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Statistical Analysis Plan

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Protocol Title:	STAMPOUT: Study of Antibody for Methamphetamine Outpatient Therapy
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1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	W. Brooks Gentry, MD, Chief Medical Officer
Signature of Sponsor Representative / Date:	W. Brooks Gentry, MD Digitally signed by W. Brooks Gentry, MD Date: 2020.04.08 15:48:53 -05'00'
Name of Author / Title:	Reilly Reis / Biostatistician
Signature of Author / Date:	Reilly Reis Signed by: ReisReilly Biostatistician Reason: I am approving this document. Date & Time: 09 Apr 2020 11:05 AM -05:00

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3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under InterveXion Therapeutics, LLC Protocol M200C-1801.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 30-MAY-2018 (including all amendments up to this protocol date) and the SAP has been amended to follow the amended protocol dated 20-AUG-2019 and the final eCRF(s) dated 09-MAR-2020.

An approved and signed SAP is a requirement for interim analysis and database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the pharmacokinetic (PK), pharmacodynamic (PD), and safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in Section 9.8.2 of the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first amendment to the SAP. Changes made include:

- Update to the number of subjects per dose group in Cohort 3 per Protocol Version 7.0 (10-JUL-2019).
- Update to randomization information due to the addition of Anaheim Clinical Trials site.
- Documentation of the Inpatient Completion Analyses planned following first database lock, and Final Analyses planned following final database lock.
- Updates to clarity of PK parameter handling based on diagnostic parameters
- Summaries of AEs broken out by inpatient and outpatient periods based on subject discharge date
- Addition of summaries of Immunogenicity

5.0 Study Objectives and Endpoints

5.1 Primary Objective

To determine the effect of IXT-m200 on methamphetamine (METH) PK parameters relative to Placebo.

5.1.1 Primary Endpoint

Change in plasma METH area under the curve (AUC) and maximum concentration (Cmax) resulting from METH challenge doses following single intravenous (IV) doses of IXT-m200.

5.2 Secondary Objectives

To determine the effect of IXT-m200 on METH subjective effects.

To evaluate the safety and tolerability and PK of a single IV dose of IXT-m200 with concomitant weekly IV METH challenges in subjects with METH use disorders.

5.2.1 Secondary Endpoints

- Subjective effects of METH challenge doses as measured by the Drug Effects Questionnaire (DEQ) (i.e., reduction of 'High' or 'Liking').
- Safety and tolerability of IXT-m200 with concomitant weekly METH challenges as measured by physical examinations and vital signs, adverse events (AEs), electrocardiograms (ECGs), and clinical laboratory testing, and immune response by measurement of anti-IXT-m200 antibody levels.
- Pharmacokinetics of IXT-m200 following single administration.

5.3 Study Hypothesis

This is primarily a PK and safety study that is not evaluating any formal hypotheses.

Primary: Treatment with IXT-m200 will increase systemic METH exposure (Cmax, AUC) following METH administration compared to Placebo. (Analysis will be Day 1 METH exposure compared to Day 5 [primary] and Day 12, Day 19, Day 26 [all secondary] for each dose level of IXT-m200 compared to Placebo.)

Secondary: Treatment with IXT-m200 will decrease subjective effects of METH compared to Placebo. (Analysis will be Day 1 METH subjective effects [Drug Liking, etc.] minus Day 5, Day 12, Day 19, and Day 26 for each dose level of IXT-m200 compared to Placebo)

6.0 Study Design

A dose run-up approach to a random-block dose assignment will be used. Approximately 126 subjects will be enrolled into the study in 4 cohorts in order to have 42 subjects complete the study. Subjects will be counted as completers if they receive the third METH challenge following the IXT-m200 dose and stay through the collection of the final METH PK sample 72 hours later (Day 22). Target numbers for completion are N = 10, 18, and 14 in the 6, 20, and 0 (Placebo) mg/kg IXT-m200 treatment groups, respectively. The odds of Placebo treatment is set at 33% across all 4 cohorts; the odds of high dose IXT-m200 (20 mg/kg) increases across successive cohorts. Subsequent cohorts will be enrolled 1 week after all subjects of the previous cohort complete Day 49 of the study, pending safety analysis.

Each cohort will participate in a standard, double-blind assessment of METH challenges requiring a 23 day/22-night inpatient study followed by an extended follow-up period. During the 23-day stay (Days -1 to Day 22), subjects will receive METH challenges before and after administration of IXT-m200 or Placebo. On Day 1, subjects will receive a METH challenge (Placebo [saline] and 30 mg METH, 4 hours apart, in random order, given under double-blind conditions). Those subjects who tolerate the METH doses as measured by AEs and cardiovascular parameters, and who also provide appropriate subjective responses will be randomized to treatment; those who do not will be discharged on Day 3. On Day 4, IXT-m200 (6 or 20 mg/kg) or Placebo will be administered in a double-blind manner. METH challenges will be repeated weekly for 3 weeks (Days 5, 12, and 19) to evaluate the enduring effects of METH following IXT-m200 or Placebo administration. Subjects may be discharged on Day 22 or given the option to continue into the Inpatient Extension Stay.

Subjects who successfully complete through Day 22 may remain in the study and continue into an optional Inpatient Extension Stay for an additional 7 days duration. On Day 26, subjects will receive the METH challenge dose regimen (Placebo and 30 mg METH, 4 hours apart in random order). On Day 29, subjects will be discharged from the clinic and will participate in an extended follow-up period.

Because of the expected long half-life of IXT-m200, the study will continue to monitor the safety of all study subjects in an outpatient manner through Day 126. Outpatient follow-up visits will occur weekly for several weeks and then every 3 weeks.

6.1 Sample Size Considerations

This is primarily a PK and safety study that is not evaluating any formal hypotheses.

It is planned that a targeted minimum of 10, 18, and 14 completers at the IXT-m200 6 mg/kg, 20 mg/kg, and Placebo treatments, respectively, through Day 22 will be sufficient to observe any difference in METH PK between Day 1 METH administration and METH challenges administered on Day 5, 12, and Day 19 following IXT-m200 administration on Day 4.

Approximately 21 subjects will be allowed to stay through the Inpatient Extension Stay for the Day 26 METH Challenge Day.

6.2 Randomization

Eleven independent double-blind randomization schedules will be prepared by PRA Health Sciences EDS, one for each Challenge Day for each study site (PRA Salt Lake City and Anaheim Clinical Trials, 10 total) and one for IXT-m200 treatment arm.

On Day 4 of the study, each subject will be assigned a unique randomization number beginning with 1X01 in each Cohort (where X identifies the Cohort number) that will determine the subject's treatment arm according to the following allocations:

Cohort	Dose Assignment
1 (N=18)	Randomization 2:1 (odds of Placebo = 33%)
	LOW = 6 mg/kg IXT-m200 (n=12)
	Placebo (n=6)
2 (N=18)	Randomization 1:1:1 (odds of Placebo = 33%)
	LOW = 6 mg/kg IXT-m200 (n=6)
	HIGH = 20 mg/kg IXT-m200 (n=6)
	Placebo (n=6)
3 (N=36)	Randomization 2:1 (odds of Placebo = 33%)
	HIGH = 20 mg/kg IXT-m200 (n=24)
	Placebo (n=12)
4 (N=54)	Randomization 2:1 (odds of Placebo = 33%)
	HIGH = 20 mg/kg IXT-m200 (n=36)
	Placebo (n=18)

On each Challenge Day (Day 1, 5, 12, 19 and optionally, Day 26), subjects will be assigned a unique randomization number to identify the Challenge Sequence of treatment with 30 mg METH (M) and Placebo (P): MP or PM. Randomization numbers will be assigned on Day 1 beginning with 2001, Day 5 beginning with 3001, Day 12 beginning with 4001, Day 19 beginning with 5001 and Day 26 beginning with 6001. Therefore, each Challenge Day is independent of the previous Challenge Day.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

Emin and TEmin are not calculated for Drug Effects Questionnaire (DEQ) assessments. Since Drug Liking and Drug Disliking are each captured separately on unipolar scales, the appropriate measure for evaluating Liking/Disliking is Emax, with the corresponding TEmax.

7.2 Interim Analysis

An unblinded interim review of the data will be conducted at the completion of Cohort 2 or upon request, no more than two unblinded interim reviews will be conducted throughout the study.

PK concentration data will be transferred directly to the unblinded PK Scientist for preparation of interim PK parameters. Summaries of interim PK parameters based on nominal time will be provided as unformatted

WinNonlin output to the client in a blinded format. Descriptive statistics will be used to summarize parameters by treatment (each IXT-m200 dose level and placebo) and challenge day. Number of subjects (n) and if necessary, other descriptive statistics, may be excluded to maintain the blind of individual subjects in the study. No formal statistical tests will be conducted. The PRA PK Scientist will be the only team member to have access to the unblinded PK results. No adjustments to p-values will be made as a result of interim review.

A summary of treatment emergent adverse events post-IXT-m200 dosing by system organ class and preferred term will be provided by treatment (IXT-m200 or placebo). Preferred terms and system organ class categories with fewer than 1 subject per treatment group will be excluded from the summary to maintain the blind of individual subjects.

Blinded safety excel listings will be provided directly from the study database.

An unblinded summary of METH 30 mg and Placebo PD effects (pooled across all IXT-m200 dose levels) on each Challenge Day was conducted in October 2019 using all PD data to date. Unblinded programmers were assigned to unblind the PD data to the METH/Placebo treatments, and only summary results were provided for review by blinded team members. This analysis was conducted to aid in the determination of whether or not the targeted number of completers in each dose group would be sufficient for analytical purposes.

7.3 Inpatient Completion Analysis

Upon completion of the inpatient stay (through Day 22) of the final enrolled subject, database lock activities will commence for all visits occurring through the date of the final subject's Day 22 visit. After database lock, the study will be unblinded for both METH/Placebo dosing on each Challenge Day and IXT-m200 dosing, METH/AMP PK data, safety data available to date and PD transfers will be received and a draft of the tables, listings and figures will be prepared. A draft of all Tables, Figures, and Listings (TFLs) will be provided except those relating to the IXT-m200 PK data. Sponsor comments will be incorporated, and the TFLs will be preliminarily considered final.

7.4 Final Analysis

Upon completion of all subjects follow-up visits, the IXT-m200 PK and ADA data transfer and updated safety lab transfer data will be received and the remaining visits in the database will be locked. Draft TFLs (all TFLs will be refreshed) will be provided after final database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the first draft CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the PRA Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

PK parameters and PD parameters will be rounded in the derived datasets as determined by the pharmacokineticist and statistician, respectively, and presented as such in the listings. Each parameter will have a fixed number of decimals. The pharmacokineticist/statistician will follow this rule when deciding the number of decimals for each parameter: no decimal if data for a parameter are generally greater than or equal to 100; 1 decimal if data are generally between 10 and 100; 2 decimals if data are generally between 1 and 10; 3 decimals if data are generally below 1.

The tmax and TEmax will be reported with 2 decimals.

For all summaries, the mean, median, 1st and 3rd Quartile (Q1 and Q3) will be presented to 1 decimal place greater than the data, standard deviation (SD) and standard error (SE) to 2 decimal places greater than the data, and the minimum (min) and maximum (max) will be presented to the same number of decimal places as the data. Percentages will be presented with 1 decimal.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Daylight Savings Time Adjustments

On November 4th, 2018 and November 3rd, 2019 at 2:00 am the clocks changed to 1:00 am as Daylight Savings Time ended. All clinic procedures for the remainder of the treatment period were moved back by one hour after daylight savings time ended. All duration calculations (ie, AE durations in hours, relative time from dosing for PK) for times post-daylight savings time adjustment that will be relative to a time prior to daylight savings will need to be programmatically adjusted for the hour that was gained on the mornings of November 4th, 2018 and November 3rd, 2019.

On March 10th, 2019 and March 8th, 2020 at 2:00 am the clocks changed to 3:00 am for Daylight Savings Time. All clinic procedures for the remainder of the treatment period were moved forward by one hour after daylight savings time occurs. All duration calculations for times post-daylight savings time that will be relative to a time prior to daylight savings will need to be programmatically adjusted for the hour that was lost on the mornings of March 10th, 2019 and March 8th, 2020.

9.1.4 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: number of observations (n), (arithmetic) mean, SD, min, median, and max value.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the CRF / Database.

9.1.5 Pooling

Summary statistics will be calculated by treatment (and timepoint, if applicable).

9.1.6 Unscheduled and Early Termination Measurements

Unscheduled and early termination measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for postdose evaluations is defined as the last observation recorded before the first study drug administration during the METH Challenge on Day 1. The last observation can be an unscheduled / repeated measurement.

Unless otherwise stated, predose for postdose evaluations on each Challenge Day and Day 4 is defined as the observed predose timepoint recorded for the given visit. If a predose observation is missing in a given visit, then the baseline value will be used.

9.2.2 Treatment/Subject Grouping

Label	Grouping
Study Drug	IXT-m200 or Placebo for Day 4 dosing, METH or Placebo for METH Challenges
Treatment	Day 4: Placebo = 0 mg/kg IXT-m200 LOW = 6 mg/kg IXT-m200 HIGH = 20 mg/kg IXT-m200 Challenge Days: Placebo 30 mg METH

9.2.3 Common Variable Derivations

Variable	Analysis Dataset	Definition/Calculation	Note
Change from Baseline/Predose	All	Postdose Observation minus Baseline/Predose Observation	Baseline may vary. Reference each section of the SAP for specific baseline. Note: Change from Baseline for PD parameters is reverse (Day 1 – Day X) as defined in Section 17.2.
Analysis Study Day (Prior to Dose)	All	Date of Measurement minus Dose Date	Day 1 is first day of first dose of study drug (challenge drug METH/Placebo).
Analysis Study Day (Post Dose)	All	Date of Measurement minus Dose Date +1	Day 1 is first day of first dose of study drug (challenge drug METH/Placebo).

IXT-m200 Actual Dose (Amount)	ADEX	IXT-m200 dose (mg) = dose level (mg/kg) * baseline body weight (kg) * [vol. administered (mL) / planned vol. (mL)]	Baseline Weight is the last weight measurement prior to dosing on Day 4 with IXT-m200 or Placebo.
Completed through Day 22	ADSL	Subjects will be counted as completers of the inpatient stay based on the CRF captured indication.	
Challenge Day/ PK Day (PKDY)	ADPC	For each PK profile on each Challenge Day (METH) and Day 4 (IXT-m200), PK concentrations captured from predose through 72 hours postdose will be mapped to the day of dosing.	For example, on Day 5 24 hour post start of infusion (SOI) timepoint for IXT-m200 concentrations, PKDY = 4, and on Day 8 72 hour post start of infusion timepoint, PKDY = 4.

9.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the PRA EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the primary objective of this study is to characterize the PK and assess safety and tolerability the datasets considered critical are subject level, PK, and adverse events (ADSL, ADPC, ADPP, and ADAE). As these are related to the primary objectives, these datasets will be double programmed per the QC Plan.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® version 8.1 or higher (Pharsight, Inc.). Additional PK computations may be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

The layout of TFLs will be according to the PRA EDS standards. Table shells are provided with and approved as part of this SAP. Small changes to shell layout due to the nature of the data may be required after lock at the discretion of the PRA project statistician. The TFLs will be provided as a single document in Adobe PDF format (in Letter format), and as individual files for each table, figure or listing in Rich Text Format (.rtf).

10.0 Analysis Sets

Analyses	Qualification Safety Set	Safety Set	PK Set	PD Set
Disposition Summaries	✓	✓		
Safety Assessments	✓	✓		
Demographic and Baseline Characteristics		✓	✓	
Primary Analysis			✓	
PK Concentrations		✓		
PK Parameters			✓	
PD Values and Parameters				✓

10.1 Qualification Safety Set

Subjects who receive at least one dose of METH on Day 1. This set will be summarized as treated and will be used for the disposition summaries and safety summaries prior to Day 4 dosing of IXT-m200.

10.2 Safety Set

The safety set will consist of subjects who receive at least one dose of IXT-m200 on Day 4. This set will be summarized as treated and will be used for the safety data summaries, and baseline characteristic summaries, and PK concentration summaries.

10.3 Pharmacokinetic Set

The PK set will consist of all subjects in the safety analysis set for whom at least 1 PK parameter can be calculated for METH or IXT-m200. This set will be summarized as treated and will be used for PK parameter summaries and analyses.

10.4 Pharmacodynamic Set

The PD analysis set will include all subjects in the safety analysis set who have completed all subjective response measures after at least 1 METH challenge following IXT-m200 administration. Subject exclusion may be determined on a case-by-case basis. Determination of events constituting major protocol deviations that would impact PD results, will be based on a blinded review of the protocol deviation and subject

completion listings prior to database lock. This set will be summarized as treated and will be used for the pharmacodynamic summaries and analyses.

11.0 Subject Disposition

The number and percentage of subjects randomized on Day 1 Challenge Day, subjects who discontinued prior to Day 4 randomization to treatment arm (IXT-m200 or Placebo), subjects dosed on Day 4, and members of each analysis set will be presented. The number and percentage of subjects who completed the study (per eCRF through Day 126, and per Protocol through Day 22 of the study) and withdrew from the study prematurely and reasons for withdrawal will be summarized.

12.0 Protocol Deviations and Violations

Protocol deviations/violations will be included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

All demographic data as collected during the screening visit will be listed by subject.

Subject demographics will be summarized descriptively for all subjects by treatment. The summary will include the subjects' age (in years), sex, race, ethnicity, weight (in kg), height (in cm), and BMI (in kg/m2). Demographics will be summarized for the safety, PK and PD sets.

13.2 Medical History

Medical history, categorized by preferred term according to MedDRA, will be listed by subject.

13.3 Other Baseline Characteristics

Recreational drug use history will be listed by subject. Instances of non-therapeutic METH use in lifetime, in the prior 30 days to screening and in the time between screening and Day -1 will be recorded and listed by subject.

14.0 Concomitant Medications

Concomitant medications, categorized by medication group and subgroup according to WHO Drug Dictionary, will be listed by subject. Medications with an end date prior to the first dose of IXT-m200 or Placebo on Day 4 of the study will be considered prior medications and will be noted in the listing. If a partial date allows a medication to be considered concomitant it will be categorized as such.

15.0 Treatment Compliance and Exposure

The number of subjects receiving each dose of METH and Placebo on each METH Challenge Day and number of subjects receiving each dose of IXT-m200 or Placebo within each cohort and overall will be summarized. All exposure data will be listed by subject. All drug administration data will be listed by subject.

Actual dose of IXT-m200 administered to each subject will be calculated as:

IXT-m200 dose (mg) = dose level (mg/kg) * body weight (kg) * [total vol. administered (mL) / planned vol. 225 mL]

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

16.1.1 Serum and Plasma Variables

Challenge Days Analysis Timepoints

- Plasma METH and its metabolite, amphetamine (AMP), concentrations will be collected beginning at predose, then at 0.0833, 0.25, 0.5, 1, 2, 4, 4.0833, 4.25, 5, 6, 8, 12, 16, 24, 36 and 72 hours relative to the first challenge dose on Day 1, Day 5, Day 12, Day 19 and Day 26 (as applicable).
- Scheduled timepoints as collected on the CRF will be mapped to planned timepoints relative to METH dosing per the table below.
    - Relative time from dosing of METH to each timepoint will be calculated.
    - Deviations from planned timepoints relative to METH dosing will be calculated.
- PK Day variable for each Challenge Day from predose through 72 hours after first challenge dose will be mapped to the Challenge Day of dosing.

Blood Sampling Times	Planned Timepoint Relative to METH Dosing	
Schedule Timepoint (per eCRF)	**Challenge Sequence = MP (i.e. First Challenge Dose at Time 0 is METH 30 mg)**	**Challenge Sequence = PM (i.e. Second Challenge Dose at Time 4 is METH 30 mg)**
BEFORE FIRST CHALLENGE	PREDOSE	PREDOSE
0.0833 HR AFTER FIRST CHALLENGE	0.0833 HR POST METH	
0.25 HR AFTER FIRST CHALLENGE	0.25 HR POST METH	
0.5 HR AFTER FIRST CHALLENGE	0.5 HR POST METH	
1 HR AFTER FIRST CHALLENGE	1 HR POST METH	
2 HR AFTER FIRST CHALLENGE	2 HR POST METH	
4 HR AFTER FIRST CHALLENGE*	4 HR POST METH	
4.0833 HR AFTER FIRST CHALLENGE	4.0833 HR POST METH	0.0833 HR POST METH
4.25 HR AFTER FIRST CHALLENGE	4.25 HR POST METH	0.25 HR POST METH
5 HR AFTER FIRST CHALLENGE	5 HR POST METH	1 HR POST METH
6 HR AFTER FIRST CHALLENGE	6 HR POST METH	2 HR POST METH
8 HR AFTER FIRST CHALLENGE	8 HR POST METH	4 HR POST METH
12 HR AFTER FIRST CHALLENGE	12 HR POST METH	8 HR POST METH
16 HR AFTER FIRST CHALLENGE	16 HR POST METH	12 HR POST METH
24 HR AFTER FIRST CHALLENGE	24 HR POST METH	20 HR POST METH
36 HR AFTER FIRST CHALLENGE	36 HR POST METH	32 HR POST METH
72 HR AFTER FIRST CHALLENGE	72 HR POST METH	68 HR POST METH
*Scheduled Timepoint 4 HR AFTER FIRST CHALLENGE reflects 0 HR relative to second challenge dose.		

IXT-m200 Analysis Timepoints

- Serum IXT-m200 concentrations will be measured on Day 4 at predose, 2.25, 4, 6, 12, 24 and 72 hours post start of the infusion, and then weekly until discharge (before the first dose of the METH challenge on Day 12, 19 and 26, as applicable), and at each follow-up visit (Day 28, 35, 42, 49, 56, 63, 84, 105, 126).
- Relative time from dosing of IXT-m200 to each timepoint will be calculated.
- Deviations from scheduled timepoints will be calculated.
- PK Day variable for Day 4 predose through 72 hours post start of infusion will be mapped to Day 4.
- PK Day for all weekly and follow-up PK collections will be the day of visit.

16.1.1.1 Concentrations

- Plasma concentration of METH and amphetamine (AMP)
- Serum concentration of IXT-m200

16.1.1.2 Parameters

- PK Parameters for METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26 (as applicable)
- PK Parameters for IXT-m200 following administration on Day 4

Table 1: Plasma/Serum Pharmacokinetic Parameters

Parameter	Description	Analyte/Day	SAS Programming Notes
C0	Initial concentration. Given only for bolus IV models. It is equal to the first observed concentration value if that value occurs at the dose time. Otherwise, it is estimated by back extrapolating from the first two concentration values.	METH on Day 1, Day 5, Day 12, Day 19 and Day 26	C0 from WNL
Cmax	Maximum concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	Cmax from WNL
Tmax	Time to maximum concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	Tmax from WNL
AUC0-36	Area under the concentration-time curve from time 0 to 36 hours postdose reported only for subjects who received METH as the first dose	If Challenge Sequence = MP, for METH and	AUC0-36 from WNL summary file is used if time deviation at 36 hr is ≤10%. If time

Parameter	Description	Analyte/Day	SAS Programming Notes
	of the METH challenge (Challenge Sequence = MP). AUC0-36 will be calculated by WNL to the actual time. If the nominal 36 hr concentration was taken with a time deviation greater than 10% at 36 hr or was not taken and a valid λz is available, then the data will be extrapolated to 36 hr. If the nominal 36 hr concentration was taken with a time deviation greater than 10% or was not taken and a valid λz is not available, then AUC0-36 hr will not be calculated.	AMP on Day 1, Day 5, Day 12, Day 19 and Day 26	deviation at 36 hr is >10% or if the nominal 36 hr concentration is missing, partial area reported as AUC0-36 in PARM file is used if Rsq ≥ 0 .75. If Rsq < 0.75 parameter will be flagged for exclusion in summaries and analyses.
AUC0-32	Area under the concentration-time curve from time 0 to 32 hours postdose reported only for subjects who received METH as the second dose of the METH challenge (Challenge Sequence = PM). AUC0-32 will be calculated by WNL to the actual time. If the nominal 32 hr concentration was taken with a time deviation greater than 10% at 32 hr or was not taken and a valid λz is available, then the data will be extrapolated to 32 hr. If the nominal 32 hr concentration was taken with a time deviation greater than 10% or was not taken and a valid λz is not available, then AUC0-32 hr will not be calculated.	If Challenge Sequence = PM, METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26	AUC0-32 from WNL summary file is used if time deviation at 32 hr is ≤10%. If time deviation at 32 hr is >10% or if the nominal 32 hr concentration is missing, partial area reported as AUC0-32 in PARM file is used if Rsq ≥ 0 .75. If Rsq < 0.75 parameter will be flagged for exclusion in summaries and analyses.
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	AUClast from WNL
AUCinf	Area under the concentration-time curve (time 0 to infinity). Percent extrapolation less than or equal to 30% and r^2 greater than or equal to 0.75 is required to obtain a reliable AUCinf.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	AUCINF_obs from WNL If Rsq < 0.75 or AUC_%Extrap_obs >30% then parameter will be flagged for exclusion in summaries and analyses.

Parameter	Description	Analyte/Day	SAS Programming Notes
%AUCext (listed only)	Percentage of the AUCinf that is due to the extrapolation to infinity.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	AUC_%Extrap_obs from WNL.
Lz (λz) (listed only)	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least three points and an r^2 greater than or equal to 0.75 are required to obtain a reliable λz.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	Lambda_z from WNL If Rsq < 0.75 then parameter will be flagged for exclusion in summary tables.
t1/2	Terminal phase half-life expressed in time units. r^2 greater than or equal to 0.75 is required to obtain a reliable $t_{1/2}$.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	HL_Lambda_z from WNL If Rsq < 0.75 then parameter will be flagged for exclusion in summary tables.
CL	Apparent clearance. Percent extrapolation less than or equal to 30% and r^2 greater than or equal to 0.75 is required to obtain a reliable CL.	METH on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	CL_obs for METH and IXT-m200 from WNL. If Rsq < 0.75 or AUC_%Extrap_obs > 30% then parameter will be flagged for exclusion in summary tables.
Vd	Volume of distribution. Percent extrapolation less than or equal to 30% and r^2 greater than or equal to 0.75 is required to obtain a reliable Vd.	METH on Day 1, Day 5, Day 12, Day 19 and Day 26 IXT-m200	Vz_obs for METH and IXT-m200 for AMP from WNL. If Rsq < 0.75 or AUC_%Extrap_obs > 30% then parameter will be flagged for exclusion in summary tables.
Rsq (listed only)	Goodness of fit statistic for the log-linear terminal elimination phase of the concentration-time profile identified by least-squares linear regression.	METH and AMP on Day 1, Day 5, Day 12, Day	Rsq from WNL

Parameter	Description	Analyte/Day	SAS Programming Notes
		19 and Day 26 IXT-m200	

Note: AUCs will be calculated using linear up / log down, expressed in units of concentration x time.

16.1.2 Urine Variables

Challenge Days Analysis Timepoints

- Urine will be collected beginning at predose, then for 0-4, 4-8, 8-12, 12-16, 16-24 and 24-36 hours relative to the first challenge dose on Day 1, Day 5, Day 12, Day 19 and Day 26 (as applicable).
- Scheduled timepoints as collected on the CRF will be mapped to planned timepoints relative to METH dosing per the table below.
- PK Day variable for each Challenge Day from predose through 36 hours after first challenge dose will be mapped to the Challenge Day of dosing.

Urine Sampling Times	Planned Timepoint Relative to METH Dosing	
Schedule Timepoint (per eCRF)	Challenge Sequence = MP (i.e. First Challenge Dose at Time 0 is METH 30 mg)	Challenge Sequence = PM (i.e. Second Challenge Dose at Time 4 is METH 30 mg)
Predose	PREDOSE	PREDOSE
0-4	0-4	
4-8	4-8	0-4
8-12	8-12	4-8
12-16	12-16	8-12
16-24	16-24	12-20
24-36	24-36	20-32

16.1.2.1 Amounts Excreted

- Amount of METH and AMP excreted in urine (Ae)
    - Calculated as the urine volume times the urine concentration for each interval.

16.1.2.2 Parameters

- PK Parameters for METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26

Table 2: Urine Parameters

Parameter	Description	Analyte/Day	SAS Programming Notes
Ct1-t2	Concentration (of the unchanged drug) in the collection interval t1-t2.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26	Directly from data, no calculation required.
Vt1-t2	Volume of the urine collected in the interval t1-t2	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26	Measured in the clinic, captured on the CRF, no calculation required.
Aet1-t2 (urine)	Amount of drug excreted unchanged into urine to time t2, calculated as the urine volume times the urine concentration for each interval. Intervals: 0-4, 4-8, 8-12, 12-16 (challenge sequence = MP only), 16-24 (challenge sequence = MP only), 12-20 (challenge sequence = PM only), 24-36 (challenge sequence = MP only), 20-32 hours (challenge sequence = PM only)	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26	Concentration(t1-t2) *volume(t1-t2)
Aet (urine) Ae36 and Ae32, separately	Total amount of drug excreted unchanged into urine to time t (t = 36 or 32 hours if challenge sequence = MP or PM, respectively), obtained by adding the amounts excreted over each collection interval through 36 hours post first dose of the METH challenge.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26	Summation of intervals [Aet1-t2] through 36 or 32 hours post METH.
CLr (urine)	Renal clearance. Note: Convert units of AUC to units of Aet prior to calculation.	METH and AMP on Day 1, Day 5, Day 12, Day 19 and Day 26	CLr = Aet/AUC0-t where t will be 32 hr if Challenge Sequence = PM, 36 hr if Challenge Sequence = MP.

16.2 Pharmacokinetic Summaries

16.2.1 Pharmacokinetic Concentrations

Concentrations for METH, AMP and IXT-m200 below the quantifiable limit (BQL) will be set to 0 in the computation of mean concentration values. Descriptive statistics (n, mean, geometric mean, SD, SE, coefficient of variation [%CV], median, min, and max) will be used to summarize the serum concentrations

by METH Challenge Day (as applicable) and IXT-m200 dose level at each scheduled timepoint. If over half of the subjects for a given timepoint have values BQL then the descriptive statistics will not be presented and will instead display as BQL for the mean and minimum. With the exception of max all other statistics will be missing.

Linear and semi-logarithmic plots of the following profiles will be provided:

- Mean plasma METH and AMP concentration by nominal sampling time relative to METH dosing will be provided by Challenge Day for each IXT-m200 dose level (one plot per dose level).
- Mean plasma METH and AMP concentration by nominal sampling time relative to METH dosing will be provided by IXT-m200 dose level for each Challenge Day (one plot per Challenge Day).
- Mean serum IXT-m200 concentration by nominal sampling time post IXT-m200 dosing on Day 4 will be provided by IXT-m200 dose level.

These plots will show time in hours. The plots will match the summary table results and will not have an observation at a given timepoint if more than half of the subjects have values BQL.

Linear and semi-logarithmic plots of the following individual concentration profiles will be provided:

- Individual plasma METH and AMP concentration by actual sampling time relative to METH dosing will be provided by Challenge Day for each subject (one subject per page).
- Individual serum IXT-m200 concentration by actual sampling time will be provided for each subject (one subject per page).

These plots will show time in hours. Individual plots will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

Scatter plots of individual values and mean Cmax and AUC will be provided by Challenge Day and IXT-m200 dose level.

All individual subject concentration data will be listed with both scheduled timepoints and timepoints relative to METH dosing.

16.2.2 Pharmacokinetic Parameters

PK parameters for METH and IXT-m200 will be estimated using non-compartmental methods with WinNonlin®.

The serum/plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters for IXT-m200, METH, and AMP, BQL values at the beginning of the profile will be set to zero. For IXT-m200, METH, and AMP, BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. To estimate the PK parameters for METH (METH administered via IV Bolus), concentrations that are BQL at predose or the beginning of the profile will be flagged for exclusion (assigned a value of missing) so that the initial concentration may be estimated. Actual sampling times (relative to METH dosing for METH and AMP parameters), rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time (relative to METH dosing for METH and AMP parameters) may be substituted in order to calculate the PK parameter.

Descriptive statistics (n, mean, geometric mean, SD, SE, %CV, median, min, and max) will be used to summarize the calculated PK parameters by IXT-m200 dose level and Challenge Day (as applicable). Only n, min, median, and max will be reported for tmax.

Determination of points to be included in λz range will follow the Guideline for Defining, Calculating and Summarizing Pharmacokinetic / Pharmacodynamic Parameters (EDSREP 009 R 01).

16.2.2.1 Analysis of the Primary Efficacy Endpoint

The effect of IXT-m200 on METH exposure will be evaluated with a linear mixed effects model. The response variable in the model will be the natural-log transformed change in METH exposure parameters: Cmax and AUCinf. The model will contain fixed effects for treatment, day (categorical day postdose), natural-log transformed Day 1 baseline parameter and a treatment-by-day interaction, and a random effect for subject.

Geometric LS Mean change from Day 1 for each treatment on each day will be presented. Geometric LS Means Ratios of change in METH exposure for each dose level of IXT-m200 compared to Placebo on each Day 5 (primary), Day 12, Day 19 and Day 26 will be presented along with the 95% confidence intervals.

The following SAS pseudo-code may be used:

```
Proc mixed data=params;
      by param;
      class treatment day subject;
      model lnparmchg = treat day lnbase treatment*day/s ddfm=betwithin;
      repeated day /type=ar(1) subjectID=subject;
      lsmeans treatment*day/pdiff;
run;
```

16.2.3 Pharmacokinetic Amounts Excreted

Descriptive statistics (n, arithmetic mean, geometric mean, SD, SE, %CV, median, min, and max) will be used to summarize the urine amounts excreted for METH and AMP by treatment at each nominal time interval.

All individual subject urine concentration data, volume data and parameters will be listed.

17.0 Pharmacodynamic Analysis

Subjective effects of METH will be measured by the Drug Effects VAS which will be administered within 30 minutes prior to the first dose, then 15, 30, 45, 60, 90, 120, and 180 minutes relative to each challenge (METH and Placebo) on each Challenge Day. Overall Drug Liking and Take Drug Again VAS will be measured at 180 minutes relative to each challenge.

17.1 Pharmacodynamic Variables

Assessment	Scale	Timepoints	Parameters to include in ADPDP	Notes
Balance Effects VAS				
Overall Drug Liking	Bipolar	180 min post challenge	180 min Score, Change from Baseline Score	
Take Drug Again	Bipolar	180 min post challenge	180 min Score, Change from Baseline Score	
Drug Effects (positive, negative, craving) VAS			Predose timepoint will not be used for calculation of AUEC for all below VAS assessments. Instead a time 0 value of 0 will be assumed for calculation purposes only.	
Feel	Unipolar	0 to 180 min post challenge	Emax, TEmax, AUEC and Change from Baseline Parameters	
High	Unipolar	0 to 180 min post challenge	Emax, TEmax, AUEC and Change from Baseline Parameters	
Good Effects	Unipolar	0 to 180 min post challenge	Emax, TEmax, AUEC and Change from Baseline Parameters	
Stimulated	Unipolar	0 to 180 min post challenge	Emax, TEmax, AUEC and Change from Baseline Parameters	
Dislike	Unipolar	0 to 180 min post challenge	Emax, TEmax, AUEC and Change from Baseline Parameters	
Like	Unipolar	0 to 180 min post challenge	Emax, TEmax, AUEC and Change from Baseline Parameters	
More	Unipolar	0 to 180 min post challenge	Emax, TEmax, AUEC and Change from Baseline Parameters	
Crave	Unipolar	0 to 180 min post challenge	Emax, TEmax, AUEC and Change from Baseline Parameters	
Note: Baseline for Change from Baseline parameters is defined as the parameter calculated on Day 1.				

17.2 Pharmacodynamic Parameters

PD parameters described below will be calculated for each VAS presented above for each subject for each treatment (METH and Placebo) on each Challenge Day (Day 1, 5, 12, 19, and 26). Actual assessment times will be used for calculation, if an actual time is missing, nominal time post challenge may be substituted for calculation of parameters.

Parameter	Description	SAS Programming Notes
Emax	Peak (maximum) effect postdose obtained directly from experimental data without interpolation over the 180 minutes of collection.	Maximum value post dose through sampling period.
TEmax	Time to peak effect. First observed time to reach peak effect obtained directly from the experimental data without interpolation, expressed in time units.	Time of Emax.
AUEC	Area under the effect curve from time 0 to 180 minutes post drug administration. Note, time 0 value of 0 will be assumed for calculation of 0 to 180 min. Measured “predose” values will not be used for calculation of AUEC as Drug Effects should not be evaluated prior to dosing.	AUEC from SAS using the trapezoidal rule. 1. Assume a time 0 value of 0 for all unipolar scales. 2. Calculate via trapezoidal rule from time 0 to X hours post dose.
Change from Baseline Emax, Change from Baseline AUEC, Change from Baseline 180 min Score	Change from Baseline for each Emax, AUEC and 180 min Score will be calculated for each VAS assessment for METH and Placebo on each Challenge Day 5, 12, 19 and 26. Baseline parameters are the Day 1 parameters from METH and Placebo, respectively.	Challenge Day 1 Parameter – Challenge Day X Parameter

17.3 Pharmacodynamic Summaries

17.3.1 Pharmacodynamic Assessments

Individual subject PD assessment results collected over time will be presented in data listings for each treatment on each Challenge Day.

PD assessment results collected over time will be summarized for each assessment by treatment and nominal timepoint on each Challenge Day using descriptive statistics (n, mean, median, SD, SE, Q1, Q3, min and max).

17.3.2 Pharmacodynamic Parameters

All PD parameters calculated will be presented in the data listings.

PD parameters and change from baseline parameters will be summarized by challenge (METH or Placebo), IXT-m200 dose level and Challenge Day using descriptive statistics (n, mean, median, SD, SE, Q1, Q3, min and max).

17.3.2.1 Statistical Analysis of Pharmacodynamic Parameters

The treatment effect of IXT-m200 on the subjective effects of METH will be analyzed using a 2-sample t-test on the change from baseline parameters. The analysis will compare the change from baseline values for METH between each dose level of IXT-m200 and Placebo. Mean, mean differences and corresponding 95% CIs of the mean differences will be reported.

The following SAS pseudo-code may be used:

```
proc ttest data=parm alpha=0.05;
    by test param;
    class IXTtreatment;
    var change;
run;
```

18.0 Safety Analyses

18.1 Safety Variables

The following safety variables will be summarized for the Safety Set:

- Adverse Events (AEs)
- Clinical Laboratory Evaluations
  - Cytokines
  - Clinical Chemistry – including Liver Function Tests
  - Hematology
  - Urinalysis
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
  - Pulse rate
  - Oral body temperature
  - Respiratory rate
  - Oxygen Saturation (SpO2)
- Electrocardiograms (ECG)
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - QTc (Frederica) Interval
  - ECG Evaluation
- Immunogenicity

All safety variables will be listed by subject for all subjects.

18.1.1 Adverse Events

All AE summaries will include only treatment emergent adverse events, unless otherwise noted. Treatment-emergent adverse events (TEAE) are those which occur after the first dose of study drug (METH or Placebo) on Day 1 of the study.

TEAEs occurring after first dose of study drug on Day 1 and prior to dosing of IXT-m200 on Day 4 will be summarized overall for the Qualification Safety Set. TEAEs occurring post IXT-m200 dosing on Day 4 through the end of inpatient stay and those occurring during outpatient follow-up visits will be summarized separately by IXT-m200 dose level and overall for the Safety Set. Each subject's inpatient stay ends on the date in which they are discharged from the clinic. Inpatient Discharge date is unique for each subject and is captured on the CRF as the date in which the subject was discharged from the initial clinic stay.

A breakdown of the number and percentage of subjects reporting each TEAE, categorized by body system and preferred term coded according to the Medical Dictionary for Regulatory Activities (MedDRA), will be presented. Counting will be done by subject only, not by event; subjects will only be counted once within each body system or preferred term.

Summaries of events reported, categorized by relationship to IXT-m200 and METH, will be provided. Subjects with multiple events within a particular body system or preferred term will be counted under the category of their most drug-related event within that body system or preferred term. Relationship to IXT-m200 and METH is categorized as recorded on the eCRF (or map eCRF categories to related / unrelated).

A summary of events reported, categorized by severity as recorded on eCRF, will also be provided. Subjects with multiple events within a particular body system or preferred term will be counted under the category of their most severe event within that body system or preferred term.

A listing of adverse events leading to study discontinuation will be provided.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date one minute after dosing
- Missing AE start date will be assumed to be after treatment for the determination of TEAE and on treatment for single treatment studies but will not be attributed to treatment in studies with multiple treatments

18.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events (SAE) will be provided by subject.

18.1.3 Laboratory Data

Clinical laboratory data will be presented using units from the study data tabulation model (SDTM) Controlled Terminology.

All laboratory data will be listed, including laboratory variables not listed in the protocol. A separate listing, including out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory.

Descriptive statistics summarizing continuous laboratory results for clinical chemistry, hematology and urinalysis (observed values and derived changes from baseline) by IXT-m200 dose level and visit will be included. Baseline for laboratory results is defined as the last measurement prior to first dose of study drug.

Descriptive statistics summarizing continuous laboratory results of cytokine tests (observed and derived changes from predose) by treatment and scheduled time will be included. If the predose observation is missing, and a baseline observation exists for cytokine tests, baseline may be used.

18.1.4 Vital Signs

Descriptive statistics will be used to summarize vital signs and changes from predose on each METH Challenge Day by IXT-m200 dose level, METH Challenge Sequence (MP or PM) and scheduled time.

Descriptive statistics will be provided to summarize vital signs and change from baseline by IXT-m200 dose level and scheduled time on Day 4 during and post infusion, and through each follow-up visit. Baseline for vital signs is defined as the last measurement prior to first dose of study drug (prior to dosing during Challenge Day 1).

All vital signs measures (including body weight) will be listed by subject.

18.1.5 Electrocardiograms

Descriptive statistics will be used to summarize ECG parameters (observed values and derived changes from predose) on each METH Challenge Day by IXT-m200 dose level, METH Challenge sequence and scheduled time.

Descriptive statistics will be provided to summarize ECG parameters (observed values and derived changes from baseline) by IXT-m200 dose level and scheduled time on Day 4 during and post infusion. Baseline for ECG parameters is defined as the last measurement prior to first dose of study drug (prior to dosing during Challenge Day 1).

All ECG parameters will be listed by subject.

18.1.6 Immunogenicity

Blood samples for measurement of HACA will be taken on Days 3 (baseline), 28, 63, and 126. Results from baseline and the last measurement postdose will be summarized by IXT-m200 treatment group and listed by subject.

18.1.7 Other Observations Related to Safety

Physical examination findings will be listed by subject and visit.

Drug and Alcohol screen results conducted throughout the study will be listed by subject.

Columbia-Suicide Severity Rating Scale (C-SSRS) responses will be listed by subject.

Administration of meals and snacks by study day will be listed by subject.

19.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. STAMPOUT: Study of Antibody for Methamphetamine Outpatient Therapy. Version 5.0, Final, 30 May 2018.

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Verrico CD, Mahoney JJ, Thompson-Lake DGY, Bennett RS, Newton TF, La Garza De R. Safety and efficacy of varenicline to reduce positive subjective effects produced by methamphetamine in methamphetamine-dependent volunteers. *Int J Neuropsychopharmacol*. 2014;17(2):223-233. doi:10.1017/S146114571300134X.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ADaM	Analysis data model
AMP	amphetamine
AUC	area under the concentration-time curve
AUEC	Area under the effect curve
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CSR	Clinical study report
CV	Coefficient of variation
DDT	Data definition table
DEQ	Drug effects questionnaire
DSMB	Data and Safety Monitoring Board
DSM-V or –IV	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
HACA	human anti-chimeric antibody
ICF	Informed consent form
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IV	intravenous
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
METH	methamphetamine
PD	Pharmacodynamic
PK	Pharmacokinetic
QA'd	Quality assured
QC'd	Quality controlled
SAP	Statistical analysis plan
SAE	Serious adverse event
SD	Standard deviation

Glossary of Abbreviations:	
SDTM	Study data tabulation model
SE	Standard error
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
WHO-DDE	World Health Organization – Drug Dictionary Enhanced
WNL	WinNonlin

Appendix 2: Schedule of Assessments

Inpatient Stay (Day -1 – Day 22)

		Inpatient Timeline (Days)								Follow-up (Days)	
	Screening	**-1**	**1**	**2**	**3**	**4**	**5, 12, 19**	**6, 13, 20**	**22 [p]**	**28, 35, 42, 49, 56, 63 (±2 days)**	**84, 105, 126 (±3 days), ET[q]**
Admit		X									
ICF	X										
Drug use assessment[a]	X	X								X	X
Psychiatric evaluation[b]	X								X		
Physical exam[c]	X	X		X				X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X
Clinical labs[e]	X	X		X				X		X	X
Drug and ETOH screens[f]	X	X								X	X
ECG[g]	X	X	X	X		X	X	X			
Telemetry[h]		X	X			X	X				
AE monitoring[i]		X	X	X	X	X	X	X	X	X	X
METH challenge[j]			X				X				
mAb dose[k]						X					
Blood for PK[l]			X			X	X	X		X	X
Blood for HACA[m]					X					X	X
Urine collection for PK[n]			X				X	X			
DEQ[o]			X				X				
Blood for cytokines[r]						X					
Discharge[p]									X		

AE = adverse event; DEQ = drug effects questionnaire; ECG = electrocardiogram; ET = early termination visit; ETOH = ethanol; HACA = human anti-chimeric antibody; ICF = informed consent form; mAb = monoclonal antibody; METH = methamphetamine; PK = pharmacokinetic

a. Drug use history will be taken to assess drug use over the past 30 days using DSM-5 criteria (Section **Error! Reference source not found.**).. During follow-ups, drug use history will be collected on Days 28, 63, and 105 only.
b. Psychiatric evaluations will be taken during medical history and will include the C-SSRS at Screening and again on Day 22 (C-SSRS will not be done on Day 22 if subject elects to participate in the inpatient extension stay).
c. Physical exams will be done once per day.
d. Vital sign measurements will be obtained every 0.25 hours during IXT-m200 dosing, then 0.25, 0.5, 1, 2, and 4 hours (±5 min) after dosing is completed, and as needed afterward until acceptable. On Days 1, 5, 12, and 19, vital signs will be measured within 30 min prior to the first dose, then 0.25, 1, 2, 4, 4.25, 5, 6, and 8 hours (±5 min) relative to the first METH challenge dose. Measurements will be done at least daily during the inpatient stay and at each follow-up visit.
e. Clinical laboratory assessments will be done once per day.
f. Qualitative urine drug and breath alcohol tests will be.
g. Electrocardiograms (12-lead) will be recorded at screening, on Day -1, then 3, 12, and 24 hours (±10 min) after IXT-m200 dosing on Day 4. (The 24 hour ECG will only be done at the Investigator's request for safety concerns, or if Day 5 dosing is not conducted). On Days 1, 5, 12, and 19, ECGs will

be recorded within 30 min prior to the first dose, then 1, 5, 8, and 24 hours (±10 min) relative to the first METH challenge dose.

h. Telemetry monitoring will be performed for a minimum of 4 hours on Day -1. Telemetry monitoring will be continuous from 0.5 hours before IXT-m200 or METH dosing to 8 hours and until normal: defined as heart rate within 20% of baseline at the final timepoint. Telemetry will be monitored as it is recorded, and a physician will review the data after completion of the recording.
i. Adverse event monitoring will be continuous from Day -1 through Day 126.
j. METH challenges will consist of 0 and 30 mg IV METH (randomized) and will be administered 4 hours apart.
k. IXT-m200 will be administered as a 2-hour IV infusion.
l. Serial blood samples will be taken for assessment of IXT-m200 and METH.
    - Pharmacokinetic samples for IXT-m200 will be taken predose, then 2.25, 4, 6, 12, 24, and 72 hours post start of the infusion. Subsequently, samples will be taken weekly until discharge (Days 12 and 19 before the first METH dose), then at each follow-up visit.
    - Pharmacokinetic samples for METH will be taken -0.25, 0.0833, 0.25, 0.5, 1, 2, 4, 4.0833, 4.25, 5, 6, 8, 12, 16, 24, 36, and 72 hours relative to the first METH dose. The second METH dose should be administered at 4 hours so that the subsequent sample is taken 5 minutes later (4.0833 hour timepoint).
m. Blood samples for measurement of HACA will be taken on Days 3 (baseline), 28, 63, and 126; if a sample is missed, it should be collected at the next visit.
n. Urine will be collected for analysis of METH excretion. Total urine collections will occur in increments of pre-dose (spot), 0-4, 4-8, 8-12, 12-16, 16-24, 24-36 hours relative to the first METH dose on each METH Challenge Day.
o. Subjective effects of METH will be measured by the DEQ which will be administered within 30 min prior to the first dose, then 15, 30, 45, 60, 90, 120, and 180 minutes relative to each METH dose.
p. Subjects who wish to remain in the Inpatient Extension Stay will not discharge; instead they will be subject to the procedures listed in the Inpatient Extension Stay table below.
q. Early termination visits may occur at any point during the study.
r. A blood sample will be taken prior to the IXT-m200 dose for cytokine baseline values (sample will not be analyzed if no infusion reaction occurs). If an infusion reaction occurs, samples will be taken at 1 and 4 hr post-start of the reaction for cytokine analysis.

Inpatient Extension Stay (Day 22 - Day 29)

	Inpatient Extension Stay (Days)					Follow-up (Days)	
	22	26	27	28	29	35, 42, 49, 56, 63 (±2 days)	84, 105, 126 (±3 days), ET
ICF	X						
Drug use assessment[a]						X	X
Psychiatric evaluation[b]					X		
Physical exam[c]	X		X		X	X	X
Vital signs[d]	X	X	X	X	X	X	X
Clinical labs[e]			X			X	X
Drug and ETOH screens[f]						X	X
ECG[g]		X	X				
Telemetry[h]		X					
AE monitoring[i]	X	X	X	X	X	X	X
METH challenge[j]		X					
Blood for PK[k]		X	X		X	X	X
Blood for HACA[l]				X		X	X
Urine collection for PK[m]		X	X				
DEQ[n]		X					
Discharge					X		

AE = adverse event; DEQ = drug effects questionnaire; ECG = electrocardiogram; ET = early termination visit; ETOH = ethanol; HACA = human anti-chimeric antibody; ICF = informed consent form; mAb = monoclonal antibody; METH = methamphetamine; PK = pharmacokinetic.

a. During follow-ups drug use history will be collected on Days 35, 63, and 105 only.
b. The C-SSRS only will be administered on Day 29.
c. Physical exams will be done once per day as described.
d. On Day 26 vital signs will be measured within 30 min prior to the first dose, then 0.25, 1, 2, 4, 4.25, 5, 6, and 8 hours (±5 min) relative to the first METH challenge dose. Measurements will be done at least daily during the inpatient stay and at each follow-up visit.
e. Clinical laboratory assessments will be done once per day.
f. Qualitative urine drug and breath alcohol tests will be performed.
g. On Day 26, ECGs will be recorded within 30 min prior to the first dose, then 1, 5, 8, and 24 hours (±10 min) relative to the first METH challenge dose.
h. Telemetry monitoring will be continuous from 0.5 hours before IXT-m200 or METH dosing to 8 hours and until normal: defined as heart rate within 20% of baseline at the final timepoint. Telemetry will be monitored as it is recorded, and a physician will review the data after completion of the recording.
i. Adverse event monitoring will be continuous from Day -1 through Day 126.
j. METH challenges will consist of 0 and 30 mg IV METH (randomized) and will be administered 4 hours apart.
k. Serial blood samples will be taken for assessment of IXT-m200 and METH PK.
   - Pharmacokinetic samples for IXT-m200 will be taken on Day 26 before the first METH dose, then at each follow-up visit.
   - Pharmacokinetic samples for METH will be taken -0.25, 0.0833, 0.25, 0.5, 1, 2, 4, 4.0833, 4.25, 5, 6, 8, 12, 16, 24, 36, and 72 hours relative to the first METH dose. The second METH dose should be administered at 4 hours so that the subsequent sample is taken 5 minutes later (4.0833 hour timepoint).
l. Blood samples for measurement of HACA will be taken on Days 28, 63, and 126; if a sample is missed, it should be collected at the next visit.

m. Urine will be collected for analysis of METH excretion. Total urine collections will occur in increments of pre-dose (spot), 0-4, 4-8, 8-12, 12-16, 16-24, 24-36 hours relative to the first METH dose on each METH challenge day.

Subjective effects of METH will be measured by the DEQ which will be administered within 30 min prior to the first dose, then 15, 30, 45, 60, 90, 120, and 180 minutes relative to each METH dose.

Appendix 3: List of End of Text Outputs

List of End of Text Tables and Figures:			
Output	**Title**	**Population Set**	**Final Analysis Only**
Section 14.1 – Disposition and Demographic Data			
Table 14.1.1.1	Summary of Subject Disposition – Screening and Qualification	All Subjects	
Table 14.1.1.2	Summary of Subject Disposition	Safety	
Table 14.1.2.1	Summary of Demographics	Safety	
Table 14.1.2.2	Summary of Demographics	PK	
Table 14.1.3.1	Summary of Qualification Study Drug Administration	Qualification Safety	
Table 14.1.3.2	Summary of Study Drug Administration – METH Challenges of	Safety	
Table 14.1.3.3	Summary of Study Drug Administration – IXT-m200	Safety	
Section 14.2.1 – Pharmacokinetic Data			
Table 14.2.1.1.1	Summary of METH and AMP Plasma Concentrations by Challenge Day	Safety	
Table 14.2.1.1.2	Summary of METH and AMP Pharmacokinetic Parameters by Challenge Day	PK	
Table 14.2.1.1.3	Statistical Analysis of Change in METH Pharmacokinetic Parameters following IXT-m200 Dosing	PK	
Table 14.2.1.2	Summary of METH and AMP Urine Pharmacokinetic Parameters by Challenge Day	PK	
Table 14.2.1.3.1	Summary IXT-m200 Serum Concentrations	Safety	Only at Final Lock
Table 14.2.1.3.2	Summary IXT-m200 Pharmacokinetic Parameters	PK	Only at Final Lock
Figure 14.2.1.4.1	Plot of Mean METH and AMP Plasma Concentrations versus Time on a Linear Scale by Challenge Day for each IXT-m200 Dose Level	Safety	
Figure 14.2.1.4.2	Plot of Mean METH and AMP Plasma Concentrations versus Time on a Linear Scale by IXT-m200 Dose Level for each Challenge Day	Safety	
Figure 14.2. 2.4.3	Plot of Mean METH and AMP Plasma Concentrations versus Time on a Semi-Log Scale by Challenge Day for each IXT-m200 Dose Level	Safety	

Figure 14.2.1.4.4	Plot of Mean METH and AMP Plasma Concentrations versus Time on a Semi-Log Scale by IXT-m200 Dose Level for each Challenge Day	Safety	
Figure 14.2.1.4.5	Plot of Individual METH and AMP Plasma Concentrations versus Time on a Linear Scale by Challenge Day	Safety	
Figure 14.2.1.4.6	Plot of Individual METH and AMP Plasma Concentrations versus Time on a Semi-Log Scale by Challenge Day	Safety	
Figure 14.2.1.4.7	Scatter Plot of METH Plasma Pharmacokinetic Parameters by Challenge Day for each Treatment	PK	
Figure 14.2.1.4.8	Scatter Plot of METH Plasma Pharmacokinetic Parameters by Treatment for each Challenge Day	PK	
Figure 14.2.1.5.1	Plot of Mean IXT-m200 Serum Concentrations versus Time on a Linear Scale	Safety	Only at Final Lock
Figure 14.2.1.5.2	Plot of Mean IXT-m200 Serum Concentrations versus Time on a Semi-Log Scale	Safety	Only at Final Lock
Figure 14.2.1.5.3	Plot of Individual IXT-m200 Serum Concentrations versus Time on a Linear Scale	Safety	Only at Final Lock
Figure 14.2.1.5.4	Plot of Individual IXT-m200 Serum Concentrations versus Time on a Semi-Log Scale	Safety	Only at Final Lock
Section 14.2.2 – Pharmacodynamic Data			
Table 14.2.2.1	Summary of Subjective Effects Questionnaires by Challenge Day	PD	
Table 14.2.2.2	Summary of Subjective Effects Parameters and Change from Baseline by Challenge Day	PD	
Table 14.2.2.3	Statistical Analysis of Change from Baseline Subjective Effects Parameters by Challenge Day	PD	
Section 14.3 – Safety Data			
Table 14.3.1.1.1	Summary of Adverse Events Occurring Prior to IXT-m200 Dosing on Day 4	Qualification Safety	
Table 14.3.1.1.2	Summary of Adverse Events Occurring During Inpatient Stay After IXT-m200 Dosing on Day 4	Safety	
Table 14.3.1.1.3	Summary of Adverse Events Occurring During Outpatient Follow-up	Safety	
Table 14.3.1.2.1	Summary of Treatment Emergent Adverse Events Occurring Prior to IXT-m200 Dosing on Day 4 by System Organ Class and Preferred Term	Qualification Safety	
Table 14.3.1.2.2	Summary of Treatment Emergent Adverse Events Occurring After IXT-m200 Dosing on Day 4 through End of Study by System Organ Class and Preferred Term	Safety	

Table 14.3.1.2.3	Summary of Treatment Emergent Adverse Events Occurring During Inpatient Stay After IXT-m200 Dosing on Day 4 by System Organ Class and Preferred Term	Safety	
Table 14.3.1.2.4	Summary of Treatment Emergent Adverse Events Occurring During Outpatient Follow-up by System Organ Class and Preferred Term	Safety	
Table 14.3.1.3.1	Summary of Treatment Emergent Adverse Events Occurring Prior to IXT-m200 Dosing on Day 4 by Relationship to METH Challenge Doses	Qualification Safety	
Table 14.3.1.3.2	Summary of Treatment Emergent Adverse Events Occurring During Inpatient Stay After IXT-m200 Dosing on Day 4 by Relationship to METH Challenge Doses	Safety	
Table 14.3.1.3.3	Summary of Treatment Emergent Adverse Events Occurring During Outpatient Follow-up by Relationship to METH Challenge Doses	Safety	
Table 14.3.1.4.1	Summary of Treatment Emergent Adverse Events Occurring During Inpatient Stay After IXT-m200 Dosing on Day 4 by Relationship to IXT-m200	Safety	
Table 14.3.1.4.2	Summary of Treatment Emergent Adverse Events Occurring During Outpatient Follow-up by Relationship to IXT-m200	Safety	
Table 14.3.1.5.1	Summary of Treatment Emergent Adverse Events Occurring Prior to IXT-m200 Dosing on Day 4 by Severity	Qualification Safety	
Table 14.3.1.5.2	Summary of Treatment Emergent Adverse Events Occurring During Inpatient Stay After IXT-m200 Dosing on Day 4 by Severity	Safety	
Table 14.3.1.5.3	Summary of Treatment Emergent Adverse Events Occurring During Outpatient Follow-up by Severity	Safety	
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	All Subjects	
Table 14.3.3	Not part of TFL – Reserved for Narratives in CSR		
Table 14.3.4	Listing of Abnormal Laboratory Values		
Table 14.3.5.1	Summary of Laboratory Results by Visit	Safety	
Table 14.3.5.2	Summary of Laboratory Results – Cytokines	Safety	
Table 14.3.6.1	Summary of Vital Signs by Challenge Day	Safety	
Table 14.3.6.2	Summary of Vital Signs relative to IXT-m200 Dosing	Safety	
Table 14.3.7.1	Summary of 12-Lead Electrocardiogram Results by Challenge Day	Safety	
Table 14.3.7.2	Summary of 12-Lead Electrocardiogram Results Relative to IXT-m200 Dosing	Safety	

Table 14.3.8	Summary of Immunogenicity Results	Safety	Only at Final Lock

List of End of Text Listings:		
Output	**Title**	**Final Analysis Only**
Section 16.2.1 – Disposition		
Listing 16.2.1.1	Subject Disposition	
Listing 16.2.1.2	Eligibility Criteria	
Listing 16.2.2	Not part of TFL – Reserved for protocol deviations in CSR	
Section 16.2.3 – Excluded Subjects		
Listing 16.2.3	Analysis Sets	
Section 16.2.4 – Demographics and Baseline Characteristics		
Listing 16.2.4.1	Subject Demographics	
Listing 16.2.4.2	Medical History	
Listing 16.2.4.3	Prior and Concomitant Medications	
Listing 16.2.4.4.1	DSM-V Criteria Assessments	
Listing 16.2.4.4.2	Recreational Drug Use History	
Listing 16.2.4.4.3	Record of Instances of Non-Therapeutic METH Use	
Section 16.2.5 - Compliance		
Listing 16.2.5.1	Study Drug Administration	
Listing 16.2.5.2	IXT-m200 Dosing Information	
Section 16.2.6 – Response Data		
Listing 16.2.6.1.1	METH and AMP Plasma Concentrations	
Listing 16.2.6.1.2	METH and AMP Plasma Pharmacokinetic Parameters	
Listing 16.2.6.1.3	METH and AMP Urine Concentrations and Volume	
Listing 16.2.6.1.4	METH and AMP Urine Pharmacokinetic Parameters	
Listing 16.2.6.1.5	IXT-m200 Serum Concentrations	Only at Final Lock
Listing 16.2.6.1.6	IXT-m200 Pharmacokinetic Parameters	Only at Final Lock
Listing 16.2.6.2.1	Subjective Effects Questionnaire Responses	
Listing 16.2.6.2.2	Subjective Effects Parameters and Change from Baseline	
Section 16.2.7 – Adverse Events Data		
Listing 16.2.7.1	Adverse Events	

Listing 16.2.7.2	Adverse Events Leading to Study Drug Discontinuation	
Section 16.2.8 – Laboratory Data		
Listing 16.2.8.1	Clinical Laboratory Results – Chemistry	
Listing 16.2.8.2	Clinical Laboratory Results – Hematology	
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis	
Listing 16.2.8.4	Clinical Laboratory Results - Cytokines	
Listing 16.2.8.5	Clinical Laboratory Results – Additional Assessments	
Listing 16.2.8.6	Drug and Alcohol Screen Results	
Section 16.2.9-10 – Other Safety Data		
Listing 16.2.9	Vital Signs	
Listing 16.2.10	12-Lead Electrocardiogram Results	
Listing 16.2.11	Immunogenicity Testing	Only at Final Lock
Listing 16.2.12	Physical Examination Findings	
Listing 16.2.13	Columbia-Suicide Severity Rating Scale (C-SSRS) Responses	
Listing 16.2.14	Meal Administration	

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.7	Randomization
Appendix 16.1.9.2.1	Statistical Appendix – SAS Output for Statistical Analysis of Change in METH Pharmacokinetic Parameters following IXT-m200 Dosing
Appendix 16.1.9.2.2	Statistical Appendix – SAS Output for Statistical Analysis of Change from Baseline Subjective Effects Parameters by Challenge Day

Appendix 4: Shells for Post-Text Tables, Figures and Listings

Shells are provided in a separate document.

20.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
13-MAR-2019	Reilly Reis Kimberly Martens Ryan Turncliff Emily Mick Lynne Pauley	Created from template, EDSREP 009 T 01 G.
07-APR-2020	Reilly Reis Emily Mick	Updated to include description of two separate locks and deliveries of TFLs. Updated PK parameter diagnostic criteria and immunogenicity data outputs. Updates based on protocol amendments and CRF updates.