Statistical Analysis Plan

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Sponsor Name: InterveXion Therapeutics, LLC

Protocol Number: M200C-2101

Protocol Title: Meth-OD: A Phase 2a Study of IXT-m200 in Patients with Toxicity from Methamphetamine Overdose

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Revision History

Version #	**Date** (DD-Mmm-YYYY)	**Document Owner**	**Revision Summary**
0.1	19-May-2021	Andy Torres	Initial Release Version
0.2	12-Aug-2021	Andy Torres	Revisions based on sponsor comments
1.0	27-Oct-2021	Andy Torres	Revisions based on sponsor comments
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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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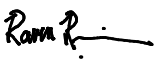
Raven Reavis, Associate Director, Biostatistics		*Electronically signed by: Raven Reavis* *Reason: I am the approver* *Date: Feb 27, 2023 12:23 CST*
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Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
ACES	Agitation-Calmness Evaluation Scale
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
CI	Confidence Interval
CRF	Case Report Form
ECG	Electrocardiogram
ED	Emergency department
DSMB	Data and Safety Monitoring Board
ICH	International Conference on Harmonization
IV	Intravenous
IXRS	Interactive Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
METH	methamphetamine
N/A	Not Applicable
NA	Not Applicable
PANSS-EC	Positive and Negative Syndrome Scale – Excited Component
PCS	Potentially clinically significant
PDNCMP	Protocol Deviation and Non-Compliance Management Plan
PT	Preferred Term
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SYNH	Syneos Health
TAU	Treatment-as-usual

Abbreviation	Description
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
UBACC	UCSD Brief Assessment of Capacity to Consent
UDS	urine drug screen
WHO-DD	World Health Organization Drug Dictionary

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings. Pharmacokinetics (PK) analysis will be carried out by Syneos Health.

2.2. Timings of Analyses

The primary analysis of safety and efficacy and/or pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

An independent Data and Safety Monitoring Board (DSMB) will review descriptive summaries of accumulating safety, subject disposition and limited efficacy data at the conclusion of cohort 1 and intermittently as necessary. Further description of the DSMB analyses can be found in the DSMB charter.

No interim analyses are planned.

3. Study Objectives

3.1. Primary Objective

To evaluate the safety and tolerability of IXT-m200 in patients with mild to moderate methamphetamine (METH) toxicity.

3.2. Secondary Objectives

- To determine the time course and degree of normalization of agitation and vital signs.
- To determine the percentage of participants requiring rescue medications for psychiatric or cardiovascular manifestations of METH intoxication.

3.3. Exploratory Objective

To determine how long patients with METH toxicity stay in the emergency department (ED).

4. Study Details/Design

4.1. Brief Description

The hypothesis of this multisite Phase 2a study is that IXT-m200 will be well-tolerated in subjects with acute mild to moderate METH toxicity. A randomized, open-label design will be used in which one dose of IXT-m200 will be compared to treatment-as-usual (TAU). Approximately 24 participants will be enrolled in 3 cohorts. A dose escalation approach will be used so that progressively higher IXT-m200 doses will be evaluated in each of the first two cohorts. In conjunction with safety monitoring, this design assures the opportunity to observe early safety findings before any participants are exposed to the next higher dose. The randomization ratio for IXT-m200 versus TAU is defined as 4:1 for each of cohorts 1 and 2, with up to an additional 4 TAU participants in cohort 3 so that the number of participants receiving TAU equals the number receiving each dose of IXT-m200 at the end of the study.

Table 4.1: Cohort Design

Cohort	IXT-m200 dose (g)	IXT-m200:TAU subject numbers
1	0.5	8:2
2	2	8:2
3	0	0:4

Agitation scales and vital signs will be recorded to track effect of the antibody treatment versus TAU over time on agitation associated with METH use. While in the ED, detailed and pertinent medical and psychiatric histories, and physical exam results will be obtained, along with laboratory assessments and electrocardiogram (ECGs). In the ED, participants will give blood samples for analysis of METH and IXT-m200 concentrations and will be followed for development of adverse events. Participants will be evaluated at 2 days and 4 weeks after discharge from the ED for adverse events and drug use history. Cohort escalation reviews will be performed by the Sponsor, Medical Monitor, and Data and Safety Monitoring Board (DSMB) after cohort 1 and the next group will not start until after completion of this review.

4.2. Subject Selection

Qualified participants will present seeking emergent treatment for unpleasant symptoms related to their recent METH use. They may also have taken other abused drugs or medications such as opioids and still qualify. They may display signs of mild to moderate METH toxicity such as dysphoria, agitation, mild paranoia, or a feeling of being unsafe. Participants will be agreeable to general study procedures (e.g., placement of an intravenous [IV] line, repeated measurement of vital signs and agitation assessments, repeated blood draws).

People with mild to moderate symptoms have been selected for this initial study in an ED setting because while they need rapid treatment, the need for rescue sedative medications will be lower and less urgent than in people suffering from acute, severe intoxication or other major health issues. Recruiting lower severity participants will allow time to determine/observe the effects of IXT-m200 doses prior to, or without the need to add, additional medications which could obscure the effects of the antibody. This initial study will establish safety and efficacy in a controlled population prior to expanding in future studies to a greater

risk, more vulnerable population who may need more intensive intervention for their acute METH intoxication.

The criteria for diagnosing METH toxicity is specified in section 5.1 of the protocol. The full list of inclusion and exclusion criteria is provided in sections 5.2 and 5.3 of the protocol.

4.3. Determination of Sample Size

No formal sample size estimation has been performed. A sample size of 8 IXT-m200 and approximately 8 TAU subjects is considered adequate to assess the safety and tolerability of IXT-m200 compared to TAU. Data from TAU subjects from each cohort will be pooled for summaries.

4.4. Treatment Assignment and Blinding

The treatment allocation ratio will be 8:2, IXT-m200 to TAU for cohort 1 and 2, with up to an additional 4 TAU participants in cohort 3. Interactive voice/web response system (IXRS) will be used to assign subjects to treatment using a list of randomization codes generated by a randomizing statistician. No stratification factors will be used.

Interactive Voice/Web Response System will be the same system for all sites so that there is no site bias to dosing. Participants will be randomized in the order they are enrolled.

This is an open-label study, in which the Sponsor and the Investigators are aware of treatment assignments on an ongoing basis to facilitate efficient dose escalation while comparing study drug to treatment as usual. While participants in cohorts 1 and 2 will not be actively informed of their group assignment, no active measures will be taken to blind participants to treatment assignment.

4.5. Administration of Study Medication

An IV line will be started and a balanced salt solution (e.g., PlasmaLyte®) will be administered at a rate of 75 mL/hr. IXT-m200 will be given over 10 min (for 0.5 g) or 20 min (for higher doses) per dosing guidelines. The IXT-m200 infusion start/stop time, infusion rate, infusion volume, whether the infusion was completed, if it was stopped, or stopped and restarted will be recorded in the electronic Case Report Form (eCRF). Participants will be asked to remain semi-reclined during dose administration and to refrain from strenuous activity from dosing through 24 hours after. If randomized to TAU, one of the following three choices will be administered as determined by the treating physician: 1) up to 4 mg lorazepam by IV push, 2) up to 5 mg haloperidol by IM or IV injection, or 3) a combination of up to 4 mg lorazepam by IV push and up to 5 mg haloperidol by IM or IV injection. IV fluids will be given as tolerated for up to 4 hours after dosing with either IXT-m200 or TAU, at which point the IV will be capped and preserved during the remainder of the ED stay. When the ED staff determine it is appropriate, a regular diet may be started. If there is an adverse reaction to study drug, the participant will be treated as outlined in protocol Section 6.5.

4.6. Study Procedures and Flowchart

The study procedures to be performed as summarized in the Schedule of Assessments, is provided in the protocol Section 1.3, Schedule of Activities.

5. Endpoints

5.1. Primary Endpoint

- Safety and tolerability of IXT-m200 as measured by physical examinations and vital sign, adverse event (AE), ECG, and clinical laboratory testing

5.2. Secondary Endpoints

- Agitation/sedation scores over time as measured by Agitation-Calmness Evaluation Scale (ACES)
- Vital signs including blood pressure, heart rate and temperature over time
- Need for rescue medications to treat:
    - agitation, dysphoria, or psychosis (central nervous system [CNS] toxicity)
    - hypertension, tachycardia, or other cardiovascular instability (CV toxicity)

5.3. Exploratory Endpoints

- ED length of stay as measured by disposition order time minus triage time, and as measured by disposition order time minus start of treatment time, with log transformation

6. Analysis Sets

6.1. Enrolled Population

The enrolled population will include all subjects who signed an informed consent.

6.2. Safety Population

The Safety Population will include all randomized subjects who receive any dose of study drug. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

6.3. Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population will include all randomized subjects. The treatment group assignment in this population will be defined by the randomized treatment. This population will be used for the analysis of efficacy.

6.4. Full Analysis Set (FAS) Population

The Full Analysis Set (FAS) population will include those in the ITT population who receive any dose of study drug and were positive for methamphetamine by urine drug screen (UDS) or blood testing during the ED stay. UDS results from data vendor Q2 Solutions or local lab will be used to derive FAS population, with subjects reporting 'Positive' result for lab test 'Amphetamines' or 'Methamphetamine'. Any subjects reporting 'Negative' result for lab test 'Amphetamines' and/or 'Methamphetamine' or the result for both lab tests are missing but have a quantifiable Day 1 pre-dose blood test for Methamphetamine will also be included in the FAS population. The treatment group assignment in this population will be defined by the randomized treatment. This population will be used for the analysis of efficacy.

6.5. Per-Protocol Population

The Per-Protocol (PP) population will include all of FAS who completed the Day 1 assessments, stay through discharge from the ED, and do not have any major protocol deviation impacting the efficacy assessments. The treatment group assignment in this population will be defined by the randomized treatment. This population will be used for the analysis of efficacy.

6.6. Pharmacokinetic (PK) Population

The PK Population will include all subjects for whom a serum concentration of IXT-m200 is available post-dose. Serum (IXT-m200) and plasma (METH) concentrations are listed for all subjects in the PK population.

6.7. Protocol Deviations

Protocol deviation management is described in the Protocol Deviation and Non-compliance Management Plan (PDNCMP). Deviations will be classified by whether or not they meet the definition of major protocol deviations. Major protocol deviations are a subset of deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Deviations will be categorized by type and will be reviewed on an ongoing basis. A protocol deviation listing will be provided. Deviations will be classified as either major (or critical) or minor if the non-compliance adversely affects the study or process.

7. General Aspects for Statistical Analysis

7.1. General Methods

All analyses and summaries will be produced using Statistical Analysis System (SAS®) version 9.4 or higher. All SAS programs used to generate analytical results will be developed and validated according to Syneos Health (SYNH) programming standards and SAS validation procedures. Summaries will be presented by treatment group and overall unless otherwise specified. Each active treatment cohort will be labeled in the outputs by its cohort number and dose level, e.g., Cohort 1 (IXT-m200 0.5 g). Additionally, overall IXT-m200 and overall TAU (treatment-as-usual) will be presented.

Unless otherwise noted, continuous variables will be summarized using the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum values as summary statistics. The minimum and maximum will be displayed to the precision with which the data were collected. The mean, median and quartiles will be displayed to one additional decimal place and the SD will be displayed to two additional decimal places, where applicable.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects with a non-missing value for the given variable will be used as the denominator for percent calculations, unless stated otherwise. All percentages will be presented with one decimal, unless otherwise specified. Percentages equal to 100 will be presented as 100, and percentages will not be presented for zero frequencies.

All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.

7.2. Key Definitions

7.2.1. Baseline

Unless otherwise specified, baseline is defined as the last non-missing observation prior to the first dose of IXT-m200 or TAU.

7.2.2. Study Hour

The hour of first dose of study drug administration is defined as study Hour 0. Subsequent hours are numbered consecutively (Hour 1, Hour 2, etc.). Prior to the hour of first dose of study drug administration, study hours are numbered sequentially with negative values (i.e., Hour -1, Hour -2, etc.).

7.2.3. Study Day

The day of first dose of study drug administration is defined as study Day 1. Subsequent days are numbered consecutively (Day 2, Day 3, etc.). Prior to the day of first dose of study drug administration, study days are numbered sequentially with negative values (i.e., Day -1, Day -2, etc.). There is no Day 0.

7.3. Missing Data

In general, missing data will not be imputed. All analyses will be based on observed cases. Sections 7.3.1 and 7.3.2 note the situations where missing data will be imputed.

7.3.1. Handling of Missing Dates/Months/Years for Prior/Concomitant Therapies

If a medication cannot be classified into concomitant or prior status due to incomplete start and/or stop date, the rules below will be applied for the classification.

For start date,

- If the year and month are observed but the day is missing, the first day of the month will be used unless month and year are the same as month and year of first dose date then impute using the day of first dose date.
- If the year is observed but the month and day are missing, the first day of the year, 01 Jan, will be used unless year is the same as first dose date then the first dose date will be used.
- If the start date is completely missing, the medication will be considered concomitant unless the stop date is before study drug administration.
- If the start and stop dates are both completely missing, a therapy will be considered concomitant.

For end date,

- If the year and month are observed but the day is missing, the last day of the month will be used unless month and year are the same as month and year of last dose date, then impute the last dose date.
- If the year is observed but the month and day are missing, the last day of the year, 31 Dec, will be used unless year is the same as last dose date then the last dose date will be used.
- If the end date is completely missing, if medication is still ongoing, then missing end date is not supposed to be imputed. If the medication is not ongoing and the start date is prior to first dose date, the end date will be imputed using 1st dose date.
- If both start and end dates are completely missing, medication will be considered concomitant.

The original partial or missing date will be shown in listings for all prior and concomitant medications.

7.3.2. Adverse Events Dates

For AEs with incomplete dates, the following rules will be used to impute start and/or stop dates for the sole purpose of determining if an AE is treatment-emergent. Imputed dates will not appear in the data listings.

For partial start dates:

- If the month and year of AE onset are provided but day is missing
  - If the month and year match the month and the year of the date of first dosing administration, then the date of first dosing administration will be used and the AE will be considered treatment-emergent.
  - Otherwise, the first day of the month will be used.
- If the year of AE onset is provided, but the month and day are missing
  - If the year matches the year of the first dosing administration, then the date of first dosing administration will be used.
  - Otherwise, 01 Jan will be used.
  - If the stop date is not missing and the imputed onset date is after the stop date, then the stop date will be used.
  - If the onset date is completely missing and the stop date is on or after the date of first dose, the event will be considered a treatment-emergent adverse event (TEAE).
  - If both onset date and stop date are missing, the event will be considered a TEAE. Partial stop dates will not be imputed in this instance.

7.4. Visit Windows

There will be no derivation for visit windows in terms of summary assessments. Nominal visits will be used for by-visit tables.

7.5. Pooling of Centers

Data from all sites will be summarized together for analyses.

7.6. Subgroups

No subgroup analyses are planned for the study.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

A summary table will be produced detailing the number of subjects screened and screen failed, the number and percentage of all subjects in each analysis population, subjects who completed or who prematurely discontinued the study. In addition, reasons leading to discontinuation from study will be summarized for each treatment group and overall. A listing of subject disposition will also be provided.

Screened subjects are defined as all subjects with a non-missing informed consent date.

8.2. Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by each treatment group and overall for the Safety Population. The characteristics being summarized which include: age at screening (in years), gender, race, ethnicity, height (cm), weight (kg), body mass index (BMI) (kg/m^2), and for females, childbearing potential. Baseline characteristics include Agitation-Calmness Evaluation Scale (ACES), Positive and Negative Syndrome Scale – Excited Component (PANSS-EC), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), and temperature (C).

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height(m)^2]

Demographics and Baseline characteristics will be listed by subject for the Safety Population.

8.3. Medical and Psychiatric History

Medical History will be summarized for the Safety Population using Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The reported medical history terms will be coded using MedDRA Version 23.0 or higher. The number of subjects with any medical or surgical history will also be summarized. A subject experiencing a medical history within more than one SOC and PT will be counted only once within that SOC and PT, respectively.

Medical history and psychiatric history findings will be listed by subject using the Safety Population. Results for "Why did the subject come to the ER today?" will be included in the listing.

8.4. Medication

Medications will be classified as prior and concomitant. All prior and concomitant medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD), March 2021.

Summaries of prior, concomitant, and rescue medications will be presented separately in tabular form using the ATC 4 level term as an upper classification level and the preferred drug name as a lower classification level. All medications will be summarized by descending frequency of ATC level 4 and preferred drug name within a given ATC level 4 term. The summary will consist of the frequency and percent of safety subjects who used the medication at least once.

For each subject, the medication will be counted only once within a level 4 ATC and only once within a given preferred drug name level. A subject may appear more than once if he/she has more than one

concomitant medication coded under different ATC categories; however, the subject will be counted only once in the overall category.

A by-subject listing with coded terms will also be provided using the Safety Population.

8.4.1. Prior Medication

Any medication that started prior and did not continue past the first dose of study treatment will be classified as prior.

8.4.2. Concomitant Medication

Concomitant medications are defined as all medications taken during the study treatment period, including those which started before study treatment, but were reported ongoing at the first administration.

8.4.3. Rescue Medication

Rescue medications will be identified in the Prior and Concomitant medications CRF and are limited to those reported prior to discharge from the ED on Day 1. Central nervous system rescue medications include lorazepam (Ativan) and haloperidol (Haldol). Cardiovascular rescue medications include labetalol, hydralazine, or other similar approaches. There is no standardized list of rescue medications as hospitals will use a wide variety. A review of the list of medications that are marked as rescue medication on the CRF page Prior and Concomitant Medications will be conducted in order to classify as either cardiovascular or psychiatric manifestations of METH intoxication. It is advised that this review will be held at the end of each cohort prior to the cohort escalation meeting.

8.5. Extent of Exposure

The following summaries will be provided for the IXT-m200 treatment groups for the Safety Population:

- Number and percentage of subjects who received the complete planned IXT-m200 infusion
- Total volume administered (mL)
- Number and percentage of subjects who received an incomplete infusion and reasons for incomplete administered,
- Number and percentage of subjects with a dose interruption and re-start and reasons for interruption

The following summaries will be provided for the TAU treatment group:

- Number and percentage of subjects receiving each dose level of TAU
- Total Lorazepam administered (mg)
- Total Haloperidol administered (mg)
- If combination of Lorazepam and Haloperidol were administered, then total dose administered of Lorazepam (mg) and Haloperidol (mg)
- Route of Administration, Haloperidol (mg)

IXT-m200 and TAU infusion details will be listed by subject using the Safety Population.

9. Efficacy

The comparison of efficacy endpoints between the treatment groups will be performed using descriptive summaries and descriptive confidence intervals (CI) and statistical tests. All efficacy parameters will be summarized and presented in tables based on the Intent-to-Treat (ITT) population, Full Analysis Set (FAS) population, and the Per-Protocol (PP) population.

9.1. Agitation/Sedation Scores Over Time as Measured by Agitation-Calmness Evaluation Scale (ACES)

ACES is a single-item scale where 1 = marked agitation; 2 = moderate agitation; 3 = mild agitation; 4 = normal; 5 = mild calmness; 6 = moderate calmness; 7 = marked calmness; 8 = deep sleep; and 9 = unable to be aroused.

Summary tables with descriptive statistics for actual values and changes from baseline will be provided for the ACES score for each scheduled timepoint by treatment group. Descriptive pairwise t-tests will be performed for the comparison of the changes from baseline of each IXT-m200 dose versus TAU using a two-sided alpha level of 5%.

The hypotheses for the t-test comparing mean change from baseline of each IXT-m200 dose group versus TAU is expressed as:

H0: $\mu 1 - \mu 2 = 0$ ("the difference in mean change from baseline is equal to 0")
H1: $\mu 1 - \mu 2 \neq 0$ ("the difference in mean change from baseline is not 0")

where $\mu 1$ and $\mu 2$ are the population mean change from baseline for IXT-m200 and TAU, respectively.

The following general form of the SAS PROC TTEST procedure will be used:

```
PROC TTEST DATA=dataset-name ALPHA=0.05;
  VAR CHG;
  CLASS TRTP;
RUN;
```

where CHG is the mean change from baseline of the ACES score, and TRTP is the planned treatment.

Shift tables will be generated for change in ACES score from baseline to all scheduled post-baseline visits. The proportions of subjects who shifted ACES score categories will be summarized by treatment group, using the following categories: Agitated (ACES 1-2), Normal (3-5), or Sedated (6-9).

In addition, analysis of ACES scores will be performed using a proportional odds model or an ordinal logistic regression for repeated measures with planned treatment , baseline ACES score category, timepoint (Day 1 – 0.5 hour, Day 1 – 1 hour, Day 1 – 2 hours), and planned treatment by timepoint interaction as independent variables. ACES category Sedated (6-9) category will be used as the reference response category. The odds ratio for this model is consistent with the ratio of one-unit increase in the ACES score category odds comparing the treatment groups. For instance, IXT-m200 may have a 1.2x higher odds of increasing from normal to agitated compared to TAU.

Interpretation of odds ratio value:

OR=1 Exposure (treatment group) does not affect odds of outcome (ACES score)
OR>1 Exposure associated with higher odds of an increase in ACES score category in group 1 vs group 2.
OR<1 Exposure associated with lower odds of an increase (or higher odds of a decrease) in ACES score category in group 1 vs group 2.

Treatment effects will be expressed as the estimated odds ratio (OR) of each active treatment over TAU. Estimated ORs, together with the associated two-sided 95% confidence interval and p-value will be calculated. Results will be plotted using a Forest plot. The following general form of the SAS PROC GENMOD procedure will be used:

```
PROC GENMOD DATA=ADQS;
  CLASS TRTP BASE VISIT SUBJID /PARAM=GLM;
  MODEL ACES = TRTP VISIT TRTP*VISIT  BASE/ DIST=MULTINOMIAL LINK=CLOGIT;
  REPEATED SUBJECT = SUBJID / TYPE=IND;
RUN;
```

where ACES is the categorized ACES score at the specified timepoint, BASE is the baseline categorized ACES score, TRTP is the planned treatment, VISIT is the scheduled timepoint.

The below are the estimate statements for Day 1 – 0.5 Hour as an example and similar logic will be applied for Day 1 -1 hour and Day 1 – 2 hour visits:

```
  estimate 'Odds (agitated) of Cohort 1 Day 1 - 0.5 Hour' intercept 1 0 TRTP 1 0 0 AVISITN 1 0 0
TRTP*VISIT 1 0 0 0 0 0 0 0 0 BASECAT1 0 1/ exp;
  estimate 'Odds (normal) of Cohort 1 Day 1 - 0.5 Hour' intercept 0 1 TRTP 1 0 0 AVISITN 1 0 0
TRTP*VISIT 1 0 0 0 0 0 0 0 0 BASECAT1 0 1/ exp;
  estimate 'Odds (agitated)of Cohort 2 Day 1 - 0.5 Hour' intercept 1 0 TRTP 0 1 0 AVISITN 1 0 0
TRTP*VISIT 0 0 0 1 0 0 0 0 0 BASECAT1 0 1/ exp;
  estimate 'Odds (normal) of Cohort 2 Day 1 - 0.5 Hour' intercept 0 1 TRTP 0 1 0 AVISITN 1 0 0
TRTP*VISIT 0 0 0 1 0 0 0 0 0 BASECAT1 0 1/ exp;
  estimate 'Odds (agitated) of Cohort 3 Day 1 - 0.5 Hour' intercept 1 0 TRTP 0 0 1 AVISITN 1 0 0
TRTP*VISIT 0 0 0 0 0 0 1 0 0 BASECAT1 0 1/  exp;
  estimate 'Odds (normal) of Cohort 3 Day 1 - 0.5 Hour' intercept 0 1 TRTP 0 0 1 AVISITN 1 0 0
TRTP*VISIT 0 0 0 0 0 0 1 0 0 BASECAT1 0 1/  exp;
  estimate 'Odds (agitated) of Pooled IXT Day 1 - 0.5 Hour' intercept 1 0 TRTP 5 .5 0 AVISITN 1 0 0
TRTP*VISIT .5 0 0 .5 0 0 0 0 0 BASECAT1 0 1/ exp;
  estimate 'Odds (normal) of Pooled IXT Day 1 - 0.5 Hour' intercept 0 1 TRTP .5 .5 0 AVISITN 1 0 0
TRTP*VISIT .5 0 0 .5 0 0 0 0 0 BASECAT1 0 1/ exp;

  lsmestimate TRTP*VISIT 'Odds Ratio C1 Versus TAU' 1 0 0 0 0 0 -1 0 0 / exp cl;
  lsmestimate TRTP*VISIT 'Odds Ratio C2 Versus TAU' 0 0 0 1 0 0 -1 0 0 / exp cl;
  lsmestimate TRTP*VISIT 'Odds Ratio Pooled IXT Versus TAU' .5 0 0 .5 0 0 -1 0 0 / exp cl;
```

In addition, figures will be provided including by-subject plots of ACES scores over time, the mean observed ACES score and standard deviation for each treatment group over time, and mean change from baseline and standard deviation for each treatment group over time.

9.2. Vital Signs including Blood Pressure and Heart Rate

The time course of actual values of vital sign parameters and of changes from baseline will be presented by treatment group in a figure using mean values and standard deviation. A shift table of post-baseline vital sign parameter values compared to baseline values will be provided by treatment group presenting the number and percentage of subjects below normal range / within normal range / above normal range. The ranges will be derived programmatically using the values specified in Table 9.2.1.

Table 9.2.1: Normal Range for Vital Signs Parameters

Vital Signs Parameter	Below Normal Range	Within Normal Range	Above Normal Range
Heart Rate (beats/min)	<40	40-100	>100
Systolic Blood Pressure (mmHg)	<90	90-140	>140
Diastolic Blood Pressure (mmHg)	<60	60-90	>90
Temperature (F)	NA	<100.4	>=100.4

The time to normalization (i.e., returning to normal range) of vital sign parameters is defined as the time from start of dosing of either IXT-m200 or TAU to first time the vital sign parameter is in normal range and remains in normal range for the remaining time-points. This time will be presented by Kaplan-Meier estimates and figure by treatment group and will be pairwise compared between each IXT-m200 dose versus TAU by the log-rank test.

The following general form of the SAS PROC LIFETEST procedure will be used:

```
PROC LIFETEST DATA=dataset-name NOTABLE;
  TIME AVAL*CENSOR(1);
  STRATA TRTP / test = LOGRANK adjust = sidak diff=control('TAU');
RUN;
```

where AVAL is the time (hours) to normalization of vital sign parameters; CENSOR is the censoring variable (1=censoring, 0=event), TRTP is the planned treatment which the subject was randomized to, and diff=control('TAU') requests comparisons of the control curve, TAU, with all other curves.

A plot of the Kaplan-Meier estimate of the survival distribution function over time will be presented. In addition, figures will be provided including by-subject plots over time, the mean observed value and 95% confidence interval for each treatment group over time, and mean change from baseline and 95% confidence interval for each treatment group over time.

9.3. Need for Rescue Medications

Number and percentage of subjects with any rescue medication (from start of study treatment until discharge) will be provided by timepoint and by treatment group, overall IXT-m200 and overall TAU. Additionally, separate tables with the number and percentage of subjects with rescue medications for psychiatric manifestations and for cardiovascular manifestations, described in section 8.4.3, will be

provided by treatment group, overall IXT-m200 and overall TAU. The proportion of subjects with any rescue medication will be compared between the IXT-m200 treatment groups (Cohorts 1-2 and overall IXT-m200) and overall TAU using a Fisher's exact test.

9.4. Emergency Department (ED) Length of Stay

ED length of stay as measured by discharge time minus triage time, and as measured by discharge time minus start of treatment time, observed values and with log transformation (natural logarithm (ln), log to the base e), will be summarized. A two-sample t-test will be used to test if the mean difference between each IXT-m200 dose versus TAU is significantly different from zero at a 5% significance level. In the two-sample t-test, we assume the differences in the log time between the two groups to be normally distributed. These assumptions will be checked using quantile-quantile (Q-Q) plots and if not satisfied, then a non-parametric Wilcoxon signed-rank test will be performed.

The following general form of the SAS PROC TTEST procedure will be used to perform a two-sample t-test:

```
PROC TTEST DATA=dataset-name;
  CLASS TRTP;
  VAR AVAL;
RUN;
```

where AVAL is the log transformation of ED length of stay, and TRTP is the planned treatment.

The following general form of the SAS PROC NPAR1WAY will be used to perform a Wilcoxon rank sum test, if necessary:

```
PROC NPAR1WAY DATA=dataset-name WILCOXON;
  CLASS TRTP;
  VAR AVAL;
RUN;
```

10. Pharmacokinetics

The PK Population will be used for the analyses specified in this section. Concentration for METH and amphetamine, if available, will be summarized as described below but no further PK analysis will be conducted.

PK analyses will be conducted for IXT-m200 by treatment group as described below. The non-compartmental analysis (NCA) will be performed using appropriate software, i.e., Phoenix™ WinNonlin® (Version 8.0 or higher, Certara Corporation). All other analyses will be performed using SAS® (Version 9.4 or higher, SAS Institute Inc.)

10.1. PK Sampling Schedule

- Blood samples will be taken for analysis of IXT-m200 in serum on Day 1 (pre-dose, 4 hours after dosing, and at discharge) and on Days 3 and 28.
- Blood samples will be taken for analysis of METH, and amphetamine in plasma on Day 1 (pre-dose, 4 hours after dosing, and at discharge).

10.2. Handling of the Difference between the Scheduled and the Actual Sampling Times

For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of start of dosing (doses will be given over varying times). The actual post-dose sampling times expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to dosing (pre-dose), which will always be treated as zero (0.000), regardless of the time difference. Scheduled sampling times will be presented in concentration tables by treatment group.

10.3. PK Endpoint

Available serum IXT-m200 data will be used to calculate pharmacokinetic parameters if the data are sufficient to generate a reliable parameter estimate:

AUC_{0-t}:	Area under the concentration-time curve from time zero to the last non-zero concentration, calculated using the linear trapezoidal method.
AUC_{0-inf}:	Area under the concentration-time curve from time zero to infinity (extrapolated), calculated as $AUC_{0-t}+C_t/K_{el,}$ where: C_t = the last observed non-zero concentration.
C_{max}:	Maximum observed concentration.
Residual area:	Residual area, calculated as $100*(1- AUC_{0-t} / AUC_{0-inf})$. If Residual area is >20%, any PK parameters derived from AUC_{0-inf} will be flagged in individual listings.
T_{max}:	Time of observed C_{max}.
$t_{½}$:	Elimination half-life, calculated as $\log(2)/K_{el}$ using the natural logarithm.
K_{el}:	Elimination rate constant. This parameter will be the negative of the estimated slope of the linear regression of the ln-transformed plasma concentration versus time profile in the terminal elimination phase. Due to the limited number of PK sample time points, manual selection using the Day 28 follow-up visit and 1 other concentration data point will be used to calculate K_{el}. The timepoint where ln-linear K_{el} calculation begins ($K_{el\ Lower}$) and the actual sampling time of the last measurable concentration used to estimate the K_{el} ($K_{el\ Upper}$), as well as the Rsq adjusted for the ln-linear regression for the calculation of the elimination rate constant will be

reported. If the K_{el} cannot be measured (e.g.: fewer than 2 non-zero concentrations in the terminal elimination phase or missing visit Day 28 follow-up sample), then elimination related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, $AUC_{0\text{-}inf}$, Rsq adjusted, Residual area, $t_{½}$, CL and V) will not be reported for PK profiles.

CL: Clearance, calculated as Dose/$AUC_{0\text{-}inf}$.

V: Volume of distribution, calculated as Dose/(K_{el} x $AUC_{0\text{-}inf}$).

10.4. Presentation of Concentration Data

10.4.1. Handling of Missing Data

Missing concentration data will be considered as non-informative and will not be imputed. No concentration estimates will be provided for missing sample values.

10.4.2. Listing and Presentation of Individual PK Data

- The sampling time of pre-dose samples relative to dosing is treated as zero for all sampling periods separately
- All concentrations are presented in original units as reported by the Bioanalytical laboratory
- All concentrations that are below the limit of quantification (BLQ) are set to zero
- Listings of PK sampling times include nominal and actual time elapsed from dose with the deviation from the nominal time and measured concentrations of the drug
- No further imputation will be applied to any missing values

Individual IXT-m200, METH, and amphetamine concentration data will be listed by subject, timepoint, and treatment group.

An overlay plot (Spaghetti plot) of subjects by treatment group will be presented graphically on both linear and semi-logarithmic scales for IXT-m200 and METH. Furthermore, an overlay plot (Spaghetti plot) of subjects by treatment group will be presented graphically on both linear and semi-logarithmic scales for change from baseline concentration of METH.

10.4.3. Summary of PK Concentration

For PK concentration summaries, the following applies:

- All concentrations that are BLQ are set to zero
- The sampling time of pre-dose samples relative to dosing will be treated as zero
- Drug concentrations will be summarized by nominal time point
- Descriptive statistics will be performed
- No further imputation is applied to any missing values

IXT-m200 and METH concentrations will be summarized by treatment group, analyte, and time point, using descriptive statistics including n, number and percentage of subjects with BLQ, arithmetic mean, geometric mean, SD, arithmetic and geometric coefficient of variation (CV) %, minimum, median and maximum. The following precision will be applied to the various descriptive statistics:

Variables	Precision
Minimum; Maximum	3 significant digits / as needed based on actual measured values
Arithmetic mean; Geometric mean; Median	4 significant digits / as needed based on actual measured values
SD	5 significant digits / as needed based on actual measured values
CV%; Geometric CV%	1 decimal place / as needed based on actual measured values

10.5. PK Parameters Derivation

For the derivation of PK parameters, the following rules will apply:

- All concentration values below the assay's lower limit of quantification (BLQ) will be treated as zero
- The sampling time of pre-dose samples relative to dosing will also be treated as zero
- Actual blood sampling times will be used to derive PK parameters (if the actual blood sampling is not present, then that timepoint and concentration will not be considered for PK analyses (except for predose, where timepoint as zero will be considered))
- No further imputation will be applied to any missing values

For PK concentration and parameter listings, the final reportable results or data will be presented by rounding off to 2 decimal digits, except for the following situations (this applies to individual data):

- PK parameters related to time such as T_{max} must be reported with the same precision as the actual sampling time: rounded off to 3 decimal digits.
- Concentration versus time data: reported as they appear in the corresponding dataset.

10.5.1. PK Parameters Summarization

PK parameters and concentrations data will be summarized using the following descriptive statistics:

Variable	Summarized with:
PK concentration at each nominal time point	n, arithmetic mean, SD, coefficient of variance (CV) %, minimum, median and maximum
AUCs, C_{max}, CL, and V	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
$t_{1/2}$, k_{el}	n, arithmetic mean, SD, CV%, minimum, median, maximum
t_{max} (actual time)	n, minimum, median, and maximum

Note: CV% = SD/mean in %. n = non-missing No. of observations.

10.6. Interim PK Analysis

No interim PK analyses are planned for this study.

11. Safety

The population used for safety analyses will be the Safety Population. Safety will be assessed based on adverse event (AE), clinical laboratory data (hematology and clinical chemistry), physical examinations, vital signs, and extent of exposure. Table summaries will be presented by treatment group (each IXT-m200 treatment group, overall IXT-m200, and TAU).

11.1. Adverse Events

All adverse events will be classified by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 23.0.

A TEAE is defined as any event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment. In addition, events with missing onset dates will be included as treatment-emergent.

An overall summary of TEAEs will be tabulated across all treatment groups, including the number and percent of subjects reporting:

- TEAEs
- TEAEs by Severity Grade
- Study Treatment-related TEAEs
- Serious TEAEs
- Study Treatment-related Serious TEAEs
- TEAEs of Special Interest
- TEAEs leading to Discontinuation of Study Treatment
- TEAEs leading to Death

A summary table of TEAEs (number and percentage of subjects who experienced an AE) grouped by primary SOC and PT will be presented across all treatment groups for the following categories of events:

- All TEAEs
- All TEAEs by maximum severity grade
- All TEAEs by maximum relationship to study treatment
- All Study Treatment-related TEAEs
- All TEAEs leading to discontinuation of study treatment
- All TEAEs leading to death
- All Serious TEAEs
- All TEAEs of Special Interest

AEs are assessed with respect to relationship status by the investigator, as unrelated, unlikely related, possibly related, probably related, and definitely related. An AE would be categorized in statistical presentations as “treatment-related” if it is assessed by the investigator as possibly related, probably related, or definitely related.

AEs of Special Interest include the following events:

- Hypertension/tachycardia
- Euphoria
- Agitation
- Insomnia

- Anxiety
- Seizures
- Mania/aggression

A subject with more than one occurrence of the same AE in a particular SOC and PT will be counted only once in the total of subjects experiencing AEs in that particular SOC and PT, respectively. If a subject experiences the same AE at more than one severity, or with more than one relationship category, the most severe rating or the stronger causal relationship will be reported.

Any missing relationship of an AE will be included as "treatment-related". Any missing severity grade of an AE will be included in the Grade 3 - Severe category.

The tables will be sorted by descending frequency of SOC and then, within a SOC, by descending frequency of PT based on the subject count for the overall IXT-m200 treatment group.

All AEs will be listed by subject and chronologically by date and time of AE onset. This listing will include all data collected in the eCRF and the coded variables. Additional listings of SAEs, treatment-related TEAEs, AEs leading to discontinuation of study treatment, and deaths will be provided.

11.2. Laboratory Evaluations

Clinical laboratory data (continuous parameters) will be summarized using descriptive statistics for each scheduled assessment time point by treatment group. Categorical laboratory data and urinary drug screen results will be presented by number and percentage of subjects in each category and scheduled time point by treatment group. Additionally, for laboratory data, frequency tables with number and percentage of subjects of scheduled time point will be provided using the categories above/within/below normal range.

Laboratory results will be displayed using standard units for all summaries and listings. Laboratory results collected in conventional units will be converted to International System of Units (SI) for all summaries and listings.

Potentially clinically significant values will be identified for Hematology and Chemistry parameters using the reference range values specified in the Q2 Solutions Range Chart V01, 27 Apr 2021. The reference ranges are included in Appendix 18.1.

All laboratory values (including values, reference ranges, and possible flags (low, high)) will be presented in the subject data listings.

11.3. Vital Signs

Vital signs will be summarized using descriptive statistics: actual values and changes from baseline will be presented for each scheduled assessment time point by treatment group, overall IXT-m200 and overall TAU.

Vital sign measurements that will be summarized include blood pressure (systolic and diastolic, mmHg), heart rate (beats per minute [bpm]), respiratory rate (breaths/min), body temperature (º Fahrenheit), pulse oximetry (%), weight (kg), and BMI (kg/m^2). Summary statistics for vital sign measurements will be presented for each scheduled time point and for the change from baseline to each time point.

Vital signs data will be listed chronologically by subject and time points for each vital sign parameter.

Potentially clinically significant values will be identified for vital sign parameters as outlined below.

Table 12.3.1: Potentially Clinically Significant Values for Vital Signs

Vital Sign Parameter	Units	Criteria for PCS Values (Observed values)	
		High	Low
Heart rate	Beats/min	>120	<40
Systolic Blood Pressure	mmHg	>180	<90
Diastolic Blood pressure	mmHg	>110	<50
Oxygen Saturation	%	NA	<92

11.4. 12-Lead ECG

An electrocardiogram (ECG; 12-lead) will be recorded after IXT-m200 or TAU dosing is complete and the participant is cooperative. Standard ECG parameters including heart rate, QRS (ms), PR (ms), QT (ms), and QTc intervals (ms) will be measured. The ECGs will be read by a study physician to assess for any abnormalities. Abnormal ECG parameters include, but are not limited to ventricular hypertrophy, left axis deviation, atrial or ventricular arrhythmias other than sinus, and prolonged QTc (greater than 500 ms).

An ECG will be performed at prespecified time points per the 'Schedule of Assessments'; table in Section 1.3 of the protocol.

Potentially clinically significant values will be identified for ECG parameters as outlined below.

Table 12.4.1: Potentially Clinically Significant Values for QT (ms), QTc intervals (ms)

ECG Parameter	Units	Criteria for PCS Values (Observed values)	
		High	Low
QT, QTc intervals	ms	>450 but <=480 >480 but <=500 >500	NA

12-Lead ECG results will be provided in a data listing.

11.5. Physical Examination

Physical examination results will be listed by subject and summarized by number and percentage of subjects in each body system category and scheduled time point.

12. Interim Analyses

No interim analyses are planned.

13. Changes from Analysis Planned in Protocol

Several instances in the protocol describe summaries by treatment group, overall IXT-m200 and total. Unless otherwise stated, all analyses will be summarized by treatment group, overall IXT-m200 and overall TAU.

Section 9.4.3 of the protocol indicates that secondary endpoint Agitation/sedation scores over time as measured by ACES will be analyzed by time to normalization of agitation using ACES. Instead, this secondary endpoint will be analyzed using methods specified in Section 9.1 of this SAP.

Section 3 of the protocol includes Tertiary/Exploratory endpoint: Emergency Department (ED) length of stay as measured by disposition order time minus triage time, and as measured by disposition order time minus start of treatment time, with log transformation. Upon evaluation of results for disposition order time minus triage time, it was determined that discharge time minus triage time is the preferred estimate for ED length of stay. Discharge time minus start of treatment time will also be applied.

14. Reference List

Protocol No. M200C-2101. Meth-OD: A Phase 2a Study of IXT-m200 in Patients with Toxicity from Methamphetamine Overdose. Version Number: 5. 22 August 2022.

15. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated TFL output will adhere to the following specifications.

15.1. General Considerations

- One SAS program can create several outputs
- Each output will be stored in a separate file
- Output files will be delivered in Word format or portable document format (pdf)
- Numbering of TFLs will follow ICH E3 guidance

15.2. Table, Figure, and Listing Format

15.2.1. General

- All TFLs will be produced in landscape format on A4/American letter size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- Legends will be used for all figures with more than one variable, group, or item displayed
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate

15.2.2. Headers

- All output should have the following header at the top left of each page:

  InterveXion Therapeutics, LLC
  Protocol: M200C-2101

- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)
- The date the output was generated will appear along with the program name as a footer on each page

15.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the body.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

15.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include 'unit' in column or row heading when appropriate
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set
- The order of treatments in the tables and listings will be Cohort 1 (IXT-m200 0.5 g), Cohort 2 (IXT-m200 2 g), Overall IXT-m200, and Overall TAU.

15.2.5. Body of the Data Display

15.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

15.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations (SD) will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value is less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the overall IXT-m200 treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing

order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'

- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

15.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time

- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study

- Units will be included where available

15.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis

15.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display

- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible

- Subject specific footnotes are avoided, where possible

- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program: myprogram.sas Listing source: 16.x.y.z')

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

16. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907).

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

17. Appendix

17.1. Q2 Solutions Range Chart

Range Values				
Analyte	**Sex**	**Age**	**Reference**	**Units**
Haematology				
WBC	Both	>=16Y	4.1-12.3	x10E3/uL
Haemoglobin	Female	12-65Y	11.6-16.2	g/dL
	Male	18-65Y	13.0-17.5	g/dL
Haematocrit	Female	12-65Y	35.0-47.0	%
	Male	18-65Y	40.0-52.0	%
RBC	Female	12-65Y	3.8-5.5	X10E6/uL
	Male	12-65Y	4.1-5.9	X10E6/uL
MCV	Female	3-110Y	79-98	fL
	Male	3-110Y	79-97	fL
MCH	Both	1-110Y	26-34	pg/cell
MCHC	Both	>=0Y	31-37	g/dL
RDW	Both	0-110Y	11.6-14.8	%
Platelet count	Both	0-110Y	140-450	X10E3/uL
Neutrophils	Both	>=16Y	40.9-77.0	%
Lymphocytes	Both	>=16Y	15.5-46.6	%
Monocytes	Both	>=16Y	3.1-12.5	%
Eosinophils	Both	>=16Y	0.0-6.0	%
Basophils	Both	>=16Y	0.0-2.4	%
Blasts	Both	0-110Y	0-0	%
Promyelocytes	Both	0-110Y	0-0	%
Myelocytes	Both	0-110Y	0-0	%
Metamyelocytes	Both	0-110Y	0-0	%
Bands	Both	0-110Y	0.0-5.0	%
Prolymphocytes	Both	0-110Y	0-0	%
Atypical lymphocytes	Both	0-110Y	0-3	%
Neutrophils Absolute	Both	>=16Y	2.03-8.36	x10E3/uL
Lymphocytes Absolute	Both	>=16Y	1.02-3.36	x10E3/uL
Monocytes Absolute	Both	>=16Y	0.18-0.90	x10E3/uL
Eosinophils Absolute	Both	>=16Y	0.00-0.56	x10E3/uL

Basophils Absolute	Both	>=16Y	0.00-0.17	x10E3/uL
Blasts Absolute	Both	0-110Y	0.00-0.00	x10E3/uL
Promyelocytes Abs	Both	0-110Y	0.00-0.00	x10E3/uL
Myelocytes Absolute	Both	0-110Y	0.00-0.00	x10E3/uL
Metamyelocytes Absolute	Both	0-110Y	0.00-0.00	x10E3/uL
Bands Absolute	Both	0-110Y	0.00-0.50	x10E3/uL
Prolymphocytes Absolute	Both	0-110Y	0.00-0.00	x10E3/uL
Atypical lymphocytes Absolute	Both	0-110Y	0.00-0.30	x10E3/uL
Nucleated RBC	Both	0-110Y	0-0	/100 WBC
Plasma cells Absolute	Both	0-110Y	0.00-0.00	x10E3/uL
Plasma cells	Both	0-110Y	0-0	%

Range Values

Analyte	Sex	Age	Reference	Units
Chemistry				
Sodium	Both	>=0Y	135-147	mEq/L
Potassium	Both	0-109Y	3.3-5.1	mEq/L
Chloride	Both	1-90Y	97-110	mEq/L
Bicarbonate	Both	16-109Y	19-29	mEq/L
BUN/Urea	Both	18-60Y	6-20	mg/dL
Creatinine	Female	>=16Y	0.51-0.95	mg/dL
	Male	>=16Y	0.67-1.17	mg/dL
Glucose	Both	16-59Y	74-106	mg/dL
Calcium	Both	12-65Y	8.4-10.3	mg/dL
ALT	Female	>=17Y	<=33	U/L
	Male	>=17Y	<=41	U/L
AST	Female	>=16Y	<=31	U/L
	Male	>=16Y	<=37	U/L
GGT	Female	>=16Y	5-36	U/L
	Male	>=16Y	8-61	U/L
Alkaline Phosphatase	Female	>=18Y	35-104	U/L
	Male	>=18Y	40-129	U/L
CPK	Female	16-110Y	26-192	U/L
	Male	16-110Y	39-308	U/L

Range Values				
Analyte	**Sex**	**Age**	**Reference**	**Units**
Urinalysis				
Urine dipstick blood	Both	>=0Y	NEGATIVE	
Urine dipstick leukocyte esterase	Both	>=0Y	NEGATIVE	
Urine dipstick protein	Both	>=0Y	NEGATIVE	
Urine microscopy	Both	>=0Y	NORMAL	
Urinalysis RBC	Male	>=0Y	0-5/HPF	
	Female	11-110Y	0-8/HPF	
Urinalysis WBC	Male	0-110Y	0-3/HPF	
	Female	13-110Y	0-12HPF	

Range Values				
Analyte	**Sex**	**Age**	**Reference**	**Units**
Urine Drug Screen				
Amphetamines	Both	>=0Y	Negative	
Barbiturates	Both	>=0Y	Negative	
Benzodiazepines	Both	>=0Y	Negative	
Cocaine	Both	>=0Y	Negative	
Marijuana Metabolites	Both	>=0Y	Negative	
Opiates	Both	>=0Y	Negative	
Phencyclidine (PCP)	Both	>=0Y	Negative	
Tested at QD Nichols Institute, Valencia, CA				
Propoxyphene	Both	>=0Y	NEGATIVE	

InterveXion_M200C-2101_SAP_v2.0

Final Audit Report 2023-02-27

Created:	2023-02-27
By:	Andy Torres (andy.torres@syneoshealth.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAA3woq7WQtgJM9sggazSqDPCyOKWq-gicn

"InterveXion_M200C-2101_SAP_v2.0" History

Document created by andy.torres@syneoshealth.com
2023-02-27 - 6:21:18 PM GMT- IP address: 165.225.218.208

Document emailed to raven.reavis@syneoshealth.com for signature
2023-02-27 - 6:22:09 PM GMT

Email viewed by raven.reavis@syneoshealth.com
2023-02-27 - 6:23:01 PM GMT- IP address: 136.226.3.29

Signer raven.reavis@syneoshealth.com entered name at signing as Raven Reavis
2023-02-27 - 6:23:34 PM GMT- IP address: 136.226.3.29

Raven Reavis (raven.reavis@syneoshealth.com) verified identity with Adobe Acrobat Sign authentication
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Document e-signed by Raven Reavis (raven.reavis@syneoshealth.com)
Signing reason: I am the approver
Signature Date: 2023-02-27 - 6:23:36 PM GMT - Time Source: server- IP address: 136.226.3.29

Document emailed to Caleb Wagner (caleb.wagner@syneoshealth.com) for signature
2023-02-27 - 6:23:38 PM GMT

Email viewed by Caleb Wagner (caleb.wagner@syneoshealth.com)
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Caleb Wagner (caleb.wagner@syneoshealth.com) verified identity with Adobe Acrobat Sign authentication
2023-02-27 - 6:45:42 PM GMT

Document e-signed by Caleb Wagner (caleb.wagner@syneoshealth.com)
Signing reason: I am the reviewer
Signature Date: 2023-02-27 - 6:45:42 PM GMT - Time Source: server- IP address: 165.225.60.215

Document emailed to andy.torres@syneoshealth.com for signature

2023-02-27 - 6:45:44 PM GMT

Signer andy.torres@syneoshealth.com entered name at signing as Andy Torres

2023-02-27 - 6:49:09 PM GMT- IP address: 165.225.218.208

Andy Torres (andy.torres@syneoshealth.com) verified identity with Adobe Acrobat Sign authentication

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Document e-signed by Andy Torres (andy.torres@syneoshealth.com)

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Document emailed to Misty Stevens (misty.stevens@intervexion.com) for signature

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Email viewed by Misty Stevens (misty.stevens@intervexion.com)

2023-02-27 - 9:12:53 PM GMT- IP address: 99.6.157.66

Misty Stevens (misty.stevens@intervexion.com) verified identity with Adobe Acrobat Sign authentication

2023-02-27 - 9:13:43 PM GMT

Document e-signed by Misty Stevens (misty.stevens@intervexion.com)

Signing reason: I am the approver

Signature Date: 2023-02-27 - 9:13:43 PM GMT - Time Source: server- IP address: 99.6.157.66

Agreement completed.

2023-02-27 - 9:13:43 PM GMT