Statistical Analysis Plan Title Page

Compound Name: **IXT-m200**

Protocol Title: **OUTLAST: A Phase 2 Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety and Efficacy of IXT-m200 in Treatment-Seeking Individuals with Methamphetamine Use Disorder**

Protocol and Version: **M200C-2201 V5**

Short Title: OUTLAST

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Regulatory Agency Identifier Number(s)

Registry	**ID**
ClinicalTrials.gov	NCT05034874

Statistical Analysis Plan Version: **V5 01MAY2024**

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Confidential Information

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Version history

Table 1 documents the changes to the SAP through all versions. Details regarding protocol changes that resulted in changes to the SAP can be found in the respective protocol amendment.

Table 1 SAP Version History Summary

SAP Version Approval Date	Rationale	Changes to SAP
1 24MAY2021	Original version	Not Applicable
2 01DEC2021		Changes to endpoints Addition of pseudo-SAS code for spaghetti plot
3 21MAR2023	The focus of the trial has shifted from a potentially pivotal trial to a purely Phase II, information gathering trial.	Change layout of SAP Incorporate suggestions from internal and FDA discussions, regarding objectives/endpoints and analyses. Addition of pseudo-R code for plots
4 01JUN2023	Fixing errors in endpoints	Fixed error in exploratory endpoint Updated table of contents
5 14JUL2023 01MAY2024	Changes to protocol Adding pharmacokinetic parameters to the analyses	Updated order of endpoints Updated study design Added pharmacokinetic endpoints Fixed discrepancy in endpoint regarding imputation of missing data

Abbreviations/Definitions

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
app	application
BMI	body mass index
BUN	blood urea nitrogen
CBT	cognitive behavioral therapy
CDFs	cumulative distribution functions
CI	confidence interval
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCFR	electronic case report form
HIPPA	Health Insurance Portability and Accountability Act of 1996
ICH	International Council for Harmonisation
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
LLOQ	lower limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
METH	methamphetamine
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
MUD	methamphetamine use disorder
PI	principal investigator
PK	pharmacokinetic

Abbreviation	Definition
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SPRHK1	SelfReportPHarmacoKinetic1

SAP Approval Signature Page

PROTOCOL TITLE	OUTLAST: A Phase 2 Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety and Efficacy of IXT-m200 in Treatment-Seeking Individuals with Methamphetamine Use Disorder
SAP Version, Date	V5, 01May2024
SAP AUTHOR	Michael C. Mosier, PhD Director, Biostatistics EMB Statistical Solutions, LLC Date
Investigational Product	IXT-m200
Protocol Number	M200C-2201
Protocol Version, Date	5 03Feb2023
Signature Statement	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Reviewers on behalf of InterveXion Therapeutics, LLC

Approver Signature _____ Date _____

Misty Stevens, MBA, PhD
Chief Operating Officer
Sponsor

1. Introduction

The purpose of this SAP is to describe the analysis variables and statistical procedures that will be used to analyze and report the results of InterveXion's protocol M200C-2201. This study is a Phase 2A study evaluating the safety, efficacy, immunogenicity, and pharmacokinetics (PK) of IXT-m200, a chimeric anti-methamphetamine monoclonal antibody treatment, in treatment-seeking individuals with methamphetamine (METH) use disorder (MUD). This statistical analysis plan (SAP) is based on InterveXion's protocol M200C-2201 version 5, dated February 3, 2023.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonization (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

Some of the analyses detailed here may be more explicit or in some respects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

Most statistical analyses will be performed using SAS® version 9.4 or later, with SAS program code prepared specifically for the project by qualified statisticians and SAS programmers. Other validated programs (e.g., S-Plus, R) may be used for graphs or for specialized analyses.

Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the SAP, so long as the changes were implemented prior to database lock. Changes in planned analyses that are decided after database lock will be documented in the clinical study report (CSR).

The formats for the tables, listings, and figures described in this SAP are provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP and will instead be described in the CSR.

Please see the study protocol for details about the study design, procedures, and schedule of assessments and see the electronic case report form (eCRF) for details about variables collected and their possible values.

1.1. Objectives, Endpoints, and Estimands

The following Table 2 lists the primary and secondary efficacy objectives of the study, along with the endpoints that will be measured, the clinical question to be addressed, as well as the *estimand*. An estimand is defined in the ICH E9(R1) guidance as *"...the target of estimation to address the scientific question of interest posed by the trial objective."*

Table 2 Primary and Secondary Efficacy Objectives, Endpoints and Estimands

Primary	
Objective: To evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use.	**Endpoints:** Percent of 20 weeks abstinent from stimulants following a 4-week grace period (between Week 5 and Week 25) as measured by saliva screens.
	Clinical Question: Does adding IXT-m200 to standardized cognitive behavioral therapy (CBT) program improve the percent of 20 weeks abstinent from stimulants following a 4-week grace period, relative to the CBT program alone, in treatment-seeking participants, regardless of IXT-m200 interruption or discontinuation, for any reason?
	Estimand: The difference in group means between the IXT-m200 and placebo groups for the percent of 20 weeks abstinent from stimulants following a 4-week grace period as measured by saliva screens in treatment-seeking individuals with MUD. All observations will be used, regardless of whether a participant discontinued treatment early. All missing values will be imputed assuming the participant is not abstinent.
Secondary	
Objective: To evaluate the efficacy of IXT-m200 in improving participant-rated quality of life.	**Endpoints:** Change from screening in participant-rated quality of life as measured by the Treatment Effectiveness Assessment (TEA) at Week 13, 25, and Week 33.
	Clinical Question: Does adding IXT-m200 to standardized CBT program improve the change from screening in participant-rated quality of life relative to the CBT program alone in treatment-seeking participants regardless of IXT-m200 interruption or discontinuation, for any reason?
	Estimand: The difference in group medians for the change from screening in participant-rated quality of life at Week 13, 25, and 33 between the IXT-m200 and placebo groups. All observations will be used, regardless of whether a participant discontinued treatment early. Missing values will not be imputed.
Objective: To evaluate the efficacy of IXT-m200 in increasing the number of participants achieving early remission.	**Endpoints:** Responders at Week 25 as measured by the DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria, while disregarding the result for craving.
	Clinical Question: Does adding IXT-m200 to standardized CBT program improve the proportion of participants achieving early remission, relative to the CBT program alone in treatment-seeking participants regardless of IXT-m200 interruption or discontinuation, for any reason?
	Estimand: The difference in the proportion of responders between the IXT-m200 and placebo groups, where a responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria, other than craving. All observations will be used, regardless of whether a participant discontinued treatment early. All missing values will be imputed assuming the participant has not achieved early remission.
Objective: To evaluate the efficacy of IXT-m200 in improving	**Endpoints:** Difference between groups in Clinical Global Impression of Change (CGIC) at Week 13, 25, and Week 33.

clinician-rated response to treatment.	**Clinical Question:** Does adding IXT-m200 to standardized CBT program improve CGIC at Week 13, 25, and Week 33, relative to the CBT program alone in treatment-seeking participants regardless of IXT-m200 interruption or discontinuation, for any reason?
	Estimand: The difference in CGIC at Week 13, 25, and Week 33, between the IXT-m200 and placebo groups in treatment-seeking individuals with MUD. All observations will be used, regardless of whether a participant discontinued treatment early. Missing values will not be imputed.
Objective: To evaluate the efficacy of IXT-m200 in improving patient-rated response to treatment.	**Endpoints:** Difference between groups in Patient Global Impression of Change (PGIC) at Week 13, 25, and Week 33.
	Clinical Question: Does adding IXT-m200 to standardized CBT program improve PGIC at Week 13, 25, and Week 33, relative to the CBT program alone in treatment-seeking participants regardless of IXT-m200 interruption or discontinuation, for any reason?
	Estimand: The difference in CGIC at Week 13, 25, and Week 33, between the IXT-m200 and placebo groups in treatment-seeking individuals with MUD. All observations will be used, regardless of whether a participant discontinued treatment early. Missing values will not be imputed.

Table 3 Exploratory Efficacy Objectives and Endpoints

Exploratory Objectives	Endpoints
To evaluate the efficacy of IXT-m200 in increasing the number of participants achieving early remission.	Responders at Week 33 as measured by DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria while disregarding the result for craving.
To evaluate the efficacy of IXT-m200 in reducing the number of adverse outcomes from the Adverse Outcomes Assessment.	The difference between groups in the number of adverse outcomes reported at Week 13, 25, and Week 33.
To evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use, as measured by self-report surveys.	Percent of days abstinent from stimulants following a 4-week grace period (between Week 5 and Week 25) as measured by self-report.
To evaluate the efficacy of IXT-m200 in improving the length of sustained abstinence.	Number of sequential weeks of abstinence from the end of treatment visit (Week 25), defined as four weeks after the final planned dose of study drug (at Week 21), as measured by saliva screens.
To evaluate the efficacy of IXT-m200 in improving post-treatment abstinence.	Point prevalence abstinence (last 7 days) as measured by saliva screens at Week 25, Week 29, and Week 33.
To evaluate the efficacy of	Complete abstinence during the last month of study drug treatment (between Week 21 and Week 25), as measured by saliva screens.

IXT-m200 in improving the proportion of participants achieving stimulant abstinence.	
To evaluate the efficacy of IXT-m200 in reducing the frequency of METH use over time, as measured by self-report.	Difference between groups in the trend over time in the number of use days per week, as measured by self-report for Weeks 5 through 25.
To evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use, as measured by self-report.	Proportion of participants with *n* or fewer use days between Week 5 and Week 25 measured by self-report.
To evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use, as measured by saliva screens.	Proportion of participants with *n* or fewer use days between Week 5 and Week 25 measured by saliva screens.

1.2. Study Design

InterveXion's protocol M200C-2201 is a Phase 2, double-blind, placebo-controlled, multiple-dose study of the safety and efficacy of monthly intravenous (IV) doses of IXT-m200 in treatment-seeking individuals with METH use disorder. The study was stopped before enrolling Cohort 2. As such, any reference to Cohort 2 in this document no longer applies, but has been retained for reference.

The study consists of two cohorts:

- In Cohort 1, approximately 60 participants will be randomized in a 2:1 ratio to IXT-m200 1.5 g or placebo (saline).
- In Cohort 2, approximately 60 participants will be randomized in a 2:1 ratio to the recommended dose of IXT-m200 or placebo based on the interim analysis at the end of Cohort 1. If the interim analysis recommends maintaining a dose of 1.5 g, then the sample size will be recalculated.

In each cohort, participants will receive either study drug (IXT-m200 at the cohort-specific dose or placebo) at the beginning of Weeks 1, 5, 9, 13, 17, and 21. All participants will also participate in seven sessions of a standardized cognitive behavioral therapy (CBT) program which will be delivered by a trained therapist; the first dose of IXT-m200 or placebo is intended to be given on the same day of initiation of CBT. For Cohort 1, the participants will participate in the CBT sessions during their monthly visits. For Cohort 2, participants will go to the clinic weekly for saliva drug tests and will participate in CBT sessions every two weeks, starting with Week 1. Participants will be followed at monthly intervals through Week 33. Cohort 1 will use app-based assessments to monitor between visits and Cohort 2 will use TLFB to monitor between visits. Schema 1.2 in the protocol displays the schematic of the study design for Cohort 1, and Appendix 1 shows the schedule of events. The first four weeks of treatment will be considered a grace period, designed to accommodate the likelihood that participants will relapse initially and experience the effects of IXT-m200. It further allows participants time to absorb and incorporate some of the skills taught by cognitive behavior therapy. METH use endpoints will be analyzed in the weeks following the grace period.

The cohorts will enroll sequentially, beginning with Cohort 1. Once the last participant in Cohort 1 has available Week 25 data (or has previously discontinued), the Data and Safety Monitoring Board (DSMB) will review an interim analysis report that includes efficacy and safety data. Based on that interim analysis, the DSMB may recommend whether to proceed to Cohort 2 and which dose to use for the IXT-m200 group (e.g., escalate to 3.0 g, continue at 1.5 g, or reduce). If the DSMB recommends continuing dosing at 1.5 g in Cohort 2, the sample size will be re-calculated based on the pooled standard deviation of the observed primary endpoint estimate in Cohort 1. The DSMB may also recommend that the study be stopped early if there is sufficient evidence that any of the circumstances in protocol section 10.1.2 apply.

The Sponsor will make the ultimate decision as to whether to accept the DSMB's recommendation. The Sponsor may have access to group-level data but will not have access to unblinded participant-level data at the time of the interim analysis. The Sponsor will have ongoing access to blinded individual participant data from saliva tests and daily self-reported drug use surveys.

Participants will continue the study in Cohort 1 through Week 33 while the interim analysis is ongoing.

2. Statistical Hypotheses and Testing

2.1. Statistical Hypotheses

The null hypothesis corresponding to the primary estimand is:

- Null hypothesis H0: IXT-m200 is not different from placebo with respect to the group means for the percent of 20 weeks abstinent from stimulants.
- Alternative hypothesis H1: There is a difference between IXT-m200 and placebo with respect to the group means for the percent of 20 weeks abstinent from stimulants.

The null and alternative hypotheses for all secondary estimands will be defined similarly, with the null hypothesis being "no difference" between groups, and the alternative hypothesis being "there is a difference," (i.e. a two-tailed alternative).

2.2. Sample Size Determination

As this is an exploratory Phase 2A study, the sample size was not set to power the study to statistically detect any particular treatment effect. Instead, it was chosen to balance the need to gather sufficient information regarding treatment effect and variability to plan for Phase 3, while not exposing more subjects than necessary to any yet unknown safety concerns.

Still, an assessment of the potential power of the study for statistical testing is provided in Table 4. These estimates assume that cohort 2 (if conducted) receives a different dose of IXT-m200, and provide the power for comparing *each* dose group to placebo. The primary endpoint will be based on Cohort 2, but cohorts may be pooled to perform additional analyses.

Table 4. Minimum detectable difference between *each* IXT-m200 group versus the placebo group

Power	Detectable difference	Examples of detectable differences with varying pooled SD		
		20%	25%	30%
Cohort 1/Cohort 2 only (n_1=40 vs n_2=20)				
0.80	0.78 × pooled SD	15.6% (3.1 more weeks)	19.5% (3.9 more weeks)	23.4% (4.7 more weeks)
0.85	0.84 × pooled SD	16.7% (3.3 more weeks)	20.9% (4.2 more weeks)	25.1% (5.0 more weeks)
0.90	0.90 × pooled SD	18.1% (3.6 more weeks)	22.5% (4.5 more weeks)	27.1% (5.4 more weeks)
Cohorts 1 and 2 pooled (n_1=40 vs n_2=40)				
0.80	0.63 × pooled SD	12.6% (2.5 more weeks)	15.8% (3.2 more weeks)	18.9% (3.8 more weeks)
0.85	0.68 × pooled SD	13.6% (2.7 more weeks)	17.0% (3.4 more weeks)	20.4% (4.1 more weeks)
0.90	0.73 × pooled SD	14.6% (2.9 more weeks)	18.3% (3.7 more weeks)	21.9% (4.4 more weeks)

The detectable differences were calculated in SAS Proc Power using a two-sample t-test assuming equal variance a two-sided 5% alpha. SD = standard deviation.

The literature suggests that dropout rates in the study population may be up to 50%**Error! Bookmark not defined.**, and therefore the analyses will account for missing data.

2.3. Multiplicity Adjustment

As this is an exploratory Phase 2 study, no adjustments for multiplicity will be made.

2.4. Interim Analyses

An interim analysis will be conducted after the last participant in Cohort 1 has available Week 25 data (or has previously discontinued). This interim analysis will include an unblinded review of efficacy, in addition to the typical safety report content.

As a Phase 2 study, there will not be formal statistical stopping rules for efficacy or futility. A Data Safety Monitoring Board (DSMB) will review the interim report (see the following Section 2.4.1 for further details) and provide a non-binding recommendation to the sponsor regarding the conduct of the study moving forward.

2.4.1. Data Safety Monitoring Board

The DSMB will review an interim analysis report after the last participant in Cohort 1 has available Week 25 data (or has previously discontinued) at which time the DSMB will review efficacy in addition to the typical safety report content. On the basis of the Week 25 interim analysis, the DSMB may recommend whether to proceed to Cohort 2, and if proceeding, which dose to use for the IXT-m200 group (e.g., escalate to 3.0 g, continue at 1.5 g, or reduce). If the DSMB recommends continuing dosing at 1.5 g in Cohort 2, a sample size recalculation will be executed using the pooled standard deviation of the primary endpoint in Cohort 1. The DSMB may also recommend that the study be stopped early if there is sufficient evidence that any of the following circumstances apply.

- Determination of unexpected, significant, or unacceptable risk to participants either related to the study intervention or unrelated events (such as a national health emergency);
- Demonstration of efficacy that would warrant early termination;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination that the primary endpoint has been met;
- Determination of futility.

The Sponsor will make the ultimate decision as to whether to accept the DSMB's recommendation. The Sponsor may have access to group-level data but will not have access to unblinded participant-level data at the time of the interim analysis. The Sponsor will have ongoing access to blinded individual participant data from saliva tests and daily self-reported drug use surveys. Participants will continue the study in Cohort 1 through Week 33 while the interim analysis is ongoing.

3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Table 5 Analysis Populations

Participant Analysis Set	Description
Intent-to-treat (ITT)	The intent-to-treat (ITT) population will be comprised of all randomized participants categorized by their randomized treatment assignment.
Modified intent-to-treat (mITT)	The modified ITT (mITT) population will be comprised of all randomized participants who received at least one dose of study drug. Participants will be analyzed according to their randomized treatment assignment.
Per protocol (PP)	The per-protocol (PP) population will be comprised of participants in the mITT population who had no major protocol deviations with the potential to impact efficacy assessments. Participants will be analyzed according to the treatment which they received (i.e., a participant randomized to placebo who received only active study drug in error will be analyzed with active participants, and a participant randomized to active who received only placebo will be analyzed with the placebo participants). The PP population will exclude participants who received some active drug and some placebo. InterveXion will conduct a blinded review of the protocol deviations prior to database lock to determine if any participant should be excluded from the PP population.
Safety	The safety population will be comprised of all randomized participants receiving at least one dose of study drug. Subjects will be classified according to drug actually received.
Pharmacokinetic (PK)	The pharmacokinetic population will include all subjects for whom a serum concentration of IXT-m200 is available post-dose.
PK Concentration	This set will include subjects who received at least one dose of study drug and have at least one quantifiable serum concentration of IXT-m200 post-dose. Subjects with an insufficient number of PK samples to derive PK parameters or those not in the PK subset will still be used for listing and summary of PK concentrations, along with any graphical presentations of concentration-time data.
PK Parameter	Any subjects in the PK subset for whom the PK profile can be adequately characterized. These will be decided by Pharmacokinetic Personnel.

The ITT population will be used to analyze endpoints related to the efficacy objectives, and the safety analysis set will be used to analyze all endpoints and assessments related to safety. If less than 90% of the ITT population is in the PP population, then efficacy objectives will also be

analyzed using the PP population as sensitivity analyses. Immunogenicity will be assessed using the mITT population. PK concentrations will be derived using the PK concentration set and PK parameters will be derived using the PK parameter set.

4. Statistical Analyses

4.1. General Considerations

While statistical inference regarding the treatment effect of IXT-m200 on MUD is an important aspect of the analysis of this trial, it should be noted that this trial is also intended to gather information regarding the feasibility of various endpoints and measures of MUD treatment response. There has been relatively little described in the literature with respect to pharmacological treatments, and thus there is a lack of precedence with regard to the most efficient measures. Therefore, this analysis plan incorporates a range of endpoints/estimands and sensitivity analyses, from primary through exploratory, which vary the definition of response to treatment, and will allow an assessment of the utility of each to measure treatment effect.

4.1.1. Common Statistical Methods and Data Presentations

Descriptive and inferential statistics will summarize results. Unless otherwise indicated, the pre-specified efficacy analyses will be conducted using the ITT population. The study will use an overall nominal two-sided Type I error rate of 5%; results will be reported with a two-sided 95% confidence interval (CI) and nominal p-value. For primary and selected secondary and exploratory efficacy outcomes, plots of the cumulative distribution functions (CDFs) will show differences by treatment arm.

Categorical variables will be summarized with the frequency count and percentage of participants with non-missing data. Continuous variables will be summarized using appropriate summary statistics (e.g., the number of non-missing observations, mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, maximum; geometric mean and 95% confidence intervals (CIs) may also be presented, as appropriate).

All summaries will be by treatment group. Tabular presentations will display a separate column for each treatment regimen and graphical summaries will color-code each treatment regimen.

In addition to tabular and graphical summaries, by-participant listings will present all relevant electronic case report form (eCRF) data, sorted by treatment group and participant identifier.

4.1.2. Other Missing Data, and Data Errors

Any missing values for treatment responder endpoints will be imputed as “non-responder.” Missing values for global impressions scales will be imputed as the neutral result of “No Change.”

For endpoints related to saliva screens or self-report surveys, if a participant withdraws from the study, all remaining days following withdrawal will be imputed as not abstinent.

Missing values for quality of life, as measured by the Treatment Effectiveness Assessment, will not be imputed. Participants who withdraw or discontinue prior to Week 5, or do not have any reported saliva or self-report use data between Weeks 5 and 25 will not be included in the analysis.

In general, missing and partial dates will be displayed as captured in participant listing displays.

For adverse events:

- Missing start day: first of the month will be used unless this is before the start date of study drug; if the partial date is the same month as the first dose of study drug, the treatment start day will be used and the event will be considered treatment-emergent.
- Missing stop day: the last day of the month will be used.
- Completely missing start or end dates will remain missing, with no imputation applied. Time to onset will be missing, and duration will be considered ongoing.

For concomitant medications/medical history:

- If the partial date is a start date, January and 1 will be used for a missing month and missing day, respectively.
- If the partial date is a stop date, December will be used for a missing month, and the end of the month will be used for a missing day (i.e., 28/29/30/31 dependent on the month and year of the partial date).

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

4.1.3. Clinical Laboratory LLOQ Values

Clinical laboratory results that are below the lower limit of quantification (LLOQ) will be imputed as half of the LLOQ.

4.1.4. Coding of Concomitant Medications and Adverse Events

All adverse events (AEs) will be coded using MedDRA terms. The number and percent of participants with any treatment-emergent AE will be presented by MedDRA SOC and PT in descending frequency of occurrence. If a participant reports more than one AE that was coded to the same SOC or PT, the participant will be counted only once for that specific SOC or PT.

4.1.5. Definition of Study Time Points

Baseline is the latest pre-dose assessment with a non-missing value on or before the date of randomization (Day 1). If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. If baseline data are missing, no derivation will be performed, and baseline will be set to missing.

The following conversion factors will be used to convert days to weeks, months, and years: 1 week = 7 days, 1 month = 30.4375 days, and 1 year = 365.25 days.

For all randomized participants, Day 1 is the date of randomization. Day 1 is the planned timepoint for the first dose administration. Day 1 is also the start of “Week 1”.

For assessments on or after the randomization date, time is calculated in days as:

Study Day = Assessment Date – Randomization Date + 1 (positive number)

For assessments prior to the randomization date, time is calculated in days as:

Study Day = Assessment Date – Randomization Date

For other time variables based on two dates, Duration (days) = End Date – Start Date + 1.

4.2. Participant Accounting

The number of subjects who were enrolled, treated with at least one dose of study drug, who completed the study, as well as the reasons for withdrawal, will be summarized with counts and percentages by treatment group. This table will also include number of screening failures and reasons for screening failures.

4.3. Participant Disposition

The number and percentage of participants who are randomized, receive treatment, complete treatment, discontinue treatment early, discontinue study early, and complete study will be presented by treatment group. For participants who discontinue study or treatment early, the number and percentage discontinuing by reason and most recent dosing visit will be presented. The number and percentage of participants in each analysis population will also be presented.

4.4. Baseline Characteristics and Participant History

Demographic and baseline characteristics (age, sex, race, ethnicity, body weight, height, body mass index [BMI], and days per month of METH use) will be summarized by treatment group using descriptive statistics.

4.5. Study Intervention and Concomitant Medications

4.5.1. Extent of Exposure

Study drug exposure will be summarized for all participants by treatment group. Study drug exposure will be summarized as the number and percentage of participants receiving at least one dose (i.e., in the safety population) using the number randomized as the denominator. In addition, the number of participants who completed each dosing visit and the number of doses will be summarized by treatment group, using the number in the safety population as the denominator.

4.5.2. Treatment Compliance

Study drug is administered by intravenous infusion by qualified personnel who are blinded to the treatment assignment of the participant. Compliance with dosing will be verified by reference to the electronic case report form (eCRF) documentation of dosing. CBT session attendance will be documented by the site and captured in the eCRF.

4.5.3. Concomitant Medications

All concomitant medications (i.e., prescription medications, over-the-counter medications, non-prescription medications, and supplements) taken during study participation will be recorded on the eCRF. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

The use of concomitant medications will be summarized by therapeutic class and generic medication name using descriptive statistics. Concomitant medications will include all medications taken from randomization through follow-up.

In addition, any behavioral therapy sessions with a trained provider outside the protocol will be recorded as concomitant therapy.

4.6. Primary Estimand Analysis

The primary objective of the study is to evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use.

4.6.1. Main analytical approach

The primary efficacy analysis will use the ITT population and is based on a test of the mean difference between each IXT-m200 group and the placebo group in percent weeks abstinent, as estimated using an analysis of covariance (ANCOVA). The dependent variable in the model is percent weeks abstinent; the independent variables in the model are the following:

- Treatment group assignment (discrete); and
- Stratification level of past-month METH use at screening (discrete).

The data for this primary endpoint will have shown efficacy if the test of mean percent weeks abstinent between Week 5 and Week 25 shows nominal statistically significant benefit in any IXT-m200 group relative to the placebo group.

Adjusted means and standard errors for each treatment group and the estimated difference between the groups and associated 95% confidence intervals and two-sided p-values will be reported. A plot of all saliva screen results for each individual subject throughout the study will be provided. Pseudo-R code for the plot is included in Exhibit 2. The data should be divided into subsets based on the value of the saliva test value for methamphetamine, including ‘positive’, ‘negative’, ‘missed’, ‘invalid’. If the result of a saliva screen is not one that is listed, the sponsor should be contacted to receive instruction on how to code the value. If a saliva screen test is missed, that week will be imputed assuming the participant is not abstinent. If a participant withdraws from the study, then all weeks following withdrawal will be assumed as not abstinent. For the *n* subjects, each subject should be assigned a value from 1 to *n* for the purpose of plotting. Participants will be grouped by study treatment. An example plot is available in Exhibit 3.

Exhibit 2 Pseudo-R Code for Saliva Screen Data Plot

```
par(mfrow=c(1,2))
par(mar=c(5,4,4,1))
plot(NA,NA,xlim=c(0,175),ylim=c(0,25),xlab='Study Day',ylab='Participant',main='Placebo
Saliva Screen Results',
       yaxt='n',xaxt='n')
axis(1, at=seq(0, 175, by=7))
axis(2, at=seq(0,25,by=5))

for(i in 0:15){
  polygon(c(14*i+.5,14*i+7.5,14*i+7.5,14*i+.5), c(-5,-
5,75,75),col=rgb(0,0,0,.025),border=rgb(0,0,0,.025))
```

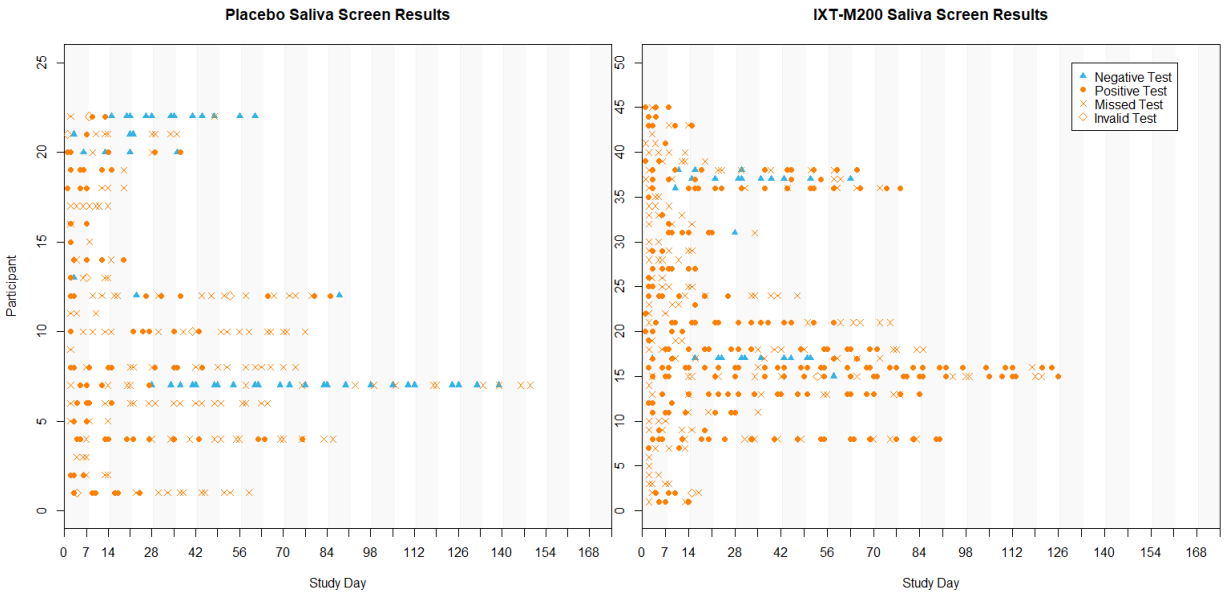
```
}
points(neg_placebo$DAY,neg_placebo$SUBJIDN,col=rgb(0.2,0.7,0.9,1),pch=17,cex=1)
points(pos_placebo$DAY,pos_placebo$SUBJIDN,col=rgb(1,0.5,0,1),pch=19,cex=1)
points(miss_placebo$DAY,miss_placebo$SUBJIDN,col=rgb(1,0.5,0,1),pch=4)
points(inv_placebo$DAY,inv_placebo$SUBJIDN,col=rgb(1,0.5,0,1),pch=5)

par(mar=c(5,1,4,2))
plot(NA,NA,xlim=c(0,175),ylim=c(0,50),xlab='Study Day',ylab='',main='IXT-M200 Saliva
Screen Results',
      yaxt='n',xaxt='n')
axis(1, at=seq(0, 175, by=7))
axis(2, at=seq(0,50,by=5))

for(i in 0:15){
  polygon(c(14*i+.5,14*i+7.5,14*i+7.5,14*i+.5), c(-5,-
5,75,75),col=rgb(0,0,0,.025),border=rgb(0,0,0,.025))
}
points(neg_trt$DAY,neg_trt$SUBJIDN,col=rgb(0.2,0.7,0.9,1),pch=17,cex=1)
points(pos_trt$DAY,pos_trt$SUBJIDN,col=rgb(1,0.5,0,1),pch=19,cex=1)
points(miss_trt$DAY,miss_trt$SUBJIDN-22,col=rgb(1,0.5,0,1),pch=4)
points(inv_trt$DAY,inv_trt$SUBJIDN,col=rgb(1,0.5,0,1),pch=5)

legend(130, 50, legend=c("Negative Test","Positive Test","Missed Test",'Invalid Test'),
      col = c(rgb(0.2,0.7,0.9,1),rgb(1,0.5,0,1),rgb(1,0.5,0,1),rgb(1,0.5,0,1)),pch=c(17,19,4,5))
```

Exhibit 3 Plot of Saliva Screen Results



4.6.2. Sensitivity analyses

To assess the robustness of findings from the primary analysis, the following set of sensitivity analyses will be performed:

- Analyses that involve imputing missing values for saliva screens or self-report surveys will be repeated without imputing missing values. That is, they will be left as missing, and proportions will use the total number non-missing values available as the denominator. The primary analysis will be repeated for the PP population as defined in Section 3 if less than 90% of the ITT population is in the PP population.

4.7. Secondary Estimand Analyses

The secondary efficacy objectives are:

1. To evaluate the efficacy of IXT-m200 in improving participant-rated quality of life.
2. To evaluate the efficacy of IXT-m200 in increasing the number of participants achieving early remission.
3. To evaluate the efficacy of IXT-m200 in improving clinician-rated response to treatment.
4. To evaluate the efficacy of IXT-m200 in improving patient-rated response to treatment.

4.7.1.1. Definition of endpoints

The corresponding secondary endpoints are:

1. Change from screening in participant-rated quality of life as measured by the Treatment Effectiveness Assessment (TEA) at Week 13, 25, and Week 33.
2. Responders at Week 25 as measured by the DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria, while disregarding the result for craving.
3. Difference between groups in Clinical Global Impression of Change (CGIC) at Week 13, 25, and Week 33.
4. Difference between groups in Patient Global Impression of Change (PGIC) at Week 13, 25, and Week 33.

4.7.1.2. Main analytical approaches

All secondary analyses will use the ITT population.

Quality of life analysis

A secondary objective is to evaluate the efficacy of IXT-m200 in improving patient-rated quality of life, as measured by change from screening in the Treatment Effectiveness Assessment score at Week 13, Week 25, and Week 33.

The Treatment Effectiveness Assessment includes four items with 10 ordinal response options ranging from “not well at all” to “extremely well” (Likert scale), where higher values indicate better quality of life. The Treatment Effectiveness Assessment score is the sum of the four responses (minimum = 4, maximum = 40); the Treatment Effectiveness Assessment score will not be computed if the participant did not respond to all four items.

As the sum of four ordinal items, a nonparametric approach to the analysis will be used since it is unlikely the values will meet the necessary normality assumptions for MMRM or ANCOVA

methods. Therefore, the change from screening in Treatment Effectiveness Assessment score at each post-screening timepoint will be compared in each IXT-m200 group versus the placebo group using a Kruskal-Wallis test.

For each comparison and timepoint, the Hodges-Lehmann estimate and 95% confidence intervals for the difference in group medians, and two-sided p-values will be reported.

A waterfall plot, depicting the median change from baseline at each timepoint will be provided for each treatment group. Pseudo-R code for the plot is included in Exhibit 4. Exhibit 5 contains an example of the waterfall plot.

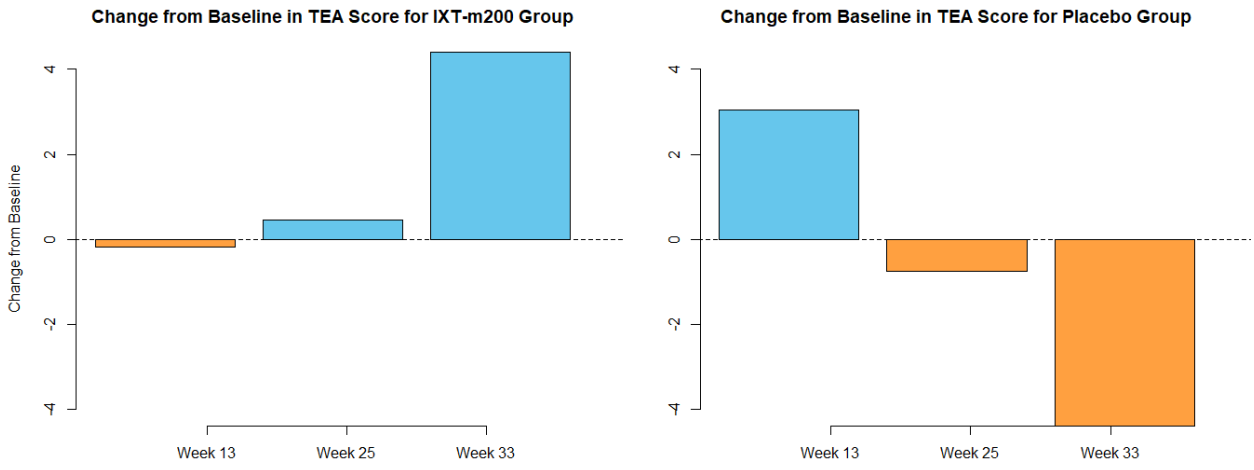
Exhibit 4 Pseudo-R Code for TEA Waterfall Plot

```
coltrt <- ifelse(medstrt >= 0,rgb(0.2,0.7,0.9,.75), rgb(1,0.5,0,.75))
colplcbo <- ifelse(medsplcbo >= 0,rgb(0.2,0.7,0.9,.75), rgb(1,0.5,0,.75))

par(mfrow=c(1,2))
barplot(medstrt,ylim=c(min(c(medstrt,medsplcbo)),max(c(medstrt,medsplcbo))),col=coltrt,yla
b="Change from Baseline")
segments(x0=0,x1=4,y0=0,y1=0,lty="dashed")

title('Change from Baseline in TEA Score for IXT-m200 Group')
axis(1, at=1:3, labels=c("Week 13","Week 25", "Week 33"))
barplot(medsplcbo,ylim=c(min(c(medstrt,medsplcbo)),max(c(medstrt,medsplcbo))),col=colplc
bo)
title('Change from Baseline in TEA Score for Placebo Group')
axis(1, at=1:3, labels=c("Week 13","Week 25", "Week 33"))
segments(x0=0,x1=4,y0=0,y1=0,lty="dashed")
```

Exhibit 5 TEA Waterfall Plot



Proportion of responders meeting early remission criteria

A secondary objective is the proportion of responders at Week 25 as measured by DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria, while disregarding the result for craving. All other criteria, 10 in total, will be counted. Participants that withdraw or discontinue prior to Week 5, or do not have any reported saliva or self-report use data between Weeks 5 and 25 will not be included in the analysis.

The proportion of participants achieving a response will be compared in each IXT-m200 dose group versus the placebo group using a stratified Mantel-Haenszel statistic with stratification level of past-month METH use at screening (discrete). The output will provide the risk difference between each IXT-m200 dose group and the placebo group, two-sided p-values, and 95% confidence intervals using the Miettinen-Nurminen (score) confidence limits[4].

Clinician-rated response to treatment

A secondary objective is to evaluate the efficacy of IXT-m200 in improving clinician-rated response to treatment, as measured by Clinical Global Impression of Change (CGIC) at Week 13, 25, and Week 33. The CGIC is completed by the clinician and has seven ordinal responses (Likert scale) ranging from "very much improved" to "very much worse". The comparison between groups will be conducted using a nonparametric Kruskal-Wallis test. The percentage of subjects in each scale category will be tabulated by treatment group and timepoint, and a graphical display using a frequency polygon will be produced for the Week 25 values.

Patient-rated response to treatment

Another secondary objective is to evaluate the efficacy of IXT-m200 in improving patient-rated response to treatment as measured by the Patient Global Impression of Change (PGIC) at Week 13, 25, and Week 33. PGIC is completed by the patient and has seven ordinal responses (Likert scale) ranging from "very much improved" to "very much worse".

The comparison between groups will be conducted using a nonparametric Kruskal-Wallis test. The percentage of subjects in each scale category will be tabulated by treatment group and timepoint, and a graphical display using a frequency polygon will be produced for the Week 25 values.

4.8. Exploratory Analyses

Exploratory analyses will be performed on the ITT population.

Proportion of responders meeting early remission criteria at Week 33

An additional exploratory objective is the proportion of responders at Week 33 as measured by DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria, while disregarding the result for craving. All other criteria, 10 in total, will be counted. Participants that withdraw or discontinue prior to Week 5, or do not have any reported saliva or self-report use data between Weeks 5 and 25 will not be included in the analysis.

The proportion of participants achieving a response will be compared in each IXT-m200 dose group versus the placebo group using a stratified Mantel-Haenszel statistic with stratification

level of past-month METH use at screening (discrete). The output will provide the risk difference between each IXT-m200 dose group and the placebo group, two-sided p-values, and 95% confidence intervals using the Miettinen-Nurminen (score) confidence limits.

Adverse Outcomes

An exploratory objective is to evaluate the efficacy of IXT-m200 in reducing the number of adverse outcomes from the Adverse Outcome Assessment. The assessment will be conducted at Screening, and Weeks 13, 25, and 33. All responses should be counted over the past 3 months. A summary table will provided, showing the mean, standard deviation, median, and min and max for each treatment group, at each of the given weeks. No formal statistical testing will be performed for this endpoint.

Percent of days abstinent from stimulants between Week 5 and Week 25

A secondary objective is to evaluate the efficacy of IXT-m200 in preventing or reducing the relapse to stimulant use, as measured by the percent of days abstinent from stimulants following a 4-week grace period (between Week 5 and Week 25) using self-report surveys via smartphone app.

Participants are to self-report their use/abstinence for each day of the study via the smartphone app. Missing survey data will be imputed assuming a use day. The analysis will be repeated without the imputation of missing data.

The difference in percentage of days abstinent from stimulants will be compared in each IXT-m200 group versus the placebo group using a t-test. For each comparison, the point estimate and 95% confidence intervals for the difference in group means, and two-sided p-values will be reported.

A plot of all self-report survey results for each individual participant throughout the study will be provided. Pseudo-R code for the plot is included in Exhibit 6. Observations should be sorted first by the highest study day where the survey was filled out and then by the number of use days.

Exhibit 6 Pseudo-R Code for Survey Data Plot

```
par(mfrow=c(2,1))
par(mar=c(3,4,2,1))
plot(NA,NA,xlim=c(0,175),ylim=c(0,25),xlab='',
    ylab='Placebo Participant',
    main='Meth Survey Responses for Individual Subjects',yaxt='n',xaxt='n')
axis(1, at=seq(0, 175, by=7))
axis(2, at=seq(0,25,by=5))

for(i in 0:15){
  polygon(c(14*i+.5,14*i+7.5,14*i+7.5,14*i+.5), c(-5,-
5,75,75),col=rgb(0,0,0,.025),border=rgb(0,0,0,.025))
}

points(nodrug_placebo$DAY,nodrug_placebo$SUBJIDN,col=rgb(0.2,0.7,0.9,1),pch=17,cex=1,yaxt='n')
points(drug_placebo$DAY,drug_placebo$SUBJIDN,col=rgb(1,0.5,0,1),pch=19,cex=1)
```

```
points(missed_placebo$DAY,missed_placebo$SUBJIDN,col=rgb(1,0.5,0,1),pch=4,cex=1)

legend(150, 25, legend=c("Answered No","Answered Yes","Missed"),
       col = c(rgb(0.2,0.7,0.9,1),rgb(1,0.5,0,1),rgb(1,0.5,0,1)),pch=c(17,19,4))

par(mar=c(5,4,0,1))
plot(NA,NA,xlim=c(0,175),ylim=c(0,45),xlab='Study Day',ylab='IXT-M200 Participant',
     main='',yaxt='n',xaxt='n')
axis(1, at=seq(0, 175, by=7))
axis(2, at=seq(0,45,by=5))

for(i in 0:15){
  polygon(c(14*i+.5,14*i+7.5,14*i+7.5,14*i+.5), c(-5,-
5,75,75),col=rgb(0,0,0,.025),border=rgb(0,0,0,.025))
}

points(nodrug_trt$DAY,nodrug_trt$SUBJIDN-22,col=rgb(0.2,0.7,0.9,1),pch=17,cex=1)
points(drug_trt$DAY,drug_trt$SUBJIDN-22,col=rgb(1,0.5,0,1),pch=19,cex=1)
points(missed_trt$DAY,missed_trt$SUBJIDN-22,col=rgb(1,0.5,0,1),pch=4,cex=1)
```

Sequential weeks of abstinence from the end of treatment visit (Week 25)

An exploratory objective is to evaluate the efficacy of IXT-m200 in improving the length of sustained abstinence. Sequential weeks of abstinence counting backwards from the end of treatment visit (Week 25), defined as four weeks after the final planned treatment visit (Week 21), as measured by saliva screens in each IXT-m200 group will be compared to the placebo group. In the event there is no Week 25 visit, then the endpoint is counted from four weeks after the last dosing visit attended.

A “use day” or “abstinent day” will be derived as described for the primary endpoint. For each participant, sequential weeks abstinent counting backwards from the Week 25 visit will be calculated based on use/abstinent days, for a minimum of 0 weeks and maximum of 24 weeks of abstinence. Participants that withdraw or discontinue prior to Week 5, or do not have any reported saliva screen data between Weeks 5 and 25 will not be included in the analysis.

The difference between each IXT-m200 group and the placebo group in sequential weeks of abstinence counting backward from Week 25 will be estimated using an ANCOVA model. The independent variables in the model will be treatment group and stratification level of past-month METH use at screening. Adjusted means and standard errors for each treatment group and the estimated difference between the groups and associated 95% confidence intervals and two-sided p-values will be reported. Figures and tables will summarize the outcomes and analysis results.

This analysis will be repeated with the PP population.

Point prevalence abstinence (last 7 days)

One exploratory objective is to evaluate the efficacy of IXT-m200 in improving post-treatment abstinence. Point prevalence abstinence (last 7 days) by saliva screens at Week 25, Week 29, and Week 33 will be compared between each IXT-m200 group and the placebo group.

For each visit of interest, abstinence or use will be based on the saliva screens in the previous seven days. A "use day" or "abstinent day" will be derived as described for the primary endpoint. A participant will be categorized as fully abstinent if their saliva screens are negative (responder); a participant will be categorized as not abstinent if any of their saliva screens are positive (failure). The generalized linear mixed model assumes that data are missing at random.

A generalized linear mixed model regressing binary abstinence on treatment group, visit, stratification level of past-month METH use at screening, and a treatment group by visit interaction term. For each comparison, the odds ratio, 95% confidence interval, and two-sided p-value will be reported. Figures and tables will summarize the outcomes and analysis results. Within-subject correlations will be modeled using an unstructured covariance structure. If the model does not converge (i.e., the study has too few observations for the number of parameters estimated), the model will sequentially use the heterogeneous Toeplitz structure, homogeneous Toeplitz structure, or compound symmetry structure, each requiring successively fewer parameters.

Complete abstinence between Week 21 and Week 25 responder analysis

A secondary objective is to evaluate the efficacy of IXT-m200 in improving the proportion of participants achieving stimulant abstinence, defined as complete abstinence during the last scheduled month of study drug treatment (between Week 21 and Week 25), as measured by saliva screens.

A participant will be categorized as fully abstinent if they have zero days of use (between Week 21 and Week 25); otherwise, a participant will be categorized as not abstinent (failure). Participants who withdraw or discontinue prior to Week 5, or do not have any reported saliva or self-report use data between Weeks 5 and 25 will not be included in the analysis.

The proportion of participants achieving a response will be compared in each IXT-m200 group versus the placebo group using a stratified Mantel-Haenszel statistic with stratification level of past-month METH use at screening (discrete). The output will provide the risk difference between each IXT-m200 dose group and the placebo group, two-sided p-values, and 95% confidence intervals using the Miettinen-Nurminen (score) confidence limits.

Reduction in the frequency of METH use over time

An additional exploratory objective is to evaluate the efficacy of IXT-m200 in reducing the frequency of METH use over time. For each day from the start of Week 5 through the end of Week 25, abstinence or use will be based on the self-reported use in the previous seven days. The number of use days in each week will then be determined.

The weekly total for a subject will be derived by counting the number of use days among the non-missing days and normalizing to a seven-day period. For example, for a subject with 1 use day among 4 non-missing days and 3 missing days in a given week, the number of use days (X) will be derived as $X = (1/4)*7 = 1.75$. No rounding will be performed. If a subject has all missing days in a given week, that week will not be imputed and therefore will not contribute to the analysis.

The number of use days per week will be summarized in a table presenting the mean and standard deviation for each treatment group, at each of the weeks from 5 to 25. No formal statistical testing will be performed for this endpoint. A plot of these group means across weeks will be provided.

A spaghetti plot will also be provided to show the use days per week by subject throughout the study. Pseudo-R code for the plot is included in Exhibit 7, and an example of the plot is included in Exhibit 8.

Exhibit 7 Pseudo-R Code for Weekly Meth Use Days Spaghetti Plot

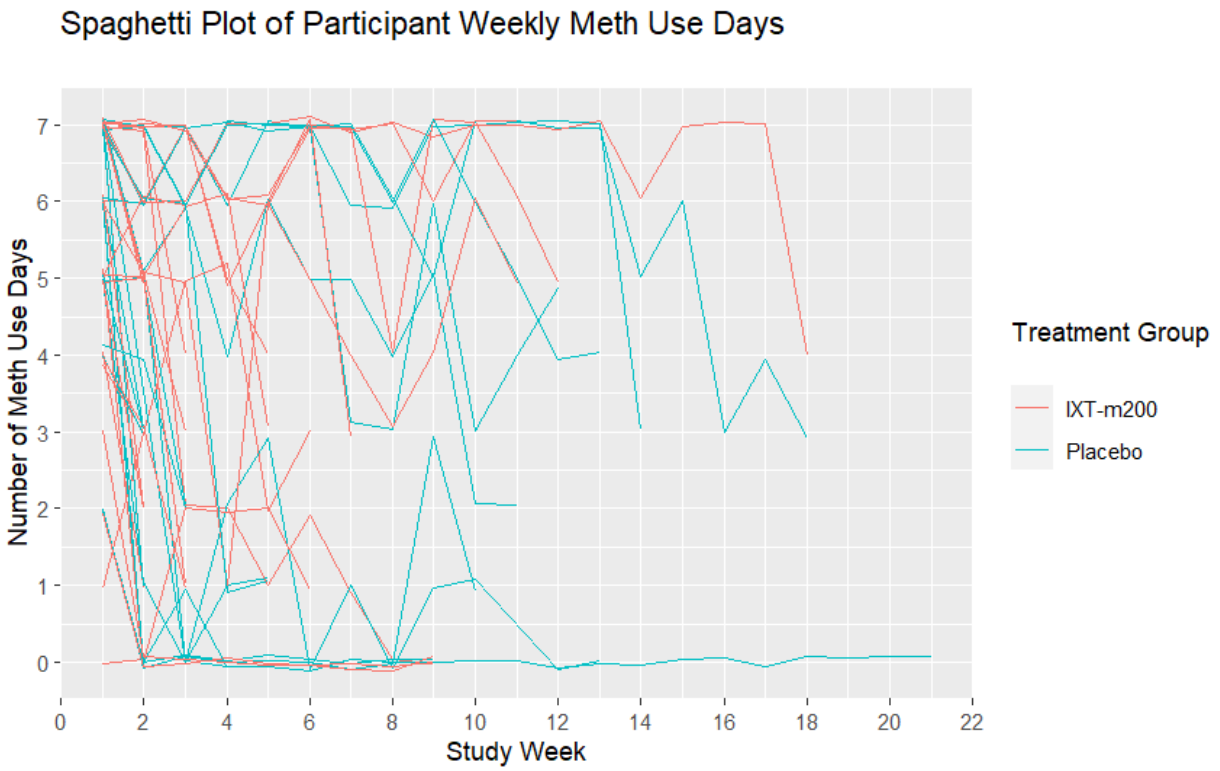
```
survey$DATE <- as.Date(survey$date)
startday <- aggregate(DATE ~ SUBJID, survey, function(x) min(x))

### RESPID is response ID, a sequential numbering of the dataset observations
### SUBJIDN is an integer valued SUBJID, a sequential numbering of unique subjects
for(i in 1:length(survey$RESPID)) {
  for(j in 1:max(SUBJIDN)) {
    if(survey$SUBJID[i]==startday$SUBJID[j]) {
      survey$DAY[i] <- as.numeric(survey$DATE[i]) - as.numeric(startday$DATE[j])
      survey$WEEK[i] <- (as.numeric(survey$DAY[i]) %/% 7)+1
      survey$METH01[i] <- as.integer(survey$METH[i]=='Methamphetamine')
      if(is.na(survey$METH01[i])) {survey$METH01[i]=0}
    }
  }
}

setDT(survey)
weeksdat <- survey[ ,list(usedays=sum(METH01)), by=.(TRT_GRP,SUBJID,WEEK)]

# Add some jittering to be able to distinguish and follow individual participants
for(i in 1:length(weeksdat$usedays)) {
  weeksdat$usedays_j[i] = weeksdat$usedays[i]+rnorm(1,mean=0,sd=.05)
}
# Spaghetti plot
plot <-ggplot(data=weeksdat, aes(x=WEEK, y=usedays_j, group=SUBJID))
plot +
  geom_line(aes(col = TRT_GRP)) +
  #geom_point() +#
  xlim(0,25) +
  ylim(-.25,7.25) +
  labs(title = "Spaghetti Plot of Participant Weekly Meth Use Days\n",
       x="Study Week", y="Number of Meth Use Days", color="Treatment Group\n") +
  scale_x_continuous(breaks=seq(0,26,2)) +
  scale_y_continuous(breaks=seq(0,7,1))
  theme_bw()
```

Exhibit 8 Weekly Meth Use Days Spaghetti Plot



Proportion of participants with *n* or fewer use days between Week 5 and Week 25 Measured by Self-Report

The proportion of participants with *n* or fewer use days between Week 5 and Week 25, where *n* ranges from 0 to 20 will be summarized. A secondary endpoint is Complete Abstinence during the last 4 weeks. This analysis will expand that to the last 20 weeks and explore a range of use days from 0 (complete abstinence) to 20 (an average of one use day a week).

A "use day" or "abstinent day" will be based on self-report surveys. Missing survey responses will be imputed assuming use for that day. The summary will be descriptive only, presenting the number and percentage of "responders," defined as subjects with *n* or fewer use days between Week 5 and Week 25 (Study days 29 to 169). A continuous responder curve will be produced with the number of use days on the horizontal axis and percent of subjects on the vertical axis, with a line for each treatment group. Since the criteria for a responder becomes less strict as *n* increases, both curves would be expected to be near 0% at *n=0,* and increase as they move to the right. The graph will allow a visual examination of potential separation between treatment groups. Pseudo-R code for the plot is included in Exhibit 9. For number of use-days from 0 to 140 (20 weeks), calculate the proportion of subjects with *n* use-days or less. Exhibit 10 shows an example of the plot.

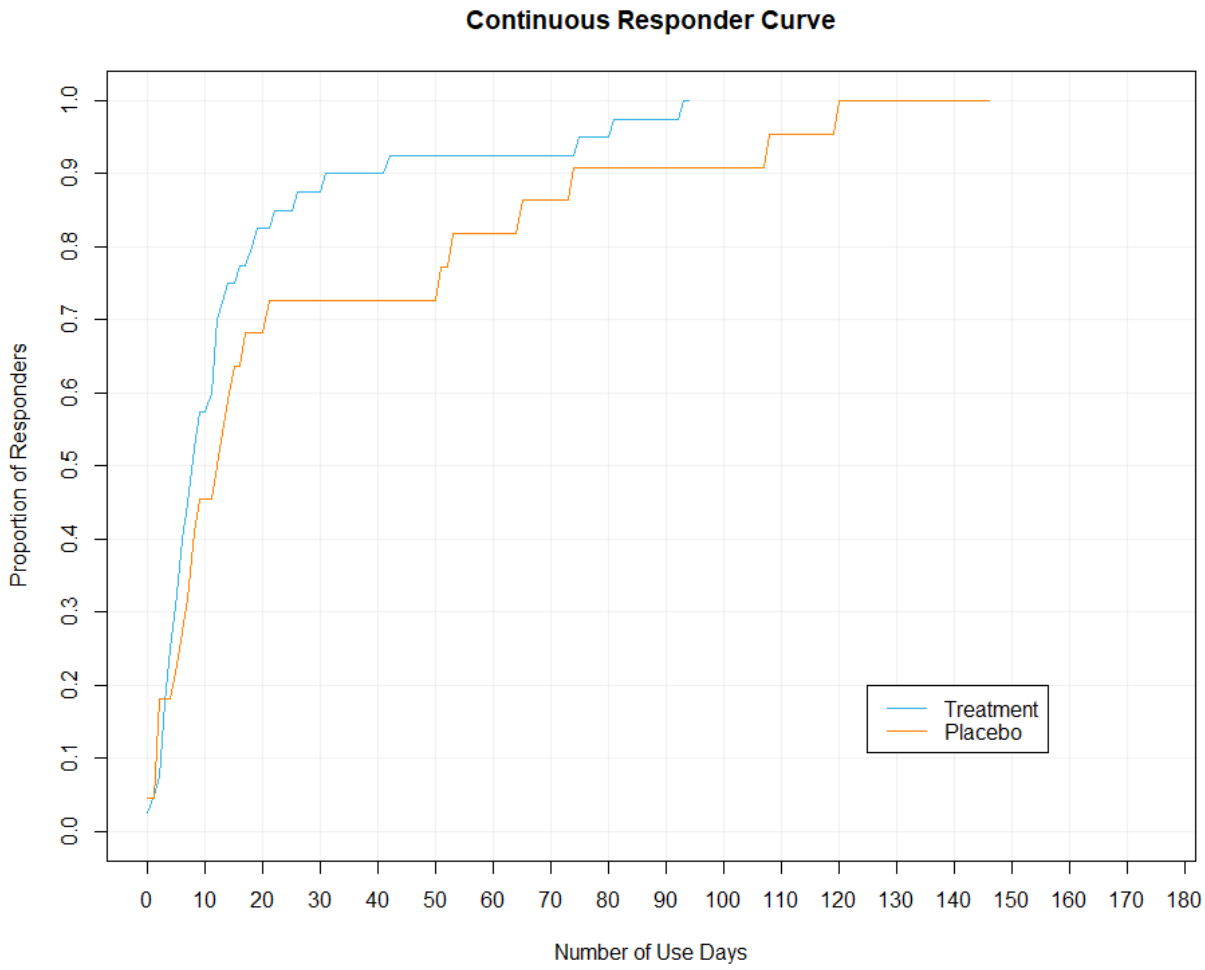
Exhibit 9 Pseudo-R Code for Continuous Responder Curve Plot

```
plot(NA,NA,xlim=c(0,175),ylim=c(0,1),xaxt='n',yaxt='n',xlab='Number of Use Days',
ylab='Proportion of Responders',main='Continuous Response Curve')
for(i in 1:18){
```

```
  abline(v=(i-1)*10,col=rgb(0,0,0,0.05))
 }
 for(i in 1:11){
  abline(h=(i-1)/10,col=rgb(0,0,0,0.05))
 }
 lines(seq(0,max(trt$DAY)),prop_resp_t,col=rgb(0.2,0.7,0.9,1))
 lines(seq(0,max(placebo$DAY)),prop_resp_c,col=rgb(1,0.5,0,1))
 axis(1,seq(0,180,10))
 axis(2,seq(0,1,0.1))

 legend(125, 0.2, legend=c('Treatment','Placebo'),
        col = c(rgb(0.2,0.7,0.9,1),rgb(1,0.5,0,1)),lwd=c(1,1))
```

Exhibit 10 Continuous Responder Curve Plot



Proportion of participants with *n* or fewer use days between Week 5 and Week 25 Measured by Saliva Screens

The proportion of participants with *n* or fewer use days between Week 5 and Week 25, where *n* ranges from 0 to 20 will be summarized. A secondary endpoint is Complete Abstinence during the last 4 weeks. This analysis will expand that to the last 20 weeks and explore a range of use days from 0 (complete abstinence) to 20 (an average of one use day a week).

A "use day" or "abstinent day" will be derived using the following algorithm.

- If a participant has two positive tests, misses two tests, or has one positive and one missing test in a given week, then impute 7 use days for that week.
- If a participant has one positive/missing test and one negative test, then impute 4 use days for that week.
- If a participant tests negative for both tests, then impute 0 use days for that week.

The summary will be descriptive only, presenting the number and percentage of "responders," defined as subjects with *n* or fewer use days between Week 5 and Week 25. A continuous responder curve will be produced with the number of use days on the horizontal axis and percent of subjects on the vertical axis, with a line for each treatment group. Since the criteria for a responder becomes less strict as *n* increases, both curves would be expected to be near 0% at *n=0,* and increase as they move to the right. The graph will allow a visual examination of potential separation between treatment groups.

4.9. Pharmacokinetics Endpoints

The PK Concentration Set will be used for serum concentration summaries and listings and the PK Parameter Set will be used for PK parameter summaries and listings as specified in this section.

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 8.3 or higher, Certara Corporation). All other analyses will be performed using SAS® (Version 9.4 or higher, SAS Institute Inc).

4.9.1. PK Sampling Schedule

Section 1.3.2 of the protocol contains the full participant schedule for the PK subset.

- In all main study subjects, blood samples will be taken for analysis of IXT-m200 in serum on Day 1, Day 29, Day 57, Day 85, Day 113, and Day 141 at pre-dose (≤30 min prior) and 4 hours (±10 min) after the start of dosing, and once each visit on Day 169, Day 197, Day 225, and at early termination.
- In subjects in the PK subset, blood samples will be taken for analysis of IXT-m200 in serum on Day 1 and Day 141 at pre-dose (≤30 min prior), 1 hour (±10 min) and 4 hours (±10 min) after the start of dosing, and once at each visit on Day 2, Day 8, Day 15, Day 22, Day 142, Day 148, Day 155, and Day 162. Blood samples will also be taken at pre-dose and 4 hours after the start of dosing on Day 29, Day 57, Day 85, and Day 113, and once each visit on Day 169, Day 197, Day 225, and at early termination.

4.9.2. 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. 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.

4.9.3. PK Endpoint

Available serum IXT-m200 data up to 28 days after dosing on Day 1 and Day 141 from the PK Parameter Set will be used to calculate the PK parameters.

The following PK parameters will be calculated for Day 1, 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 up, log down trapezoidal method.

AUC_{0-28d}: Area under the concentration-time curve from time zero to day 28, calculated using the linear up, log down 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 serum concentration versus time profile in the terminal elimination phase. The Best-fit method, in Phoenix WinNonlin, will be used to calculate the K_{el} from at least 3 concentration data points excluding the C_{max}. Rsq adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of K_{el} must be ≥ 0.8. 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 3 non-zero concentrations in the terminal elimination phase or Rsq adjusted <0.8), then elimination related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, AUC_{0-inf}, Rsq adjusted, Residual area, $t_{½}$, CL and V) will be presented in the listing with a flag and excluded from descriptive statistics.

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

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

The following PK parameters will be calculated for Day 141, if the data are sufficient to generate a reliable parameter estimate:

$AUC_{0\text{-}t}$: Area under the concentration-time curve from time zero to the last non-zero concentration, calculated using the linear up, log down trapezoidal method.

$AUC_{0\text{-}tau}$: Area under the concentration-time curve over the dosing interval (tau = 28 days) at steady-state.

$C_{max,ss}$: Maximum observed concentration at steady-state.

$T_{max,ss}$: Time of observed C_{max} at steady-state.

$t_{½}$: 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 serum concentration versus time profile in the terminal elimination phase. The Best-fit method, in Phoenix WinNonlin, will be used to calculate the K_{el} from at least 3 concentration data points excluding the C_{max}. Rsq adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of K_{el} must be ≥ 0.8. 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 3 non-zero concentrations in the terminal elimination phase or Rsq adjusted <0.8), then elimination related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, Rsq adjusted, $t_{½}$, and V_{ss}) will be presented in the listing with a flag and excluded from descriptive statistics.

CL_{ss}: Clearance at steady-state, calculated as Dose/$AUC_{0\text{-}tau}$.

V_{ss}: Volume of distribution at steady-state, calculated as Dose/(K_{el} x $AUC_{0\text{-}tau}$).

RC_{max}: Accumulation ratio based on C_{max}, calculated as C_{max} on Day 141/Day 1

RAUC: Accumulation ratio based on AUC, calculated as $AUC_{0\text{-}tau}$ Day 141/$AUC_{0\text{-}28d}$ Day 1

4.9.4. Presentation of Concentration Data

4.9.4.1. 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.

4.9.4.2. 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 concentration data will be listed by subject, visit, 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.

4.9.4.3. 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 concentrations will be summarized by treatment group, visit, and time point.
- Mean (±SD) serum concentration versus time will be presented graphically on both linear and semi-logarithmic scales by treatment for IXT-m200.

4.9.5. 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

Individual IXT-m200 PK parameters will be listed by subject, visit, and treatment group.

Additionally, box plots of PK exposure parameters (e.g., AUC, C_{max}) and HACA results may be presented, as appropriate.

4.9.5.1. 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, number and percentage of subjects with BLQ, arithmetic mean, SD, coefficient of variance (CV) %, minimum, median, maximum, geometric mean and geometric CV%
$AUC_{0\text{-}t}$, $AUC_{0\text{-}28d}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}tau}$, C_{max}, $C_{max,ss}$, CL, CL_{ss}, V and V_{ss}	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
$t_{1/2}$, k_{el} and ratios (RC_{max} and RAUC)	n, arithmetic mean, SD, CV%, minimum, median, maximum
T_{max} and $T_{max,ss}$ (actual time)	n, minimum, median, and maximum

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

4.9.5.2. PK Reporting Precision

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

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):

- K_{el} data, and Rsq adjusted: rounded off to four decimal digits.
- PK parameters related to time such as T_{max}. $T_{max,ss,}$ $K_{el\ Lower}$, and $K_{el\ Upper}$ 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.

4.10. Safety Analyses

Primary analyses of safety will be summarized for the Safety population.

4.10.1. Adverse Events

All adverse events (AEs) will be coded using MedDRA terms. The number and percent of participants with any treatment-emergent AE will be presented by MedDRA SOC and PT in descending frequency of occurrence. If a participant reports more than one AE that was coded to the same SOC or PT, the participant will be counted only once for that specific SOC or PT.

Summaries of AEs by MedDRA SOC and PT will be provided for the following:

- AEs (overall and by severity)
- AEs reported as potentially related to IXT-m200 (including those with missing
- relatedness designation) (overall and by severity)
- Serious adverse events (SAEs)
- AEs leading to study withdrawal
- AEs leading to treatment discontinuation

Summaries will be presented by treatment group and for all participants. A listing will include all events for each participant, along with study day of onset, duration, severity, seriousness, relatedness, action taken (e.g., treatment discontinued, study discontinued, treatment interrupted, none), and outcome (e.g., recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown). Separate participant listings of SAEs and AEs leading to withdrawal will also be presented.

If any participant dies during the study, a listing of the fatal AE will also be provided along with a participant narrative that will include all relevant information.

4.10.2. Clinical Laboratory Analyses

All quantitative centrally reviewed clinical laboratory results other than urinalysis results will be presented in standardized units. Both observed values and changes from baseline will be summarized for each scheduled timepoint. Figures will be used if appropriate and would include shading between the lower and upper limits of normal, as applicable.

4.10.3. Electrocardiograms

Electrocardiogram (ECG) measurement data will be summarized descriptively by timepoint. Both observed values and changes from baseline will be summarized for each scheduled timepoint, as well as depicted in figures. Abnormal values will be indicated in listings.

4.10.4. Vital Signs

Vital signs results (heart rate, diastolic and systolic blood pressure, temperature, and respiratory rate) will be summarized descriptively by treatment and planned timepoint. Both observed values and changes from baseline will be summarized for each scheduled timepoint and depicted in figures.

4.10.5. Physical Examination

Physical examination findings will be listed by treatment group, participant, and visit.

4.10.6. Psychiatric evaluation

Psychiatric evaluation findings will be listed by treatment group, participant, and visit.

4.11. Immunogenicity

The primary analysis of immunogenicity will be conducted using the ITT population. Secondary analyses of immunogenicity will be conducted using the mITT population. The secondary endpoint of the number and percentage of participants with anti-IXT-m200 antibody levels that are confirmed positive and have titers more than three times the minimum required dilution will be summarized by treatment group and overall. For participants with positive screen results whose samples underwent immunodepletion, the number and percentage of participants with each titer category will be presented.

4.12. Subgroup analyses

Primary and secondary efficacy analyses may be performed in the following subgroups:

- Sex: male versus female
- Gender (as collected on eCRF)
- BMI categorized as under/normal/overweight
- Abstinent during the grace period: abstinent versus not abstinent
- Baseline METH use as randomized: <18 days versus ≥18 days
- Treatment compliance: above versus below median doses of study drug received
- Preferred route of administration of methamphetamine
- CBT attendance compliance: above versus below median number of sessions attended
- Participants who received additional therapy outside of the study versus those who did not
- If at least 10% participants are in the ITT population but not the PP population, the PP population will be analyzed as a subgroup.

4.13. Changes to Protocol-Planned Analyses

- There are no changes to the analyses planned in the protocol.

5. Supporting Documentation

5.1. Appendix 1: Schedule of Events

Assessment [a]	Screening	Dosing (-2/+7 days)						Follow-up (±3 days)			ET
Study Week	**≤-1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**NA**
Study Day	**-60 to -1**	**1[b]**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**NA**
Informed consent	X										
Initial evaluations Eligibility criteria Demographics Medical history and medications Vital signs [c] Physical and psychiatric exam Urine pregnancy test Saliva drug screen	X										
Laboratory tests [d]	X	X	X	X	X	X	X	X			X
Electrocardiogram (ECG) [e]	X	X	X	X	X	X	X				
App training App download and tutorial Saliva drug screens until acceptable	X										
Quality of Life Assessments [f]	X				X			X		X	X
Methamphetamine Use Assessments	X							X		X	X
Randomization		X									
Blood for PK/HACA & Cytokines [g]		X	X	X	X	X	X	X	X	X	X
Dose administration [h]		X	X	X	X	X	X				
Cognitive behavioral therapy		X	X	X	X	X	X		X		
Wellness check Update medical history Update medications Brief psychiatric evaluation Vital signs [c] Targeted physical exam Urine pregnancy test		X	X	X	X	X	X	X	X	X	X
Continuous events AE monitoring [i] Recovery coaching [j] Self-report daily drug use by app Random saliva drug screens [k]		Continuous									

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

[a] Descriptions of assessments are in Section 8.1 (efficacy) or 8.2 (safety).
[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 dosing days 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 2-hr post-dose completion (±10 min) on dose days.
[e] ECGs are to be done 30-min post dose completion (±15 min) on dosing days.
[f] Quality of Life Assessments include TEA, PGIC, and CGIC.
[g] PK samples are to be taken pre-dose (≤30 min prior), then 4 hr (±10 min) after the start of each infusion on dosing days. Participants should be kept on site until 4 hr post infusion start to collect samples. All other PK samples are to be collected once each visit. For participants in the PK subset (12 active and 4 placebo participants per cohort), additional samples should be taken on Day 1 at 1 hr (±10 min) post-start of infusion, Days 2 (+1), 8 (±2), 15 (±3), and 22 (±3); then also Day 141 at 1 hr (±10 min) post-start of infusion, Days 142 (+1), 148 (+2), 155 (±3), and 162 (±3). HACA samples are to be taken pre-dose (≤60 min prior) on visit Days 1, 57, 113, 169, and 225. Cytokine samples are to be taken pre-dose (≤60 min prior) on each dosing day. If a participant has an infusion reaction, cytokine sampling at 1- and 4-hours post-dose (±10 min) should be performed.
[h] Doses will be given over 30 min by intravenous (IV) infusion.
[i] AEs will be collected by phone call at 1 day and 1 week (±2 days) post-dose throughout the study.
[j] Recovery coaching will occur weekly via phone or video for the first three months, then taper off.
[k] Saliva drug screens will be done remotely and monitored by smartphone app.

6. References

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical principles for clinical trials (E9). International Conference on Harmonization, 1998.

2. International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Estimands and sensitivity analysis in clinical trials E9 (R1). International Conference on Harmonization, 2017.

3. Trivedi, M. H., et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. *The New England Journal of Medicine*. 2021, 384: 140-153.

4. Miettinen, O. S., and Nurminen, M. M. (1985). "Comparative Analysis of Two Rates." *Statistics in Medicine* 4:213–226.

5. Cook R, Quinn B, Heinzerling K, et al. Dropout in clinical trials of pharmacological treatment for methamphetamine dependence: the role of initial abstinence. *Addiction.* 2017; 112: 1077–1085.