dosing)
- Rel. Day in trial of AE = start date of the event – date of First Admin (for AEs before the day of dosing of the trial only)

Repeated and unscheduled laboratory assessments will be included and flagged as repeats in the subject data listings, but not used for summary tables statistics (unless the scheduled measurement was considered unreliable, e.g. due to technical reasons, and needed to be replaced by an unscheduled repeat measurement).

In this Phase I PK trial missing observations will be assumed to be missing completely at random (MCAR). No action will be taken to handle missing data. A subject who withdraws prior to the

last planned observation in a trial period will be included in the analyses up to the time of discontinuation.

The following treatment labels will be used:

- 5 x 100 mg TF3
- 2 x 250 mg TF3

Details of the statistical analysis will be provided in the subsequent sections.

10 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Subjects and Discontinuations

The following will be presented in a summary table:

- Total number of subjects screened (i.e. subjects who gave informed consent)
- Number of screened subjects who discontinued from the trial prior to treatment overall and grouped by the main reason for discontinuation:
 - Subject did not meet all eligibility criteria
 - Withdrew consent
 - Adverse event
 - Lost to follow-up
 - Death
 - Other
- Number of treated subjects by treatment and overall
- Number and percentage of treated subjects who completed trial by treatment and overall
- Number and percentage of treated subjects who discontinued the trial, with the primary reason of discontinuation by treatment and overall:
 - Adverse event
 - Lost to follow-up

- Protocol non-compliance
- Death
- Withdrew consent
- Other

A listing of discontinued subjects will be provided.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

Listings of important protocol deviations will be provided including the date and relative day in relation to dosing in the relevant period.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

All criteria/reasons leading to the exclusion of a subject from an analysis set (including clinically important protocol deviations) will be listed based on the safety set.

Reasons for excluding individual PK concentrations will also be listed separately and flagged in the main listing based on the safety analysis set.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Summaries will be given for both the safety and the PK set, if different.

Demographic characteristics will be listed by subject and summarized using the following information from the Screening/Baseline Visit electronic Case Report Form (eCRF) pages.

Demographic characteristics:

- Sex: male, female
- Race: Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, White, Other
- Ethnic origin: Hispanic or Latino , Not Hispanic or Latino , Japanese, Not Japanese
- Age (years): summary statistics
- Height (cm) at Baseline: summary statistics

- Weight (kg) at Baseline: summary statistics
- BMI (kg/m²) at Baseline: summary statistics

Age will be taken from the eCRF and cannot be derived from the data because only the year of birth is collected in the eCRF.

BMI will be re-derived (i.e. not taken directly from the database) according to the following formula:

- $\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / (\text{height (m)} * \text{height (m)})$

11.2 Medical History

The medical history will be listed by subject including the preferred term (PT) and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) body term using MedDRA latest version.

11.3 Other Baseline Characteristics

Other baseline characteristics will be listed by subject and summarized using the following information from the Screening/Baseline Visit eCRF pages.

Other baseline characteristics:

- Smoking status
- Alcohol consumption

12 Previous or Concomitant Medications/Procedures

Previous medications are medications, other than trial medications and pre-medications for trial drug, which started and stopped before first administration of trial drug.

Concomitant treatments are medications, other than trial medications, which are taken by subjects any time on-trial (on or after the first day of trial drug treatment for each subject).

In case the date values will not allow to unequivocally allocate a medication to previous or concomitant medication the medication will be considered as concomitant medication.

Any previous and concomitant medication will be encoded with WHO-DD, latest version. Prior and concomitant medications will be listed by subject (all subjects).

The following information will be displayed in a listing: generic or trade name (as reported in CRF), WHO drug name (including ATC-2nd level and PT), dose/unit, route, frequency, reason for use, start/end date and time.

Concomitant procedures will be presented in a data listing.

13 Treatment Compliance and Exposure

A listing of date and time of each drug administration and each blood sampling including time deviations will be provided sorted by subject.

14 Efficacy Analyses

Not applicable.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

Safety data analysis will be conducted on the Safety Analysis Set.

15.1 Adverse Events

The number and percentage of subjects experiencing at least one TEAE will be summarized by treatment as well as the number of events. A TEAE is an AE with onset after start of treatment. Tables by relationship to trial drug and by severity will be generated. AEs will be coded using MedDRA terminology, latest version.

If an event was reported more than once, the worst severity will be tabulated.

Incomplete TEAE-related dates will be flagged in listings and handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year or the onset year are equal to the start of trial treatment, then the onset date will be replaced by the minimum of start of trial treatment and TEAE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed.

15.1.1 All Adverse Events

All AEs recorded during the course of the trial (i.e. assessed from signature of informed consent until the end of the Follow-up/End of Trial visit) will be coded according to MedDRA latest version and assigned to a SOC and PT.

TEAEs will be summarized by severity, using MedDRA latest version, with PT as event category and MedDRA primary SOC body term as body system category. The severity of AEs will be graded using the “National Cancer Institute - Common Terminology Criteria for Adverse Events” (NCI-CTCAE) guideline, version 5.0 (publication date: 27 Nov 2017), as detailed in the trial protocol.

TEAEs related to trial treatment are those events with relationship missing, unknown or related.

The following will be summarized in an overview table with the number and percentage of subjects (and the number of events) by treatment and overall:

- Any TEAEs
- Any trial treatment related TEAEs
- Any serious TEAEs
- Any trial treatment related serious TEAEs
- Any TEAE (grade ≥ 3)
- Any trial treatment related TEAEs (grade ≥ 3)
- Any TEAEs leading to death
- Any trial treatment related TEAEs leading to death

TEAEs will be summarized by treatment and overall in tables with:

- The number and percentage of subjects by treatment with at least one TEAE and the number of events overall and by SOC and PT. Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency.
- The number and percentage of subjects by treatment with at least one non-serious TEAE and the number of non-serious TEAE applying frequency threshold of 5%. Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency.

In addition the following tables will be provided. Group/SOC terms will be sorted alphabetically and PTs within each group/SOC term will be sorted by descending frequency (based on all treatment groups combined):

- A table by severity of TEAEs with the number and percentage of subjects by treatment with at least one TEAE and the number of events by SOC and PT.
- A table by relationship to trial treatment with the number and percentage of subjects by treatment with at least one TEAE and the number of events by SOC and PT.

Pre-treatment AEs (AEs with onset after informed consent but before start of treatment) and TEAEs will be listed separately.

15.1.2 Adverse Events Leading to Treatment Discontinuation

TEAEs leading to permanent discontinuation of trial treatment will be summarized by treatment and overall including number of subjects, percentage and number of events.

A listing of TEAEs leading to permanent discontinuation of a trial treatment will additionally be provided.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

All deaths as well as reason for death will be based on information from the “Report of Subject Death” CRFs.

Listing of deaths, if any, will be provided displaying date and cause of death (including TEAE leading to death and relatedness to trial treatment, when applicable), and date and time of treatment administration.

15.2.2 Serious Adverse Events

A summary table of serious adverse events (SAEs), if any, by treatment and overall will be provided displaying the number and percentage of subjects by treatment with at least one SAE and the number of SAE overall and by system organ class and preferred term. Group/SOC terms and PTs within each group/SOC term will be sorted alphabetically.

Listing of SAEs, if any, will be provided in addition.

15.2.3 Other Significant Adverse Event

15.2.3.1 Adverse Events of Special Interest

Healthy subjects might experience asymptomatic elevations in serum lipase and amylase. Any elevation in serum lipase and amylase of Grade ≥ 3 will lead to the recording of an adverse event of special interest (AESI). The severity of these AEs should be defined based on clinical judgment of the Investigator and defined according to NCI-CTCAE Severity Scale.

AESIs will be presented in a separate data listing.

15.3 Clinical Laboratory Evaluation

All laboratory data will be reported with SI units. Laboratory parameters will be listed by subject and time-point and summarized indicating the treatment at the respective time-point using descriptive statistics for absolute values and change from baseline over time and by post-dose CTCAE grade shift relative to baseline. Shift tables will be based on NCI-CTCAE grades, where possible, and on normal ranges otherwise.

Shift tables will be presented for:

- End of Trial/Follow-up versus Screening
- Discharge Day 4 versus Pre-dose/Baseline (Tepotinib administration) within periods.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and NCI-CTCAE grade. Any out-of-range values will additionally be listed separately including NCI-CTCAE grade.

See section 7.4.3 of the clinical study protocol for a table of the safety laboratory evaluations.

Safety laboratory values are separated into:

- Hematology
- Biochemistry
- Urinalysis
- Other tests

Tables will be produced for the groups Hematology and Biochemistry.

15.4 Vital Signs

Vital signs will be listed by subject and time-point and summarized for absolute values and changes-from-baseline (period-baseline) by visit and treatment using descriptive statistics. Descriptive statistics tables will start at baseline.

15.5 ECG Evaluation

Electrocardiogram (ECG) data will be listed by subject and time-point and summarized by absolute values and changes-from-baseline (period-baseline) by treatment group using descriptive statistics. Baseline is the pre-dose assessment in each period. See section 9 for a description of how missing baseline values are handled. Descriptive statistics tables will start at baseline. Clinically significant ECG findings for individual subjects will be listed and summarized.

The time intervals (PR, QRS, RR, QT and corrected QT intervals [based on Fridericia's formula, QTcF]) will be summarized descriptively by treatment. In case of triplicate ECGs, the mean of these measurements will be considered in summary tables.

The Fridericia's Correction (QTcF) is derived as follows:

$$\text{Fridericia's Correction (QTcF)} \quad QTc_f = \frac{QT}{\sqrt[3]{RR}}$$

where: RR = RR-interval measured in seconds.

QTcF values will be categorized according to their absolute values into the categories:

- ≤ 430 ms,
- > 430 and ≤ 450 ms,
- > 450 and ≤ 480 ms,
- > 480 and ≤ 500 ms, and
- > 500 ms,

and categorized according to their absolute change from period baseline into the categories:

- ≤ 30 ms,
- > 30 and ≤ 60 ms, and
- > 60 ms.

The number and percentage of subjects by these categories at any post-dose assessment will be tabulated by treatment group. All ECG measurements and changes from period baseline will be listed, with abnormalities (as reported of the Investigator on the ECG eCRF page) indicated.

Investigator reported interpretation results will also be tabulated by treatment using the number and percentage of subjects for each interpretation category (Normal, Abnormal Not Clinically Significant [NCS], Abnormal Clinically Significant [CS]). In case of triplicate ECGs, the worst interpretation will be considered in these frequency tables.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

General Specifications for Plasma Concentration Data

Concentrations of tepotinib and its metabolites in plasma will be presented in tables and descriptively summarized by treatment and nominal time point using number of observations (n), Mean, SD, SEM, median, Min, Max, and CV%. Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max: 3 significant digits

SD, SEM: 4 significant digits

CV%: 1 decimal place

Values below the LLOQ of the assay will be taken as zero for summary statistics of PK concentration data. For final evaluations values greater than the upper limit of quantification (ULOQ) are not accepted and should be replaced by valid numeric values from dilution measurement. Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as “no result” (“N.R.”). Pre-dose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration.

All available concentration data will be listed. Data of participants not in the PK analysis set or invalid data will be flagged accordingly. Any flags will be included in ADaM, respectively.

General Specifications for PK Parameter Data

PK parameter data will be descriptively summarized: n, Mean, SEM, SD, CV%, Min, median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM).

PK parameter C_{\max} will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI: 3 significant digits

SD, SEM: 4 significant digits

CV%, GeoCV%: 1 decimal place

Ratio of GeoMean and 95% CI 4 decimal places

To ensure a reliable estimate of the extent of exposure, AUC_{extra} should be less than or equal to 20%. If AUC_{extra} is greater than 20%, all parameters derived using λ_z (i.e. λ_z , $t_{1/2}$, $AUC_{0-\infty}$, AUC_{extra} , V_z/f , CL/F) will be listed, but set to missing for the calculation of descriptive statistics.

All statistical analyses and descriptive summaries of PK data will be performed on the PK Analysis Set. All available concentration/PK data will be listed. Data of subjects not in the PK Analysis Set or invalid data will be flagged accordingly. Any flags will be included in ADaM, respectively.

16.1.1 Primary Endpoints

The primary endpoints will be descriptively summarized. Scatter plots will be produced for the individual PK parameters by treatment group indicating the geometric means within each treatment group.

Statistical Hypotheses (Bioequivalence)

The following null hypothesis for the ratio of the geometric means will be used to assess bioequivalence:

$H_0: \mu_T/\mu_R \leq 0.8000 \text{ or } 1.2500 \leq \mu_T/\mu_R \text{ for at least one parameter (AUC}_{0-t} \text{ or}$

$AUC_{0-\infty} \text{ or } C_{\max})$

$H_1: 0.8000 < \mu_T/\mu_R < 1.2500 \text{ for all parameters (AUC}_{0-t} \text{ and } AUC_{0-\infty} \text{ and } C_{\max})$

where μ_T and μ_R are the geometric means for the test and reference treatment respectively.

The test treatment is 5 tablets of the 100 mg dose strength of TF3 and reference is 2 tablets of the 250 mg dose strength of TF3, both under fasting condition.

An analysis of variance (ANOVA) model with TREATMENT, PERIOD, SEQUENCE as fixed effects and SUBJECT(SEQUENCE) as random effect will be fitted to log-transformed primary endpoints AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} based on the PK analysis set.

Treatment differences 5 x 100 mg TF3 – 2 x 250 mg TF3 under fasting condition on the log scale will be estimated for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ together with their 90% CIs. Point estimates and CIs will be back-transformed to the original scale.

The null hypothesis will be rejected if the 90% CI for the ratio of the geometric mean lies within the interval 0.8000 to 1.2500 for all parameters.

16.1.2 Secondary Endpoints

The secondary PK endpoints will be descriptively summarized by treatment and listed.

16.1.3 Exploratory Endpoints

The PK endpoints AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , t_{max} , $t_{1/2}$ of tepotinib metabolites observed from time zero to 168 h post-dose of each period for the tepotinib metabolites MSC2571109A and MSC2571107A will be descriptively summarized by treatment and listed.

Similar analyses as for the primary endpoints will be performed for the parameters based on the metabolites of tepotinib, using 90% CIs for the comparison 5 x 100 mg TF3 - 2 x 250 mg TF3, both under fasting condition.

The ANOVA model will have the same effects as the primary analysis applied to log-transformed PK parameters C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$.

A mixed model with TREATMENT, PERIOD, SEQUENCE as fixed effects and SUBJECT(SEQUENCE) as random effect will be applied.

16.1.4 Plasma Concentration Data

The following figures will be produced for the tepotinib and metabolites (MSC2571109A and MSC2571107A) plasma concentrations:

- Arithmetic mean plasma concentration-time profiles overlaying all treatments on linear and semi-logarithmic scale
- Arithmetic mean plasma concentration-time profiles overlaying all treatments on linear scale including SD error bars
- Individual plasma concentration-time profiles overlaying subjects, for each treatment separately on linear and semi-logarithmic scale

- Individual plasma concentration-time profiles overlaying all treatments, separately for each subject on linear and semi-logarithmic scale

The following listings will be produced for the tepotinib and metabolites plasma concentrations:

- Plasma concentrations will be listed by nominal time by treatment. Excluded plasma concentrations will be flagged.

16.1.5 Estimation of Individual Pharmacokinetic Parameters

The following non-compartmental PK parameters (see will be calculated from the individual plasma total tepotinib and metabolites concentration-time data using commercial software such as Phoenix[®]/WinNonlin[®] (Version 6.4 or higher) at Nuvisan GmbH.

Table 1 Definition of PK Parameters for Tepotinib and its Metabolites After Single Dose Administration

Symbol	Definition
AUC_{0-t}	Area under the plasma concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification (LLOQ), calculated using the mixed log linear trapezoidal rule (ie linear up/log down)
AUC_{0-t}/D	AUC_{0-t} divided by dose
AUC_{0-24}	AUC from 0 to 24 hours, calculated using mixed log linear trapezoidal rule (linear up, log down)
AUC_{0-24}/D	AUC_{0-24} divided by dose
$AUC_{0-\infty}$	AUC from time zero (= dosing time) extrapolated to infinity, calculated as $AUC_{0-t} + AUC_{extra}$. AUC_{extra} represents the extrapolated part of $AUC_{0-\infty}$ calculated by $C_{lastpred}/\lambda_z$, where $C_{lastpred}$ is the predicted plasma concentration at the last sampling time point, calculated from the log-linear regression line for λ_z determination at which the measured plasma concentration is at or above LLOQ
$AUC_{0-\infty}/D$	$AUC_{0-\infty}$ divided by dose
C_{max}	Maximum plasma concentration observed
C_{max}/D	C_{max} divided by dose

Symbol	Definition
t_{last}	The last sampling time at which the plasma concentration is at or above the lower limit of quantification
t_{max}	Time to reach the maximum observed plasma concentration
$t_{1/2}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$
λ_z	Terminal rate constant determined from the terminal slope of the log-transformed plasma concentration curve using linear regression on terminal data points of the curve
CL/F	Apparent total body clearance of drug from plasma following extravascular administration, calculated as $\text{dose}/\text{AUC}_{0-\infty}$
V_z/f	Apparent volume of distribution during the terminal phase following extravascular administration
AUC_{extra}	The AUC from time t_{last} extrapolated to infinity
$\text{AUC}_{extra\%}$	$\text{AUC}_{extra} / \text{AUC}_{0-\infty} \times 100$.

Individual PK parameters will be calculated using actual sampling times. If the actual sampling time is missing, then the nominal sampling times will be used instead. The pre-dose sample will be considered as if it had been taken simultaneously with the administration of study drug. PK variables will be evaluated and listed for all subjects who provide sufficient concentration-time data.

Plasma concentrations below LLOQ will be taken as zero for calculating the AUC. Plasma concentrations below LLOQ after the last quantifiable data point will not be considered for the determination of λ_z .

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression ($\lambda_{z \text{ low}}$, $\lambda_{z \text{ upp}}$) to determine λ_z .
- Number of data points included in the log-linear regression analysis to determine λ_z .
- Goodness of fit statistic (Rsqr) for calculation of λ_z .

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best fit methodology will be used as standard. The last quantifiable concentration

should always be included in the regression analysis, while the concentration at t_{\max} and any <LLOQ concentrations that occur after the last quantifiable data point should not be used.

The coefficient of correlation (R^2) should be ≥ 0.8 and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If these criteria are not met, then the corresponding values should be flagged in the listing displaying Individual Plasma Pharmacokinetic Diagnostic Parameters for Each Treatment. Any flags should be included in the study specific SDTM/ADaM. Then the rate constants and all derived parameters (e.g. $AUC_{0-\infty}$, $\%AUC_{\text{extra}}$, CL/f , $t_{1/2}$, and V_Z/f) will be included in the parameter listings and will be discussed appropriately in alignment with the protocol lead and quantitative pharmacology representative.

The following interpolation or extrapolation rules apply when calculating AUC_{0-24} :

- If the time point 24 hours falls within the time range in which samples were taken, but does not coincide with an observed data point, then a linear interpolation is performed to estimate the corresponding concentration value.
- If the time point 24 hours occurs after the last measurable concentration and the terminal regression (λ_z) is estimable, then λ_z is used to estimate the concentration at time 24 hours. If λ_z cannot be estimated the partial area will not be calculated.

The IMP dose administered is given for the monohydrate hydrochloride salt (i.e. 500 mg IMP). A conversion factor for the freebase IMP was calculated and will be applied when ‘dose’ is used in deriving PK parameter formulas needing a dose value (CL/f).

Conversion factor = Molecular weight (MW) of base IMP divided by MW of salt form IMP = $492.574 \text{ g/mol} / 547.05 \text{ g/mol} = 0.9004$

Amount of dose * conversion factor = actual dose of IMP: $500 \text{ mg} * 0.9004 = 450 \text{ mg}$

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

16.2 Pharmacogenetics

Pharmacogenetic sampling is mandatory for trial participation. An additional separate ICF will be used. One blood sample should be collected in duplicate on Day -1 of the first treatment period prior to administration. The pharmacogenetic samples will be analyzed conditionally in case of unexpected PK profiles. The results of the PGx analysis, as applicable, will be described in a separate report.

17 References

N.A.

18 Appendices

None.

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16.1.9.2: Statistical Analysis Output

Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-inf (h*ng/mL) for Tepotinib

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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16.1: Study Information

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16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-inf (h*ng/mL) for Tepotinib

The Mixed Procedure

Class Level Information

Class	Levels	Values
-------	--------	--------

USUBJID	18	
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PI



T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-inf (h*ng/mL) for Tepotinib

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	35

Number of Observations

Number of Observations Read	35
Number of Observations Used	35
Number of Observations Not Used	0

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020
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16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-inf (h*ng/mL) for Tepotinib

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	27.82729226	
1	2	14.18487139	0.00009191
2	1	14.18286276	0.00000010
3	1	14.18286061	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.08236
Residual	0.02311

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-inf (h*ng/mL) for Tepotinib

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	14.2
AIC (smaller is better)	18.2
AICC (smaller is better)	18.6
BIC (smaller is better)	20.0

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	15	3.34	0.0875
APERIOD	1	15	5.68	0.0308
SEQUENCE	1	16	1.42	0.2502

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020
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16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-inf (h*ng/mL) for Tepotinib

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	9.7527	0.07654	15	127.41	<.0001	0.1	9.6186	9.8869
TRTA1	T	9.6576	0.07747	15	124.66	<.0001	0.1	9.5218	9.7934

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	-0.09516	0.05206	15	-1.83	0.0875	0.1	-0.1864	-0.00390

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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16.1.9.2: Statistical Analysis Output
Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-t (h*ng/mL) for Tepotinib

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020
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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

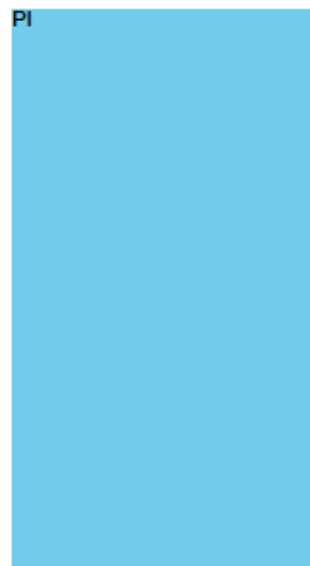
Parameter: AUC0-t (h*ng/mL) for Tepotinib

The Mixed Procedure

Class Level Information

Class	Levels	Values
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USUBJID	18	PI
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T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-t (h*ng/mL) for Tepotinib

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	35

Number of Observations

Number of Observations Read	35
Number of Observations Used	35
Number of Observations Not Used	0

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020
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16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-t (h*ng/mL) for Tepotinib

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	26.34579623	
1	2	13.26462856	0.00006316
2	1	13.26322330	0.00000005
3	1	13.26322224	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.07738
Residual	0.02303

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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16.1.9.2: Statistical Analysis Output
Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-t (h*ng/mL) for Tepotinib

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	13.3
AIC (smaller is better)	17.3
AICC (smaller is better)	17.7
BIC (smaller is better)	19.0

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	15	3.18	0.0947
APERIOD	1	15	6.09	0.0261
SEQUENCE	1	16	1.40	0.2546

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020
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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: AUC0-t (h*ng/mL) for Tepotinib

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	9.7125	0.07469	15	130.04	<.0001	0.1	9.5816	9.8434
TRTA1	T	9.6198	0.07563	15	127.19	<.0001	0.1	9.4872	9.7524

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	-0.09269	0.05197	15	-1.78	0.0947	0.1	-0.1838	-0.00159

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: Cmax (ng/mL) for Tepotinib

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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16.1: Study Information

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16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

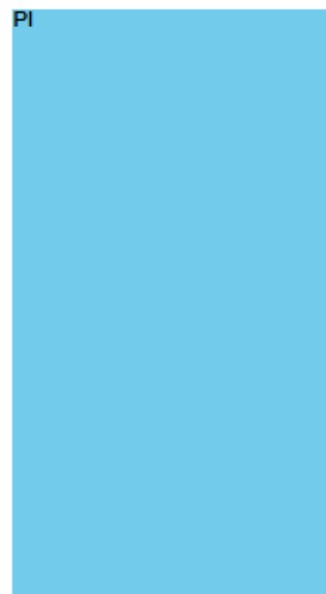
Parameter: Cmax (ng/mL) for Tepotinib

The Mixed Procedure

Class Level Information

Class	Levels	Values
-------	--------	--------

USUBJID	18	
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T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-prim-anova.sas, 28JAN2020 12:59

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16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: Cmax (ng/mL) for Tepotinib

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	36

Number of Observations

Number of Observations Read	36
Number of Observations Used	36
Number of Observations Not Used	0

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: Cmax (ng/mL) for Tepotinib

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	7.31480767	
1	1	2.58411332	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.02709
Residual	0.02645

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-prim-anova.sas, 28JAN2020 12:59

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16.1.9: Documentation of Statistical Methods
16.1.9.2: Statistical Analysis Output
Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: Cmax (ng/mL) for Tepotinib

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	2.6
AIC (smaller is better)	6.6
AICC (smaller is better)	7.0
BIC (smaller is better)	8.4

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	16	0.69	0.4173
APERIOD	1	16	3.61	0.0754
SEQUENCE	1	16	0.38	0.5462

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020
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16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.1: Statistical Output of Primary Analysis

Parameter: Cmax (ng/mL) for Tepotinib

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	5.4826	0.05454	16	100.52	<.0001	0.1	5.3874	5.5778
TRTA1	T	5.5277	0.05454	16	101.35	<.0001	0.1	5.4325	5.6230

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	0.04515	0.05422	16	0.83	0.4173	0.1	-0.04951	0.1398

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.12; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

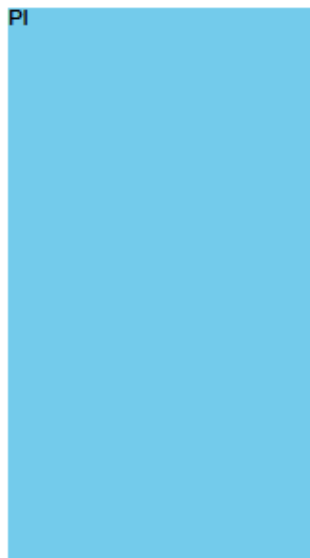
Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Class Level Information

Class	Levels	Values
-------	--------	--------

USUBJID	18	PI
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T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	35

Number of Observations

Number of Observations Read	35
Number of Observations Used	34
Number of Observations Not Used	1

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	31.53030633	
1	2	16.76697914	0.00007090
2	1	16.76559433	0.00000005
3	1	16.76559328	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.09898
Residual	0.02278

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	16.8
AIC (smaller is better)	20.8
AICC (smaller is better)	21.2
BIC (smaller is better)	22.5

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	14	2.11	0.1685
APERIOD	1	14	3.75	0.0731
SEQUENCE	1	16	0.71	0.4120

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	9.3035	0.08311	14	111.94	<.0001	0.1	9.1571	9.4499
TRTA1	T	9.2264	0.08311	14	111.01	<.0001	0.1	9.0801	9.3728

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	-0.07708	0.05308	14	-1.45	0.1685	0.1	-0.1706	0.01641

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

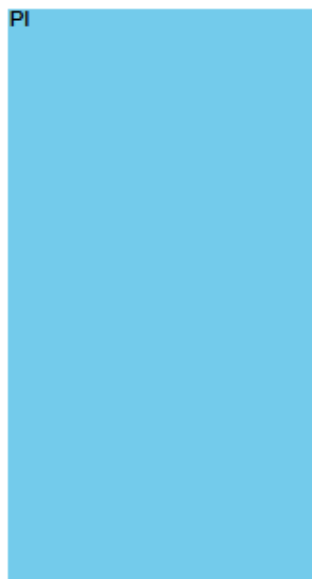
Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Class Level Information

Class	Levels	Values
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USUBJID	18	PI
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T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	35

Number of Observations

Number of Observations Read	35
Number of Observations Used	35
Number of Observations Not Used	0

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	26.81517413	
1	2	11.88675358	0.00035958
2	1	11.87830803	0.00000157
3	1	11.87827247	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.08272
Residual	0.02009

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	11.9
AIC (smaller is better)	15.9
AICC (smaller is better)	16.3
BIC (smaller is better)	17.7

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	15	2.29	0.1511
APERIOD	1	15	4.59	0.0491
SEQUENCE	1	16	0.68	0.4226

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020
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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	9.2341	0.07558	15	122.18	<.0001	0.1	9.1016	9.3666
TRTA1	T	9.1606	0.07641	15	119.90	<.0001	0.1	9.0267	9.2946

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	-0.07348	0.04856	15	-1.51	0.1511	0.1	-0.1586	0.01166

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: Cmax (ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

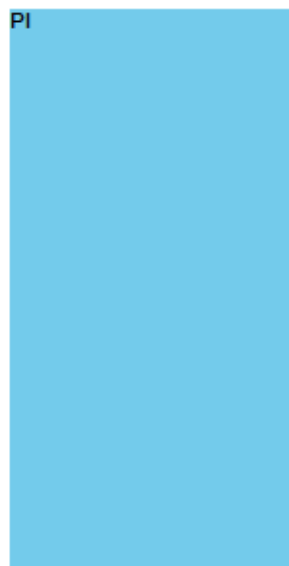
Parameter: Cmax (ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Class Level Information

Class	Levels	Values
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USUBJID	18	PI
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T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: Cmax (ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	36

Number of Observations

Number of Observations Read	36
Number of Observations Used	36
Number of Observations Not Used	0

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: Cmax (ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	15.17122702	
1	1	6.48385334	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.04430
Residual	0.02414

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020
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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: Cmax (ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	6.5
AIC (smaller is better)	10.5
AICC (smaller is better)	10.9
BIC (smaller is better)	12.3

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	16	0.19	0.6704
APERIOD	1	16	4.23	0.0563
SEQUENCE	1	16	0.33	0.5736

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.2: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571109A

Parameter: Cmax (ng/mL) for Metabolite MSC2571109A

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	4.7859	0.06166	16	77.61	<.0001	0.1	4.6782	4.8935
TRTA1	T	4.7634	0.06166	16	77.25	<.0001	0.1	4.6558	4.8711

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	-0.02246	0.05179	16	-0.43	0.6704	0.1	-0.1129	0.06796

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.13; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

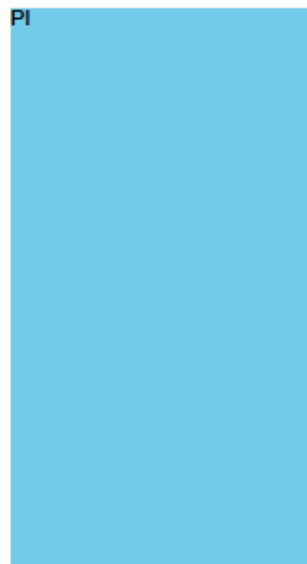
Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Class Level Information

Class	Levels	Values
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USUBJID	18	PI
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T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	35

Number of Observations

Number of Observations Read	35
Number of Observations Used	34
Number of Observations Not Used	1

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	39.33425405	
1	3	22.75268267	0.00020766
2	1	22.74922662	0.00000039
3	1	22.74922033	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.1279
Residual	0.02641

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	22.7
AIC (smaller is better)	26.7
AICC (smaller is better)	27.2
BIC (smaller is better)	28.5

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	14	1.97	0.1821
APERIOD	1	14	3.43	0.0854
SEQUENCE	1	16	1.19	0.2917

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-inf (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	6.5721	0.09348	14	70.30	<.0001	0.1	6.4074	6.7367
TRTA1	T	6.4918	0.09348	14	69.44	<.0001	0.1	6.3271	6.6564

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	-0.08030	0.05719	14	-1.40	0.1821	0.1	-0.1810	0.02042

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

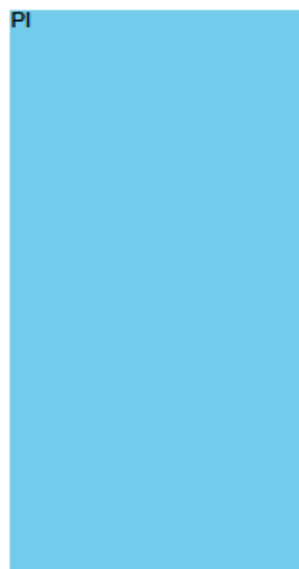
Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Class Level Information

Class	Levels	Values
-------	--------	--------

USUBJID	18	
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T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

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16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	35

Number of Observations

Number of Observations Read	35
Number of Observations Used	35
Number of Observations Not Used	0

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	35.34606855	
1	2	18.61144132	0.00000217
2	1	18.61139966	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.1093
Residual	0.02369

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020
Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	18.6
AIC (smaller is better)	22.6
AICC (smaller is better)	23.0
BIC (smaller is better)	24.4

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	15	2.60	0.1276
APERIOD	1	15	4.91	0.0425
SEQUENCE	1	16	1.38	0.2571

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: AUC0-t (h*ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	6.5079	0.08596	15	75.71	<.0001	0.1	6.3572	6.6586
TRTA1	T	6.4228	0.08683	15	73.97	<.0001	0.1	6.2706	6.5751

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	-0.08507	0.05274	15	-1.61	0.1276	0.1	-0.1775	0.007396

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: Cmax (ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Model Information

Data Set	WORK.PKPARS
Dependent Variable	LOGAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
TRTA1	2	R T
APERIOD	2	1 2

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

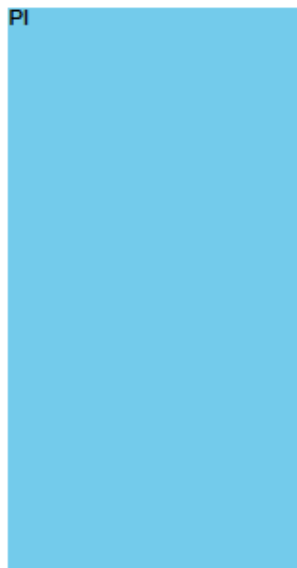
Parameter: Cmax (ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Class Level Information

Class	Levels	Values
-------	--------	--------

USUBJID	18	PI
---------	----	----



T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: Cmax (ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Class Level Information

Class	Levels	Values
SEQUENCE	2	RT TR

Dimensions

Covariance Parameters	2
Columns in X	7
Columns in Z	18
Subjects	1
Max Obs Per Subject	36

Number of Observations

Number of Observations Read	36
Number of Observations Used	36
Number of Observations Not Used	0

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: Cmax (ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	18.54420114	
1	1	6.94881662	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
USUBJID(SEQUENCE)	0.05461
Residual	0.02145

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020
Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: Cmax (ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	6.9
AIC (smaller is better)	10.9
AICC (smaller is better)	11.4
BIC (smaller is better)	12.7

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA1	1	16	0.13	0.7220
APERIOD	1	16	5.50	0.0323
SEQUENCE	1	16	1.69	0.2126

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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Protocol: MS200095-0038

16.1: Study Information

16.1.9: Documentation of Statistical Methods

16.1.9.2: Statistical Analysis Output

Listing 16.1.9.2.3: Statistical Output of Exploratory Analysis - Tepotinib Metabolite MSC2571107A

Parameter: Cmax (ng/mL) for Metabolite MSC2571107A

The Mixed Procedure

Least Squares Means

Effect	TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	R	2.1436	0.06500	16	32.98	<.0001	0.1	2.0301	2.2571
TRTA1	T	2.1260	0.06500	16	32.71	<.0001	0.1	2.0125	2.2394

Differences of Least Squares Means

Effect	TRTA1	_TRTA1	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA1	T	R	-0.01768	0.04881	16	-0.36	0.7220	0.1	-0.1029	0.06755

T: 5 x 100 mg TF3; R: 2 x 250 mg TF3

Source: ADPP 22JAN2020 13:55; Listing 16.2.5.14; SDTM package: 15JAN2020

Program: J:\BIO\J19\N-A-PH1-19-070\tables\tr-expl-anova.sas, 28JAN2020 13:02

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WinNonlin Core Output - Tepotinib

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.050	0.0000			0.0000	0.0000	
1.500	10.70			2.408	3.611	
2.000	14.50			8.708	14.87	
3.000	34.10			33.01	80.52	
4.000	48.20			74.16	228.1	
6.000	105.0			227.4	1051.	
8.017	117.0			451.2	2632.	
12.00	218.0			1118.	9710.	
16.03	222.0			2006.	2.216e+004	
24.00	257.0			3914.	6.091e+004	
36.07 *	197.0	187.8	9.198	6637.	1.420e+005	1.000
48.00 *	148.0	143.5	4.524	8681.	2.273e+005	1.000
60.00 *	110.0	109.4	0.5533	1.022e+004	3.099e+005	1.000
72.00 *	76.50	83.49	-6.989	1.133e+004	3.825e+005	1.000
96.00 *	45.90	48.58	-2.682	1.276e+004	5.018e+005	1.000
120.0 *	30.70	28.27	2.430	1.367e+004	5.990e+005	1.000
144.0 *	15.10	16.45	-1.350	1.420e+004	6.679e+005	1.000
168.0 *	10.20	9.572	0.6275	1.450e+004	7.145e+005	1.000

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

Final Parameters

Rsqr 0.9960
Rsqr_adjusted 0.9953
Corr_XY -0.9980
No_points_lambda_z 8
Lambda_z 1/h 0.0226
Lambda_z_lower h 36.0667
Lambda_z_upper h 168.0000
HL_Lambda_z h 30.7238
Tlag h 1.0500
Tmax h 24.0000
Cmax ng/mL 257.0000

Cmax_D	ng/mL/mg	0.5711
Tlast	h	168.0000
Clast	ng/mL	10.2000
AUClast	h*ng/mL	14497.1496
AUCall	h*ng/mL	14497.1496
AUCINF_obs	h*ng/mL	14949.2650
AUCINF_D_obs	h*ng/mL/mg	33.2206
AUC_%Extrap_obs	%	3.0243
Vz_F_obs	L	1334.2643
Cl_F_obs	L/h	30.1018
AUCINF_pred	h*ng/mL	14921.4501
AUCINF_D_pred	h*ng/mL/mg	33.1588
AUC_%Extrap_pred	%	2.8436
Vz_F_pred	L	1336.7515
Cl_F_pred	L/h	30.1579
AUMClast	h*h*ng/mL	714474.9371
AUMCINF_obs	h*h*ng/mL	810470.3763
AUMC_%Extrap_obs	%	11.8444
AUMCINF_pred	h*h*ng/mL	804564.5644
AUMC_%Extrap_pred	%	11.1973
MRTlast	h	49.2838
MRTINF_obs	h	54.2147
MRTINF_pred	h	53.9200
AUC0_24	h*ng/mL	3913.7658

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	5.860			0.7325	0.5494	
1.000	12.50			3.028	2.661	
1.500	24.70			12.33	15.05	
2.000	38.60			28.15	43.61	
3.000	76.10			85.50	196.4	
4.000	95.60			171.4	501.7	
6.000	256.0			523.0	2420.	
8.000	228.0			1006.	5795.	
12.00	231.0			1924.	1.499e+004	
16.00	225.0			2836.	2.775e+004	
24.02	239.0			4696.	6.518e+004	
36.00	240.0			7566.	1.513e+005	
48.00	232.0		1.040e+004	2.702e+005		
60.00	249.0		1.328e+004	4.266e+005		
72.00	199.0		1.596e+004	6.027e+005		

96.00	137.0			1.995e+004	9.345e+005	
120.0 *	76.30	75.83	0.4695	2.244e+004	1.200e+006	1.000
144.0 *	47.20	47.79	-0.5863	2.389e+004	1.391e+006	1.000
168.0 *	30.30	30.11	0.1864	2.480e+004	1.533e+006	1.000

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

Final Parameters

Rsqr		0.9995
Rsqr_adjusted		0.9989
Corr_XY		-0.9997
No_points_lambda_z		3
Lambda_z	1/h	0.0192
Lambda_z_lower	h	120.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	36.0262
Tlag	h	0.5000
Tmax	h	6.0000
Cmax	ng/mL	256.0000
Cmax_D	ng/mL/mg	0.5689
Tlast	h	168.0000
Clast	ng/mL	30.3000
AUClast	h*ng/mL	24804.7480
AUCall	h*ng/mL	24804.7480
AUCINF_obs	h*ng/mL	26379.5832
AUCINF_D_obs	h*ng/mL/mg	58.6213
AUC_%Extrap_obs	%	5.9699
Vz_F_obs	L	886.6191
Cl_F_obs	L/h	17.0586
AUCINF_pred	h*ng/mL	26369.8930
AUCINF_D_pred	h*ng/mL/mg	58.5998
AUC_%Extrap_pred	%	5.9353
Vz_F_pred	L	886.9449
Cl_F_pred	L/h	17.0649
AUMClast	h*h*ng/mL	1532953.4265
AUMCINF_obs	h*h*ng/mL	1879377.4103
AUMC_%Extrap_obs	%	18.4329
AUMCINF_pred	h*h*ng/mL	1877245.8165
AUMC_%Extrap_pred	%	18.3403
MRTlast	h	61.8008
MRTINF_obs	h	71.2436
MRTINF_pred	h	71.1890
AUC0_24	h*ng/mL	4692.2430

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h ² *ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	7.790			0.9738	0.4869	
0.7500	16.90			4.060	2.558	
1.000	32.90			10.29	8.255	
1.500	69.20			35.81	42.43	
2.000	96.00			77.11	116.4	
3.000	120.0			185.1	392.4	
4.000	142.0			316.1	856.4	
6.000	172.0			630.1	2456.	
8.000	192.0			994.1	5024.	
12.00	206.0			1790.	1.304e+004	
16.00	197.0			2596.	2.431e+004	
24.00	230.0			4304.	5.900e+004	
36.00	278.0			7352.	1.522e+005	
48.00	232.0			1.040e+004	2.798e+005	
60.00 *	215.0	222.4	-7.439	1.308e+004	4.243e+005	1.000
72.02 *	179.0	179.5	-0.4744	1.545e+004	5.797e+005	1.000
96.00 *	115.0	116.9	-1.942	1.891e+004	8.681e+005	1.000
120.0 *	87.70	76.18	11.52	2.133e+004	1.128e+006	1.000
144.1 *	46.30	49.56	-3.261	2.289e+004	1.332e+006	1.000
168.0 *	31.70	32.32	-0.6217	2.381e+004	1.475e+006	1.000

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

Final Parameters

Rsq		0.9907
Rsq_adjusted		0.9883
Corr_XY		-0.9953
No_points_lambda_z		6
Lambda_z	1/h	0.0179
Lambda_z_lower	h	60.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	38.8093
Tlag	h	0.2500
Tmax	h	36.0000
Cmax	ng/mL	278.0000
Cmax_D	ng/mL/mg	0.6178
Tlast	h	168.0000
Clast	ng/mL	31.7000
AUClast	h*ng/mL	23813.9884
AUCall	h*ng/mL	23813.9884
AUCINF_obs	h*ng/mL	25588.8703
AUCINF_D_obs	h*ng/mL/mg	56.8642
AUC_%Extrap_obs	%	6.9361
Vz_F_obs	L	984.6267
Cl_F_obs	L/h	17.5858
AUCINF_pred	h*ng/mL	25623.6769
AUCINF_D_pred	h*ng/mL/mg	56.9415
AUC_%Extrap_pred	%	7.0626
Vz_F_pred	L	983.2892
Cl_F_pred	L/h	17.5619
AUMClast	h ² *ng/mL	1475092.5334
AUMCINF_obs	h ² *ng/mL	1872648.2664
AUMC_%Extrap_obs	%	21.2296
AUMCINF_pred	h ² *ng/mL	1880444.6104
AUMC_%Extrap_pred	%	21.5562
MRTlast	h	61.9423
MRTINF_obs	h	73.1821
MRTINF_pred	h	73.3870
AUC0_24	h*ng/mL	4303.9760

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI ,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

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AUC_%Extrap_obs	%	1.8710
Vz_F_obs	L	1008.3388
CL_F_obs	L/h	25.9036
AUCINF_pred	h*ng/mL	17351.8162
AUCINF_D_pred	h*ng/mL/mg	38.5596
AUC_%Extrap_pred	%	1.7562
Vz_F_pred	L	1009.5189
CL_F_pred	L/h	25.9339
AUMClast	h*h*ng/mL	780914.2247
AUMCINF_obs	h*h*ng/mL	848173.1252
AUMC_%Extrap_obs	%	7.9299
AUMCINF_pred	h*h*ng/mL	843970.8712
AUMC_%Extrap_pred	%	7.4714
MRTlast	h	45.8092
MRTINF_obs	h	48.8238
MRTINF_pred	h	48.6388
AUC0_24	h*ng/mL	5224.6947

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI ,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	16.30			2.038	2.038	
1.500	70.30			23.69	32.48	
2.000	135.0			75.01	126.3	
3.000	210.0			247.5	576.3	
4.000	263.0			484.0	1417.	
6.000	273.0			1020.	4107.	
8.000	280.0			1573.	7985.	
12.00	227.0			2583.	1.802e+004	
16.00	196.0			3428.	2.980e+004	
24.02 *	211.0	205.9	5.061	5059.	6.268e+004	1.000
36.00 *	174.0	170.7	3.337	7359.	1.312e+005	1.000
48.00 *	129.0	141.4	-12.39	9163.	2.065e+005	1.000
60.00 *	116.0	117.1	-1.143	1.063e+004	2.856e+005	1.000
72.02 *	96.00	97.03	-1.026	1.190e+004	3.692e+005	1.000
96.00 *	68.80	66.62	2.184	1.386e+004	5.324e+005	1.000
120.3 *	51.50	45.52	5.978	1.531e+004	6.885e+005	1.000
144.0 *	29.90	31.40	-1.502	1.625e+004	8.118e+005	1.000
168.1 *	20.70	21.50	-0.8036	1.686e+004	9.056e+005	1.000

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

Final Parameters

Rsqr		0.9940
Rsqr_adjusted		0.9931
Corr_XY		-0.9970
No_points_lambda_z		9
Lambda_z	1/h	0.0157
Lambda_z_lower	h	24.0167
Lambda_z_upper	h	168.1167
HL_Lambda_z	h	44.2083
Tlag	h	0.7500
Tmax	h	8.0000
Cmax	ng/mL	280.0000
Cmax_D	ng/mL/mg	0.6222
Tlast	h	168.1167
Clast	ng/mL	20.7000
AUClast	h*ng/mL	16855.7226
AUCall	h*ng/mL	16855.7226
AUCINF_obs	h*ng/mL	18175.9510
AUCINF_D_obs	h*ng/mL/mg	40.3910
AUC_%Extrap_obs	%	7.2636
Vz_F_obs	L	1579.0435
CL_F_obs	L/h	24.7580
AUCINF_pred	h*ng/mL	18227.2059
AUCINF_D_pred	h*ng/mL/mg	40.5049
AUC_%Extrap_pred	%	7.5244
Vz_F_pred	L	1574.6032
CL_F_pred	L/h	24.6884
AUMClast	h*h*ng/mL	905589.6981
AUMCINF_obs	h*h*ng/mL	1211745.1415
AUMC_%Extrap_obs	%	25.2657
AUMCINF_pred	h*h*ng/mL	1223630.9399
AUMC_%Extrap_pred	%	25.9916
MRTlast	h	53.7259
MRTINF_obs	h	66.6675
MRTINF_pred	h	67.1321
AUC0_24	h*ng/mL	5055.6666

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	

0.7500	0.0000			0.0000	0.0000
1.000	0.0000			0.0000	0.0000
1.500	21.40			5.350	8.025
2.000	16.70			14.83	24.51
3.000	52.60			49.48	120.1
4.000	53.30			102.4	305.6
6.000	100.0			255.7	1119.
8.000	107.0			462.7	2575.
12.00	170.0			1017.	8367.
16.00	175.0			1707.	1.805e+004
24.00	173.0			3099.	4.588e+004
36.00	208.0			5385.	1.157e+005
48.00	136.0			7418.	2.003e+005
60.03	103.0			8847.	2.770e+005
72.00	70.10			9870.	3.442e+005
96.00 *	32.80	31.77	1.029	1.105e+004	4.414e+005
120.0 *	17.20	18.28	-1.081	1.163e+004	5.033e+005
144.0 *	10.80	10.52	0.2805	1.196e+004	5.466e+005
168.0 *	6.070	6.053	0.01687	1.216e+004	5.771e+005

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

Final Parameters

Rsqr		0.9965
Rsqr_adjusted		0.9947
Corr_XY		-0.9982
No_points_lambda_z		4
Lambda_z	1/h	0.0230
Lambda_z_lower	h	96.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	30.1010
Tlag	h	1.0000
Tmax	h	36.0000
Cmax	ng/mL	208.0000
Cmax_D	ng/mL/mg	0.4622
Tlast	h	168.0000
Clast	ng/mL	6.0700
AUClast	h*ng/mL	12155.8917
AUCall	h*ng/mL	12155.8917
AUCINF_obs	h*ng/mL	12419.4909
AUCINF_D_obs	h*ng/mL/mg	27.5989
AUC_%Extrap_obs	%	2.1225
Vz_F_obs	L	1573.4902
CL_F_obs	L/h	36.2334
AUCINF_pred	h*ng/mL	12418.7581
AUCINF_D_pred	h*ng/mL/mg	27.5972
AUC_%Extrap_pred	%	2.1167
Vz_F_pred	L	1573.5831
CL_F_pred	L/h	36.2355
AUMClast	h*h*ng/mL	577097.4841
AUMCINF_obs	h*h*ng/mL	632829.3454
AUMC_%Extrap_obs	%	8.8068
AUMCINF_pred	h*h*ng/mL	632674.4096
AUMC_%Extrap_pred	%	8.7844
MRTlast	h	47.4747
MRTINF_obs	h	50.9545
MRTINF_pred	h	50.9451
AUC0_24	h*ng/mL	3098.7112

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535

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CL_F_pred	L/h	22.5195
AUMClast	h*h*ng/mL	1080950.4897
AUMCINF_obs	h*h*ng/mL	1333031.7987
AUMC_%Extrap_obs	%	18.9104
AUMCINF_pred	h*h*ng/mL	1337815.7841
AUMC_%Extrap_pred	%	19.2003
MRTlast	h	57.4438
MRTINF_obs	h	66.7818
MRTINF_pred	h	66.9487
AUC0_24	h*ng/mL	4766.7594

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:21

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5167	0.0000			0.0000	0.0000	
0.7500	6.050			0.7058	0.5294	
1.000	7.990			2.461	2.095	
1.500	18.40			9.058	10.99	
2.000	89.20			35.96	62.49	
3.000	76.80			118.8	268.6	
4.000	122.0			218.2	627.8	
6.000	249.0			589.2	2610.	
8.000	304.0			1142.	6536.	
12.00	351.0			2452.	1.982e+004	
16.00	309.0			3770.	3.822e+004	
24.00	255.0			6020.	8.292e+004	
36.00	193.0			8690.	1.623e+005	
48.00	162.0			1.081e+004	2.512e+005	
60.00	122.0			1.251e+004	3.421e+005	
72.00	75.50			1.367e+004	4.183e+005	
96.00	59.00			1.528e+004	5.524e+005	
120.0 *	30.10	29.74	0.3605	1.631e+004	6.623e+005	1.000
144.0 *	16.90	17.31	-0.4122	1.686e+004	7.341e+005	1.000
168.0 *	10.20	10.08	0.1221	1.717e+004	7.835e+005	1.000

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

Final Parameters

Rsqr 0.9985
Rsqr_adjusted 0.9970
Corr_XY -0.9993

No_points_lambda_z		3
Lambda_z	1/h	0.0225
Lambda_z_lower	h	120.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	30.7457
Tlag	h	0.5167
Tmax	h	12.0000
Cmax	ng/mL	351.0000
Cmax_D	ng/mL/mg	0.7800
Tlast	h	168.0000
Clast	ng/mL	10.2000
AUClast	h*ng/mL	17174.0467
AUCall	h*ng/mL	17174.0467
AUCINF_obs	h*ng/mL	17626.4846
AUCINF_D_obs	h*ng/mL/mg	39.1700
AUC_%Extrap_obs	%	2.5668
Vz_F_obs	L	1132.4150
Cl_F_obs	L/h	25.5298
AUCINF_pred	h*ng/mL	17621.0665
AUCINF_D_pred	h*ng/mL/mg	39.1579
AUC_%Extrap_pred	%	2.5368
Vz_F_pred	L	1132.7632
Cl_F_pred	L/h	25.5376
AUMClast	h*h*ng/mL	783474.7942
AUMCINF_obs	h*h*ng/mL	879552.9950
AUMC_%Extrap_obs	%	10.9235
AUMCINF_pred	h*h*ng/mL	878402.4272
AUMC_%Extrap_pred	%	10.8069
MRTlast	h	45.6197
MRTINF_obs	h	49.8995
MRTINF_pred	h	49.8496
AUC0_24	h*ng/mL	6019.5094

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2667	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	7.380			0.9225	0.6919	
1.000	9.900			3.083	2.621	
1.500	26.40			12.16	15.00	
2.000	51.40			31.61	50.60	
3.000	95.70			105.2	245.5	
4.000	126.0			216.0	641.1	
6.000	174.0			516.0	2189.	

8.000	160.0			849.8	4521.	
12.00 *	153.0	158.3	-5.302	1476.	1.077e+004	1.000
16.00 *	144.0	145.0	-1.024	2070.	1.907e+004	1.000
24.00 *	120.0	121.7	-1.715	3123.	4.001e+004	1.000
36.00 *	92.20	93.58	-1.384	4388.	7.765e+004	1.000
48.00 *	77.40	71.95	5.445	5404.	1.201e+005	1.000
60.00 *	53.50	55.32	-1.824	6180.	1.618e+005	1.000
72.00 *	46.30	42.54	3.762	6778.	2.011e+005	1.000
96.00 *	23.80	25.15	-1.347	7589.	2.682e+005	1.000
120.2 *	15.30	14.82	0.4824	8054.	3.180e+005	1.000
144.0 *	8.630	8.789	-0.1586	8332.	3.544e+005	1.000
168.0 *	5.130	5.196	-0.06559	8493.	3.794e+005	1.000

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

Final Parameters

Rsqr		0.9985
Rsqr_adjusted		0.9984
Corr_XY		-0.9993
No_points_lambda_z		11
Lambda_z	1/h	0.0219
Lambda_z_lower	h	12.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	31.6478
Tlag	h	0.5000
Tmax	h	6.0000
Cmax	ng/mL	174.0000
Cmax_D	ng/mL/mg	0.3867
Tlast	h	168.0000
Clast	ng/mL	5.1300
AUClast	h*ng/mL	8493.2403
AUCall	h*ng/mL	8493.2403
AUCINF_obs	h*ng/mL	8727.4667
AUCINF_D_obs	h*ng/mL/mg	19.3944
AUC_%Extrap_obs	%	2.6838
Vz_F_obs	L	2354.1972
Cl_F_obs	L/h	51.5614
AUCINF_pred	h*ng/mL	8730.4613
AUCINF_D_pred	h*ng/mL/mg	19.4010
AUC_%Extrap_pred	%	2.7172
Vz_F_pred	L	2353.3897
Cl_F_pred	L/h	51.5437
AUMClast	h*h*ng/mL	379413.2473
AUMCINF_obs	h*h*ng/mL	429457.6382
AUMC_%Extrap_obs	%	11.6529
AUMCINF_pred	h*h*ng/mL	430097.4552
AUMC_%Extrap_pred	%	11.7844
MRTlast	h	44.6724
MRTINF_obs	h	49.2076
MRTINF_pred	h	49.2640
AUC0_24	h*ng/mL	3122.6100

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI ,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00

MRTINF_obs	h	65.2297
MRTINF_pred	h	65.1955
AUC0_24	h*ng/mL	3422.5197

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.033	0.0000			0.0000	0.0000	
1.500	6.060			1.414	2.121	
2.000	13.30			6.254	11.04	
3.000	39.70			32.75	83.89	
4.000	49.00			77.10	241.4	
6.000	227.0			353.1	1799.	
8.000	231.0			811.1	5009.	
12.00	241.0			1755.	1.449e+004	
16.00	205.0			2645.	2.690e+004	
24.00	195.0			4245.	5.884e+004	
36.00 *	181.0	185.7	-4.703	6500.	1.263e+005	1.000
48.02 *	145.0	147.9	-2.936	8451.	2.078e+005	1.000
60.00 *	125.0	117.9	7.076	1.007e+004	2.948e+005	1.000
72.00 *	92.50	93.97	-1.471	1.136e+004	3.799e+005	1.000
96.00 *	59.80	59.67	0.1271	1.316e+004	5.295e+005	1.000
120.0 *	38.00	37.89	0.1069	1.431e+004	6.530e+005	1.000
144.0 *	24.80	24.06	0.7374	1.506e+004	7.504e+005	1.000
168.0 *	14.80	15.28	-0.4801	1.552e+004	8.225e+005	1.000

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

Final Parameters

Rsq		0.9988
Rsq_adjusted		0.9986
Corr_XY		-0.9994
No_points_lambda_z		8
Lambda_z	1/h	0.0189
Lambda_z_lower	h	36.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	36.6333
Tlag	h	1.0333
Tmax	h	12.0000

Cmax	ng/mL	241.0000
Cmax_D	ng/mL/mg	0.5356
Tlast	h	168.0000
Clast	ng/mL	14.8000
AUClast	h*ng/mL	15520.8814
AUCall	h*ng/mL	15520.8814
AUCINF_obs	h*ng/mL	16303.0722
AUCINF_D_obs	h*ng/mL/mg	36.2290
AUC_%Extrap_obs	%	4.7978
Vz_F_obs	L	1458.7943
CL_F_obs	L/h	27.6022
AUCINF_pred	h*ng/mL	16328.4450
AUCINF_D_pred	h*ng/mL/mg	36.2854
AUC_%Extrap_pred	%	4.9457
Vz_F_pred	L	1456.5275
CL_F_pred	L/h	27.5593
AUMClast	h*h*ng/mL	822459.3369
AUMCINF_obs	h*h*ng/mL	995206.7539
AUMC_%Extrap_obs	%	17.3579
AUMCINF_pred	h*h*ng/mL	1000810.3660
AUMC_%Extrap_pred	%	17.8207
MRTlast	h	52.9905
MRTINF_obs	h	61.0441
MRTINF_pred	h	61.2924
AUC0_24	h*ng/mL	4244.8300

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7667	7.930			1.057	0.8106	
1.000	10.20			3.173	2.710	
1.500	41.80			16.17	20.93	
2.000	67.90			43.60	70.56	
3.000	102.0			128.5	291.5	
4.000	130.0			244.5	704.5	
6.000	186.0			560.5	2340.	
8.017	234.0			984.0	5357.	
12.00	222.0			1892. 1.443e+004		
16.00	261.0			2858. 2.811e+004		
24.02	267.0			4974. 7.055e+004		
36.00 *	180.0	178.9	1.097	7619. 1.489e+005		1.000
48.00 *	142.0	139.5	2.496	9542. 2.292e+005		1.000
60.00 *	111.0	108.8	2.219	1.105e+004 3.104e+005		1.000

72.00 *	85.00	84.82	0.1753	1.222e+004	3.872e+005	1.000
96.00 *	49.90	51.58	-1.677	1.380e+004	5.184e+005	1.000
120.0 *	29.10	31.36	-2.261	1.473e+004	6.174e+005	1.000
144.0 *	19.60	19.07	0.5309	1.531e+004	6.931e+005	1.000
168.0 *	12.00	11.59	0.4051	1.568e+004	7.507e+005	1.000

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

Final Parameters

Rsqr		0.9986
Rsqr_adjusted		0.9984
Corr_XY		-0.9993
No_points_lambda_z		8
Lambda_z	1/h	0.0207
Lambda_z_lower	h	36.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	33.4379
Tlag	h	0.5000
Tmax	h	24.0167
Cmax	ng/mL	267.0000
Cmax_D	ng/mL/mg	0.5933
Tlast	h	168.0000
Clast	ng/mL	12.0000
AUClast	h*ng/mL	15676.9265
AUCall	h*ng/mL	15676.9265
AUCINF_obs	h*ng/mL	16255.8149
AUCINF_D_obs	h*ng/mL/mg	36.1240
AUC_%Extrap_obs	%	3.5611
Vz_F_obs	L	1335.4184
CL_F_obs	L/h	27.6824
AUCINF_pred	h*ng/mL	16236.2731
AUCINF_D_pred	h*ng/mL/mg	36.0806
AUC_%Extrap_pred	%	3.4450
Vz_F_pred	L	1337.0257
CL_F_pred	L/h	27.7157
AUMClast	h*h*ng/mL	750689.4744
AUMCINF_obs	h*h*ng/mL	875868.7062
AUMC_%Extrap_obs	%	14.2920
AUMCINF_pred	h*h*ng/mL	871642.9765
AUMC_%Extrap_pred	%	13.8765
MRTlast	h	47.8850
MRTINF_obs	h	53.8803
MRTINF_pred	h	53.6849
AUC0_24	h*ng/mL	4969.9879

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:21

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	0.0000			0.0000	0.0000	
1.500	17.50			4.375	6.563	
2.000	20.20			13.80	23.23	
3.000	70.40			59.10	149.0	
4.000	106.0			147.3	466.6	
6.000	202.0			455.3	2103.	
8.000	203.0			860.3	4939.	
12.00	172.0			1609. 1.238e+004		
16.00	147.0			2245. 2.126e+004		
24.00	129.0			3348. 4.321e+004		
36.00 *	122.0	119.3	2.733	4853. 8.830e+004		1.000
48.00 *	86.30	87.78	-1.479	6091. 1.398e+005		1.000
60.00 *	64.40	64.60	-0.2049	6989. 1.881e+005		1.000
72.00 *	48.40	47.55	0.8514	7661. 2.322e+005		1.000
96.00 *	25.30	25.76	-0.4562	8515. 3.029e+005		1.000
120.0 *	13.40	13.95	-0.5517	8965. 3.509e+005		1.000
144.0 *	7.850	7.557	0.2926	9214. 3.835e+005		1.000
168.0	0.0000			9308. 3.971e+005		

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

Final Parameters

Rsqr 0.9993
Rsqr_adjusted 0.9991
Corr_XY -0.9996
No_points_lambda_z 7
Lambda_z 1/h 0.0255
Lambda_z_lower h 36.0000
Lambda_z_upper h 144.0000
HL_Lambda_z h 27.1346
Tlag h 1.0000
Tmax h 8.0000
Cmax ng/mL 203.0000
Cmax_D ng/mL/mg 0.4511
Tlast h 144.0000
Clast ng/mL 7.8500
AUClast h*ng/mL 9213.9288
AUCall h*ng/mL 9308.1288
AUCINF_obs h*ng/mL 9521.2320

AUCINF_D_obs	h*ng/mL/mg	21.1583
AUC_%Extrap_obs	%	3.2276
Vz_F_obs	L	1850.1917
Cl_F_obs	L/h	47.2628
AUCINF_pred	h*ng/mL	9509.7772
AUCINF_D_pred	h*ng/mL/mg	21.1328
AUC_%Extrap_pred	%	3.1110
Vz_F_pred	L	1852.4203
Cl_F_pred	L/h	47.3197
AUMClast	h*h*ng/mL	383506.7812
AUMCINF_obs	h*h*ng/mL	439788.4020
AUMC_%Extrap_obs	%	12.7974
AUMCINF_pred	h*h*ng/mL	437690.4856
AUMC_%Extrap_pred	%	12.3795
MRTIast	h	41.6225
MRTINF_obs	h	46.1903
MRTINF_pred	h	46.0253
AUC0_24	h*ng/mL	3347.7131

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	5.330			0.6663	0.4997	
1.017	9.260			2.612	2.288	
1.500	17.80			9.151	11.02	
2.000	46.00			25.10	40.69	
3.000	83.40			89.80	211.8	
4.000	115.0			189.0	566.9	
6.000	245.0			549.0	2497.	
8.000	263.0			1057.	6071.	
12.00	257.0			2097.	1.646e+004	
16.00	270.0			3151.	3.127e+004	
24.02	279.0			5352.	7.544e+004	
36.00	261.0			8586.	1.723e+005	
48.00	255.0			1.168e+004	3.022e+005	
60.00	201.0			1.440e+004	4.486e+005	
72.00	174.0			1.665e+004	5.966e+005	
96.00	95.40			1.979e+004	8.565e+005	
120.0 *	49.00	48.84	0.1551	2.146e+004	1.035e+006	1.000
144.0 *	30.80	31.00	-0.1956	2.240e+004	1.158e+006	1.000
168.1 *	19.70	19.64	0.06215	2.300e+004	1.251e+006	1.000

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

Final Parameters

Rsqr		0.9999
Rsqr_adjusted		0.9997
Corr_XY		-0.9999
No_points_lambda_z		3
Lambda_z	1/h	0.0190
Lambda_z_lower	h	120.0333
Lambda_z_upper	h	168.0500
HL_Lambda_z	h	36.5265
Tlag	h	0.5000
Tmax	h	24.0167
Cmax	ng/mL	279.0000
Cmax_D	ng/mL/mg	0.6200
Tlast	h	168.0500
Clast	ng/mL	19.7000
AUClast	h*ng/mL	23000.4030
AUCall	h*ng/mL	23000.4030
AUCINF_obs	h*ng/mL	24038.5264
AUCINF_D_obs	h*ng/mL/mg	53.4189
AUC_%Extrap_obs	%	4.3186
Vz_F_obs	L	986.4780
Cl_F_obs	L/h	18.7199
AUCINF_pred	h*ng/mL	24035.2514
AUCINF_D_pred	h*ng/mL/mg	53.4117
AUC_%Extrap_pred	%	4.3055
Vz_F_pred	L	986.6124
Cl_F_pred	L/h	18.7225
AUMClast	h*h*ng/mL	1250878.2518
AUMCINF_obs	h*h*ng/mL	1480040.4739
AUMC_%Extrap_obs	%	15.4835
AUMCINF_pred	h*h*ng/mL	1479317.5414
AUMC_%Extrap_pred	%	15.4422
MRTlast	h	54.3851
MRTINF_obs	h	61.5695
MRTINF_pred	h	61.5478
AUC0_24	h*ng/mL	5346.8801

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:21

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 18
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	

0.5000	0.0000			0.0000	0.0000
0.7500	5.000			0.6250	0.4688
1.000	10.30			2.538	2.225
1.500	22.00			10.61	13.05
2.000	38.80			25.81	40.70
3.000	107.0			98.71	240.0
4.000	143.0			223.7	686.5
6.000	244.0			610.7	2723.
8.000	240.0			1095.	6109.
12.00	201.0			1974.	1.485e+004
16.00	147.0			2665.	2.445e+004
24.00	112.0			3694.	4.485e+004
36.00	92.60			4918.	8.134e+004
48.00 *	68.80	68.47	0.3324	5880.	1.214e+005
60.00 *	54.90	55.43	-0.5344	6619.	1.612e+005
72.00 *	45.10	44.88	0.2179	7217.	2.005e+005

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

Final Parameters

Rsqr		0.9984
Rsqr_adjusted		0.9968
Corr_XY		-0.9992
No_points_lambda_z		3
Lambda_z	1/h	0.0176
Lambda_z_lower	h	48.0000
Lambda_z_upper	h	72.0000
HL_Lambda_z	h	39.3907
Tlag	h	0.5000
Tmax	h	6.0000
Cmax	ng/mL	244.0000
Cmax_D	ng/mL/mg	0.5422
Tlast	h	72.0000
Clast	ng/mL	45.1000
AUClast	h*ng/mL	7216.8292
AUCall	h*ng/mL	7216.8292
AUCINF_obs	h*ng/mL	9779.8055
AUCINF_D_obs	h*ng/mL/mg	21.7329
AUC_%Extrap_obs	%	26.2068
Vz_F_obs	L	2614.8715
Cl_F_obs	L/h	46.0132
AUCINF_pred	h*ng/mL	9767.4225
AUCINF_D_pred	h*ng/mL/mg	21.7054
AUC_%Extrap_pred	%	26.1133
Vz_F_pred	L	2618.1866
Cl_F_pred	L/h	46.0715
AUMClast	h*h*ng/mL	200528.3458
AUMCINF_obs	h*h*ng/mL	530713.3641
AUMC_%Extrap_obs	%	62.2153
AUMCINF_pred	h*h*ng/mL	529118.0731
AUMC_%Extrap_pred	%	62.1014
MRTlast	h	27.7862
MRTINF_obs	h	54.2662
MRTINF_pred	h	54.1717
AUC0_24	h*ng/mL	3694.4375

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI ,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

AUMC_%Extrap_obs	%	11.6469
AUMCINF_pred	h*ng/mL	474991.6570
AUMC_%Extrap_pred	%	10.8133
MRTlast	h	43.9893
MRTINF_obs	h	48.4922
MRTINF_pred	h	48.1395
AUC0_24	h*ng/mL	3639.0276

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	0.0000			0.0000	0.0000	
1.500	0.0000			0.0000	0.0000	
2.000	0.0000			0.0000	0.0000	
3.000	11.60			5.800	17.40	
4.000	30.20			26.70	95.20	
6.000	106.0			162.9	852.0	
8.000	109.0			377.9	2360.	
12.00	100.0			795.6	6525.	
16.00	90.50			1176. 1.184e+004		
24.00	100.0			1938. 2.723e+004		
36.00 *	96.70	94.41	2.286	3118. 6.260e+004		1.000
48.00 *	68.60	71.08	-2.480	4101. 1.035e+005		1.000
60.00 *	51.90	53.51	-1.613	4819. 1.421e+005		1.000
72.00 *	41.00	40.29	0.7125	5374. 1.786e+005		1.000
96.00 *	24.10	22.83	1.265	6137. 2.419e+005		1.000
120.0 *	12.70	12.94	-0.2424	6564. 2.875e+005		1.000
144.0 *	7.260	7.336	-0.07559	6798. 3.180e+005		1.000
168.0	0.0000			6885. 3.306e+005		

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

Final Parameters

Rsqr		0.9988
Rsqr_adjusted		0.9985
Corr_XY		-0.9994
No_points_lambda_z		7
Lambda_z	1/h	0.0237
Lambda_z_lower	h	36.0000

Lambda_z_upper	h	144.0000
HL_Lambda_z	h	29.2999
Tlag	h	2.0000
Tmax	h	8.0000
Cmax	ng/mL	109.0000
Cmax_D	ng/mL/mg	0.2422
Tlast	h	144.0000
Clast	ng/mL	7.2600
AUClast	h*ng/mL	6797.6504
AUCall	h*ng/mL	6884.7704
AUCINF_obs	h*ng/mL	7104.5362
AUCINF_D_obs	h*ng/mL/mg	15.7879
AUC_%Extrap_obs	%	4.3196
Vz_F_obs	L	2677.4229
Cl_F_obs	L/h	63.3398
AUCINF_pred	h*ng/mL	7107.7313
AUCINF_D_pred	h*ng/mL/mg	15.7950
AUC_%Extrap_pred	%	4.3626
Vz_F_pred	L	2676.2193
Cl_F_pred	L/h	63.3113
AUMClast	h*h*ng/mL	318043.2142
AUMCINF_obs	h*h*ng/mL	375207.0721
AUMC_%Extrap_obs	%	15.2353
AUMCINF_pred	h*h*ng/mL	375802.2394
AUMC_%Extrap_pred	%	15.3695
MRTlast	h	46.7872
MRTINF_obs	h	52.8123
MRTINF_pred	h	52.8723
AUC0_24	h*ng/mL	1938.3255

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI ,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	7.290			0.9113	0.9113	
1.500	15.70			6.659	8.621	
2.000	35.70			19.51	32.36	
3.000	78.50			76.61	185.8	
4.000	106.0			168.9	515.6	
6.000	175.0			449.9	1990.	
8.017	214.0			842.1	4778.	
12.00	246.0			1758.	1.407e+004	
16.00	252.0			2754.	2.804e+004	

24.00	262.0			4810. 6.932e+004	
36.00	267.0			7984. 1.647e+005	
48.00	281.0			1.127e+004 3.033e+005	
60.03	245.0			1.443e+004 4.736e+005	
72.00	201.0			1.709e+004 6.486e+005	
96.03 *	105.0	103.5	1.511	2.065e+004 9.426e+005	1.000
120.0 *	64.50	65.17	-0.6747	2.264e+004 1.156e+006	1.000
144.0 *	40.10	41.02	-0.9190	2.387e+004 1.317e+006	1.000
168.0 *	26.30	25.82	0.4838	2.465e+004 1.439e+006	1.000

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

Final Parameters

Rsqr		0.9989
Rsqr_adjusted		0.9984
Corr_XY		-0.9995
No_points_lambda_z		4
Lambda_z	1/h	0.0193
Lambda_z_lower	h	96.0333
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	35.9271
Tlag	h	0.7500
Tmax	h	48.0000
Cmax	ng/mL	281.0000
Cmax_D	ng/mL/mg	0.6244
Tlast	h	168.0000
Clast	ng/mL	26.3000
AUClast	h*ng/mL	24654.2933
AUCall	h*ng/mL	24654.2933
AUCINF_obs	h*ng/mL	26017.4726
AUCINF_D_obs	h*ng/mL/mg	57.8166
AUC_%Extrap_obs	%	5.2395
Vz_F_obs	L	896.4883
CL_F_obs	L/h	17.2961
AUCINF_pred	h*ng/mL	25992.3942
AUCINF_D_pred	h*ng/mL/mg	57.7609
AUC_%Extrap_pred	%	5.1480
Vz_F_pred	L	897.3533
CL_F_pred	L/h	17.3128
AUMClast	h*h*ng/mL	1439103.8570
AUMCINF_obs	h*h*ng/mL	1738774.1565
AUMC_%Extrap_obs	%	17.2346
AUMCINF_pred	h*h*ng/mL	1733261.1376
AUMC_%Extrap_pred	%	16.9713
MRTlast	h	58.3713
MRTINF_obs	h	66.8310
MRTINF_pred	h	66.6834
AUC0_24	h*ng/mL	4810.2671

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values

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WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	6.740			0.8425	0.8425	
1.500	15.70			6.453	8.415	
2.000	39.40			20.23	34.00	
3.000	88.80			84.33	206.6	
4.000	106.0			181.7	551.8	
6.017	168.0			458.0	1999.	
8.000	178.0			801.1	4413.	
12.00	182.0			1521.	1.163e+004	
16.10	190.0			2284.	2.238e+004	
24.07	187.0			3785.	5.252e+004	
36.00	179.0			5969.	1.180e+005	
48.00 *	149.0	159.1	-10.12	7931.	2.001e+005	1.000
60.02 *	122.0	120.4	1.631	9554.	2.874e+005	1.000
72.00 *	96.70	91.13	5.573	1.086e+004	3.732e+005	1.000
96.17 *	55.70	51.99	3.713	1.265e+004	5.222e+005	1.000
120.0 *	28.40	29.89	-1.489	1.362e+004	6.254e+005	1.000
146.9 *	14.70	15.99	-1.290	1.418e+004	6.993e+005	1.000
168.0 *	10.40	9.803	0.5968	1.444e+004	7.404e+005	1.000

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

Final Parameters

Rsq 0.9961
Rsq_adjusted 0.9953
Corr_XY -0.9981
No_points_lambda_z 7
Lambda_z 1/h 0.0232
Lambda_z_lower h 48.0000
Lambda_z_upper h 168.0000
HL_Lambda_z h 29.8456
Tlag h 0.7500
Tmax h 16.1000
Cmax ng/mL 190.0000
Cmax_D ng/mL/mg 0.4222
Tlast h 168.0000

Clast	ng/mL	10.4000
AUClast	h*ng/mL	14442.9440
AUCall	h*ng/mL	14442.9440
AUCINF_obs	h*ng/mL	14890.7483
AUCINF_D_obs	h*ng/mL/mg	33.0906
AUC_%Extrap_obs	%	3.0073
Vz_F_obs	L	1301.2206
Cl_F_obs	L/h	30.2201
AUCINF_pred	h*ng/mL	14865.0506
AUCINF_D_pred	h*ng/mL/mg	33.0334
AUC_%Extrap_pred	%	2.8396
Vz_F_pred	L	1303.4700
Cl_F_pred	L/h	30.2723
AUMClast	h*h*ng/mL	740382.3484
AUMCINF_obs	h*h*ng/mL	834895.0777
AUMC_%Extrap_obs	%	11.3203
AUMCINF_pred	h*h*ng/mL	829471.3823
AUMC_%Extrap_pred	%	10.7405
MRTlast	h	51.2626
MRTINF_obs	h	56.0680
MRTINF_pred	h	55.8001
AUC0_24	h*ng/mL	3772.9450

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	7.880			0.9850	0.9850	
1.500	12.80			6.155	7.755	
2.000	23.70			15.28	24.41	
3.000	74.60			64.43	160.0	
4.000	121.0			162.2	513.9	
6.000	215.0			498.2	2288.	
8.000	231.0			944.2	5426.	
12.00	210.0			1826.	1.421e+004	
16.00	186.0			2617.	2.525e+004	
24.02	166.0			4026.	5.335e+004	
36.00	189.0			6153.	1.180e+005	
48.00	175.0			8336.	2.095e+005	
60.00	156.0			1.032e+004	3.164e+005	
72.00	118.0			1.195e+004	4.238e+005	
96.00	92.70			1.447e+004	6.339e+005	
120.0 *	54.60	54.45	0.1531	1.620e+004	8.188e+005	1.000

144.0 *	33.10	33.29	-0.1864	1.723e+004	9.538e+005	1.000
168.0 *	20.40	20.34	0.05717	1.786e+004	1.051e+006	1.000

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

Final Parameters

Rsqr		0.9999
Rsqr_adjusted		0.9998
Corr_XY		-1.0000
No_points_lambda_z		3
Lambda_z	1/h	0.0205
Lambda_z_lower	h	120.0167
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	33.7833
Tlag	h	0.7500
Tmax	h	8.0000
Cmax	ng/mL	231.0000
Cmax_D	ng/mL/mg	0.5133
Tlast	h	168.0000
Clast	ng/mL	20.4000
AUClast	h*ng/mL	17858.0511
AUCall	h*ng/mL	17858.0511
AUCINF_obs	h*ng/mL	18852.3253
AUCINF_D_obs	h*ng/mL/mg	41.8941
AUC_%Extrap_obs	%	5.2740
Vz_F_obs	L	1163.3854
Cl_F_obs	L/h	23.8697
AUCINF_pred	h*ng/mL	18849.5389
AUCINF_D_pred	h*ng/mL/mg	41.8879
AUC_%Extrap_pred	%	5.2600
Vz_F_pred	L	1163.5573
Cl_F_pred	L/h	23.8733
AUMClast	h*h*ng/mL	1051407.0812
AUMCINF_obs	h*h*ng/mL	1266905.0092
AUMC_%Extrap_obs	%	17.0098
AUMCINF_pred	h*h*ng/mL	1266301.0863
AUMC_%Extrap_pred	%	16.9702
MRTlast	h	58.8758
MRTINF_obs	h	67.2015
MRTINF_pred	h	67.1794
AUC0_24	h*ng/mL	4023.2390

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI ,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

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

h	ng/mL	ng/mL	ng/mL	h*ng/mL	h*h*ng/mL	
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	6.030			0.7538	0.7538	
1.500	20.50			7.386	9.949	
2.000	35.80			21.46	35.54	
3.000	112.0			95.36	239.3	
4.000	176.0			239.4	759.3	
6.000	212.0			627.4	2735.	
8.000	224.0			1063.	5799.	
12.00	233.0			1977.	1.498e+004	
16.00	213.0			2869.	2.743e+004	
24.02	231.0			4648.	6.333e+004	
36.00	225.0			7381.	1.452e+005	
48.00	175.0			9768.	2.449e+005	
60.00	176.0			1.187e+004	3.587e+005	
72.00	164.0			1.391e+004	4.931e+005	
96.00	112.0			1.719e+004	7.655e+005	
120.0 *	59.10	59.20	-0.1041	1.917e+004	9.775e+005	1.000
144.0 *	35.50	35.38	0.1248	2.028e+004	1.123e+006	1.000
168.0 *	21.10	21.14	-0.03717	2.095e+004	1.226e+006	1.000

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

Final Parameters

Rsqr		1.0000
Rsqr_adjusted		0.9999
Corr_XY		-1.0000
No_points_lambda_z		3
Lambda_z	1/h	0.0215
Lambda_z_lower	h	120.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	32.3033
Tlag	h	0.7500
Tmax	h	12.0000
Cmax	ng/mL	233.0000
Cmax_D	ng/mL/mg	0.5178
Tlast	h	168.0000
Clast	ng/mL	21.1000
AUClast	h*ng/mL	20947.0902
AUCall	h*ng/mL	20947.0902
AUCINF_obs	h*ng/mL	21930.4314
AUCINF_D_obs	h*ng/mL/mg	48.7343
AUC_%Extrap_obs	%	4.4839
Vz_F_obs	L	956.2845
Cl_F_obs	L/h	20.5194
AUCINF_pred	h*ng/mL	21932.1638
AUCINF_D_pred	h*ng/mL/mg	48.7381
AUC_%Extrap_pred	%	4.4915
Vz_F_pred	L	956.2089
Cl_F_pred	L/h	20.5178
AUMClast	h*h*ng/mL	1225971.4686
AUMCINF_obs	h*h*ng/mL	1437000.2689
AUMC_%Extrap_obs	%	14.6854
AUMCINF_pred	h*h*ng/mL	1437372.0569
AUMC_%Extrap_pred	%	14.7074
MRTlast	h	58.5271
MRTINF_obs	h	65.5254
MRTINF_pred	h	65.5372
AUC0_24	h*ng/mL	4644.6133

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI ,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI

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CLF_obs	L/h	37.8337
AUCINF_pred	h*ng/mL	11863.9452
AUCINF_D_pred	h*ng/mL/mg	26.3643
AUC_%Extrap_pred	%	2.5832
Vz_F_pred	L	1675.8349
CLF_pred	L/h	37.9300
AUMClast	h*h*ng/mL	541364.5996
AUMCINF_obs	h*h*ng/mL	612799.7356
AUMC_%Extrap_obs	%	11.6572
AUMCINF_pred	h*h*ng/mL	606390.8933
AUMC_%Extrap_pred	%	10.7235
MRTlast	h	46.8411
MRTINF_obs	h	51.5211
MRTINF_pred	h	51.1121
AUC0_24	h*ng/mL	3679.1063

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:21

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.033	11.10			1.572	1.625	
1.500	26.90			10.44	13.72	
2.017	34.20			26.22	41.96	
3.000	167.0			125.1	322.2	
4.000	154.0			285.6	882.6	
6.000	230.0			669.6	2879.	
8.000	255.0			1155.	6299.	
12.00	291.0			2247.	1.736e+004	
16.00	298.0			3425.	3.388e+004	
24.03	312.0			5875.	8.315e+004	
36.00 *	260.0	265.8	-5.800	9288.	1.850e+005	1.000
48.00 *	214.0	201.5	12.52	1.212e+004	3.035e+005	1.000
60.00 *	144.0	152.7	-8.726	1.424e+004	4.172e+005	1.000
72.00 *	117.0	115.8	1.231	1.580e+004	5.198e+005	1.000
96.00 *	62.60	66.52	-3.920	1.789e+004	6.926e+005	1.000
120.3 *	43.60	37.99	5.613	1.917e+004	8.295e+005	1.000
144.0 *	20.90	21.96	-1.062	1.990e+004	9.252e+005	1.000
168.0 *	12.40	12.62	-0.2189	2.029e+004	9.858e+005	1.000

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

Final Parameters

Rsqr		0.9961
Rsqr_adjusted		0.9954
Corr_XY		-0.9980
No_points_lambda_z		8
Lambda_z	1/h	0.0231
Lambda_z_lower	h	36.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	30.0227
Tlag	h	0.7500
Tmax	h	24.0333
Cmax	ng/mL	312.0000
Cmax_D	ng/mL/mg	0.6933
Tlast	h	168.0000
Clast	ng/mL	12.4000
AUClast	h*ng/mL	20289.2653
AUCall	h*ng/mL	20289.2653
AUCINF_obs	h*ng/mL	20826.3535
AUCINF_D_obs	h*ng/mL/mg	46.2808
AUC_%Extrap_obs	%	2.5789
Vz_F_obs	L	935.8865
CL_F_obs	L/h	21.6072
AUCINF_pred	h*ng/mL	20835.8369
AUCINF_D_pred	h*ng/mL/mg	46.3019
AUC_%Extrap_pred	%	2.6232
Vz_F_pred	L	935.4606
CL_F_pred	L/h	21.5974
AUMClast	h*h*ng/mL	985802.1871
AUMCINF_obs	h*h*ng/mL	1099296.2082
AUMC_%Extrap_obs	%	10.3242
AUMCINF_pred	h*h*ng/mL	1101300.1855
AUMC_%Extrap_pred	%	10.4874
MRTlast	h	48.5874
MRTINF_obs	h	52.7839
MRTINF_pred	h	52.8561
AUC0_24	h*ng/mL	5864.3265

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

7.0.0.2535

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	7.290			0.9113	0.4556	
0.7500	16.00			3.823	2.411	
1.000	21.90			8.560	6.649	

1.500	39.40			23.89	26.90
2.000	69.90			51.21	76.62
3.000	97.10			134.7	292.2
4.000	195.0			280.8	827.8
6.000	343.0			818.8	3666.
8.000	363.0			1525.	8628.
12.00	301.0			2849.	2.179e+004
16.00	278.0			4006.	3.796e+004
24.00 *	273.0	286.3	-13.34	6210.	8.201e+004 1.000
36.00 *	229.0	231.6	-2.642	9214.	1.716e+005 1.000
48.00 *	193.0	187.4	5.607	1.174e+004	2.773e+005 1.000
60.00 *	149.0	151.6	-2.596	1.378e+004	3.869e+005 1.000
72.00 *	130.0	122.6	7.363	1.545e+004	4.970e+005 1.000
96.00 *	78.70	80.26	-1.559	1.791e+004	7.006e+005 1.000
120.0 *	53.00	52.52	0.4752	1.947e+004	8.679e+005 1.000
144.0 *	37.50	34.36	3.136	2.054e+004	1.009e+006 1.000
168.0 *	20.60	22.50	-1.896	2.122e+004	1.114e+006 1.000

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

Final Parameters

Rsqr		0.9964
Rsqr_adjusted		0.9958
Corr_XY		-0.9982
No_points_lambda_z		9
Lambda_z	1/h	0.0177
Lambda_z_lower	h	24.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	39.2372
Tlag	h	0.2500
Tmax	h	8.0000
Cmax	ng/mL	363.0000
Cmax_D	ng/mL/mg	0.8067
Tlast	h	168.0000
Clast	ng/mL	20.6000
AUClast	h*ng/mL	21218.2736
AUCall	h*ng/mL	21218.2736
AUCINF_obs	h*ng/mL	22384.3851
AUCINF_D_obs	h*ng/mL/mg	49.7431
AUC_%Extrap_obs	%	5.2095
Vz_F_obs	L	1137.9946
CL_F_obs	L/h	20.1033
AUCINF_pred	h*ng/mL	22491.7155
AUCINF_D_pred	h*ng/mL/mg	49.9816
AUC_%Extrap_pred	%	5.6618
Vz_F_pred	L	1132.5641
CL_F_pred	L/h	20.0074
AUMClast	h*h*ng/mL	1113944.4494
AUMCINF_obs	h*h*ng/mL	1375861.6680
AUMC_%Extrap_obs	%	19.0366
AUMCINF_pred	h*h*ng/mL	1399968.8604
AUMC_%Extrap_pred	%	20.4308
MRTlast	h	52.4993
MRTINF_obs	h	61.4652
MRTINF_pred	h	62.2438
AUC0_24	h*ng/mL	6210.2217

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
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AUMCINF_obs	h*h*ng/mL	809099.4814
AUMC_%Extrap_obs	%	13.5804
AUMCINF_pred	h*h*ng/mL	798791.8736
AUMC_%Extrap_pred	%	12.4653
MRTlast	h	49.9341
MRTINF_obs	h	55.7361
MRTINF_pred	h	55.2093
AUC0_24	h*ng/mL	3865.0356

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	0.0000			0.0000	0.0000	
1.500	0.0000			0.0000	0.0000	
2.000	8.690			2.173	4.345	
3.000	15.40			14.22	36.14	
4.000	37.30			40.57	133.8	
6.000	164.0			241.9	1267.	
8.000	176.0			581.9	3659.	
12.00	217.0			1368.	1.168e+004	
16.00	226.0			2254.	2.412e+004	
24.00	194.0			3931.	5.749e+004	
36.00	117.0			5758.	1.114e+005	
48.00	106.0			7095.	1.674e+005	
60.00	80.60			8207.	2.272e+005	
72.00	53.60			9002.	2.793e+005	
96.00 *	42.20	40.78	1.415	1.015e+004	3.748e+005	1.000
120.0 *	21.70	23.24	-1.535	1.089e+004	4.538e+005	1.000
144.0 *	13.70	13.24	0.4631	1.130e+004	5.085e+005	1.000
168.0 *	7.540	7.541	-0.001047	1.155e+004	5.468e+005	1.000

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

Final Parameters

Rsqr	0.9956
Rsqr_adjusted	0.9934
Corr_XY	-0.9978
No_points_lambda_z	4
Lambda_z	1/h 0.0234

Lambda_z_lower	h	96.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	29.5663
Tlag	h	1.5000
Tmax	h	16.0000
Cmax	ng/mL	226.0000
Cmax_D	ng/mL/mg	0.5022
Tlast	h	168.0000
Clast	ng/mL	7.5400
AUClast	h*ng/mL	11550.5353
AUCall	h*ng/mL	11550.5353
AUCINF_obs	h*ng/mL	11872.1556
AUCINF_D_obs	h*ng/mL/mg	26.3826
AUC_%Extrap_obs	%	2.7090
Vz_F_obs	L	1616.7953
Cl_F_obs	L/h	37.9038
AUCINF_pred	h*ng/mL	11872.2003
AUCINF_D_pred	h*ng/mL/mg	26.3827
AUC_%Extrap_pred	%	2.7094
Vz_F_pred	L	1616.7892
Cl_F_pred	L/h	37.9037
AUMClast	h*h*ng/mL	546801.8568
AUMCINF_obs	h*h*ng/mL	614552.8489
AUMC_%Extrap_obs	%	11.0244
AUMCINF_pred	h*h*ng/mL	614562.2575
AUMC_%Extrap_pred	%	11.0258
MRTlast	h	47.3400
MRTINF_obs	h	51.7642
MRTINF_pred	h	51.7648
AUC0_24	h*ng/mL	3930.6117

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	0.0000			0.0000	0.0000	
1.500	0.0000			0.0000	0.0000	
2.000	16.20			4.050	8.100	
3.000	27.60			25.95	65.70	
4.000	57.30			68.40	221.7	
6.000	109.0			234.7	1105.	
8.000	164.0			507.7	3071.	
12.00	215.0			1266.	1.085e+004	

16.00	223.0			2142.2315e+004	
24.00	272.0			4122.6353e+004	
36.00 *	234.0	225.3	8.735	7152.1540e+005	1.000
48.00 *	172.0	174.1	-2.053	9569.2548e+005	1.000
60.00 *	131.0	134.5	-3.484	1.138e+004 3.518e+005	1.000
72.00 *	110.0	103.9	6.089	1.282e+004 4.468e+005	1.000
96.00 *	56.20	62.04	-5.835	1.474e+004 6.057e+005	1.000
120.0 *	38.80	37.04	1.765	1.587e+004 7.266e+005	1.000
144.0 *	20.90	22.11	-1.210	1.656e+004 8.174e+005	1.000
168.0 *	13.90	13.20	0.7000	1.697e+004 8.813e+005	1.000

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

Final Parameters

Rsqr		0.9968
Rsqr_adjusted		0.9963
Corr_XY		-0.9984
No_points_lambda_z		8
Lambda_z	1/h	0.0215
Lambda_z_lower	h	36.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	32.2501
Tlag	h	1.5000
Tmax	h	24.0000
Cmax	ng/mL	272.0000
Cmax_D	ng/mL/mg	0.6044
Tlast	h	168.0000
Clast	ng/mL	13.9000
AUClast	h*ng/mL	16974.2217
AUCall	h*ng/mL	16974.2217
AUCINF_obs	h*ng/mL	17620.9485
AUCINF_D_obs	h*ng/mL/mg	39.1577
AUC_%Extrap_obs	%	3.6702
Vz_F_obs	L	1188.1994
Cl_F_obs	L/h	25.5378
AUCINF_pred	h*ng/mL	17588.3816
AUCINF_D_pred	h*ng/mL/mg	39.0853
AUC_%Extrap_pred	%	3.4918
Vz_F_pred	L	1190.3995
Cl_F_pred	L/h	25.5851
AUMClast	h*h*ng/mL	881344.2543
AUMCINF_obs	h*h*ng/mL	1020084.6943
AUMC_%Extrap_obs	%	13.6009
AUMCINF_pred	h*h*ng/mL	1013098.1999
AUMC_%Extrap_pred	%	13.0051
MRTlast	h	51.9225
MRTINF_obs	h	57.8905
MRTINF_pred	h	57.6004
AUC0_24	h*ng/mL	4121.7000

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,

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AUC0_24

h*ng/mL

3882.1260

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: P|

Date: 09/23/2023
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

7.0.0.2535

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration

Number of nonmissing observations: 22

Dose time: 0.00

Dose amount: 450.00

Calculation method: Linear Trapezoidal Rule for for Increasing Values.

Log Trapezoidal Rule for Decreasing Values

Weighting for lambda_z calculations: Uniform weighting

Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	7.060			0.8825	0.4413	
0.7500	17.20			3.915	2.495	
1.000	25.50			9.253	7.295	
1.500	38.30			25.20	28.03	
2.000	39.40			44.63	62.10	
3.000	67.20			97.93	202.3	
4.000	109.0			186.0	521.1	
6.000	173.0			468.0	1995.	
8.000	218.0			859.0	4777.	
12.00	227.0			1749.	1.371e+004	
16.00	237.0			2677.	2.675e+004	
24.00	290.0			4785.	6.975e+004	
36.00	267.0			8125.	1.697e+005	
48.00	234.0			1.113e+004	2.954e+005	
60.00 *	195.0	199.7	-4.686	1.369e+004	4.335e+005	1.000
72.00 *	166.0	159.4	6.581	1.586e+004	5.758e+005	1.000
96.00 *	100.0	101.6	-1.608	1.898e+004	8.352e+005	1.000
120.0 *	65.80	64.76	1.039	2.094e+004	1.045e+006	1.000
144.0 *	39.70	41.28	-1.576	2.218e+004	1.208e+006	1.000
168.0 *	26.90	26.31	0.5922	2.297e+004	1.330e+006	1.000

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

Final Parameters

Rsq		0.9985
Rsq_adjusted		0.9981
Corr_XY		-0.9992
No_points_lambda_z		6
Lambda_z	1/h	0.0188
Lambda_z_lower	h	60.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	36.9336
Tlag	h	0.2500
Tmax	h	24.0000
Cmax	ng/mL	290.0000
Cmax_D	ng/mL/mg	0.6444

Tlast	h	168.0000
Clast	ng/mL	26.9000
AUClast	h*ng/mL	22970.4375
AUCall	h*ng/mL	22970.4375
AUCINF_obs	h*ng/mL	24403.7739
AUCINF_D_obs	h*ng/mL/mg	54.2306
AUC_%Extrap_obs	%	5.8734
Vz_F_obs	L	982.5426
CL_F_obs	L/h	18.4398
AUCINF_pred	h*ng/mL	24372.2207
AUCINF_D_pred	h*ng/mL/mg	54.1605
AUC_%Extrap_pred	%	5.7516
Vz_F_pred	L	983.8146
CL_F_pred	L/h	18.4636
AUMClast	h*h*ng/mL	1330242.4556
AUMCINF_obs	h*h*ng/mL	1647416.7110
AUMC_%Extrap_obs	%	19.2528
AUMCINF_pred	h*h*ng/mL	1640434.4943
AUMC_%Extrap_pred	%	18.9091
MRTlast	h	57.9111
MRTINF_obs	h	67.5066
MRTINF_pred	h	67.3076
AUC0_24	h*ng/mL	4785.0275

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

7.0.0.2535

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
 Number of nonmissing observations: 22
 Dose time: 0.00
 Dose amount: 450.00
 Calculation method: Linear Trapezoidal Rule for for Increasing Values,
 Log Trapezoidal Rule for Decreasing Values
 Weighting for lambda_z calculations: Uniform weighting
 Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2667	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.017	0.0000			0.0000	0.0000	
1.500	14.20			3.432	5.147	
2.000	38.30			16.56	29.62	
3.000	73.90			72.66	178.8	
4.000	129.0			174.1	547.6	
6.000	233.0			536.1	2462.	
8.000	274.0			1043.	6052.	
12.00	297.0			2185.	1.756e+004	
16.00	290.0			3359.	3.399e+004	
24.00	299.0			5715.	8.125e+004	
36.00	268.0			9114.	1.828e+005	
48.00	223.0			1.205e+004	3.057e+005	
60.00	170.0			1.440e+004	4.316e+005	
72.73	125.0			1.626e+004	5.547e+005	
96.03	81.80			1.863e+004	7.530e+005	

120.0 *	42.50	42.21	0.2920	2.007e+004	9.065e+005	1.000
144.0 *	24.40	24.74	-0.3387	2.085e+004	1.009e+006	1.000
168.0 *	14.60	14.50	0.1003	2.131e+004	1.080e+006	1.000

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

Final Parameters

Rsqr		0.9995
Rsqr_adjusted		0.9990
Corr_XY		-0.9998
No_points_lambda_z		3
Lambda_z	1/h	0.0223
Lambda_z_lower	h	120.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	31.1386
Tlag	h	1.0167
Tmax	h	24.0000
Cmax	ng/mL	299.0000
Cmax_D	ng/mL/mg	0.6644
Tlast	h	168.0000
Clast	ng/mL	14.6000
AUClast	h*ng/mL	21311.5822
AUCall	h*ng/mL	21311.5822
AUCINF_obs	h*ng/mL	21967.4656
AUCINF_D_obs	h*ng/mL/mg	48.8166
AUC_%Extrap_obs	%	2.9857
Vz_F_obs	L	920.2511
CL_F_obs	L/h	20.4848
AUCINF_pred	h*ng/mL	21962.9600
AUCINF_D_pred	h*ng/mL/mg	48.8066
AUC_%Extrap_pred	%	2.9658
Vz_F_pred	L	920.4399
CL_F_pred	L/h	20.4890
AUMClast	h*h*ng/mL	1079987.9763
AUMCINF_obs	h*h*ng/mL	1219640.9871
AUMC_%Extrap_obs	%	11.4503
AUMCINF_pred	h*h*ng/mL	1218681.6380
AUMC_%Extrap_pred	%	11.3806
MRTlast	h	50.6761
MRTINF_obs	h	55.5203
MRTINF_pred	h	55.4880
AUC0_24	h*ng/mL	5715.0510

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7333	0.0000			0.0000	0.0000	
1.000	0.0000			0.0000	0.0000	
1.500	11.00			2.750	4.125	
2.000	27.00			12.25	21.75	
3.000	75.70			63.60	162.3	
4.000	111.0			157.0	497.9	
6.000	153.0			421.0	1860.	
8.050	176.0			758.2	4253.	
12.00	211.0			1523.	1.205e+004	
16.05	211.0			2377.	2.404e+004	
24.02	218.0			4086.	5.838e+004	
36.00	194.0			6552.	1.321e+005	
48.00 *	149.0	151.1	-2.125	8598.	2.175e+005	1.000
60.00 *	109.0	106.2	2.809	1.013e+004	2.999e+005	1.000
72.00 *	75.20	74.62	0.5832	1.123e+004	3.716e+005	1.000
95.73 *	37.20	37.13	0.06842	1.251e+004	4.773e+005	1.000
120.0 *	17.10	18.19	-1.090	1.313e+004	5.440e+005	1.000
144.0 *	9.350	8.981	0.3687	1.344e+004	5.843e+005	1.000
168.0	0.0000			1.356e+004	6.005e+005	

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

Final Parameters

Rsqr		0.9989
Rsqr_adjusted		0.9987
Corr_XY		-0.9995
No_points_lambda_z		6
Lambda_z	1/h	0.0294
Lambda_z_lower	h	48.0000
Lambda_z_upper	h	144.0000
HL_Lambda_z	h	23.5718
Tlag	h	1.0000
Tmax	h	24.0167
Cmax	ng/mL	218.0000
Cmax_D	ng/mL/mg	0.4844
Tlasi	h	144.0000
Clasi	ng/mL	9.3500
AUClasi	h*ng/mL	13443.0163
AUCall	h*ng/mL	13555.2163
AUCINF_obs	h*ng/mL	13760.9804
AUCINF_D_obs	h*ng/mL/mg	30.5800
AUC_%Extrap_obs	%	2.3106
Vz_F_obs	L	1112.0636
Cl_F_obs	L/h	32.7012
AUCINF_pred	h*ng/mL	13748.4425
AUCINF_D_pred	h*ng/mL/mg	30.5521
AUC_%Extrap_pred	%	2.2215
Vz_F_pred	L	1113.0777
Cl_F_pred	L/h	32.7310
AUMClasi	h*h*ng/mL	584346.9180
AUMCINF_obs	h*h*ng/mL	640946.7075
AUMC_%Extrap_obs	%	8.8307
AUMCINF_pred	h*h*ng/mL	638714.8799
AUMC_%Extrap_pred	%	8.5121
MRTlasi	h	43.4684
MRTINF_obs	h	46.5771
MRTINF_pred	h	46.4573
AUC0_24	h*ng/mL	4082.2668

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=pi,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

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Vz_F_obs	L	1493.7034
Cl_F_obs	L/h	27.4937
AUCINF_pred	h*ng/mL	16370.7366
AUCINF_D_pred	h*ng/mL/mg	36.3794
AUC_%Extrap_pred	%	5.2307
Vz_F_pred	L	1493.3982
Cl_F_pred	L/h	27.4881
AUMClast	h*h*ng/mL	822206.6838
AUMCINF_obs	h*h*ng/mL	1011845.4005
AUMC_%Extrap_obs	%	18.7419
AUMCINF_pred	h*h*ng/mL	1012588.9412
AUMC_%Extrap_pred	%	18.8015
MRTlast	h	52.9963
MRTINF_obs	h	61.8208
MRTINF_pred	h	61.8536
AUC0_24	h*ng/mL	4081.4941

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:22

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	0.0000			0.0000	0.0000	
1.500	7.410			1.853	2.779	
2.000	10.80			6.405	10.96	
3.000	37.80			30.71	78.46	
4.000	68.10			83.66	271.4	
6.000	198.0			349.8	1732.	
8.067	221.0			782.7	4802.	
12.00	202.0			1614.	1.312e+004	
16.00	190.0			2398.	2.407e+004	
24.02	203.0			3973.	5.580e+004	
36.00 *	172.0	175.3	-3.261	6215.	1.227e+005	1.000
48.00 *	146.0	137.0	9.014	8119.	2.023e+005	1.000
60.00 *	108.0	107.1	0.9303	9631.	2.836e+005	1.000
72.00 *	81.60	83.69	-2.087	1.076e+004	3.578e+005	1.000
96.07 *	51.90	51.06	0.8442	1.234e+004	4.892e+005	1.000
120.0 *	27.70	31.22	-3.523	1.326e+004	5.877e+005	1.000
144.0 *	19.80	19.08	0.7189	1.383e+004	6.619e+005	1.000
168.0 *	12.10	11.65	0.4510	1.420e+004	7.201e+005	1.000

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

Final Parameters

Rsqr		0.9966
Rsqr_adjusted		0.9961
Corr_XY		-0.9983
No_points_lambda_z		8
Lambda_z	1/h	0.0205
Lambda_z_lower	h	36.0000
Lambda_z_upper	h	168.0333
HL_Lambda_z	h	33.7575
Tlag	h	1.0000
Tmax	h	8.0667
Cmax	ng/mL	221.0000
Cmax_D	ng/mL/mg	0.4911
Tlast	h	168.0333
Clast	ng/mL	12.1000
AUClast	h*ng/mL	14204.1004
AUCall	h*ng/mL	14204.1004
AUCINF_obs	h*ng/mL	14793.3920
AUCINF_D_obs	h*ng/mL/mg	32.8742
AUC_%Extrap_obs	%	3.9835
Vz_F_obs	L	1481.4590
CL_F_obs	L/h	30.4190
AUCINF_pred	h*ng/mL	14771.4261
AUCINF_D_pred	h*ng/mL/mg	32.8254
AUC_%Extrap_pred	%	3.8407
Vz_F_pred	L	1483.6620
CL_F_pred	L/h	30.4642
AUMClast	h*h*ng/mL	720112.4562
AUMCINF_obs	h*h*ng/mL	847832.6414
AUMC_%Extrap_obs	%	15.0643
AUMCINF_pred	h*h*ng/mL	843071.8634
AUMC_%Extrap_pred	%	14.5847
MRTlast	h	50.6975
MRTINF_obs	h	57.3116
MRTINF_pred	h	57.0745
AUC0_24	h*ng/mL	3969.7088

WinNonlin 7.0.0.2535

PARAMCD=TEPO,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:23:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	7.590			0.9488	0.7116	

WinNonlin Core Output - Tepotinib Metabolite MSC2571107A

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2667	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.017	0.0000			0.0000	0.0000	
1.500	0.2140			0.05172	0.07757	
2.000	0.4690			0.2225	0.3923	
3.000	1.240			1.077	2.721	
4.000	2.380			2.887	9.341	
6.000	2.850			8.117	35.96	
8.000	4.150			15.12	86.26	
12.00	4.780			32.98	267.4	
16.00	6.450			55.44	588.5	
24.00	7.650			111.8	1736.	
36.00	5.910			192.7	4142.	
48.00	6.360			266.4	7250.	
60.00	4.160			328.6	1.058e+004	
72.73	3.870			379.7	1.397e+004	
96.03	3.130			460.9	2.079e+004	
120.0 *	2.060	2.025	0.03491	522.2	2.736e+004	1.000
144.0 *	1.050	1.087	-0.03652	558.2	3.206e+004	1.000
168.0 *	0.5930	0.5829	0.01005	577.4	3.504e+004	1.000

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

Final Parameters

Rsqr 0.9977
Rsqr_adjusted 0.9955
Corr_XY -0.9989
No_points_lambda_z 3
Lambda_z 1/h 0.0259
Lambda_z_lower h 120.0000
Lambda_z_upper h 168.0000
HL_Lambda_z h 26.7180
Tlag h 1.0167
Tmax h 24.0000
Cmax ng/mL 7.6500

Cmax_D	ng/mL/mg	0.0170
Tlast	h	168.0000
Clast	ng/mL	0.5930
AUClast	h*ng/mL	577.3723
AUCall	h*ng/mL	577.3723
AUCINF_obs	h*ng/mL	600.2301
AUCINF_D_obs	h*ng/mL/mg	1.3338
AUC_%Extrap_obs	%	3.8082
Vz_F_obs	L	28898.3851
Cl_F_obs	L/h	749.7125
AUCINF_pred	h*ng/mL	599.8427
AUCINF_D_pred	h*ng/mL/mg	1.3330
AUC_%Extrap_pred	%	3.7460
Vz_F_pred	L	28917.0494
Cl_F_pred	L/h	750.1967
AUMClast	h*h*ng/mL	35035.3710
AUMCINF_obs	h*h*ng/mL	39756.5470
AUMC_%Extrap_obs	%	11.8752
AUMCINF_pred	h*h*ng/mL	39676.5285
AUMC_%Extrap_pred	%	11.6975
MRTlast	h	60.6807
MRTINF_obs	h	66.2355
MRTINF_pred	h	66.1449
AUC0_24	h*ng/mL	111.8370

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	0.1010			0.01263	0.01263	
1.500	0.1960			0.08688	0.1114	
2.000	0.3280			0.2179	0.3489	
3.000	0.7880			0.7759	1.859	
4.000	1.350			1.845	5.741	
6.000	2.130			5.325	23.92	
8.000	3.030			10.48	60.94	
12.00	3.960			24.46	204.5	
16.00	4.790			41.96	452.8	
24.00	9.560			99.36	1677.	
36.00	8.510			207.7	4913.	
48.00	11.20			325.9	9977.	
60.00	10.10			453.6	1.686e+004	
72.00	12.20			587.4	2.577e+004	

96.00 *	10.50	10.78	-0.2835	859.3 4.852e+004	1.000
120.0 *	7.720	7.328	0.3921	1076. 7.182e+004	1.000
144.0 *	4.860	4.980	-0.1197	1225. 9.126e+004	1.000
168.0 *	3.380	3.384	-0.003920	1322. 1.064e+005	1.000

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

Final Parameters

Rsqr		0.9946
Rsqr_adjusted		0.9920
Corr_XY		-0.9973
No_points_lambda_z		4
Lambda_z	1/h	0.0161
Lambda_z_lower	h	96.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	43.0607
Tlag	h	0.7500
Tmax	h	72.0000
Cmax	ng/mL	12.2000
Cmax_D	ng/mL/mg	0.0271
Tlast	h	168.0000
Clast	ng/mL	3.3800
AUClast	h*ng/mL	1322.3614
AUCall	h*ng/mL	1322.3614
AUCINF_obs	h*ng/mL	1532.3387
AUCINF_D_obs	h*ng/mL/mg	3.4052
AUC_%Extrap_obs	%	13.7031
Vz_F_obs	L	18243.7204
Cl_F_obs	L/h	293.6688
AUCINF_pred	h*ng/mL	1532.5822
AUCINF_D_pred	h*ng/mL/mg	3.4057
AUC_%Extrap_pred	%	13.7168
Vz_F_pred	L	18240.8217
Cl_F_pred	L/h	293.6221
AUMClast	h*h*ng/mL	106446.9712
AUMCINF_obs	h*h*ng/mL	154767.6771
AUMC_%Extrap_obs	%	31.2214
AUMCINF_pred	h*h*ng/mL	154823.7155
AUMC_%Extrap_pred	%	31.2463
MRTlast	h	80.4976
MRTINF_obs	h	101.0010
MRTINF_pred	h	101.0215
AUC0_24	h*ng/mL	99.3649

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h ² *ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.033	0.0000			0.0000	0.0000	
1.500	0.0000			0.0000	0.0000	
2.000	0.2340			0.05850	0.1170	
3.000	0.6310			0.4910	1.298	
4.000	1.170			1.392	4.584	
6.000	2.050			4.612	21.56	
8.000	2.730			9.392	55.70	
12.00	3.830			22.51	191.3	
16.00	4.180			38.53	417.0	
24.00	6.540			81.41	1312.	
36.00	5.230			151.7	3406.	
48.00	5.570			216.5	6140.	
60.00	3.810			272.2	9122.	
72.00	4.250			320.5	1.233e+004	
96.00 *	3.040	2.942	0.09836	407.2	1.955e+004	1.000
120.0 *	1.670	1.708	-0.03760	462.1	2.541e+004	1.000
144.0 *	0.9390	0.9912	-0.05224	492.5	2.940e+004	1.000
168.0 *	0.6010	0.5754	0.02559	510.7	3.222e+004	1.000

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

Final Parameters

Rsqr		0.9957
Rsqr_adjusted		0.9935
Corr_XY		-0.9978
No_points_lambda_z		4
Lambda_z	1/h	0.0227
Lambda_z_lower	h	96.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	30.5867
Tlag	h	1.5000
Tmax	h	24.0000
Cmax	ng/mL	6.5400
Cmax_D	ng/mL/mg	0.0145
Tlast	h	168.0000
Clast	ng/mL	0.6010
AUClast	h*ng/mL	510.7214
AUCall	h*ng/mL	510.7214
AUCINF_obs	h*ng/mL	537.2419
AUCINF_D_obs	h*ng/mL/mg	1.1939
AUC_%Extrap_obs	%	4.9364
Vz_F_obs	L	36961.4899
Cl_F_obs	L/h	837.6116
AUCINF_pred	h*ng/mL	536.1125
AUCINF_D_pred	h*ng/mL/mg	1.1914
AUC_%Extrap_pred	%	4.7362
Vz_F_pred	L	37039.3505
Cl_F_pred	L/h	839.3760
AUMClast	h ² *ng/mL	32221.9479
AUMCINF_obs	h ² *ng/mL	37847.6627
AUMC_%Extrap_obs	%	14.8641
AUMCINF_pred	h ² *ng/mL	37608.0990
AUMC_%Extrap_pred	%	14.3218
MRTlast	h	63.0910
MRTINF_obs	h	70.4481
MRTINF_pred	h	70.1496
AUC0_24	h*ng/mL	81.4115

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=P1,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

AUC_%Extrap_obs	%	6.0859
Vz_F_obs	L	27115.4992
CL_F_obs	L/h	591.9313
AUCINF_pred	h*ng/mL	760.0826
AUCINF_D_pred	h*ng/mL/mg	1.6891
AUC_%Extrap_pred	%	6.0685
Vz_F_pred	L	27120.5212
CL_F_pred	L/h	592.0410
AUMClast	h*h*ng/mL	47483.5017
AUMCINF_obs	h*h*ng/mL	57375.6966
AUMC_%Extrap_obs	%	17.2411
AUMCINF_pred	h*h*ng/mL	57345.5984
AUMC_%Extrap_pred	%	17.1977
MRTlast	h	66.5075
MRTINF_obs	h	75.4722
MRTINF_pred	h	75.4465
AUC0_24	h*ng/mL	86.3275

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:27

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	0.0000			0.0000	0.0000	
1.500	0.0000			0.0000	0.0000	
2.000	0.2530			0.06325	0.1265	
3.000	0.4760			0.4278	1.094	
4.000	0.9520			1.142	3.712	
6.000	1.690			3.784	17.66	
8.000	2.800			8.274	50.20	
12.00	4.360			22.59	199.6	
16.00	6.300			43.91	505.9	
24.00	7.890			100.7	1667.	
36.00	4.610			173.9	3825.	
48.00	5.970			237.4	6540.	
60.00	3.580			293.5	9540.	
72.00 *	3.430	3.624	-0.1935	335.5	1.231e+004	1.000
96.00 *	2.510	2.346	0.1636	406.2	1.821e+004	1.000
120.0 *	1.430	1.519	-0.08936	452.3	2.313e+004	1.000
144.0 *	1.130	0.9838	0.1462	482.9	2.715e+004	1.000
168.0 *	0.5820	0.6371	-0.05508	502.7	3.022e+004	1.000

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

Final Parameters

Rsqr		0.9800
Rsqr_adjusted		0.9733
Corr_XY		-0.9899
No_points_lambda_z		5
Lambda_z	1/h	0.0181
Lambda_z_lower	h	72.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	38.2800
Tlag	h	1.5000
Tmax	h	24.0000
Cmax	ng/mL	7.8900
Cmax_D	ng/mL/mg	0.0175
Tlast	h	168.0000
Clast	ng/mL	0.5820
AUClast	h*ng/mL	502.7147
AUCall	h*ng/mL	502.7147
AUCINF_obs	h*ng/mL	534.8564
AUCINF_D_obs	h*ng/mL/mg	1.1886
AUC_%Extrap_obs	%	6.0094
Vz_F_obs	L	46464.5032
CL_F_obs	L/h	841.3473
AUCINF_pred	h*ng/mL	537.8982
AUCINF_D_pred	h*ng/mL/mg	1.1953
AUC_%Extrap_pred	%	6.5409
Vz_F_pred	L	46201.7451
CL_F_pred	L/h	836.5895
AUMClast	h*h*ng/mL	30221.0222
AUMCINF_obs	h*h*ng/mL	37395.8970
AUMC_%Extrap_obs	%	19.1863
AUMCINF_pred	h*h*ng/mL	38074.9136
AUMC_%Extrap_pred	%	20.6275
MRTlast	h	60.1157
MRTINF_obs	h	69.9176
MRTINF_pred	h	70.7846
AUC0_24	h*ng/mL	100.6738

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5333	0.0000			0.0000	0.0000	

0.7500	0.0000			0.0000	0.0000
1.000	0.0000			0.0000	0.0000
1.500	0.0000			0.0000	0.0000
2.000	0.2030			0.05075	0.1015
3.000	0.5050			0.4048	1.062
4.000	1.110			1.212	4.040
6.000	1.630			3.952	18.26
8.000	2.750			8.332	50.04
12.00	4.120			22.07	192.9
16.00	5.480			41.27	467.2
24.02	8.200			96.11	1608.
36.00	6.740			185.3	4268.
48.00	7.440			270.4	7867.
60.02	4.510			340.8	1.163e+004
72.00 *	4.640	4.819	-0.1787	395.6	1.525e+004
96.00 *	3.090	3.021	0.06895	487.1	2.287e+004
120.0 *	2.100	1.894	0.2060	548.6	2.946e+004
144.0 *	1.050	1.187	-0.1375	585.0	3.421e+004
168.0 *	0.7710	0.7445	0.02653	606.6	3.758e+004

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

Final Parameters

Rsqr		0.9869
Rsqr_adjusted		0.9825
Corr_XY		-0.9934
No_points_lambda_z		5
Lambda_z	1/h	0.0195
Lambda_z_lower	h	72.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	35.6302
Tlag	h	1.5000
Tmax	h	24.0167
Cmax	ng/mL	8.2000
Cmax_D	ng/mL/mg	0.0182
Tlast	h	168.0000
Clast	ng/mL	0.7710
AUClast	h*ng/mL	606.6329
AUCall	h*ng/mL	606.6329
AUCINF_obs	h*ng/mL	646.2650
AUCINF_D_obs	h*ng/mL/mg	1.4361
AUC_%Extrap_obs	%	6.1325
Vz_F_obs	L	35792.7014
Cl_F_obs	L/h	696.3087
AUCINF_pred	h*ng/mL	644.9014
AUCINF_D_pred	h*ng/mL/mg	1.4331
AUC_%Extrap_pred	%	5.9340
Vz_F_pred	L	35868.3832
Cl_F_pred	L/h	697.7811
AUMClast	h*h*ng/mL	37580.0970
AUMCINF_obs	h*h*ng/mL	46275.5166
AUMC_%Extrap_obs	%	18.7905
AUMCINF_pred	h*h*ng/mL	45976.3356
AUMC_%Extrap_pred	%	18.2621
MRTlast	h	61.9487
MRTINF_obs	h	71.6045
MRTINF_pred	h	71.2920
AUC0_24	h*ng/mL	95.9696

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535

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CL_F_pred	L/h	330.0405
AUMClast	h*h*ng/mL	87479.5168
AUMCINF_obs	h*h*ng/mL	130072.5656
AUMC_%Extrap_obs	%	32.7456
AUMCINF_pred	h*h*ng/mL	131143.1515
AUMC_%Extrap_pred	%	33.2946
MRTlast	h	74.2963
MRTINF_obs	h	95.7185
MRTINF_pred	h	96.1835
AUC0_24	h*ng/mL	132.7461

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.033	0.1370			0.01941	0.02006	
1.500	0.3340			0.1293	0.1700	
2.017	0.6180			0.3752	0.6214	
3.000	1.760			1.544	3.830	
4.000	2.430			3.639	11.33	
6.000	3.230			9.299	40.43	
8.000	3.700			16.23	89.41	
12.00	4.640			32.91	260.0	
16.00	5.720			53.63	554.4	
24.03	8.570			111.0	1749.	
36.00	6.430			200.2	4399.	
48.00	6.360			276.9	7622.	
60.00	4.490			341.4	1.108e+004	
72.00 *	4.330	4.450	-0.1201	394.3	1.457e+004	1.000
96.00 *	3.060	2.841	0.2195	482.1	2.188e+004	1.000
120.3 *	1.680	1.804	-0.1241	537.9	2.786e+004	1.000
144.0 *	1.190	1.157	0.03269	571.6	3.229e+004	1.000
168.0 *	0.7360	0.7387	-0.002710	594.3	3.581e+004	1.000

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

Final Parameters

Rsqr 0.9940
Rsqr_adjusted 0.9920
Corr_XY -0.9970

No_points_lambda_z		5
Lambda_z	1/h	0.0187
Lambda_z_lower	h	72.0000
Lambda_z_upper	h	168.0000
HL_Lambda_z	h	37.0548
Tlag	h	0.7500
Tmax	h	24.0333
Cmax	ng/mL	8.5700
Cmax_D	ng/mL/mg	0.0190
Tlast	h	168.0000
Clast	ng/mL	0.7360
AUClast	h*ng/mL	594.3188
AUCall	h*ng/mL	594.3188
AUCINF_obs	h*ng/mL	633.6645
AUCINF_D_obs	h*ng/mL/mg	1.4081
AUC_%Extrap_obs	%	6.2092
Vz_F_obs	L	37964.0342
CL_F_obs	L/h	710.1550
AUCINF_pred	h*ng/mL	633.8094
AUCINF_D_pred	h*ng/mL/mg	1.4085
AUC_%Extrap_pred	%	6.2307
Vz_F_pred	L	37955.3550
CL_F_pred	L/h	709.9927
AUMClast	h*h*ng/mL	35805.1167
AUMCINF_obs	h*h*ng/mL	44518.5627
AUMC_%Extrap_obs	%	19.5726
AUMCINF_pred	h*h*ng/mL	44550.6517
AUMC_%Extrap_pred	%	19.6305
MRTlast	h	60.2456
MRTINF_obs	h	70.2557
MRTINF_pred	h	70.2903
AUC0_24	h*ng/mL	110.7421

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time h	Conc. ng/mL	Pred. ng/mL	Residual ng/mL	AUC h*ng/mL	AUMC h*h*ng/mL	Weight
0.0000	0.0000			0.0000	0.0000	
0.2500	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
0.7500	0.0000			0.0000	0.0000	
1.000	0.0000			0.0000	0.0000	
1.500	0.0000			0.0000	0.0000	
2.000	0.1420			0.03550	0.07100	
3.000	0.5740			0.3935	1.074	
4.000	0.9620			1.162	3.859	
6.000	2.620			4.744	23.43	

8.067	3.960			11.54	72.68	
12.00	4.660			28.50	245.5	
16.00	5.570			48.96	535.6	
24.02	8.080			103.7	1671.	
36.00 *	6.450	7.315	-0.8655	190.4	4253.	1.000
48.00 *	7.090	5.952	1.138	271.6	7688.	1.000
60.00 *	4.450	4.842	-0.3921	339.6	1.133e+004	1.000
72.00 *	4.170	3.939	0.2306	391.3	1.474e+004	1.000
96.07 *	2.890	2.604	0.2856	475.3	2.174e+004	1.000
120.0 *	1.390	1.725	-0.3353	524.4	2.697e+004	1.000
144.0 *	1.250	1.142	0.1077	556.0	3.114e+004	1.000
168.0 *	0.7560	0.7557	0.0003353	579.7	3.480e+004	1.000

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

Final Parameters

Rsqr		0.9744
Rsqr_adjusted		0.9701
Corr_XY		-0.9871
No_points_lambda_z		8
Lambda_z	1/h	0.0172
Lambda_z_lower	h	36.0000
Lambda_z_upper	h	168.0333
HL_Lambda_z	h	40.3139
Tlag	h	1.5000
Tmax	h	24.0167
Cmax	ng/mL	8.0800
Cmax_D	ng/mL/mg	0.0180
Tlast	h	168.0333
Clast	ng/mL	0.7560
AUClast	h*ng/mL	579.6538
AUCall	h*ng/mL	579.6538
AUCINF_obs	h*ng/mL	623.6233
AUCINF_D_obs	h*ng/mL/mg	1.3858
AUC_%Extrap_obs	%	7.0506
Vz_F_obs	L	41968.1021
CL_F_obs	L/h	721.5895
AUCINF_pred	h*ng/mL	623.6038
AUCINF_D_pred	h*ng/mL/mg	1.3858
AUC_%Extrap_pred	%	7.0477
Vz_F_pred	L	41969.4145
CL_F_pred	L/h	721.6121
AUMClast	h*h*ng/mL	34796.5459
AUMCINF_obs	h*h*ng/mL	44742.1674
AUMC_%Extrap_obs	%	22.2287
AUMCINF_pred	h*h*ng/mL	44737.7564
AUMC_%Extrap_pred	%	22.2211
MRTlast	h	60.0299
MRTINF_obs	h	71.7455
MRTINF_pred	h	71.7407
AUC0_24	h*ng/mL	103.5346

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840. 841. 842. 843. 844. 845. 846. 847. 848. 849. 850. 851. 852. 853. 854. 855. 856. 857. 858. 859. 860. 861. 862. 863. 864. 865. 866. 867. 868. 869. 870. 871. 872. 873. 874. 875. 876. 877. 878. 879. 880. 881. 882. 883. 884. 885. 886. 887. 888. 889. 890. 891. 892. 893. 894. 895. 896. 897. 898. 899. 900. 901. 902. 903. 904. 905. 906. 907. 908. 909. 910. 911. 912. 913. 914. 915. 916. 917. 918. 919. 920. 921. 922. 923. 924. 925. 926. 927. 928. 929. 930. 931. 932. 933. 934. 935. 936. 937. 938. 939. 940. 941. 942. 943. 944. 945. 946. 947. 948. 949. 950. 951. 952. 953. 954. 955. 956. 957. 958. 959. 960. 961. 962. 963. 964. 965. 966. 967. 968. 969. 970. 971. 972. 973. 974. 975. 976. 977. 978. 979. 980. 981. 982. 983. 984. 985. 986. 987. 988. 989. 990. 991. 992. 993. 994. 995. 996. 997. 998. 999. 1000.

| | | |
|-------------|---------|---------|
| MRTINF_obs | h | 57.6716 |
| MRTINF_pred | h | 57.7456 |
| AUC0_24 | h*ng/mL | 99.1593 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7333 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.1030 | | | 0.01373 | 0.01373 | |
| 1.500 | 0.2560 | | | 0.1035 | 0.1355 | |
| 2.000 | 0.5180 | | | 0.2970 | 0.4905 | |
| 3.000 | 1.390 | | | 1.251 | 3.093 | |
| 4.000 | 2.120 | | | 3.006 | 9.418 | |
| 6.000 | 2.510 | | | 7.636 | 32.96 | |
| 8.050 | 3.240 | | | 13.53 | 75.13 | |
| 12.00 | 3.820 | | | 27.47 | 217.2 | |
| 16.05 | 4.580 | | | 44.48 | 458.9 | |
| 24.02 | 6.260 | | | 87.66 | 1351. | |
| 36.00 | 4.660 | | | 152.6 | 3281. | |
| 48.00 * | 4.790 | 4.434 | 0.3562 | 209.3 | 5667. | 1.000 |
| 60.00 * | 2.660 | 3.282 | -0.6221 | 252.8 | 7988. | 1.000 |
| 72.00 * | 3.010 | 2.430 | 0.5805 | 286.8 | 1.025e+004 | 1.000 |
| 95.73 * | 1.360 | 1.340 | 0.01979 | 336.1 | 1.430e+004 | 1.000 |
| 120.0 * | 0.6590 | 0.7295 | -0.07048 | 359.6 | 1.680e+004 | 1.000 |
| 144.0 * | 0.3480 | 0.3997 | -0.05173 | 371.3 | 1.833e+004 | 1.000 |
| 168.0 * | 0.2530 | 0.2190 | 0.03397 | 378.4 | 1.944e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|-----|----------|
| Rsqr | | 0.9810 |
| Rsqr_adjusted | | 0.9772 |
| Corr_XY | | -0.9905 |
| No_points_lambda_z | | 7 |
| Lambda_z | 1/h | 0.0251 |
| Lambda_z_lower | h | 48.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 27.6541 |
| Tlag | h | 0.7333 |
| Tmax | h | 24.0167 |

| | | |
|-------------------|------------|------------|
| Cmax | ng/mL | 6.2600 |
| Cmax_D | ng/mL/mg | 0.0139 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 0.2530 |
| AUClast | h*ng/mL | 378.4066 |
| AUCall | h*ng/mL | 378.4066 |
| AUCINF_obs | h*ng/mL | 388.5004 |
| AUCINF_D_obs | h*ng/mL/mg | 0.8633 |
| AUC_%Extrap_obs | % | 2.5981 |
| Vz_F_obs | L | 46212.0324 |
| Cl_F_obs | L/h | 1158.2999 |
| AUCINF_pred | h*ng/mL | 387.1453 |
| AUCINF_D_pred | h*ng/mL/mg | 0.8603 |
| AUC_%Extrap_pred | % | 2.2572 |
| Vz_F_pred | L | 46373.7922 |
| Cl_F_pred | L/h | 1162.3544 |
| AUMClast | h*h*ng/mL | 19440.8740 |
| AUMCINF_obs | h*h*ng/mL | 21539.3383 |
| AUMC_%Extrap_obs | % | 9.7425 |
| AUMCINF_pred | h*h*ng/mL | 21257.6061 |
| AUMC_%Extrap_pred | % | 8.5463 |
| MRTlast | h | 51.3756 |
| MRTINF_obs | h | 55.4423 |
| MRTINF_pred | h | 54.9086 |
| AUC0_24 | h*ng/mL | 87.5583 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.1250 | | | 0.01563 | 0.01563 | |
| 1.600 | 0.2270 | | | 0.1212 | 0.1621 | |
| 2.217 | 0.4870 | | | 0.3414 | 0.6069 | |
| 3.000 | 1.370 | | | 1.069 | 2.639 | |
| 4.000 | 2.050 | | | 2.779 | 8.794 | |
| 6.000 | 2.970 | | | 7.799 | 34.81 | |
| 8.000 | 3.980 | | | 14.75 | 84.47 | |
| 12.00 | 4.200 | | | 31.11 | 249.0 | |
| 16.00 | 5.090 | | | 49.69 | 512.6 | |
| 24.02 | 7.640 | | | 100.7 | 1575. | |
| 36.00 | 5.950 | | | 181.7 | 3985. | |
| 48.02 | 6.530 | | | 256.7 | 7156. | |
| 60.00 | 4.320 | | | 320.8 | 1.059e+004 | |

| | | | | | | |
|---------|-------|-------|----------|-------|------------|-------|
| 72.00 * | 4.640 | 4.654 | -0.01418 | 374.6 | 1.415e+004 | 1.000 |
| 96.02 * | 3.330 | 3.176 | 0.1541 | 469.4 | 2.206e+004 | 1.000 |
| 120.0 * | 2.010 | 2.168 | -0.1582 | 532.1 | 2.877e+004 | 1.000 |
| 144.1 * | 1.510 | 1.478 | 0.03242 | 574.2 | 3.430e+004 | 1.000 |
| 168.0 * | 1.020 | 1.010 | 0.009878 | 604.1 | 3.894e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|------------|
| Rsqr | | 0.9942 |
| Rsqr_adjusted | | 0.9922 |
| Corr_XY | | -0.9971 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0159 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 43.5572 |
| Tlag | h | 0.7500 |
| Tmax | h | 24.0167 |
| Cmax | ng/mL | 7.6400 |
| Cmax_D | ng/mL/mg | 0.0170 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 1.0200 |
| AUClast | h*ng/mL | 604.0927 |
| AUCall | h*ng/mL | 604.0927 |
| AUCINF_obs | h*ng/mL | 668.1893 |
| AUCINF_D_obs | h*ng/mL/mg | 1.4849 |
| AUC_%Extrap_obs | % | 9.5926 |
| Vz_F_obs | L | 42320.1954 |
| CL_F_obs | L/h | 673.4618 |
| AUCINF_pred | h*ng/mL | 667.5686 |
| AUCINF_D_pred | h*ng/mL/mg | 1.4835 |
| AUC_%Extrap_pred | % | 9.5085 |
| Vz_F_pred | L | 42359.5480 |
| CL_F_pred | L/h | 674.0881 |
| AUMClast | h*h*ng/mL | 38939.8758 |
| AUMCINF_obs | h*h*ng/mL | 53735.9159 |
| AUMC_%Extrap_obs | % | 27.5347 |
| AUMCINF_pred | h*h*ng/mL | 53592.6206 |
| AUMC_%Extrap_pred | % | 27.3410 |
| MRTlast | h | 64.4601 |
| MRTINF_obs | h | 80.4202 |
| MRTINF_pred | h | 80.2803 |
| AUC0_24 | h*ng/mL | 100.5875 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Page 146 of 331

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.2120 | | | 0.05300 | 0.07950 | |
| 2.000 | 0.3270 | | | 0.1878 | 0.3225 | |
| 3.000 | 0.6210 | | | 0.6618 | 1.581 | |
| 4.000 | 0.9700 | | | 1.457 | 4.453 | |
| 6.000 | 1.590 | | | 4.017 | 17.87 | |
| 8.000 | 1.960 | | | 7.567 | 43.09 | |
| 12.00 | 2.990 | | | 17.47 | 146.2 | |
| 16.00 | 3.520 | | | 30.49 | 330.6 | |
| 24.00 | 5.850 | | | 67.97 | 1117. | |
| 36.00 | 6.530 | | | 142.2 | 3370. | |
| 48.00 * | 6.200 | 5.763 | 0.4373 | 218.6 | 6574. | 1.000 |
| 60.03 * | 3.890 | 4.333 | -0.4435 | 278.2 | 9767. | 1.000 |
| 72.00 * | 3.440 | 3.264 | 0.1762 | 322.0 | 1.265e+004 | 1.000 |
| 96.00 * | 1.660 | 1.849 | -0.1885 | 380.7 | 1.749e+004 | 1.000 |
| 120.0 * | 1.190 | 1.047 | 0.1431 | 414.6 | 2.113e+004 | 1.000 |
| 144.0 * | 0.5790 | 0.5929 | -0.01395 | 434.9 | 2.379e+004 | 1.000 |
| 168.0 * | 0.3310 | 0.3358 | -0.004825 | 445.6 | 2.544e+004 | 1.000 |

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

Final Parameters

Rsqr 0.9929
Rsqr_adjusted 0.9915
Corr_XY -0.9964
No_points_lambda_z 7
Lambda_z 1/h 0.0237
Lambda_z_lower h 48.0000
Lambda_z_upper h 168.0000
HL_Lambda_z h 29.2614
Tlag h 1.0000
Tmax h 36.0000
Cmax ng/mL 6.5300
Cmax_D ng/mL/mg 0.0145
Tlast h 168.0000
Clast ng/mL 0.3310
AUClast h*ng/mL 445.5607
AUCall h*ng/mL 445.5607
AUCINF_obs h*ng/mL 459.5339

| | | |
|-------------------|------------|------------|
| AUCINF_D_obs | h*ng/mL/mg | 1.0212 |
| AUC_%Extrap_obs | % | 3.0407 |
| Vz_F_obs | L | 41339.3706 |
| CL_F_obs | L/h | 979.2530 |
| AUCINF_pred | h*ng/mL | 459.7376 |
| AUCINF_D_pred | h*ng/mL/mg | 1.0216 |
| AUC_%Extrap_pred | % | 3.0837 |
| Vz_F_pred | L | 41321.0542 |
| CL_F_pred | L/h | 978.8191 |
| AUMClast | h*h*ng/mL | 25437.2620 |
| AUMCINF_obs | h*h*ng/mL | 28374.6483 |
| AUMC_%Extrap_obs | % | 10.3522 |
| AUMCINF_pred | h*h*ng/mL | 28417.4685 |
| AUMC_%Extrap_pred | % | 10.4872 |
| MRTlast | h | 57.0905 |
| MRTINF_obs | h | 61.7466 |
| MRTINF_pred | h | 61.8124 |
| AUC0_24 | h*ng/mL | 67.9673 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.5800 | | | 0.1450 | 0.2175 | |
| 2.000 | 1.280 | | | 0.6100 | 1.075 | |
| 3.000 | 3.020 | | | 2.760 | 6.885 | |
| 4.000 | 4.860 | | | 6.700 | 21.14 | |
| 6.000 | 5.460 | | | 17.02 | 73.34 | |
| 8.000 | 6.340 | | | 28.82 | 156.8 | |
| 12.00 | 6.020 | | | 53.53 | 403.5 | |
| 16.00 | 7.440 | | | 80.45 | 786.1 | |
| 24.02 | 8.680 | | | 145.1 | 2099. | |
| 36.00 | 7.300 | | | 240.6 | 4948. | |
| 48.00 | 4.870 | | | 312.6 | 7945. | |
| 60.00 | 3.910 | | | 365.1 | 1.077e+004 | |
| 72.02 | 4.110 | | | 413.3 | 1.395e+004 | |
| 96.00 | 3.730 | | | 507.2 | 2.183e+004 | |
| 120.3 * | 3.900 | 3.740 | 0.1599 | 599.9 | 3.187e+004 | 1.000 |
| 144.0 * | 2.110 | 2.292 | -0.1825 | 668.9 | 4.091e+004 | 1.000 |
| 168.1 * | 1.450 | 1.392 | 0.05834 | 711.4 | 4.750e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|------------|
| Rsqr | | 0.9793 |
| Rsqr_adjusted | | 0.9586 |
| Corr_XY | | -0.9896 |
| No_points_lambda_z | | 3 |
| Lambda_z | 1/h | 0.0207 |
| Lambda_z_lower | h | 120.2833 |
| Lambda_z_upper | h | 168.1167 |
| HL_Lambda_z | h | 33.5377 |
| Tlag | h | 1.0000 |
| Tmax | h | 24.0167 |
| Cmax | ng/mL | 8.6800 |
| Cmax_D | ng/mL/mg | 0.0193 |
| Tlast | h | 168.1167 |
| Clast | ng/mL | 1.4500 |
| AUClast | h*ng/mL | 711.3561 |
| AUCall | h*ng/mL | 711.3561 |
| AUCINF_obs | h*ng/mL | 781.5139 |
| AUCINF_D_obs | h*ng/mL/mg | 1.7367 |
| AUC_%Extrap_obs | % | 8.9772 |
| Vz_F_obs | L | 27860.1940 |
| Cl_F_obs | L/h | 575.8055 |
| AUCINF_pred | h*ng/mL | 778.6913 |
| AUCINF_D_pred | h*ng/mL/mg | 1.7304 |
| AUC_%Extrap_pred | % | 8.6472 |
| Vz_F_pred | L | 27961.1811 |
| Cl_F_pred | L/h | 577.8926 |
| AUMClast | h*h*ng/mL | 47504.9820 |
| AUMCINF_obs | h*h*ng/mL | 62694.2573 |
| AUMC_%Extrap_obs | % | 24.2275 |
| AUMCINF_pred | h*h*ng/mL | 62083.1634 |
| AUMC_%Extrap_pred | % | 23.4817 |
| MRTlast | h | 66.7809 |
| MRTINF_obs | h | 80.2215 |
| MRTINF_pred | h | 79.7276 |
| AUC0_24 | h*ng/mL | 144.9242 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |

| | | | | | |
|---------|--------|-------|---------|---------|------------------|
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 |
| 0.7833 | 0.0000 | | | 0.0000 | 0.0000 |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 |
| 1.500 | 0.0000 | | | 0.0000 | 0.0000 |
| 2.000 | 0.1960 | | | 0.04900 | 0.09800 |
| 3.000 | 0.7990 | | | 0.5465 | 1.493 |
| 4.000 | 1.930 | | | 1.911 | 6.551 |
| 6.000 | 3.630 | | | 7.471 | 36.05 |
| 8.000 | 4.620 | | | 15.72 | 94.79 |
| 12.00 | 5.790 | | | 36.54 | 307.7 |
| 16.00 | 6.000 | | | 60.12 | 638.6 |
| 24.00 | 8.500 | | | 118.1 | 1839. |
| 36.00 | 5.930 | | | 203.8 | 4378. |
| 48.00 | 6.750 | | | 279.9 | 7602. |
| 60.00 | 5.750 | | | 354.7 | 1.163e+004 |
| 72.00 * | 6.700 | 6.909 | -0.2088 | 429.4 | 1.660e+004 1.000 |
| 96.00 * | 4.920 | 4.753 | 0.1673 | 567.7 | 2.813e+004 1.000 |
| 120.0 * | 3.070 | 3.270 | -0.1996 | 661.9 | 3.821e+004 1.000 |
| 144.0 * | 2.600 | 2.249 | 0.3508 | 729.8 | 4.715e+004 1.000 |
| 168.0 * | 1.420 | 1.547 | -0.1273 | 776.6 | 5.440e+004 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|------------|
| Rsqr | | 0.9760 |
| Rsqr_adjusted | | 0.9679 |
| Corr_XY | | -0.9879 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0156 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 44.4717 |
| Tlag | h | 1.5000 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 8.5000 |
| Cmax_D | ng/mL/mg | 0.0189 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 1.4200 |
| AUClast | h*ng/mL | 776.5863 |
| AUCall | h*ng/mL | 776.5863 |
| AUCINF_obs | h*ng/mL | 867.6923 |
| AUCINF_D_obs | h*ng/mL/mg | 1.9282 |
| AUC_%Extrap_obs | % | 10.4998 |
| Vz_F_obs | L | 33274.0250 |
| Cl_F_obs | L/h | 518.6170 |
| AUCINF_pred | h*ng/mL | 875.8598 |
| AUCINF_D_pred | h*ng/mL/mg | 1.9464 |
| AUC_%Extrap_pred | % | 11.3344 |
| Vz_F_pred | L | 32963.7376 |
| Cl_F_pred | L/h | 513.7808 |
| AUMClast | h*h*ng/mL | 54396.3729 |
| AUMCINF_obs | h*h*ng/mL | 75547.4595 |
| AUMC_%Extrap_obs | % | 27.9971 |
| AUMCINF_pred | h*h*ng/mL | 77443.6381 |
| AUMC_%Extrap_pred | % | 29.7600 |
| MRTlast | h | 70.0455 |
| MRTINF_obs | h | 87.0671 |
| MRTINF_pred | h | 88.4201 |
| AUC0_24 | h*ng/mL | 118.1210 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:27

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

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| | | |
|-------------------|---------|-------------|
| Vz_F_pred | L | 39739.4753 |
| Cl_F_pred | L/h | 376.8262 |
| AUMClast | h*ng/mL | 67713.0139 |
| AUMCINF_obs | h*ng/mL | 133753.1096 |
| AUMC_%Extrap_obs | % | 49.3746 |
| AUMCINF_pred | h*ng/mL | 133942.2754 |
| AUMC_%Extrap_pred | % | 49.4461 |
| MRTlast | h | 71.1276 |
| MRTINF_obs | h | 112.0687 |
| MRTINF_pred | h | 112.1621 |
| AUC0_24 | h*ng/mL | 128.1248 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-----------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.5000 | 0.2060 | | | 0.05150 | 0.07725 | |
| 2.0000 | 0.4930 | | | 0.2263 | 0.4010 | |
| 3.0000 | 1.030 | | | 0.9878 | 2.439 | |
| 4.0000 | 1.810 | | | 2.408 | 7.604 | |
| 6.0000 | 2.680 | | | 6.898 | 30.92 | |
| 8.0000 | 3.650 | | | 13.23 | 76.20 | |
| 12.00 | 5.840 | | | 32.21 | 274.8 | |
| 16.00 | 7.130 | | | 58.15 | 643.1 | |
| 24.00 | 10.20 | | | 127.5 | 2079. | |
| 36.03 | 9.030 | | | 243.0 | 5533. | |
| 48.00 | 8.760 | | | 349.5 | 1.000e+004 | |
| 60.00 | 5.560 | | | 433.9 | 1.453e+004 | |
| 72.00 | 4.820 | | | 496.1 | 1.862e+004 | |
| 96.00 | 3.130 | | | 590.1 | 2.643e+004 | |
| 120.0 * | 1.390 | 1.399 | -0.008729 | 641.5 | 3.190e+004 | 1.000 |
| 144.0 * | 0.9030 | 0.8918 | 0.01124 | 668.6 | 3.546e+004 | 1.000 |
| 168.0 * | 0.5650 | 0.5685 | -0.003548 | 685.9 | 3.814e+004 | 1.000 |

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

Final Parameters

Rsq 0.9994
Rsq_adjusted 0.9988

| | | |
|--------------------|------------|------------|
| Corr_XY | | -0.9997 |
| No_points_lambda_z | | 3 |
| Lambda_z | 1/h | 0.0188 |
| Lambda_z_lower | h | 120.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 36.9583 |
| Tlag | h | 1.0000 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 10.2000 |
| Cmax_D | ng/mL/mg | 0.0227 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 0.5650 |
| AUClast | h*ng/mL | 685.8936 |
| AUCall | h*ng/mL | 685.8936 |
| AUCINF_obs | h*ng/mL | 716.0191 |
| AUCINF_D_obs | h*ng/mL/mg | 1.5912 |
| AUC_%Extrap_obs | % | 4.2074 |
| Vz_F_obs | L | 33509.9715 |
| Cl_F_obs | L/h | 628.4748 |
| AUCINF_pred | h*ng/mL | 716.2083 |
| AUCINF_D_pred | h*ng/mL/mg | 1.5916 |
| AUC_%Extrap_pred | % | 4.2327 |
| Vz_F_pred | L | 33501.1202 |
| Cl_F_pred | L/h | 628.3088 |
| AUMClast | h*h*ng/mL | 38139.9732 |
| AUMCINF_obs | h*h*ng/mL | 44807.3395 |
| AUMC_%Extrap_obs | % | 14.8801 |
| AUMCINF_pred | h*h*ng/mL | 44849.2085 |
| AUMC_%Extrap_pred | % | 14.9595 |
| MRTlast | h | 55.6063 |
| MRTINF_obs | h | 62.5784 |
| MRTINF_pred | h | 62.6203 |
| AUC0_24 | h*ng/mL | 127.4678 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.1400 | | | 0.01750 | 0.01313 | |
| 1.000 | 0.2360 | | | 0.06450 | 0.05575 | |
| 1.500 | 0.6430 | | | 0.2843 | 0.3559 | |
| 2.000 | 1.030 | | | 0.7025 | 1.112 | |
| 3.000 | 1.830 | | | 2.133 | 4.887 | |
| 4.000 | 2.730 | | | 4.413 | 13.09 | |

| | | | | | |
|---------|-------|-------|---------|-------|------------|
| 6.000 | 3.290 | | | 10.43 | 43.75 |
| 8.000 | 4.070 | | | 17.79 | 96.05 |
| 12.00 | 5.010 | | | 35.95 | 281.4 |
| 16.00 | 6.230 | | | 58.43 | 601.0 |
| 24.00 | 8.700 | | | 118.2 | 1835. |
| 36.00 | 7.870 | | | 217.5 | 4805. |
| 48.00 | 9.130 | | | 319.5 | 9134. |
| 60.00 | 7.900 | | | 421.5 | 1.463e+004 |
| 72.02 | 7.720 | | | 515.3 | 2.082e+004 |
| 96.00 | 5.010 | | | 665.7 | 3.332e+004 |
| 120.0 * | 5.270 | 5.068 | 0.2022 | 789.0 | 4.668e+004 |
| 144.1 * | 2.680 | 2.899 | -0.2188 | 881.2 | 5.873e+004 |
| 168.0 * | 1.730 | 1.663 | 0.06675 | 933.1 | 6.679e+004 |

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

Final Parameters

| | | |
|--------------------|------------|------------|
| Rsqr | | 0.9853 |
| Rsqr_adjusted | | 0.9707 |
| Corr_XY | | -0.9926 |
| No_points_lambda_z | | 3 |
| Lambda_z | 1/h | 0.0232 |
| Lambda_z_lower | h | 120.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 29.8629 |
| Tlag | h | 0.5000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 9.1300 |
| Cmax_D | ng/mL/mg | 0.0203 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 1.7300 |
| AUClast | h*ng/mL | 933.1420 |
| AUCall | h*ng/mL | 933.1420 |
| AUCINF_obs | h*ng/mL | 1007.6757 |
| AUCINF_D_obs | h*ng/mL/mg | 2.2393 |
| AUC_%Extrap_obs | % | 7.3966 |
| Vz_F_obs | L | 19239.7000 |
| Cl_F_obs | L/h | 446.5723 |
| AUCINF_pred | h*ng/mL | 1004.8000 |
| AUCINF_D_pred | h*ng/mL/mg | 2.2329 |
| AUC_%Extrap_pred | % | 7.1316 |
| Vz_F_pred | L | 19294.7628 |
| Cl_F_pred | L/h | 447.8503 |
| AUMClast | h*ng/mL | 66785.9287 |
| AUMCINF_obs | h*ng/mL | 82518.7298 |
| AUMC_%Extrap_obs | % | 19.0657 |
| AUMCINF_pred | h*ng/mL | 81911.7235 |
| AUMC_%Extrap_pred | % | 18.4660 |
| MRTlast | h | 71.5710 |
| MRTINF_obs | h | 81.8902 |
| MRTINF_pred | h | 81.5204 |
| AUC0_24 | h*ng/mL | 118.1525 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:27

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22

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| | | |
|-------------|---------|---------|
| MRTlast | h | 63.5371 |
| MRTINF_obs | h | 71.4680 |
| MRTINF_pred | h | 71.8122 |
| AUC0_24 | h*ng/mL | 95.9402 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:27

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 2.000 | 0.1130 | | | 0.02825 | 0.05650 | |
| 3.000 | 0.2980 | | | 0.2338 | 0.6165 | |
| 4.000 | 0.6840 | | | 0.7248 | 2.432 | |
| 6.000 | 1.910 | | | 3.319 | 16.63 | |
| 8.000 | 2.730 | | | 7.959 | 49.93 | |
| 12.03 | 4.330 | | | 22.20 | 199.0 | |
| 16.00 | 5.310 | | | 41.32 | 470.9 | |
| 24.00 | 7.840 | | | 93.92 | 1563. | |
| 36.00 | 5.480 | | | 173.0 | 3907. | |
| 48.00 * | 5.960 | 5.814 | 0.1456 | 241.6 | 6808. | 1.000 |
| 60.00 * | 3.910 | 4.436 | -0.5265 | 300.0 | 9934. | 1.000 |
| 72.00 * | 3.750 | 3.385 | 0.3649 | 345.9 | 1.297e+004 | 1.000 |
| 96.07 * | 2.060 | 1.968 | 0.09214 | 413.8 | 1.859e+004 | 1.000 |
| 120.1 * | 1.160 | 1.146 | 0.01389 | 451.4 | 2.261e+004 | 1.000 |
| 144.0 * | 0.5890 | 0.6680 | -0.07902 | 471.6 | 2.525e+004 | 1.000 |
| 168.0 * | 0.4160 | 0.3889 | 0.02708 | 483.5 | 2.710e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|-----|----------|
| Rsqr | | 0.9920 |
| Rsqr_adjusted | | 0.9903 |
| Corr_XY | | -0.9960 |
| No_points_lambda_z | | 7 |
| Lambda_z | 1/h | 0.0225 |
| Lambda_z_lower | h | 48.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 30.7528 |
| Tlag | h | 1.5000 |

| | | |
|-------------------|------------|------------|
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 7.8400 |
| Cmax_D | ng/mL/mg | 0.0174 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 0.4160 |
| AUClast | h*ng/mL | 483.5428 |
| AUCall | h*ng/mL | 483.5428 |
| AUCINF_obs | h*ng/mL | 501.9995 |
| AUCINF_D_obs | h*ng/mL/mg | 1.1156 |
| AUC_%Extrap_obs | % | 3.6766 |
| Vz_F_obs | L | 39771.2079 |
| Cl_F_obs | L/h | 896.4152 |
| AUCINF_pred | h*ng/mL | 500.7980 |
| AUCINF_D_pred | h*ng/mL/mg | 1.1129 |
| AUC_%Extrap_pred | % | 3.4455 |
| Vz_F_pred | L | 39866.6228 |
| Cl_F_pred | L/h | 898.5658 |
| AUMClast | h*h*ng/mL | 27099.5522 |
| AUMCINF_obs | h*h*ng/mL | 31019.1346 |
| AUMC_%Extrap_obs | % | 12.6360 |
| AUMCINF_pred | h*h*ng/mL | 30763.9841 |
| AUMC_%Extrap_pred | % | 11.9114 |
| MRTlast | h | 56.0437 |
| MRTINF_obs | h | 61.7912 |
| MRTINF_pred | h | 61.4299 |
| AUC0_24 | h*ng/mL | 93.9158 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.2630 | | | 0.06575 | 0.09863 | |
| 2.000 | 0.3670 | | | 0.2233 | 0.3808 | |
| 3.000 | 1.010 | | | 0.9118 | 2.263 | |
| 4.000 | 1.950 | | | 2.392 | 7.678 | |
| 6.000 | 3.120 | | | 7.462 | 34.20 | |
| 8.000 | 4.360 | | | 14.94 | 87.80 | |
| 12.00 | 5.840 | | | 35.34 | 297.7 | |
| 16.00 | 7.500 | | | 62.02 | 677.9 | |
| 24.02 | 11.30 | | | 137.4 | 2247. | |
| 36.00 | 10.10 | | | 265.5 | 6076. | |
| 48.00 | 11.00 | | | 392.1 | 1.143e+004 | |

| | | | | | |
|---------|-------|-------|----------|--------|------------|
| 60.00 | 8.970 | | | 511.5 | 1.785e+004 |
| 72.00 | 9.890 | | | 624.6 | 2.535e+004 |
| 96.00 | 8.430 | | | 844.0 | 4.371e+004 |
| 120.0 * | 5.550 | 5.592 | -0.04182 | 1009.6 | 1.143e+004 |
| 144.0 * | 3.500 | 3.448 | 0.05215 | 1116.7 | 7.542e+004 |
| 168.0 * | 2.110 | 2.126 | -0.01590 | 1182.8 | 5.63e+004 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9993 |
| Rsqr_adjusted | | 0.9986 |
| Corr_XY | | -0.9996 |
| No_points_lambda_z | | 3 |
| Lambda_z | 1/h | 0.0201 |
| Lambda_z_lower | h | 120.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 34.4026 |
| Tlag | h | 1.0000 |
| Tmax | h | 24.0167 |
| Cmax | ng/mL | 11.3000 |
| Cmax_D | ng/mL/mg | 0.0251 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 2.1100 |
| AUClast | h*ng/mL | 1182.0003 |
| AUCall | h*ng/mL | 1182.0003 |
| AUCINF_obs | h*ng/mL | 1286.7247 |
| AUCINF_D_obs | h*ng/mL/mg | 2.8594 |
| AUC_%Extrap_obs | % | 8.1388 |
| Vz_F_obs | L | 17357.7026 |
| Cl_F_obs | L/h | 349.7252 |
| AUCINF_pred | h*ng/mL | 1287.5138 |
| AUCINF_D_pred | h*ng/mL/mg | 2.8611 |
| AUC_%Extrap_pred | % | 8.1951 |
| Vz_F_pred | L | 17347.0644 |
| Cl_F_pred | L/h | 349.5108 |
| AUMClast | h*h*ng/mL | 85634.6553 |
| AUMCINF_obs | h*h*ng/mL | 108426.0761 |
| AUMC_%Extrap_obs | % | 21.0202 |
| AUMCINF_pred | h*h*ng/mL | 108597.8077 |
| AUMC_%Extrap_pred | % | 21.1451 |
| MRTlast | h | 72.4489 |
| MRTINF_obs | h | 84.2652 |
| MRTINF_pred | h | 84.3469 |
| AUC0_24 | h*ng/mL | 137.1901 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

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WinNonlin 7.0.0.2535
 PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
 Time: 09:27:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
 7.0.0.2535
 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
 Number of nonmissing observations: 22
 Dose time: 0.00
 Dose amount: 450.00
 Calculation method: Linear Trapezoidal Rule for Increasing Values,
 Log Trapezoidal Rule for Decreasing Values
 Weighting for lambda_z calculations: Uniform weighting
 Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.1430 | | | 0.03575 | 0.05363 | |
| 2.000 | 0.4110 | | | 0.1743 | 0.3128 | |
| 3.000 | 0.9090 | | | 0.8343 | 2.087 | |
| 4.000 | 1.650 | | | 2.114 | 6.751 | |
| 6.017 | 2.300 | | | 6.097 | 27.36 | |
| 8.000 | 3.110 | | | 11.46 | 65.76 | |
| 12.00 | 4.290 | | | 26.26 | 218.5 | |
| 16.10 | 5.790 | | | 46.93 | 515.1 | |
| 24.07 | 7.830 | | | 101.2 | 1637. | |
| 36.00 | 5.950 | | | 182.9 | 4069. | |
| 48.00 | 6.410 | | | 257.0 | 7200. | |
| 60.02 | 4.190 | | | 319.8 | 1.056e+004 | |
| 72.00 * | 5.150 | 5.541 | -0.3912 | 375.8 | 1.429e+004 | 1.000 |
| 96.17 * | 3.410 | 3.241 | 0.1689 | 477.7 | 2.278e+004 | 1.000 |
| 120.0 * | 1.940 | 1.910 | 0.03020 | 539.9 | 2.943e+004 | 1.000 |
| 146.9 * | 1.190 | 1.051 | 0.1395 | 581.2 | 3.490e+004 | 1.000 |
| 168.0 * | 0.5850 | 0.6582 | -0.07322 | 599.1 | 3.770e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|----------|----------|
| Rsqr | | 0.9872 |
| Rsqr_adjusted | | 0.9829 |
| Corr_XY | | -0.9936 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0222 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 31.2343 |
| Tlag | h | 1.0000 |
| Tmax | h | 24.0667 |
| Cmax | ng/mL | 7.8300 |
| Cmax_D | ng/mL/mg | 0.0174 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 0.5850 |
| AUClast | h*ng/mL | 599.1435 |
| AUCall | h*ng/mL | 599.1435 |

| | | |
|-------------------|------------|------------|
| AUCINF_obs | h*ng/mL | 625.5045 |
| AUCINF_D_obs | h*ng/mL/mg | 1.3900 |
| AUC_%Extrap_obs | % | 4.2144 |
| Vz_F_obs | L | 32418.1193 |
| CL_F_obs | L/h | 719.4193 |
| AUCINF_pred | h*ng/mL | 628.8041 |
| AUCINF_D_pred | h*ng/mL/mg | 1.3973 |
| AUC_%Extrap_pred | % | 4.7170 |
| Vz_F_pred | L | 32248.0091 |
| CL_F_pred | L/h | 715.6442 |
| AUMClast | h*h*ng/mL | 37701.8848 |
| AUMCINF_obs | h*h*ng/mL | 43318.3955 |
| AUMC_%Extrap_obs | % | 12.9656 |
| AUMCINF_pred | h*h*ng/mL | 44021.4077 |
| AUMC_%Extrap_pred | % | 14.3556 |
| MRTIast | h | 62.9263 |
| MRTINF_obs | h | 69.2535 |
| MRTINF_pred | h | 70.0081 |
| AUC0_24 | h*ng/mL | 100.6572 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2667 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.1140 | | | 0.01425 | 0.01425 | |
| 1.500 | 0.3890 | | | 0.1400 | 0.1886 | |
| 2.000 | 0.7540 | | | 0.4258 | 0.7115 | |
| 3.000 | 1.500 | | | 1.553 | 3.716 | |
| 4.000 | 2.770 | | | 3.688 | 11.51 | |
| 6.000 | 4.180 | | | 10.64 | 47.67 | |
| 8.000 | 7.520 | | | 22.34 | 132.9 | |
| 12.00 | 9.070 | | | 55.52 | 470.9 | |
| 16.00 | 12.20 | | | 98.06 | 1079. | |
| 24.00 | 20.40 | | | 228.5 | 3818. | |
| 36.00 | 13.60 | | | 429.7 | 9774. | |
| 48.00 | 16.20 | | | 608.5 | 1.738e+004 | |
| 60.00 | 10.20 | | | 764.1 | 2.571e+004 | |
| 72.00 * | 9.940 | 9.861 | 0.07859 | 885.0 | 3.368e+004 | 1.000 |
| 96.00 * | 6.410 | 6.340 | 0.06952 | 1078. | 4.973e+004 | 1.000 |
| 120.0 * | 4.160 | 4.077 | 0.08334 | 1203. | 6.312e+004 | 1.000 |
| 144.0 * | 2.360 | 2.621 | -0.2611 | 1279. | 7.309e+004 | 1.000 |
| 168.0 * | 1.800 | 1.685 | 0.1147 | 1329. | 8.080e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsq | | 0.9919 |
| Rsq_adjusted | | 0.9892 |
| Corr_XY | | -0.9959 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0184 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 37.6646 |
| Tlag | h | 0.7500 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 20.4000 |
| Cmax_D | ng/mL/mg | 0.0453 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 1.8000 |
| AUClast | h*ng/mL | 1328.8158 |
| AUCall | h*ng/mL | 1328.8158 |
| AUCINF_obs | h*ng/mL | 1426.6251 |
| AUCINF_D_obs | h*ng/mL/mg | 3.1703 |
| AUC_%Extrap_obs | % | 6.8560 |
| Vz_F_obs | L | 17139.9782 |
| CL_F_obs | L/h | 315.4298 |
| AUCINF_pred | h*ng/mL | 1420.3908 |
| AUCINF_D_pred | h*ng/mL/mg | 3.1564 |
| AUC_%Extrap_pred | % | 6.4472 |
| Vz_F_pred | L | 17215.2070 |
| CL_F_pred | L/h | 316.8142 |
| AUMClast | h*h*ng/mL | 80803.2468 |
| AUMCINF_obs | h*h*ng/mL | 102550.0171 |
| AUMC_%Extrap_obs | % | 21.2060 |
| AUMCINF_pred | h*h*ng/mL | 101163.9117 |
| AUMC_%Extrap_pred | % | 20.1264 |
| MRTlast | h | 60.8085 |
| MRTINF_obs | h | 71.8829 |
| MRTINF_pred | h | 71.2226 |
| AUC0_24 | h*ng/mL | 228.4578 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |

| | | | | | |
|---------|--------|-------|----------|---------|------------|
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 |
| 1.500 | 0.1910 | | | 0.04775 | 0.07163 |
| 2.000 | 0.5420 | | | 0.2310 | 0.4143 |
| 3.000 | 1.190 | | | 1.097 | 2.741 |
| 4.000 | 2.030 | | | 2.707 | 8.586 |
| 6.000 | 3.610 | | | 8.347 | 38.37 |
| 8.017 | 4.360 | | | 16.38 | 95.45 |
| 12.00 | 5.270 | | | 35.56 | 291.0 |
| 16.00 | 6.310 | | | 58.72 | 619.4 |
| 24.00 | 8.520 | | | 118.0 | 1841. |
| 36.00 | 6.670 | | | 208.7 | 4540. |
| 48.00 | 9.440 | | | 305.4 | 8699. |
| 60.03 | 7.370 | | | 406.0 | 1.411e+004 |
| 72.00 * | 7.300 | 7.075 | 0.2253 | 493.8 | 1.990e+004 |
| 96.03 * | 4.520 | 4.603 | -0.08263 | 633.2 | 3.148e+004 |
| 120.0 * | 2.940 | 2.998 | -0.05792 | 721.2 | 4.091e+004 |
| 144.0 * | 1.890 | 1.952 | -0.06153 | 778.2 | 4.839e+004 |
| 168.0 * | 1.320 | 1.270 | 0.04963 | 816.4 | 5.431e+004 |

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

Final Parameters

| | | |
|--------------------|------------|------------|
| Rsqr | | 0.9977 |
| Rsqr_adjusted | | 0.9970 |
| Corr_XY | | -0.9989 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0179 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 38.7500 |
| Tlag | h | 1.0000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 9.4400 |
| Cmax_D | ng/mL/mg | 0.0210 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 1.3200 |
| AUClast | h*ng/mL | 816.3601 |
| AUCall | h*ng/mL | 816.3601 |
| AUCINF_obs | h*ng/mL | 890.1539 |
| AUCINF_D_obs | h*ng/mL/mg | 1.9781 |
| AUC_%Extrap_obs | % | 8.2900 |
| Vz_F_obs | L | 28261.3909 |
| Cl_F_obs | L/h | 505.5306 |
| AUCINF_pred | h*ng/mL | 887.3796 |
| AUCINF_D_pred | h*ng/mL/mg | 1.9720 |
| AUC_%Extrap_pred | % | 8.0033 |
| Vz_F_pred | L | 28349.7466 |
| Cl_F_pred | L/h | 507.1110 |
| AUMClast | h*h*ng/mL | 54311.3950 |
| AUMCINF_obs | h*h*ng/mL | 70834.1596 |
| AUMC_%Extrap_obs | % | 23.3260 |
| AUMCINF_pred | h*h*ng/mL | 70212.9858 |
| AUMC_%Extrap_pred | % | 22.6476 |
| MRTlast | h | 66.5287 |
| MRTINF_obs | h | 79.5752 |
| MRTINF_pred | h | 79.1240 |
| AUC0_24 | h*ng/mL | 118.0432 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:26

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| | | |
|-------------------|---------|------------|
| AUC_%Extrap_pred | % | 4.2327 |
| Vz_F_pred | L | 65833.1146 |
| CL_F_pred | L/h | 1413.8941 |
| AUMClast | h*ng/mL | 18127.7153 |
| AUMCINF_obs | h*ng/mL | 20845.0826 |
| AUMC_%Extrap_obs | % | 13.0360 |
| AUMCINF_pred | h*ng/mL | 21018.1307 |
| AUMC_%Extrap_pred | % | 13.7520 |
| MRTlast | h | 59.4744 |
| MRTINF_obs | h | 65.6614 |
| MRTINF_pred | h | 66.0387 |
| AUC0_24 | h*ng/mL | 50.2685 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-----------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.8167 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.017 | 0.1080 | | | 0.01080 | 0.01098 | |
| 1.500 | 0.2230 | | | 0.09079 | 0.1184 | |
| 2.000 | 0.4240 | | | 0.2525 | 0.4140 | |
| 3.000 | 1.390 | | | 1.160 | 2.923 | |
| 4.000 | 2.450 | | | 3.080 | 9.908 | |
| 6.000 | 3.290 | | | 8.820 | 39.45 | |
| 8.033 | 4.460 | | | 16.70 | 95.94 | |
| 12.00 | 4.680 | | | 34.83 | 278.4 | |
| 16.00 | 5.860 | | | 55.91 | 578.2 | |
| 24.00 | 5.950 | | | 103.1 | 1524. | |
| 36.00 | 4.540 | | | 165.7 | 3384. | |
| 48.02 | 4.320 | | | 218.9 | 5617. | |
| 60.08 | 3.120 | | | 263.4 | 8008. | |
| 72.00 | 2.140 | | | 294.4 | 1.004e+004 | |
| 95.73 * | 1.320 | 1.320 | 0.0003104 | 334.7 | 1.338e+004 | 1.000 |
| 120.1 * | 0.8940 | 0.8927 | 0.001303 | 361.4 | 1.624e+004 | 1.000 |
| 144.0 * | 0.6070 | 0.6090 | -0.002041 | 379.0 | 1.856e+004 | 1.000 |
| 171.8 * | 0.3910 | 0.3904 | 0.0006497 | 392.7 | 2.070e+004 | 1.000 |

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

Final Parameters

Rsqr 1.0000

| | | |
|--------------------|------------|------------|
| Rsquared | | 1.0000 |
| Corr_XY | | -1.0000 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0160 |
| Lambda_z_lower | h | 95.7333 |
| Lambda_z_upper | h | 171.7667 |
| HL_Lambda_z | h | 43.2657 |
| Tlag | h | 0.8167 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 5.9500 |
| Cmax_D | ng/mL/mg | 0.0132 |
| Tlast | h | 171.7667 |
| Clast | ng/mL | 0.3910 |
| AUClast | h*ng/mL | 392.6793 |
| AUCall | h*ng/mL | 392.6793 |
| AUCINF_obs | h*ng/mL | 417.0852 |
| AUCINF_D_obs | h*ng/mL/mg | 0.9269 |
| AUC_%Extrap_obs | % | 5.8515 |
| Vz_F_obs | L | 67345.1331 |
| CL_F_obs | L/h | 1078.9162 |
| AUCINF_pred | h*ng/mL | 417.0447 |
| AUCINF_D_pred | h*ng/mL/mg | 0.9268 |
| AUC_%Extrap_pred | % | 5.8424 |
| Vz_F_pred | L | 67351.6817 |
| CL_F_pred | L/h | 1079.0211 |
| AUMClast | h*h*ng/mL | 20701.6217 |
| AUMCINF_obs | h*h*ng/mL | 26417.1454 |
| AUMC_%Extrap_obs | % | 21.6357 |
| AUMCINF_pred | h*h*ng/mL | 26407.6485 |
| AUMC_%Extrap_pred | % | 21.6075 |
| MRTlast | h | 52.7189 |
| MRTINF_obs | h | 63.3375 |
| MRTINF_pred | h | 63.3209 |
| AUC0_24 | h*ng/mL | 103.1464 |

WinNonlin 7.0.0.2535
PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 18
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.1310 | | | 0.01638 | 0.01638 | |
| 1.500 | 0.2120 | | | 0.1021 | 0.1286 | |
| 2.000 | 0.3430 | | | 0.2409 | 0.3796 | |
| 3.000 | 1.250 | | | 1.037 | 2.598 | |

| | | | | | | |
|---------|-------|-------|----------|-------|-------|-------|
| 4.000 | 2.360 | | | 2.842 | 9.193 | |
| 6.000 | 3.540 | | | 8.742 | 39.87 | |
| 8.000 | 4.870 | | | 17.15 | 100.1 | |
| 12.00 | 4.990 | | | 36.87 | 297.8 | |
| 16.00 | 5.560 | | | 57.97 | 595.4 | |
| 24.00 | 6.110 | | | 104.7 | 1538. | |
| 36.00 * | 4.470 | 4.527 | -0.05666 | 167.6 | 3407. | 1.000 |
| 48.00 * | 3.790 | 3.548 | 0.2423 | 217.1 | 5476. | 1.000 |
| 60.00 * | 2.530 | 2.780 | -0.2504 | 254.5 | 7481. | 1.000 |
| 72.00 * | 2.270 | 2.179 | 0.09094 | 283.3 | 9377. | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|------------|
| Rsqr | | 0.9516 |
| Rsqr_adjusted | | 0.9274 |
| Corr_XY | | -0.9755 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0203 |
| Lambda_z_lower | h | 36.0000 |
| Lambda_z_upper | h | 72.0000 |
| HL_Lambda_z | h | 34.1316 |
| Tlag | h | 0.7500 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 6.1100 |
| Cmax_D | ng/mL/mg | 0.0136 |
| Tlast | h | 72.0000 |
| Clast | ng/mL | 2.2700 |
| AUClast | h*ng/mL | 283.2524 |
| AUCall | h*ng/mL | 283.2524 |
| AUCINF_obs | h*ng/mL | 395.0305 |
| AUCINF_D_obs | h*ng/mL/mg | 0.8778 |
| AUC_%Extrap_obs | % | 28.2961 |
| Vz_F_obs | L | 56093.4985 |
| CL_F_obs | L/h | 1139.1526 |
| AUCINF_pred | h*ng/mL | 390.5524 |
| AUCINF_D_pred | h*ng/mL/mg | 0.8679 |
| AUC_%Extrap_pred | % | 27.4739 |
| Vz_F_pred | L | 56736.6747 |
| CL_F_pred | L/h | 1152.2143 |
| AUMClast | h*h*ng/mL | 9376.8831 |
| AUMCINF_obs | h*h*ng/mL | 22929.0119 |
| AUMC_%Extrap_obs | % | 59.1047 |
| AUMCINF_pred | h*h*ng/mL | 22386.0770 |
| AUMC_%Extrap_pred | % | 58.1129 |
| MRTlast | h | 33.1043 |
| MRTINF_obs | h | 58.0437 |
| MRTINF_pred | h | 57.3190 |
| AUC0_24 | h*ng/mL | 104.6524 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840. 841. 842. 843. 844. 845. 846. 847. 848. 849. 850. 851. 852. 853. 854. 855. 856. 857. 858. 859. 860. 861. 862. 863. 864. 865. 866. 867. 868. 869. 870. 871. 872. 873. 874. 875. 876. 877. 878. 879. 880. 881. 882. 883. 884. 885. 886. 887. 888. 889. 890. 891. 892. 893. 894. 895. 896. 897. 898. 899. 900. 901. 902. 903. 904. 905. 906. 907. 908. 909. 910. 911. 912. 913. 914. 915. 916. 917. 918. 919. 920. 921. 922. 923. 924. 925. 926. 927. 928. 929. 930. 931. 932. 933. 934. 935. 936. 937. 938. 939. 940. 941. 942. 943. 944. 945. 946. 947. 948. 949. 950. 951. 952. 953. 954. 955. 956. 957. 958. 959. 960. 961. 962. 963. 964. 965. 966. 967. 968. 969. 970. 971. 972. 973. 974. 975. 976. 977. 978. 979. 980. 981. 982. 983. 984. 985. 986. 987. 988. 989. 990. 991. 992. 993. 994. 995. 996. 997. 998. 999. 1000.

135.0296

PARAMCD=M7A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Time: 09:27:26

Core Version 04Jun2007

[illegible]

Lambda z method: Find best fit for lambda z, Log regression

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h ² *ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.1860 | | | 0.04650 | 0.06975 | |
| 2.000 | 0.3530 | | | 0.1813 | 0.3160 | |
| 3.000 | 0.9730 | | | 0.8443 | 2.129 | |
| 4.000 | 1.850 | | | 2.256 | 7.288 | |
| 6.000 | 3.210 | | | 7.316 | 33.95 | |
| 8.000 | 4.180 | | | 14.71 | 86.65 | |
| 12.00 | 4.810 | | | 32.69 | 269.0 | |
| 16.00 | 5.180 | | | 52.67 | 550.2 | |
| 24.00 | 6.560 | | | 99.63 | 1511. | |
| 36.00 | 4.490 | | | 165.1 | 3452. | |
| 48.00 * | 4.820 | 4.658 | 0.1622 | 221.0 | 5810. | 1.000 |
| 60.00 * | 3.210 | 3.532 | -0.3216 | 268.5 | 8357. | 1.000 |
| 72.00 * | 2.730 | 2.678 | 0.05231 | 304.1 | 1.070e+004 | 1.000 |
| 96.00 * | 1.680 | 1.539 | 0.1406 | 356.0 | 1.501e+004 | 1.000 |
| 120.0 * | 0.8000 | 0.8850 | -0.08496 | 384.5 | 1.804e+004 | 1.000 |
| 144.0 * | 0.5740 | 0.5088 | 0.06524 | 400.8 | 2.019e+004 | 1.000 |
| 168.0 * | 0.2740 | 0.2925 | -0.01848 | 410.5 | 2.169e+004 | 1.000 |

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

1000

| | | |
|----------------|----------|----------|
| | | 0.9927 |
| adjusted | | 0.9912 |
| _XY | | -0.9963 |
| oints_lambda_z | | 7 |
| oda_z | 1/h | 0.0231 |
| oda_z_lower | h | 48.0000 |
| oda_z_upper | h | 168.0000 |
| ambda_z | h | 30.0508 |
| | h | 1.0000 |
| x | h | 24.0000 |
| x | ng/mL | 6.5600 |
| x_D | ng/mL/mg | 0.0146 |

| | | |
|-------------------|------------|------------|
| Tlast | h | 168.0000 |
| Clast | ng/mL | 0.2740 |
| AUClast | h*ng/mL | 410.5374 |
| AUCall | h*ng/mL | 410.5374 |
| AUCINF_obs | h*ng/mL | 422.4164 |
| AUCINF_D_obs | h*ng/mL/mg | 0.9387 |
| AUC_%Extrap_obs | % | 2.8122 |
| Vz_F_obs | L | 46185.1053 |
| CL_F_obs | L/h | 1065.2996 |
| AUCINF_pred | h*ng/mL | 423.2174 |
| AUCINF_D_pred | h*ng/mL/mg | 0.9405 |
| AUC_%Extrap_pred | % | 2.9961 |
| Vz_F_pred | L | 46097.6871 |
| CL_F_pred | L/h | 1063.2832 |
| AUMClast | h*h*ng/mL | 21691.3891 |
| AUMCINF_obs | h*h*ng/mL | 24202.0695 |
| AUMC_%Extrap_obs | % | 10.3738 |
| AUMCINF_pred | h*h*ng/mL | 24371.3761 |
| AUMC_%Extrap_pred | % | 10.9965 |
| MRTlast | h | 52.8366 |
| MRTINF_obs | h | 57.2943 |
| MRTINF_pred | h | 57.5859 |
| AUC0_24 | h*ng/mL | 99.6258 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:24

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

7.0.0.2535

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.050 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 2.017 | 0.0000 | | | 0.0000 | 0.0000 | |
| 3.000 | 0.2540 | | | 0.1249 | 0.3746 | |
| 4.000 | 0.4630 | | | 0.4834 | 1.682 | |
| 6.000 | 0.9970 | | | 1.943 | 9.516 | |
| 8.000 | 1.880 | | | 4.820 | 30.54 | |
| 12.00 | 3.440 | | | 15.46 | 143.2 | |
| 16.00 | 5.380 | | | 33.10 | 397.9 | |
| 24.00 | 8.540 | | | 88.78 | 1562. | |
| 36.00 | 7.510 | | | 184.9 | 4435. | |
| 48.00 | 8.340 | | | 280.0 | 8459. | |
| 60.00 | 5.230 | | | 360.0 | 1.274e+004 | |
| 72.00 * | 5.150 | 5.444 | -0.2944 | 422.3 | 1.685e+004 | 1.000 |
| 96.07 * | 3.580 | 3.484 | 0.09622 | 526.2 | 2.551e+004 | 1.000 |

| | | | | | | |
|---------|--------|--------|----------|-------|------------|-------|
| 120.0 * | 2.300 | 2.235 | 0.06526 | 595.4 | 3.292e+004 | 1.000 |
| 144.1 * | 1.550 | 1.429 | 0.1214 | 641.3 | 3.894e+004 | 1.000 |
| 168.6 * | 0.8360 | 0.9074 | -0.07141 | 669.6 | 4.333e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|------------|
| Rsqr | | 0.9911 |
| Rsqr_adjusted | | 0.9881 |
| Corr_XY | | -0.9955 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0186 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.5833 |
| HL_Lambda_z | h | 37.3639 |
| Tlag | h | 2.0167 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 8.5400 |
| Cmax_D | ng/mL/mg | 0.0190 |
| Tlast | h | 168.5833 |
| Clast | ng/mL | 0.8360 |
| AUClast | h*ng/mL | 669.5743 |
| AUCall | h*ng/mL | 669.5743 |
| AUCINF_obs | h*ng/mL | 714.6386 |
| AUCINF_D_obs | h*ng/mL/mg | 1.5881 |
| AUC_%Extrap_obs | % | 6.3059 |
| Vz_F_obs | L | 33943.1733 |
| CL_F_obs | L/h | 629.6889 |
| AUCINF_pred | h*ng/mL | 718.4881 |
| AUCINF_D_pred | h*ng/mL/mg | 1.5966 |
| AUC_%Extrap_pred | % | 6.8079 |
| Vz_F_pred | L | 33761.3157 |
| CL_F_pred | L/h | 626.3152 |
| AUMClast | h*h*ng/mL | 43329.7220 |
| AUMCINF_obs | h*h*ng/mL | 53355.9896 |
| AUMC_%Extrap_obs | % | 18.7913 |
| AUMCINF_pred | h*h*ng/mL | 54212.4459 |
| AUMC_%Extrap_pred | % | 20.0742 |
| MRTlast | h | 64.7123 |
| MRTINF_obs | h | 74.6615 |
| MRTINF_pred | h | 75.4535 |
| AUC0_24 | h*ng/mL | 88.7804 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7667 | 0.1070 | | | 0.01427 | 0.01094 | |
| 1.000 | 0.2280 | | | 0.05335 | 0.04711 | |
| 1.500 | 0.6630 | | | 0.2761 | 0.3527 | |
| 2.000 | 1.230 | | | 0.7494 | 1.216 | |
| 3.000 | 2.320 | | | 2.524 | 5.926 | |
| 4.000 | 3.350 | | | 5.359 | 16.11 | |
| 6.000 | 4.170 | | | 12.88 | 54.53 | |
| 8.017 | 5.570 | | | 22.70 | 124.8 | |
| 12.00 | 6.490 | | | 46.72 | 368.8 | |
| 16.00 | 8.380 | | | 76.46 | 792.7 | |
| 24.02 | 12.80 | | | 161.4 | 2562. | |
| 36.00 | 8.250 | | | 285.5 | 6233. | |
| 48.00 | 8.230 | | | 384.4 | 1.039e+004 | |
| 60.00 | 5.030 | | | 462.4 | 1.456e+004 | |
| 72.00 * | 5.480 | 5.497 | -0.01679 | 525.4 | 1.874e+004 | 1.000 |
| 96.00 * | 3.840 | 3.623 | 0.2174 | 636.1 | 2.796e+004 | 1.000 |
| 120.0 * | 2.130 | 2.387 | -0.2574 | 705.7 | 3.539e+004 | 1.000 |
| 144.0 * | 1.680 | 1.573 | 0.1066 | 751.2 | 4.138e+004 | 1.000 |
| 168.0 * | 1.030 | 1.037 | -0.006921 | 783.1 | 4.632e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|------------|
| Rsqr | | 0.9882 |
| Rsqr_adjusted | | 0.9843 |
| Corr_XY | | -0.9941 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0174 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 39.8956 |
| Tlag | h | 0.5000 |
| Tmax | h | 24.0167 |
| Cmax | ng/mL | 12.8000 |
| Cmax_D | ng/mL/mg | 0.0284 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 1.0300 |
| AUClast | h*ng/mL | 783.1276 |
| AUCall | h*ng/mL | 783.1276 |
| AUCINF_obs | h*ng/mL | 842.4114 |
| AUCINF_D_obs | h*ng/mL/mg | 1.8720 |
| AUC_%Extrap_obs | % | 7.0374 |
| Vz_F_obs | L | 30745.9066 |
| Cl_F_obs | L/h | 534.1808 |
| AUCINF_pred | h*ng/mL | 842.8098 |
| AUCINF_D_pred | h*ng/mL/mg | 1.8729 |
| AUC_%Extrap_pred | % | 7.0813 |
| Vz_F_pred | L | 30731.3737 |
| Cl_F_pred | L/h | 533.9283 |
| AUMClast | h*h*ng/mL | 46323.1661 |
| AUMCINF_obs | h*h*ng/mL | 59695.0555 |
| AUMC_%Extrap_obs | % | 22.4003 |
| AUMCINF_pred | h*h*ng/mL | 59784.9126 |
| AUMC_%Extrap_pred | % | 22.5170 |
| MRTlast | h | 59.1515 |
| MRTINF_obs | h | 70.8621 |
| MRTINF_pred | h | 70.9352 |
| AUC0_24 | h*ng/mL | 161.1433 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=pj,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

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| | | |
|-------------------|------------|------------|
| Vz_F_obs | L | 35112.3993 |
| Cl_F_obs | L/h | 665.5952 |
| AUCINF_pred | h*ng/mL | 676.7689 |
| AUCINF_D_pred | h*ng/mL/mg | 1.5039 |
| AUC_%Extrap_pred | % | 6.7187 |
| Vz_F_pred | L | 35077.0009 |
| Cl_F_pred | L/h | 664.9242 |
| AUMClast | h*h*ng/mL | 39029.9218 |
| AUMCINF_obs | h*h*ng/mL | 48916.9406 |
| AUMC_%Extrap_obs | % | 20.2119 |
| AUMCINF_pred | h*h*ng/mL | 49067.5565 |
| AUMC_%Extrap_pred | % | 20.4568 |
| MRTlast | h | 61.8248 |
| MRTINF_obs | h | 72.3531 |
| MRTINF_pred | h | 72.5027 |
| AUC0_24 | h*ng/mL | 117.9921 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:25

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.8167 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.017 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.1290 | | | 0.03117 | 0.04676 | |
| 2.000 | 0.2920 | | | 0.1364 | 0.2411 | |
| 3.000 | 0.9400 | | | 0.7524 | 1.943 | |
| 4.000 | 1.370 | | | 1.907 | 6.093 | |
| 6.000 | 2.170 | | | 5.447 | 24.59 | |
| 8.000 | 2.860 | | | 10.48 | 60.49 | |
| 12.00 | 4.110 | | | 24.42 | 204.9 | |
| 16.00 | 5.630 | | | 43.90 | 483.7 | |
| 24.00 | 8.360 | | | 99.86 | 1647. | |
| 36.00 | 10.00 | | | 210.0 | 5010. | |
| 48.00 | 11.60 | | | 339.6 | 1.051e+004 | |
| 60.00 | 9.000 | | | 462.6 | 1.712e+004 | |
| 72.00 * | 9.380 | 9.797 | -0.4167 | 572.8 | 2.441e+004 | 1.000 |
| 96.00 * | 7.050 | 6.670 | 0.3804 | 768.7 | 4.075e+004 | 1.000 |
| 120.0 * | 4.730 | 4.541 | 0.1894 | 908.2 | 5.571e+004 | 1.000 |
| 144.0 * | 2.870 | 3.091 | -0.2212 | 997.5 | 6.741e+004 | 1.000 |
| 168.0 * | 2.150 | 2.104 | 0.04551 | 1057. | 7.671e+004 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9915 |
| Rsqr_adjusted | | 0.9887 |
| Corr_XY | | -0.9958 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0160 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 43.2660 |
| Tlag | h | 1.0167 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 11.6000 |
| Cmax_D | ng/mL/mg | 0.0258 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 2.1500 |
| AUClast | h*ng/mL | 1057.3563 |
| AUCall | h*ng/mL | 1057.3563 |
| AUCINF_obs | h*ng/mL | 1191.5586 |
| AUCINF_D_obs | h*ng/mL/mg | 2.6479 |
| AUC_%Extrap_obs | % | 11.2628 |
| Vz_F_obs | L | 23573.2159 |
| Cl_F_obs | L/h | 377.6566 |
| AUCINF_pred | h*ng/mL | 1188.7181 |
| AUCINF_D_pred | h*ng/mL/mg | 2.6416 |
| AUC_%Extrap_pred | % | 11.0507 |
| Vz_F_pred | L | 23629.5458 |
| Cl_F_pred | L/h | 378.5591 |
| AUMClast | h*h*ng/mL | 76708.7918 |
| AUMCINF_obs | h*h*ng/mL | 107631.6638 |
| AUMC_%Extrap_obs | % | 28.7303 |
| AUMCINF_pred | h*h*ng/mL | 106977.1495 |
| AUMC_%Extrap_pred | % | 28.2942 |
| MRTlast | h | 72.5477 |
| MRTINF_obs | h | 90.3285 |
| MRTINF_pred | h | 89.9937 |
| AUC0_24 | h*ng/mL | 99.8574 |

WinNonlin 7.0.0.2535

PARAMCD=M7A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:27:26

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2667 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |

□ □ □ □

WinNonlin Core Output - Tepotinib Metabolite MSC2571109A

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 1.080 | | | 0.1350 | 0.1350 | |
| 1.600 | 1.850 | | | 1.014 | 1.347 | |
| 2.217 | 4.960 | | | 3.114 | 5.650 | |
| 3.000 | 10.20 | | | 9.051 | 21.94 | |
| 4.000 | 16.60 | | | 22.45 | 70.44 | |
| 6.000 | 24.10 | | | 63.15 | 281.4 | |
| 8.000 | 34.30 | | | 121.6 | 700.4 | |
| 12.00 | 42.00 | | | 274.2 | 2257. | |
| 16.00 | 52.20 | | | 462.6 | 4936. | |
| 24.02 | 85.10 | | | 1013. | 1.648e+004 | |
| 36.00 | 79.70 | | | 2000. | 4.603e+004 | |
| 48.02 | 97.90 | | | 3067. | 9.151e+004 | |
| 60.00 | 72.60 | | | 4081. | 1.460e+005 | |
| 72.00 | 70.50 | | | 4940. | 2.026e+005 | |
| 96.02 * | 52.40 | 52.27 | 0.1324 | 6405. | 3.248e+005 | 1.000 |
| 120.0 * | 32.90 | 32.66 | 0.2448 | 7410. | 4.324e+005 | 1.000 |
| 144.1 * | 19.90 | 20.36 | -0.4553 | 8033. | 5.141e+005 | 1.000 |
| 168.0 * | 12.90 | 12.74 | 0.1618 | 8419. | 5.740e+005 | 1.000 |

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

Final Parameters

Rsqr 0.9993
Rsqr_adjusted 0.9990
Corr_XY -0.9997
No_points_lambda_z 4
Lambda_z 1/h 0.0196
Lambda_z_lower h 96.0167
Lambda_z_upper h 168.0000
HL_Lambda_z h 35.3421
Tlag h 0.7500
Tmax h 48.0167
Cmax ng/mL 97.9000

| | | |
|-------------------|------------|-------------|
| Cmax_D | ng/mL/mg | 0.2176 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 12.9000 |
| AUClast | h*ng/mL | 8418.6346 |
| AUCall | h*ng/mL | 8418.6346 |
| AUCINF_obs | h*ng/mL | 9076.3791 |
| AUCINF_D_obs | h*ng/mL/mg | 20.1697 |
| AUC_%Extrap_obs | % | 7.2468 |
| Vz_F_obs | L | 2527.9436 |
| Cl_F_obs | L/h | 49.5792 |
| AUCINF_pred | h*ng/mL | 9068.1286 |
| AUCINF_D_pred | h*ng/mL/mg | 20.1514 |
| AUC_%Extrap_pred | % | 7.1624 |
| Vz_F_pred | L | 2530.2436 |
| Cl_F_pred | L/h | 49.6244 |
| AUMClast | h*h*ng/mL | 573981.3758 |
| AUMCINF_obs | h*h*ng/mL | 718019.4828 |
| AUMC_%Extrap_obs | % | 20.0605 |
| AUMCINF_pred | h*h*ng/mL | 716212.7199 |
| AUMC_%Extrap_pred | % | 19.8588 |
| MRTlast | h | 68.1799 |
| MRTINF_obs | h | 79.1086 |
| MRTINF_pred | h | 78.9813 |
| AUC0_24 | h*ng/mL | 1011.4778 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7333 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.6050 | | | 0.08067 | 0.08067 | |
| 1.500 | 2.360 | | | 0.8219 | 1.117 | |
| 2.000 | 5.220 | | | 2.717 | 4.612 | |
| 3.000 | 12.80 | | | 11.73 | 29.03 | |
| 4.000 | 21.10 | | | 28.68 | 90.43 | |
| 6.000 | 26.90 | | | 76.68 | 336.2 | |
| 8.050 | 37.00 | | | 142.2 | 807.0 | |
| 12.00 | 47.70 | | | 309.5 | 2526. | |
| 16.05 | 60.30 | | | 528.2 | 5645. | |
| 24.02 | 86.20 | | | 1112. | 1.775e+004 | |
| 36.00 | 85.00 | | | 2137. | 4.851e+004 | |
| 48.00 | 91.00 | | | 3193. | 9.308e+004 | |
| 60.00 | 58.80 | | | 4078. | 1.405e+005 | |
| 72.00 * | 63.10 | 56.58 | 6.516 | 4810. | 1.889e+005 | 1.000 |

| | | | | | |
|---------|-------|-------|---------|------------------|-------|
| 95.73 * | 26.90 | 27.77 | -0.8672 | 5817. 2.717e+005 | 1.000 |
| 120.0 * | 12.00 | 13.41 | -1.410 | 6265. 3.193e+005 | 1.000 |
| 144.0 * | 5.800 | 6.528 | -0.7281 | 6470. 3.460e+005 | 1.000 |
| 168.0 * | 3.700 | 3.178 | 0.5220 | 6582. 3.634e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9881 |
| Rsqr_adjusted | | 0.9842 |
| Corr_XY | | -0.9941 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0300 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 23.1091 |
| Tlag | h | 0.7333 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 91.0000 |
| Cmax_D | ng/mL/mg | 0.2022 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 3.7000 |
| AUClast | h*ng/mL | 6582.0447 |
| AUCall | h*ng/mL | 6582.0447 |
| AUCINF_obs | h*ng/mL | 6705.4004 |
| AUCINF_D_obs | h*ng/mL/mg | 14.9009 |
| AUC_%Extrap_obs | % | 1.8396 |
| Vz_F_obs | L | 2237.4090 |
| Cl_F_obs | L/h | 67.1101 |
| AUCINF_pred | h*ng/mL | 6687.9971 |
| AUCINF_D_pred | h*ng/mL/mg | 14.8622 |
| AUC_%Extrap_pred | % | 1.5842 |
| Vz_F_pred | L | 2243.2311 |
| Cl_F_pred | L/h | 67.2847 |
| AUMClast | h*h*ng/mL | 363436.8272 |
| AUMCINF_obs | h*h*ng/mL | 388273.1926 |
| AUMC_%Extrap_obs | % | 6.3966 |
| AUMCINF_pred | h*h*ng/mL | 384769.2189 |
| AUMC_%Extrap_pred | % | 5.5442 |
| MRTlast | h | 55.2164 |
| MRTINF_obs | h | 57.9045 |
| MRTINF_pred | h | 57.5313 |
| AUC0_24 | h*ng/mL | 1110.2790 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h ² *ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.6840 | | | 0.08550 | 0.06413 | |
| 1.000 | 1.620 | | | 0.3735 | 0.3308 | |
| 1.500 | 4.940 | | | 2.014 | 2.588 | |
| 2.000 | 8.610 | | | 5.401 | 8.746 | |
| 3.000 | 16.00 | | | 17.71 | 41.36 | |
| 4.000 | 21.30 | | | 36.36 | 108.0 | |
| 6.033 | 27.10 | | | 85.56 | 360.8 | |
| 8.000 | 43.00 | | | 154.5 | 859.8 | |
| 12.00 | 52.80 | | | 346.1 | 2815. | |
| 16.03 | 73.20 | | | 600.2 | 6460. | |
| 24.00 | 106.0 | | | 1314. | 2.127e+004 | |
| 36.00 | 101.0 | | | 2556. | 5.846e+004 | |
| 48.00 | 132.0 | | | 3954. | 1.183e+005 | |
| 60.00 | 84.00 | | | 5228. | 1.865e+005 | |
| 72.00 | 92.50 | | | 6287. | 2.567e+005 | |
| 96.00 | 50.30 | | | 7950. | 3.944e+005 | |
| 120.0 * | 19.00 | 18.81 | 0.1944 | 8721. | 4.762e+005 | 1.000 |
| 144.0 * | 9.760 | 9.963 | -0.2030 | 9054. | 5.197e+005 | 1.000 |
| 168.0 * | 5.340 | 5.285 | 0.05474 | 9230. | 5.469e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|-----------------------|-------------|
| Rsqr | | 0.9992 |
| Rsqr_adjusted | | 0.9984 |
| Corr_XY | | -0.9996 |
| No_points_lambda_z | | 3 |
| Lambda_z | 1/h | 0.0264 |
| Lambda_z_lower | h | 119.9833 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 26.2226 |
| Tlag | h | 0.5000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 132.0000 |
| Cmax_D | ng/mL/mg | 0.2933 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 5.3400 |
| AUClast | h*ng/mL | 9229.8441 |
| AUCall | h*ng/mL | 9229.8441 |
| AUCINF_obs | h*ng/mL | 9431.8627 |
| AUCINF_D_obs | h*ng/mL/mg | 20.9597 |
| AUC_%Extrap_obs | % | 2.1419 |
| Vz_F_obs | L | 1804.9497 |
| Cl_F_obs | L/h | 47.7106 |
| AUCINF_pred | h*ng/mL | 9429.7918 |
| AUCINF_D_pred | h*ng/mL/mg | 20.9551 |
| AUC_%Extrap_pred | % | 2.1204 |
| Vz_F_pred | L | 1805.3460 |
| Cl_F_pred | L/h | 47.7211 |
| AUMClast | h ² *ng/mL | 546937.6967 |
| AUMCINF_obs | h ² *ng/mL | 588519.4215 |
| AUMC_%Extrap_obs | % | 7.0655 |
| AUMCINF_pred | h ² *ng/mL | 588093.1737 |
| AUMC_%Extrap_pred | % | 6.9981 |
| MRTlast | h | 59.2575 |
| MRTINF_obs | h | 62.3969 |
| MRTINF_pred | h | 62.3654 |
| AUC0_24 | h*ng/mL | 1314.0077 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

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| | | |
|-------------------|------------|-------------|
| AUC_%Extrap_obs | % | 5.0286 |
| Vz_F_obs | L | 2492.1375 |
| CL_F_obs | L/h | 52.8860 |
| AUCINF_pred | h*ng/mL | 8521.6327 |
| AUCINF_D_pred | h*ng/mL/mg | 18.9370 |
| AUC_%Extrap_pred | % | 5.1708 |
| Vz_F_pred | L | 2488.4063 |
| CL_F_pred | L/h | 52.8068 |
| AUMClast | h*h*ng/mL | 520000.0031 |
| AUMCINF_obs | h*h*ng/mL | 612060.0678 |
| AUMC_%Extrap_obs | % | 15.0410 |
| AUMCINF_pred | h*h*ng/mL | 614805.1625 |
| AUMC_%Extrap_pred | % | 15.4204 |
| MRTlast | h | 64.3485 |
| MRTINF_obs | h | 71.9320 |
| MRTINF_pred | h | 72.1464 |
| AUC0_24 | h*ng/mL | 1050.1452 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.033 | 0.8570 | | | 0.1214 | 0.1255 | |
| 1.500 | 2.350 | | | 0.8697 | 1.155 | |
| 2.017 | 4.400 | | | 2.613 | 4.357 | |
| 3.000 | 13.90 | | | 11.61 | 29.22 | |
| 4.000 | 20.70 | | | 28.91 | 91.47 | |
| 6.000 | 29.50 | | | 79.11 | 351.3 | |
| 8.000 | 39.50 | | | 148.1 | 844.3 | |
| 12.00 | 61.70 | | | 350.5 | 2957. | |
| 16.00 | 77.30 | | | 628.5 | 6911. | |
| 24.03 | 113.0 | | | 1393. | 2.279e+004 | |
| 36.00 | 127.0 | | | 2829. | 6.639e+004 | |
| 48.00 | 133.0 | | | 4389. | 1.321e+005 | |
| 60.00 | 99.30 | | | 5773. | 2.065e+005 | |
| 72.00 | 94.70 | | | 6937. | 2.832e+005 | |
| 96.00 * | 77.00 | 73.84 | 3.155 | 8990. | 4.548e+005 | 1.000 |
| 120.3 * | 39.90 | 44.30 | -4.405 | 1.036e+004 | 6.011e+005 | 1.000 |
| 144.0 * | 29.20 | 26.88 | 2.318 | 1.117e+004 | 7.081e+005 | 1.000 |
| 168.0 * | 15.90 | 16.22 | -0.3189 | 1.170e+004 | 7.894e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsq | | 0.9846 |
| Rsq_adjusted | | 0.9769 |
| Corr_XY | | -0.9923 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0211 |
| Lambda_z_lower | h | 96.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 32.9246 |
| Tlag | h | 0.7500 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 133.0000 |
| Cmax_D | ng/mL/mg | 0.2956 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 15.9000 |
| AUClast | h*ng/mL | 11697.6472 |
| AUCall | h*ng/mL | 11697.6472 |
| AUCINF_obs | h*ng/mL | 12452.9008 |
| AUCINF_D_obs | h*ng/mL/mg | 27.6731 |
| AUC_%Extrap_obs | % | 6.0649 |
| Vz_F_obs | L | 1716.4757 |
| CL_F_obs | L/h | 36.1362 |
| AUCINF_pred | h*ng/mL | 12468.0506 |
| AUCINF_D_pred | h*ng/mL/mg | 27.7068 |
| AUC_%Extrap_pred | % | 6.1790 |
| Vz_F_pred | L | 1714.3901 |
| CL_F_pred | L/h | 36.0923 |
| AUMClast | h*h*ng/mL | 789355.4269 |
| AUMCINF_obs | h*h*ng/mL | 952112.7497 |
| AUMC_%Extrap_obs | % | 17.0943 |
| AUMCINF_pred | h*h*ng/mL | 955377.5311 |
| AUMC_%Extrap_pred | % | 17.3776 |
| MRTlast | h | 67.4798 |
| MRTINF_obs | h | 76.4571 |
| MRTINF_pred | h | 76.6261 |
| AUC0_24 | h*ng/mL | 1389.1184 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:13

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |

| | | | | | |
|---------|--------|-------|---------|---------|------------------|
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 |
| 1.000 | 0.5660 | | | 0.07075 | 0.07075 |
| 1.500 | 0.9810 | | | 0.4575 | 0.5801 |
| 2.000 | 2.040 | | | 1.213 | 1.968 |
| 3.000 | 4.780 | | | 4.623 | 11.18 |
| 4.000 | 11.10 | | | 12.56 | 40.55 |
| 6.000 | 16.50 | | | 40.16 | 183.9 |
| 8.000 | 28.70 | | | 85.36 | 512.5 |
| 12.00 | 53.00 | | | 248.8 | 2244. |
| 16.00 | 78.30 | | | 511.4 | 6021. |
| 24.00 | 119.0 | | | 1301. | 2.246e+004 |
| 36.00 | 93.30 | | | 2568. | 6.018e+004 |
| 48.00 | 110.0 | | | 3788. | 1.120e+005 |
| 60.00 | 75.00 | | | 4885. | 1.708e+005 |
| 72.00 | 69.80 | | | 5753. | 2.281e+005 |
| 96.00 * | 64.30 | 63.99 | 0.3098 | 7361. | 3.629e+005 1.000 |
| 120.0 * | 32.70 | 35.39 | -2.692 | 8483. | 4.825e+005 1.000 |
| 144.0 * | 22.60 | 19.57 | 3.025 | 9139. | 5.686e+005 1.000 |
| 168.0 * | 10.10 | 10.83 | -0.7263 | 9511. | 6.262e+005 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9822 |
| Rsqr_adjusted | | 0.9733 |
| Corr_XY | | -0.9911 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0247 |
| Lambda_z_lower | h | 96.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 28.0887 |
| Tlag | h | 0.7500 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 119.0000 |
| Cmax_D | ng/mL/mg | 0.2644 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 10.1000 |
| AUClast | h*ng/mL | 9511.4885 |
| AUCall | h*ng/mL | 9511.4885 |
| AUCINF_obs | h*ng/mL | 9920.7752 |
| AUCINF_D_obs | h*ng/mL/mg | 22.0462 |
| AUC_%Extrap_obs | % | 4.1256 |
| Vz_F_obs | L | 1838.1174 |
| Cl_F_obs | L/h | 45.3594 |
| AUCINF_pred | h*ng/mL | 9950.2083 |
| AUCINF_D_pred | h*ng/mL/mg | 22.1116 |
| AUC_%Extrap_pred | % | 4.4092 |
| Vz_F_pred | L | 1832.6802 |
| Cl_F_pred | L/h | 45.2252 |
| AUMClast | h*h*ng/mL | 626161.4043 |
| AUMCINF_obs | h*h*ng/mL | 711507.2909 |
| AUMC_%Extrap_obs | % | 11.9951 |
| AUMCINF_pred | h*h*ng/mL | 717644.7709 |
| AUMC_%Extrap_pred | % | 12.7477 |
| MRTlast | h | 65.8321 |
| MRTINF_obs | h | 71.7189 |
| MRTINF_pred | h | 72.1236 |
| AUC0_24 | h*ng/mL | 1300.5628 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535

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| | | |
|-------------------|-----------|--------------|
| CL_F_pred | L/h | 21.2205 |
| AUMClast | h*h*ng/mL | 1462502.4585 |
| AUMCINF_obs | h*h*ng/mL | 2115761.4405 |
| AUMC_%Extrap_obs | % | 30.8758 |
| AUMCINF_pred | h*h*ng/mL | 2160427.5432 |
| AUMC_%Extrap_pred | % | 32.3050 |
| MRTlast | h | 80.3874 |
| MRTINF_obs | h | 100.6875 |
| MRTINF_pred | h | 101.8783 |
| AUC0_24 | h*ng/mL | 1353.5810 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5333 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 1.160 | | | 0.2900 | 0.4350 | |
| 2.000 | 1.880 | | | 1.050 | 1.810 | |
| 3.000 | 5.630 | | | 4.805 | 12.14 | |
| 4.000 | 10.60 | | | 12.92 | 41.78 | |
| 6.000 | 16.90 | | | 40.42 | 185.6 | |
| 8.000 | 27.90 | | | 85.22 | 510.2 | |
| 12.00 | 48.90 | | | 238.8 | 2130. | |
| 16.00 | 66.00 | | | 468.6 | 5416. | |
| 24.02 | 91.50 | | | 1100. | 1.846e+004 | |
| 36.00 | 102.0 | | | 2259. | 5.363e+004 | |
| 48.00 | 112.0 | | | 3543. | 1.079e+005 | |
| 60.02 | 92.00 | | | 4765. | 1.737e+005 | |
| 72.00 * | 77.40 | 77.13 | 0.2688 | 5778. | 2.403e+005 | 1.000 |
| 96.00 * | 48.90 | 49.49 | -0.5938 | 7267. | 3.641e+005 | 1.000 |
| 120.0 * | 32.50 | 31.76 | 0.7406 | 8231. | 4.673e+005 | 1.000 |
| 144.0 * | 19.90 | 20.38 | -0.4795 | 8847. | 5.481e+005 | 1.000 |
| 168.0 * | 13.20 | 13.08 | 0.1228 | 9239. | 6.089e+005 | 1.000 |

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

Final Parameters

| | |
|---------------|---------|
| Rsqr | 0.9993 |
| Rsqr_adjusted | 0.9991 |
| Corr_XY | -0.9997 |

| | | |
|--------------------|------------|-------------|
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0185 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 37.4961 |
| Tlag | h | 1.0000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 112.0000 |
| Cmax_D | ng/mL/mg | 0.2489 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 13.2000 |
| AUClast | h*ng/mL | 9238.7096 |
| AUCall | h*ng/mL | 9238.7096 |
| AUCINF_obs | h*ng/mL | 9952.7703 |
| AUCINF_D_obs | h*ng/mL/mg | 22.1173 |
| AUC_%Extrap_obs | % | 7.1745 |
| Vz_F_obs | L | 2445.8495 |
| Cl_F_obs | L/h | 45.2135 |
| AUCINF_pred | h*ng/mL | 9946.1262 |
| AUCINF_D_pred | h*ng/mL/mg | 22.1025 |
| AUC_%Extrap_pred | % | 7.1125 |
| Vz_F_pred | L | 2447.4834 |
| Cl_F_pred | L/h | 45.2437 |
| AUMClast | h*h*ng/mL | 608898.1387 |
| AUMCINF_obs | h*h*ng/mL | 767487.8146 |
| AUMC_%Extrap_obs | % | 20.6635 |
| AUMCINF_pred | h*h*ng/mL | 766012.1980 |
| AUMC_%Extrap_pred | % | 20.5106 |
| MRTlast | h | 65.9073 |
| MRTINF_obs | h | 77.1130 |
| MRTINF_pred | h | 77.0161 |
| AUC0_24 | h*ng/mL | 1098.4079 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.033 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.6930 | | | 0.1617 | 0.2426 | |
| 2.000 | 2.370 | | | 0.9275 | 1.687 | |
| 3.000 | 7.170 | | | 5.697 | 14.81 | |
| 4.000 | 13.00 | | | 15.78 | 51.57 | |
| 6.000 | 21.90 | | | 50.68 | 235.0 | |

| | | | | | |
|---------|-------|-------|---------|-------|------------|
| 8.000 | 31.00 | | | 103.6 | 614.4 |
| 12.00 | 47.20 | | | 260.0 | 2243. |
| 16.00 | 66.50 | | | 487.4 | 5504. |
| 24.00 | 78.60 | | | 1068. | 1.731e+004 |
| 36.00 | 85.30 | | | 2051. | 4.705e+004 |
| 48.00 | 97.50 | | | 3148. | 9.355e+004 |
| 60.00 | 77.70 | | | 4195. | 1.498e+005 |
| 72.00 | 69.20 | | | 5075. | 2.078e+005 |
| 96.00 * | 48.90 | 48.76 | 0.1356 | 6478. | 3.247e+005 |
| 120.0 * | 28.30 | 28.04 | 0.2587 | 7382. | 4.214e+005 |
| 144.0 * | 15.70 | 16.12 | -0.4248 | 7895. | 4.885e+005 |
| 168.0 * | 9.410 | 9.272 | 0.1377 | 8190. | 5.342e+005 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9993 |
| Rsqr_adjusted | | 0.9990 |
| Corr_XY | | -0.9997 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0231 |
| Lambda_z_lower | h | 96.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 30.0649 |
| Tlag | h | 1.0333 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 97.5000 |
| Cmax_D | ng/mL/mg | 0.2167 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 9.4100 |
| AUClast | h*ng/mL | 8190.3625 |
| AUCall | h*ng/mL | 8190.3625 |
| AUCINF_obs | h*ng/mL | 8598.5159 |
| AUCINF_D_obs | h*ng/mL/mg | 19.1078 |
| AUC_%Extrap_obs | % | 4.7468 |
| Vz_F_obs | L | 2269.9838 |
| CL_F_obs | L/h | 52.3346 |
| AUCINF_pred | h*ng/mL | 8592.5451 |
| AUCINF_D_pred | h*ng/mL/mg | 19.0945 |
| AUC_%Extrap_pred | % | 4.6806 |
| Vz_F_pred | L | 2271.5612 |
| CL_F_pred | L/h | 52.3710 |
| AUMClast | h*h*ng/mL | 534231.3564 |
| AUMCINF_obs | h*h*ng/mL | 620504.5365 |
| AUMC_%Extrap_obs | % | 13.9037 |
| AUMCINF_pred | h*h*ng/mL | 619242.4596 |
| AUMC_%Extrap_pred | % | 13.7282 |
| MRTlast | h | 65.2268 |
| MRTINF_obs | h | 72.1641 |
| MRTINF_pred | h | 72.0674 |
| AUC0_24 | h*ng/mL | 1067.7825 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00

| | | |
|-------------|---------|-----------|
| MRTINF_obs | h | 100.1916 |
| MRTINF_pred | h | 100.0458 |
| AUC0_24 | h*ng/mL | 1197.8551 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|-----------------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 2.000 | 1.650 | | | 0.4125 | 0.8250 | |
| 3.000 | 4.080 | | | 3.278 | 8.595 | |
| 4.000 | 8.480 | | | 9.558 | 31.68 | |
| 6.000 | 14.20 | | | 32.24 | 150.8 | |
| 8.000 | 24.20 | | | 70.64 | 429.6 | |
| 12.00 | 47.00 | | | 213.0 | 1945. | |
| 16.00 | 61.40 | | | 429.8 | 5038. | |
| 24.00 | 129.0 | | | 1191. 2.135e+004 | | |
| 36.00 | 131.0 | | | 2751. 6.822e+004 | | |
| 48.00 | 156.0 | | | 4473. 1.414e+005 | | |
| 60.00 | 110.0 | | | 6053. 2.262e+005 | | |
| 72.00 | 116.0 | | | 7409. 3.159e+005 | | |
| 96.00 * | 90.90 | 93.68 | -2.781 | 9880. 5.223e+005 | | 1.000 |
| 120.0 * | 58.80 | 57.56 | 1.239 | 1.165e+004 7.117e+005 | | 1.000 |
| 144.0 * | 37.10 | 35.37 | 1.733 | 1.278e+004 8.600e+005 | | 1.000 |
| 168.0 * | 20.90 | 21.73 | -0.8309 | 1.346e+004 9.649e+005 | | 1.000 |

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

Final Parameters

| | | |
|--------------------|-----|----------|
| Rsqr | | 0.9957 |
| Rsqr_adjusted | | 0.9935 |
| Corr_XY | | -0.9978 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0203 |
| Lambda_z_lower | h | 96.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 34.1553 |
| Tlag | h | 1.5000 |
| Tmax | h | 48.0000 |

| | | |
|-------------------|------------|--------------|
| Cmax | ng/mL | 156.0000 |
| Cmax_D | ng/mL/mg | 0.3467 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 20.9000 |
| AUClast | h*ng/mL | 13456.8835 |
| AUCall | h*ng/mL | 13456.8835 |
| AUCINF_obs | h*ng/mL | 14486.7451 |
| AUCINF_D_obs | h*ng/mL/mg | 32.1928 |
| AUC_%Extrap_obs | % | 7.1090 |
| Vz_F_obs | L | 1530.6443 |
| CL_F_obs | L/h | 31.0629 |
| AUCINF_pred | h*ng/mL | 14527.6863 |
| AUCINF_D_pred | h*ng/mL/mg | 32.2837 |
| AUC_%Extrap_pred | % | 7.3708 |
| Vz_F_pred | L | 1526.3307 |
| CL_F_pred | L/h | 30.9753 |
| AUMClast | h*h*ng/mL | 964871.5723 |
| AUMCINF_obs | h*h*ng/mL | 1188635.4435 |
| AUMC_%Extrap_obs | % | 18.8253 |
| AUMCINF_pred | h*h*ng/mL | 1197530.9708 |
| AUMC_%Extrap_pred | % | 19.4283 |
| MRTlast | h | 71.7010 |
| MRTINF_obs | h | 82.0499 |
| MRTINF_pred | h | 82.4309 |
| AUC0_24 | h*ng/mL | 1191.4375 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|------------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2667 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.017 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 1.700 | | | 0.4108 | 0.6162 | |
| 2.000 | 4.060 | | | 1.851 | 3.284 | |
| 3.000 | 11.70 | | | 9.731 | 24.89 | |
| 4.000 | 22.70 | | | 26.93 | 87.84 | |
| 6.000 | 26.70 | | | 76.33 | 338.8 | |
| 8.000 | 44.10 | | | 147.1 | 851.8 | |
| 12.00 | 63.60 | | | 362.5 | 3084. | |
| 16.00 | 81.20 | | | 652.1 | 7209. | |
| 24.00 | 122.0 | | | 1465. 2.412e+004 | | |
| 36.00 | 108.0 | | | 2843. 6.530e+004 | | |
| 48.00 | 126.0 | | | 4247. 1.249e+005 | | |
| 60.00 | 99.10 | | | 5591. 1.972e+005 | | |

| | | | | | |
|---------|-------|-------|--------|----------------|------------|
| 72.73 | 89.60 | | | 6792.2767e+005 | |
| 96.03 | 74.40 | | | 8697.4368e+005 | |
| 120.0 * | 52.40 | 50.19 | 2.210 | 1.020e+004 | 5.982e+005 |
| 144.0 * | 23.80 | 25.94 | -2.143 | 1.107e+004 | 7.116e+005 |
| 168.0 * | 14.00 | 13.41 | 0.5906 | 1.151e+004 | 7.803e+005 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9874 |
| Rsqr_adjusted | | 0.9747 |
| Corr_XY | | -0.9937 |
| No_points_lambda_z | | 3 |
| Lambda_z | 1/h | 0.0275 |
| Lambda_z_lower | h | 120.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 25.2082 |
| Tlag | h | 1.0167 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 126.0000 |
| Cmax_D | ng/mL/mg | 0.2800 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 14.0000 |
| AUClast | h*ng/mL | 11513.9438 |
| AUCall | h*ng/mL | 11513.9438 |
| AUCINF_obs | h*ng/mL | 12023.0928 |
| AUCINF_D_obs | h*ng/mL/mg | 26.7180 |
| AUC_%Extrap_obs | % | 4.2348 |
| Vz_F_obs | L | 1361.1727 |
| Cl_F_obs | L/h | 37.4280 |
| AUCINF_pred | h*ng/mL | 12001.6152 |
| AUCINF_D_pred | h*ng/mL/mg | 26.6703 |
| AUC_%Extrap_pred | % | 4.0634 |
| Vz_F_pred | L | 1363.6086 |
| Cl_F_pred | L/h | 37.4950 |
| AUMClast | h*h*ng/mL | 780326.2198 |
| AUMCINF_obs | h*h*ng/mL | 884379.8860 |
| AUMC_%Extrap_obs | % | 11.7657 |
| AUMCINF_pred | h*h*ng/mL | 879990.5652 |
| AUMC_%Extrap_pred | % | 11.3256 |
| MRTlast | h | 67.7723 |
| MRTINF_obs | h | 73.5568 |
| MRTINF_pred | h | 73.3227 |
| AUC0_24 | h*ng/mL | 1464.9308 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

0

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7667 | 0.5190 | | | 0.06920 | 0.05305 | |
| 1.000 | 1.020 | | | 0.2488 | 0.2185 | |
| 1.500 | 4.760 | | | 1.694 | 2.258 | |
| 2.000 | 7.340 | | | 4.719 | 7.713 | |
| 3.000 | 16.70 | | | 16.74 | 40.10 | |
| 4.000 | 24.60 | | | 37.39 | 114.4 | |
| 6.000 | 28.40 | | | 90.39 | 383.2 | |
| 8.017 | 42.00 | | | 161.4 | 894.5 | |
| 12.00 | 52.60 | | | 349.8 | 2822. | |
| 16.00 | 78.60 | | | 612.2 | 6600. | |
| 24.02 | 139.0 | | | 1484. | 2.502e+004 | |
| 36.00 | 89.00 | | | 2828. | 6.475e+004 | |
| 48.00 | 122.0 | | | 4094. | 1.191e+005 | |
| 60.00 | 76.70 | | | 5266. | 1.818e+005 | |
| 72.00 | 86.40 | | | 6244. | 2.468e+005 | |
| 96.00 * | 62.30 | 62.69 | -0.3926 | 8013. | 3.942e+005 | 1.000 |
| 120.0 * | 34.80 | 34.98 | -0.1822 | 9146. | 5.153e+005 | 1.000 |
| 144.0 * | 20.10 | 19.52 | 0.5801 | 9789. | 5.994e+005 | 1.000 |
| 168.0 * | 10.70 | 10.89 | -0.1920 | 1.015e+004 | 6.548e+005 | 1.000 |

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

Final Parameters

Rsqr 0.9993
Rsqr_adjusted 0.9989
Corr_XY -0.9996
No_points_lambda_z 4
Lambda_z 1/h 0.0243
Lambda_z_lower h 96.0000
Lambda_z_upper h 168.0000
HL_Lambda_z h 28.5145
Tlag h 0.5000
Tmax h 24.0167
Cmax ng/mL 139.0000
Cmax_D ng/mL/mg 0.3089
Tlast h 168.0000
Clast ng/mL 10.7000
AUClast h*ng/mL 10146.7471
AUCall h*ng/mL 10146.7471
AUCINF_obs h*ng/mL 10586.9216

| | | |
|-------------------|------------|-------------|
| AUCINF_D_obs | h*ng/mL/mg | 23.5265 |
| AUC_%Extrap_obs | % | 4.1577 |
| Vz_F_obs | L | 1748.5734 |
| CL_F_obs | L/h | 42.5053 |
| AUCINF_pred | h*ng/mL | 10594.8198 |
| AUCINF_D_pred | h*ng/mL/mg | 23.5440 |
| AUC_%Extrap_pred | % | 4.2292 |
| Vz_F_pred | L | 1747.2699 |
| CL_F_pred | L/h | 42.4736 |
| AUMClast | h*h*ng/mL | 654771.4914 |
| AUMCINF_obs | h*h*ng/mL | 746828.6060 |
| AUMC_%Extrap_obs | % | 12.3264 |
| AUMCINF_pred | h*h*ng/mL | 748480.4180 |
| AUMC_%Extrap_pred | % | 12.5199 |
| MRTlast | h | 64.5302 |
| MRTINF_obs | h | 70.5426 |
| MRTINF_pred | h | 70.6459 |
| AUC0_24 | h*ng/mL | 1482.0848 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.050 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 2.017 | 0.9720 | | | 0.2511 | 0.5064 | |
| 3.000 | 2.510 | | | 1.963 | 5.172 | |
| 4.000 | 4.580 | | | 5.508 | 18.10 | |
| 6.000 | 10.60 | | | 20.69 | 100.0 | |
| 8.000 | 20.50 | | | 51.79 | 327.6 | |
| 12.00 | 40.10 | | | 173.0 | 1618. | |
| 16.00 | 61.70 | | | 376.6 | 4555. | |
| 24.00 | 108.0 | | | 1055. | 1.887e+004 | |
| 36.00 | 124.0 | | | 2447. | 6.121e+004 | |
| 48.00 | 150.0 | | | 4091. | 1.312e+005 | |
| 60.00 | 108.0 | | | 5626. | 2.135e+005 | |
| 72.00 * | 100.0 | 106.1 | -6.101 | 6873. | 2.958e+005 | 1.000 |
| 96.07 * | 69.70 | 67.16 | 2.538 | 8893. | 4.641e+005 | 1.000 |
| 120.0 * | 43.20 | 42.62 | 0.5787 | 1.022e+004 | 6.060e+005 | 1.000 |
| 144.1 * | 29.70 | 26.95 | 2.746 | 1.109e+004 | 7.201e+005 | 1.000 |
| 168.6 * | 15.50 | 16.93 | -1.433 | 1.162e+004 | 8.030e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|--------------|
| Rsqr | | 0.9895 |
| Rsqr_adjusted | | 0.9860 |
| Corr_XY | | -0.9947 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0190 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.5833 |
| HL_Lambda_z | h | 36.4801 |
| Tlag | h | 1.5000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 150.0000 |
| Cmax_D | ng/mL/mg | 0.3333 |
| Tlast | h | 168.5833 |
| Clast | ng/mL | 15.5000 |
| AUClast | h*ng/mL | 11622.1791 |
| AUCall | h*ng/mL | 11622.1791 |
| AUCINF_obs | h*ng/mL | 12437.9382 |
| AUCINF_D_obs | h*ng/mL/mg | 27.6399 |
| AUC_%Extrap_obs | % | 6.5586 |
| Vz_F_obs | L | 1904.1201 |
| Cl_F_obs | L/h | 36.1796 |
| AUCINF_pred | h*ng/mL | 12513.3305 |
| AUCINF_D_pred | h*ng/mL/mg | 27.8074 |
| AUC_%Extrap_pred | % | 7.1216 |
| Vz_F_pred | L | 1892.6479 |
| Cl_F_pred | L/h | 35.9616 |
| AUMClast | h*h*ng/mL | 802966.8658 |
| AUMCINF_obs | h*h*ng/mL | 983423.3415 |
| AUMC_%Extrap_obs | % | 18.3498 |
| AUMCINF_pred | h*h*ng/mL | 1000101.1085 |
| AUMC_%Extrap_pred | % | 19.7114 |
| MRTlast | h | 69.0892 |
| MRTINF_obs | h | 79.0664 |
| MRTINF_pred | h | 79.9229 |
| AUC0_24 | h*ng/mL | 1055.3881 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2667 | 0.0000 | | | 0.0000 | 0.0000 | |

| | | | | | |
|---------|--------|-------|-----------|--------|------------------|
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 |
| 1.000 | 0.9330 | | | 0.1166 | 0.1166 |
| 1.500 | 2.800 | | | 1.050 | 1.400 |
| 2.000 | 5.830 | | | 3.207 | 5.365 |
| 3.000 | 12.10 | | | 12.17 | 29.34 |
| 4.000 | 19.80 | | | 28.12 | 87.09 |
| 6.000 | 28.20 | | | 76.12 | 335.5 |
| 8.000 | 43.60 | | | 147.9 | 853.5 |
| 12.00 | 50.00 | | | 335.1 | 2751. |
| 16.00 | 66.50 | | | 568.1 | 6079. |
| 24.00 | 84.70 | | | 1173. | 1.847e+004 |
| 36.00 | 71.60 | | | 2109. | 4.638e+004 |
| 48.00 | 82.90 | | | 3036. | 8.572e+004 |
| 60.00 | 47.60 | | | 3799. | 1.265e+005 |
| 72.00 | 52.30 | | | 4398. | 1.663e+005 |
| 96.00 * | 24.50 | 25.16 | -0.6629 | 5278. | 2.388e+005 1.000 |
| 120.2 * | 16.20 | 15.36 | 0.8446 | 5763. | 2.908e+005 1.000 |
| 144.0 * | 9.180 | 9.428 | -0.2481 | 6058. | 3.294e+005 1.000 |
| 168.0 * | 5.770 | 5.771 | -0.001056 | 6234. | 3.567e+005 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9964 |
| Rsqr_adjusted | | 0.9947 |
| Corr_XY | | -0.9982 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0205 |
| Lambda_z_lower | h | 96.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 33.8921 |
| Tlag | h | 0.7500 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 84.7000 |
| Cmax_D | ng/mL/mg | 0.1882 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 5.7700 |
| AUClast | h*ng/mL | 6233.8544 |
| AUCall | h*ng/mL | 6233.8544 |
| AUCINF_obs | h*ng/mL | 6515.9838 |
| AUCINF_D_obs | h*ng/mL/mg | 14.4800 |
| AUC_%Extrap_obs | % | 4.3298 |
| Vz_F_obs | L | 3376.7981 |
| Cl_F_obs | L/h | 69.0609 |
| AUCINF_pred | h*ng/mL | 6516.0354 |
| AUCINF_D_pred | h*ng/mL/mg | 14.4801 |
| AUC_%Extrap_pred | % | 4.3306 |
| Vz_F_pred | L | 3376.7713 |
| Cl_F_pred | L/h | 69.0604 |
| AUMClast | h*h*ng/mL | 356739.5529 |
| AUMCINF_obs | h*h*ng/mL | 417932.2728 |
| AUMC_%Extrap_obs | % | 14.6418 |
| AUMCINF_pred | h*h*ng/mL | 417943.4680 |
| AUMC_%Extrap_pred | % | 14.6441 |
| MRTlast | h | 57.2262 |
| MRTINF_obs | h | 64.1396 |
| MRTINF_pred | h | 64.1408 |
| AUC0_24 | h*ng/mL | 1172.9224 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

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| | | |
|-------------------|---------|--------------|
| Vz_F_pred | L | 1738.6070 |
| Cl_F_pred | L/h | 28.7614 |
| AUMClast | h*ng/mL | 1037749.8400 |
| AUMCINF_obs | h*ng/mL | 1431322.9332 |
| AUMC_%Extrap_obs | % | 27.4972 |
| AUMCINF_pred | h*ng/mL | 1435098.3570 |
| AUMC_%Extrap_pred | % | 27.6879 |
| MRTlast | h | 74.6227 |
| MRTINF_obs | h | 91.5787 |
| MRTINF_pred | h | 91.7233 |
| AUC0_24 | h*ng/mL | 1147.1918 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 18
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.7480 | | | 0.09350 | 0.09350 | |
| 1.500 | 1.590 | | | 0.6780 | 0.8768 | |
| 2.000 | 3.230 | | | 1.883 | 3.088 | |
| 3.000 | 8.730 | | | 7.863 | 19.41 | |
| 4.000 | 16.40 | | | 20.43 | 65.31 | |
| 6.000 | 25.90 | | | 62.73 | 286.3 | |
| 8.000 | 41.20 | | | 129.8 | 771.3 | |
| 12.00 | 48.60 | | | 309.4 | 2597. | |
| 16.00 | 68.10 | | | 542.8 | 5943. | |
| 24.00 | 76.80 | | | 1122. | 1.767e+004 | |
| 36.00 * | 61.70 | 62.22 | -0.5229 | 1950. | 4.232e+004 | 1.000 |
| 48.00 * | 56.30 | 52.89 | 3.408 | 2658. | 7.197e+004 | 1.000 |
| 60.00 * | 40.70 | 44.96 | -4.261 | 3235. | 1.029e+005 | 1.000 |
| 72.00 * | 40.00 | 38.22 | 1.782 | 3719. | 1.349e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|-----|---------|
| Rsqr | | 0.8921 |
| Rsqr_adjusted | | 0.8382 |
| Corr_XY | | -0.9445 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0135 |
| Lambda_z_lower | h | 36.0000 |

| | | |
|-------------------|------------|-------------|
| Lambda_z_upper | h | 72.0000 |
| HL_Lambda_z | h | 51.1963 |
| Tlag | h | 0.7500 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 76.8000 |
| Cmax_D | ng/mL/mg | 0.1707 |
| Tlast | h | 72.0000 |
| Clast | ng/mL | 40.0000 |
| AUClast | h*ng/mL | 3718.7655 |
| AUCall | h*ng/mL | 3718.7655 |
| AUCINF_obs | h*ng/mL | 6673.1936 |
| AUCINF_D_obs | h*ng/mL/mg | 14.8293 |
| AUC_%Extrap_obs | % | 44.2731 |
| Vz_F_obs | L | 4980.7212 |
| Cl_F_obs | L/h | 67.4340 |
| AUCINF_pred | h*ng/mL | 6541.6103 |
| AUCINF_D_pred | h*ng/mL/mg | 14.5369 |
| AUC_%Extrap_pred | % | 43.1521 |
| Vz_F_pred | L | 5080.9075 |
| Cl_F_pred | L/h | 68.7904 |
| AUMClast | h*h*ng/mL | 134890.2742 |
| AUMCINF_obs | h*h*ng/mL | 565825.2498 |
| AUMC_%Extrap_obs | % | 76.1604 |
| AUMCINF_pred | h*h*ng/mL | 546632.4136 |
| AUMC_%Extrap_pred | % | 75.3234 |
| MRTlast | h | 36.2729 |
| MRTINF_obs | h | 84.7908 |
| MRTINF_pred | h | 83.5624 |
| AUC0_24 | h*ng/mL | 1122.4280 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.5330 | | | 0.06663 | 0.06663 | |
| 1.500 | 1.650 | | | 0.6124 | 0.8186 | |
| 2.000 | 3.140 | | | 1.810 | 3.007 | |
| 3.000 | 8.460 | | | 7.610 | 18.84 | |
| 4.000 | 15.50 | | | 19.59 | 62.53 | |
| 6.000 | 24.80 | | | 59.89 | 273.3 | |
| 8.000 | 37.00 | | | 121.7 | 718.1 | |
| 12.00 | 49.90 | | | 295.5 | 2508. | |
| 16.00 | 60.70 | | | 516.7 | 5648. | |

| | | | | | |
|---------|-------|-------|---------|------------------|-------|
| 24.00 | 93.90 | | | 1135. 1.855e+004 | |
| 36.00 | 79.60 | | | 2174. 4.953e+004 | |
| 48.00 | 82.00 | | | 3143. 9.034e+004 | |
| 60.00 | 59.50 | | | 3985. 1.355e+005 | |
| 72.00 | 46.60 | | | 4619. 1.772e+005 | |
| 96.00 * | 34.80 | 33.44 | 1.360 | 5588. 2.581e+005 | 1.000 |
| 120.0 * | 14.10 | 15.87 | -1.772 | 6138. 3.165e+005 | 1.000 |
| 144.0 * | 8.470 | 7.533 | 0.9366 | 6404. 3.512e+005 | 1.000 |
| 168.0 * | 3.440 | 3.576 | -0.1356 | 6537. 3.719e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9890 |
| Rsqr_adjusted | | 0.9835 |
| Corr_XY | | -0.9945 |
| No_points_lambda_z | | 4 |
| Lambda_z | 1/h | 0.0311 |
| Lambda_z_lower | h | 96.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 22.3233 |
| Tlag | h | 0.7500 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 93.9000 |
| Cmax_D | ng/mL/mg | 0.2087 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 3.4400 |
| AUClast | h*ng/mL | 6537.4920 |
| AUCall | h*ng/mL | 6537.4920 |
| AUCINF_obs | h*ng/mL | 6648.2798 |
| AUCINF_D_obs | h*ng/mL/mg | 14.7740 |
| AUC_%Extrap_obs | % | 1.6664 |
| Vz_F_obs | L | 2179.9013 |
| CL_F_obs | L/h | 67.6867 |
| AUCINF_pred | h*ng/mL | 6652.6473 |
| AUCINF_D_pred | h*ng/mL/mg | 14.7837 |
| AUC_%Extrap_pred | % | 1.7310 |
| Vz_F_pred | L | 2178.4702 |
| CL_F_pred | L/h | 67.6422 |
| AUMClast | h*h*ng/mL | 371890.3110 |
| AUMCINF_obs | h*h*ng/mL | 394070.6732 |
| AUMC_%Extrap_obs | % | 5.6285 |
| AUMCINF_pred | h*h*ng/mL | 394945.0669 |
| AUMC_%Extrap_pred | % | 5.8375 |
| MRTlast | h | 56.8858 |
| MRTINF_obs | h | 59.2741 |
| MRTINF_pred | h | 59.3666 |
| AUC0_24 | h*ng/mL | 1135.0899 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values

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WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 2.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 3.000 | 1.690 | | | 0.8450 | 2.535 | |
| 4.000 | 4.270 | | | 3.825 | 13.61 | |
| 6.000 | 13.90 | | | 22.00 | 114.1 | |
| 8.000 | 19.40 | | | 55.30 | 352.7 | |
| 12.00 | 29.20 | | | 152.5 | 1364. | |
| 16.00 | 36.00 | | | 282.9 | 3217. | |
| 24.00 | 60.70 | | | 669.7 | 1.135e+004 | |
| 36.00 | 65.90 | | | 1429. | 3.432e+004 | |
| 48.00 | 64.80 | | | 2213. | 6.725e+004 | |
| 60.00 | 51.30 | | | 2907. | 1.045e+005 | |
| 72.00 * | 45.80 | 46.81 | -1.009 | 3489. | 1.429e+005 | 1.000 |
| 96.00 * | 27.80 | 26.11 | 1.694 | 4354. | 2.147e+005 | 1.000 |
| 120.0 * | 14.80 | 14.56 | 0.2405 | 4849. | 2.675e+005 | 1.000 |
| 144.0 * | 7.100 | 8.120 | -1.020 | 5101. | 3.004e+005 | 1.000 |
| 168.0 * | 4.890 | 4.529 | 0.3614 | 5243. | 3.225e+005 | 1.000 |

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

Final Parameters

Rsq 0.9917
Rsq_adjusted 0.9889
Corr_XY -0.9958
No_points_lambda_z 5
Lambda_z 1/h 0.0243
Lambda_z_lower h 72.0000
Lambda_z_upper h 168.0000
HL_Lambda_z h 28.4898
Tlag h 2.0000
Tmax h 36.0000
Cmax ng/mL 65.9000
Cmax_D ng/mL/mg 0.1464
Tlast h 168.0000

| | | |
|-------------------|------------|-------------|
| Clast | ng/mL | 4.8900 |
| AUClast | h*ng/mL | 5242.9444 |
| AUCall | h*ng/mL | 5242.9444 |
| AUCINF_obs | h*ng/mL | 5443.9334 |
| AUCINF_D_obs | h*ng/mL/mg | 12.0976 |
| AUC_%Extrap_obs | % | 3.6920 |
| Vz_F_obs | L | 3397.5292 |
| Cl_F_obs | L/h | 82.6608 |
| AUCINF_pred | h*ng/mL | 5429.0808 |
| AUCINF_D_pred | h*ng/mL/mg | 12.0646 |
| AUC_%Extrap_pred | % | 3.4285 |
| Vz_F_pred | L | 3406.8240 |
| Cl_F_pred | L/h | 82.8870 |
| AUMClast | h*h*ng/mL | 322456.6593 |
| AUMCINF_obs | h*h*ng/mL | 364483.8764 |
| AUMC_%Extrap_obs | % | 11.5306 |
| AUMCINF_pred | h*h*ng/mL | 361378.1689 |
| AUMC_%Extrap_pred | % | 10.7703 |
| MRTlast | h | 61.5030 |
| MRTINF_obs | h | 66.9523 |
| MRTINF_pred | h | 66.5634 |
| AUC0_24 | h*ng/mL | 669.6950 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.5060 | | | 0.06325 | 0.06325 | |
| 1.500 | 1.780 | | | 0.6348 | 0.8573 | |
| 2.000 | 4.280 | | | 2.150 | 3.665 | |
| 3.000 | 8.890 | | | 8.735 | 21.28 | |
| 4.000 | 16.60 | | | 21.48 | 67.81 | |
| 6.000 | 26.40 | | | 64.48 | 292.6 | |
| 8.017 | 37.60 | | | 129.0 | 756.3 | |
| 12.00 | 48.50 | | | 300.5 | 2516. | |
| 16.00 | 62.10 | | | 521.7 | 5667. | |
| 24.00 | 94.40 | | | 1148. | 1.870e+004 | |
| 36.00 | 82.00 | | | 2204. | 5.025e+004 | |
| 48.00 | 117.0 | | | 3398. | 1.017e+005 | |
| 60.03 | 110.0 | | | 4764. | 1.753e+005 | |
| 72.00 * | 109.0 | 109.7 | -0.7457 | 6074. | 2.618e+005 | 1.000 |
| 96.03 * | 69.80 | 69.67 | 0.1272 | 8188. | 4.375e+005 | 1.000 |
| 120.0 * | 44.10 | 44.29 | -0.1880 | 9529. | 5.812e+005 | 1.000 |

| | | | | | | |
|---------|-------|-------|---------|------------|------------|-------|
| 144.0 * | 29.00 | 28.13 | 0.8657 | 1.039e+004 | 6.946e+005 | 1.000 |
| 168.0 * | 17.50 | 17.87 | -0.3725 | 1.094e+004 | 7.793e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9993 |
| Rsqr_adjusted | | 0.9991 |
| Corr_XY | | -0.9997 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0189 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 36.6643 |
| Tlag | h | 0.7500 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 117.0000 |
| Cmax_D | ng/mL/mg | 0.2600 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 17.5000 |
| AUClast | h*ng/mL | 10940.1694 |
| AUCall | h*ng/mL | 10940.1694 |
| AUCINF_obs | h*ng/mL | 11865.8382 |
| AUCINF_D_obs | h*ng/mL/mg | 26.3685 |
| AUC_%Extrap_obs | % | 7.8011 |
| Vz_F_obs | L | 2006.0035 |
| Cl_F_obs | L/h | 37.9240 |
| AUCINF_pred | h*ng/mL | 11885.5403 |
| AUCINF_D_pred | h*ng/mL/mg | 26.4123 |
| AUC_%Extrap_pred | % | 7.9540 |
| Vz_F_pred | L | 2002.6782 |
| Cl_F_pred | L/h | 37.8611 |
| AUMClast | h*h*ng/mL | 779292.5903 |
| AUMCINF_obs | h*h*ng/mL | 983768.5418 |
| AUMC_%Extrap_obs | % | 20.7850 |
| AUMCINF_pred | h*h*ng/mL | 988120.6513 |
| AUMC_%Extrap_pred | % | 21.1339 |
| MRTlast | h | 71.2322 |
| MRTINF_obs | h | 82.9076 |
| MRTINF_pred | h | 83.1364 |
| AUC0_24 | h*ng/mL | 1147.6956 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

7.0.0.2535

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

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

| h | ng/mL | ng/mL | ng/mL | h*ng/mL | h*h*ng/mL |
|---------|--------|-------|--------|---------|------------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 |
| 0.8167 | 0.0000 | | | 0.0000 | 0.0000 |
| 1.017 | 0.5110 | | | 0.05110 | 0.05195 |
| 1.500 | 1.450 | | | 0.5250 | 0.7031 |
| 2.000 | 3.040 | | | 1.648 | 2.767 |
| 3.000 | 9.990 | | | 8.163 | 20.79 |
| 4.000 | 18.00 | | | 22.16 | 71.78 |
| 6.000 | 25.10 | | | 65.26 | 294.4 |
| 8.033 | 39.90 | | | 131.3 | 773.4 |
| 12.00 | 49.70 | | | 309.0 | 2592. |
| 16.00 | 72.10 | | | 552.6 | 6092. |
| 24.00 | 81.40 | | | 1167. | 1.852e+004 |
| 36.00 * | 71.30 | 76.84 | -5.544 | 2082. | 4.585e+004 |
| 48.02 * | 70.40 | 61.56 | 8.840 | 2933. | 8.160e+004 |
| 60.08 * | 49.60 | 49.27 | 0.3295 | 3650. | 1.201e+005 |
| 72.00 * | 42.30 | 39.54 | 2.756 | 4196. | 1.561e+005 |
| 95.73 * | 23.70 | 25.52 | -1.819 | 4958. | 2.191e+005 |
| 120.1 * | 13.30 | 16.27 | -2.967 | 5397. | 2.660e+005 |
| 144.0 * | 11.30 | 10.47 | 0.8282 | 5690. | 3.046e+005 |
| 171.8 * | 6.700 | 6.273 | 0.4269 | 5935. | 3.429e+005 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9851 |
| Rsqr_adjusted | | 0.9826 |
| Corr_XY | | -0.9925 |
| No_points_lambda_z | | 8 |
| Lambda_z | 1/h | 0.0185 |
| Lambda_z_lower | h | 36.0000 |
| Lambda_z_upper | h | 171.7667 |
| HL_Lambda_z | h | 37.5598 |
| Tlag | h | 0.8167 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 81.4000 |
| Cmax_D | ng/mL/mg | 0.1809 |
| Tlast | h | 171.7667 |
| Clast | ng/mL | 6.7000 |
| AUClast | h*ng/mL | 5934.5185 |
| AUCall | h*ng/mL | 5934.5185 |
| AUCINF_obs | h*ng/mL | 6297.5733 |
| AUCINF_D_obs | h*ng/mL/mg | 13.9946 |
| AUC_%Extrap_obs | % | 5.7650 |
| Vz_F_obs | L | 3872.0115 |
| CL_F_obs | L/h | 71.4561 |
| AUCINF_pred | h*ng/mL | 6274.4383 |
| AUCINF_D_pred | h*ng/mL/mg | 13.9432 |
| AUC_%Extrap_pred | % | 5.4175 |
| Vz_F_pred | L | 3886.2883 |
| CL_F_pred | L/h | 71.7196 |
| AUMClast | h*h*ng/mL | 342895.3193 |
| AUMCINF_obs | h*h*ng/mL | 424928.9793 |
| AUMC_%Extrap_obs | % | 19.3053 |
| AUMCINF_pred | h*h*ng/mL | 419701.5427 |
| AUMC_%Extrap_pred | % | 18.3002 |
| MRTlast | h | 57.7798 |
| MRTINF_obs | h | 67.4750 |
| MRTINF_pred | h | 66.8907 |
| AUC0_24 | h*ng/mL | 1166.6475 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI

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| | | |
|-------------------|------------|--------------|
| CL_F_obs | L/h | 25.7033 |
| AUCINF_pred | h*ng/mL | 17459.5559 |
| AUCINF_D_pred | h*ng/mL/mg | 38.7990 |
| AUC_%Extrap_pred | % | 10.2442 |
| Vz_F_pred | L | 1447.5440 |
| CL_F_pred | L/h | 25.7739 |
| AUMClast | h*h*ng/mL | 1177233.9428 |
| AUMCINF_obs | h*h*ng/mL | 1588918.6096 |
| AUMC_%Extrap_obs | % | 25.9097 |
| AUMCINF_pred | h*h*ng/mL | 1578171.0701 |
| AUMC_%Extrap_pred | % | 25.4052 |
| MRTlast | h | 75.1220 |
| MRTINF_obs | h | 90.7564 |
| MRTINF_pred | h | 90.3901 |
| AUC0_24 | h*ng/mL | 1471.3888 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|------------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.5120 | | | 0.1280 | 0.1920 | |
| 2.000 | 1.060 | | | 0.5210 | 0.9140 | |
| 3.000 | 3.050 | | | 2.576 | 6.549 | |
| 4.000 | 8.270 | | | 8.236 | 27.66 | |
| 6.000 | 19.40 | | | 35.91 | 177.1 | |
| 8.000 | 32.40 | | | 87.71 | 552.7 | |
| 12.03 | 53.60 | | | 261.1 | 2376. | |
| 16.00 | 72.50 | | | 511.2 | 5956. | |
| 24.00 | 107.0 | | | 1229. 2.087e+004 | | |
| 36.00 | 102.0 | | | 2483. 5.842e+004 | | |
| 48.00 | 123.0 | | | 3833. 1.159e+005 | | |
| 60.00 | 76.90 | | | 5011. 1.789e+005 | | |
| 72.00 * | 73.50 | 72.12 | 1.377 | 5913. 2.384e+005 | | 1.000 |
| 96.07 * | 44.20 | 41.73 | 2.473 | 7300. 3.535e+005 | | 1.000 |
| 120.1 * | 23.10 | 24.19 | -1.087 | 8080. 4.368e+005 | | 1.000 |
| 144.0 * | 12.00 | 14.03 | -2.031 | 8485. 4.899e+005 | | 1.000 |
| 168.0 * | 9.220 | 8.130 | 1.090 | 8739. 5.292e+005 | | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9848 |
| Rsqr_adjusted | | 0.9797 |
| Corr_XY | | -0.9924 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0227 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 30.4843 |
| Tlag | h | 1.0000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 123.0000 |
| Cmax_D | ng/mL/mg | 0.2733 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 9.2200 |
| AUClast | h*ng/mL | 8738.5962 |
| AUCall | h*ng/mL | 8738.5962 |
| AUCINF_obs | h*ng/mL | 9144.0870 |
| AUCINF_D_obs | h*ng/mL/mg | 20.3202 |
| AUC_%Extrap_obs | % | 4.4345 |
| Vz_F_obs | L | 2164.3238 |
| CL_F_obs | L/h | 49.2121 |
| AUCINF_pred | h*ng/mL | 9096.1409 |
| AUCINF_D_pred | h*ng/mL/mg | 20.2136 |
| AUC_%Extrap_pred | % | 3.9307 |
| Vz_F_pred | L | 2175.7321 |
| CL_F_pred | L/h | 49.4715 |
| AUMClast | h*h*ng/mL | 529238.5537 |
| AUMCINF_obs | h*h*ng/mL | 615194.2807 |
| AUMC_%Extrap_obs | % | 13.9721 |
| AUMCINF_pred | h*h*ng/mL | 605030.6982 |
| AUMC_%Extrap_pred | % | 12.5270 |
| MRTlast | h | 60.5633 |
| MRTINF_obs | h | 67.2778 |
| MRTINF_pred | h | 66.5151 |
| AUC0_24 | h*ng/mL | 1229.2377 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

7.0.0.2535

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
 Number of nonmissing observations: 22
 Dose time: 0.00
 Dose amount: 450.00
 Calculation method: Linear Trapezoidal Rule for Increasing Values,
 Log Trapezoidal Rule for Decreasing Values
 Weighting for lambda_z calculations: Uniform weighting
 Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.5200 | | | 0.0000 | 0.0000 | |
| 0.2667 | 0.0000 | | | 0.06933 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.06933 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.06933 | 0.0000 | |
| 1.000 | 0.9000 | | | 0.1818 | 0.1125 | |

| | | | | | |
|---------|-------|-------|--------|------------|------------|
| 1.500 | 2.810 | | | 1.109 | 1.391 |
| 2.000 | 6.160 | | | 3.352 | 5.525 |
| 3.000 | 13.50 | | | 13.18 | 31.94 |
| 4.000 | 23.00 | | | 31.43 | 98.19 |
| 6.000 | 29.90 | | | 84.33 | 369.6 |
| 8.000 | 60.40 | | | 174.6 | 1032. |
| 12.00 | 75.30 | | | 446.0 | 3806. |
| 16.00 | 98.10 | | | 792.8 | 8752. |
| 24.00 | 197.0 | | | 1973. | 3.394e+004 |
| 36.00 | 147.0 | | | 4023. | 9.482e+004 |
| 48.00 | 193.0 | | | 6063. | 1.822e+005 |
| 60.00 | 113.0 | | | 7856. | 2.780e+005 |
| 72.00 * | 139.0 | 133.8 | 5.249 | 9368. | 3.788e+005 |
| 96.00 * | 76.20 | 81.55 | -5.347 | 1.188e+004 | 5.864e+005 |
| 120.0 * | 53.80 | 49.72 | 4.082 | 1.342e+004 | 7.521e+005 |
| 144.0 * | 27.20 | 30.31 | -3.113 | 1.436e+004 | 8.744e+005 |
| 168.0 * | 19.60 | 18.48 | 1.119 | 1.491e+004 | 9.609e+005 |

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

Final Parameters

| | | |
|--------------------|------------|--------------|
| Rsqr | | 0.9889 |
| Rsqr_adjusted | | 0.9852 |
| Corr_XY | | -0.9944 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0206 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 33.6205 |
| Tlag | h | 0.0000 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 197.0000 |
| Cmax_D | ng/mL/mg | 0.4378 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 19.6000 |
| AUClast | h*ng/mL | 14912.4021 |
| AUCall | h*ng/mL | 14912.4021 |
| AUCINF_obs | h*ng/mL | 15863.0829 |
| AUCINF_D_obs | h*ng/mL/mg | 35.2513 |
| AUC_%Extrap_obs | % | 5.9930 |
| Vz_F_obs | L | 1375.9529 |
| Cl_F_obs | L/h | 28.3678 |
| AUCINF_pred | h*ng/mL | 15808.8258 |
| AUCINF_D_pred | h*ng/mL/mg | 35.1307 |
| AUC_%Extrap_pred | % | 5.6704 |
| Vz_F_pred | L | 1380.6752 |
| Cl_F_pred | L/h | 28.4651 |
| AUMClast | h*h*ng/mL | 960877.0560 |
| AUMCINF_obs | h*h*ng/mL | 1166703.3585 |
| AUMC_%Extrap_obs | % | 17.6417 |
| AUMCINF_pred | h*h*ng/mL | 1154956.4826 |
| AUMC_%Extrap_pred | % | 16.8040 |
| MRTlast | h | 64.4348 |
| MRTINF_obs | h | 73.5483 |
| MRTINF_pred | h | 73.0577 |
| AUC0_24 | h*ng/mL | 1973.2318 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

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| | | |
|-------------------|-----------|-------------|
| AUMCINF_obs | h*h*ng/mL | 796632.2851 |
| AUMC_%Extrap_obs | % | 17.1957 |
| AUMCINF_pred | h*h*ng/mL | 820586.4230 |
| AUMC_%Extrap_pred | % | 19.6129 |
| MRTlast | h | 68.3280 |
| MRTINF_obs | h | 77.5158 |
| MRTINF_pred | h | 79.0092 |
| AUC0_24 | h*ng/mL | 1163.1212 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.8690 | | | 0.1086 | 0.1086 | |
| 1.500 | 1.890 | | | 0.7984 | 1.035 | |
| 2.000 | 3.160 | | | 2.061 | 3.323 | |
| 3.000 | 8.650 | | | 7.966 | 19.46 | |
| 4.000 | 18.50 | | | 21.54 | 69.43 | |
| 6.000 | 27.80 | | | 67.84 | 310.2 | |
| 8.000 | 38.90 | | | 134.5 | 788.2 | |
| 12.00 | 50.90 | | | 314.1 | 2632. | |
| 16.00 | 62.20 | | | 540.3 | 5844. | |
| 24.02 | 80.70 | | | 1113. | 1.760e+004 | |
| 36.00 | 78.30 | | | 2066. | 4.616e+004 | |
| 48.00 | 102.0 | | | 3148. | 9.245e+004 | |
| 60.00 | 67.00 | | | 4147. | 1.460e+005 | |
| 72.00 | 66.00 | | | 4945. | 1.986e+005 | |
| 96.00 * | 58.00 | 57.98 | 0.01543 | 6431. | 3.231e+005 | 1.000 |
| 120.0 * | 40.10 | 38.06 | 2.040 | 7596. | 4.480e+005 | 1.000 |
| 144.0 * | 22.50 | 25.00 | -2.496 | 8326. | 5.436e+005 | 1.000 |
| 168.0 * | 17.30 | 16.41 | 0.8884 | 8801. | 6.175e+005 | 1.000 |

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

Final Parameters

| | |
|--------------------|------------|
| Rsqr | 0.9816 |
| Rsqr_adjusted | 0.9724 |
| Corr_XY | -0.9908 |
| No_points_lambda_z | 4 |
| Lambda_z | 1/h 0.0175 |

| | | |
|-------------------|------------|-------------|
| Lambda_z_lower | h | 96.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 39.5398 |
| Tlag | h | 0.7500 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 102.0000 |
| Cmax_D | ng/mL/mg | 0.2267 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 17.3000 |
| AUClast | h*ng/mL | 8800.9454 |
| AUCall | h*ng/mL | 8800.9454 |
| AUCINF_obs | h*ng/mL | 9787.8039 |
| AUCINF_D_obs | h*ng/mL/mg | 21.7507 |
| AUC_%Extrap_obs | % | 10.0825 |
| Vz_F_obs | L | 2622.6240 |
| Cl_F_obs | L/h | 45.9756 |
| AUCINF_pred | h*ng/mL | 9737.1274 |
| AUCINF_D_pred | h*ng/mL/mg | 21.6381 |
| AUC_%Extrap_pred | % | 9.6146 |
| Vz_F_pred | L | 2636.2733 |
| Cl_F_pred | L/h | 46.2149 |
| AUMClast | h*h*ng/mL | 617454.0793 |
| AUMCINF_obs | h*h*ng/mL | 839540.5034 |
| AUMC_%Extrap_obs | % | 26.4533 |
| AUMCINF_pred | h*h*ng/mL | 828136.0830 |
| AUMC_%Extrap_pred | % | 25.4405 |
| MRTlast | h | 70.1577 |
| MRTINF_obs | h | 85.7741 |
| MRTINF_pred | h | 85.0493 |
| AUC0_24 | h*ng/mL | 1111.7870 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:13

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.050 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 1.350 | | | 0.3038 | 0.4556 | |
| 2.000 | 3.350 | | | 1.479 | 2.637 | |
| 3.000 | 6.890 | | | 6.599 | 16.32 | |
| 4.000 | 14.40 | | | 17.24 | 55.46 | |
| 6.000 | 18.60 | | | 50.24 | 224.7 | |
| 8.017 | 31.70 | | | 101.0 | 593.4 | |
| 12.00 | 55.70 | | | 275.0 | 2431. | |

| | | | | | |
|---------|-------|-------|--------|------------|------------|
| 16.03 | 72.10 | | | 532.8 | 6110. |
| 24.00 | 154.0 | | | 1433. | 2.544e+004 |
| 36.07 | 115.0 | | | 3045. | 7.336e+004 |
| 48.00 | 148.0 | | | 4614. | 1.405e+005 |
| 60.00 | 87.60 | | | 5996. | 2.144e+005 |
| 72.00 * | 112.0 | 111.5 | 0.4918 | 7194. | 2.943e+005 |
| 96.00 * | 64.50 | 63.59 | 0.9050 | 9260. | 4.656e+005 |
| 120.0 * | 35.10 | 36.27 | -1.169 | 1.042e+004 | 5.894e+005 |
| 144.0 * | 20.80 | 20.68 | 0.1150 | 1.108e+004 | 6.753e+005 |
| 168.0 * | 11.90 | 11.80 | 0.1030 | 1.146e+004 | 7.346e+005 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9996 |
| Rsqr_adjusted | | 0.9994 |
| Corr_XY | | -0.9998 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0234 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 29.6236 |
| Tlag | h | 1.0500 |
| Tmax | h | 24.0000 |
| Cmax | ng/mL | 154.0000 |
| Cmax_D | ng/mL/mg | 0.3422 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 11.9000 |
| AUClast | h*ng/mL | 11457.7246 |
| AUCall | h*ng/mL | 11457.7246 |
| AUCINF_obs | h*ng/mL | 11966.3048 |
| AUCINF_D_obs | h*ng/mL/mg | 26.5918 |
| AUC_%Extrap_obs | % | 4.2501 |
| Vz_F_obs | L | 1607.1816 |
| Cl_F_obs | L/h | 37.6056 |
| AUCINF_pred | h*ng/mL | 11961.9025 |
| AUCINF_D_pred | h*ng/mL/mg | 26.5820 |
| AUC_%Extrap_pred | % | 4.2149 |
| Vz_F_pred | L | 1607.7731 |
| Cl_F_pred | L/h | 37.6194 |
| AUMClast | h*h*ng/mL | 734572.8306 |
| AUMCINF_obs | h*h*ng/mL | 841749.9263 |
| AUMC_%Extrap_obs | % | 12.7327 |
| AUMCINF_pred | h*h*ng/mL | 840822.1979 |
| AUMC_%Extrap_pred | % | 12.6364 |
| MRTlast | h | 64.1116 |
| MRTINF_obs | h | 70.3433 |
| MRTINF_pred | h | 70.2917 |
| AUC0_24 | h*ng/mL | 1433.3963 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,

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$h^* \text{ ng/mL}$

1381.0613

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

PI

Core Version 04Jun2007

00000000

Model: Plasma Data, Extravascular Administration

Number of nonmissing observations: 22

Dose time: 0.00

Dose amount: 450.00

Calculation method: Linear Trapezoidal Rule for for Increasing Values.

Log Trapezoidal Rule for Decreasing Values

Weighting for lambda z calculations: Uniform weighting

Lambda_z method: Find best fit for lambda_z, Log regression

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.6120 | | | 0.07650 | 0.07650 | |
| 1.500 | 1.530 | | | 0.6120 | 0.8033 | |
| 2.000 | 4.120 | | | 2.025 | 3.437 | |
| 3.000 | 8.820 | | | 8.495 | 20.79 | |
| 4.000 | 17.20 | | | 21.50 | 68.42 | |
| 6.000 | 22.90 | | | 61.60 | 274.6 | |
| 8.000 | 34.00 | | | 118.5 | 684.0 | |
| 12.00 | 59.60 | | | 305.7 | 2658. | |
| 16.00 | 79.70 | | | 584.3 | 6639. | |
| 24.00 | 117.0 | | | 1371. | 2.297e+004 | |
| 36.03 | 118.0 | | | 2785. | 6.545e+004 | |
| 48.00 | 118.0 | | | 4197. | 1.248e+005 | |
| 60.00 | 80.80 | | | 5376. | 1.880e+005 | |
| 72.00 * | 79.00 | 83.55 | -4.553 | 6335. | 2.512e+005 | 1.000 |
| 96.00 * | 51.00 | 44.13 | 6.870 | 7870. | 3.789e+005 | 1.000 |
| 120.0 * | 22.10 | 23.31 | -1.208 | 8700. | 4.671e+005 | 1.000 |
| 144.0 * | 11.10 | 12.31 | -1.211 | 9083. | 5.172e+005 | 1.000 |
| 168.0 * | 6.960 | 6.502 | 0.4580 | 9296. | 5.502e+005 | 1.000 |

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

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| | | |
|--------------------|----------|----------|
| Rsq | | 0.9897 |
| Rsq_adjusted | | 0.9863 |
| Corr_XY | | -0.9949 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0266 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 26.0605 |
| Tlag | h | 0.7500 |
| Tmax | h | 36.0333 |
| Cmax | ng/mL | 118.0000 |
| Cmax_D | ng/mL/mg | 0.2622 |

| | | |
|-------------------|------------|-------------|
| Tlast | h | 168.0000 |
| Clast | ng/mL | 6.9600 |
| AUClast | h*ng/mL | 9295.8206 |
| AUCall | h*ng/mL | 9295.8206 |
| AUCINF_obs | h*ng/mL | 9557.4986 |
| AUCINF_D_obs | h*ng/mL/mg | 21.2389 |
| AUC_%Extrap_obs | % | 2.7379 |
| Vz_F_obs | L | 1770.2161 |
| CL_F_obs | L/h | 47.0834 |
| AUCINF_pred | h*ng/mL | 9540.2794 |
| AUCINF_D_pred | h*ng/mL/mg | 21.2006 |
| AUC_%Extrap_pred | % | 2.5624 |
| Vz_F_pred | L | 1773.4111 |
| CL_F_pred | L/h | 47.1684 |
| AUMClast | h*h*ng/mL | 550187.6112 |
| AUMCINF_obs | h*h*ng/mL | 603987.9364 |
| AUMC_%Extrap_obs | % | 8.9075 |
| AUMCINF_pred | h*h*ng/mL | 600447.7210 |
| AUMC_%Extrap_pred | % | 8.3704 |
| MRTlast | h | 59.1866 |
| MRTINF_obs | h | 63.1952 |
| MRTINF_pred | h | 62.9382 |
| AUC0_24 | h*ng/mL | 1371.1045 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=2,TRTA=2 x 250 mg TF3

Date: PI
Time: 09:24:12

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

7.0.0.2535

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration

Number of nonmissing observations: 22

Dose time: 0.00

Dose amount: 450.00

Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values

Weighting for lambda_z calculations: Uniform weighting

Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.5070 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.5350 | | | 0.1303 | 0.01672 | |
| 0.5000 | 0.5140 | | | 0.2614 | 0.06577 | |
| 0.7500 | 0.6730 | | | 0.4097 | 0.1610 | |
| 1.000 | 1.110 | | | 0.6326 | 0.3628 | |
| 1.500 | 2.000 | | | 1.410 | 1.390 | |
| 2.000 | 3.470 | | | 2.778 | 3.875 | |
| 3.000 | 7.310 | | | 8.168 | 18.31 | |
| 4.000 | 11.00 | | | 17.32 | 51.28 | |
| 6.000 | 20.60 | | | 48.92 | 218.9 | |
| 8.000 | 31.10 | | | 100.6 | 591.3 | |
| 12.00 | 48.90 | | | 260.6 | 2262. | |
| 16.00 | 71.90 | | | 502.2 | 5737. | |
| 24.02 | 104.0 | | | 1207. | 2.036e+004 | |
| 36.00 | 96.60 | | | 2409. | 5.632e+004 | |
| 48.00 | 124.0 | | | 3732. | 1.129e+005 | |
| 60.00 | 112.0 | | | 5147. | 1.892e+005 | |
| 72.00 | 122.0 | | | 6551. | 2.822e+005 | |
| 96.00 | 90.60 | | | 9084. | 4.934e+005 | |

| | | | | | | |
|---------|-------|-------|---------|------------|------------|-------|
| 120.0 * | 57.60 | 57.14 | 0.4626 | 1.083e+004 | 6.807e+005 | 1.000 |
| 144.0 * | 46.50 | 47.26 | -0.7560 | 1.208e+004 | 8.444e+005 | 1.000 |
| 168.0 * | 39.40 | 39.08 | 0.3164 | 1.311e+004 | 1.005e+006 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|--------------|
| Rsqr | | 0.9946 |
| Rsqr_adjusted | | 0.9892 |
| Corr_XY | | -0.9973 |
| No_points_lambda_z | | 3 |
| Lambda_z | 1/h | 0.0079 |
| Lambda_z_lower | h | 120.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 87.6115 |
| Tlag | h | 0.0000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 124.0000 |
| Cmax_D | ng/mL/mg | 0.2756 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 39.4000 |
| AUClast | h*ng/mL | 13105.0983 |
| AUCall | h*ng/mL | 13105.0983 |
| AUCINF_obs | h*ng/mL | 18085.1283 |
| AUCINF_D_obs | h*ng/mL/mg | 40.1892 |
| AUC_%Extrap_obs | % | 27.5366 |
| Vz_F_obs | L | 3145.0435 |
| CL_F_obs | L/h | 24.8823 |
| AUCINF_pred | h*ng/mL | 18045.1310 |
| AUCINF_D_pred | h*ng/mL/mg | 40.1003 |
| AUC_%Extrap_pred | % | 27.3760 |
| Vz_F_pred | L | 3152.0145 |
| CL_F_pred | L/h | 24.9375 |
| AUMClast | h*h*ng/mL | 1004510.3979 |
| AUMCINF_obs | h*h*ng/mL | 2470614.7820 |
| AUMC_%Extrap_obs | % | 59.3417 |
| AUMCINF_pred | h*h*ng/mL | 2458839.7159 |
| AUMC_%Extrap_pred | % | 59.1470 |
| MRTlast | h | 76.6504 |
| MRTINF_obs | h | 136.6103 |
| MRTINF_pred | h | 136.2606 |
| AUC0_24 | h*ng/mL | 1205.5557 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7833 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 0.7050 | | | 0.1763 | 0.2644 | |
| 2.000 | 1.770 | | | 0.7950 | 1.414 | |
| 3.000 | 6.240 | | | 4.800 | 12.54 | |
| 4.000 | 12.40 | | | 14.12 | 46.70 | |
| 6.000 | 25.20 | | | 51.72 | 247.5 | |
| 8.000 | 35.40 | | | 112.3 | 681.9 | |
| 12.00 | 53.00 | | | 289.1 | 2520. | |
| 16.00 | 63.90 | | | 522.9 | 5837. | |
| 24.00 | 100.0 | | | 1179. | 1.953e+004 | |
| 36.00 | 91.60 | | | 2327. | 5.389e+004 | |
| 48.00 | 112.0 | | | 3549. | 1.059e+005 | |
| 60.00 | 100.0 | | | 4820. | 1.744e+005 | |
| 72.00 * | 109.0 | 114.6 | -5.600 | 6074. | 2.575e+005 | 1.000 |
| 96.00 * | 84.20 | 79.75 | 4.450 | 8379. | 4.500e+005 | 1.000 |
| 120.0 * | 52.10 | 55.50 | -3.398 | 9984. | 6.218e+005 | 1.000 |
| 144.0 * | 45.50 | 38.62 | 6.879 | 1.115e+004 | 7.758e+005 | 1.000 |
| 168.0 * | 24.20 | 26.88 | -2.677 | 1.196e+004 | 9.011e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|--------------|
| Rsqr | | 0.9652 |
| Rsqr_adjusted | | 0.9537 |
| Corr_XY | | -0.9825 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0151 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 45.8851 |
| Tlag | h | 1.0000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 112.0000 |
| Cmax_D | ng/mL/mg | 0.2489 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 24.2000 |
| AUClast | h*ng/mL | 11963.2267 |
| AUCall | h*ng/mL | 11963.2267 |
| AUCINF_obs | h*ng/mL | 13565.2245 |
| AUCINF_D_obs | h*ng/mL/mg | 30.1449 |
| AUC_%Extrap_obs | % | 11.8096 |
| Vz_F_obs | L | 2195.9987 |
| Cl_F_obs | L/h | 33.1731 |
| AUCINF_pred | h*ng/mL | 13742.4177 |
| AUCINF_D_pred | h*ng/mL/mg | 30.5387 |
| AUC_%Extrap_pred | % | 12.9467 |
| Vz_F_pred | L | 2167.6838 |
| Cl_F_pred | L/h | 32.7453 |
| AUMClast | h*h*ng/mL | 901108.7591 |
| AUMCINF_obs | h*h*ng/mL | 1276293.8569 |
| AUMC_%Extrap_obs | % | 29.3965 |
| AUMCINF_pred | h*h*ng/mL | 1317792.1958 |
| AUMC_%Extrap_pred | % | 31.6198 |
| MRTlast | h | 75.3232 |
| MRTINF_obs | h | 94.0857 |
| MRTINF_pred | h | 95.8923 |
| AUC0_24 | h*ng/mL | 1178.5200 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=pj,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

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| | | |
|-------------------|------------|-------------|
| Vz_F_obs | L | 1753.2571 |
| Cl_F_obs | L/h | 42.1696 |
| AUCINF_pred | h*ng/mL | 10676.2794 |
| AUCINF_D_pred | h*ng/mL/mg | 23.7251 |
| AUC_%Extrap_pred | % | 7.1353 |
| Vz_F_pred | L | 1752.4203 |
| Cl_F_pred | L/h | 42.1495 |
| AUMClast | h*h*ng/mL | 712752.7128 |
| AUMCINF_obs | h*h*ng/mL | 871424.9340 |
| AUMC_%Extrap_obs | % | 18.2084 |
| AUMCINF_pred | h*h*ng/mL | 872493.5266 |
| AUMC_%Extrap_pred | % | 18.3085 |
| MRTlast | h | 71.8900 |
| MRTINF_obs | h | 81.6615 |
| MRTINF_pred | h | 81.7226 |
| AUC0_24 | h*ng/mL | 1516.6890 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=1,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:11

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
7.0.0.2535
Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 1.500 | 1.520 | | | 0.3800 | 0.5700 | |
| 2.000 | 2.410 | | | 1.363 | 2.345 | |
| 3.000 | 6.010 | | | 5.573 | 13.77 | |
| 4.000 | 8.680 | | | 12.92 | 40.15 | |
| 6.000 | 13.50 | | | 35.10 | 155.9 | |
| 8.000 | 18.50 | | | 67.10 | 384.9 | |
| 12.00 | 34.20 | | | 172.5 | 1502. | |
| 16.00 | 44.70 | | | 330.3 | 3753. | |
| 24.00 | 69.50 | | | 787.1 | 1.329e+004 | |
| 36.00 | 93.60 | | | 1766. | 4.351e+004 | |
| 48.00 | 107.0 | | | 2969. | 9.454e+004 | |
| 60.03 | 65.40 | | | 3986. | 1.490e+005 | |
| 72.00 * | 56.90 | 56.02 | 0.8754 | 4717. | 1.971e+005 | 1.000 |
| 96.00 * | 29.60 | 31.70 | -2.096 | 5719. | 2.800e+005 | 1.000 |
| 120.0 * | 18.50 | 17.93 | 0.5678 | 6286. | 3.407e+005 | 1.000 |
| 144.0 * | 11.00 | 10.15 | 0.8548 | 6632. | 3.860e+005 | 1.000 |
| 168.0 * | 5.410 | 5.740 | -0.3297 | 6821. | 4.153e+005 | 1.000 |

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

Final Parameters

| | | |
|--------------------|------------|-------------|
| Rsqr | | 0.9951 |
| Rsqr_adjusted | | 0.9935 |
| Corr_XY | | -0.9976 |
| No_points_lambda_z | | 5 |
| Lambda_z | 1/h | 0.0237 |
| Lambda_z_lower | h | 72.0000 |
| Lambda_z_upper | h | 168.0000 |
| HL_Lambda_z | h | 29.2058 |
| Tlag | h | 1.0000 |
| Tmax | h | 48.0000 |
| Cmax | ng/mL | 107.0000 |
| Cmax_D | ng/mL/mg | 0.2378 |
| Tlast | h | 168.0000 |
| Clast | ng/mL | 5.4100 |
| AUClast | h*ng/mL | 6821.3604 |
| AUCall | h*ng/mL | 6821.3604 |
| AUCINF_obs | h*ng/mL | 7049.3110 |
| AUCINF_D_obs | h*ng/mL/mg | 15.6651 |
| AUC_%Extrap_obs | % | 3.2337 |
| Vz_F_obs | L | 2689.7336 |
| Cl_F_obs | L/h | 63.8360 |
| AUCINF_pred | h*ng/mL | 7063.2019 |
| AUCINF_D_pred | h*ng/mL/mg | 15.6960 |
| AUC_%Extrap_pred | % | 3.4240 |
| Vz_F_pred | L | 2684.4438 |
| Cl_F_pred | L/h | 63.7105 |
| AUMClast | h*h*ng/mL | 415268.7757 |
| AUMCINF_obs | h*h*ng/mL | 463169.1793 |
| AUMC_%Extrap_obs | % | 10.3419 |
| AUMCINF_pred | h*h*ng/mL | 466088.1406 |
| AUMC_%Extrap_pred | % | 10.9034 |
| MRTlast | h | 60.8777 |
| MRTINF_obs | h | 65.7042 |
| MRTINF_pred | h | 65.9882 |
| AUC0_24 | h*ng/mL | 787.0975 |

WinNonlin 7.0.0.2535

PARAMCD=M9A,SUBJID=PI,APERIOD=2,TRTAN=1,TRTA=5 x 100 mg TF3

Date: PI
Time: 09:24:10

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM 7.0.0.2535 Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 22
Dose time: 0.00
Dose amount: 450.00
Calculation method: Linear Trapezoidal Rule for Increasing Values,
Log Trapezoidal Rule for Decreasing Values
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

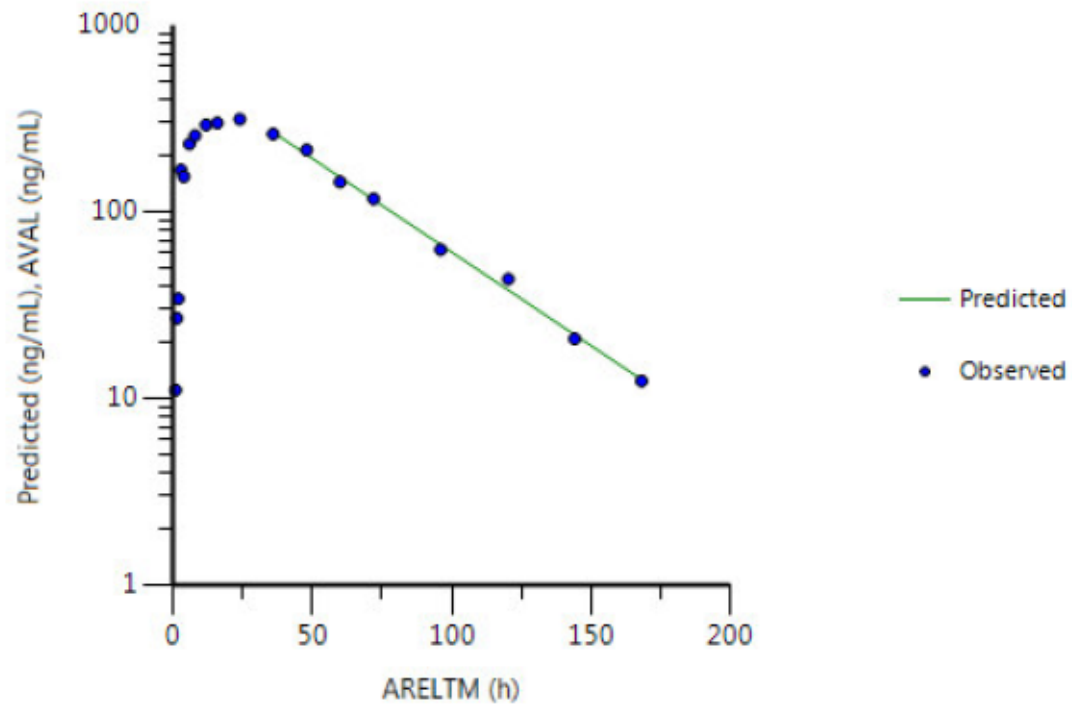
Summary Table

| Time
h | Conc.
ng/mL | Pred.
ng/mL | Residual
ng/mL | AUC
h*ng/mL | AUMC
h*h*ng/mL | Weight |
|-----------|----------------|----------------|-------------------|----------------|-------------------|--------|
| 0.0000 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.2500 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.5167 | 0.0000 | | | 0.0000 | 0.0000 | |
| 0.7500 | 0.5200 | | | 0.06067 | 0.04550 | |

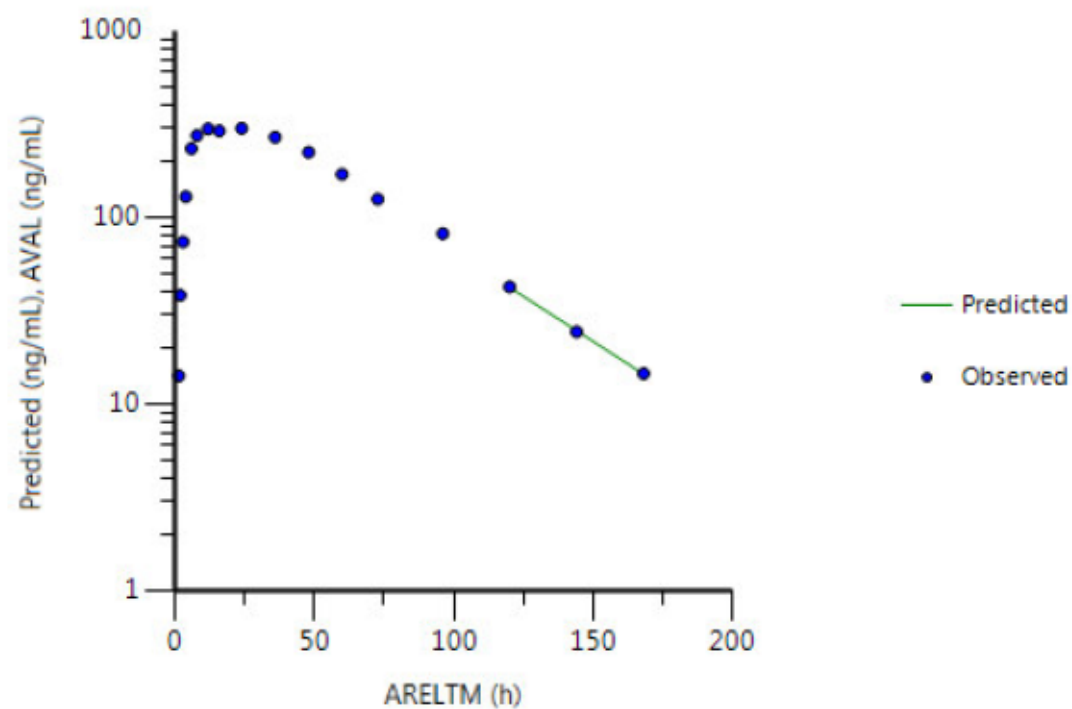
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WinNonlin Plots - Tepotinib

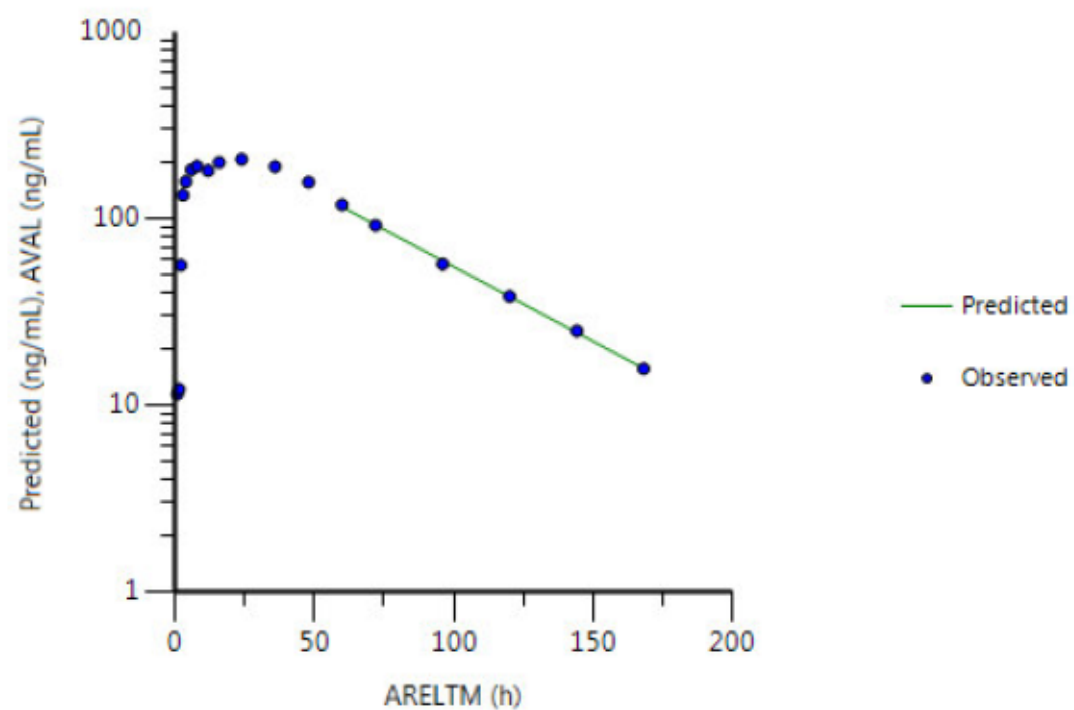
PARAMCD=TEPO, SUBJID=PI, APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9961 Rsquared_adjusted=0.9954 HL_Lambda_z=30.0227
8 points used in calculation



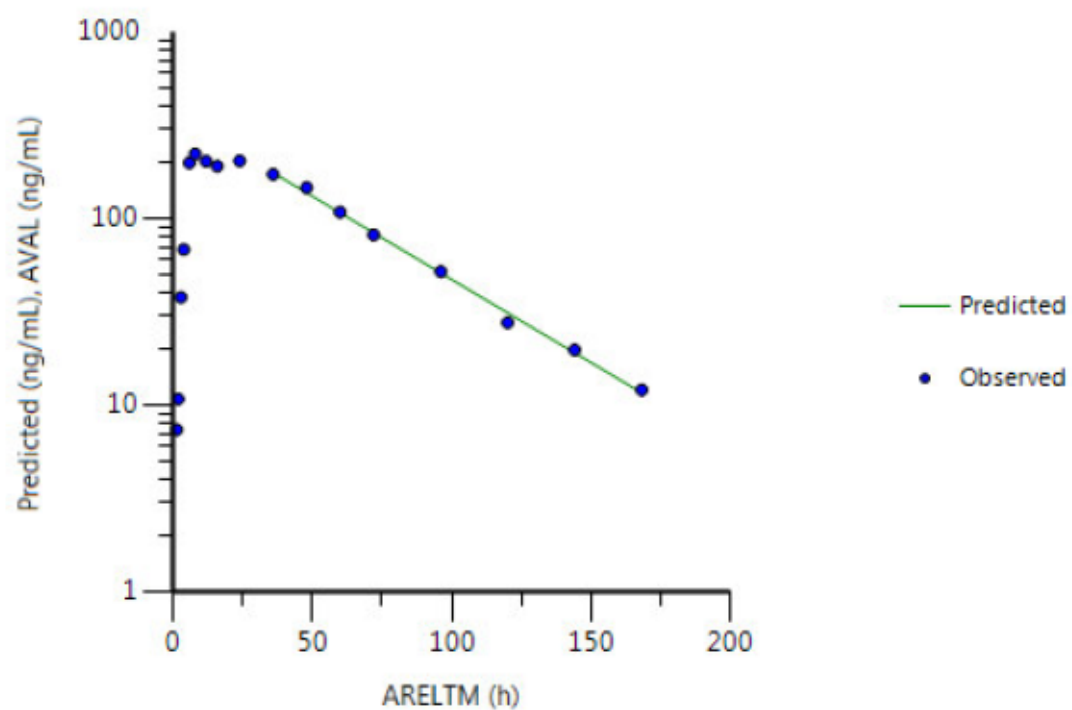
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9995 Rsquared_adjusted=0.999 HL_Lambda_z=31.1386
3 points used in calculation



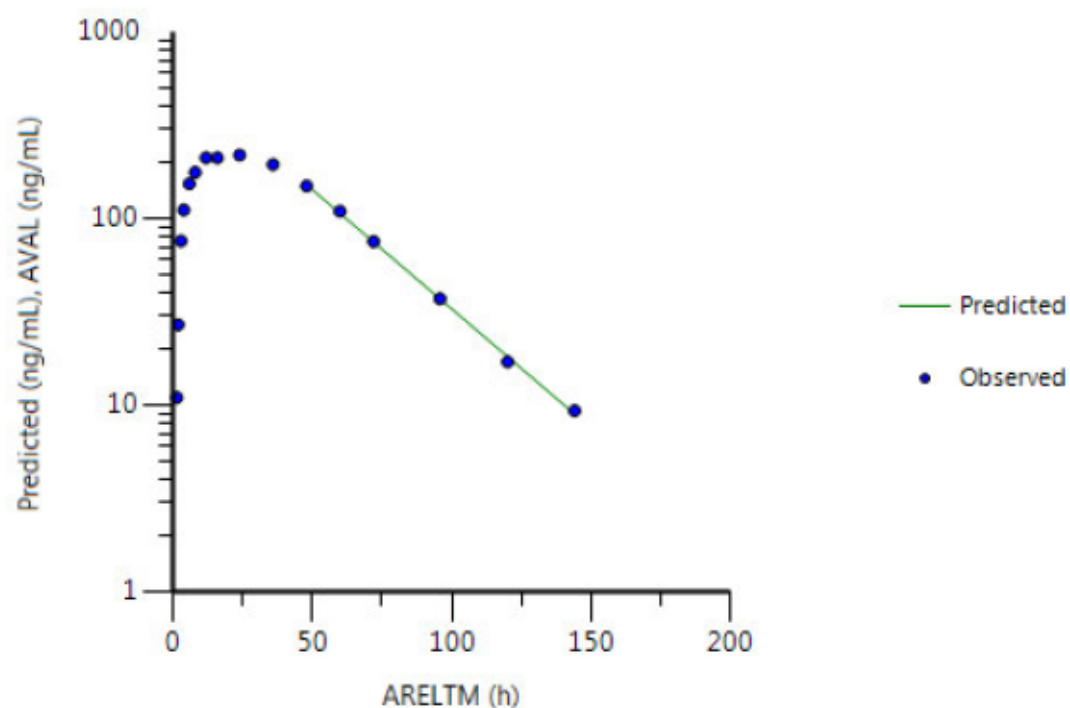
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9991 Rsquared_adjusted=0.9989 HL_Lambda_z=37.658
6 points used in calculation



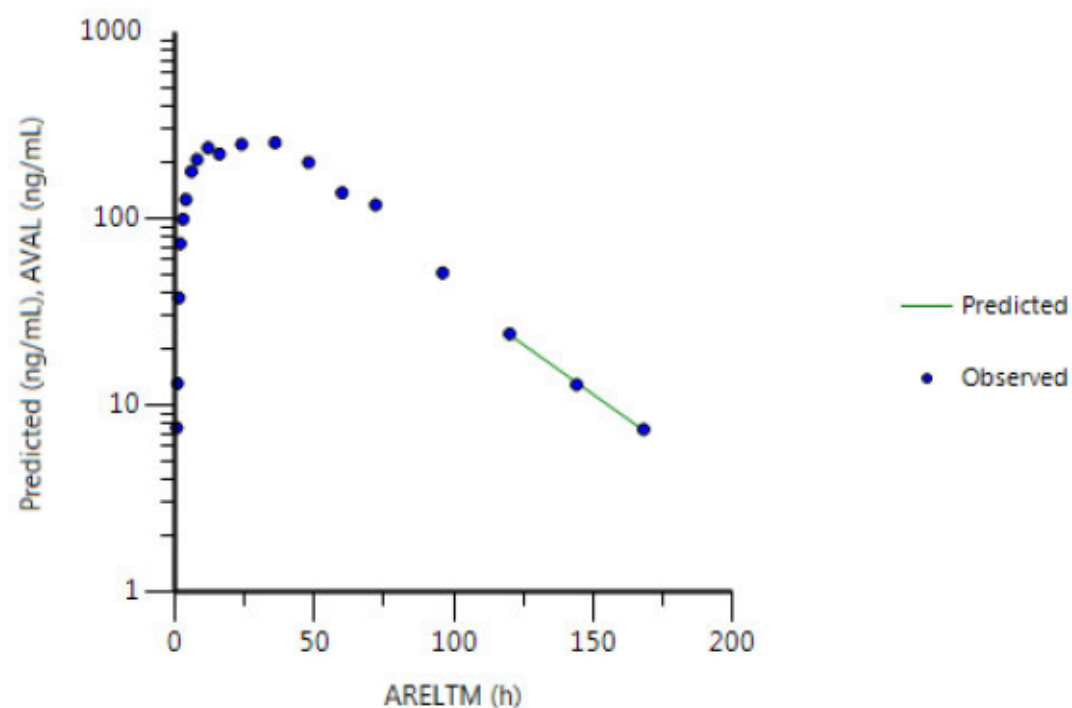
PARAMCD=TEPO, SUBJID=PI, APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsqu=0.9966 Rsqu_adjusted=0.9961 HL_Lambda_z=33.7575
8 points used in calculation



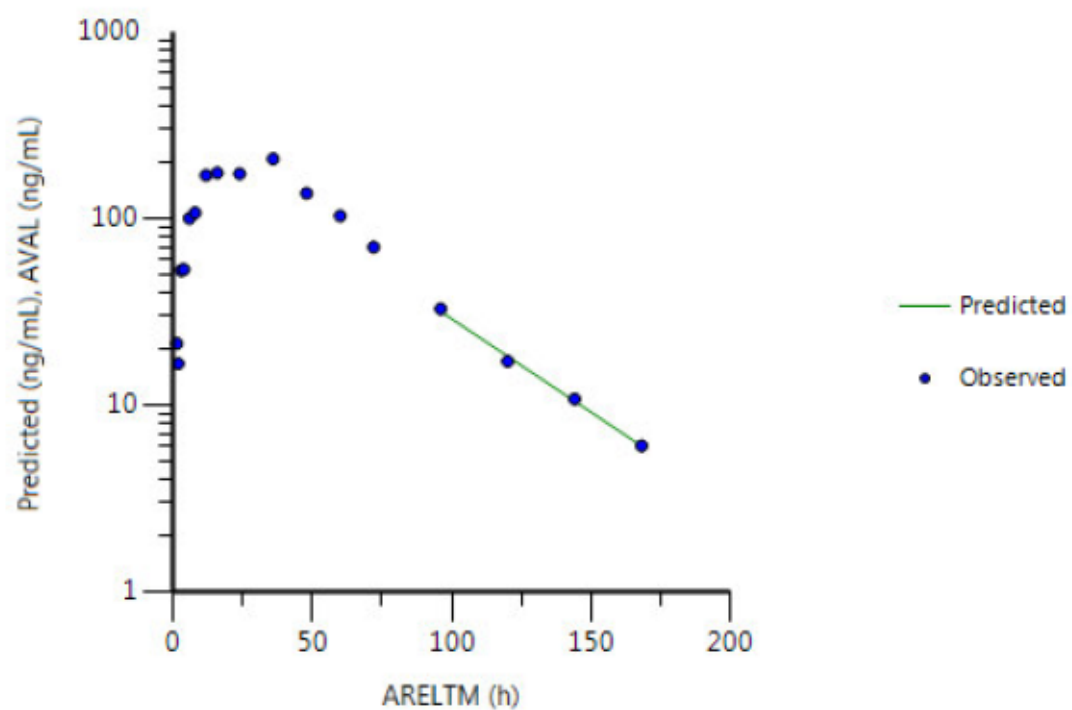
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9989 Rsquared_adjusted=0.9987 HL_Lambda_z=23.5718
6 points used in calculation



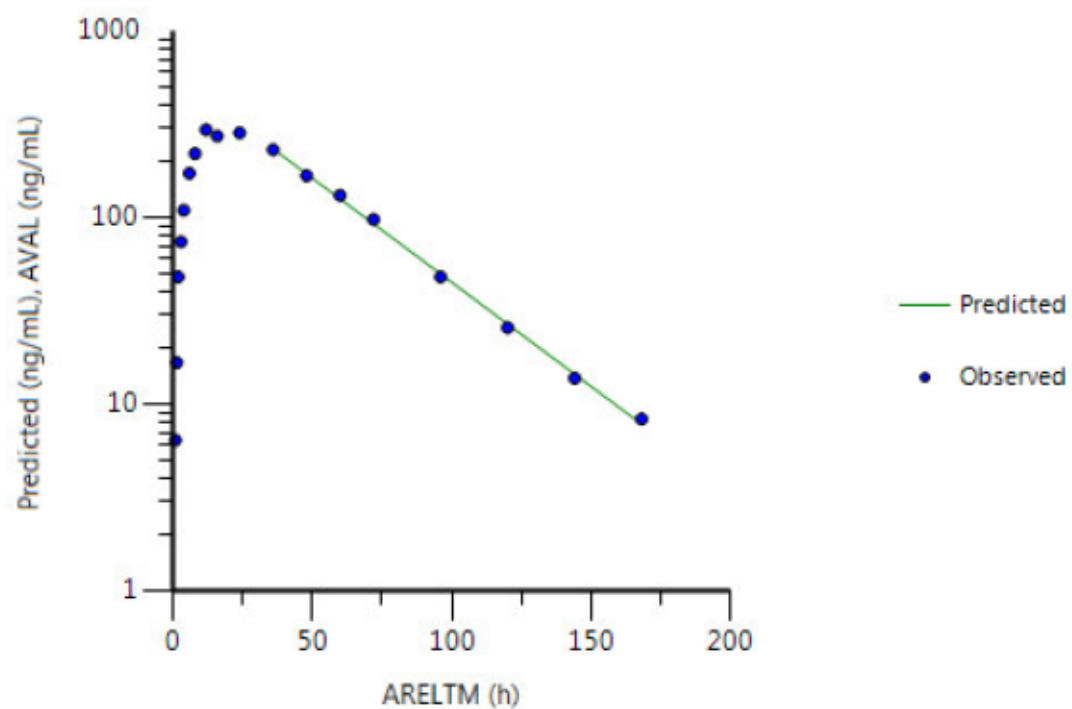
PARAMCD=TEPO, SUBJID=PI, APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9987 Rsquared_adjusted=0.9974 HL_Lambda_z=28.3168
3 points used in calculation



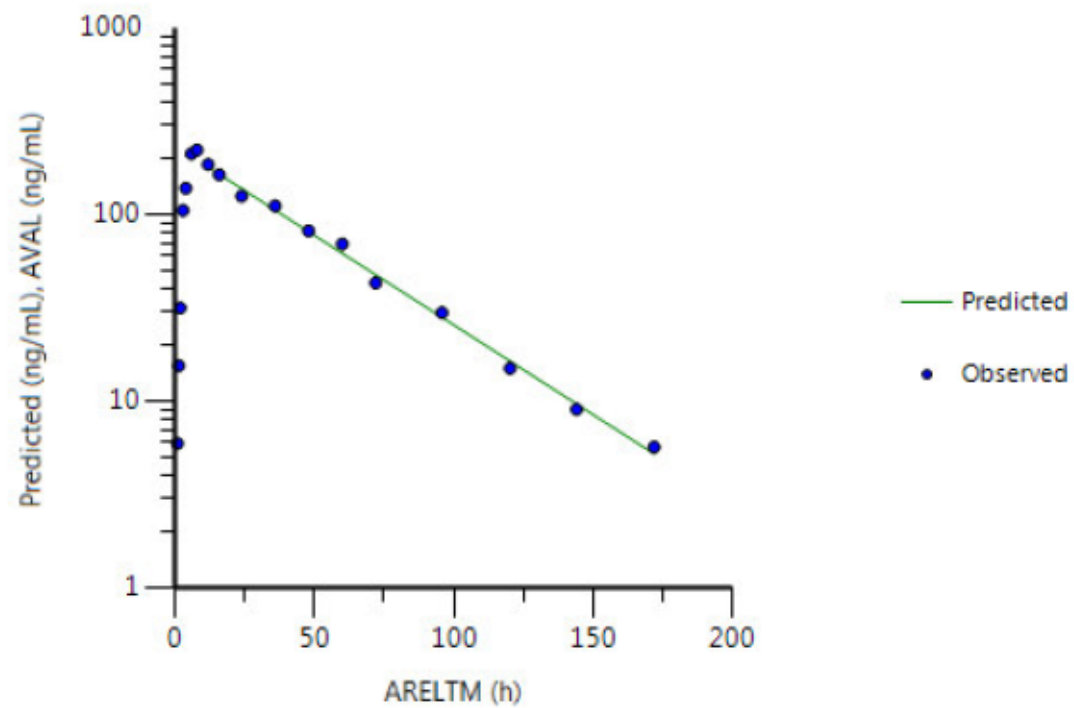
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9965 Rsquared_adjusted=0.9947 HL_Lambda_z=30.101
4 points used in calculation



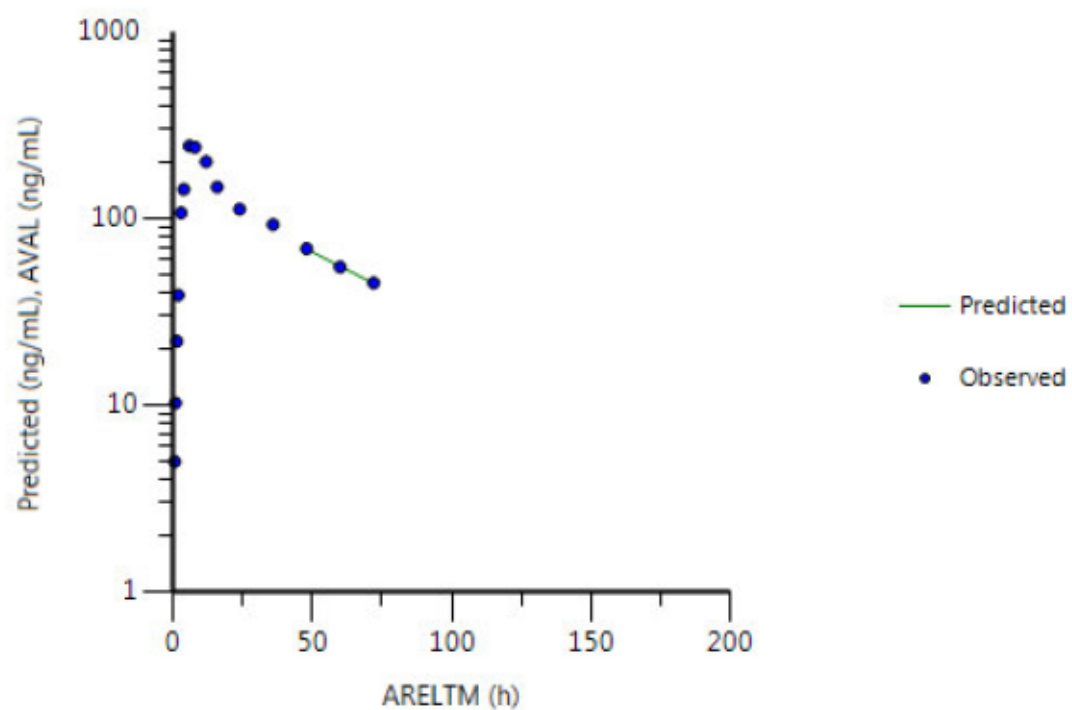
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9985 Rsquared_adjusted=0.9983 HL_Lambda_z=26.9819
8 points used in calculation



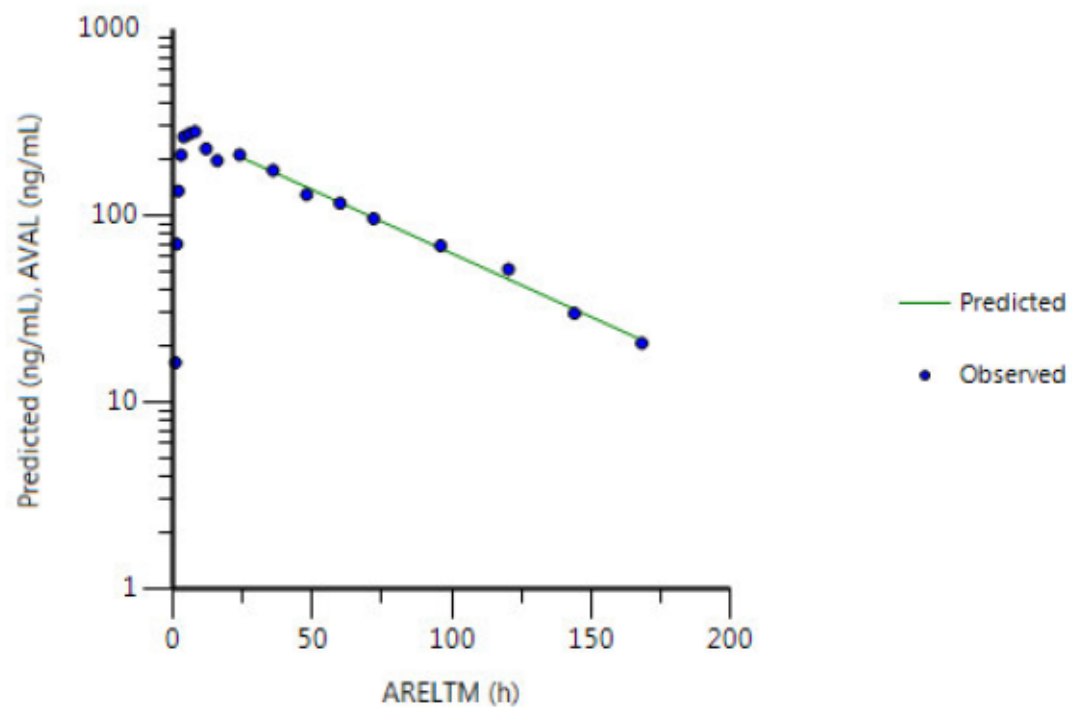
PARAMCD=TEPO, SUBJID=PI, APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9959 Rsquared_adjusted=0.9954 HL_Lambda_z=31.35
11 points used in calculation



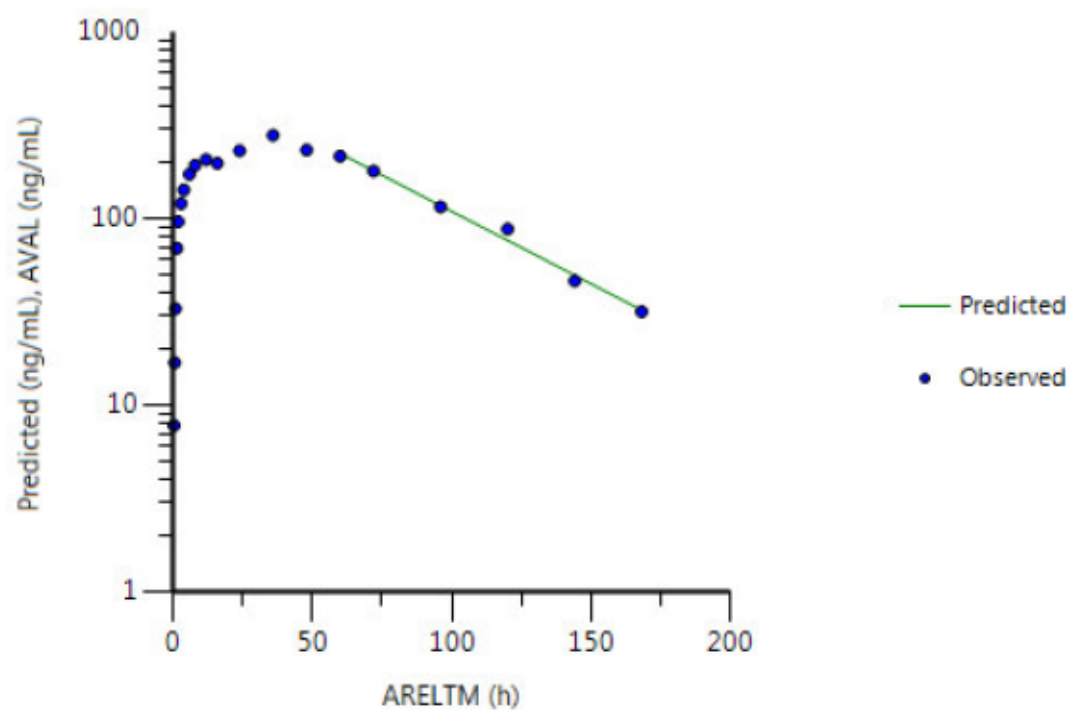
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9984 Rsquared_adjusted=0.9968 HL_Lambda_z=39.3907
3 points used in calculation



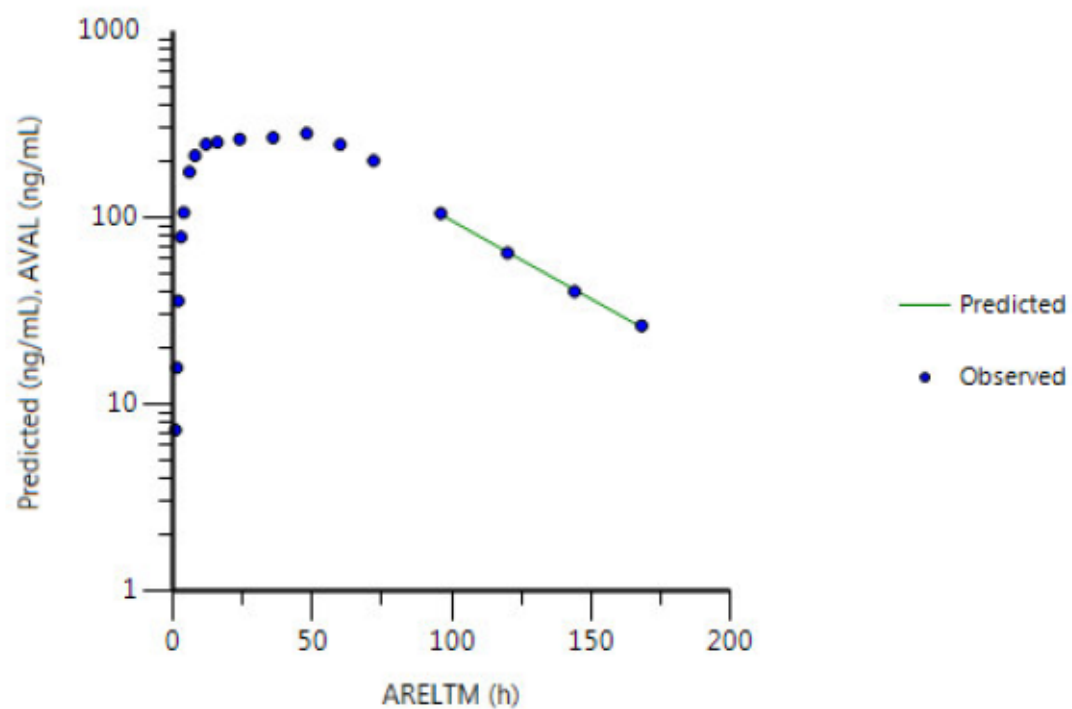
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.994 Rsquared_adjusted=0.9931 HL_Lambda_z=44.2083
9 points used in calculation



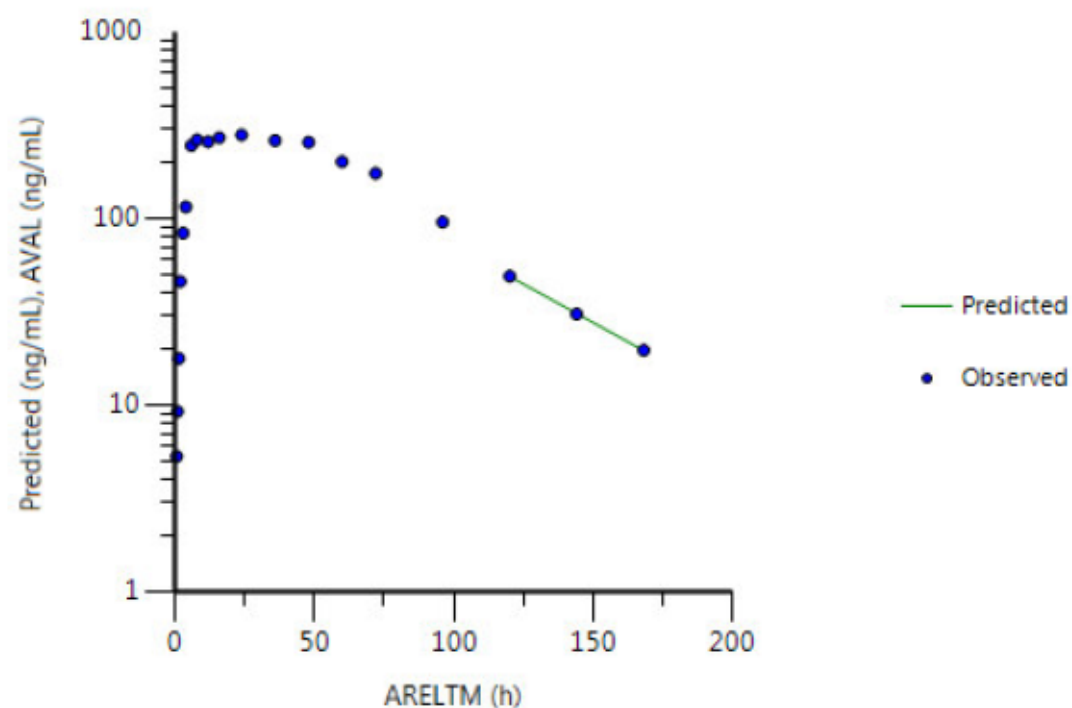
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9907 Rsquared_adjusted=0.9883 HL_Lambda_z=38.8093
6 points used in calculation



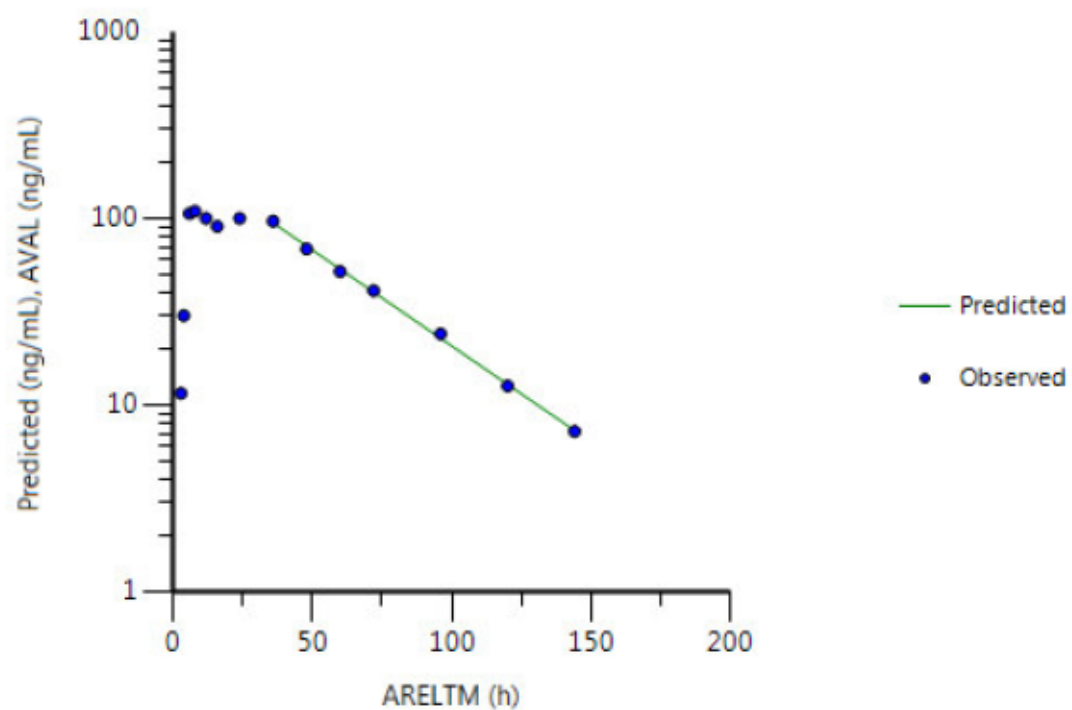
PARAMCD=TEPO, SUBJID=PI, APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9989 Rsquared_adjusted=0.9984 HL_Lambda_z=35.9271
4 points used in calculation



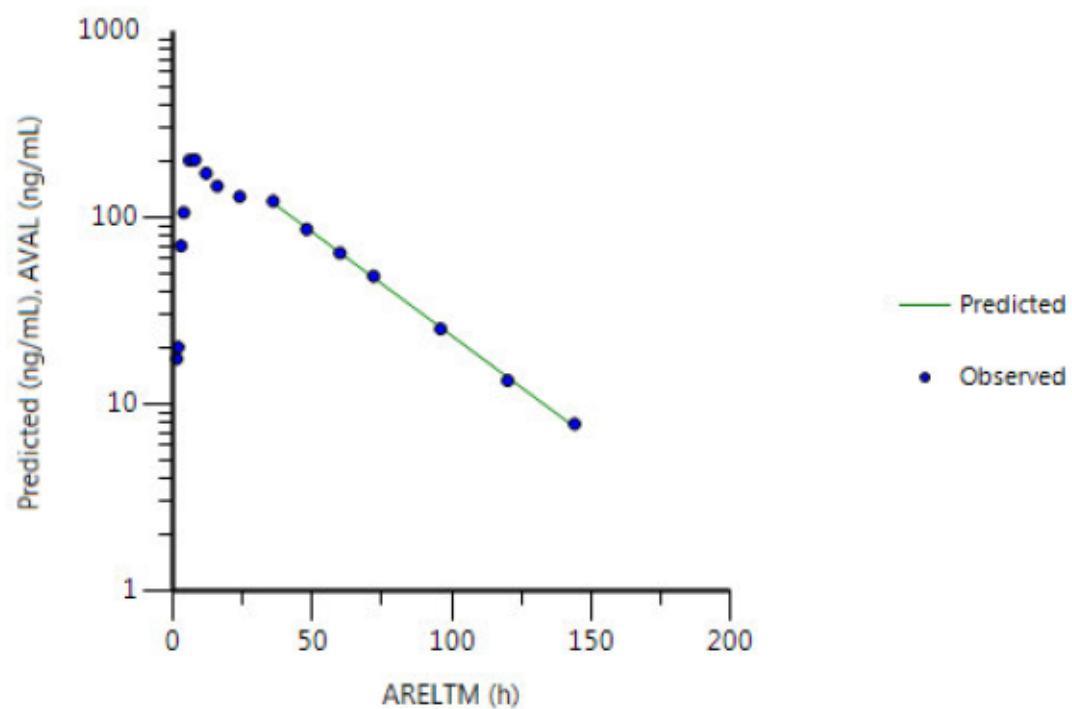
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9999 Rsquared_adjusted=0.9997 HL_Lambda_z=36.5265
3 points used in calculation



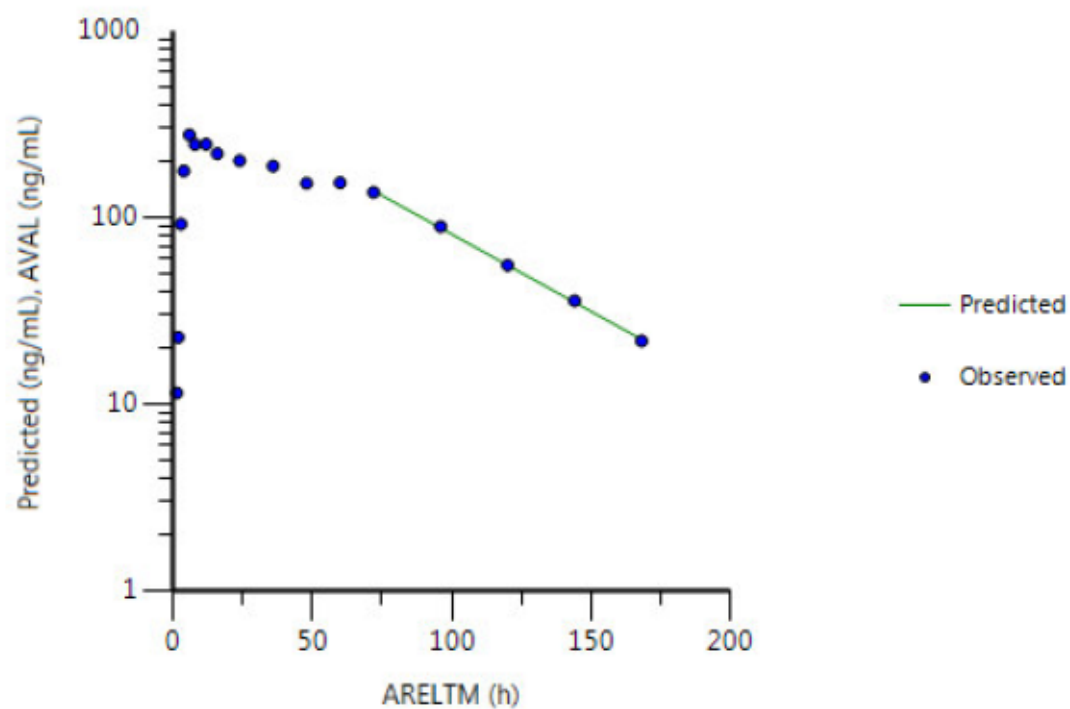
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9988 Rsquared_adjusted=0.9985 HL_Lambda_z=29.2999
7 points used in calculation



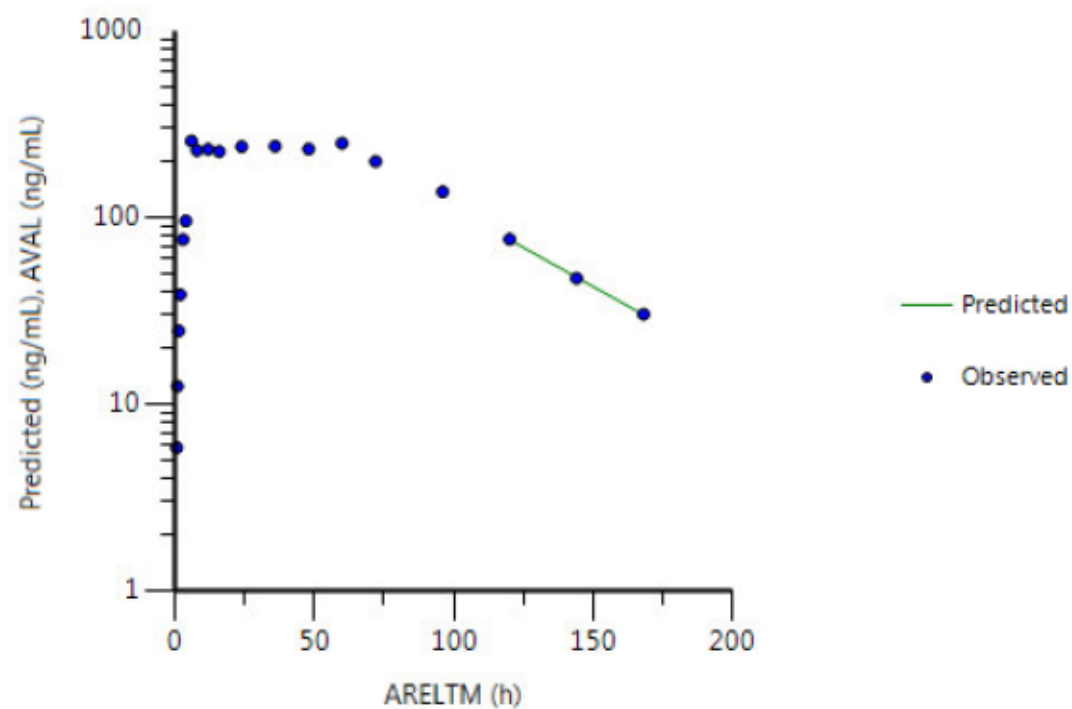
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9993 Rsquared_adjusted=0.9991 HL_Lambda_z=27.1346
7 points used in calculation



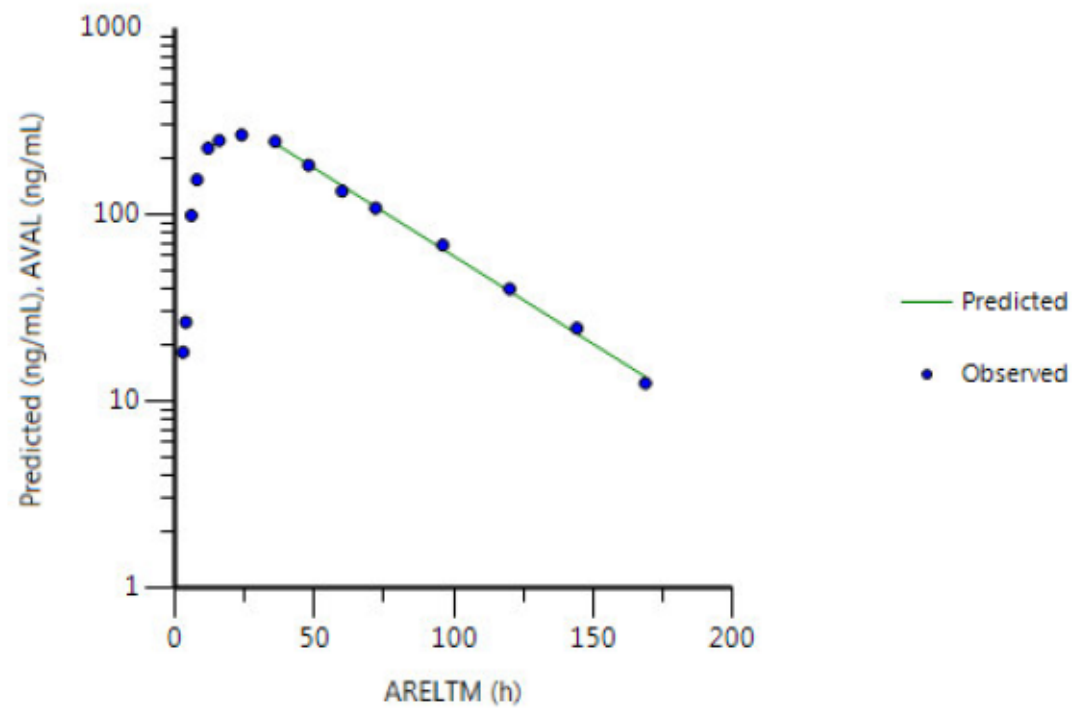
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9993 Rsquared_adjusted=0.9991 HL_Lambda_z=36.3575
5 points used in calculation



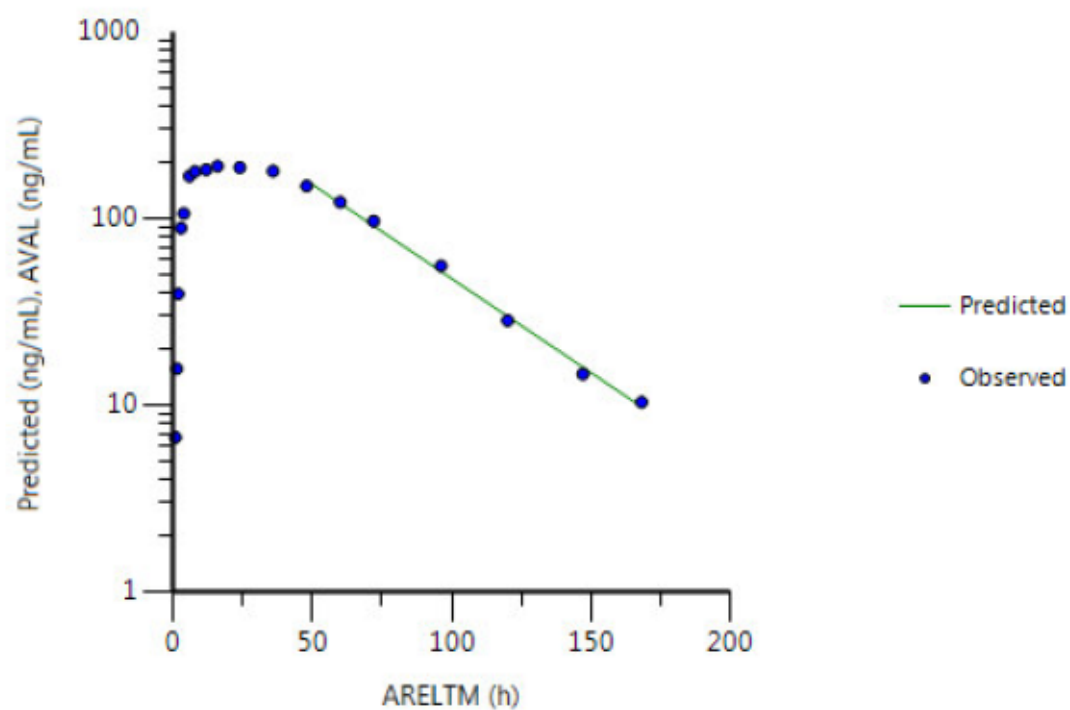
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9995 Rsquared_adjusted=0.9989 HL_Lambda_z=36.0262
3 points used in calculation



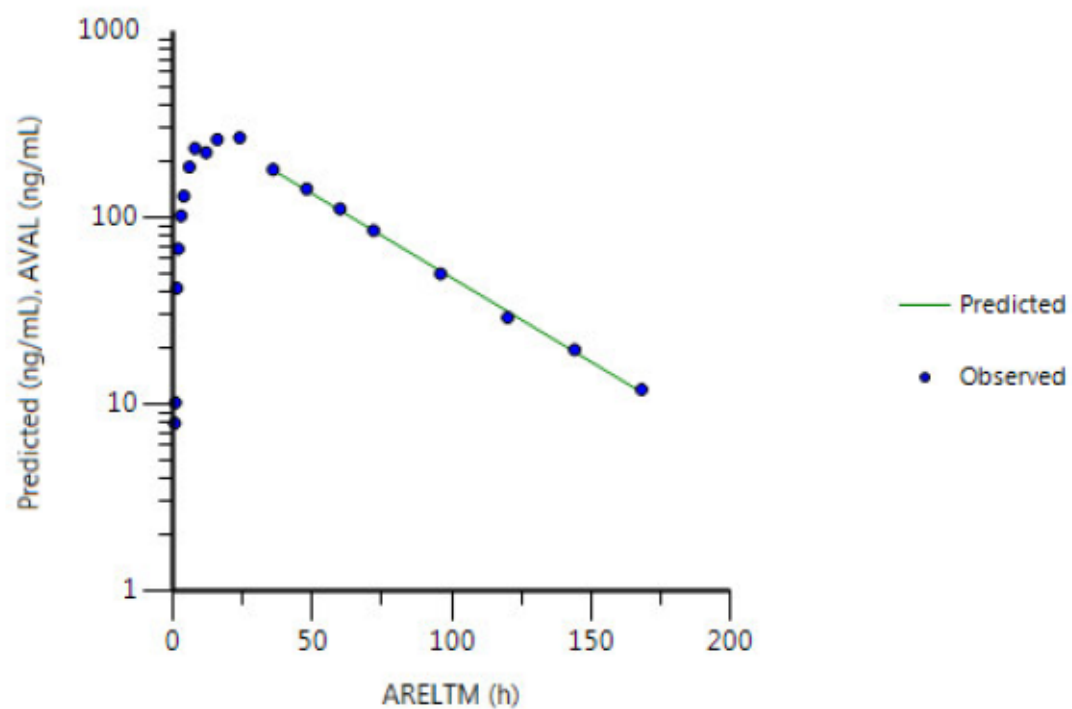
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9974 Rsquared_adjusted=0.9969 HL_Lambda_z=31.988
8 points used in calculation



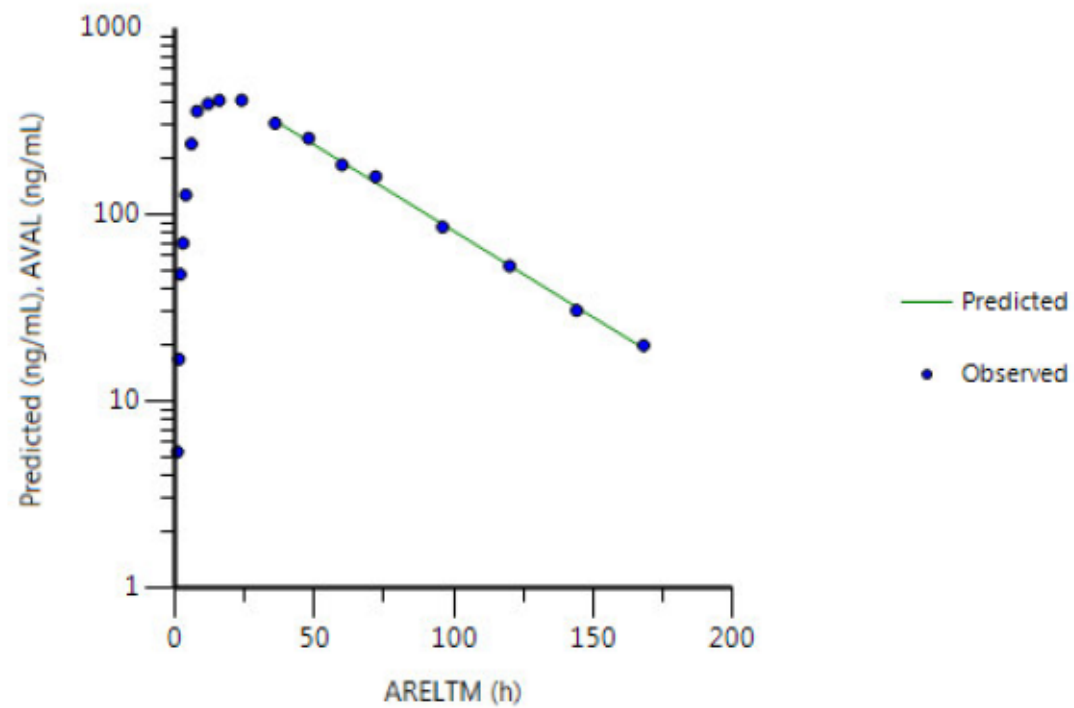
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9961 Rsquared_adjusted=0.9953 HL_Lambda_z=29.8456
7 points used in calculation



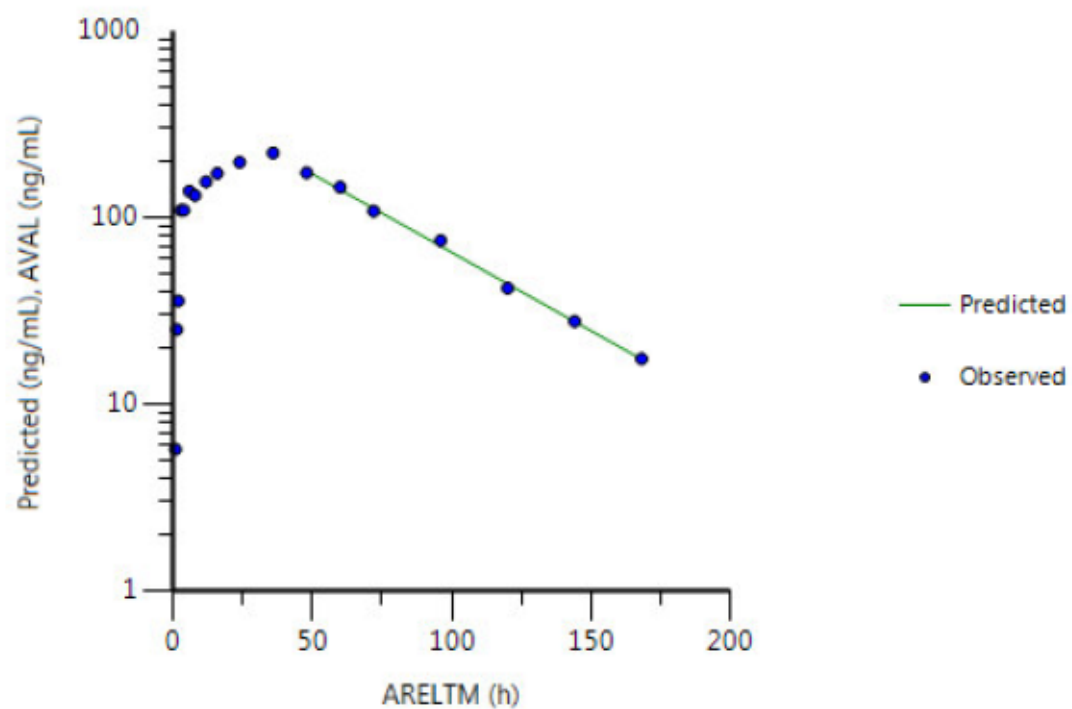
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9986 Rsquared_adjusted=0.9984 HL_Lambda_z=33.4379
8 points used in calculation



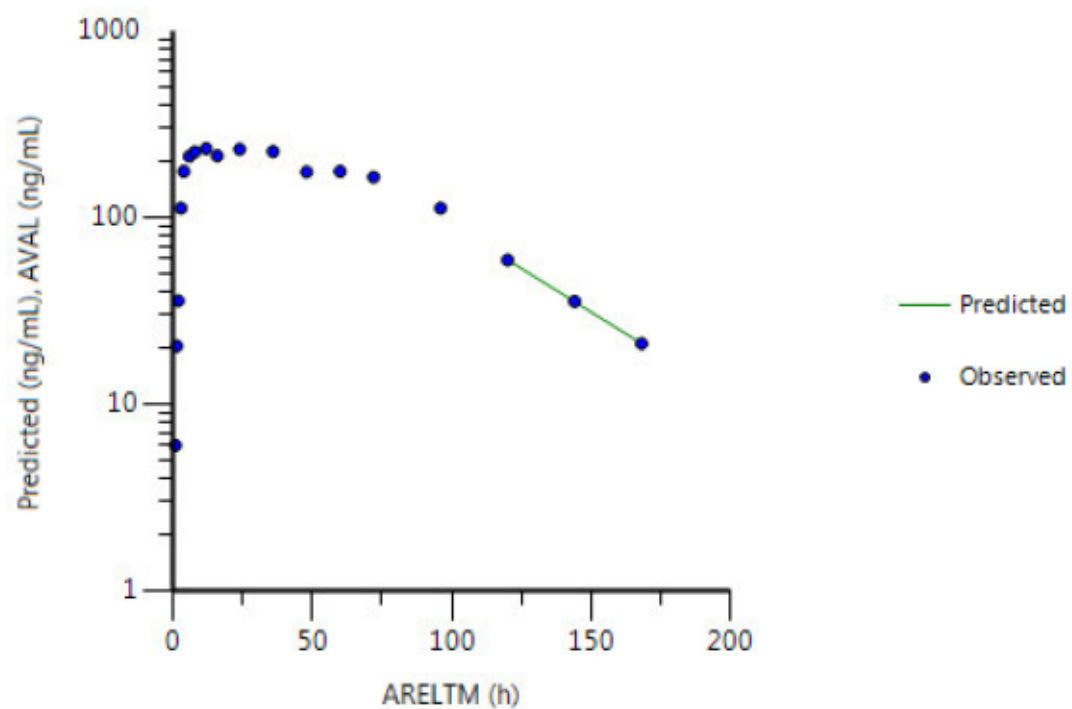
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9981 Rsquared_adjusted=0.9978 HL_Lambda_z=32.62
8 points used in calculation



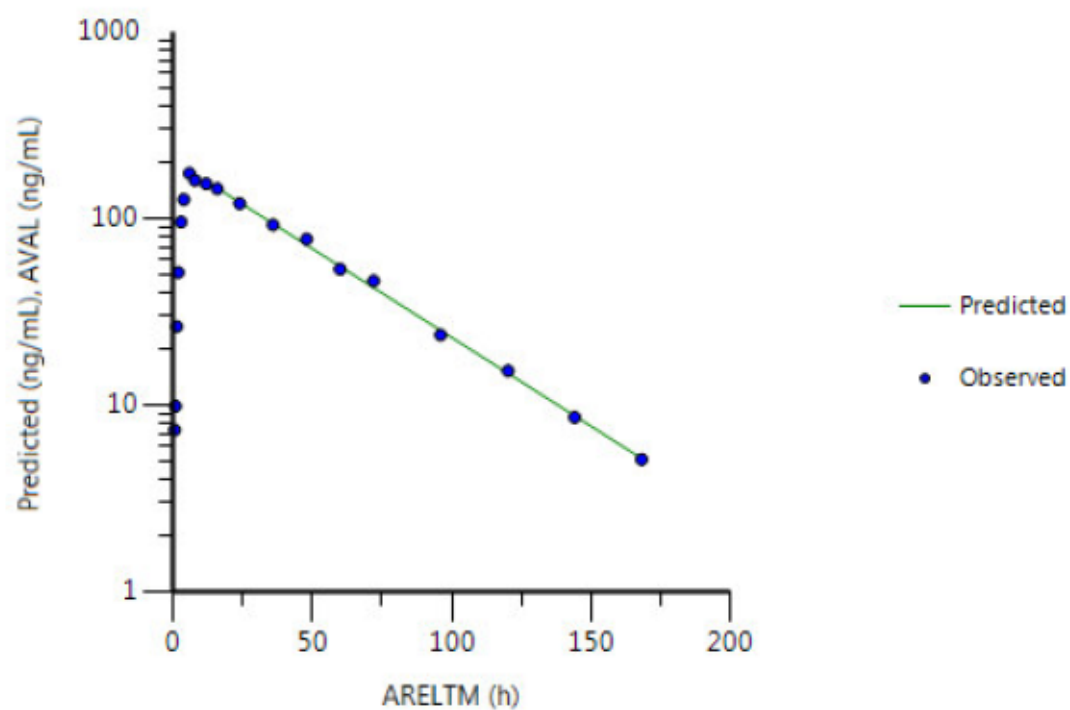
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9977 Rsquared_adjusted=0.9973 HL_Lambda_z=35.8565
7 points used in calculation



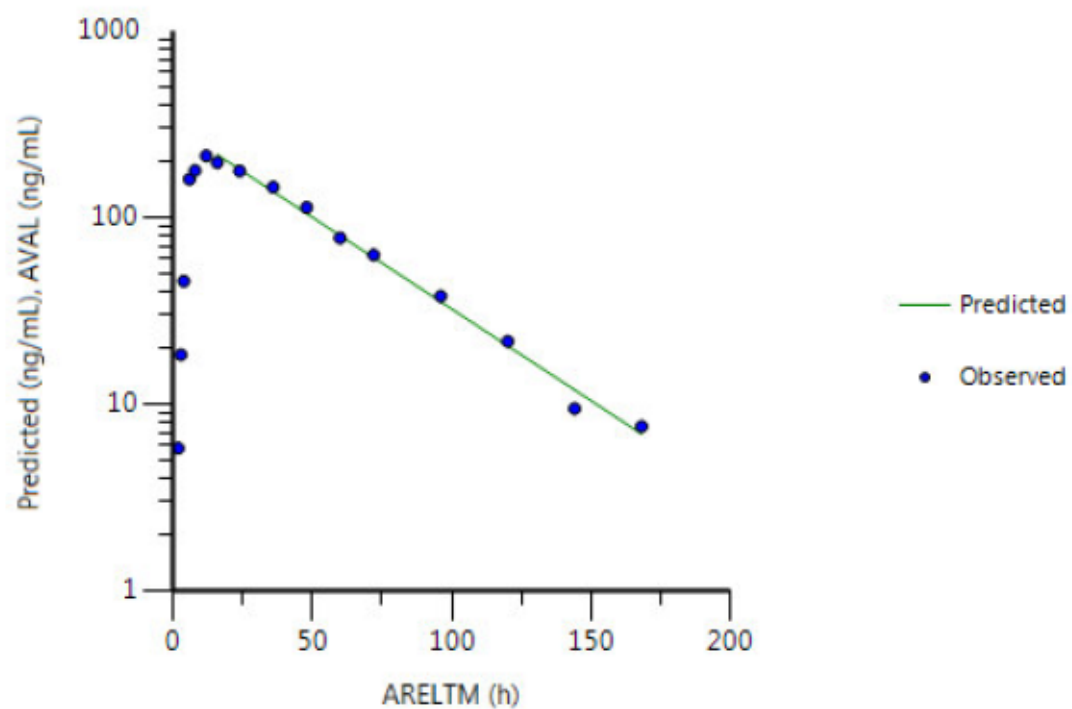
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsqr=1.0 Rsqr_adjusted=0.9999 HL_Lambda_z=32.3033
3 points used in calculation



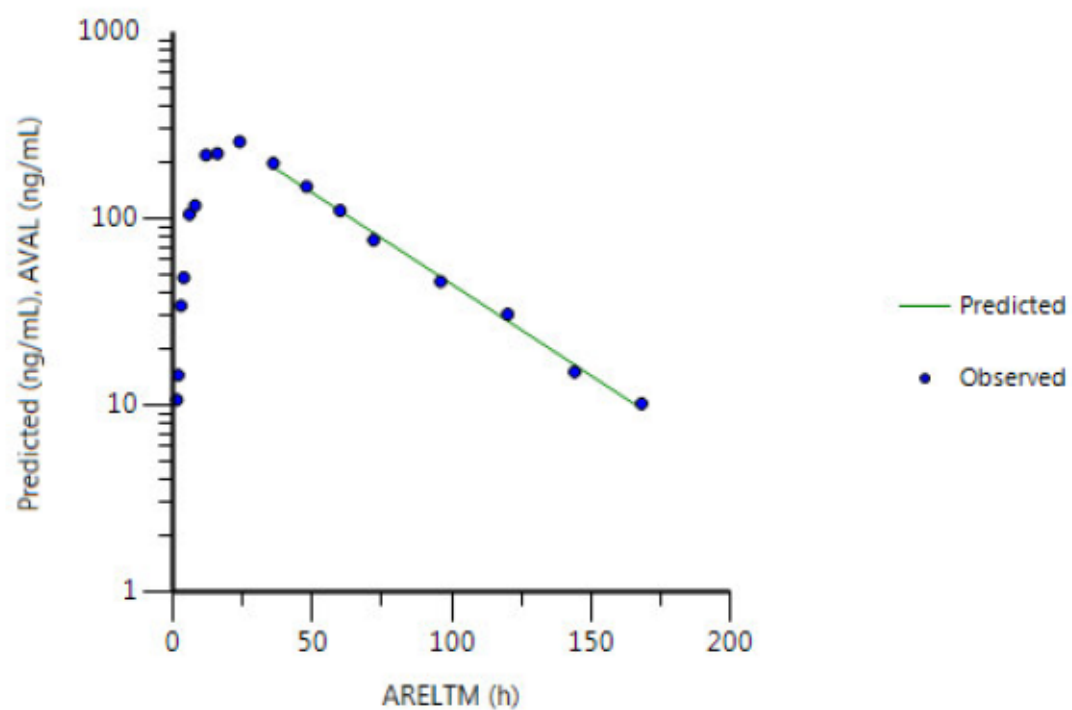
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9985 Rsquared_adjusted=0.9984 HL_Lambda_z=31.6478
11 points used in calculation



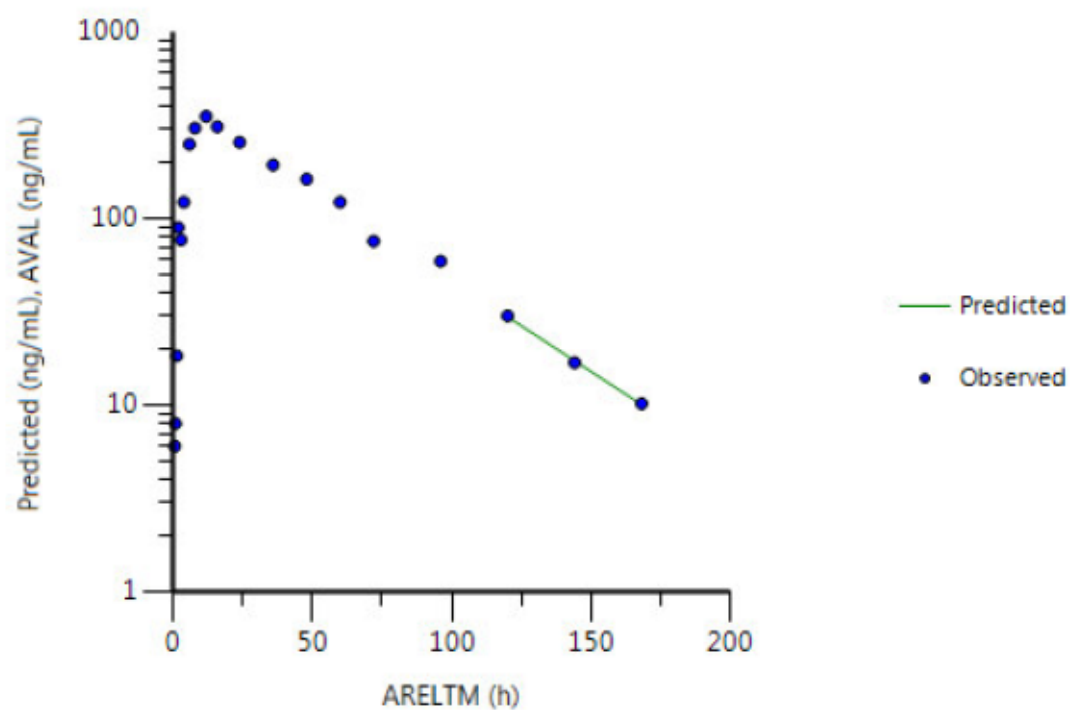
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9928 Rsquared_adjusted=0.9919 HL_Lambda_z=30.6248
10 points used in calculation



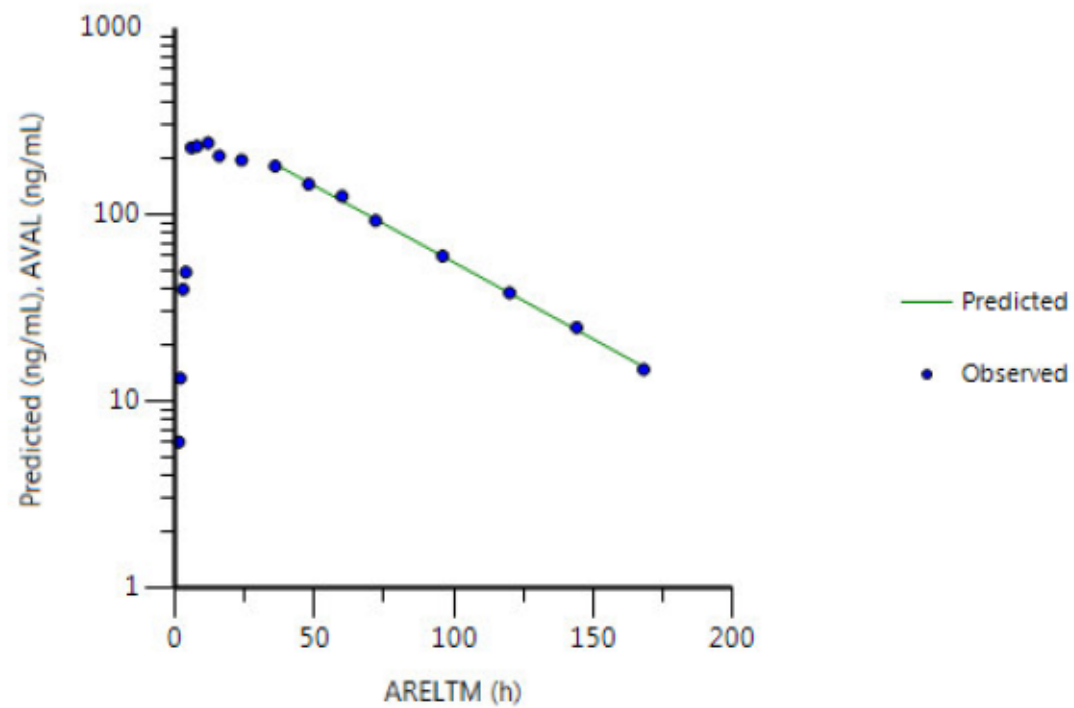
PARAMCD=TEPO, SUBJID=PI, APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.996 Rsquared_adjusted=0.9953 HL_Lambda_z=30.7238
8 points used in calculation



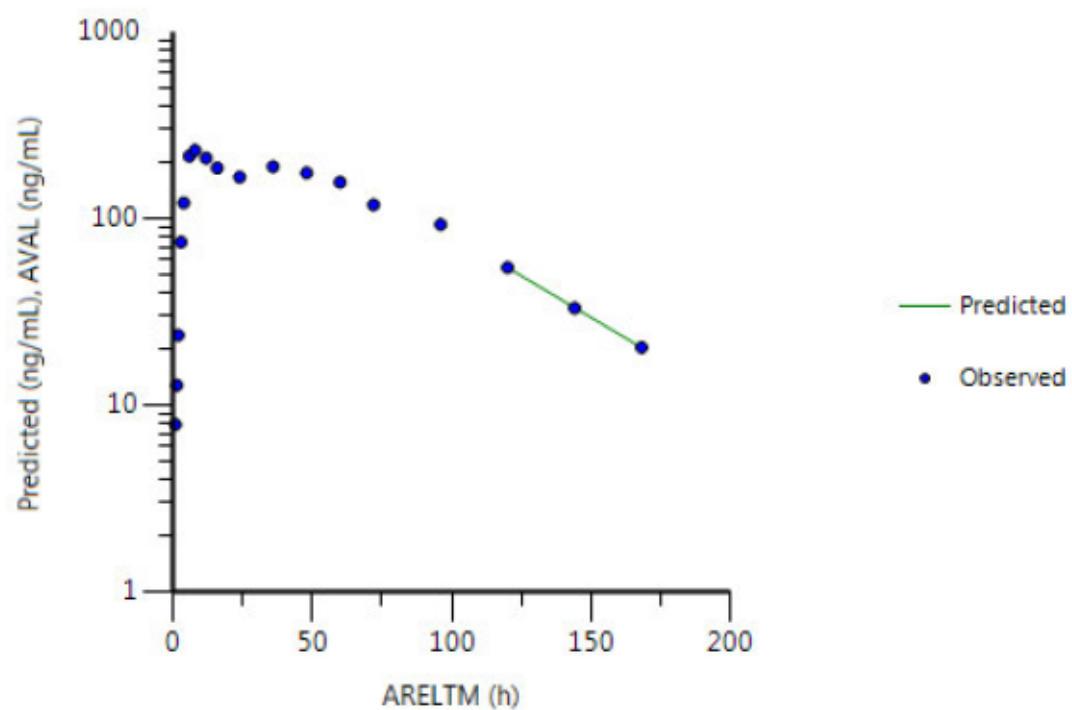
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9985 Rsquared_adjusted=0.997 HL_Lambda_z=30.7457
3 points used in calculation



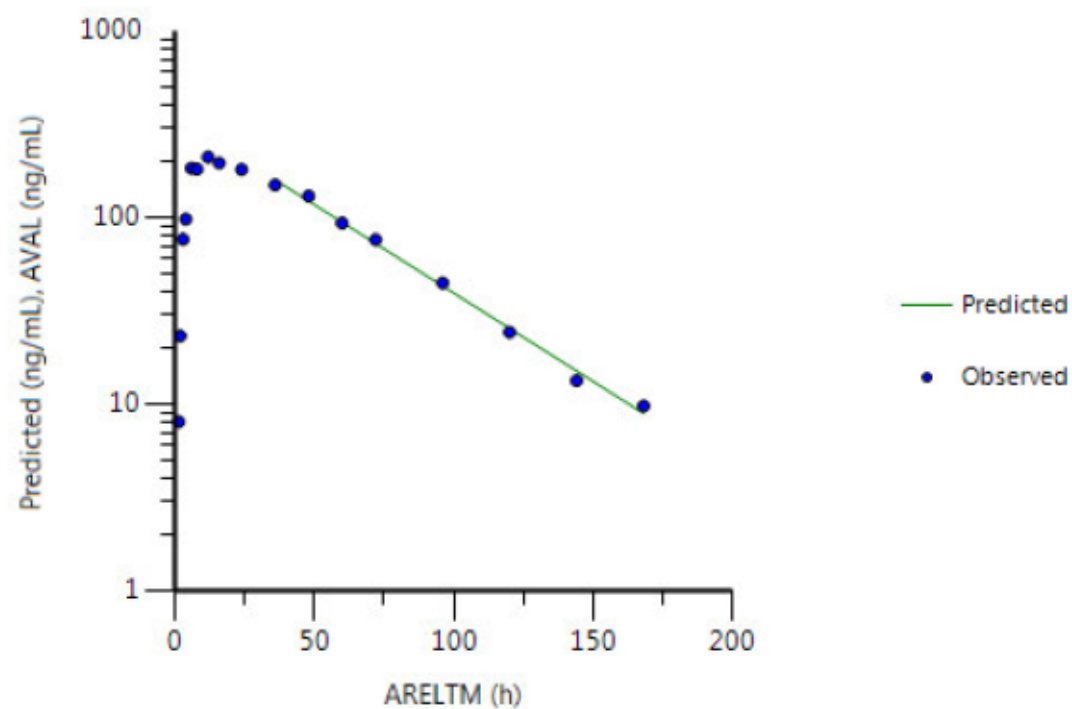
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9988 Rsquared_adjusted=0.9986 HL_Lambda_z=36.6333
8 points used in calculation



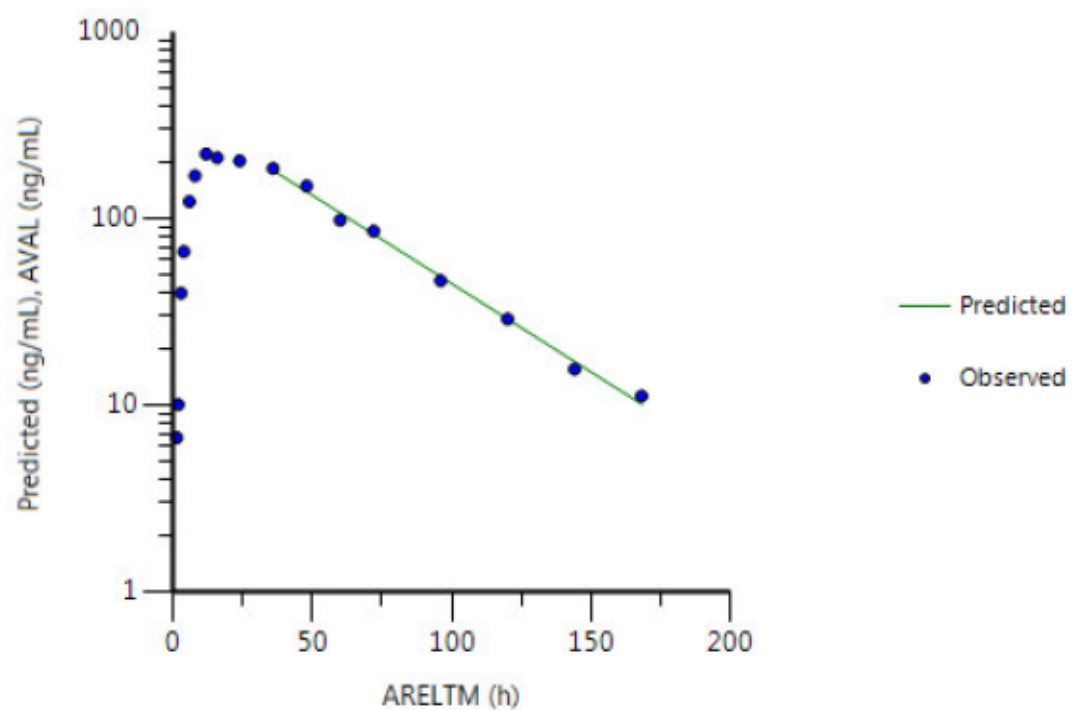
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9999 Rsquared_adjusted=0.9998 HL_Lambda_z=33.7833
3 points used in calculation



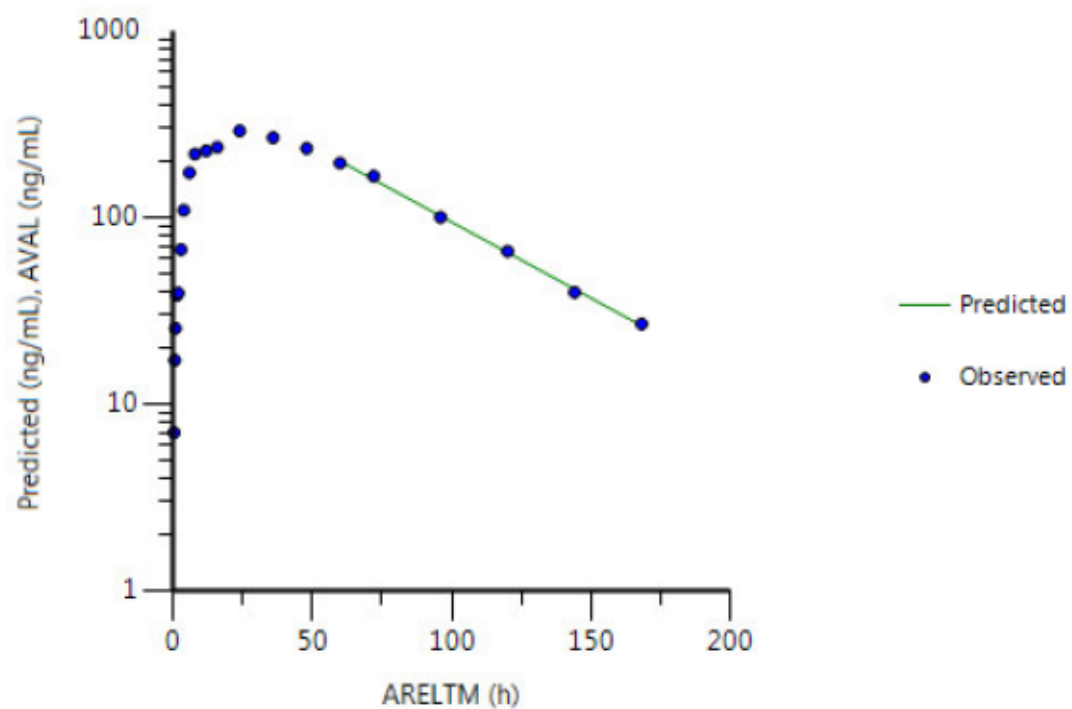
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9952 Rsquared_adjusted=0.9944 HL_Lambda_z=31.792
8 points used in calculation



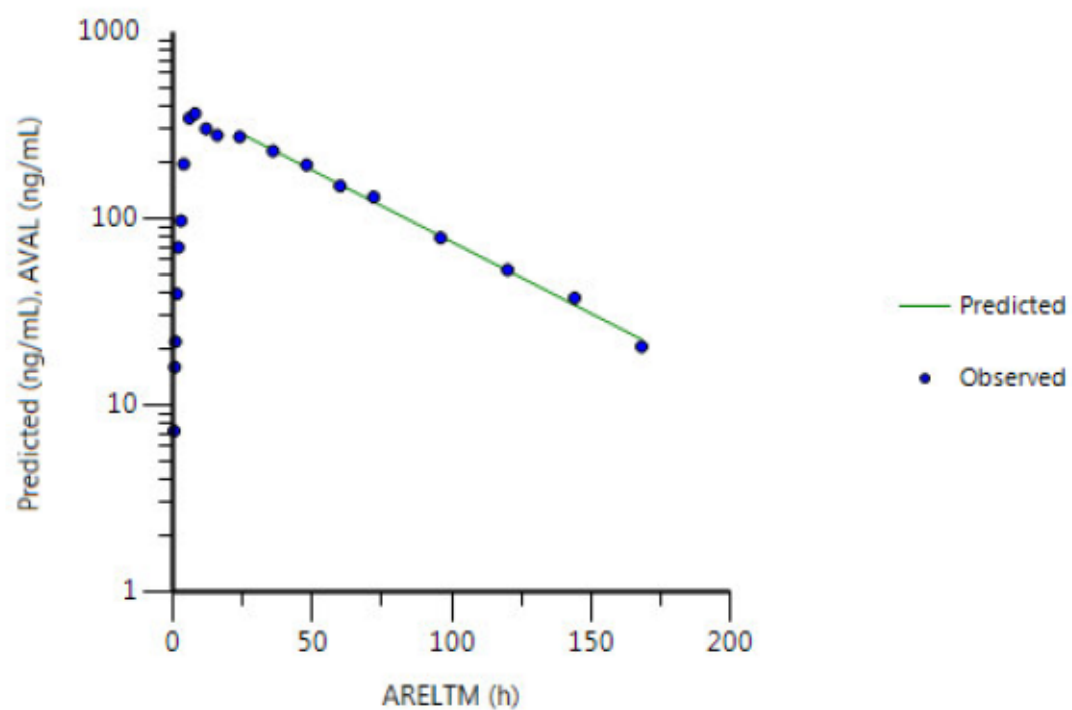
PARAMCD=TEPO, SUBJID=PI, APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9953 Rsquared_adjusted=0.9945 HL_Lambda_z=31.7958
8 points used in calculation



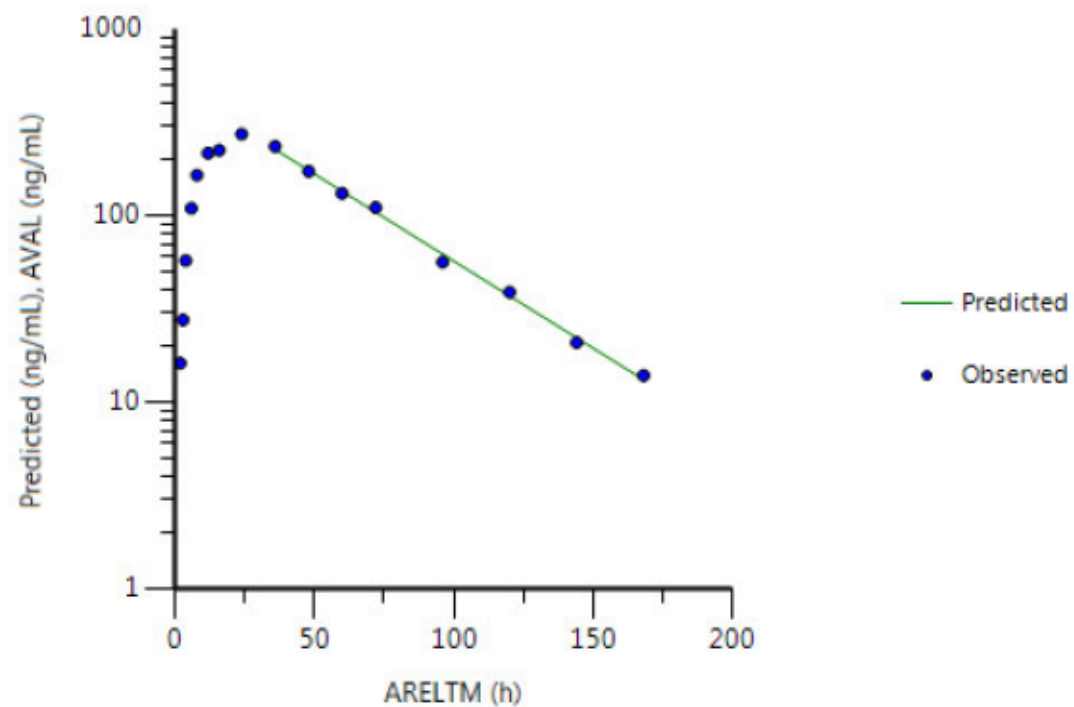
PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9985 Rsquared_adjusted=0.9981 HL_Lambda_z=36.9336
6 points used in calculation



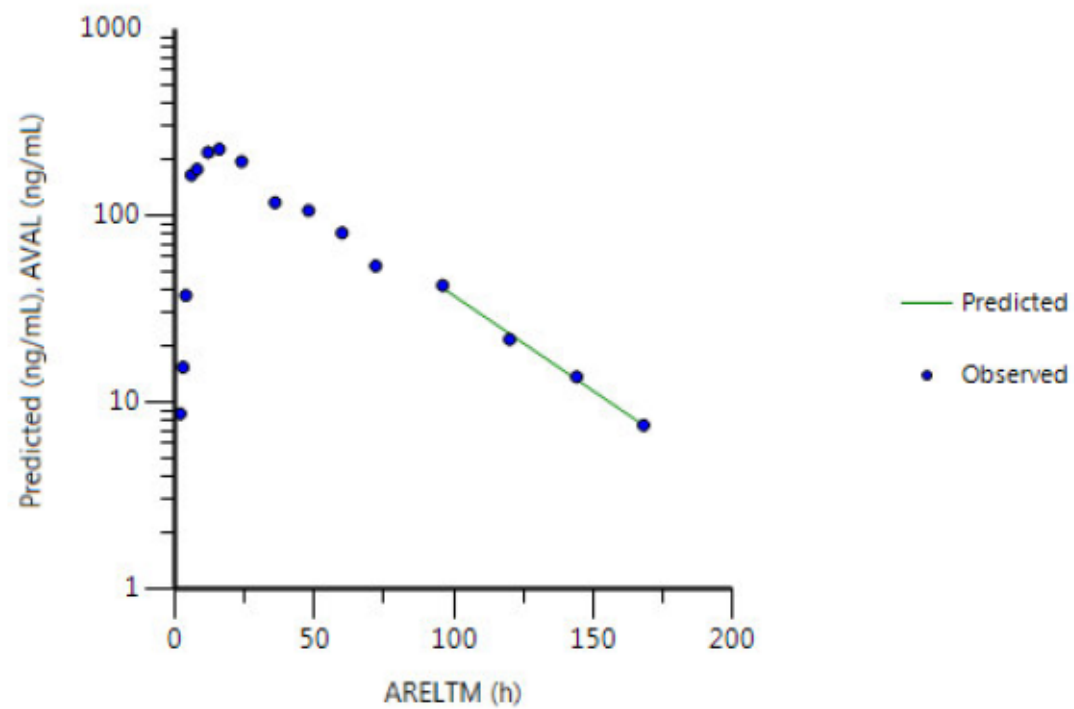
PARAMCD=TEPO, SUBJID=PI, APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9964 Rsquared_adjusted=0.9958 HL_Lambda_z=39.2372
9 points used in calculation



PARAMCD=TEPO, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9968 Rsquared_adjusted=0.9963 HL_Lambda_z=32.2501
8 points used in calculation



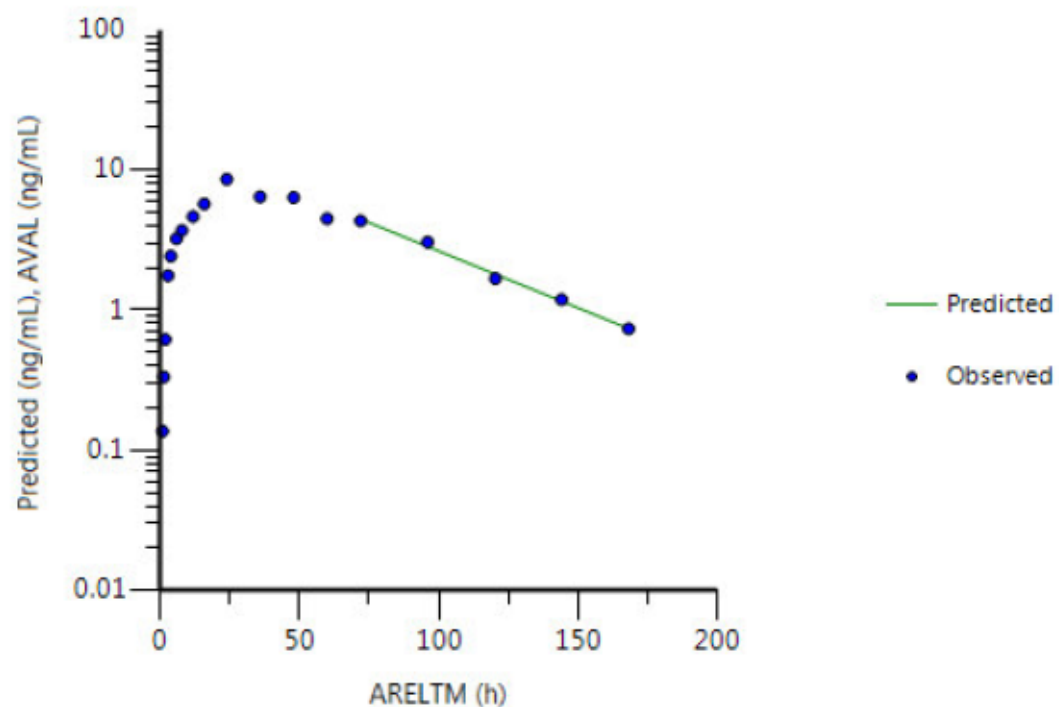
PARAMCD=TEPO, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9956 Rsquared_adjusted=0.9934 HL_Lambda_z=29.5663
4 points used in calculation



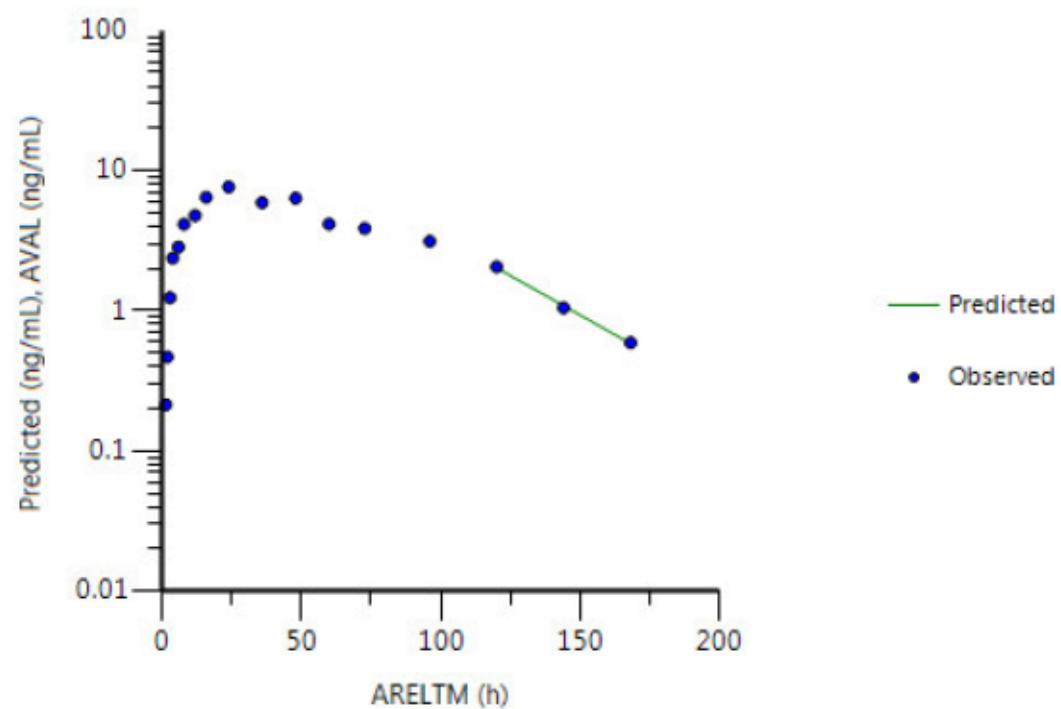
WinNonlin Plots - Tepotinib Metabolite MSC2571107A

PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3

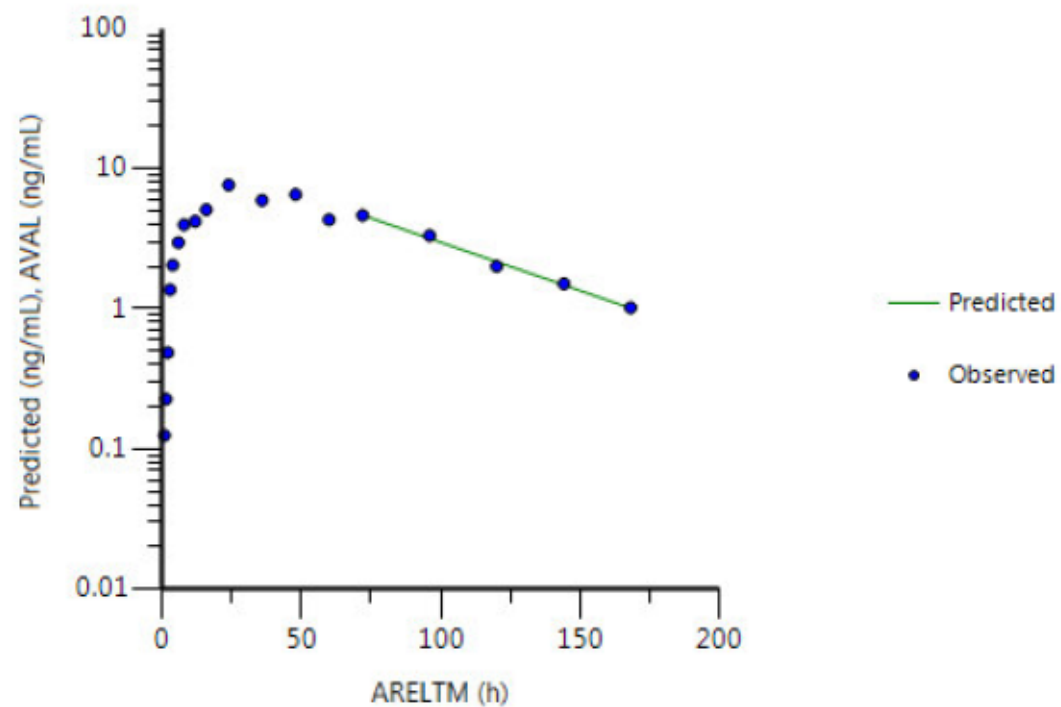
Rsquared=0.994 Rsquared_adjusted=0.992 HL_Lambda_z=37.0548
5 points used in calculation



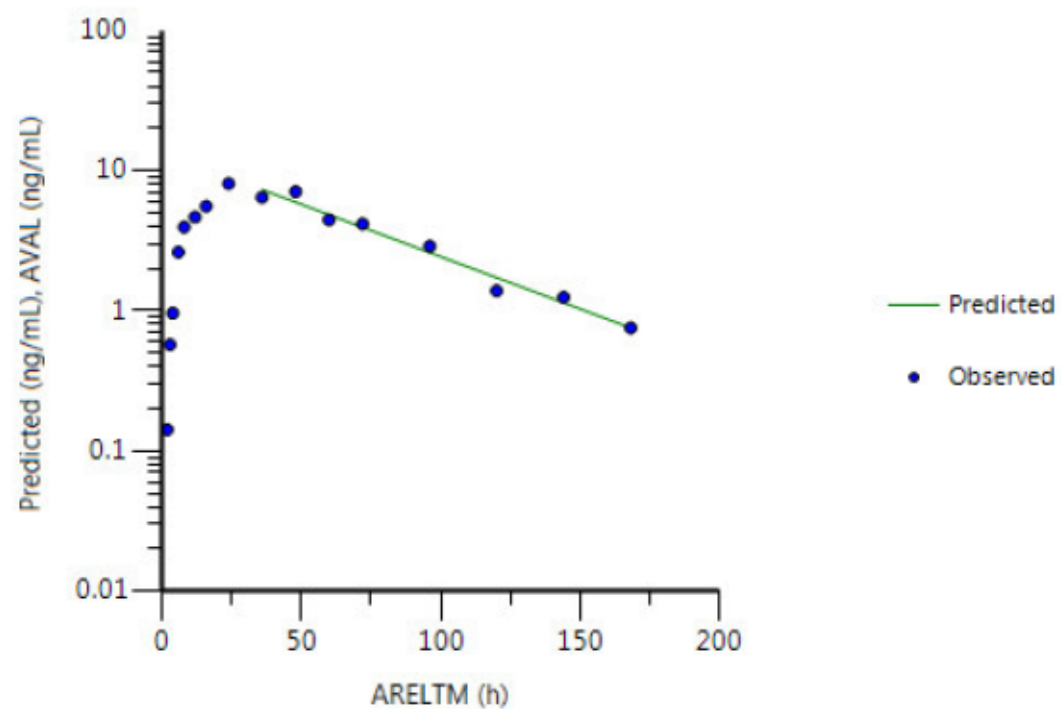
PARAMCD=M7A, SUBJID=PI, APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9977 Rsquared_adjusted=0.9955 HL_Lambda_z=26.718
3 points used in calculation



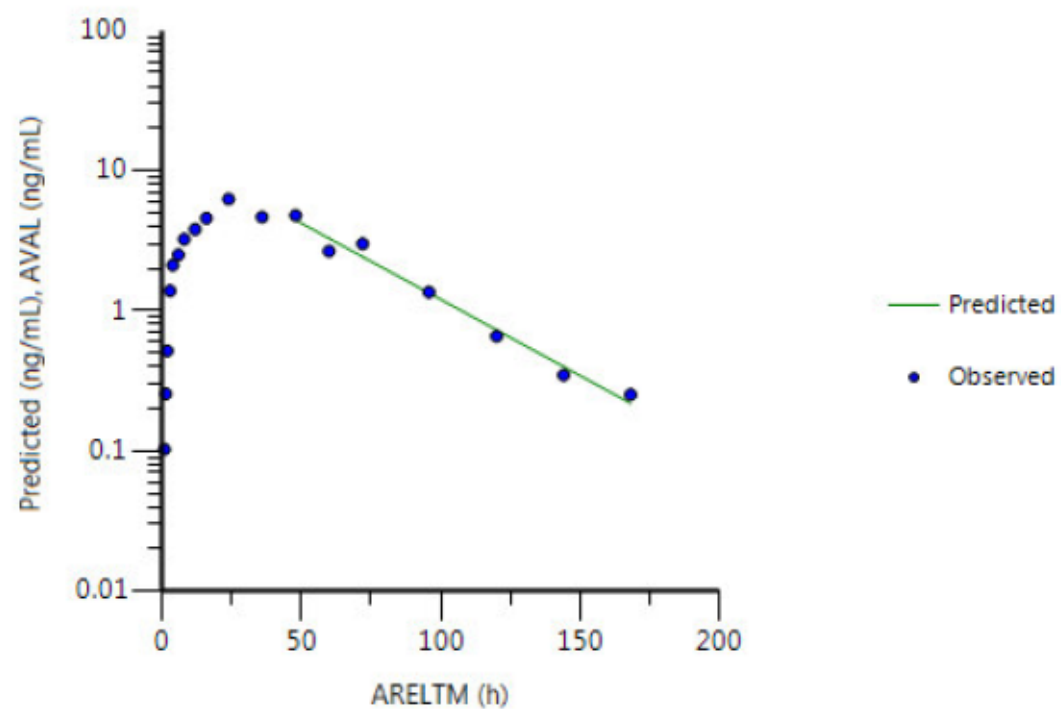
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9942 Rsquared_adjusted=0.9922 HL_Lambda_z=43.5572
5 points used in calculation



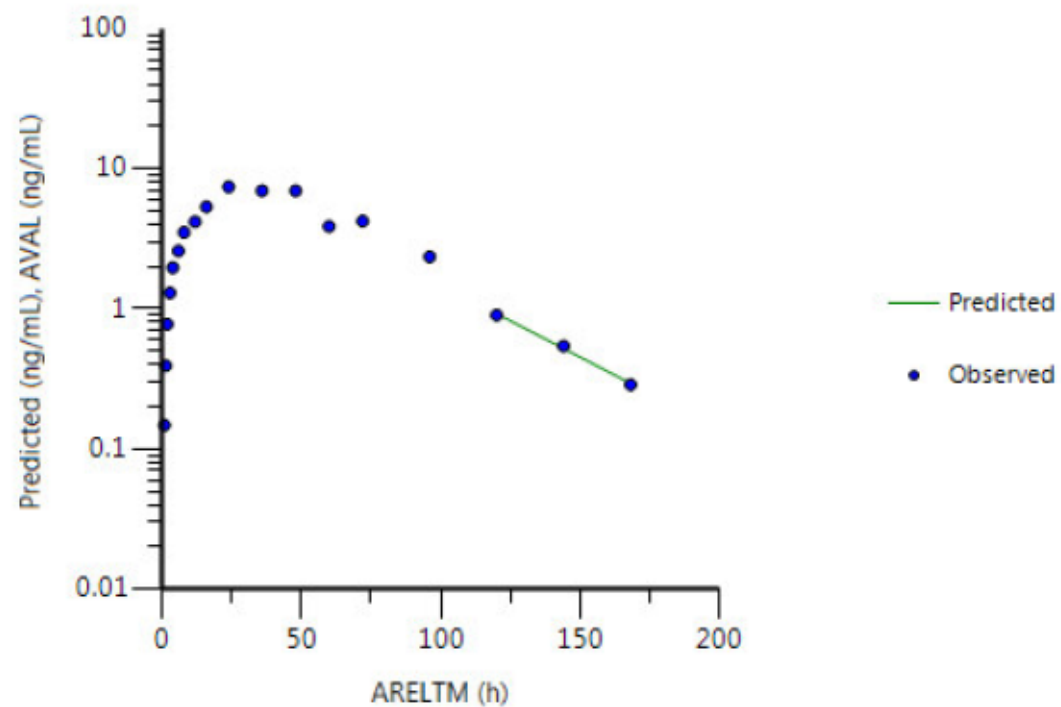
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9744 Rsquared_adjusted=0.9701 HL_Lambda_z=40.3139
8 points used in calculation



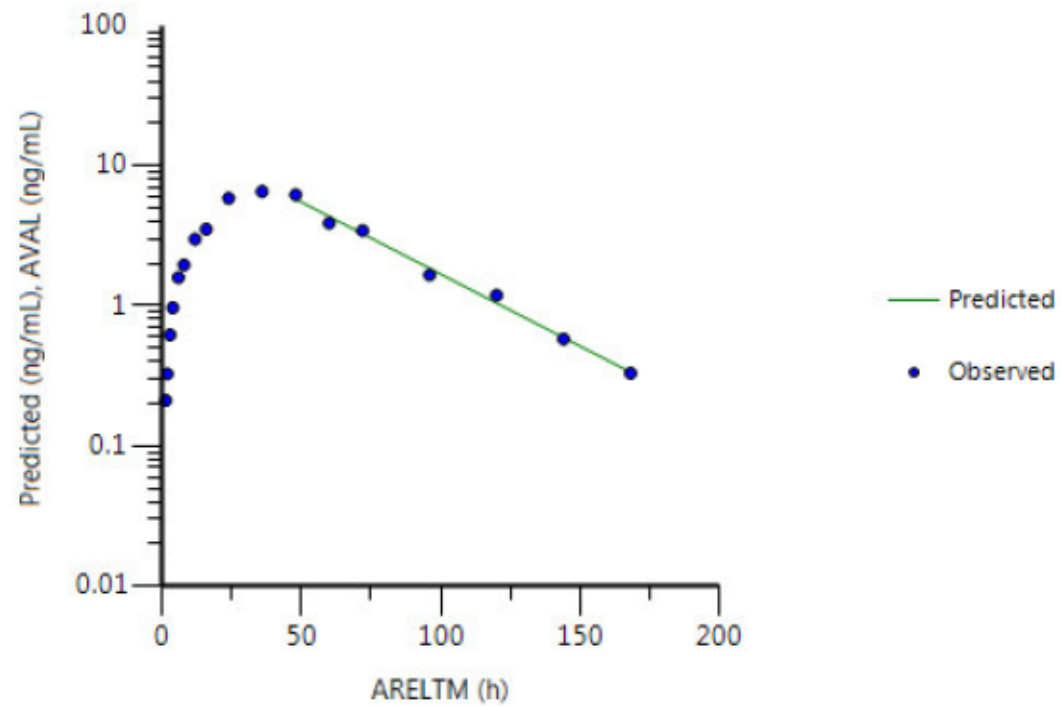
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.981 Rsquared_adjusted=0.9772 HL_Lambda_z=27.6541
7 points used in calculation



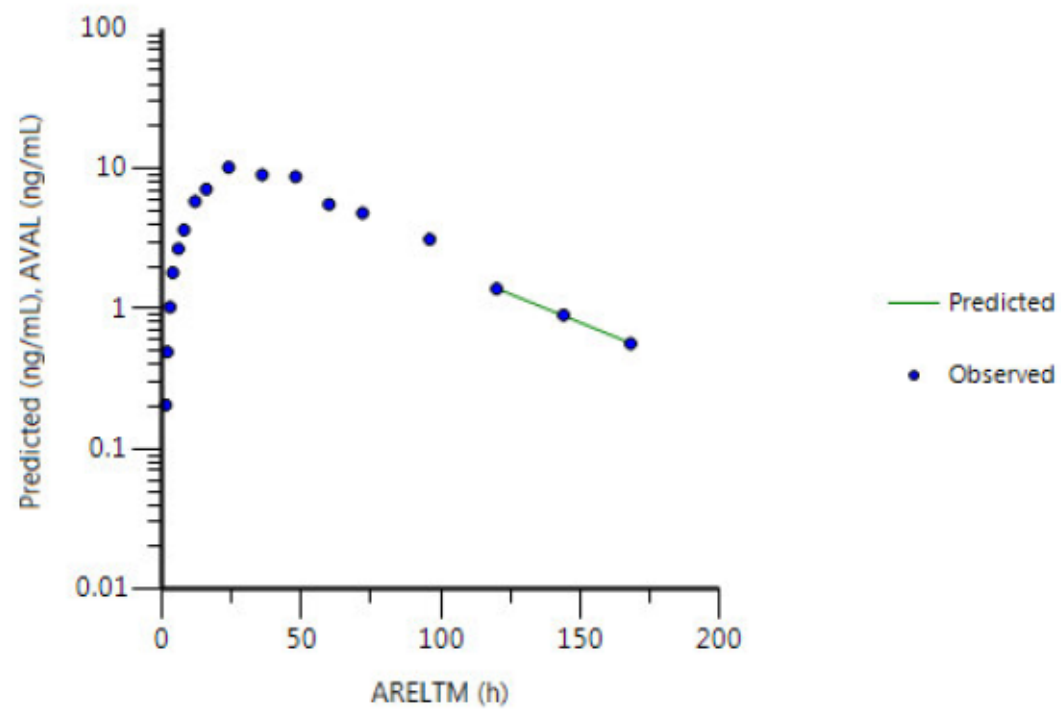
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9959 Rsquared_adjusted=0.9918 HL_Lambda_z=29.1258
3 points used in calculation



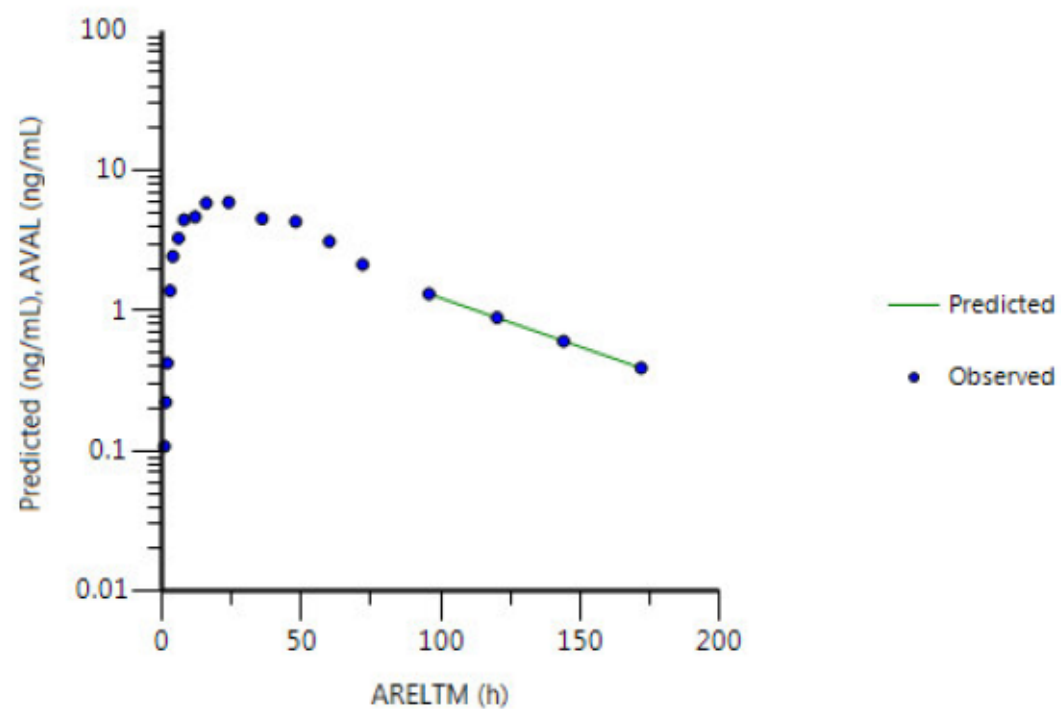
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9929 Rsquared_adjusted=0.9915 HL_Lambda_z=29.2614
7 points used in calculation



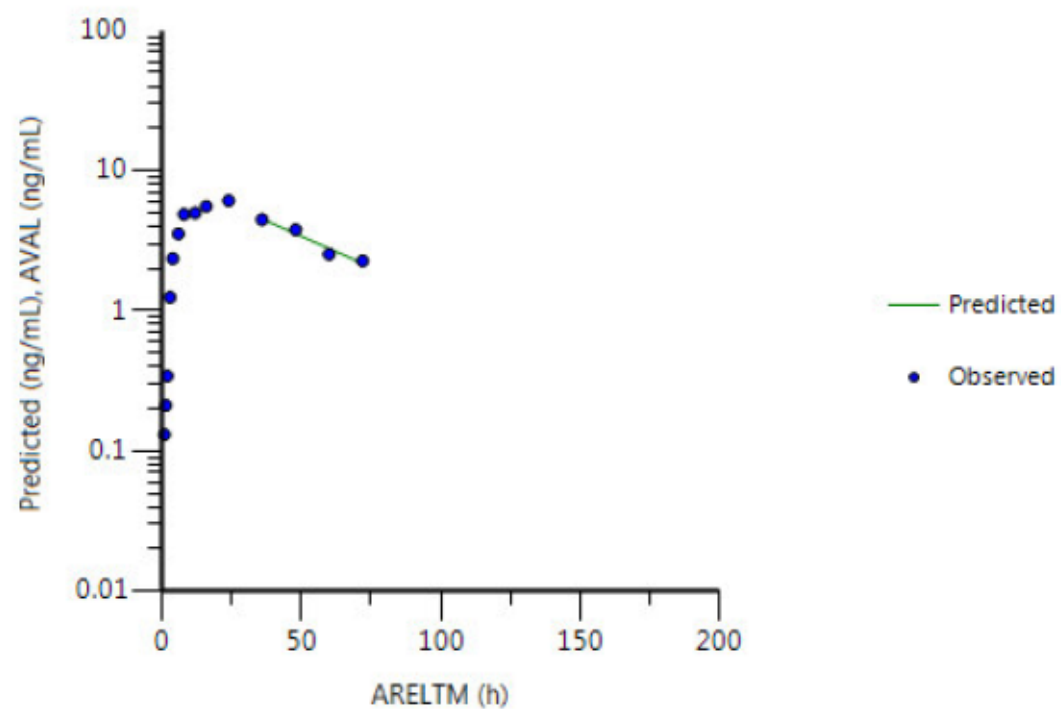
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9994 Rsquared_adjusted=0.9988 HL_Lambda_z=36.9583
3 points used in calculation



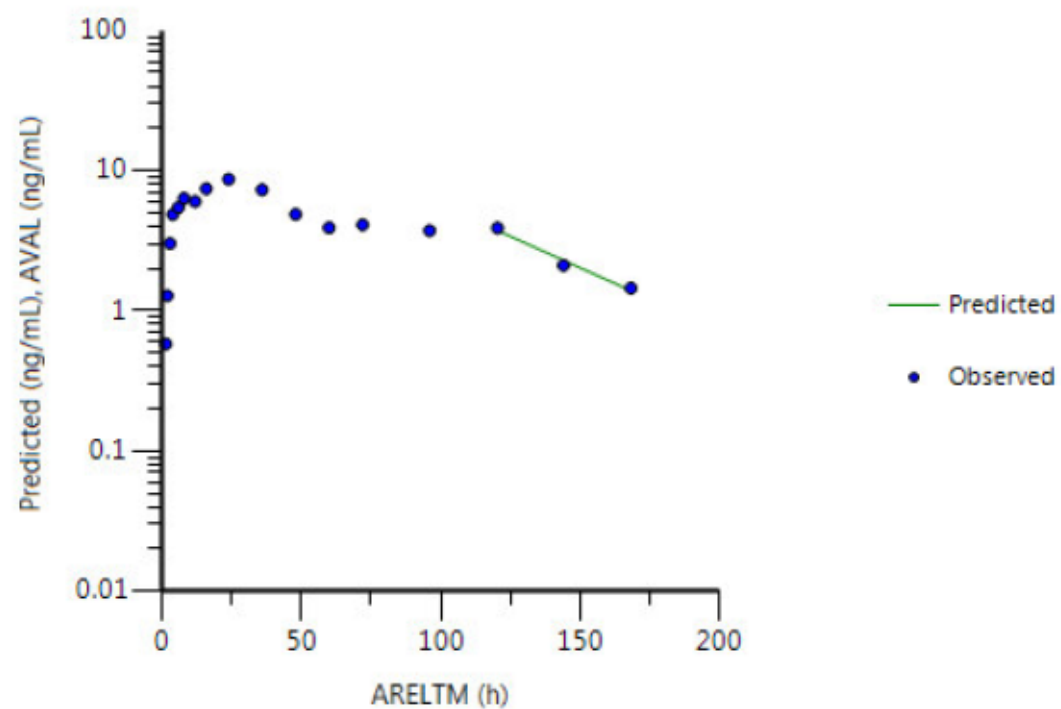
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=1.0 Rsquared_adjusted=1.0 HL_Lambda_z=43.2657
4 points used in calculation



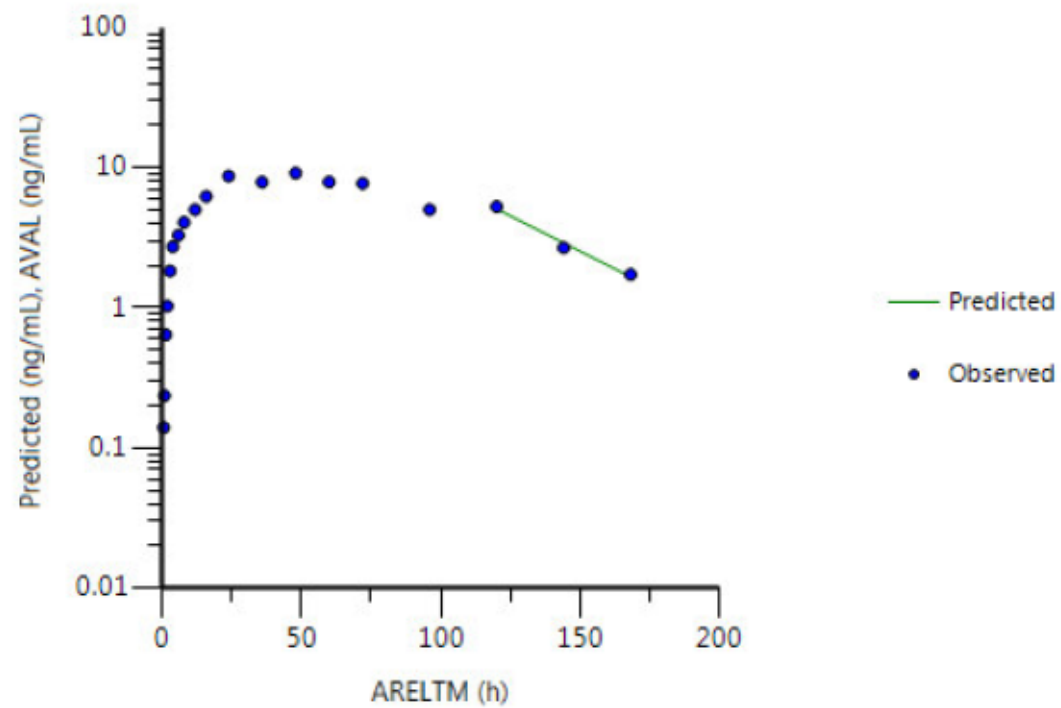
PARAMCD=M7A, SUBJID=PI, APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9516 Rsquared_adjusted=0.9274 HL_Lambda_z=34.1316
4 points used in calculation



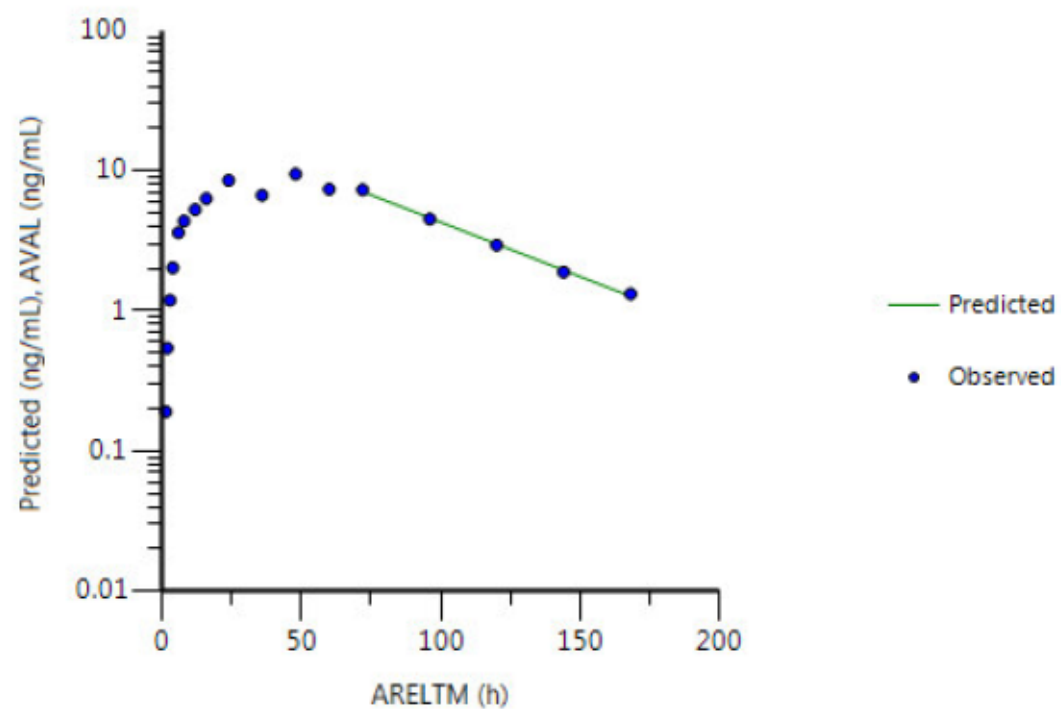
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9793 Rsquared_adjusted=0.9586 HL_Lambda_z=33.5377
3 points used in calculation



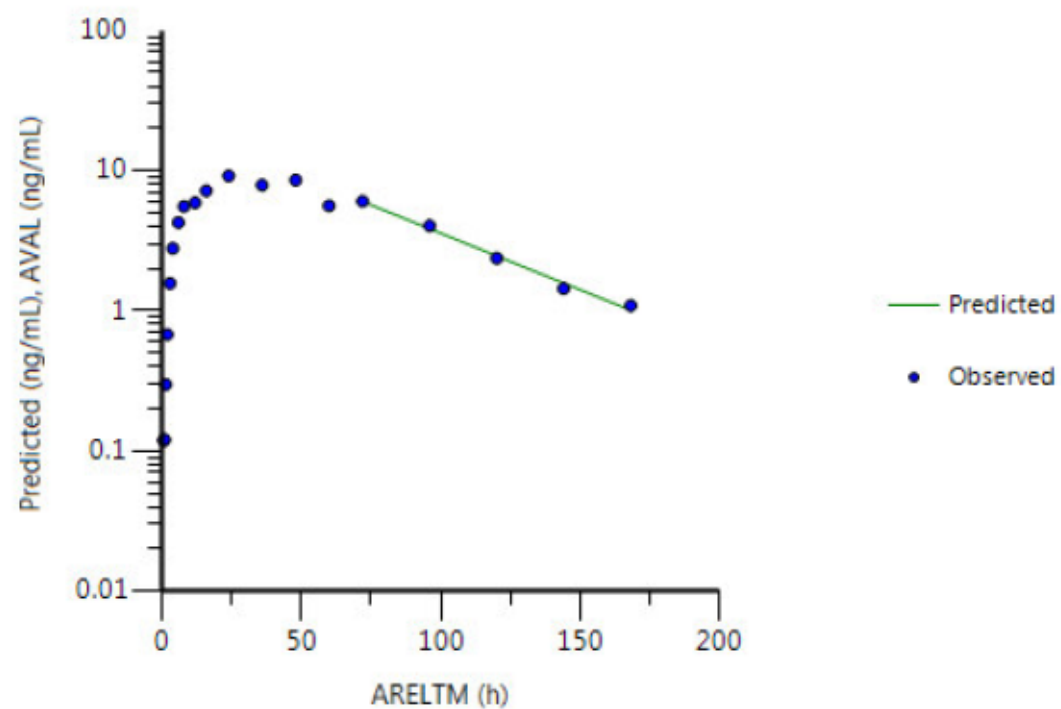
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsqu=0.9853 Rsqu_adjusted=0.9707 HL_Lambda_z=29.8629
3 points used in calculation



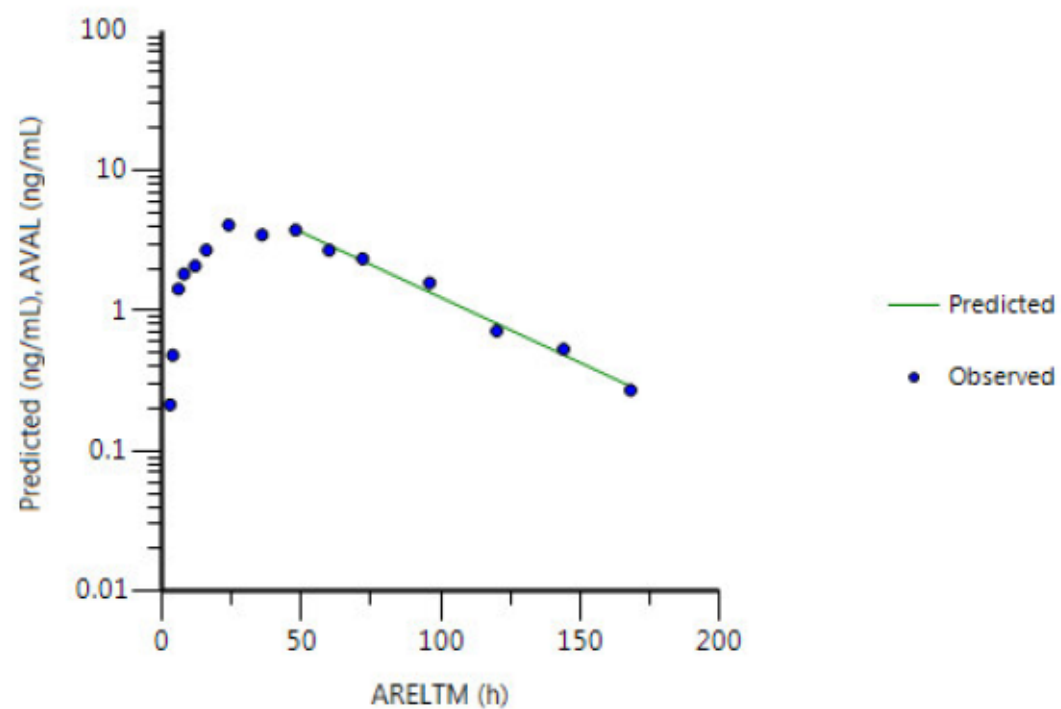
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9977 Rsquared_adjusted=0.997 HL_Lambda_z=38.75
5 points used in calculation



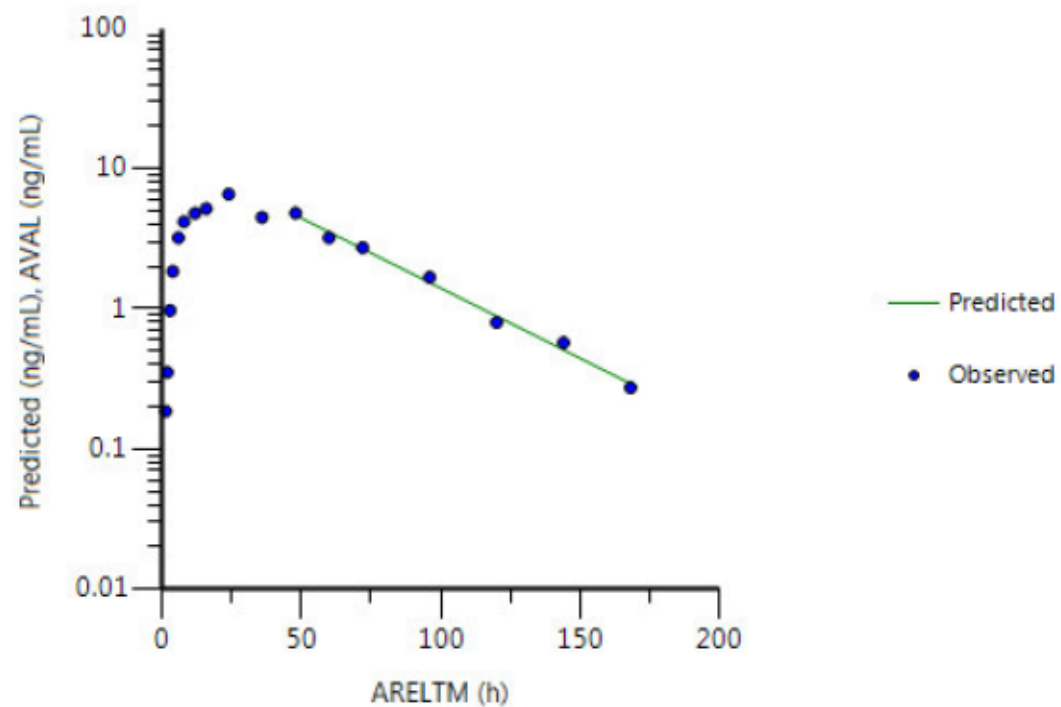
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.991 Rsquared_adjusted=0.9879 HL_Lambda_z=37.3489
5 points used in calculation



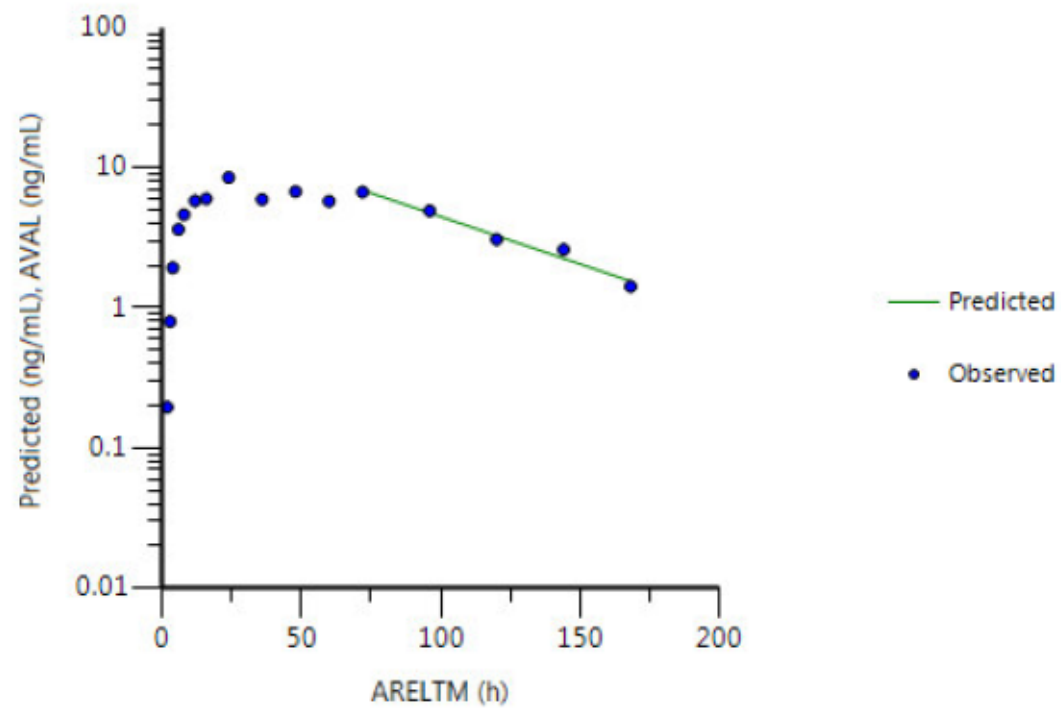
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9895 Rsquared_adjusted=0.9873 HL_Lambda_z=32.274
7 points used in calculation



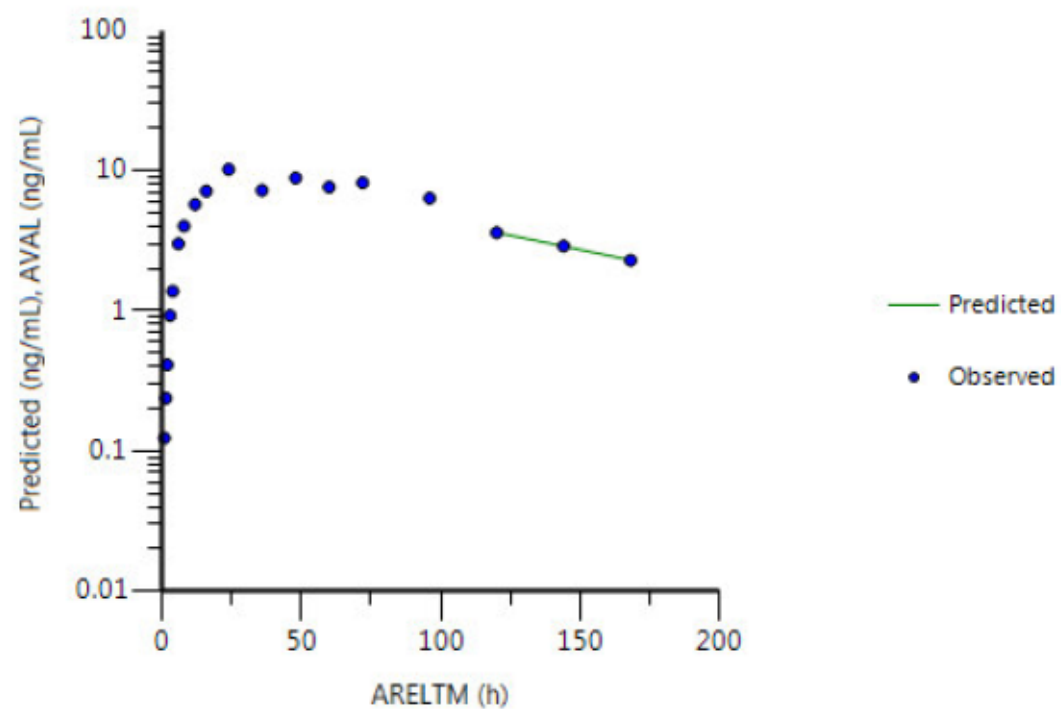
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9927 Rsquared_adjusted=0.9912 HL_Lambda_z=30.0508
7 points used in calculation



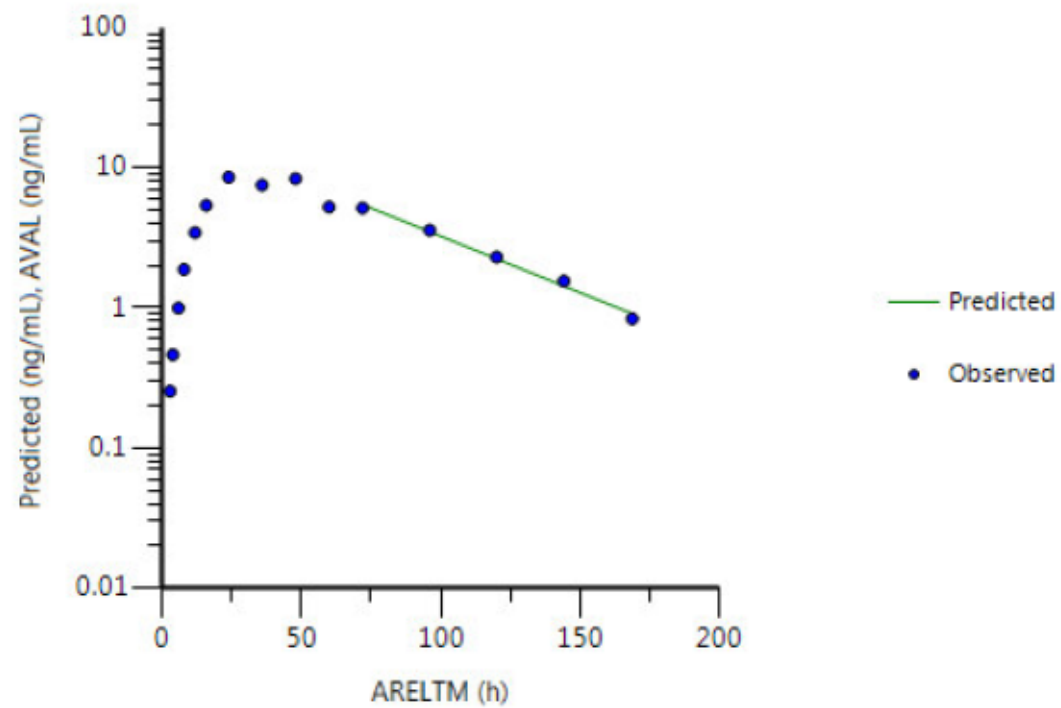
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.976 Rsquared_adjusted=0.9679 HL_Lambda_z=44.4717
5 points used in calculation



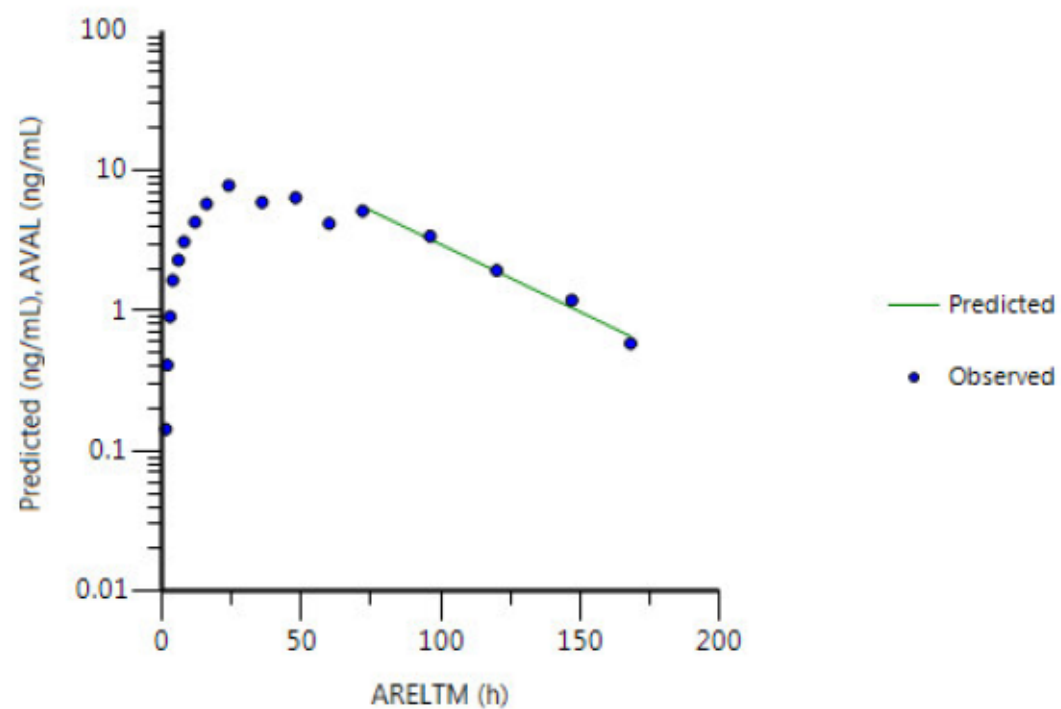
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9995 Rsquared_adjusted=0.9991 HL_Lambda_z=73.0982
3 points used in calculation



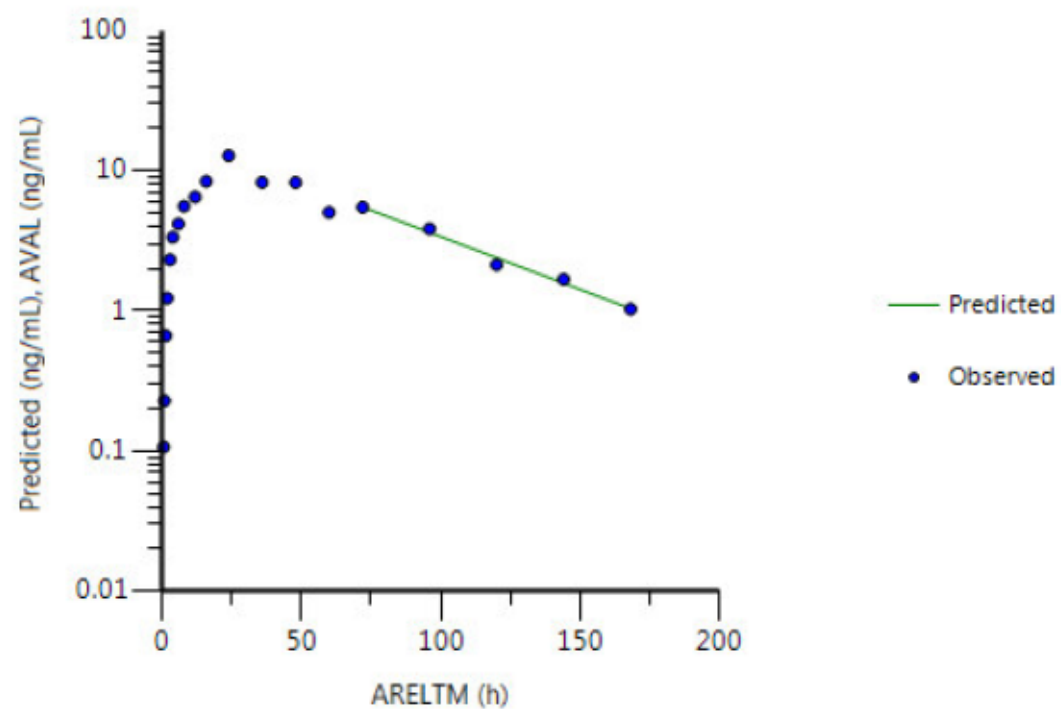
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9911 Rsquared_adjusted=0.9881 HL_Lambda_z=37.3639
5 points used in calculation



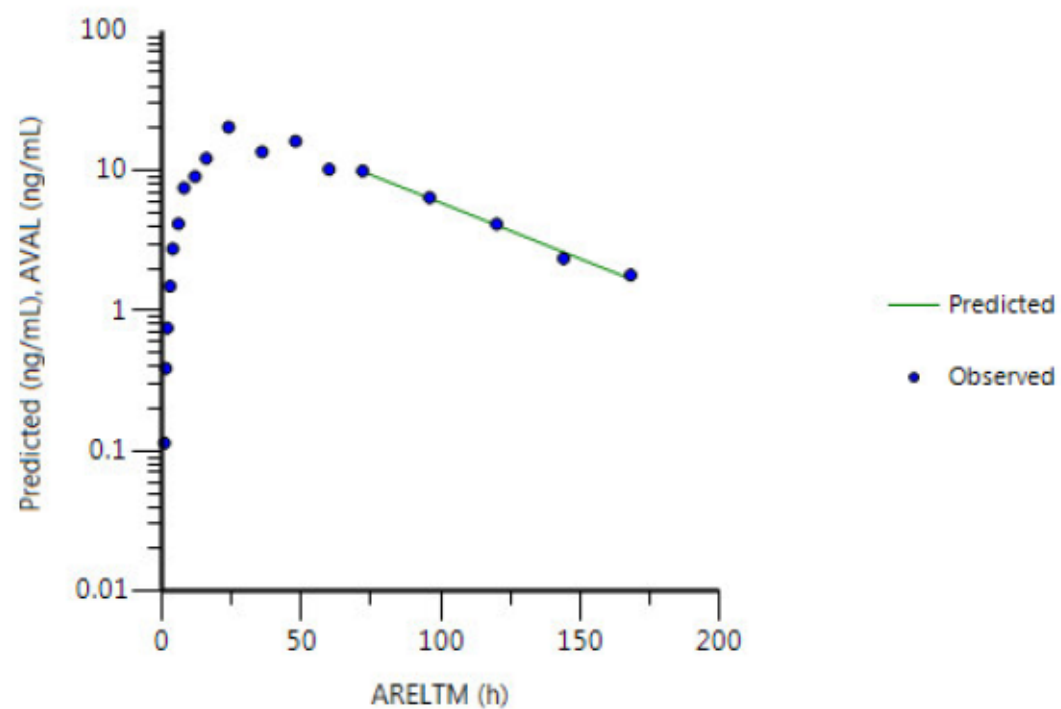
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9872 Rsquared_adjusted=0.9829 HL_Lambda_z=31.2343
5 points used in calculation



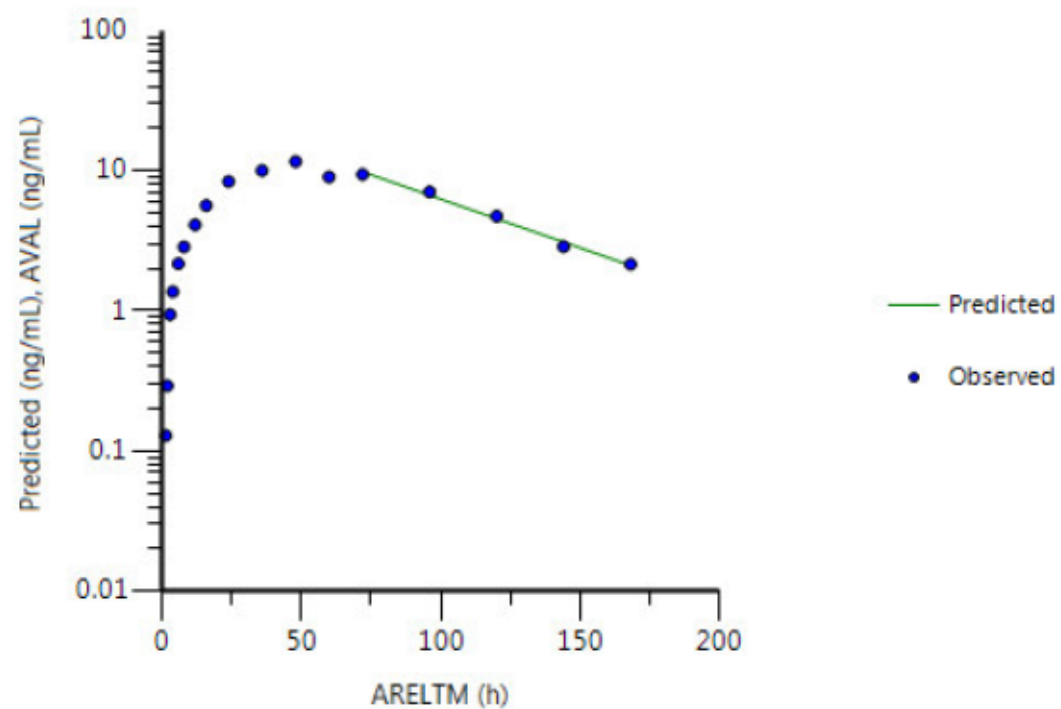
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9882 Rsquared_adjusted=0.9843 HL_Lambda_z=39.8956
5 points used in calculation



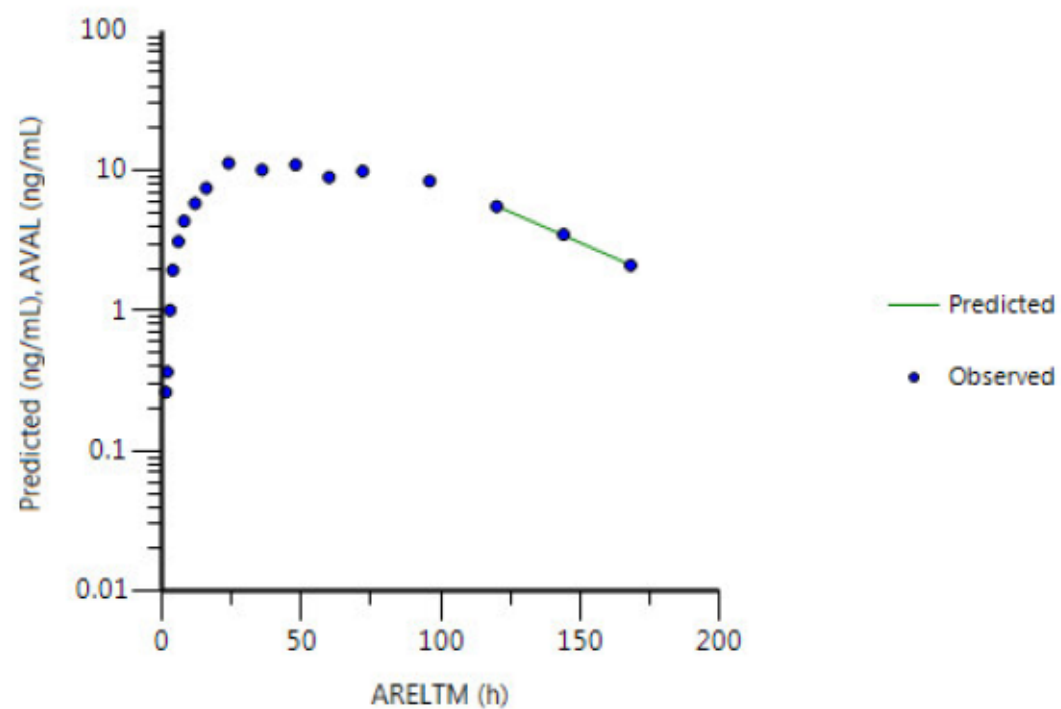
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9919 Rsquared_adjusted=0.9892 HL_Lambda_z=37.6646
5 points used in calculation



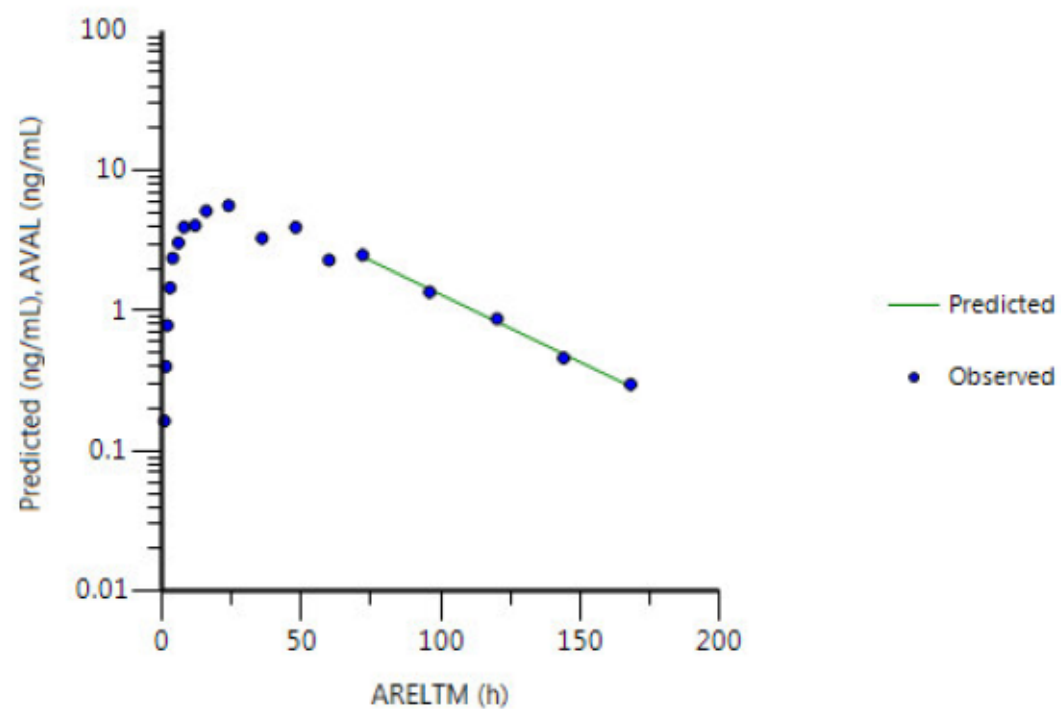
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9915 Rsquared_adjusted=0.9887 HL_Lambda_z=43.266
5 points used in calculation



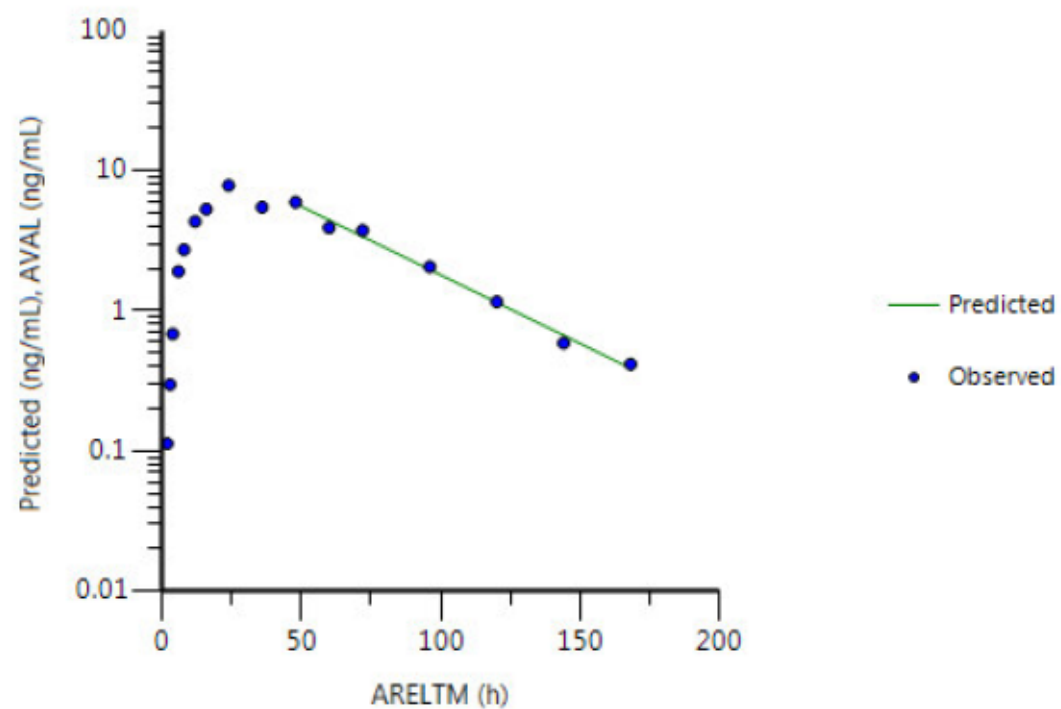
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9993 Rsquared_adjusted=0.9986 HL_Lambda_z=34.4026
3 points used in calculation



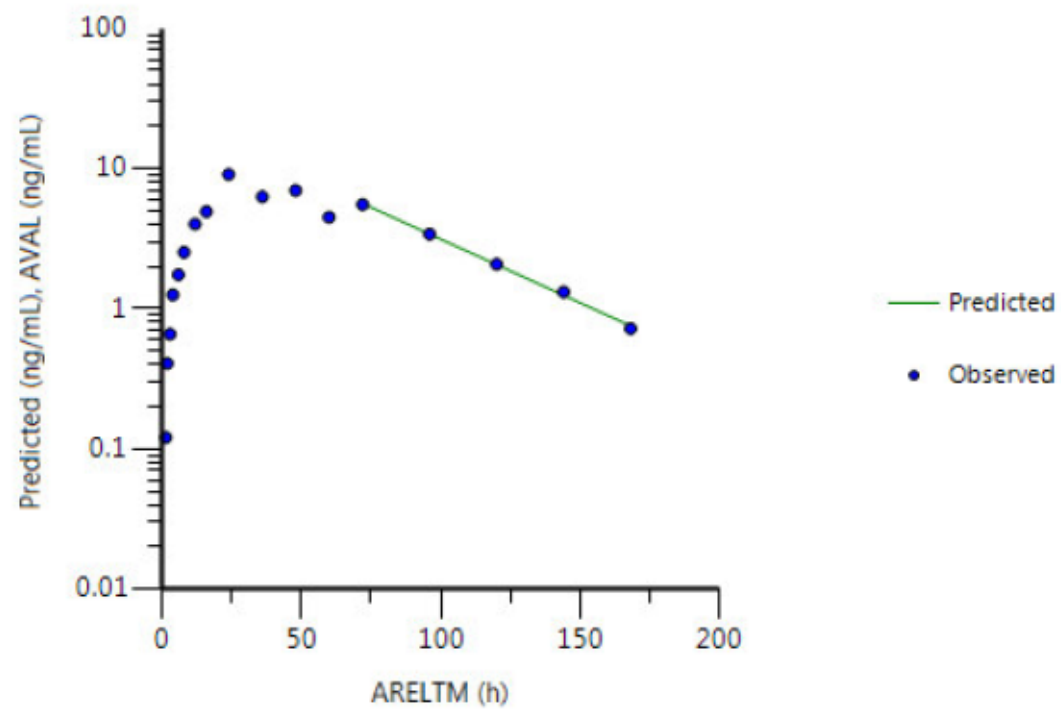
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9962 Rsquared_adjusted=0.9949 HL_Lambda_z=31.2185
5 points used in calculation



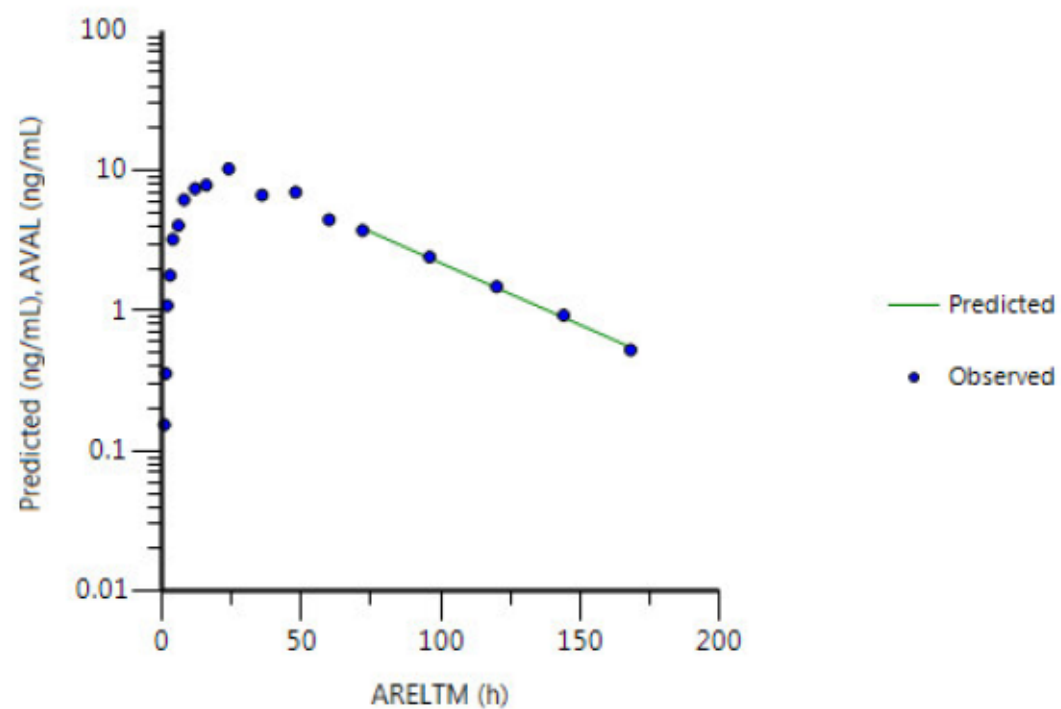
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.992 Rsquared_adjusted=0.9903 HL_Lambda_z=30.7528
7 points used in calculation



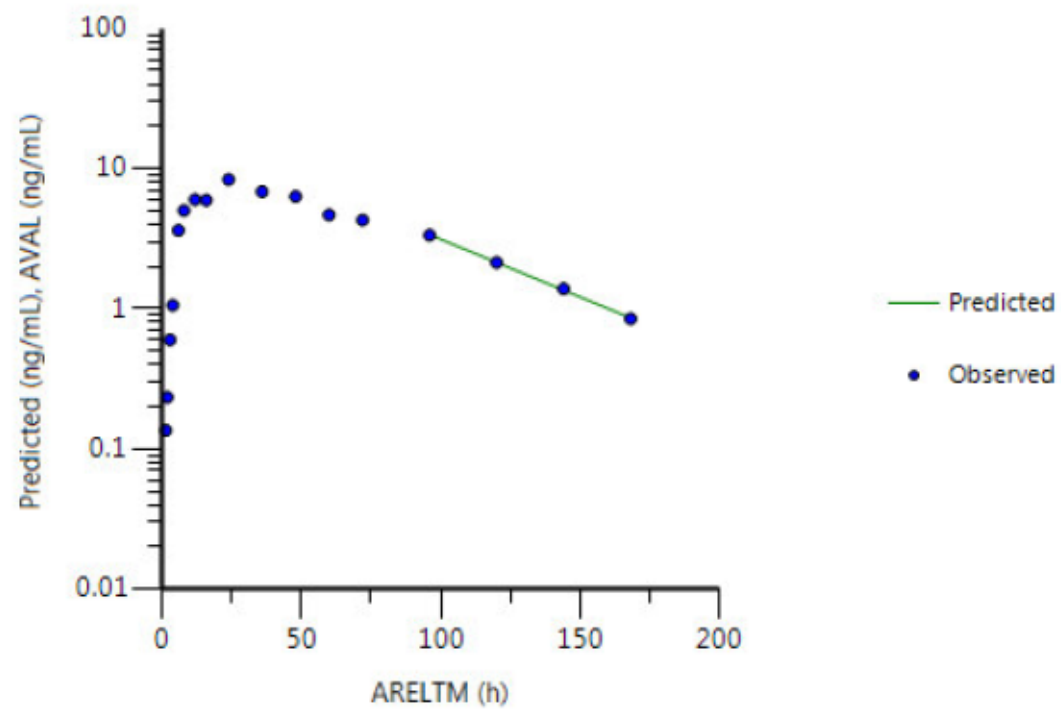
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9979 Rsquared_adjusted=0.9972 HL_Lambda_z=33.1269
5 points used in calculation



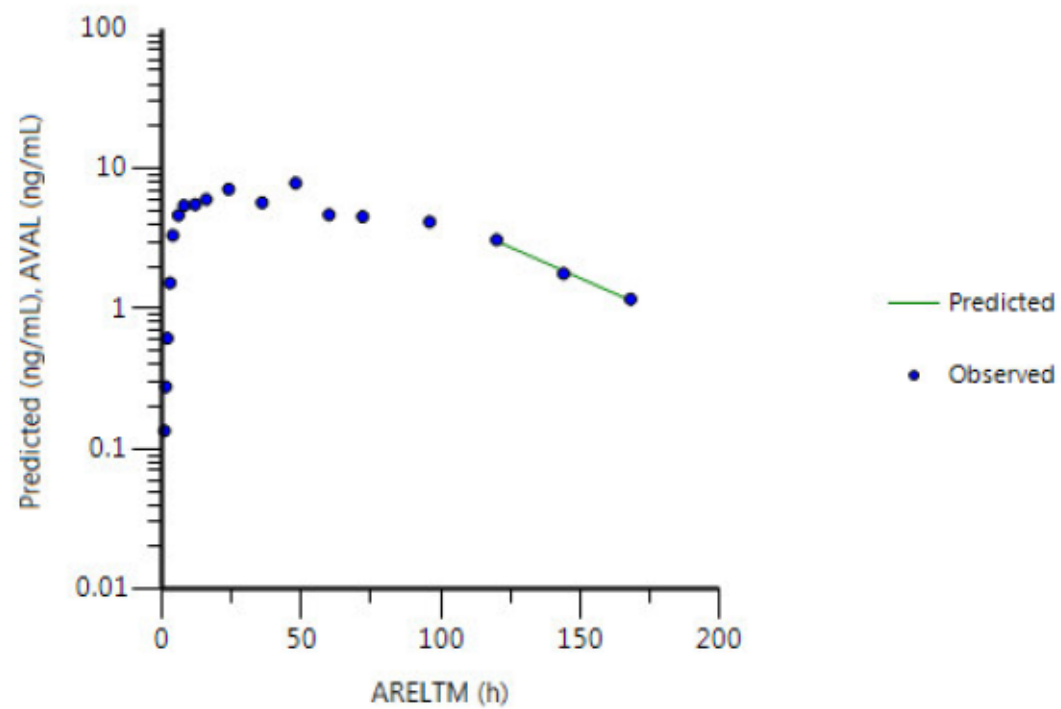
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9979 Rsquared_adjusted=0.9972 HL_Lambda_z=34.0485
5 points used in calculation



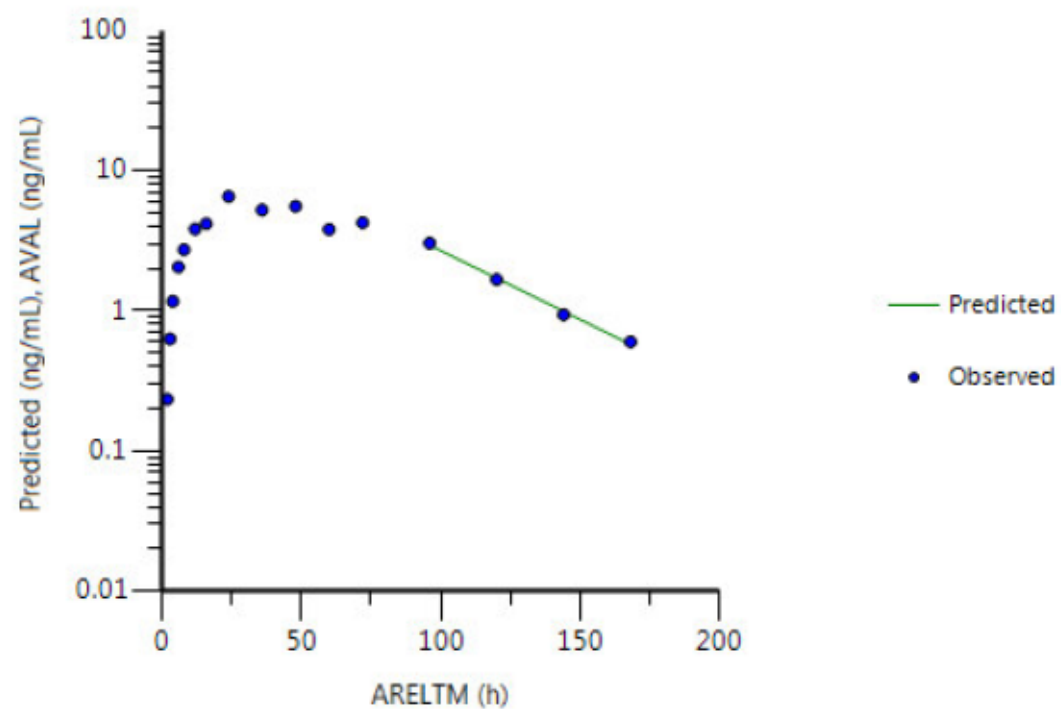
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9992 Rsquared_adjusted=0.9988 HL_Lambda_z=36.5659
4 points used in calculation



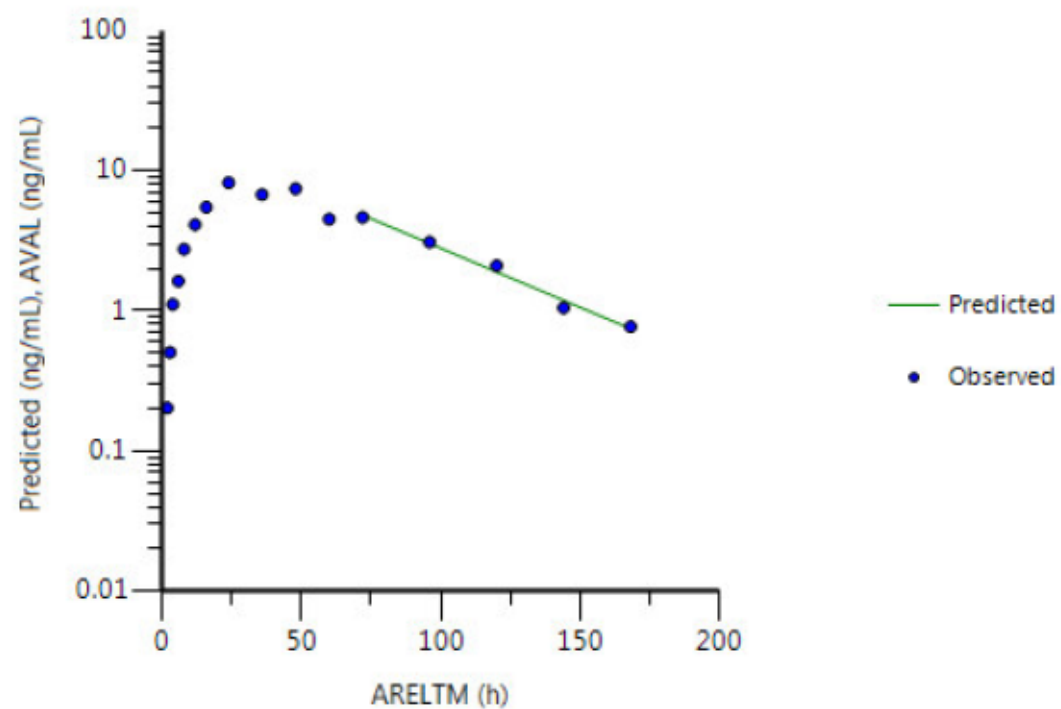
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9933 Rsquared_adjusted=0.9867 HL_Lambda_z=34.0215
3 points used in calculation



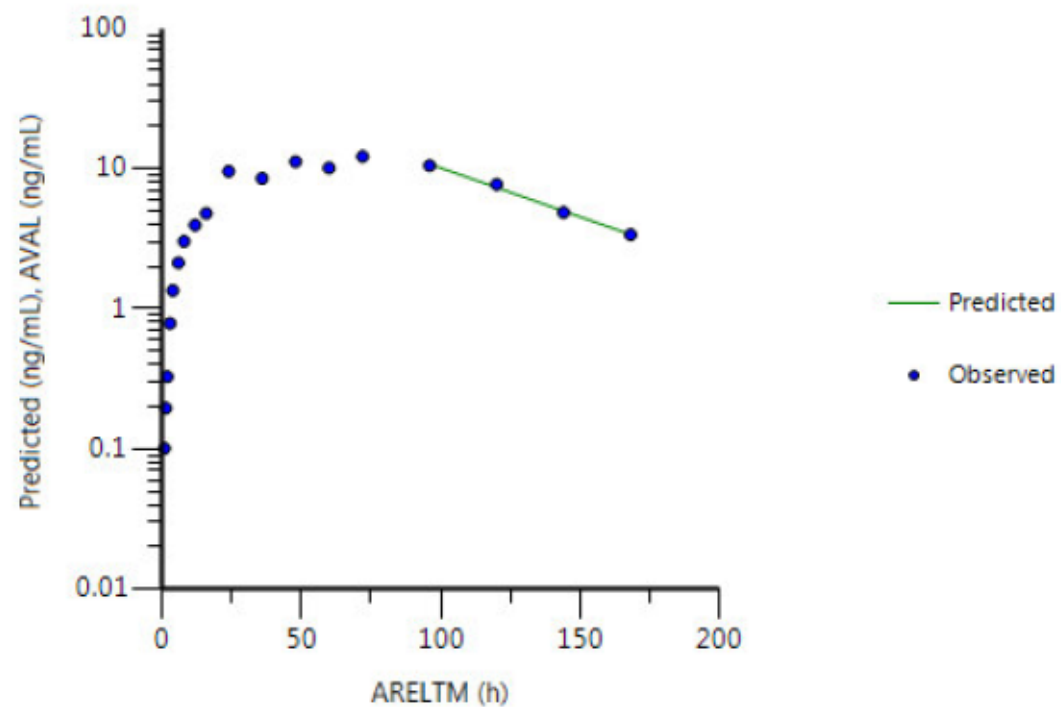
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9957 Rsquared_adjusted=0.9935 HL_Lambda_z=30.5867
4 points used in calculation



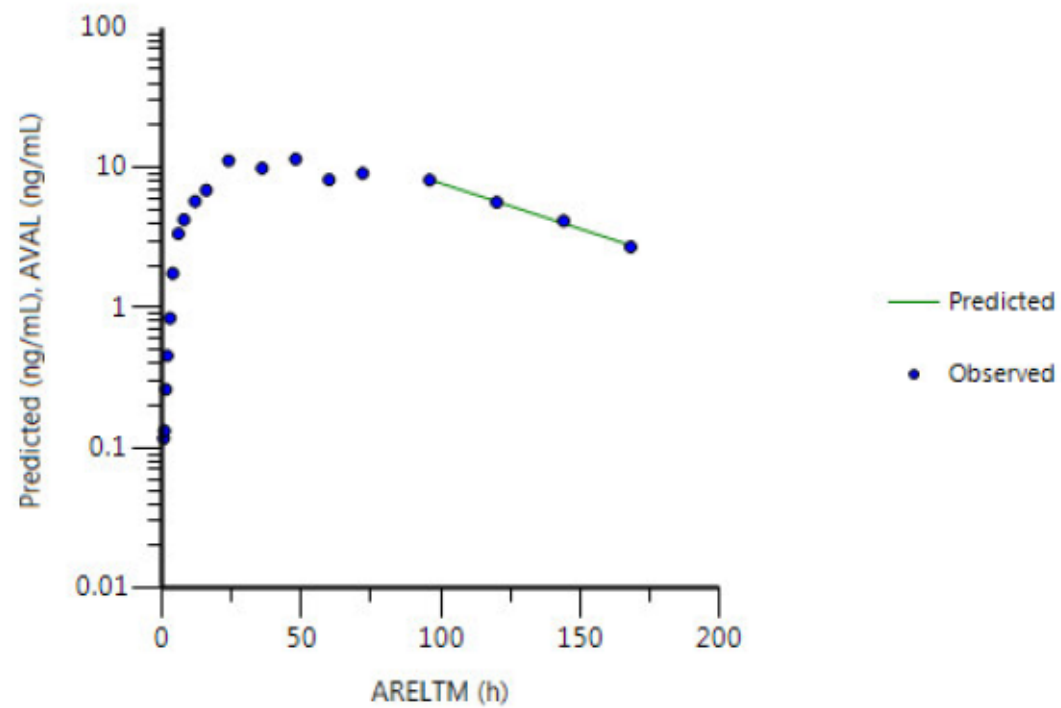
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9869 Rsquared_adjusted=0.9825 HL_Lambda_z=35.6302
5 points used in calculation



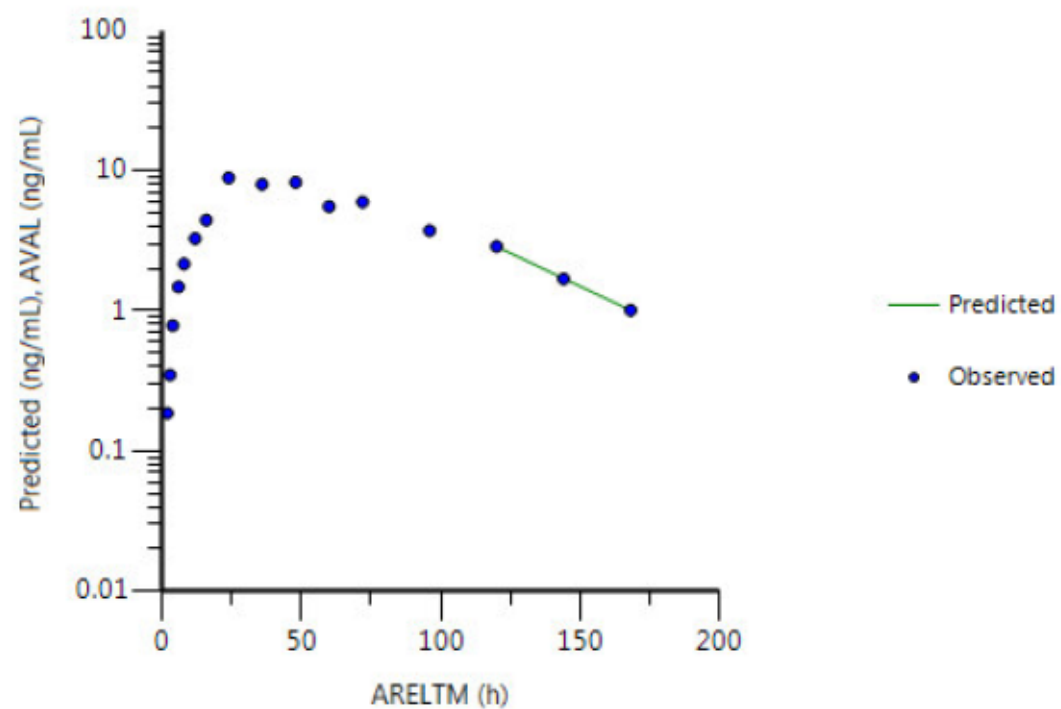
PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9946 Rsquared_adjusted=0.992 HL_Lambda_z=43.0607
4 points used in calculation



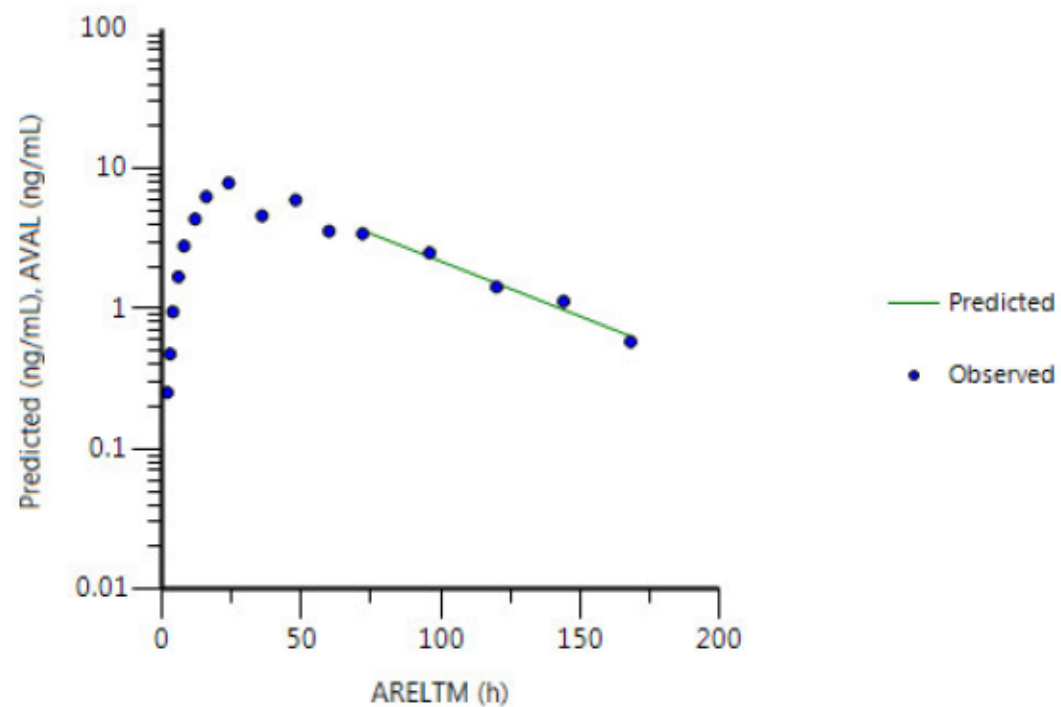
PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9959 Rsquared_adjusted=0.9939 HL_Lambda_z=46.2438
4 points used in calculation



PARAMCD=M7A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9999 Rsquared_adjusted=0.9998 HL_Lambda_z=31.752
3 points used in calculation

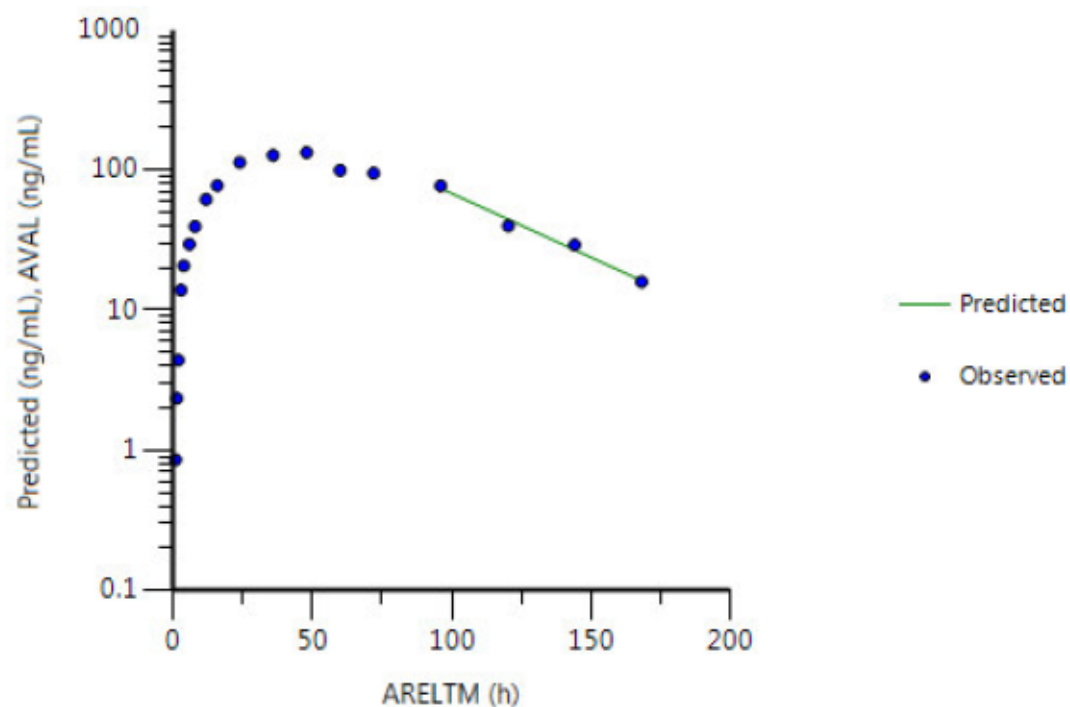


PARAMCD=M7A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.98 Rsquared_adjusted=0.9733 HL_Lambda_z=38.28
5 points used in calculation

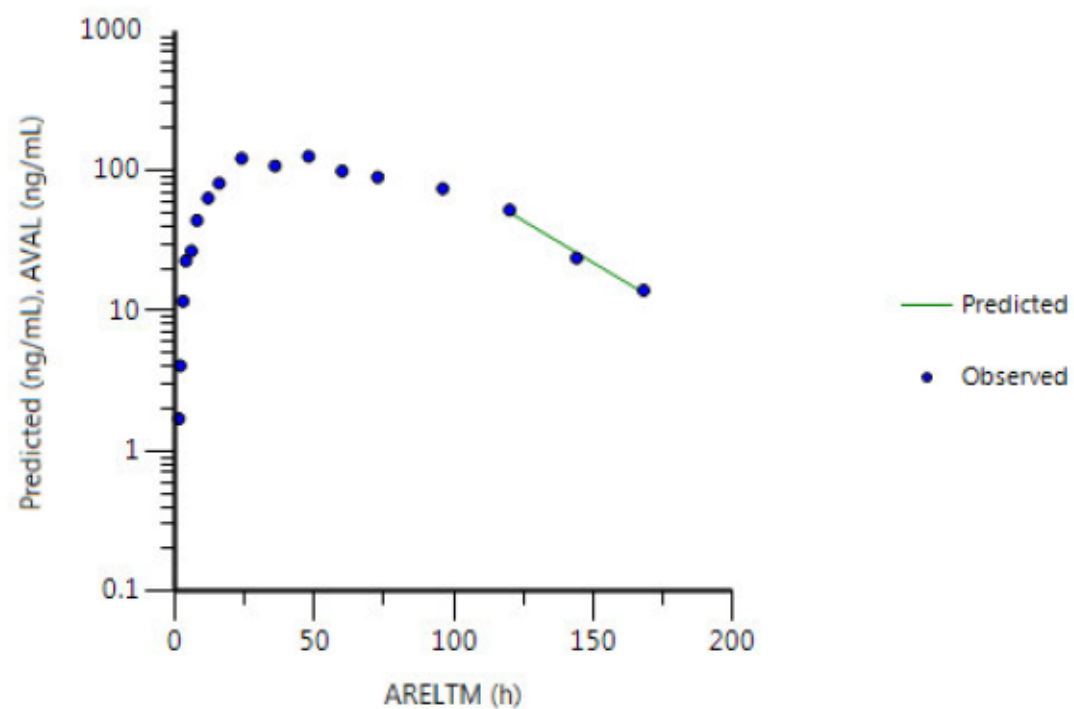


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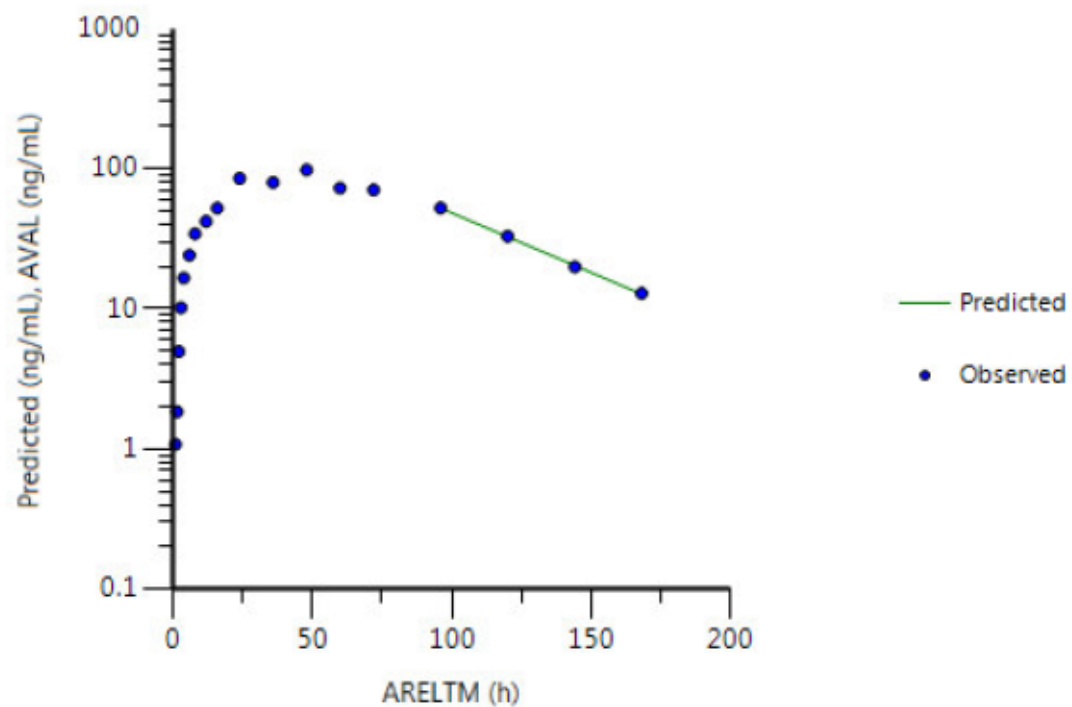
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9846 Rsquared_adjusted=0.9769 HL_Lambda_z=32.9246
4 points used in calculation



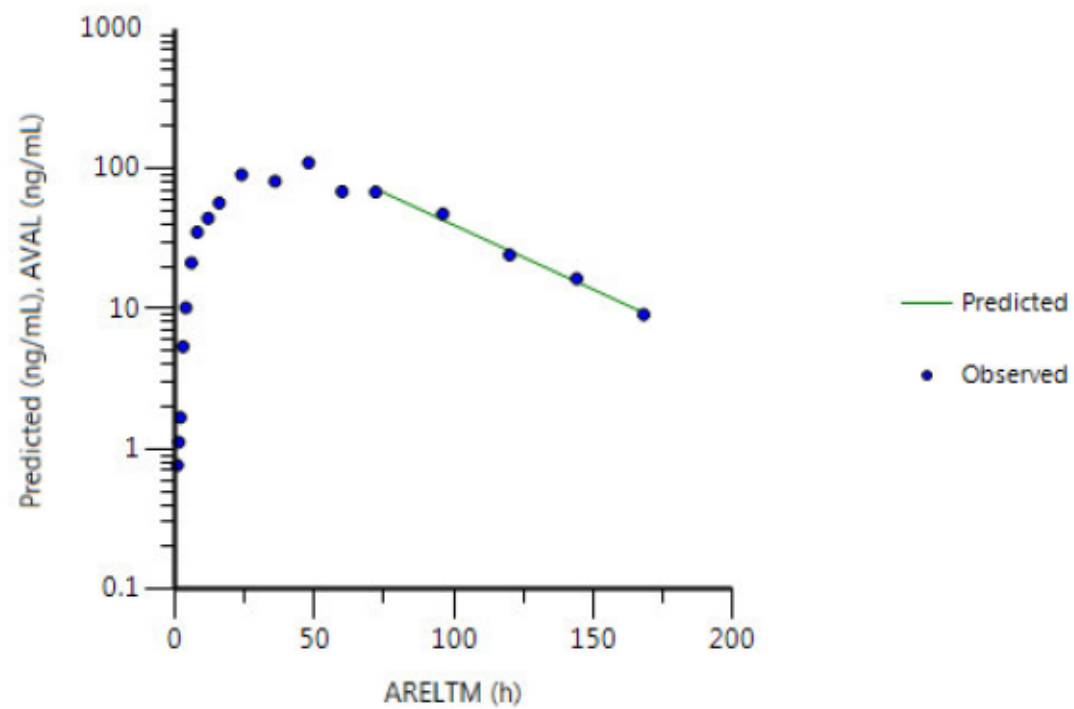
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9874 Rsquared_adjusted=0.9747 HL_Lambda_z=25.2082
3 points used in calculation



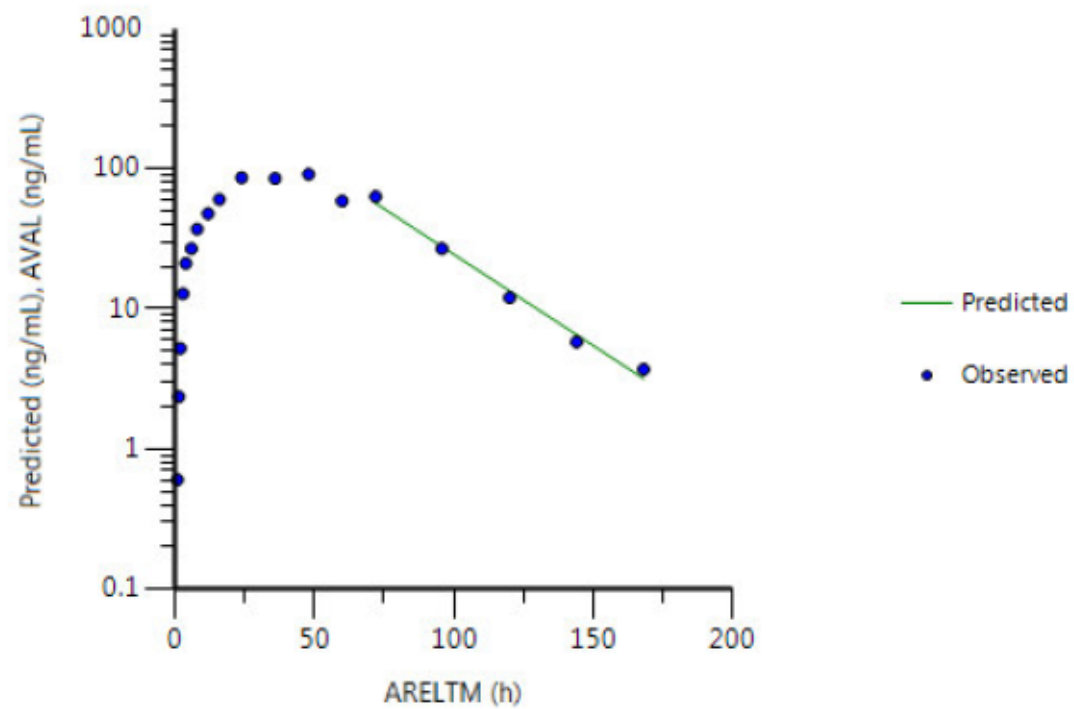
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9993 Rsquared_adjusted=0.999 HL_Lambda_z=35.3421
4 points used in calculation



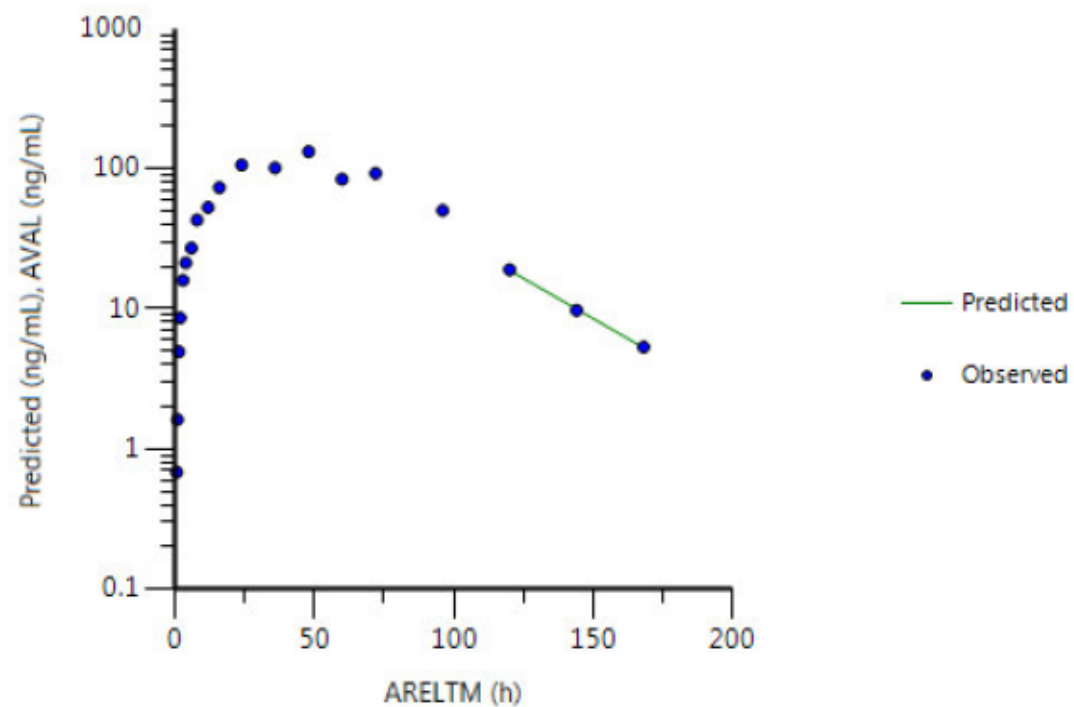
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9921 Rsquared_adjusted=0.9895 HL_Lambda_z=32.6631
5 points used in calculation



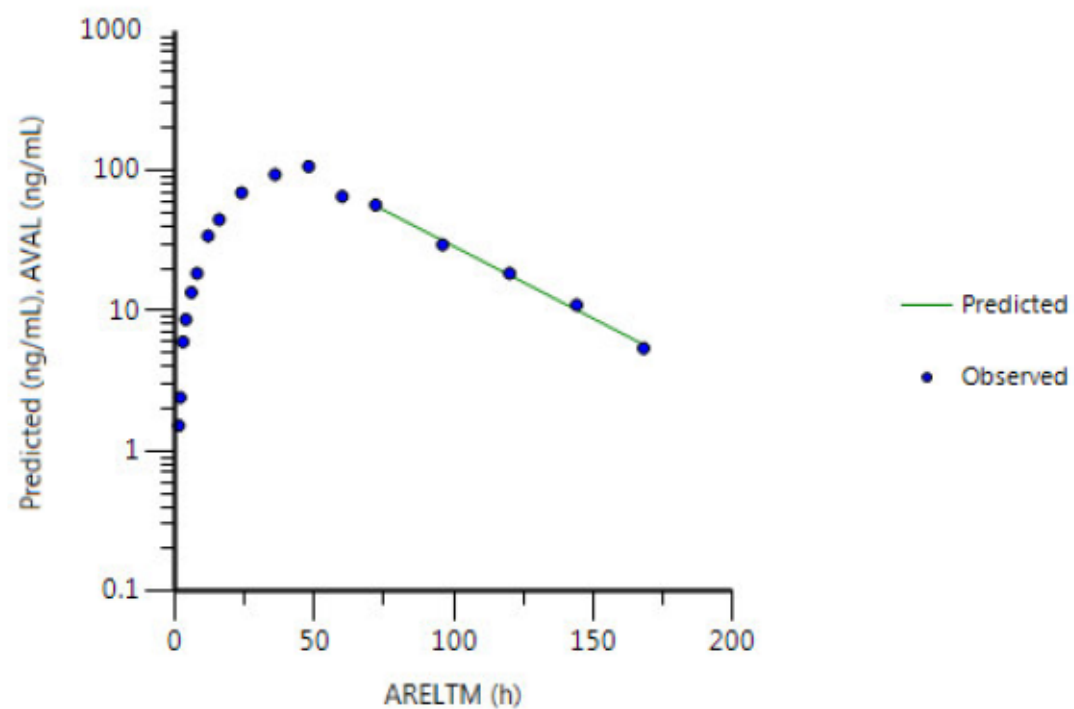
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsqr=0.9881 Rsqr_adjusted=0.9842 HL_Lambda_z=23.1091
5 points used in calculation



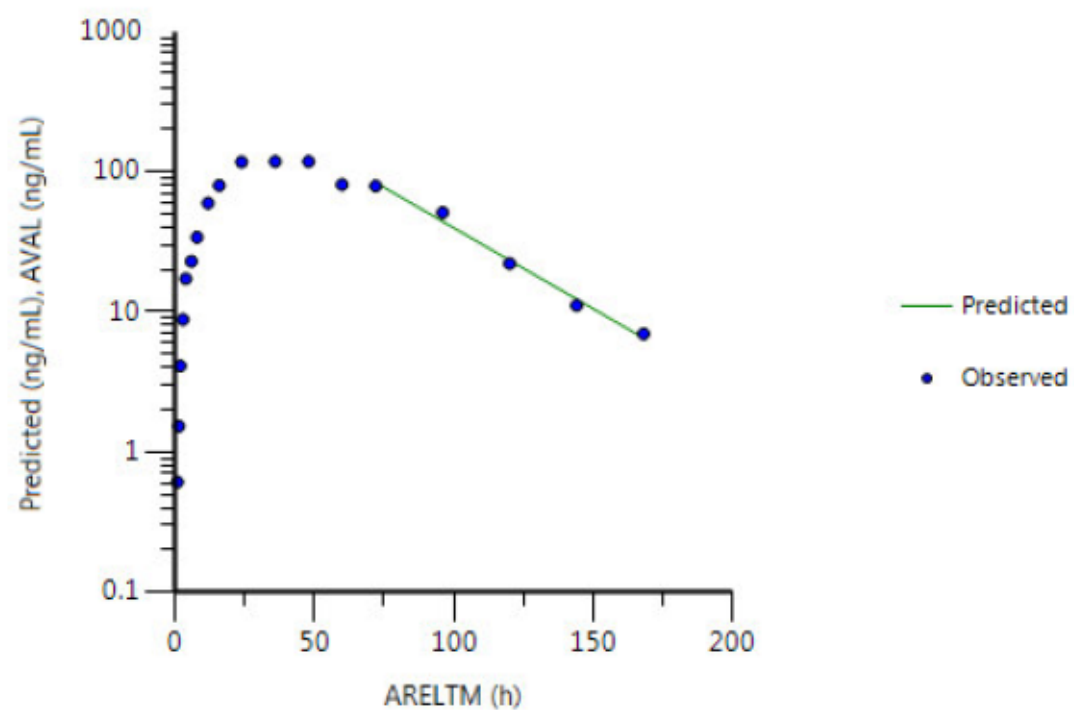
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9992 Rsquared_adjusted=0.9984 HL_Lambda_z=26.2226
3 points used in calculation



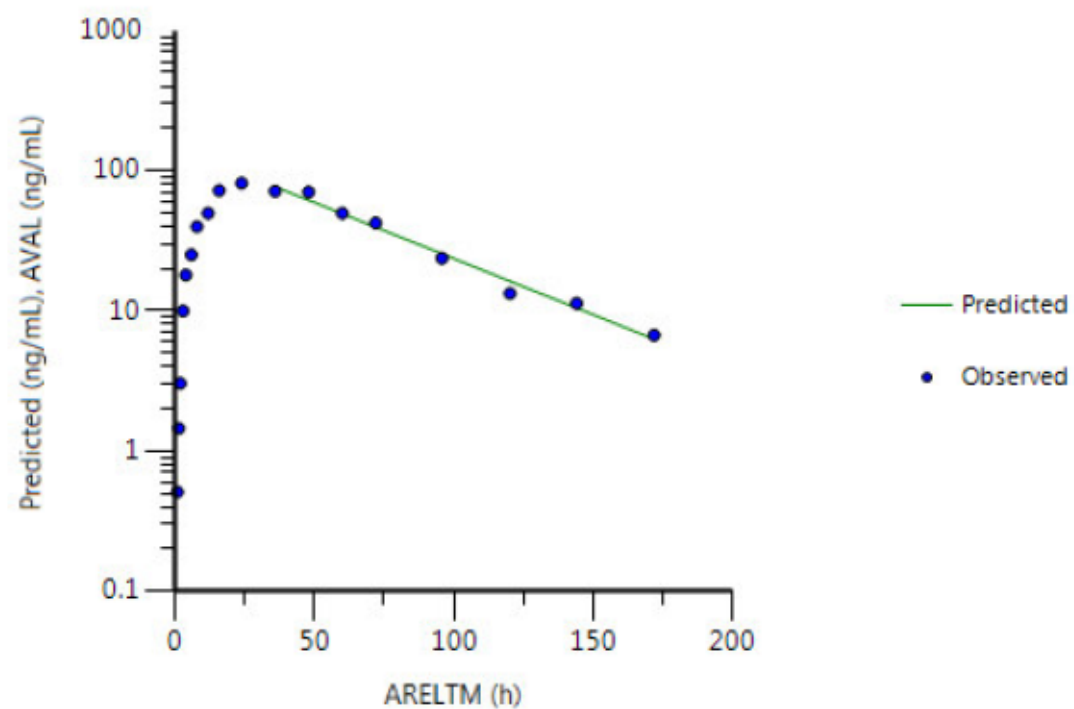
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9951 Rsquared_adjusted=0.9935 HL_Lambda_z=29.2058
5 points used in calculation



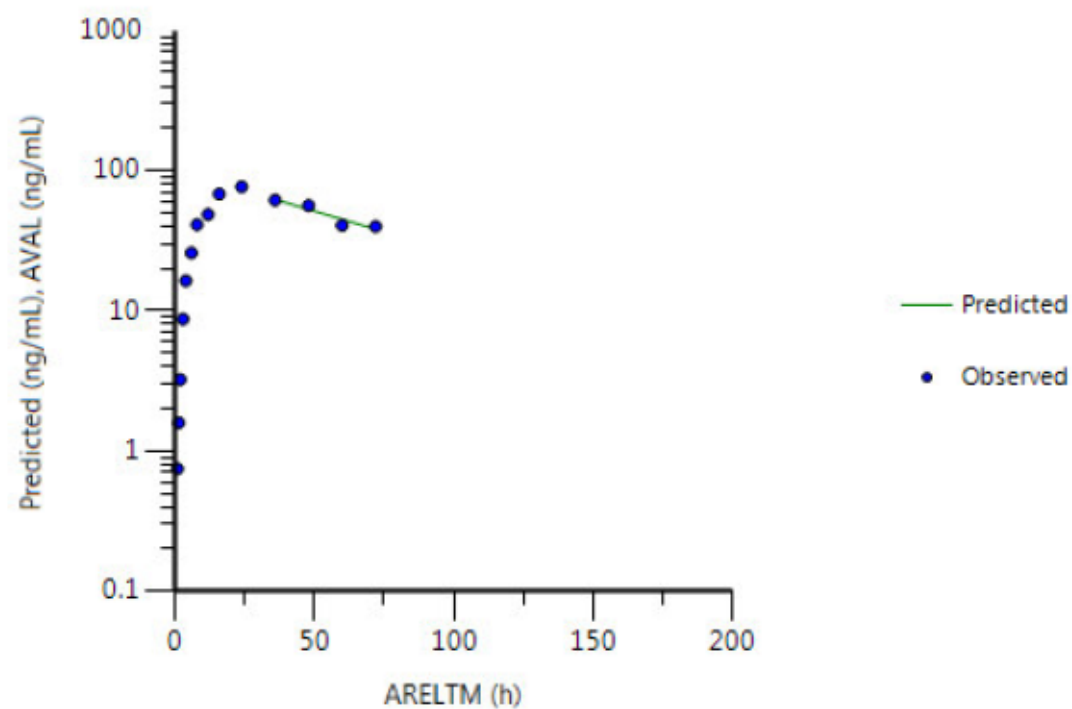
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9897 Rsquared_adjusted=0.9863 HL_Lambda_z=26.0605
5 points used in calculation



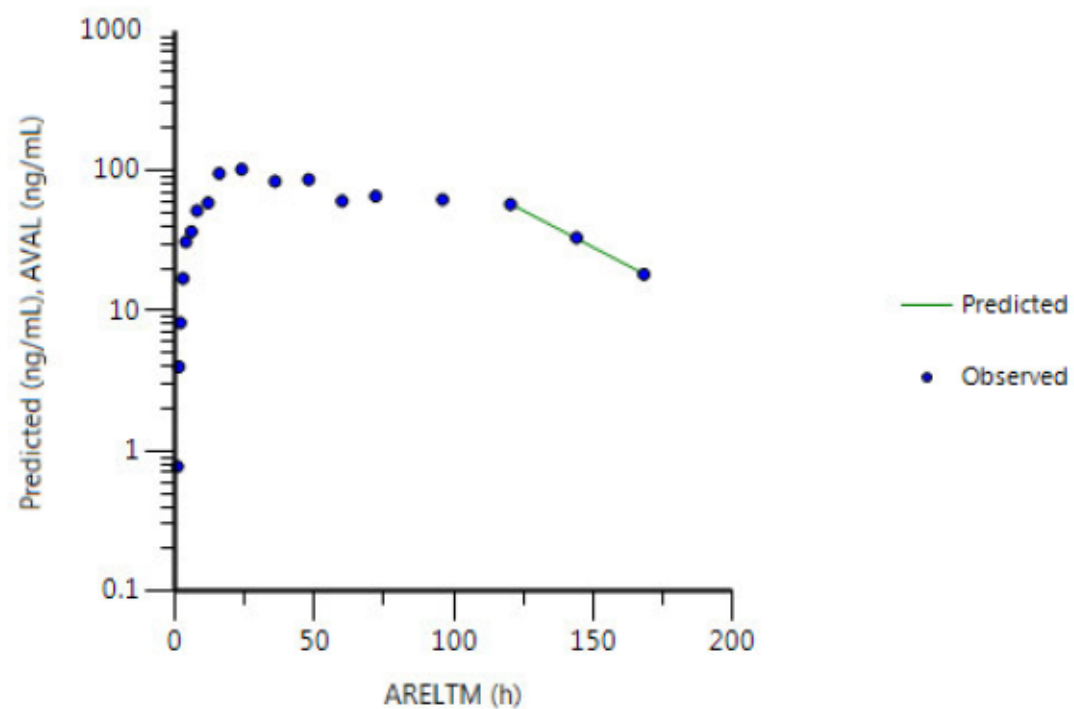
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9851 Rsquared_adjusted=0.9826 HL_Lambda_z=37.5598
8 points used in calculation



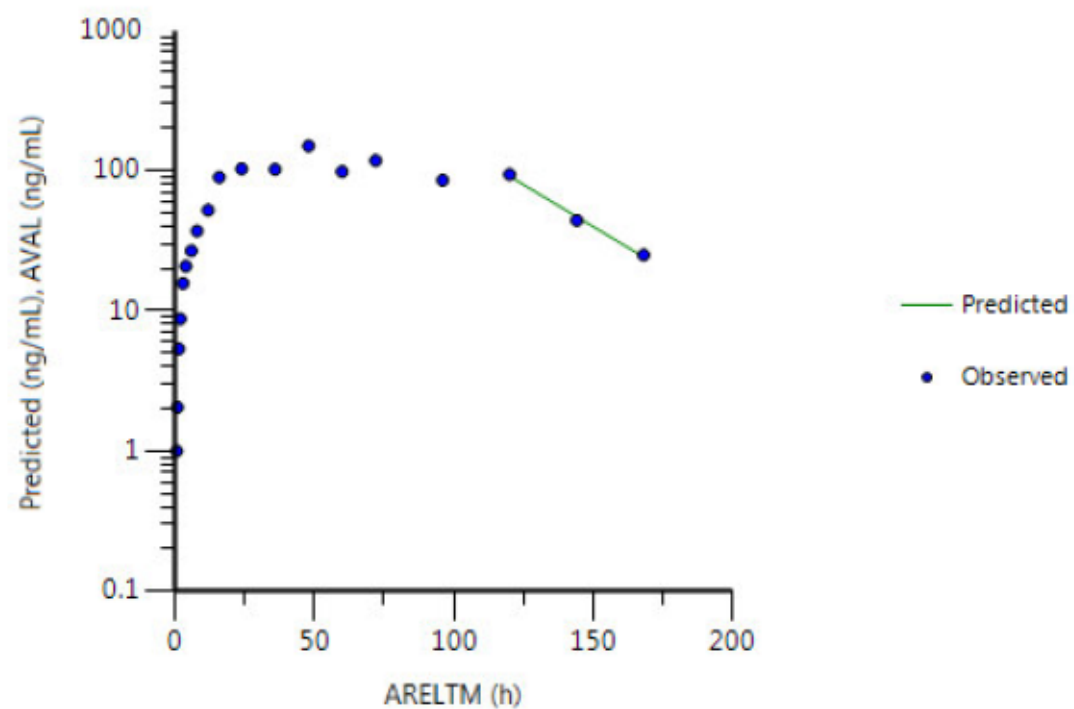
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.8921 Rsquared_adjusted=0.8382 HL_Lambda_z=51.1963
4 points used in calculation



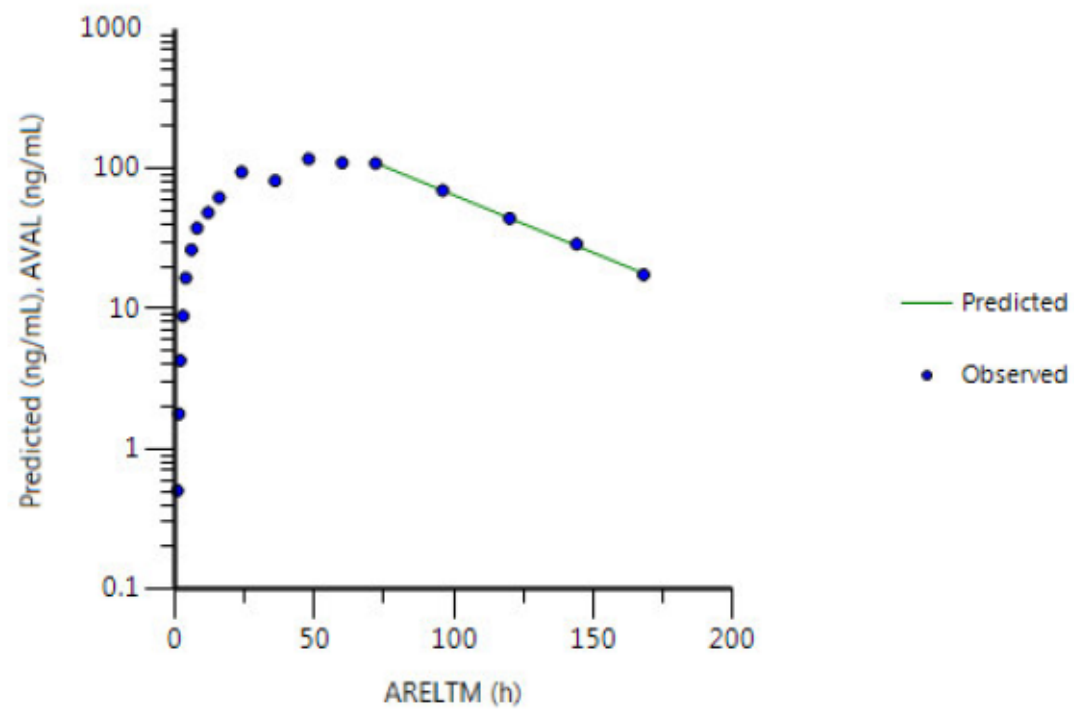
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9996 Rsquared_adjusted=0.9992 HL_Lambda_z=28.8185
3 points used in calculation



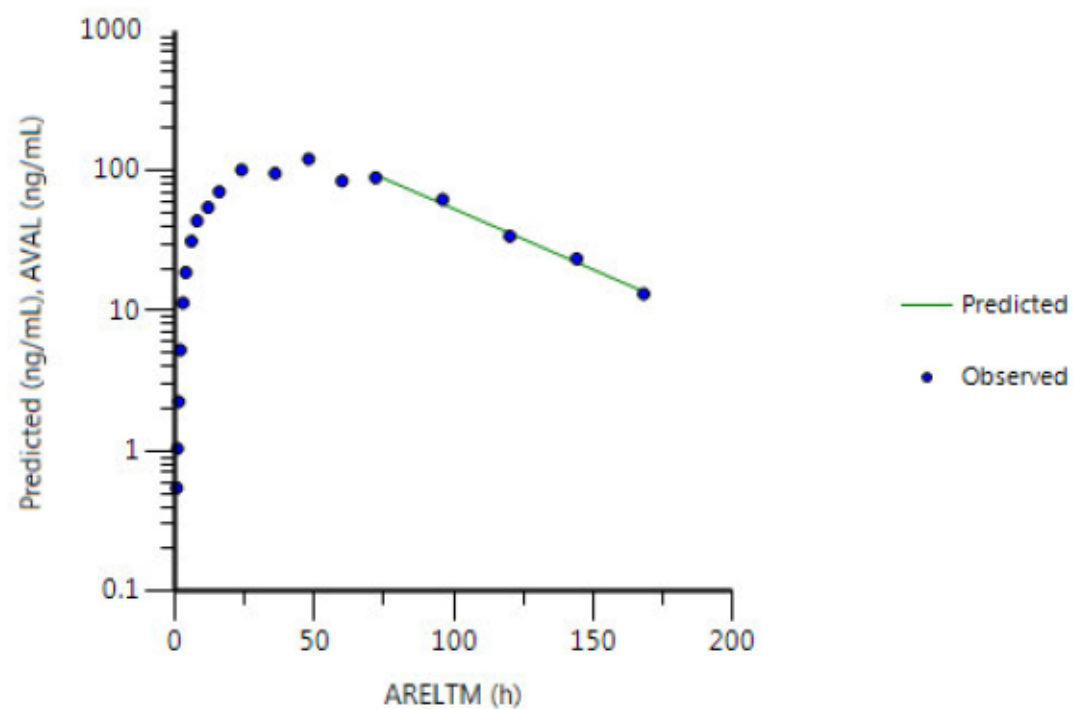
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9936 Rsquared_adjusted=0.9871 HL_Lambda_z=25.1382
3 points used in calculation



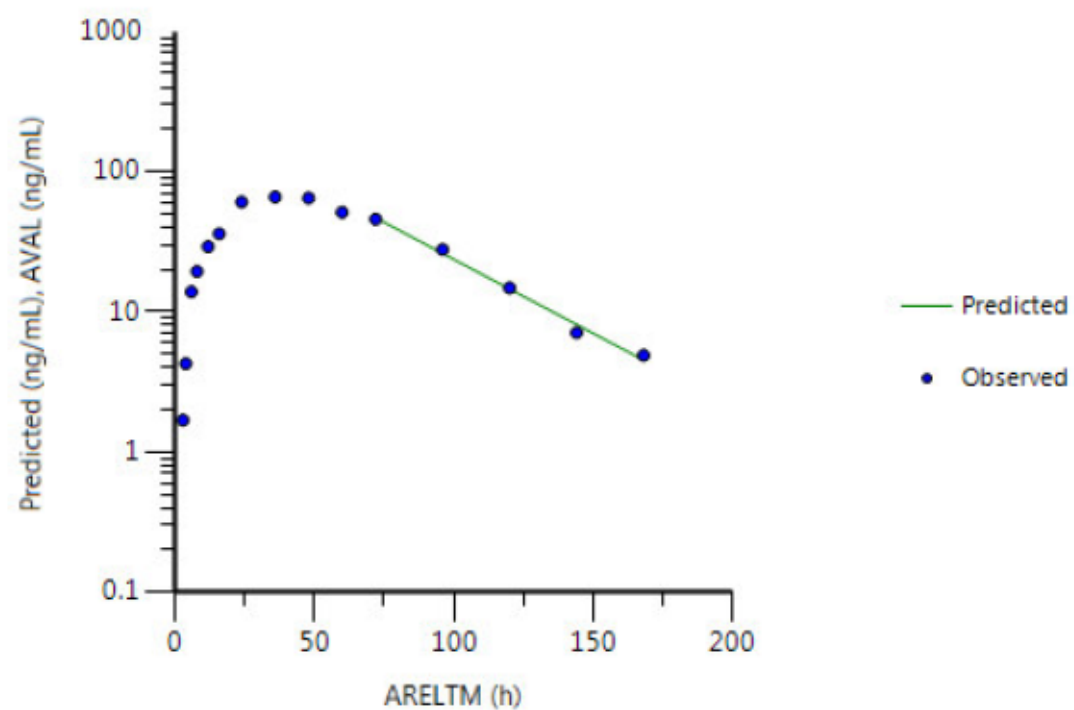
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9993 Rsquared_adjusted=0.9991 HL_Lambda_z=36.6643
5 points used in calculation



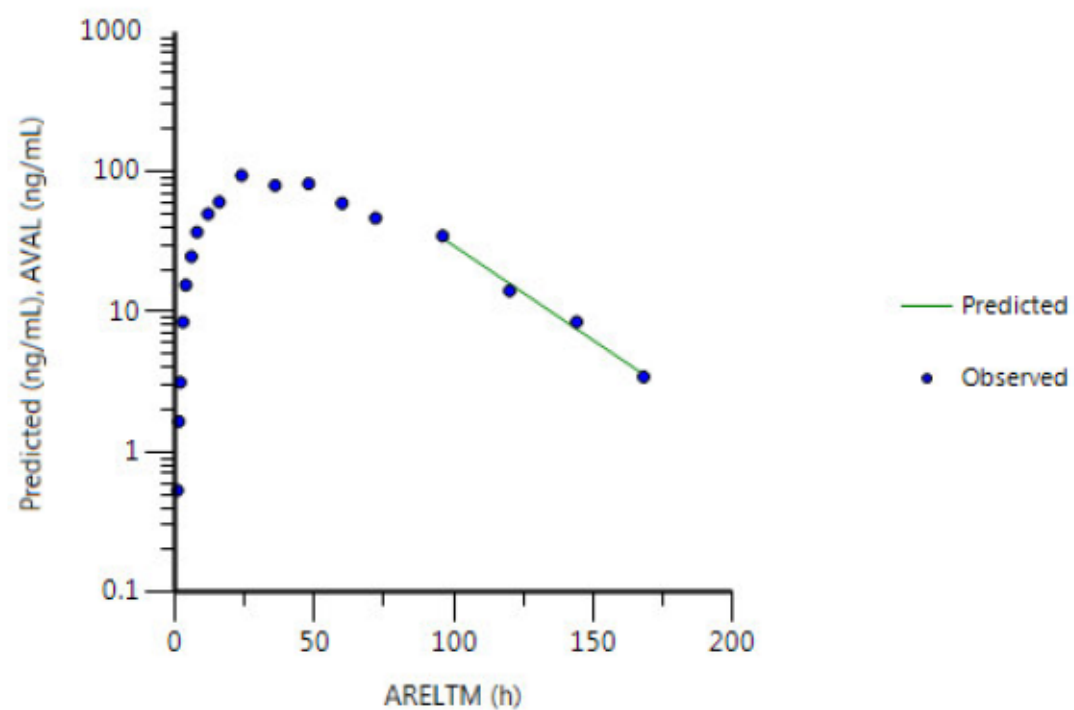
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9935 Rsquared_adjusted=0.9914 HL_Lambda_z=34.7254
5 points used in calculation



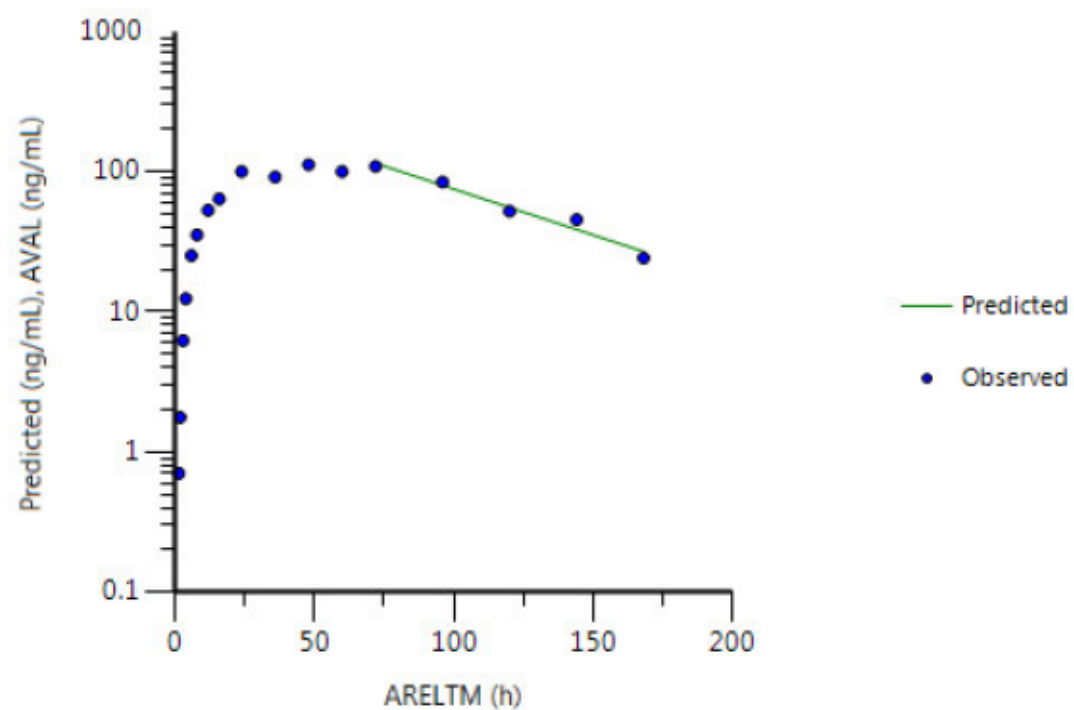
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9917 Rsquared_adjusted=0.9889 HL_Lambda_z=28.4898
5 points used in calculation



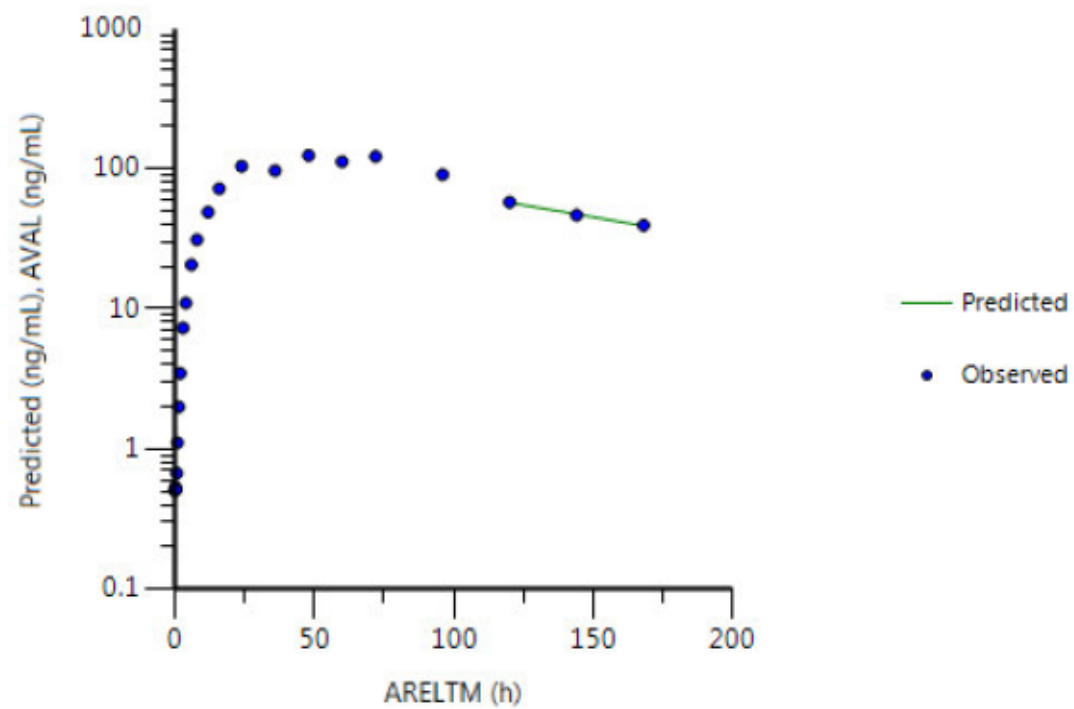
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.989 Rsquared_adjusted=0.9835 HL_Lambda_z=22.3233
4 points used in calculation



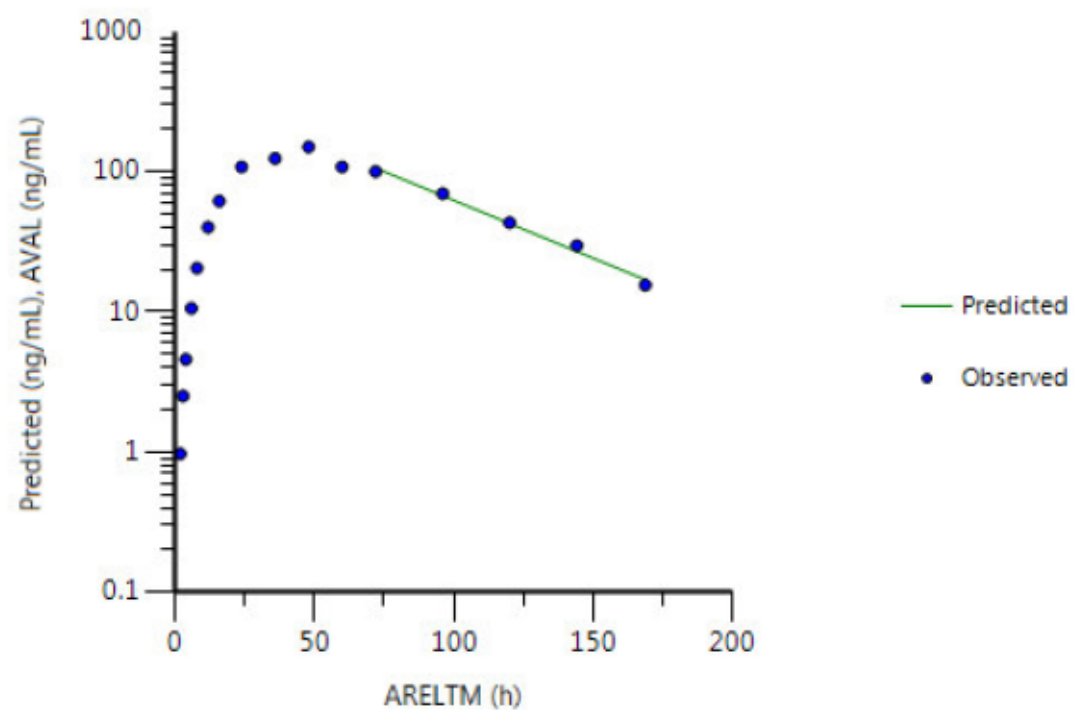
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9652 Rsquared_adjusted=0.9537 HL_Lambda_z=45.8851
5 points used in calculation



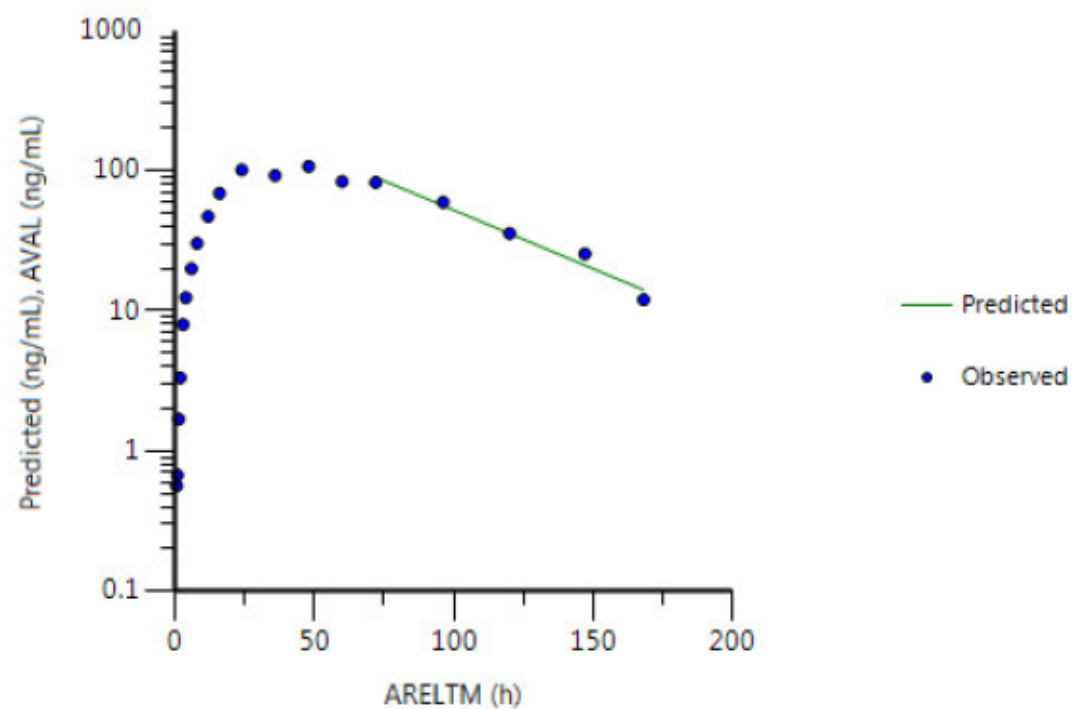
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9946 Rsquared_adjusted=0.9892 HL_Lambda_z=87.6115
3 points used in calculation



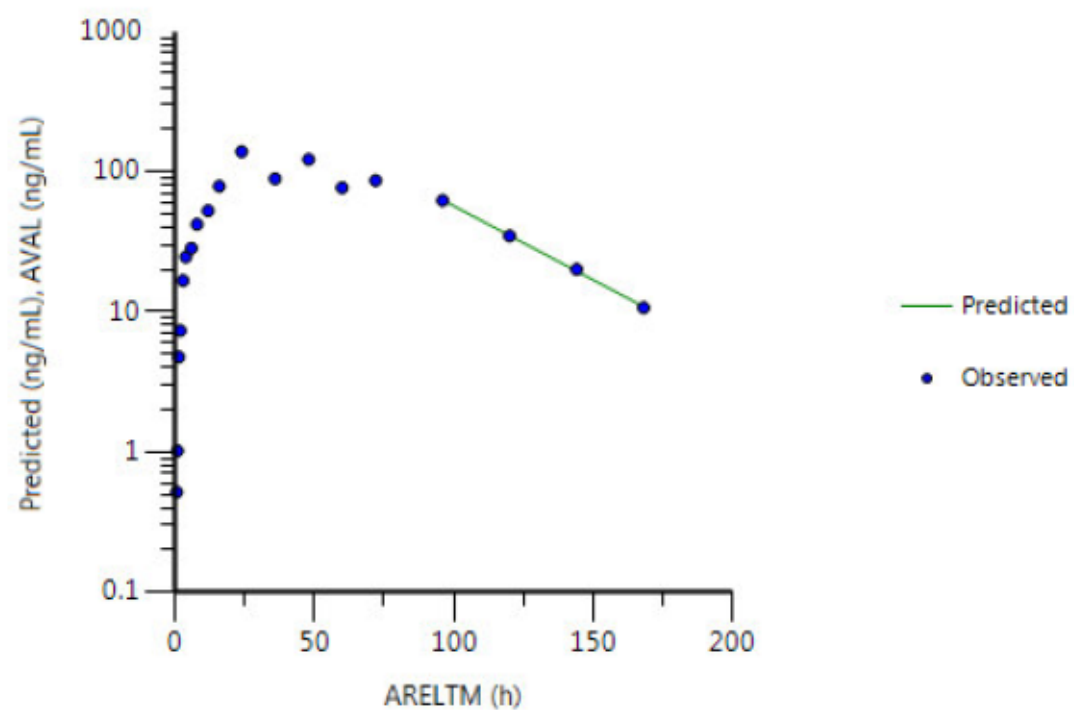
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9895 Rsquared_adjusted=0.986 HL_Lambda_z=36.4801
5 points used in calculation



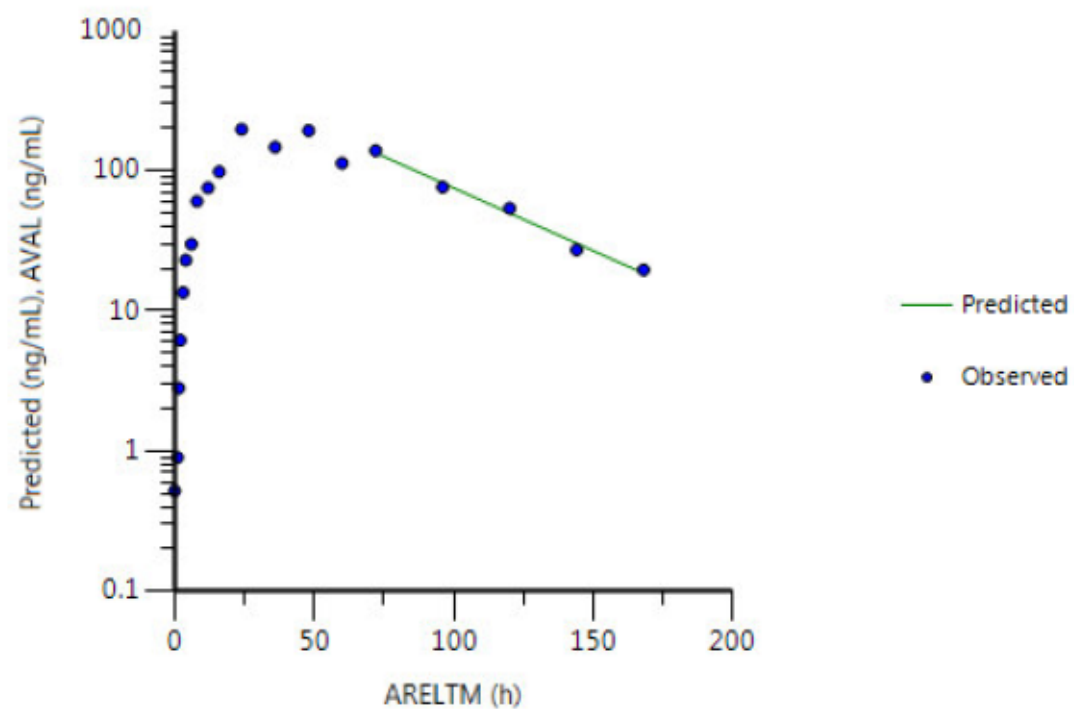
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9684 Rsquared_adjusted=0.9579 HL_Lambda_z=35.9813
5 points used in calculation



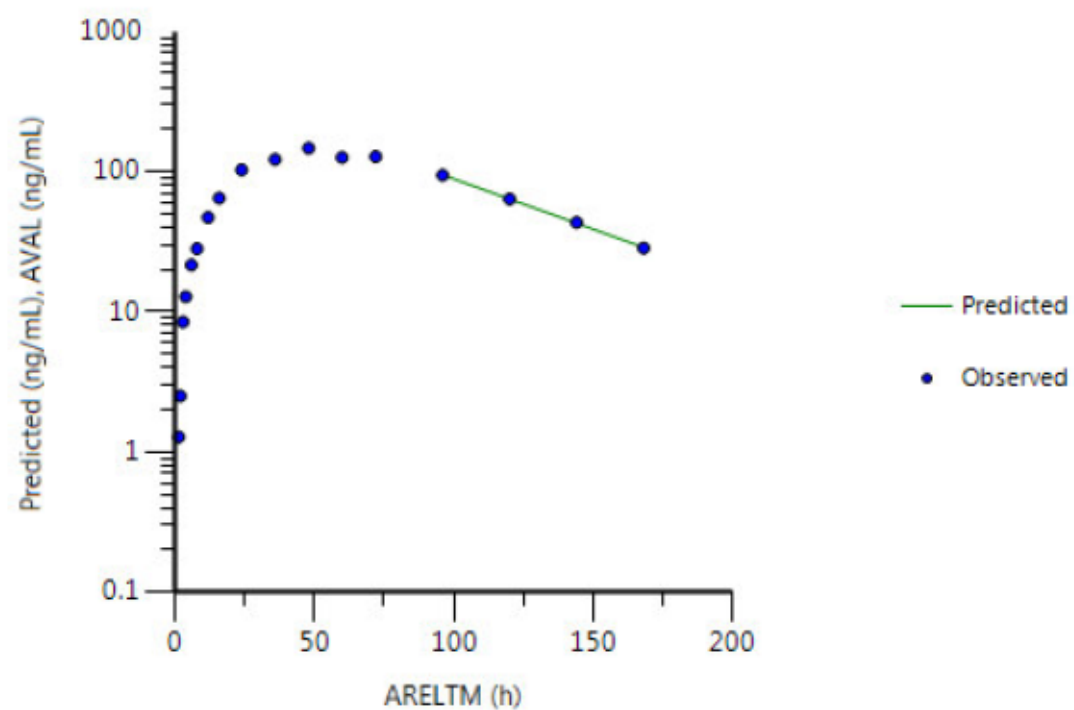
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9993 Rsquared_adjusted=0.9989 HL_Lambda_z=28.5145
4 points used in calculation



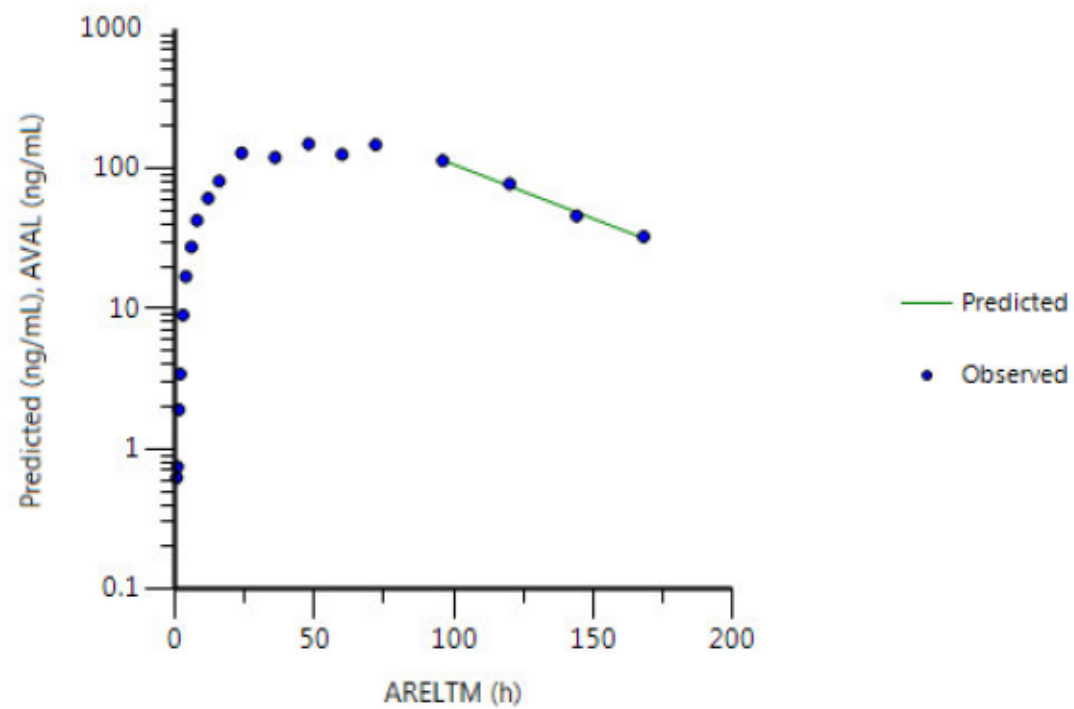
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9889 Rsquared_adjusted=0.9852 HL_Lambda_z=33.6205
5 points used in calculation



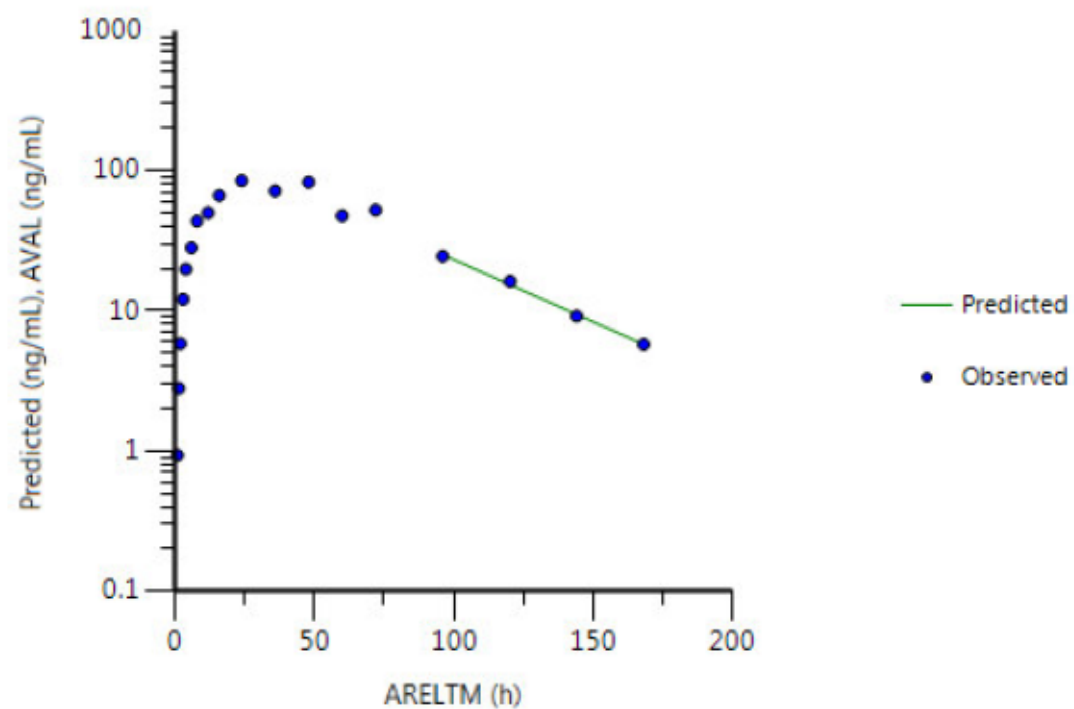
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9996 Rsquared_adjusted=0.9994 HL_Lambda_z=41.9002
4 points used in calculation



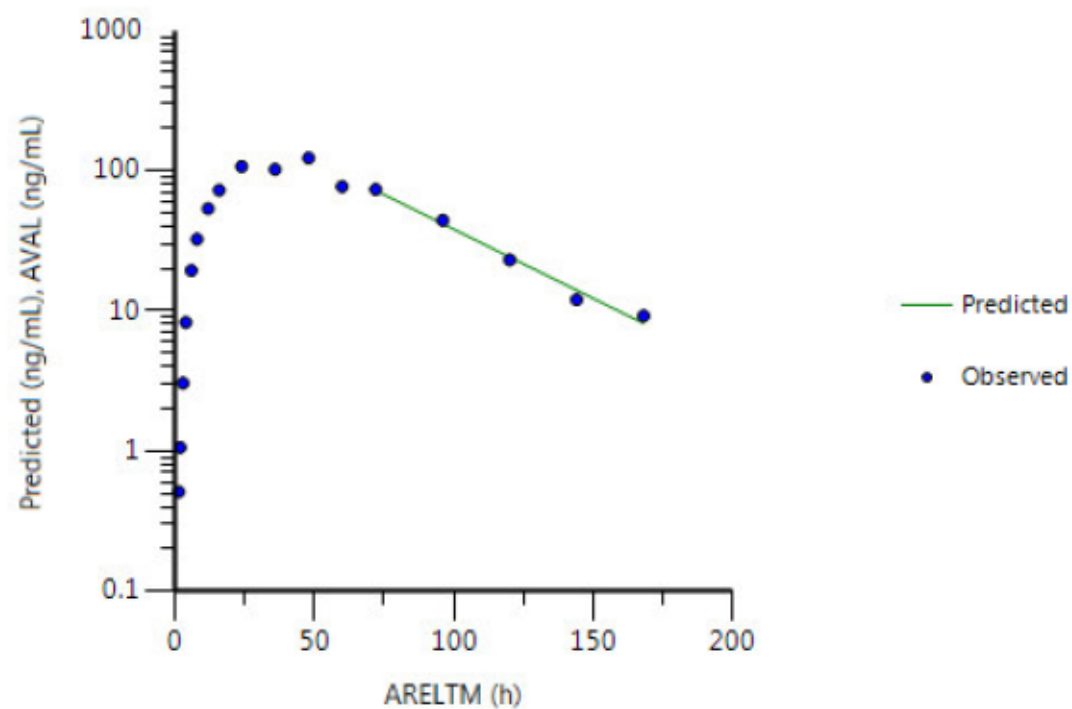
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9936 Rsquared_adjusted=0.9904 HL_Lambda_z=38.9294
4 points used in calculation



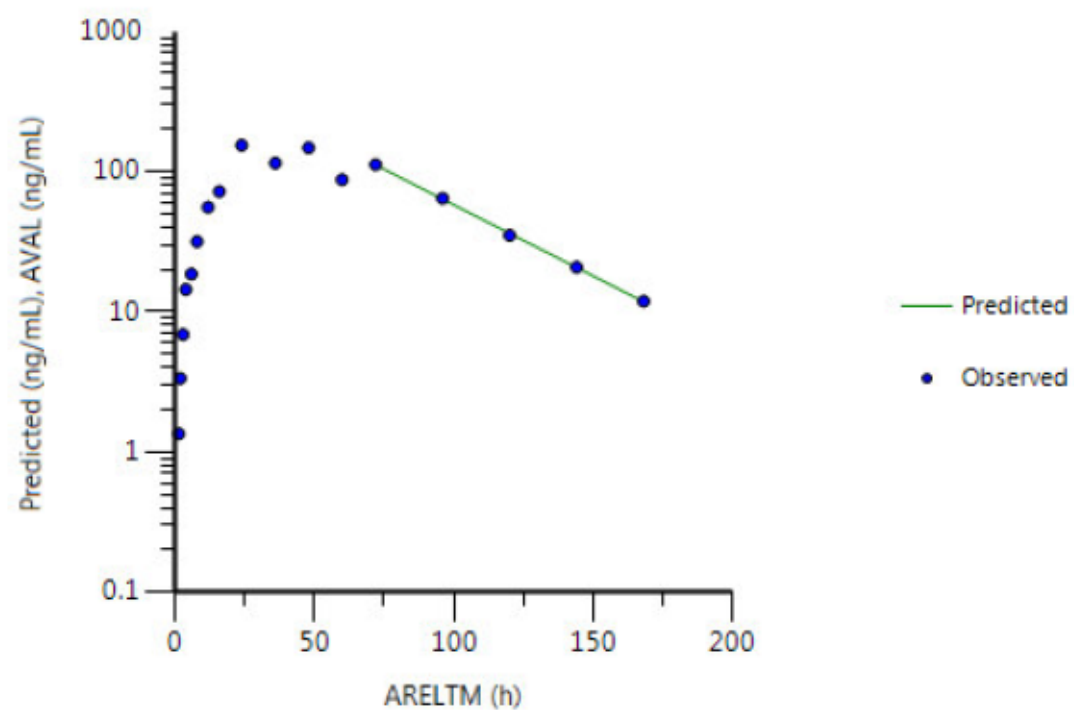
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9964 Rsquared_adjusted=0.9947 HL_Lambda_z=33.8921
4 points used in calculation



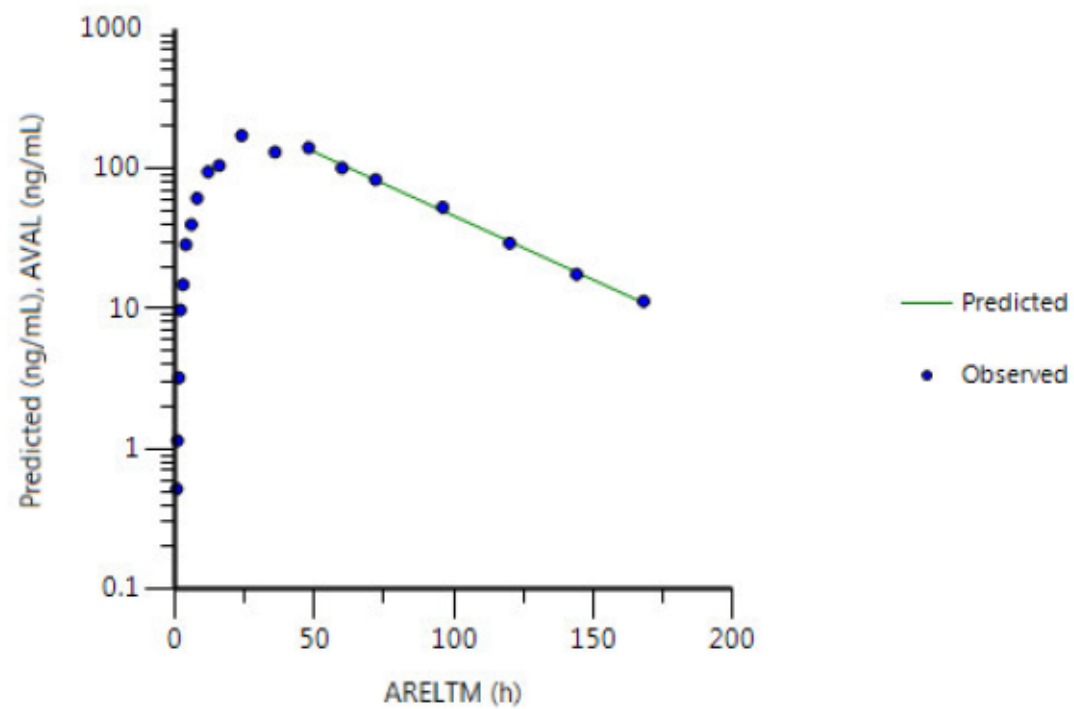
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9848 Rsquared_adjusted=0.9797 HL_Lambda_z=30.4843
5 points used in calculation



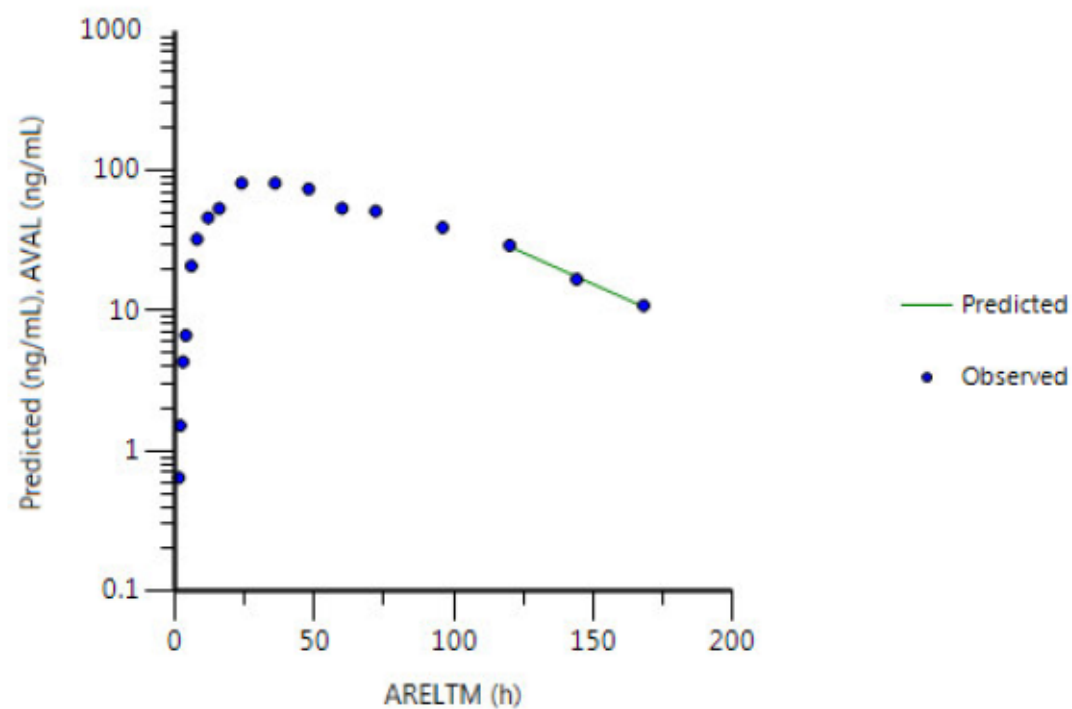
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9996 Rsquared_adjusted=0.9994 HL_Lambda_z=29.6236
5 points used in calculation



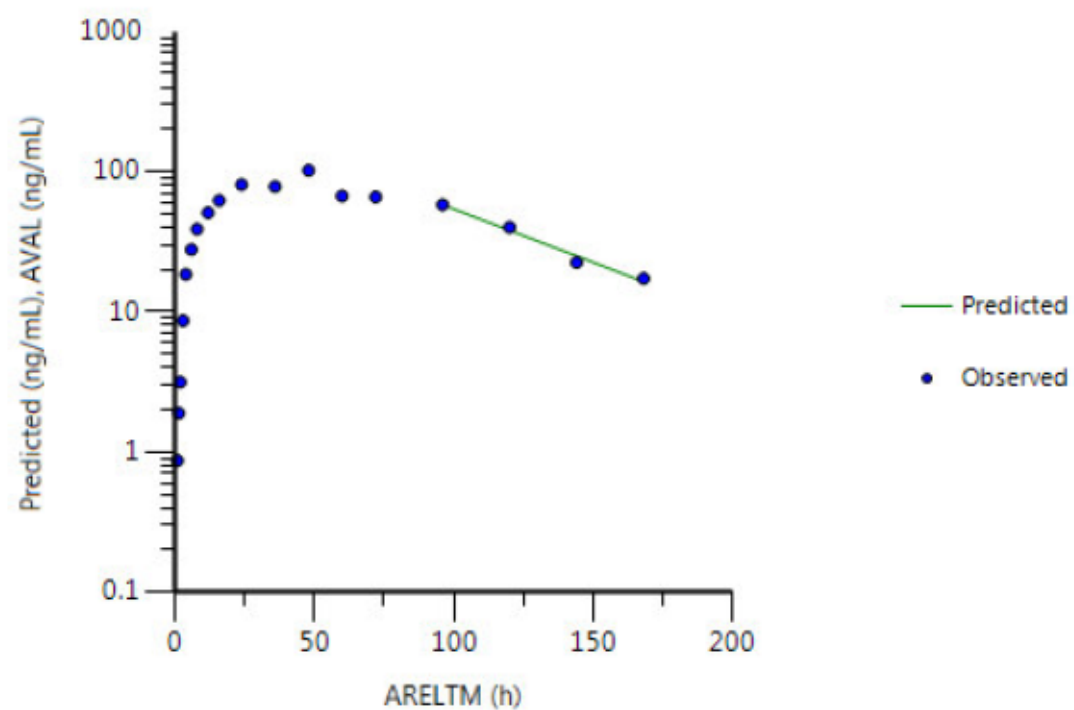
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9982 Rsquared_adjusted=0.9979 HL_Lambda_z=32.9681
7 points used in calculation



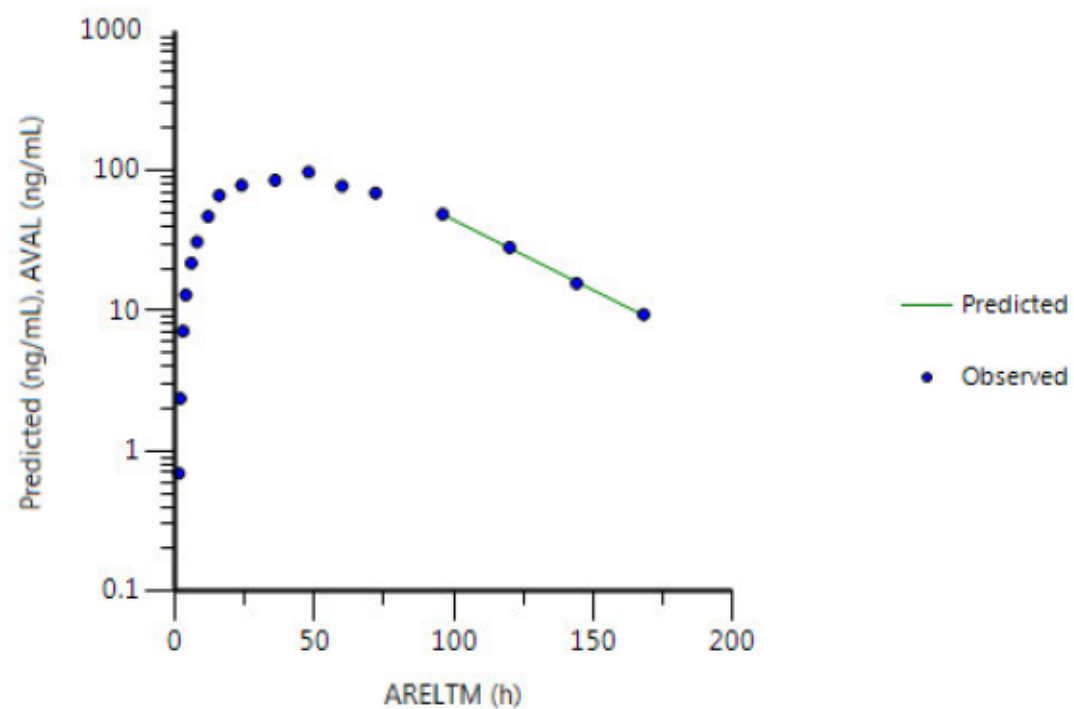
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9948 Rsquared_adjusted=0.9896 HL_Lambda_z=33.6471
3 points used in calculation



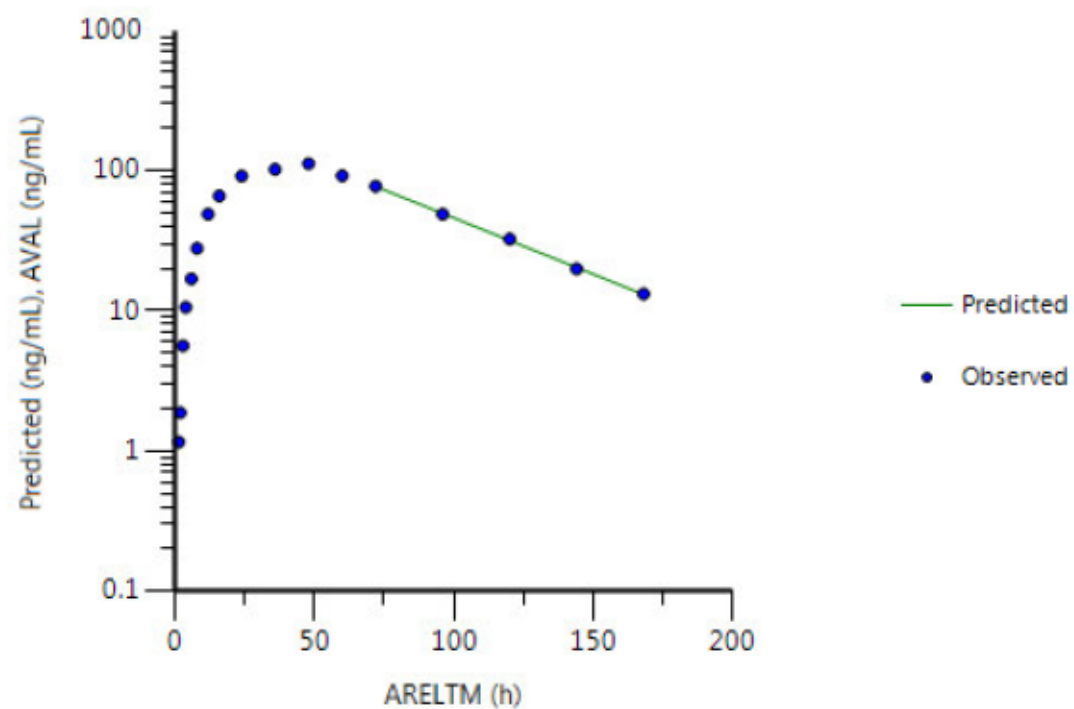
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9816 Rsquared_adjusted=0.9724 HL_Lambda_z=39.5398
4 points used in calculation



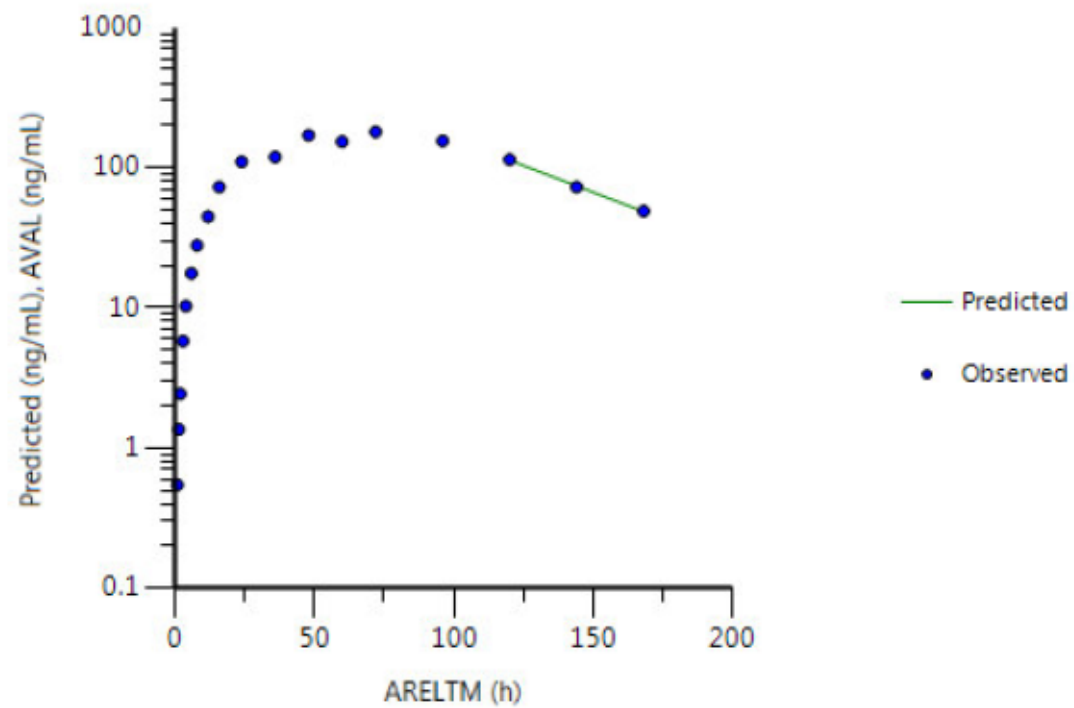
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9993 Rsquared_adjusted=0.999 HL_Lambda_z=30.0649
4 points used in calculation



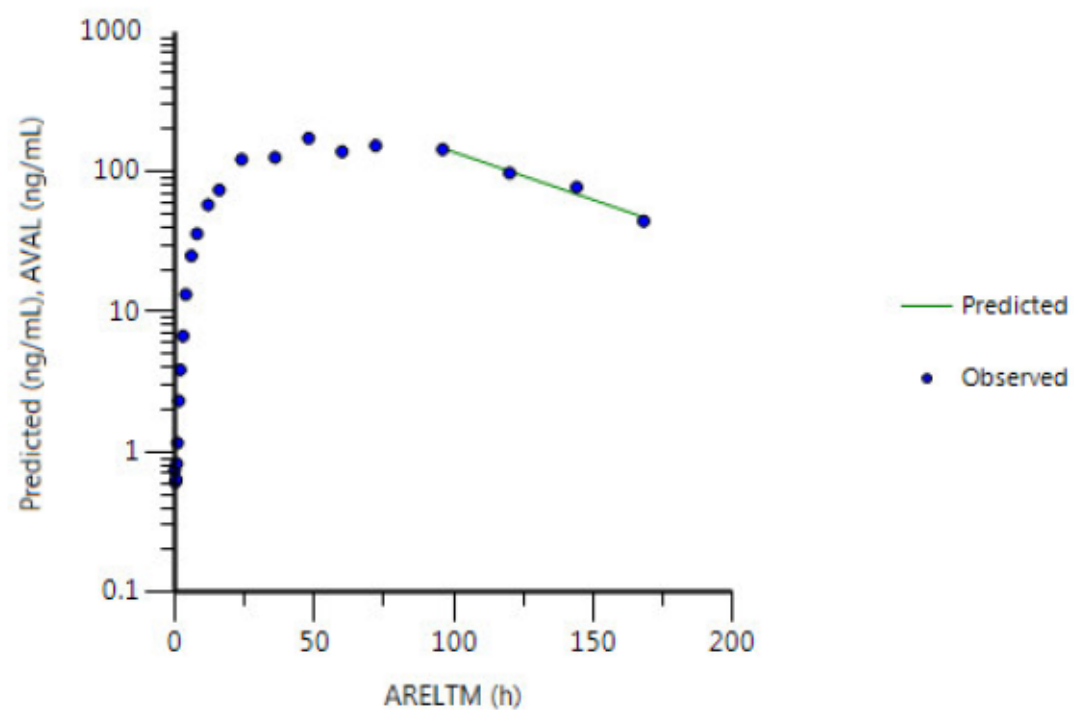
PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9993 Rsquared_adjusted=0.9991 HL_Lambda_z=37.4961
5 points used in calculation



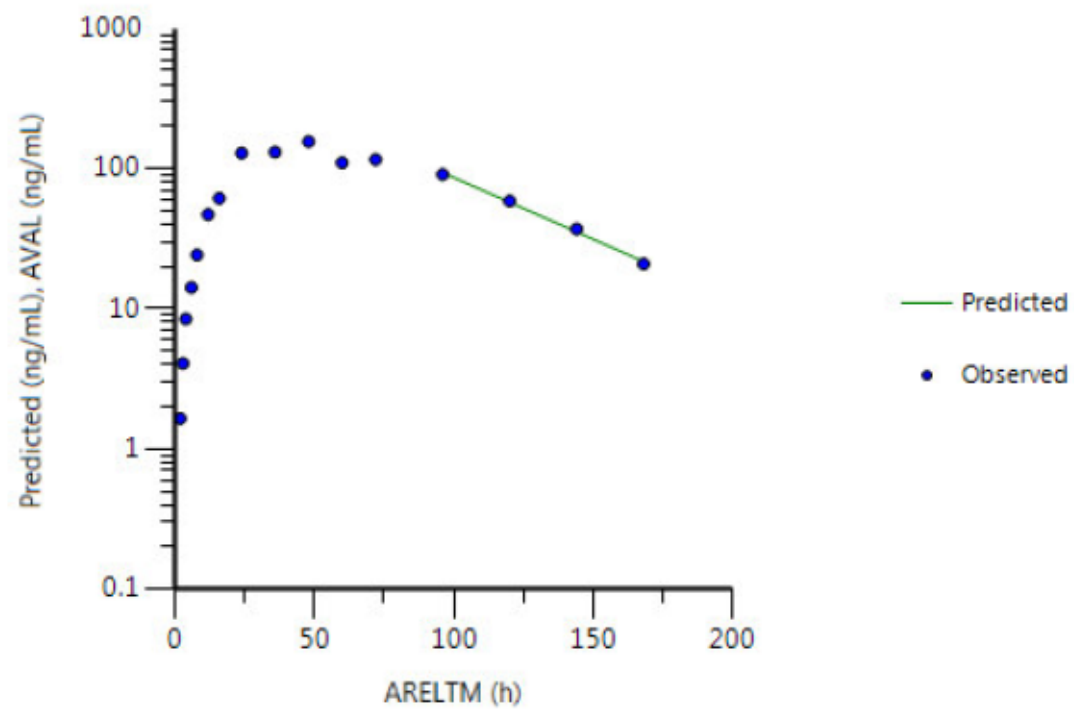
PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9986 Rsquared_adjusted=0.9971 HL_Lambda_z=39.403
3 points used in calculation



PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9746 Rsquared_adjusted=0.9619 HL_Lambda_z=44.1229
4 points used in calculation



PARAMCD=M9A, SUBJID=PI APERIOD=1, TRTAN=2, TRTA=2 x
250 mg TF3
Rsquared=0.9957 Rsquared_adjusted=0.9935 HL_Lambda_z=34.1553
4 points used in calculation



PARAMCD=M9A, SUBJID=PI APERIOD=2, TRTAN=1, TRTA=5 x
100 mg TF3
Rsquared=0.9822 Rsquared_adjusted=0.9733 HL_Lambda_z=28.0887
4 points used in calculation

