16.1.9 Documentation of Statistical Methods, Pharmacokinetic Analysis

Statistical Analysis Plan, Version 1.0: 15 December 2021

WinNonlin Supplemental Appendix 16.1.9

PROTOCOL M200C-2102

A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single-Dose Intravenous Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of IXT-m200 in Healthy Participants

STATISTICAL ANALYSIS PLAN – V1.0

December 15, 2021

CONFIDENTIAL

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AUC_{inf}	Area under the serum concentration-time curve from zero (start of the infusion) extrapolated to infinity
AUC_{last}	Area under the serum concentration-time curve from zero (start of the infusion) to last quantifiable time point
CL	Clearance
C_{last}	Serum concentration at last measurable time point (observed)
C_{max}	Maximum serum concentration (observed)
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
ET	Early termination visit
GLP	Good Laboratory Practices
HACA	Human Anti-Chimeric Antibodies
HIPAA	Health Insurance Portability and Accountability Act
IgG	Immunoglobulin G
IV	Intravenous
IXT-m200	InterveXion investigational medicinal product, a high-affinity chimeric anti-METH monoclonal antibody
K_{el}	Elimination rate constant associated with the terminal elimination phase (also referred to as λ_z)
MedDRA	Medical Dictionary for Regulatory Activities
METH	Methamphetamine
MDA	Methylenedioxyamphetamine
MDMA	MethylenedioxyMETH
MRT_{inf}	Mean residence time extrapolated to infinity
MRT_{last}	Mean residence time from zero to last quantifiable time point
PK	Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
STAMPOUT	Study of Antibody for Methamphetamine Outpatient Therapy
T½	Terminal elimination half-life

Abbreviation	Definition
TEAE	Treatment Emergent Adverse Event
T_{last}	Time to last measurable serum concentration (observed)
T_{max}	Time to maximum serum concentration (observed)
Vd	Volume of Distribution
Vz	Volume of distribution based on the terminal phase
Vss	An estimate of volume of distribution at steady-state

Table of Contents

1. Introduction

This Statistical Analysis Plan (SAP) is based on study procedures and analyses described in the protocol Number: M200C-2102 dated August 25, 2021. Table/Figure shells and mock listings corresponding to the contents of this document will be in a separate file.

1.1 Background

IXT-m200, also called ch-mAb7F9, binds METH with high selectivity and affinity. The product contains a murine METH-binding variable region and the constant domains of a human immunoglobulin G (IgG) 2κ. This antibody isotype was chosen because of the lower risk of immune response compared to an IgG1 or IgG3. IXT-m200 targets METH, does not rely on binding to any endogenous target for its action, and has been well-tolerated in previous clinical studies (see below).

Through the binding of METH in the bloodstream, it is anticipated that IXT-m200 will alter the pharmacokinetics (PK) of METH and decrease concentrations of METH reaching its active sites in the brain. The presence of IXT-m200 should therefore decrease the perceived pleasurable effects of METH. Over the longer term, when combined with behavioral therapy, IXT-m200 should reduce the frequency of METH use over time.

1.2 IXT-m200 Pharmacokinetics in Healthy Volunteers

A Phase 1 study of the safety of single doses of IXT-m200 in healthy humans has been completed[1]. In this first clinical study, 42 participants (17 females) were dosed in 5 groups (0.2, 0.6, 2, 6, or 20 mg/kg IXT-m200), with 10 participants receiving placebo (saline). Pharmacokinetic results indicated that IXT-m200 is similar to other IgGs, with an elimination half-life of ~18 days, volume of distribution (Vd) of ~5 L and clearance of ~200 mL/d. The disposition of IXT-m200 did not appear to be affected by dose.

1.3 IXT-m200 Safety and Tolerability

There were no serious adverse events (SAEs) or serious adverse reactions during the conduct of the Phase 1 study. There were 3 adverse events in 2 participants that were attributed to IXT-m200. A mild infusion reaction (Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 Grade 3) and bronchospasm (Grade 2) occurred in the same participant. The symptoms included a brief period of bronchospasm with no drop in oxygen saturation that resolved with stopping the infusion. A separate participant experienced an AE of mild proteinuria (Grade 1). Both participants were in the same dose group (2 mg/kg IXT-m200).

Samples from all participants were tested for immunogenicity, i.e., anti-IXT-m200 antibodies. Samples from only 4 (12.5%) IXT-m200 treated participants were confirmed to have low titers. One of these 4 participants also provided a pre-dose sample that screened positive for

[1] Stevens MW, Henry RL, Owens SM, Schutz R, Gentry WB. First human study of a chimeric anti-methamphetamine monoclonal antibody in healthy volunteers. mAbs 2014; 6:1649–56.

anti-IXT-m200 antibodies. The development of anti-IXT-m200 antibodies did not appear to be dose-related. Overall, there were no apparent safety or tolerability concerns identified when IXT-m200 was dosed over the range from 0.2 to 20 mg/kg. Therefore, a maximum tolerated dose was not reached.

Following the Phase 1 study, a Phase 2 study of IXT-m200 was conducted (STAMPOUT: Study of Antibody for Methamphetamine Outpatient Therapy, NCT03336866). This was a parallel-group, placebo-controlled, double-blind study in otherwise healthy, non-treatment seeking participants who use METH. Those who qualified received single doses of IXT-m200 (6 or 20 mg/kg) or placebo followed by weekly METH challenges for up to 4 weeks. The challenges consisted of METH (30 mg, intravenous) and placebo, separated by 4 hours. Safety, METH and IXT-m200 PK, and pharmacodynamic data were collected for up to 126 days.

In the STAMPOUT study, all AEs were grade 1 or grade 2. Common AEs included palpitations, tachycardia, dry mouth, nausea, injection site pain, headache, euphoria, hypervigilance, and hyperhidrosis. All of these AEs are expected in people receiving METH, and all participants in this study received METH. Of these, only blurred vision, nausea, feeling abnormal, and dry mouth were considered by the investigator as probably related to IXT-m200; each AE was reported by only one participant who received IXT-m200. Furthermore, none of the AEs associated with METH appeared to be exacerbated by IXT-m200. For example, an analysis of heart rate changes following METH administration demonstrated that average percent heart rate increase, and average peak heart rates were not changed in the presence of IXT-m200. Plus, the individual maximum attained heart rate in each group was 139 (placebo), 142 (6 mg/kg), and 144 (20 mg/kg). Finally, as in the Phase 1 study, samples from all participants were tested for HACA. Only one participant in each IXT-m200 dose group had notable titers of anti-IXT-m200 antibodies, and the PK of IXT-m200 in these participants did not differ from other participants in the dose group.

1.4 Justification for IXT-m200 Dose

The IXT-m200 dose of 3 g was selected for this study because it is potentially effective in reducing METH effects for several weeks, and will be used in an upcoming repeat-dose Phase 2 clinical study in patients with METH use disorder. Prior to this Phase 2 study, safety and pharmacokinetics of a single 3-g dose in healthy volunteers will be established. IXT-m200 will be administered via IV infusion over 30 min. This is necessary because it is a protein medication and would be metabolized to inactive components in the gastrointestinal tract if administered orally. The volume that must be given is too large to allow for intramuscular or subcutaneous administration based on the current formulation. This will result in a rate of 40 mg/kg/hr in a 75-kg person, which is significantly lower than doses given during a multiple-dose GLP toxicology study in which the slowest rate for the high dose was 1800 mg/kg/hr.

2. Trial Design and Methods

2.1 Study Objectives

2.1.1 Primary Objectives

- To evaluate the safety and tolerability of a single 3-g intravenous dose of IXT-m200 in healthy participants.

2.1.2 Secondary Objectives

- To characterize the pharmacokinetics of IXT-m200 following a single 3-g intravenous dose of IXT-m200 in healthy participants.

2.2 Study Overview

Approximately 9 participants will be enrolled in the study in a single cohort. Participants will be randomized to 3 g IXT-m200 or placebo at a 7:2 ratio. Each will receive their dose as a 30-min IV infusion, then remain at the study site overnight to complete Day 1 and Day 2 assessments (e.g., ECG, laboratory assessments, blood draws, and vital signs). Following discharge on Day 2, participants will return to the clinic for follow-up PK and safety assessments on Day 8, then every 1-3 weeks thereafter until Day 127.

2.3 Sample Size Considerations

Nine healthy adults will be randomized into the study. The sample size chosen for this study is not based on statistical considerations. The number of participants within each dose group was chosen based on historical experience with safety and pharmacokinetic trials and to match the study design used in the previous Phase 1 study with IXT-m200 which provided adequate safety and pharmacokinetic data. The sample size falls within the range of those used in other studies of this nature.

2.4 Selection and Withdrawal of Participants

2.4.1 Inclusion Criteria

Participants must meet the following inclusion criteria:

1. Be at least 18 years of age at the time of study consent;
2. Be able and willing to read, comprehend, and give Authorization for Use/Disclosure of Health Information (HIPAA) and informed consent;
3. Be healthy, based on the pre-study medical evaluation (medical history and physical exam, vital signs, ECG, and clinical laboratory evaluations);
4. Be willing to comply with study instructions and dosing, agree to make all appointments, and complete the entire course of the study;
5. Be of nonchildbearing potential or agree to use protocol-specified method(s) of birth control throughout study participation;

6. Agree to adhere to Lifestyle Considerations throughout study duration (see protocol section 5.3).

2.4.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Have a history of treatment with a monoclonal antibody in the past year;
2. Have a known contraindication or sensitivity to IXT-m200 based on known allergies to other mAbs, any inactive ingredient of IXT-m200, or any other products required for the study procedures;
3. Have a history of alcohol and/or drug use disorder, as determined by DSM-5 criteria;
4. Have a history of stimulant use, including methamphetamine and amphetamine;
5. Be currently taking certain other drugs and medications, including: "designer drugs" (e.g., 3,4-methylenedioxyMETH (MDMA, Ecstasy, Adam, XTC) and its N-dimethyl metabolite methylenedioxyamphetamine (MDA), anti-orexigenic drugs (including over-the-counter medications for weight loss), or be chronic users of phenethylamine compounds (e.g., phenylpropanolamine, ephedrine, pseudoephedrine, amphetamine, phentermine, phenmetrazine, methylphenidate, diethylpropion, and propylhexedrine);
6. Have a positive drug screen for any psychoactive substances (legal or nonlegal) on Day 1 prior to dosing;
7. Have a history of severe allergy (rash, hives, breathing difficulty, etc.) to any medications;
8. Have a history of allergic or environmental bronchial asthma within the past 3 years;
9. Have a clinically significant history of or current abnormality or disease of any organ system, including renal, hepatic, gastrointestinal, cardiovascular, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous (e.g., psychiatric conditions), or hematologic systems, or recent clinically significant surgery,
10. Have a history of seizure, epilepsy, severe head injury, multiple sclerosis, or other known neurological conditions,
11. Have a planned or scheduled surgical procedure during the study;
12. Have recently donated blood or plasma (within 30 days of study drug dose);
13. Have a current diagnosis of anorexia nervosa or bulimia disorder;
14. Be currently participating or has participated within the last 30 days prior to the start of this study in a drug, device, or other interventional research study;
15. Be pregnant or lactating;
16. In the Investigator's or Sponsor's (or designee) opinion, be inappropriate for the study.

2.5 Criteria for Individual Participant Discontinuation of Protocol Therapy

The Investigator may discontinue a participant from study drug administration for the following reasons:

- the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation, such as an infusion reaction,
- any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant,
- significant non-compliance by the participant,
- if, in the Investigator's opinion, continuation with study drug administration would be detrimental to the participant's well-being,
- at the specific request of InterveXion (Sponsor) or the Investigator.

In all cases, the reason for withdrawal or discontinuation must be recorded in the CRF and in the participant's medical records. If the reason is not known, an attempt must be made to follow up with the participant to establish whether the reason was an AE, and, if so, this AE must be reported. Once the participant has been contacted and expresses their decision to withdraw from further participation in the study, the research staff will cease to try to make further contact.

2.6 Criteria for Individual Participation Discontinuation from the Trial

Participants who withdraw consent for future study visits (following early termination assessments) will be considered 'withdrawn'. Participants are free to withdraw at any time upon request; they will be asked to complete early termination assessments as soon as possible. Participants that receive less than the complete single dose of study drug but agree to continue participation in other study procedures and assessments will be considered 'discontinued'. Participants are free to discontinue at any time during dosing upon request.

2.7 Handling of Participant Withdrawals or Discontinuation of Study Intervention

Participants will be encouraged to complete study visits and assessments, even if they elect to discontinue study drug administration. In this case, all study activities will be completed per protocol with the exception of dose administration.

2.8 Replacement of Participants

Participants who withdraw or are discontinued may be replaced at the Sponsor's discretion until there are 6 participants who have completed the protocol through Day 63.

2.9 IXT-m200 Dosing and Administration

Participants will only be randomized and dosed with study drug if they have passed all screening requirements before or on Day 1. Participants will be randomized on Day 1 to receive 3 g IXT-m200 or placebo (7:2).

Each participant will receive 1 dose of assigned study drug on Day 1. Participants should lie supine or semi-reclined during dose administration. Each dose will be given with an infusion

pump over 30 minutes with a 50-mL saline flush dispensed after the dose to ensure the entire dose is flushed through the infusion set. The study drug infusion start/stop time, infusion rate, infusion volume, whether the infusion was completed, if it was stopped, or stopped and restarted will be recorded.

2.10 Schedule of Events

Table 2-1 Schedule of Events

Assessment [a]	**Screening**	**Inpatient**		**Follow-up (±1 day)**	**Follow-up (±3 days)**		**ET**
Study Week	**≤-1**	**1**		**2**	**3-17**	**18**	**NA**
Study Day	**-30 to -1**	**1**[b]	**2**	**8**	**15, 22, 29, 36, 43, 64, 85, 106**	**127**	**NA**
Informed consent	X						
Initial evaluations Eligibility criteria Demographics Medical history and medications Vital signs [c] Physical exam Psychiatric evaluation Urine pregnancy test	X						
Laboratory tests [d]	X	X	X	X	X (29 and 64 only)		X
Urine drug screen		X					
Wellness check Update medical history Update medications Vital signs [c] Targeted physical exam		X	X	X	X	X	X
ECG [e]		X					
Urine pregnancy test		X				X	X
Blood for cytokines [f]		X					
Blood for PK [g]		X	X	X	X	X	X
Blood for HACA [h]		X				X	X
Randomization		X					
Dose administration [i]		X					
AE monitoring		Continuous					X

Abbreviations: ECG – electrocardiogram; ET – early termination visit; HACA – human anti-chimeric antibodies; NA – not applicable; PK – pharmacokinetic

a) Descriptions of assessments are in Section 8.1 of the Protocol.
b) Study Day -1 is the day prior to the first dose. Study Day 1 is the day of the first dose.
c) Vital sign measurements will be taken on Day 1 starting with a pre-dose measurement (≤30 min prior), then 0.25, 0.5, 1, 2, and 4 hours (±5 min) after dosing starts, and as needed afterward until normalization. Measurements will be obtained once on each non-dosing day. Each test may be repeated once at each time point if the initial result is out of range.
d) Laboratory tests require blood and urine sampling for hematology, serum chemistry, and urinalysis. Samples are to be taken at screening, pre-dose and 2-hr post-dose completion (±10 min) on Day 1, and once on Days 2, 8, 29, and 64.

e) ECGs are to be done pre-dose (up to 2 hr prior) and 30-min post-dose completion (±15 min) on Day 1.
f) Cytokine samples are to be taken pre-dose (≤60 min prior) on Day 1. If a participant has an infusion reaction, cytokine sampling at 1- and 4-hours post-dose (±10 min) should be performed. If no infusion reaction is observed, pre-dose samples will not be analyzed.
g) PK samples are to be taken pre-dose (≤30 min prior), then 1, 4, and 8 hr (±10 min) and 24 hr (±30 min) after the start of the infusion on Day 1. All other PK samples are to be collected once each visit.
h) HACA samples are to be taken pre-dose (≤60 min prior) on Day 1 and once on Day 127.
i) Doses will be given over 30 min by IV infusion

2.11 Study Endpoints

2.11.1 Primary Endpoints

The primary endpoint for the study is number of participants with treatment-related AEs assessed by physical examinations and vital sign, ECG, and clinical laboratory testing.

2.11.2 Secondary Endpoints

The secondary endpoint is the time course of IXT-m200 concentrations. This will be examined by determining the IXT-m200 serum pharmacokinetic (PK) parameters derived from the serial serum concentrations following single-dose IV administration, including C_{max}, T_{max}, K_{el} (λ_z), AUC_{last}, AUC_{inf}, MRT, CL, and Vd and other PK parameters as data permit.

3. Efficacy Assessments

Not Applicable.

4. Pharmacokinetic Assessments

Serum IXT-m200 PK parameters will be calculated from serum concentration data determined using a validated bioanalytical method. Pharmacokinetic parameters will be calculated using noncompartmental analysis methods suitable for intravenous infusion. Pharmacokinetic parameters that will be calculated if data permit are presented in **Table 4-1**.

Table 4-1 Pharmacokinetic Parameters

Parameter	Description	Method of Determination
C_{max}	Maximum serum concentration (observed)	Observed directly from data
T_{max}	Time to maximum serum concentration (observed)	Observed directly from data
C_{last}	Serum concentration at last measurable time point (observed)	Observed directly from data

T_{last}	Time to last measurable serum concentration (observed)	Observed directly from data
AUC_{last}	Area under the serum concentration-time curve from zero (start of infusion) to last quantifiable time point	AUC =Σ Δt* (C1 + C2)/2
AUC_{inf}	Area under the serum concentration-time curve from zero (start of infusion) extrapolated to infinity	$AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$
K_{el} or λ_z	Elimination rate constant associated with the terminal elimination phase	K_{el} is calculated by a linear regression of the log-linear concentration-time curve.
$t_{½}$	Terminal elimination half life	$t_{1/2} = \text{In } (2) /\lambda_z$
CL	Systemic clearance	$CL = Dose/AUC_{inf}$
Vz	Volume of distribution based on the terminal phase.	$Vz = Dose/[\lambda_z(AUC_{inf})]$
V_{ss}	An estimate of the volume of distribution at steady-state	$V_{ss} = MRT_{inf} * CL$
MRT_{last}	Mean residence time (MRT) from zero to last quantifiable time point	$AUMC_{last}/AUC_{last} – TI/2$ TI is the length of infusion
MRT_{inf}	Mean residence time (MRT) extrapolated to infinity	$AUMC_{inf}/AUC_{inf} – TI/2$ TI is the length of infusion

5. Safety Assessments

All safety analyses will be performed on the Safety population. Descriptive statistics will be used to summarize AEs, serious AEs, AEs causing withdrawal or discontinuation from the study, AEs judged by the Investigator as potentially related to study drug, changes in laboratory and vital signs, and immune response by measurement of anti-IXT-m200 antibody levels. AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term.

Other safety observations and measurements will include vital signs, physical exam, pregnancy test, laboratory tests, and ECG. Descriptive statistics will be used to summarize continuous variables and change from baseline. Frequency and shift tables will be created for categorical variables.

6. Data Analysis and Statistical Considerations

6.1 General Considerations

Sample size was selected empirically without consideration of statistical power. As a result, no formal statistical hypothesis will be evaluated. Draft statistical summaries will be provided during the course of the study using dummy treatment code. The final report will be generated when all corresponding data are collected and database locked and treatment code released per Symbiance SOP. Statistical tables, data listings, and graphs will be prepared using SAS Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

6.2 Analysis Populations

Pharmacokinetic Population: All participants who receive active study drug and have at least one measured IXT-m200 concentration at a scheduled PK time point after start of dosing comprise the PK Population. If participants do not receive a complete dose or have incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis. This population will be used for all PK summaries.

6.3 Safety Population: All participants who receive exposure to study drug, including placebo comprise the Safety Population. This population will be used for all demographic and safety summaries.Safety Analyses

Safety analyses will be presented by IXT-m200 and placebo groups and for all participants in the safety population.

Treatment-emergent adverse events (TEAEs) and serious TEAEs will be summarized by SOC and preferred term, and by severity (Grades 1, 2, 3, or 4) and relationship to treatment for IXT-m200 and placebo groups. The analysis of TEAEs by severity will count TEAEs by worst severity if an individual participant has a TEAE with more than one severity. The analysis of TEAEs by relationship to treatment will define treatment-related TEAEs as including all TEAEs assessed as definitely, probably, or possibly related to treatment, and non-treatment-related TEAEs as including all TEAEs assessed as unlikely and unrelated to treatment.

Vital signs, physical exam, pregnancy test, laboratory tests, and ECG will be tabulated. Descriptive statistics will be used to summarize continuous variables and change from baseline, which is defined as the most recent observation before dosing. Frequency and shift tables will be created for categorical variables.

6.4 Pharmacokinetic Analyses

Pharmacokinetic parameters will be calculated using Phoenix WinNonlin Version 8.3 or higher (Certara USA, Princeton, New Jersey, USA).

6.4.1 Serum Concentrations

Serum concentrations of IXT-m200 will be listed with nominal sampling times for all participants in the PK Population.

Serum concentrations will be summarized using descriptive statistics for each treatment. Below the limit of quantitation (BLQ) concentrations will be treated as zero for the computation of descriptive statistics. Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics.

Mean and individual IXT-m200 serum concentration versus nominal time will be displayed in the figures (linear and semi-logarithmic scale) by dose and participant. Graphs may be generated in SAS or WinNonlin (or both) applications.

6.4.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived from IXT-m200 serum concentrations using actual doses administered and actual sampling times of blood collection for each participant in the PK Population. Descriptive statistics will be summarized by dose. Descriptive statistics (mean, standard deviation (SD), coefficient of variation (CV%), geometric mean, geometric SD, geometric CV%) will be reported for all PK parameters, except for T_{max} where N, median, min, and max will be reported.

Predose samples that are BLQ or missing will be assigned a numerical value of zero for the calculation of area under the concentration-time curve (AUC). Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if reanalysis or exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating AUC. If BLQ values occur at the end of the collection interval (after the last quantifiable concentration), these will be treated as missing data. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile.

The linear-log trapezoidal rule will be applied for the calculation of AUC parameters in the noncompartmental analysis model. Pharmacokinetic parameters presented in **Table 4-1** will be listed by participant and summarized. Graphical presentations of PK data may be added at the discretion of the PK scientist.

Pharmacokinetic parameters derived with K_{el} such as $t_{1/2}$ and AUC_{inf}, will be listed but excluded from descriptive statistics if R^2_adjusted < 0.8 in K_{el} estimation.

For determination of AUC_{inf}, if the percentage of extrapolated AUC is more than 20% of AUC_{inf} from t_{last} to infinity, then individual AUC_{inf} result and the PK parameters depending on AUC_{inf} (CL, Vz, and MRT_{inf}) will be listed but flagged as not reliable calculations. AUC_{inf} and

the PK parameters depending on AUC_{inf} for these flagged participants will not be included in the descriptive statistics table.

6.5 Immunogenicity and Cytokines Analyses

Human anti-chimeric antibody (HACA) samples are to be taken pre-dose (≤60 min prior to the start of the infusion) on Day 1 and once on Day 127. HACA results, including screening, confirmation, and titer results as available, will be summarized by group and individual and in a descriptive statistics table if appropriate.

A cytokine panel including at a minimum IL-6, IL-8, and TNFα levels will be determined only if any study drug infusion reaction occurs. If cytokines are measured, the results will be presented in a listing and the participant will be presented in a narrative.

7. Data Handling

7.1 Handling of Missing Data

All missing data will be queried. With the exception of the treatment of BLQ values for the pharmacokinetic analyses described in section 6.4, no missing values imputation will be applied. Pooling of centers not required as this is a single-center study.

7.2 Drop-outs, Withdrawals, Replacement Policy

Participants who withdraw or are discontinued may be replaced at the Sponsor's discretion until there are 6 participants who have completed the protocol through Day 63. In case a discontinued participant is replaced, both the original and replacing participants will be included in the relevant listings and AE reporting.

8. Changes to the Planned Analyses

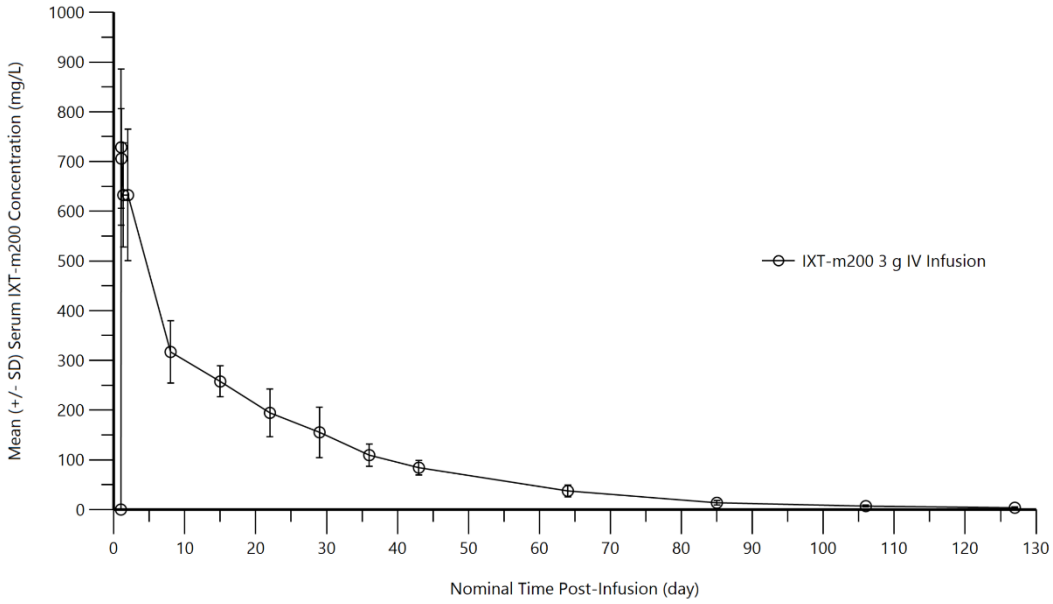
Any deviation(s) of consequence from the Statistical Analysis Plan during the data analysis will be documented and justified in an amended Statistical Analysis Plan and/or in the final study report or addressed in a separate document, as appropriate.

9. Revision History

Version	Date	Comments
1.0	15 December 2021	Original Statistical Analysis Plan

Appendix 16.1.9 Supplement: WinNonlin Figures and Output

Supplemental Summary Figure 1 – Mean (±SD) Serum IXT-m200 Concentration-Time Profile following IXT-m200 3 g IV infusion, Linear Plot, PK Population



Supplemental Summary Figure 2 – Mean (±SD) Serum IXT-m200 Concentration-Time Profile following IXT-m200 3 g IV infusion, Semi-log Plot, PK Population

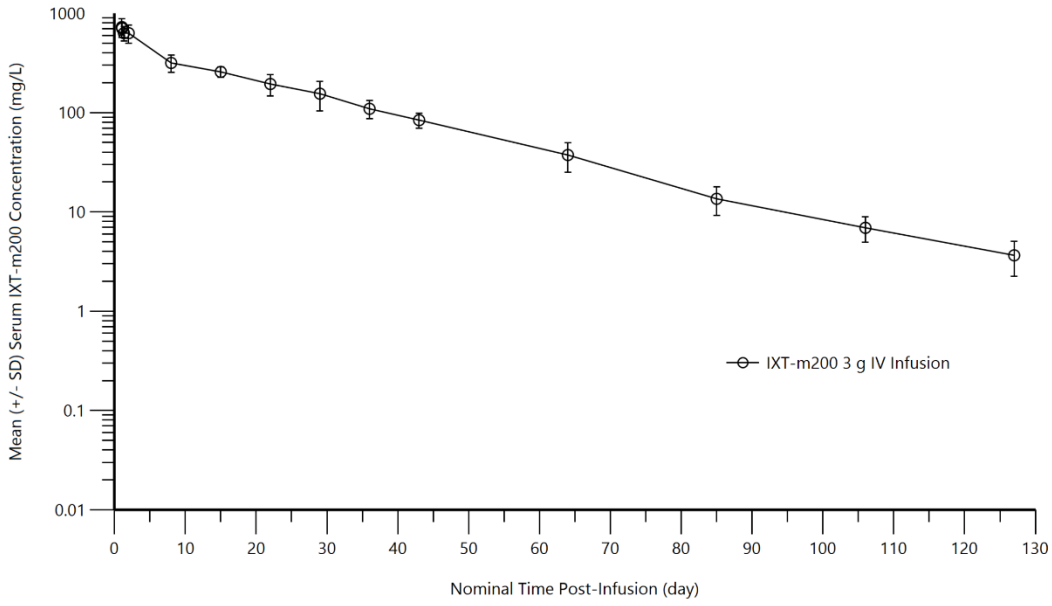


Figure 14.2.4.1 Individual Linear Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1002) – PK Population

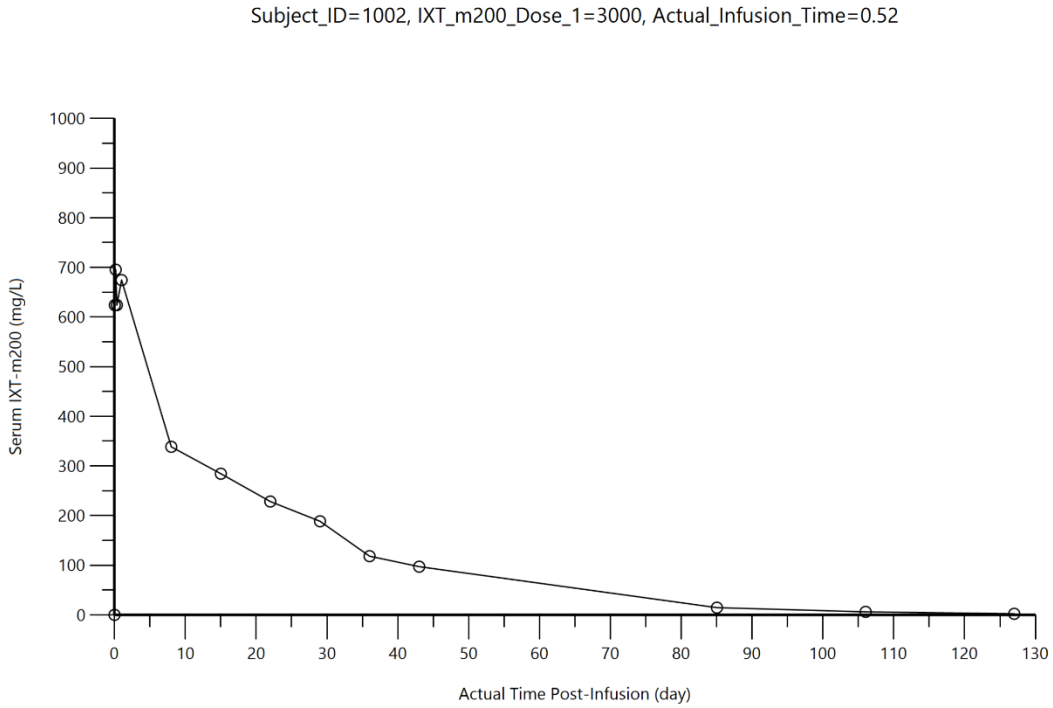


Figure 14.2.4.2 Individual Linear Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1003) – PK Population

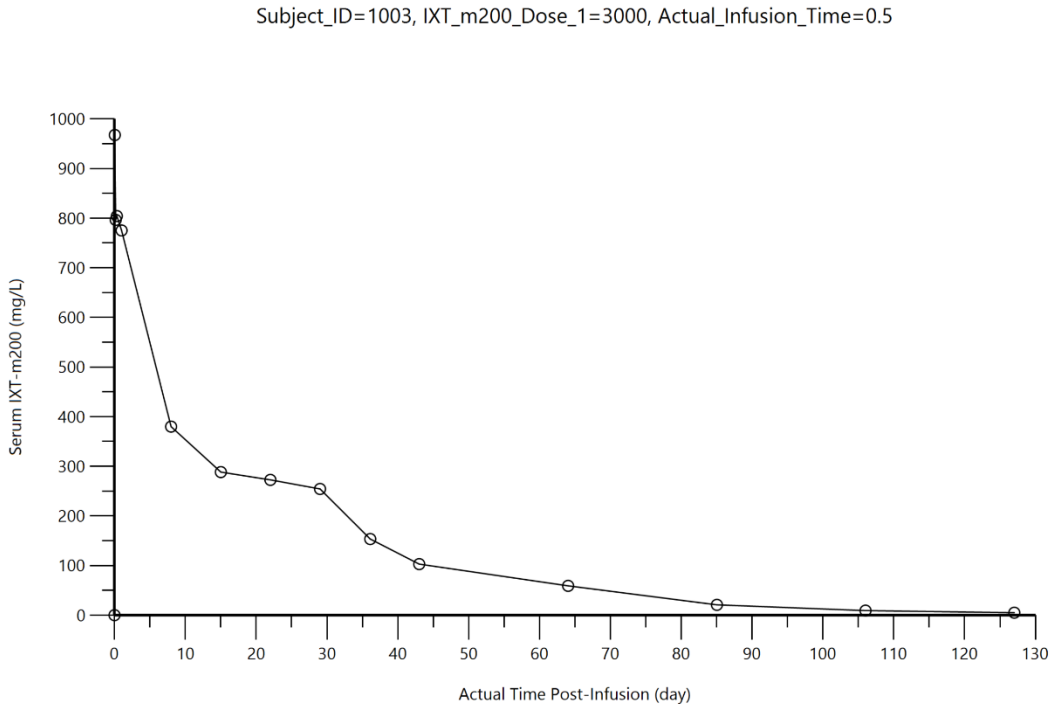


Figure 14.2.4.3 Individual Linear Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1011) – PK Population

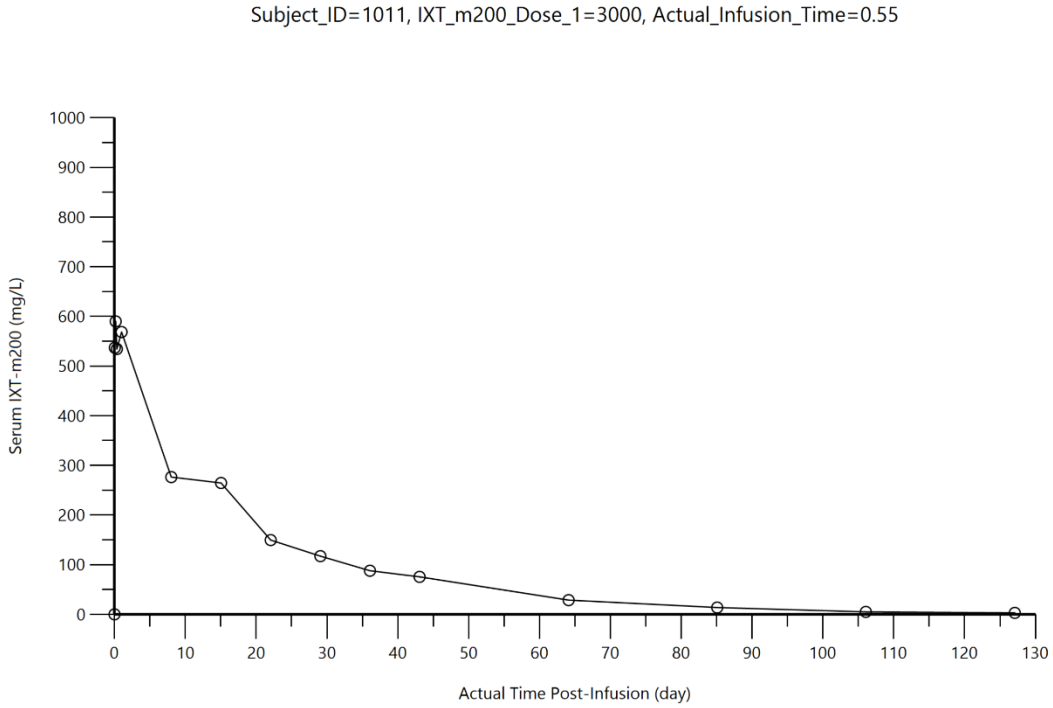


Figure 14.2.4.4 Individual Linear Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1012) – PK Population

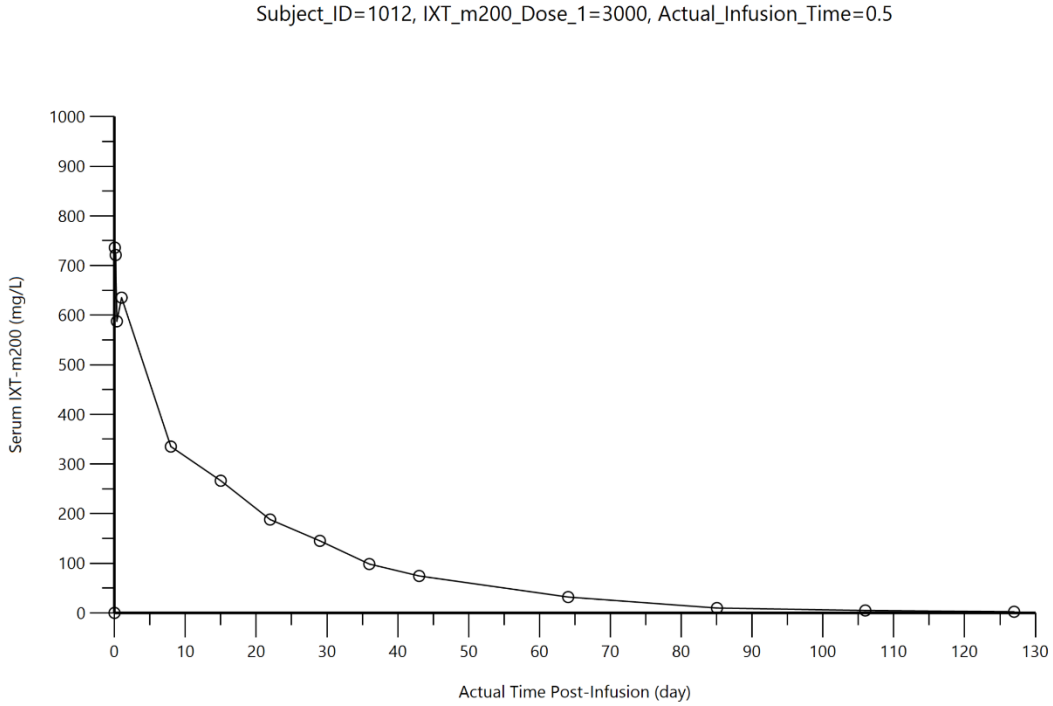


Figure 14.2.4.5 Individual Linear Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1018) – PK Population

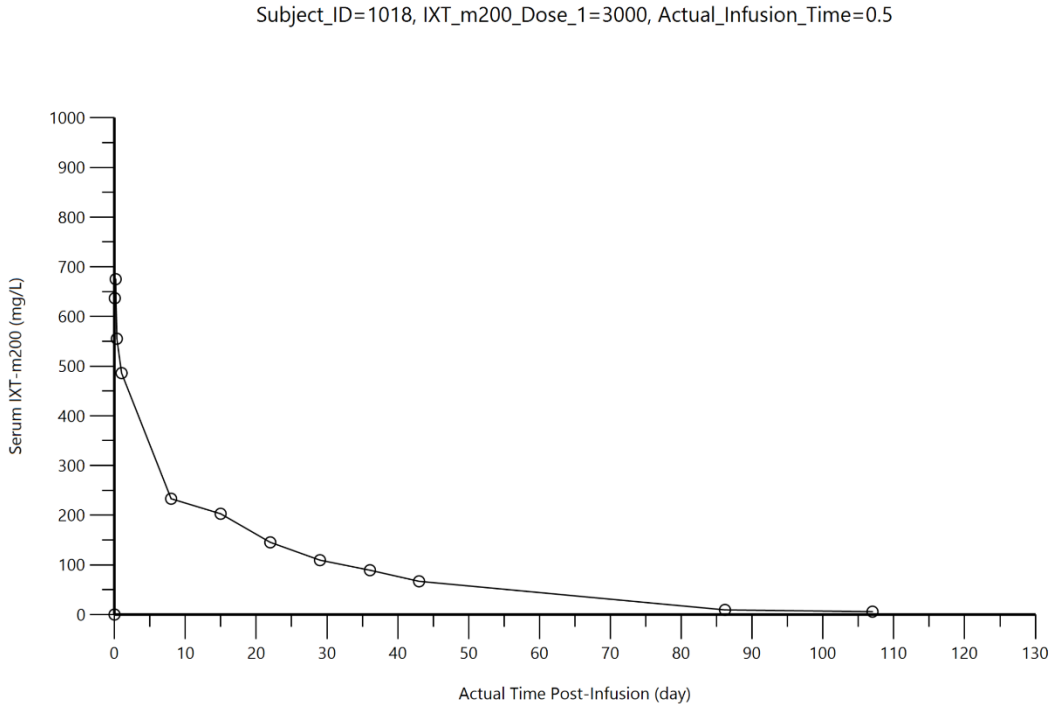


Figure 14.2.4.6 Individual Linear Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1023) – PK Population

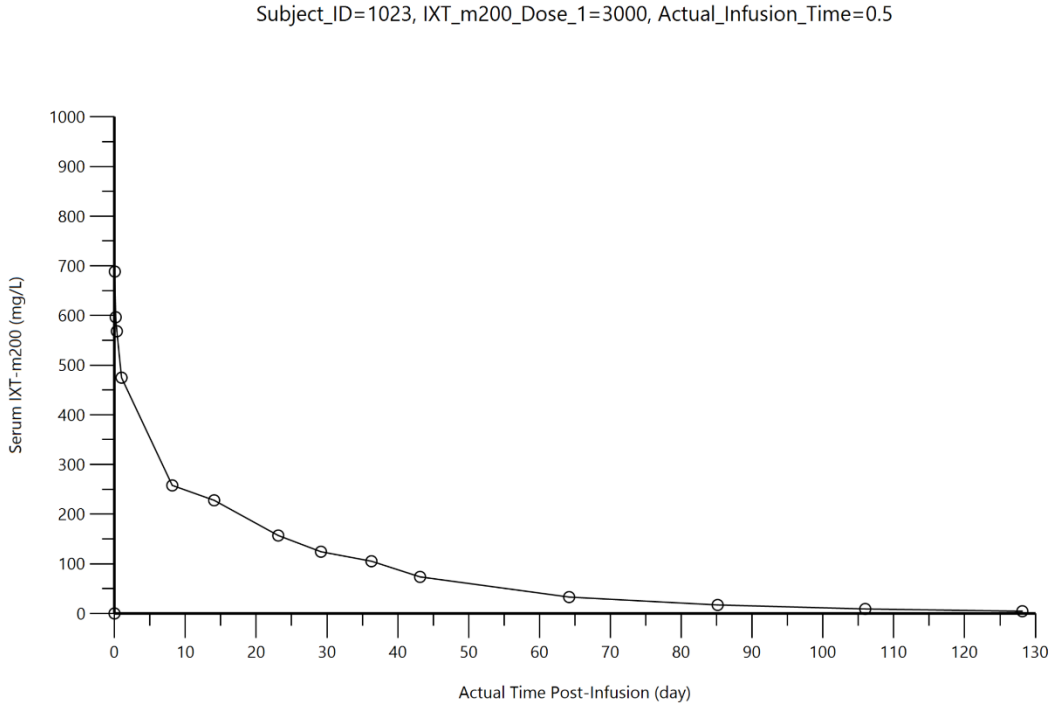


Figure 14.2.4.7 Individual Linear Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1024) – PK Population

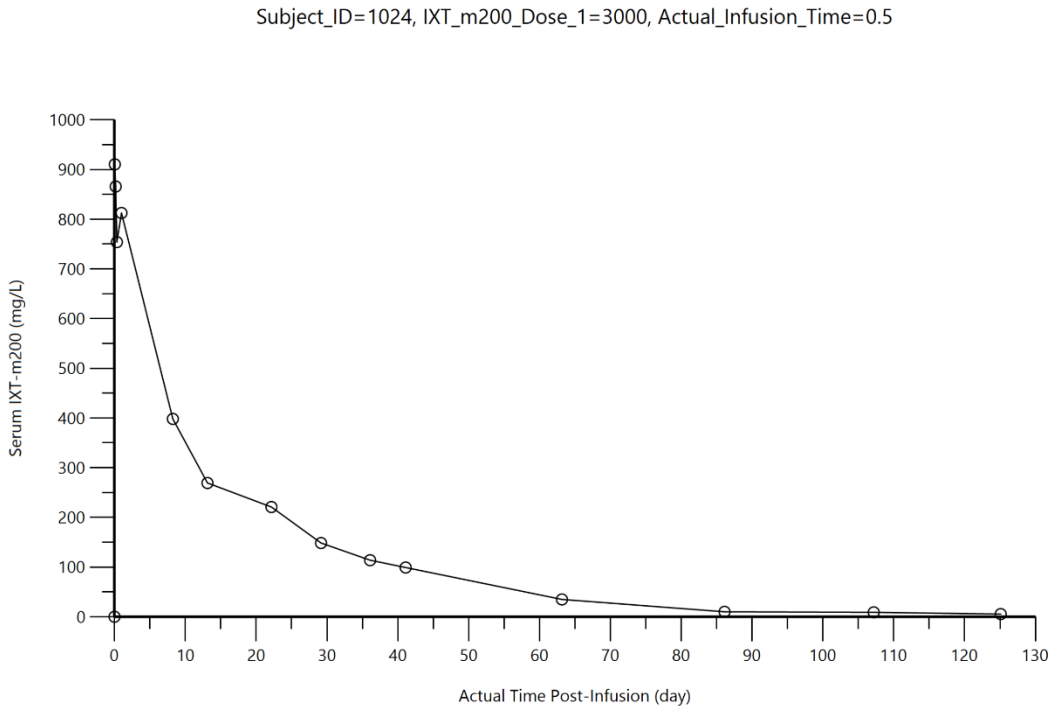


Figure 14.2.4.8 Individual Semi-log Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1002) – PK Population

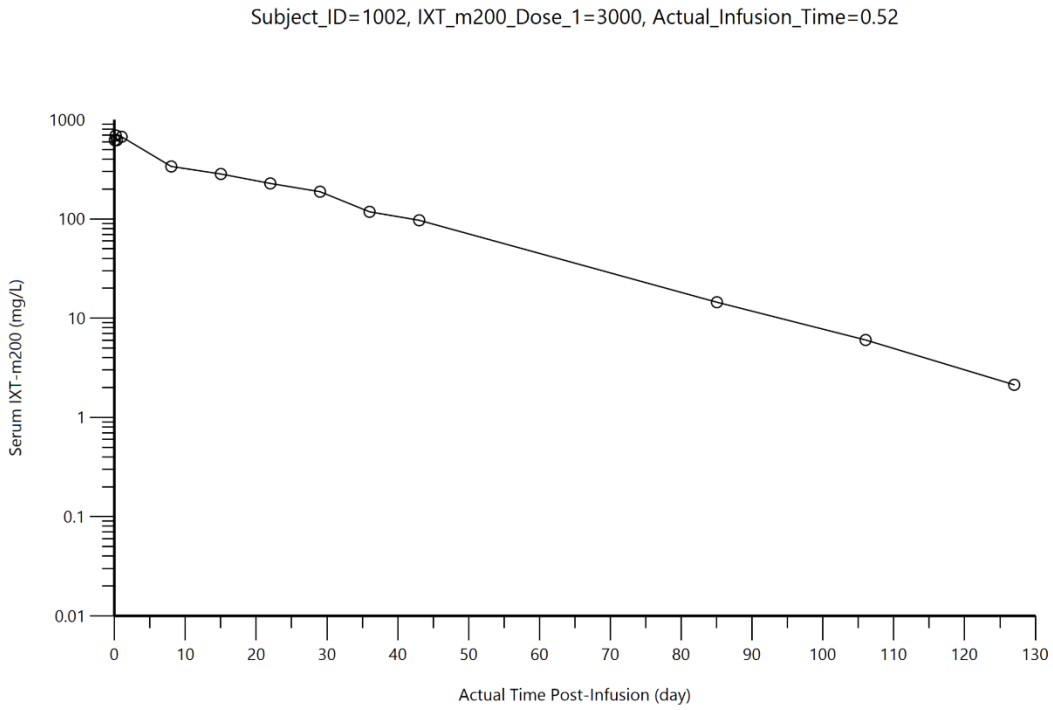


Figure 14.2.4.9 Individual Semi-log Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1003) – PK Population

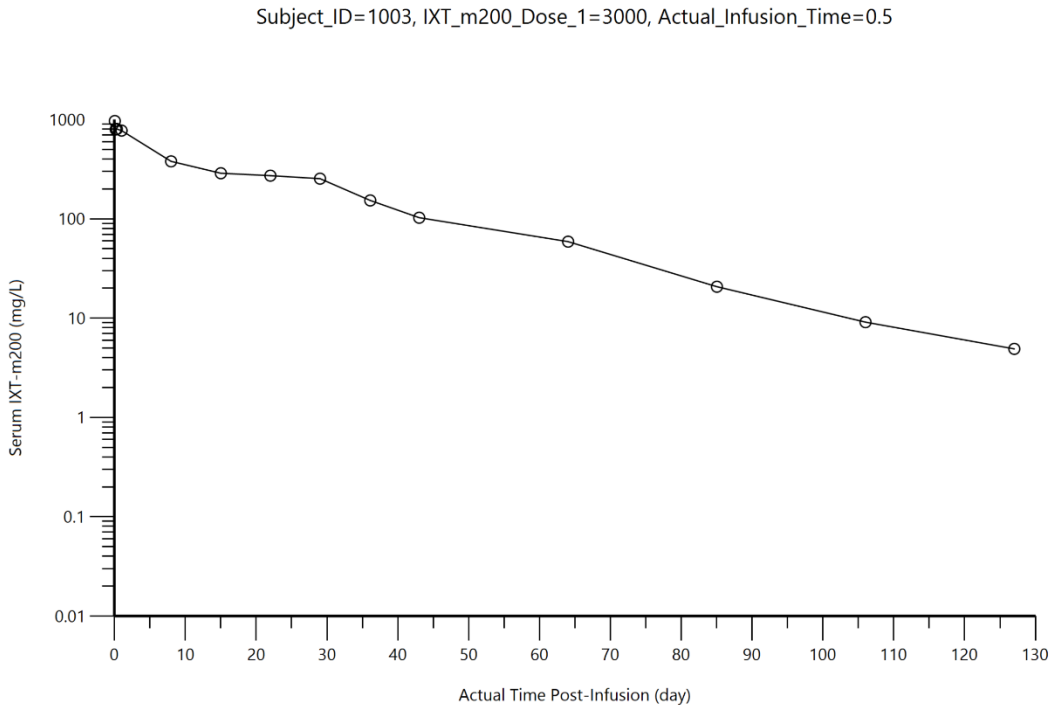


Figure 14.2.4.10 Individual Semi-log Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1011) – PK Population

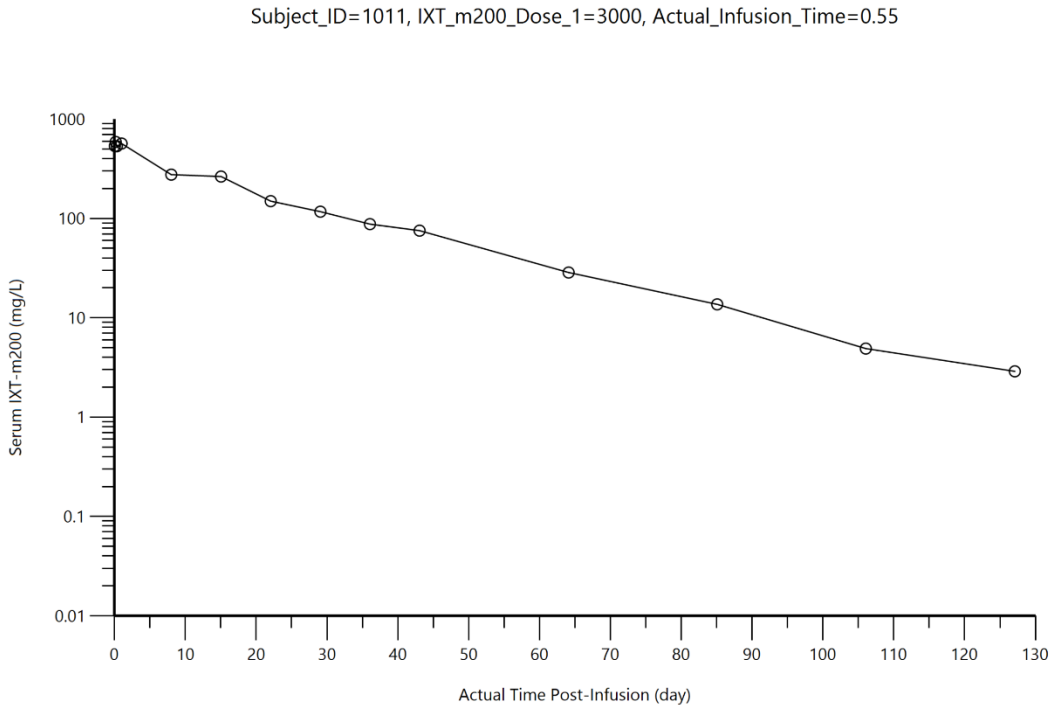


Figure 14.2.4.11 Individual Semi-log Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1012) – PK Population

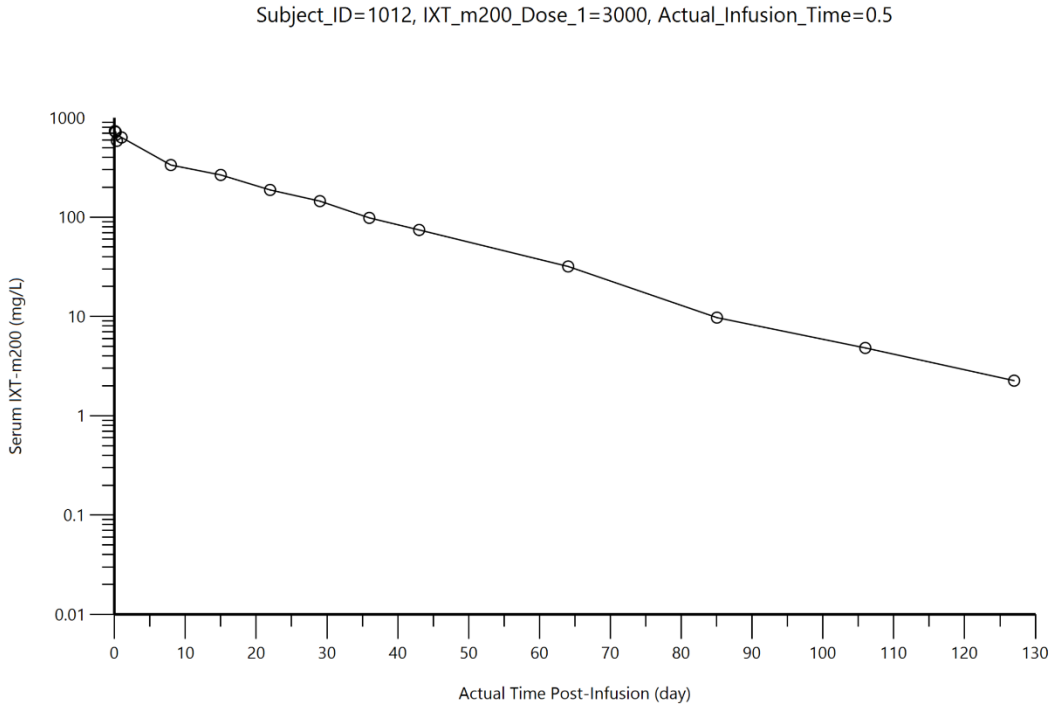


Figure 14.2.4.12 Individual Semi-log Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1018) – PK Population

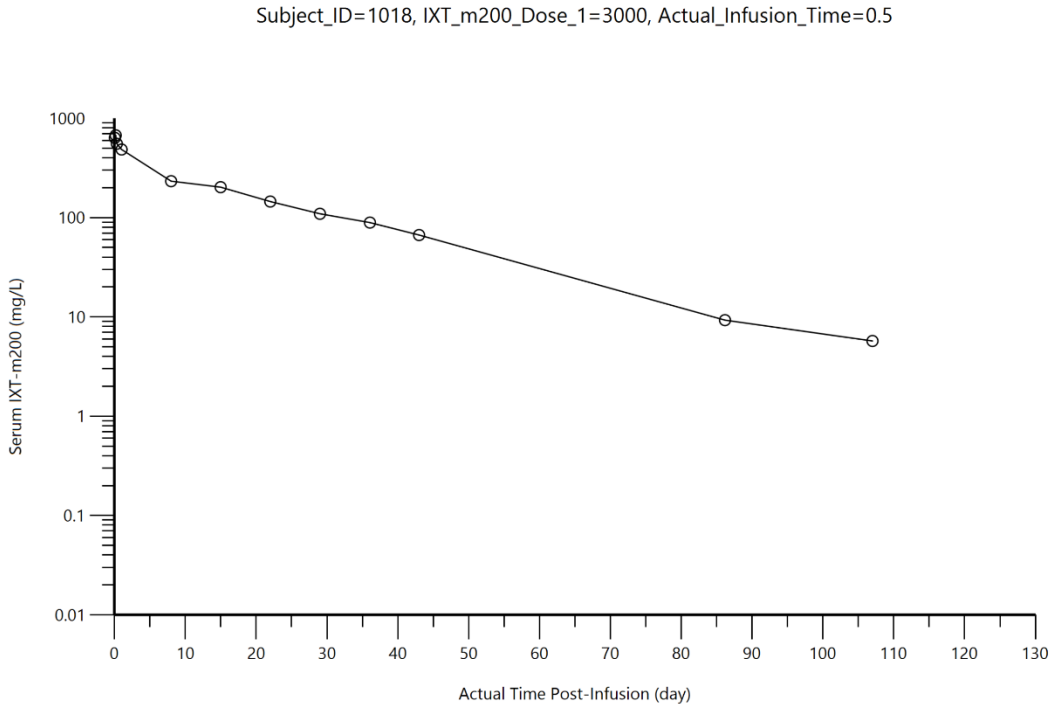


Figure 14.2.4.13 Individual Semi-log Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1023) – PK Population

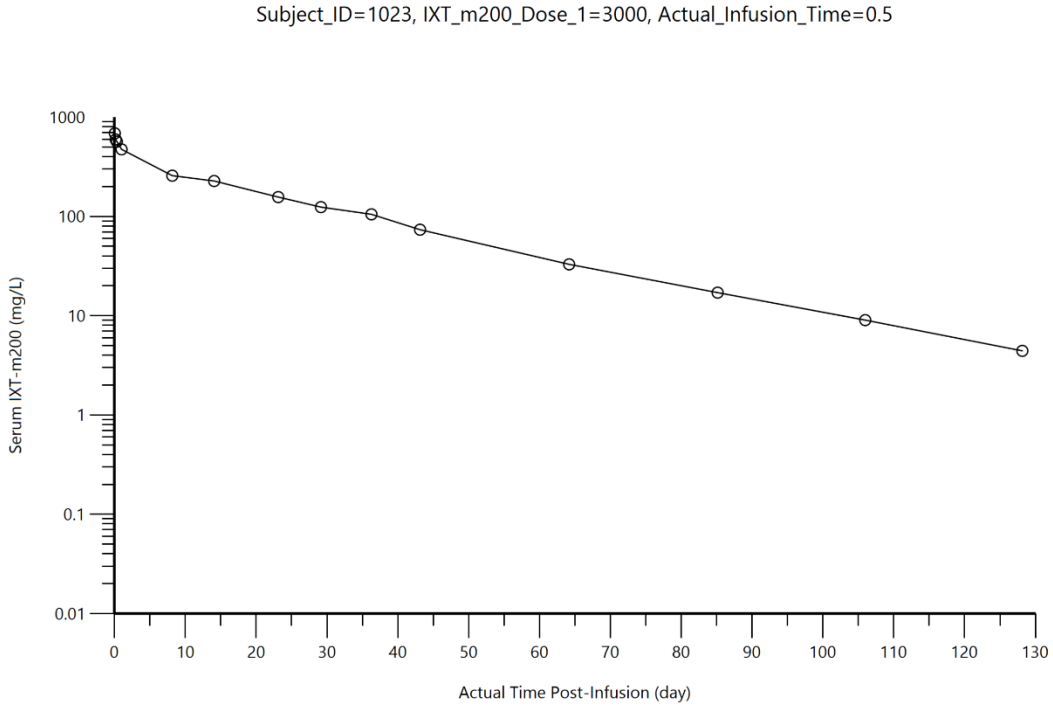
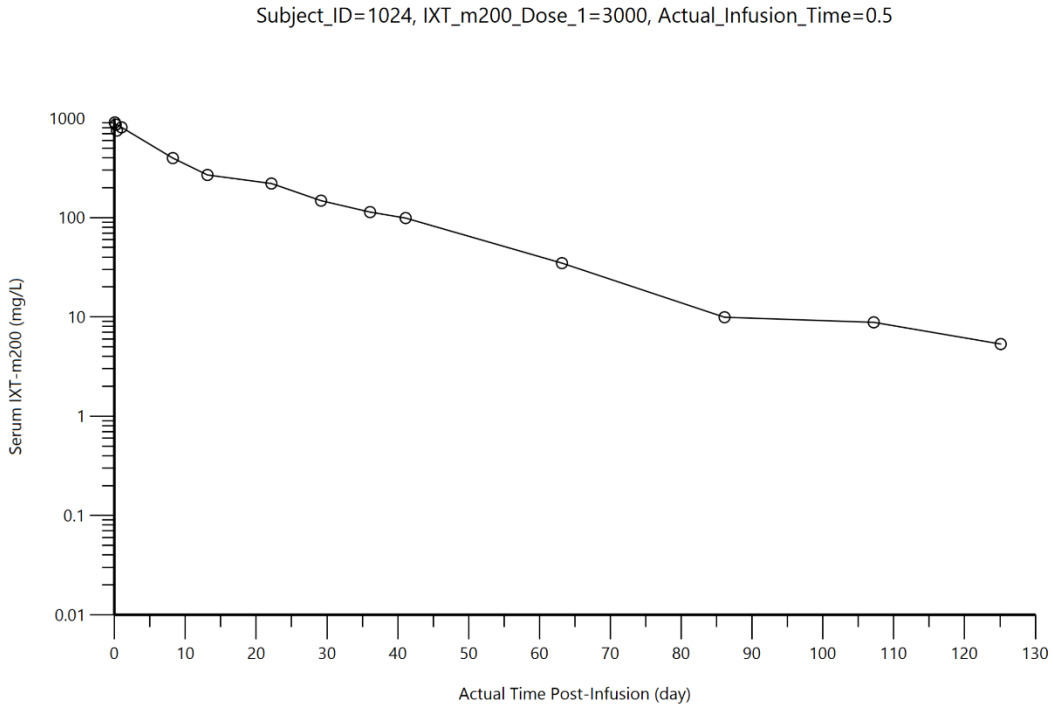
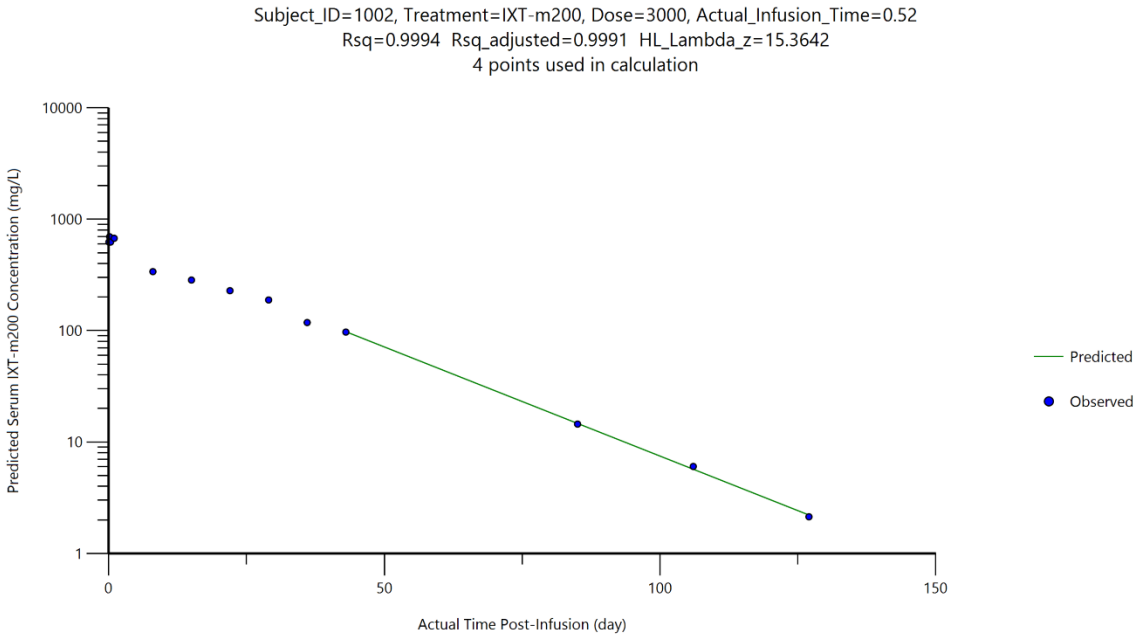
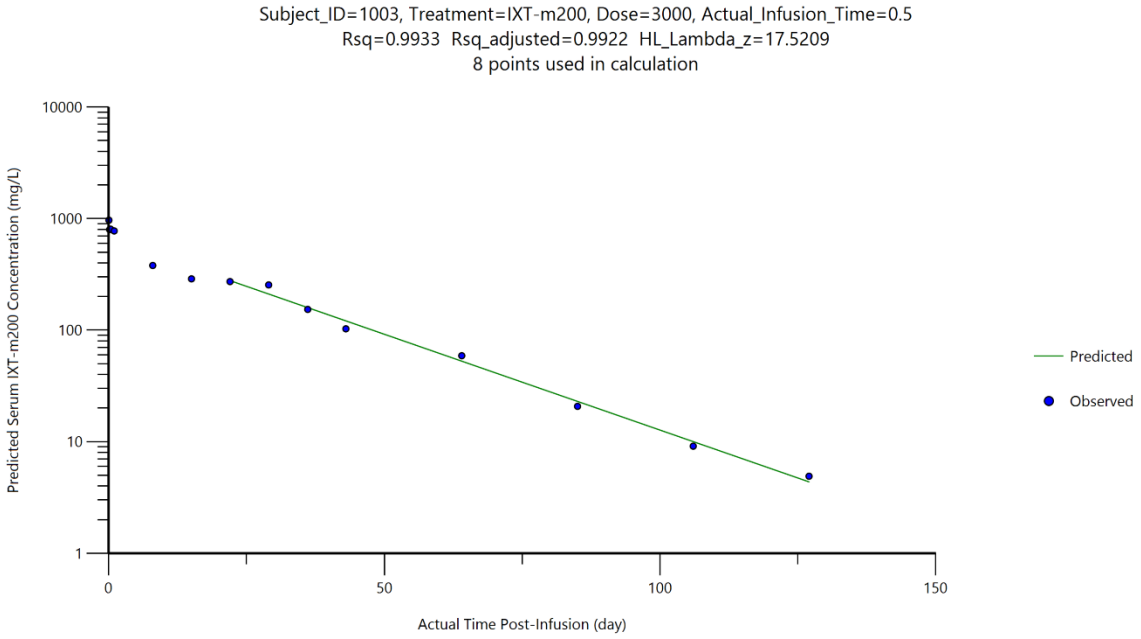


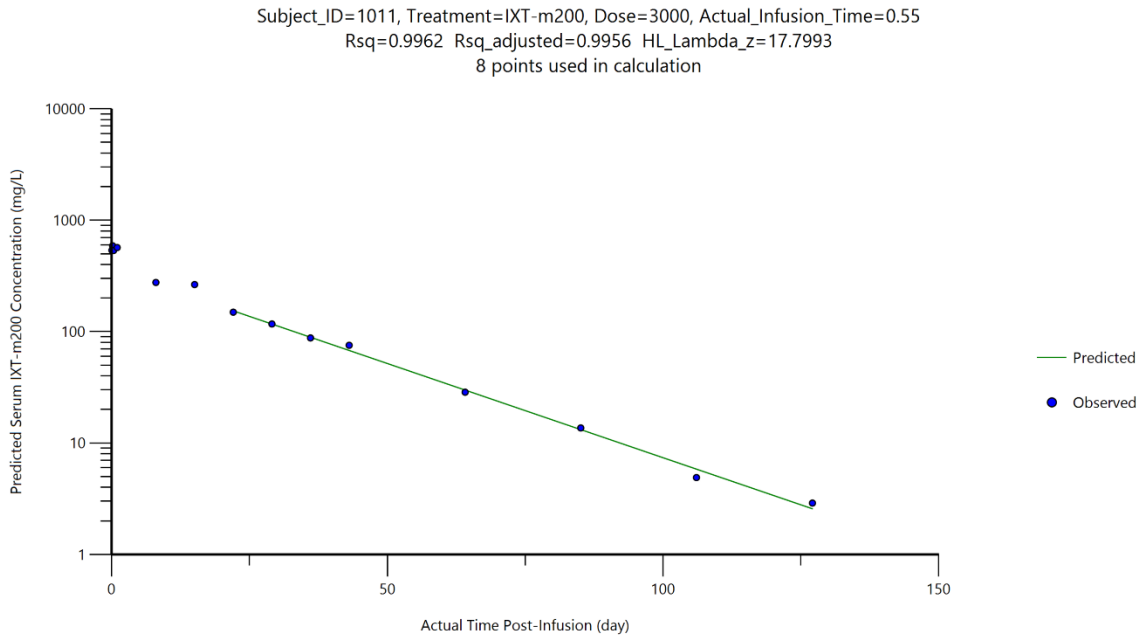
Figure 14.2.4.14 Individual Semi-log Plot of Serum IXT-m200 Concentration-Time Profiles (Subject 1024) – PK Population

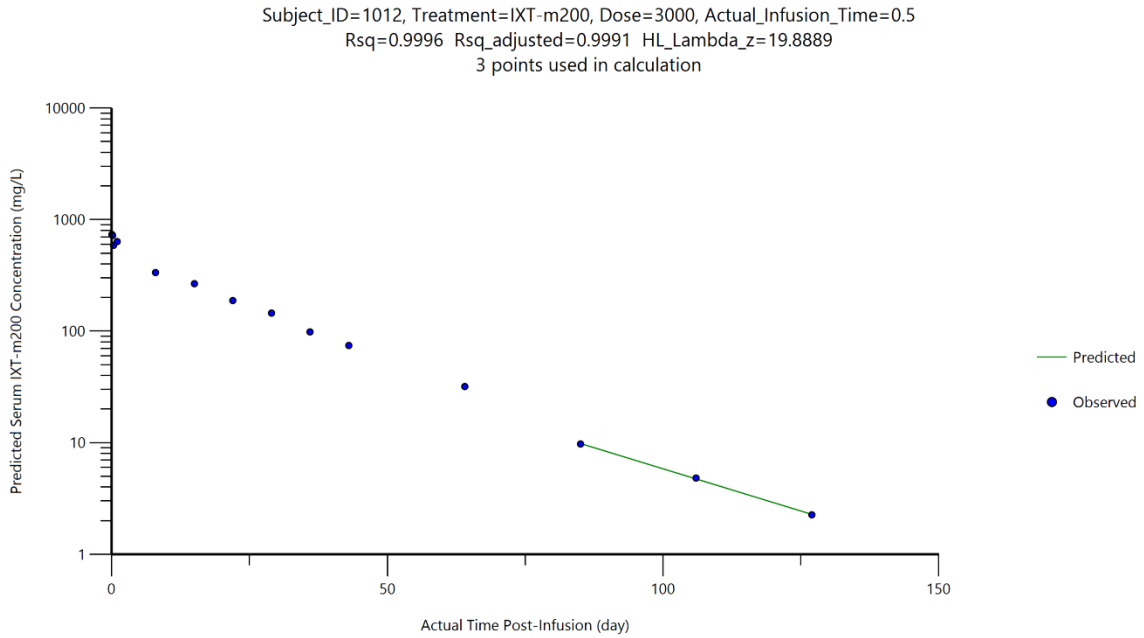


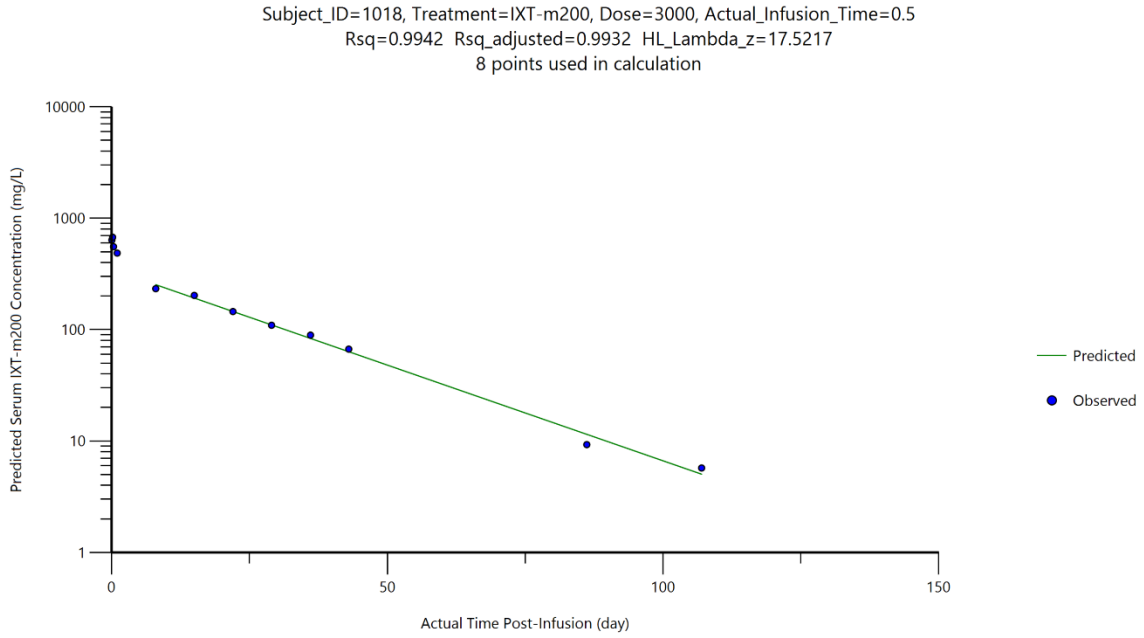
WinNonlin Fitted Plots

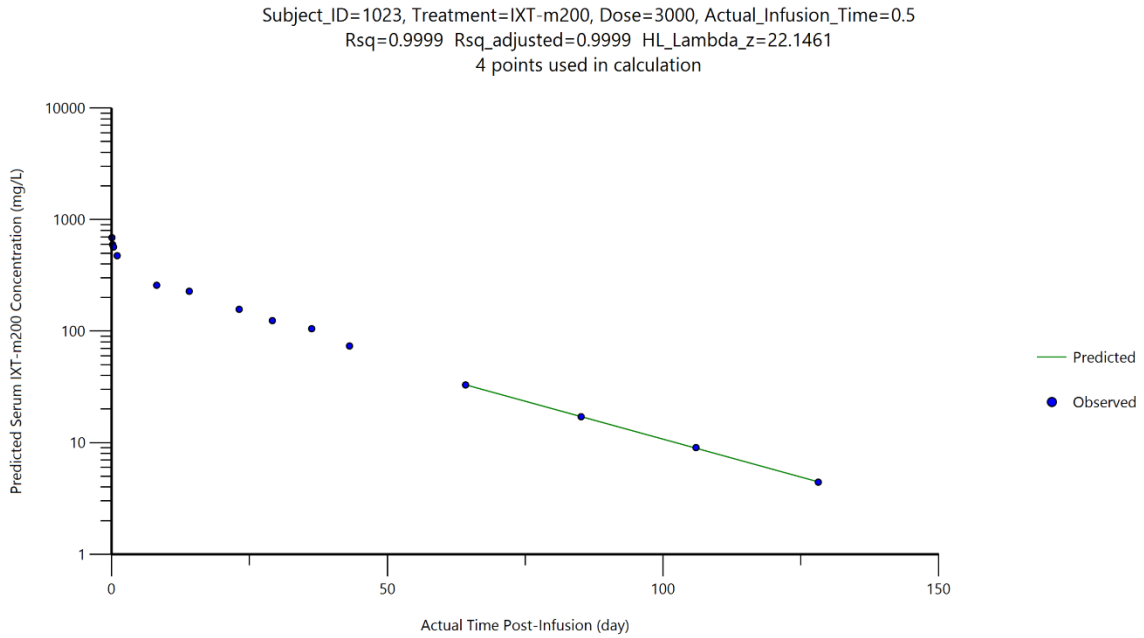


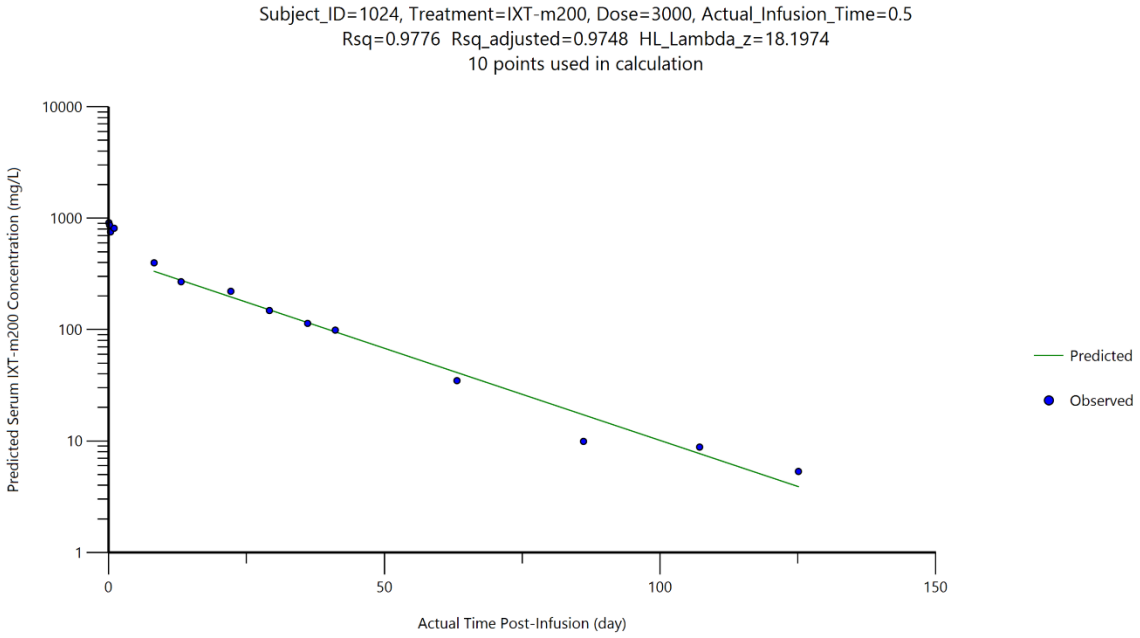



Subject_ID=1011, Treatment=IXT-m200, Dose=3000, Actual_Infusion_Time=0.55
Rsq=0.9962 Rsq_adjusted=0.9956 HL_Lambda_z=17.7993
8 points used in calculation
Predicted Serum IXT-m200 Concentration (mg/L)
10000
1000
100
10
1
0
50
100
150
Actual Time Post-Infusion (day)
Predicted
Observed


Subject_ID=1012, Treatment=IXT-m200, Dose=3000, Actual_Infusion_Time=0.5
Rsq=0.9996 Rsq_adjusted=0.9991 HL_Lambda_z=19.8889
3 points used in calculation
Predicted Serum IXT-m200 Concentration (mg/L)
10000
1000
100
10
1
0
50
100
150
Actual Time Post-Infusion (day)
Predicted
Observed


Subject_ID=1018, Treatment=IXT-m200, Dose=3000, Actual_Infusion_Time=0.5
Rsq=0.9942 Rsq_adjusted=0.9932 HL_Lambda_z=17.5217
8 points used in calculation
Predicted Serum IXT-m200 Concentration (mg/L)
10000
1000
100
10
1
0
50
100
150
Actual Time Post-Infusion (day)
Predicted
Observed


Subject_ID=1023, Treatment=IXT-m200, Dose=3000, Actual_Infusion_Time=0.5
Rsq=0.9999 Rsq_adjusted=0.9999 HL_Lambda_z=22.1461
4 points used in calculation
Predicted Serum IXT-m200 Concentration (mg/L)
10000
1000
100
10
1
0
50
100
150
Actual Time Post-Infusion (day)
Predicted
Observed


Subject_ID=1024, Treatment=IXT-m200, Dose=3000, Actual_Infusion_Time=0.5
Rsq=0.9776 Rsq_adjusted=0.9748 HL_Lambda_z=18.1974
10 points used in calculation
Predicted Serum IXT-m200 Concentration (mg/L)
10000
1000
100
10
1
0
50
100
150
Actual Time Post-Infusion (day)
Predicted
Observed

WinNonlin Core Output

```
WinNonlin 8.3.3.33
Subject_ID=1002,Treatment=IXT-m200,Dose=3000,Actual_Infusion_Time=0.52

                                                    Date:    5/09/2022
                                                    Time:     03:47:44


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                      8.3.3.33
                                Core Version 06Feb2020

Settings
--------
Model:  Plasma Data, Constant Infusion Administration
Number of nonmissing observations:   14
Dose time:      0.00
Dose amount:     3000.00
Length of Infusion:      0.52
Calculation method:  Linear/Log Trapezoidal
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
Lambda_z Acceptance Criterion, Min Rsq_Adjusted:  0.8000
Lambda_z Acceptance Criterion, Max AUC_%Extrap_obs:   20.00


Summary Table
-------------
      Time          Conc.       Pred.     Residual       AUC        AUMC       Weight
        day         mg/L         mg/L         mg/L    day*mg/L  day*day*mg/L
-------------------------------------------------------------------------------------
      0.000         0.000                              0.000      0.000
    0.04236         624.0                              13.22     0.5598
     0.1667         695.4                              95.22      9.406
     0.3333         624.0                              205.1      36.70
      1.000         674.4                              637.7      327.0
      8.013         338.5                              4055.  1.436e+04
      15.01         284.3                              6229.  3.917e+04
      21.99         228.3                              8011.  7.191e+04
      29.01         188.5                              9469.  1.089e+05
      36.00         118.2                          1.052e+04  1.429e+05
      43.01 *       97.07       97.81    -0.7463   1.127e+04  1.725e+05       1.000
      85.04 *       14.49       14.69    -0.1956   1.310e+04  2.778e+05       1.000
      106.0 *       6.035       5.698     0.3371   1.330e+04  2.969e+05       1.000
      127.0 *       2.133       2.212   -0.07910   1.338e+04  3.059e+05       1.000


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

Final Parameters

N_Samples		14
Dose	mg	3000.0000
Rsq		0.9994
Rsq_adjusted		0.9991
Flag_Rsq_adjusted		Accepted
Corr_XY		-0.9997
No_points_lambda_z		4
Lambda_z	1/day	0.0451
Lambda_z_intercept		6.5234
Lambda_z_lower	day	43.0104
Lambda_z_upper	day	127.0021
HL_Lambda_z	day	15.3642
Span		5.4667
Tmax	day	0.1667
Cmax	mg/L	695.3830
Cmax_D	mg/L/mg	0.2318
Tlast	day	127.0021
Clast	mg/L	2.1327
Clast_pred	mg/L	2.2118
AUClast	day*mg/L	13380.1269
AUClast_D	day*mg/L/mg	4.4600
AUCall	day*mg/L	13380.1269
AUCINF_obs	day*mg/L	13427.4011
AUCINF_D_obs	day*mg/L/mg	4.4758
AUC_%Extrap_obs	%	0.3521
Flag_AUC_%Ext_obs		Accepted
Vz_obs	L	4.9524
Cl_obs	mL/day	223.4237
AUCINF_pred	day*mg/L	13429.1545
AUCINF_D_pred	day*mg/L/mg	4.4764
AUC_%Extrap_pred	%	0.3651
Vz_pred	L	4.9517
Cl_pred	mL/day	223.3946
AUMClast	day*day*mg/L	305922.4560
AUMCINF_obs	day*day*mg/L	312974.2497
AUMC_%Extrap_obs	%	2.2532
AUMCINF_pred	day*day*mg/L	313235.8048
AUMC_%Extrap_pred	%	2.3348
MRTlast	day	22.6039
MRTINF_obs	day	23.0486
MRTINF_pred	day	23.0651
Vss_obs	L	5.1496
Vss_pred	L	5.1526

```
WinNonlin 8.3.3.33
Subject_ID=1003,Treatment=IXT-m200,Dose=3000,Actual_Infusion_Time=0.5

                                                    Date:    5/09/2022
                                                    Time:     03:47:44


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                       8.3.3.33
                                 Core Version 06Feb2020

Settings
--------
Model:  Plasma Data, Constant Infusion Administration
Number of nonmissing observations:   15
Dose time:      0.00
Dose amount:     3000.00
Length of Infusion:      0.50
Calculation method:  Linear/Log Trapezoidal
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
Lambda_z Acceptance Criterion, Min Rsq_Adjusted:  0.8000
Lambda_z Acceptance Criterion, Max AUC_%Extrap_obs:   20.00


Summary Table
-------------
      Time          Conc.       Pred.     Residual       AUC        AUMC       Weight
        day         mg/L         mg/L         mg/L    day*mg/L  day*day*mg/L
-------------------------------------------------------------------------------------
      0.000         0.000                              0.000       0.000
    0.04167         967.6                              20.16      0.8399
     0.1674         796.4                              130.7       12.17
     0.3333         804.2                              263.5       45.44
      1.000         775.2                              789.9       395.3
      7.987         379.9                              4662.   1.620e+04
      15.02         288.2                              6995.   4.266e+04
      22.00 *       272.6       278.1     -5.508       8954.   7.884e+04       1.000
      29.01 *       254.2       210.7      43.53   1.080e+04   1.259e+05       1.000
      36.10 *       153.4       159.2     -5.831   1.221e+04   1.715e+05       1.000
      43.01 *       102.8       121.1     -18.29   1.309e+04   2.059e+05       1.000
      64.03 *       59.01       52.73      6.282   1.475e+04   2.930e+05       1.000
      85.03 *       20.75       22.97     -2.220   1.552e+04   3.489e+05       1.000
      106.0 *       9.117       10.02    -0.9005   1.581e+04   3.769e+05       1.000
      127.0 *       4.904       4.364     0.5394   1.595e+04   3.933e+05       1.000


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

Final Parameters

N_Samples		15
Dose	mg	3000.0000
Rsq		0.9933
Rsq_adjusted		0.9922
Flag_Rsq_adjusted		Accepted
Corr_XY		-0.9967
No_points_lambda_z		8
Lambda_z	1/day	0.0396
Lambda_z_intercept		6.4983
Lambda_z_lower	day	22.0021
Lambda_z_upper	day	127.0160
HL_Lambda_z	day	17.5209
Span		5.9936
Tmax	day	0.0417
Cmax	mg/L	967.5700
Cmax_D	mg/L/mg	0.3225
Tlast	day	127.0160
Clast	mg/L	4.9037
Clast_pred	mg/L	4.3643
AUClast	day*mg/L	15954.9717
AUClast_D	day*mg/L/mg	5.3183
AUCall	day*mg/L	15954.9717
AUCINF_obs	day*mg/L	16078.9254
AUCINF_D_obs	day*mg/L/mg	5.3596
AUC_%Extrap_obs	%	0.7709
Flag_AUC_%Ext_obs		Accepted
Vz_obs	L	4.7162
Cl_obs	mL/day	186.5796
AUCINF_pred	day*mg/L	16065.2902
AUCINF_D_pred	day*mg/L/mg	5.3551
AUC_%Extrap_pred	%	0.6867
Vz_pred	L	4.7202
Cl_pred	mL/day	186.7380
AUMClast	day*day*mg/L	393335.5205
AUMCINF_obs	day*day*mg/L	412212.8480
AUMC_%Extrap_obs	%	4.5795
AUMCINF_pred	day*day*mg/L	410136.2960
AUMC_%Extrap_pred	%	4.0964
MRTlast	day	24.4028
MRTINF_obs	day	25.3868
MRTINF_pred	day	25.2793
Vss_obs	L	4.7367
Vss_pred	L	4.7206

```
WinNonlin 8.3.3.33
Subject_ID=1011,Treatment=IXT-m200,Dose=3000,Actual_Infusion_Time=0.55

                                                    Date:    5/09/2022
                                                    Time:     03:47:44


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                       8.3.3.33
                                 Core Version 06Feb2020

Settings
--------
Model:  Plasma Data, Constant Infusion Administration
Number of nonmissing observations:   15
Dose time:      0.00
Dose amount:     3000.00
Length of Infusion:      0.55
Calculation method:  Linear/Log Trapezoidal
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
Lambda_z Acceptance Criterion, Min Rsq_Adjusted:  0.8000
Lambda_z Acceptance Criterion, Max AUC_%Extrap_obs:   20.00


Summary Table
-------------
      Time         Conc.      Pred.    Residual      AUC       AUMC      Weight
        day        mg/L        mg/L        mg/L    day*mg/L day*day*mg/L
-------------------------------------------------------------------------------
      0.000        0.000                            0.000      0.000
    0.04167        536.9                            11.19     0.4661
     0.1674        589.9                            82.00      8.076
     0.3333        534.3                            175.2      31.28
      1.000        568.5                            542.7      277.5
      8.013        276.4                            3383.  1.189e+04
      15.04        264.5                            5283.  3.374e+04
      22.05 *      149.5      153.6     -4.116      6696.  5.947e+04      1.000
      29.06 *      117.1      116.9     0.2140      7626.  8.311e+04      1.000
      36.06 *      87.77      89.03     -1.253      8338.  1.062e+05      1.000
      43.06 *      75.42      67.77      7.650      8908.  1.287e+05      1.000
      64.10 *      28.58      29.87     -1.291      9924.  1.814e+05      1.000
      85.08 *      13.65      13.20     0.4566  1.035e+04  2.125e+05      1.000
      106.1 *      4.897      5.830    -0.9332  1.053e+04  2.293e+05      1.000
      127.1 *      2.890      2.570     0.3195  1.061e+04  2.385e+05      1.000


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

Final Parameters

N_Samples		15
Dose	mg	3000.0000
Rsq		0.9962
Rsq_adjusted		0.9956
Flag_Rsq_adjusted		Accepted
Corr_XY		-0.9981
No_points_lambda_z		8
Lambda_z	1/day	0.0389
Lambda_z_intercept		5.8931
Lambda_z_lower	day	22.0479
Lambda_z_upper	day	127.0889
HL_Lambda_z	day	17.7993
Span		5.9014
Tmax	day	0.1674
Cmax	mg/L	589.8678
Cmax_D	mg/L/mg	0.1966
Tlast	day	127.0889
Clast	mg/L	2.8896
Clast_pred	mg/L	2.5702
AUClast	day*mg/L	10606.7945
AUClast_D	day*mg/L/mg	3.5356
AUCall	day*mg/L	10606.7945
AUCINF_obs	day*mg/L	10680.9970
AUCINF_D_obs	day*mg/L/mg	3.5603
AUC_%Extrap_obs	%	0.6947
Flag_AUC_%Ext_obs		Accepted
Vz_obs	L	7.2125
Cl_obs	mL/day	280.8727
AUCINF_pred	day*mg/L	10672.7935
AUCINF_D_pred	day*mg/L/mg	3.5576
AUC_%Extrap_pred	%	0.6184
Vz_pred	L	7.2181
Cl_pred	mL/day	281.0885
AUMClast	day*day*mg/L	238532.8682
AUMCINF_obs	day*day*mg/L	249868.6319
AUMC_%Extrap_obs	%	4.5367
AUMCINF_pred	day*day*mg/L	248615.3968
AUMC_%Extrap_pred	%	4.0555
MRTlast	day	22.2137
MRTINF_obs	day	23.1188
MRTINF_pred	day	23.0193
Vss_obs	L	6.4934
Vss_pred	L	6.4705

```
WinNonlin 8.3.3.33
Subject_ID=1012,Treatment=IXT-m200,Dose=3000,Actual_Infusion_Time=0.5

                                                  Date:    5/09/2022
                                                  Time:     03:47:44


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                       8.3.3.33
                                 Core Version 06Feb2020

Settings
--------
Model:  Plasma Data, Constant Infusion Administration
Number of nonmissing observations:   15
Dose time:      0.00
Dose amount:     3000.00
Length of Infusion:      0.50
Calculation method:  Linear/Log Trapezoidal
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
Lambda_z Acceptance Criterion, Min Rsq_Adjusted:  0.8000
Lambda_z Acceptance Criterion, Max AUC_%Extrap_obs:   20.00


Summary Table
-------------
      Time         Conc.      Pred.    Residual      AUC       AUMC      Weight
        day         mg/L        mg/L        mg/L    day*mg/L day*day*mg/L
-------------------------------------------------------------------------------
      0.000        0.000                            0.000      0.000
    0.04167        736.1                            15.33     0.6389
     0.1667        721.3                            106.4      10.11
     0.3347        587.6                            216.0      37.27
      1.000        635.3                            622.6      310.4
      7.955        335.1                            3887.  1.372e+04
      15.00        266.4                            5996.  3.765e+04
      21.96        188.1                            7562.  6.628e+04
      28.99        145.2                            8727.  9.578e+04
      35.97        98.44                            9567.  1.228e+05
      43.00        74.40                        1.017e+04  1.466e+05
      64.04        31.89                        1.123e+04  2.016e+05
      85.04 *      9.741      9.829   -0.08753  1.162e+04  2.300e+05      1.000
      106.0 *      4.823      4.738    0.08539  1.177e+04  2.438e+05      1.000
      127.0 *      2.258      2.278   -0.02023  1.184e+04  2.520e+05      1.000


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

Final Parameters

N_Samples		15
Dose	mg	3000.0000
Rsq		0.9996
Rsq_adjusted		0.9991
Flag_Rsq_adjusted		Accepted
Corr_XY		-0.9998
No_points_lambda_z		3
Lambda_z	1/day	0.0349
Lambda_z_intercept		5.2490
Lambda_z_lower	day	85.0410
Lambda_z_upper	day	126.9868
HL_Lambda_z	day	19.8889
Span		2.1090
Tmax	day	0.0417
Cmax	mg/L	736.0651
Cmax_D	mg/L/mg	0.2454
Tlast	day	126.9868
Clast	mg/L	2.2581
Clast_pred	mg/L	2.2783
AUClast	day*mg/L	11836.0573
AUClast_D	day*mg/L/mg	3.9454
AUCall	day*mg/L	11836.0573
AUCINF_obs	day*mg/L	11900.8503
AUCINF_D_obs	day*mg/L/mg	3.9670
AUC_%Extrap_obs	%	0.5444
Flag_AUC_%Ext_obs		Accepted
Vz_obs	L	7.2332
Cl_obs	mL/day	252.0828
AUCINF_pred	day*mg/L	11901.4307
AUCINF_D_pred	day*mg/L/mg	3.9671
AUC_%Extrap_pred	%	0.5493
Vz_pred	L	7.2328
Cl_pred	mL/day	252.0705
AUMClast	day*day*mg/L	251984.8306
AUMCINF_obs	day*day*mg/L	262071.8305
AUMC_%Extrap_obs	%	3.8489
AUMCINF_pred	day*day*mg/L	262162.1803
AUMC_%Extrap_pred	%	3.8821
MRTlast	day	21.0396
MRTINF_obs	day	21.7713
MRTINF_pred	day	21.7778
Vss_obs	L	5.4882
Vss_pred	L	5.4895

```
WinNonlin 8.3.3.33
Subject_ID=1018,Treatment=IXT-m200,Dose=3000,Actual_Infusion_Time=0.5

                                                    Date:    5/09/2022
                                                    Time:     03:47:44


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                       8.3.3.33
                                 Core Version 06Feb2020

Settings
--------
Model:  Plasma Data, Constant Infusion Administration
Number of nonmissing observations:   13
Dose time:      0.00
Dose amount:     3000.00
Length of Infusion:      0.50
Calculation method:  Linear/Log Trapezoidal
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
Lambda_z Acceptance Criterion, Min Rsq_Adjusted:  0.8000
Lambda_z Acceptance Criterion, Max AUC_%Extrap_obs:   20.00


Summary Table
-------------
      Time         Conc.      Pred.    Residual      AUC       AUMC      Weight
        day        mg/L        mg/L        mg/L    day*mg/L day*day*mg/L
-------------------------------------------------------------------------------
      0.000        0.000                           0.000      0.000
    0.04167        636.8                           13.27     0.5528
     0.1667        675.1                           95.26      9.244
     0.3333        555.2                           197.5      34.52
      1.000        486.1                           544.1      263.0
      7.989 *      233.1      253.1     -20.00      2950.  1.006e+04      1.000
      14.98 *      202.8      191.9      10.88      4472.  2.741e+04      1.000
      21.99 *      145.3      145.5    -0.1663      5680.  4.952e+04      1.000
      29.00 *      109.4      110.2    -0.8202      6567.  7.198e+04      1.000
      36.06 *      89.21      83.39      5.818      7266.  9.461e+04      1.000
      42.99 *      66.84      63.38      3.458      7803.  1.158e+05      1.000
      86.17 *      9.283      11.48     -2.200      9062.  1.887e+05      1.000
      107.0 *      5.727      5.039     0.6876      9215.  2.033e+05      1.000


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

Final Parameters

N_Samples		13
Dose	mg	3000.0000
Rsq		0.9942
Rsq_adjusted		0.9932
Flag_Rsq_adjusted		Accepted
Corr_XY		-0.9971
No_points_lambda_z		8
Lambda_z	1/day	0.0396
Lambda_z_intercept		5.8499
Lambda_z_lower	day	7.9889
Lambda_z_upper	day	106.9951
HL_Lambda_z	day	17.5217
Span		5.6505
Tmax	day	0.1667
Cmax	mg/L	675.1326
Cmax_D	mg/L/mg	0.2250
Tlast	day	106.9951
Clast	mg/L	5.7266
Clast_pred	mg/L	5.0389
AUClast	day*mg/L	9215.2150
AUClast_D	day*mg/L/mg	3.0717
AUCall	day*mg/L	9215.2150
AUCINF_obs	day*mg/L	9359.9739
AUCINF_D_obs	day*mg/L/mg	3.1200
AUC_%Extrap_obs	%	1.5466
Flag_AUC_%Ext_obs		Accepted
Vz_obs	L	8.1021
Cl_obs	mL/day	320.5137
AUCINF_pred	day*mg/L	9342.5914
AUCINF_D_pred	day*mg/L/mg	3.1142
AUC_%Extrap_pred	%	1.3634
Vz_pred	L	8.1171
Cl_pred	mL/day	321.1101
AUMClast	day*day*mg/L	203338.3361
AUMCINF_obs	day*day*mg/L	222486.1011
AUMC_%Extrap_obs	%	8.6063
AUMCINF_pred	day*day*mg/L	220186.8568
AUMC_%Extrap_pred	%	7.6519
MRTlast	day	21.8155
MRTINF_obs	day	23.5199
MRTINF_pred	day	23.3181
Vss_obs	L	7.5385
Vss_pred	L	7.4877

```
WinNonlin 8.3.3.33
Subject_ID=1023,Treatment=IXT-m200,Dose=3000,Actual_Infusion_Time=0.5

                                                    Date:    5/09/2022
                                                    Time:     03:47:44


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                       8.3.3.33
                                 Core Version 06Feb2020

Settings
--------
Model:  Plasma Data, Constant Infusion Administration
Number of nonmissing observations:   15
Dose time:      0.00
Dose amount:     3000.00
Length of Infusion:      0.50
Calculation method:  Linear/Log Trapezoidal
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
Lambda_z Acceptance Criterion, Min Rsq_Adjusted:  0.8000
Lambda_z Acceptance Criterion, Max AUC_%Extrap_obs:   20.00


Summary Table
-------------
      Time          Conc.       Pred.     Residual       AUC        AUMC       Weight
        day         mg/L         mg/L         mg/L    day*mg/L  day*day*mg/L
-------------------------------------------------------------------------------------
      0.000         0.000                              0.000       0.000
    0.04167         688.5                              14.34      0.5976
     0.1667         596.5                              94.52       8.830
     0.3333         568.3                              191.6       33.03
     0.9944         474.8                              535.4       257.9
      8.153         257.8                              3079.   1.097e+04
      14.06         227.8                              4512.   2.681e+04
      23.11         156.9                              6234.   5.832e+04
      29.14         124.3                              7077.   8.026e+04
      36.27         105.1                              7893.   1.069e+05
      43.13         73.60                              8500.   1.308e+05
      64.18 *       32.95       33.03    -0.08146      9564.   1.865e+05       1.000
      85.14 *       17.09       17.14    -0.04422   1.007e+04  2.237e+05       1.000
      106.0 *       9.037       8.928      0.1090   1.033e+04  2.486e+05       1.000
      128.1 *       4.428       4.460    -0.03147   1.048e+04  2.651e+05       1.000


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

Final Parameters

N_Samples		15
Dose	mg	3000.0000
Rsq		0.9999
Rsq_adjusted		0.9999
Flag_Rsq_adjusted		Accepted
Corr_XY		-1.0000
No_points_lambda_z		4
Lambda_z	1/day	0.0313
Lambda_z_intercept		5.5060
Lambda_z_lower	day	64.1771
Lambda_z_upper	day	128.1486
HL_Lambda_z	day	22.1461
Span		2.8886
Tmax	day	0.0417
Cmax	mg/L	688.4733
Cmax_D	mg/L/mg	0.2295
Tlast	day	128.1486
Clast	mg/L	4.4282
Clast_pred	mg/L	4.4597
AUClast	day*mg/L	10477.0455
AUClast_D	day*mg/L/mg	3.4923
AUCall	day*mg/L	10477.0455
AUCINF_obs	day*mg/L	10618.5271
AUCINF_D_obs	day*mg/L/mg	3.5395
AUC_%Extrap_obs	%	1.3324
Flag_AUC_%Ext_obs		Accepted
Vz_obs	L	9.0267
Cl_obs	mL/day	282.5251
AUCINF_pred	day*mg/L	10619.5326
AUCINF_D_pred	day*mg/L/mg	3.5398
AUC_%Extrap_pred	%	1.3417
Vz_pred	L	9.0258
Cl_pred	mL/day	282.4983
AUMClast	day*day*mg/L	265138.6729
AUMCINF_obs	day*day*mg/L	287789.6942
AUMC_%Extrap_obs	%	7.8707
AUMCINF_pred	day*day*mg/L	287950.6725
AUMC_%Extrap_pred	%	7.9222
MRTlast	day	25.0566
MRTINF_obs	day	26.8526
MRTINF_pred	day	26.8652
Vss_obs	L	7.5865
Vss_pred	L	7.5894

```
WinNonlin 8.3.3.33
Subject_ID=1024,Treatment=IXT-m200,Dose=3000,Actual_Infusion_Time=0.5

                                                    Date:    5/09/2022
                                                    Time:     03:47:44


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                       8.3.3.33
                                 Core Version 06Feb2020

Settings
--------
Model:  Plasma Data, Constant Infusion Administration
Number of nonmissing observations:   15
Dose time:      0.00
Dose amount:     3000.00
Length of Infusion:      0.50
Calculation method:  Linear/Log Trapezoidal
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
Lambda_z Acceptance Criterion, Min Rsq_Adjusted:  0.8000
Lambda_z Acceptance Criterion, Max AUC_%Extrap_obs:   20.00


Summary Table
-------------
      Time          Conc.       Pred.     Residual       AUC        AUMC       Weight
        day         mg/L         mg/L         mg/L    day*mg/L  day*day*mg/L
-------------------------------------------------------------------------------------
      0.000         0.000                              0.000       0.000
    0.04167         910.4                              18.97      0.7903
     0.1667         865.8                              130.0       12.29
     0.3340         754.0                              265.3       45.91
     0.9889         812.6                              778.0       387.1
      8.233 *       398.1       334.0       64.15       4986.   1.799e+04       1.000
      13.12 *       269.1       277.2      -8.055       6597.   3.494e+04       1.000
      22.15 *       220.8       196.6       24.25       8801.   7.348e+04       1.000
      29.15 *       148.3       150.5      -2.192   1.008e+04   1.059e+05       1.000
      36.08 *       113.8       115.6      -1.856   1.098e+04   1.352e+05       1.000
      41.10 *       99.04       95.51       3.532   1.151e+04   1.558e+05       1.000
      63.16 *       34.83       41.21      -6.382   1.287e+04   2.239e+05       1.000
      86.11 *       9.927       17.19      -7.266   1.332e+04   2.568e+05       1.000
      107.2 *       8.825       7.709       1.116   1.352e+04   2.758e+05       1.000
      125.1 *       5.333       3.895       1.439   1.365e+04   2.901e+05       1.000


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

Final Parameters

N_Samples		15
Dose	mg	3000.0000
Rsq		0.9776
Rsq_adjusted		0.9748
Flag_Rsq_adjusted		Accepted
Corr_XY		-0.9887
No_points_lambda_z		10
Lambda_z	1/day	0.0381
Lambda_z_intercept		6.1246
Lambda_z_lower	day	8.2333
Lambda_z_upper	day	125.0972
HL_Lambda_z	day	18.1974
Span		6.4220
Tmax	day	0.0417
Cmax	mg/L	910.3975
Cmax_D	mg/L/mg	0.3035
Tlast	day	125.0972
Clast	mg/L	5.3333
Clast_pred	mg/L	3.8947
AUClast	day*mg/L	13645.1032
AUClast_D	day*mg/L/mg	4.5484
AUCall	day*mg/L	13645.1032
AUCINF_obs	day*mg/L	13785.1184
AUCINF_D_obs	day*mg/L/mg	4.5950
AUC_%Extrap_obs	%	1.0157
Flag_AUC_%Ext_obs		Accepted
Vz_obs	L	5.7134
Cl_obs	mL/day	217.6260
AUCINF_pred	day*mg/L	13747.3505
AUCINF_D_pred	day*mg/L/mg	4.5825
AUC_%Extrap_pred	%	0.7438
Vz_pred	L	5.7291
Cl_pred	mL/day	218.2239
AUMClast	day*day*mg/L	290143.5780
AUMCINF_obs	day*day*mg/L	311334.9490
AUMC_%Extrap_obs	%	6.8066
AUMCINF_pred	day*day*mg/L	305618.7579
AUMC_%Extrap_pred	%	5.0636
MRTlast	day	21.0136
MRTINF_obs	day	22.3349
MRTINF_pred	day	21.9811
Vss_obs	L	4.8606
Vss_pred	L	4.7968